Effective Health Care Program

Comparative Effectiveness Review
Number 37

Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment

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Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. HHSA 290-2007-10064-I

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AHRQ Publication No. 11(12)-EHC075-EF
January 2012

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None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.

Suggested citation: Fink HA, Ishani A, Taylor BC, Greer NL, MacDonald, R, Rossini D, Sadiq S, Lankireddy S, Kane RL, Wilt TJ. Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment. Comparative Effectiveness Review No. 37. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. HHSA 290-2007-10064-I.) AHRQ Publication No. 11(12)-EHC075-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

We would like to thank Marilyn Eells for outstanding editing support. We also would like to thank James Tacklind and Indulis Rutks for their literature searching expertise, database management, extracting skills, and all-around general support. Finally, we would like to thank Nino Alapishvili, M.D., Milind Junghare, M.D., and Wei Yen Kong, M.D., for their assistance with abstract triaging and data extraction.

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Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment

Structured Abstract

Objective. The objective was to systematically review and synthesize evidence regarding benefits and harms of screening for and monitoring and treatment of chronic kidney disease (CKD) stages 1–3.

Data Sources. The data sources were MEDLINE® and Cochrane Database of Systematic Reviews electronic databases, hand searches of references from relevant systematic reviews and eligible trials, and references from expert consultants.

Review Methods. We screened abstracts and full text articles of identified references for eligibility and reviewed randomized controlled trials (RCTs) for evidence on benefits and harms of CKD treatments. We reviewed RCTs and observational studies for evidence regarding possible benefits and harms of CKD screening or monitoring. For all included RCTs, data were extracted, quality was rated, and strength of evidence was graded. Evidence on the benefits and harms of CKD treatments was quantitatively synthesized when possible. Additional evidence on CKD screening and monitoring was qualitatively described.

Results. We found no RCTs of CKD screening or monitoring. In treatment RCTs, several interventions significantly reduced clinical events. In patients with proteinuria, nearly all with diabetes and hypertension, angiotensin converting enzyme inhibitors (ACEIs) (relative risk [RR], 0.60, 95 percent confidence interval [CI], 0.43 to 0.83) and angiotensin receptor blockers (ARBs) (RR 0.77, 95 percent CI, 0.66 to 0.90) significantly reduced risk of end-stage renal disease (ESRD) versus placebo. In patients with microalbuminuria who had cardiovascular disease or diabetes with other cardiovascular risk factors, ACEI treatment reduced mortality risk (RR 0.79, 95 percent CI, 0.66 to 0.96) versus placebo. In individuals with hyperlipidemia and impaired estimated glomerular filtration rate (eGFR) or creatinine clearance, HMG CoA-reductase inhibitors (statins) reduced risk of mortality (RR 0.80, 95 percent CI, 0.68 to 0.95), myocardial infarction (MI), and stroke compared with placebo. However, limited data addressed whether these effects differed between patients with and without CKD or as a function of CKD severity. In RCTs that directly compared different treatments, including high dose versus low dose, combination versus monotherapy, and strict versus standard control, it was unclear whether intensification of treatment improves clinical outcomes. Reporting of study withdrawals and adverse events was limited. Based on treatment RCT findings and additional indirect data, including high CKD prevalence, low CKD recognition and limited CKD monitoring in usual care, uncertain sensitivity of screening and monitoring measures for CKD, and insufficient evidence on CKD screening and monitoring harms, the overall benefits of CKD screening and monitoring are unclear. The likelihood of benefit, if present, appears to be greater in specific subgroups. For example, individuals not being treated with ACEIs or ARBs who have cardiovascular disease or diabetes combined with other cardiovascular risk factors may benefit from screening for albuminuria. Individuals not being treated with a statin who have hyperlipidemia and no cardiovascular disease may benefit from screening for impaired eGFR. Younger patients, and those without diabetes, hypertension, cardiovascular disease, or obesity,

are the least likely to benefit from CKD screening. Individuals with impaired eGFR and at high risk for cardiovascular complications who are not being treated with ACEIs or ARBs may benefit from monitoring for incident albuminuria.

Conclusions. No trials directly show a benefit for CKD screening or monitoring. The likelihood of benefit, if present, appears to be greater in specific subgroups. Screening and monitoring harms are poorly described. In selected CKD patients, ACEI or ARB treatment reduces ESRD risk, ACEI treatment reduces mortality risk, and statin treatment reduces risk of mortality, MI, and stroke. Many of these patients may already warrant treatment with these therapies regardless of CKD status. Many knowledge gaps remain, and additional research should increase understanding regarding optimal approaches to CKD screening, monitoring, and treatment.

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Executive Summary

Objectives

This systematic review evaluates the evidence regarding the potential benefits and harms of: (1) screening adults for early-stage chronic kidney disease (CKD stages 1–3); (2) monitoring adults with CKD stages 1–3 for progression of kidney dysfunction and/or kidney damage; and (3) treating adults with CKD stages 1–3.

This report's scope is limited to CKD stages 1–3 to inform patient care decisions of primary care physicians. Management of patients with CKD stages 4–5, generally performed by nephrologists, is outside the scope of the report. An additional aim of the report is to provide a synthesis of evidence to assist groups developing clinical practice recommendations regarding CKD screening and management.

Background

Definition of CKD

In CKD, the kidneys are damaged and/or cannot filter blood normally.[1] CKD increases the risk for many adverse health outcomes, including cardiovascular disease, end-stage renal disease (ESRD), and mortality. However, CKD is usually asymptomatic until its most advanced state.

CKD has been defined as decreased kidney function and/or kidney damage persistent for at least 3 months. Kidney dysfunction is indicated by a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2, while kidney damage most frequently is manifested as increased urinary albumin excretion.[2] Within this framework, CKD has been categorized into five stages:

- Stage 1: Kidney damage with GFR ≥90 mL/min/1.73 m^2.
- Stage 2: Kidney damage with GFR 60–89 mL/min/1.73 m^2.
- Stage 3: GFR 30–59 mL/min/1.73 m^2 regardless of kidney damage.
- Stage 4: GFR 15–29 mL/min/1.73 m^2 regardless of kidney damage.
- Stage 5: GFR <15 mL/min/1.73 m^2 regardless of kidney damage, or kidney failure treated by dialysis or transplantation.

A recent series of meta-analyses of large prospective cohort studies demonstrated the independent associations of each level of estimated GFR (eGFR) and albuminuria or dipstick proteinuria with total and cardiovascular mortality, ESRD, and acute kidney injury (AKI).[3,4] These associations were independent of cardiovascular risk factors. Informed by these results, a CKD consensus conference concluded that CKD staging should be modified:[5]

- Divide Stage 3 into 3a (GFR 45–59 mL/min/1.73m^2) and 3b (GFR 30–44 mL/min/1.73m^2).
- Add albuminuria strata within each GFR stage (urine albumin-creatinine ratio <30 mg/g [normoalbuminuria], 30–299 mg/g [microalbuminuria], or >300 mg/g [macroalbuminuria]).
- Identify the cause of CKD when possible.

Epidemiology of CKD

Approximately 11 percent of U.S. adults age 20 or older (23.5 million persons) have CKD.[6] Of these, nearly half are stage 1 or 2, nearly another half are stage 3, fewer than 4 percent are stage 4, and fewer than 2 percent are stage 5 and receive dialysis. Also, about half have albuminuria without impaired GFR, one-third have decreased GFR without albuminuria, and one-sixth have albuminuria plus impaired GFR. Of individuals with albuminuria, nearly 85 percent have microalbuminuria and the remainder have macroalbuminuria. Data from the National Health and Nutrition Examination Survey (NHANES) suggest that the prevalence of CKD is rising, particularly for stage 3.[7]

Etiology of CKD

Infrequently, CKD is caused by primary kidney disease (e.g., glomerular diseases, tubulointerstitial diseases, obstruction, and polycystic kidney disease). But in the vast majority of cases, it is associated with other medical conditions, such as diabetes and hypertension. For example, excluding those with ESRD, in 2008, 48 percent of Medicare patients with CKD had diabetes, 91 percent had hypertension, and 46 percent had atherosclerotic heart disease.[1] Other risk factors for CKD include older age, obesity, family history, and African American, Native American, or Hispanic ethnicity.

Screening for Early-Stage CKD

The rationale for considering screening for early-stage CKD includes the high and rising prevalence of CKD, its known risk factors, its numerous adverse health consequences, its long asymptomatic phase, the availability of potential screening tests for CKD, and the availability of treatments that may alter the course of early-stage CKD and reduce complications of early-stage CKD or its associated health conditions.

Some organizations already recommend CKD screening in selected populations. Kidney Disease: Improving Global Outcomes (KDIGO) recommends screening of all patients with hypertension, diabetes, or cardiovascular disease.[8] The American Diabetes Association recommends annual screening of all adults with diabetes, based on "expert consensus or clinical experience."[9] The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommends annual screening of all patients with combined hypertension and diabetes.[10] Also advocating selected screening, the National Kidney Foundation sponsors free CKD screening for all adults with hypertension, diabetes, or a primary relative with a history of kidney disease, hypertension, or diabetes.[11]

Nevertheless, the benefit of screening for early-stage CKD is uncertain. For screening to be beneficial, it should improve important clinical outcomes (while limiting harms) for screened individuals identified with CKD compared with individuals with CKD whose treatment started at a later time or stage. However, potential CKD treatments may be indicated for conditions associated with CKD. So demonstration of benefit from CKD screening requires that the treatment benefits CKD populations who would have had no indication for such treatment in the absence of CKD or that, among patients with an indication for the treatment, those with CKD have a relatively greater treatment benefit or benefit from the treatment at doses or treatment targets different from those of non-CKD patients.

Monitoring Early-Stage CKD for Progression

In most patients with CKD stages 1–3, GFR declines slowly.[12] However, the rate of decline varies among individuals, and many factors appear to impact progression.[13] Because CKD stages 1–3 usually progress asymptomatically, detection of early-stage CKD requires laboratory testing.

Some organizations recommend monitoring for changes in kidney function or damage in patients with CKD. For example, the Kidney Disease Outcomes Quality Initiative (KDOQI) recommends at least annual eGFR measurement in adults with CKD in order to predict onset of ESRD and evaluate the effect of CKD treatments.[13] JNC7 recommends annual quantitative measurement of albuminuria in all patients with "kidney disease."[14] KDOQI also recommends more frequent monitoring of CKD patients with worsening kidney function.[15]

Confirming the benefits of monitoring patients with CKD stages 1–3 for changes in kidney function and/or damage requires evidence similar to that for CKD screening. Treatment modified because of monitoring results would need to improve important clinical outcomes more than treatment modified at a later time or stage does, while limiting harms.

Treatment of CKD Stages 1–3

In most patients with nonprimary CKD stages 1–3, treatment is not directed at the CKD but at associated conditions or cardiovascular risk factors, such as diabetes and hypertension.[16] In efforts to reduce the risk of complications from these conditions, therapeutic goals are sometimes set more strictly for CKD patients than non-CKD patients. For example, JNC7 recommends a blood pressure goal of <130/80 mm Hg for patients with CKD or diabetes.[14] It has been suggested that medications such as angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may specifically treat CKD. However, whether their impact on CKD outcomes (e.g., incident ESRD) or markers (e.g., albuminuria)[17] is independent of their effect to lower blood pressure is not clear.[18]

Analytic Framework and Key Questions

During this project's topic refinement, we received feedback regarding the scope and relevance of draft Key Questions and feedback regarding the details of a draft protocol. The feedback came from the topic nominators, public reviewers, and a Technical Expert Panel (TEP) composed of researchers, clinicians, and representatives from numerous interested professional organizations and Federal and State agencies. These parties agreed that an independent comprehensive review of the issues introduced above would provide helpful guidance to clinicians and policymakers regarding diagnosis and management of early-stage CKD. There was consensus that the analytic framework, shown in Figure A, and Key Questions addressed the most important issues regarding CKD stages 1–3.

Key Question 1. In asymptomatic adults with or without recognized risk factors for CKD incidence, progression, or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?

Key Question 2. What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression, or complications?

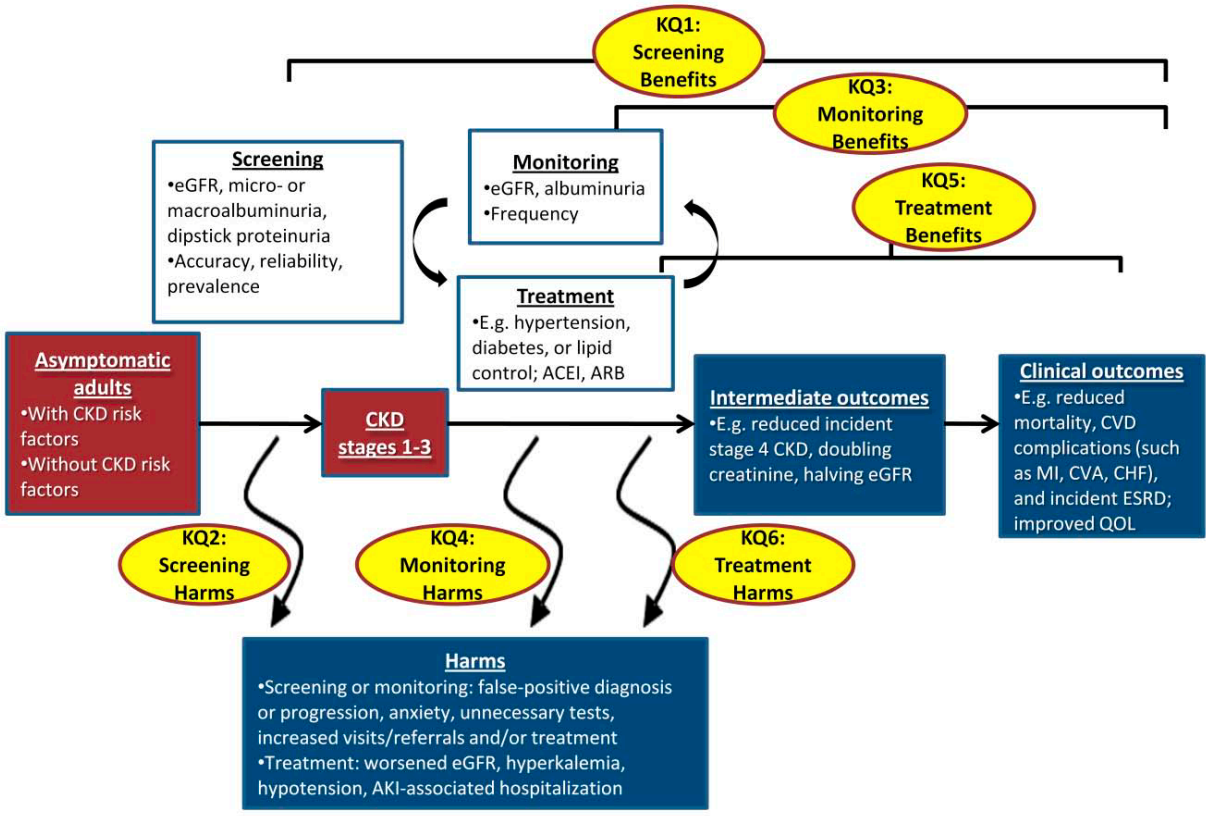
Key Question 3. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?

Key Question 4. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function and/or kidney damage?

Key Question 5. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?

Key Question 6. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

Figure A. Analytic framework for screening, monitoring, and treatment of chronic kidney disease stages 1–3



ACEI = angiotensin converting enzyme inhibitor; AKI = acute kidney injury; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; MI = myocardial infarction; QOL = quality of life.

Methods

We searched MEDLINE® and the Cochrane Database of Systematic Reviews (January 1985 to January 2011) to identify randomized controlled trials (RCTs) and controlled clinical trials (CCTs) of screening for and monitoring and treatment of patients with CKD. When no RCTs were identified that evaluated a CKD screening or monitoring intervention and reported outcomes, indirect evidence was reviewed regarding possible benefits and harms. This indirect evidence included observational studies on CKD prevalence, progression, and clinical recognition as well as accuracy and reliability of CKD screening and monitoring tests, and RCTs of CKD treatments. Although these observational studies were not identified through a comprehensive literature search, whenever possible we evaluated data from large representative U.S. cohorts. Assessment of CKD treatment benefits and harms was based strictly on direct evidence from RCTs. All titles and abstracts were assessed for eligibility based on Key Question–specific inclusion/exclusion criteria. For treatment intervention studies, data were extracted pertaining to study quality, trial characteristics, population characteristics, efficacy outcomes, and withdrawals and adverse events. Study quality for each trial was rated to formally assess risk of bias.[19] For each treatment comparison and major outcome, overall strength of evidence for the RCTs was evaluated using methods developed by the Agency for Healthcare Research and Quality and the Effective Health Care Program.[20] Briefly, strength of the evidence was evaluated based on four required domains: risk of bias, consistency, directness, and precision. Based on these four domains, the overall evidence was rated as: (1) high, indicating high confidence that further research is very unlikely to change the confidence in the estimate of effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, indicating low confidence that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; and (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion. If heterogeneity of patient populations, interventions, and outcomes was minimal, we pooled results using Review Manager 5.0.[21] Random effects models were used to generate pooled estimates of relative risks and 95 percent confidence intervals. Statistical heterogeneity was summarized using the I^2 statistic.[22] Additional evidence on CKD screening and monitoring was qualitatively described.

Results

We found no direct RCT evidence that addressed whether systematic CKD screening or monitoring improves clinical outcomes or increases harms. Indirect evidence that these interventions improve outcomes would need to include evidence that CKD treatment improves outcomes. Therefore, the ordering of the Results section has been changed from that of the Key Questions to be consistent with this logical flow.

CKD Treatment Benefits and Harms

- In RCTs of patients with CKD stages 1–3, several treatments reduced the risk of clinical outcomes, but the benefits appeared to be limited to specific CKD subgroups, some of which already had a clinical indication for the treatment studied (Table A).
- Only limited data addressed whether the relative effectiveness of treatment differed between patients with and without CKD or between patients with different severities of CKD.

- Trials used heterogeneous entrance criteria for renal function and damage, which often did not match KDOQI definitions for CKD stages 1–3 precisely, so we considered reasonable overlap sufficient for inclusion in this evidence synthesis. Because trials also rarely reported outcomes stratified by CKD stage or other CKD markers, it often was difficult to determine if trial clinical benefits applied to patients within individual CKD stages or eGFR or albuminuria categories.
  - ACEI and/or ARB treatment significantly reduced ESRD risk in patients with proteinuria (macroalbuminuria), most of whom had diabetes and hypertension. ESRD was not significantly reduced in patients with CKD stages 1–3 who did not have proteinuria. Patients with proteinuria, diabetes, and hypertension may benefit from ACEI or ARB treatment.
  - ACEI treatment significantly reduced mortality risk in patients known to have microalbuminuria who had either cardiovascular disease or the combination of diabetes and other cardiovascular risk factors. Relative risk reduction was not significantly different than in similar patients who did not have microalbuminuria. Patients who had microalbuminuria and were at high risk for cardiovascular complications may benefit from ACEI treatment at adequate doses.
  - Statins significantly reduced the risk of mortality, myocardial infarction (MI), and stroke in patients with hyperlipidemia and impaired eGFR or creatinine clearance, including those without coronary artery disease. Patients with hyperlipidemia and no coronary artery disease may not otherwise have an indication for statins, but the subset with CKD may benefit from treatment. No statin trials reported clinical outcomes data for patients with albuminuria.
  - Beta blockers significantly reduced the risk of mortality, MI, and congestive heart failure (CHF) events in patients with CHF and impaired eGFR, most of whom already were treated with an ACEI or ARB. Patients with systolic CHF already have an indication for beta blockers, regardless of whether they have CKD.
  - In RCTs that compared different active treatments head to head (e.g., ACEI versus ARB, ACEI versus beta blocker), there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.
  - In RCTs that compared high- versus low-dose treatment (ARB, statin), strict versus standard control (blood pressure, glycemia), combination versus monotherapy, and intensive multidisciplinary interventions (simultaneous targeting of blood pressure, diabetes, cholesterol, and/or reducing nephrotoxic drug exposure) versus usual care, there was no consistent significant difference in clinical outcomes between treatments, with strength of evidence ranging between low and insufficient for different comparisons.
  - Low-protein diets did not significantly reduce risk of mortality, ESRD, or any clinical vascular outcome compared with usual protein diets; risk for a composite renal outcome was significantly reduced in one trial, but this study also included participants with CKD stages 4–5.
- Few RCTs reported information on study withdrawals. When reported, withdrawals were often high and infrequently were separated by treatment group.

- Few trials reported adverse events. When reported, adverse events often did not appear to be predefined, were not systematically collected or reported, and often were not reported separately by treatment group.
- Although limitations in reporting impeded the quantitative synthesis of withdrawal and adverse events data from different studies, adverse events reported generally were consistent with known potential adverse effects of these treatments (e.g., hypotension with antihypertensives; cough with ACEIs; edema with calcium channel blockers; hyperkalemia with ACEIs, ARBs, and aldosterone).

CKD Screening Benefits and Harms

- We found no direct RCT evidence that addressed whether systematic screening of adults for CKD improves clinical outcomes or increases harms.
- Results from studies not directly linking systematic CKD screening to clinical outcomes contributed indirect evidence regarding whether CKD screening improves clinical outcomes.
  - Microalbuminuria and eGFR are sensitive screening tests for detecting one-time kidney abnormalities that may reflect CKD, but false positive rates are substantial, particularly for microalbuminuria; their sensitivity and specificity for CKD as defined by kidney dysfunction or damage lasting 3 months or longer is unknown.
  - Most patients with CKD stages 1–3 are clinically unrecognized. Because even populations with a high CKD prevalence (e.g., diabetes, hypertension, cardiovascular disease, older age) are not routinely tested for CKD, especially for albuminuria, systematic screening likely would lead to a large increase in CKD diagnoses.
  - Because of the above-noted treatment benefits in patients who have cardiovascular disease or diabetes combined with other cardiovascular risk factors (e.g., hypertension) and are known to have albuminuria, screening such patients for microalbuminuria or macroalbuminuria could lead to early initiation of ACEI or ARB treatment and reduced risk of mortality or ESRD.
  - Because of the above-noted treatment benefits in patients who have hyperlipidemia without cardiovascular disease and are known to have impaired eGFR or creatinine clearance, screening such patients for impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.
  - Virtually no RCTs of CKD treatments identified participants through screening, so the generalizability of treatment RCT results to patients with CKD stages 1–3 identified through screening is unknown.
- We found insufficient strength of evidence addressing potential harms associated with systematic CKD screening.

CKD Monitoring Benefits and Harms

- We found no direct RCT evidence regarding whether systematic monitoring of adults with CKD stages 1–3 for worsening kidney function or damage improves clinical outcomes.
- Results from studies not directly linking systematic CKD monitoring to clinical outcomes contributed indirect evidence regarding whether CKD monitoring improves clinical outcomes.

- Because of the above-noted treatment benefits in patients with albuminuria who have cardiovascular disease or have diabetes combined with other cardiovascular risk factors (e.g., hypertension), monitoring patients with impaired eGFR for development of albuminuria could lead to early initiation of ACEI or ARB treatment and reduced mortality or ESRD risk.
- Because of the above-noted treatment benefits in patients with hyperlipidemia who have impaired eGFR or creatinine clearance, monitoring such patients for development of impaired eGFR could lead to early initiation of statin treatment and reduced risk of mortality, MI, or stroke.
- In patients with CKD stages 1–3, kidney function usually slowly worsens over years, but may worsen faster in selected subgroups (e.g., those with diabetes, proteinuria, hypertension, older age, obesity, or dyslipidemia).
- The sensitivity and specificity of eGFR and albuminuria for identifying CKD progression in patients with CKD stages 1–3 are unknown.
- The vast majority of patients with recognized CKD stages 1–3 have serum creatinine measured regularly, so implementation of systematic eGFR monitoring may have only a limited impact on current practice. Because only a minority of patients with CKD stages 1–3 are annually tested for albuminuria, systematic albuminuria monitoring likely would lead to an increase in patients identified with clinical worsening of CKD.

- We found insufficient strength of evidence addressing potential harms associated with systematic CKD monitoring.

Table A summarizes the evidence for specific comparative effectiveness studies addressed in Key Question 5.

Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3

Treatment, Trials, Number of Patients	Level of Evidence	Summary, Conclusion, Comments
ACEI vs. placebo 17 trials; 11,661 patients	Mortality: moderate ESRD: moderate	• There was no significant difference in risk of all-cause or cardiovascular mortality, MI, or stroke overall, but significantly reduced risk of mortality in patients at high risk for cardiovascular complications who had microalbuminuria. • ACEI did not significantly reduce risk of all-cause or cardiovascular mortality, MI, or stroke. • ACEI significantly reduced ESRD risk in patients with overt proteinuria. • ACEI significantly reduced risk of all examined composite renal outcomes, but of few examined composite vascular outcomes. • Limits: Few studies were designed to assess clinical outcomes; there was considerable variability in the definitions of clinical outcomes.
ACEI vs. ARB 6 trials; 4,799 patients	Mortality: low ESRD: insufficient	• There was no significant difference in risk of all-cause or cardiovascular mortality, MI, or CHF; no data for stroke, ESRD, or composite vascular outcomes. • Results from the CKD subset of the ONTARGET study, whether defined by GFR <60 ml/min/1.73m^2 or albuminuria, showed no difference in risk of composite renal outcome. • Limits: There were small sample sizes in all but one trial; few trials reported most outcomes; there were few events in trials reporting.

Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

Treatment, Trials, Number of Patients	Level of Evidence	Summary, Conclusion, Comments
ACEI vs. CCB 6 trials; 4,357 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause or cardiovascular mortality, stroke, CHF, any composite vascular endpoint, or ESRD. • ACEI significantly reduced risk of composite renal outcome in one of three trials. • Limits: Several studies were not designed for/reported no clinical outcomes; most outcomes were reported in few trials; there were few events in trials reporting.
ACEI vs. BB 3 trials; 1,080 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause or cardiovascular mortality, stroke, CHF, composite vascular endpoints, or ESRD. • In one trial, ACEI significantly reduced risk of composite renal outcome. • Limits: Only one trial was designed to evaluate clinical vascular outcomes.
ACEI vs. diuretic 2 trials; 4,716 patients	Mortality: insufficient ESRD: low	• There was no significant difference in risk of all-cause mortality, stroke, ESRD, or composite vascular or renal outcomes. • Limits: One trial was not designed for clinical events; one trial was post hoc subgroup analysis with no mortality data by CKD status.
ARB vs. placebo 5 trials; 5,769 patients	Mortality: high ESRD: high	• There was no significant difference in risk of all-cause mortality, cardiovascular mortality, MI, or composite vascular outcomes. • ARB significantly reduced risk of CHF hospitalization and ESRD; results were mixed regarding risk of composite renal outcomes. • Limits: Several outcomes came from only one trial or were not reported.
ARB vs. CCB 3 trials; 3,924 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause mortality, stroke, composite vascular outcomes, or ESRD. • Limits: Most outcomes were uncommon or reported in only one trial.
ACEI+ARB vs. ACEI 6 trials; 7,357 patients	Mortality: moderate ESRD: insufficient	• There was no significant difference in risk of all-cause mortality. • Few vascular outcomes were reported, although combination significantly reduced risk of composite vascular outcome in one trial. • Limits: There were few clinical events and little data on renal outcomes.
ACEI+ARB vs. ARB 3 trials; approximately 4,300 patients	Mortality: insufficient ESRD: insufficient	• Only one trial reported all-cause mortality (no deaths in any treatment group); no trials reported information on vascular outcomes or ESRD. • Limits: There were few clinical events.
ACEI+ARB vs. ACEI or ARB 1 trial; 8,933 patients	Mortality: moderate ESRD: low	• There was no significant difference in risk of all-cause mortality, cardiovascular mortality, ESRD, or single composite vascular outcome reported. • Limits: This was a single post hoc analysis.
ACEI+CCB vs. ACEI 1 trial; 481 patients	Mortality: insufficient ESRD: insufficient	• No data were reported for mortality or individual vascular or renal outcomes. • There was no significant difference in risk of composite vascular outcome of serious cardiovascular events. • Limits: Few events were reported.
ACEI+CCB vs. ACEI+diuretic 2 trials; 1,425 patients	Mortality: insufficient ESRD: insufficient	• There was no significant difference in risk of mortality, "cardiac disorders," "vascular disorders," or a single composite renal outcome. • Limits: There were few deaths or renal events; no other clinical outcomes were reported.
ACEI+diuretic vs. placebo 1 trial; 4,526 patients	Mortality: low ESRD: insufficient	• There was no significant difference in risk of all-cause or cardiovascular mortality, MI, stroke, composite vascular outcome, or composite renal outcome. • Limits: This was a single post hoc analysis.

Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

Treatment, Trials, Number of Patients	Level of Evidence	Summary, Conclusion, Comments
ARB vs. different ARB 2 trials; 1,745 patients	Mortality: Telmisartan vs. losartan low; telmisartan vs. valsartan low ESRD: Telmisartan vs. losartan insufficient; telmisartan vs. valsartan low	• Compared with losartan, telmisartan significantly reduced risk of mortality and one composite vascular outcome but not a composite renal outcome. • There was no significant difference between telmisartan and valsartan in risk of all-cause or cardiovascular mortality, MI, stroke, CHF hospitalization, ESRD, or composite vascular or renal outcomes. • Limits: There were few clinical events; no studies compared losartan and valsartan.
ARB vs. ARB (high vs. low dose) 3 trials; 998 patients	Mortality: insufficient ESRD: insufficient	• One trial reported three total deaths; a second trial reported that there were no deaths in any treatment groups. • No other cardiovascular or renal outcomes were reported. • Limits: There were few clinical events.
BB vs. placebo 2 trials; 2,173 patients	Mortality: low ESRD: insufficient	• BB significantly reduced risk of all-cause mortality, CHF hospitalizations, and CHF death; reduced composite vascular outcomes risk in one of two trials. • There was no significant difference in risk of cardiovascular mortality. • Inconsistent data suggested greater relative risk reduction for several clinical vascular outcomes in lower eGFR category. • Limits: This was a post hoc analysis from two CHF treatment trials in which CKD was defined only by impaired eGFR; no renal outcomes were reported.
CCB vs. placebo 2 trials; 1,226 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause or cardiovascular mortality, stroke, CHF, ESRD, or composite vascular or renal outcomes. • CCB significantly reduced risk of MI. • Limits: Outcomes were mainly derived from one trial.
CCB vs. BB 3 trials; 12,766 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause mortality, ESRD, or composite renal outcome. • Limits: Most outcomes were not reported by treatment group in more than one study; 95% of subjects were derived from one post hoc analysis, in which it is uncertain if "renal dysfunction" meets CKD criteria.
CCB vs. diuretic 1 trial; 4,129 patients	Mortality: insufficient ESRD: low	• There was no significant difference in risk of stroke, ESRD, or any composite clinical vascular or renal outcomes. • Limits: This was a post hoc subgroup analysis; no results were reported for risk of mortality or MI between treatment groups.
Diuretic vs. placebo 1 trial; 393 patients	Mortality: low ESRD: insufficient	• There was no significant difference in risk of all-cause mortality. • Diuretic significantly reduced risk of stroke and one of two composite vascular outcomes. • Limits: There were few patients; this was a single post hoc subgroup analysis; no renal outcomes were reported.
ACEI vs. non-ACEI (other BP control) 1 trial; 131 patients	Mortality: insufficient ESRD: low	• There was no significant difference in risk for ESRD or a composite renal outcome. • Limits: Sample size was small; there were few clinical events; no data were reported for mortality or other clinical vascular or renal outcomes.
Strict BP control vs. usual BP control 6 trials; 2,520 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause or cardiovascular mortality, MI, stroke, ESRD, or several composite renal outcomes. • Limits: Generalizability is limited for some of the older included studies; there was heterogeneity in patient populations and antihypertensive regimens; there were few vascular events.

Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

Treatment, Trials, Number of Patients	Level of Evidence	Summary, Conclusion, Comments
Statins vs. placebo or usual care 12 trials; 17,460 patients	Mortality: high ESRD: low	• Statins significantly reduced risk of all-cause mortality, MI, stroke, and most composite vascular outcomes reported. • There was no significant difference in risk of CHF hospitalization, ESRD, or composite renal outcome. • Limits: All but one study were post hoc analyses in which CKD was defined by impaired eGFR or creatinine clearance; most trials excluded patients with moderate or severe renal impairment.
Statin vs. statin (high vs. low dose) 2 trials; 4,793 patients	Mortality: low ESRD: insufficient	• There was no significant difference in risk of all-cause mortality. • High-dose statin significantly reduced risk of CHF hospitalization and reduced risk of all composite vascular endpoints in one of two trials. • Limits: These were post hoc analyses; no outcomes were reported for MI, stroke, or renal outcomes.
Gemfibrozil vs. placebo 1 trial; 470 patients	Mortality: low ESRD: insufficient	• There was no significant difference in risk of mortality. • Gemfibrozil significantly reduced risk of one of two composite vascular outcomes. • Limits: This was a post hoc analysis; no ESRD events were reported; no data were reported for other renal outcomes.
Gemfibrozil vs. low-triglyceride diet 1 trial; 57 patients	Mortality: insufficient ESRD: insufficient	• There was no significant difference in risk of ESRD. • Limits: There were few patients and only three ESRD events; no data were reported for mortality or clinical vascular outcomes.
Low-protein diet vs. usual protein diet 6 trials; 1,480 patients	Mortality: low ESRD: low	• Low-protein diet did not significantly reduce risk of all-cause or cardiovascular mortality, or of ESRD. • Low-protein diet was associated with significant reduction in risk of composite renal outcome of dialysis. • Limits: Few vascular outcomes were reported; at least four trials also included participants with CKD stages 4 and/or 5.
Low-protein diet vs. low-carb, low-iron-available, polyphenol-enriched diet 1 trial; 191 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause mortality or ESRD. • Treatment with low-protein diet significantly increased risk of composite outcome of mortality and ESRD. • Limits: This was a small trial; there were few outcomes.
Low-protein, low-phosphate diet vs. low-phosphate diet vs. usual diet 1 trial; 98 patients	Mortality: insufficient ESRD: low	• There was no significant difference in risk of all-cause mortality or ESRD. • Limits: This was a small trial with few deaths; no data were reported for clinical vascular outcomes; trial was restricted to participants with deteriorating renal function and appears to have included many with eGFR <30 mg/ml/1.73m^2.
Intensive vs. standard glycemic control studies 2 trials; 1,861 patients	Mortality: insufficient ESRD: insufficient	• Limits: No data were reported for mortality, ESRD, or other clinical vascular or renal outcomes.

Table A. Summary of evidence for Key Question 5: Benefits of treatment for patients with CKD stages 1–3 (continued)

Treatment, Trials, Number of Patients	Level of Evidence	Summary, Conclusion, Comments
Intensive multicomponent intervention vs. control studies 4 trials; 892 patients	Mortality: low ESRD: low	• There was no significant difference in risk of all-cause mortality, MI, fatal stroke, or ESRD. • Multicomponent intervention significantly reduced risk of nonfatal stroke, a composite vascular endpoint, in single trials reporting that endpoint. • Limits: There was heterogeneity between interventions.

Note: For all-cause mortality and end-stage renal disease, the strength of the evidence was evaluated based on: (1) risk of bias, (2) consistency, (3) directness, and (4) precision. Based on these four domains, the overall evidence was rated as: (1) high, meaning high confidence that the evidence reflects the true effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; BP = blood pressure; CCB = calcium channel blocker; CHF = congestive heart failure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GFR = glomerular filtration rate; MI = myocardial infarction; ONTARGET = Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial.

Discussion

For CKD screening or monitoring to be of benefit, each would need to improve clinically important outcomes, presumably by leading to specific changes in treatment. However, we identified no RCTs that randomized individuals without known CKD to CKD screening, or randomized those with CKD stages 1–3 to CKD monitoring, and collected and reported associated clinical outcomes.

With no direct link between screening or monitoring and clinical outcomes, concluding that there is a likely benefit to screening or monitoring requires, at minimum, the availability of accurate screening tests and sufficient evidence that treatment for CKD stages 1–3 improves clinically important outcomes while limiting harms. For treatment benefits in CKD patients to be relevant to screening or monitoring, treatments also would need to improve outcomes in individuals who would not otherwise receive them; i.e., patients without specific treatment indications in the absence of a CKD diagnosis. In patients with other treatment indications, diagnosis of CKD or of CKD progression might be beneficial if outcomes in these patients are significantly improved with a higher treatment dose or by treatment to a stricter target than indicated in individuals with no or less severe CKD. Finally, any treatment benefit would need to outstrip treatment harms and potential screening and monitoring harms, and the applicability of treatment RCT results to screening or monitoring would be increased if subjects were identified for participation in these treatment trials through screening.

In this synthesis of RCT evidence, several treatments reduced the risk of clinical events in patients with CKD stages 1–3. Compared with placebo, ACEI and ARB treatment significantly reduced the risk of ESRD in patients with proteinuria, nearly all of whom had concomitant diabetes and hypertension. While there was no significant reduction in the risk of ESRD with ACEIs or ARBs in patients without proteinuria, the present analysis had limited statistical power to detect such a difference because of the low rate of progression to ESRD in these patients. While it does not constitute direct evidence that testing patients with diabetes and hypertension for proteinuria will reduce ESRD risk, it suggests that knowledge of these results might inform the treatment decision in patients not currently being treated with ACEIs or ARBs. Also, compared with placebo, ACEIs significantly reduced the risk of mortality in patients with

microalbuminuria who had cardiovascular disease or had diabetes and other cardiovascular risk factors. Although the relative reduction in mortality risk appeared to be slightly greater in patients with microalbuminuria than in those without microalbuminuria, the difference was not statistically significant, suggesting that such patients may have an indication for ACEI treatment regardless of CKD status.

In individuals with hyperlipidemia and impaired eGFR or creatinine clearance, we found that statins significantly reduced the risk of mortality, MI, and stroke compared with placebo, including the risk in patients without coronary artery disease. This does not constitute direct evidence that testing patients with hyperlipidemia for eGFR will reduce the risk of these outcomes, in part because some of these patients already have a clinical indication for statin treatment. Determining CKD status in these patients would not alter their management. Specifically, as previously documented, patients with hyperlipidemia and coronary artery disease randomized to statins have a significantly reduced risk of mortality compared with placebo;[23] they have an indication for statin treatment regardless of their CKD status. In contrast, as also previously documented, hyperlipidemic patients without coronary artery disease, taken as a whole, did not have a significant mortality benefit from statins.[24] The current results suggest that knowledge of impaired eGFR might inform the treatment decision in patients with hyperlipidemia and no coronary artery disease who are not being treated with a statin.

In individuals with CHF and impaired eGFR, beta blockers significantly reduced the risk of mortality, MI, and CHF events compared with placebo. Patients in all eGFR strata had a significant reduction in the risk of these clinical outcomes. Inconsistent results suggested possibly a greater relative risk reduction with beta blockers in patients with lower eGFR than in those with higher eGFR. However, as patients with systolic CHF already have an indication for beta blocker treatment, testing for eGFR is not likely to inform this treatment decision.

With regard to patients with CKD stages 1–3 already receiving treatments for conditions associated with CKD (e.g., ACEIs for treatment of hypertension), no clear RCT evidence showed whether intensification of treatment improves clinical outcomes. We identified no eligible RCTs that compared clinical outcomes in CKD patients randomized to different fixed ACEI doses, although separate trials suggested that ramipril at 1.25 mg per day in patients with albuminuria lacks the mortality benefit of ramipril at 10 mg per day in patients with microalbuminuria. For other treatments in CKD patients, we did not find evidence of significant or consistent benefit in clinical outcomes in high-dose versus low-dose ARBs, strict versus standard blood pressure control, high-dose versus low-dose statins, tight versus standard glycemic control, intensive multidisciplinary interventions versus standard care, or combination treatment versus monotherapy. While data limited to these latter trials suggest an absence of evidence for benefit from intensification of therapy as a justification for either CKD screening or monitoring, most had low statistical power to detect a significant difference in clinical outcomes.

In RCTs included in this evidence synthesis, many treatments reduced the risk of doubling of serum creatinine and progression from microalbuminuria to macroalbuminuria. However, these renal endpoints are not clinical outcomes. Although impaired GFR and albuminuria are unquestionably adverse prognostic markers, treatments that target and even improve these measures will not necessarily reduce the risk of mortality, ESRD, or important clinical vascular outcomes. Findings reported from the large Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study[25]—in which patients with diabetes and at least one additional CKD risk factor were randomized to ARB versus non-ARB blood pressure control—illustrated the potential danger of utilizing albuminuria as a surrogate marker for

clinical outcomes in kidney disease. Although blood pressure control was significantly better and time to onset of microalbuminuria was significantly delayed in the ARB treatment group, these patients also experienced a significant increase in fatal cardiovascular events.

As we have noted, establishing the benefit of CKD screening and/or monitoring requires evidence of treatment benefit. Yet treatment benefit does not by itself prove screening or monitoring benefit. First, the accuracy of available screening and monitoring measures for persistent CKD and progressive CKD is uncertain. Second, only two of the dozens of RCTs included in this evidence synthesis reported that study participants were identified through screening.[26,27] Consequently, patients with CKD stages 1–3 enrolled in all these trials may not be representative of those who would be identified through systematic screening. For example, patients identified through screening may be earlier in their course of CKD, less likely to progress during treatment followup, and thus less likely to benefit from treatment intervention than those not identified through screening. In addition, formal diagnosis of CKD requires that impairment in kidney function or kidney damage persist for at least 3 months. The vast majority of trials included in this evidence synthesis categorized patients as having CKD based on one-time abnormalities. Other trials that required repeated or sustained kidney abnormalities for entry did not mandate persistence for 3 months. Study participants thus may have had transient impairments, been more likely to improve regardless of treatment, and been less likely to develop progressive CKD than patients with CKD confirmed over 3 months duration. Finally, we identified no evidence to quantify harms that may be associated with CKD screening and monitoring. Potential harms of systematic CKD screening could include adverse effects from screening and followup tests, including followup of false positive tests, psychological effects from labeling asymptomatic individuals as diseased, medication adverse effects, increased medical visits, and increased difficulty keeping health insurance coverage. Analogously, potential harms of systematic monitoring of patients with CKD stages 1–3 for worsening kidney function or damage could include adverse effects from monitoring and followup tests, including potentially unnecessary testing, medication adverse effects, and increased medical visits. Accurate information on screening and monitoring harms is needed to evaluate their overall impact in CKD.

Considering these issues, if there is a benefit from CKD screening, evidence suggests that the likelihood of benefit is greatest in individuals with diabetes, cardiovascular disease, and possibly hyperlipidemia. For other populations with a high prevalence of CKD, such as patients with hypertension, obesity, and older age, evidence for benefit from screening appears to be weaker. Individuals under 50 years old and without diabetes, hypertension, cardiovascular disease, or obesity infrequently have CKD and seem least likely to benefit from CKD screening, although this also is based only on indirect data.

Finally, because of the imprecision and high intraindividual variability of eGFR and albuminuria, providers who monitor patients with CKD stages 1–3 for worsening kidney function and/or damage will identify both declines and improvements in these measures, including many that are transient and/or clinically insignificant. We identified no RCTs that assigned patients with CKD stages 1–3 to systematic monitoring versus control, or that modified treatment based on followup levels of eGFR or albuminuria and evaluated clinical outcomes. Rather, trials either assigned participants to a fixed dose to be maintained throughout the trial or titrated upward from an initial dose to achieve a specific target dose or clinical target (e.g., systolic blood pressure less than 140 mm Hg). Although treatment RCT results suggest that monitoring could inform decisions regarding whether to start ACEI or ARB treatment in patients

with diabetes and hypertension who develop albuminuria, or statin treatment in patients with hyperlipidemia who develop impaired eGFR, considering the uncertainty in the accuracy of monitoring tests for identifying CKD progression and the uncertainty regarding possible monitoring harms, the relative benefits and harms of CKD monitoring are unclear.

Future Research Recommendations

Key Question 1. CKD Screening Benefits

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD screening improves clinical outcomes.
- The sensitivity and specificity of one-time measures of microalbuminuria, macroalbuminuria, and eGFR for persistent (at least 3 months' duration) CKD is unknown; the impact of patient factors on persistence also is unknown.
- Only two trials were performed in patients with CKD identified through screening.

Research Recommendations

- Long-term RCTs of systematic CKD screening versus usual care that are adequately powered to evaluate impact on clinical outcomes.
  - Target populations with high CKD prevalence and high risk for complications.
  - May test different screening measures (e.g., microalbuminuria, macroalbuminuria, eGFR, combination).
- Modeling studies evaluating efficacy and harms of different CKD screening strategies versus usual care. In addition to parameters in published models, consider impact of:
  - Variations in target populations.
  - Variations in screening measures and frequency.
  - Prevalence in the target population of indications for and use of specific CKD treatments.
  - Yield of one-time screening tests based on actual association with persistent CKD.
  - Take into account potential screening harms.
- Determine eGFR and albuminuria from baseline and followup blood and urine available from large prospective cohorts or RCT/CCT control groups (or collect new samples).
  - Estimate the proportion of individuals with abnormal one-time abnormalities who meet the criteria for CKD for at least 3 months.
  - Evaluate the impact of patient factors (e.g., eGFR severity, albuminuria, age) on persistence.

Key Question 2. CKD Screening Harms

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD screening increases harms.

Research Recommendations

- Long-term RCTs comparing systematic CKD screening versus usual care to assess potential screening harms.
  - Predefine potential harms, and collect and report them in all study participants.
  - May include as potential harms adverse effects from screening/followup tests, including from false positive tests; psychological effects of labeling asymptomatic individuals as diseased; medication adverse effects; increased medical visits; increased costs; difficulty keeping health insurance.
- Prospectively collect predefined harms data from all participants in large observational CKD screening cohort studies.
- Conduct modeling studies evaluating the effectiveness and harms of different CKD screening strategies versus usual care.

Key Question 3. CKD Monitoring Benefits

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD monitoring for worsened kidney function or damage improves clinical outcomes.
- The sensitivity and specificity of changes in eGFR and albuminuria for CKD progression are unknown.
- Only limited RCT data address whether treatment relative risk reduction for clinical outcomes differs based on CKD severity. Such information could inform decisions regarding whether to change treatment in patients identified by monitoring with worsened CKD severity.
- No RCT data address whether treatments have different relative risk reduction in clinical outcomes for patients with recently worsened kidney function or damage, as detectable by monitoring, compared with those with stable CKD.

Research Recommendations

- Long-term RCTs of systematic CKD monitoring versus usual care that are adequately powered to evaluate impact on clinical outcomes.
  - Target populations with high risk for CKD complications.
  - Consider testing different monitoring measures, alone and in combination (e.g., quantitative microalbuminuria, macroalbuminuria, eGFR).
- Modeling studies evaluating the efficacy and harms of different CKD monitoring strategies compared with usual care. Parameters of these models may include:
  - Variations in monitoring measures and frequency (quantitative albuminuria, eGFR, or a combination).
  - Variations in baseline CKD severity (i.e., stage, eGFR, quantitative albuminuria).
  - Variations in CKD patient characteristics (e.g., diabetes, hypertension, age, cardiovascular disease, hyperlipidemia, race/ethnicity), including possible indications for specific CKD treatments and prevalence of use of these treatments.
  - Take into account potential monitoring harms.

Key Question 4. CKD Monitoring Harms

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD monitoring for worsening kidney function or damage increases harms.

Research Recommendations

- Long-term RCTs comparing systematic CKD monitoring versus usual care to assess potential monitoring harms.
  - Predefine potential harms associated with monitoring, and collect and report them in all study participants.
  - May include as potential harms adverse effects from monitoring/followup tests, including from false positive tests (for progression); medication adverse effects; increased medical visits; increased costs.
- Prospectively collect predefined harms data from all participants in large observational CKD monitoring cohort studies.
- Conduct modeling studies evaluating the effectiveness and harms of different CKD monitoring strategies versus usual care.

Key Question 5. CKD Treatment Benefits

Knowledge Gaps

- Only limited RCT data address whether the relative efficacy of treatments differs between patients with and without CKD.
- Only limited RCT data address whether treatment risk reduction differs based on CKD severity.
- Only limited RCT data address whether treatments improved outcomes in CKD subgroups in which treatments were not already indicated.
- In RCTs of high versus low dose, combination versus monotherapy, and strict versus standard control, it was unclear whether intensification of treatment improves clinical outcomes.
- The effect of diet interventions on clinical outcomes in patients with CKD stages 1–3 is unclear because diet intervention RCTs were small, included patients with both stage 1–3 and stage 4–5 CKD, and did not separate results by CKD stage or severity.
- In head-to-head RCTs, there was little evidence of a significant difference in mortality or any clinical vascular outcome between different active treatment groups.
- Trials used heterogeneous eligibility criteria for kidney function and damage, and rarely reported outcomes stratified by CKD stage or albuminuria category, impeding evidence synthesis.

Research Recommendations

- Post hoc analyses of ongoing or completed RCTs that already have collected or are collecting clinical outcomes.

    - Determine baseline eGFR and quantitative albuminuria, categorize participants by CKD stage and albuminuria category, and perform analyses to evaluate the relative effectiveness of treatment versus control on clinical outcomes within these strata.
- Merge data from large-scale treatment RCTs with Medicare data to identify incident ESRD cases occurring in the post-trial followup period.
- Long-term RCTs of CKD treatment adequately powered to evaluate impact on clinical outcomes.
    - In addition to mortality, ESRD, and clinical vascular outcomes, consider additional clinical outcomes for evaluation, including quality of life, acute kidney injury complications (e.g., hospitalization), health care utilization, physical function, and cognitive function.
    - If composite outcomes are reported, also report complete data for individual composite components.
    - To increase trial relevance to a screened population, consider recruitment using population-based sampling.
    - Stratify results by CKD stage, albuminuria category, and other characteristics associated with CKD complications, including diabetes, hypertension, cardiovascular disease, older age, race/ethnicity, obesity, and hyperlipidemia.
    - Consider future RCTs of statins in patients with albuminuria, ACEI or ARB treatment in patients with macroalbuminuria, ACEI or ARB treatment in combination with other therapy, and treatments other than ACEIs or ARBs.
    - Consider trials of dietary interventions restricted to patients with CKD stages 1–3.
    - Consider trials comparing system-level interventions to aid providers in avoidance of nephrotoxic agents, medication renal dose adjustment, and other measures targeted to reduce CKD-associated complications compared with complications in usual care.
- Patient-level meta-analyses of treatment RCTs to evaluate the effect of treatments relative to control in relevant CKD subgroups.
- Analysis of administrative data to evaluate the effect of nephrology referral on clinical outcomes, performing propensity analysis to account for factors associated with early referral.

Key Question 6. CKD Treatment Harms

Knowledge Gaps

- Withdrawals and adverse events were reported in few RCTs.
- Withdrawals often were not reported separately by treatment group; adverse events often did not appear to be predefined, systematically collected and reported, or separated by treatment group.

Research Recommendations

- In future RCTs, predefine withdrawals and adverse effects, and collect and report them in all patients with CKD stages 1–3.
- May report withdrawal and adverse effects stratified by CKD stage, albuminuria category, and other patient characteristics.

Glossary

ACEI	Angiotensin converting enzyme inhibitor
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
CCT	Controlled clinical trial
CHF	Congestive heart failure
CKD	Chronic kidney disease
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
JNC7	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
MI	Myocardial infarction
RCT	Randomized controlled trial

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Introduction

Scope and Purpose

The objective of this systematic review is to evaluate the evidence for the potential benefits and harms of: (1) screening adults for chronic kidney disease (CKD) stages 1–3, (2) monitoring adults with CKD stages 1–3 for progression of kidney dysfunction and/or damage, and (3) treatment of adults with CKD stages 1–3.

This report's scope is limited to early stage CKD because it is intended to inform patient care decisions of primary care physicians. This report also is intended as background material to assist groups developing clinical practice recommendations.

Definition of CKD

CKD is a condition in which the kidneys are damaged and/or cannot filter blood normally.[1] CKD usually is asymptomatic, except in its most advanced state. Consequently, blood and/or urine tests generally are required to make a diagnosis.

There has been substantial debate regarding how to define early stages of CKD. The definition of CKD developed by Kidney Disease Outcomes Quality Initiative (KDOQI)[2] was:

1. Kidney damage present at least 3 months, as defined by structural or functional abnormalities (most often based on increased albuminuria, e.g., urinary albumin-creatinine ratio [UACR] ≥30 mg/g); and/or
2. Glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 present at least 3 months.

Within this framework, KDOQI then classified CKD into five stages, as follows:

- Stage 1: Kidney damage with GFR ≥90 mL/min/1.73 m2.
- Stage 2: Kidney damage with GFR 60-89 mL/min/1.73 m2.
- Stage 3: GFR 30-59 mL/min/1.73 m2.
- Stage 4: GFR 15-29 mL/min/1.73 m2.
- Stage 5: GFR <15 mL/min/1.73 m2 or kidney failure treated by dialysis or transplantation.

A limitation of the KDOQI definition and staging was that they were based on cross sectional data, and that there were limited data associating adverse clinical outcomes with specific levels of GFR, albuminuria, or proteinuria. However, results of a recent series of meta-analyses of multiple large prospective cohort studies clearly demonstrated the independent associations of each level of GFR and albuminuria (or alternatively of dipstick proteinuria), with total and cardiovascular mortality, ESRD and acute kidney injury (AKI).[3-6] These associations were independent of cardiovascular risk factors. Based in part on these data, a consensus conference led by Kidney Disease: Improving Global Outcomes (KDIGO), on Chronic Kidney Disease: Definition, Classification and Prognosis, concluded that the current CKD definition should be preserved. However, the conference recommended that staging be altered to subdivide stage 3 into 3a (GFR 45-59 mL/min/1.73 m^2) and 3b (GFR 30-44 mL/min/1.73 m^2), to add albuminuria strata within each GFR stage (UACR <30 mg/g, 30-299 mg/g, or ≥300 mg/g), and to assign a cause of CKD when possible.[7]

Prevalence of CKD

In the United States, based on data from the 1999-2006 National Health and Nutrition Examination Survey (NHANES) study, an estimated 11.1 percent (22.4 million) of adults aged 20 or older have CKD stages 1–3.[8] Because this estimate was based on one-time measurements of urinary albumin-creatinine ratio (UACR) and serum creatinine, and the definition of CKD requires persistent kidney abnormalities, statistical adjustments were made to estimate persistence. An additional 0.8 million U.S. adults aged 20 or older have CKD stage 4, and more than 0.3 million have stage 5 CKD and receive hemodialysis.[9]

Among adults with CKD stages 1–3, approximately half have either stage 1 or 2 CKD (increased albuminuria with normal GFR), and half have stage 3 CKD (low GFR, with approximately one third of these having increased albuminuria and two thirds having normal albuminuria).[8] Of individuals with albuminuria, nearly 85 percent have microalbuminuria (UACR 30-299 mg/g).

Analyses of NHANES data between 1988-1994 and 1999-2004 suggest that the prevalence of CKD is rising for every CKD stage, but with a particular increase in the prevalence of individuals classified with CKD stage 3.[10] The number of patients with stage 5 CKD requiring dialysis also has increased.[9] It has been estimated that more than 700,000 individuals will have end-stage renal disease (ESRD) by 2015.[11]

Factors Associated With CKD

Prevalence of CKD stages 1–3 in U.S. adults rises from 3.1 percent among those aged 20-39 years, to 6.7 percent in those aged 40-59, 17.6 percent in those aged 60-69, and 44.4 percent among adults aged 70 years or older.[8] CKD prevalence is somewhat higher in women (12.6 percent) than in men (9.7 percent) and is similar in whites (11.6 percent) and blacks (11.2 percent).

Although CKD can be caused by primary kidney disease (predominantly glomerular diseases, tubulointerstitial diseases, obstruction, and polycystic kidney disease), in the vast majority of patients with CKD, the kidney damage is associated with other medical conditions such as diabetes and hypertension. Other risk factors for CKD include older age, cardiovascular disease, obesity, family history, and African American, Native American, or Hispanic ethnicity. With respect to diabetes as a CKD risk factor, based on NHANES 1999-2006 data, prevalence of diabetes was approximately 5 percent in individuals without CKD and 20 percent in individuals with CKD stages 1–3.[12] Prevalence of hypertension was 24 percent among individuals without CKD, but rose from 36 percent in those with CKD stage 1 to 64 percent in those with CKD stage 3. Similarly, prevalence of cardiovascular disease was 6 percent among individuals without CKD, and rose from 7 percent in those with CKD stage 1 to 36 percent in those with CKD stage 3. Compared with the NHANES population, the prevalence of comorbidities was higher in the older Medicare population. Excluding those with ESRD, in 2008, 48 percent of Medicare patients with CKD had diabetes, 91 percent had hypertension, and 46 percent had atherosclerotic heart disease.[12]

Association of CKD With Adverse Outcomes

CKD has been associated with numerous adverse health outcomes. Many studies have reported that a GFR of 30-59 mL/min/1.73 m^2 is associated with an increased risk of mortality,[3,13] cardiovascular disease,[14] fractures,[15] bone loss,[16] infections,[17] cognitive

impairment,[18] and frailty.[19] Similarly, there appears to be a graded relationship between the severity of proteinuria or albuminuria and adverse health outcomes, including mortality,[3,20] ESRD,[21] and cardiovascular disease.[22] Further, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria (or proteinuria) appears to be independent and multiplicative.[3,21]

A number of possible explanations exist for the observed association of CKD with adverse health outcomes. First, CKD shares many of the same risk factors as other vascular diseases, such as older age, hypertension, and diabetes, so CKD may be a marker for undiagnosed vascular disease or for a worsened prognosis among individuals with known vascular disease. Second, CKD may be associated with a number of nontraditional risk factors for vascular disease and mortality, such as increased inflammation or bone mineral disorders. Third, CKD may be a marker for individuals less likely to receive proven medical therapies. For example, among individuals with myocardial infarction, those with CKD are less likely to receive proven effective therapies such as coronary artery bypass grafting, angiotensin converting enzyme inhibitors (ACEI), beta-blockers, or HMG CoA-reductase inhibitors (i.e., statins).[23] Therefore, systematic undertreatment may in part underlie the association between CKD and adverse health outcomes. Finally, the associations of CKD with adverse health outcomes and increased healthcare costs may be related to a combination of the above mechanisms.

Rationale for CKD Screening

Factors that impact the potential benefit of screening adults for CKD stages 1–3 include: (1) whether undiagnosed CKD is sufficiently prevalent in the population, overall or in certain high risk groups; (2) whether CKD is associated with significant adverse health consequences and/or healthcare costs; (3) whether CKD is accurately diagnosable while asymptomatic; (4) whether there are valid and reliable screening tests for CKD that are acceptable to patients and available in primary care settings; and (5) whether there are treatments for patients with CKD that improve clinically important health outcomes.

Going further, determination that CKD screening is beneficial would require evidence that treatment of screen-detected CKD is associated with an improvement in health outcomes compared with treatment initiated once an individual is symptomatic or has CKD detected through usual care, while limiting harms. In addition, since potential CKD treatments often are indicated for conditions associated with CKD, such as diabetes, hypertension, or cardiovascular disease, demonstration that CKD screening is beneficial may require evidence that treatment benefits CKD populations who don't have another indication for treatment or, that among patients with another indication for treatment, those with CKD experience a greater relative treatment benefit than those without CKD. Alternatively, because patients with diabetes, hypertension, and/or cardiovascular disease who also have CKD are at significantly higher risk for adverse health outcomes than patients with these comorbid conditions who don't have CKD, diagnosis of CKD resulting from screening patients with these conditions would identify a group, if currently untreated, who could derive a greater absolute benefit in health outcomes even if the relative benefit of treatment versus no treatment was similar in CKD and non-CKD patients.

Several organizations have made recommendations regarding screening for CKD. KDIGO recommends screening for CKD in patients with hypertension, diabetes, or cardiovascular disease using both a urine test for proteinuria and a blood test for creatinine to estimate GFR.[24] KDIGO further recommends that CKD screening be considered in patients who are older, have a family history of kidney disease, have other cardiovascular disease risk factors, have certain

chronic infections or cancers, or are treated with potentially nephrotoxic drugs, and that screening need not be performed more often than annually. The American Diabetes Association (ADA) recommends that all adults with diabetes undergo annual measurement of serum creatinine to estimate GFR, and that all type 2 diabetics and all type 1 diabetics with a diabetes duration of at least 5 years undergo annual measurement of urinary albumin excretion.[25] Ongoing CKD screening programs include the National Kidney Foundation's Kidney Early Evaluation Program (KEEP®), which offers free screening for all adults with hypertension, diabetes, or a first degree relative with a history of kidney disease, hypertension, or diabetes.[26]

Rationale for Monitoring for Progression of CKD

Because CKD in stages 1–3 is usually asymptomatic, monitoring these patients for worsening kidney function or damage requires laboratory testing (i.e., measures to estimate GFR, albuminuria).

Factors that impact the potential benefit of monitoring adults with CKD stages 1–3 for worsening kidney function or damage include: (1) whether undiagnosed progression of patients with CKD stages 1–3 to worse kidney function or damage is sufficiently frequent in the population, overall or in certain high risk groups; (2) whether CKD that has progressed from stages 1–3 is associated with significant adverse health consequences and/or healthcare costs; (3) whether CKD that has progressed from stages 1–3 is diagnosable while asymptomatic; (4) whether there are valid and reliable monitoring tests for CKD stages 1–3 that are acceptable to patients and available in primary care settings; and (5) whether there are treatments for patients whose CKD has progressed from stages 1–3 that improve clinically important health outcomes.

Strictly considered, determination that monitoring patients with CKD stages 1–3 for worsened kidney function or damage is beneficial would require evidence that modified treatment of worsened CKD detected by monitoring is associated with an improvement in health outcomes compared with treatment modified once an individual becomes symptomatic or has CKD worsening detected through usual care, while limiting harms.

Several organizations have made recommendations regarding monitoring kidney function and/or damage in patients with CKD. KDOQI recommends that adults with CKD receive monitoring of urinary albumin or protein to creatinine ratio, though no frequency of monitoring was recommended.[27] The U.K. National Health Service (NHS) National Institute for Health and Clinical Excellence (NICE) guidelines suggest "more frequent monitoring" in CKD patients with worsening kidney function and a "relaxed frequency" of estimated GFR measurements in patients with stable kidney function.[28]

Rationale for Treatment of CKD

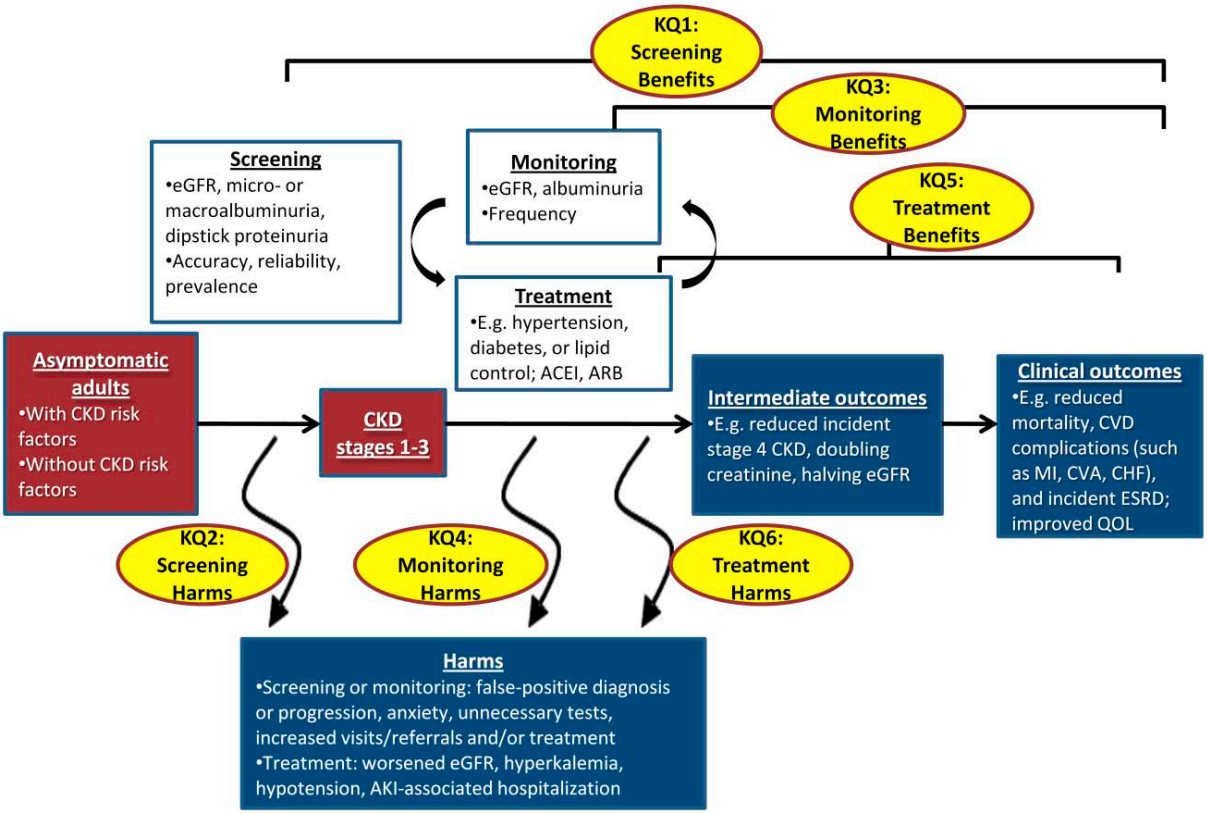
In patients treated for nonprimary CKD, treatment most often is not directed specifically at the CKD but rather at the associated underlying conditions or cardiovascular risk factors, such as hypertension or diabetes,[29] with therapeutic goals for these conditions sometimes set more strictly for CKD patients than for non-CKD patients.[30] An aim of this systematic review is to evaluate the evidence regarding whether the benefits and harms of treatment differ between patients with and without CKD, both in patients with and without other indications for treatments. Medications such as ACEI and angiotensin receptor blockers (ARB) potentially could be directed specifically towards treatment of CKD. However, whether their impact on CKD outcomes or markers (e.g., incident ESRD, albuminuria severity[31]) is independent of their blood pressure lowering effect is not clear.[32] Additional nonspecific therapies may include other

medications and nonpharmacological interventions targeted, for example, at blood pressure control, glycemic control, cholesterol control, and obesity treatment.

Analytic Framework and Key Questions

During this project's topic development, the topic nominators and other interested parties agreed that an independent, comprehensive review of the issues introduced above would provide helpful guidance to clinicians and policymakers regarding diagnosis and management of early stage CKD. There was consensus that the following analytic framework (Figure 1) and Key Questions addressed the most important issues regarding CKD stages 1–3:

Figure 1. Analytic framework for screening, monitoring, and treatment of chronic kidney disease stages 1–3



Key Question 1. In asymptomatic adults with or without recognized risk factors for chronic kidney disease (CKD) incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?

- In asymptomatic adults with or without risk factors for CKD incidence, progression, or complications, what is the accuracy and reliability of CKD screening and the prevalence of CKD identifiable by screening?
- Does initiating treatment for CKD as a result of systematic screening improve clinical outcomes compared with treatment initiated after incidental CKD diagnosis during routine clinical practice?
- How do patient factors and CKD screening thresholds modify the yield of CKD screening and its association with clinical benefits?

Key Question 2. What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?

- How do patient factors and CKD screening thresholds modify the association of CKD screening with harms?

Key Question 3. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?

- How do patient factors, CKD severity/stage, and CKD monitoring intervals modify the association of CKD monitoring with clinical benefits?

Key Question 4. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function/kidney damage?

- How do patient factors, CKD severity/stage, and CKD monitoring intervals modify the association of CKD monitoring with harms?

Key Question 5. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?

- Does the presence of CKD modify the likelihood of improvement in clinical outcomes associated with treatment of vascular disease or vascular risk factors?
- Among adults with CKD, what patient factors modify the association of specific treatments with improved clinical outcomes?

Key Question 6. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

- Does the presence of CKD modify the likelihood of harms associated with treatment of vascular disease or of vascular risk factors?
- How do patient factors and CKD severity/stage modify the association of CKD treatment with harms?

Methods

Topic Refinement

The initial nominator of this topic, first titled "Management of Mild Renal Impairment," proposed questions related to clinical typology, frequency of monitoring, calculation of creatinine clearance, management, and secondary prevention of mild renal impairment. Subsequently, a second nominator proposed questions related to screening for and treatment of screen-detected CKD. It was determined to be feasible to combine the two sets of questions. The scope of the combined questions explicitly excluded management of patients with more advanced kidney disease.

Key Questions were drafted with input from representatives of the nominating organizations. These Key Questions and project scope were submitted for AHRQ approval and then posted on the Effective Health Care web site for public comment.

Comparative Effectiveness Review

Public comments were reviewed with AHRQ and the nominators, and incorporated as appropriate in a draft protocol. The draft protocol was circulated to a Technical Expert Panel (TEP) composed of researchers, clinicians, and representatives from professional organizations and federal and state agencies including the American College of Physicians, United States Preventive Services Task Force, National Kidney Foundation, American Association for Clinical Chemistry, Centers for Disease Control and Prevention, American Academy of Family Practice, and KDIGO. Based on TEP feedback, including on the relevance and scope of the review, the protocol was revised and a final protocol, including the revised Key Questions and proposed project methods, was approved by the Agency for Healthcare Research and Quality (AHRQ) and posted on the Effective Health Care website.

Based on feedback received during protocol development, the terminology used in this project was changed to be consistent with the currently accepted terminology for referring to impairments in kidney function and kidney damage as established by the National Kidney Foundation's KDOQI[2] and later modified by the KDIGO.[33] In addition, its title was changed for the protocol to "Screening for and Management of Chronic Kidney Disease Stages 1–3." Finally, based on public and peer reviewer feedback to the draft report, the final report title was changed to more accurately and transparently reflect its content and organization: "Chronic Kidney Disease Stages 1–3: Screening, Monitoring, and Treatment."

Systematic Review

Search Strategy

We developed separate search strategies for the screening, monitoring, and treatment Key Questions. Search strings were developed and tested to identify randomized controlled trials (RCTs) or controlled clinical trials (CCTs). We included studies that enrolled an adult population (18 years of age and older), were published since 1985, and were written in the English language. Evidence suggests that for systematic reviews of conventional medicine, as were evaluated in the present review, restriction to include only English language trials should not bias estimates of the effectiveness of the interventions.[34] Only full articles were included. We

searched MEDLINE® and the Cochrane Database of Systematic Reviews. Details of the major search strategies are provided in Appendix A.

To identify systematic reviews related to the three topic areas, we completed a search of MEDLINE® and the Cochrane Database of Systematic Reviews using the same search strategies as above with the addition of publication type terms to identify systematic reviews. We manually searched the reference lists of the identified systematic reviews to identify any RCTs or CCTs not detected in our electronic literature search. We also manually searched reference lists of the primary reports that were eligible for inclusion in the review. Per project protocol, because we did not find evidence from RCTs or CCTs to directly address whether screening or monitoring impact clinical outcomes or harms, we conducted a nonsystematic search for observational studies to identify indirect evidence regarding the benefits and harms of screening for and monitoring of CKD. All citations then were imported into EndNote X and Excel for abstract review and database management.

A broad search of the grey literature was completed by the AHRQ Scientific Resource Center librarian. Grey literature, which by definition is literature that is not systematically stored or indexed,[35] included abstracts presented at conferences, unpublished trial data, government documents, and pharmaceutical company scientific information packets on medications evaluated in this topic.

We conducted the initial searches in March and April of 2010. All searches were updated in January 2011.

Inclusion/Exclusion Criteria

We developed criteria for inclusion and exclusion of studies based on patient populations, interventions, outcome measures, and types of evidence relevant to the Key Questions. Within the sections for each pair of Key Questions immediately below, inclusion criteria are detailed in the 'Patients' sections and exclusion criteria are detailed in the 'Study Selection' sections. We retrieved full-text articles of potentially relevant abstracts and conducted a second review for inclusion by reapplying the inclusion criteria. If no abstract was available electronically, the full text of the article was obtained for review.

Key Questions 1 and 2

Patients

We restricted the review to studies that enrolled adults who were without known CKD, were with or without recognized risk factors for CKD, and who were systematically screened for CKD. Because much of our search period preceded the development and wide implementation of the current CKD staging system, studies whose definitions of CKD at least closely approximated the current KDOQI and KDIGO definitions for CKD stages 1–3 were considered eligible.

Study Selection

We sought RCTs or CCTs that assessed the direct impact of systematic screening for CKD stages 1–3 on clinical outcomes and harms. Examples of tests to screen for CKD that were considered eligible were direct measurements of GFR or creatinine clearance, estimation of GFR or creatinine clearance with creatinine-based formulae, serum creatinine, albuminuria, proteinuria, albumin/creatinine ratio, and cystatin C. The screening method must have been feasible within a primary care setting. Our exclusion criteria were as follows: nonadult

population, study participants already diagnosed with CKD, not an RCT that assigned participants to systematic screening for CKD versus usual care or a comparator intervention, study followup duration less than 1 year, and sample size less than 1,000 randomized participants.

When no RCTs were identified that evaluated a CKD screening intervention and reported clinical outcomes and harms, indirect evidence was reviewed regarding its possible benefits and harms. This indirect evidence included observational studies on CKD prevalence, clinical recognition, accuracy and reliability of CKD screening tests, and RCTs of CKD treatments. Although these observational studies were not identified through a comprehensive literature search, whenever possible we evaluated data from large representative U.S. cohorts. Assessment of CKD treatment benefits and harms was based strictly on direct evidence from RCTs.

Comparators

Studies were to compare systematic screening for CKD stages 1–3 with no CKD screening, usual care, or an alternative CKD screening regimen. Any monitoring or treatment interventions that followed screening were allowed.

Outcomes

We restricted the review to studies that reported clinical outcomes or harms. Clinical outcomes included: all-cause mortality, cardiovascular mortality, MI (any, fatal, nonfatal), stroke (any, fatal, nonfatal), CHF (hospitalization, death), composite vascular outcomes, composite renal outcomes, ESRD (progression to kidney transplant or dialysis), quality of life, physical function, and activities of daily living. Intermediate outcomes included: progression to stage 4 or stage 5 kidney disease, composite renal outcomes, doubling of serum creatinine or halving of GFR, and conversion from microalbuminuria to macroalbuminuria. Harms included: any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

Study Designs

We initially included only RCTs. As described above, when no relevant RCTs were identified, we expanded our search to include observational studies that could provide indirect evidence regarding these questions.

Key Questions 3 and 4

Patients

We restricted the review to studies that enrolled adults with CKD stages 1–3 who were systematically monitored for worsening of kidney function and/or damage. As above, studies whose definitions of CKD stages 1–3 at least closely approximated the current KDOQI and KDIGO definitions were considered eligible.

Study Selection

We sought RCTs or CCTs that assessed the direct impact of monitoring on clinical outcomes and harms. Examples of tests to monitor for worsening kidney function and/or damage that were considered eligible were direct measurements of GFR or creatinine clearance, estimation of GFR or creatinine clearance with creatinine-based formulae, serum creatinine, albuminuria, proteinuria, albumin/creatinine ratio, and cystatin C. The monitoring method must have been

feasible within a primary care setting. Our exclusion criteria were as follows: nonadult population, population entirely or predominately not CKD stages 1–3, not an RCT that assigned participants to systematic monitoring for worsening of kidney function and/or damage versus usual care or a comparator intervention, and sample size of less than 50 randomized participants.

When no RCTs were identified that evaluated a CKD monitoring intervention and reported clinical outcomes or harms, indirect evidence was reviewed regarding its possible benefits and harms. This indirect evidence included observational studies on CKD progression, clinical recognition, accuracy and reliability of CKD monitoring tests, and RCTs of CKD treatments. Although these observational studies were not identified through a comprehensive literature search, whenever possible we evaluated data from large representative U.S. cohorts. Assessment of CKD treatment benefits and harms was based strictly on direct evidence from RCTs.

Comparators

Studies were to compare systematic monitoring of patients with CKD stages 1–3 for changes in kidney function and/or damage with usual care or an alternative CKD monitoring regimen. Any interventions that followed CKD monitoring were allowed.

Outcomes

We restricted the review to studies that reported clinical outcomes or harms. Clinical outcomes included: all-cause mortality, cardiovascular mortality, MI (any, fatal, nonfatal), stroke (any, fatal, nonfatal), CHF (hospitalization, death), composite vascular outcomes, composite renal outcomes, ESRD (progression to kidney transplant or dialysis), quality of life, physical function, and activities of daily living. Intermediate outcomes included: progression to stage 4 or stage 5 kidney disease, composite renal outcomes, doubling of serum creatinine or halving of GFR, and conversion from microalbuminuria to macroalbuminuria. Harms included: any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

Study Designs

We initially included only RCTs. As described above, when no relevant RCTs were identified, we expanded our search to include observational studies that could provide indirect evidence regarding these questions.

Key Questions 5 and 6

Patients

We restricted the review to studies that enrolled adults with CKD stages 1–3. Again, studies whose definitions of CKD stages 1–3 at least closely approximated the current KDOQI and KDIGO definitions were considered eligible.

Interventions

We included studies of both CKD specific and nonspecific treatments. Specifically, we attempted to identify studies of ACEI, ARB, calcium channel blockers (CCB), aldosterone antagonists, alpha blockers, beta blockers (BB), loop diuretics, thiazide and related diuretics, combination antihypertensive regimens, targeting thresholds of blood pressure control independent of specific antihypertensive agent(s), insulin, sulfonylureas, thiazolidinediones, biguanides (e.g., Metformin), targeting thresholds for glycemic control, HMG CoA-reductase

inhibitors (i.e., statins), bile acid sequestrants, cholesterol absorption inhibitors (e.g., Ezetimibe), anorexiants, lipase inhibitors, low protein diets, and other diets.

Comparators

These studies compared active treatment of patients with CKD stages 1–3 with placebo, usual care/no treatment, or with other active treatments, including combination treatment and comparisons with the same active treatments using different dose levels or targeting different treatment thresholds.

Outcomes

We restricted the review to studies that reported clinical outcomes or harms. Clinical outcomes included: all-cause mortality, cardiovascular mortality, MI (any, fatal, nonfatal), stroke (any, fatal, nonfatal), CHF (hospitalization, death), composite vascular outcomes, composite renal outcomes, ESRD (progression to kidney transplant or dialysis), quality of life, physical function, and activities of daily living. Intermediate outcomes included: progression to stage 4 or stage 5 kidney disease, composite renal outcomes, doubling of serum creatinine or halving of GFR, and conversion from microalbuminuria to macroalbuminuria. Harms included: any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

Study Designs

We only included RCTs.

Study Selection

Separate literature searches were completed for the three main topic areas: screening, monitoring, and treatment. Results of each literature search were imported to a spreadsheet for screening. Trained reviewers examined all titles and abstracts for eligibility based on the inclusion/exclusion criteria for the topic area of the search. Titles and abstracts with insufficient information to determine eligibility were pulled for full article text review. If the initial reviewer was uncertain about eligibility, one of the physician project leads reviewed the abstract (or article) and made a final decision about inclusion or exclusion. We selected a 10 percent sample (representing the work of all abstract reviewers) for repeat review. Based on discrepancies between the results of one initial reviewer and the second reviewer, all abstracts reviewed by that initial reviewers were reviewed a second time. Overall, we asked abstract reviewers to err on the side of inclusion rather than exclusion. Reasons for exclusion were tallied in the spreadsheet and entered in an EndNote file for reference list management. We also applied the inclusion/ exclusion criteria to studies identified in the hand search of reference lists and in the review of studies cited in relevant systematic reviews. Additional references suggested by members of our TEP and by the public during the comment period also were reviewed for eligibility. A list of excluded studies is included in Appendix B.

Data Extraction

For the treatment interventions, trained clinicians or research assistants extracted data onto a spreadsheet. After verifying study eligibility, we extracted the following data from each trial:

- Study quality: Allocation concealment, intention-to-treat analysis, blinding, withdrawals, and dropouts adequately described;

- Study characteristics: Location, number of sites, subject inclusion and exclusion criteria, source of study subjects, total number randomized, details of treatment and control group interventions;
- Baseline participant data: age, weight, body mass index, gender, race/ethnicity, CKD stage, estimated or directly measured GFR, serum creatinine, urinary albumin or protein excretion rate, creatinine clearance, urine albumin or protein creatinine ratio, glycosylated hemoglobin or hemoglobin A_{1c} (HbA_{1c}), blood pressure, cholesterol, smoking status, and history of diabetes, hypertension, dyslipidemia, coronary artery disease, congestive heart failure (CHF), peripheral arterial disease, myocardial infarction (MI), stroke, and history of acute kidney injury;
- Efficacy outcomes: Duration of followup, all-cause mortality, cardiovascular mortality, MI (any, fatal, nonfatal), stroke (any, fatal, nonfatal), CHF (hospitalization, death), composite vascular outcomes, ESRD (progression to kidney transplant or dialysis), progression to stage 4 or stage 5 kidney disease, composite renal outcomes, doubling of serum creatinine or halving of GFR, conversion from microalbuminuria to macroalbuminuria, whether continuous renal outcomes were reported, and whether quality of life, physical function or activities of daily living were reported; and
- Withdrawals and adverse events: any withdrawals, withdrawals due to adverse events, any adverse events, serious adverse events, specific adverse events, and any renal adverse events.

Articles identified as not meeting eligibility criteria during the extraction phase were tallied and documented on the study flow diagram. In preparing the tables and text, a second clinician or research assistant confirmed the accuracy of the extracted information by comparing the extracted information with the original article. A physician project lead verified all entries in tables included in the review and appendices.

Quality Assessment

Study quality for the individual RCTs was rated by using the following criteria based on the domains the Cochrane Collaboration recommends to assess the risk of bias of studies included in a systematic review:[36] (1) adequate allocation concealment, based on the approach by Schulz and Grimes;[37] (2) blinding methods (participant, investigator, and/or outcome assessor); (3) how incomplete data are addressed (did the study analyze the data based on the intention-to-treat principle, i.e., were all participants who were randomized included in the outcomes analyses); and (4) whether reasons for dropouts/attrition were reported. Studies were rated as good, fair, or poor quality. A rating of good generally indicated that the trial reported adequate allocation concealment, blinding, analysis by intent-to-treat, and reasons for dropouts/attrition were reported. Studies were generally rated poor if the method of allocation concealment was inadequate or not defined, blinding was not defined, analysis by intent-to-treat was not utilized, and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition.

Rating the Body of Evidence

The overall strength of evidence for the randomized trials was evaluated using methods developed by AHRQ and the Effective Health Care Program.[38] For each of several important clinical outcomes within each comparison evaluated, the strength of the evidence was evaluated

based on four required domains: (1) risk of bias (do the studies for a given outcome or comparison have good internal validity); (2) consistency (the degree of similarity in the effect sizes, i.e., same direction of effect, of the included studies); (3) directness (reflecting a single, direct link between the intervention of interest and the outcome); and (4) precision (degree of certainty surrounding an effect estimate of a given outcome). The risk of bias, based on study design and conduct, is rated low, medium, or high. Consistency is rated consistent, inconsistent, or unknown/not applicable (e.g., a single study was evaluated). Directness can either be direct or indirect and precision is either precise or imprecise. A precise estimate is one that would yield a clinically meaningful conclusion. Based on these four domains, the overall evidence was rated as: (1) high, indicating high confidence that further research is very unlikely to change the confidence in the estimate of effect, meaning that the evidence reflects the true effect; (2) moderate, indicating moderate confidence that further research may change our confidence in the estimate of effect and may change the estimate; (3) low, indicating low confidence that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate, meaning there is low confidence that the evidence reflects the true effect; and (4) insufficient, indicating that evidence either is unavailable or does not permit a conclusion. An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias, with consistent, direct, and precise domains.

Applicability

Applicability of the results reported in this review is affected by the representativeness of the patient samples in the included studies to general populations and specific subpopulations of nonstudy patients with CKD stages 1–3, both those identified through screening and through other means. All treatment trials included patients with CKD stages 1–3, but because of the variability in CKD definitions used in identified studies, some trials also included some patients outside the bounds defined by CKD stages 1–3. This may limit the applicability of results reported here to patients who meet the currently accepted definition for CKD stages 1–3. Incomplete reporting of patient characteristics in many included trials also limits our ability to judge applicability of study results to specific CKD patient populations. The evidence tables in Appendix C identify reported details on the patient inclusion and exclusion criteria, as well as baseline patient characteristics.

Data Synthesis

Text; evidence, outcomes, and summary tables; and figures were organized by intervention. If clinical heterogeneity of patient populations, interventions, and outcomes was minimal, we pooled results. For many interventions, there were only one or two trials and reported outcomes did not overlap. Narratives provide details on study populations, interventions, clinical outcomes, and harms. Data were analyzed in Review Manager 5.0.[39] Random effects models were used to generate pooled estimates of relative risks (RR) and 95 percent confidence intervals (CI). Statistical heterogeneity was summarized using the I^2 statistic (50 percent indicates moderate heterogeneity and 75 percent or greater indicates high heterogeneity).[40]

Publication Bias

Grey literature was searched for relevant trials and other material to estimate the likelihood of publication bias. Sources of regulatory documents included Federal Drug Administration –

Medical Reviews and Statistical Reviews, Health Canada – Drug Monographs, and Authorized Medicines for the European Union. Clinical trial registries accessed were ClinicalTrials.gov, Current Controlled Trials, Clinical Study Results, and World Health Organization's Clinical Trials. Conference papers and abstracts were identified from the CSA Conference Papers Index and Scopus.

Results

Our literature search was designed to identify RCTs and CCTs of screening to identify patients with CKD stages 1–3, and monitoring and treatment of patients with CKD stages 1–3. For the screening questions, our search yielded 324 references (Key Questions 1 and 2; Figure 2). We excluded 315 references in the initial review of titles and abstracts and we excluded the remaining nine references based on a full text review. The results were similar for the monitoring questions (Key Questions 3 and 4; Figure 3). Of 816 references identified in the search, we excluded 803 in title and abstract review and excluded the remaining 13 after obtaining the full text. For the treatment questions, 4,706 references were identified by the literature search (Key Questions 5 and 6; Figure 4). We excluded 3,676 references during title and abstract review and excluded an additional 939 when we reviewed the full text. In addition to the 91 eligible references identified from the literature search, an additional eight eligible references were identified by hand searching reference lists of related articles or systematic reviews or were suggested by members of our TEP or reviewers of our protocol.

The grey literature search yielded 1,899 documents or citations; 1,065 from regulatory sources, 416 from clinical trials, and 418 conference papers and abstracts. Of the treatments analyzed for this report, our literature review yielded the most references for ACEIs. We therefore looked at the grey literature for ACEI studies not identified in our literature search. In the conference abstract and papers grey literature, there were 74 references pertaining to ACEIs. Ten of the references were identified in our literature search. The remainder did not meet inclusion criteria. In the clinical trials grey literature, there were 13 citations pertaining to ACEIs. Nine did not meet inclusion criteria. The four remaining studies are in progress with no results reported, to date. We concluded that our literature search adequately identified the relevant studies.

Figure 2. Reference flow chart for CKD literature search—screening

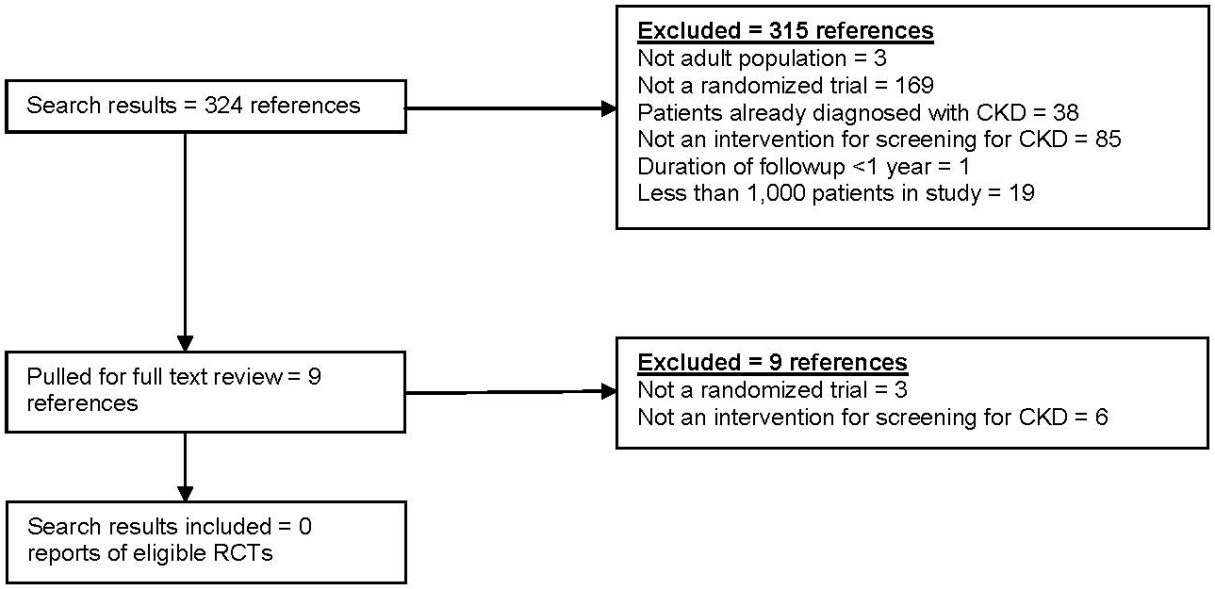


Figure 3. Reference flow chart for CKD literature search—monitoring

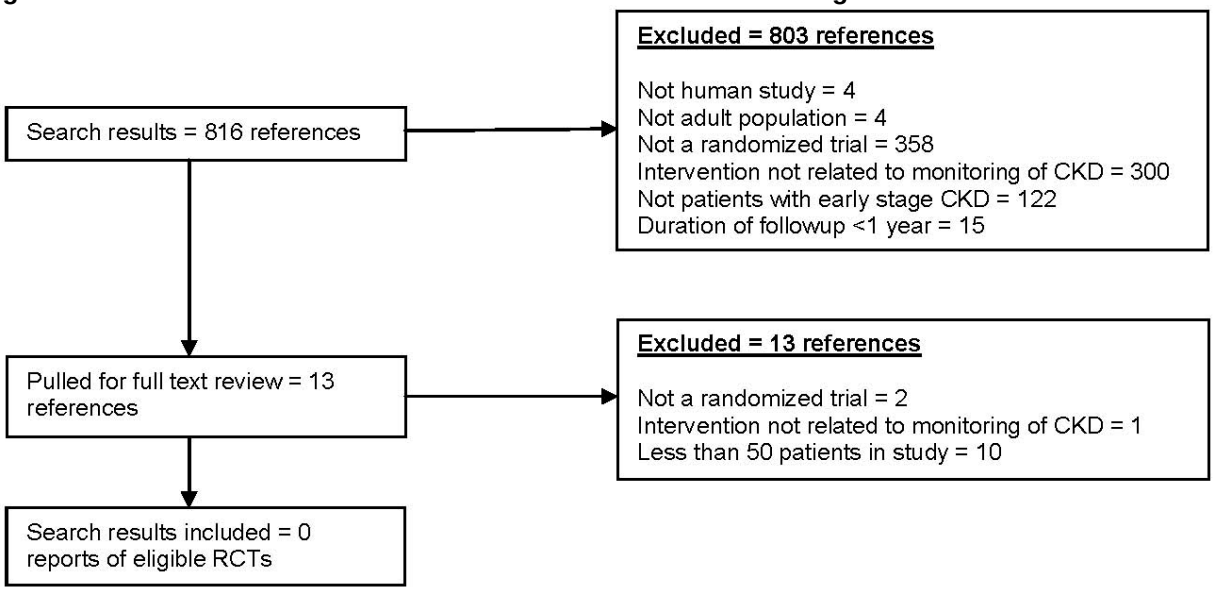
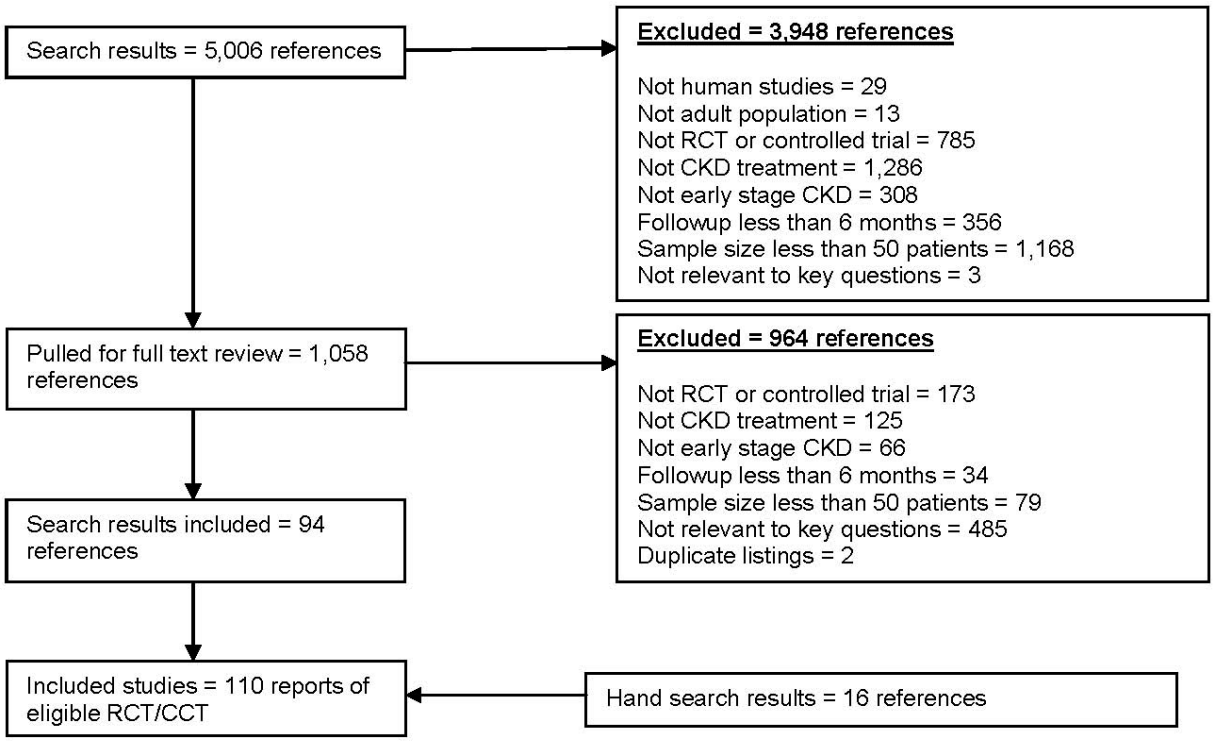


Figure 4. Reference flow chart for CKD literature search—treatment



Key Question 1. In asymptomatic adults with or without recognized risk factors for chronic kidney disease (CKD) incidence, progression or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?

We found insufficient evidence regarding whether systematic screening for CKD improves clinical outcomes.

Direct Evidence

We identified no RCTs that compared systematic CKD screening versus no CKD screening, versus usual care, or versus an alternative CKD screening regimen and evaluated clinical outcomes.

Indirect Evidence

Not finding direct evidence regarding whether systematic CKD screening improved clinical outcomes, we nevertheless identified data to address at least some parameters that would be needed to indirectly assess the potential clinical benefits of systematic CKD screening.

Is Undiagnosed CKD Stages 1–3 Sufficiently Prevalent?

Determination of how many individuals need to be screened to identify each new case of CKD in the population overall and within high risk groups will be a function both of the prevalence of undiagnosed CKD in these groups and the frequency with which such patients already are tested for CKD in usual practice.

As described earlier, approximately 11.1 percent (22.4 million) of U.S. adults age 20 or older have CKD stages 1–3.[8] This estimate is derived from the NHANES population by using the CKD-EPI formula to estimate GFR and the urine albumin-creatinine ratio to estimate kidney damage. Of individuals with CKD stages 1–3, half have increased albuminuria only (nearly all with microalbuminuria), one-third have decreased GFR only, and the remainder have both abnormalities. Of individuals with albuminuria, nearly 85 percent have microalbuminuria, with the remainder (approximately 1 percent of NHANES participants) having macroalbuminuria. In another population-based sample, prevalence of macroalbuminuria among adults aged 28 to 75 years was 0.6 percent.[41] Compared with the overall population, prevalence of CKD stages 1–3 is higher among older adults, including 17.6 percent in those aged 60-69, and 44.4 percent among adults aged 70 years or older[8] Also based on NHANES data, prevalence of CKD stages 1–3 is 39.0 percent in patients with diabetes, 27.8 percent in patients with hypertension, and 37.9 percent in those with cardiovascular disease[42] (Table 1) Combining these risk factors, NHANES data have been used to stratify individuals into different groups with respect to their likelihood of having CKD[9] (Tables 2 and 3). For example, only 5 percent of individuals less than 52 years old and without diabetes, hypertension, or obesity were estimated to have CKD compared with 68 percent of those aged 81 years or older.

Other data suggest that most individuals with CKD stages 1–3 are not clinically recognized to have this diagnosis. In one study, among patients with GFR <60 ml/min/1.73m^2, just 26.5 percent were documented to have a clinical diagnosis of CKD.[43] In 2008 data from the VA system, even in patients with CKD stages 3-5, only 33 percent had a provider-coded ICD-9 diagnosis for CKD.[44] Awareness of CKD appears even lower in patients. According to the CDC

CKD Surveillance Project 2009 Report, among NHANES participants in 1999-2006, fewer than 5 percent with proteinuria and an estimated GFR ≥60 ml/min/1.73m^2 (based on a single measurement) reported being aware of having CKD, and only 7.5 percent of participants with a GFR between 30-59 ml/min/1.73m^2 were aware of having CKD.[44]

Most patients without CKD, even those in high risk groups, do not appear to be undergoing CKD testing in usual clinical care. Based on 2007-2008 Medicare data, among patients without CKD who had diabetes, the annual probability of urine microalbumin testing was just over 30 percent.[12] In those without CKD who had hypertension, the annual probability of urine microalbumin testing was 4 percent. Based on 2004 Medicare data, among patients without CKD who had either diabetes or hypertension, the annual probability of serum creatinine measurement was less than 20 percent.[45]

Is CKD Stages 1–3 Associated With Sufficient Adverse Health Consequences?

As described earlier, early stage CKD is usually asymptomatic. However, data from many studies indicate that a GFR 30-59 mL/min/1.73 m^2 (stage 3 CKD) is associated with an increased risk of mortality,[3,13] cardiovascular disease,[14] fractures,[15] bone loss,[16] infections,[17] cognitive impairment,[18] and frailty. Similarly, albuminuria and proteinuria (stage 1–4 CKD) are associated with an increased risk of mortality,[3,20] ESRD,[21] and cardiovascular disease,[22] with risk increasing according to the severity of albuminuria or proteinuria. Further, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria or proteinuria appear independent and multiplicative.[3,21]

Are There Valid, Reliable, and Clinically Available CKD Screening Tests?

Serum creatinine is measured from a simple blood test. Formulas to estimate GFR are now automatically reported in many clinical labs from serum creatinine and are highly correlated (i.e., >0.9)[46] with direct GFR measurement based on urinary clearance of ^{125}I-iothalamate. At present, the Modification of Diet in Renal Disease (MDRD) formula is the one most commonly used in clinical practice. A large external validation study indicated that compared with measured GFR the CKD-EPI formula had a small median bias (measured GFR minus estimated GFR) of +/-4 ml/min/1.73m^2 or less at all levels of measured GFR.[47] This represents a significant improvement in accuracy compared with the MDRD formula for measured GFR ≥30 ml/min/1.73m^2, which is known to underestimate measured GFR above this level, particularly in individuals with GFR ≥60 ml/min/1.73m^2. However, the precision of both formulas are limited in that the percentage of their estimates that diverge by more than 30 percent from measured GFR exceeds 15 percent.[8] Framed differently, the sensitivity and specificity of a one-time estimate of GFR <60 mL/min/1.73m^2 for detection of a one-time direct measurement of GFR <60 mL/min/1.73m^2 were 91 percent and 87 percent according to the CKD-EPI equation and 95 percent and 82 percent according to the MDRD Study equation.[8] These data correspond to a false-positive rate of 13 percent and 18 percent for GFR estimation with CKD-EPI and MDRD, respectively. We did not identify studies that compared estimated GFR with directly measured GFR based on two or more measurements three or more months apart as would be consistent with the definition of CKD. It would be expected that when compared with persistently abnormal measured GFR, the false-positive rate of one-time estimated GFR would be higher.

There are many sources of variability in measurement of urinary albumin excretion. Intra-individual variability is high, with many published coefficients of variance estimates clustering around 30 to 50 percent.[48] Factors that can impact urinary albumin excretion include body position, exercise, and fever.[48] While most groups recommend use of spot tests and calculation of the urine albumin-creatinine ratio, methodology for its collection and for measurement of both urinary albumin and creatinine has yet to be standardized. Although these are additional sources of variation, they appear considerably smaller in magnitude than the intra-individual variability.[48-50] Impacted by these issues, among individuals with one-time microalbuminuria and GFR ≥60 ml/min/1.73m^2 in the NHANES study, only 63 percent had either microalbuminuria or macroalbuminuria on repeat testing two months later.[51] Further, even in a diabetic population with persistent microalbuminuria, as defined by repeated UACR measurements during a 2-year period, regression of the microalbuminuria to normal occurred in 59 percent patients over a subsequent 6-year evaluation period.[52]

Unfortunately, we did not identify any population-based studies that tested the sensitivity or specificity of one-time screening using both estimated GFR and albuminuria for diagnosis of CKD as defined by persistence of impaired GFR and/or albuminuria for at least 3 months (the current "gold standard"). We also did not identify any data on the validity and reliability of repeated screening for CKD.

Do Treatments for Screen-Detected CKD Patients Improve Important Clinical Outcomes?

We did not identify RCTs involving treatment of CKD patients identified through systematic screening, but did systematically review the RCT evidence on the effectiveness of treatments of CKD patients identified more generally in the Results section for Key Question 5.

Table 1. Percentage of U.S. adult population age 20 years or older with each stage of CKD, overall and within subgroups defined by age, gender, race, and comorbidities using the creatinine based CKD-Epi formula for estimating GFR

Population Characteristic	% of Population With Stage 1 CKD	% of Population With Stage 2 CKD	% of Population With Stage 3 CKD	% of Population With Stages 4–5 CKD
Overall	4.3	3.2	6.3	0.6
Age 20-39	4.7	0.7	0.2*	0.1*
Age 40-59	4.9	2.5	2.0	0.2
Age 60+	2.4	8.6	24.3	2.1
Male	3.5	3.4	5.2	0.6
Female	5.0	3.0	7.4	0.6
Non-Hispanic white	3.2	3.3	7.4	0.6
Non-Hispanic African American	6.3	3.4	4.9	1.2
Diabetes (SR)	11.8	10.2	17.0	3.1
Hypertension (SR)	5.4	5.9	14.6	1.7
CVD (SR)	3.3	8.7	25.9	4.3
Current smoker	5.9	2.3	2.4	0.5
Obese (BMI ≥30)	5.5	4.2	6.6	0.6

*Not Reliably Estimated. SR= Self-Reported
CKD Stages defined as:
Stage 1: eGFR ≥90 mL/min/1.73 m^2, UACR ≥30 mg/g
Stage 2: eGFR 60–89 mL/min/1.73 m^2, UACR ≥30 mg/g
Stage 3: eGFR 30–59 mL/min/1.73 m^2
Stage 4: eGFR 15–29 mL/min/1.73 m^2
Stage 5: eGFR <15 with dialysis patients excluded from this analysis
Note: Adapted from USRDS Annual Report 2010.[12]

Table 2. Sensitivity and specificity of different population characteristics for identifying individuals who would have one-time eGFR <60 ml/min/1.73 m^2: using creatinine and CKD-Epi formula

Screened Population	Sensitivity of Demographic Characteristics	Specificity of Demographic Characteristics
Age 20+	100.0	0
Age 50+	94.6	65.7
Age 50+ or <50 with DM or HTN	98.0	55.4
Age 50+ or <50 with DM, HTN, or CVD	98.6	54.7
Age 60+	85.3	82.3
Age 60+ or <60 with DM or HTN	94.6	65.5
Age 60+ or <60 with DM, HTN, or CVD	95.4	64.2

CKD-Epi Formula: estimated GFR = 141 * min(Scr /κ, 1)**α* max(Scr/κ, 1)**(-1.209) * 0.993**age * 1.018 [if female] * 1.159 [if African American], where Scr is standardized serum creatinine in mg/dl, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/κ or 1.

DM=Diabetes Mellitus, HTN=Hypertension, CVD=Cardiovascular Disease.

Note: Adapted from USRDS Annual Report 2010.[12]

Table 3. Sensitivity and specificity of different population characteristics for identifying individuals who would have one-time UACR ≥30 mg/g

Screened Population	Sensitivity	Specificity
Age 20+	100.0	0
Age 50+	60.5	64.3
Age 50+ or <50 with DM or HTN	73.3	54.9
Age 50+ or <50 with DM, HTN, or CVD	73.9	54.1
Age 60+	44.9	80.5
Age 60+ or <60 with DM or HTN	67.6	65.1
Age 60+ or <60 with DM, HTN, or CVD	68.6	63.7

ACR: urinary Albumin (mg/l) to urinary Creatinine (mg/dl) Ratio.

DM=Diabetes Mellitus, HTN=Hypertension, CVD=Cardiovascular Disease.

Note: Adapted from USRDS Annual Report 2010.[12]

Key Question 2. What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression, or complications?

We found insufficient evidence to address the question regarding whether systematic CKD screening causes adverse effects for patients.

Direct Evidence

We identified no RCTs that compared systematic CKD screening versus no CKD screening, versus usual care, or versus an alternative CKD screening regimen and evaluated adverse effects for patients.

Indirect Evidence

We considered numerous potential adverse effects of systematic CKD screening (Table 4), but found only very limited literature addressing this issue.[53] Based on expert opinion only, the primary harms from CKD screening are likely to be misclassification of patients with CKD, unnecessary tests and their associated adverse effects (e.g., from phlebotomy or renal biopsies), psychological effects of being labeled with CKD, adverse events associated with

pharmacological treatments initiated or changed following a CKD diagnosis, and possible financial and insurance ramifications of a new CKD diagnosis.

Table 4. Potential harms associated with screening for CKD

A)	Psychological effects of screening tests
B)	Adverse physical effects of screening tests (e.g., phlebotomy-associated bruising)
C)	Misclassification/false positive diagnosis
D)	Unnecessary tests to further evaluate patients with positive screening test and their associated effects, e.g., phlebotomy-associated bruising; pain, bleeding with need for transfusion, and infection associated with renal biopsy
E)	Psychological effects associated with CKD diagnostic label and of further evaluations following diagnosis
F)	Increased visits to primary provider, increased referrals to specialists
G)	Adverse effects associated with increased treatment, possibly including worsened estimated GFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
H)	Increased difficulty obtaining/keeping health insurance coverage

Psychological Effects of Screening

We did not identify any studies that reported on the psychological effects of screening tests for CKD.

Adverse Physical Effects of Screening Tests and of Followup Tests To Evaluate Abnormal Screening Test

Phlebotomy required to measure serum creatinine may be associated with a small degree of bruising or discomfort. In a small number of patients, postscreening evaluation will include a renal biopsy, which has an associated risk of pain, bleeding, and infection.

Misclassification/False Positive Test for CKD

We did not identify any studies that reported on the effects of a false positive result from tests used to screen for CKD. False positive results may be common with tests for microalbuminuria. As described above, intra-individual variability in albuminuria is high. In one study, more than one-third of individuals with microalbuminuria and normal GFR on first testing regressed to normoalbuminuria on repeat testing two months later.[51] Raising questions about the sufficiency of the requirement that albuminuria be persistent for at least 3 months to diagnose CKD, in a second study, 59 percent of individuals with persistent microalbuminuria over a 2 year period regressed to normal during a subsequent 6 year evaluation period.[52] We did not identify any studies that reported the specificity of a single measurement of GFR estimated from serum creatinine for a diagnosis of CKD defined by abnormalities in kidney function or damage that persist for at least 3 months.

Labeling of an Individual With CKD

We did not identify any studies that reported on the effects of labeling an individual with CKD.

Increased Clinic Visits to Primary and/or Specialist Providers

We did not identify any studies that reported on the effect of CKD screening tests on subsequent patient visits to primary or specialist providers. However, to the extent that their provider is aware of it, individuals who have an abnormal result on CKD screening, seem likely to be seen more frequently in primary and specialty clinics. These visits may be for further evaluation to confirm the abnormal screening test, or providers may follow and treat these

patients under the assumption that they have diagnosed CKD. According to recent U.S. Renal Data System (USRDS) data, in the year following a claim-documented CKD diagnosis, approximately 90 percent of individuals have at least one physician visit and 30 percent have a visit with a nephrologist.[12]

Adverse Effects Associated With Treatment

We systematically reviewed the RCT evidence on adverse effects of treatments of CKD patients in the Results section for Key Question 6.

Impact on Insurance Coverage

We did not identify any studies that reported the effects of being diagnosed with CKD on obtaining or keeping health insurance coverage.

Key Question 3. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?

We found insufficient evidence regarding whether systematic monitoring of individuals with CKD stages 1–3 for worsening kidney function and/or kidney damage improves clinical outcomes.

Direct Evidence

We identified no RCTs that compared systematic monitoring of individuals with CKD stages 1–3 for changes in kidney function and/or damage versus no CKD monitoring, versus usual care, or versus an alternative CKD monitoring regimen and evaluated clinical outcomes.

Indirect Evidence

Though we did not find direct evidence regarding whether systematic monitoring of individuals with CKD stages 1–3 for changes in kidney function and/or damage improved clinical outcomes, we identified data to address at least some parameters that would be needed to indirectly assess the potential clinical benefits of such systematic monitoring in these patients.

Is Undiagnosed Worsening of Kidney Function and/or Damage Sufficiently Frequent in Patients With CKD Stages 1–3?

Determination of whether and how frequently individuals with CKD stages 1–3 need to be monitored to identify patients with CKD progression, overall and within high risk groups, will be a function both of the incidence of undiagnosed CKD progression in these groups, the incidence of CKD regression (e.g., to normoalbuminuria), and the frequency with which these patients already have their level of kidney function and/or damage tested in usual practice.

In patients with CKD, reported rates of CKD progression vary widely. Mean annual GFR decline may range from approximately 1 to >10 ml/min/1.73m^2.[27] Factors shown in at least some studies to predict faster decline include diabetes, proteinuria, increased blood pressure, older age, obesity, dyslipidemia, smoking, male gender, and etiology of primary kidney disease. The high intra-individual variation in albuminuria makes it harder to estimate rates at which albuminuria increases in CKD. However, in several RCTs that randomized individuals with diabetes and

microalbuminuria to either ACEI or ARB versus placebo,[54-59] the average annual progression rate to macroalbuminuria was approximately 5 to 9 percent (Table 5). A lower annual conversion rate of 2.8 percent was reported in the United Kingdom Prospective Diabetes Study.[60] However, these estimates of progression in albuminuria from RCTs are limited both in that being derived from RCTs they may not be representative of all patients with microalbuminuria, and in that a substantial portion of individuals with microalbuminuria also will regress (i.e., to normoalbuminuria) over time.

Contrasted to the lower frequency of testing among individuals who do not carry a CKD diagnosis, most patients with CKD stages 1–3 appear to be undergoing at least some CKD testing in usual clinical care. Based on 2008 data, the annual probability that patients with CKD stages 1–3 receive serum creatinine testing is about 95 percent in the Medicare population and about 80 percent in a younger privately insured population.[12] By comparison, the annual probability that patients with CKD stages 1–3 get albuminuria measured is between 30 and 40 percent.

Table 5. Rate of progression from microalbuminuria to macroalbuminuria

Trial	Baseline CKD Level	Followup Duration	Incidence of Macroalbuminuria
O'Hare, 2000[58] (ATLANTIS)	N=46 100% had microalbuminuria; 100% Insulin Dependent Diabetics GFR (ioexol) mean±SD= 100 ± 23ml/min	2 years	10.9% (5/46) ~5% per year
Strippoli, 2006[54] MICRO HOPE 2000[56]	N=587 100% had microalbuminuria 100% Diabetics	Median 4.5 years	21.6% (127/587) ~5% per year
Crepaldi, 1998[55]	N=34 100% had microalbuminuria 100% Insulin Dependent Diabetics	3 years	20.6% (7/34) ~7% per year
Laffel, 1995[57]	N=70 100% had microalbuminuria; 100% Insulin Dependent Diabetics CrCl (mean±SD)= 80 ± 22 mL/min per 1.73m^2 at baseline	2 years	18.6% (13/70) ~9% per year
Ravid, 1993[59]	N=45 100% had microalbuminuria 100% Type 2 Diabetics Proteinuria mean±SD= 123 ± 58 mg/24 h	5 years	42.2% (19/45) ~8% per year

In Patients With CKD Stages 1–3, Is CKD Progression Associated With Sufficient Adverse Health Consequences?

As described earlier, data from many studies indicate that a GFR 30-59 mL/min/1.73 m^2 (stage 3 CKD) is associated with an increased risk of mortality,[3,13] cardiovascular disease,[14] fractures,[15] bone loss,[16] infections,[17] cognitive impairment,[18] and frailty. Similarly, albuminuria and proteinuria are associated with an increased risk of mortality,[3,20] ESRD,[21] and cardiovascular disease,[22] with risk increasing according to the severity of albuminuria or proteinuria. Further, the risk for adverse outcomes conferred by reduced GFR and increased albuminuria or proteinuria is independent and multiplicative.[3,21]

We did not identify studies that longitudinally recalibrated risk of adverse health consequences among individuals with CKD stages 1–3 as their CKD progressed. However, a large, recent meta-analysis of prospective cohort studies reported risk of all-cause and

cardiovascular mortality for different strata defined by baseline eGFR and albuminuria as follows:[3]

- Within individuals who had albuminuria and GFR >60 ml/min/1.73m^2 (CKD stages 1–2):
  - Mortality risk was higher in those with macroalbuminuria than in those with microalbuminuria.
  - A lower GFR within this range was not associated with a higher mortality risk.
  - Mortality is increased for each lower level of eGFR below 60 ml/min/1.73m^2, higher for 45–59 (CKD stage 3), still higher for 30–44, and higher for GFR <30 ml/min/1.73m^2 (CKD stage 4).
- Within individuals with GFR <60 ml/min/1.73m2 (CKD stage 3):
  - Mortality risk is increased for each lower level of eGFR, lowest for 45–59, higher for 30–44, and higher for GFR <30 ml/min/1.73m2 (CKD stage 4).
  - Mortality risk is lowest in those without albuminuria, higher in those with microalbuminuria, and highest in those with macroalbuminuria.

Are There Valid, Reliable, and Clinically Available Tests To Monitor CKD Progression in Patients With CKD Stages 1–3?

Tests used to monitor CKD progression in patients with CKD stages 1–3, most typically quantitative measures of albuminuria and estimates of GFR calculated from serum creatinine, are derived from simple blood and urine tests that are widely available in primary care settings.

As described earlier in the section on screening, formulas to estimate GFR are automatically reported in many clinical labs from serum creatinine and are highly correlated with direct GFR measurement.[46] Compared with measured GFR, the CKD-EPI formula to estimate GFR has only a small bias at all levels of measured GFR,[47] which represents an improvement in accuracy compared with the MDRD formula, particularly in individuals with GFR ≥60 ml/min/1.73m^2. Both formulas suffer from some imprecision, however, as more than 15 percent of their estimates diverge from measured GFR by at least 30 percent.[8] Still, they appear to perform well for one-time classification of individuals as either having CKD or not. The sensitivity and specificity of estimated GFR <60 mL/min/1.73m^2 for detection of directly measured GFR <60 mL/min/1.73m^2 were 91 percent and 87 percent according to the CKD-EPI equation and 95 percent and 82 percent according to the MDRD Study equation.[8] Unfortunately, we did not identify data regarding the accuracy and precision of these formulas for assessing change in GFR within individuals over time, or their sensitivity and specificity for detecting change in GFR category over time (e.g., a decline from a GFR of 30 to 59 ml/min/1.73m2 to one of <30 ml/min/1.73m^2).

Also as described in the section on screening, inter-assay and intra-assay coefficient of variance for urinary albumin is less than 5 percent.[49,50] However, as is the case for individuals without CKD, intra-individual variation of urinary albumin excretion is high in individuals with CKD. The impact of hydration can be addressed by accounting for urine output (e.g., using urine albumin-to-creatinine ratio), but nonhydration factors that may impact estimates of urinary albumin excretion include body position, exercise, certain medications, fever, and urinary tract infections.[27] As an illustration of this variability, based on NHANES data, among individuals with one-time microalbuminuria and GFR ≥60 ml/min/1.73m^2, only 63 percent had either microalbuminuria or macroalbuminuria on repeat testing two months later.[51] Further, even in a diabetic population with persistent microalbuminuria over a 2-year period, regression of the microalbuminuria to normal occurred in 59 percent patients during a subsequent 6-year

evaluation period.[52] This variability makes it more difficult to determine whether longitudinal changes in measured albuminuria represent progression of CKD.

In Patients With CKD Stages 1–3 Whose CKD Has Progressed, Do Treatments Improve Important Clinical Outcomes?

For monitoring to improve clinical outcomes, changes in CKD status (such as the patient reaching a specific threshold or rate of change in kidney function or damage) would need to impact patient behavior or provider treatment in ways that improve these outcomes. RCT evidence that certain treatments had differential effects on clinical outcomes between patients with CKD stages 1–3 and those with CKD stage 4, or differential effects between different categories of patients within CKD stages 1–3 might suggest that treatment should be modified when change in CKD status is identified. While RCT data on CKD treatments are reviewed in greater detail elsewhere in this report, there is limited evidence to suggest that some treatments may have such differential effects based on CKD stage. For example, in RCTs comparing ACEI versus placebo treatment, a significant 40 percent reduction in relative risk of ESRD with ACEI is evident in trials comprised of patients with macroalbuminuria. By comparison, in ACEI versus placebo trials comprised of patients with microalbuminuria only, with very low power to detect changes in ESRD events, the pooled effect size suggests no difference between treatments. In a post hoc analysis in CHF patients with CKD, tests for interaction between study participants with GFR of >60, 45 to 60, and 30 to 44 ml/min/1.73m^2 suggest that benefit of beta blocker treatment versus placebo may be greater in the lower GFR group for reducing risk of hospitalizations due to CHF (p=.038), of two composite outcomes including all-cause mortality and hospitalization (both p <.05), and may be borderline significant with regard to all-cause mortality (p=.095).

Key Question 4. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function/kidney damage?

We found insufficient evidence to address the question regarding whether systematic monitoring of patients with CKD stages 1–3 for worsening kidney function or kidney damage causes adverse effects for patients.

Direct Evidence

We identified no RCTs that compared systematic monitoring of patients with CKD stages 1–3 for worsening kidney function or kidney damage versus no CKD monitoring, versus usual care, or versus an alternative CKD monitoring regimen and evaluated adverse effects for patients.

Indirect Evidence

We considered numerous potential adverse effects of systematic monitoring of patients with CKD stages 1–3 for worsening kidney function or kidney damage (Table 6), but found no literature directly addressing this issue. The primary harms from such monitoring are likely to be incorrect reclassification of patients as having improved or worsened CKD, unnecessary tests and their associated adverse effects (e.g., from phlebotomy or renal biopsies), psychological effects of being labeled with progressive or regressed CKD, adverse events associated with pharmacological treatments initiated or changed following testing that indicates that CKD has

worsened or improved, and possible financial and insurance ramifications of a more advanced CKD diagnosis.

Table 6. Potential harms associated with monitoring patients with CKD stages 1–3 for worsening kidney function

A)	Psychological effects of monitoring tests
B)	Adverse physical effects of screening tests (e.g., phlebotomy-associated bruising)
C)	Incorrect reclassification of CKD severity
D)	Unnecessary tests and associated effects, e.g., phlebotomy-associated bruising; pain, bleeding with need for transfusion, and infection associated with renal biopsy
E)	Psychological effects associated with label of worse CKD stage and of further evaluations following diagnosis
F)	Increased visits to primary provider, increased referrals to specialists
G)	Adverse effects associated with increased treatment, possibly including worsened estimated GFR, hyperkalemia, hypotension, cough, hospitalization for AKI, cardiovascular morbidity, other
H)	increased difficulty obtaining/keeping health insurance coverage

Psychological Effects of Monitoring

We did not identify any studies that reported on the psychological effects of monitoring tests for CKD.

Adverse Physical Effects of Monitoring Tests and of Followup Tests To Further Evaluate Monitoring Tests

Phlebotomy required to measure serum creatinine may be associated with a small degree of bruising or discomfort. In a small number of patients, postscreening evaluation will include a renal biopsy, which has an associated risk of pain, bleeding, and infection.

Incorrect Reclassification of CKD Severity

We did not identify any studies that reported on the effects of testing that incorrectly reclassifies patients with CKD stage 1–3 as having worse or improved CKD, or even no CKD. Limitations in the precision of formulas that estimate GFR means there is a reasonable likelihood that any one test will suggest that a patient's CKD has changed or remained stable when this isn't the case. However, the small bias, in particular of the CKD-EPI formula, suggests that multiple GFR estimates will cluster accurately around true measured GFR. The high intra-individual variability of albuminuria in the absence of changes in underlying disease means there is at least a modest likelihood that findings of any one quantitative test will be inaccurate, whether it indicates that a patient's albuminuria is improving, stable, or worsening. As an example, in one study cited above, more than half of individuals with persistent microalbuminuria during a 2-year period regressed to normal over a subsequent 6-year evaluation period.[52]

Labeling of an Individual With More Advanced CKD Stage

We did not identify any studies that reported on the effects of labeling an individual with a more advanced CKD stage.

Increased Clinic Visits to Primary and/or Specialist Providers

We did not identify any studies that reported on the effect of CKD monitoring tests on subsequent patient visits to primary or specialist providers. However, individuals whose monitoring tests indicate progression of their CKD seem likely to be seen more frequently in primary and specialty clinics. These visits may be for further evaluation to confirm the abnormal

monitoring test, or providers may follow and treat these patients under the assumption that they have more severe CKD.

Adverse Effects Associated With Treatment

We systematically reviewed the RCT evidence on adverse effects of treatments of CKD patients in the Results section for Key Question 6.

Impact on Insurance Coverage

We did not identify any studies that reported the effects of being diagnosed with worsening CKD on obtaining or keeping health insurance coverage.

Key Question 5. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?

and

Key Question 6. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

ACE Inhibitor Monotherapy Versus Placebo/No Treatment Trials (n=17)

Overview

In patients with CKD, compared with placebo, we found moderate strength of evidence that ACEI treatment does not reduce risk of all-cause mortality more than placebo, and low strength of evidence that ACEI treatment does reduce risk of ESRD. Compared with placebo, ACEI treatment did not appear to reduce risk of MI or stroke, but significantly reduced risk of doubling serum creatinine and risk of progression from microalbuminuria to macroalbuminuria.

Description of Studies

Seventeen trials met all eligibility criteria and randomized participants with CKD (n=11,661, range 52 to 4,912) to an ACEI versus placebo (n=16 trials).[55,57-59,61-72] or no treatment (n=1 trial).[73] Two of the included reports were post hoc analyses performed within subsets of participants with CKD from larger trial populations that were not originally limited to subjects with CKD.[61,66] Detailed baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 7,537 participants were randomized to ramipril versus placebo (n=7 trials),[58,63,65,66,68,69,71] 1,757 to perindopril versus placebo (n=1 trial),[61] 864 to fosinopril versus placebo (n=1 trial),[62] 665 to captopril versus placebo (n=4 trials)[57,64,67,72] 583 to benazepril versus placebo (n=1 trial),[70] 108 to enalapril versus placebo (n=1 trial),[59] 97 to lisinopril versus placebo (n=1 trial),[55] and 52 to enalapril versus no treatment (n=1 trial).[73] The mean age of subjects was 60 years (range 33 to 70; n=16 trials), and men constituted 66 percent (range 35 to 82; n=15 trials) of all patients randomized. Among the five trials reporting ethnicity, the patients were mostly of white race (77 percent).[57,61,62,67,72] Most trials were conducted in Europe (including North Africa and Israel), three were conducted primarily or partially in the United

States, and two were conducted in Japan. Mean or median study duration ranged from 6 months to 5 years. Seven trials had a followup of 3 years or longer and 12 trials had a followup of at least 2 years. Only one trial had a study duration of less than 1 year.[71] One trial was conducted in a subset of individuals who previously had responded to an effort to screen all city residents aged 28 to 75 years for albuminuria.[62]

Renal Function

One of the two post hoc analyses restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse.[61] Otherwise, no trial based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. In 15 of 17 trials, participants were required to have albuminuria or proteinuria. In 10 of these trials, participants must have been microalbuminuric,[55,57-59,62,65-67,71,73] most commonly with a urinary albumin excretion rate of 20 to 200 µg/minute. In three of the 15 trials, they were required to have overt proteinuria, with minimum thresholds ranging from ≥500 mg/day,[72] to ≥1 but ≤3 g/day,[68] and to >3 g/day.[69] In the last two of the 15 trials, both microalbuminuric and macroalbuminuric participants were allowed,[63,64] with approximately three-quarters of the participants in one of these trials being microalbuminuric,[63] but no similar data reported for the other trial. Among the 15 trials requiring participants to have albuminuria or proteinuria, seven required that participants also have normal creatinine, creatinine clearance or GFR,[55,57,58,62,67,71,73] three allowed some participants with abnormal levels for these renal function measures but mandated a maximally abnormal limit,[63,66,72] and the remaining five trials did not specify an eligibility requirement with respect to these measures.[59,64,65,68,69] Finally, inclusion in two of 17 studies was based strictly on elevated serum creatinine, or reduced creatinine clearance or GFR.[61,70]

Among the 10 trials restricted to microalbuminuric patients, mean baseline urinary albumin excretion rate was reported as 61.0 µg/min (range 53 to 71.5) in five trials[55,57,58,67,71] and as 25.6 mg/24 hour (range 23 to 72) in two trials,[62,73] and mean urinary protein excretion rate was 133 mg/24 hours in one trial.[59] Among the three trials restricted to patients with overt proteinuria, mean urinary protein excretion was 3.0 g/day (range 1.7 to 5.3).[68,69,72] In the two trials that permitted inclusion of both microalbuminuric and macroalbuminuric patients, one reported mean baseline urinary albumin excretion rate of 711 mg/24 hours.[64] One of two trials that did not require albuminuria for inclusion nevertheless had an elevated mean baseline urinary protein excretion rate of 1.8 g/day,[70] while the other did not report baseline albuminuria or proteinuria.[61] In trials reporting, mean baseline serum creatinine was 1.0 mg/dL (range 0.8 to 2.4; n=10 trials),[55,57,59,62-64,68-70,72] mean creatinine clearance was 64.1 ml/min/1.73m^2 (range 43 to 114; n=8 trials),[55,57,64,68-70,72,73] and mean GFR was 68.5 ml/min/1.73m^2 (range 39 to 114; n=5 trials).[55,58,67-69]

Baseline Comorbidities

Twelve of 17 studies were restricted to patients with diabetes, including seven limited to those with type 1 diabetes,[55,57-59,64,65,72] four limited to those with type 2 diabetes,[63,67,71,73] and one analysis that was open to both types of diabetics.[66] Among the five trials that did not report restricting enrollment solely to diabetics,[61,62,68-70] two nevertheless excluded participants with type 1 diabetes,[69,70] and three reported no data on baseline prevalence of diabetes[68-70] Mean glycosylated hemoglobin was 8.2 percent (range 7.1 to 11.7, n=10 trials).[55,57-59,63-65,71-73]

Seven trials excluded participants with hypertension,[55,57-59,62,65,73] including five that mandated that blood pressure be controlled without antihypertensive medications.[57,58,62,73] Four

additional trials excluded participants only for severe hypertension.[68-71] In addition, though information on hypertension was not available for all participants from two studies, prevalence was at least 35 percent[71] and 53 percent[61] in these two trials. Prevalence of hypertension across all trials excluding these two with incomplete information was 49.8 percent (n=14 trials). Mean systolic and diastolic blood pressures at baseline were 144 mm Hg (range 126 to 149) and 83 mm Hg (range 74 to 92), respectively.

One trial reported data on prevalence of "cardiovascular disease," at 24 percent.[63] Another trial was comprised entirely of participants with a history of cerebrovascular disease, including 71 percent with ischemic stroke, 10 percent with hemorrhagic stroke, and 7 percent with a stroke of unknown type.[61] Prevalence of specific cardiovascular conditions was reported in few trials, including coronary artery disease (18.5 percent, range 0 to 20, n=2 trials),[57,61] myocardial infarction (5.1 percent, range 0 to 6, n=3 trials),[57,62,63] and stroke (3.5 percent, range 0.8 to 4; n=2 trials).[62,63] Participants with CHF were excluded from four trials,[57,62,63,66] and prevalence of CHF was not reported in other trials.

Study Quality (Appendix Table C140)

Among the 17 studies, five were rated good quality and 12 were rated fair quality. Allocation concealment was adequate in seven trials and unclear in the remaining studies. All 16 placebo-controlled trials were double blinded. Nine trials reported outcomes assessment by blinded adjudication committees. Analysis by intention-to-treat principle was reported in nine trials. All trials adequately described reasons for study withdrawal except for the two reports that were post hoc subgroup analyses from larger trials. Percentages of study withdrawals ranged from 7 to 32 percent, including nine trials with withdrawal rates greater than 20 percent.[55,57,58,62,64,68-70,72] No data were reported on withdrawals in the two studies that were post hoc analyses of CKD subsets from larger trial populations not limited to CKD.[61,66]

Results

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1)

All-Cause Mortality

Patients with CKD randomized to ACEIs did not have a significantly reduced risk of all-cause mortality compared with those assigned placebo (RR 0.94, 95% CI, 0.80 to 1.12; n=16 trials, 11,536 patients). In two trials reporting, effect of ACEI versus placebo on mortality risk appeared similar in patients with and without CKD. In the HOPE trial,[66,74] relative risk of mortality was 0.77 [95% CI, 0.64 to 0.93] in patients with microalbuminuria and 0.90 [95% CI, 0.78 to 1.04] in patients without microalbuminuria (p=0.20 for interaction). In a second trial,[61] relative risk of mortality was 1.04 [95% CI, 0.83 to 1.31] in patients with creatinine clearance <60 ml/min and 0.84 [95% CI, 0.68 to 1.04] in patients with creatinine clearance ≥60 ml/min (p=0.1 for interaction).

Cardiovascular Mortality

Compared with placebo treatment, trial participants assigned to ACEIs also were not at lower risk for cardiovascular mortality (RR 1.03, 95% CI, 0.86 to 1.23).[61-63] Effect of treatment appeared similar in patients with and without CKD.[61]

Vascular Outcomes (Table 7, Appendix Tables C3-5, and Appendix Figure C1)

Myocardial Infarction

Compared with CKD patients randomized to placebo, risk for myocardial infarction was not significantly reduced in those assigned ACEI (2.4 versus 3.1 percent; RR=0.79, 95% CI 0.57 to 1.09; n=3 trials, 5,100 patients).[55,63,71]

Stroke

Compared with CKD patients randomized to placebo, those assigned to ACEI did not have a significant reduction in risk for stroke (6.0 versus 7.2 percent; RR=0.80, 95% CI, 0.52 to 1.23; n=4 trials, 7,719 patients).[61-63,68] However, there was evidence of substantial heterogeneity between the trials (I^2=68 percent). Two trials reported significant reductions in risk of stroke in ACEI patients compared with those assigned placebo (0.2 versus 2.3 percent; RR 0.10, 95% CI, 0.01 to 0.78; n=864 patients)[62] and (12.5 versus 17.6 percent; RR 0.71, 95% CI, 0.57 to 0.89; n=1,757 patients).[61] This latter trial, a post hoc analysis in patients with cerebrovascular disease, reported a similar relative reduction in stroke risk in patients with or without CKD.[61] A third trial reported no difference in risk of stroke between ACEI and placebo groups (4.8 versus 4.7 percent; RR 1.03, 95% CI, 0.80 to 1.32; n=4,912 patients),[63] while there was only one stroke in both treatment groups in the fourth trial.[68]

Other Vascular Outcomes

Seven trials reported a composite vascular endpoint (Appendix Table C5). Due to variability in these composite outcome definitions, results were not pooled between trials. Two of seven trials reported significant reductions in risk of their defined composite vascular outcome with ACEI treatment compared with placebo (Appendix Figure C1),[61,66] both of which further reported that this ACEI benefit was similar regardless of whether or not patients had microalbuminuria[56] or whether or not they had impaired creatinine clearance.[61] No trials reported a significant increase in risk of the composite vascular outcome in the ACEI group.

Renal Outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1)

End-Stage Renal Disease

In CKD patients overall, ACEIs significantly reduced the risk of ESRD versus placebo (1.7 versus 2.6 percent; RR 0.65, 95% CI, 0.49 to 0.88; n=7 trials, 7,490 patients).[59,63,66,68-70,72]

Other Renal Outcomes

CKD patients assigned ACEI treatment had a significantly reduced risk compared with placebo for doubling of baseline serum creatinine (RR 0.60, 95% CI, 0.40 to 0.89; n=7 trials), and in progression from microalbuminuria to macroalbuminuria (RR 0.38, 95% CI, 0.18 to 0.84; n=7 trials). Three trials defined composite renal outcomes (Appendix Table C7), as doubling of serum creatinine or ESRD in one trial,[69] doubling of serum creatinine or need for dialysis in a second trial,[70] and as death, dialysis or renal transplantation in the third trial.[72] In each of these studies, participants randomized to ACEI were about half as likely to reach the composite outcome as participants assigned to placebo, a statistically significant finding in all three trials. In

the two trials in which doubling of serum creatinine was part of the composite renal outcome definition, it accounted for 21 percent[69] and 98 percent of the composite events,[70] respectively.

Study Withdrawals and Adverse Events (Appendix Table C8)

Overall study withdrawal rates were comparable in the ACEI and placebo groups, 17.3 percent versus 16.3 percent (RR 1.06, 95% CI, 0.96 to 1.17; 12 trials; n=7,336). Patients allocated to an ACEI were more likely to withdraw from treatment due to any or a serious adverse event than patients assigned placebo (20.7 percent versus 18.7 percent; RR 1.12, 95% CI, 1.02 to 1.23; 14 trials; n=7,055). Worsening renal insufficiency leading to study withdrawal was reported in three trials, with four events (0.8 percent) in the ACEI group compared with eight (1.7 percent) in the placebo group.[68-70] Specific adverse events were not often reported. Cough was the most commonly reported adverse event and was significantly more likely in the ACEI group compared with placebo (4.7 percent versus 1.8 percent; RR 2.33, 95% CI, 1.49 to 3.63; 10 trials; n=7,361). Hyperkalemia was not significantly increased with use of an ACEI (1.3 percent versus 0.9 percent; RR 1.08, 95% CI, 0.53 to 2.23; 8 trials; n=2,758).

Subgroup Results

Albuminuria or Impaired eGFR (Figures 5 and 6)

In trials restricted to patients with overt proteinuria at baseline, there was no significant difference in risk between those assigned ACEI versus placebo for all-cause mortality (RR 0.71, 95% CI, 0.33 to 1.54; n=3 trials, 761 patients). However, there was a significant 40 percent relative reduction in risk of ESRD (12.0 versus 20.7 percent; RR 0.60, 95% CI, 0.43 to 0.83; n=861 patients).[68,69,72] In trials restricted to patients with microalbuminuria, mortality risk was significantly reduced in the ACEI group versus placebo (9.3 versus 12.1 percent; RR 0.79, 95% CI, 0.66 to 0.96; n=3,440 patients), with similar results in the diabetic (RR 0.78, 95% CI, 0.61 to 1.00; n=1,140 patients) and nondiabetic (RR 0.75, 95% CI, 0.55 to 1.02; n=816 patients) microalbuminuria subgroups. However, there was no significant reduction in risk of ESRD between ACEI and placebo groups (0.8 versus 0.9 percent; RR 0.88, 95% CI, 0.27 to 2.88; n=1,234 patients).[59,66] In trials restricted to patients with microalbuminuria or worse, there was no significant difference between treatment groups in risk of ESRD (0.4 versus 0.5 percent; RR 0.93, 95% CI, 0.42 to 2.03; n=5,495 patients)[63,70] or mortality (RR 0.92, 95% CI, 0.74 to 1.15; n=9,192 patients). However, the two trials that together contributed more than 95 percent of the deaths for the ACEI versus placebo albuminuria subgroup analyses presented contrasting results, with a significant reduction in mortality risk in the HOPE trial[66,74] (15.7 versus 20.3 percent; RR 0.77, 95% CI, 0.64 to 0.93) but not the DIABHYCAR trial[63] (13.7 versus 13.1 percent; RR 1.04, 95% CI, 0.90 to 1.20). In the overall HOPE study population, 80 percent of participants had a history of coronary artery disease, including 52 percent with a history of MI, and 38 percent had diabetes, though comorbidity data were not reported for the subset with CKD. HOPE study participants were randomized to ramipril 10 mg per day versus placebo, and those with CKD were defined as having microalbuminuria. In the DIABHYCAR trial, prevalence of cardiovascular disease was lower at 24 percent, with only 6 percent having a history of MI, and 100 percent had diabetes. Participants were randomized to ramipril 1.25 mg per day versus placebo. Those with CKD were defined as having either microalbuminuria or macroalbuminuria. In results from two trials restricted to patients with impaired eGFR, there was no significant difference between treatments in risk of mortality (RR 2.14, 95% CI, 0.34 to 13.39).

Diabetes

In 12 trials restricted to patients with diabetes, there was no significantly reduced risk with ACEI versus placebo for mortality (RR 0.91, 95% CI, 0.70 to 1.18, n=11 trials), ESRD (RR 0.73, 95% CI 0.48 to 1.10, n=4 trials), MI, stroke, or doubling of serum creatinine (RR 0.69, 95% CI, 0.44 to 1.09, n=5 trials). With respect to mortality risk, results appeared clinically heterogeneous between diabetic participants from the HOPE trial[66,74] (16.3 versus 20.8 percent; RR 0.78, 95% CI, 0.61 to 1.00) and those from the DIABHYCAR trial[63] (13.7 versus 13.1 percent; RR 1.04, 95% CI, 0.90 to 1.20). In contrast, diabetic participants randomized to ACEI had a significant reduction in risk of conversion from microalbuminuria to macroalbuminuria (RR 0.38, 95% CI, 0.18 to 0.84, n=7 trials). In four trials reporting a composite vascular outcome, risk was significantly reduced in the ACEI group in one trial.[66,74]

Hypertension

No trials were restricted to patients with hypertension, but in seven trials that excluded patients with hypertension, there was a significantly reduced risk of stroke (RR 0.10, 95% CI, 0.01 to 0.78, n=1 trial), doubling of serum creatinine (RR 0.15, 95% CI, 0.04 to 0.65), and conversion from microalbuminuria to macroalbuminuria (RR 0.29, 95% CI, 0.13 to 0.64), but no significant treatment group difference in mortality (RR 1.87, 95% CI, 0.65 to 5.37; n=7 trials, 1,454 patients) or other clinical vascular outcomes.

Congestive Heart Failure

No trials were restricted to patients with CHF, but in four trials that excluded patients with CHF, there was no significant difference between ACEI and placebo treatment groups in risk of mortality (RR 1.07, 95% CI, 0.52 to 2.18; n=4 trials, 1,192 patients), ESRD, or any other vascular or renal outcome.

Cerebrovascular Disease

In one trial restricted to patients with a history of cerebrovascular disease, risk of stroke was significantly reduced with ACEI versus placebo (RR 0.71, 95% CI, 0.57 to 0.89).However, there was no significant difference in risk of mortality (RR 1.07, 95% CI, 0.87 to 1.32), and no other vascular or renal outcomes were reported. Otherwise, no trials were limited to or excluded participants with cardiovascular disease.

Summary

In patients with CKD stages 1–3, compared with placebo, ACEI monotherapy did not significantly reduce risk of all-cause mortality in results overall. However, results appeared discordant between the two trials that together reported nearly all the deaths. In a study comprised of patients with microalbuminuria, and a high prevalence of cardiovascular disease who were treated with ramipril 10 mg per day versus placebo, mortality risk was significantly reduced. Results were similar in study subsets with and without diabetes. In a study comprised of patients with diabetes, microalbuminuria or macroalbuminuria, and a low prevalence of cardiovascular disease who were treated with ramipril 1.25 mg per day versus placebo, mortality was not significantly reduced. Because the latter trial appeared to be comprised of participants at only slightly lower absolute mortality risk and had a large total number of deaths, the difference between ramipril treatment doses seems the most likely explanation for the difference in outcomes. There was no significant difference between ACEI and placebo in risk of cardiovascular mortality, or MI. Overall, there was no significant reduction in risk of stroke,

though results appeared heterogeneous between trials, with two moderate-sized trials reporting a significant reduction in stroke risk and another one finding no difference. Two of seven trials reporting found a significantly reduced risk in a composite vascular outcome in participants randomized to ACEI. Overall, subjects assigned to ACEIs had a significant 35 percent reduction in risk of ESRD compared with patients assigned to placebo. This risk reduction appeared restricted to studies that enrolled only patients with overt proteinuria. CKD patients assigned to ACEIs had a significant 40 percent reduction in risk of doubling serum creatinine, 62 percent reduction in risk of converting from microalbuminuria to macroalbuminuria, and approximately 50 percent reductions in all composite renal outcomes reported. Overall study withdrawals were not significantly different between ACEI and placebo groups. ACEIs increased risk of cough, but there was little apparent difference from placebo subjects in hyperkalemia. Results were limited in that few trials were of sufficient size to assess mortality or clinical vascular outcomes.

Figure 5. ACEI versus placebo: All-cause mortality by albuminuria subgroups

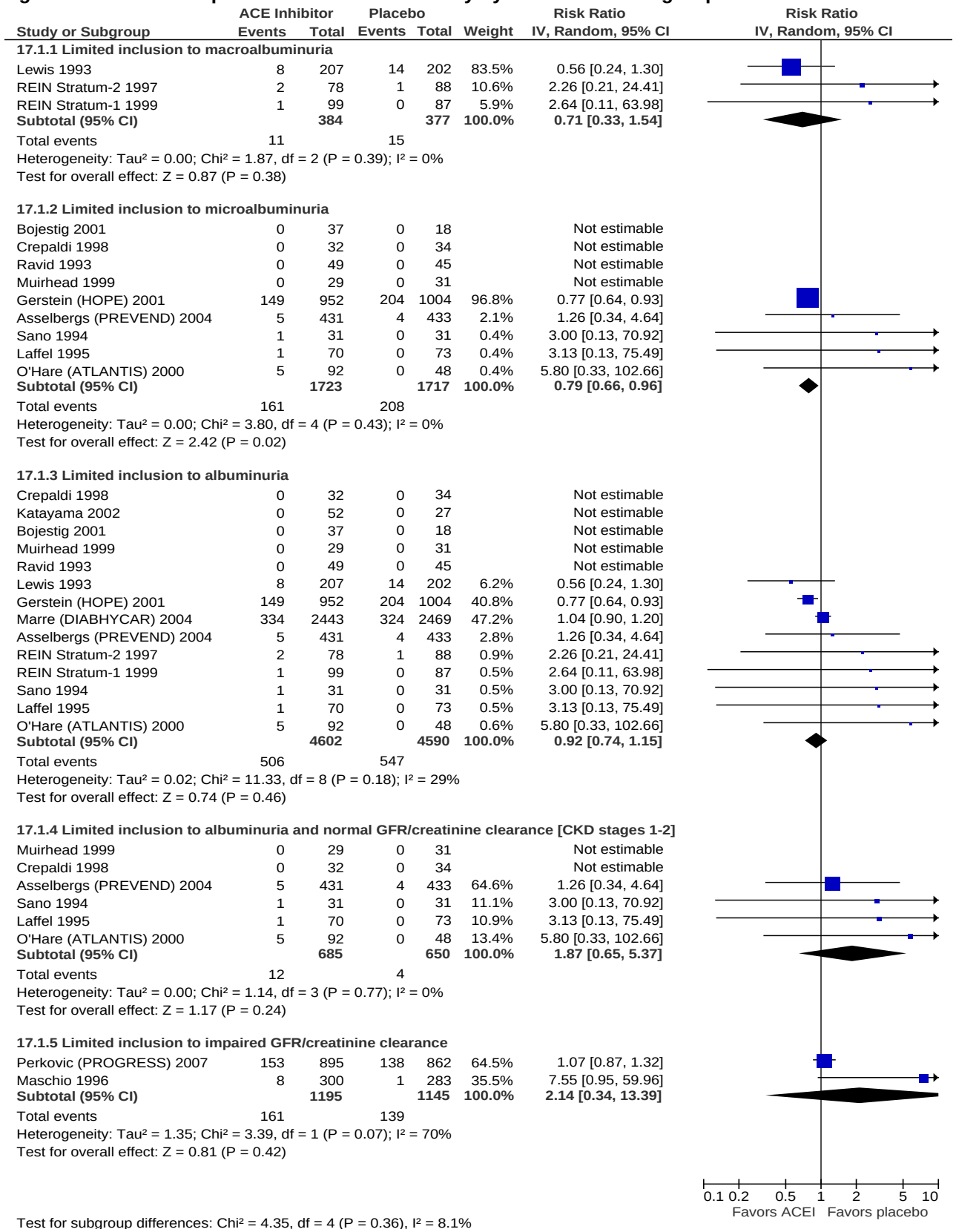
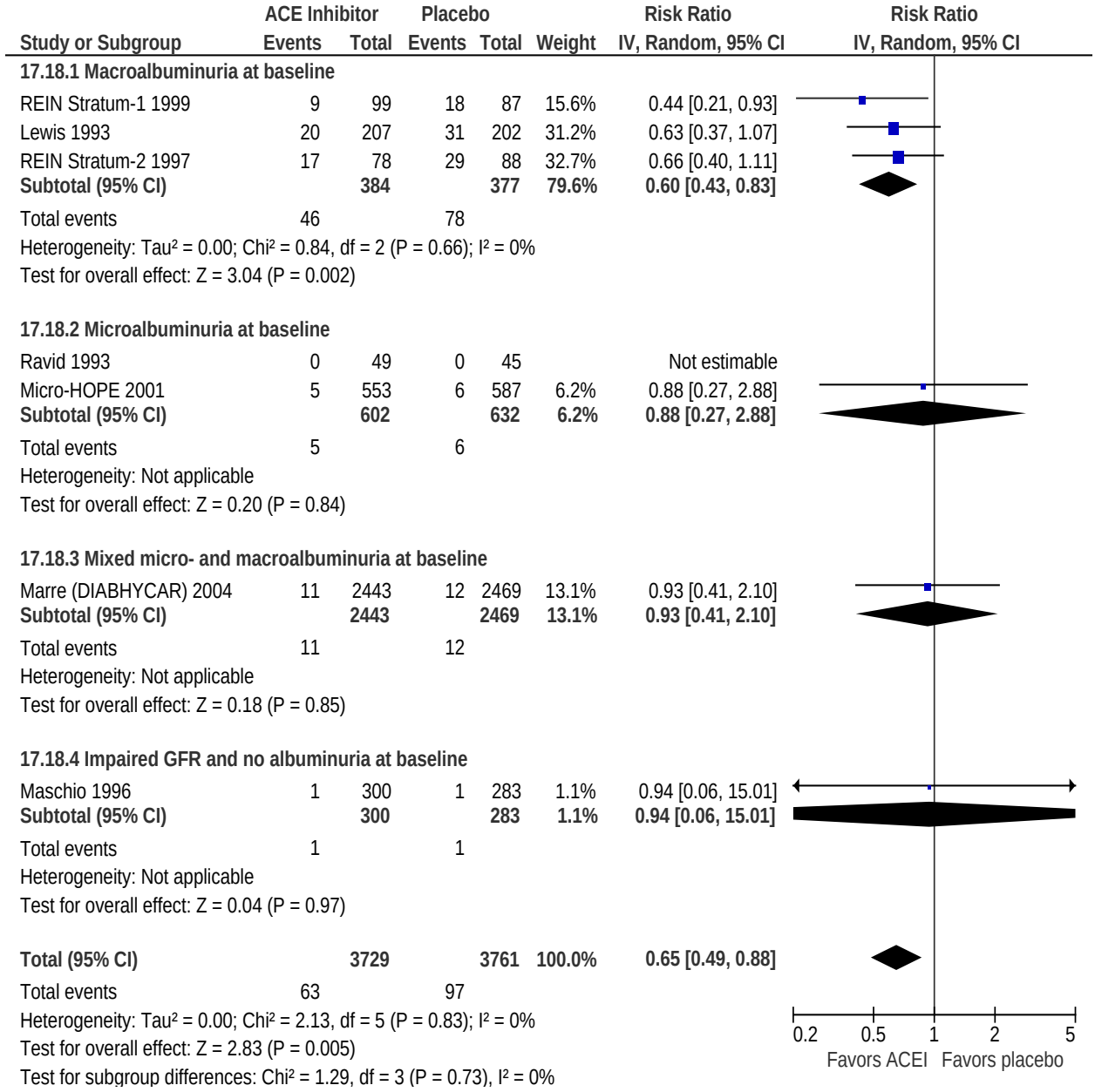


Figure 6. ACEI versus placebo: End-stage renal disease by albuminuria subgroups



ACE Inhibitor Monotherapy Versus ARB Monotherapy Trials (n=6)

Overview

In patients with CKD, we found low strength of evidence suggesting that there is no difference between ACEI and ARB treatment for the outcome of all-cause mortality. We found insufficient evidence regarding whether there is a difference between these treatments for ESRD.

Description of Studies

Six trials met all eligibility criteria and randomized participants (n=4,799, range 90 to 4,046) to ACEI monotherapy versus ARB monotherapy.[67,75-79] Detailed baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 4,046 participants were randomized to ramipril versus ARB (n=1 trial), 353 were randomized to enalapril versus ARB (n=2 trials), 309 were randomized to lisinopril versus ARB (n=2 trials), 91 were randomized to captopril versus ARB (n=1 trial), 4,515 were randomized to telmisartan versus ACEI (n=3 trials), 181 were randomized to valsartan versus ACEI (n=2 trials), and 103 were randomized to losartan versus ACEI (n=1 trial). While five of the six trials maintained the ACEI versus ARB comparison throughout the entire treatment period, in a single partial crossover trial, after 24 weeks patients initially assigned to ACEI were randomized to ACEI plus ARB versus continued ACEI monotherapy, and patients initially assigned to ARB monotherapy were randomized to ARB plus ACEI versus continued ARB monotherapy.[77] By far the largest study, comparing ramipril versus telmisartan, was a post hoc analysis performed within the subset of ONTARGET trial participants with CKD (n=4,046 out of 25,620).[75] The mean age of subjects was 59 years (range 56 to 61; n=5 trials) and men constituted 62 percent (range 37 to 81; n=5 trials) of all patients evaluated. The ethnicity of patients in the three trials reporting was nearly all white race (96 percent).[67,78,79] Two trials were conducted exclusively in Canada, two exclusively in Europe, one in Turkey, and one trial included sites in the United States, Canada, and Europe, as well as Asia, Africa, and Australia. Mean or median study duration was 1 year in three trials, 2.5 years in one trial, and about 5 years in two trials.

Renal Function

The single post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse,[75] and a second trial required participants to have microalbuminuria and a GFR $\geq$60 ml/min/1.73m^2, by definition CKD stages 1–2.[67] Otherwise, no trial based study eligibility on CKD stage and no trial reported baseline distribution of participants by CKD stage. Among the six trials, five required participants to be albuminuric, including four restricted to patients with microalbuminuria,[67,76,77,79] and one that allowed subjects to have either microalbuminuria or macroalbuminuria.[78] Among the five trials requiring participants to have albuminuria, two required that they also have normal creatinine or GFR,[67,78] and three allowed some participants with abnormal levels for these renal function measures but mandated a maximally abnormal limit.[76,77,79] One trial determined eligibility based only on impaired GFR.[75] Within trials, measures of baseline renal function were inconsistently reported. The ONTARGET post hoc analysis reported no data on baseline renal function in its CKD population.[75] In other trials, the most commonly reported measure was urinary albumin excretion rate (UAER), with mean UAER 62 μg/min in two trials[67,79] and 260 mg/24 hours in one trial,[77] and median UAER 46 μg/min (ACEI treatment arm) to 60 μg/min (ARB treatment arm) in one trial.[78] The mean GFR was 92 ml/min/1.73 m^2 (range 91 to 96, n=3 trials).[67,78,79] In two trials, mean baseline serum creatinine was 1.0 mg/dL in both trials.[77,78] Mean creatinine clearance was 101 ml/min/1.73 m^2 (range 97 to 112, n=2 trials).[76,77]

Baseline Comorbidities

The study within the subset of ONTARGET participants with impaired GFR did not report any data on their baseline characteristics,[75] though the main study required subjects to have established atherosclerotic vascular disease or diabetes associated with end-organ damage. In the main study, prevalence of comorbidities included diabetes 37.3 percent, hypertension 68.3 percent, and MI 48.7 percent.[80] Within the five other trials, prevalence of diabetes was 97 percent, including four trials comprised entirely of subjects with type 2 diabetes[67,77-79] and another that excluded type 1 diabetics and had a prevalence of type 2 diabetes of 74 percent.[76] Nearly all study participants were hypertensive at baseline (94 percent; range 33 to 100), including four trials that enrolled only patients with hypertension.[76-79] Five trials excluded patients with severe hypertension,[75-79] and mean baseline systolic and diastolic blood pressure measurements were 151 and 87 mm Hg, respectively. Nearly half the enrollees from one trial had cardiovascular disease,[78] a history of non-MI cardiac disorder was reported in 19 percent of subjects in another trial,[76] and two trials excluded participants with CHF.[76,79] Otherwise, studies reported no data on baseline cardiovascular disease.

Study Quality (Appendix Table C140)

Among the six trials, two were rated good quality and four were rated fair quality. Allocation concealment was adequate in three trials[75,76,78] and unclear in the remaining trials. All trials were double blinded except one open-label study.[77] Analysis by the intention-to-treat principle was reported in two trials.[75,78] All trials adequately described reasons for study withdrawals. No data on study withdrawals were reported in one trial.[75] Otherwise, withdrawals were 33 percent in one trial,[78] and ranged between 11 and 14 percent in the other trials.

Results

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1)

All-Cause Mortality

There were few deaths in trials reporting this outcome. Between CKD patients assigned to ACEI versus those assigned to ARB, there was no significant difference in risk of all-cause mortality (2.7 versus 2.2 percent; RR 1.04, 95% CI, 0.37 to 2.95; n=4 trials, 534 patients). Due to wide confidence intervals around this estimate, results are unable to exclude a meaningful advantage for either ACEI or ARB for this outcome.

Cardiovascular Mortality

There were few deaths in trials reporting this outcome. Between CKD patients assigned to ACEI versus those assigned to ARB, there was no significant difference in risk of cardiovascular mortality (1.2 versus 1.0 percent; RR 0.88, 95% CI, 0.19 to 4.13; n=4 trials, 534 patients). Due to wide confidence intervals around this estimate, results are unable to exclude a meaningful advantage for either ACEI or ARB for this outcome.

Vascular Outcomes (Table 7, Appendix Tables C3 and C4, and Appendix Figure C1)

Only two trials reported data for cardiovascular outcomes, one of which reported no events.[79] In the other small trial, there were relatively few events.[78]

Myocardial Infarction

There was a nonsignificant 38 percent lower risk of MI in the group of CKD patients receiving ACEI compared with the group receiving ARB (3 versus 5.2 percent for MI; RR 0.62, 95% CI, 0.23 to 1.68; n=353 patients).

Stroke

No studies of ACEI versus ARB in CKD patients reported results for stroke.

Other Vascular Outcomes

For patients with CKD, there was a 28 percent lower risk of CHF with ACEI compared with ARB but the result was not significant (3.9 versus 5.2 percent for CHF; RR 0.72, 95% CI, 0.28 to 1.87; n=353 patients). No studies of ACEI versus ARB in CKD patients reported results for composite cardiovascular events.

Renal Outcomes (Appendix Table C6)

End-Stage Renal Disease

None of the trials reported data for ESRD.

Other Renal Outcomes

None of the trials reported data for doubling of serum creatinine as an individual endpoint. With regard to progression from microalbuminuria to macroalbuminuria, though this outcome was reported in the ONTARGET trial, results for the number of participants with baseline microalbuminuria were inconsistent throughout the paper, could not be verified, and could not be incorporated in a pooled analysis. In the only other trial that reported this outcome, it occurred in only two participants.[67] The ONTARGET trial reported results for a composite renal outcome, defined as first occurrence of either dialysis, renal transplantation, doubling of baseline serum creatinine, or death.[75] Based on graphical display of the data (risk ratios and number of events in each treatment arm were not reported), there appeared to be no significant difference between ACEI and ARB for reaching this endpoint in either the ONTARGET subgroup with GFR <60 ml/min/1.73m^2 or the subgroup with baseline microalbuminuria.[75] Further, that the relative reduction in risk of the composite renal outcome between treatment groups in ONTARGET was not significantly different in the CKD subgroup than in ONTARGET participants without CKD (p for interaction 0.84).

Study Withdrawals and Adverse Events (Appendix Table C8)

Overall study withdrawal rates were comparable in the ACEI and ARB groups, 20.2 percent versus 18.1 percent (RR 1.07, 95% CI, 0.80 to 1.42; 5 trials; n=753). Though patients assigned ACEI treatment appeared possibly more likely to withdraw from a study due to an adverse event compared with ARB treatment, 14.4 percent versus 9.7 percent (4 trials, n=534), respectively, this difference was not statistically significant. Renal adverse events were rarely reported. Laboratory abnormalities led to four study discontinuations in the DETAIL trial, two cases of raised serum creatinine levels (both < 2.3mg/dL) in both the ACEI and ARB arms.[78] One subject receiving an ARB in the Muirhead study was withdrawn from treatment due to a decreased GFR and creatinine clearance.[67] Cough was the most commonly reported specific adverse event, and was significantly more likely in participants assigned to ACEI treatment compared with those

allocated to ARB treatment (4.7 percent versus 1.8 percent; RR 4.10, 95% CI, 1.47 to 11.48; 3 trials; n=284).

Summary

In trials comparing ACEI and ARB treatments individuals with CKD, there were very few vascular events reported, based on which there was no significant difference between treatments for the outcomes of all-cause mortality, cardiovascular mortality, MI, or CHF. No data were reported for stroke, ESRD, or any composite vascular outcome. Results from the CKD subset of the ONTARGET study population, whether defined by GFR <60 ml/min/1.73m^2 or by albuminuria, appeared to show no difference in the risk of the composite renal outcome of doubling creatinine, dialysis, renal transplant, or death. Results were limited by small sample sizes in all but one trial, and by the small number of events among trials reporting them. Because no trial provided followup beyond 5 years, longer term effects of ACEI monotherapy versus ARB monotherapy in CKD patients could not be determined from these trials. Overall study withdrawals were not significantly different between ACEI and ARB treatment groups, though cough was significantly more likely in participants assigned to ACEI.

ACE Inhibitor Monotherapy Versus CCB Monotherapy Trials (n=6)

Overview

In comparing ACEI versus CCB for treatment of patients with CKD, we found low strength of evidence, suggesting that there was no difference in risk of all-cause mortality or ESRD. We found no significant difference between treatment groups in risk of cardiovascular mortality, stroke, or halving of GFR.

Description of Studies

Six trials met all eligibility criteria and randomized participants (n=4,357, range 88 to 3,049) to ACEI monotherapy versus CCB monotherapy.[55,81-88] Baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 3,137 participants were randomized to lisinopril versus CCB (n=2 trials), 653 were randomized to ramipril versus CCB (n=1 trial), 446 were randomized to fosinopril versus CCB (n=2 trials), 121 were randomized to captopril versus CCB (n=1 trial), 3,907 were randomized to amlodipine versus ACEI (n=3 trials), and 450 were randomized to nifedipine versus ACEI (n=3 trials). By far the largest eligible study was a post hoc analysis performed in the subset of 3,049 individuals with GFR <60 ml/min/ 1.73m^2 from the larger Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (N= 42,418).[81-83] In the AASK trial, designed as a 3x2 factorial study, besides randomizing 653 participants to ACEI versus CCB, an additional 441 were randomized to beta blocker, and all participants also were randomized to one of two blood pressure target groups.[89,90] The CCB treatment arm was stopped early by recommendation of the data and safety monitoring board, with patients switched to open label medication. The mean age of study participants was 66 years (range 37 to 71; n=6 trials) and men constituted 51 percent (range 48 to 69) of all subjects studied. In the two trials that reported race/ethnicity,[81-83,85] 48 percent of participants were white and 38 percent were African American, including one trial comprised entirely of African American participants.[85] Two trials were conducted primarily in the United States,[81-83,85] three

trials were conducted in Italy, and one was performed in Spain. Mean or median study duration ranged from 3 to approximately 5 years.

Renal Function

The single post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse,[81] and a second trial required participants to have microalbuminuria and a GFR ≥80 ml/min/1.73m^2, by definition CKD stages 1-2.[55] Otherwise, no trial based study eligibility on CKD stage and no trial reported baseline distribution of participants by CKD stage. Among the six trials, two required that participants have microalbuminuria to be included,[55,84] while four determined eligibility based only on impaired creatinine or GFR.[81-83,85-88] Within included participants, there was no single measure of renal function or damage that was reported in every trial. The most commonly reported measure of baseline renal function was serum creatinine, with a mean of 2 mg/dL (range 0.96 to 2.8, n=5 trials)[55,84-88] The mean baseline GFR, reported in three trials, was 50 ml/min/1.73m2 (range 46 to 120),[55,81-83,85] and the mean baseline creatinine clearance concentration was 66 ml/min/1.73m^2 (range 36 to 109, n=3 trials).[55,84,86] Mean proteinuria was 0.94 gm/24 hours (range 1.7 to 1.8, n=3 trials),[85-88] and mean urinary albumin excretion rate was 89 μg/min (range 61 to 97, n=2 trials).[55,84]

Baseline Comorbidities

Thirty percent of study participants had diabetes, which included two trials that restricted enrollment to participants with diabetes[55,84] and three trials that excluded patients with diabetes.[85-88] In two trials reporting data, mean baseline hemoglobin A_{1c} was 7.2.[55,84] Ninety-nine percent of study participants had hypertension, which included five trials that restricted enrollment to participants with hypertension and one small trial that excluded patients with hypertension.[55] Mean baseline systolic and diastolic blood pressure measurements were 149 and 87 mm Hg, respectively. One trial excluded any participants with a history of coronary artery disease,[84] three excluded participants with either recent[55,86] or severe[87,88] cardiovascular events but provided no data on past history of coronary artery disease, while the remaining two trials reported that 29 percent[81-83] and 52 percent[85] of randomized participants, respectively, had a history of coronary artery disease.

Study Quality (Appendix Table C140)

Among the six trials, two were rated good quality and four were rated fair quality. Allocation concealment was adequate in three of six trials and three trials were double blinded. Analysis by the intention-to-treat principle was reported in four trials[81-83,85-88] All trials, except the single post hoc analysis, adequately described reasons for study withdrawal. Withdrawals across studies ranged from 0 to 37 percent.

Results

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1)

All-Cause Mortality

Risk of all-cause mortality, reported in five studies, was not significantly different in individuals with CKD randomized to ACEI treatment compared with those allocated to CCB

therapy (5.4 versus 6.2 percent; RR 0.75, 95% CI, 0.48 to 1.16; n=1,307). The estimate of effect was driven primarily by data from the AASK trial, which accounted for 75 percent of the weight and deaths.[85,91] All-cause mortality data for the largest study, ALLHAT, was not available.

Cardiovascular Mortality

Cardiovascular mortality was reported in three trials totaling 1,014 patients,[85-88,91] including one small 3-year trial not designed to evaluate the effect of therapy on clinical outcomes. As with all-cause mortality, risk of cardiovascular mortality was not significantly different in individuals with CKD randomized to ACEI treatment compared with those allocated to CCB therapy (RR 0.75, 95% CI, 0.36 to 1.57), and the estimate of effect again was driven primarily by data from the AASK trial.

Vascular Outcomes (Table 7, Appendix Tables C3–C5, and Appendix Figure C1)

Myocardial Infarction

Myocardial infarction was reported in only one small trial (n=64 participants).[55] In this trial, there were no myocardial infarctions in either treatment group; therefore, the relative risk for this outcome between CKD patients randomized to ACEI versus CCB treatment could not be determined.

Stroke

Risk of stroke, reported in three trials,[82,83,86,91] was not significantly different between CKD patients assigned an ACEI versus CCB treatment (RR 1.00, 95% CI, 0.78 to 1.28; n=3,943 participants). This estimate was driven mainly by the ALLHAT study, which comprised 88 percent of the weight. There was a 27 percent increased relative risk for stroke in the ACEI group in the AASK trial but this was not statistically significant.[91]

Other Vascular Outcomes

Based on pooled data from two studies, there was no apparent difference in risk for CHF between CKD patients allocated to ACEI versus CCB treatment (RR 1.09, 95% CI, 0.91 to 1.32).[82,91] Two trials reported data on one or more composite cardiovascular outcomes (Appendix Table C5), which, because of their different components, were not pooled.[82,91] There was no statistically significant difference between ACEI and CCB treatment in CKD patients for any composite cardiovascular outcome in any trial. The ALLHAT trial performed additional analyses of clinical outcomes among CKD patients with diabetes.[82] In this subgroup, there was no statistically significant difference between treatment groups in risk of stroke, CHF, or either of two composite vascular endpoints.

Renal Outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1)

End-Stage Renal Disease

Overall risk of ESRD, reported in three trials, was not significantly different between CKD patients randomized to ACEI versus CCB treatment (RR 0.89, 95% CI, 0.66 to 1.21; n=3,823 patients).[81,85,87,88,90] However, there was evidence of low heterogeneity (I^2=29 percent), with results suggesting benefit in those assigned to ACEI treatment versus CCB treatment in the

AASK (RR 0.86, 95% CI, 0.59 to 1.25) and Zucchelli (RR 0.51, 95% CI, 0.22 to 1.17) studies, respectively, but not in the ALLHAT study (RR 1.06, 95% CI, 0.77 to 1.48), with none of the results from the individual trials achieving statistical significance. Of note, the definitions of ESRD varied slightly between these studies, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis in the ALLHAT study; as need for renal replacement therapy in the AASK study; and as need for dialysis (creatinine clearance below 4 ml/minute) in the Zucchelli study.

Other Renal Outcomes

Overall risk of 50 percent or greater decline in GFR, reported in two trials, was not significantly different between CKD patients randomized to ACEI treatment versus CCB treatment (RR 1.02, 95% CI, 0.55 to 1.91, n=3,702).[81,85] However, there was evidence of substantial heterogeneity (I^2=71 percent), and though differences were not statistically significant in either trial, results from the AASK trial appeared to favor ACEI treatment (10.1 percent versus 13.4 percent), while results from the ALLHAT trial appeared worse in the ACEI group (2.3 percent versus 1.6 percent).

Three trials reported data on composite renal outcomes, which, because of their different components, detailed in Appendix Table C7, were not pooled.[81,86,91] In the AASK trial, in which the composite renal outcome included ESRD (i.e., need for renal replacement therapy), death, or reduction from baseline GFR by 50 percent or by 25 mL/min/1.73m^2, CKD patients randomized to ACEI treatment had a nonsignificantly lower risk of this composite outcome than those assigned to CCB treatment (20 versus 26 percent, RR 0.77, 95% CI, 0.58 to 1.04).[85] Approximately half of these incident renal events were attributed to halving of GFR (73 of 143 composite events). In the ALLHAT trial, in which the composite renal outcome included ESRD (death due to kidney disease, dialysis, or renal transplantation), reduction in GFR by 50 percent or by 25 mL/min/1.73 m^2, but did not include all-cause death, the risk of a composite renal event was similar in both treatment groups (7 versus 6 percent, RR 1.16, 95% CI, 0.89 to 1.53).[81] Approximately one-third of these incident renal events appeared to be attributed to halving of GFR. In the ESPIRAL trial, in which the composite renal outcome included need for dialysis or doubling of serum creatinine, the risk of a composite renal event was significantly lower in CKD patients allocated to ACEI versus CCB treatment (RR 0.59, 95% CI, 0.39 to 0.89).[86] In this trial, it was not reported what proportion of incident cases were due to doubling of serum creatinine.

The ALLHAT trial performed additional analyses of renal outcomes among CKD patients with diabetes and reported that there were no statistically significant differences in risk of ESRD or the above described composite renal outcome between treatment groups[82]

Study Withdrawals and Adverse Events (Appendix Table C8)

CKD patients randomized to treatment with an ACEI were no more likely to withdraw from treatment (13.3 versus 18.4 percent, p=0.81) or withdraw from treatment due to an adverse event (3.2 versus 4.7 percent, p=0.77) compared with patients assigned to treatment with a CCB. No patient in the AASK trial was reported to have withdrawn from treatment or was lost to followup.[89,90] No study withdrawal or adverse event data were reported for the ALLHAT CKD subgroup.[81-83]

In the AASK trial, adverse events were reported as percentage per patient year. Compared with study participants randomized to CCB, those assigned to ACEI had a significantly higher rate of cough (55 versus 46 percent), angioedema (6 versus 2 percent), and syncope (7 versus 2 percent).[89,90] In contrast, edema was significantly more frequent in the CCB group compared

with the ACEI group, 60 versus 46 percent. Hyperkalemia was reported for three ACEI group patients and none in the CCB group. In the ESPIRAL trial, withdrawals due to adverse events occurred in small numbers of CKD patients in both groups, for cough (n=3 in the ACEI group versus n=0 in the CCB group), hyperkalemia (n=6 versus n=0), edema (n=1 versus n=10), and impaired renal function (n=4 versus n=1).[86] In the study by Zucchelli, cough led to study withdrawal in two ACEI patients and severe edema led to study withdrawal in three CCB patients.[87] In the trial by Fogari, two subjects each in the ACEI and CCB groups were withdrawn from treatment due to worsening kidney function.[84]

Summary

In patients with CKD, there was no apparent difference between treatment with ACEI monotherapy and CCB monotherapy for the outcomes of all-cause mortality, cardiovascular mortality, stroke, CHF, any composite vascular endpoint, or ESRD. Relative risk of MI could not be determined. While results for the composite renal outcome indicated significant benefit for ACEI treatment compared with CCB in one trial,[86] there was no between-treatment group difference in the composite renal endpoints reported in two other trials.[81-83,85] Results were limited in that several studies were not designed for and reported no clinical outcomes data, and the modest number of clinical events overall may have limited power to detect differences between treatment groups. Further, no trial provided followup beyond 5 years; therefore, longer term effects of ACE-inhibitor monotherapy versus CCB monotherapy cannot be determined from these data. Withdrawals appeared similar between treatment groups, with cough appearing more common in patients assigned ACEI and edema more common in patients assigned CCB.

ACE Inhibitor Monotherapy Versus Beta Blocker Trials (n=3)

Overview

In comparing ACEI versus beta blocker treatment in patients with CKD, there was low strength of evidence that there is no difference in risk of all-cause mortality and ESRD. We found no significant difference between treatments for risk of cardiovascular mortality, stroke, or heart failure.

Description of Studies

Three trials met all eligibility criteria and randomized participants (n=1,080, range 100 to 877) to ACEI versus beta blocker monotherapy.[90,92,93] Baseline characteristics are presented in Appendix Tables C1 and C2.

Among eligible trials, 877 participants were randomized to ramipril versus metoprolol (n=1 trial),[90] 103 were randomized to enalapril versus atenolol (n=1 trial),[92] and 100 were randomized to enalapril versus either atenolol or acebutelol (n=1 trial).[93] The mean age of study participants was 54 years, and men constituted 61 percent of patients studied. In the single trial that reported race/ethnicity, 100 percent of participants self-identified as African American.[90] One trial was conducted in the United States,[90] while two trials were performed in Europe.[92,93] Mean or median study durations were three years or greater in all trials.

Renal Function

No trial based study eligibility on CKD stage and no trial reported baseline distribution of participants by CKD stage. All three trials based eligibility on impairment in GFR (20 to 65

ml/min/1.73m^2),[90] creatinine clearance (30 to 90 ml/min),[92] or creatinine (2.3 to 5.2 mg/dL).[93] None based inclusion on the presence of albuminuria, though one excluded patients with urinary protein-creatinine ratio >2.5,[90] and another excluded participants with nephrotic syndrome.[93] Mean serum creatinine, reported in all three trials, was 2.0 mg/dL (range 1.8 to 3.0). Mean baseline GFR was 47 ml/min/1.73m^2 (range 46 to 53, n=2 trials).[90,92] Urinary protein excretion ranged from 0.5 g/24 hour[90] to 2.2 g/24 hour[93] in two trials. In the third trial, median urinary protein excretion was 3.3 g/24 hour.[92]

Baseline Comorbidities

All three trials excluded individuals with diabetes. Approximately 51 percent of participants had a history of heart disease in one trial,[90,91] patients with coronary artery disease were excluded from one trial,[93] and no data were reported regarding cardiovascular disease in the third trial.[92] While two trials were limited to patients with hypertension,[90,93] more than half of the participants in the third trial were reported to have diastolic blood pressure less than 90 mm Hg off antihypertensive medications.[92] Overall, 96 percent of participants in the three trials had hypertension. Mean baseline systolic and diastolic blood pressure measurements were 152 and 95 mm Hg, respectively.

Study Quality (Appendix Table C140)

Among the three trials, one was rated good quality and two were rated fair quality. Allocation concealment was adequate in two trials,[90,93] two trials were double blinded,[90,92] and analysis was performed by intention-to-treat in two trials.[90,93] All trials adequately described reasons for study withdrawal. Percentages of study withdrawals ranged from 0 to 23 percent. The AASK trial reported that no participants withdrew from treatment or were lost to followup.[90]

Results

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1)

All-Cause Mortality

For patients with CKD, risk of all-cause mortality between those randomized to ACEI and those assigned beta blocker monotherapy was not significantly different (6.9 versus 9.6 percent; RR 0.71, 95% CI, 0.48 to 1.07; n=3 trials, 1,080 patients). The estimate of effect was driven primarily by data from the AASK trial, which accounted for 94 percent of the weight and 93 percent of deaths.[91]

Cardiovascular Mortality

In two trials reporting, there were relatively few cardiovascular deaths, and, though confidence intervals were wide, no difference in risk of cardiovascular mortality between CKD patients assigned to ACEI and those assigned to beta blocker (2.9 versus 2.6 percent; RR 1.08, 95% CI, 0.51 to 2.28).[91,92] As with all-cause mortality, the estimate of effect was again driven primarily by data from the AASK trial.

Vascular Outcomes (Table 7, Appendix Tables C3-C5, and Appendix Figure C1)

Myocardial Infarction

Two trials reported no data on myocardial infarctions,[90,93] and the third reported that two participants in the ACEI group (4.7 percent) and one in the beta blocker group (2.2 percent) experienced a fatal myocardial infarction.[92]

Stroke

In data derived entirely from the AASK trial, there was no difference for CKD patients allocated to ACEI versus beta blocker treatment groups for the outcomes of stroke (RR 1.01, 95% CI, 0.58 to 1.78).[91]

Other Vascular Outcomes

There were no differences between treatment groups for heart failure (RR 0.92, 95% CI, 0.51 to 1.66), or for the composite outcome of coronary artery disease hospitalization or coronary artery disease-related death (4.4 versus 4.1 percent; RR 1.07, 95% CI 0.57 to 2.01) or the composite outcome of first cardiovascular hospitalization or cardiovascular death (14.0 versus 14.7 percent; RR 0.95, 95% CI, 0.69 to 1.31).[91]

Renal Outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1)

End-Stage Renal Disease

In pooled results, among these CKD patients there was no significant reduction in risk of end-stage renal disease with ACEI compared with beta blocker treatment (RR 0.81,95% CI, 0.50 to 1.33; n=3 trials, 1,080 patients). However, the estimate of effect varied substantially between trials, ranging from RR 0.54 (95% CI, 0.28 to 1.07)[93] to RR 2.45 (95% CI, 0.50 to 12.07)[92] in two small trials, with an intermediate result in the largest trial (RR 0.86, 95% CI, 0.63 to 1.17).[90]

Other Renal Outcomes

The AASK trial reported that CKD patients assigned ACEI versus beta blocker treatment had a statistically significantly reduced risk of the composite renal outcome of >50 percent reduction in GFR, need for dialysis or transplant, or death (28.9 versus 35.1 percent; RR 0.82,95% CI, 0.68 to 1.00; p=0.048).[90] Results for halving of GFR as an isolated endpoint, doubling of baseline creatinine, or conversion from microalbuminuria to macroalbuminuria were not reported.

Study Withdrawals and Adverse Events (Appendix Table C8)

In results pooled from all three trials, patients assigned to an ACEI were not more likely to withdraw from treatment (3.7 versus 3.1 percent, p=0.76) or withdraw from treatment due to an adverse event (2.2 versus 1.5 percent, p=0.39) compared with patients receiving a beta blocker. No patient in the AASK was reported to have withdrawn from treatment.[90] Hyperkalemia, though uncommon, appeared slightly more frequent in subjects randomized to the ACEI group in all three trials at 2.9 versus 0 percent of patients in two trials,[92,93] and as 0.7 versus 0.2 percent per patient year in the AASK trial.[90] The AASK trial reported significant differences between ACEI and beta blocker subjects in angioedema (6.4 versus 2.7 percent per patient year) and cough (54.9 versus 41.5 percent per patient year).[90]

Summary

In patients with CKD, there was no significant difference between ACEI and beta blocker treatment for risk of all-cause mortality, cardiovascular mortality, stroke, heart failure, or either of two composite vascular endpoints. Overall, there was no difference between ACEI and beta blocker treatment for risk of ESRD, but results were heterogeneous between trials. However, ACEI treatment was associated with a significantly lower risk of the composite renal outcome of >50 percent reduction in GFR, need for dialysis or transplant, or death. With respect to adverse effects, ACEI treatment was associated with a significantly higher rate of cough and angioedema. Results were limited in that only one study, the AASK trial, was designed to evaluate the effect of ACEI and beta blocker treatment on clinical cardiovascular outcomes. The two smaller trials reported few or no events for most vascular endpoints and had very limited power to detect differences in these outcomes between treatment groups. No trial provided mean or median followup beyond 5 years; therefore, longer term effects of ACEI monotherapy versus beta blocker monotherapy cannot be determined from these study results.

ACE Inhibitor Monotherapy Versus Diuretic Trials (n=2)

Overview

In patients with CKD there was insufficient strength of evidence that there was no difference in risk of all-cause mortality risk between those assigned to ACEI and those allocated to diuretic treatment. There was low strength of evidence that there was no difference between ACEI and diuretic in risk of ESRD. There was no significant difference between treatment groups in risk of stroke or multiple composite cardiovascular outcomes, but there was a significantly increased risk of CHF in the group assigned to ACEI. Our confidence in these estimates is limited because they are based almost entirely on results reported from a post hoc analysis in a single large trial.

Description of Studies

Two trials met all eligibility criteria and randomized participants (n=4,716, range 570 to 4,146) to ACEI monotherapy versus diuretic monotherapy.[81-83,94] Detailed baseline characteristics are presented in Appendix Tables C1 and C2). One of the included reports was a post hoc analysis performed within a subset of participants with CKD from the ALLHAT trial, a population that was not originally limited to subjects with CKD.

In one study, from the ALLHAT trial, 4,146 participants were randomized to lisinopril versus chlorthalidone,[81-83] while in the second study, the NESTOR trial, 570 participants were randomized to enalapril versus indapamide.[94] The mean age in these two trials was 70 years (range 60 to 71), and men comprised slightly over half of all patients studied (51 percent; range 49 to 65). The most common race/ethnicity of patients in the two trials was white (61 percent), followed by black (23 percent).[81-83,94] Hispanics comprised 11 percent of participants in the ALLHAT study.[81-83] The NESTOR trial was conducted in Europe,[94] while the ALLHAT study was performed primarily in the United States.[81-83] Study durations were 1 year[94] and 4.9 years, respectively.[81-83]

Renal Function

The single post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse, and reported a mean baseline GFR of 50 ml/min/1.73m^2.[81] The second study, the NESTOR trial, did not base eligibility on CKD stage

and neither trial reported baseline distribution of participants by CKD stage. In the NESTOR trial, participants were required to have microalbuminuria for inclusion, and the mean baseline urinary albumin excretion rate was 58 μg/min, the urinary albumin/creatinine ratio was 6.2 mg/g, and the creatinine clearance was 92 ml/min/1.73m^2.[94] The two studies excluded subjects with baseline creatinine levels exceeding 1.7 mg/dL[94] and 2 mg/dL,[81-83] respectively.

Baseline Comorbidities

Both studies were limited to patients with hypertension, with mean blood pressures at baseline being 147/83 mm Hg in the ALLHAT study[81-83] and 161/94 mm Hg in the NESTOR trial.[94] In the ALLHAT study, 61 percent of participants reported cardiovascular disease, 31 percent reported coronary artery disease, and 31 percent were diabetic. In the NESTOR trial, however, prevalence of type 2 diabetes was 100 percent (mean hemoglobin A_{1c} 7.6 percent), but no information was reported regarding history of any cardiovascular disease.

Study Quality (Appendix Table C140)

Of the two eligible trials, one was rated good quality and one was rated fair quality. Allocation concealment was adequate in the ALLHAT study and unclear in the NESTOR trial. Both trials were double blinded. Analysis by the intention-to-treat principle was reported in ALLHAT. However, the NESTOR trial excluded one randomized participant from analyses who was reported to not have been exposed to study drug.[94] The NESTOR trial reported an 11 percent withdrawal rate and adequately described reasons for study withdrawal. By contrast, the ALLHAT study reported no data regarding withdrawals.

Results

Mortality (Table 7, Appendix Table C3, and Appendix Figure C1)

Data for all-cause mortality was reported only in the NESTOR trial, in which there were only three total deaths, all of which were cardiovascular. There was one death within subjects assigned to ACEI treatment (0.3 percent) and two deaths in participants within the diuretic group (0.7 percent).

Vascular Outcomes (Table 7, Appendix Tables C3-C5, and Appendix Figure C1)

Myocardial Infarction

The NESTOR trial reported that within the diuretic group one patient had a fatal MI and two others discontinued treatment after an MI.[94] It was not clear whether this was a complete accounting of all MIs.

Stroke

In the ALLHAT study, among the CKD subgroup evaluated in this post hoc analysis, there was no significant difference between ACEI and diuretic treatment assignment in risk of stroke (6.5 versus 6.0 percent; RR 1.07, 95% CI, 0.84 to 1.37).[81-83]

Other Vascular Outcomes

In the ALLHAT study, there was a significantly increased risk of heart failure (included fatal, hospitalized, or treated nonhospitalized) in the ACEI treatment group (12.5 versus 9.9 percent;

RR 1.26, 95% CI, 1.05 to 1.50).[81-83] In data available only from the ALLHAT study, there was no significant between-treatment difference for the composite vascular outcome of nonfatal MI or coronary heart disease death (RR 0.99, 95% CI, 0.83 to 1.17), or for the composite outcome that included death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, or peripheral arterial disease requiring hospitalization or outpatient revascularization (RR1.07, 95% CI, 0.98 to 1.17).[81-83] The ALLHAT trial reported additional results within CKD patients with diabetes.[82] In this subgroup, there was no statistically significant difference between treatment groups in risk of stroke or the two composite cardiovascular endpoints described in detail above. However, risk of heart failure was significantly greater in CKD patients with diabetes randomized to ACEI treatment compared with diuretic treatment (RR 1.37, 95% CI, 1.05 to 1.79; n=1,382).

Renal Outcomes (Table 7, Appendix Tables C6 and C7, and Appendix Figure C1)

End-Stage Renal Disease

The ALLHAT study reported that ACEI and diuretic treatment were comparable in CKD patients regarding the risk of ESRD, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis (RR 0.9, 95% CI, 0.72 to 1.28).[81]

Other Renal Outcomes

The ALLHAT trial reported no difference between treatment groups in risk of the incident composite renal outcome defined by ESRD or >50 percent decline in GFR (7 versus 7 percent, RR 1.00, 95% CI, 0.80 to 1.27).[81] The ALLHAT trial also performed additional analyses of renal outcomes among CKD patients with diabetes and reported that there were no statistically significant differences in reduction in risk of ESRD or the above described composite renal outcome between treatment groups.[82] The NESTOR trial reported that CKD subjects with microalbuminuria who were assigned to ACEI were less likely than diuretic subjects to convert to macroalbuminuria (6 versus 9 percent; RR 0.69, 95% CI, 0.38 to 1.22),[94] though this result was not statistically significant.

Study Withdrawals and Adverse Events (Appendix Table C8)

No study withdrawal or adverse event data were reported for the ALLHAT CKD subgroup.[81-83] In the NESTOR trial, CKD patients randomized to ACEI treatment were not more likely to withdraw from treatment, withdraw from treatment due to an adverse event, or withdraw from treatment due to a "medical reason" compared with patients assigned a diuretic.[94]

Summary

Within the two eligible trials of patients with CKD, there was no apparent difference between the ACEI and diuretic monotherapy treatment groups in risk of all-cause or cardiovascular mortality, MI, stroke, ESRD, or other composite clinical vascular or renal outcomes. There was a statistically significantly greater risk of heart failure among CKD patients allocated to ACEI therapy versus diuretic treatment. Results were limited in that one trial was a 1 year bioequivalence study not designed to evaluate the effect of these treatments on clinical events[94] and that the second study was a post hoc subgroup analysis. The large ALLHAT study also did not provide mortality data based on CKD status. Also, since mean followup did not extend

beyond 5 years, longer term effects of ACE-inhibitor monotherapy versus diuretic monotherapy cannot be determined from these data. Withdrawals were not significantly different between treatment groups in the one trial reporting, and no adverse events data were available.

Table 7. Pooled clinical and renal outcomes, ACEI monotherapy versus control treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI Events/N (%)	Control Events/N (%)	Relative Risk (95% CI)	I^2 Test for Heterogeneity
ACEI vs. placebo trials (n=17)						
All-cause mortality	16	Good	667/5786 (11.5)	686/5750 (11.9)	0.94 [0.80-1.12]	33%
Cardiovascular mortality	3	Good	231/3769 (6.1)	222/3764 (5.9)	1.03 [0.86-1.23]	0%
Myocardial infarction, any	3	Fair	62/2535 (2.4)	80/2565 (3.1)	0.79 [0.57-1.09]	0%
Myocardial infarction, fatal	2	Fair	4/378 (1.1)	0/371	4.84 [0.55-2.34]	0%
Myocardial infarction, nonfatal	7	Fair	71/3436 (2.1)	76/3417 (2.2)	0.93 [0.67-1.28]	0%
Stroke	4	Good	232/3868 (6.0)	278/3851 (7.2)	0.80 [0.52-1.23]	68%
Stroke, nonfatal	2	Fair	91/2743 (3.3)	87/2752 (3.2)	0.62 [0.12-3.18]	0%
PREVEND trial composite vascular outcome[a]*	1	Fair	17/431 (3.9)	28/433 (6.5)	0.61 [0.34-1.10]	NA
DIABHYCAR trial composite vascular outcome[b]	1	Good	362/2443 (14.8)	377/2469 (15.3)	0.97 [0.85-1.11]	NA
HOPE trial composite vascular outcome[c]	1	Good	186/952 (19.5)	265/1004 (26.4)	0.74 [0.63-0.87]	NA
ATLANTIS trial composite vascular outcome[d]	1	Fair	16/92 (17.4)	8/46 (17.4)	1.00 [0.46-2.16]	NA
PROGRESS trial composite vascular outcome[e]	1	Good	178/895 (19.9)	222/862 (25.8)	0.77 [0.65-0.92]	NA
REIN, Stratum 1 trial composite vascular outcome[f]	1	Good	2/99 (2.0)	3/87 (3.4)	0.59 [0.10-3.43]	NA
REIN, Stratum 2 trial composite vascular outcome[g]	1	Fair	4/78 (5.1)	3/88 (3.4)	1.50 [0.35-6.51]	NA
End-stage renal disease	7	Good	63/3729 (1.7)	97/3761 (2.6)	0.65 [0.49-0.88]	0%
Doubling of serum creatinine concentration	7	Fair	129/3682 (3.5)	202/3710 (5.5)	0.60 [0.40-0.89]	58%
ACEI versus angiotensin II receptor blocker trials (n=6)						
All-cause mortality	4	Fair	7/257 (2.7)	6/277 (2.2)	1.04 [0.37-2.95]	0%
Cardiovascular mortality	4	Fair	3/257 (1.2)	3/277 (1.0)	0.88 [0.19-4.13]	0%
Myocardial infarction, nonfatal	2	Fair	6/181 (3.3)	9/172 (5.2)	0.62 [0.23-1.68]	NA**
Congestive heart failure	2	Fair	7/181 (3.9)	9/172 (5.2)	0.72 [0.28-1.87]	NA**
ACEI versus calcium channel blocker trials (n=6)						
All-cause mortality	5	Fair	42/774 (5.4)	33/533 (6.2)	0.75 [0.48-1.16]	0%
Cardiovascular mortality	3	Fair	16/625 (2.6)	13/389 (3.3)	0.75 [0.36-1.57]	0%
Congestive heart failure	2	Good	211/1969 (10.7)	182/1733 (10.5)	1.09 [0.91-1.32]	0%
Stroke, any	3	Good	123/2098 (5.9)	111/1845 (6.0)	1.00 [0.78-1.28]	0%
AASK trial composite vascular outcome #1†	1	Good	61/436 (14.0)	23/217 (10.6)	1.32 [0.84-2.07]	NA
AASK trial composite vascular outcome #2†	1	Good	19/436 (4.4)	5/217 (2.3)	1.89 [0.72-5.00]	NA
ALLHAT trial composite vascular outcome #1‡	1	Good	547/1533 (35.7)	537/1516 (35.4)	1.01 [0.92-1.11]	NA
ALLHAT trial composite vascular outcome #2‡	1	Good	184/1533 (12.0)	194/1516 (12.8)	0.94 [0.78-1.13]	NA
End-stage renal disease	3	Good	139/2029 (6.9)	115/1794 (6.4)	0.89 [0.66-1.21]	29%
Halving of GFR	2	Good	80/1969 (4.1)	54/1733 (3.1)	1.02 [0.55-1.91]	71%
AASK trial composite renal outcome¥	1	Good	87/436 (20.0)	56/217 (25.8)	0.77 [0.58-1.04]	NA
ALLHAT trial composite renal outcome§	1	Good	106/1533 (6.9)	90/1516 (5.9)	1.16 [0.89-1.53]	NA

Table 7. Pooled clinical and renal outcomes, ACEI monotherapy versus control treatment trials (continued)

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI Events/N (%)	Control Events/N (%)	Relative Risk (95% CI)	I^2 Test for Heterogeneity
ACEI versus beta blocker trials (n=3)						
All-cause mortality	3	Fair	37/540 (6.9)	52/540 (9.6)	0.71 [0.48-1.07]	0%
Cardiovascular mortality	2	Fair	14/488 (2.9)	13/492 (2.6)	1.08 [0.51-2.28]	0%
AASK trial composite vascular outcome #2†	1	Good	19/436 (4.4)	18/441 (4.1)	1.07 [0.57-2.01]	NA
Stroke	1	Good	23/436 (5.3)	23/441 (5.2)	1.01 [0.58-1.78]	NA
Congestive heart failure	1	Good	20/436 (4.6)	22/441 (5)	0.92 [0.51-1.66]	NA
AASK trial composite vascular outcome #1†	1	Good	61/436 (14)	65/441 (14.7)	0.95 [0.69-1.31]	NA
End-stage renal disease	3	Fair	77/540 (14.3)	92/540 (17.0)	0.81 [0.50-1.33]	40%
AASK trial composite renal outcome¥	1	Good	126/436 (28.9)	155/441 (35.1)	0.82 [0.68-1.00]	NA
ACEI versus diuretics trials (n=2)						
All-cause mortality	1	Fair	1/286 (0.3)	2/284 (0.7)	0.50 [0.05-5.44]	NA
Cardiovascular mortality	1	Fair	1/286 (0.3)	2/284 (0.7)	0.50 [0.05-5.44]	NA
Stroke	1	Good	99/1533 (6.5)	157/2613 (6.0)	1.07 [0.84-1.37]	NA
Congestive heart failure	1	Good	191/1533 (12.5)	259/2613 (9.9)	1.26 [1.05-1.50]	NA
ALLHAT trial composite vascular outcome #1‡	1	Good	547/1533 (35.7)	870/2613 (33.3)	1.07 [0.98-1.17]	NA
ALLHAT trial composite vascular outcome #2‡	1	Good	184/1533 (12.0)	318/2613 (12.2)	0.99 [0.83-1.17]	NA
End-stage renal disease	1	Good	70/1533 (4.6)	124/2613 (4.7)	0.96 [0.72-1.28]	NA
ALLHAT trial composite renal outcome§	1	Good	106/1533 (6.9)	180/2613 (6.9)	1.00 [0.80-1.27]	NA

NA = not applicable; RR = relative risk reduction; ACEI = angiotensin converting enzyme inhibitor

[a]PREVEND = Cardiovascular death and hospitalization for cardiovascular morbidity, defined as hospitalization for documented (1) nonfatal MI or myocardial ischemia, (2) heart failure, (3) PVD, and/or (4) CVA.

[b]DIABHYCAR = Cardiovascular death (including sudden death), nonfatal acute MI, stroke, heart failure requiring admission to hospital, and end stage renal failure (defined as dialysis or kidney transplant)

[c]Micro-HOPE = Cardiovascular death, MI, stroke

[d]ATLANTIS = Not clearly defined, noted as "cardiovascular adverse events." Incidences of death, MI and angina/chest pain provided.

[e]PROGRESS = Major cardiovascular events, defined as the composite of nonfatal stroke, nonfatal MI, and cardiovascular death.

[f]REIN, Stratum 1 = Incidence of "non-fatal cardiovascular events" reported but not defined.

[g]REIN, Stratum 2 = Non-fatal cardiovascular events include MI, aortic aneurysm, and uncontrolled HTN.

**Pooling data was not possible for this outcome because only one trial reported events.

† In AASK study, two composite vascular endpoints were defined, as follows: (1) Cardiovascular mortality or first cardiovascular hospitalization; and (2) "Coronary heart disease event" defined as CAD hospitalization (probable MI) and/or fatal coronary heart disease death

‡ In ALLHAT study, two composite vascular endpoints were defined, as follows: (1) Death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease requiring hospitalization or outpatient revascularization; and (2) "Coronary heart disease event" defined as nonfatal MI or fatal coronary heart disease death

¥End stage renal disease (need for renal replacement therapy), reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs, or death.

§End stage renal disease (death due to kidney disease, dialysis, or renal transplantation) or reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs.

ARB Monotherapy Versus Placebo Trials (n=5)

Overview

In patients with CKD, we found high strength of evidence that ARB treatment reduces risk of ESRD compared with placebo. These results are based entirely on data from trials enrolling CKD patients with overt albuminuria. We found high strength of evidence that ARB treatment does not reduce risk of all-cause mortality compared with placebo. While patients with CKD randomized to ARB versus placebo had a significantly lower risk of progression from microalbuminuria to macroalbuminuria, we found no statistically significant difference between treatment groups for risk of MI, and mixed results regarding risk for CHF hospitalization. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events in some trials, and the heterogeneity of the study populations.

Description of Studies

Five trials met all eligibility criteria and randomized participants with CKD (n=5,769, range 527 to 1,991) to an ARB versus placebo.[95-99] Detailed baseline characteristics are presented in Appendix Tables C9 and C10. One of the included reports was a post hoc analysis[99] performed within a subset of participants with CKD from the TRANSCEND trial, a population that was not originally limited to subjects with CKD.

Among eligible trials, 1,738 participants were randomized to irbesartan versus placebo (n=2 trials), 1,513 participants (n=1 trial) to losartan versus placebo, and 2,518 participants (n=2 trials) to telmisartan versus placebo. The mean age of subjects was 62.7 years (range 58 to 68.7; n=5 trials), and men constituted 60.0 percent (range 51 to 69; n=4 trials) of all patients randomized. Four trials reported race/ethnicity, within which 64 percent of subjects were white. One trial was conducted in the United States,[97] one in Japan,[95] and three were multinational.[96,98,99]

Renal Function

In four trials, patients were required to have albuminuria or proteinuria. In two of these trials, patients must have been microalbuminuric, with a urinary albumin excretion rate between 20-200 µg/min in one study[96] and a urinary albumin-creatinine ratio between 100-300 mg/g in the second study.[95] Both of these trials also were restricted to participants with a normal serum creatinine, defining them as CKD stages 1-2. In the other two trials that required albuminuria or proteinuria for entry, patients must have been overtly albuminuric or proteinuric, with either an albumin-creatinine ratio ≥300 mg/g or urinary protein excretion rate ≥0.5 g/day,[98] or a 24 hour urine protein excretion ≥900 mg.[97] These two trials required participants to be within a range that included both normal and moderately elevated serum creatinine values (e.g., between 1.0 and 3.0 mg/dL), so that it was not possible to determine CKD stage.[97,98] The fifth trial, a post hoc analysis of TRANSCEND study participants who had either impaired eGFR or albuminuria, excluded participants with serum creatinine >3.0 mg/dL. This study categorized participants with eGFR <60 ml/min/1.73m^2 versus ≥60 ml/min/1.73m^2, and with normoalbuminuria versus microalbuminuria versus macroalbuminuria, and all possible combinations so that they further could be categorized as either CKD stages 1-2 or CKD stages 3-4. At baseline, serum creatinine was the measure of renal function most frequently reported, with a mean of 1.5 mg/dL (range 1.2

to 1.9; n=4 trials). Two trials reported urinary albumin excretion rate, with results of 55.5 µg/min (0.08 g/day)[96] and 1.9 g/day,[97] respectively. Median urinary albumin-creatinine ratio reported in one trial was 1,250 mg/g.[98] One trial reported no baseline data on renal function/damage for its participants.[95]

Baseline Comorbidities

Four studies were restricted to subjects with type 2 diabetes, and three further specified exclusion of patients with any nondiabetic kidney disease.[95,96,98] Two trials also were limited to subjects with hypertension,[96,97] while in two trials 81 and 93.5 percent of participants had a diagnosis of hypertension.[98,99] In the fifth trial, the prevalence of hypertension was not reported, though patients with severe hypertension (>180/100 mm Hg) were excluded and mean baseline blood pressure was 137/77 mm Hg.[95] Across all five trials, mean baseline blood pressures were 149/83 mm Hg (range 137/77 to 159/90 mm Hg). In one trial 28 percent of participants reported a history of cardiovascular disease.[97] In a second trial, cardiovascular disease was more common, including 73 percent of participants with coronary artery disease and 22 percent with stroke.[99] However, in the two other trials reporting data,[96,98] cardiovascular disease was uncommon, including myocardial infarction (8.9 percent, range 3 to 11.2, n=2 trials), coronary artery disease (4.5 percent, n=1 trial), stroke (0.9 percent, range 0.1 to 3.1, n=2 trials). Two trials explicitly excluded patients with CHF,[96,99] and another excluded patients with an indication for ACEIs or ARBs, likely indicating an exclusion of patients with CHF.[96] Finally, in one trial no entrance criteria related to cardiovascular disease were listed and no baseline data on cardiovascular disease were reported.[95]

Study Quality (Appendix Table C140)

Of the five eligible trials, three were rated good quality and two were rated fair quality. Allocation concealment was adequate in three trials[97-99] and unclear in two trials.[95,96] All trials were double blinded. All but one trial[95] performed analyses using the intention-to-treat principle. All trials adequately described study withdrawal and reasons for withdrawals, with withdrawals ranging from 0.8 to 13.1 percent of randomized participants.

Results

Mortality (Table 8, Appendix Table C11, and Appendix Figure C2)

All-Cause Mortality

Among these CKD patients studied, overall incidence of death in trials reporting this outcome ranged from less than 1 percent of study participants in one trial,[96] to between 16 and 20 percent in the other three trials.[97-99] Nevertheless, no individual trial results suggested a difference in risk of death among CKD patients randomized to ARB versus those allocated to placebo. In pooled results, there was no between-treatment difference in mortality risk (RR 1.04, 95% CI, 0.92 to 1.18, n=4 trials, 5,242 patients). Only one trial reported results stratified by baseline category of albuminuria in patients with and without an eGFR <60 mL/min/1.73m^2. There was no difference in mortality stratified by baseline category of albuminuria in patients with and without an eGFR <60 mL/min/1.73m^2.[99]

Cardiovascular Mortality

In a single trial that reported data on cardiovascular mortality, there was no significant difference in risk between study participants randomized to ARB versus placebo (RR 1.03, 95% CI, 0.80 to 1.31).[99]

Vascular Outcomes (Table 8, Appendix Tables C11–C13, and Appendix Figure C2)

Myocardial Infarction

In the one trial reporting data, among CKD patients there was a 25 percent reduction in risk of MI between ARB and placebo that was not statistically significant (6.7 versus 8.9 percent; RR 0.75, 95% CI, 0.53 to 1.06).[98]

Stroke

No trials reported data on risk of stroke.

Other Vascular Outcomes

One trial reported a significant reduction in risk of hospitalization for CHF (11.9 versus 16.7 percent; RR 0.71, 95% CI, 0.55 to 0.91; n=1,513 patients.[98] A second trial reported that CKD patients assigned to ARB had a rate of hospitalization for CHF that was 23 percent lower than placebo, a difference that was not stated to be statistically significant.[97] This study did not report the proportion of patients with one or more CHF hospitalizations, overall or by treatment group. On the other hand, ARB treatment did not significantly reduce risk of composite vascular events (Appendix Table C13) compared with placebo in any of three trials reporting, (RR 0.94, 95% CI, 0.81 to 1.08;[98] RR 0.95, 95% CI, 0.80 to 1.12;[99] and RR 0.94, 95% CI, 0.77 to 1.15),[97] respectively.

Renal Outcomes (Table 8, Appendix Tables C14 and C15, and Appendix Figure C2)

End-Stage Renal Disease

In three trials reporting incident ESRD, subjects with CKD assigned to ARB treatment were 22 percent less likely to progress to ESRD than those allocated to placebo treatment, a statistically significant result (10.0 versus 12.9 percent; RR 0.78, 95% CI, 0.67 to 0.90; n=4,652 patients)[97-99] (Figure 7). Two of these trials were comprised entirely of participants with proteinuria, whereas the third trial reported results for risk of ESRD stratified by albuminuria groups.[99] It reported no interaction between category of albuminuria (normal, microalbuminuria, or macroalbuminuria) and the relative reduction in risk of ESRD with ARB treatment versus placebo.

Other Renal Outcomes

In three trials reporting, CKD patients randomized to ARB treatment were significantly less likely to develop a doubling of their baseline serum creatinine (11.8 versus 15.2 percent; RR 0.78, 95% CI, 0.68 to 0.90; n=4,652 patients).[97-99] Risk of conversion from microalbuminuria to macroalbuminuria was 58 percent lower in CKD patients assigned to ARB compared with those allocated to placebo (13.2 versus 31.2 percent; RR 0.42, 95% CI, 0.33 to 0.52; n=2 trials, 1,104 patients).[95,96] One or more composite renal outcomes were reported in three trials (Appendix

Table C15),[97,98] with all suggesting that assignment to ARB reduces risk of the composite outcome compared with placebo, though not all differences were statistically significant.

Study Withdrawals and Adverse Events (Appendix Table C16)

Among CKD patients allocated to either ARB or placebo treatment, 12.2 percent withdrew from studies (range 0.8 to 24.4; n=5 trials). One trial reported that patients assigned to ARB treatment had a significantly lower rate of adverse events per 1,000 treatment days than those assigned to placebo.[97] Another trial reported that more than 90 percent of participants had at least one adverse event,[95] but no trials reported data on the proportion of patients with any adverse event by treatment group. This study further reported that 61 percent of all subjects had a serious adverse event and that there was no between-group difference for this outcome. Again no results were reported by treatment group. A second trial also reported that fewer ARB patients than those assigned placebo had a serious adverse event (15.4 versus 22.9 percent, n=590 participants), and further that ARB patients were not more likely than those assigned to placebo to withdraw from the study due to an adverse event (6.7 versus 8.5 percent).[96] Hyperkalemia necessitating discontinuation of study medication occurred in a significantly higher proportion of patients randomized to ARB treatment than placebo (3.2 versus 1.3 percent; RR 2.38, 95% CI, 1.57 to 3.61; n=3 trials, 4,652 patients). In one study reporting, relative risk of hyperkalemia with ARB versus placebo did not differ by baseline category of albuminuria.[99] In one study reporting, serum creatinine elevation necessitating discontinuation of study medication appeared similar between treatment groups (ARB 1.5 percent versus placebo 1.2 percent). Another study reported one episode of an early increase in serum creatinine concentration suggestive of renal artery stenosis that necessitated stopping the study medication but did not indicate in which treatment group this adverse event occurred.

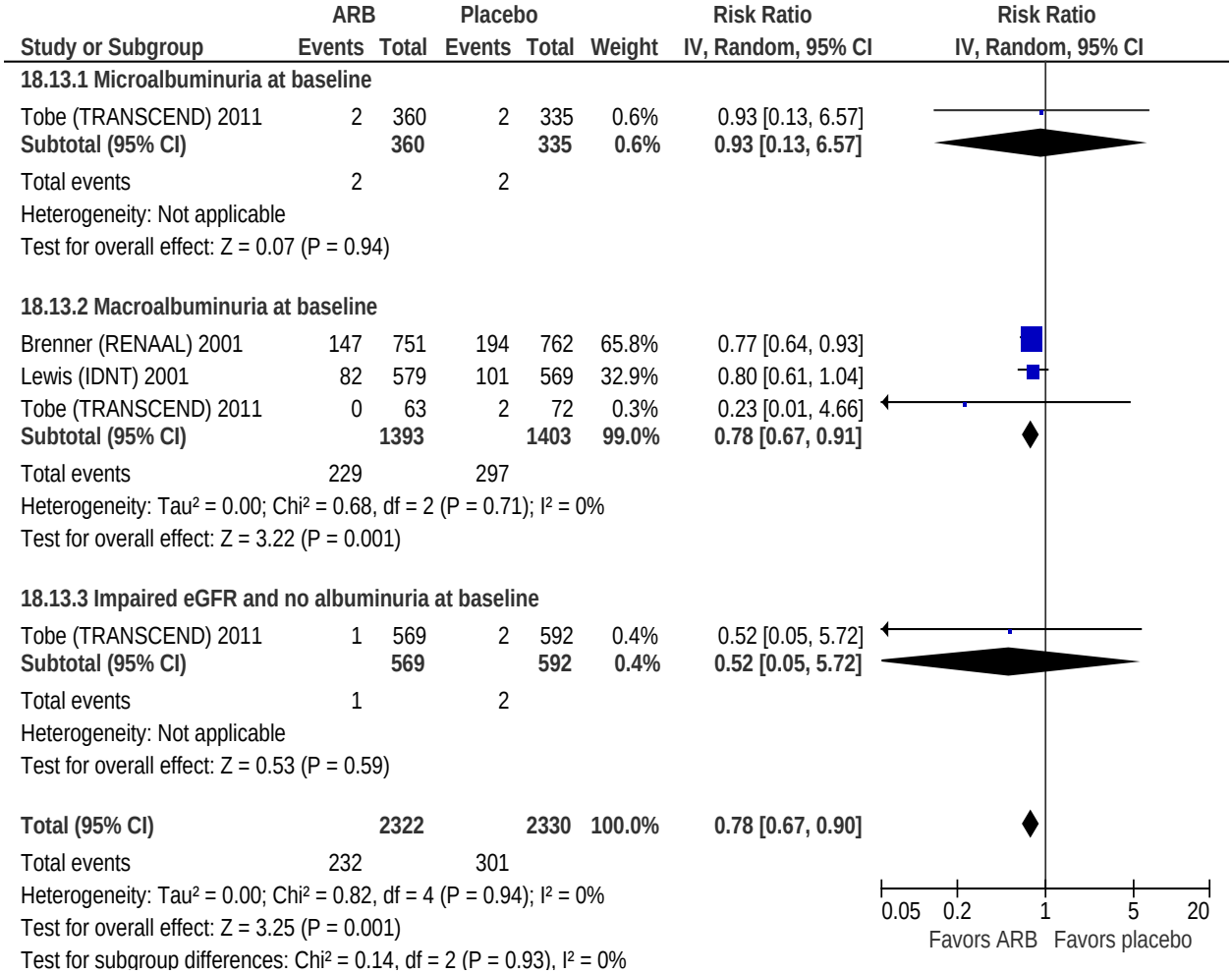
Subgroup Results

No trials reported outcomes stratified by any participant characteristic. In four trials restricted to patients with diabetes, all of which also required that participants have albuminuria, there was no significantly reduced risk with ARB versus placebo for mortality (RR 0.99, 95% CI 0.85 to 1.17; n=3 trials), MI, or composite vascular outcome. In the two trials restricted to diabetic participants with macroalbuminuria, those randomized to ARB had a significant reduction in risk of ESRD (RR 0.78, 95% CI 0.67 to 0.91; n=3 trials), CHF hospitalization (RR 0.71, 95% CI 0.55 to 0.91; n=1 trial), and doubling of serum creatinine (RR 0.78, 95% CI 0.68 to 0.91; n=2 trials). In the two trials restricted to diabetic participants with microalbuminuria, both of which also required normal eGFR for entry, participants randomized to ARB had a significant reduction in risk of conversion from microalbuminuria to macroalbuminuria (RR 0.42, 95% CI 0.33 to 0.52; n=2 trials). In two trials restricted to patients with hypertension, there was no significant difference between treatment groups in risk of mortality, ESRD or one composite vascular outcome reported, but there were statistically significant reductions in risk of doubling baseline creatinine, conversion from microalbuminuria to macroalbuminuria, and a single composite renal outcome reported. In three trials in which patients with CHF were excluded, there was a significant reduction in risk of CHF hospitalization (RR 0.71, 95% CI, 0.55 to 0.91), ESRD (RR 0.76, 95 percent CI, 0.63 to 0.92), and in doubling of baseline creatinine and conversion from microalbuminuria to macroalbuminuria. No trials were restricted to or excluded patients with cardiovascular disease.

Summary

In individuals with CKD, compared with placebo, assignment to ARB treatment was associated with significant reductions in risk of ESRD (reported only in patients with macroalbuminuria), and of doubling of serum creatinine and conversion from microalbuminuria to macroalbuminuria (both reported only in patients with microalbuminuria at baseline). Assignment to ARB treatment also was associated with reduction in risk in one of two composite renal outcomes, and in risk of CHF hospitalization. There was no significant difference between treatment groups for the outcomes of all-cause mortality, MI, or any reported composite vascular outcomes. No trials reported results for stroke. Results were limited in that several outcomes were reported in only one trial or not at all, in particular with neither of the studies that limited enrollment to microalbuminuric patients reporting results for MI, stroke, CHF, ESRD, or a composite vascular or renal endpoint. Though withdrawal and adverse event reporting were limited, individuals with CKD allocated to ARB were significantly more likely to experience hyperkalemia requiring discontinuation of study medication. In one trial that reported results stratified by baseline albuminuria category, there was no significant difference between these groups in the relative risk between ARB and placebo for any outcome or adverse event.

Figure 7. ARB versus placebo: End-stage renal disease by albuminuria subgroups



ARB Versus CCB Trials (n=4)

Overview

In patients with CKD, we found low strength of evidence that ARB treatment does not reduce risk of all-cause mortality or ESRD relative to CCB. We found that patients assigned ARB treatment were significantly less likely to experience doubling of baseline creatinine, but that there was no significant difference between treatment groups for risk of stroke, or conversion from microalbuminuria to macroalbuminuria. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events in some trials, and the heterogeneity of the study populations.

Description of Studies

Three trials met all eligibility criteria and randomized participants with CKD (n=3,924 patients, range 58 to 2,720) to an ARB versus CCB.[97,100,101] Detailed baseline characteristics are presented in Appendix Tables C9 and C10.

Among eligible trials, one compared candesartan to amlodipine (n=2,720 patients),[100] one compared irbesartan to amlodipine (n=1,146 patients),[97] and one compared candesartan to nifedipine (n=58 patients).[101] In total, there were 2,778 participants randomized to candesartan versus a CCB and 3,866 participants randomized to amlodipine versus an ARB. The mean age of subjects was 63.2 years (range 59 to 65; n=3 trials), and men constituted 55.4 percent (range 46.6 to 64.3; n=3 trials) of all patients randomized. Just one trial reported race/ethnicity, in which 72.1 percent of subjects were white.[97] Two other trials were conducted in Japan.[100,101] Median study durations ranged from 1.8 to 3.2 years.

Renal Function

In two trials, the initial study design specified restriction to patients with albuminuria (repeated urinary albumin-creatinine ratio 100-300 mg/g)[101] or proteinuria (urinary protein excretion ≥900 mg/24 hours).[97] In the third study, the current report[100] was a secondary analysis conducted in patients with either GFR <60ml/min/1.73m^2 or a positive dipstick test for proteinuria from among a larger trial population with either serum creatinine >1.3 mg/dL or undefined proteinuria.[101,102] Among the 2,720 participants enrolled in this study, 330 were reported in combined CKD stages 1 or 2, 2,265 were CKD stage 3, and 125 were CKD stage 4. No other study based inclusion on or reported distribution of participants by CKD stage. The only measure of renal function reported in more than one trial was serum creatinine, which ranged from 0.74 to 1.66 mg/dL in two trials reporting,[97,101] and was by definition >1.3 mg/dL in all participants in the third trial.[100] The baseline level of albuminuria differed considerably in two trials reporting, from an albumin-creatinine ratio of 237 mg/g[101] to a 24 hour urinary albumin excretion of 1.9 g.[97] Neither baseline GFR nor creatinine clearance was reported in any trials.

Baseline Comorbidities

All three studies included only subjects with hypertension and type 2 diabetes. Mean baseline systolic and diastolic blood pressures was 162/90 mmHg. Two trials excluded subjects with severe hypertension (systolic >200mmHg and/or diastolic >110 or 120 mmHg).[100,101] Trials provided little information on participant history of cardiovascular disease. In one trial, 28.7 percent of subjects had a history of cardiovascular disease,[97] while in a second trial 4.8 percent of participants had a history of MI.[100] One trial excluded subjects with "severe cerebral or

cardiovascular diseases,"[101] while a second trial excluded participants with MI or stroke ≤6 months before screening, coronary angioplasty or bypass ≤6 months before screening or currently scheduled, current treatment for class II-IV CHF or ejection fraction <40 percent, or coronary artery disease requiring BB or CCB.[100]

Study Quality (Appendix Table C140)

Among the three eligible trials, one was rated good quality and two were rated fair quality. Allocation concealment was adequate in two trials[97] and unclear in two trials.[100,101] One trial was double blinded.[97] Two trials were single blinded, one to the assessors only[100] and one to the patients only.[101] Analysis by the intention-to-treat principle was performed in two trials[97,100] and was unclear in one trial.[101] Two trials adequately described reasons for study withdrawals, with withdrawals ranging from 0.6 to 3.4 percent of randomized participants.[97,101] The third trial did not report any data on withdrawals.[100]

Results

Mortality (Table 8, Appendix Table C11, and Appendix Figure C2)

All-Cause Mortality

Results were heterogeneous between these two trials in that one reported no deaths among its 58 participants (and thus, no cardiovascular deaths),[101] while among the 1,146 participants in the other trial, 15.0 percent died in the ARB group versus 14.6 percent in the CCB group.[97] In pooled results, compared with CCB treatment, assignment to ARB therapy did not reduce risk of all-cause mortality among individuals with CKD (14.1 percent for ARB versus 14.2 percent for CCB; RR 1.03, 95% CI, 0.78 to 1.35; n=2 trials, 1,206 patients).

Vascular Outcomes (Table 8, Appendix Tables C11-C13, and Appendix Figure C2)

Myocardial Infarction

No trial reported results for MI.

Stroke

One trial reported stroke events, finding no difference in risk of stroke between CKD subjects randomized to ARB compared with those assigned to CCB (RR 1.07, 95% CI, 0.70 to 1.64).[100]

Other Vascular Outcomes

Two trials reporting a composite vascular outcome as a study endpoint found no significant difference between treatment groups (0.95, 95% CI, 0.73 to 1.24[100] and 1.06, 95% CI, 0.86 to 1.31),[97] respectively. In one trial that reported results for three composite vascular outcomes stratified by baseline CKD stage, cardiovascular events, cerebrovascular events, and cardiac events, respectively, there was no significant difference in risk of any of these composite outcomes between treatment groups for participants in CKD stages 1 or 2, or for participants in CKD stage 3.[100]

Renal Outcomes (Table 8, Appendix Tables C14 and C15, and Appendix Figure C2)

End-Stage Renal Disease

In the only trial that reported ESRD events, subjects with CKD assigned to ARB treatment were 23 percent less likely to progress to ESRD than those allocated to CCB treatment, though these results were not statistically significant (14.2 percent versus 18.3 percent; RR 0.77, 95% CI, 0.59 to 1.01; n=1,146 patients).[97]

Other Renal Outcomes

In one trial reporting, CKD patients randomized to ARB treatment were significantly less likely to develop a doubling of their baseline serum creatinine (16.9 versus 25.4 percent, RR 0.67, 95% CI, 0.53 to 0.84; n=1,146 patients).[97] In data based on one small trial, risk of conversion from microalbuminuria to macroalbuminuria was not statistically significantly lower in CKD subjects assigned to ARB treatment (10.0 versus 27.8 percent; RR 0.36, 95% CI, 0.11 to 1.18; n=58 patients).[101] A composite renal outcome was reported in two trials. In one trial, there was a significant reduction in risk among CKD patients assigned to ARB versus CCB (32.6 versus 42.1 percent; RR 0.80, 95% CI, 0.68 to 0.93).[97] In the second trial, there were few renal events and there was no significant difference in risk of this outcome between treatment groups, including 1.2 versus 1.9 percent (p=0.58) for participants with CKD stages 1 or 2, and 1.2 versus 0.8 percent (p=0.31) for participants with CKD stage 3.[100] It appeared that incidence of events included in the composite renal outcome definition in both trials (doubling of creatinine, ESRD) was far higher in the first trial,[97] suggesting that its CKD population had a substantially higher baseline risk for these events, possibly in part associated with a higher baseline level of proteinuria.

Study Withdrawals and Adverse Events (Appendix Table C16)

Few CKD patients allocated to either ARB or CCB treatment withdrew from studies (0.8 versus 0.7 percent, respectively, n=2 trials reporting). One trial reported that ARB subjects had a significantly lower rate of adverse events per 1,000 days than did CCB subjects but did not report the proportion of study participants with adverse events in each treatment group.[97] This study further reported that 61 percent of all subjects had a serious adverse event and that there was no between-group difference for this outcome. However, again no results were reported by treatment group. Hyperkalemia was significantly more frequent among CKD patients allocated to ARB than to CCB (1.9 versus 0.5 percent, $p<0.05$), though this outcome also was reported in only one trial.[97]

Summary

In individuals with CKD, compared with CCB, assignment to ARB treatment was associated with a significant 33 percent reduction in risk of doubling serum creatinine, but no significant difference in risk of all-cause mortality, MI, stroke, ESRD, or at least two defined composite vascular outcomes. Risk for a composite renal outcome including doubling creatinine, ESRD, or death was significantly lower with ARB in one trial that enrolled CKD patients with substantial baseline proteinuria. In another study of CKD patients at lower risk for these renal outcomes, there was no significant reduction in risk. Results were limited in that most outcomes were reported in only one trial or were uncommon. Evaluated CKD study populations appeared

heterogeneous with respect to risk of clinical events. However, small sample sizes and few clinical events in some studies, and the limited reported data on baseline vascular disease and renal function/damage, limited evaluation as to whether there are differences in the relative effect of ARB and CCB treatment according to these patient characteristics.

Table 8. Pooled clinical and renal outcomes, ARB monotherapy versus control treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	ARB Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
ARB versus placebo trials (n=5)						
All-cause mortality	4	Good	432/2711 (15.9)	415/2531 (16.4)	1.04 [0.92-1.18]	0%
Cardiovascular mortality	1	Good	114/992 (11.5)	112/999 (11.2)	1.03 [0.80-1.31]	NA
Myocardial infarction, any	1	Good	50/751 (6.7)	68/762 (8.9)	0.75 [0.53-1.06]	NA
CHF hospitalization	1	Good	89/751 (11.9)	127/762 (16.7)	0.71 [0.55-0.91]	NA
Composite vascular outcome, TRANSCEND study[a]	1	Good	205/992 (20.7)	218/999 (21.8)	0.95 [0.80-1.12]	NA
Composite vascular outcome, RENAAL study[b]	1	Good	247/751 (32.9)	268/762 (35.2)	0.94 [0.81-1.08]	NA
Composite vascular outcome, IDNT study[c]	1	Good	138/579 (23.8)	144/569 (25.3)	0.94 [0.77-1.15]	NA
End-stage renal disease	3	Good	232/2322 (10.0)	301/2330 (12.9)	0.77 [0.66-0.90]	0%
Doubling of serum creatinine concentration	3	Good	275/2322 (11.8)	354/2330 (15.2)	0.78 [0.68-0.90]	1%
Progression from micro to macroalbuminuria	2	Good	96/729 (13.2)	117/375 (31.2)	0.42 [0.33-0.52]	0%
Composite renal outcome, TRANSCEND study[d]	1	Good	16/992 (1.6)	27/999 (2.7)	0.60 [0.32-1.10]	NA
Composite renal outcome, RENAAL study[e]	1	Good	327/751 (43.5)	359762 (47.1)	0.92 [0.83-1.03]	NA
Composite renal outcome, IDNT study[f]	1	Good	189/579 (32.6)	144/569 (39.0)	0.84 [0.72-0.98]	NA
ARB versus CCB trials (n=4)						
All-cause mortality	2	Fair	87/619 (14.1)	93/587 (15.8)	0.92 [0.70-1.20]	NA
Stroke	1	Fair	44/1376 (3.1)	40/1344 (3.0)	1.07 [0.70-1.64]	NA
Composite vascular outcome, CASE-J study†	1	Fair	99/1376 (7.2)	102/1344 (7.6)	0.95 [0.73-1.24]	NA
Composite vascular outcome, IDNT study[c]	1	Good	138/579 (23.8)	128/567 (22.6)	1.06 [0.86-1.31]	NA
End-stage renal disease	1	Good	82/579 (14.2)	104/567 (18.3)	0.77 [0.59-1.01]	NA
Doubling of serum creatinine concentration	1	Good	98/579 (16.9)	144/567 (25.4)	0.67 [0.53-0.84]	NA
Progression from micro to macroalbuminuria	1	Fair	4/40 (10.0)	5/18 (27.8)	0.36 [0.11-1.18]	NA
Composite renal outcome, CASE-J study††	1	Fair	19/1376 (1.4)	26/1344 (1.9)	0.71 [0.40-1.28]	NA
Composite renal outcome, IDNT study[f]	1	Good	189/579 (32.6)	233/567 (41.1)	0.80 [0.68- 0.93]	NA

ARB = angiotensin receptor blocker; RR = relative risk; NA = not applicable; CHF = congestive heart failure; CCB = calcium channel blocker

[a]TRANSCEND = Cardiovascular death, MI, fatal or nonfatal stroke, or hospitalization for heart failure.

[b]RENAAL = MI, stroke, first hospitalization from heart failure or unstable angina, coronary or peripheral revascularization, or death from cardiovascular causes.

[c]IDNT = Death from cardiovascular causes, nonfatal MI, heart failure resulting in hospitalization, stroke resulting in permanent neurological defect, lower limb AKA.

[d]TRANSCEND = Doubling of baseline serum creatinine or chronic dialysis.

[e]RENAAL = Time to doubling serum creatinine, incident ESRD (hemodialysis or renal transplant), or death.

[f]IDNT = Doubling of baseline serum creatinine, incident ESRD (hemodialysis, renal transplant, serum creatinine concentration at least 6.0mg/dl), or death from any cause.

†First cardiovascular event defined as any of the following: sudden death (unexpected death within 24 h without external cause); cerebrovascular event (stroke or transient ischemic attack); cardiac event (heart failure, angina pectoris, or acute myocardial infarction); renal event (included serum creatinine concentration of 4.0 mg/dl or higher, doubling of serum creatinine concentration, or end-stage renal disease); and/or vascular event (dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery).

††Serum creatinine concentration of 4.0 mg/dl or higher, doubling of the serum creatinine concentration or end-stage renal disease.

ACE Inhibitor Plus ARB Therapy Versus ACE Inhibitor Alone Trials (n=6)

Overview

In patients with CKD, we found moderate strength of evidence that there is no difference between ACEI plus ARB combination therapy versus ACEI monotherapy for the outcome of all-cause mortality. We found insufficient strength of evidence that there is no difference between these treatments for ESRD. We found no significant difference between treatment groups in risk of stroke, CHF, doubling of serum creatinine, or progression from microalbuminuria to macroalbuminuria. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events in some trials, and the heterogeneity of the study populations.

Description of Studies

Six trials met eligibility criteria and randomized participants with CKD (N=7,233, range of 54 to 3,988) to combination therapy with an ACEI plus an ARB versus ACEI therapy alone.[75-77,103-105] One of the included reports was a post-hoc analysis performed within a subset of participants with CKD from a larger trial population that was not originally limited to subjects with CKD,[105] while a second report was a post hoc analysis from a larger trial that evaluated outcomes in multiple participant subgroups, including impaired GFR and albuminuria.[75] Detailed baseline characteristics are presented in Appendix Tables C17 and C18.

The mean age of study subjects was 65 years (range of study means 51–66; n=5 trials), and men constituted 83 percent (range 37 to 88; n=5 trials) of all participants randomized. Among the three trials that reported race/ethnicity, one was entirely comprised of Japanese participants,[104] one reported only that 91 percent of participants were white,[105] and, in third trial, 45 percent of participants were Hispanic, 34 percent were black, and 19 percent were white.[103] Two studies were conducted solely in the United States,[103,105] one study was conducted in Japan[104] one study was conducted in Turkey,[77] and two studies were multinational.[75,76] The mean or median study duration ranged from 30 weeks to 3.1 years. All studies but two[76,103] had followup durations of at least 1 year.

Renal Function

One post hoc analysis restricted inclusion to participants with GFR <60 ml/min/1.73m^2, by definition CKD stage 3 or worse,[105] while a second post hoc analysis reported results for a subgroup defined by GFR <60 ml/min/1.73m^2 as well as for a subgroup defined by albuminuria, the latter by definition could have included CKD stages 1–4.[75] Otherwise, no trial based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Of the six trials, two required that participants have microalbuminuria,[76,77] two required that participants have macroalbuminuria or overt proteinuria,[103,104] and one reported a post hoc analysis of participants with either microalbuminuria or macroalbuminuria.[75] Among these trials that required participants to have albuminuria or proteinuria, one required that participants also have a normal creatinine,[77] three allowed participants to have abnormal levels for creatinine or creatinine clearance but mandated a maximally abnormal limit,[76,103,105] while one required that participants also had an elevated creatinine between 1.2 and 5 mg/dL.[104]

Overall, four studies reported on some measure of proteinuria at baseline.[75-77,103,104] One reported a mean 24 hour proteinuria of 1.7 g/d,[104] one reported a mean urinary albumin: creatinine ratio of 9.4 mg/mmol,[76] one reported a mean 24 hour albumin excretion rate of 260 mg,[77] and one study reported a mean urinary albumin:creatinine ratio of 907 mg/g.[103] The study by Anand reported only on dipstick proteinuria.[105] Several measures of renal function were reported by the studies, including a mean serum creatinine 1.5 mg/dL (range 1 to 3, n=3 trials),[77,103,104] a mean creatinine clearance of 96 ml/min/1.73m2 (range 65 to 112, n=3 trials),[76,77,103] and a mean eGFR of 50 (range 48 to 51, n=2 trials).[75,105]

Baseline Comorbidities

Two of six trials were restricted to patients with diabetes,[77,103] including one limited to participants with type 2 diabetes.[77] Among the remaining trials, only two report data on diabetes prevalence, with 29 percent[105] and 74 percent[76] of study participants, respectively.

Three trials were restricted to participants with hypertension,[76,77,104] two trials excluded participants with hypertension,[75,103] while prevalence of hypertension in the remaining study was 15 percent.[105] Mean baseline blood pressures was 127/76 mmHg.

Three trials excluded participants with heart failure,[76,103,104] while one included only participants with heart failure.[105] Four trials excluded participants with a recent stroke or ischemic cardiac event. Prevalence of other cardiovascular disease was reported only in that heart failure was attributed to ischemic disease in 36 percent of participants in one trial,[105] and a history of MI or coronary artery procedure was reported in fewer than 10 percent of participants in a second study.[103,104]

Study Quality (Appendix Table C140)

Among six eligible trials, two were rated as good quality and four were rated as fair quality. Allocation concealment was adequate in three trials and unclear in the remaining studies. Four trials were double blinded.[75,76,103,105] Two studies were not blinded.[77,104] For the outcomes presented here, only two studies analyzed results according to the intention-to-treat principle.[75,105] All studies adequately described reasons for study withdrawals. Withdrawals ranged from 5 to 24 percent (n=4 trials).

Results

Mortality (Table 9, Appendix Table C19, and Appendix Figure C3)

All-Cause Mortality

Overall, there was no significant difference in risk of all-cause mortality between CKD patients randomized to ACEI+ARB versus those allocated to ACEI alone (RR 1.03, 95% CI, 0.91 to 1.18). More than 99 percent of events occurred in only one trial.[105]

Cardiovascular Mortality

No study reported data for cardiovascular mortality.

Vascular Outcomes (Table 9, Appendix Tables C19–C21, and Appendix Figure C3)

Myocardial Infarction

No study reported on MI (fatal or nonfatal).

Stroke

Only one study reported on nonfatal stroke,[103] with only two stroke events occurring during the study, one in each study arm.

Other Vascular Outcomes

Congestive heart failure events were reported only by one study[103] in which two CHF events occurred in participants randomized to ACEI+ARB versus no events in the ACE monotherapy group. A composite cardiovascular outcome was also only reported in one study.[105] This study had a broad outcome definition for their cardiovascular composite outcome (Appendix Table C21). Combination ACEI+ARB therapy was associated with a modest but statistically significant 11 percent relative risk decrease in CVD events (95% CI, 0.80 to 0.98).

Renal Outcomes (Table 9, Appendix Tables C22 and C23, and Appendix Figure C3)

End-Stage Renal Disease

Only one study reported results for ESRD.[104] The risk of ESRD was equivalent in those on combination ACEI+ARB therapy compared with ACEI therapy alone (HR 1.0, 95% CI, 0.2 to 6.8). This trial reported only four ESRD events, with two occurring in each arm.

Other Renal Outcomes

One study reported on the outcome of doubling of serum creatinine.[104] In this study, combination ACEI+ARB therapy was associated with a nonsignificant reduction in the risk for doubling of creatinine compared with solitary ACEI therapy (HR 0.07, 95% CI, 0.0 to 1.13). This outcome occurred in only seven study participants, though all had been assigned to the ACEI monotherapy group. Three trials reported on progression from microalbuminuria to macroalbuminuria.[75-77] Although by far the most events for this outcome were reported in the ONTARGET trial, results reported by this trial for the number of participants with baseline microalbuminuria were inconsistent throughout the paper and could not be incorporated in a pooled analysis. The ONTARGET trial reported results for a composite renal outcome, defined as first occurrence of either dialysis, renal transplantation, doubling of baseline serum creatinine, or death.[75] Based on graphical display of the data (risk ratios and number of events in each treatment arm were not reported), there appeared to be no significant difference between ACEI and ACEI+ARB for reaching this endpoint in either the ONTARGET subgroup with GFR <60 ml/min/1.73m^2 or the subgroup with baseline microalbuminuria.[75] Further, that the relative reduction in risk of the composite renal outcome between treatment groups in ONTARGET was not significantly different in the CKD subgroup than in ONTARGET participants without CKD (p for interaction 0.80).

Study Withdrawals and Adverse Events (Appendix Table C24)

Overall study withdrawals, reported in all four studies, ranged from 6 to 24 percent. Only one study reported on adverse events leading to withdrawal,[76] which was similar in both study arms. Two studies reported on any adverse events[76,103] that appeared to be similar between groups. The most common adverse events reported were hypotension and hyperkalemia. Hyperkalemia was more common in the combination therapy group in one study[105] but not in another.[76]

Summary

In patients with CKD, compared with ACEI monotherapy, assignment to combination ACEI+ARB therapy did not significantly reduce risk of all-cause mortality but was associated with significant reductions in risk of the one composite vascular outcome reported and in risk of progression from microalbuminuria to macroalbuminuria. Results suggested that combination treatment might reduce risk of doubling creatinine, but they did not achieve statistical significance. Too few events were reported for all other outcomes for the results to be clinically meaningful, including for stroke, MI, and ESRD. Reporting on study withdrawals and adverse effects was limited. No trial provided followup beyond 4 years.

Table 9. Pooled clinical and renal outcomes, ACE inhibitor plus ARB versus ACE inhibitor trials

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI+ARB Events/N (%)	ACEI Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	3	Fair	363/1546 (23.5)	342/1513 (22.6)	1.03 [0.91-1.18]	0%
Stroke, nonfatal	1	Fair	1/26 (3.8)	1/27 (3.7)	1.04 [0.07- 15.75]	NA
CHF	1	Fair	2/26 (7.6)	0/27 (0)	5.19 [0.26- 103.11]	NA
Composite vascular outcome**	1	Good	499/1477 (33.8)	549/1439 (38.2)	0.89 [0.80- 0.98]	NA
End stage renal disease	1	Fair	2/45 (4.4)	2/45 (4.4)	1.00 [0.15- 6.79]	NA
Doubling of serum creatinine	1	Fair	0/45 (0)	7/45 (15.6)	0.07 [0.00-1.13]	NA
Progression to macroalbuminuria	2	Fair	1/139 (0.7)	3/95(3.2)	0.36 [0.04-3.37]	NA

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; RR = relative risk reduction; NA = not applicable

**Death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasodilator drugs for 4 hours or more without hospitalization

ACE Inhibitor Plus ARB Therapy Versus ARB Alone Trials (n=3)

Overview

In patients with CKD, we found insufficient evidence regarding whether there is a difference between ACEI+ARB combination therapy versus ARB monotherapy for all-cause mortality (no events) or ESRD (no data reported). Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events, and the heterogeneity of the study populations.

Description of Studies

Three trials met eligibility criteria and randomized participants with CKD (n=approximately 4,300) to combination therapy with an ACEI+ARB versus ARB therapy alone.[75-77] Baseline characteristics are presented in Appendix Tables C17, C18, and C25.

Among eligible trials, the mean age of study subjects was 57 years (range of study means 57 to 58; n=2 trials reporting), and men constituted 46 percent (range 37 to 69; n=2 trials reporting) of all participants. Ethnicity was not reported by any study. Two studies were multinational[75,76] and one was conducted in Turkey.[77] The mean or median study duration ranged from 30 weeks to 4.7 years. Two studies had a duration of followup of 1 year or greater.[75,77]

Renal Function

One post hoc analysis reported results for a subgroup defined by GFR <60 ml/min/1.73m^2 as well as for a subgroup defined by albuminuria, the latter by definition could have included CKD stages 1–4 but did not state the total number of participants with CKD.[75] Otherwise, no trial based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Of the three trials, two required that participants have microalbuminuria,[76,77] and one reported a post hoc analysis of participants with either microalbuminuria or macroalbuminuria.[75] Of the two trials that required participants to have albuminuria or proteinuria, one required that participants also have a normal creatinine,[77] and one allowed participants to have abnormal levels for creatinine or creatinine clearance but mandated a maximally abnormal limit.[76]

Two studies reported on some measure of proteinuria at baseline.[76,77] One reported a mean urinary albumin:creatinine ratio of 9.4 mg/mmol,[76] and the other reported a mean 24-hour albumin excretion rate of 260 mg.[77] Two studies reported a mean creatinine clearance of 101 ml/min/1.73m2 (range 97 to 112, n=2 trials),[76,77] one reported a mean serum creatinine of 1.0 mg/dL,[77] and one reported a mean eGFR of 50 mL/min/1.73m2.[75]

Baseline Comorbidities

One trial was restricted to patients with type 2 diabetes.[77] In the only other study that reported data, diabetes prevalence was 74 percent.[76] Two trials were restricted to participants with hypertension,[76,77] and one trial excluded participants with hypertension.[75] Mean baseline blood pressures was 152/90 mmHg. One trial excluded participants with heart failure,[76] but otherwise the presence of cardiovascular disease at baseline was not reported in any study.

Study Quality (Appendix Table C140)

Among the three trials, one was rated good quality and two were rated fair quality. Allocation concealment was adequate in two studies and unclear the third study. Two studies

were double blinded.[75,76] The other study was not blinded.[77] For the outcomes presented here, only one study analyzed results according to the intention-to-treat principle.[75] All studies adequately described reasons for study withdrawals. Withdrawals ranged from 12 to 14 percent (n=2 trials).

Results

Mortality (Table 10, Appendix Table C19, and Appendix Figure C4)

Of the three studies, only one reported on mortality during the trial.[76] In this study of 86 patients with CKD there were no deaths.

Vascular Outcomes (Table 10, Appendix Tables C19–C20)

Myocardial Infarction

No study reported on MI events (fatal or nonfatal).

Stroke

No study reported on stroke events.

Other Vascular Outcomes

No studies reported on CHF events or any composite cardiovascular outcomes.

Renal Outcomes (Table 10, Appendix Table C22, and Appendix Figure C4)

End-Stage Renal Disease

No study reported on ESRD.

Other Renal Outcomes

No study reported on the outcome of doubling of serum creatinine. With regard to the outcome of progression from microalbuminuria to macroalbuminuria, it was reported that no events occurred in one trial,[77] and only four events in a second trial.[76] Although by far the most events for this outcome were reported in the ONTARGET trial, results reported by this trial for the number of participants with baseline microalbuminuria were impossibly inconsistent throughout the paper and could not be incorporated in a pooled analysis. No study reported on any renal composite outcomes.

Study Withdrawals and Adverse Events (Appendix Table C24)

Overall study withdrawals were reported in only one study at 14 percent. One study reported on adverse events leading to withdrawal,[76] which was similar in both study arms. One study reported on any serious adverse events,[76] which were more common in the combination therapy group (9.3 percent) versus the ARB alone group (2.3 percent). The most common adverse events reported were hypotension, hyperkalemia, and cough. In one study cough was more common in the combination therapy group that in the ARB alone group (4.3 percent versus 0 percent).

Summary

In individuals with CKD, trials comparing ACEI+ARB combination therapy versus ARB alone reported few or no clinical outcomes, including no deaths in one trial reporting this

outcome. No trials reported data on MI, stroke, CHF, ESRD, doubling of serum creatinine, or any composite vascular or renal outcome. Though trials reported data for progression from microalbuminuria to macroalbuminuria, all had either few events or errors in reporting that impeded interpretation. Reporting on study withdrawals and adverse effects was limited. No trial provided followup beyond 5 years.

Table 10. Pooled clinical and renal outcomes, ACE inhibitor plus ARB versus ARB trials

Outcome	Number of Trials Reporting	Quality of the Studies	ACEI+ARB Events/N (%)	ARB Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	1	Fair	0/43 (0)	0/43 (0)	-	NA
Progression to macroalbuminuria	2	Fair	1/139 (0.7)	3/91 (3.3)	0.33 [0.04-3.08]	NA

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; RR = relative risk reduction; NA = not applicable

ACE Inhibitor Plus ARB Therapy Versus ACE Inhibitor or ARB (Monotherapy) Trial (n=1)

Overview

In patients with CKD, we found moderate strength of evidence that combination ACEI and ARB treatment did not reduce risk of all-cause mortality compared with ACEI or ARB monotherapy. We found low strength of evidence that that there was no difference in risk of ESRD between treatment groups. There was no significant difference between treatment groups for risk of cardiovascular mortality, a composite vascular outcome, doubling of serum creatinine, or a composite renal outcome defined as doubling of serum creatinine or ESRD. Our confidence in these estimates is limited as data were drawn from only one trial.

Description of Studies

One trial met all eligibility criteria and randomized participants with CKD to either ACEI monotherapy, ARB monotherapy, or combined ACEI plus ARB treatment. Detailed baseline characteristics are presented in Appendix Tables C17 and C18. From the larger ONTARGET trial (n=23,422), this post hoc analysis was limited to 8,933 participants with either eGFR ≤60 ml/min/1.73m^2 or albuminuria and reported results only for combination therapy versus the pooled monotherapy arms.

In this post hoc analysis,[99] 2,943 participants were randomized to ramipril 10 mg/d plus telmisartan 80 mg/d versus either ramipril or telmisartan monotherapy (n=5,990). The mean age of subjects was 68.2 years, and men constituted 68.0 percent of patients randomized. Race was reported as 70 percent European and 16 percent Asian. This trial was multinational.[99]

Renal Function

Participants were excluded if they had a serum creatinine >3 mg/dL with no restriction on albuminuria. At baseline, mean serum creatinine was 1.1 mg/dL, mean eGFR was 73.6 ml/min/1.73m^2, and mean urinary albumin:creatinine ratio was 129.1 mg/g. In this post hoc analysis, 5,623 participants (62.9 percent) had eGFR <60 ml/min/1.73m^2, 2,631 (29.5 percent) had isolated microalbuminuria, and 679 (7.6 percent) had isolated macroalbuminuria.

Baseline Comorbidities

Participants were included if they were >55 years with established cardiovascular disease or with diabetes associated with end organ damage. Seventy-seven percent of participants had hypertension with a mean blood pressure of 144/82 mm Hg. Diabetes was present in 49 percent of participants. The prevalence of cardiovascular disease was 70 percent, including 45 percent with a previous myocardial infarction, 20 percent with a prior stroke and 17 percent with prior peripheral vascular disease.

Study Quality (Appendix Table C140)

The study was rated good quality. It was double blinded, performed analyses using the intention-to-treat principle, and adequately described study withdrawals and reasons for withdrawals. Study withdrawals occurred in 29 percent of participants.

Results

Mortality (Table 8, Appendix Table C19, and Appendix Figure C5)

All-Cause Mortality

Overall, incidence of all-cause mortality was 17.4 percent, with no difference between patients randomized to combination therapy versus monotherapy (RR 1.02, 95% CI, 0.93 to 1.13). However, there was a significant interaction between baseline albuminuria category and the association between treatment group and mortality (p=0.03). Relative risk of mortality with combination therapy versus monotherapy was 1.15 (95% CI, 1.02 to 1.24) in patients with normoalbuminuria, 1.09 (95% CI, 0.93 to 1.29) in patients with microalbuminuria, and 0.80 (95% CI, 0.64 to 1.01) in patients with macroalbuminuria. This association was independent of baseline eGFR.

Cardiovascular Mortality

Risk of cardiovascular death was not significantly different between combination therapy and monotherapy (RR 1.01, 95% CI, 0.86 to 1.19). This result did not differ by albuminuria status.

Vascular Outcomes (Table 8, Appendix Tables C19-C21, and Appendix Figure C5)

Myocardial Infarction

Risk of myocardial infarction was not reported.

Stroke

Risk of stroke was not reported.

Other Vascular Outcomes

There was no difference between treatment groups in risk of a single composite outcome defined as death from cardiovascular causes, myocardial infarction, stroke or hospitalization for heart failure (RR 0.97, 95% CI, 0.89 to 1.05).

Renal Outcomes (Table 8, Appendix Tables C22 and C23, and Appendix Figure C5)

End-Stage Renal Disease

ESRD occurred in a similar percentage of participants randomized to combination therapy as assigned monotherapy (RR 1.19, 95% CI, 0.77 to 1.85).

Other Renal Outcomes

There was no significant difference between treatment groups in risk of doubling of serum creatinine (RR 1.25, 95% CI, 0.96 to 1.63) or for the composite outcome of doubling of serum creatinine or ESRD (RR 1.22, 95% CI, 0.96 to 1.55).

Study Withdrawals and Adverse Events (Appendix Table C24)

Overall, 24.7 percent of individuals in this post hoc analysis withdrew from therapy. Risk of withdrawal was significantly greater in the group assigned combination treatment (RR 1.17, 95%

CI, 1.10 to 1.25). Risk for most specific adverse effects was greater in participants randomized to combination therapy, including need for acute dialysis (RR 1.95, 95% CI, 1.09 to 3.49), hyperkalemia (potassium > 5.5 meq/dL) (RR 1.65, 95% CI, 1.4 to 1.95), hypotension (RR 1.66, 95% CI, 1.29 to 2.12), cough (RR 1.72, 95% CI, 1.34 to 2.20), and syncope (RR 2.44, 95% CI, 0.75 to 8.00).

Summary

In individuals with CKD, compared with ACEI or ARB monotherapy, assignment to ACEI plus ARB combination treatment was associated with a similar risk of all-cause mortality, cardiovascular mortality, a composite vascular outcome, ESRD, and doubling of serum creatinine. However, there was a significant interaction between baseline category of albuminuria and the association of treatment assignment on risk of all cause mortality. While those with normoalbuminuria had an increased risk of death with combination therapy, those with macroalbuminuria demonstrated a trend towards a decreased risk of mortality. Results were limited in that they are derived from only one trial. Adverse effects were more likely in patients randomized to combination ACEI and ARB therapy compared with monotherapy with either an ACEI or ARB.

ACE Inhibitor Plus ARB Versus ACE Inhibitor Plus Aldosterone Antagonist Trial

Overview

In comparing ACEI plus ARB versus ACEI plus aldosterone antagonist, we found insufficient evidence regarding whether there is a difference between treatments in risk of mortality or ESRD. Our confidence in these estimates is limited because data are drawn from only one trial and because of the small number of clinical events.

Description of Study

One trial met all eligibility criteria and randomized 54 participants with CKD and taking an ACEI (lisinopril 80 mg/day) to the addition of either an ARB (losartan) or of an aldosterone antagonist (spironolactone).[103] A third arm of the trial, discussed elsewhere, involved addition of placebo to lisinopril. Detailed baseline characteristics are presented in Appendix Table C26.

The mean age of trial participants was 52 years, and males constituted 49 percent of study subjects. Most patients (55 percent) were Hispanic, with an additional 28 percent black, 15 percent white, and 2 percent Native American. The study duration was 48 weeks.

Renal Function

Patients were included if they had macroalbuminuria, defined as a urinary albumin to creatinine ratio of 300 mg/g or higher despite treatment with an ACEI or ARB for at least 3 months prior to study entry. Females with a serum creatinine greater than 3.0 mg/dl and males with a serum creatinine greater than 4.0 mg/dl were excluded. Baseline renal function for trial participants included mean urine albumin to creatinine ratio of 997.4 mg/g, mean baseline serum creatinine of 1.8 mg/dl, and mean creatinine clearance of 58.0 ml/min.

Baseline Comorbidities

All study participants were required to have hypertension, with a systolic blood pressure on antihypertensive treatment of greater than 130 mm Hg. Mean baseline blood pressure was 134.0/72.5 mm Hg. Trial participants also were required to have diabetes, but with an HbA_{1c} at or below 11 percent. The mean HbA_{1c} at baseline was 7.5 percent. Patients with any history of heart failure, or with a stroke or MI in the past 12 months were excluded. A history of either MI, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty was reported by 7.5 percent of the patients.

Study Quality (Appendix Table C140)

The trial was rated fair quality. The method used for treatment allocation was not clearly described. The study was double blinded; however, the analysis was not completed using intention-to-treat principles. From the 54 randomized participants, 35.2 percent withdrew, with reasons for withdrawals adequately explained.

Results

Mortality (Appendix Table C27 and Appendix Figure C6)

The trial reported one death in the ACEI plus ARB treatment group and no deaths in the ACEI plus aldosterone antagonist group.

Vascular Outcomes (Appendix Table C27 and Appendix Figure C6)

Myocardial Infarction

The trial reported no MIs in the ACEI plus ARB treatment group and one MI in the ACEI plus aldosterone antagonist group.

Stroke

No stroke events were reported.

Other Vascular Outcomes

The trial reported two hospitalizations attributed to heart failure in the ACEI plus ARB treatment group. This compared with two hospitalizations attributed to heart failure in the ACEI plus aldosterone antagonist group. No composite vascular outcomes were reported.

Renal Outcomes (Appendix Table C28 and Appendix Figure C6)

End-Stage Renal Disease

The trial did not report results for end-stage renal disease.

Other Renal Outcomes

There was no significant difference between treatment groups in risk of doubling of baseline serum creatinine (RR=1.04, 95% CI, 0.60 to 1.80).

Study Withdrawals and Adverse Events (Appendix Table C29)

Withdrawals occurred in 33.3 percent of study participants randomized to the ACEI plus ARB treatment arm versus 37.0 percent of the ACEI plus aldosterone antagonist arm. There were

more withdrawals due to adverse events in the ACEI plus aldosterone antagonist group (25.9 percent versus 7.7 percent). Two patients (7.4 percent) in the ACEI plus aldosterone antagonist group and none in the ACEI plus ARB group experienced recurrent hyperkalemia. Similarly, one patient (3.7 percent) in the ACEI plus aldosterone antagonist group and none in the ACEI plus ARB group withdrew from the study because of an increase in serum creatinine.

Summary (Appendix Table C140)

In this trial of diabetic, hypertensive CKD patients already on ACEI, there appeared to be no difference between subjects randomized to additional ARB versus additional aldosterone antagonist for the outcome of doubling of baseline creatinine. Few or no results were reported with respect to risk of all-cause mortality, MI, stroke, CHF, or ESRD. Withdrawals due to adverse events appeared possibly were more likely with ACEI combined with aldosterone antagonist. Results were limited in that they are based on only one small trial that reported few clinical endpoints. Further, the withdrawal rate was high and followup duration was less than 1 year.

ACE Inhibitor Plus CCB Versus ACE Inhibitor Monotherapy or CCB Monotherapy Trial

Overview

In patients with CKD, we found insufficient evidence regarding whether there is a difference between ACEI monotherapy, CCB monotherapy, and ACE+CCB combination therapy for reducing risk of mortality or any clinical vascular or renal outcome.

Description of Study

We identified one trial that met all eligibility criteria. Patients with CKD were randomized to receive ACEI and CCB combined, ACEI alone, or CCB alone.[84] Detailed baseline characteristics are presented in Appendix Table C30.

After randomization to CCB (amlodipine at 5 to 15 mg/day), ACEI (fosinopril at 10 to 30 mg/day), or the combination, participants began a three month dose titration phase to a goal diastolic blood pressure less than 90 mm Hg for the monotherapy groups and less than 85 mm Hg for the combination therapy group. Patients judged nonresponders or who complained of side effects during the titration phase were withdrawn (n=144 overall, with no data reported by treatment group) and were not entered into the subsequent treatment phase. Study followup during the treatment phase was 4 years.

Renal Function

Study participants were required to have microalbuminuria, defined by UAER 30 to 300 mg/24 hours. For the patients entered in the treatment phase into either the ACEI plus CCB group or the ACEI alone group, the mean baseline serum creatinine was 1.0 mmol/L, mean creatinine clearance was 89.9 mg/min, and mean UAER was 97.9 µg/min. For the patients entered into either the ACEI plus CCB group or the CCB alone group, baseline characteristics were similar. Mean serum creatinine was 1.0 mg/dL, creatinine clearance was 89.3 mg/min, and UAER was 96.6 µg/min.

Baseline Comorbidities

Study participants were required to have hypertension (diastolic blood pressure 90 to 110 mm Hg) and type 2 diabetes (well controlled without insulin). Patients with a history of coronary heart disease, CHF, MI, or stroke were excluded. For patients entered in the treatment phase into either the ACEI plus CCB group or the ACEI alone group, mean baseline blood pressure was 160/99 mm Hg and baseline HbA_{1c} was 7.1 percent. For the patients entered into either the ACEI plus CCB group or the CCB alone group, mean baseline blood pressure was 161/99 mm Hg and HbA_{1c} was 7.0 percent.

Study Quality (Appendix Table C140)

The trial was rated fair quality. Concealment of treatment allocation was adequate. This open-label study did not perform analysis according to the intention-to-treat principle. In addition to participants excluded during the dose titration phase, additional participants withdrew during treatment, resulting in 47 percent total withdrawals.

Results

Mortality (Appendix Table C31 and Appendix Figures C6 and C7)

All-Cause Mortality

The trial reported deaths in few participants, with 2.9 percent, 3.9 percent, and 1.9 percent in ACEI monotherapy, CCB monotherapy, and ACEI+CCB combination groups respectively. There were no significant differences in risk of all-cause mortality between any of these treatment groups.

Cardiovascular Mortality

The trial reported cardiovascular deaths in few participants, with 1.9 percent, 1.9 percent, and 1.0 percent in ACEI monotherapy, CCB monotherapy, and ACEI+CCB combination groups respectively. There were no significant differences in risk of all-cause mortality between any of these treatment groups.

Vascular Outcomes (Appendix Tables C31 and C32 and Appendix Figures C6 and C7)

Myocardial Infarction

There were few events and no difference between the ACEI plus CCB combination compared with either ACEI alone or CCB alone for all-cause MI.

Stroke

There were few events and no difference between the ACEI plus CCB combination compared with either ACEI alone or CCB alone for stroke.

Other Vascular Outcomes

No other vascular or composite vascular outcomes were reported.

Renal Outcomes

End-Stage Renal Disease

No outcomes were reported for end-stage renal disease.

Other Renal Outcomes

No other renal or composite renal outcomes were reported.

Study Withdrawals and Adverse Events (Appendix Table C33)

The overall withdrawal rate for the study was 45 percent. Thirty two percent withdrew during the titration period (treatment group not stated). Excluding deaths, an additional 20 percent withdrew during the study period (22 percent CCB, 23 percent ACE, 15 percent ACEI plus CCB). Between 1 and 2 percent of the patients in each group discontinued study medication due to worsening kidney function. Other reported adverse events (also reported for less than 2 percent of the patients in any treatment group) were cough and edema.

Summary

In one study of patients with CKD, hypertension, and diabetes without a history of cardiovascular disease, few participants died or experienced clinical vascular or renal events. There was no significant difference for any of these outcomes between ACEI plus CCB versus either ACEI monotherapy or CCB monotherapy groups, but wide confidence intervals around all estimates could not exclude large between-group differences. Adverse events were infrequent and risk did not appear significantly different between treatment groups. There were no data on clinical renal outcomes. The study was limited by its exclusion of one-third of randomized participants from the analyses, the large number of additional withdrawals during treatment, the small number of clinical vascular events, and the absence of any reported clinical renal outcomes.

ACE Inhibitor Plus Diuretic Versus ACE Inhibitor Plus CCB Trials (n=2)

Overview

In patients with CKD we found insufficient evidence regarding whether there is any difference between combination therapy with an ACEI and a diuretic and combination therapy with an ACEI and CCB for risk of mortality or ESRD. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events, and the heterogeneity of the study populations.

Description of Study

Two trials met all eligibility criteria. One trial randomized 332 patients with CKD to ACEI plus diuretic versus ACEI plus CCB.[106] The second trial reported results from 1,093 patients with CKD enrolled in a trial of 11,506 patients with hypertension and randomized to ACEI plus diuretic or ACEI plus CCB.[107,108] Detailed baseline characteristics are presented in Appendix Table C34.

In the first trial, patients randomized to the ACEI plus CCB group received benazepril and amlodipine. Those randomized to the ACEI plus diuretic group received benazepril and

hydrochlorothiazide (HCTZ). Doses were titrated to reach a blood pressure target below 130/80 mm Hg, and additional antihypertensives were added as needed with the exception of ACEI, ARB, or aldosterone receptor antagonists. The mean age of study participants was 58 years, and men constituted 65 percent of subjects. Patients were mostly white race (60 percent), with blacks comprising another 26 percent of participants. Study followup duration was 12 months.[106]

The protocol was similar in the second trial. The mean age of the subgroup with CKD was 70.9 years and 67 percent were men. Approximately 77 percent of the patients were white; 20 percent were black. The followup period was 2.9 years.[107]

Renal Function

In the first study, participants were required to have either microalbuminuria or macroalbuminuria (UACR 20 to 500 mg/g), and to have serum creatinine ≤1.3 mg/dl for women and ≤1.5 mg/dl for men. In data available only for the 304 patients who completed followup, the median UACR was 60.6 mg/g, and the median estimated GFR was 90.6 ml/min/1.73m^2.[106]

Patients eligible for the second trial had hypertension and were at high risk for cardiovascular events based on evidence of cardiovascular or renal disease or target organ damage. Criteria for renal disease included serum creatinine >1.5 mg/dL for women or >1.7 mg/dL for men or macroalbuminuria (UACR > 300 mg/g or > 200 mg/g if receiving an ACEI or aldosterone receptor blocker).[107]

Baseline Comorbidities

Trial participants in the first study were required to have hypertension (mean systolic blood pressure 130 to 179 mm Hg and diastolic blood pressure 80 to 109 mm Hg). Mean baseline blood pressure was 151/88 mm Hg. Individuals with CHF, type 1 diabetes or uncontrolled type 2 diabetes were excluded, as were those with a cardiovascular disease event in the past 6 months (MI, stroke, transient ischemic attack, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty).[106]

The second study enrolled patients age 60 and older with systolic blood pressure of 160 mm Hg or higher (or currently on antihypertensive therapy). Within the participants with CKD, mean systolic blood pressure was 145 mm Hg and 59 percent had diabetes. Vascular and hypertension-related reasons for study exclusion included: current evidence for angina pectoris, history of symptomatic heart failure or evidence of left ventricular ejection fraction <40 percent, acute MI or revascularization in the prior month, stroke or other ischemic cerebrovascular events in the prior 3 months, or hypertension that is severe, refractory to treatment, or known to have a secondary cause.[107]

Study Quality (Appendix Table C140)

The first study was rated fair quality. Treatment allocation concealment was adequate. The study was double blinded. Analysis was not according to the intention-to-treat principle. Withdrawals were 19 percent.[106] The second study was rated good quality. Treatment allocation was adequate, the study was double-blinded, analysis was by intention to treat, and withdrawals were adequately reported.[107]

Results

Mortality (Appendix Table C35 and Appendix Figure C8)

In the first study, among 166 patients allocated to ACEI plus diuretic, there were two deaths. Among 166 patients allocated to ACEI plus CCB, there was one death.[106] The second study did not report mortality.

Vascular Outcomes (Appendix Tables C35 and C36 and Appendix Figure C9)

Myocardial Infarction

There were no reports of MI in either study.

Stroke

There were no reports of stroke in either study.

Other Vascular Outcomes

Three patients in the ACEI plus diuretic group were reported to have undefined "cardiac disorders," and two were reported to have undefined "vascular disorders." In the ACEI plus CCB group, two patients were reported to have "cardiac disorders," and none had a "vascular disorder." There was no significant difference between treatment groups for any of these outcomes.[106] The second study did not report any other vascular outcomes.[107]

Renal Outcomes (Appendix Tables C37 and C38 and Appendix Figure C9)

End-Stage Renal Disease

No data were reported for end-stage renal disease in either study.

Other Renal Outcomes

In the first study, the risk of progression from microalbuminuria to macroalbuminuria was not significantly different between the ACEI plus diuretic group and the ACEI plus CCB group (4.0 versus 4.6 percent, RR0.84, 95% C 0.29 to 2.44).[106] The second study reported composite renal outcomes only for patients with CKD and diabetic nephropathy. In 644 patients, the risk of doubling of serum creatinine, ESRD, or need for chronic dialysis was not significantly different between the ACEI plus diuretic group and the ACEI plus CCB group (5.5 versus 5.8 percent, RR 1.15, 95% CI, 0.59 to 2.24). Similar results were observed when cardiovascular mortality was added to the renal outcome defined above (9.7 versus 8.4 percent, RR 1.16, 95% CI, 0.71 to 1.90).[107]

Study Withdrawals and Adverse Events (Appendix Table C39)

For the first study, 47 percent of participants withdrew after randomization, most of whom withdrew during the dose titration period for nonresponse or adverse effects, during which these results were not reported by treatment group. The overall withdrawal rate during the study period was 18.7 percent (21.7 percent in the ACEI plus diuretic group and 15.7 percent in the ACEI plus CCB group). During the study period, adverse events resulted in study withdrawal for 10.8 percent of the ACEI plus diuretic group and 5.4 percent of the ACEI plus CCB group, but details were not provided regarding specific adverse events that led to withdrawal. Reported adverse events in the ACEI plus CCB group and ACEI plus diuretic group, respectively, included edema

in 17.5 percent and 7.2 percent, cough in 13.9 percent and 10.3 percent, and dizziness in 9.0 percent and 6.6 percent.[106] The second study was a subgroup analysis and did not report study withdrawals for the CKD patients. Adverse events included edema (33.7 percent of the ACEI plus CCB group, 16.0 percent of the ACEI plus diuretic group), dizziness (25.1 and 24.2 percent, respectively), cough 21.4 and 17.5 percent, respectively), hypotension (4.3 and 5.5 percent, respectively), and hyperkalemia (0.0 and 0.2 percent, respectively).[107]

Summary

In one study of patients with CKD defined by albuminuria, hypertension with no recent cardiovascular events, and no heart failure, there was no significant difference between patients allocated to ACEI plus diuretic versus ACEI plus CCB in risk of mortality, or of unspecified "cardiac disorders" or "vascular disorders." However, there were very few events for any of these outcomes, and confidence intervals around risk estimates were wide. No data were reported for MI, stroke, CHF, ESRD, or any transparently defined composite vascular or renal outcome. The risk of progression from microalbuminuria to macroalbuminuria appeared similar between treatment groups, but again confidence intervals were wide. A second study reported no difference between treatment groups for two composite renal outcomes assessed in patients with CKD and diabetic nephropathy. Risk of edema appeared somewhat higher in the ACEI plus CCB group in the first study and was significantly higher in the second study. Cough and dizziness appeared somewhat higher in the ACEI plus CCB groups in both studies.

ACE Inhibitor Plus Diuretic Versus ACE Inhibitor Monotherapy Trial

Overview

In patients with CKD, we found insufficient evidence regarding whether treatments differ for risk of mortality or ESRD. There was a significantly reduced risk of achieving the composite vascular outcome in the ACEI plus diuretic group. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Study

One trial met all eligibility criteria and randomized 481 patients with CKD to receive either an ACEI and diuretic or a different ACEI alone.[109] Detailed baseline characteristics are presented in Appendix Table C40 for the 457 patients who took at least one dose of study medication and who had albuminuria measured at least once during treatment.

The ACEI plus diuretic group received perindopril and indapamide, while the ACEI monotherapy group received enalapril. Both groups were titrated to achieve a blood pressure goal of less than 140/90 mm Hg. The mean age of subjects was 59 years and 61 percent of study participants were male. Ninety-one percent of the study participants were white. Mean followup duration was 10.7 months.

Renal Function

Study participants were required to have albuminuria (UAER of 20 to 499 µg/min) and to have a serum creatinine less than approximately 1.6 mg/dl. Mean UAER was 92.1µg/min and the mean urine albumin/creatinine ratio was 8.5 mg/mmol.

Baseline Comorbidities

Study participants were required to have type 2 diabetes with HbA_{1c} less than 9 percent in the 3 months prior to the study. Mean baseline HbA_{1c} was 7.2 percent. Participants also were required to have hypertension (systolic blood pressure 140 to 179 mm Hg and diastolic blood pressure less than 110 mm Hg). Mean baseline blood pressure was 158/93 mm Hg.

Study Quality (Appendix Table C140)

Study quality was rated fair. Though the study was double blind, allocation concealment was unclear and analysis was not intention-to-treat. Withdrawals were 23 percent and were not adequately described.

Results

Mortality

The number of deaths during the study could not be determined.

Vascular Outcomes (Appendix Tables C41 and C42 and Appendix Figure C10)

Myocardial Infarction

The number of MIs during the study could not be determined.

Stroke

The number of strokes during the study could not be determined.

Other Vascular Outcomes

The only clinical outcome reported was serious (fatal or requiring prolonged hospitalization) cardiovascular events (defined by ICD9-1975 revision codes for sudden death and many other cardiovascular conditions). There was a significantly reduced risk of achieving the composite vascular outcome in the ACEI plus diuretic group (RR 0.39, 95% CI, 0.15 to 0.98).

Renal Outcomes

End-Stage Renal Disease

There were no reports of end-stage renal disease.

Other Renal Outcomes

There were no other renal outcomes reported.

Study Withdrawals and Adverse Events (Appendix Table C43)

The overall withdrawal rate for the study was 23 percent, including 21 percent in the ACEI plus diuretic group and 25 percent in the ACEI group. Adverse events related to drug treatment were similar for the two groups (14 percent and 15 percent for the ACEI plus diuretic and ACEI groups, respectively) as were withdrawals due to adverse events (8 percent and 9 percent, respectively). Specific adverse events included hyperkalemia in 3.3 percent of the ACEI

plus diuretic group and 5.5 percent of the ACEI group and cough in 3.7 percent of the ACEI plus diuretic group and 2.1 percent of the ACEI group.

Summary

In patients with CKD, hypertension, and type 2 diabetes, a combination of ACEI and diuretics was associated with a significant reduction in risk of serious cardiovascular events compared with treatment with ACEI monotherapy. The risk of adverse events was similar in the two groups. Results were limited because there were no data on mortality or specific cardiovascular or renal outcomes. Further, analysis was not based on intention-to-treat principles and the study withdrawals or dropouts were not adequately described. Mean followup for this study was 10.7 months.

ACE Inhibitor Plus Diuretic Versus Placebo Trial

Overview

In patients with CKD, we found a low strength of evidence that combination therapy with an ACEI and a diuretic did not significantly reduce mortality compared with placebo. We found insufficient evidence that there was no difference between treatments in risk of ESRD.[110] We found no significant difference between treatment groups for risk of cardiovascular mortality; risk of major cardiovascular events, major coronary events, or major cerebrovascular events; or risk of a composite renal outcome. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events for several outcomes.

Description of Study

A subgroup analysis of a larger trial of patients with type 2 diabetes met all eligibility criteria. The analysis included 2,482 patients with stage 1 or 2 CKD and 2,044 patients with stage 3 CKD who had been randomized to receive either an ACEI and diuretic or placebo[109] Detailed baseline characteristics are presented in Appendix Table C44).

The ACEI plus diuretic group received perindopril and indapamide. The mean age of subjects in the subgroup analysis was 67 years and 53 percent of study participants were male. Race/ethnicity data were not reported. Mean followup duration was 4.3 years.

Renal Function

For inclusion in this post hoc analysis, study participants were required to have CKD. As noted above, 2,482 participants had CKD stages 1–2, and 2,044 had CKD stage 3 or worse. Mean urine albumin-creatinine ratio was 48.1 µg/mg, and mean eGFR was 70.7 ml/min/1.73m^2.

Baseline Comorbidities

Study participants were required to be age 55 or older, diagnosed with type 2 diabetes at age 30 or older. Mean baseline HbA_{1c} was 7.7 percent. A history of macrovascular disease was reported in 34.7 percent of participants, and 12.8 percent reported a history of MI, and 10.8 percent reported a history of stroke. Mean baseline blood pressure was 148/81 mm Hg.

Study Quality (Appendix Table C140)

Study quality was rated as good. Treatment allocation concealment was adequate, the study was double-blind, the study was analyzed as intention to treat, and withdrawals were adequately reported.

Results

Mortality (Appendix Table C45 and Appendix Figure C11)

All-Cause Mortality

There was no significant difference in risk of all-cause mortality between treatment groups for the subgroups of patients with CKD stages 1–2 (RR 0.91, 95% CI, 0.72 to 1.16), or CKD stages 3 or worse (RR 0.88, 95% CI, 0.70 to 1.11)). In patients without CKD, there also was no significant difference in risk for all-cause mortality between treatment groups (RR 0.91, 95% CI, 0.73 to 1.13). In pooled analyses including all CKD and non-CKD study participants, risk of all-cause mortality was significantly reduced in the group randomized to ACEI plus diuretic as compared with the placebo group (RR 0.86, 95% CI, 0.75 to 0.98). The p-value for trend was 0.74 between the three subgroups.

Cardiovascular Mortality

There was no significant difference in risk of cardiovascular mortality between treatment groups for the subgroups of patients with CKD stages 1–2 (RR 0.77, 95% CI, 0.55 to 1.06), or CKD stages 3 or worse (RR 0.81, 95% CI, 0.59 to 1.11). In patients without CKD, there also was no significant difference in risk for cardiovascular mortality between treatment groups (RR 1.00, 95% CI, 0.72 to 1.39). In pooled analyses including all CKD and non-CKD study participants, risk of cardiovascular mortality was significantly reduced in the group randomized to ACEI plus diuretic as compared with the placebo group (RR 0.82, 95% CI, 0.68 to 0.98). The p-value for trend was 0.36 between the three subgroups.

Vascular Outcomes (Appendix Tables C45-C47 and Appendix Figure C11)

Myocardial Infarction

No study data were reported for myocardial infarctions.

Stroke

No study data were reported for stroke.

Other Vascular Outcomes

Among study participants with CKD, there was no significant difference between treatment groups in risk of major cardiovascular events, major coronary events, or major cerebrovascular events. For major cardiovascular events, there was no reduced risk either for participants with CKD stages 1-2 (RR 0.89, 95% CI, 0.70 to 1.13), or for patients with CKD stages 3 or worse (RR 0.87, 95% CI, 0.68 to 1.10). For major coronary events, there was no reduced risk either for participants with CKD stages 1-2 (RR 0.89, 95% CI, 0.64 to 1.23), or for patients with CKD stages 3 or worse (RR 0.85, 95% CI, 0.62 to 1.1). For major cerebrovascular events, there was no reduced risk either for participants with CKD stages 1-2 (RR 0.88, 95% CI, 0.61 to 1.26), or for patients with CKD stages 3 or worse (RR 0.84, 95% CI, 0.58 to 1.22). For all these outcomes,

there also was no significant difference in risk between treatments for patients without CKD, or for patients considered overall. For all outcomes, the p-value for trend between subgroups was not statistically significant. Results were similar in analyses in which patients were stratified by eGFR or by urine albumin-creatinine ratio.

Renal Outcomes (Appendix Tables C48 and C49 and Appendix Figure C11)

End-Stage Renal Disease

No study data were reported for end-stage renal disease.

Other Renal Outcomes

Among study participants with CKD, there was no significant difference between treatment groups in risk of a composite renal outcome defined as occurrence of either incident macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for renal replacement therapy, or death due to renal illness. Stratified by baseline CKD, there was a statistically significant reduction in risk in participants with CKD stages 1–2 (RR 0.69, 95% CI, 0.51 to 0.93), but not for patients with CKD stages 3 or worse (RR 0.93, 95% CI, 0.66 to 1.31), However, the p-value for trend between subgroups was 0.79. In results stratified by eGFR or by urine albumin-creatinine ratio, there was no significant difference between treatment groups for risk of the composite renal outcome within any stratum.

Study Withdrawals and Adverse Events (Appendix Table C50)

Adverse events leading to discontinuation of the treatment (including serious adverse events, dough, and hypotension/dizziness), regardless of whether they were considered to be drug related, are presented in Table C50. The incidence was higher in the active treatment group but no differences were observed for the subgroups based on CKD stage.

Summary

In a subgroup of patients with CKD, type 2 diabetes, and at high risk for vascular events, a combination of ACEI and diuretic was not associated with a significant reduction in risk of mortality or clinical cardiovascular or renal events compared with treatment with placebo. Risk for the composite renal outcome were significantly reduced with ACEI plus diuretic in patients with CKD stages 1-2, but given that this finding was not observed in analyses stratified by eGFR or albuminuria, and tests for interaction by CKD strata were not significant, the probability of this being a chance finding is substantial.

ARB (Higher Dose) Versus ARB (Lower Dose) Trial

Overview

We found insufficient strength of evidence regarding whether there is any difference between higher and lower dose ARB in risk of mortality or ESRD. We found that higher dose ARB significantly reduces risk of conversion from microalbuminuria to macroalbuminuria. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Studies

Three trials met eligibility criteria and randomized participants with CKD to at least two different fixed doses of ARB treatment. One trial randomized 269 participants to three different doses of candesartan (16 mg/day, 64 mg/day, and 128 mg/day.[111] A second trial randomized participants to telmisartan 40 mg/day versus 80 mg/day).[95] A third trial randomized participants to irbesartan 150 mg/day versus 300 mg/day.[96] Detailed baseline characteristics are presented in Appendix Tables C51 and C52.

Mean age of study participants was 58.5 years. Men constituted 73 percent of all study participants (2 trials reporting). In two studies reporting race/ethnicity, 91 percent of participants were white. The studies were conducted in Canada, Japan, and multinational. Median followup durations ranged from 7 months to 2 years.

Renal Function

Two trials required participants to have microalbuminuria, defined in one study by urinary albumin:creatinine ratio of 100-300 mg/g and in the other study by repeated urinary albumin excretion rate of 20-200 micrograms/minute. Both of these studies excluded participants with serum creatinine greater than 1.5 mg/dl in men and either greater than 1.1 or 1.3 mg/dl in women. The third study required repeated urinary protein excretion of at least 1 g/day and excluded participants with serum creatinine >3.4 mg/dl. One trial reported a mean serum creatinine of 1.44 mg/dl, eGFR of 52.0 ml/min/1.73m^2 and proteinuria of 2.83 g/day. A second trial reported a mean serum creatinine of 1.05 mg/dl, creatinine clearance of 109 ml/min/1.73m^2 and albuminuria of 55.9 micrograms/day. The third trial provided no data on baseline renal function. Mean serum creatinine in two trials reporting was 1.21 mg/dl.

Baseline Comorbidities

All participants in two trials were required to have hypertension, and all participants in two trials were required to have diabetes. One trial each provided no information on prevalence of diabetes or hypertension. Mean baseline blood pressure was 142/82 mm Hg. In one trial reporting, prevalence of cardiovascular disease was rare.

Study Quality (Appendix Table C140)

Two trials were rated as fair quality and one was rated as good quality. All trials were double blinded but only one reported using adequate concealment methods for treatment allocation. Results were analyzed according to the intention-to-treat principle in two studies and withdrawal and dropouts were adequately described in all trials. Withdrawals ranged from 12 to 14 percent in two trials reporting.[96,111]

Results

Mortality (Appendix Tables C53)

One trial reported deaths in 1.5 percent of participants randomized to high dose irbesartan versus in none of those assigned to low dose irbesartan. A second trial reported that there were no deaths in any of the three candesartan dose groups.

Vascular Outcomes (Appendix Tables C53–C55)

Myocardial Infarction

There were no reports of myocardial infarction.

Stroke

There were no reports of stroke.

Other Vascular Outcomes

No other vascular outcomes were reported.

Renal Outcomes (Appendix Tables C56 and C57)

End-Stage Renal Disease

There were no reports of end-stage renal disease.

Other Renal Outcomes

Risk of conversion from microalbuminuria to macroalbuminuria with high dose telmisartan was not significantly different than for low dose telmisartan (RR 0.74, 95% CI, 0.48 to 1.14) and also was not significantly different for high dose irbesartan than for low dose irbesartan (RR 0.53, 95% CI, 0.25 to 1.11). In pooled results, reduction in risk was significantly lower with higher dose ARB than lower dose ARB (RR 0.68, 95% CI, 0.46 to 0.98). No other renal outcomes were reported.

Study Withdrawals and Adverse Events (Appendix Table C58)

Study withdrawals ranged from 2.4 to 14 percent between trials. In the candesartan trial, withdrawals were 20 percent in the 16 mg/day candesartan group, 6.7 percent in the 64 mg/day group, and 15.7 percent in the 128 mg/day group. In the irbesartan trial, 13.8 percent of participants withdrew from the low dose group compared with 10.3 percent from the high dose group. Withdrawals were not reported by treatment group for the telmisartan trial. Study withdrawals due to serious adverse effects were 12.2 percent in the 16 mg/day candesartan group, 5.5 percent in the 64 mg/day group, and 9.0 percent in the 128 mg/day group. Withdrawals due to serious adverse effects were reported in 9.2 percent of individuals assigned to low dose irbesartan compared with 4.1 percent of those assigned high dose irbesartan. The incidence of hyperkalemia was reported in only one trial and was between 3.3 and 4.4 percent for each of the three candesartan dose groups.

Summary

In these three small trials of CKD patients with albuminuria, high dose ARB treatment was associated with a significant reduction in risk of conversion from microalbuminuria to macroalbuminuria. Trials reported very few deaths and no other vascular or renal outcomes. Withdrawals and adverse events did not appear higher in the higher dose ARB groups compared with the low dose group in either trial reporting these data.

ARB Versus Different ARB Trials (n=2)

Overview

In patients with CKD, we found a low level of evidence that telmisartan significantly reduces risk of all-cause mortality compared with losartan and a low level of evidence that there is no difference in risk of all-cause mortality between telmisartan and valsartan. In addition, we found a low level of evidence that there is no difference in risk of ESRD between telmisartan and losartan and insufficient (no) evidence regarding whether risk for ESRD differs between telmisartan and valsartan. Our confidence in these estimates is limited by the small number of trials reporting different outcomes and the small number of clinical events.

Description of Studies

Two trials met all eligibility criteria and randomized 1,745 participants with CKD to treatment comparing two different ARBs.[112,113] Detailed baseline characteristics are presented in Appendix Tables C51 and C52.

One trial randomized 860 participants to telmisartan versus losartan.[112] The second trial randomized 885 participants to telmisartan versus valsartan.[113] The mean age of study participants was 61 years (range 60 to 61) and men constituted 63 percent (range 62 to 64) of all participants studied. Both trials reported race/ethnicity, and 63 percent of participants were white, 30 percent were Asian, and 7 percent were black. Both were multinational studies and followup duration ranged from 10.7 to 12 months.

Renal Function

Both trials required that participants have overt proteinuria, and allowed subjects with either normal or elevated serum creatinine levels, setting an upper abnormal limit. In one trial, participants had to have proteinuria of 900 mg/24 hours or greater and a serum creatinine of 3.0 mg/dl or less.[113] This study reported a mean baseline proteinuria of 2.78 g/day. In the second trial, patients had to have a urine protein-creatinine ratio at least 700 mg/g and a serum creatinine <3.0 mg/dl in women and <3.2 mg/dl in men.[112] At baseline, this study reported a mean urine protein-creatinine ratio of 1,991 mg/g, mean urine albumin-creatinine ratio of 1,394 mg/g, and a mean serum creatinine of 1.55 mg/dl. For both trials considered together, the mean baseline GFR was 53.2 ml/min/1.73m^2 (range 49.6 to 56.6).

Baseline Comorbidities

Both trials were restricted to patients with type 2 diabetes and hypertension. At baseline, mean HbA_{1c} was 7.85 percent and mean blood pressure was 146/81 mm Hg. One trial excluded patients with a history of "clinically significant" heart disease or stroke, which was presumed to exclude patients with a history of coronary artery disease, MI, or congestive heart failure.[112] The second study excluded patients with any history of congestive heart failure and those with a "recent acute cardiovascular event."[113] It did not report data on prevalence of coronary artery disease, MI, or stroke.

Study Quality (Appendix Table C140)

Both trials were rated as fair quality. Allocation concealment was unclear in both studies. Both were double blinded. One study analyzed results according to the intention-to-treat principal and adequately described the 19.1 percent of subjects who withdrew from the study.[113]

The second study did not include an intention-to-treat analysis and did not adequately describe the 18.4 percent of participants who withdrew.[112]

Results

Mortality (Table 11, Appendix Table C53, and Figure C12)

All-Cause Mortality

Among these patients with CKD, those randomized to telmisartan had a significant 84 percent reduction in risk of all-cause mortality compared with those randomized to losartan (0.5 versus 2.9 percent; RR 0.16, 95% CI, 0.04 to 0.71).[112] However, the risk of all-cause mortality was higher, although not significantly so, for patients assigned telmisartan versus valsartan (3.5 versus 1.9 percent; RR 1.88, 95% CI, 0.81 to 4.39).[113] Results from these trials were not pooled as the results suggested large differences in the direction of the effect of losartan and valsartan compared with telmisartan. This was reflected in the I^2 of 75 percent.

Cardiovascular Mortality

One study reported no significant difference between the telmisartan or valsartan treatment groups for cardiovascular mortality (RR 1.34, 95% CI, 0.47 to 3.82).[113]

Vascular Outcomes (Table 11, Appendix Tables C53-C55 and Appendix Figure C12)

Myocardial Infarction

In one trial reporting, there was no significant difference between telmisartan and valsartan in risk of myocardial infarction (RR 0.36, 95% CI, 0.12 to 1.14).[113]

Stroke

In the same trial, there was no significant difference between telmisartan and valsartan in the risk of stroke (RR 2.21, 95% CI, 0.77 to 6.29).[113]

Other Vascular Outcomes

Again in one trial reporting, there was no significant difference between telmisartan and valsartan in the risk of hospitalization for congestive heart failure (RR 1.17, 95% CI, 0.39 to 3.52).[113] Both trials defined and reported results for composite vascular endpoints. One reported a borderline statistically significant 40 percent reduction in risk of cardiovascular mortality or cardiovascular morbidity (not defined) in its CKD population assigned to telmisartan versus those assigned to losartan (RR 0.60, 95% CI, 0.36 to 1.00).[112] The second trial reported no difference between its participants with CKD allocated to telmisartan versus valsartan for the composite outcome of MI, stroke, hospitalization for CHF or unstable angina, or coronary or peripheral revascularization (RR 0.94, 95% CI, 0.59 to 1.51).[113]

Renal Outcomes (Table 11, Appendix Tables C56 and C57, and Appendix Figure C10)

End-Stage Renal Disease

In the one trial reporting this outcome, there was no apparent difference in risk for ESRD between CKD patients randomized to telmisartan versus valsartan (RR 0.88, 95% CI, 0.32 to 2.40).[113]

Other Renal Outcomes

One trial reported that there was no difference between subjects randomized to telmisartan versus valsartan for doubling of serum creatinine (RR 1.0, 95% CI, 0.20 to 4.94).[113] Both trials reported no significant difference between assigned ARBs in risk of a composite renal outcome defined as doubling of serum creatinine, ESRD, or death. One trial reported a nonsignificant 41 percent reduced risk with telmisartan compared with losartan (RR 0.59, 95% CI 0.31 to 1.12),[112] but the other trial reported a nonsignificant 23 percent increased risk with telmisartan compared with valsartan (RR 1.23, 95% CI, 0.42 to 1.75).[113] Neither study reported results for halving of GFR or progression from microalbuminuria to macroalbuminuria.

Study Withdrawals and Adverse Events (Appendix Table C58)

Overall study withdrawals were comparable in the two studies at 18.4 percent[112] and 19.1 percent.[113] There were fewer serious adverse events in the telmisartan group (15.5 percent) than in the losartan group (22.4 percent)[112] but more serious adverse events in the telmisartan group (26.2 percent) than in the valsartan group (23.5 percent).[113] Overall withdrawals for serious adverse events were low (3.2 percent or less in all groups). Similarly, the incidence of hyperkalemia was low in all groups (<2.9 percent).

Summary

In individuals with CKD, type 2 diabetes mellitus, and hypertension, compared with losartan, telmisartan was associated with a significant 84 percent reduction in all-cause mortality and a borderline significant 40 percent reduction in cardiovascular morbidity or cardiovascular mortality. In addition, telmisartan was associated with a nonsignificant 41 percent reduction in risk of the composite endpoint of doubling of serum creatinine, ESRD, or death, and with fewer serious adverse events. However, compared with valsartan, CKD patients randomized to telmisartan appeared to have a nonsignificantly higher risk of all-cause and cardiovascular mortality, stroke, and CHF, but a lower risk of MI. There was little difference in the composite vascular outcome or in any of the adverse event measures recorded. Results were limited by relatively small sample size and number of clinical events, with most outcomes reported only in one trial, and heterogeneity in comparison groups and outcomes that prevented statistical pooling. This resulted in there being low statistical power to determine if even large differences in outcomes between treatment groups were statistically significant. Results also were limited in that there were no studies that directly compared losartan and valsartan. Because no trial was longer than 1 year, it was not possible from these studies to determine the longer term effects of telmisartan versus losartan or valsartan.

Table 11. Pooled clinical and renal outcomes, ARB versus ARB trials

Outcome	Number of Trials Reporting	Quality of the Studies	Intervention Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
Telmisartan vs. Different ARB						
All-cause mortality	2	Fair	17/847 (2.0)	21/870 (2.4)	0.59 [0.05-6.88]	88%
Bakris, 2008[112]	1	Fair	2/419 (0.5)	13/441 (2.9)	0.16 [0.04-0.71]	NA
Galle, 2008[113]	1	Fair	15/428 (3.5)	8/429 (1.9)	1.88 [0.81-4.39]	NA
Cardiovascular mortality	1	Fair	8/428 (1.9)	6/429 (1.4)	1.34 [0.47-3.82]	NA
Myocardial infarction	1	Fair	4/428 (0.9)	11/429 (2.6)	0.36 [0.12-1.14]	NA
Stroke	1	Fair	11/428 (2.6)	5/429 (1.2)	2.21 [0.77-6.29]	NA
CHF hospitalization	1	Fair	7/428 (1.6)	6/429 (1.4)	1.17 [0.40-3.45]	NA
Composite vascular† Bakris, 2008[112]	1	Fair	21/419 (5.0)	37/441 (8.4)	0.60 [0.36-1.00]	NA
Composite vascular* Galle, 2008[113]	1	Fair	31/428 (7.2)	33/429 (7.7)	0.94 [0.59-1.51]	NA
End-stage renal disease	1	Fair	7/428 (1.6)	8/429 (1.9)	0.88 [0.32-2.40]	NA
Doubling of serum creatinine	1	Fair	3/428 (0.7)	3/429 (0.7)	1.00 [0.20-4.94]	NA
Composite renal outcome**						
Bakris, 2008[112]	1	Fair	14/419 (3.3)	25/441 (5.7)	0.59 [0.31-1.12]	NA
Galle, 2008[113]	1	Fair	22/428 (5.1)	18/429 (4.1)	1.23 [0.67- 2.25]	NA

MI = myocardial infarction; NA = not applicable; RR = relative risk reduction

†Bakris = Cardiovascular morbidity (not defined) or mortality.

*Galle = Myocardial infarction, stroke, or hospitalization for heart failure or unstable angina, coronary or peripheral revascularization.

**Doubling of serum creatinine concentration, end-stage renal disease (need for long-term dialysis, renal transplantation, or serum creatinine ≥ 6 mg/dl), or death.

ACE Inhibitor Plus Aldosterone Antagonist Versus ACE Inhibitor Plus Placebo Trial

Overview

In patients with CKD, we found insufficient evidence regarding whether there is a difference between ACEI plus aldosterone antagonist versus ACEI alone for risk of all-cause mortality or ESRD. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Study

We identified one trial that met all eligibility criteria and randomized 54 patients with CKD being treated with ACEI to either additional aldosterone antagonist or placebo.[103] Detailed baseline characteristics for this comparison are presented in Appendix Table C59. Data regarding a third treatment arm, the addition of ARB to ACEI are discussed separately.

Mean age of randomized participants was 51 years, and men constituted 46 percent of the subjects. Fifty-four percent of patients were Hispanic, 32 percent were black, 11 percent were non-Hispanic white, and 3 percent were Native American. Mean study followup duration was 11.1 months.

Renal Function

For inclusion, participants were required to have macroalbuminuria (UACR at least 300 mg/g) despite run-in treatment. Women with serum creatinine above 3.0 mg/dL and men with creatinine above 4.0 mg/dL were excluded from the study. Among randomized participants, mean baseline UACR was 1,006 mg/g, mean serum creatinine was 1.6 mg/dL, and mean creatinine clearance was 62 ml/min.

Baseline Comorbidities

All study participants were required to be hypertensive prior to screening but were treated with diet and ACEI during a pre-randomization 3 month run-in period to a target systolic blood pressure of less than 130 mm Hg. Mean blood pressure at randomization was 132/74 mm Hg study participants also were required to have diabetes, and mean HbA_{1c} was 7.8 percent. Patients with a history of heart failure, and those with a stroke or MI within 12 months were excluded from the trial. A history of either MI, CABG, or PTCA was reported by 9.3 percent.

Study Quality (Appendix Table C140)

Study quality was rated fair. The trial was double blinded, but allocation concealment was unclear. While the overall study analysis was not by intention-to-treat, this pertained to exclusion from analyses of a single participant randomized into the ACEI plus ARB treatment group that is not the focus of this section of the report. Withdrawals were 30 percent.

Results

Mortality (Appendix Table C60)

There were no deaths during the followup period.

Vascular Outcomes (Appendix Tables C60 and C61 and Appendix Figure C13)

Myocardial Infarction

Among participants in the ACEI plus aldosterone antagonist group, there was one subject with MI, while in the ACEI plus placebo group, no subjects had an MI.

Stroke

Among participants in the ACEI plus aldosterone antagonist group, there were two subjects with stroke. In the ACEI plus placebo group, one subject had a stroke.

Other Vascular Outcomes

Among participants in the ACEI plus aldosterone antagonist group, two subjects were hospitalized for heart failure. In the ACEI plus placebo group, no subjects were hospitalized for heart failure. The study did not report results for any composite vascular outcomes.

Renal Outcomes

End-Stage Renal Disease

The study did not report results for ESRD.

Other Renal Outcomes

The study did not report results for doubling baseline creatinine, halving GFR, or for any composite renal outcome.

Study Withdrawals and Adverse Events (Appendix Table C62)

In the ACEI plus aldosterone antagonist group, withdrawals and withdrawals due to adverse effects occurred in 37 percent and 26 percent of participants respectively, as compared with 22 percent and 7 percent, respectively, in the ACEI plus placebo group. Adverse effects attributing to withdrawal were hyperkalemia (n=2), stroke (n=2), symptomatic hypotension (n=1), gynecomastia (n=1), and increased serum creatinine (n=1) in the ACEI plus aldosterone antagonist group, and stroke (n=1) and increased serum creatinine (n=1) in the ACEI plus placebo group.

Summary

In this small, short duration study of CKD patients with macroalbuminuria, hypertension, and diabetes, but with no history of heart failure and with a low prevalence of other cardiovascular disease, there were no deaths and very few cardiovascular outcomes. Differences in individual cardiovascular outcomes were not statistically significant. Participants in the ACEI plus aldosterone group appeared to be at higher risk for adverse events leading to discontinuation of treatment and study withdrawal. Results were limited by the short study duration, and small number of individual clinical vascular events. Also, no clinical renal outcomes data were reported.

ACE Inhibitor/ARB Plus Aldosterone Antagonist Versus ACE Inhibitor/ARB Plus Placebo Trial

Overview

In patients with CKD, there was insufficient evidence regarding whether, in comparison to treatment with ACEI or ARB plus placebo, treatment with ACEI or ARB plus aldosterone antagonist reduces mortality or ESRD. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Study

One trial met all eligibility criteria and randomized 59 participants with CKD and taking ACEI or ARB at baseline to the addition of an aldosterone antagonist versus addition of placebo.[114] Detailed baseline characteristics are presented in Appendix Table C63.

Participants using an ACEI or ARB in recommended dosages for at least 1 year were randomized to addition of the aldosterone antagonist, spironolactone, 50 mg daily versus placebo. Mean age in study participants was 52 years and 66 percent of subjects were men. Study followup duration was 1 year.

Renal Function

Eligible participants were required to have albuminuria, defined as either 24 hour urinary albumin excretion greater than 300 mg or UACR greater than 20 mg/mmol. Mean serum creatinine was 98.2 μmol/l, mean UACR was 81 mg/mmol, and mean protein-to-creatinine ratio was 128.5 mg/mmol. The mean estimated GFR was 70.5 ml/min/1.73m^2.

Baseline Comorbidities

All participants had type 2 diabetes. Patients with MI or stroke within the past 3 months or with unstable angina pectoris were excluded. Mean blood pressure was 146/81 mm Hg and mean HbA_{1c} was 8.1 percent.

Study Quality (Appendix Table C140)

Study quality was rated fair. Treatment allocation concealment was adequate. The study was double blinded. Analysis was not performed according to the intention to treat principle. Withdrawals were 11.9 percent and were adequately described.

Results

Mortality (Appendix Table C64 and Appendix Figure C14)

There were two deaths in the placebo group due to complications following an MI (RR 0.21, 95% CI, 0.01 to 4.13).

Vascular Outcomes (Appendix Table C64)

Myocardial Infarction

As noted above, there were two fatal MIs in the placebo group.

Stroke
There were no reports of stroke.

Other Vascular Outcomes
No other vascular outcomes were reported.

Renal Outcomes

End-Stage Renal Disease
There were no reports of end-stage renal disease.

Other Renal Outcomes
No other renal outcomes were reported.

Study Withdrawals and Adverse Events (Appendix Table C65)
Of 59 patients randomized, six (17.2 percent) in the aldosterone antagonist group and one (3.3 percent) in the placebo group discontinued treatment as a result of hyperkalemia developed during the first 2 to 12 weeks of treatment. During the rest of the study, two additional patients in the aldosterone antagonist group and one in the placebo group discontinued treatment.

Summary
In one trial in patients with CKD and diabetes, already on ACEI or ARB, there was no significant difference in risk of all-cause or cardiovascular mortality between those randomized to addition of aldosterone antagonist versus placebo. No data were reported for other vascular or clinical renal outcomes. Results were limited in that they were based on only one small study with low statistical power for clinical events, which do not appear to have been a priori study outcomes.

Beta Blocker (BB) Versus Placebo Trials (n=2)

Overview
We found low strength of evidence that in patients with heart failure and CKD who are on optimal medical therapy for their heart failure, treatment with BB significantly reduced risk of all-cause mortality. We found insufficient evidence in this population regarding whether there is a difference between BB and placebo regarding risk of ESRD as neither trial reported ESRD outcomes. Participants with CKD assigned to BB had a significantly lower risk of CHF complications, MI, or cardiac death. Our confidence in these estimates is limited by the small number of trials reporting different outcomes and the small number of clinical events.

Description of Study
We identified two trials that met all eligibility criteria and randomized participants with CKD to BB versus placebo.[115,116] One study was a post hoc subgroup analysis of 1,469 subjects with eGFR ≤60 ml/min/1.73m^2 from the larger MERIT-HF heart failure trial (n=3,991)[115] The second study was a post hoc subgroup analysis of 704 patients with eGFR <55.5 ml/min/1.73m^2 from the larger SENIORS heart failure trial (n=2,135). Detailed baseline characteristics are presented in Appendix Table C66.

All participants in MERIT-HF were required to have been on optimum heart failure therapy consisting of any combination or diuretics and an ACEI, with hydralazine, long acting nitrate, or ARB if an ACEI was not tolerated. Patients then were randomized to the BB, metoprolol XL/CR versus placebo. At baseline, 88 percent of the patients were taking an ACEI and 94 percent were taking diuretics. The mean age of study participants was 68 years and 68 percent of subjects were male. No data were reported on race/ethnicity in this multinational study. Study followup duration was 1 year.

Participants in the SENIORS trial had a documented clinical history of heart failure and were receiving optimal standard therapy. Patients were randomized to receive either BB (nebivolol) or placebo. Baseline use of other medications was not reported according to eGFR levels but it was noted that among participants with poorer renal function, more were taking diuretics and ARB and fewer were taking ACEI. The mean age of the CKD subgroup was 77 years and 59 percent were male. The study was conducted in 11 European countries, but no race/ethnicity data were reported. Mean followup was 21 months.

Renal Function

For inclusion in the post hoc analysis of the MERIT-HF trial, participants were required to have eGFR ≤60 ml/min/1.73m^2. There were 976 participants with eGFR 45 to 60 ml/min/1.73m^2, and 493 with eGFR <45 ml/min/1.73m^2. In these two strata combined, mean GFR was 48 ml/min/1.73m^2 and mean serum creatinine was 1.5 mg/dL. For the post hoc analysis of the SENIORS trial, tertiles of eGFR were created. In the tertile with eGFR <55.5 ml/min/1.73m^2, the mean eGFR was 43 ml/min/1.73m^2 and mean serum creatinine was 1.6 mg/dL.

Baseline Comorbidities

All participants in the MERIT-HF and SENIORS trials were required to have symptomatic or documented heart failure. Among participants in the MERIT-HF post hoc analysis, diabetes was reported for 29 percent, a history of hypertension for 49 percent, and a history of myocardial infarction for 55 percent. Mean baseline blood pressure was 130/77 mm Hg. Among participants in the SENIORS post hoc analysis, diabetes was reported for 29 percent, and 46 percent had a history of myocardial infarction. Mean baseline blood pressure was 134/78 mm Hg.

Study Quality (Appendix Table C140)

Study quality was rated as good for one trial and fair for one trial. Concealment of treatment allocation in both double-blind trials was adequate. Analyses were performed according to the intention-to-treat principle in the MERIT-HF trial; however, 23 randomized patients were excluded from the SENIORS trial post hoc analysis. No data on withdrawals were reported for the CKD subgroups.

Results

Mortality (Appendix Table C67 and Appendix Figure C15)

All-Cause Mortality

In the patients with CKD and heart failure, there was a significant reduction in the risk of all-cause mortality in those treated with BB versus placebo (12.4 versus 18.1 percent, RR 0.69, 95%

CI, 0.53 to 0.91). In both studies, results were stratified by baseline eGFR. The MERIT-HF study reported an adjusted HR 0.41, 95% CI, 0.25 to 0.68 for patients with eGFR <45 ml/min/1.73m^2, HR 0.68, 95% CI, 0.45 to 1.02 for patients with eGFR 45 to 60 ml/min/1.73m^2, and HR 0.71, 95% CI, 0.54 to 0.95 for those with eGFR greater than 60 ml/min/1.73m^2, with a test for interaction of p=.095. Similarly, in the SENIORS trial, the adjusted HR values were 0.76, 95% CI, 0.56 to 1.03 for patients with eGFR <55.5 ml/min/1.73m^2, 1.14, 95% CI, 0.78 to 1.66 for patients with eGFR of 55.6 to 72.8 ml/min/1.73m^2, and 0.82, 95% CI, 0.53 to 1.25 for patients with eGFR >72.8 ml/min/1.73m^2. The test for interaction was not significant (p=.521). No mortality data were reported for other patient subgroups.

Cardiovascular Mortality

In the SENIORS trial, in the subgroup with CHF and CKD there was no significant reduction in risk of cardiovascular mortality with BB versus placebo (HR 0.72, 95% CI, 0.50 to 1.04). There also was no significant reduction in risk in the non-CKD subgroups, with HR 1.11, 95% CI, 0.74 to 1.69 for patients with eGFR of 55.6 to 72.8 ml/min/1.73m^2, and HR 0.81, 95% CI, 0.49 to 1.35 for patients with eGFR >72.8 ml/min/1.73m^2. The test for interaction was not significant (p=.494).

Vascular Outcomes (Appendix Tables C67–C69 and Appendix Figure C15)

Myocardial Infarction

Neither study reported results for myocardial infarction as an isolated outcome.

Stroke

Neither study reported results for stroke.

Other Vascular Outcomes

In MERIT-HF study results in which all participants with eGFR ≤60 ml/min/1.73m^2 were pooled, assignment to BB treatment was associated with significant reductions in risks for hospitalization for CHF (12.2 versus 20.0 percent; RR 0.61, 95% CI, 0.48 to 0.78) and CHF death (2.0 versus 4.9 percent; RR 0.42, 95% CI, 0.23 to 0.75). Similarly, compared with placebo, CKD study participants randomized to BB had significant reductions in risk of the composite vascular outcomes of all cause mortality and hospitalization for CHF (18.5 versus 29.2 percent; RR 0.63, 95% CI, 0.53 to 0.77) and cardiac death or nonfatal MI (8.7 versus 14.6 percent; RR 0.60, 95% CI 0.45 to 0.80). In results stratified by baseline eGFR (<45, 45-60, and >60 ml/min/1.73m^2), the study consistently reported the numerically lowest HR for each of these outcomes in the patients with eGFR <45 ml/min/1.73m^2. The p-value for interaction between baseline eGFR stratum and treatment assignment was 0.038 for CHF hospitalization, 0.16 for CHF death, 0.011 for the composite outcome of all cause mortality and CHF hospitalization, and >0.2 for the composite outcome of cardiac death or nonfatal MI. In the SENIORS trial, treatment with BB was associated with a nonsignificant reduction in risk of a composite vascular outcome of all-cause mortality or cardiovascular hospitalization in the subgroup with eGFR <55.5 ml/min/1.73m^2 (37.1 versus 43.9 percent; RR 0.86, 95% CI, 0.72 to 1.03). The p value for the interaction across tertiles of eGFR was p=.442. No vascular outcomes data were reported for other patient subgroups.

Renal Outcomes

End-Stage Renal Disease

Neither study reported results for ESRD.

Other Renal Outcomes

Neither study reported results for other individual or composite clinical renal outcomes.

Study Withdrawals and Adverse Events (Appendix Table C70)

Neither study reported data on withdrawals within the CKD subgroups. In the MERIT-HF study, rate of study treatment discontinuation due to adverse events appeared higher in participants with worse eGFR, but not worse in those assigned to BB versus placebo. In patients with eGFR 45 to 60 ml/min/1.73m^2, the rate of discontinuations due to adverse events was 13.6 and 13.5 per 100 person years for those assigned BB versus placebo, respectively. In patients with eGFR <45 ml/min/1.73m^2, the rate was 16.9 and 20.8 per 100 person years for those assigned BB versus placebo, respectively. The most commonly reported adverse event resulting in discontinuation was heart failure. Fatigue, bradycardia, dizziness, and hypotension were also reported. In the SENIORS study, adverse event data were reported for patients with baseline eGFR <60 ml/min/1.73m^2 or ≥60 ml/min/1.73m^2. In the BB group, there was a higher incidence of bradycardia and any adverse event in patients with lower eGFR. In the placebo group, no significant differences were reported. In the total study group, patients treated with BB had significantly higher rates of hypotension and any adverse event.

Subgroup Results

No trials reported outcomes stratified by any participant characteristic. However, both trials were restricted to patients with CHF and impaired eGFR, so all results reported above apply to these subgroups. No other subgroup results are available since no trials were restricted to patients with albuminuria, or with a history of diabetes, hypertension, or cardiovascular disease, and no trials excluded patients with these conditions.

Summary

In two post hoc analyses, patients with well controlled heart failure and CKD who were randomized to BB versus placebo had a significantly lower risk of all-cause mortality. One trial also reported significantly lower risks of hospitalizations for CHF, CHF deaths, and of the composite vascular outcomes of all cause mortality or CHF hospitalization and of cardiac death or nonfatal MI. Analyses stratified by eGFR subgroup suggested that the relative benefit of BB versus placebo may be greatest in patients with eGFR <45 ml/min/1.73m^2 (MERIT-HF) or eGFR < 55.5 ml/min/1.73m^2 (SENIORS), though the statistical tests for interaction by eGFR strata did not approach statistical significance. Results were limited in that both studies were post hoc subgroup analyses, there were no measures of albuminuria available, and no clinical renal outcomes and little adverse events data were reported. Because trial followup was a mean of 21 months or less, longer term effects of BB monotherapy versus placebo in this population cannot be determined from these data.

CCB Versus Placebo Trials (n=2)

Overview

In patients with CKD, we found low strength of evidence that there is no difference in risk of all-cause mortalityor ESRD between participants randomized to CCB versus placebo. In participants randomized to CCB versus placebo, there was a statistically significant reduction in risk of MI and conversion from microalbuminuria to macroalbuminuria, but there was no significant difference between treatment groups for the outcomes of cardiovascular mortality, stroke, doubling of baseline creatinine, or any composite vascular or renal outcomes. Our confidence in these estimates is limited by the small number of trials reporting different outcomes and the small number of clinical events.

Description of Studies

Two trials met all eligibility criteria and randomized 1,226 participants (range 90 to 1,136) with CKD to CCB versus placebo.[55,97,117] Detailed baseline characteristics are presented in Appendix Tables C71 and C72.

The larger trial, IDNT, randomized 1,136 hypertensive, type 2 diabetic individuals to amlodipine versus placebo.[97,117] This trial also included an ARB treatment arm discussed elsewhere in this report. Mean age of study participants was 59 years, 67 percent of all subjects were male and 71 percent of participants were white. The study was multinational and followup duration was 2.6 years.

A second trial randomized 90 normotensive, type 1 diabetic subjects to nifedipine versus placebo,[55] and also included an ACEI treatment arm discussed elsewhere in this report. After randomization, 22 participants were excluded for having UAER outside the 20 to 200 µg/min range and an additional seven for adverse clinical events. Baseline data were only reported on these 61 participants. Within these participants, mean age was 37 years and 70 percent of all subjects were male. No information was reported on race/ethnicity, though the study was conducted in Italy. Followup duration was 3 years.

Renal Function

For inclusion in the IDNT trial, participants were required to have both elevated serum creatinine (1.0 to 3.0 mg/dL for women and 1.2 to 3.0 mg/dL for men) and proteinuria >900 mg/day. At baseline, mean serum creatinine was 1.7 mg/dL, mean proteinuria was 2.9 g/day, and mean albuminuria was 1.9 g/day.

For inclusion in the smaller trial, participants were required to have microalbuminuria, with a UAER of 20 to 200 µg/min, a GFR of 80 ml/min/1.73m^2 or greater, and a serum creatinine <10 percent higher than the upper limit of normal. After randomization, 22 participants were excluded for having UAER outside the 20 to 200 µg/min range. Within participants not withdrawn after baseline, baseline median UAER was 80.2 µg/min, mean serum creatinine was 0.97 mg/dL, mean creatinine clearance was 107.8 mL/min, and mean GFR was 111.8 ml/min/1.73m^2.

Baseline Comorbidities

In the IDNT trial, all participants were required to have hypertension, Mean baseline blood pressure was 159/87 mm Hg. All participants also were required to have diabetes, and mean

baseline HbA_{1c} was 8.2 percent. Thirty percent of study subjects had a history of cardiovascular disease.

In the smaller trial, participants with hypertension were excluded and no information on baseline blood pressure was reported. All participants were required to have type 1 diabetes. Baseline HbA_{1c} was not reported, though those with HbA_{1c} 11 percent or greater were excluded. The study did not report any information on the prevalence of cardiovascular disease, though patients with an MI in the prior 3 months were excluded.

Study Quality (Appendix Table C140)

Of the two studies, one was rated good quality and one was rated fair quality. The IDNT reported adequate concealment of treatment allocation, while concealment was unclear for the other study. Both trials were double blinded. The IDNT trial performed analyses according to the intention-to-treat principle, but the other study excluded 24 percent of participants after randomization from analyses. Withdrawals ranged from 0.5 percent in the IDNT trial to 32 percent in the other study.

Results

Mortality (Table 12, Appendix Table C73 and Appendix Figure C16)

All-Cause Mortality

In the IDNT trial,[97,117] there was a nonsignificant reduction in risk of all-cause mortality (14.6 versus 16.3 percent; RR 0.90, 95% CI, 0.68 to 1.18). In the smaller study, only one death occurred, in an individual assigned to the CCB group.[55] In pooled results, risk with CCB treatment was nonsignificantly decreased for all-cause mortality (RR 0.90, 95% CI, 0.69 to 1.19).

Cardiovascular Mortality

In the IDNT trial,[97,117] there was a nonsignificant reduction in risk of cardiovascular mortality (6.5 versus 8.1 percent; RR 0.81, 95% CI, 0.53 to 1.22). In the smaller study, only one cardiovascular death occurred, in an individual assigned to the CCB group.[55] In pooled results, risk with CCB treatment was nonsignificantly decreased for cardiovascular mortality (RR 0.83, 95% CI, 0.55 to 1.25).

Vascular Outcomes (Table 12, Appendix Tables C73-C75 and Appendix Figure C16)

Myocardial Infarction

In the IDNT trial, there was a significant 41 percent reduction in risk of MI in CCB subjects compared with those assigned placebo (4.8 versus 8.1 percent; RR 0.59, 95% CI, 0.37 to 0.93). In the smaller study, there was only one MI, which occurred in an individual assigned to the placebo group.

Stroke

In the IDNT trial, participants assigned CCB had a nonsignificant reduction in risk of stroke compared with placebo (2.6 versus 4.6 percent; RR 0.58, 95% CI, 0.31 to 1.08).

Other Vascular Outcomes

In the IDNT trial, in the CCB group compared with the placebo group, there was a nonsignificant increase in risk of CHF (16.4 versus 12.7 percent; RR 1.30, 95% CI, 0.97 to 1.72). There was no significant difference between CCB and placebo for either of two composite vascular outcomes. For an outcome that included MI, CHF, neurologic deficit attributed to stroke, or unplanned revascularization, there was a nonsignificant 13 percent reduction in risk in the CCB group (28.4 versus. 32.5 percent; RR 0.87, 95% CI, 0.73 to 1.04). For an outcome that included death from cardiovascular causes, nonfatal MI, hospitalization for CHF, neurologic deficit, or lower limb amputation, there was a nonsignificant 11 percent reduction in risk in the CCB group (22.6 versus 25.3 percent; RR 0.89, 95% CI, 0.72 to 1.10).

Renal Outcomes (Table 12, Appendix Tables C76 and C77, and Appendix Figure C16)

End-Stage Renal Disease

In results reported only in the IDNT trial, in patients with CKD there was no significant difference between CCB and placebo groups in risk of ESRD (RR 1.03, 95% CI, 0.81 to 1.32).

Other Renal Outcomes

In results reported only in the IDNT trial, in patients with CKD there was no significant difference between CCB and placebo groups in risk of doubling of baseline creatinine (RR 1.07, 95% CI, 0.87 to 1.31), or in the composite renal outcome of doubling of serum creatinine, ESRD, or death (RR 1.05, 95% CI, 0.91 to 1.21).[97,117] The smaller of the studies reported a nonsignificant 63 percent reduction in risk of progression from microalbuminuria to macroalbuminuria in the CCB group versus the placebo group (7.7 versus 20.6 percent; RR 0.37, 95% CI, 0.08 to 1.65).[55]

Study Withdrawals and Adverse Events (Appendix Table C78)

There were few withdrawals in the larger study, just 0.4 percent of the CCB group and 0.7 percent of the placebo group.[97,117] It was reported that 61 percent of the study participants (including those in an ARB arm) had at least one serious adverse event, but the results were not presented by treatment group. Treatment was discontinued due to adverse events by 9.0 percent of the CCB group and 7.2 percent of the placebo group. Hyperkalemia was reported by 0.5 percent of the CCB group and 0.4 percent of the placebo group. There was one report of an early increase in serum creatinine suggestive of renal artery stenosis, but the group assignment of that patient was not given. In the smaller study, 36.6 percent of the CCB group and 30.6 percent of the placebo group withdrew.[55] Three of the withdrawals from the placebo group were a result of adverse events during the run-in phase; six were from adverse events during the randomized phase.

Summary

In two trials of patients with CKD and diabetes, treatment with CCB as compared with placebo was associated with nonsignificant reductions in risk of all-cause mortality, cardiovascular mortality, MI, stroke, and two different composite vascular outcomes. Risk of congestive heart failure was nonsignificantly higher for patients with CKD. The risk between treatment groups appeared similar for ESRD, doubling of creatinine, and a composite renal

outcome, including both of these events as well as death. The rate of withdrawals in the smaller study was high. In both trials, adverse event rates were difficult to interpret due to incomplete reporting. Results were limited in that nearly all were derived from only one trial. The multiple post-randomization exclusions from the smaller trial and its apparent nonsystematic reporting of outcomes lowered our confidence in its reported results. Because the followup of the IDNT trial was 2.6 years, it is not possible to determine from these results the longer term effects of CCB versus placebo in patients with CKD.

Table 12. Pooled clinical and renal outcomes, CCB versus placebo trials

Outcome	Number of Trials Reporting	Quality of the Studies	CCB Events/N (%)	Placebo Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	2	Fair	84/608 (13.8)	93/618 (15.0)	0.90 [0.69-1.19]	0%
Cardiovascular mortality	2	Fair	38/608 (6.3)	46/618 (7.4)	0.83 [0.55-1.25]	0%
Myocardial infarction	2	Fair	27/608 (4.4)	47/618 (7.6)	0.58 [0.37-0.92]	0%
Stroke	1	Good	15/567 (2.6)	26/569 (4.6)	0.58 [0.31-1.08]	NA
Congestive heart failure	1		93/567 (16.4)	72/569 (12.7)	1.30 [0.97-1.72]	NA
Composite vascular*	1	Good	161/567 (28.4)	185/569 (32.5)	0.87 [0.73-1.04]	NA
Lewis (A)[97]			128/567 (22.6)	144/569 (25.3)	0.89 [0.72-1.10]	
Lewis (B)[97]						
End-stage renal disease	1	Good	104/567 (18.3)	101/569 (17.8)	1.03 [0.81-1.32]	NA
Doubling of serum creatinine	1	Good	144/567 (25.4)	135/569 (23.7)	1.07 [0.87-1.31]	NA
Progression to macroalbuminuria	1	Fair	2/26 (7.7)	7/34 (20.6)	0.37 [0.08-0.65]	NA
Composite renal outcome**, Lewis[97]	1	Good	233/567 (41.1)	222/569 (39.0)	1.05 [0.91-1.21]	NA

CCB = calcium channel blocker; NA = not applicable; RR = relative risk reduction

*A = Myocardial infarction, heart failure, permanent neurologic deficit of at least 24-hour duration attributed to stroke, or unplanned (at time of randomization) coronary artery revascularization procedure (all before renal failure, death, or censorship).

*B= Death from cardiovascular causes, nonfatal myocardial infarction, heart failure resulting in hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle.

**Doubling of baseline serum creatinine concentration, onset of end-stage renal disease (initiation of dialysis, renal transplantation, or serum creatinine concentration ≥ 6.0 mg/dL), or death from any cause

Diuretic Versus Placebo Trial

Overview

In patients with CKD, we found low strength of evidence that there is no difference between treatments in risk of all-cause mortality. We found insufficient evidence regarding whether treatments differ for risk of ESRD. There was a statistically significant reduction in risk of stroke in the diuretic group versus placebo. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Study

One trial met all eligibility criteria and randomized CKD patients (n=393) to diuretic versus placebo.[118] Detailed baseline characteristics are presented in Appendix Table C79.

The single eligible study was a subgroup analysis in patients with CKD from within the larger SHEP study (n=4,736), a randomized trial comparing chlorthalidone versus placebo in older patients with hypertension. Mean subject age was 74 years, and men constituted 76 percent of participants. Seventy-six percent of study participants were white, 20 percent were black, and 3 percent were Asian. The study was performed in the United States and followup duration was 5 years.

Renal Function

Participants included in this post hoc analysis were the subgroup from the larger study with a baseline creatinine of 1.35 mg/dL or higher, the level considered to represent the upper threshold of normal in the SHEP trial. Within this subgroup, no measures of baseline renal function were reported.

Baseline Comorbidities

For inclusion in the SHEP trial, participants were required to have isolated systolic hypertension, with a systolic blood pressure of 160 to 219 mm Hg, and a diastolic blood pressure less than 90 mm Hg. Mean baseline blood pressure within patients with CKD was 172/77 mm Hg. A history of myocardial infarction was reported by 5 percent, a history of stroke by 4 percent, and a history of diabetes by 12 percent. Patients were excluded from participation in SHEP for any recent myocardial infarction or stroke or for insulin-treated diabetes.

Study Quality (Appendix Table C140)

Study quality was rated as good. Concealment of treatment allocation was adequate and the study was reported to be double blind, though it is not clear whether open-label potassium supplementation for potassium levels <3.5 mmol/L could have compromised blinding. Analysis was performed according to intention-to-treat principles. Study withdrawals were not reported for the CKD subgroup, but were adequately reported for the overall SHEP trial.

Results

Mortality (Appendix Table C80 and Appendix Figure C17)

The risk of all-cause mortality was nonsignificantly higher in CKD study participants randomized to the diuretic group compared with placebo (17.1 versus 14.7 percent; RR 1.17, 95% CI, 0.74 to 1.85).

Vascular Outcomes (Appendix Tables C80-C82 and Appendix Figure C17)

Myocardial Infarction

The study did not report results for myocardial infarction.

Stroke

In subjects assigned to diuretic, there was a significant 51 percent reduction in the risk of stroke (6.5 versus 12.4 percent; RR 0.49, 95% CI, 0.24 to 0.99).

Other Vascular Outcomes

Two composite vascular outcomes were reported (Appendix Table C81 and C82), with a significant 37 percent reduction in the risk of any cardiovascular event (16.7 versus 26.6 percent; RR 0.63, 95% CI, 0.43 to 0.93), and a nonsignificant 38 percent reduction in the risk of fatal or nonfatal coronary heart disease (7.4 versus 11.9 percent; RR 0.62, 95% CI, 0.34 to 1.16).

Renal Outcomes

End-Stage Renal Disease

The study did not report on ESRD for the CKD subgroup.

Other Renal Outcomes

There were two renal deaths in the CKD subgroup, both in participants allocated to diuretic (0.9 percent). No other clinical renal outcomes were reported.

Study Withdrawals and Adverse Events (Appendix Table C83)

Neither study withdrawals nor adverse events data were reported within the CKD subgroup.

Summary

In this analysis of a subgroup of patients with CKD from a larger trial of older patients with systolic hypertension, diuretic treatment compared with placebo significantly reduced risk of stroke and of one of two composite vascular outcomes. There was no significant difference between treatment groups in all-cause mortality. Results were limited by the small number of patients with CKD, with insufficient statistical power to determine whether large magnitude differences in risk for clinical outcomes were statistically significant. Results also were limited in that this was a post hoc subgroup analysis without confirmation of findings in another study population. Further, results were not reported for several vascular events of interest, including cardiovascular mortality, MI and heart failure, and no clinical renal outcomes were reported.

ACE Inhibitor Versus Non-ACE Inhibitor Antihypertensive Therapy Trial

Overview

In patients with CKD, we found insufficient evidence that ACEI therapy as compared with non-ACEI antihypertensive therapy is associated with a reduced risk of all-cause mortality and low level of evidence that ACEI therapy compared with non-ACEI antihypertensive therapy does not significantly reduce the risk of ESRD. There was no statistically significant difference between treatment groups for risk of halving of GFR or for one reported composite renal outcome. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Study

We identified one trial that met all eligibility criteria and randomized 131 participants with CKD to ACEI versus non-ACEI hypertension treatment.[119] Detailed baseline characteristics are presented in Appendix Table C84.

Randomized subjects assigned to ACEI were treated with lisinopril or lisinopril in combination with another antihypertensive agent versus a non-ACEI antihypertensive treatment regimen. Prior to randomization, 139 hypertensive patients underwent a run-in period, during which they were to follow a 0.8 g/kg protein and 3–4 g salt intake per day, and non-ACEI antihypertensive agents were used to obtain diastolic blood pressure of 90 mm Hg or less. Only patients achieving this target on two or fewer drugs, judged compliant, and with stable renal function were eligible to proceed to randomization.

Mean age of randomized study participants was 51 years, and men constituted 66 percent of all subjects. Race/ethnicity of study participants was not reported, though the study was conducted in Italy. Mean followup was 1.9 years.

Renal Function

Participants were required to have creatinine clearance between 20 and 50 ml/min/1.73m^2 and were excluded if they had proteinuria of ≥1 gram/day. Among those enrolled, mean creatinine clearance was 36 ml/min/1.73m^2, mean GFR was 36 ml/min/1.73m^2, mean creatinine was 2.4 mg/dL, and mean proteinuria was 512 mg/day.

Baseline Comorbidities

All study participants had hypertension, with an untreated diastolic blood pressure of ≥95 mm Hg prior to run-in, and a stable treated diastolic blood pressure <90 mm Hg prior to randomization. Patients with malignant hypertension were excluded. Among subjects randomized, mean baseline blood pressure was 142/86 mm Hg. Patients with diabetes, heart failure or another major (undefined) cardiac disease, or a recent history of MI or stroke were excluded from study entry.

Study Quality (Appendix Table C140)

Study quality was rated as fair. This study was open-label and concealment of treatment allocation was unclear. Analyses were conducted according to the intention-to-treat principle. No information was reported regarding withdrawals.

Results

Mortality

No data were reported on mortality.

Vascular Outcomes (Appendix Table C85 and Appendix Figure C18)

Myocardial Infarction

The study reported just one myocardial infarction, in a subject assigned to non-ACEI antihypertensive treatment

Stroke

There were no reports of stroke.

Other Vascular Outcomes

There were no reports of heart failure or any composite vascular outcomes.

Renal Outcomes (Appendix Tables C86 and C87 and Appendix Figure C18)

End-Stage Renal Disease

There was a nonstatistically significant 61 percent reduction in risk of ESRD in those assigned to ACEI treatment as compared with those allocated to non-ACEI treatment (3.0 versus 7.6 percent; RR 0.39, 95% CI, 0.08 to 1.96).

Other Renal Outcomes

There was a nonstatistically significant 58 percent reduction in risk of halving of GFR in those assigned to ACEI treatment as compared with those allocated to non-ACEI treatment (4.5 versus 10.6 percent; RR 0.42, 95% CI, 0.11 to 1.56). Similarly, There was a nonstatistically significant 59 percent reduction in risk of the composite renal outcome of halving of GFR or need for dialysis in those assigned to ACEI treatment as compared with those allocated to non-ACEI treatment (7.6 versus 18.2 percent; RR 0.41, 95% CI, 0.15 to 1.10). However, there were only a small number of events for all these outcomes and none of these differences was clinically significant.

Study Withdrawals and Adverse Events (Appendix Table C88)

No data on study withdrawals were reported. Treatment was discontinued due to adverse events by 6.1 percent of the study participants assigned to the ACEI group and 4.6 percent in the non-ACEI antihypertensive therapy group. There was one incidence of hyperkalemia and one incidence of uncontrolled hypotension in the ACEI group. No hyperkalemia or hypotension events were reported for the non-ACEI antihypertensive therapy group.

Summary

In a single study of patients with hypertension and CKD, antihypertensive treatment with ACEIs in comparison to that without ACEIs was associated with nonsignificant reductions in the risk for MI, ESRD, halving of GFR, and a composite renal outcome including ESRD and GFR. Mortality data and other cardiovascular or renal outcomes were not reported, nor were study

withdrawals or serious adverse events. Results were limited by the small sample size, small number of clinical events, and short followup duration.

CCB Versus BB Trials (n=3)

Overview

In patients with CKD, we found low strength of evidence that treatment with CCB does not significantly reduce the risk of all-cause mortality compared with BB, and low strength of evidence that there is no difference between treatments in risk of ESRD. Participants assigned CCB were statistically significantly less likely to experience one composite vascular outcome. Our confidence in these estimates is limited by the small number of trials reporting different outcomes and the small number of clinical events.

Description of Studies

Three trials met all eligibility criteria and randomized participants with CKD (n=12,766, range 34 to 12,074) to CCB versus BB.[89,90,120,121] Detailed baseline characteristics of patients enrolled in the three trials are presented in Appendix Tables C80 and C81.

Among eligible trials, most data were derived from a subgroup analysis reported in a subset of 12,074 patients with undefined "renal dysfunction" from the larger ASCOT-BPLA trial (n=19,257).[121] In this study, participants were randomized to amlodipine versus atenolol. As needed to meet blood pressure targets (<140/90 mm Hg for patients without diabetes and <130/90 mm Hg for patients with diabetes), participants randomized to amlodipine could have had an ACEI added and subjects randomized to atenolol could have had a diuretic added. In the AASK trial, designed as a 3x2 factorial study, besides randomizing 658 participants to amlodipine versus metoprolol, an additional 436 were randomized to an ACEI, and all participants also were randomized to one of two blood pressure target groups as described elsewhere in this report.[89,90] In this trial, the amlodipine treatment arm was stopped early by recommendation of the data and safety monitoring board with patients switched to open label medication. Results presented here compare outcomes including followup until the time blinded amlodipine was discontinued. In the smallest trial,[120] 34 participants were randomized to one of two CCBs (verapamil or diltiazem) versus atenolol. This study also included an additional ACEI treatment arm that is reviewed elsewhere in this report.

The mean age of study participants across all three trials was 55 years (range 55 to 62) and men constituted 60 percent (range 44 to 61, n=2 trials) of all subjects studied. In the two trials that reported race/ethnicity,[89,90,120] 98 percent of participants were African American, including 100 percent of subjects in the AASK trial.[89,90] Two studies were conducted in the United States, and the large subgroup analysis was conducted in Europe. Median study duration ranged from 3 to 5.5 years.

Renal Function

Among eligible trials, one required that participants have impaired GFR (20 to 65 ml/min/1.73m^2)[89,90] and reported a mean baseline GFR of 46 ml/min/1.73m^2, a mean creatinine of 2.0 mg/dL, and mean proteinuria of 0.5 g/day. A second trial required that participants have both impaired creatinine clearance (<70 ml/min) and at least 2 g/day proteinuria, and reported a mean baseline creatinine clearance of 61 ml/min/1.73m^2, a mean creatinine of 1.9 mg/dL, and

mean proteinuria of 4.4 g/day.[120] The third study reported no information on the baseline renal function in its "renal dysfunction" subgroup.

Baseline Comorbidities

In all three studies, all participants were required to be hypertensive. In two trials reporting, mean baseline blood pressure was 150/95 mm Hg.[89,90,120] Patients with heart failure were excluded from all three trials, and patients with a history of MI[121] or of any documented coronary artery disease[120] were excluded in two trials. While one trial required that participants be diabetic,[120] a second trial excluded diabetic patients,[89,90] and the third study reported no information on participants' diabetes status.[121]

Study Quality (Appendix Table C140)

Study quality was rated good for two trials and fair for one trial. Two of the trials reported adequate treatment allocation concealment.[89,90,121] One study was open-label,[121] a second study was double blind with respect to medication assignment but not to blood pressure target.[89,90] Both reported that endpoint adjudicators were blinded to treatment allocation. The third study provided no information with respect to blinding.[120] Two of the three studies performed analyses according to the intention-to-treat principle. Withdrawals ranged from 0 to 11.5 percent between studies.

Results

Mortality (Table 13, Appendix Table C91, and Appendix Figure C19)

All-Cause Mortality

In two trials of CKD patients reporting mortality data, those randomized to CCB versus BB had a nonsignificant 38 percent reduction in risk of all-cause mortality (6.0 versus 9.2 percent; RR 0.62, 95% CI, 0.31 to 1.22; n=692 patients).[89,90,120]

Cardiovascular Mortality

One study reported cardiovascular deaths per patient year of followup (CCB 0.9 percent, BB 0.8 percent) but did not report the number and percentage of participants with this outcome by treatment group.[89,90] A second study reported cardiovascular deaths (9.6 percent) but did not report these outcomes by treatment group.[120]

Vascular Outcomes (Table 13, Appendix Tables C91-C93, and Appendix Figure C19)

Myocardial Infarction

One study reported fatal MI (7.7 percent), but did not report these outcomes by treatment group.[120]

Stroke

One study reported fatal strokes (1.9 percent), but did not report these outcomes by treatment group.[120]

Other Vascular Outcomes

No trials reported results for heart failure. Two trials reported results for a composite vascular endpoint. One reported that there was no significant difference in the rate of cardiovascular events (cardiovascular mortality or first cardiovascular hospitalization) per patient year (1.7 versus 2.9) between CCB and BB patients, but did not report the number of study participants with these events overall or by treatment group.[89,90] In the second study, though the main ASCOT-LLP study had defined six different composite vascular endpoints, results for the "renal dysfunction" subgroup were only reported for one, defined as cardiovascular mortality, nonfatal MI (symptomatic and silent), unstable angina, chronic stable angina, life threatening arrhythmias, silent nonfatal heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures, or retinal vascular thromboses.[121] Patients assigned to CCB were significantly less likely to experience this composite outcome than those assigned to BB (14.0 versus 16.0 percent; RR 0.87, 95% CI, 0.80 to 0.95; n=12,074 patients).

Renal Outcomes (Table 13, Appendix Tables C94 and C95, and Appendix Figure C19)

End-Stage Renal Disease

In one trial of patients with CKD, 9.6 percent of patients were reported to have started dialysis during the trial, but results were not reported by treatment group.[120] In a second trial, there was no significant difference in risk of ESRD between subjects randomized to CCB versus BB (16.6 versus 16.6 percent; RR 1.00, 95% CI, 0.70 to 1.44).[89,90]

Other Renal Outcomes

In one trial, there was no significant difference between treatment groups for the composite renal outcome of ESRD, death, or at least 50 percent decline in GFR (27.2 versus 26.5 percent; RR 1.02, 95% CI, 0.78 to 1.34). Similarly, there was no significant difference between treatment groups for a composite outcome of ESRD or death (22.5 versus 25.2 percent, RR 0.90, 95% CI, 0.67 to 1.20).[89,90] Doubling of serum creatinine, reported in one small study, was less frequent in the CCB group (11.1 percent versus 31.3 percent; $p<0.05$), a nonsignificant 64 percent reduction in risk (RR 0.36, 95% CI, 0.08 to 1.59).[120]

Study Withdrawals and Adverse Events (Appendix Table C96)

One study reported a withdrawal rate of 11.5 percent (six patients), but no withdrawal data were reported by treatment group.[120] Another study reported no withdrawals but noted that 23 patients in the CCB group and 30 in the BB group were no longer active study participants at the end of the study.[90] In the one study reporting withdrawals as a result of serious adverse events, there were no events in either group.[120] Specific adverse events were reported in two studies. In one study, impotence (16.7 percent versus 56.3 percent), insomnia (5.6 percent versus 37.5 percent), lethargy (0 percent versus 81.3 percent), exercise intolerance (0 percent versus 43.8 percent), and dry mouth (5.6 percent versus 81.0 percent) were less frequent in the CCB group than the BB group.[120] The second study reported percentage of patients experiencing the adverse event per patient year of followup. The results were similar for the two groups (hyperkalemia, CCB 0 versus BB 0.2 percent; angioedema, CCB 2.3 versus BB 2.7 percent; shortness of breath, CCB 44.4 versus BB 45.8 percent; syncope, CCB 2.3 versus BB 6.3 percent; dizziness, CCB 46.7 versus BB 47.8 percent; lightheadedness, CCB 48.1 versus BB 47.8 percent; edema, CCB

59.8 versus BB 51.0 percent; cough, CCB 46.3 versus BB 41.5 percent; and sexual dysfunction, CCB 25.7 versus BB 25.2 percent).[90]

Summary

In patients with CKD and hypertension, there was a nonsignificant 38 percent reduction in all-cause mortality with CCB compared with BB treatment. One of two trials reported a significant reduction in a composite vascular outcome, but this was the only one of six composite vascular endpoints collected in this trial that was reported for patients with renal dysfunction, raising uncertainty regarding whether this risk reduction is a consistent finding within this study. There was no significant difference between CCB and BB treatment groups in risk of ESRD or in risk of the composite renal outcome of ESRD, death, or greater than 50 percent decline in GFR. Both the composite outcome of ESRD or death and the risk of doubling creatinine appeared less likely in patients randomized to CCB, though results were not statistically significant. Results were limited in that most outcomes were not reported by treatment group in more than one study, and by the uncertainty regarding whether the patients in the ASCOT-BPLA study with "renal dysfunction" meet criteria for CKD.

Table 13. Pooled clinical and renal outcomes, CCB versus BB trials

Outcome	Number of Trials Reporting	Quality of the Studies	CCB Events/N (%)	BB Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	2	Fair	14/235 (6.0)	42/457 (9.2)	0.62 [0.31-1.22]	6%
Composite vascular outcome*, Dahlof, 2005[121]	1	Good	825/5893 (14.0)	989/6181 (16.0)	0.87 [0.80-0.95]	NA
End-stage renal disease	1	Good	36/217 (16.6)	73/441 (16.6)	1.00 [0.70-1.44]	NA
Doubling of serum creatinine	1	Fair	1/18 (5.6)	5/16 (31.3)	0.18 [0.02-1.37]	NA
Composite renal outcome**, AASK, Wright, 2002[90]	1	Good	59/217 (27.2)	117/441 (26.5)	1.02 [0.78-1.34]	NA

BB = beta blocker; CCB = calcium channel blocker; NA = not applicable; RR = relative risk reduction

* Cardiovascular mortality, nonfatal MI (symptomatic and silent), unstable angina, chronic stable angina, life threatening arrhythmias, silent non-fatal heart failure, non-fatal stroke, peripheral arterial disease, revascularization procedures, and retinal vascular thromboses

**GFR event (reduction in GFR by 50% or by 25 ml/min/1.73m^2 from baseline mean), ESRD (dialysis or transplantation), or death

CCB Monotherapy Versus Diuretic Trial

Overview

In patients with CKD, there was insufficient evidence regarding whether there is a difference between CCB and diuretic treatment for risk of all-cause mortality and low strength of evidence that there was no difference between CCB and diuretic treatment for risk of ESRD. There was no statistically significant difference between CCB and diuretic treatment groups in risk of stroke, CHF, or in multiple composite vascular or renal outcomes. Our confidence in these estimates is limited because they are based entirely on results reported from a post hoc analysis from a single large trial.

Description of Study

One study met all eligibility criteria and randomized 4,129 participants to CCB monotherapy versus diuretic monotherapy.[81-83] Detailed baseline characteristics are presented in Appendix Tables C97 and C98. The eligible study was a post hoc analysis performed within a subset of participants with CKD from the ALLHAT trial, a study of 23,261 subjects that was not originally limited to individuals with CKD, contained two additional antihypertensive treatment arms and, as part of a factorial design, also randomized participants to pravastatin versus control.

The CCB and diuretic utilized in this trial were amlodipine and chlorthalidone, respectively. The mean age among the 4,129 study participants assigned to CCB versus diuretic was 71 years, and men constituted 47 percent all study subjects. The most common race/ethnicity of trial participants was white non-Hispanic (57 percent), black (25 percent), and Hispanic (12 percent). The ALLHAT trial was performed primarily in the United States. The study duration was 4.9 years.

Renal Function

Patients with a baseline creatinine level >2 mg/dL were excluded from the main ALLHAT trial. Inclusion in the post-hoc analysis was limited to ALLHAT participants with a GFR <60 ml/min/ 1.73m^2. Within subjects in the CKD subgroup, mean baseline GFR was 50 ml/min/1.73m^2. No baseline data on albuminuria was reported.

Baseline Comorbidities

Enrollment was limited to patients with hypertension, with the mean blood pressure at baseline 147/83 mm Hg. Thirty-four percent of participants reported diabetes at baseline, 60 percent reported cardiovascular disease, and 30 percent reported coronary artery disease.

Study Quality (Appendix Table C140)

Study quality was rated as good. Allocation concealment was adequate. The trial was double blinded and analysis by the intention-to-treat principle was reported. No data regarding withdrawals was reported.

Results

Mortality

Neither all-cause mortality nor cardiovascular mortality data were reported.

Vascular Outcomes (Appendix Tables C99–C100 and Appendix Figure C20)

Myocardial Infarction

No data were reported for risk of MI as an isolated outcome.

Stroke

In patients with CKD, there was no significant difference between those assigned CCB versus diuretic treatment for risk of stroke (6.6 versus 6.0 percent; RR 1.10, 95% CI, 0.86 to 1.40). Among patients with diabetes, there was no statistically significant difference between treatment groups for risk of stroke

Other Vascular Outcomes

Similarly, in this CKD subgroup, there was no significant difference between those assigned CCB versus diuretic treatment for CHF (11.5 versus 9.9 percent; RR 1.16, 95% CI, 0.97 to 1.39). There also was no significant between-treatment difference for the composite vascular outcome of nonfatal MI or coronary heart disease death (RR 1.05, 95% CI, 0.89 to 1.24), or for the composite vascular outcome that included death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, or peripheral arterial disease requiring hospitalization or outpatient revascularization (RR 1.06, 95% CI, 0.98 to 1.16).

The ALLHAT trial reported additional results for CKD patients with diabetes. In this subgroup, risk of CHF was significantly greater in patients randomized to CCB treatment compared with diuretic treatment (RR 1.46, 95% CI, 1.12 to 1.89; n=1,387). There was no statistically significant difference between treatment groups for risk of the composite cardiovascular endpoint of nonfatal MI or coronary heart disease death. For the more comprehensive composite cardiovascular endpoint described above, risk of occurrence was significantly greater in patients randomized to CCB treatment compared with diuretic treatment (RR 1.20, 95% CI, 1.05 to 1.36; n=1,387).

Renal Outcomes (Appendix Tables C102 and C103 and Appendix Figure C20)

End-Stage Renal Disease

In CKD patients, CCB and diuretic treatments were comparable in CKD patients regarding the risk of ESRD, defined as death due to kidney disease, kidney transplantation, or start of long-term renal dialysis (RR 0.90, 95% CI 0.67 to 1.21). Results were similar in diabetics with CKD.

Other Renal Outcomes

In CKD patients, there was no statistically significant difference between CCB and diuretic treatment groups in risk of the composite renal outcome defined by ESRD or ≥50 percent decline in GFR (6 versus 7 percent, RR 0.86, 95% CI, 0.67 to 1.10). Results were similar in diabetics with CKD.

Study Withdrawals and Adverse Events

No study withdrawal or adverse event data were reported for the ALLHAT CKD subgroup.

Summary

Within the one eligible trial of patients with CKD, there was no apparent difference between the CCB and diuretic monotherapy treatment groups in risk of stroke, ESRD, or other composite clinical vascular or renal outcomes. Results were limited in that the study was a post hoc subgroup analysis. The ALLHAT study also did not report results for risk of mortality or risk of MI in the subgroup of CKD patients. In addition, mean followup did not extend beyond 5 years, so longer term effects of CCB monotherapy versus diuretic monotherapy cannot be determined from these data.

Strict Versus Standard Blood Pressure Target Treatment Trials (n=6)

Overview

In patients with CKD, we found a low strength of evidence regarding whether antihypertensive treatment targeting stricter blood pressure targets reduces risk of all-cause mortality compared with treatment targeting standard blood pressure control targets. We found a low strength of evidence regarding whether there was a difference between treatments for risk of ESRD. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events, and heterogeneity between studies.

Description of Studies

Six trials met all eligibility criteria and randomized participants with CKD (n=2,520, range 77 to 1,094) to treatment aimed to reach different target blood pressures, i.e., "strict" versus "standard" blood pressure targets.[90,122-127] One study was not limited to individuals with CKD but presented subgroup results for the approximately 3 percent of participants whose baseline creatinine was >1.7 mg/dL.[126] Detailed baseline characteristics are presented in Appendix Tables C104 and C105.

In general, studies established blood pressure targets for their strict control group about 10-15 mm Hg lower than for their standard control group, though there was variability between trials in the absolute blood pressure targets selected. The most common treatment target, used in three trials, was a mean arterial blood pressure (MAP) of ≤92 mm Hg versus a MAP of 100 to 107.[90,123,125] Two trials set diastolic blood pressure (DBP) targets, <90 mm Hg for the strict target versus >90 mm Hg for the standard target in one trial,[126] and 65 to 80 mm Hg for the strict target versus 85 to 95 mm Hg for the standard target in the second trial.[124] The most recent trial compared treatment to achieve blood pressure <130/80 mm Hg versus a DBP target of <90 mm Hg.[122] The specific antihypertensive agents utilized to achieve these blood pressure targets varied between trials. The oldest trial, published in 1989,[126] used diuretics, adrenergic receptor blockers, and vasodilators, while all three trials published in the 1990s used ACEIs with or without diuretics as first-line treatment.[123-125] A trial published in 2002, structured as a 3 x 2 factorial design, assigned participants to initial treatment with either an ACEI, beta blocker or calcium channel blocker.[90] Finally, the most recent trial, published in 2005,[122] titrated all participants with an ACEI prior to randomization and then used a long-acting CCB to compare strict versus standard blood pressure control.

The mean age of study subjects was 53 years (range of study means 37 to 56; n=5 trials), and men constituted 63 percent (range 47 to 75; n=6 trials) of all patients evaluated. Among five trials reporting race/ethnicity, three were predominately[124,126] or entirely[90] comprised of

blacks/African Americans. In two other trials, more than 85 percent of participants were white.[123,125] All trials were conducted in the United States, except for one performed in Italy.[122] Mean or median study duration ranged from 19 months to 5 years, with all but one trial having a followup duration of at least 2 years.

Renal Function

Among the six trials, two required that participants have proteinuria to be included,[122,123] and one trial excluded participants with proteinuria.[90] Five trials required decreased GFR or creatinine clearance or elevation in serum creatinine for entry,[90,122,124-126] including one study that was a subgroup analysis of participants from a larger trial with baseline creatinine >1.7 mg/dL.[126] Measures of baseline renal function were reported in all but one trial.[126] Mean GFR was 43 ml/min/1.73m^2 (range 35 to 63), mean serum creatinine was 2.0 mg/dL (range 1.3 to 2.7), and mean proteinuria was 1.0 gm/day (range 0.36 to 2.85). Creatinine clearance, reported in only two trials, averaged 46.2 ml/min/1.73m^2.[122,125]

Baseline Comorbidities

In five trials reporting data, approximately 95 percent of study participants had a history of hypertension. In the sixth trial, though information on history of hypertension was not reported, approximately two-thirds of the subjects were receiving blood pressure lowering drugs at baseline.[122] Mean blood pressures at baseline were 142/89 mm Hg (MAP 106 mm Hg). Overall, few study participants had diabetes, though among individual trials one included only patients with type 1 diabetes,[123] two excluded all diabetic patients,[90,124] one had about 15 percent diabetic patients[126] and two studies provided no information regarding whether participants had a history of diabetes.[122,125] While only one trial reported baseline prevalence of cardiovascular disease, at 36 percent,[124] several reported exclusions of such participants, including exclusion of all subjects with recent MI or stroke,[122,124] exclusion of all participants with a history of any past MI or stroke,[123] and exclusion of any participants with clinical or overt heart failure.[90,122] One further trial documented enrollment of individuals with cardiovascular disease but did not report baseline prevalence.[126]

Study Quality (Appendix Table C140)

Among the six trials, study quality was rated as good in one trial and as fair in five trials. Allocation concealment was adequate in three trials and unclear in the remaining studies. Three trials were not blinded,[90,122,126] one was double blinded,[124] and blinding was unclear for two trials.[123,125] For the outcomes presented here, four of six trials analyzed results according to the intention-to-treat principal.[90,123-125] Three trials adequately described reasons for study withdrawal.[90,122,125] Percentages of study withdrawals ranged from 0 to 16 percent (n=4 trials).

Results

Mortality (Table 14, Appendix Table C106, and Appendix Figure C21)

All-Cause Mortality

Compared with standard blood pressure control, there was no significant reduction in risk of all-cause mortality with strict blood pressure control (RR 0.86, 95% CI, 0.68 to 1.09; n=4 trials, 1,803 patients). These results were driven almost entirely by two trials that, though they each

reported a 12 to 15 percent relative reduction in mortality with strict compared with standard blood pressure control, differed markedly in other respects. In the trial by Shulman, 35 percent of participants assigned strict blood pressure control versus 41 percent assigned standard control died during a 5-year followup period, compared with 6.9 percent versus 7.8 percent, respectively, in an approximately 4-year followup period, in the trial by Wright.[90,126] Other differences between these trials included the substantially higher baseline blood pressure, most of which had been untreated, among participants in the Shulman trial,[126] and lower blood pressure targets for both treatment groups, and use of ACEIs and BB only in the trial by Wright.[90]

Cardiovascular Mortality

Compared with standard blood pressure control, there was no significant reduction in risk of cardiovascular mortality with strict blood pressure control (RR 0.83, 95% CI, 0.54 to 1.26). Nearly all the weight contributing to this pooled estimate was derived from one trial, in which 20.1 percent versus 23.9 percent of participants experienced a cardiovascular death (RR 0.84, 95% CI, 0.55 to 1.29),[126] while fewer than 1 percent of participants died due to cardiovascular causes in the only other trial reporting this outcome.[122]

Vascular Outcomes (Table 14, Appendix Tables C106-C108, and Appendix Figure C21)

Myocardial Infarction

Incidence of fatal MI was reported in few trials and among these trials occurred in less than 5 percent of participants in all treatment groups. Based on these very limited data, there was no significant difference in risk of fatal MI (RR 1.01, 95% CI, 0.06 to 15.95; n=1 trial, 335 patients) between the strict and standard blood pressure control groups. However, the 95% CI estimating risk for this outcome is wide and cannot exclude either a clinically important benefit or harm.

Stroke

Similar findings were reported for stroke. As with MI, there was no evidence of reduced risk of fatal stroke (RR 1.09, 95% CI, 0.34 to 3.47; n=2 trials, 632 patients) between the strict and standard blood pressure control groups. Again, the 95% CI estimating risk is wide and cannot exclude either a clinically important benefit or harm.

Other Vascular Outcomes

Only one trial reported a composite vascular endpoint, in this case, a composite of cardiovascular mortality and first cardiovascular hospitalization. Incidence appeared similar between participants assigned to strict versus standard blood pressure control (2.3 percent versus 2.7 percent per patient year, respectively).

Renal Outcomes (Table 14, Appendix Tables C109 and C110, and Appendix Figure C21)

End-Stage Renal Disease

Though five trials reported outcomes for ESRD, results were reported separately by treatment group in only three trials. Among these trials, there was no significant reduction in risk for ESRD between strict and standard blood pressure control (16.8 percent versus 16.6 percent; RR 1.03, 95% CI, 0.77 to 1.38, n=3 trials, 1,506 patients).

Other Renal Outcomes

No trials comparing strict versus standard blood pressure targets reported results separately by treatment group for the individual outcomes of doubling of serum creatinine, halving of GFR, or progression from microalbuminuria to macroalbuminuria. Assignment to a strict blood pressure target group did not appear to decrease risk of experiencing any of several study-defined composite renal outcomes (Appendix Table C110), including ESRD, or death (RR 0.91, 95% CI, 0.73 to 1.13);[90] halving of GFR, ESRD, or death (RR 1.06, 95% CI, 0.89 to 1.27);[90] or 50 percent decline in GFR, doubled serum creatinine, ESRD, or death (RR 1.43, 95% CI, 0.63 to 3.23).[124]

Study Withdrawals and Adverse Events (Appendix Table C111)

Overall study withdrawals, reported in four trials, ranged from 0 to 16 percent, with results appearing to be similar between treatment groups in two trials reporting these data. In the only trial to report serious adverse events and withdrawals due to serious adverse events, incidence of these outcomes appeared possibly more frequent in the strict blood pressure control group.[122] Specific adverse events also were infrequently reported, with cough[90] and postural hypotension[123] each being significantly more frequent in the strict blood pressure target group compared with the standard blood pressure target group in one trial.

Subgroup Results

No trials reported outcomes stratified by any participant characteristic. In trials restricted to patients with diabetes, outcomes reported were limited to the finding of no significant difference in risk of conversion from microalbuminuria to macroalbuminuria in one trial (RR 0.70, 95% CI, 0.36 to 1.36). In one trial that excluded participants with cardiovascular disease, no results were reported by treatment group. In two trials restricted to participants with proteinuria, only one of which reported results by treatment group, there was no significant difference in risk of ESRD (RR 1.12, 95% CI 0.75 to 1.69), and clinical vascular events and deaths were rare. In trials restricted to participants with decreased eGFR or creatinine clearance or increased serum creatinine, there was no significant difference between strict and standard blood pressure control groups in all-cause mortality (RR 0.86, 95% CI, 0.68 to 1.09, n=4 trials), cardiovascular mortality, MI, fatal stroke, ESRD (RR 1.03, 95% CI, 0.77 to 1.38, n=3 trials), or any of four composite renal outcomes. In one trial restricted to African American participants, which also excluded patients with CHF, there was no significant difference between tight and standard blood pressure control groups for risk of mortality (RR 0.88, 95% CI, 0.58 to 1.35, ESRD (RR 0.92, 95% CI, 0.70 to 1.22), or either of two composite renal outcomes.

Summary (Appendix Table C140)

In individuals with CKD, compared with targeting standard blood pressure control, assignment to targeting strict control was associated with 14 percent and 17 percent relative reductions in risk of all-cause mortality and cardiovascular mortality, respectively, which were not statistically significant. There were no significant differences between treatment groups for the outcomes of MI, stroke, ESRD, or, in individual trials, for several composite renal outcomes. Findings for the mortality and ESRD outcomes were driven mostly by a single trial conducted more than 20 years ago that may have limited generalizability to current patient populations and available antihypertensive treatment options. Results for MI and stroke in particular were limited by small sample sizes and could not exclude either clinically meaningful benefits or harms. Overall results were further limited by heterogeneity in patient populations (i.e., baseline level of

renal function, comorbidities), and heterogeneity in blood pressure targets. Subgroup analyses, though limited, did not identify any comorbid conditions or category of renal function in which there was a significant difference between strict and standard blood pressure control for any clinical outcome. Reporting on study withdrawals and adverse effects was limited. Finally, no trial provided followup beyond 5 years; therefore, longer term effects of different blood pressure targets cannot be determined from these studies.

Table 14. Pooled clinical and renal outcomes, strict versus standard blood pressure target treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	Strict BP Events/N (%)	Usual BP Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
All-cause mortality	4	Fair	96/908 (10.6)	103/895 (11.5)	0.86 [0.68-1.09]	0%
Cardiovascular mortality	2	Fair	33/326 (10.1)	35/306 (11.4)	0.83 [0.54-1.26]	0%
Fatal MI	1	Fair	1/167 (0.6)	1/168 (0.6)	1.01 [0.06-15.95]	NA
Stroke, fatal	2	Fair	6/326 (1.8)	5/306 (1.6)	1.09 [0.34-3.47]	0%
End-stage renal disease	3	Fair	126/749 (16.8)	126/757 (16.6)	1.03 [0.77-1.38]	22%
Composite renal outcome*, Wright A[90]	1	Good	173/540 (32.0)	167/554 (30.1)	1.06 [0.89-1.27]	NA
Composite renal outcome*, Wright B[90]	1	Good	118/540 (21.9)	133/554 (24.0)	0.91 [0.73-1.13]	NA
Composite renal outcome**, Toto A[124]	1	Fair	12/42 (28.6)	7/35 (20.0)	1.43 [0.63-3.23]	NA
Composite renal outcome**, Toto B[124]	1	Fair	4/42 (9.5)	5/35 (14.3)	0.67 [0.19-2.29]	NA

BP = blood pressure; MI = myocardial infarction; NA = not applicable; RR = relative risk reduction

* (A) 50% or 25 mL/min reduction in GFR, ESRD (dialysis or transplantation), or death; (B) ESRD or death

** (A) 50% decline in GFR, doubled serum creatinine, ESRD, or death; (B) 50% decline in GFR or doubled serum creatinine.

Low Protein Diet Versus Usual Protein Diet Trials (n=6)

Overview

In patients with CKD, we found a low level of evidence that, compared with usual protein diets, a low protein did not significantly reduce risk of all-cause mortality nor increase risk of ESRD. We found no statistically significant difference between treatment groups in risk of doubling baseline creatinine, or halving GFR. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events, and heterogeneity between studies.

Description of Studies

Six trials met all eligibility criteria and randomized 1,480 (range 63 to 585) participants with CKD to a low protein diet (typically 0.6 or 0.8 g protein per kg of ideal/lean body weight per day) versus a usual diet (typical protein intake less than 1.3 g/kg/day).[125,127-135] Detailed baseline characteristics are presented in Appendix Tables C112 and C113.

Mean participant age was 52 years (range 49 to 58; n=5 trials), and men constituted 59 percent (range 54 to 83; n=5 trials) of all study participants. In the one trial reporting ethnicity, 85 percent of participants were white. One study was conducted in the United States.[125,127,130,131] Of the remaining studies, two were conducted in Italy[132,133] and one each was conducted in Japan,[128] France,[129] and the United Kingdom.[134,135] Followup periods ranged from 2 to 3.5 years.

Renal Function

Two of the six eligible trials required that participants have albuminuria, with some limitation in the severity of their renal function. In one of these studies, all subjects had to have macroalbuminuria (UAER >200 µg/min) or proteinuria (urine protein excretion rate, i.e., urine protein excretion rate (UPER), >1 g/day) and serum creatinine <2.0 mg/dl (i.e., CKD stages 1–3).[128] In the second study, patients were required to have UAER >30 mg/day (i.e., at least microalbuminuria) and GFR of at least 15 ml/min (i.e., CKD stages 1-4).[129] The remaining four trials required that participants have either an elevated serum creatinine or a reduced GFR or creatinine clearance, and three also imposed limits on UPER. Thresholds for eligibility in these trials included creatinine 1.2 to 7.0 mg/dl in women and 1.4 to 7.0 mg/dl in men, with UPER less than 10 g/day (i.e., CKD stages 1-5);[131] creatinine 1.35 to 7.0 mg/dl in women and 1.5 to 7.0 mg/dl in men, with GFR <60 ml/min, and UPER <3 g/day (i.e., CKD stages 3-5);[133] creatinine clearance 15 to 70 ml/min and UPER <3 g/day (i.e., CKD stages 1-4);[132] and GFR 10 to 60 ml/min (i.e., CKD stages 3-5).[134,135] Among all six eligible trials, baseline mean UPER ranged from 0.28 g/day/1.73m^2 to 1.5 g/day (n=3 trials), mean UAER was reported in only one trial (366 mg/day), mean serum creatinine was 1.7 mg/dl (range 1.1 to 1.9, n=3 trials), and mean GFR was 45 ml/min/1.73m^2 (range 39 to 86, n=3 trials).

Baseline Comorbidities

Two trials enrolled only patients with diabetes,[128,129] two trials excluded patients with diabetes,[132,133] and two trials did not report baseline prevalence of diabetes[131,134,135] Among two trials reporting,[128,131] mean blood pressure was 132/80 mm Hg. One trial excluded all patients with CHF,[128] another trial excluded patients with either class III or IV CHF,[131] and two trials

excluded participants with a recent MI[128,133] or stroke.[128] However, no additional information on baseline cardiovascular morbidity was reported in any trial.

Study Quality (Appendix Table C140)

Study quality was rated as fair in all six trials. Allocation concealment was adequate in three studies and unclear in three studies. One trial reported that measures of GFR were blinded,[131] but the other trials were not reported as blinded. Five trials did not perform analyses using intention-to-treat principles, and it was unclear in one study.[131] Withdrawals were adequately described in all but two studies.[132,134,135] Study withdrawals ranged from 2 to 25 percent.

Results

Mortality (Table 15, Appendix Table C114, and Appendix Figure C22)

All-Cause Mortality

In the CKD patients studied in eligible trials, low protein diets were associated with a nonsignificant 42 percent reduction in risk of all-cause mortality compared with usual protein diets (1.9 versus 3.3 percent; RR 0.58, 95% CI, 0.29 to 1.16; n=4 trials).[128,131,133,135] All individual trials suggested a lower mortality risk with low protein diets, but the difference was not statistically significant in any trial.

Cardiovascular Mortality

Only one trial reported cardiovascular mortality, in which there were four such events (1.4 percent) in the low protein diet group and five cardiovascular deaths (1.7 percent) in the usual protein diet group.[131]

Vascular Outcomes (Table 15, Appendix Tables C114 and C115, and Appendix Figure C22)

Myocardial Infarction

One trial reported a single fatal MI (2.0 percent) in the usual protein diet group and none in the low protein diet group.[128]

Stroke

One trial reported two nonfatal strokes (0.7 percent) in the low protein diet group and none in the usual protein diet group.[131]

Other Vascular Outcomes

No other cardiovascular events were reported in any trial.

Renal Outcomes (Table 15, Appendix Tables C116 and C117, and Appendix Figure C22)

End-Stage Renal Disease

In three trials reporting, none of which had more than 10 cases of ESRD, low protein diets were associated with a nonstatistically significant 62 percent increase in risk of ESRD compared with usual protein diets (7.1 versus 4.1 percent; RR=1.62, 95% CI, 0.62 to 4.21; n=302

patients).[128,129,135] One additional trial reported that 12 participants (2.1 percent) developed ESRD, but did not report this result separately for the two treatment groups.[131]

Other Renal Outcomes

One trial reported no significant difference between low and usual protein diet groups in risk of doubling of plasma creatinine (RR 0.93, 95% CI, 0.53 to 1.64),[128] while a second trial reported no significant difference between these groups in risk of halving GFR (RR 0.71, 95% CI, 0.44 to 1.17).[132] One trial reported a significant 37 percent lower risk of the composite renal outcome of dialysis or doubling of plasma creatinine concentration in CKD subjects randomized to low protein diet versus usual protein diet (11.7 versus 18.6 percent; RR 0.63, 95% CI, 0.40 to 0.99).[133] A second trial reported that 60 patients reached a study stopping point due to "rapidly declining glomerular filtration rate."[131] Though it did not report this result separately for the two treatment groups, it did report that there was no significant difference in this outcome between the two groups. No other clinical renal events were reported in any trial.

Withdrawals and Adverse Events (Appendix Table C118)

Withdrawals were reported in 10.0 percent of randomized participants (range 1.9 to 27.7, n=6 trials). In the four trials that reported withdrawals by treatment group, withdrawals were 13.5 percent and 15.4 percent in low protein diet subjects and usual protein diet subjects, respectively. No data were reported on serious adverse events or withdrawals due to serious adverse events. One trial reported that 2.0 and 2.1 percent of participants in low protein diet and usual protein diet groups, respectively, stopped the trial due to a "serious medical condition."[131] In the low protein diet group, these conditions were pregnancy (n=1), stroke (n=2), acute renal failure (n=1), diabetes necessitating insulin (n=1), and cancer (n=1). In the usual protein diet group, these conditions were diabetes necessitating insulin (n=3), cardiomyopathy (n=1), cancer (n=1), and severe liver disease (n=1). In the same trial, additional outcomes reported as adverse events in the low protein diet group were weight loss (29 percent), weight gain (25 percent), and hyperkalemia (10 percent). Additional outcomes reported as adverse events in the usual protein diet group were weight loss (18 percent), weight gain (40 percent), and hyperkalemia (17 percent).

Subgroup Results

No trials reported outcomes stratified by any participant characteristic. In two small trials restricted to patients with diabetes, both of which also required participants to have albuminuria, there was no significant difference between low protein and usual protein treatment groups in risk of mortality or ESRD, though there were few clinical events. There also was no difference between treatment groups for doubling serum creatinine (RR 0.93, 95% CI, 0.53 to 1.64, n=1 trial). In two trials restricted to patients without diabetes, while there was no significant difference in risk of mortality, a significantly lower risk of experiencing a composite renal outcome (RR 0.63, 95% CI, 0.40 to 0.99) was seen in one trial reporting, and no ESRD events were reported. In one trial that excluded participants with CHF, there was no significant difference between low protein and usual protein treatment groups in risk of mortality or ESRD, though again there were few clinical events. No trials were either restricted to or excluded participants with hypertension or other cardiovascular conditions.

Summary

In six trials conducted in patients with CKD, low protein diets were associated with a nonsignificant 42 percent reduction in all-cause mortality compared with usual protein diets. In one trial reporting, the small number of cardiovascular deaths appeared similar in both diet intervention groups. No other vascular outcome was reported in more than two cases in any trial. In three trials reporting, all with fewer than 10 cases of ESRD, low protein diets were associated with a nonsignificant 62 percent increase in risk of ESRD compared with usual protein diets. One trial reported a significant 37 percent lower risk of the composite renal outcome of dialysis or doubling of plasma creatinine concentration in CKD subjects randomized to low protein diet versus usual protein diet. Applicability to patients with CKD stages 1–3 may be limited since at least four of six trials also included individuals in CKD stages 4–5. Withdrawals ranged widely between trials but did not appear greater in the low protein diet group in any trial. Results were limited by small sample sizes, few trials reporting clinical vascular or renal outcomes, and almost no events in the trials that reported these outcomes. Judging applicability was limited because of the variability in renal function reported between trials and scant data reported on comorbid conditions. Trials did not systematically report adverse events.

Other Dietary Intervention Trials (n=3)

Overview

In patients with CKD, we found a low level of evidence that, compared with a low protein diet, the CR-LIPE diet reduced risk of mortality or ESRD. There was a low level of evidence that diets altering phosphate intake impacted risk of ESRD and insufficient evidence regarding whether it impacted risk of mortality. There was insufficient evidence regarding whether a low triglyceride diet and pharmacological treatment to lower triglycerides differ regarding risk of mortality or ESRD. Our confidence in these estimates is limited because for each comparison data are drawn from only one trial and there were few reported clinical events.

Description of Studies

Three trials met all eligibility criteria and randomized participants with CKD to a diet intervention versus a control treatment group. Detailed baseline characteristics are presented in Appendix Tables C112 and C113.

Among the three trials, one randomized 191 participants to a carbohydrate restricted, low-iron-available, polyphenol-enriched diet (CR-LIPE) versus a low protein diet.[136] Mean age of study participants was 60 years and 53 percent of study participants were men. The study was conducted in the United States. Followup duration was 3.9 years.

A second trial randomized 57 participants to a triglyceride lowering diet versus gemfibrozil, a triglyceride lowering medication.[137] Mean age of study participants was 51 years and 75 percent of study subjects were men. The study was conducted in Sweden. Followup duration was 1 year.

The third trial randomized 98 participants to either a low protein-low phosphate diet, a low phosphate diet with phosphate binders, or an unrestricted diet.[138] Mean age of study participants was 45 years and 66 percent of study subjects were men. The study was conducted in the United Kingdom. Followup duration was 1.6 years.

Renal Function

For inclusion in the CR-LIPE versus low protein diet trial, participants were required to have GFR 15 to 75 ml/min and UPER 0.35 to 12 g/day. Baseline renal function was reported as mean GFR 63 ml/min, mean UPER 2.47 g/day, and mean creatinine 1.84 mg/dl.[136] For inclusion in the triglyceride lowering diet versus gemfibrozil trial, participants were required to have a GFR of 10 to 70 ml/min/1.73m^2. Baseline renal function was reported as mean GFR of 35.5 ml/min/1.73m^2, mean serum creatinine of 2.4 mg/dl, and mean UAER of 0.95 g/day.[137] For inclusion in the low protein low phosphate diet, low phosphate diet, or unrestricted diet trial, participants were required to have a serum creatinine between 1.7 and 10.2 mg/dl. At baseline, mean serum creatinine was 4.5 mg/dl, mean UPER was 3.15 g/day, and mean creatinine clearance was 26.8 ml/min/1.73m2.[138]

Baseline Comorbidities

For inclusion in the CR-LIPE versus low protein trial, participants were required to be diabetic.[136] No additional information was reported on comorbid conditions. For inclusion in the triglyceride lowering diet versus gemfibrozil trial, participants were required to be nondiabetic. No additional information was reported on comorbid conditions.[137] For the third trial, no information was reported on comorbid conditions.[138]

Study Quality (Appendix Table C140)

All three trials were rated as fair quality. Allocation concealment was adequate in one trial[138] and unclear in the other two studies. One study reported that study personnel were blinded to the aims of the study, but it was unclear if the outcome assessment was blinded.[136] The remaining two studies were unblinded. None of the studies analyzed by the intention-to-treat principle. Withdrawals ranged from 5.3 to 15.8 percent, and reasons for withdrawals were adequately explained in two of the three trials.[136,137]

Results

Mortality (Table 15, Appendix Table C114, Appendix Figure C22)

In one trial, reported all-cause mortality was 8.8 percent in CKD subjects assigned to the CR-LIPE diet compared with 17.7 percent in the low-protein diet group.[136] In a second trial, risk of all-cause mortality was not significantly different between treatment groups, at 3.0 percent, 13.3 percent, and 3.1 percent in the low protein-low phosphate, low phosphate-phosphate binding, and control diet groups.[138] The triglyceride lowering diet trial did not report mortality data.

Vascular Outcomes

Myocardial Infarction

No data were reported for MI.

Stroke

No studies reported on stroke.

Other Vascular Outcomes

No heart failure or composite vascular outcomes were reported.

Renal Outcomes (Table 15, Appendix Tables C116 and C117, and Appendix Figure C22)

End-Stage Renal Disease

In one trial, ESRD occurred in 11.0 percent of CKD subjects allocated to the CR-LIPE diet versus 21.5 percent assigned to the low protein diet group.[136] In a second trial, ESRD occurred in 54.8 percent, 48.3 percent, and 51.7 percent of the low protein-low phosphate diet group, low phosphate-phosphate binding group, and control diet group, respectively.[138] In the trial that compared a low triglyceride diet versus gemfibrozil, progression to ESRD was reported for 3.4 percent and 7.1 percent of these treatment groups, respectively.[137]

Other Renal Outcomes

In one study, participants randomized to a CR-LIPE diet appeared less likely than those assigned to a low protein diet to experience either a doubling in creatinine (20.9 versus 39.2 percent), or the composite renal outcome of renal replacement therapy or death (19.8 versus 39.2 percent, $p<0.05$).[136]

Withdrawals and Adverse Events (Appendix Table C118)

In the trial comparing the CR-LIPE diet and low protein diet, withdrawals by treatment group were 9.0 percent and 13.2 percent respectively.[136] In the trial comparing a low triglyceride diet to gemfibrozil, no withdrawals were reported in the diet group compared with 21.4 percent withdrawals in the gemfibrozil group, with all attributed to mild gastrointestinal symptoms.[137] In the third trial, 5.3 percent of the participants withdrew, but no data were reported according to treatment group.[138] No other adverse events data were reported from any trial.

Summary

In one trial, CKD patients randomized to a carbohydrate-restricted, low iron available, polyphenol-enriched diet (CR-LIPE) appeared to have lower all-cause mortality, lower risk of ESRD, and lower risk of the composite endpoint of ESRD or death compared with participants assigned to a low protein diet. In a second trial, study participants allocated to a low phosphate-phosphate binding diet appeared to have a higher risk of all-cause mortality than did patients assigned to either a low protein-low phosphate diet or to a control diet. There was no apparent difference between these three diet groups in risk of ESRD. In the third trial, results suggested that CKD patients randomized to a low triglyceride diet may have a lower risk of ESRD and fewer gastrointestinal side effects than patients assigned to gemfibrozil. Results were limited in that all trials were small, reported few clinical outcomes, and did not conduct their analyses according to an intention-to-treat principle.

Table 15. Pooled clinical and renal outcomes, dietary intervention trials

Outcome	Number of Trials Reporting	Quality of the Studies	Low Protein Diet Events /N (%)	Usual Protein Diet Events/N (%)	RR [95% CI]*	I^2 test for Heterogeneity
Low-protein diet versus usual protein diet (N=6)						
All-cause mortality	4	Fair	12/642 (1.9)	21/638 (3.3)	0.58 [0.29-1.16]	0%
Cardiovascular death	1	Fair	4/291 (1.4)	5/294 (1.7)	0.81 [0.22-2.98]	NA
Myocardial infarction, fatal	1	Fair	0/47 (0)	1/41 (2.4)	0.29 [0.01-6.97]	NA
Stroke, nonfatal	1	Fair	2/291 (0.7)	0/294 (0)	5.05 [0.24-104.76]	NA
End-stage renal disease	3	Fair	11/154 (7.1)	6/148 (4.1)	1.62 [0.62-4.21]	0%
Doubling of serum creatinine	1	Fair	16/47 (34.0)	15/41 (36.6)	0.93 [0.53-1.64]	NA
Halving of GFR**	1	Fair	18/63 (28.6)	26/65 (40.0)	0.71 [0.44-1.17]	NA
Composite renal outcome†	1	Fair	27/230 (11.7)	42/226 (18.6)	0.63 [0.40-0.99]	NA
Low-protein/low phosphate diet versus low phosphate diet (N=1)						
All-cause mortality	1	Fair	1/31 (3.2)	4/29 (13.8)	0.23 [0.03-1.97]	NA
End-stage renal disease	1	Fair	17/31 (54.8)	14/29 (48.3)	1.14 [0.69-1.86]	NA
Low-protein/low phosphate diet versus usual diet (N=1)						
All-cause mortality	1	Fair	1/31 (3.2)	1/29 (3.4)	0.94 [0.06-14.27]	NA
End-stage renal disease	1	Fair	17/31 (54.8)	15/29 (51.7)	1.06 [0.66-1.70]	NA
Low-protein versus other diet††						
All-cause mortality	1	Fair	14/79 (17.7)	8/91 (8.8)	2.02 [0.89-4.55]	NA
End-stage renal disease	1	Fair	17/79 (21.5)	10/91 (11.0)	1.96 [0.95-4.03]	NA
Doubling of serum creatinine	1	Fair	31/79 (39.2)	19/91 (20.9)	1.88 [1.16-3.05]	NA
Composite renal outcome§	1	Fair	31/79 (39.2)	18/91 (19.8)	1.98 [1.21-3.26]	NA
Low-triglyceride diet versus gemfibrozil (N=1)						
End-stage renal disease	1	Fair	1/29 (3.4)	2/28 (7.1)	0.48 [0.05-5.03]	NA

*RR = relative risk reduction; **GFR = reported as halving of creatinine clearance; NA = not applicable

†Need for dialysis or doubling of baseline plasma creatinine concentration.

††50% carbohydrate restricted, low-iron-available, polyphenol-enriched diet.

§Renal replacement therapy or death.

Glycemic Control Trials (n=2)

Overview

In diabetic patients with CKD, we found insufficient evidence regarding whether there is a difference between treatments in risk of mortality or ESRD. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events, and heterogeneity between studies.

Description of Studies

Two trials met all eligibility criteria and randomized participants with diabetes and CKD to intensive versus standard glycemic control.[139,140] Detailed baseline characteristics are presented in Appendix Tables C119 and C120.

In the first study, conducted in 70 patients, those assigned intensive diabetes control (treatment targets HbA_{1c} ≤7.5percent, fasting blood glucose 72 to 108 mg/dL, and 2 hour postprandial blood glucose ≤180 mg/dL) were treated using insulin by continuous infusion or multiple daily injections. Frequent visits and medication adjustment were made as needed, and 24 hour/day consultation was available. Participants assigned to conventional therapy (no glycemic targets) generally were treated using two daily insulin injections, adjusted only for symptoms, along with conventional education about diet, exercise, and blood glucose monitoring. Standard control patients were seen every 3 months. No changes were made to the usual diabetic diet of participants in either treatment group, and all patients were treated to keep their blood pressure <160/95 mm Hg.[140] Mean age was 37 years, 73 percent of participants were male, and no data was reported on ethnicity.

In the second study, a subgroup analysis within 491 patients with microalbuminuria from a larger diabetes treatment trial (n=1,791), trial participants allocated to the intensive control group were started on maximal doses of oral therapy, and insulin was added as needed to achieve a target HbA_{1c} <6 percent.[139] Participants assigned to standard control were started on one-half of maximal doses of oral therapy and insulin was added as needed to achieve a target HbA_{1c} <9 percent. No data on age, gender, or ethnicity was reported for the subgroup with microalbuminuria.

Renal Function

Both trials were restricted to participants with microalbuminuria. In one study this was defined as UAER between 30 and 200 μg/min.[140] In the second trial, in which subgroup results were reported for conversion from microalbuminuria to macroalbuminuria, no definition of microalbuminuria was reported. Participants in this second trial further were restricted to those with serum creatinine ≤1.6 mg/dl.[139] Participant mean baseline GFR was 116.7 ml/min/1.73m^2 and mean UAER was 47.9 μg/min.

Baseline Comorbidities

Both trials were restricted to participants with diabetes. The first trial enrolled patients with baseline blood pressure <160/95 mm Hg and no evidence of diabetic macrovascular complications.[140] Participant mean HbA_{1c} was 10.1 percent. The second trial enrolled individuals with type 2 diabetes who had HbA_{1c} >7.5 percent, despite maximal doses of oral agents or on insulin.[139] In this second trial, no baseline characteristics were reported for the subgroup of

participants with microalbuminuria, though overall study excluded patients with a cardiovascular event during the previous 6 months, advanced CHF, or severe angina.

Results

Mortality (Appendix Table C121)

During median followup durations of about 5 years, neither trial reported results comparing intensive versus standard glycemic control within their CKD population for the outcome of mortality. One trial reported that one CKD patient died (2.7 percent) but did not report the group assignment of the patient.[140]

Vascular Outcomes

Myocardial Infarction

Neither trial reported on MI.

Stroke

Neither trial reported stroke outcomes.

Other Vascular Outcomes

Neither trial reported any composite vascular outcomes.

Renal Outcomes (Table 16, Appendix Table C122)

End-Stage Renal Disease

There were no reports of ESRD.

Other Renal Outcomes (Appendix Figure C23)

One trial reported that one patient experienced acute renal failure (2.7 percent) but did not report the group assignment of the patient.[140] In data from both trials, compared with conventional treatment, participants allocated to intensive diabetes treatment had a nonsignificant 31 percent relative reduction in risk of conversion from microalbuminuria to macroalbuminuria (8.7 versus 12.8 percent; RR 0.69, 95% CI, 0.42 to 1.12; n=561 patients). Neither study reported on any other renal outcomes.

Study Withdrawals and Adverse Events (Appendix Table C123)

Only one of the two trials reported study withdrawals,[140] with 13.9 percent versus 8.8 percent in the intensive versus conventional treatment groups, respectively. While it further noted that 4.3 percent (three of 70) of study participants withdrew due to serious adverse events, including one death, one leukemia, and one acute renal failure, it did not report these outcomes by treatment group. In one trial, neither incidence of severe hypoglycemia or diabetic ketoacidosis appeared to differ between CKD patients assigned to the two treatment groups.[139] In the second trial, risk of hypoglycemia was not reported for the CKD subgroup, but in the larger overall study population frequency of hypoglycemic events and frequency of severe hypoglycemic events was significantly greater in the intensive control group ($p<0.001$).[140]

Subgroup Results

No trials reported outcomes stratified by any participant characteristic. However, both trials were restricted to patients with diabetes and microalbuminuria, so all results reported above apply to these subgroups. No other subgroup results are available since no trials were restricted to patients with impaired eGFR, or with a history of hypertension or cardiovascular disease, and no trials excluded patients with these conditions. Since both trials were limited to participants with microalbuminuria, no data for patients with macroalbuminuria are available.

Summary

In diabetic individuals with CKD, compared with conventional treatment, assignment to intensive diabetes treatment was associated with an approximately 31 percent relative reduction in risk of conversion from microalbuminuria to macroalbuminuria that was not statistically significant. There were no data regarding the relative risk between these treatment strategies for all-cause or cardiovascular mortality, MI, stroke, ESRD, doubling of serum creatinine, halving of GFR, or any composite vascular or renal endpoint. Reporting on withdrawals and adverse effects associated with these treatment regimens in CKD patients was limited. Results were limited by the small number of trials, few outcomes reported, the heterogeneity of patient populations, and the heterogeneity in intensity of treatment regimens.

Table 16. Pooled clinical and renal outcomes, glycemic control trials

Outcome	Number of Trials Reporting	Quality of the Studies	Intensive Treatment Events/N (%)	Conventional Treatment Events/N (%)	Relative Risk [95% CI]	I^2 test for Heterogeneity
Intensive treatment versus conventional treatment trials (n=2)						
Progression from micro- to macroalbuminuria	2	Good	25/287	35/274	0.69 [0.42-1.12]	0%

HMG-CoA Reductase Inhibitors (Statins) Versus Control Trials (n=12)

Overview

In patients with CKD defined by impaired GFR, in comparison to control treatment, there is a high level of evidence that statins reduce risk of all-cause mortality. There is a low level of evidence that there is no difference between statins and control treatment for risk of ESRD. Compared with participants assigned to control, those randomized to statin had a statistically significantly lower risk of MI, stroke, and most composite cardiovascular outcomes, but no statistically significant difference in risk of cardiovascular mortality, CHF hospitalization, or a single composite renal outcome. Our confidence in these estimates is limited by the heterogeneity between studies and because all outcomes data are drawn from post hoc analyses.

Description of Studies

Twelve trials met all eligibility criteria and randomized participants with CKD (n=17,460, range 304 to 4,491) to statin therapy versus control.[62,83,141-149] One study, the CARE trial, was reported both by itself[148] and as part of a pooled subject-level meta-analysis of three trials of pravastatin versus placebo.[149] All but one study[62] were post hoc analyses performed within subsets of participants with CKD from larger trial populations not originally limited to subjects with CKD. Detailed baseline characteristics are presented in Appendix Tables C124 and C125.

Among eligible trials, 9,890 participants were randomized to pravastatin versus control, including 5,355 versus placebo (n=2 trials),[62,149] 2,978 versus diet (n=1 trial),[142] and 1,557 versus usual care (n=1 trial).[83] In addition, 4,902 participants were randomized to rosuvastatin versus placebo (n=2 trials),[146,150] and 1,549 participants were randomized to atorvastatin versus control, including 970 versus placebo (n=1 trial)[143] and 579 versus usual care (n=1 trial).[144] There also were several smaller studies, in which 505 participants were randomized to simvastatin versus placebo (n=1 trial),[145] 310 participants were randomized to fluvastatin versus placebo (n=1 trial),[147] and 304 participants were randomized to lovastatin versus placebo (n=1 trial).[141] The mean age of subjects was 65 years (range 51 to 71; n=10 trials), and men constituted 53 percent (range 24 to 82; n=10 trials) of all patients randomized. Among the six trials that reported race/ethnicity, 79 percent of participants were white. The majority of trials were multinational.[83,143,145-147,149,150] Mean or median study duration ranged from 1.9 to 5.4 years, with most trials having a followup of at least 4 years.

Renal Function

All studies except one were post hoc analyses from large statin trials, performed in subsets of participants with decreased GFR or creatinine clearance from the larger trial populations. Most of these analyses defined impaired GFR or creatinine clearance as <60 ml/min/1.73m^2,[83,141-144,149,150](i.e., CKD stage 3 or worse) or at least provided data for patients under this threshold.[145] No other trials based study eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Instead, individual studies defined impairment as GFR <51 ml/min/1.73m^2,[146] and creatinine clearance of <55.9 ml/min[147] and <75 ml/min.[148] In trials reporting, mean baseline serum creatinine was 1.3 mg/dL (range 1.0 to 1.5, n=9 trials), mean GFR was 54 ml/min/1.73m^2 (range 50 to 56; n=10 trials), and mean creatinine clearance was 59 ml/min (range 47 to 61; n=2 trials). Most of the larger trials on which the post hoc analyses were

based excluded at least some patients with impaired renal function, with exclusion thresholds ranging from creatinine >1.5 to 1.8 mg/dL,[142,143,147,149] >2.0 mg/dL,[150] >2.5 mg/dL,[146,148] to >4.5 mg/dL.[149] One trial excluded participants with creatinine clearance less than 60 percent of the age-based normal.[62] Just one trial required participants to have microalbuminuria for inclusion,[62] and this was also the only trial to report mean baseline urinary albumin excretion (23 mg/24 hours).

Baseline Comorbidities

One trial was restricted to patients with diabetes,[143] and the mean prevalence of diabetes among 11 trials reporting was 22 percent (range 2 to 100). One trial was restricted to patients with hypertension,[83] while hypertensive patients were excluded from one trial.[62] The mean prevalence of hypertension was 49 percent among nine trials reporting. Mean systolic blood pressure was 136 mm Hg (range 131 to 146; n=10 trials) and mean diastolic blood pressure was 80 mm Hg (range 75 to 84; n=9 trials). Six trials were restricted to patients with coronary artery disease (secondary prevention studies),[144-149] including one restricted to patients with a history of myocardial infarction,[148] while patients with coronary artery disease were excluded from five trials (primary prevention studies).[141-143,149,150] The mean prevalence of coronary artery disease was 46 percent in 12 trials reporting. One trial was restricted to patients with CHF,[146] while patients with CHF were excluded from one trial.[62] The mean prevalence of CHF in four trials reporting was 39 percent. Mean baseline total cholesterol and low density lipoprotein (LDL) cholesterol were 220 mg/dL (range 189 to 265) and 142 mg/dL (range 109 to 192), respectively (n=12 trials).

Study Quality (Appendix Table C140)

Study quality was rated as good in eight trials and as fair in four trials. The method of allocation concealment was adequate in nine trials[83,142-146,148-150] but was unclear in three studies.[83,145,149] Nine trials were double blinded, of which eight explicitly stated that outcomes were adjudicated by blinded assessors.[62,141,143,145-147,149,150] Three trials were open label studies,[83,142,144] though one stated that outcomes were adjudicated by blinded assessors.[83] Analysis was by intention to treat in eleven studies[62,83,141-144,146-150] and not by intention to treat in one study.[145] None of the post hoc analyses reported the number of withdrawals within the subgroup of participants with impaired GFR. Only the trial that enrolled participants on the basis of microalbuminuria reported withdrawals (23 percent).[62]

Results

Mortality (Table 17, Appendix Table C126, and Appendix Figure C24)

All-Cause Mortality

In CKD patients assigned to statins versus control, there was a significant 20 percent reduction in all-cause mortality (7.1 versus 8.7 percent; RR 0.80, 95% CI, 0.68 to 0.95; n=8 trials, 13,964 patients).[62,142-145,147,149,150] However, in three trials that limited entry to patients with coronary artery disease, the 11 percent reduced all-cause mortality among patients randomized to statin treatment was not statistically significant (12.8 versus 14.3 percent; RR 0.89, 95% CI, 0.68 to 1.15; n=1,394 patients)[144,145,147] (Figure 8). In three trials that limited enrollment to patients without coronary artery disease, the 37 percent relative reduction in all-cause mortality was

statistically significant (2.1 versus 3.4 percent; RR 0.63, 95%CI, 0.44 to 0.90; n=7,215 patients)[142,143,150] (Figure 8).

Cardiovascular Mortality

In the four trials reporting data for cardiovascular mortality, there were few events (2.4 versus 3.4 percent for statin and control groups, respectively), with a nonsignificant 29 percent relative risk reduction in this outcome in participants randomized to statin treatment versus control (RR 0.71, 95% CI, 0.43 to 1.71; n=2,057 patients).[62,141,144,147] There also was no significant difference in risk of cardiovascular mortality between subjects assigned to statin versus control groups in two trials limited to patients with coronary artery disease (4.6 versus 6.6 percent; RR 0.69, 95% CI, 0.40 to 1.19; n=889 patients)[144,147] or in one trial limited to patients without coronary artery disease (0 versus 0.6 percent).[141]

Vascular Outcomes (Table 17, Appendix Tables C126–C128, and Appendix Figure C24)

Myocardial Infarction

In patients with CKD, assignment to statin treatment versus control was associated with a significant 28 percent reduction in risk of MI (RR 0.72, 95% CI, 0.54 to 0.98; n=2 trials, 2,015 patients).[141,148] In one secondary prevention trial, there was no statistically significant reduction in risk of MI between treatment groups (RR 0.74, 95% CI, 0.55 to 1.01; n=1,911 patients).[148] Similarly, in one primary prevention trial with few events, there was no significant reduction in risk of MI between treatment groups (RR 0.37, 95% CI, 0.07 to 1.78; n=304 patients).[141] Nonfatal MI was reported in one primary prevention and one secondary prevention trial. The primary prevention study alone demonstrated a significant reduction in the risk of nonfatal MI in the statin group compared with the placebo group (0.5 versus 1.2 percent; RR 0.40, 95% CI, 0.18 to 0.90). In the secondary prevention study, there was no significant reduction in risk of this outcome in statin subjects compared with those assigned to control (5.9 versus 9.9 percent; RR 0.60, 95% CI, 0.34 to 1.07).[144]

Stroke

In patients with CKD, assignment to statin treatment versus control significantly reduced the risk of stroke (1.4 versus 2.3 percent; RR 0.62, 95% CI, 0.41 to 0.95; n=6 trials, 10,369 patients).[62,142-144,148,150] The reduction in risk of stroke did not reach statistical significance in two secondary prevention trials (3.5 versus 5.0 percent; RR 0.71% 95% CI, 0.48 to 1.05; n=2,290 patients).[144,148] However, in three primary prevention trials, risk of stroke was significantly lower in statin patients than in those allocated to control (0.7 versus 1.6 percent; RR 0.43, 95% CI, 0.25 to 0.75; n=7,215 patients).[142,143,150]

Other Vascular Outcomes

In two trials reporting data, including one with fewer than 0.5 percent clinical events in either treatment group,[62] risk of hospitalization due to CHF in individuals with CKD was not significantly different between those who were randomized to statin treatment versus control (RR 0.7, 95% CI, 0.38 to 1.32; n=1,443 patients).[62,144] Nearly all trials reported multiple composite cardiovascular outcomes. For every composite cardiovascular outcome for every trial, the risk of the composite outcome was numerically lower (RR range 0.42 to 0.99) in study participants with CKD assigned to the statin group versus those allocated to control. This

difference was statistically significant in the majority of comparisons. Because the definition of the composite cardiovascular outcomes varied between trials, no pooled risk estimate was calculated

Renal Outcomes (Table 17, Appendix Tables C129 and C130, and Appendix Figure C24)

End-Stage Renal Disease

Only one trial reported results for ESRD.[83] In this trial of individuals with CKD with and without coronary artery disease there was no difference in risk of ESRD between study participants with CKD allocated to statin versus control treatment (4.1 versus 4.0 percent; RR 1.05, 95% CI, 0.64 to 1.73; n=1,557 patients).

Other Renal Outcomes

Similarly, this study reported no difference between treatment groups in the risk of experiencing the composite renal outcome of ESRD or ≥50 percent decline in renal function (6.4 versus 6.7 percent, RR 0.97, 95% CI, 0.66 to 1.43).[83] Only one trial reported on doubling of serum creatinine,[150] and there was no difference between groups for this rare outcome.

Study Withdrawals and Adverse Events (Appendix Table C131)

One trial provided data on withdrawals within patients with CKD, reporting 20 percent in the statin subjects and 26 percent in the placebo subjects.[62] However, the study included within these totals, 5 percent and 8 percent in each group withdrawn for "other medical reasons," which in part were comprised of subjects reaching study endpoints (i.e., cardiovascular mortality or hospitalization). A second trial reported no withdrawals among 1,711 subjects in both treatment groups.[148] No other post hoc analyses reported information on withdrawals for CKD patients.

Only five trials reported any data on adverse events within study participants with CKD. Four trials reported on the incidence of elevated creatine kinase, with two trials reporting only one control patient with creatine kinase exceeding ten times the upper limit of normal,[141,144] one trial reporting 0.7 and 0.3 percent of statin and control subjects, respectively, with creatine kinase levels exceeding three times the upper limit of normal,[148] and one trial reporting that 2.6 percent of participants in both treatment groups had a creatine kinase level greater than 500 IU.[142] In four trials reporting, rhabdomyolysis occurred in one of 2,913 (0.03 percent) statin subjects and four of 2,958 (0.1 percent) control group subjects.[141,144,148,150] Four trials reported incidence of abnormal liver function tests.[142,144,148,150] In all, the incidence was low, and in three trials that reported results for both statin and control groups,[142,148,150] there was no difference between these groups.

Subgroup Results

No trials reported outcomes stratified by any participant characteristic within CKD subjects. As noted above, in secondary prevention trials, compared with those assigned placebo, participants randomized to statins had no significant reduction in all-cause mortality (12.8 versus 14.3 percent; RR 0.89, 95% CI, 0.68 to 1.15; n=3 trials, 1,394 patients)[144,145,147] (Figure 8), cardiovascular mortality (RR 0.69, 95% CI, 0.40 to 1.19; n=2 trials, 889 patients), MI (RR 0.74, 95% CI, 0.55 to 1.01, n=1 trial, 1,711 patients), or stroke (RR 0.71, 95% CI, 0.48 to 1.05; n=2 trials, 2,290 patients), but were significantly less likely to experience a CHF hospitalization (RR

0.55, 95% CI, 0.39 to 0.77, n=1 trial, 3,107 patients). In addition, in primary prevention trials, compared with those assigned placebo, participants randomized to statins had a significant reduction in all-cause mortality (2.1 versus 3.4 percent; RR 0.63, 95% CI, 0.44 to 0.90; n=3 trials, 7,215 patients) (Figure 8), stroke (RR 0.43, 95% CI, 0.25 to 0.75; n=3 trials, 7,215 patients). None of these primary or secondary prevention trials reported any renal outcome measure.

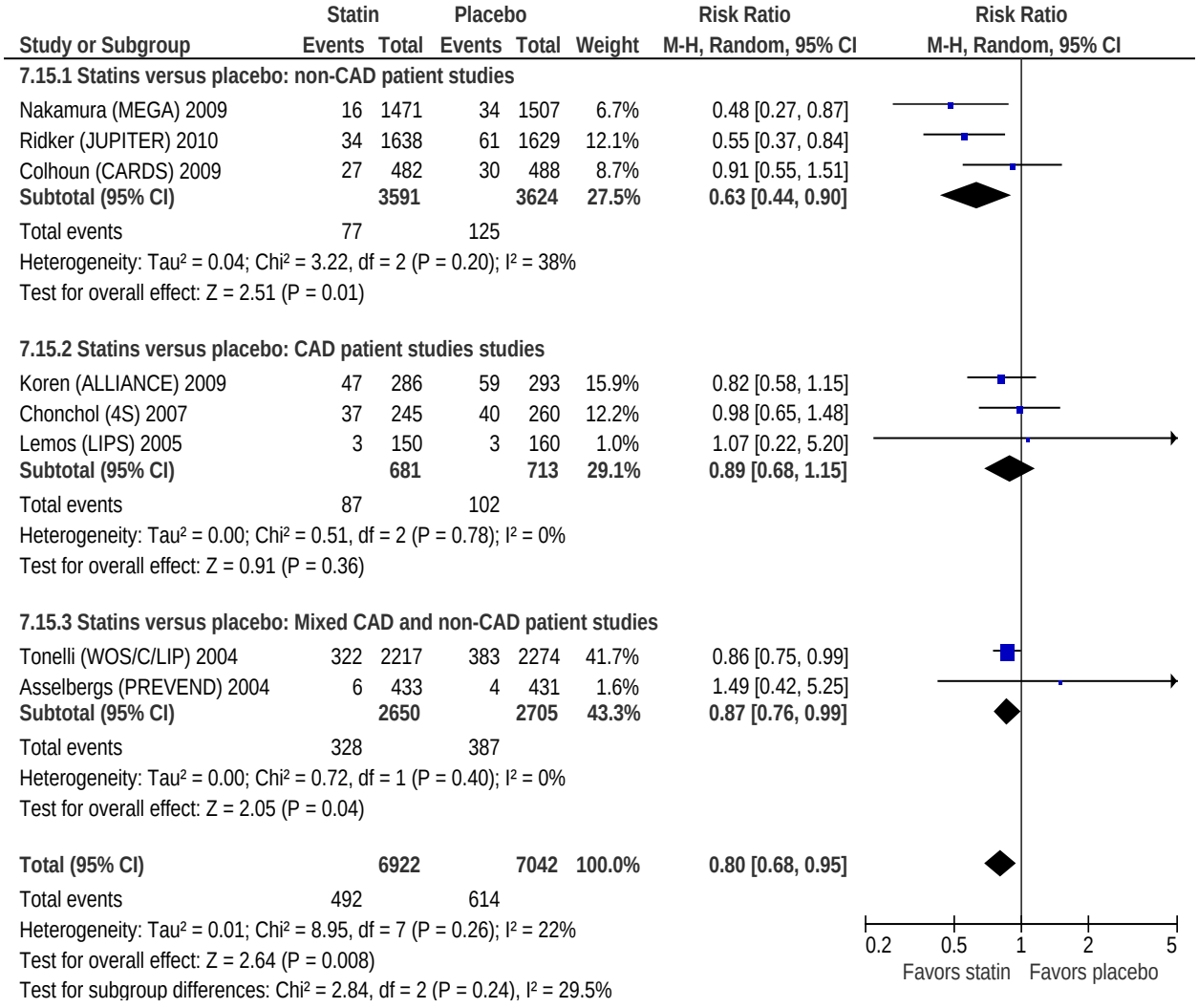
In one trial limited to participants with diabetes, there was no significant between treatment difference in risk of all-cause mortality (RR 0.91, 95% CI, 0.55 to 1.51) or stroke (RR 0.40, 95% CI, 0.16 to 1.04), and mixed results for several composite vascular outcomes reported. In one trial limited to participants with hypertension, there was no difference between statins and placebo in risk of ESRD (RR 1.03, 95% CI, 0.64 to 1.67) or of a composite renal outcome, and no results were reported for mortality, MI, stroke, or other renal outcomes. In one trial limited to participants with CHF, there was no between treatment difference in risk of a composite vascular outcome and no results were reported for mortality, MI, stroke, CHF events, or any renal outcomes. In one trial that excluded patients with either CHF or hypertension, and was the only trial to require microalbuminuria for inclusion, participants randomized to statins did not have a significant reduction in risk of mortality (RR 1.49, 95% CI, 0.42 to 5.25), stroke (RR 1.74, 95% CI, 0.51 to 5.91), CHF hospitalization (RR 1.00, 95% CI, 0.06 to 15.86), or either of two composite vascular outcomes. No trials required macroalbuminuria for entry.

Summary

In individuals with CKD, statin treatment, as compared with control, was associated with significant relative reductions in risk of all-cause mortality (20 percent), MI (28 percent), and stroke (38 percent). Results appear to favor statin in both patients with and without a history of coronary artery disease, though results were statistically significant only for patients without coronary artery disease for mortality and stroke outcomes. Overall results were statistically nonsignificant but in favor of statin versus control for risk of hospitalization due to congestive heart failure. Risk for most composite vascular outcomes was significantly lower in CKD patients assigned statin treatment. In results available from only one trial, there was no difference between statin and control treatment groups regarding risk of ESRD or a composite outcome of ESRD or GFR decline by at least 50 percent. Only one trial reported on doubling of serum creatinine, but it had very few events.

While the magnitude of effect sizes favoring statins for many vascular outcomes, if real, seemed large enough to be clinically meaningful, results were limited by the small number of events in many studies and by small sample sizes in some others, in particular for analyses evaluating results in separate primary and secondary prevention subgroups. Results also were limited because, with one exception, studies were post hoc subgroup analyses from large statin trials that were not originally designed to evaluate CKD patients and renal outcomes. Consequently, there are almost no data on any renal outcome or on any vascular or renal outcome as a function of baseline albuminuria. Because most trials excluded patients with moderate and/or severely impaired renal function, available results may not be generalizable to these populations. Another limitation was that though composite vascular endpoints were reported in nearly all trials, the variability in their definitions prevented statistical pooling. Finally, few studies provided data on withdrawals or adverse events, so there was little information available regarding the relative tolerability and safety of statins versus control treatments in this population.

Figure 8. Statins versus placebo: Mortality by coronary artery disease (CAD) subgroups



High-Dose Versus Low-Dose HMG-CoA Reductase Inhibitors Trials

Overview

In patients with CKD, there is a low level of evidence that there is no difference in risk of mortality between treatment with high versus low dose statin. There is insufficient evidence regarding whether there is a difference between high and low dose statin in risk of ESRD. Our confidence in these estimates is limited by the small number of trials reporting different outcomes and the small number of clinical events.

Description of Study

Two trials met all eligibility criteria and randomized participants with CKD to high versus low dose HMG-CoA reductase inhibitor treatment.[151,152] The first study was a post hoc analysis in 3,107 individuals with eGFR <60 ml/min/1.73m^2 from among the 10,003 enrolled in the TNT trial. The second study was a post hoc analysis in 1,686 individuals with a eGFR <60 ml/min/1.73m^2 from among the 12,064 enrolled in the SEARCH trial. Detailed baseline characteristics are presented in Appendix Tables C124 and C125.

Patients were randomized to atorvastatin 10 mg daily versus atorvastatin 80 mg daily in the TNT trial and to simvastatin 20 mg daily versus simvastatin 80 mg daily in the SEARCH trial. Only the TNT trial provided baseline characteristics for the CKD participants. The mean age of participants in the TNT post hoc analysis was 66 years, and men constituted 68 percent of patients. Ninety-five percent of study participants were white. Both trials were multinational. Mean or median study duration ranged from 5.0 to 6.7 years.

Renal Function

Study participants were required to have eGFR <60 ml/min/1.73m^2 (i.e., CKD stage 3 or worse), but did not otherwise report participant distribution by CKD stage. Mean eGFR was 53 ml/min/1.73m^2 in the TNT study. No other measures of renal function were reported.

Baseline Comorbidities

All participants in the TNT trial had coronary artery disease and hyperlipidemia while off cholesterol medications, while participants in the SEARCH trial had a history of myocardial infarction and either were taking or considered to have a clear indication for statin therapy. Additional comorbid conditions from TNT participants included hypertension (63 percent) and diabetes (18 percent). Mean baseline blood pressure was 133/78 mm Hg. In the TNT trial, all participants completed an 8 week open-label run-in of atorvastatin 10 mg daily, and only those with LDL cholesterol less than 130 mg/dL were considered for enrollment, mean baseline total cholesterol and LDL cholesterol were 176 mg/dL and 96 mg/dL, respectively. In the SEARCH trial, all participants completed a run-in period of treatment with 20 mg of simvastatin daily.

Study Quality (Appendix Table C140)

Study quality was rated as fair in one trial and good in one trial. Both trials reported that they were double blind. However, in the TNT post hoc analysis it was unclear whether allocation concealment was adequate, and analysis was not by intention to treat. Only 0.4 percent of TNT participants withdrew from the overall study, but withdrawals in the CKD subset were not reported. In the SEARCH trial, allocation concealment was adequate, analysis was intention to treat, and withdrawals were adequately reported.

Results

Mortality (Table 17, Appendix Table C126, and Appendix Figure C24)

In participants with CKD, only the TNT trial reported on this outcome. There was no significant difference between high and low dose statin groups regarding risk of all-cause mortality (7.0 versus 7.5 percent; RR 0.93, 95% CI, 0.72 to 1.20).

Vascular Outcomes (Table 17, Appendix Tables C126-C128, and Appendix Figure C24)

Myocardial Infarction

No results were reported for MI.

Stroke

No results were reported for stroke.

Other Vascular Outcomes

Risk for hospitalization due to CHF (3.1 versus 5.5 percent; RR 0.55, 95% CI, 0.39 to 0.77) and for all of the five defined composite vascular outcomes in the TNT trial was significantly lower in CKD patients assigned to high dose statin as compared with low dose statin. The composite vascular outcome was not different between groups in the SEARCH trial.

Renal Outcomes

End-Stage Renal Disease

No results were reported for ESRD.

Other Renal Outcomes

No results were reported for doubling of serum creatinine, halving of GFR, progression from microalbuminuria to macroalbuminuria, or for any composite renal outcome.

Withdrawals and Adverse Events (Appendix Table C131)

Only the TNT trial reported on these events. Less than 0.5 percent of participants with CKD withdrew from the study in both high and low dose statin groups. Treatment related adverse effects (8.7 versus 5.2 percent) and treatment discontinuations attributed to adverse effects (4.2 versus 1.9 percent) both were more common in study participants assigned high dose statins. Liver function abnormalities occurred in 1.4 versus 0.1 percent of patients on high versus low dose statin, respectively.

Summary

In individuals with CKD defined by reduced eGFR, high dose statin did not reduce all-cause mortality but significantly reduced risk of hospitalization attributed to CHF and risk of all defined composite vascular endpoints in the TNT trial, but did not reduce risk of the single reported composite vascular outcome in the SEARCH trial. There were no data reported for the individual outcomes of MI, stroke, ESRD, doubling of serum creatinine, halving of GFR, progression from microalbuminuria to macroalbuminuria, or for any composite renal outcome. Results were limited because they were based on two post hoc analyses, there were no data comparing treatment results in patients with albuminuria, and results were not reported for many vascular outcomes or any renal outcomes of clinical interest.

HMG-CoA Reductase Inhibitor Versus Bile Acid Sequestrant Trial

Overview

In patients with CKD, there is insufficient evidence regarding whether there is any difference between these treatments for the outcomes of mortality or ESRD. Our confidence in these estimates is limited because data are drawn from only one trial and there were few reported clinical events.

Description of Study

One trial met all eligibility criteria and randomized 86 participants with CKD to an HMG-CoA reductase inhibitor versus a bile acid sequestrant.[153] Detailed baseline characteristics are presented in Appendix Tables C124 and C125.

Participants were randomized to simvastatin versus cholestyramine. The mean age of subjects was 62 years. No data on gender or race/ethnicity was reported. Followup duration for this study, based in a single site in Italy, was 4 years.

Renal Function

The study did not base eligibility on CKD stage or report baseline distribution of participants by CKD stage. All participants were required to have microalbuminuria (urine albumin-to-creatinine ratio between 30 and 300 µg/mg) and at least a small measurable decline in GFR in the past 3 years. Mean GFR was 91 ml/min/1.73m2. Mean urine albumin/creatinine ratio was 83 µg/mg

Baseline Comorbidities

Eligible patients had treated hypertension and type 2 diabetes. Mean systolic blood pressure was 131 mm Hg and mean diastolic blood pressure was 76 mm Hg. No information on other comorbid conditions was reported.

Study Quality (Appendix Table C140)

Study quality was rated as fair. Though the adequacy of treatment allocation concealment was unclear, the study was double blinded and analysis was conducted using the intention-to-treat principle. Withdrawals were adequately described and five percent of participants withdrew from the study.

Results

Mortality

No information on mortality was reported.

Vascular Outcomes (Appendix Table C126)

Myocardial Infarction

The study reported that one participant experienced an MI, but did not indicate this patient's treatment group.

Stroke

No stroke outcomes were reported.

Other Vascular Outcomes

No information on CHF or any other vascular outcome was reported.

Renal Outcomes (Appendix Table C129)

End-Stage Renal Disease

No results were reported for ESRD.

Other Renal Outcomes

The study reported that conversion from microalbuminuria to macroalbuminuria occurred in 4 percent of participants randomized to simvastatin versus 15 percent of those assigned to

cholestyramine ($p<0.01$), but did not provide results for the number of participants experiencing these events in each treatment group or the denominators on which these calculations were derived. No results were reported for other renal outcomes.

Withdrawals and Adverse Events (Appendix Table C131)

Withdrawals, all due to adverse events, were reported in 2.3 percent (n=1) versus 7.0 percent (n=3) of CKD patients allocated to simvastatin and cholestyramine treatment, respectively. The study reported that these adverse events included renal cancer (n=2), and three- to four-fold increase of liver function tests above baseline levels (n=1), but did not indicate any patient's treatment group.

Summary

In patients with CKD defined by microalbuminuria, hypertension and diabetes, simvastatin significantly reduced risk of conversion to macroalbuminuria as compared with cholestyramine. There were no between-treatment group data for the endpoints of mortality, MI, stroke, CHF, ESRD, doubling of serum creatinine, halving of GFR, or for any composite vascular or renal outcome. Results were limited because they were based on a single small trial, and there were no between-treatment results for any vascular outcome or any other renal outcomes of clinical interest.

Gemfibrozil Versus Placebo or Control Trials (n=2)

Overview

In CKD patients defined by impaired GFR, we found a low level of evidence that there is no difference between gemfibrozil and placebo for risk of mortality. There was insufficient evidence regarding whether gemfibrozil and a low triglyceride diet differ for risk of mortality. There was insufficient evidence regarding whether gemfibrozil differs from either placebo or a low triglyceride diet for risk of ESRD. Our confidence in these estimates is limited because for each comparison data are drawn from only one trial and there were few reported clinical events.

Description of Studies

Two trials met all eligibility criteria and randomized participants with CKD to gemfibrozil versus a control treatment.[137,149,154] The largest of the two trials involved a post hoc analysis involving 470 participants with GFR <60 ml/min/1.73m^2 from the larger (n=2,531) VA-HIT trial. Detailed baseline characteristics are presented in Appendix Tables C124 and C125.

Participants in the post hoc VA-HIT trial analysis were randomized to gemfibrozil versus placebo. The mean age of participants in this analysis was 67 years, all participants were male U.S. veterans, and 91 percent of study participants were white. Followup for this multinational study was 5.3 years.[149,154] The second study randomized 57 nondiabetic patients to gemfibrozil versus a low triglyceride diet. The mean age of study participants was 51 years, and men constituted 75 percent of study participants. No data on race/ethnicity were reported. Followup for this single-site Swedish study was 1 year.[137]

Renal Function

In the VA-HIT post hoc analysis, participants were required to have GFR <60 ml/min/1.73m^2 (CKD stage 3 or worse).[149,154] All participants in the larger VA-HIT study had been required to

have baseline serum creatinine ≤2.0 mg/dL. Mean GFR was 52 ml/min/1.73m^2. Mean creatinine clearance was 60 ml/min/1.73m^2. The second study did not base eligibility on CKD stage. The second study enrolled patients with impaired GFR (10 to 70 ml/min/1.73m^2).[137] Mean GFR was 36 ml/min/1.73m^2 and mean albuminuria was 0.95 g/24 hours. Mean serum creatinine was 2.4 mg/dL. Neither study reported baseline distribution of participants by CKD stage

Baseline Comorbidities

All participants in the VA-HIT trial had coronary heart disease, LDL cholesterol ≤140 mg/dL, and HDL cholesterol ≤40 mg/dL. Additional comorbid conditions included hypertension (67 percent) and diabetes (30 percent). Mean baseline systolic blood pressure was 134 mm Hg, and mean diastolic blood pressure was 77 mm Hg. Mean total and LDL cholesterol were 176 mg/dL and 111 mg/dL, respectively. The second study excluded individuals with diabetes.[137] Mean baseline systolic blood pressure was 137 mm Hg, and mean diastolic blood pressure was 84 mm Hg. Mean total and LDL cholesterol were 244 mg/dL and 170 mg/dL, respectively. No other comorbidity data were reported.

Study Quality (Appendix Table C140)

Study quality of the VA-HIT post hoc analysis was rated as good. The adequacy of treatment allocation concealment in the first study was clear. The study was double blinded, including outcome adjudication by a blinded endpoint committee. Analysis was performed using the intention-to-treat principle. No study participants were reported as lost to followup.[149,154] Study quality of the second study was rated as fair. The adequacy of treatment allocation concealment in the second study was unclear. The study was open label, and analysis was not performed using the intention-to-treat principle. Withdrawals were adequately described, and 11 percent of study participants withdrew from the study.[137]

Results

Mortality (Table 17, Appendix Table C126, and Appendix Figure C24)

In the VA-HIT study, there was no significant difference in risk of all-cause mortality between CKD patients assigned to gemfibrozil versus placebo (10.0 versus 11.0 percent; RR 0.91, 95% CI, 0.52 to 1.62, n=399 patients).[149,154] The gemfibrozil versus low triglyceride diet trial did not report results for mortality.[137]

Vascular Outcomes (Table 17, Appendix Table C126-C128 and Appendix Figure C24)

Myocardial Infarction

No between-treatment results were reported for MI for either study.[137,149,154]

Stroke

No between-treatment results were reported for stroke for either study.[137,149,154]

Other Vascular Outcomes

In patients with CKD within the VA-HIT study, no between-treatment results were reported for the primary composite vascular outcome. For a second composite vascular outcome that included fatal CHD, nonfatal MI, and stroke, risk was significantly lower in participants assigned

to gemfibrozil versus placebo (24.0 versus 32.9 percent; RR 0.73, 95% CI, 0.54 to 0.97, n=470 patients).[149,154] The gemfibrozil versus low triglyceride diet trial did not report results for any vascular outcome.[137]

Renal Outcomes (Table 17, Appendix Table C129, and Appendix Figure C24)

End-Stage Renal Disease

In the VA-HIT study, no patient in either the gemfibrozil or placebo treatment groups experienced ESRD.[149,154] In the gemfibrozil versus low triglyceride diet trial, two of 28 (7.1 percent) CKD participants randomized to gemfibrozil and one of 29 (3.4 percent) allocated to diet developed ESRD.[137]

Other Renal Outcomes

Neither study reported results for doubling of serum creatinine, halving of GFR, or for any composite renal outcome.

Withdrawals and Side Effects (Appendix Table C131)

The VA-HIT trial reported no withdrawals and no cases of rhabdomyolysis or elevation of creatine kinase more than three times the upper limit of normal in either treatment group. The gemfibrozil versus low triglyceride diet trial reported withdrawals in 21.4 percent of gemfibrozil participants, all of which were attributed to "mild gastrointestinal symptoms," while there were no withdrawals or gastrointestinal side effects reported in the diet group.

Summary

In male veterans with CKD defined by impaired GFR, coronary artery disease, LDL ≤140 mg/dL and HDL ≤40 mg/dL, gemfibrozil did not reduce all-cause mortality compared with placebo. In the one composite vascular endpoint reported of the two the study defined, gemfibrozil significantly reduced risk of fatal CHD, nonfatal MI, or stroke. In both studies, too few (or no) patients developed ESRD to effectively compare risk between gemfibrozil and either placebo or low triglyceride diet. The gemfibrozil versus diet study suggested an increased risk of gastrointestinal side effects with gemfibrozil, but the VA-HIT CKD study reported no information on the incidence of adverse gastrointestinal symptoms. Results were limited because they were based on small studies, with few reported outcomes and small numbers of clinical events. Results from the VA-HIT study were limited because they were a post hoc analysis from a larger trial not designed to look at CKD patients or renal outcomes. Studies are limited in that they do not also report results based on baseline albuminuria.

Table 17. Pooled clinical and renal outcomes, anti-lipid agents versus control trials

Outcome	Number of Trials Reporting	Quality of the Studies	Anti-lipid Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
HMG-CoA reductase inhibitors versus placebo (N=12)						
All-cause mortality	**8**	**Good**	**492/6922 (7.1)**	**614/7042 (8.7)**	**0.80 [0.68-0.95]**	**22%**
All-cause mortality; non-CAD patients	*3*	*Good*	*77/3591 (2.1)*	*125/3624 (3.4)*	*0.63 [0.44-0.90]*	*38%*
All-cause mortality; CAD patients	*3*	*Fair*	*87/681 (12.8)*	*102/713 (14.3)*	*0.89 [0.68-1.15]*	*0%*
All-cause mortality; CAD and non-CAD patients	*2*	*Fair*	*328/2650 (12.4)*	*387/2705 (14.3)*	*0.87 [0.76-0.99]*	*0%*
Cardiovascular mortality	**4**	**Fair**	**24/1014 (2.4)**	**35/1043 (3.4)**	**0.71 [0.43-1.17]**	**0%**
Cardiovascular mortality; non-CAD patients	*1*	*Fair*	*0/145*	*1/159 (0.6)*	*0.37 [0.01-8.90]*	*NA*
Cardiovascular mortality; CAD patients	*2*	*Fair*	*20/436 (4.6)*	*30/453 (6.6)*	*0.69 [0.40-1.19]*	*0%*
Cardiovascular mortality; CAD and non-CAD patients	*1*	*Fair*	*4/433 (0.9)*	*4/431 (0.9)*	*1.00 [0.28-3.95]*	*NA*
Myocardial infarction, any	**2**	**Fair**	**67/989 (6.8)**	**96/1026 (9.4)**	**0.72 [0.54-0.98]**	**0%**
Myocardial infarction, any; non-CAD patients	*1*	*Fair*	*2/145 (1.4)*	*6/159 (3.8)*	*0.37 [0.07-1.78]*	*NA*
Myocardial infarction, any; CAD patients	*1*	*Good*	*65/844 (7.7)*	*90/867 (10.4)*	*0.74 [0.55-1.01]*	*NA*
Myocardial infarction, nonfatal	**2**	**Good**	**25/1924 (1.3)**	**49/1922 (2.5)**	**0.52 [0.33-0.84]**	**0%**
Stroke, any	**6**	**Good**	**71/5154(1.4)**	**120/5215(2.3)**	**0.62 [0.41-0.95]**	**42%**
Stroke; non-CAD patients	*3*	*Good*	*24/3591 (0.7)*	*58/3624 (1.6)*	*0.43 [0.25-0.75]*	*24%*
Stroke; CAD patients	*2*	*Good*	*40/1130 (3.5)*	*58/1160 (5.0)*	*0.71 [0.48-1.05]*	*0%*
Stroke; CAD and non-CAD patients	*1*	*Fair*	*7/433 (1.6)*	*4/431 (0.9)*	*1.74 [0.51-5.91]*	*NA*
CHF hospitalization	**2**	**Fair**	**16/719 (2.2)**	**23/724 (3.2)**	**0.71 [0.38-1.32]**	**0%**
CHF hospitalization; CAD patients	*1*	*Good*	*15/286 (5.2)*	*22/293 (7.5)*	*0.70 [0.37-1.32]*	*NA*
CHF hospitalization; CAD and non-CAD patients	*1*	*Fair*	*1/433 (0.2)*	*1/431 (0.2)*	*1.00 [0.06-15.86]*	*NA*
Composite vascular outcomes						
Composite vascular outcome*; Kendrick[141] (AFCAPS), definition B[a]	1	Fair	8/145 (5.5)	21/159 (13.2)	0.42 [0.19-0.91]	NA
Composite vascular outcome; Kendrick[141] (AFCAPS), definition C[a]	1	Fair	7/145 (4.8)	18/159 (11.3)	0.43 [0.18-0.99]	NA
Composite vascular outcome; Nakamura[142] (MEGA), definition A[b]	1	Good	21/1471 (1.2)	40/1507 (5.7)	0.54 [0.32-0.91]	NA
Composite vascular outcome; Nakamura[142] (MEGA), definition B[b]	1	Good	25/1471 (3.7)	60/1507 (8.7)	0.43 [0.27-0.68]	NA
Composite vascular outcome; Nakamura[142] (MEGA), definition C[b]	1	Good	33/1471 (4.9)	71/1507 (10.3)	0.48 [0.32-0.72]	NA
Composite vascular outcome; Ridker (JUPITER), definition A[cx]	1	Good	40/1638 (2.4)	71/1629 (4.4)	0.56 [0.38-0.82]	NA
Composite vascular outcome; Ridker (JUPITER), definition B[c]	1	Good	64/1638 (3.9)	114/1629 (7.0)	0.56 [0.41-0.75]	NA

Table 17. Pooled clinical and renal outcomes, anti-lipid agents versus control trials (continued)

Outcome	Number of Trials Reporting	Quality of the Studies	Anti-lipid Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
Composite vascular outcome; Ridker (JUPITER), definition C[c]	1	Good	69/1638 (4.2)	127/1629 (7.8)	0.54 [0.41-0.72]	NA
Composite vascular outcome; Ridker (JUPITER), definition D[c]	1	Good	24/1638 (1.5)	40/1629 (2.5)	0.60 [0.36-0.99]	NA
Composite vascular outcome; Colhoun[143] (CARDS), definition A[d]	1	Good	25/482 (5.2)	42/488 (8.6)	0.63 [0.39-1.02]	NA
Composite vascular outcome; Colhoun[143] (CARDS), definition A-albuminuric patients[d]	1	Good	24/276 (8.7)	38/275 (13.8)	0.60 [0.37-0.97]	NA
Composite vascular outcome; Colhoun[143] (CARDS), definition B[d]	1	Good	18/482 (3.7)	27/488 (5.5)	0.67 [0.38-1.21]	NA
Composite vascular outcome; Koren[144] (ALLIANCE), definition A[e]	1	Good	78/286 (27.3)	105/293 (35.8)	0.76 [0.60-0.97]	NA
Composite vascular outcome; Koren[144] (ALLIANCE), definition B[e]	1	Good	73/286 (25.5)	85/293 (29.0)	0.88 [0.67-1.15]	NA
Composite vascular outcome; Koren[144] (ALLIANCE), definition C[e]	1	Good	32/286 (11.2)	54/293 (18.4)	0.61 [0.40-0.91]	NA
Composite vascular outcome; Chonchol[145] (4S), definition A[f]	1	Fair	53/245 (21.6)	77/260 (29.6)	0.73 [0.54-0.99]	NA
Composite vascular outcome; Kjekhus[146] (CORONA), definition A[g]	1	Good	288/791 (15.8)	309/844 (16.3)	0.99 [0.88-1.13]	NA
Composite vascular outcome; Lemos[147] (LIPS), definition A[h]	1	Fair	23/150 (15.3)	47/160 (29.4);	0.52 [0.33-0.82]	NA
Composite vascular outcome; Lemos[147] (LIPS), definition B[h]	1	Fair	7/150 (4.7)	13/160 (8.1)	0.57 [0.24-1.40]	NA
Composite vascular outcome; Lemos[147] (LIPS), definition C[h]	1	Fair	7/150 (4.7)	13/160 (8.1)	0.57 [0.24-1.40]	NA
Composite vascular outcome; Asselbergs[62] (PREVD), definition A[i]	1	Fair	21/433 (4.8)	24/431 (5.6)	0.87 [0.49-1.54]	NA
Composite vascular outcome; Asselbergs[62] (PREVD), definition B[i]	1	Fair	8/433 (1.8)	15/431 (3.5)	0.53 [0.23-1.24]	NA
Composite vascular outcome; Tonelli[149] (WOSCOPS/ CARE/ LIPID), definition A[j]	1	Good	492/2217 (22.2)	647/2274 (28.5)	0.78 [0.70-0.86]	NA
Composite vascular outcome; Tonelli[149] (WOSCOPS/ CARE/ LIPID), definition B[j]	1	Good	573/2217 (25.9)	730/2274 (32.1)	0.81 [0.73-0.88]	NA
Composite vascular outcome; Tonelli[148] (CARE), definition A[k]	1	Good	89/844 (10.5)	126/867 (14.5)	0.73 [0.56-0.94]	NA
Composite vascular outcome; Tonelli[148] (CARE), definition B[k]	1	Good	171/844 (20.3)	237/867 (27.0)	0.74 [0.62-0.88]	NA
End-stage renal disease	**1**	**Good**	**32/779 (4.1)**	**31/778 (4.0)**	**1.03 [0.64-1.67]**	**NA**
Composite renal outcome (ALLHAT)[l]	1	Good	50/779 (6.4)	52/778 (6.7)	0.96 [0.66-1.40]	NA
High- versus low-dose HMG-CoA reductase inhibitors (n=2)						
All-cause mortality	1	Fair	112/1602 (7.0)	113/1505 (7.5)	0.93 [0.72-1.20]	NA
CHF hospitalization	1	Fair	49/1602 (3.1)	84/1505 (5.6)	0.55 [0.39-0.77]	NA

Table 17. Pooled clinical and renal outcomes, anti-lipid agents versus control trials (continued)

Outcome	Number of Trials Reporting	Quality of the Studies	Anti-lipid Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
Composite vascular outcome; Shepard[151] (TNT), definition A[m]	1	Fair	149/1602 (9.3)	202/1505 (13.4)	0.69 [0.57-0.85]	NA
Composite vascular outcome; Shepard[151] (TNT), definition B[m]	1	Fair	489/1602 (30.5)	574/1505 (38.1)	0.80 [0.73-0.88]	NA
Composite vascular outcome; Shepard[151] (TNT), definition C[m]	1	Fair	110/1602 (6.9)	157/1505 (10.4)	0.66 [0.52-0.83]	NA
Composite vascular outcome; Shepard[151] (TNT), definition D[m]	1	Fair	356/1602 (22.2)	431/1505 (28.6)	0.78 [0.69-0.88]	NA
Composite vascular outcome; Shepard[151] (TNT), definition E[m]	1	Fair	74/1602 (4.6)	104/1505 (6.9)	0.67 [0.50-0.89]	NA
Composite vascular outcome; SEARCH trial[n]	1	Fair	265/820 (32.3)	292/866 (33.7)	0.96 [0.84-1.10]	NA
Gemfibrozil versus placebo trials (n=1)						
All-cause mortality	1	Good	20/199 (10)	22/200 (11.0)	0.91 [0.52-1.62]	NA
Composite vascular outcome; Tonelli[154] (VA-HIT), definition B[o]	1	Good	58/242 (24.0)	75/228 (32.9)	0.73 [0.54-0.97]	NA
End-stage renal disease	2	Fair	2/227 (0.9)	1/229 (0.4)	2.07 [0.20-21.58]	NA

CHF = congestive heart failure; NA = not applicable; RR = relative risk reduction

[a](B)Fatal and nonfatal cardiovascular events; (C) Fatal and nonfatal coronary events

[b](A)First occurrence of a CHD event, including fatal and nonfatal MI, angina pectoris, cardiac/sudden death, and coronary revascularization. Additional composite endpoints included; (B)first CHD event or ischemic stroke; (C) total CVD events, which was not defined

[c](A) nonfatal myocardial infarction, nonfatal stroke, hospital stay for unstable angina, arterial revascularization, or confirmed cardiovascular death; (B) same as A plus any death; (C) same as A plus any death plus venous thromboembolism; (D) non-fatal myocardial infarction, nonfatal stroke, or confirmed cardiovascular death

[d](A) Major cardiovascular disease, including acute CHD event (MI, including silent MI, unstable angina, acute CHD death, or resuscitated cardiac arrest), stroke, coronary revascularization, or death; (B) acute CHD event as defined above

[e](A) First primary cardiovascular event, including cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, or unstable angina requiring hospitalization; (B) All-cause mortality, peripheral revascularization, hospitalization for CHF, or stroke; (C) Nonfatal MI or cardiac death

[f](A) Major coronary event, including coronary death, nonfatal MI, resuscitated cardiac arrest, ECG confirmed silent MI

[g](A) Cardiovascular death, nonfatal MI, or nonfatal stroke

[h](A) Adverse coronary atherosclerotic events, which included cardiac death, nonfatal MI, and all surgical or percutaneous coronary interventions not caused by restenosis after an index percutaneous coronary intervention; (B) Cardiac death or MI; (C) All-cause mortality or MI

[i](A) Cardiovascular mortality or hospitalization for any of the following: nonfatal MI, myocardial ischemia, CHF, PVD or stroke; (B) Hospitalization for nonfatal MI or myocardial ischemia

[j](A) Cardiovascular mortality or hospitalization for any of the following: nonfatal MI, myocardial ischemia, CHF, PVD or stroke; (B) Hospitalization for nonfatal MI or myocardial ischemia

[k](A) Death from coronary disease (including fatal MI, sudden death, death during a coronary intervention, and death from other coronary causes) or a symptomatic nonfatal biochemically confirmed myocardial infarction; (B) Major coronary events, defined as fatal coronary disease, nonfatal MI, CABG, or coronary angioplasty

[l](A) ESRD (start of long-term dialysis, death due to kidney disease, or kidney transplantation) or ≥50% decline in GFR; and (B) ESRD or ≥50% decline in GFR

[m](A) Major cardiovascular events, which included CHD death, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, and stroke; (B) Any cardiovascular event (defined as CHD death, nonfatal MI, resuscitation from cardiac arrest, revascularization procedure, documented angina, stroke, TIA, CABG, or CHF hospitalization); (C) Major coronary event (defined as CHD death, nonfatal nonprocedure-related MI, or resuscitation from cardiac arrest); (D) Any coronary event (defined as CHD death, nonfatal MI, resuscitation from cardiac arrest, revascularization procedure, or documented angina); and (E) Cerebrovascular event (stroke or TIA)

[n] first major vascular event, including coronary death, myocardial infarction, any stroke, or any arterial revascularization

[o](B) Major cardiovascular event, which included fatal CHD, nonfatal MI, and stroke

Intensive Multicomponent Intervention Trials (n=4)

Overview

In patients with CKD, we found a low strength of evidence that there is no difference between intensive, multicomponent treatment and conventional treatment for risk of all-cause mortality or ESRD. We found no statistically significant difference between treatment groups in risk of cardiovascular mortality, MI, or stroke. Risk of conversion from microalbuminuria was statistically significantly lower in the intensive treatment group. Our confidence in these estimates is limited by the small number of trials reporting different outcomes, the small number of clinical events, and heterogeneity between studies.

Description of Studies

Five reports of four unique trials met all eligibility criteria and randomized participants with CKD (n=892 patients, range 90 to 437) to an intensive multicomponent treatment intervention versus usual care.[155-159] Detailed baseline characteristics are presented in Appendix Tables C132 and C133.

In all eligible trials, the intensive treatment arm was implemented by a multidisciplinary research team, comprised of at least a physician, a nurse, and a dietitian. In three of these trials, conducted entirely in patients with diabetes, the research team met with the patients at least every three months and directly intervened in their care, treating them to achieve explicit targets for blood pressure (systolic <130 to 140 mm Hg, diastolic <80 to 85 mm Hg), diabetes (HbA_{1c} targets ranged from <6.5 to <8 percent), and lipid control (cholesterol <154 to 193 mg/dL, LDL <100 mg/dL, HDL >42 mg/dL, triglycerides <66 to 75 mg/dL).[155,156,158] The interventions were introduced in a stepwise fashion, including behavior modification and pharmacologic therapy, as necessary. In the fourth trial, the research team implementing the intensive treatment arm met with patients every 3 to 6 months and utilized a mix of direct intervention and letters sent with management recommendations to the patients' primary care providers.[159] In this latter trial, while improved blood pressure control was a stated aim, no explicit blood pressure target was reported, and the study did not discuss management of diabetes or lipids. An emphasis was placed on improving medication compliance and decreasing nephrotoxic drug exposure. In three trials, ACEIs or ARBs were to be initiated in all intensive treatment group participants,[155,156,159] and although the fourth trial did not state that these medications were mandated, it reported ACEI use in 95 percent of enrolled participants at followup.[158] Within the intensive treatment intervention groups, dietary recommendations in three trials included low protein,[155,158,159] with low potassium recommended in two trials.[155,159] Low fat[156] and low sodium[158] each were part of diet recommendations in one trial.

By comparison with the intensive intervention arms, all study participants assigned to control treatment groups were managed by their primary physician. In two trials, their management was left entirely to the discretion of their primary physician.[155,159] However, in two other trials their doctors were to target explicit goals for blood pressure, diabetes, and lipid control, aiming either for the same thresholds being used for treatment of the intensive treatment group,[158] or following national guidelines that were modestly less strict than the thresholds targeted for the intensive treatment group.[156]

The mean age of subjects was 65 years (range 55 to 68; n=4 trials) and men constituted 52 percent (range 34 to 74; n=4 trials) of all patients randomized. In the only trial that reported data

on ethnicity/race, 80 percent of participants were African American.[159] Two trials were conducted in Europe (including Scotland and Denmark),[156,158] one was conducted primarily in the United States,[159] and one was conducted in China.[155] Mean or median study durations ranged from 2 to 7.8 years.

Renal Function

No study based eligibility on CKD stage or reported baseline distribution of participants by CKD stage. Among the four eligible trials, two based participant eligibility on presence of albuminuria,[156,158] while two others determined eligibility based on impaired creatinine clearance and/or elevated serum creatinine.[155,159] In trials reporting these data, mean baseline creatinine clearance was 37.6 mL/min (range 34 to 55, n=2 trials),[158,159] mean baseline serum creatinine was 1.8 (range 0.9 to 2.1, n=2 trials),[156,159] and urinary albumin excretion rate ranged from a mean of 73.5 mg/24 hours in one trial[156] to a median of 755 mg/24 hours in a second trial.[158] In addition, one trial reported a baseline mean GFR of 117 ml/min/1.73m^2,[156] and another reported a mean albumin-to-creatinine ratio of 79 mg/mmol.[158]

Baseline Comorbidities

Hypertension prevalence was reported in three trials, within which 98 percent of participants had a diagnosis of hypertension.[155,158,159] Mean systolic and diastolic blood pressure measurements were 147 and 82 mm Hg, respectively (n=4 trials). Three trials were comprised entirely of type 2 diabetic patients,[155,156,158] with the fourth trial including 44 percent diabetic participants.[159] In the two diabetic trials reporting, mean baseline HbA_{1c} was 8.3 percent (range 7.9 to 8.6).[156,158] The prevalence of other comorbidities included coronary artery disease 35 percent (range 16 to 48, n=3 trials), CHF 30 percent (range 7 to 40, n=2 trials), MI 26 percent (range 2 to 37, n=2 trials), and stroke 16 percent (range 3 to 20, n=3 trials).

Study Quality (Appendix Table C140)

Among the four eligible trials, study quality was rated as good for one trial and as fair for three trials. Allocation concealment was adequate in three trials and unclear in the remaining study. All of these intensive multicomponent intervention trials were open label. Analysis by the intention-to-treat principle was performed in two trials. Reasons for study withdrawal were adequately described in all reports, and 2.6 percent (range 0 to 17) of randomized participants withdrew from trials overall.

Results

Mortality (Table 18, Appendix Table C134, and Appendix Figure C25)

All-Cause Mortality

Compared with control treatment, assignment of CKD patients to an intensive, multicomponent intervention did not significantly reduce risk of all-cause mortality (19.5 percent versus 23.3 percent; RR 0.86, 95% CI, 0.67 to 1.10; n=4 trials, 892 patients).

Cardiovascular Mortality

Assignment to the multicomponent treatment group was not associated with a significant difference in risk of cardiovascular mortality compared with control treatment (RR 1.07, 95% CI, 0.47 to 2.43; n=2 trials).

Vascular Outcomes (Table 18, Appendix Tables C134-C136, and Appendix Figure C25)

Myocardial Infarction

Compared with control treatment, allocation of patients with CKD to intensive, multicomponent treatment was not associated with a significant reduction in MI (RR 0.97, 95% CI, 0.25 to 3.78), fatal MI (RR 1.83, 95% CI, 0.17 to 19.47) or nonfatal MI (RR 0.50, 95% CI, 0.16 to 1.59). However, each of these outcomes was reported only in one trial with a small sample size and few events.

Stroke

Compared with control treatment, allocation of patients with CKD to intensive, multicomponent treatment was not associated with a significant reduction in fatal stroke (RR 0.31, 95% CI, 0.01 to 7.31). In contrast, participants assigned to intensive, multicomponent treatment had a significantly lower risk of nonfatal stroke (3.8 percent versus 13.8 percent; RR 0.27, 95% CI, 0.08 to 0.94). Again, this outcome was reported only in one trial with a small sample size and few events.

Other Vascular Outcomes

Two trials reported a composite vascular endpoint as a main outcome,[155,156] with a significant reduction in risk associated with intensive, multicomponent treatment in one of these trials (RR 0.54, 95% CI, 0.34 to 0.86, n=160 patients)[156] but not in the other (RR 1.07, 95% CI, 0.62 to 1.87).[155]

Renal Outcomes (Table 18, Appendix Tables C137 and C138, and Appendix Figure C25)

End-Stage Renal Disease

In three trials reporting, compared with control treatment, assignment of CKD patients to an intensive, multicomponent intervention was associated with a 53 percent relative reduction in risk of ESRD that was not statistically significant (6.9 versus 9.4 percent, RR 0.47, 95% CI, 0.10 to 2.20; n=3 trials, 455 patients). More than 80 percent of ESRD events occurred in one trial[155] and there was substantial heterogeneity between trials (I^2=43 percent).

Other Renal Outcomes

In the single trial reporting, intensive multicomponent treatment significantly reduced risk of progression of CKD patients from microalbuminuria to macroalbuminuria compared with conventional treatment (20.0 versus 38.8 percent, RR 0.52, 95% CI, 0.31 to 0.87; n=160 patients).[156] A composite renal outcome was reported in only one trial, and risk appeared no different between treatment groups (23.1 versus 23.8 percent).[155]

Study Withdrawals and Adverse Events (Appendix Table C139)

CKD patients allocated to intensive multicomponent treatment were no more likely to have withdrawn from treatment than those assigned to control treatment (0.9 versus 0.8 percent; n=3 trials, 687 patients). Adverse events data were only reported in one trial.[156] In this trial, risk of major hypoglycemic events that impaired consciousness and required help from another person was not higher in the intensive, multicomponent treatment group as compared with the

conventionally treated group (6.3 versus 15.0 percent, p=0.12). In this trial, there also was no between-group difference in the proportion of patients with at least one minor hypoglycemic event (48.8 versus 52.5 percent, p=0.50).

Subgroup Results

No trials reported outcomes stratified by any participant characteristic. In three trials restricted to patients with diabetes, all of which tested an intervention that explicitly targeted diabetes, blood pressure, and lipid control, there was no significant difference between intensive multicomponent and control treatment in risk of mortality (RR 0.86, 95% CI, 0.52 to 1.43), cardiovascular mortality, MI, or CHF hospitalization. However, risk of stroke was significantly reduced in one of these trials (RR 0.27, 95% CI, 0.08 to 0.94), a small study in which participants also were albuminuric. Also in this single trial, there was a significant reduction in risk of one reported composite vascular outcome, and of conversion from microalbuminuria to macroalbuminuria. There was no difference between treatment groups in risk of mortality (RR 0.99, 95% CI, 0.49 to 2.02), cardiovascular mortality, MI, or ESRD. In two trials in which decreased creatinine clearance or increased serum creatinine was required for inclusion, there was no significant difference between treatment groups in any of the few clinical outcomes reported.

Summary

In individuals with CKD, compared with usual care, assignment to intensive, multicomponent intervention was not associated with a significant reduction in risk of all-cause mortality. Further, there was no significant association between treatment groups and risk of MI, fatal stroke, and ESRD. In data from single trials only, there was a significantly reduced risk with intensive, multicomponent treatment for the outcomes of nonfatal stroke, a composite vascular endpoint, and conversion from microalbuminuria to macroalbuminuria. Results for all outcomes, with the possible exception of all-cause mortality, were limited by small sample sizes and few events and could not exclude either clinically meaningful benefits or harms. Overall results were further limited by heterogeneity in patient populations and in treatment protocols, including those for both the intensive intervention groups and the usual care groups. Reporting on study withdrawals and adverse effects was limited. Finally, no trial provided followup beyond 5 years; therefore, longer term effects of intensive, multicomponent interventions cannot be determined from these studies.

Table 18. Pooled clinical and renal outcomes, INT versus control treatment trials

Outcome	Number of Trials Reporting	Quality of the Studies	Intensive Events/N (%)	Control Events/N (%)	RR [95% CI]	I^2 Test for Heterogeneity
INT versus control treatment trials (N=4)						
All-cause mortality	4	Fair	85/437 (19.5)	106/455 (23.3)	0.86 [0.67-1.10]	0%
Cardiovascular mortality	2	Fair	11/127 (8.7)	10/123 (8.1)	1.07 [0.47-2.43]	0%
Myocardial infarction, any	1	Good	4/104 (3.8)	4/101 (4.0)	0.97 [0.25-3.78]	NA
Myocardial infarction, fatal	1	Fair	2/47 (4.25)	1/43 (2.3)	1.83 [0.17-19.47]	NA
Myocardial infarction, nonfatal	1	Fair	4/80 (5.0)	4/80 (10.0)	0.50 [0.16-1.59]	NA
Stroke, nonfatal	1	Fair	3/80 (3.8)	11/80 (13.8)	0.27 [0.08-0.94]	NA
Stroke, fatal	1	Fair	0/47 (0)	1/43(2.3)	0.31 [0.01-7.31]	NA
CHF hospitalization	1	Good	13/104(12.5)	15/101(14.8)	0.84 [0.42-1.68]	NA
Composite vascular outcome* Chan, 2009[155]	1	Good	4/104 (3.8)	4/101 (4.0)	0.97 [0.25-3.78]	NA
Composite vascular outcome** Gaede (A), 2003[156]	1	Fair	19/80 (23.8)	35/80 (43.8)	0.54 [0.34-0.86]	NA
End-stage renal disease	3	Fair	16/231 (6.9)	21/224 (9.4)	0.47 [0.10-2.20]	43%
Progression from micro to macroalbuminuria	1	Fair	16/80 (20.0)	31/80 (38.8)	0.52 [0.31-0.87]	NA
Composite renal outcome***, Chan, 2009[155]	1	Good	24/104(23.1)	24/101 (23.8)	0.97 [0.59-1.59]	NA

CHF = congestive heart failure; CI = confidence interval; INT = Intensive Multi-Component Intervention; NA = not applicable; RR = relative risk reduction;
*Hospitalization for heart failure, hospitalization for angina, hospitalization for arrhythmia, MI, coronary revascularization (PTCA/CABG), other revascularization, CVA or transient ischemic attack, and lower limb amputation.
** (A) death from cardiovascular causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation as a result of ischemia, or surgery for peripheral atherosclerotic artery disease.
***ESRD (defined as the need for dialysis, or plasma creatinine level ≥500 μmol/l) or death.

Strength of Evidence for Key Question 5

The strength of evidence for Key Question 5 is presented in Table 19.

Table 19. Strength of evidence for Key Question 5

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
ACEI Monotherapy Studies							
ACEI versus placebo (n=17)	All-cause mortality	16; 11,536	RCTs/good	Inconsistent	Direct	Precise	Moderate
	ESRD	7; 7490	RCTs/good	Consistent	Direct	Imprecise	Moderate
ACEI versus ARB (n=6)	All-cause mortality	4; 534	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	none	-	-	-	-	Insufficient
ACEI versus CCB (n=6)	All-cause mortality	5; 1307	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 3823	RCTs/good	Inconsistent	Direct	Imprecise	Low
ACEI versus beta blocker (n=3)	All-cause mortality	3; 1080	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 1080	RCTs/fair	Inconsistent	Direct	Imprecise	Low
ACEI versus diuretic (n=2)	All-cause mortality	1; 570	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	1; 4146	RCT/good	Unknown	Direct	Imprecise	Low
ARB Monotherapy Studies							
ARB versus placebo (n=4)	All-cause mortality	4; 5242	RCTs/good	Consistent	Direct	Precise	High
	ESRD	3; 4652	RCTs/good	Consistent	Direct	Precise	High
ARB versus CCB (n=3)	All-cause mortality	2; 1206	RCTs/fair	Unknown	Direct	Imprecise	Low
	ESRD	1; 1148	RCT/good	Unknown	Direct	Imprecise	Low
ACEI+ARB Versus Other Studies							
ACEI+ARB versus ACE (n=6)	All-cause mortality	3; 3059	RCTs/fair	Consistent	Direct	Precise	Moderate
	ESRD	1; 90	RCT/poor	Unknown	Direct	Imprecise	Insufficient
ACEI+ARB versus ARB (n=3)	All-cause mortality	1; 86	RCTs/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+ARB versus ACEI or ARB (n=1)	All-cause mortality	1; 8933	RCT/good	Unknown	Direct	Precise	Moderate
	ESRD	1; 8933	RCT/good	Unknown	Direct	Imprecise	Low

Table 19. Strength of evidence for Key Question 5 (continued)

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
ACEI+ARB versus ACEI+aldosterone antagonist (n=1)	All-cause mortality	1; 53	RCT/poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+CCB or Diuretic Versus Other Studies							
ACEI+CCB versus ACE (n=1)	All-cause mortality	1; 207	RCT/poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+CCB versus CCB (n=1)	All-cause mortality	1; 207	RCT/poor	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+CCB versus ACEI+ diuretic (n=2)	All-cause mortality	1; 332	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ACEI+ diuretic versus placebo (n=1)	All-cause mortality	1; 4519	RCT/good (post-hoc)	Unknown	Direct	Precise	Low
	ESRD	none	-	-	-	-	Insufficient
ACEI+ aldosterone antagonist versus ACE (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient
ARB Versus ARB Studies							
ARB (Telmisartan) versus different ARB (n=2)	All-cause mortality versus losartan	1; 860	RCT/poor	Inconsistent	Direct	Precise	Low
	All-cause mortality versus valsartan	1; 857	RCT/fair	Inconsistent	Direct	Imprecise	Low
	ESRD versus losartan	none	-	-	-	-	Insufficient
	ESRD versus valsartan	1; 857	RCTs/fair	Unknown	Direct	Imprecise	Insufficient
ARB (High Dose) versus ARB (Standard Dose)	All-cause mortality candesartan	1; 269	RCT/good	-	-	-	Insufficient
	ESRD candesartan	none	-	-	-	-	Insufficient

Table 19. Strength of evidence for Key Question 5 (continued)

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
	All-cause mortality Irbesartan	1; 389	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD Irbesartan	none	-	-	-	-	Insufficient
	All-cause mortality Telmisartan	none	-	-	-	-	Insufficient
	ESRD Telmisartan	none	-	-	-	-	Insufficient
Aldosterone Antagonist Studies							
ACEI+ Aldosterone antagonist versus ACEI (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Aldosterone antagonist (+ACE/ ARB) versus placebo (+ACE/ ARB) (n=1)	All-cause mortality	1; 59	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Miscellaneous Blood Pressure Control Versus Other Studies							
Beta blocker versus placebo (n=2)	All-cause mortality	2; 2173	RCT/fair (post-hoc)	Inconsistent	Direct	Precise	Low
	ESRD	none	-	-	-	-	Insufficient
CCB versus placebo (n=2)	All-cause mortality	2; 1226	RCTs/fair	Unknown	Direct	Imprecise	Low
	ESRD	1; 1136	RCT/good	Unknown	Direct	Imprecise	Low
CCB versus diuretic (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1; 4129	RCT/good (post-hoc)	Unknown	Direct	Imprecise	Low
CCB versus beta blocker (n=3)	All-cause mortality	2; 692	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	1; 658	RCT/good	Unknown	Direct	Imprecise	Low
Diuretic versus placebo (n=1)	All-cause mortality	1; 393	RCT/good (post-hoc)	Unknown	Direct	Imprecise	Low
	ESRD	none	-	-	-	-	Insufficient

Table 19. Strength of evidence for Key Question 5 (continued)

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
ACEI versus non-ACE (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1;	RCT/fair	Unknown	Direct	Imprecise	Low
Strict BP control versus Usual BP control (n=6)	All-cause mortality	4; 1803	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 1506	RCTs/fair	Consistent	Direct	Imprecise	Low
Non-Blood Pressure Control Interventions Section: Anti-Lipid Treatment Trials							
HMG-CoA Reductase Inhibitors versus control (n=12)	All-cause mortality	8; 13964	RCTs/good	Consistent	Direct	Precise	High
	ESRD	1; 1557	RCT/good	Unknown	Direct	Imprecise	Low
High versus low-dose HMG-CoA Reductase Inhibitors (n=2)	All-cause mortality	1; 3107	RCT/good	Unknown	Direct	Imprecise	Low
	ESRD	none	-	-	-	-	Insufficient
Gemfibrozil versus Placebo (n=1)	All-cause mortality	1; 399	RCT/good	Unknown	Direct	Imprecise	Low
	ESRD	1; 399	RCT/good	Unknown	Direct	Imprecise	Insufficient
Gemfibrozil versus Low triglyceride diet (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1; 57	RCT/fair	Unknown	Direct	Imprecise	Insufficient
Non-Blood Pressure Control Interventions Section: Dietary Intervention and Weight Loss							
Low protein diet versus usual protein diet (n=6)	All-cause mortality	4; 1280	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3:302	RCTs/fair	Consistent	Direct	Imprecise	Low
Low protein diet versus other diet (n=1)	All-cause mortality	1; 170	RCT/fair	Unknown	Direct	Imprecise	Low
	ESRD	1; 170	RCT/fair	Unknown	Direct	Imprecise	Low
Low protein-low phosphate diet versus low phosphate diet versus usual diet (n=1)	All-cause mortality	1; 98	RCT/fair	Unknown	Direct	Imprecise	Insufficient
	ESRD	1; 98	RCT/fair	Unknown	Direct	Imprecise	Low
Low triglyceride diet versus gemfibrozil trials (n=1)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	1; 57	RCT/fair	Unknown	Direct	Imprecise	Insufficient

Table 19. Strength of evidence for Key Question 5 (continued)

Comparison	Outcome, Control	Number of Studies; Number of Subjects	Risk of Bias Design; Quality	Consistency	Directness	Precision	Strength of Evidence
Non-Blood Pressure Control Interventions Section: Glycemic Control Studies							
Intensive versus standard glycemic control studies (n=2)	All-cause mortality	none	-	-	-	-	Insufficient
	ESRD	none	-	-	-	-	Insufficient
Non-Blood Pressure Control Interventions Section: Intensive Multi-Component Intervention Studies							
Intensive multi-component intervention versus control studies (n=4)	All-cause mortality	4; 892	RCTs/fair	Consistent	Direct	Imprecise	Low
	ESRD	3; 455	RCTs/fair	Inconsistent	Direct	Imprecise	Low

ACEI = Angiotensin-converting Enzyme inhibitor; ARB= angiotensin II receptor blocker; BP = blood pressure; CCB = calcium channel blocker; ESRD = End-stage renal disease

Discussion

For CKD screening or monitoring to be of benefit, each would need to improve clinically important outcomes, presumably by leading to specific changes in treatment. However, we identified no RCTs that randomized individuals without known CKD to CKD screening, or those with CKD stages 1–3 to CKD monitoring, and collected and reported associated clinical outcomes.

With no direct link between screening or monitoring and clinical outcomes, concluding likely benefit of screening or monitoring requires, at minimum, the availability of accurate screening tests, and sufficient evidence that treatment for CKD stages 1–3 improves clinically important outcomes while limiting harms. For treatment benefits in CKD patients to be relevant to screening or monitoring, treatments also would need to improve these outcomes in individuals who would not otherwise receive them; i.e., patients without specific treatment indications in the absence of a CKD diagnosis. In patients with other treatment indications, diagnosis of CKD or of CKD progression might be beneficial if outcomes in these patients are significantly improved with a higher treatment dose or by treatment to a stricter target than indicated in individuals with no or less severe CKD. Finally, any treatment benefit would need to outstrip treatment harms and potential screening and monitoring harms, and applicability of treatment RCT results to screening or monitoring would be increased if subjects were identified for participation in these treatment trials through screening.

In this synthesis of RCT evidence, several treatments reduced risk of clinical events in patients with CKD stages 1–3. Compared with placebo, ACEI and ARB significantly reduced risk of ESRD in patients with proteinuria, nearly all of whom had concomitant diabetes and hypertension. While there was no significant reduction in risk of ESRD with ACEI or ARB in patients without proteinuria, because of the low rate of progression to ESRD in these patients, the present analysis had limited statistical power to detect such a difference. This is not direct evidence that testing patients with diabetes and hypertension for proteinuria will reduce ESRD risk, but it suggests, in patients not currently being treated with ACEI or ARB, that knowledge of these results might inform this treatment decision. Also compared with placebo, ACEI significantly reduced risk of mortality in patients with microalbuminuria who had cardiovascular disease or had diabetes and other cardiovascular risk factors. Though the relative reduction in mortality risk appeared slightly greater in patients with microalbuminuria compared with those without microalbuminuria, this difference was not statistically significant, suggesting that such patients may have an indication for ACEI regardless of CKD status.

In individuals with hyperlipidemia and impaired eGFR or creatinine clearance, we found that statins significantly reduced risk of mortality, MI, and stroke compared with placebo, including in patients without coronary artery disease. This is not direct evidence that testing patients with hyperlipidemia for eGFR will reduce risk of these outcomes, in part because some of these patients already have a clinical indication for statin treatment. Determining CKD status in these patients wouldn't alter their management. Specifically, as previously documented, patients with hyperlipidemia and coronary artery disease randomized to statins have a significantly reduced risk of mortality compared with placebo,[160] They have an indication for statin treatment regardless of their CKD status. In contrast, also previously documented, hyperlipidemic patients without coronary artery disease taken as a whole did not have a significant mortality benefit from statins.[161] The current results suggest that, in patients with hyperlipidemia and no coronary artery

disease who are not currently being treated with a statin, knowledge of impaired eGFR might inform this treatment decision.

In individuals with CHF and impaired eGFR, beta blockers significantly reduced risk of mortality, MI, and CHF events compared with placebo. Patients in all eGFR strata had a significant reduction in risk of these clinical outcomes. Inconsistent results suggested possibly a greater relative risk reduction with beta blockers in patients with lower eGFR. However, as patients with systolic CHF already have an indication for beta blocker treatment, testing for eGFR is not likely to inform this treatment decision.

With regard to patients with CKD stages 1–3 already receiving treatments for conditions associated with CKD (e.g., ACEI for treatment of hypertension), no clear RCT evidence showed whether intensification of treatment improves clinical outcomes. We identified no eligible RCTs that compared clinical outcomes in CKD patients randomized to different fixed ACEI doses, though separate trials suggested that ramipril at 1.25 mg per day in patients with albuminuria lacks the mortality benefit of ramipril at 10 mg per day in patients with microalbuminuria. For other treatments in CKD patients, we did not find evidence of significant or consistent benefit in clinical outcomes in high versus low dose ARB, strict versus standard blood pressure control, high versus low dose statin, tight versus standard glycemic control, intensive multidisciplinary interventions versus standard care, and combination treatment versus monotherapy. While data limited to these latter trials suggests an absence of evidence for benefit from intensification of therapy as a justification for either CKD screening or monitoring, most had low statistical power to detect a significant difference in clinical outcomes.

In RCTs included in this evidence synthesis, many treatments reduced the risk of doubling of serum creatinine and progression from microalbuminuria to macroalbuminuria. However, these renal endpoints are not clinical outcomes. Although impaired GFR and albuminuria are unquestionably adverse prognostic markers, treatments that target and even improve these measures will not necessarily reduce risk of mortality, ESRD or important clinical vascular outcomes. Findings reported from the large ROADMAP study[162]—in which patients with diabetes and at least one additional CKD risk factor were randomized to ARB versus non-ARB blood pressure control—illustrated the potential danger of utilizing albuminuria as a surrogate marker for clinical outcomes in kidney disease. Though blood pressure control was significantly better and time to onset of microalbuminuria was significantly delayed in the ARB treatment group, these patients also experienced a significant increase in fatal cardiovascular events.

As we have noted, establishing the benefit of CKD screening and/or monitoring requires evidence of treatment benefit. Yet, treatment benefit does not by itself prove screening or monitoring benefit. First, the accuracy of available screening and monitoring measures for persistent CKD and progressive CKD, respectively, is uncertain. Second, only two of the dozens of RCTs included in this evidence synthesis reported that study participants were identified through screening.[26,27] Consequently, patients with CKD stages 1–3 enrolled in all these trials may not be representative of those who would be identified through systematic screening. For example, patients identified through screening may be earlier in their course of CKD, less likely to progress during treatment followup, and thus less likely to benefit from treatment intervention. In addition, formal diagnosis of CKD requires that impairment in kidney function or kidney damage persists for at least 3 months. The vast majority of trials included in this evidence synthesis categorized patients as having CKD based on one-time abnormalities. Other trials that required repeated or sustained kidney abnormalities for entry did not mandate persistence for 3 months. Study participants thus may have had transient impairments, been more likely to

improve regardless of treatment, and less likely to develop progressive CKD than patients with CKD confirmed over 3 months duration. Finally, we identified no evidence to quantify harms that may be associated with CKD screening and monitoring. Potential harms of systematic CKD screening could include adverse effects from screening and followup tests, including following false positive tests; psychological effects from labeling asymptomatic individuals as diseased; medication adverse effects; increased medical visits; and increased difficulty keeping health insurance coverage. Analogously, potential harms of systematic monitoring of patients with CKD stages 1–3 for worsening kidney function or damage could include adverse effects from monitoring and followup tests, including potentially unnecessary testing; medication adverse effects; and increased medical visits. Accurate information on screening and monitoring harms is needed to evaluate their overall impact in CKD.

Considering these issues, if there is a benefit from CKD screening, evidence suggests the likelihood of benefit is greatest in individuals with diabetes, cardiovascular disease, and possibly hyperlipidemia. For other populations with a high prevalence of CKD, such as patients with hypertension, obesity, and older age, evidence for benefit from screening appears weaker. Though also based only on indirect data, individuals under 50 years old and without diabetes, hypertension, cardiovascular disease, or obesity infrequently have CKD and seem least likely to benefit from CKD screening.

Finally, because of the imprecision and high intra-individual variability of eGFR and albuminuria, providers who monitor patients with CKD stages 1–3 for worsening kidney function and/or damage will identify both declines and improvements in these measures, including many that are transient and/or clinically insignificant. We identified no RCTs that assigned patients with CKD stages 1–3 to systematic monitoring versus control, or that modified treatment based on followup levels of eGFR or albuminuria and evaluated clinical outcomes. Rather, trials either assigned participants to a fixed dose to be maintained throughout the trial or titrated upward from an initial dose to achieve a specific target dose or clinical target (e.g., systolic blood pressure less than 140 mm Hg). Although treatment RCT results suggest that monitoring could inform decisions regarding whether to start ACEI or ARB treatment in patients with diabetes and hypertension who develop albuminuria, or statin treatment in patients with hyperlipidemia who develop impaired eGFR, considering uncertainty in the accuracy of monitoring tests for identifying CKD progression and uncertainty regarding possible monitoring harms, the relative benefits and harms of CKD monitoring are unclear.

Future Research Recommendations

Key Question 1. In asymptomatic adults with or without recognized risk factors for CKD incidence, progression, or complications, what direct evidence is there that systematic CKD screening improves clinical outcomes?

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD screening improves clinical outcomes.
- Sensitivity and specificity of one-time measures of microalbuminuria, macroalbuminuria and eGFR for persistent (at least 3 months' duration) CKD is unknown; impact of patient factors on persistence also is unknown.
- Only two trials were performed in patients with CKD identified through screening.

Research Recommendations

- Long-term RCTs of systematic CKD screening versus usual care adequately powered to evaluate impact on clinical outcomes.
  - Target populations with high CKD prevalence and high risk for complications.
  - May test different screening measures (e.g., microalbuminuria, macroalbuminuria, eGFR, combination).
- Modeling studies evaluating efficacy and harms of different CKD screening strategies versus usual care. In addition to parameters in published models, consider impact of:
  - Variations in target populations.
  - Variations in screening measures and frequency.
  - Prevalence in target population of indications for and use of specific CKD treatments.
  - Yield of one-time screening tests based on actual association with persistent CKD.
  - Take into account potential screening harms.
- Determine eGFR and albuminuria from baseline and followup blood and urine available from large prospective cohorts or RCT/CCT control groups (or collect new samples).
  - Estimate the proportion of individuals with abnormal one-time abnormalities who meet criteria for CKD for at least 3 months.
  - Evaluate impact of patient factors on persistence (e.g., eGFR severity, albuminuria, age)

Key Question 2. What harms result from systematic CKD screening in asymptomatic adults with or without recognized risk factors for CKD incidence, progression or complications?

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD screening increases harms.

Research Recommendations

- Long-term RCT comparing systematic CKD screening versus usual care to assess potential screening harms.
  - Potential harms should be predefined, and collected and reported in all study participants.
  - Potential harms may include adverse effects from screening/followup tests, including from false positive tests; psychological effects of labeling asymptomatic individuals as diseased; medication adverse effects; increased medical visits; increased costs; difficulty keeping health insurance.
- Prospectively collect predefined harms data (see above list) from all participants in large, observational CKD screening cohort studies.
- As above, conduct modeling studies evaluating the effectiveness and harms of different CKD screening strategies versus usual care.

Key Question 3. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that monitoring for worsening kidney function and/or kidney damage improves clinical outcomes?

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD monitoring for worsened kidney function or damage improves clinical outcomes.
- Sensitivity and specificity of changes in eGFR and albuminuria for CKD progression is unknown.
- Limited RCT data address whether treatment relative risk reduction for clinical outcomes differs based on CKD severity that could inform decisions regarding whether to change treatment in patients identified by monitoring with worsened CKD severity..
- No RCT data address whether treatments have different relative risk reduction in clinical outcomes between patients with recently worsened kidney function or damage, as detectable by monitoring, compared with in those with stable CKD.

Research Recommendations

- Long-term RCTs of systematic CKD monitoring versus usual care adequately powered to evaluate impact on clinical outcomes.
  - Target populations with high risk for CKD complications.
  - Consider testing different monitoring measures, alone and in combination (e.g., quantitative microalbuminuria, macroalbuminuria, eGFR)
- Modeling studies evaluating efficacy and harms of different CKD monitoring strategies versus usual care. Parameters these models may include:
  - Variations in monitoring measures and frequency (quantitative albuminuria, eGFR, or a combination)
  - Variations in baseline CKD severity (i.e., stage, eGFR, quantitative albuminuria)

- Variations in CKD patient characteristics (e.g., diabetes, hypertension, age, cardiovascular disease, hyperlipidemia, race/ethnicity), including possible indication for specific CKD treatments and prevalence of use of these treatments
- Take into account potential monitoring harms

Key Question 4. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from monitoring for worsening kidney function and/or kidney damage?

Knowledge Gaps

- No RCT evidence directly addresses whether systematic CKD monitoring for worsening kidney function or damage increases harms.

Research Recommendations

- Long term RCT comparing systematic CKD monitoring versus usual care to assess potential monitoring harms.
  - Potential harms associated with monitoring should be predefined and collected and reported in all study participants.
  - Potential harms may include adverse effects from monitoring/followup tests, including from false positive (for progression) tests; medication adverse effects; increased medical visits; increased costs.
- Prospectively collect predefined harms data (see above list) from all participants in large, observational CKD monitoring cohort studies.
- As above, conduct modeling studies evaluating the effectiveness and harms of different CKD monitoring strategies versus usual care.

Key Question 5. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what direct evidence is there that treatment improves clinical outcomes?

Knowledge Gaps

- Limited RCT data address whether relative efficacy of treatments differs between patients with and without CKD.
- Limited RCT data address whether treatment risk reduction differs based on CKD severity.
- Limited RCT data address whether treatments improved outcomes in CKD subgroups in whom treatments were not already indicated.
- In RCTs of high versus low dose, combination versus monotherapy, and strict versus standard control, it was unclear whether intensification of treatment improves clinical outcomes.
- Effect of diet interventions on clinical outcomes in patients with CKD stages 1–3 is unclear because diet intervention RCTs were small, included both patients with CKD stages 1–3 and 4–5, and did not separate results by CKD stage or severity.
- In head-to-head RCTs, there was little evidence of a significant difference in mortality or any clinical vascular outcome between different active treatment groups.

- Trials used heterogeneous eligibility criteria for kidney function and damage, and rarely reported outcomes stratified by CKD stage or albuminuria category, impeding evidence synthesis.

Research Recommendations

- Post hoc analyses of ongoing or completed RCTs that already have or are collecting clinical outcomes.
  - Determine baseline eGFR and quantitative albuminuria, categorize participants by CKD stage and albuminuria category, and perform analyses to evaluate relative effectiveness of treatment versus control on clinical outcomes within these strata.
- Merge data from large scale treatment RCTs with Medicare data to identify incident ESRD cases occurring in post-trial followup period.
- Long-term RCTs of CKD treatment adequately powered to evaluate impact on clinical outcomes.
  - In addition to mortality, ESRD, and clinical vascular outcomes, additional clinical outcomes to consider for evaluation include quality of life, acute kidney injury complications (e.g., hospitalization), healthcare utilization, physical function, and cognitive function.
  - If composite outcomes reported, complete data also should be reported for individual composite components.
  - To increase trial relevance to a screened population, consider recruitment using population-based sampling.
  - Stratify results by CKD stage, albuminuria category, and other characteristics associated with CKD complications, including diabetes, hypertension, cardiovascular disease, older age, race/ethnicity, obesity, and hyperlipidemia.
  - Consider future RCTs of statins in patients with albuminuria, AECI, or ARB in patients with macroalbuminuria, ACEI or ARB in combination with other therapy, and of treatments other than ACEI or ARB.
  - Consider trials of dietary interventions restricted to patients with CKD stages 1–3.
  - Consider trials comparing system level interventions to aid providers in avoidance of nephrotoxic agents, medication renal dose adjustment, and other measures targeted to reduce CKD associated complications versus usual care.
- Patient level meta-analyses of treatment RCTs to evaluate the effect of treatments relative to control in relevant CKD subgroups.
- Analysis of administrative data to evaluate effect of nephrology referral on clinical outcomes, performing propensity analysis to account for factors associated with early referral.

Key Question 6. Among adults with CKD stages 1–3, whether detected by systematic screening or as part of routine care, what harms result from treatment?

Knowledge Gaps

- Withdrawals and adverse events were reported in few RCTs.

- Withdrawals often were not reported separately by treatment group; adverse events often did not appear predefined, systematically collected and reported, or separated by treatment group.

Research Recommendations

- In future RCTs, withdrawals and adverse effects should be predefined and collected and reported in all patients with CKD stages 1–3.
- Withdrawal and adverse effects may be reported stratified by CKD stage and albuminuria category, and other patient characteristics.

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Acronyms and Abbreviations

ACEI	Angiotensin converting enzyme inhibitors
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
ADA	American Diabetes Association
AHRQ	Agency for Healthcare Research and Quality
ALLHAT	Antihypertensive Lipid Lowering Treatment to Prevent Heart Attack
BB	Beta blocker
CCB	Calcium channel blocker
CCT	Controlled clinical trial
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
GFR	Glomerular filtration rate
HbA_{1c}	Hemoglobin A_{1c}
HCTZ	Hydrochlorothiazide
JNC7	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
KDIGO	Kidney Disease: Inspiring Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KEEP	Kidney Early Evaluation Program
LDL	Low density lipoprotein
MAP	Mean arterial blood pressure
MDRD	Modification of Diet in Renal Disease
MI	Myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
RCT	Randomized controlled trial
ROADMAP	Randomized Olmesartan and Diabetes Microalbuminuria Prevention
RR	Relative risk
TEP	Technical expert panel
UACR	Urinary albumin-creatinine ratio
UAER	Urinary albumin excretion rate
UPER	Urine protein excretion rate
USRDS	U.S. Renal Data System

Appendix A. Search Strings

Screening (KQ1, KQ2)

Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp mass screening/ or screening.tw. or exp early diagnosis/
2 (expression screening or throughput screening or molecular screening or pharmaceutical screening or mutation screening or genetic screening).tw. or exp genetic screening/ or cancer screening.tw. or compound screening.tw. or drug screening.tw. or exp drug evaluation, preclinical/
3 1 not 2
4 (randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/
5 exp albuminuria/ or exp proteinuria/ or exp glomerular filtration rate/ or exp creatinine/ or exp kidney function tests/ or exp cystatins/ or exp kidney diseases/ or kidney$.ti. or nephr$.ti. or renal.ti. or exp kidney/
6 3 and 4 and 5
7 exp animals/ not humans.sh.
8 6 not 7
9 limit 8 to english language
10 limit 9 to yr="1985 -Current"
11 limit 10 to "all child (0 to 18 years)"
12 limit 10 to "all adult (19 plus years)"
13 11 not 12
14 10 not 13

Monitoring (KQ3, KQ4)

Database: Ovid MEDLINE(R)
Search Strategy:

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1 monitoring.tw. or exp disease progression/
2 cardiac monitoring.tw. or exp drug monitoring/ or exp environmental monitoring/ or drug monitoring.tw. or exp blood glucose self-monitoring/ or exp blood gas monitoring, transcutaneous/ or exp clinical trials data monitoring committees/ or exp esophageal pH monitoring/ or exp monitoring, immunologic/ or exp uterine monitoring/ or exp monitoring, intraoperative/ or exp radiation monitoring/ or exp monitoring, physiologic/
3 1 not 2
4 (randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/
5 exp albuminuria/ or exp proteinuria/ or exp glomerular filtration rate/ or exp creatinine/ or exp kidney function tests/ or exp cystatins/ or exp kidney diseases/ or kidney$.ti. or nephr$.ti. or renal.ti. or exp kidney/
6 3 and 4 and 5

7 exp animals/ not humans.sh.
8 6 not 7
9 limit 8 to english language
10 limit 9 to yr="1985 -Current"
11 limit 10 to "all child (0 to 18 years)"
12 limit 10 to "all adult (19 plus years)"
13 11 not 12
14 10 not 13

Treatment (KQ5, KQ6)

Database: Ovid MEDLINE(R)
Search Strategy:

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1 exp albuminuria/co, de, dh, dt, mo, pc, th or exp proteinuria/co, de, dh, dt, mo, pc, th or exp glomerular filtration rate/ or exp kidney diseases/co, de, dh, dt, mo, pc, th or exp kidney/co, de, dh, dt, mo, pc, th or exp diabetic nephropathies/co, de, dh, dt, mo, pc, th or exp kidney failure, chronic/co, de, dh, dt, mo, pc, th or exp chronic renal insufficiency/co, de, dh, dt, mo, pc, th or exp renal insufficiency/co, de, dh, dt, mo, pc, th or exp renal insufficiency, chronic/co, de, dh, dt, mo, pc, th
2 exp *renal replacement therapy/ or exp renal dialysis/ or exp *kidney neoplasms/ or *nephritis/ or exp *urinary tract infections/ or exp *urolithiasis/ or exp anuria/ or exp diabetes insipidus/ or exp fanconi syndrome/ or exp hepatorenal syndrome/ or exp hydronephrosis/ or exp kidney cortex necrosis/ or exp Kidney Diseases, Cystic/ or kidney papillary necrosis/ or exp nephritis/ or exp renal artery obstruction/ or exp Renal Tubular Transport, Inborn Errors/ or exp Tuberculosis, Renal/ or exp Zellweger syndrome/ or exp AIDS-Associated Nephropathy/ or exp Hyperoxaluria/ or exp Nephrocalcinosis/ or exp Perinephritis/ or exp Renal Osteodystrophy/
3 1 not 2
4 (randomized controlled trial or controlled clinical trial).pt. or random*.ti,ab. or placebo.ab. or exp Double-Blind Method/ or randomized controlled trials as topic/
5 3 and 4
6 exp animals/ not humans.sh.
7 5 not 6
8 limit 7 to english language
9 limit 8 to yr="1985 -Current"
10 limit 9 to "all child (0 to 18 years)"
11 limit 9 to "all adult (19 plus years)"
12 10 not 11
13 9 not 12

Appendix B. Excluded Studies

(Note that this set of references is different from those in the text, and the numbers are different.)

CKD Screening (KQ1, KQ2)

1. Microalbuminuria in type I diabetic patients. Prevalence and clinical characteristics. Microalbuminuria Collaborative Study Group. Diabetes Care 1992; 15(4):495-501. *Not a randomized trial*
2. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. New England Journal of Medicine 1993; 329(14):977-86. *Not an intervention for screening for CKD*
3. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 1995; 44(8):968-83. *Not a randomized trial*
4. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. Lancet 2000; 355(9200):253-9. *Not an intervention for screening for CKD*
5. Abetimus: Abetimus sodium, LJP 394. Biodrugs 2003; 17(3):212-5. *Less than 1000 patients in study*
6. Accetta NA, Gladstone EH, DiSogra C, et al. Prevalence of estimated GFR reporting among US clinical laboratories. American Journal of Kidney Diseases 2008; 52(4):778-87. *Not a randomized trial*
7. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney International 2003; 63(1):225-32. *Not an intervention for screening for CKD*
8. Agarwal A, Silver MR, Walczyk M, et al. Once-monthly darbepoetin alfa for maintaining hemoglobin levels in older patients with chronic kidney disease. Journal of the American Medical Directors Association 2007; 8(2):83-90. *Not a randomized trial*
9. Agodoa LY, Francis ME, Eggers PW. Association of analgesic use with prevalence of albuminuria and reduced GFR in US adults. American Journal of Kidney Diseases 2008; 51(4):573-83. *Not a randomized trial*
10. Agrawal A, Sautter MC, Jones NP. Effects of rosiglitazone maleate when added to a sulfonylurea regimen in patients with type 2 diabetes mellitus and mild to moderate renal impairment: a post hoc analysis. Clinical Therapeutics 2003; 25(11):2754-64. *Duration of follow-up less than 1 year*

11. Ahmedani MY, Hydrie MZI, Iqbal A, et al. Prevalence of microalbuminuria in type 2 diabetic patients in Karachi: Pakistan: a multi-center study.[Erratum appears in J Pak Med Assoc. 2005 Nov;55(11):523].[Erratum appears in J Pak Med Assoc. 2005 Dec;55(12):570]. JPMA - Journal of the Pakistan Medical Association 2005; 55(9):382-6. *Not a randomized trial*

12. Ahn CW, Song YD, Kim JH, et al. The validity of random urine specimen albumin measurement as a screening test for diabetic nephropathy. Yonsei Medical Journal 1999; 40(1):40-5. *Less than 1000 patients in study*

13. Akanji AO, Mainasara AS, Akinlade KS. Urinary iodine excretion in mothers and their breast-fed children in relation to other childhood nutritional parameters. European Journal of Clinical Nutrition 1996; 50(3):187-91. *Not an intervention for screening for CKD*

14. Al-Maskari F, El-Sadig M, Obineche E. Prevalence and determinants of microalbuminuria among diabetic patients in the United Arab Emirates. BMC Nephrology 2008; 9:1. *Not a randomized trial*

15. Alsuwaida A, Abdulkareem A, Alwakeel J. The Gulf Survey on Anemia Management (GSAM 2005). Saudi Journal of Kidney Diseases & Transplantation 2007; 18(2):206-14. *Patients already diagnosed with CKD*

16. Amato D, Alvarez-Aguilar C, Castaneda-Limones R, et al. Prevalence of chronic kidney disease in an urban Mexican population. Kidney International - Supplement 2005; (97):S11-7. *Not a randomized trial*

17. Andrassy J, Zeier M, Andrassy K. Do we need screening for thrombophilia prior to kidney transplantation? Nephrology Dialysis Transplantation 2004; 19 Suppl 4:iv64-8. *Not a randomized trial*

18. Atkins RC, Briganti EM, Zimmet PZ, et al. Association between albuminuria and proteinuria in the general population: the AusDiab Study. Nephrology Dialysis Transplantation 2003; 18(10):2170-4. *Not a randomized trial*

19. Atthobari J, Asselbergs FW, Boersma C, et al. Cost-effectiveness of screening for albuminuria with subsequent fosinopril treatment to prevent cardiovascular events: A pharmacoeconomic analysis linked to the prevention of renal and vascular endstage disease (PREVEND) study and the prevention of renal and vascular endstage disease intervention trial (PREVEND IT). Clinical Therapeutics 2006; 28(3):432-44. *Not an intervention for screening for CKD*

20. Atthobari J, Brantsma AH, Gansevoort RT, et al. The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study. Nephrology Dialysis Transplantation 2006; 21(11):3106-14. *Less than 1000 patients in study*

21. Atthobari J, Gansevoort RT, Visser ST, et al. The effect of screening for cardio-renal risk factors on drug use in the general population. British Journal of Clinical Pharmacology 2007; 64(6):810-8. *Not an intervention for screening for CKD*

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23. Azizi M, Menard J, Peyrard S, et al. Assessment of patients' and physicians' compliance to an ACE inhibitor treatment based on urinary N-acetyl Ser-Asp-Lys-Pro determination in the Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study. Diabetes Care 2006; 29(6):1331-6. *Not a randomized trial*

24. Bakris G. Inclusion of albuminuria in hypertension and heart guidelines. Kidney International - Supplement 2004; (92):S124-5. *Not a randomized trial*

25. Bakris G, Hester A, Weber M, et al. The diabetes subgroup baseline characteristics of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial. J Cardiometab Syndr 2008; 3(4):229-33. *Not an intervention for screening for CKD*

26. Bakris GL, Fonseca V, Katholi RE, et al. Differential effects of beta-blockers on albuminuria in patients with type 2 diabetes. Hypertension 2005; 46(6):1309-15. *Not an intervention for screening for CKD*

27. Bang H, Mazumdar M, Newman G, et al. Screening for kidney disease in vascular patients: SCreening for Occult REnal Disease (SCORED) experience. Nephrology Dialysis Transplantation 2009; 24(8):2452-7. *Not a randomized trial*

28. Barbanel CS, Winkelman JW, Fischer GA, et al. Confirmation of the Department of Transportation criteria for a substituted urine specimen. Journal of Occupational & Environmental Medicine 2002; 44(5):407-16. *Not a randomized trial*

29. Barrett BJ, Katzberg RW, Thomsen HS, et al. Contrast-induced nephropathy in patients with chronic kidney disease undergoing computed tomography: a double-blind comparison of iodixanol and iopamidol.[Erratum appears in Invest Radiol. 2007 Feb;42(2):94 Note: Ni, Zhao-hui [added]]. Investigative Radiology 2006; 41(11):815-21. *Patients already diagnosed with CKD*

30. Baskar V, Kamalakannan D, Holland MR, et al. Uncertain clinical utility of contemporary strategies for microalbuminuria testing. Diabetes, Obesity & Metabolism 2003; 5(4):262-6. *Not a randomized trial*

31. Baxter GM, Aitchison F, Sheppard D, et al. Colour Doppler ultrasound in renal artery stenosis: intrarenal waveform analysis. British Journal of Radiology 1996; 69(825):810-5. *Not a randomized trial*

32. Beatovic S, Jaksic ED, Han RS. Measurement of renal function by calculation of fractional uptake of technetium-99m dimercaptosuccinic acid. Nucl Med Rev Cent East Eur 2004; 7(1):49-52. *Not an intervention for screening for CKD*

33. Beatty OL, Ritchie CM, Hadden DR, et al. Is a random urinary albumin concentration a useful screening test in insulin-treated diabetic patients? Irish Journal of Medical Science 1994; 163(9):406-9. *Not a randomized trial*

34. Beaulieu AJ, Gohh RY, Han H, et al. Enhanced reduction of fasting total homocysteine levels with supraphysiological versus standard multivitamin dose folic acid supplementation in renal transplant recipients. Arteriosclerosis, Thrombosis & Vascular Biology 1999; 19(12):2918-21. *Patients already diagnosed with CKD*

35. Beevers DG, Lip GY. Does non-malignant essential hypertension cause renal damage? A clinician's view. Journal of Human Hypertension 1996; 10(10):695-9. *Not a randomized trial*

36. Bellizzi V, Scalfi L, Terracciano V, et al. Early changes in bioelectrical estimates of body composition in chronic kidney disease. Journal of the American Society of Nephrology 2006; 17(5):1481-7. *Not a randomized trial*

37. Beresford TP, Blow FC, Hill E, et al. Comparison of CAGE questionnaire and computer-assisted laboratory profiles in screening for covert alcoholism. Lancet 1990; 336(8713):482-5. *Not an intervention for screening for CKD*

38. Berland LL, Koslin DB, Routh WD, et al. Renal artery stenosis: prospective evaluation of diagnosis with color duplex US compared with angiography. Work in progress. Radiology 1990; 174(2):421-3. *Not a randomized trial*

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CKD Treatment (KQ5, KQ6)

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Appendix C. Evidence Tables and Other Supporting Tables and Figures

Tables

Figures

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ACE inhibitor monotherapy versus placebo/no treatment trials (n=17 trials)				
Perkovic, 2007[1] PROGRESS Multinational (Europe, Asia, Australia) Funding Source: Industry and other	Inclusion Criteria: history of cerebrovascular disease (ischemic stroke, hemorrhagic stroke, or transient ischemic attack but not subarachnoid hemorrhage) within the previous 5 years and no clear indication for or contraindication to treatment with an ACE inhibitor. Exclusion Criteria: not described.	N=1757 patients with CKD (Baseline GFR <60 ml/min/ 1.73m^2) of 6105 randomized. Age (yr): 70 Gender (Male %): 55 Race/Ethnicity (%): Asian 37 BMI: 24 Systolic BP (mm Hg): 149 Diastolic BP (mm Hg): 84 Serum creatinine (mg/dL): 1.2 (median) Creatinine clearance (ml/min/1.73m^2) (median): 50 Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 11 History of HTN (%): NR (study reported 53% on HTN medication but did not report prevalence of untreated HTN) History of CHD (%): 20 History of CHF (%): NR History of MI (%): NR History of Stroke (ischemic) (%): 71 History of Stroke (hemorrhagic) (%): 10 History of transient ischemic attack (%): 22 Peripheral arterial disease (%): NR Current smoker (%): 16	Perindopril 4 mg/d (n=895) Placebo (n=862) Followup period: mean 4 years Study withdrawals (%): NR	Allocation Concealment: adequate (central) Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: NA, post hoc analysis

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Asselbergs, 2004[2] PREVEND IT The Netherlands Funding Source: Industry and other	Inclusion Criteria: persistent microalbuminuria (urinary albumin concentration >10 mg/L in 1 early morning spot urine sample and a concentration of 15 to 300 mg/24 hours in 2 24-hour urine samples at least once); BP <160/100 mm Hg and no use of antihypertensive medication; total cholesterol level <8.0 mmol/L, or <5.0 mmol/L in case of previous MI, and no use of lipid-lowering medication. Exclusion Criteria: creatinine clearance <60% of the normal age adjusted value; use of ACE inhibitors or ARB antagonists.	N=864 Age (yr): 51 Gender (Male %): 65 Race/Ethnicity (%): white 96 BMI: 26 Systolic BP (mm Hg): 130 Diastolic BP (mm Hg): 76 Albuminuria (mg/24 h): 23 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): 222 LDL cholesterol (mg/dL): 157 Diabetes (%): 2.5 History of HTN (%): 0 (exclusion criterion) History of CVD (%): NR History of CHF (%): 0 History of MI (%): 0.5 History of Stroke (%): 0.8 Peripheral arterial disease (%): 0.6 Current/ever smoker (%): 73	Fosinopril 20 mg/d (n=431) Placebo (n=433) Followup period: mean 3.8 years Study withdrawals (%): 28 Note: 2 x 2 factorial design with pravastatin	Allocation Concealment: unclear Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes
Marre, 2004[3] DIABHYCAR Multinational (Europe and North Africa) Funding Source: Industry and other	Inclusion Criteria: persistent micro-albuminuria or proteinuria (urinary albumin excretion ≥20 mg/L, in two successive random urine samples); <50 years of age; and type 2 diabetes (defined on the basis of receiving current treatment with at least one oral antidiabetic agent). Exclusion Criteria: serum creatinine concentration >150 mmol/L; treatment with insulin, an ACE inhibitor, or ARB blocker; documented CHF; MI during the past three months; urinary tract infection; previous intolerance to an ACE inhibitor.	N=4,912 Age (yr): 65 Gender (Male %): 70 Race/Ethnicity (%): NR BMI: 29 Systolic BP (mm Hg): 145 Diastolic BP (mm Hg): 82 Microalbuminuria (%): 74 Proteinuria (%): 26 Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m^2): NR HbA_{1c}(%): 7.8 Diabetes (%): 100 History of HTN (%): 56 History of CVD (%): 24 History of CHF (%): 0 History of MI (%): 6 History of Stroke (%): 4 Peripheral arterial disease (%): 10 Current smoker (%): 15	Ramipril 1.25 mg/d (n=2443) Placebo (n=2469) Followup period: median 4 years Study withdrawals (%): 17	Allocation Concealment: adequate Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Katayama, 2002[4] JAPAN-IDDM Sarafidis review Japan Funding Source: Other	Inclusion Criteria: UAE >30 mg/24 h at the time of screening in two consecutive sterile urine samples collected overnight; onset of type 1 diabetes before 20 years; and aged between 20 and 50 years of age. Exclusion Criteria: none stated.	N=53 (imdapril arm excluded) Age (yr): 33 Gender (Male %): 35 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 127 Diastolic BP (mm Hg): 78 Albumin excretion rate (mg/day): 711 Serum creatinine (mg/dL): 0.76 Creatinine clearance (ml/min): 98.4 Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 8.8 Diabetes (%): 100 History of HTN (%): 18 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Captopril 37.5 mg (n=26) Placebo (n=27) Followup period: mean 1.5 years Study withdrawals (%): 30 (excluding subjects reaching endpoint)	Allocation Concealment: adequate Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes
Bojestig, 2001[5] Sarafidis review Sweden Funding Source: Industry	Inclusion Criteria: microalbuminuria (AER of 20–200 µg/min in two of three collections); type 1 diabetes; and normotensive (clinic diastolic <90 mmHg). Exclusion Criteria: Patients treated with any form of hypertensive medication.	N=55 Age (yr): 40 Gender (Male %): 75 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 126 (clinic) Diastolic BP (mm Hg): NR Albumin excretion rate (µg/min): median 69-103 Estimated GFR (ml/min/1.73m^2): median 100-108 HbA_{1c} (%): 7.4 Diabetes (%): 100 History of HTN (%): 0 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Ramipril 1.25 mg/d (n=19) Ramipril 15 mg/d (n=18) Placebo (n=18) Followup period: 2 years Study withdrawals (%): 7	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Gerstein HOPE Trial, 2001[6] Multinational (North and South America and in Europe) Funding Source: Industry and other	Inclusion Criteria: ≥55 years of age; history of CV disease (either CAD, stroke, or PVD) or with a history of DM; plus at least one other CV risk factor (total cholesterol >200 mg/dL, high-density lipoprotein cholesterol ≤35mg/dL, HTN, known microalbuminaria, or current smoker. Microalbuminuria was defined as an ACR of ≥2mg/mmol for both men and women; dipstick-positive (ie, ≥1+) proteinuria Exclusion Criteria: heart failure; intolerance of ACE inhibitors or vitamin E; serum creatinine concentration >200 mmol/L (2.3 mg/dL), or dipstick-positive proteinuria (>+1)	N=1,140 patients with diabetes and microalbuminuria (urinary albumin-creatinine ratio >2mg/mmol, but not dipstick positive [≥1+] proteinuria) from 1963 with microalbuminuria and 9297 randomized overall in the larger HOPE trial. Patient characteristics not described for microalbuminuric subjects	Ramipril 10 mg/d (n=553) Placebo (n=587) Followup period: median 4.5 years Study withdrawals (%): NR Note: 2 x 2 factorial design with vitamin E.	Allocation Concealment: adequate (from background paper Can J Cardiol) Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: NA, post hoc analysis

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
O'Hare, 2000[7] ATLANTIS UK and Ireland Funding Source: Industry	Inclusion Criteria: microalbuminuria, defined as overnight AER on screening of 20–200 µg/min in two of three collections; type 1 diabetes; and untreated blood pressure <150/90 mmHg for patients <50 years of age and <165/90 mmHg for patients 50–65 years of age. Exclusion Criteria: those pregnant or lactating; were women of child-bearing potential not using adequate contraception; were on concomitant therapy for HTN; were on one or more nonsteroidal anti-inflammatory drugs; history of drug or alcohol abuse; had other known renal diseases or raised creatinine levels (>120 µmol/L) or liver function twice that of normal on repeat testing; or had iodine sensitivity, making them unable to partake in GFR measurements.	N=140 Age (yr): 40 Gender (Male %): 71 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 132 Diastolic BP (mm Hg): 76 Albumin excretion rate (µg/min): 53 Estimated GFR (ml/min/1.73m^2): 104 HbA_{1c} (%): 11.4 Diabetes (%): 100 History of HTN (%): 0 (HTN was exclusion criterion) History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Ramipril 1.25 mg/d (n=47) Ramipril 5 mg/d (n=45) Placebo (n=48) Followup period: 2 years Study withdrawals (%): 30	Allocation Concealment: adequate Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Muirhead, 1999[8] Kunz review Canada Funding Source: Industry	Inclusion Criteria: incipient diabetic nephropathy, defined as AER between 20 to 300 µg/min and a GFR 60 ≥ ml/min/1.73m^2 at visit 1; aged ≥18 years; type 2 DM Exclusion Criteria: "brittle" diabetes (increased risk of hypoglycemia) or patients with a history of noncompliance with medical regimens.	N=60 (excluding valsartan arms) Age (yr): 56 Gender (Male %): 82 Race/Ethnicity (%): white 87, black 2, Asian 5 BMI: NR Systolic BP (mm Hg): 136 Diastolic BP (mm Hg): 84 Serum creatinine (mg/dL): NR Albumin excretion rate (µg/min): 53.4 Estimated GFR (ml/min/1.73m^2): 87 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR HbA_{1c} (%): NR Diabetes (%): 100 History of HTN (%):47% on HTN medication History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Captopril 75 mg/d (n=29) Placebo (n=31) Follow-p period: 1 year Study withdrawals (%): 18	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Ruggenenti, 1999[9] REIN, proteinuria stratum 1: ≥1 g to <3g/24 h Italy Funding Source: Industry	Inclusion Criteria: chronic nephropathy; persistent proteinuria (≥1 g to <3 g); aged 18 to 70 years; has not received ACEI for 2 months, corticosteroids, NSAIDS, immunosuppressive drugs for 6 months. Exclusion Criteria: treatment with corticosteroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs; acute MI or cerebrovascular accident in the previous 6 months; severe uncontrolled hypertension (diastolic BP ≥115 and/or systolic BP ≥220 mm Hg); evidence or suspicion of renovascular disease, obstructive uropathy, insulin-dependent diabetes mellitus, collagen disease, cancer, higher serum aminotransferase concentrations, or chronic cough; drug or alcohol abuse; pregnancy; breast feeding; and ineffective contraception.	N=186 Age (yr): 50 Gender (Male %): 75 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 143 Diastolic BP (mm Hg): 89 Urinary protein excretion (g/day): 1.7 Serum creatinine (mg/dL): 2.0 Creatinine clearance (ml/min/1.73m^2): 52 Estimated GFR (ml/min/1.73m^2): 46 Total cholesterol (mg/dL): 229 Diabetes (%): NR History of HTN (%): 82 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Ramipril 1.25 mg/d (n=99) Placebo (n=87) Followup period: median 2.6 years Study withdrawals (%): 22 (excluding subjects reaching endpoint)	Allocation Concealment: adequate (*based on GISEN report*) Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Crepaldi, 1998[10] Sarafidis review Italy Funding Source: None stated	Inclusion Criteria: overt albuminuria - median AER value between 20 and 200 µg/min from 3 timed overnight urine collections; GFR ≥80 ml/min/1.73m^2 at randomization; aged 18 to 70 years; onset of insulin-dependent DM before age 35 and insulin treatment within 3 years of diagnosis; clinical stability of DM during past 12 months; standing systolic BP ≥115 and ≤145 mmHg (without HTN therapy) and diastolic BP ≥75 and ≤90 mmHg. Exclusion Criteria: impaired renal function (defined as serum creatinine >10% above the upper limit of normal (125 µmol/L) and median AER >200 µg/min at entry and visit 3 after randomization); nondiabetic renal disease; hematuria; evidence of clinically significant liver or hematological disease; evidence of aortic or mitral valve obstruction; arrhythmias; unstable angina; history of MI within previous 3 months; systemic malignancy; hyperkalemia, serum trigylcerides >3.4mmol/L, or total cholesterol >6.5 mmol/L.	N=96 (66 included in the baseline characteristics and nifedipine arm excluded) Age (yr): 37 Gender (Male %): 67 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 128 Diastolic BP (mm Hg): 83 Albumin excretion rate (µg/min): 71.5 Serum creatinine (mg/dL): 0.98 Creatinine clearance (ml/min/1.73m^2): 114 Estimated GFR (ml/min/1.73m^2): 114 HbA_{1c} (%): 8.6 Diabetes (%): 100 History of HTN (%): 0 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 58	Lisinoprol 2.5-20 mg/d (n=47) Placebo (n=49) Followup period: 3 years Study withdrawals (%): 32 (includes 21 patients excluded for not having AER values between 20 and 200 µg/min)	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
The GISEN Group, 1997[11] REIN, proteinuria stratum 2: ≥3 g/ 24 h Italy Funding Source: Industry	Inclusion Criteria: chronic nephropathy; persistent proteinuria (≥3 g); aged 18 to 70 years; has not received ACEI for 2 months, corticosteroids, NSAIDS, immunosuppressive drugs for 6 months. Exclusion Criteria: treatment with corticosteroids, nonsteroidal anti-inflammatory drugs, or immunosuppressive drugs; acute MI or cerebrovascular accident in the previous 6 months; severe uncontrolled hypertension (diastolic blood pressure ≥115 and/or systolic blood pressure ≥220 mm Hg); evidence or suspicion of renovascular disease, obstructive uropathy, insulin-dependent diabetes mellitus, collagen disease, cancer, higher serum aminotransferase concentrations, or chronic cough; drug or alcohol abuse; pregnancy; breast feeding; and ineffective contraception.	N=166 Age (yr): 49 Gender (Male %): 78 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 149 Diastolic BP (mm Hg): 92 Urinary protein excretion (g/day): 5.3 Serum creatinine (mg/dL): 2.4 Creatinine clearance (ml/min/1.73m^2): 45 Estimated GFR (ml/min/1.73m^2): 39 Diabetes (%): NR History of HTN (%): 87 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Ramipril 1.25 mg/d (n=78) Placebo (n=88) Followup period: mean 1.3 years Study withdrawals (%): 21 (excluding subjects reaching endpoint) Note: combined endpoint stratified by baseline AER	Allocation Concealment: adequate Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Maschio, 1996[12] Europe Funding Source: Industry	Inclusion Criteria: chronic renal insufficiency caused by various diseases (glomerular disease (in 192 patients), interstitial nephritis (in 105), nephrosclerosis (in 97), polycystic kidney disease (in 64), diabetic nephropathy (in 21) unknown (in 104)); aged 18 to 70 years; serum creatinine concentration of 1.5 to 4.0 mg/dL and a 24-hour estimated creatinine clearance of 30 to 60 ml/min, with variations of <30 percent in at least three measurements of creatinine clearance during a three-month screening period and <15 percent during a subsequent two-week, single-blind placebo period. Exclusion Criteria: therapy-resistant edema; treatment with corticosteroids, nonsteroidal antiinflammatory drugs, or immunosuppressive drugs; a value for urinary protein excretion over 10 g/24 h and a value for serum albumin under 25 g/L (each measured at least three times, and twice during the screening period); renovascular hypertension; malignant HTN or a MI or CVA in the six months preceding the study; congestive heart failure (New York Heart Association class III or IV); insulin-dependent DM; elevated serum amino-transferase concentrations; collagen disease; obstructive uropathy; cancer; chronic cough; history of allergy to ACEI; drug or alcohol abuse; and pregnancy.	N=583 Age (yr): 51 Gender (Male %): 72 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 143 Diastolic BP (mm Hg): 87 Urinary protein excretion (g/day): 1.8 Serum creatinine (mg/dL): 2.1 Creatinine clearance (ml/min): 43 Estimated GFR (ml/min/1.73m^2): NR Diabetes (%): 4 (n=21) have diabetic nephropathy History of HTN (%): 82 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR Severity of renal dysfunction: Creatinine clearance 46 to 60 ml/min) (%): 39 Creatinine clearance 30 to 45 ml/min) (%): 61	Benazepril 10 mg/d (n=300) Placebo (n=283) Followup period: median 3 years Study withdrawals (%): 23 (excluding subjects reaching endpoint)	Allocation Concealment: unclear Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Trevisan, 1995[13] Italy Funding Source: Industry	Inclusion Criteria: persistent microalbuminuria (AER 20-200 µg/min at screening and in at least two of three consecutive sterile urine samples collected overnight); aged 18 to 65 years; had non-insulin-dependent DM (diagnosed according to World Health Organization criteria) of at least 6 months duration; had stable metabolic control with a glycated hemoglobin concentration <10%. Exclusion Criteria: systolic blood pressure was ≥180 mm Hg or diastolic blood pressure ≥105 mm Hg; unstable angina, heart failure; serum creatinine >1.5 mg/dL; history of poor compliance; high serum potassium levels (>5.5 mEq/L); or liver, gastrointestinal, and connective tissue diseases.	N=122 Age (yr): 57 Gender (Male %): 77 Race/Ethnicity: NR BMI: 29 Systolic BP (mm Hg): 149 Diastolic BP (mm Hg): 91 Albumin excretion rate (µg/min): 67 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.1 Diabetes (%): 100 History of HTN (%): NR (among 108 who completed study, 43 (39.8%) had baseline BP ≥160/95 mm Hg) History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 22	Ramipril 1.25 mg/d (n=60) Placebo (n=62) Followup period: 6 months Study withdrawals (%): 11	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Laffel, 1995[14] North American Micro-albuminuria Study Sarafidis review USA and Canada Funding Source: Industry	Inclusion Criteria: microalbuminaria - overnight AER 20–200 µg/min; aged 14 to 57 years with at least 4 years documented insulin-dependent DM before age 45; normotensive Exclusion Criteria: HbA_{1c} ≥11.5%; body weight outside of 75% to 125% of ideal; serum creatinine and potassium levels beyond normal ranges; white blood cell count <3500/mm^3; BP ≥140/90 mm Hg; antihypertensive therapy; pregnancy/lactation; histories of renal, cardiac, hepatic, gastrointestinal, or autoimmune diseases. No use of CCB, beta-blockers, and non-steroidal agents.	N=143 Age (yr): 33 Gender (Male %): 50 Race/Ethnicity (%): white 92 BMI: NR Systolic BP (mm Hg): 140 Diastolic BP (mm Hg): 90 Albumin excretion rate (µg/min): 62 Serum creatinine (mg/dL): 1.1 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (ml/min/1.73m^2): 80 HbA_{1c} (%): 7.8 Diabetes (%): 100 History of HTN (%): 0 History of CAD (%): 0 History of CHF (%): 0 History of MI (%): 0 History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 29	Captopril 100 mg (n=70) Placebo (n=73) Followup period: 2 years Study withdrawals (%): 30	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes
Sano 1994[15] Sarafidis review Japan Funding Source: None stated	Inclusion Criteria: noninsulin dependent diabetes mellitus; persistent microalbuminuria (AER 20-300 mg/24 h on 3-4 separate occasions over a 3 month period; aged 50 to 76 years; serum creatinine <1.2 mg/dL; systolic BP <150 mmHg and diastolic <90 mmHg over a long period; HbA_{1c} <10%; no history of nondiabetic renal disease; no medications other than oral hypoglycemic agents. Exclusion Criteria: none stated.	N=52 (48 included in the baseline characteristics) Age (yr): 64 Gender (Male %): NR Race/Ethnicity (%): NR BMI: 24 Systolic BP (mm Hg): 136 Diastolic BP (mm Hg): 74 Albumin excretion rate (mg/day): 72 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (ml/min): 90 HbA_{1c} (%): 8.2 Diabetes (%): 100 History of HTN (%): 0 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Enalapril (n=26) No enalapril (n=26) Followup period: 2 years Study withdrawals (%): 8	Allocation Concealment: unclear Blinding: no Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Lewis, 1993[16] USA Funding Source: Industry and other	Inclusion Criteria: urinary protein excretion of ≥ 500 mg/24 h, and a serum creatinine concentration of ≤ 2.5 mg/dL; aged 18 to 49 years; insulin-dependent DM for ≥7 years, with an onset before the age of 30 years, and had diabetic retinopathy; Patients satisfying these criteria during a single examination were eligible for the study, regardless of previous BP status or a previous need for antihypertensive medication. Patients who were receiving ACE inhibitors or CCBs were eligible provided their BP could be maintained within the BP goals required by the trial without these drugs Exclusion Criteria: pregnancy; dietary evaluation that indicated marked departure from standard dietary recommendations; white-cell count <2500 per cubic millimeter; CHF (New York Heart Association class III or worse); and serum potassium concentration of ≥6 mmol/L.	N=409 Age (yr): 35 Gender (Male %): 53 Race/Ethnicity (%): white 89; black 7 BMI: NR Systolic BP (mm Hg): 138 Diastolic BP (mm Hg): 85 Urinary protein excretion (g/day): 2.7 Serum creatinine (mg/dL): 1.3 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (ml/min): 82 HbA_{1c} (%): 11.7 Diabetes (%): 100 History of HTN (%): 76 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Captopril 75 mg (n=207) Placebo (n=202) Followup period: median 3 years Study withdrawals (%): 26	Allocation Concealment: unclear Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Ravid, 1993[17] Sarafidis review Israel Funding Source: Other	Inclusion Criteria: microabluminuria (urinary protein excretion 30 to 300 mg/24h on two consecutive visits without evidence of a urinary tract infection; type 1 diabetes <10 years with no evidence of systemic, renal, cardiac, or hepatic disease; age <50 years; BMI <27; normal BP on two consecutive examinations (systolic ≤140 mm Hg; diastolic ≤90 mm Hg; Exclusion Criteria: none stated.	N=108 (94 included in the baseline characteristics) Age (yr): 44 Gender (Male %): 45 Race/Ethnicity (%): NR BMI: 24 Mean BP (mm Hg): 98 Proteinuria (mg/day): 133 Serum creatinine (mg/dL): 1.2 Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 10.4 Diabetes (%): 100 History of HTN (%): 0 History of CAD (%):NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Enalapril 10 mg (n=56) Placebo (n=52) Followup period: 5 years Study withdrawals (%): 13	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes
ACE inhibitor monotherapy versus ARB trials (n=6 trials)				
Mann, 2008[18] ONTARGET Multinational Funding Source: Industry	Inclusion Criteria: aged 55 years or older with established atherosclerotic vascular disease or with diabetes with endorgan damage. Exclusion Criteria: major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration above 265 µmol/L, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic), symptomatic congestive heart failure..	N=4,046 for patients with a baseline GFR <60 ml/min/ 1.73m^2 (of a total of 17,118 randomized to ramipril vs. telmisartan, and not including 8502 subjects randomized to combination ramipril + telmisartan). 2673 patients had micro or macroalbuminuria. Patient characteristics not described for CKD subjects	Ramipril 10 mg/day (n NR for CKD patients) Telmisartan 80 mg/day (n NR for CKD patients) Followup period: median 4.7 years Study withdrawals (%): NR	Allocation Concealment: adequate Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Menne, 2008[19] VALERIA Germany and Hungary Funding Source: Industry	Inclusion Criteria: microalbuminuria (urine albumin creatinine ratio for women ≥3.5 mg/ mmol/L and ≤35.0 mg/mmol and men ≥2.5 mg/ mmol/L and ≤25.0 mg/ mmoL); aged 18 to 75 years; essential hypertension [defined as mean sitting diastolic BP ≥85 mmHg and <110 mm Hg]. To fulfill the criteria of microalbuminuria, two of three first morning void urines needed to be positive during the screening phase. Exclusion Criteria: primary kidney disease, renal impairment (creatinine clearance <30ml/min using the Cockroft and Gault formula; serum potassium values >5.5mmol/L; heart failure, significant arrhythmias or bradycardia; relevant valvular disease, type I DM, uncontrolled type II DM with HbA_{1c} >8.0%; history of MI; percutaneous transluminal coronary angioplasty, bypass surgery or stroke within the last 12 months prior to study inclusion; unstable angina pectoris; renal transplantation; severe hepatic disease or hepatic failure; malignant concomitant diseases or history of malignant diseases within the last 5 years; systemic inflammatory diseases; pregnancy or breast feeding; psychiatric disease; either history of alcohol or drug abuse or both.	N=90 (133 total with combination arm) Age (yr): 58 Gender (Male %): 69 Race/Ethnicity (%): NR BMI: 32 Systolic BP (mm Hg): 153 Diastolic BP (mm Hg): 91 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 112 Urine albumin creatinine ratio (mg/ mmol): 9.4 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR HbA_{1c} (%): NR Diabetes (%): 74 History of HTN (%): 100 History of CAD “Cardiac disorders”(%): 19 History of CHF (%): 0 (exclusion criterion) History of MI (%): 0 (exclusion criterion) History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Lisinopril 40 mg/d (n=47) Valsartan 320 mg/d (n=43) *Lisinopril + Valsartan (n=43)* Followup period: 2.5 years Study withdrawals (%): 14	Allocation Concealment: adequate Blinding: double plus outcome assessors and data analysts Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Sengul, 2006[20] Turkey Funding Source: none stated	Inclusion Criteria: Type 2 diabetes, microalbuminuria (AER rate 30 to 300 mg/24 h for a minimum of three consecutive occasions); aged 40 to 65 years; previously diagnosed hypertension (systolic BP ≥ 140 mm Hg or diastolic BP ≥90 mm Hg), despite receiving ACE inhibitor monotherapy for ≥6 months. Exclusion Criteria: type 1 DM; BMI ≥ 40; secondary diabetes; alcoholism; thyroid disease; systolic BP >200 mm Hg, any non-diabetic cause of secondary HTN (including bilateral renal artery stenosis); urinary tract infection; persistent hematuria; chronic liver disease; overt carcinoma; any cardiovascular event in the previous 6 months; serum creatinine ≥ 150 mmol/L; serum potassium ≥ 5.5 mmol/L; or pregnancy.	N=219 Age (yr): 57 Gender (Male %): 37 Race/Ethnicity (%): NR BMI: 30 Systolic BP (mm Hg): 151 Diastolic BP (mm Hg): 89 Urinary AER (mg/24 h): 260 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 97 Total cholesterol (mg/dL): 211 LDL cholesterol (mg/dL): 135 HbA_{1c} (%): 7.9 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 37	Lisinopril 20 mg/d (n=110) Telmisartan 80 mg/d (n=109) After 24 weeks, half of the patients receiving lisinopril were randomized to receive telmisartan in addition. Similarly, half the patients initially treated with telmisartan received a combination of lisinopril plus telmisartan. The remaining patients continued to be treated with monotherapy. Followup period: 1 year Study withdrawals (%): 12	Allocation Concealment: unclear Blinding: open-label Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Barnett, 2004[21] DETAIL Europe Funding Source: Industry	Inclusion Criteria: urinary albumin excretion rate (mean of three consecutive overnight values) between 11 and 999 µg per minute, with two values > 10 µg per minute; aged 35 to 80 years; type 2 DM treated by diet, diet plus oral hypoglycemic drugs (for at least one year), or insulin preceded by treatment with oral agents (also for at least one year). Among those treated with insulin, onset of diabetes had to have occurred after the age of 40 years with a BMI >25 at the time of diagnosis; mild-to-moderate HTN, with a resting BP of less than 180/95 mm Hg after ≥3 months of ACE-inhibitor therapy before entry into the study; normal renal morphology; glycosylated hemoglobin value <12 %; serum creatinine <1.6 mg/dL; GFR >70 ml/min/1.73m^2. Exclusion Criteria: any condition (other than cardiovascular disease) that could restrict long-term survival and known allergy to study drugs or iohexol.	N=250 Age (yr): 61 Gender (Male %): 73 Race/Ethnicity (%): white 98 BMI: 31 Systolic BP (mm Hg): 152 Diastolic BP (mm Hg): 86 Microabluminuria (%): 82 Macroabluminuria (%): 18 Urinary AER (µg/min): median 46 to 60 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m^2): 93 Total cholesterol (mg/dL): 223 LDL cholesterol (mg/dL): 137 HbA_{1c} (%): 8.3 Diabetes (%): 100 History of HTN (%): 100 History of CVD (%): 49 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 25	Enalapril 20 mg/d (n=130) Telmisartan 80 mg/d (n=120) Followup period: 5 years Study withdrawals (%): 33	Allocation Concealment: adequate Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Lacourcière, 2000[22] Canada Funding Source: Industry	Inclusion Criteria: early nephropathy characterized by a UAE rate 20 to 350 µg/min without evidence of urinary tract infection; type 2 diabetes diagnosed at 30 years of age or later; mild to moderate essential HTN (sitting diastolic BP 90 to 115 mm Hg); Exclusion Criteria: evidence or suspicion of renovascular disease; history of malignant hypertension; systolic BP > 210 mm Hg; cerebrovascular accident in the previous 12 months or current transient ischemic attacks; myocardial infarction within the previous 12 months; clinically significant arteriovenous (AV) conduction disturbances and/or arrhythmias; unstable angina; history of heart failure, serum creatinine ≥ 200 mmol/L; serum potassium ≥ 5.5 mmol/L or ≤ 3.5 mmol/L; treatment with oral corticosteroids; concomitant use of agents that may affect BP except β-blockers and nitrates used in the treatment of stable angina; drug or alcohol abuse; pregnancy, breast feeding, and ineffective contraception.	N=103 Age (yr): 59 Gender (Male %): 81 Race/Ethnicity (%): white 96; Asian 3; black 1 BMI: NR Systolic BP (mm Hg): 160 Diastolic BP (mm Hg): 96 Urinary AER (µg/min): 69 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): 96 HbA_{1c} (%): NR Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): 0 (exclusion criterion) History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Enalapril 5 mg/d (n=51) Losartan 50 mg/d (n=52) Followup period: 1 year Study withdrawals (%): 11	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Muirhead, 1999[8] Kunz review Canada Funding Source: Industry	Inclusion Criteria: incipient diabetic nephropathy, defined as AER between 20 to 300 µg/min and a GFR 60 ≥ ml/min/1.73m^2 at visit 1; aged ≥ 18 years; type 2 DM Exclusion Criteria: "brittle" diabetes (increased risk of hypoglycemia) or patients with a history of non compliance with medical regimens.	N=91 (excluding placebo arm) Age (yr): 56 Gender (Male %): 67 Race/Ethnicity (%): white 90, black 1, Asian 4 BMI: NR Systolic BP (mm Hg): 136 Diastolic BP (mm Hg): 83 Urinary AER (µg/min): 54 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): 91 HbA_{1c} (%): NR Diabetes (%): 100 History of HTN (%): 33% on HTN medication History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Captopril 75 mg/d (n=29) Valsartsan 80 mg/d (n=31) Valsartsan 160 mg/d (n=31) Followup period: 1 year Study withdrawals (%): 13	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ACE inhibitor monotherapy versus Calcium channel blocker trials (n=6 trials)				
Rahman, 2005[23] ALLHAT USA and Canada Funding Source: Industry and other	Inclusion Criteria: aged 55 years or older who had stage 1 or stage 2 hypertension; at least 1 additional risk factor for CHD events (previous (> 6 months) MI or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 DM, current cigarette smoking, high-density lipoprotein cholesterol level < 35 mg/dL, or documentation of other atherosclerotic cardiovascular disease). Exclusion Criteria: history of symptomatic heart failure and/or a known left ventricular ejection fraction <35%; serum creatinine level > 2 mg/dL as reported by the investigator.	N=3049 for patients with a baseline GFR <60 ml/min/ 1.73m^2 (of a total of 17,118 randomized and minus the chlorthalidone arm) Age (yr): 70 Gender (Male %): 48 Race/Ethnicity (%): white 58; black 25; Hispanic 13 BMI: 29 Systolic BP (mm Hg): 147 Diastolic BP (mm Hg): 83 Albuminuria: NR Serum creatinine (mmol/L): NR Estimated GFR (ml/min/1.73m^2): 50 HbA_{1c} (%): NR Diabetes (%): 33 History of HTN (%): 100 History of CAD (%): 29 History of CHF (%): NR History of MI or stroke (%): 27 Peripheral arterial disease (%): NR Current smoker (%): 18	Lisinopril up to 40 mg/d (n=1533) Amlodipine up to 10 mg/d (n=1516) *Chlorthalidone arm* 3 x 2 factorial design, Followup period: mean 4.9 years Study withdrawals (%):Not reported for CKD subgroup	Allocation Concealment: adequate (from background paper) Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: Not reported for CKD subgroup

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Fogari, 2002[24] Italy Funding Source: none stated	Inclusion Criteria: microalbuminuria; essential HTN and type 2 DM and noted by sitting diastolic BP values >90 mm Hg and <110 mm Hg; type 2 DM well controlled by diet or by metformin alone or metformin plus a sulfanylurea; UAE ≥30 and ≤300 mg/24 h in two distinct 24-h urine collections during 7 days before enrollment; BMI < 30 kg/m^2; serum creatinine <1.5 mg/dL. Exclusion Criteria: history of previous CHD, stroke, CHF, cancer; smoking habits; electrocardiogram showing left ventricular hypertrophy; total cholesterol values >240 mg/dL; use of diuretics or b-blockers.	N=205 (minus combination arm) Age (yr): 63 Gender (Male %): 58 Race/Ethnicity (%): NR BMI: 28 Systolic BP (mm Hg): 160 Diastolic BP (mm Hg): 99 Urinary AER (µg/min): 97 Serum creatinine (mmol/L): 1 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 90 HbA_{1c} (%): 7 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): 0 History of CHF (%): 0 History of MI (%): 0 History of Stroke (%): 0 Peripheral arterial disease (%): NR Current smoker (%): NR	Fosinopril 10-30 mg/d (n=102) Amlodipine up to 10 mg/d (n=103) *Combination arm* Followup period: 4 years Study withdrawals (%): 32% of all subjects (including combination arm) in titration period, 26% during study period.	Allocation Concealment: adequate Blinding: open-label Intention to Treat Analysis: no, 453 were randomized to a 3-month titration period but 144 were removed due to non response or adverse events Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Agodoa, 2002[25] Wright, 2002[26] Norris, 2006[27] (AASK) USA Funding Source: Industry and other	Inclusion Criteria: self-identified African Americans with HTN; aged 18 to 70 years; GFR between 20 and 65 mL/min/1.73 m2 and no other identified causes of renal insufficiency. Exclusion Criteria: diastolic BP of <95 mm Hg; known history of DM (fasting glucose ≥140 mg/dL or random glucose >200 mg/dL); urinary protein to creatinine ratio >2.5; accelerated or malignant HTN within 6 months; secondary HTN; evidence of non–BP-related causes of chronic kidney disease; serious systemic disease; clinical CHF; or specific indication for or contraindication to a study drug or study procedure.	N=653 (minus metoprolol arm of 1,094 randomized) Age (yr): 54 Gender (Male %): 61 Race/Ethnicity (%): African American 100 BMI: NR Systolic BP (mm Hg): 151 Diastolic BP (mm Hg): 96 Proteinuria (g/24 h): 0.5 (pooled men and women) Serum creatinine (mg/dL): 2.21 men; 1.76 women Estimated GFR (ml/min/1.73m^2): 46.3 Diabetes (%): 0 History of HTN (%): 100 History of CAD (%): 52 History of CHF (%): 0 History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Ramipril 2.5-10 mg/d (n=436) Amlodipine 5-10 mg/d (n=217) *Metoprolol arm* 3 x 2 factorial design with lower and usual blood pressure goal arms Followup period: mean 4 years (Norris 2006) Study withdrawals (%): 0 (not counting death or dialysis, or no GFR assessment)	Allocation Concealment: adequate (from background paper) Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Marin, 2001[28] ESPIRAL Spain Funding Source: None stated	Inclusion Criteria: aged 18 to 75 years; serum creatinine values between 1.5 and 5 mg/dl; hypertension (BP >140/90 mmHg, or by the use of antihypertensive agent(s); proven progression of chronic renal failure in the previous 2 years (increase by more than 25% or > 0.5 mg/dl in serum creatinine). Exclusion Criteria: DM; recent history of cardiovascular disease (stroke, myocardial infarction, or heart failure); taking concomitant medications that could interfere with study results (steroids, immuno-suppressant drugs, or NSAIDS); presenting intolerance to fosinopril or nifedipine.	N=241 Age (yr): 56 Gender (Male %): 59 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 156 Diastolic BP (mm Hg): 96 Albuminuria (g/dL): 4.3 Proteinuria (g/24 h): 1.7 Serum creatinine (mg/dL): 2.8 Creatinine clearance (ml/min/1.73m^2): 36 Estimated GFR (ml/min/1.73m^2): NR Diabetes (%): 0 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Fosinopril 10-30 mg/d (n=129) Nifedepine 30-60 mg/d (n=112) Followup period: minimum 3 years Study withdrawals (%): 34 (excluding death)	Allocation Concealment: unclear Blinding: open-label Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Crepaldi, 1998[10] Sarafidis review Italy Funding Source: None stated	Inclusion Criteria: age 18 to 70 years; onset of insulin-dependent DM before age 35 and insulin treatment within 3 years of diagnosis; clinical stability of DM during past 12 months; median AER value between 20 and 200 µg/min from 3 timed overnight urine collections; GFR ≥80 ml/min/1.73m^2 at randomization; standing systolic BP ≥115 and ≤145 mmHg (without HTN therapy) and diastolic BP ≥75 and ≤90 mmHg. Exclusion Criteria: impaired renal function (defined as serum creatinine >10% above the upper limit of normal (125 µmol/L) and median AER >200 µg/min at entry and visit 3 after randomization); nondiabetic renal disease; hematuria; evidence of clinically significant liver or hematological disease; evidence of aortic or mitral valve obstruction; arrhythmias; unstable angina; history of MI within previous 3 months; systemic malignancy; hyperkalemia, serum trigylcerides >3.4mmol/L, or total cholesterol >6.5 mmol/L.	N=88 (58 included in the baseline characteristics and nifedipine arm excluded) Age (yr): 37 Gender (Male %): 69 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 128 Diastolic BP (mm Hg): 83 Albumin excretion rate (µg/min): 61.2 Albumin (g/dL): 4.4 Serum creatinine (mg/dL): 0.96 Creatinine clearance (ml/min/1.73m^2): 109 Estimated GFR (ml/min/1.73m^2): 120 HbA_{1c} (%): 8.1 Diabetes (%): 100 (type 1) History of HTN (%): 0 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 57	Lisinoprol 2.5-20 mg/d (n=48) Nifedepine 10-20 mg/d (n=41) Followup period: 3 years Study withdrawals (%): 37 (includes 27 patients excluded for not having AER values between 20 and 200 µg/min)	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Zucchelli, 1995/1992[29,30] Italy Funding Source: None stated	Inclusion Criteria: aged 18 to 70 years of age; established chronic renal failure (serum creatinine ranging between 1.8 to 5 mg/dL); variation in plasma creatinine < 50% during 3 month observation period; HTN - baseline diastolic BP ≥ 95 mmHg; good general health. Exclusion Criteria: DM; potentially reversible renal disease; systemic diseases; severe cardiac or hepatic dysfunction; peripheral edema; proteinuria >5 g/24 h.	N=121 Age (yr): 55 Gender (Male %): 58 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 165 Diastolic BP (mm Hg): 100 Proteinuria (g/24 h): 1.8 Serum creatinine (mg/dL): 3.0 Estimated GFR (ml/min/1.73m^2): NR Diabetes (%): 0 History of HTN (%): 100 History of CAD (%): NR (none with severe disease) History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Captopril 25-100 mg/d (n=60) Nifedepine 20-40 mg/d (n=61) Followup period: 3 years Study withdrawals (%): 26	Allocation Concealment: unclear Blinding: none stated Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ACE inhibitor monotherapy versus beta-blocker trials (n=3 trials)				
Wright, 2002[26] Norris, 2006[27] (AASK) USA Funding Source: Industry and other	Inclusion Criteria: self-identified African Americans with HTN; aged 18 to 70 years; GFR between 20 and 65 mL/min/1.73 m2 and no other identified causes of renal insufficiency. Exclusion Criteria: diastolic BP of less <95 mm Hg; known history of DM (fasting glucose ≥140 mg/dL or random glucose >200 mg/dL); urinary protein to creatinine ratio >2.5; accelerated or malignant HTN within 6 months; secondary HTN; evidence of non–BP-related causes of chronic kidney disease; serious systemic disease; clinical CHF; or specific indication for or contraindication to a study drug or study procedure.	n=877 (minus amlodipine arm of 1,094 randomized) Age (yr): 55 Gender (Male %): 61.5 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 150.5 Diastolic BP (mm Hg): 95.5 Albuminuria: NR Serum creatinine (mg/dL): 2.15 Estimated GFR (ml/min/1.73m^2): 45.6 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 History of HTN (%): 100 History of CAD (%): NR History of “heart disease” (%): 51 History of CHF (%): 0 History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Ramipril 2.5-10.0 mg/d (n=436) Metoprolol 50-200 mg/d (n=441) 3 x 2 factorial design with lower and usual blood pressure goal arms Followup period: 4 years Study withdrawals (%):0 (not counting death or dialysis, or no GFR)	Allocation Concealment: adequate (from background paper) Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
van Essen, 1997[31] The Netherlands Funding Source: Industry	Inclusion Criteria: modest chronic renal insufficiency defined as a creatinine clearance of 30-90 mL/min; aged 18 to 65 years old; no need for immunosuppressive agents or non-steroidal anti-inflammatory drugs; no proven renal artery stenosis, or other conditions for which beta blocking drugs or ACEI are contraindicated. Both patients with and without proteinuria could be included. Exclusion Criteria: NR	N=103 (89 with baseline characteristics and evaluated) Age (yr): 50 Gender (Male %): 64 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 152 Diastolic BP (mm Hg): 90 Proteinuria (g/24h): median 3.3 Serum creatinine (mg/dL): 1.8 Creatinine clearance (ml/min/1.73m^2): 55 Estimated GFR (ml/min/1.73m^2): 53 Diabetes (%): 0 History of HTN (%): 53% were reported to have untreated diastolic BP < 90 mm Hg History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Enalapril 10 mg/d (n=52) Atenolol 50 mg/d (n=51) Followup period: median 3.9 years Study withdrawals (%): 14	Allocation Concealment: unclear Blinding: double Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Hannedouche, 1994[32] France Funding Sources: Industry	Inclusion Criteria: aged 18 to 70 years; chronic renal failure as defined by a serum creatinine concentration of 200-400 µmol/L Exclusion Criteria: patients with the nephrotic syndrome (serum albumin concentration <30 g/L); systemic diseases including diabetes, malignant hypertension, renovascular hypertension, evolving obstructive nephropathy, and serious extrarenal disorders including malignancy, heart failure, and coronary artery disease; also excluded were women who were breast feeding, pregnant, or intending to become pregnant and patients who had taken converting enzyme inhibitors in the three months before inclusion; had contraindications to converting enzyme inhibitors or (B blockers; were unlikely to comply; or were unwilling to give consent	N=100 Age (yr): 51 Gender (Male %): 53 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 167 Diastolic BP (mm Hg): 102 Proteinuria (g/24h): 2.2 Serum creatinine (mg/dL): 3.0 Estimated GFR (ml/min/1.73m^2): NR Diabetes (%): 0 History of HTN (%): 100 History of CAD (%): 0 History of CHF (%): NR History of MI (%): 0 History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Enalapril 5-10 mg/d (n=52) Acebutolol 400 mg/d or Atenolol 100 mg/d (n=48) Followup period: 3 years Study withdrawals (%): 23	Allocation Concealment: adequate Blinding: open-label Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ACE inhibitor monotherapy versus diuretic trials (n= 2 trials)				
Rahman, 2005[23] ALLHAT USA and Canada Funding Source: Industry and other	Inclusion Criteria: aged 55 years or older who had stage 1 or stage 2 hypertension; at least 1 additional risk factor for CHD events (previous (> 6 months) MI or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 DM, current cigarette smoking, high-density lipoprotein cholesterol level <35 mg/dL, or documentation of other atherosclerotic cardiovascular disease). Exclusion Criteria: history of symptomatic heart failure and/or a known left ventricular ejection fraction <35%; serum creatinine level > 2 mg/dL as reported by the investigator.	N=4,146 for patients with a baseline GFR <60 ml/min/ 1.73m^2 (of a total of 17,118 randomized and minus the amlodipine arm) Age (yr): 71 Gender (Male %): 49 Race/Ethnicity (%): white 57; black 26; Hispanic 12 BMI: 29 Systolic BP (mm Hg): 147 Diastolic BP (mm Hg): 83 Albuminuria: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): 50 Diabetes (%): 33 (type 2) History of HTN (%): 100 History of CAD (%): 31 History of CVD (%): 61 History of CHF (%): 0 (by exclusion criteria) History of MI or stroke (%): 29 Peripheral arterial disease (%): NR Current smoker (%): 18	Lisinopril up to 40 mg/d (n=1533) Chlorthalidone up to 25 mg/d (n=2613) 3 x 2 factorial design, Followup period: mean 4.9 years Study withdrawals (%): Not reported for CKD subgroup	Allocation Concealment: adequate (from background paper) Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: Not reported for CKD subgroup

Appendix Evidence Table C1. Overview of ACEI monotherapy versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Marre, 2004[33] NESTOR France Funding Sources: Industry	Inclusion Criteria: aged between 35 and 80 years; type 2 DM; persistent micro-albuminuria (AER between 20 and 200 µg/min on at least two of three overnight urine collections); essential HTN. Diabetes was required to be controlled by diet with or without one or more oral antidiabetic treatment, unchanged for at least 3 months. For selection, microalbuminuria had to be documented within the previous year. Exclusion Criteria: severe HTN; BMI > 40 kg/m^2; ventricular rhythm disorders on ECG; urinary tract infection, haematuria or leucocyturia; plasma creatinine > 150 µmol/l; kalaemia < 3.5 mmol/l or > 5.5 mmol/l; uric acid > 536 µmol/l; treatment with potassium supplement or insulin and poor placebo compliance during the run-in period. Previously known intolerance to ACEI or diuretics was also a criterion for exclusion.	N=570 Age (yr): 60 Gender (Male %): 65 Race/Ethnicity (%): white 86; black 4; Asian 2 BMI: 30 Systolic BP (mm Hg): 161 Diastolic BP (mm Hg): 94 Albumin excretion rate (µg/min): 58 Urinary albumin: creatinine ratio: 6.2 Serum creatinine (mg/dL): NR Creatinine clearance (ml/min/1.73m^2): 92 Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.6 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 14	Enalapril 10 mg/d (n=286) Indapamide 1.5 mg/d (n=284) Followup period: 1 year Study withdrawals (%): 11.4	Allocation Concealment: Unclear Blinding: double Intention to Treat Analysis: no (one subject excluded) Withdrawals/Dropouts adequately described: yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C2. Summary of study baseline characteristics for ACEI monotherapy versus control treatment trials

Characteristic	Mean (Range) *Unless Otherwise Noted*	Number of Trials Reporting
ACEI versus placebo		**17**
Total number of patients evaluated	11,661 (52-4,912)	17
Age of subjects, years	60 (33-70)	16
Gender, male (%)	66 (35-82)	15
Race/ethnicity, white (%)	77 (63-96)	5
Body Mass Index	28 (24-29)	5
Patients with diabetes (%)	65 (0-100)	17
Patients with diabetic nephropathy‡, n	6,193 (21-4,912)	13
% HbA_{1c} in patients with diabetes	8.2 (7.1-11.0)	10
Estimated GFR ml/min/1.73m^2	68.5 (39-114)	5
Serum creatinine, mg/dL	1.0 (0.8-2.4)	10
Creatinine clearance, ml/min/1.73m^2	64.1 (43-114)	8
Albumin excretion rate, µg/min	61.0 (53-71.5)	5
Albuminuria, mg/24 h	63.2 (72-711)	3
Proteinuria, g/24 h	2.34 (0.13-5.3)	5
Systolic blood pressure, mm Hg	144 (126-149)	15
Diastolic blood pressure, mm Hg	83 (74-92)	14
Patients with hypertension, %	50 (0-100)	16
Patients with cardiovascular disease, %	38 (0-100)	5
Patients randomized to Ramipril versus placebo, n	7,537 (65%) (55-4,912)	7
Patients randomized to Captopril versus placebo, n	665 (6%) (81-409)	4
Patients randomized to Perindopril versus placebo, n	1,757	1
Patients randomized to Fosinopril versus placebo, n	864	1
Patients randomized to Benazepril versus placebo, n	583	1
Patients randomized to Enalapril versus placebo, n	108	1
Patients randomized to Lisinopril versus placebo, n	97	1
Patients randomized to Enalopril versus no treatment, n	52	1
ACEI versus ARB		**6**
Total number of patients evaluated, n	4,799 (90-4,046)	6
Age of subjects, years	59 (56-61)	5
Gender, male, %	62 (37-81)	5
Race/ethnicity, white, %	96 (91-98)	3
Body Mass Index	31 (30-32)	3
Patients with diabetes, %	97 (76-100)	5
Patients with diabetic nephropathy‡, n	730 (67-250)	5
% HbA_{1c} %in patients with diabetes	8.1 (7.9-8.3)	2
Estimated GFR, ml/min/1.73m^2	92 (91-96)	3
Serum creatinine, mg/dL	1.0 (1.0-1.0)	2
Creatinine clearance, ml/min/1.73m^2	101 (97-112)	2
Albumin excretion rate, µg/min	62 (53-69)	2
Systolic blood pressure, mm Hg	151 (136-160)	5
Diastolic blood pressure, mm Hg	87 (83-91)	5
Patients with hypertension, %	94 (33-100)	5
Patients with cardiovascular disease, %	99 (19-100)	3
Patients randomized to Ramipril versus ARB, n	4046	1
Patients randomized to Enalapril versus ARB, n	353 (103-250)	2
Patients randomized to Lisinopril versus ARB, n	309 (90-219)	2
Patients randomized to Captopril versus ARB, n	91	1
Patients randomized to Telmisartan versus ACEI, n	4,515 (219-4,046)	3
Patients randomized to Valsartan versus ACEI, n	181 (90-91)	2
Patients randomized to Losartan versus ACEI, n	103	1

Appendix Table C2. Summary of study baseline characteristics for ACEI monotherapy versus control treatment trials (continued)

Characteristic	Mean (Range) *Unless Otherwise Noted*	Number of Trials Reporting
ACEI versus CCB		**6**
Total number of patients evaluated, n	4,357 (88-3,049)	6
Age of subjects, years	66 (37-71)	6
Gender, male, %	51 (48-69)	6
Race/ethnicity, white, %	48 (0-58)	2
Body Mass Index	29 (28 to 29)	2
Patients with diabetes, %	30 (0-100)	6
Patients with diabetic nephropathy‡, n	293 (88-205)	2
Patients with	1,015 (121-653)	3
% HbA_{1c} in patients with diabetes	7.2 (7.0-8.1)	2
Estimated GFR, ml/min/1.73m^2	50 (46-120)	3
Serum creatinine, mg/dL	2.0 (1.0-3.0)	5
Proteinuria, g/24 h	0.9 (0.5-1.8)	3
Systolic blood pressure, mm Hg	149 (128-165)	6
Diastolic blood pressure, mm Hg	87 (83-100)	6
Patients with hypertension, %	99 (0-100)	6
Patients with cardiovascular disease, %	29 (0-52)	5
Patients randomized to Lisinopril versus CCB, n	3,137 (88-3,049)	2
Patients randomized to Ramipril versus CCB, n	653	1
Patients randomized to Fosinopril versus CCB, n	446 (205-241)	2
Patients randomized to Captopril versus CCB, n	121	1
Patients randomized to Amlodipine versus ACEI, n	3,907 (205-3,049)	3
Patients randomized to Nifedipine versus ACEI, n	450 (88-241)	3
ACEI versus BB		**3**
Total number of patients evaluated, n	1,080 [100-877]	3
Age of subjects, years	54 [50-55]	3
Gender, male, %	61 (53-64)	3
Race/ethnicity, white, %	0*	1
Patients with diabetes, %	0	3
Estimated GFR, ml/min/1.73m^2	47 [46-53]	2
Serum creatinine, mg/dL	2.0 [1.8-3.0]	3
Proteinuria, g/24 h	0.7 [0.5-2.2]	2
Systolic blood pressure, mm Hg	152 (150-167)	3
Diastolic blood pressure, mm Hg	95 (90-102)	3
Patients with hypertension, %	96 (47-100)	3
Patients randomized to Ramipril versus BB, n	877	1
Patients randomized to Enalapril versus BB, n	203 (100-103)	2
Patients randomized to Metropolol versus ACEI, n	877	1
Patients randomized to Atenolol or Acebutelol versus ACEI, n†	203 (100-103)	2
ACEI versus Diuretics		**2**
Total number of patients evaluated, n	4,716 [570-4,146]	2
Age of subjects, years	70 [60-71]	2
Gender, male, %	51 [49-65]	2
Race/ethnicity, white, %	61 [57-85]	2
Patients with diabetes, %	41 [33-100]	2
Estimated GFR, ml/min/1.73m^2	50	1
Creatinine clearance, ml/min/1.73m^2	92	1
Albumin excretion rate, µg/min	58	1
Systolic blood pressure, mm Hg	149 (147-161)	2
Diastolic blood pressure, mm Hg	84 (83-94)	2
Patients with hypertension, %	100	2
Patients randomized to Lisinopril versus Diuretic, n	4,146	1

Appendix Table C2. Summary of study baseline characteristics for ACEI monotherapy versus control treatment trials (continued)

Characteristic	Mean (Range) *Unless Otherwise Noted*	Number of Trials Reporting
Patients randomized to Enalapril versus Diuretic, n	570	1
Patients randomized to Chlorthalidone versus ACEI, n	4,146	1
Patients randomized to Indapimide versusACEI, n	570	1

ACEI = angiotension converting enzyme inhibitor; HbA_{1c} = hemoglobin A_{1c}; GFR = glomerular filtration rate; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; BB = beta blocker

* Only one trial reported ethnicity, the AASK study which limited enrollment to self-identified African Americians.

†In one trial, all participants assigned BB were assigned atenolol while in the other trial, all participants assigned BB were assigned to either atenolol or acebutolol.

‡Diabetic nephropathy defined as present in patients with diabetes and albuminuria or proteinuria.

Appendix Table C3. Clinical outcomes (outcomes part A), ACEI monotherapy versus control treatment trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke or CVA, Any n/N (%)	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus placebo/no treatment trials (n=17)												
Perkovic, 2007[1] (PROGRESS)	153/895* (17.1)	138/862* (16.0)	85/895* (9.5)	86/862* (10.0)							112/895* (12.5)	152/862* (17.6)
Asselbergs, 2004[2] (PREVD)	5/431 (1.2)	4/433 (0.9)	5/431 (1.2)	3/433 (0.7)					12/431 (2.8)	11/433 (2.5)	1/431 (0.2)*	10/433 (2.3)
Marre, 2004[3] (DIAB)	334/2443 (13.7)	324/2469 (13.1)	179/2443 (7.3)	175/2469 (7.1)	61/2443 (2.5)	78/2469 (3.2)			52/2443 (2.1)	59/2469 (2.4)	118/2443 (4.8)	116/2469 (4.7)
Katayama, 2002[4]	0/52	0/27										
Bojestig, 2001[5]	0/37	0/18										
Gerstein, 2001[6] (MICROHOPE)	90/553 (16.3)	122/587 (20.8)										
O'Hare, 2000[7] (ATLANTIS)	5/92 (5.4)	0/48							3/92 (3.3)	1/48 (2.1)		
Muirhead, 1999[8]												
REIN, 1999[9] stratum 1	1/99 (1.0)	0/87									1/99 (1.0)	0/87
Crepaldi, 1998[10]	0/32	0/34			0/32	1/34 (2.9)			0/32	1/34 (2.9)		
REIN, 1997[11] stratum 2	2/78 (2.6)	1/88 (1.1)					1/78 (1.3)	0/88	1/78 (1.3)	1/88 (1.1)		
Maschio, 1996[12]	8/300 (2.7)	1/283 (0.4)					3/300 (1.0)	0/283	2/300 (0.7)	2/283 (0.7)		
Trevisan, 1995[13]					1/60 (1.7)	1/62 (1.6)			1/60 (1.7)	1/62 (1.6)		
Laffel, 1995[14]	1/70 (1.4)	0/73										
Sano, 1994[15]	1/31 (3.2)	0/31										
Lewis, 1993[16]	8/207 (3.9)	14/202 (6.9)										
Ravid, 1993[17]	0/49	0/45										

Appendix Table C3. Clinical outcomes (outcomes part A), ACEI monotherapy versus control treatment trials (continued)

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke or CVA, Any n/N (%)	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus ARB trials (n=6)												
Perkovic, 2007[1] (PROGRESS)	153/895* (17.1)	138/862* (16.0)	85/895* (9.5)	86/862* (10.0)							112/895* (12.5)	152/862* (17.6)
Asselbergs, 2004[2] (PREVD)	5/431 (1.2)	4/433 (0.9)	5/431 (1.2)	3/433 (0.7)					12/431 (2.8)	11/433 (2.5)	1/431 (0.2)*	10/433 (2.3)
Marre, 2004[3] (DIAB)	334/2443 (13.7)	324/2469 (13.1)	179/2443 (7.3)	175/2469 (7.1)	61/2443 (2.5)	78/2469 (3.2)			52/2443 (2.1)	59/2469 (2.4)	118/2443 (4.8)	116/2469 (4.7)
Katayama, 2002[4]	0/52	0/27										
Bojestig, 2001[5]	0/37	0/18										
Gerstein, 2001[6] (HOPE)	149/952† (15.7)	204/1004† (20.3)										
O'Hare, 2000[7] (ATLANTIS)	5/92 (5.4)	0/48							3/92 (3.3)	1/48 (2.1)		
Muirhead, 1999[8]												
REIN, 1999[9] stratum 1	1/99 (1.0)	0/87									1/99 (1.0)	0/87
Crepaldi, 1998[10]	0/32	0/34			0/32	1/34 (2.9)			0/32	1/34 (2.9)		
REIN, 1997[11] stratum 2	2/78 (2.6)	1/88 (1.1)					1/78 (1.3)	0/88	1/78 (1.3)	1/88 (1.1)		
Maschio, 1996[12]	8/300 (2.7)	1/283 (0.4)					3/300 (1.0)	0/283	2/300 (0.7)	2/283 (0.7)		
Trevisan, 1995[13]					1/60 (1.7)	1/62 (1.6)			1/60 (1.7)	1/62 (1.6)		
Laffel, 1995[14]	1/70 (1.4)	0/73										
Sano, 1994[15]	1/31 (3.2)	0/31										
Lewis, 1993[16]	8/207 (3.9)	14/202 (6.9)										
Ravid, 1993[17]	0/49	0/45										

Appendix Table C3. Clinical outcomes (outcomes part A), ACEI monotherapy versus control treatment trials (continued)

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke or CVA, Any n/N (%)	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus CCB trials (n=6)												
Rahman, 2006[34] ALLHAT											99/1533 (6.5)	100/1516 (6.6)
Rahman, 2006[34] ALLHAT, DM patients*											33/501 (6.6)	42/506 (8.3)
Fogari, 2002[24]	3/102 (2.9)	4/103 (3.9)										
Norris, 2006[27] Agodoa 2001[25] (AASK)	34/436 (7.8)	22/217 (10.1)	12/436 (2.8)	7/217 (3.2)							23/436 (5.3)	9/217 (4.1)
Marin, 2001[28] ESPIRAL	4/129 (3.1)	6/112 (5.4)	3/129 (2.3)	6/112 (5.4)							1/129 (0.8)	2/112 (1.8)
Crepaldi, 1998[10]	0/48	1/41 (2.4)			0/32	0/26			0/32	0/26		
Zucchelli, 1995[29]	1/60 (1.7)	0/61	1/60 (1.7)	0/61								
ACEI versus BB trials (n=3)												
Norris, 2006[27] (AASK)	34/436 (7.8)	49/441 (11.1)	12/436 (2.8)	12/441 (2.7)							23/436 (5.3)	23/441 (5.2)
van Essen, 1997[31]	2/43 (4.7)	1/46 (2.2)	2/43 (4.7)	1/46 (2.2)			2/43 (4.7)	1/46 (2.2)				
Hannedouche, 1994[32]	1/52 (1.9)	2/48 (4.2)										

Appendix Table C3. Clinical outcomes (outcomes part A), ACEI monotherapy versus control treatment trials (continued)

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke or CVA, Any n/N (%)	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus diuretics trials (n=2)												
Rahman, 2006[34] ALLHAT											99/1533 (6.5)	157/2613 (6.0)
Rahman, 2006[34] ALLHAT, DM patients**											33/501 (6.6)	63/881 (7.2)
Marre, 2004[33] NESTOR	1/286 (0.3)	2/284 (0.7)	1/286 (0.3)	2/284 (0.7)			0/286	1/284 (0.3)				

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor II blocker; CCB = calcium channel blocker; BB = beta blocker ; CVA = cerebrovascular accident (i.e., stroke); DM = diabetes mellitus

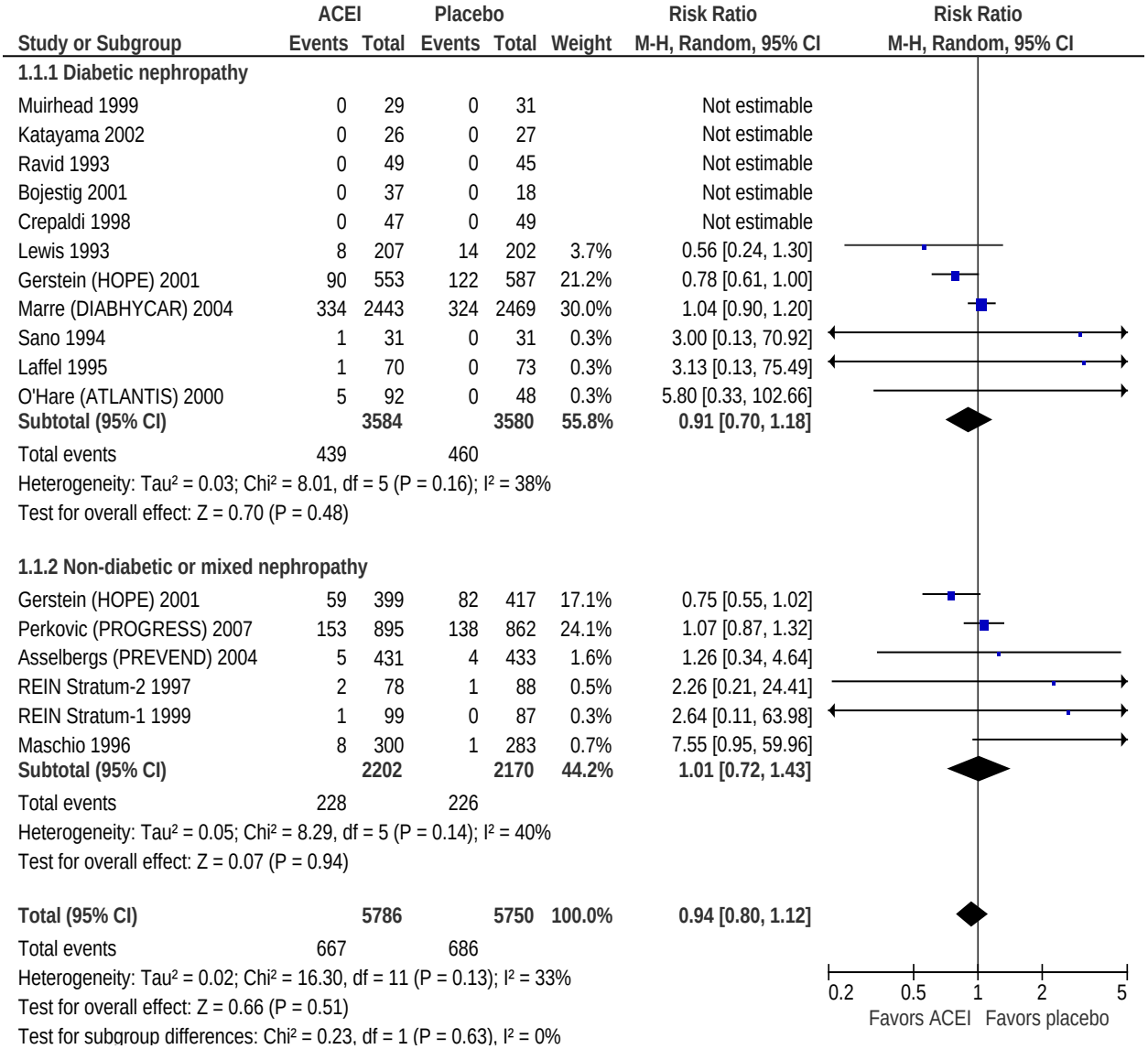
*Patients with CKD, defined as creatinine clearance <60 ml/min

†Patients with CKD, defined as presence of microalbuminuria

**Rahman 2006 ALLHAT DM patients is a report on the subgroup of diabetic patients from the overall ALLHAT study

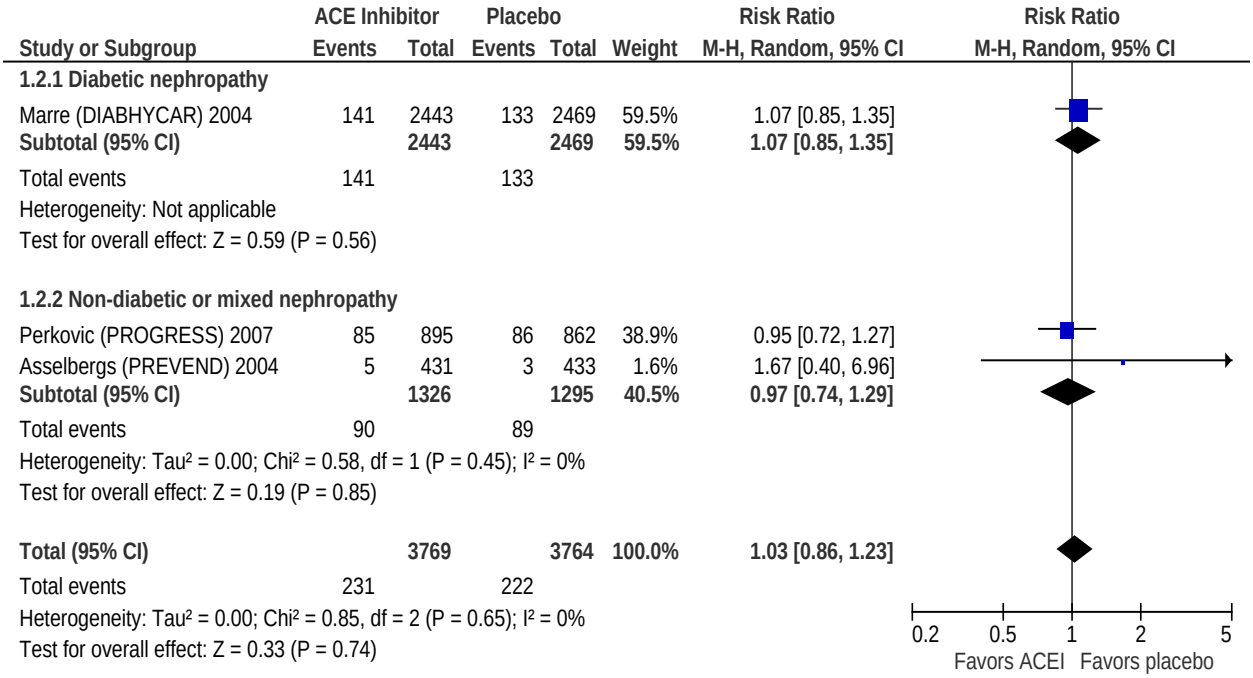
Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials
ACEI VERSUS PLACEBO

All-cause mortality

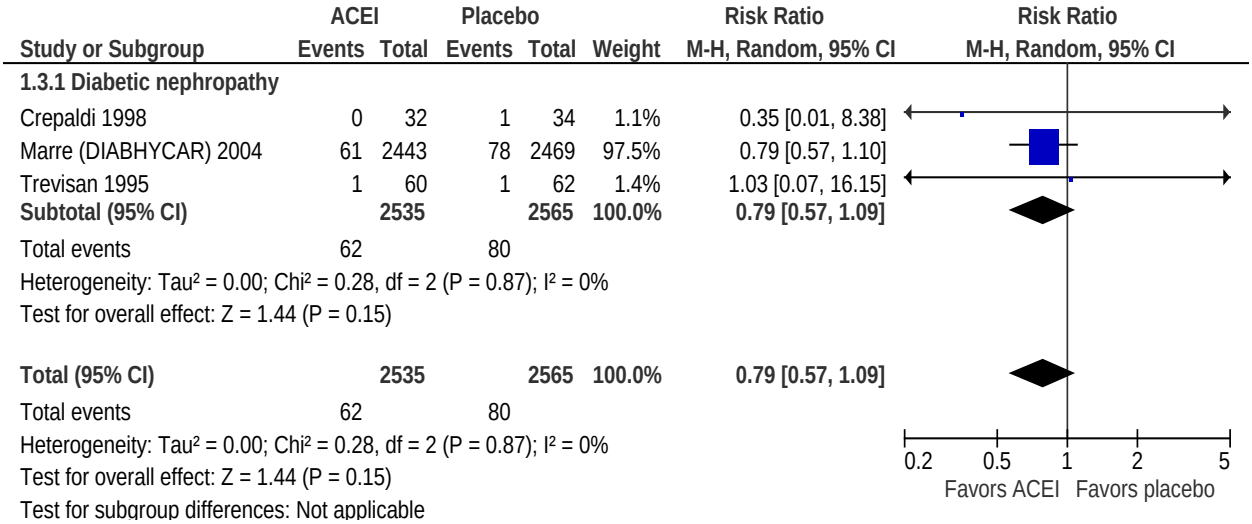


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Cardiovascular mortality



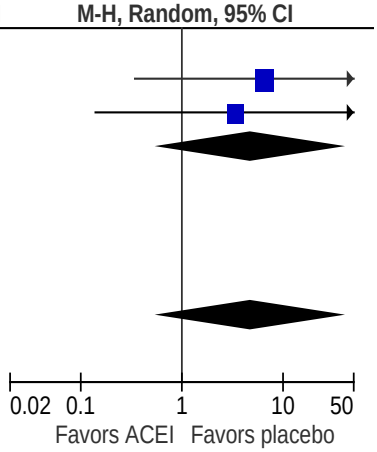
Myocardial infarction (any)



Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

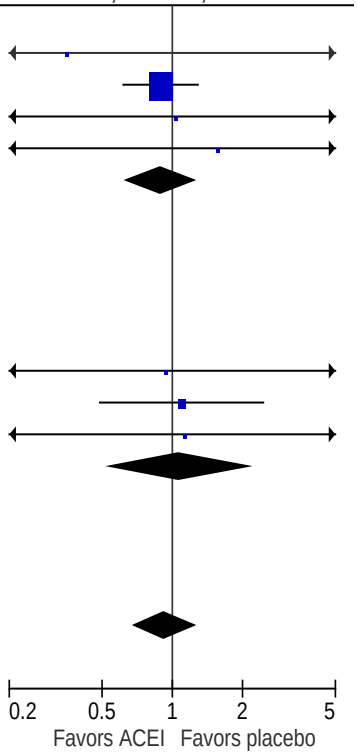
Myocardial infarction (fatal)

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Non-diabetic or mixed nephropathy						
Maschio 1996	3	300	0	283	53.7%	6.60 [0.34, 127.30]
REIN Stratum-2 1997	1	78	0	88	46.3%	3.38 [0.14, 81.78]
Subtotal (95% CI)		**378**		**371**	**100.0%**	**4.84 [0.55, 42.34]**
Total events	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**378**		**371**	**100.0%**	**4.84 [0.55, 42.34]**
Total events	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Test for subgroup differences: Not applicable						



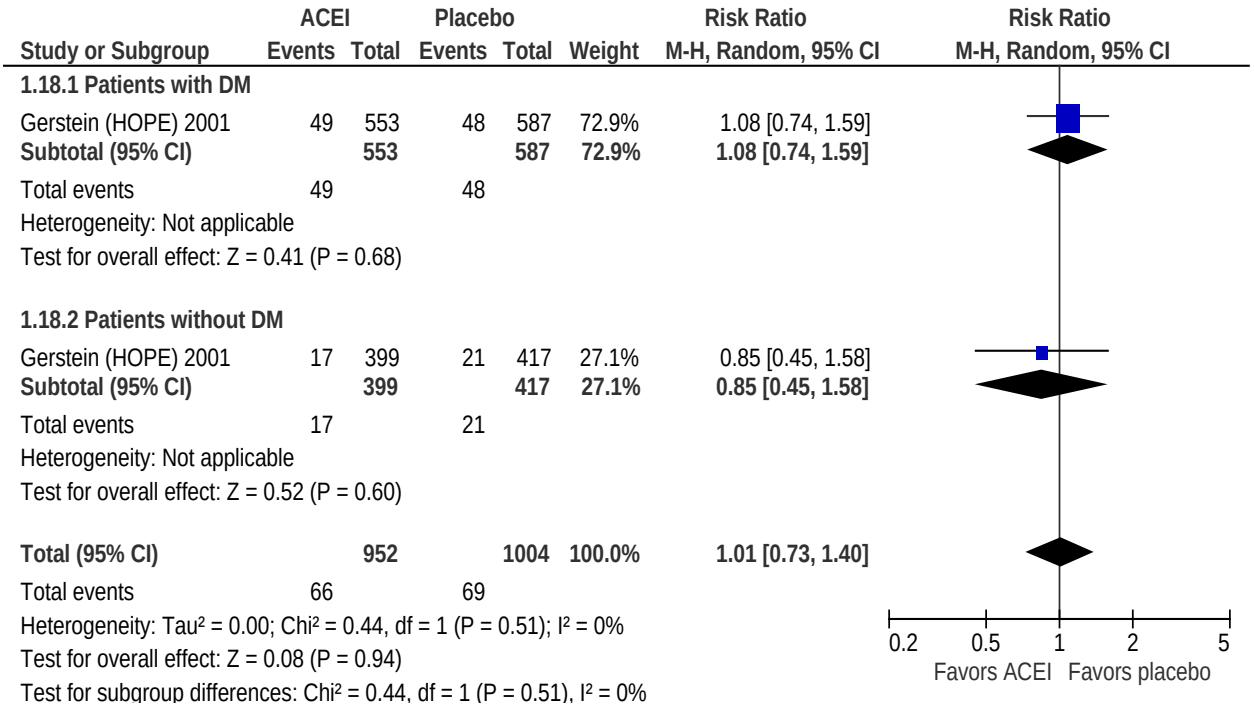
Myocardial infarction (nonfatal)

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Diabetic nephropathy						
Crepaldi 1998	0	32	1	34	1.0%	0.35 [0.01, 8.38]
Marre (DIABHYCAR) 2004	52	2443	59	2469	75.7%	0.89 [0.62, 1.29]
Trevisan 1995	1	60	1	62	1.4%	1.03 [0.07, 16.15]
O'Hare (ATLANTIS) 2000	3	92	1	48	2.1%	1.57 [0.17, 14.65]
Subtotal (95% CI)		**2627**		**2613**	**80.2%**	**0.90 [0.63, 1.28]**
Total events	56		62			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 3 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.5.2 Non-diabetic or mixed nephropathy						
Maschio 1996	2	300	2	283	2.7%	0.94 [0.13, 6.65]
Asselbergs (PREVEND) 2004	12	431	11	433	15.8%	1.10 [0.49, 2.46]
REIN Stratum-2 1997	1	78	1	88	1.4%	1.13 [0.07, 17.74]
Subtotal (95% CI)		**809**		**804**	**19.8%**	**1.08 [0.52, 2.21]**
Total events	15		14			
Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Total (95% CI)		**3436**		**3417**	**100.0%**	**0.93 [0.67, 1.28]**
Total events	71		76			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 6 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%						

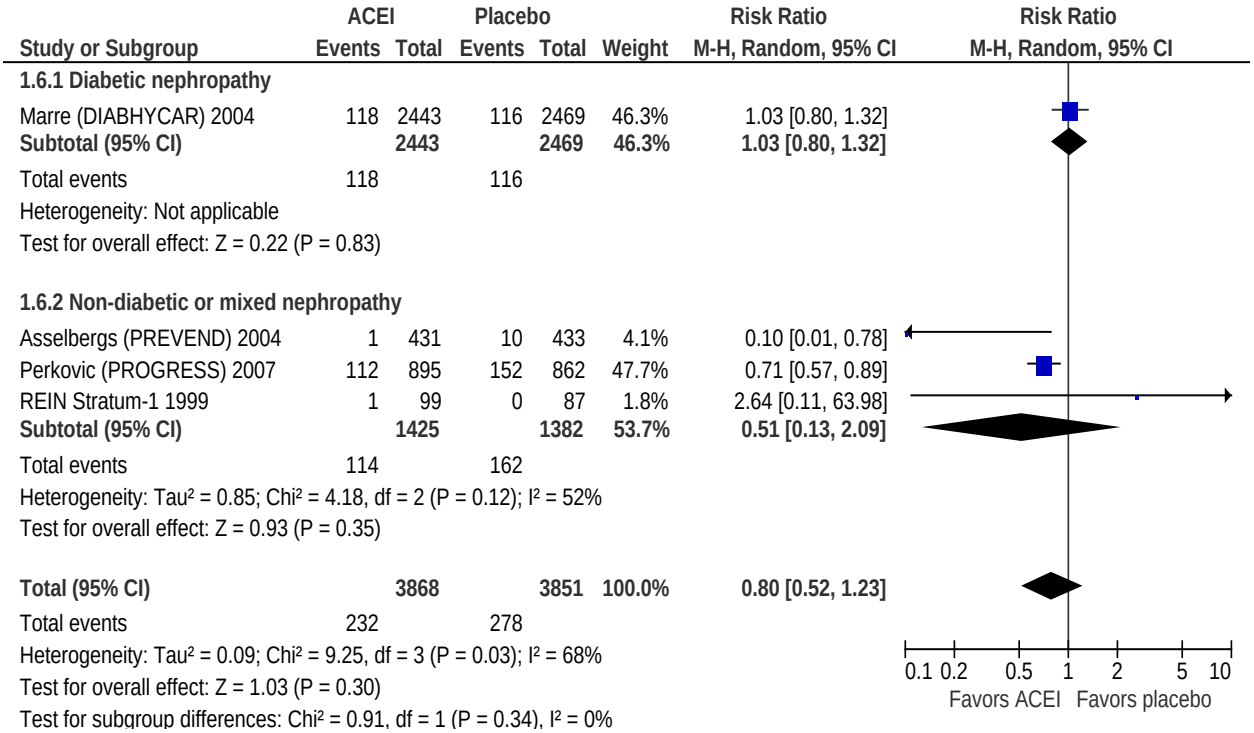


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Congestive heart failure hospitalization



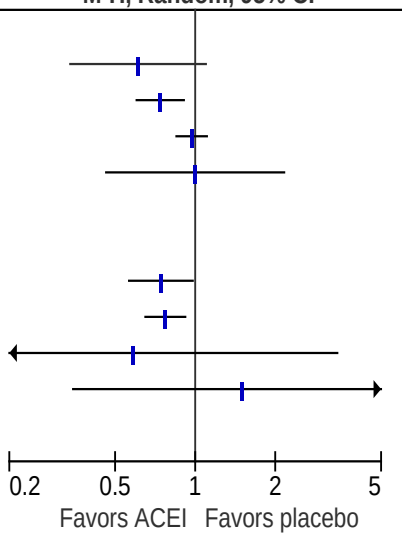
Stroke



Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

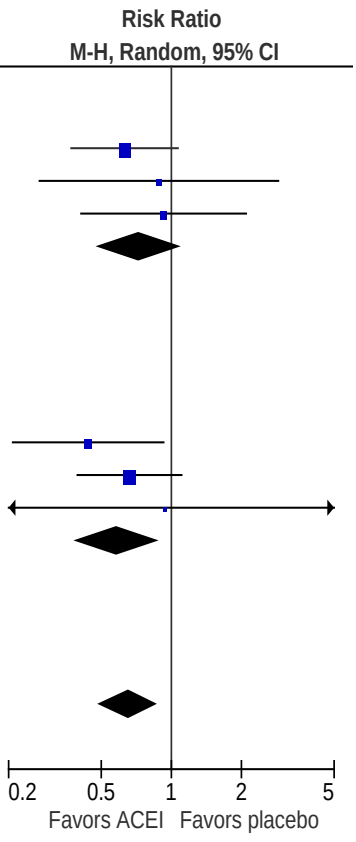
Composite vascular outcome (see Table C5 for definitions)

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
1.8.1 Diabetic nephropathy					
Asselbergs (PREVEND) 2004	17	431	28	433	0.61 [0.34, 1.10]
Gerstein (HOPE) 2001	117	553	168	587	0.74 [0.60, 0.91]
Marre (DIABHYCAR) 2004	362	2443	377	2469	0.97 [0.85, 1.11]
O'Hare (ATLANTIS) 2000	16	92	8	46	1.00 [0.46, 2.16]
1.8.2 Non-diabetic or mixed nephropathy					
Gerstein (HOPE) 2001	69	399	97	417	0.74 [0.56, 0.98]
Perkovic (PROGRESS) 2007	178	895	222	862	0.77 [0.65, 0.92]
REIN Stratum-1 1999	2	99	3	87	0.59 [0.10, 3.43]
REIN Stratum-2 1997	4	78	3	88	1.50 [0.35, 6.51]



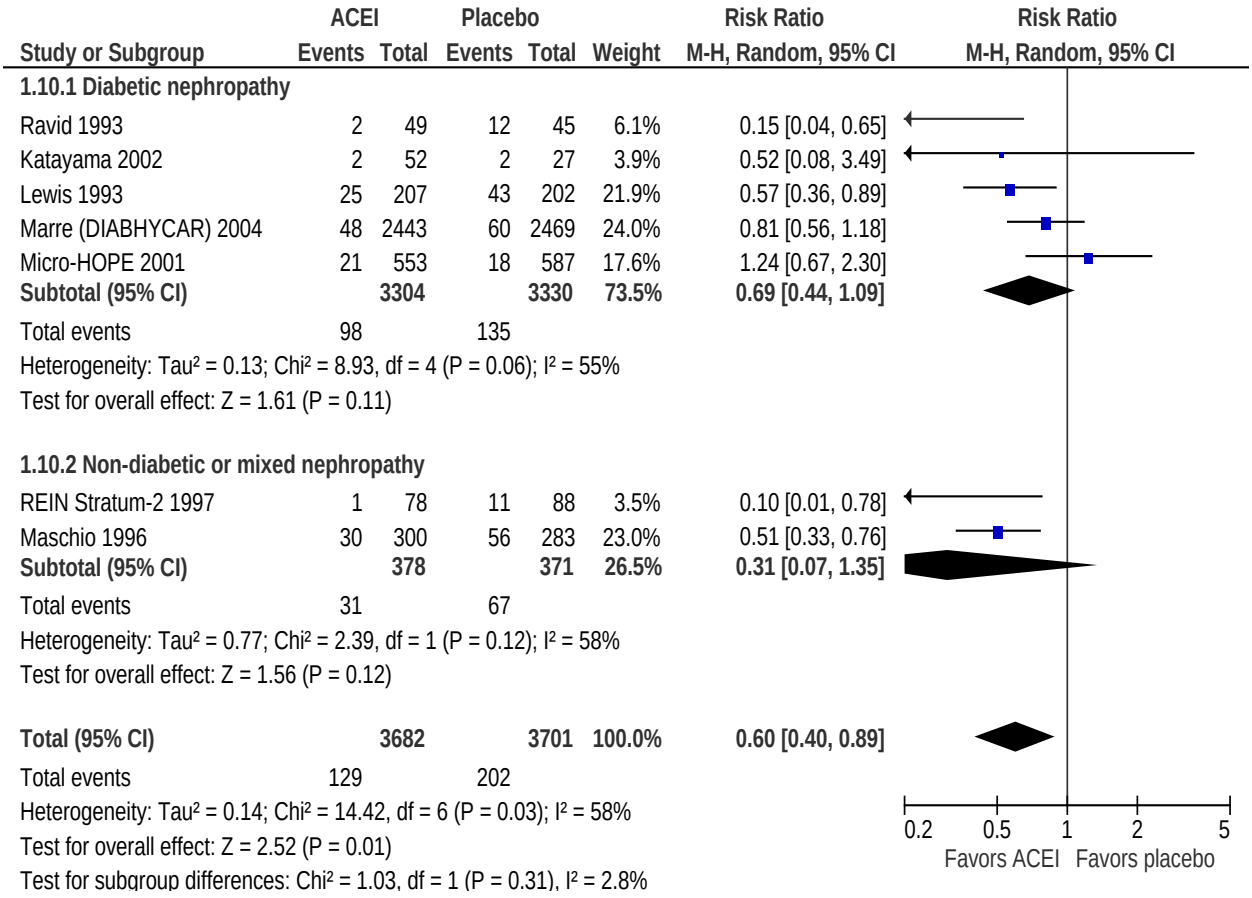
End-stage renal disease

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.9.1 Diabetic nephropathy						
Ravid 1993	0	49	0	45		Not estimable
Lewis 1993	20	207	31	202	31.2%	0.63 [0.37, 1.07]
Micro-HOPE 2001	5	553	6	587	6.2%	0.88 [0.27, 2.88]
Marre (DIABHYCAR) 2004	11	2443	12	2469	13.1%	0.93 [0.41, 2.10]
Subtotal (95% CI)		**3252**		**3303**	**50.5%**	**0.73 [0.48, 1.10]**
Total events	36		49			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						
1.9.2 Non-diabetic or mixed nephropathy						
REIN Stratum-1 1999	9	99	18	87	15.6%	0.44 [0.21, 0.93]
REIN Stratum-2 1997	17	78	29	88	32.7%	0.66 [0.40, 1.11]
Maschio 1996	1	300	1	283	1.1%	0.94 [0.06, 15.01]
Subtotal (95% CI)		**477**		**458**	**49.5%**	**0.59 [0.39, 0.89]**
Total events	27		48			
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 2 (P = 0.64); I² = 0%						
Test for overall effect: Z = 2.50 (P = 0.01)						
Total (95% CI)		**3729**		**3761**	**100.0%**	**0.65 [0.49, 0.88]**
Total events	63		97			
Heterogeneity: Tau² = 0.00; Chi² = 2.13, df = 5 (P = 0.83); I² = 0%						
Test for overall effect: Z = 2.83 (P = 0.005)						
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%						

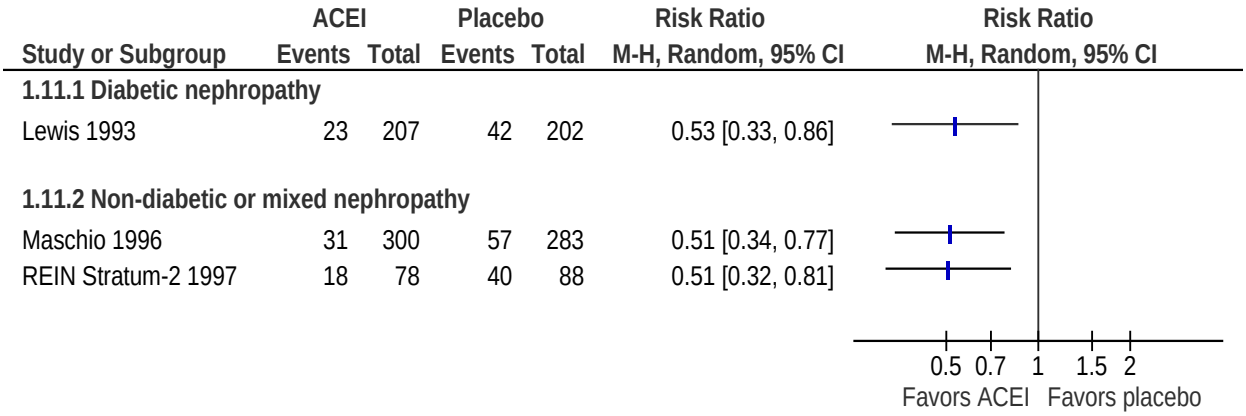


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Doubling of serum creatinine



Composite renal outcome (see Table C7 for defintions)

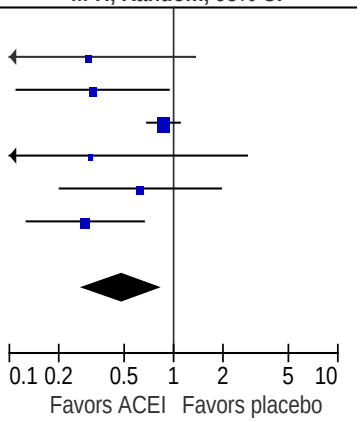


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	ACEI Events	ACEI Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bojestig 2001	0	37	0	18		Not estimable
Crepaldi 1998	2	32	7	34	10.3%	0.30 [0.07, 1.35]
Laffel 1995	4	67	13	70	15.8%	0.32 [0.11, 0.94]
Micro-HOPE 2001	104	553	127	587	33.2%	0.87 [0.69, 1.10]
Muirhead 1999	1	29	3	27	5.7%	0.31 [0.03, 2.81]
O'Hare (ATLANTIS) 2000	6	88	5	46	14.8%	0.63 [0.20, 1.95]
Ravid 1993	6	49	19	45	20.3%	0.29 [0.13, 0.66]
Total (95% CI)		**855**		**827**	**100.0%**	**0.48 [0.27, 0.85]**
Total events	123		174			

Heterogeneity: Tau² = 0.24; Chi² = 11.30, df = 5 (P = 0.05); I² = 56%
Test for overall effect: Z = 2.52 (P = 0.01)

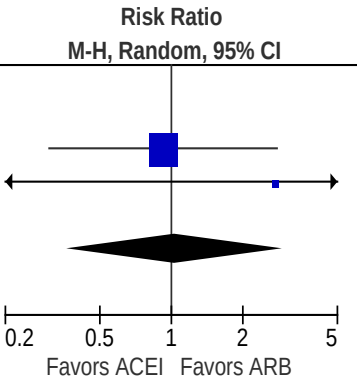


ACEI VERSUS ARB

All-cause mortality

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Lacourcière 2000	0	51	0	52		Not estimable
Muirhead 1999	0	29	0	62		Not estimable
Barnett (DETAIL) 2004	6	130	6	120	89.2%	0.92 [0.31, 2.78]
Menne (VALERIA) 2008	1	47	0	43	10.8%	2.75 [0.12, 65.76]
Total (95% CI)		**257**		**277**	**100.0%**	**1.04 [0.37, 2.95]**
Total events	7		6			

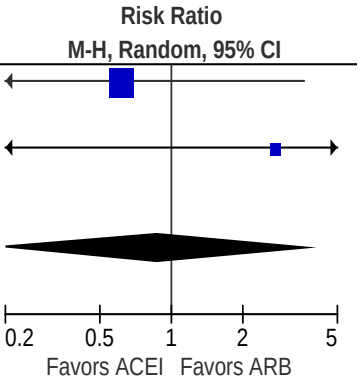
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.94)



Cardiovascular mortality

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnett (DETAIL) 2004	2	130	3	120	76.2%	0.62 [0.10, 3.62]
Lacourcière 2000	0	51	0	52		Not estimable
Menne (VALERIA) 2008	1	47	0	43	23.8%	2.75 [0.12, 65.76]
Muirhead 1999	0	29	0	62		Not estimable
Total (95% CI)		**257**		**277**	**100.0%**	**0.88 [0.19, 4.13]**
Total events	3		3			

Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

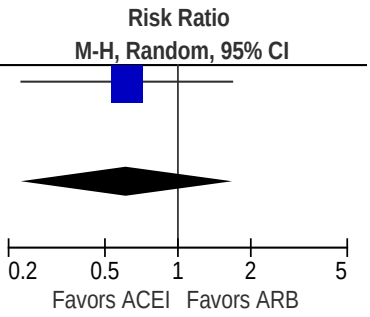


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Myocardial infarction (nonfatal)

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnett (DETAIL) 2004	6	130	9	120	100.0%	0.62 [0.23, 1.68]
Lacourcière 2000	0	51	0	52		Not estimable
Total (95% CI)		**181**		**172**	**100.0%**	**0.62 [0.23, 1.68]**
Total events	6		9			

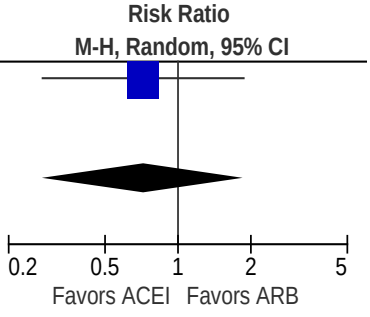
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



Congestive heart failure

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnett (DETAIL) 2004	7	130	9	120	100.0%	0.72 [0.28, 1.87]
Lacourcière 2000	0	51	0	52		Not estimable
Total (95% CI)		**181**		**172**	**100.0%**	**0.72 [0.28, 1.87]**
Total events	7		9			

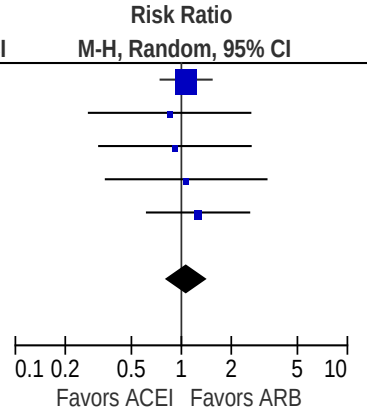
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



Any study withdrawal

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnett (DETAIL) 2004	44	130	38	120	63.8%	1.07 [0.75, 1.53]
Lacourcière 2000	5	51	6	52	6.4%	0.85 [0.28, 2.61]
Menne (VALERIA) 2008	6	47	6	43	7.3%	0.91 [0.32, 2.62]
Muirhead 1999	4	29	8	62	6.5%	1.07 [0.35, 3.26]
Sengul 2006	15	109	12	110	16.0%	1.26 [0.62, 2.57]
Total (95% CI)		**366**		**387**	**100.0%**	**1.07 [0.80, 1.42]**
Total events	74		70			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.45$, df = 4 (P = 0.98); $I^2 = 0\%$
Test for overall effect: Z = 0.46 (P = 0.64)

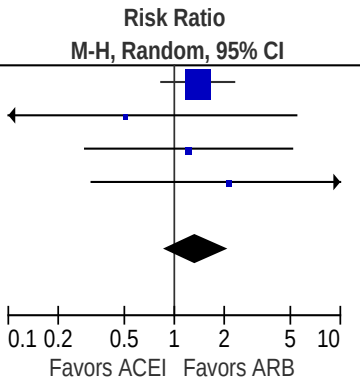


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Study withdrawal due to AE

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Barnett (DETAIL) 2004	30	130	20	120	80.5%	1.38 [0.83, 2.30]
Lacourcière 2000	1	51	2	52	3.7%	0.51 [0.05, 5.45]
Menne (VALERIA) 2008	4	47	3	43	10.1%	1.22 [0.29, 5.14]
Muirhead 1999	2	29	2	62	5.7%	2.14 [0.32, 14.43]
Total (95% CI)		**257**		**277**	**100.0%**	**1.35 [0.86, 2.13]**
Total events	37		27			

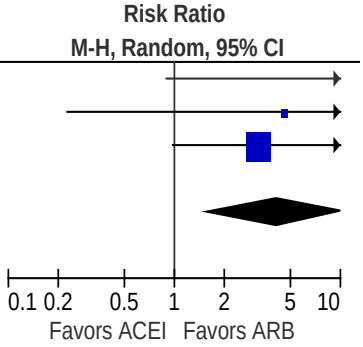
Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)



Cough

Study or Subgroup	ACEI Events	ACEI Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Lacourcière 2000	7	51	0	52	13.1%	15.29 [0.90, 260.90]
Menne (VALERIA) 2008	2	47	0	43	11.7%	4.58 [0.23, 92.86]
Muirhead 1999	6	29	4	62	75.2%	3.21 [0.98, 10.50]
Total (95% CI)		**127**		**157**	**100.0%**	**4.10 [1.47, 11.48]**
Total events	15		4			

Heterogeneity: Tau² = 0.00; Chi² = 1.16, df = 2 (P = 0.56); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)

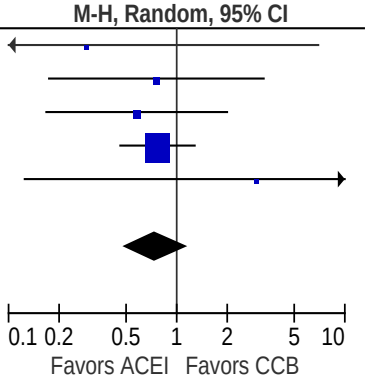


ACEI VERSUS CCB

All-cause mortality

Study or Subgroup	ACE-I Events	ACE-I Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Crepaldi 1998	0	47	1	41	1.9%	0.29 [0.01, 6.97]
Fogari 2002	3	102	4	103	9.0%	0.76 [0.17, 3.30]
Marin (ESPIRAL) 2001	4	129	6	112	12.7%	0.58 [0.17, 2.00]
Norris (AASK) 2006	34	436	22	217	74.5%	0.77 [0.46, 1.28]
Zucchelli 1992	1	60	0	60	1.9%	3.00 [0.12, 72.20]
Total (95% CI)		**774**		**533**	**100.0%**	**0.75 [0.48, 1.16]**
Total events	42		33			

Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 4 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.30 (P = 0.19)

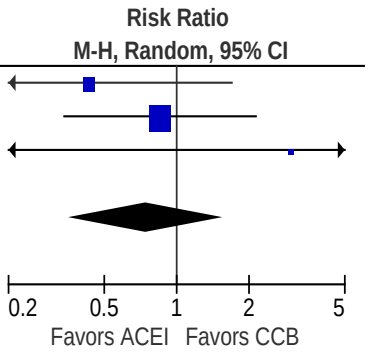


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Cardiovascular mortality

Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Marin (ESPIRAL) 2001	3	129	6	112	29.5%	0.43 [0.11, 1.70]
Norris (AASK) 2006	12	436	7	217	65.1%	0.85 [0.34, 2.14]
Zucchelli 1992	1	60	0	60	5.4%	3.00 [0.12, 72.20]
Total (95% CI)		**625**		**389**	**100.0%**	**0.75 [0.36, 1.57]**
Total events	16		13			

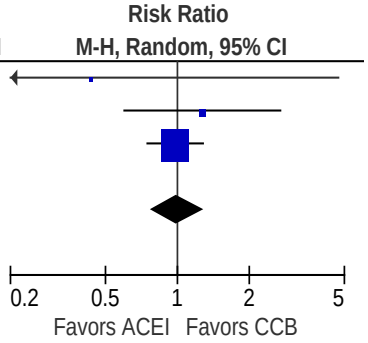
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)



Stroke

Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Marin (ESPIRAL) 2001	1	129	2	112	1.1%	0.43 [0.04, 4.72]
Norris (AASK) 2006	23	436	9	217	11.2%	1.27 [0.60, 2.70]
Rahman (ALLHAT) 2006	99	1533	100	1516	87.7%	0.98 [0.75, 1.28]
Total (95% CI)		**2098**		**1845**	**100.0%**	**1.00 [0.78, 1.28]**
Total events	123		111			

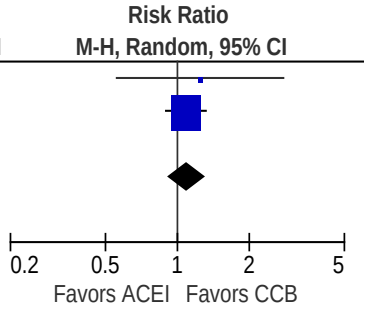
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)



Congestive heart failure

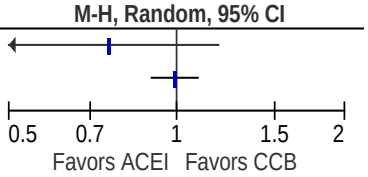
Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	20	436	8	217	5.4%	1.24 [0.56, 2.78]
Rahman (ALLHAT) 2006	191	1533	174	1516	94.6%	1.09 [0.90, 1.32]
Total (95% CI)		**1969**		**1733**	**100.0%**	**1.09 [0.91, 1.32]**
Total events	211		182			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)



Composite vascular outcome (1)* (see Table C5 for definitions)

Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	23	217	61	436		0.76 [0.48, 1.19]
Rahman (ALLHAT) 2006	537	1516	547	1533		0.99 [0.90, 1.09]

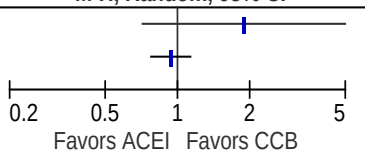


*First outcome identified for each study

Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Composite vascular outcome (2)* (see Table C5 for defintions)

Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	19	436	5	217		1.89 [0.72, 5.00]
Rahman (ALLHAT) 2006	184	1533	194	1516		0.94 [0.78, 1.13]

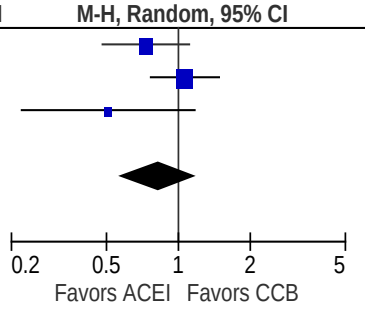


*Second outcome identified for each study

End stage renal disease

Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	47	436	32	217	38.0%	0.73 [0.48, 1.11]
Rahman (ALLHAT) 2006	70	1533	65	1516	46.4%	1.06 [0.77, 1.48]
Zucchelli 1992	7	60	14	61	15.6%	0.51 [0.22, 1.17]
Total (95% CI)		**2029**		**1794**	**100.0%**	**0.82 [0.57, 1.19]**
Total events	124		111			

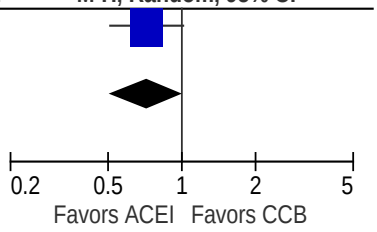
Heterogeneity: Tau² = 0.05; Chi² = 3.71, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 1.03 (P = 0.30)



Composite renal outcome (see Table C7 for definition)

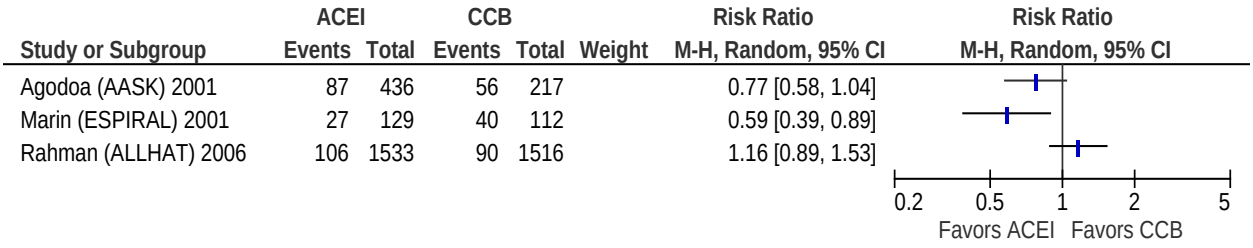
Study or Subgroup	ACEI Events	ACEI Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	65	436	45	217	100.0%	0.72 [0.51, 1.01]
Total (95% CI)		**436**		**217**	**100.0%**	**0.72 [0.51, 1.01]**
Total events	65		45			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)

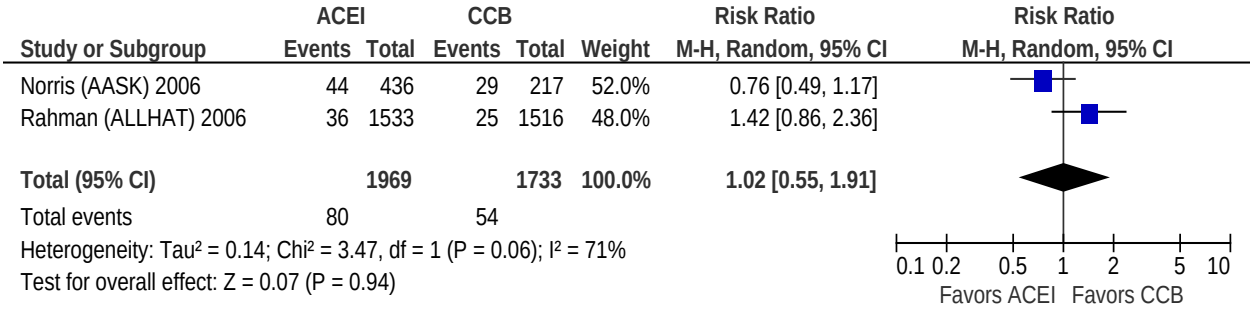


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Composite renal outcome (see Table C7 for defintions)

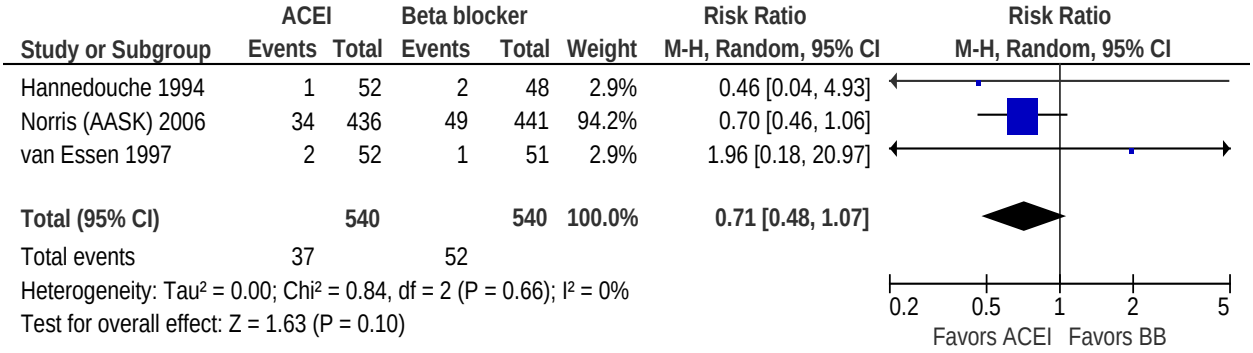


Halving of GFR



ACEI VS. BB

All-cause mortality

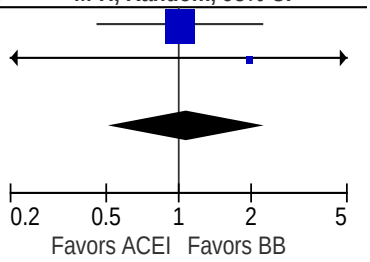


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Cardiovascular mortality

Study or Subgroup	ACEI Events	ACEI Total	Beta blocker Events	Beta blocker Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	12	436	12	441	90.0%	1.01 [0.46, 2.23]
van Essen 1997	2	52	1	51	10.0%	1.96 [0.18, 20.97]
Total (95% CI)		**488**		**492**	**100.0%**	**1.08 [0.51, 2.28]**
Total events	14		13			

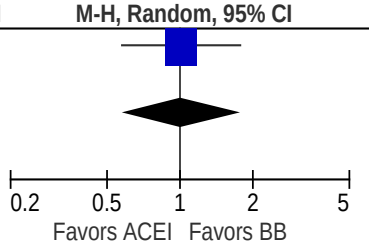
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)



Stroke

Study or Subgroup	ACEI Events	ACEI Total	Beta blocker Events	Beta blocker Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	23	436	23	441	100.0%	1.01 [0.58, 1.78]
Total (95% CI)		**436**		**441**	**100.0%**	**1.01 [0.58, 1.78]**
Total events	23		23			

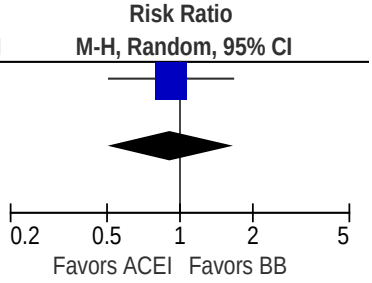
Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)



Congestive heart failure

Study or Subgroup	ACEI Events	ACEI Total	Beta blocker Events	Beta blocker Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	20	436	22	441	100.0%	0.92 [0.51, 1.66]
Total (95% CI)		**436**		**441**	**100.0%**	**0.92 [0.51, 1.66]**
Total events	20		22			

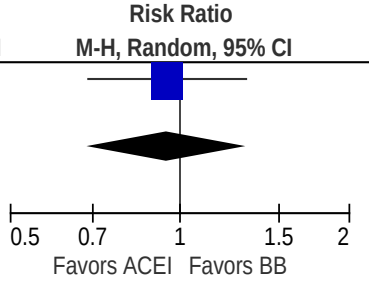
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)



Composite vascular outcome (A) (See Table C5 for definition)

Study or Subgroup	ACEI Events	ACEI Total	Beta blocker Events	Beta blocker Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	61	436	65	441	100.0%	0.95 [0.69, 1.31]
Total (95% CI)		**436**		**441**	**100.0%**	**0.95 [0.69, 1.31]**
Total events	61		65			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)

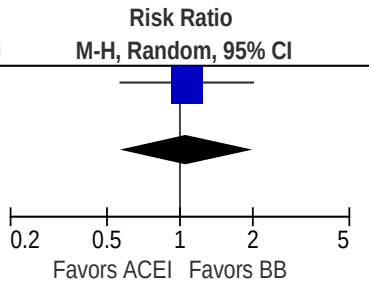


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Composite vascular outcome (B) (see Table C5 for definition)

Study or Subgroup	ACEI Events	ACEI Total	Beta blocker Events	Beta blocker Total	Weight	Risk Ratio M-H, Random, 95% CI
Norris (AASK) 2006	19	436	18	441	100.0%	1.07 [0.57, 2.01]
Total (95% CI)		**436**		**441**	**100.0%**	**1.07 [0.57, 2.01]**
Total events	19		18			

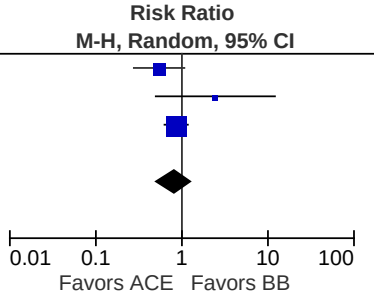
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



End stage renal disease

Study or Subgroup	ACE Events	ACE Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Hannedouche 1994	10	52	17	48	31.8%	0.54 [0.28, 1.07]
van Essen 1997	5	52	2	51	8.6%	2.45 [0.50, 12.07]
Wright 2002	62	436	73	441	59.6%	0.86 [0.63, 1.17]
Total (95% CI)		**540**		**540**	**100.0%**	**0.81 [0.50, 1.33]**
Total events	77		92			

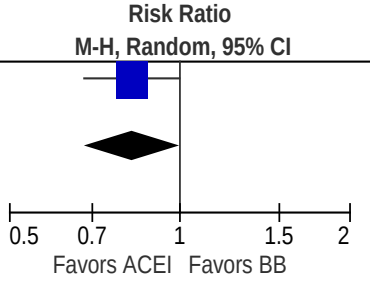
Heterogeneity: Tau² = 0.08; Chi² = 3.34, df = 2 (P = 0.19); I² = 40%
Test for overall effect: Z = 0.82 (P = 0.41)



Composite renal outcome (see Table C7 for definition)

Study or Subgroup	ACEI Events	ACEI Total	Beta blocker Events	Beta blocker Total	Weight	Risk Ratio M-H, Random, 95% CI
Wright (AASK) 2002	126	436	155	441	100.0%	0.82 [0.68, 1.00]
Total (95% CI)		**436**		**441**	**100.0%**	**0.82 [0.68, 1.00]**
Total events	126		155			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)

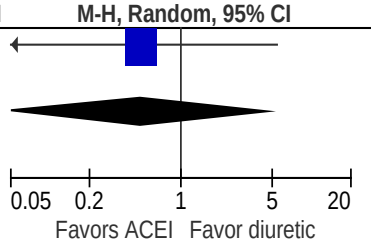


ACEI VERSUS DIURETICS

All-cause mortality

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Marre (NESTOR) 2004	1	286	2	284	100.0%	0.50 [0.05, 5.44]
Total (95% CI)		**286**		**284**	**100.0%**	**0.50 [0.05, 5.44]**
Total events	1		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)

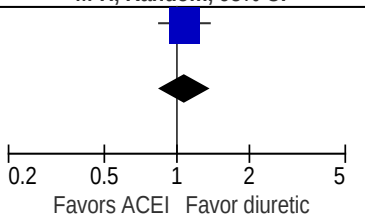


Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

Stroke

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	99	1533	157	2613	100.0%	1.07 [0.84, 1.37]
Total (95% CI)		**1533**		**2613**	**100.0%**	**1.07 [0.84, 1.37]**
Total events	99		157			

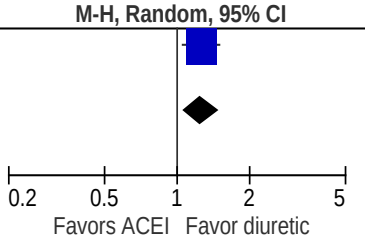
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Congestive heart failure

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	191	1533	259	2613	100.0%	1.26 [1.05, 1.50]
Total (95% CI)		**1533**		**2613**	**100.0%**	**1.26 [1.05, 1.50]**
Total events	191		259			

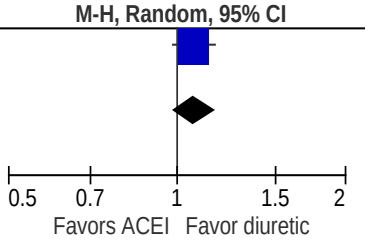
Heterogeneity: Not applicable
Test for overall effect: Z = 2.55 (P = 0.01)



Composite vascular outcome (1) (see Table C5 for definition)

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	547	1533	870	2613	100.0%	1.07 [0.98, 1.17]
Total (95% CI)		**1533**		**2613**	**100.0%**	**1.07 [0.98, 1.17]**
Total events	547		870			

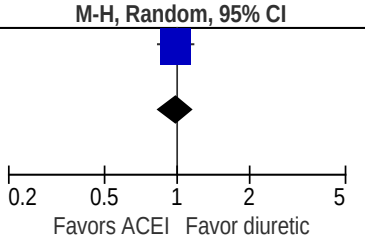
Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)



Composite vascular outcome (2) (see Table C5 for definition)

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	184	1533	318	2613	100.0%	0.99 [0.83, 1.17]
Total (95% CI)		**1533**		**2613**	**100.0%**	**0.99 [0.83, 1.17]**
Total events	184		318			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.16 (P = 0.87)



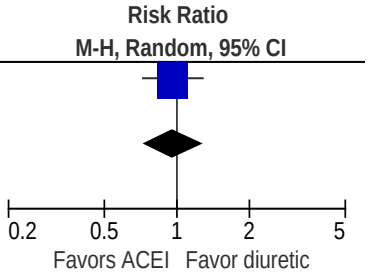
Appendix Figure C1. Forest plots for ACEI monotherapy versus control treatment trials (continued)

End-stage renal disease

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	70	1533	124	2613	100.0%	0.96 [0.72, 1.28]
Total (95% CI)		**1533**		**2613**	**100.0%**	**0.96 [0.72, 1.28]**
Total events	70		124			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.26 (P = 0.79)

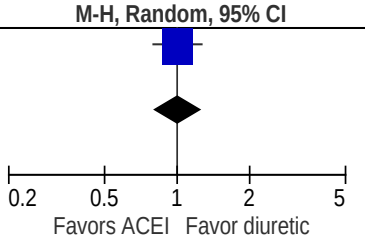


Composite renal outcome (see Table C7 for definition)

Study or Subgroup	ACEI Events	ACEI Total	Diuretic Events	Diuretic Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	106	1533	180	2613	100.0%	1.00 [0.80, 1.27]
Total (95% CI)		**1533**		**2613**	**100.0%**	**1.00 [0.80, 1.27]**
Total events	106		180			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.03 (P = 0.97)



Appendix Table C4. Clinical outcomes (outcomes part B), ACEI monotherapy versus control treatment trials

Study	Stroke or CVA, Nonfatal n/N (%)		Stroke or CVA, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) or Any (C) n/N (%)		Composite Vascular Outcome n/N (%)*	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus placebo/no treatment trials (n=17)										
Perkovic, 2007[1] (PROGRESS)									(1) 178/895 (19.9) (2) 46/895 (5.1)	(1) 222/862 (25.8) (2) 52/862 (6.0)
Asselbergs, 2004[2] (PREVD)					0/431	2/433 (0.5)			17/431 (3.9)	28/433 (6.5)
Marre, 2004[3] (DIAB)	89/2443 (3.6)	84/2469 (3.4)			76/2443 (3.1)	91/2469 (3.7)	85/2443 (3.5) (C)	102/2469 (4.1) (C)	362/2443 (14.8)	377/2469 (15.3)
Katayama, 2002[4]										
Bojestig, 2001[5]										
Gerstein, 2001[6] (HOPE)							66/952 (6.9) (A)	69/1004 (6.9) (A)	186/952 (19.5)	265/1004 (26.4)
O'Hare, 2000[7] (ATLANTIS)									16/92 (17.4)	8/46 (17)
Muirhead, 1999[8]										
REIN, 1999[9] stratum 1					0/99	2/87 (2.3)			2/99 (2.0)	3/87 (3.4)
Crepaldi, 1998[10]										
REIN, 1997[11] stratum 2									4/78 (5.1)	3/88 (3.4)
Maschio, 1996[12]	2/300 (0.7)	3/283 (1.1)								
Trevisan, 1995[13]										
Laffel,1995[14]										
Sano, 1994[15]										
Lewis, 1993[16]										
Ravid, 1993[17]										
(ACEI) versus ARB trials (n=6)										
Mann, 2008[18] ONTARGET										
Menne, 2008[19] VALERIA										
Sengul, 2006[20]										

Appendix Table C4. Clinical outcomes (outcomes part B), ACEI monotherapy versus control treatment trials (continued)

Study	Stroke or CVA, Nonfatal n/N (%)		Stroke or CVA, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) or Any (C) n/N (%)		Composite Vascular Outcome n/N (%)*	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
Barnett, 2004[21] DETAIL					7/130 (5.4)	9/120 (7.5)				
Lacourcière, 2000[22]	0/51	0/52	0/51	0/52	0/51	0/52	0/51 (C)	0/52 (C)		
Muirhead, 1999[8]										
ACEI versus CCB trials (n=5)										
Rahman, 2005/2006[23,34] ALLHAT					191/1533 (12.5)	174/1516 (11.5)			(1) 547/1533 (35.7); (2) 184/1533 (12.0)	(1) 537/1516 (35.4); (2) 194/1516 (12.8)
Rahman, 2006[34] ALLHAT, DM patients					81/501 (16.2)	87/506 (17.2)			(1) 193/501 (38.5); (2) 76/501 (15.2)	(1) 224/506 (44.3); (2) 83/506 (16.4)
Fogari, 2002[24]										
Norris, 2006[27] Agodoa 2001[25] (AASK)					20/436 (4.6)	8/217 (3.7)			(1) 61/436 (14.0); (2) 19/436 (4.4)	(1) 23/217 (10.6); (2) 5/217 (2.3)
Marin, 2001[28] ESPIRAL										
Crepaldi, 1998[10]										
Zucchelli, 1995[29]										
ACEI versus BB trials (n=3)										
Norris, 2006[27] Agodoa 2001[25] (AASK)					20/436 (4.6)	22/441 (5.0)			(2) 19/436 (4.4)	(2) 18/441 (4.1)
van Essen, 1997[31]										
Hannedouche 1994[32]										
ACEI versus diuretics (n=2)										
Rahman, 2006[34] ALLHAT					191/1533 (12.5)	259/2613 (9.9)			(1) 547/1533 (35.7); (2) 184/1533 (12.0)	(1) 870/2613 (33.3); (2) 318/2613 (12.2)
Rahman, 2006[34] ALLHAT, DM patients					81/501 (16.2)	104/881 (11.8)			(1) 193/501 (38.5); (2) 76/501 (15.2)	(1) 326/881 (37.0); (2) 132/881 (15.0)

Appendix Table C4. Clinical outcomes (outcomes part B), ACEI monotherapy versus control treatment trials (continued)

Study	Stroke or CVA, Nonfatal n/N (%)		Stroke or CVA, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) or Any (C) n/N (%)		Composite Vascular Outcome n/N (%)*	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
Marre, 2004[33] NESTOR										

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor II blocker; CCB = calcium channel blocker; BB = beta blocker; CVA = cerebrovascular accident (or stroke); CHF = congestive heart failure; DM = diabetes mellitus; CAD = coronary artery disease.
*See Composite vascular outcome definitions table.

Appendix Table C5. Composite vascular outcome definitions for ACEI monotherapy versus control treatment trials

Study	Definition
ACEI versus placebo/no treatment trials	
Perkovic, 2007[1] PROGRESS	(1) "Major cardiovascular events," defined as any of the following: nonfatal stroke, nonfatal MI, or cardiovascular death; and (2) Major "Coronary heart disease event," defined as nonfatal myocardial infarction or death ascribed to coronary heart disease.
Asselbergs, 2004[2] PREVEND IT	Cardiovascular death or hospitalization for cardiovascular morbidity (latter defined as hospitalization for either nonfatal MI or myocardial ischemia, heart failure, peripheral vascular disease, and/or cerebrovascular accident).
Marre, 2004[3] DIABHYCAR	Cardiovascular death (including sudden death), nonfatal acute MI, stroke, heart failure requiring admission to hospital, or end stage renal failure (defined as dialysis or kidney transplant)
Gerstein, 2001[6] Micro-HOPE	Cardiovascular death, MI, or stroke
O'Hare, 2000[7] ATLANTIS	Incident "cardiovascular adverse events" reported but not defined. Incidence of death, MI and angina/chest pain separately provided.
REIN, 1999[9] stratum 1	Incident "nonfatal cardiovascular events" reported but not defined.
REIN, 1997[11] stratum 2	Nonfatal cardiovascular events included any of the following: MI, aortic aneurysm, or uncontrolled hypertension.
Maschio, 1996[12]	Nonfatal cardiovascular events included any of the following: MI, stroke, transient ischemic attack, hypertensive crisis, angina, hypotension or dizziness.
ACEI versus CCB trials	
Rahman, 2006[34] ALLHAT	Defined two composite vascular endpoints, as follows: (1) Death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease requiring hospitalization or outpatient revascularization; and (2) "Coronary heart disease event" defined as nonfatal MI or fatal coronary heart disease death
Norris, 2006[27] Wright, 2002[26] AASK	Defined two composite vascular endpoints, as follows: (1) Cardiovascular mortality or first cardiovascular hospitalization and (2) "Coronary heart disease event" defined as CAD hospitalization (probable MI) and/or fatal coronary heart disease death.
ACEI versus BB trial	
Norris, 2006 AASK[27]	(A) Cardiovascular mortality or first cardiovascular hospitalization (B) Coronary heart disease event" defined as CAD hospitalization (probable MI) and/or fatal coronary heart disease death.
ACEI versus diuretic trials	
Rahman, 2006[34] ALLHAT	Defined two composite vascular endpoints, as follows: (1) Death from coronary heart disease, nonfatal MI, stroke, coronary revascularization procedures, hospitalized or treated angina, treated or hospitalized heart failure, and peripheral arterial disease requiring hospitalization or outpatient revascularization and (2) "Coronary heart disease event" defined as nonfatal MI or fatal coronary heart disease death

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor II blocker; CCB = calcium channel blocker; BB = beta blocker; MI = myocardial infarction; CAD = coronary artery disease

Appendix Table C6. Clinical renal outcomes (outcomes part C), ACEI monotherapy versus control treatment trials

Study	End-Stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)*	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus placebo trials (n=17)										
Perkovic, 2007[1] (PROGRESS)										
Asselbergs, 2004[2] (PREVD)										
Marre, 2004[3] (DIAB)	11/2443 (0.5)	12/2469 (0.5)	48/2443 (2.0)	60/2469 (2.4)						
Katayama, 2002[4]			2/52 (3.8)	2/27 (7.4)						
Bojestig, 2001[5]							0/37	0/18		
Gerstein, 2001[6] (MICROHOPE)†	5/553 (0.9)	6/587 (1.0)	21/553 (3.8)*	18/587 (3.1)			104/553 (18.8)	127/587 (21.6)		
O'Hare, 2000[7] (ATLANTIS)							6/88 (6.8)	5/46 (10.9)		
Muirhead, 1999[8]							1/29 (3.4)	3/27 (11.1)		
REIN, 1999[9] stratum 1	9/99 (9.1)	18/87 (20.7)								
Crepaldi, 1998[10]							2/32 (6.3)	7/34 (20.6)		
REIN, 1997[11] stratum 2	17/78 (21.8)	29/88 (33.0)	1/78 (1.3)	11/88 (12.5)					18/78 (23.1)	40/88 (45.5)
Maschio, 1996[12]	1/300* (0.3)	1/283 (0.4)	30/300 (10)*	56/283 (19.8)					31/300 (10.3)	57/283 (20.1)
Trevisan, 1995[13]										
Laffel, 1995[14]							4/67 (6.0)	13/70 (18.6)		
Sano, 1994[15]										
Lewis, 1993[16]	20/207 (9.7)	31/202 (15.3)	25/207 (12.1)	43/202 (21.3)					23/207 (11.1)	42/202 (20.8)
Ravid, 1993†[17]	0/49*	0/45	2/49 (4.1)*	12/45 (26.7)			2/49 (4.1)	22/45 (48.9)		
ACEI versus ARB trials (n=6)										
Mann, 2008[18] ONTARGET							§	§	*Numbers not provided for CKD subgroup*	
Menne, 2008[18] VALERIA										
Sengul, 2006[20]							0/110	0/109		
Barnett, 2004[21] DETAIL										
Lacourcière, 2000[22]							NR‡	NR‡		

Appendix Table C6. Clinical renal outcomes (outcomes part C), ACEI monotherapy versus control treatment trials (continued)

Study	End-Stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)*	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
Muirhead, 1999[8]							1/29 (3.4)	1/62 (1.6)		
ACEI versus CCB trials (n=6)										
Rahman, 2005[23] ALLHAT	70/1533 (4.6)	65/1516 (4.3)					36/1533 (2.3)	25/1516 (1.6)	106/1533 (6.9)	90/1516 (5.9)
Rahman, 2005[23] ALLHAT, DM patients††									61/501 (12.2)	56/506 (11.1)
Fogari, 2002[24]										
Agodoa, 2001 (AASK)	47/436 (10.8)	32/217 (14.7)					44/436 (10.1)	29/217 (13.4)	(1) 70/436 (16.1); (2) 87/436 (20.0)	(1) 43/217 (19.8); (2) 56/217 (25.8)
Marin, 2001[28] ESPIRAL									27/129 (20.9)	40/112 (35.7)
Crepaldi, 1998[10]										
Zucchelli, 1995[29]	7/60 (11.7)	14/61 (23.0)								
ACEI versus BB trials (n=3)										
Wright, 2002[26]	62/436 (14.2)	73/441 (16.6)							126/436 (28.9)	155/441 (35.1)
van Essen, 1997[31]	5/52 (9.6)	2/51 (3.9)								
Hannedouche, 1994[32]	10/52 (19.2)	17/48 (35.4)								
ACEI versus diuretic trials (n=3)										
Rahman, 2006[34] ALLHAT	70/1533 (4.6)	124/2613 (4.7)							106/1533 (6.9)	180/2613 (6.9)
Rahman, 2006[34] ALLHAT, DM patients	41/501 (8.2)	68/881 (7.7)							61/501 (12.1)	96/881 (10.9)
Marre, 2004[33] NESTOR							18/286 (6.3)	26/283 (9.2)		

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor II blocker; CCB = calcium channel blocker; BB = beta blocker; GFR = glomerular filtration rate

*See Composite renal outcome definitions table

† Data obtained from Ksirsagar Am J Kidney Dis 2000;35(4):695-707) or Stroppoli BMJ/Cochrane review 2004.

‡Study reported that 3/103 participants converted from micro- to microalbuminuria, but did not report results by treatment group.

§Study reported in text that progression from microalbuminuria to microalbuminuria occurred in 166 (2.12%) of ramipril subjects, 138 (1.8%) of telmisartan subjects, but this is not possible given that in figure study reports that 2673 subjects had either microalbuminuria or macroalbuminuria at baseline.

††Rahman 2006 ALLHAT DM patients is a report on the subgroup of diabetic patients from the overall ALLHAT study.

Appendix Table C7. Composite renal outcome definitions for ACEI versus control treatment trials

Study	Definition
ACEI versus placebo/no treatment trials	
REIN, 1997[11] stratum 2	Doubling of baseline serum creatinine concentration or end stage renal disease.
Maschio, 1996[12]	Doubling of baseline serum creatinine concentration or the need for dialysis.
Lewis, 1993[16]	Death, dialysis, or renal transplantation.
ACEI versus ARB trials	
Mann, 2008[18] ONTARGET	Dialysis, renal transplantation, doubling of serum creatinine, or death.
ACEI versus CCB trials	
Rahman, 2005[23] ALLHAT	End stage renal disease (death due to kidney disease, dialysis, or renal transplantation) or reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs.
Agodoa, 2001[25] AASK	End stage renal disease (need for renal replacement therapy), reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs, or death.
Marin. 2001[28] ESPIRAL	Doubling of baseline serum creatinine concentration or the need for dialysis.
ACEI versus BB trials	
Wright, 2002[26] (AASK)	End stage renal disease (need for renal replacement therapy), reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs, or death.
ACEI versus diuretic trials	
Rahman, 2005[23] ALLHAT	End stage renal disease (death due to kidney disease, dialysis, or renal transplantation) or reduction in GFR by 50% or by 25 mL/min/1.73 m^2 from the mean of the two baseline GFRs.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor II blocker; CCB = calcium channel blocker; BB = beta blocker; GFR = glomerular filtration rate

Appendix Table C8. Study withdrawals and adverse events (outcomes Part D), ACEI monotherapy versus control treatment trials

Study	Any Study Withdrawals		Any or Serious Adverse Events Leading to Study Withdrawal		Adverse Event: Cough		Adverse Event: Hyperkalemia		Renal Adverse Events Leading to Withdrawal*		Renal Adverse Events	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
ACEI versus placebo/no treatment trials (n=17)												
Perkovic, 2007[1] (PRGRESS)												
Asselbergs, 2004[2] (PREVD)	103/431 (24)	110/433 (25.4)										
Marre, 2004[3] (DIAB)	334/2443 (13.7)**	324/2469 (13.1)**	609/2443 (24.9)	554/2469 (22.4)	80/2443 (3.3)	21/2469 (0.9)						
Katayama, 2002[4]	12/52 (23.1)	10/27 (37)	2/52 (3.8)	1/27 (3.7)								
Bojestig, 2001[5]	4/37 (10.8)	0/18	3/37 (8.1)	0/18	1/37 (2.7)	0/18						
Gerstein, 2001[6] (MICROHOPE)												
O'Hare, 2000[7] (ATLANTIS)	31/92 (33.7)	11/48 (22.9)	15/92 (16.3)	5/48 (10.4)								
Muirhead, 1999[8]	4/29 (13.8)	7/31 (22.6)	2/29 (6.9)	0/31	6/29 (20.7)	1/31 (3.2)						
REIN, 1999[9 11] Stratum 1	20/99 (20.2)†	20/87 (23)†	11/99 (11.1)	6/87 (6.9)	1/99 (1.0)	0/87	0/99	1/87 (1.1)	1/99 (1.0)	0/87	Worsening renal insufficiency	
Crepaldi, 1998[10]	2/32 (6.3)	6/34 (17.6)	1/32 (3.1)	6/34 (17.6)					0/32	1/34 (2.9)	Diabetic nephropathy	
REIN, 1997[11] Stratum 2	14/78 (17.9) †	21/88 (23.9) †	9/78 (11.5)	11/88 (12.5)			1/78 (1.3)	1/88 (1.1)	0/78	2/88 (2.3)	Worsening renal insufficiency	
Maschio, 1996[12]	68/300 (22.7)	61/283 (21.6)	52/300 (17.3)	41/283 (14.5)	25/300 (8.3)	10/283 (3.5)	5/300 (1.7)	3/283 (1.1)	3/300 (1.0)	6/283 (2.1)	Worsening renal insufficiency	
Trevisan, 1995[13]	6/60 (10)	8/62 (12.9)	4/60 (6.7)	7/62 (11.3)	1/60 (1.7)	1/62 (1.6)						
Laffel, 1995[14]	22/70 (31.4)	21/73 (28.8)	4/70 (5.7)	5/73 (6.8)	15/70 (21.4)	16/73 (21.9)	0/70	0/73				
Sano, 1994[15]			0/26	0/26	0/26	0/26	0/26	0/26				
Lewis, 1993[16]			46/207 (22.2)	58/202 (28.7)			3/207 (1.4)	0/202				

Appendix Table C8. Study withdrawals and adverse events (outcomes Part D), ACEI monotherapy versus control treatment trials (continued)

Study	Any Study Withdrawals		Any or Serious Adverse Events Leading to Study Withdrawal		Adverse Event: Cough		Adverse Event: Hyperkalemia		Renal Adverse Events Leading to Withdrawal*		Renal Adverse Events	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
Ravid, 1993[17]	3/56 (5.3)	3/52 (5.8)	4/56 (7.1)	3/52 (5.8)	4/56 (7.1)	2/52 (3.8)						
ACEI versus ARB trials (n=6)												
Mann, 2008[18] ONTARGET												
Menne, 2008[19] VALERIA	6/47 (12.8)	6/43 (14.0)	4/47 (8.5)	3/43 (7)	2/47 (4.3)	0/43	1/47 (2.1)	1/43 (2.3)				
Sengul, 2006[20]	15/109 (13.8)	12/110 (10.9)										
Barnett, 2004[21] DETAIL	44/130 (33.8)	38/120 (31.7)	30/130 (23.1)	20/120 (16.7)					2/130 (1.5)	2/120 (1.7)	Elevated serum creatinine	
Lacourcière, 2000[22]	5/51 (9.8)	6/52 (11.5)	1/51 (2)	2/52 (3.8)	7/51 (13.7)	0/52						
Muirhead, 1999[8]	4/29 (13.8)	8/62 (12.9)	2/29 (6.9)	2/62 (3.2)	6/29 (20.7)	4/62 (6.5)			0/29 0	1/62 (1.6)	Decreased GFR and creatinine clearance	
ACEI versus CCB trials (n=5)												
Rahman, 2006[34] ALLHAT												
Fogari, 2002[24]	26/102 (25.5)	27/103 (26.2)	3/102 (2.9)	4/103 (3.9)	2/102 (2.0)	0/103			2/102 (2.0)	2/103 (1.9)	Worsening kidney function	
Wright, 2002[26] (AASK)	0/436	0/217	0/436	0/217	54.9*	46.3*	3/436 (0.7)	0/217				
Wright, 2002[26] (AASK)	Other adverse events that were significantly different between groups (p<0.5): angioedema ACE 6.4* vs. 2.3* for CCB; Syncope ACE 6.7* vs. 2.3* for CCB; Edema ACE 46* vs. 59.8* for CCB											
Marin, 2001[28] ESPIRAL	45/129 (34.9)	38/112 (33.9)	15/129 (11.6)	12/112 (10.7)	3/129 (2.63)	0/112			4/129 (3.1)	1/112 (0.9)	Impaired kidney function	
Crepaldi, 1998[10]	17/47 (36.2)	17/41 (41.2)	1/32 (3.1)	0/26					0/32	0/26		
Zucchelli, 1995[29]	15/60 (25)	16/61 (26)	5/60 (8.3)	7/61 (11.5)	2/60 (3.3)	0/61						
ACEI versus BB trials (n=3)												
Wright, 2002[26] (AASK)	0/436	0/441	0/436	0/441	54.9*	41.5*	3/436 (0.7)	1/441 (0.2)				
van Essen, 1997[31]	9/52 (17.3)	5/51 (9.8)	9/52 (17.3)	5/51 (9.8)			1/52 (1.9)	0/51				

Appendix Table C8. Study withdrawals and adverse events (outcomes Part D), ACEI monotherapy versus control treatment trials (continued)

Study	Any Study Withdrawals		Any or Serious Adverse Events Leading to Study Withdrawal		Adverse Event: Cough		Adverse Event: Hyperkalemia		Renal Adverse Events Leading to Withdrawal*		Renal Adverse Events	
	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control	ACEI	Control
Hannedouche, 1994[32]	11/52 (21.2)	12/48 (25.0)	3/52 (5.8)	3/48 (6.3)			2/52 (3.8)	0/48				
ACEI versus diuretics (n=2)												
Rahman, 2006[34] ALLHAT												
Marre, 2004[33] NESTOR	30/286 (10.5)	35/284 (12.3)	15/286 (5.2)	14/284 (4.9)								

* Results reported as percent of patients experiencing adverse event per patient year of followup (patients were followed up for 3 to 6.4 years)
ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor II blocker; CCB = calcium channel blocker; BB = beta blocker

Appendix Evidence Table C9. Overview of ARB monotherapy trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ARB versus placebo/no treatment trials (n= 5 trials)				
Tobe, 2011[35] TRANSCEND Location Multinational (40 countries) Funding Source Industry	Inclusion Criteria: patients intolerant to ACE inhibitors were enrolled if they had established coronary artery, peripheral vascular or CVD, or diabetes with end-organ damage. Intolerance to ACE inhibitors was defined as previous discontinuation by a physician because of intolerance, with a specific documented cause. Exclusion Criteria: heart failure, significant primary valvular or cardiac outflow tract obstruction, constrictive pericarditis, complex congenital heart disease, unexplained syncope, planned cardiac surgery or cardiac revascularization within the previous 3 months, systolic BP >160 mm Hg, heart transplantation, subarachnoid hemorrhage, significant renal artery stenosis, creatinine levels >265 µmol/L, proteinuria, or hepatic dysfunction.	5926 total were randomized, 1480 had a GFR <60 ml/min/1.73m^2 and an additional 511 had micro or macroalbuminuria with a GFR ≥60 ml/min/ 1.73m^2 (n=1991). *Demographic data for the 1991 unless noted*. N=1991 Age (yr): 68.7 Gender (Male %): 51 Race/Ethnicity (%): European 59, Asian 23 BMI: 28 Systolic BP (mm Hg): 143 Diastolic BP (mm Hg): 82 Albuminuria-to-creatinine ratio (ACR): 6.8 (4.4 GFR <60; 6.8 with micro and GFR ≥60; 52.1 with macro and GFR ≥60) Serum creatinine (mg/dL): 1.2 (1.3 GFR <60; 0.95 with micro and GFR ≥60; 0.98 with macro and GFR ≥60) Estimated GFR (ml/min/1.73m^2): 57.7 (50.1 GFR <60; 79.7 with micro and GFR ≥60; 78.8 with macro and GFR ≥60) Total cholesterol (mg/dL): 201 LDL cholesterol (mg/dL): 120 Diabetes (%): 41 History of HTN (%): 81 History of CAD (%): 73 History of CHF (%): 0 (see exclusion criteria) History of MI (%): 45 History of Stroke (%): 22 Peripheral arterial disease (%): 12 Current smoker (%): 8	Telmisartan 80mg/day (n=729 plus 226 with micro and GFR ≥60 and 37 with macro and GFR ≥60) Placebo (n=751 plus 208 with micro and GFR ≥60 and 40 with macro and GFR ≥60) Study duration: median 4.7 years (all subjects) Study withdrawals (%):	Allocation Concealment : adequate (main publication)* Blinding: double, endpoints adjudication committee Intention to Treat Analysis (ITT): yes (for all subjects) Withdrawals/Dropouts adequately described: yes (for all subjects) * TRANSCEND, Lancet 2008;372:1174-83.[36] Note: Post-hoc analysis

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Makino, 2007[37] Location Japan Funding Source NR	Inclusion Criteria: Age 30 to 74, type 2 DM and urinary albumin-to-creatinine ratio 100-300 mg/g, serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women). Exclusion Criteria: DM type 1, age of diabetes onset <30 years, seated systolic blood pressure (SBP)/diastolic blood pressure (DBP) >180/100 mmHg, and definable chronic kidney disease other than diabetic nephropathy	N=527 Age (yr): 61.7 Gender (Male %): NR Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 137 Diastolic BP (mm Hg): 77 Albuminuria: NR, see Inc. criteria Serum creatinine (mg/dL): NR, see Inc. criteria Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): NR History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	n= 168 to Telmisartan 80mg/day n= 172 to Telmisartan 40mg/day n= 174 to placebo period: median 1.3 +/- 0.5 years Study withdrawals (%): 2.4 % excluded from primary analysis due to suspected type 1 DM or for missing UACR measurements	Allocation Concealment Unclear Blinding: Double blinded Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Brenner, 2001[38] RENAAL Location Multinational Funding Source Industry	Inclusion Criteria: Age 31 to 70 years with type 2 DM and nephropathy defined as 2 occasions of urinary albumin/creatinine ratio ≥300 mg/g (or urinary protein excretion ≥0.5 g/day) and serum creatinine 1.3 – 3.0 mg/dL with lower limit of 1.5 mg/dL for male patients weighing >60kg. Exclusion Criteria: Type 1 DM or nondiabetic renal disease including renal-artery stenosis. MI or CABG within the previous month, PCI within the previous six months, CVA or TIA within the previous year. History of CHF. Patients on ACEI or ARB prior to study had these medications stopped.	N=1513 Age (yr): 60 Gender (Male %): 63.2 Race/Ethnicity (%): Asian: 16.7, Black: 15.2, White: 48.6, Hispanic: 18.2, Other: 1.3 BMI: 29 Systolic BP (mm Hg): 153 Diastolic BP (mm Hg): 82 Albuminuria: Median Urine Alb/Cr: 1250 mg/g Serum creatinine (mg/dL): 1.9 Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): 228 LDL cholesterol (mg/dL): 142 Diabetes (%): 100 History of HTN (%): 93.5 History of CAD (%): 0.1 (not all CAD as only refers to history of coronary revascularization procedure) History of CHF (%): 0 History of MI (%): 11.2 History of Stroke (%): 0.1 Peripheral arterial disease (%): NR Current smoker (%): 18.3	n= 751 for 50-100mg/day Losartan (71% reached 100 mg/day) n= 762 Placebo All patients also given “standard antihypertensive therapy” (CCB, Diuretics, Alpha blockers, Beta-blockers and centrally acting agents) to maintain BP<140/90. Followup period: median 3.4 years Study withdrawals (%): 7.8 46.5 Losartan	Allocation Concealment Adequate Blinding: Double blind Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Parving, 2001[39] IRMA-2 Location: 96 centers worldwide Funding Source Industry	Inclusion Criteria: HTN, age 30 to 70, type 2 DM, persistent microalbuminuria (UAER 20 to 200 µg/min in 2 of 3 consecutive, sterile, overnight samples), serum creatinine ≤1.5 mg/dl for men and ≤1.1 mg/dl for women. Exclusion Criteria: Nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within two years, and an indication for ACEI or ARBs.	N=590 Age (yr): 58 Gender (Male %): 68.5 Race/Ethnicity (%): White: 97.3, Non-White: 2.7 BMI: 30 Systolic BP (mm Hg): 153 Diastolic BP (mm Hg): 90 Albuminuria: 55.5 µg/min Serum creatinine (mg/dL): 1.18 Estimated GFR (ml/min/1.73m2):NR Total cholesterol (mg/dL): 224 LDL cholesterol (mg/dL): 140 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): 4.5 History of CHF (%): NR History of MI (%): 3.0 History of Stroke (%): 3.1 Peripheral arterial disease (%): 5.2 Current smoker (%): 18.6	n= 201 placebo n= 195 Irbesartan 150mg n= 194 Irbesartan 300mg Followup period: median 2 years Study withdrawals (%): 13	Allocation Concealment: Not defined Blinding: Double blind Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Lewis, 2001[40] IDNT Location USA Funding Source: Industry	Inclusion Criteria: Age 30 - 70, documented diagnosis of type 2 DM, HTN (SBP>135 mm Hg, DBP>85 mm Hg, or documented treatment with antihypertensive agents), proteinuria (urinary protein excretion $\geq$ 900 mg per 24 hours), serum creatinine 1.0 - 3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men Exclusion Criteria: NR	N=1,148 Age (yr): 59 Gender (Male %): 68 Race/Ethnicity (%): White 74.3 Hispanic 4.7 Black 12.3 Asian 4.4 Other 4.3 BMI: 30.7 Systolic BP (mm Hg): 159 Diastolic BP (mm Hg): 87 Albuminuria: NR Median Urine Protein Excretion 2.9 g/24hr Median Urine Albumin Excretion 1.9 g/24hr Serum creatinine (mg/dL): 1.68 Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100% History of HTN (%): 100% History of CAD (%): 28.0 with history of "cardiovascular disease" History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	n= 579 Irbesartan 300 n= 569 Placebo Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85. Followup period: median 2.6 years Study withdrawals (%): 0.8	Allocation Concealment : Adequate Blinding: Patients, investigators, and assessors Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: yes

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ARB versus CCB trials (n=4 trials)				
Saruta, 2009[41] CASE-J Location Japan Funding Source Industry and Government	Inclusion Criteria: For main study, inclusion criteria were: SBP >180mmHg or DBP >110mmHg, type II diabetes, history of stroke or transient ischemic attack, left-ventricular hypertrophy, angina pectoris or a history of myocardial infarction, proteinuria or a serum creatinine ≥1.3mg/dL, or arteriosclerotic peripheral artery obstruction. For this post-hoc analysis, CKD defined as proteinuria (positive urine dipstick) and/or decreased GFR (<60ml/min/1.73m2). Exclusion Criteria: SBP ≥200 mmHg or DBP ≥120 mmHg, Type I DM, MI or CVA ≤6 months before screening, PTCA or CABG ≤6 months before screening or currently scheduled, current treatment for CHF (New York Heart Association functional class II-IV) or ejection fraction <40%, CAD requiring beta blocker or calcium channel blocker, atrial fibrillation or atrial flutter, serum creatinine ≥3 mg/dL, AST and/or ALT ≥100 IU/L, malignancy ≤5 years before enrollment, suspected contraindication for candesartan or amlodipine, pregnancy, possible pregnancy, or plan to conceive a child within 5 years of enrollment, not suited to the clinical trial as judged by a collaborating physician, inability to give informed consent.	N= 2720 (subset with GFR <60ml/min/1.73m2 from among larger study cohort of 4728) Age (yr): 65 Gender (Male %): 51.8 Race/Ethnicity (%): NR BMI: 24.5 Systolic BP (mm Hg): 163 Diastolic BP (mm Hg): 91 Albuminuria: NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL):NR Diabetes (%): 42.4 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): 4.8 History of Stroke (%): 11.8 Peripheral arterial disease (%): 1.2 Current smoker (%): NR	n=1376 Candesartan 4 to 12mg daily titrated to target BP n=1344 Amlodipine 2.5 to 10mg daily titrated to target BP Doses titrated to goal BP <130/85 for ages <60 years <140/90 for ages 60-69 <150/90 for ages 70-79 <160/90 for ages >80 Followup period: Total 36 months Study withdrawals (%):No data were reported	Allocation Concealment: Not defined Blinding: Assessor Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Inadequate

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Ogawa, 2007[42] Location Japan Funding Source NR	Inclusion/Exclusion Criteria: Type 2 DM outpatients who previously had untreated moderate hypertension (130/80 – 200/110 mmHg); microalbuminuria with repeat x 3 urinary albumin-to-creatinine ratio (ACR) of 100-300 mg/g; glycated hemoglobin Alc (HbAlc)<8.0%; no changes in medications or hospitalization during past 3 years; body mass index (BMI)<30 kg/m2; serum creatinine < 1.2 mg/dl; no other renal diseases; no severe cerebral or cardiovascular diseases or liver dysfunction; and no active retinopathy.	N=58 Age (yr): 62.7 Gender (Male %): 46.6 Race/Ethnicity (%): NR BMI: 23.6 Systolic BP (mm Hg): 152 Diastolic BP (mm Hg): 90 Albuminuria: 100% Mean urine Alb/Cr ratio: 237 Serum creatinine (mg/dL): 0.74 Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): 199.6 LDL cholesterol (mg/dL): NR Diabetes (%): 100% History of HTN (%): 100% Peripheral arterial disease (%): NR Current smoker (%): NR History of CHF (%): NR History of CAD (%): NR History of MI (%): NR History of Stroke (%): NR	n=40 Candesartan 4 - 8mg/d n=18 Nifedipine 20 - 40mg/d Followup period: median 56 weeks Study withdrawals (%): 2/58 (3.4) Candesartan and Nifedipine doses were 4 mg and 20mg daily, respectively, for first 48 weeks, then doses increased to 8mg and 40 mg daily, respectively.	Allocation Concealment: Not defined Blinding: Patient only Intention to Treat Analysis (ITT): Unclear Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Viberti, 2002[43] MARVAL Location 31 centers in the United Kingdom Funding Source Industry	Inclusion Criteria: 35 to 75 years of age, type 2 diabetes mellitus, persistent microalbuminuria (median UAER of 3 nonconsecutive timed overnight urine collections 20 to 200 g/min during 5 week period before entry), normal serum creatinine, BP <180/105 mm Hg. Exclusion Criteria: Type 1 DM (onset at <35 years of age and requiring insulin within the first year), use of ACEIs, alpha 2 blockers, or CCB ≤5 weeks before random assignment; child-bearing potential for women; heart failure within preceding 6 months requiring ACE inhibitor therapy; MI, PTCA or CVA within the preceding 3 months; severe diabetic neuropathy; history of hypertensive or hepatic encephalopathy; hepatic disease.	N=332 Age (yr): 58 Gender (Male %): 79.8 Race/Ethnicity (%): White: 86.5 Asian: 10 BMI: 30.8 Systolic BP (mm Hg): 148 Diastolic BP (mm Hg): 86 Albuminuria: 100% Baseline UAER: 56.7 μg/min Serum creatinine (mg/dL): 1.08 Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): 198.5 LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 65 History of CAD (%): NR History of CHF (%): NR History of MI (%): 0 History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	n= 169 valsartan initiated at 80 mg/d, could be titrated to 160 mg/d to reach target BP 135/85 mm Hg n= 163 amlodipine initiated at 5 mg/d, could be titrated to 10 mg/d to reach target BP 135/85 mm Hg Mean daily doses at end of study were 122 mg valsartan and 8 mg amlodipine. If BP target not reached with maximum study drug dose, 2.5 mg/d bendrofluazide could be added. Followup period: median 12 weeks, total 24 weeks Study withdrawals (%): 12.3	Allocation Concealment: Yes Blinding: Patients, investigators Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C9. Overview of ARB monotherapy trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Lewis, 2001[40] IDNT Location USA Funding Source Industry	Inclusion Criteria: Age 30 – 70 yrs, type 2 DM, HTN (SBP >135 or DBP >85 mm Hg, or treatment with antihypertensive agents), proteinuria (urinary protein excretion ≥900 mg per 24 hours), serum creatinine 1.0 - 3.0 mg/dL in women and 1.2 - 3.0 mg/dL in men Exclusion Criteria: NR	N=1,146 Age (yr): 59 Gender (Male %): 64.3 Race/Ethnicity (%): White 72.1 Hispanic 5.0 Black 13.0 Asian 5.1 Other 4.7 BMI: 30.9 Systolic BP (mm Hg): 160 Diastolic BP (mm Hg): 87 Albuminuria: NR Median Urine Protein Excretion: 2.9 g/24hr Median Urine Albumin Excretion: 1.9 g/24hr Serum creatinine (mg/dL): 1.66 Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100% History of HTN (%): 100% History of CAD (%): 28.7 with history of "cardiovascular disease" History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	n=579 Irbesartan 300 mg daily n= 567 Amlodipine 10mg daily Additional antihypertensives (excluding ACEI, ARB or CCB) allowed to maintain SBP <135mmHg (or 10mmHg less than baseline if SBP >145) and DBP <85. Followup period: 2.6 years Study withdrawals (%): 0.6	Allocation Concealment : Yes Blinding: Patients, investigators, assessors Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Adequate

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ALT = alanine aminotransferase; ARB = angiotensin II receptor blocker; AST = aspartate aminotransferase; BB = bete blocker; BMI = body mass index; BP = blood pressure; DBP=diastolic blood pressure; CABG= coronary artery bypass grafting; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP=diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PTCA= percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP=systolic blood pressure; TIA = transient ischemic attack; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin

Appendix Table C10. Summary of study baseline characteristics for ARB monotherapy trials

Characteristic	Mean (Range) *(unless otherwise noted)*	Number of Trials Reporting
ARB versus placebo trials		*5*
Patients randomized, n	5769 (527-1513)	5
Age of subjects, years	62.7 (58-68.7)	5
Male gender, %	60 (51-69)	4
White race/ethnicity, %	64 (49-97)	4
Body Mass Index	29 (28-31)	4
Patients with diabetic nephropathy, n	3,778 (527-1,513)	4
Serum creatinine, mg/dL	1.5 (1.2-1.9)	4
Estimated GFR, TRANSCEND, GFR <60 ml/min/1.73m^2	50.1	1
Estimated GFR, TRANSCEND, GFR ≥60 and microalbuminuria	79.7	
Estimated GFR, TRANSCEND, GFR ≥60 and macroalbuminuria	78.8	
ACR, TRANSCEND, GFR <60 ml/min/1.73m^2	4.4	
ACR, TRANSCEND, GFR ≥60 and microalbuminuria	6.8	
ACR, TRANSCEND, GFR ≥60 and macroalbuminuria	52.1	
Albuminuria, μg/min	55.5	*1
Systolic blood pressure, mm Hg	149 (137-159)	5
Diastolic blood pressure, mm Hg	83 (77-90)	5
History of Hypertension, %	91 (81-100)	4
History of Diabetes, %	80 (41-100)	5
History of Cardiovascular disease, %	28	1
History of CAD, %	57 (5-73)	2
History of MI, %	26 (3-45)	3
Patients randomized to Irbesartan versus placebo, n	1,738 (590-1,148)	2
Patients randomized to Losartan versus placebo, n	1,513	1
Patients randomized to Telmisartan versus placebo, n	2526 (527-1991)	2
ARB versus CCB trials		3
Patients randomized, n	3,924 (58-2,720)	3
Age of subjects, years	63.2 (59 - 65)	3
Male gender, %	55.4 (46.6-64.3)	3
Race/ethnicity, white, %	72.1	1
Body Mass Index	26.4 (23.6-30.9)	3
Patients with diabetic nephropathy, n	†1,204 (58-1,146)	2
Serum creatinine, mg/dL	1.6 (0.74-1.66)	2
Estimated GFR, ml/min/1.73m^2	Not reported	0
Systolic blood pressure, mm Hg	162 (152-163)	3
Diastolic blood pressure, mm Hg	90 (87-91)	3
History of HTN, %	100 (100-100)	3
History of Cardiovascular disease, %	28.7	1
History of CAD, %	Not reported	0
Patients with history of MI, %	4.8	1
Patients randomized to Candesartan versus CCB, n	2,778 (58-2,720)	2
Patients randomized to Irbesartan versus CCB, n	1146	1
Patients randomized to Amlodipine versus ARB, n	3,866 (1,146-2,720)	2
Patients randomized to Nifedipine versus ARB, n	58	1

ACR = urinary albumin-to-creatinine ratio, ARB = angiotensin receptor blocker, GFR = glomerular filtration rate, CAD = coronary artery disease, MI = myocardial infarction, CCB = calcium channel blocker

*All 4 trials that compared ARB versus placebo required that participants have albuminuria or proteinuria at baseline for entry, but all reported this measure differently, as albumin-to-creatinine ratio100-300 mg/g (no baseline mean or median reported), urinary albumin/creatinine ratio (UACR) ≥300 mg/g or urinary protein excretion ≥0.5 g/day (median UACR 1250 mg/g), urinary albumin excretion rate (UAER) 20 to 200 μg/min (mean UAER 55.5 μg/min), and urinary protein excretion ≥900 mg per 24 hours (median urinary albumin excretion 1.9gm/24 hrs), respectively.

†One additional study included 2,720 participants with diabetes and CKD, defined by either impaired GFR or proteinuria, but did not specify how many participants had proteinuria. These study subjects were not counted toward the total number of patients with diabetic nephropathy.

Appendix Table C11. Clinical outcomes (outcomes part A), ARB monotherapy trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke or CVA, Any, n/N (%)	
	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control
ARB versus placebo trials (n=5)												
Tobe, 2011[35] TRANSCEND	184/992* (18.5)	166/999* (16.6)	114/992* (11.5)	112/999* (11.2)								
Makino, 2007[37]												
Brenner, 2001[38] RENAAL	158/751 (21.0)	155/762 (20.3)			50/751 (6.7)	68/762 (8.9)						
Parving, 2001[39] IRMA-2	IRB 150mg 0/195 IRB 300mg 3/194 (1.5)	1/201 (0.5)										
Lewis, 2001[40] IDNT	87/579 (15.0)	93/569 (16.3)										
ARB versus CCB trials (n=3)												
Saruta, 2009[41] CASE-J	**NR	**NR	*NR	*NR			*NR	*NR			44/1376 (3.1)	40/1344 (3.0)
Ogawa, 2007[42]	0/40	0/18	0/40	0/18			0/40	0/18				
Lewis, 2001[40] IDNT	87/579 (15.0)	83/567 (14.6)										

ARB = angiotensin receptor blocker; IRB = irbesartan; CCB = calcium channel blocker

*Includes all subjects with a GFR <60 ml/min/1.73m^2 *and* subjects with a GFR ≥60 ml/min/1.73m^2 and micro or macroalbuminuria. **Study did not report results for all cause mortality, but reported incidence of "sudden deaths" as 8/1376 (0.6%) in candesartan (ARB) group vs. 12/1344 (0.9%) in amlodipine (CCB) group, p=0.34.

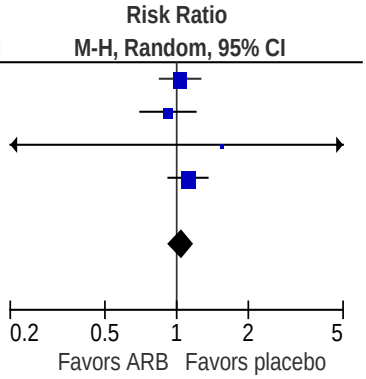
Appendix Figure C2. Forest plots for ARB monotherapy trials

ARB VERSUS PLACEBO

All-cause mortality

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) 2001	158	751	155	762	38.2%	1.03 [0.85, 1.26]
Lewis (IDNT) 2001	87	579	93	569	20.6%	0.92 [0.70, 1.20]
Parving (IRMA-2) 2001	3	389	1	201	0.3%	1.55 [0.16, 14.81]
TRANSCEND 2011	184	992	166	999	40.9%	1.12 [0.92, 1.35]
Total (95% CI)		**2711**		**2531**	**100.0%**	**1.04 [0.92, 1.18]**
Total events	432		415			

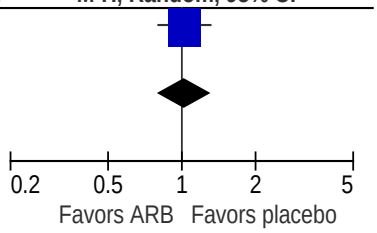
Heterogeneity: Tau² = 0.00; Chi² = 1.46, df = 3 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)



Cardiovascular mortality

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
TRANSCEND 2011	114	992	112	999	100.0%	1.03 [0.80, 1.31]
Total (95% CI)		**992**		**999**	**100.0%**	**1.03 [0.80, 1.31]**
Total events	114		112			

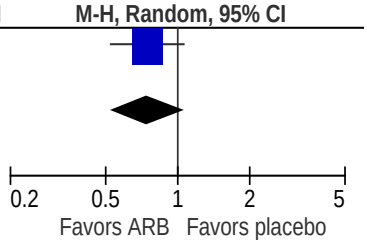
Heterogeneity: Not applicable
Test for overall effect: Z = 0.20 (P = 0.84)



MI, any

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) 2001	50	751	68	762	100.0%	0.75 [0.53, 1.06]
Total (95% CI)		**751**		**762**	**100.0%**	**0.75 [0.53, 1.06]**
Total events	50		68			

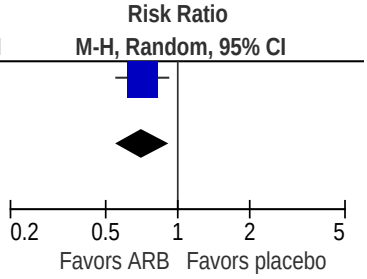
Heterogeneity: Not applicable
Test for overall effect: Z = 1.64 (P = 0.10)



Congestive heart failure hospitalization

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) 2001	89	751	127	762	100.0%	0.71 [0.55, 0.91]
Total (95% CI)		**751**		**762**	**100.0%**	**0.71 [0.55, 0.91]**
Total events	89		127			

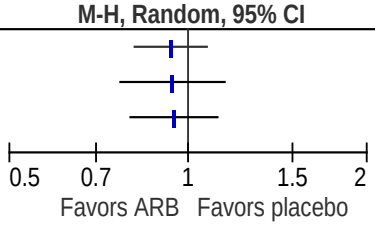
Heterogeneity: Not applicable
Test for overall effect: Z = 2.66 (P = 0.008)



Appendix Figure C2. Forest plots for ARB monotherapy trials (continued)

Composite vascular outcome (see Table C13 for definition)

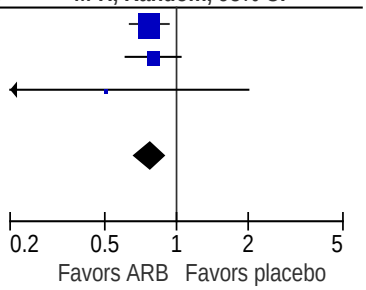
Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) 2001	247	751	268	762	0.94 [0.81, 1.08]
Lewis (IDNT) 2001	138	579	144	569	0.94 [0.77, 1.15]
TRANSCEND 2011	205	992	218	999	0.95 [0.80, 1.12]



End-stage renal disease

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) 2001	147	751	194	762	65.8%	0.77 [0.64, 0.93]
Lewis (IDNT) 2001	82	579	101	569	32.9%	0.80 [0.61, 1.04]
TRANSCEND 2011	3	992	6	999	1.2%	0.50 [0.13, 2.01]
Total (95% CI)		**2322**		**2330**	**100.0%**	**0.77 [0.66, 0.90]**
Total events	232		301			

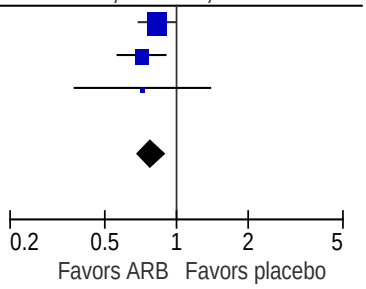
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)



Doubling of serum creatinine

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) 2001	162	751	198	762	59.4%	0.83 [0.69, 1.00]
Lewis (IDNT) 2001	98	579	135	569	36.1%	0.71 [0.57, 0.90]
TRANSCEND 2011	15	992	21	999	4.5%	0.72 [0.37, 1.39]
Total (95% CI)		**2322**		**2330**	**100.0%**	**0.78 [0.68, 0.90]**
Total events	275		354			

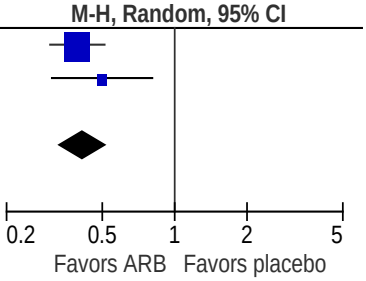
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 2 (P = 0.58); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)



Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Makino 2007	67	340	87	174	77.3%	0.39 [0.30, 0.51]
Parving (IRMA-2) 2001	29	389	30	201	22.7%	0.50 [0.31, 0.81]
Total (95% CI)		**729**		**375**	**100.0%**	**0.42 [0.33, 0.52]**
Total events	96		117			

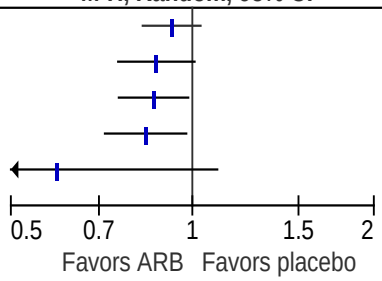
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 7.49 (P < 0.00001)



Appendix Figure C2. Forest plots for ARB monotherapy trials (continued)

Composite renal outcome (see Table C15 for definitions)

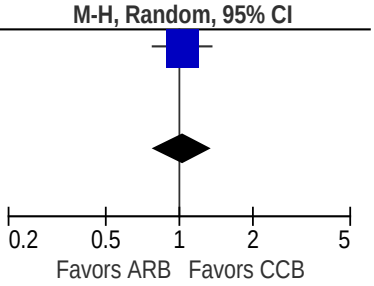
Study or Subgroup	ARB Events	ARB Total	Placebo Events	Placebo Total	Risk Ratio M-H, Random, 95% CI
Brenner (RENAAL) A	327	751	359	762	0.92 [0.83, 1.03]
Brenner (RENAAL) B	226	751	263	762	0.87 [0.75, 1.01]
Brenner (RENAAL) C	255	751	300	762	0.86 [0.75, 0.99]
Lewis (IDNT) 2001	189	579	222	569	0.84 [0.72, 0.98]
TRANSCEND 2011	16	992	27	999	0.60 [0.32, 1.10]



ARB VERSUS CCB

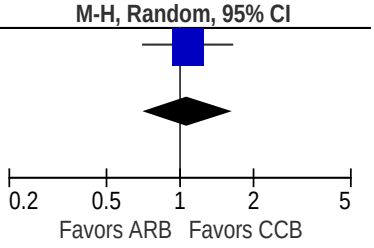
All-cause mortality

Study or Subgroup	ARB Events	ARB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	87	579	83	567	100.0%	1.03 [0.78, 1.35]
Ogawa 2007	0	40	0	18		Not estimable
Total (95% CI)		**619**		**585**	**100.0%**	**1.03 [0.78, 1.35]**
Total events	87		83			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.85)						



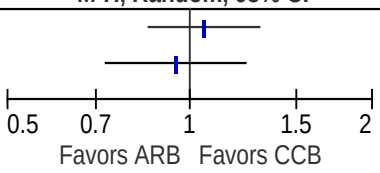
Stroke

Study or Subgroup	ARB Events	ARB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Saruta (CASE-J) 2009	44	1376	40	1344	100.0%	1.07 [0.70, 1.64]
Total (95% CI)		**1376**		**1344**	**100.0%**	**1.07 [0.70, 1.64]**
Total events	44		40			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						



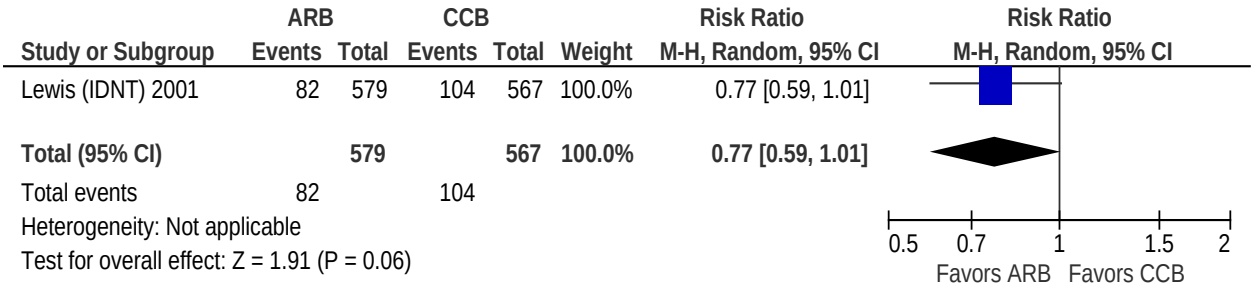
Composite vascular outcome (see Table C13 for definitions)

Study or Subgroup	ARB Events	ARB Total	CCB Events	CCB Total	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	138	579	128	567	1.06 [0.86, 1.30]
Saruta (CASE-J) 2009	99	1376	102	1344	0.95 [0.73, 1.24]

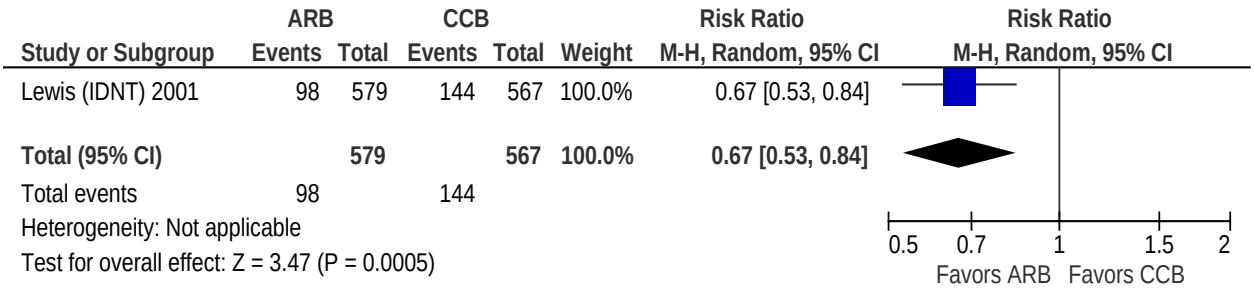


Appendix Figure C2. Forest plots for ARB monotherapy trials (continued)

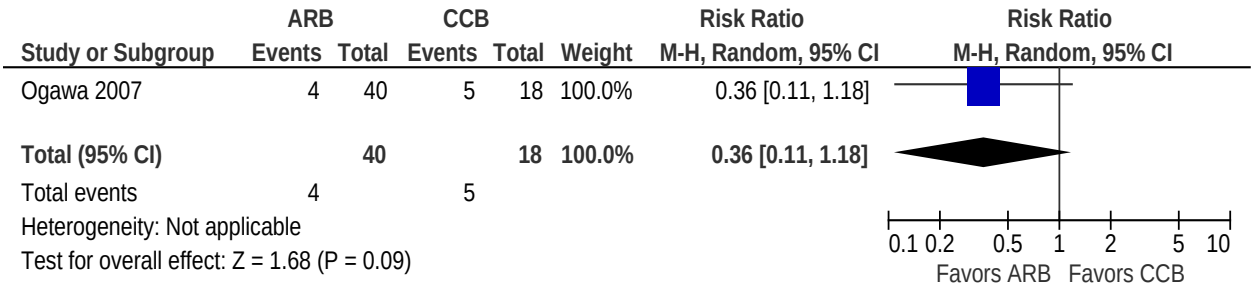
End-stage renal disease



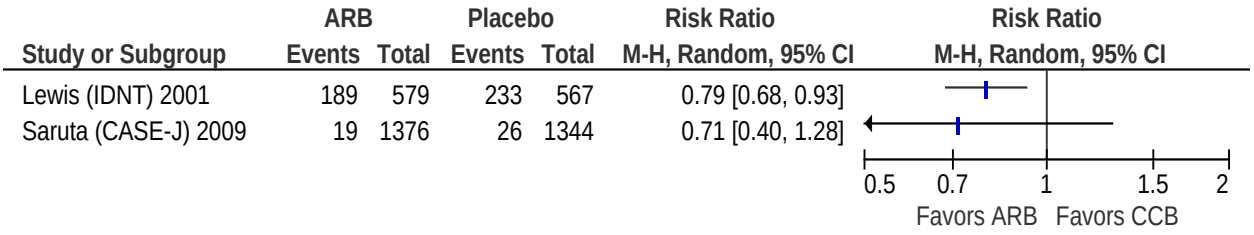
Doubling of serum creatinine



Progression from microalbuminuria to macroalbuminuria



Composite renal outcome (see Table C15 for definition)



Appendix Table C12. Clinical outcomes (outcomes part B), ARB monotherapy trials

Study	Stroke or CVA, Nonfatal n/N (%)		Stroke or CVA, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome n/N (%)**	
	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control
ARB versus placebo trials (n=5)										
Tobe, 2011[35] TRANSCEND									205/992 (20.7)	218/999 (21.8)
Makino, 2007[37]										
Brenner, 2001[38] RENAAL							(A): 89/751 (11.9)*	(A): 127/762 (16.7)	247/751 (32.9)	268/762 (35.2)
Parving, 2001[39] IRMA-2									#	#
Lewis, 2001[40] IDNT							§(A): NR	§(A): NR	138/579 (23.8)	144/569 (25.3)
ARB versus CCB trials (n=3)										
Saruta, 2009[41] CASE-J									†99/1376 (7.2)	†102/1344 (7.6)
Ogawa, 2007[42]			0/40	0/18			(B): 0/40	(B): 0/18		
Lewis, 2001[40] IDNT									138/579 (23.8)	128/567 (22.6)

ARB = angiotensin receptor blocker; CCB = calcium channel blocker; NR = not reported

* $P < 0.05$ versus control

**See Composite vascular outcome definitions table

† In addition to defined composite cardiovascular events presented in this table, study also reported results for undefined, but apparently composite "cerebrovascular events" and "cardiac events." "Cerebrovascular events" occurred in 44/1376 (3.1%) in candesartan (ARB) group vs. 40/1344 (3.0%) in amlodipine (CCB) group, p=0.73, while "cardiac events" occurred in 30/1376 (2.2%) in candesartan (ARB) group vs. 32/1344 (2.4%) in amlodipine (CCB) group, p=0.71.

§ Study did not report proportion of participants with hospitalization due to CHF, but stated that "patients assigned to receive irbesartan (ARB) had a rate of congestive heart failure necessitating hospitalization that was 23 percent lower than that among the patients assigned to receive placebo."

Study reported that nonfatal cardiovascular events (undefined) occurred in 8.7% of patients in the placebo group vs. 4.5% of those in the irbesartan (ARB) 300 mg/daily group, p=0.11, but the proportion of subjects in each group with these events was not reported and was not possible to calculate.

Appendix Table C13. Composite vascular outcome definitions for ARB monotherapy trials

Study	Definition
ARB versus placebo/no treatment trials	
Tobe, 2011[35] TRANSCEND	Cardiovascular death, MI, fatal or nonfatal stroke, or hospitalization for heart failure.
Brenner, 2001[38] RENAAL	MI, stroke, first hospitalization from heart failure or unstable angina, coronary or peripheral revascularization, or death from cardiovascular causes.
Lewis, 2001[40] IDNT	Death from cardiovascular causes, nonfatal MI, heart failure resulting in hospitalization, stroke resulting in permanent neurological defect, lower limb AKA.
ARB versus CCB trials	
Saruta, 2009[41] CASE-J	First cardiovascular event defined as any of the following: sudden death (unexpected death within 24 h without external cause); cerebrovascular event (stroke or transient ischemic attack); cardiac event (heart failure, angina pectoris, or acute myocardial infarction); renal event (included serum creatinine concentration of 4.0 mg/dl or higher, doubling of serum creatinine concentration, or end-stage renal disease); and/or vascular event (dissecting aortic aneurysm or arteriosclerotic occlusion of a peripheral artery).
Lewis, 2001[40] IDNT	Death from cardiovascular causes, nonfatal MI, heart failure resulting in hospitalization, stroke resulting in permanent neurological defect, or lower limb AKA

Abbreviations: ARB = angiotensin receptor blocker; MI = myocardial infarction; AKA = above the knee amputation

Appendix Table C14. Clinical renal outcomes (outcomes part C), ARB monotherapy trials

Study	End Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)**	
	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control
ARB versus placebo trials (n=5)										
Tobe, 2011[35] TRANSCEND	3/992 (0.3) *Chronic dialysis*	6/999 (0.6) *Chronic dialysis*	15/992 (1.5)	21/999 (2.1)					16/992 (1.6)	27/999 (2.7)
Makino, 2007[37]							<u>TEL 80 mg</u> 28/168 (16.7)* <u>TEL 40 mg</u> 39/172 (22.6)*	87/174 (49.9)		
Brenner, 2001[38] RENAAL	147/751 (19.6)*	194/762 (25.5)	162/751 (21.6)*	198/762 (26.0)					(1)327/751 (43.5)*; (2)226/751 (30.1)*; (3)255/751 (34.0)*	(1)359/762 (47.1); (2)263/762 (34.5); (3)300/762 (39.4)
Parving, 2001[39] IRMA-2							<u>IRB 150 mg</u> 19/195 (9.7) <u>IRB 300 mg</u> 10/194 (5.2)*	30/201 (14.9)		
Lewis, 2001[40] IDNT	82/579 (14.2)	101/569 (17.8)	98/579 (16.9)*	135/569 (23.7)					189/579 (32.6)*	222/569 (39.0)
ARB versus CCB trials (n=4)										
Saruta, 2009[41] CASE-J									‡19/1376 (1.4)	‡26/1244 (1.9)
Ogawa, 2007[42]							4/40 (10.0)	5/18 (27.8)		
Lewis, 2001[40] IDNT	82/579 (14.2)	104/567 (18.3)	98/579 (16.9)*	144/567 (25.4)					189/579 (32.6)*	233/567 (41.1)

ARB = angiotensin receptor blocker; TEL = telmisartan; IRB = irbesartan; CCB = calcium channel blocker; GFR = glomerular filtration rate.
*P < 0.05 versus control
**See Composite renal outcome definitions table
‡ Composite renal events reported overall, as above, and stratified by baseline CKD stage: Stage 1+2 = 2/152 (1.2%) candesartan group vs. 3/158 (1.9%) amlodipine group (p=0.58); Stage 3 = 14/1140 (1.2%) candesartan group vs. 9/1125 (0.8%) amlodipine group (p=0.32), and Stage 4 = 3/64 (4.7%) candesartan group vs. 14/61 (23.0%) amlodipine group (p=0.008).

Appendix Table C15. Composite renal outcome definitions for ARB monotherapy trials

Study	Definition
ARB versus placebo/no treatment trials	
Tobe, 2011[35] TRANSCEND	Doubling of baseline serum creatinine or chronic dialysis.
Brenner, 2001[38] RENAAL	Study defined multiple composite renal endpoints, including: (1) doubling of the serum creatinine concentration, end-stage renal disease, or death; (2) doubling of serum creatinine concentration or end-stage renal disease; and (3) end-stage renal disease or death.
Parving, 2001[39] IRMA-2	Time to first detection of overt nephropathy (overnight urinary albumin excretion rate greater than 200 µg per minute and at least 30 percent higher than baseline rate on at least two consecutive visits).
Lewis, 2001[40] IDNT	Doubling of baseline serum creatinine, incident ESRD (hemodialysis, renal transplant, serum creatinine concentration at least 6.0mg/dl), or death from any cause.
ARB versus CCB trials	
Saruta 2009[41] CASE-J	Serum creatinine concentration of 4.0 mg/dl or higher, doubling of the serum creatinine concentration or end-stage renal disease.
Lewis 2001[40] IDNT	Doubling of baseline serum creatinine, incident ESRD (hemodialysis, renal transplant, serum creatinine concentration at least 6.0mg/dl, or death from any cause.

ARB = angiotensin receptor blocker; ESRD = end stage renal disease; CCB = calcium channel blocker

Appendix Table C16. Study withdrawals and adverse events (outcomes part D), ARB monotherapy trials

Study	Study Withdrawals: Any		Serious Adverse Event: Any		Serious Adverse Event: Any Leading to Withdrawal		Adverse Event: Any		Adverse Event: Cough		Adverse Event: Hyperkalemia		Renal Adverse Events*	
	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control	ARB	Control
ARB versus placebo/no treatment trials														
Tobe, 2011[35] TRANSCEND	236/992 (23.8)	249/999 (24.9)							5/992 (0.5)	1/999 (0.1)	*>5.5 mmol/L* 56/992 (5.6)	*>5.5 mmol/L* 25/999 (2.5)	*Acute dialysis* 1/992 (0.1)	*Acute dialysis* 3/999 (0.3)
Makino, 2007[37]	#NR	#NR					NR*	NR*						
Brenner, 2001[38] RENAAL	59/751 (7.9)	59/762 (7.8)									8/751 (1.1)	4/762 (0.5)	11/751 (1.5)	9/762 (1.2)
Parving, 2001[39] IRMA-2	IRB 150mg 27/195 (13.8) IRB 300mg 20/194 (10.3)	30/201 (14.9)	§ 60/389 (15.4)	46/201 (22.9)	IRB 150mg 18/195 (9.2) IRB 300mg 8/194 (4.1)	17/201 (8.5)								
Lewis, 2001[40] IDNT	5/579 (0.9)	4/569 (0.7)	NR‡	NR‡			NR**	NR**			11/579 (1.9)†	2/569 (0.4)	NR††	NR††
ARB versus CCB trials														
Saruta, 2009[41] CASE-J														
Ogawa, 2007[42]	0/40	2/18 (11.1)			0/40	0/18								
Lewis, 2001[40] IDNT	5/579 (0.9)	2/567 (0.4)	NR‡	NR‡			NR**	NR**			11/579 (1.9)†	3/567 (0.5)	NR††	NR††

ARB = angiotensin receptor blocker; CCB = calcium channel blocker; NR = not reported

* Study reported that "one or more adverse event was recorded in >90% of patients in each treatment group;" no additional adverse events information was provided, including on specific types of adverse events.

† $p < 0.05$

‡ 61% of overall cohort had serious adverse event; results were not provided by treatment group, but were reported to not differ significantly between treatment groups.

§ Study reported serious adverse events for the two ARB treatment dose groups combined only.

#Study reported that 13 of 527 (2.4%) randomized participants were excluded from analyses** Results were not reported for the proportion of study participants with any adverse event, either overall or within groups; subjects in the irbesartan group had a significantly lower rate of adverse events per 1000 days of treatment than those in the placebo and amlodipine groups (P=0.002).

†† Study reported one episode of an early increase in serum creatinine concentration suggestive of renal artery stenosis that necessitated stopping the study medication, but did not indicate in which treatment group this adverse event occurred.

Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ONTARGET A *Dual vs monotherapy (ACEI or ARB)*Tobe 2011[35] Multinational Funding Source: Industry	Inclusion Criteria: aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage. Exclusion Criteria: major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration above 265 µmol/L, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic).	23,422 total were randomized, 5623 had a GFR <60 ml/min/1.73m^2 and an additional 3310 had micro (2631) or macroalbuminuria (679) with a GFR ≥60 ml/min/ 1.73m^2 (n=8933). *Demographic data for the 8933 unless noted*. N=8933 Age (yr): 68.2 Gender (Male %): 68 Race/Ethnicity (%): European 70, Asian 16 BMI: 28 Systolic BP (mm Hg): 144 Diastolic BP (mm Hg): 82 Albuminuria-to-creatinine ratio (ACR): 14.6 (12.2 with GFR <60; 6.7 with micro and GFR ≥60; 65.5 with macro and GFR ≥60) Serum creatinine (mg/dL): 1.2 (1.4 GFR <60; 0.96 with micro and GFR ≥60; 0.98 with macro and GFR ≥60) Estimated GFR (ml/min/1.73m^2): 61.8 (50.2 with a GFR <60; 81.7 with micro and GFR ≥60; 81.3 with macro and GFR ≥60) Total cholesterol (mg/dL): 192 LDL cholesterol (mg/dL): 115 Diabetes (%): 49 History of HTN (%): 77 History of CAD (%): 70 History of CHF (%): NR History of MI (%): 45 History of Stroke (%): 20 Peripheral arterial disease (%): 17 Current smoker (%): 12	Ramipril 10 mg/d + telmisartan 80 mg/d (n=2943) Ramipril 10 mg/d or telmisartan 80 mg/d (n=5990) Followup period: median 4.7 years (followup is for the entire cohort) Study withdrawals (%): 29 (2591/8933)	Allocation Concealment: adequate Blinding: double, endpoints adjudication committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes Note: Post-hoc analysis

Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ONTARGET B *Dual vs ACEI* Mann, 2008[18] ONTARGET Multinational Funding Source: Industry	Inclusion Criteria: aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage. Exclusion Criteria: major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration above 265 µmol/L, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic).	This was a 3-arm trial of 25,620 subjects; number with CKD is not specified Estimated GFR (ml/min/1.73m2) 51.0* Urine albumin creatinine ratio (mg/mmol): 0.81* *Patient characteristics not described for the different arms or for CKD subgroup	Ramipril 10 mg/d + telmisartan 80 mg/d (n=8502 overall) Ramipril 10 mg/d (n=8576 overall) Followup period: median 4.7 years (Followup is for the entire cohort) Study withdrawals (%): NR	Allocation Concealment: adequate Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes
Sengul, 2006[20] Turkey Funding Source: none stated	Inclusion Criteria: microalbuminuria (AER rate 30 to 300 mg/24 hours for a minimum of three consecutive occasions); aged 40 to 65 years; previously diagnosed hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), despite receiving ACEI monotherapy for ≥6 months. Exclusion Criteria: type 1 DM; BMI ≥ 40; secondary diabetes; alcoholism; thyroid disease; systolic BP >200 mm Hg, any nondiabetic cause of secondary HTN (including bilateral renal artery stenosis); urinary tract infection; persistent hematuria; chronic liver disease; overt carcinoma; any cardiovascular event in the previous 6 months; serum creatinine ≥150 mmol/L; serum potassium ≥5.5 mmol/L; or pregnancy.	N=219 Age (yr): 57 Gender (Male %): 37 Race/Ethnicity (%): NR BMI: 30 Systolic BP (mm Hg): 151 Diastolic BP (mm Hg): 89 Urinary AER (mg/24 h): 260 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 97 Total cholesterol (mg/dL): 211 LDL cholesterol (mg/dL): 135 HbA_{1c} (%): 7.9 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 37	Lisinopril 20 mg/d (n=110) Telmisartan 80 mg/d (n=109) After 24 weeks, half of the patients receiving lisinopril were randomized to receive telmisartan in addition. Similarly, half the patients initially treated with telmisartan received a combination of lisinopril plus telmisartan. Follow up for the combination period was 28 weeks. The remaining patients continued to be treated with monotherapy Followup period: 1 year Study withdrawals (%): 12	Allocation Concealment: unclear Blinding: open-label Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Menne, 2008[19] VALERIA Germany and Hungary Funding Source: Industry	Inclusion Criteria: microalbuminuria (urine albumin creatinine ratio for women ≥3.5 mg/ mmol/L and ≤35.0 mg/mmol and men ≥2.5 mg/ mmol/L and ≤25.0 mg/mmoL); aged 18 to 75 years; essential hypertension [defined as mean sitting diastolic BP ≥85 mmHg and <110 mm Hg]. To fulfill the criteria of microalbuminuria, two of three first morning void urines needed to be positive during the screening phase. Exclusion Criteria: primary kidney disease, renal impairment (creatinine clearance <30ml/min using the Cockroft and Gault formula; serum potassium values >5.5mmol/L; heart failure, significant arrhythmias or bradycardia; relevant valvular disease, type I DM, uncontrolled type II DM with HbA_{1c} >8.0%; history of MI; percutaneous transluminal coronary angioplasty, bypass surgery or stroke within the last 12 months prior to study inclusion; unstable angina pectoris; renal transplantation; severe hepatic disease or hepatic failure; malignant concomitant diseases or history of malignant diseases within the last 5 years; systemic inflammatory diseases; pregnancy or breast feeding; psychiatric disease; either history of alcohol or drug abuse or both.	N=90 (in addition, there was 3rd trial arm of ARB monotherapy with n=43) Age (yr): 58 Gender (Male %): 69 Race/Ethnicity (%): NR BMI: 32 Systolic BP (mm Hg): 153 Diastolic BP (mm Hg): 91 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 112 Urine albumin creatinine ratio (mg/ mmol): 9.4 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR HbA_{1c} (%): NR Diabetes (%): 74 History of HTN (%): 100 History of CAD “Cardiac disorders”(%): 19 History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Lisinopril 40 mg/d + Valsartan 320 mg/d (n=43) Lisinopril 40 mg/d (n=47) Followup period: 30 weeks Study withdrawals (%): 14	Allocation Concealment: adequate Blinding: double plus outcome assessors and data analysts Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Kanno, 2006[44] Japan Funding Source: none stated	Inclusion Criteria: serum creatinine concentration of between 1.2 and 5.0 mg/dl; systolic BP (SBP) of >130 and <180 mmHg; diastolic BP (DBP) >80 and <120mmHg; and a daily urinary protein excretion of >1.0g Exclusion Criteria: secondary hypertension, including patients who were on dialysis therapy or receiving renal transplantation; patients who had chronic renal diseases and were receiving corticosteroid hormone; patients with myocardial infarction or stroke within the previous 6 months or angina pectoris that required treatment with B blockers or calcium channel blocker; and patients with heart failure or left ventricular ejection fraction of 40% or less or with a disorder that in the treating physician's opinion for other types of ARB	N=90 Age (yr): 60.1 Gender (Male %): 40 Race/Ethnicity (%): 100 Japanese BMI: NR Total BP (mm Hg): 137.5 Urinary protein excretion (g/24 h): 1.7 Serum creatinine (mg/dL): 3.01 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR HbA_{1c} (%): NR Diabetes (%): NR History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): 0 History of Stroke (%): 0 Peripheral arterial disease (%): NR Current smoker (%): NR	ACEI + candesartan 2-12 mg/d (n=45) ACEI (n=45) The main ACEI used were benazepril 2.5-10 mg/d or trandolapril 2-4 mg/d Followup period: 3.1 years Study withdrawals (%): 5.6	Allocation Concealment: unclear Blinding: not blinded Intention to Treat Analysis: no Withdrawals/ Dropouts adequately described: yes

Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Mehdi, 2009[45] United States, single-site Funding Source: Government	Inclusion Criteria: Age 20 to 65; type 1 or 2 DM; seated systolic BP<130mmHg; proteinuria (2-24-h UACR≥300 mg/g despite treatment with ACEI or ARB for at least 3 months* Exclusion Criteria: BMI>45kg/m^2; serum creatinine>3.0mg/dl (females) or >4.0 mg/dl (males); known nonddiabetic kidney disease; serum potassium >5.5 mEq/L; hemoglobin A1c>11%; stroke or myocardial infarction within preceding 12 mo; heart failure; known adverse reaction to losartan or spironolactone; anticipated need for dialysis within 12 months *Effort was made to recruit younger patients with type 2 DM as recommended by study sponsor	Baseline characteristics based on 26 in losartan group (excluded 1 patient who withdrew prior to first dose) N=53 Age (yr): 50.8 Gender (Male %): 47 Race/Ethnicity (%): 45% Hispanic, 34% black, 19% non-Hispanic white, 2% Native American Weight (kg): NR BMI: 31.3 Clinic Systolic BP (mm Hg): 134.0 Clinic Diastolic BP (mm Hg): 73.0 CKD stage: NR Serum creatinine (mg/d/l): 1.6 Creatinine clearance (mL/min): 64.5 Albuminuria (µg/min): NR Proteinuria (g/day): NR Albumin/creatinine ratio (mg/g): 907.2 GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.9 Total cholesterol (mg/dl): 193.4 LDL cholesterol (mg/dl): 97.5 Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of MI, CABG, PCTA (%): 9.4 History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Losartan 50 mg/day for 1 week then 100mg/day (n=27)# Placebo (n=27)# Followup period: 48 weeks Study withdrawals (%): 24.1 #All patients were taking lisinopril 80 mg/day	Allocation Concealment: Unclear Blinding: Double blinded Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Table C17. Overview of ACEI plus ARB versus ACEI or ARB trials (n=6 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Anand, 2009[46] United States, Multi-site Funding Source: Industry	Inclusion Criteria: Ages 18 and older; stable symptomatic heart failure (HF); receiving recommended HF therapy; left ventricular ejection fraction <40%; left ventricular internal diameters in diastole adjusted for body surface area ≥2.9 cm/m^2 Exclusion Criteria: Persistent mean standing SBP <90 mm Hg or serum creatinine >2.5 mg/dL NOTE: results presented are from subgroup analysis of patients with CKD	N=2916 Age (yr): 65.9 Gender (Male %): 88 Race/Ethnicity (%): 91% white Weight (kg): NR BMI: 27 Systolic BP (mm Hg):123.8 Diastolic BP (mm Hg): 74.5 CKD stage: NR Serum creatinine (mg/d/l): NR Serum albumin (g/dL): 4.2 Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (g/day): NR Dipstick Proteinuria Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 47.8 HbA_{1c} (%): NR Total cholesterol (mg/dl): NR LDL cholesterol (mg/dl): NR Diabetes (%): 29.1 History of HTN (%): 6.9 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 100 Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Valsartan 40 mg twice per day; dose doubled every 2 weeks to reach target of 160 mg twice per day (n= 1477 with CKD)*# to Placebo (n= 1439 with CKD)# Followup period: 23 months (mean) Study withdrawals (%): 10% discontinued treatment (other withdrawals not reported for subgroup) *provided SBP ≥90 mmHg; no signs or symptoms of hypotension; serum creatinine not >150% of baseline #91% of patients in CKD subgroup were taking an ACEI at randomization	Allocation Concealment: Adequate Blinding: Double blind Intention to Treat Analysis (ITT): Yes for the outcomes we are recording Withdrawals/Dropouts adequately described: Yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C18. Summary of study baseline characteristics for ACEI plus ARB versus ACEI or ARB trials

Characteristic	Mean (Range Unless Otherwise Noted)	Number of Trials Reporting
ACEI plus ARB versus ACEI (n=6)		
Total number of patients evaluated	18962 (53 to 15594*)	6
Age of subjects, years	64.7 (51 to 66)	5
Gender, male (%)	83.4 (37 to 88)	5
Race/ethnicity, white (%)	89.7 (19 to 91)	2
Race/ethnicity, black (%)	34	1
Race/ethnicity, Asian/Pacific Islander (%)	100% (Japanese)	1
Body Mass Index	27.4 (27 to 32)	4
Weight (kg)		
SBP (mmHg)	126.6 (123.8 to 153)	4
DBP (mmHg)	75.9 (73 to 91)	4
Proteinuria or AER (g/day)	0.68 (0.26 to 1.7) #	5
Serum creatinine (mg/dL)	1.46 (1 to 3)	3
Creatinine Clearance (ml/min/1.73m2)	96.0 (64.5 to 112)	3
Estimated GFR (ml/min/1.73m^2)	49.8 (47.8 to 50.7)	2
Total cholesterol (mg/dl)	207.6 (193.4 to 211.0)	2
LDL Cholesterol (mg/dl)	127.7 (97.7 to 135.0)	2
DM (%)	36.2 (29.1 to 100)	4
HbA_{1c} (%)	7.9 (both 7.9)	2
HTN (%)	18.5 (6.9 to 100)	4
CAD (%) *	19	1
CHF (%) *	100	1
MI (%) *	3.5 (0 to 9.4)	2
Stroke **(%) ***	0	1
AKI **(%)**		
PAD **(%)**		
Current Smoker **(%)**	37	1
ACEI plus ARB versus ARB (n=3)		
Total number of patients evaluated	16143 (90 to 15834*)	3
Age of subjects, years	57.3 (57 to 58)	2
Gender, male (%)	46.3 (37 to 69)	2
Race/ethnicity, white (%)		
Race/ethnicity, black (%)		
Body Mass Index	30.6 (30 to 32)	2
Weight (kg)		
SBP (mmHg)	151.6 (151 to 153)	2
DBP (mmHg)	89.6 (89-91)	2
MAP (mmHg)		
Proteinuria or AER (g/day)	0.26 #	2
Serum creatinine (mg/dL)	1	1
Creatinine Clearance (ml/min/1.73m2)	101.4 (97 to 112)	2
Estimated GFR (ml/min/1.73m^2)	50	1
Total cholesterol (mg/dl)	211	1
LDL Cholesterol (mg/dl)	135	1
DM (%)	92.4 (74 to 100)	2
HbA_{1c} (%)	7.9	1
HTN (%)	100 (100 to 100)	2
CAD (%) *		
CHF (%) *		
MI (%) *		
Stroke **(%) ***		
AKI **(%)**		
PAD **(%)**		
Current Smoker **(%)**	37	1

Appendix Table C18. Summary of study baseline characteristics for ACEI plus ARB versus ACEI or ARB trials (continued)

Characteristic	Mean (Range Unless Otherwise Noted)	Number of Trials Reporting
ACEI plus ARB versus ACE or ARB [ONTARGET 2011] (n=1)		
Total number of patients evaluated	8933	1
Age of subjects, years	68.2	1
Gender, male (%)	68	1
Race/ethnicity, white (%)	70	1
Race/ethnicity, Asian (%)	16	1
Body Mass Index	28	1
SBP (mmHg)	144	1
DBP (mmHg)	82	1
Proteinuria or AER (g/day)		
ACR, GFR <60 ml/min/1.73m^2	12.2	1
ACR, GFR ≥60 and microalbuminuria	6.7	1
ACR, GFR ≥60 and macroalbuminuria	65.5	1
Serum creatinine (mg/dL)	1.2	1
Creatinine Clearance (ml/min/1.73m2)		
Estimated GFR, GFR <60 ml/min/1.73m^2	50.2	1
Estimated GFR, GFR ≥60 and microalbuminuria	81.7	1
Estimated GFR, GFR ≥60 and macroalbuminuria	81.3	1
Total cholesterol (mg/dl)	192	1
LDL Cholesterol (mg/dl)	115	1
DM (%)	49	1
HTN (%)	77	1
CAD (%) *	70	1
CHF (%) *		
MI (%) *	45	1
Stroke **(%) ***	20	1
PAD **(%)**	17	1
Current Smoker **(%)**	12	1

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; SBP = systolic blood pressure; DBP = diastolic blood pressure, AER = albumin excretion rate; ACR = urinary albumin-to-creatinine ratio; GFR = glomerular filtration rate; LDL = low density lipoprotein; DM = diabetes mellitus, HTN = hypertension, CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; PAD = peripheral arterial disease

*N for Mann 2008 ONTARGET study based on back calculation of reported progression to macroalbuminuria; # data from one trial not included in calculations as value in mg/mmo

Appendix Table C19. Clinical outcomes (outcomes part A), ACEI plus ARB versus ACEI or ARB trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Non-fatal n/N (%)		Stroke or CVA, Any n/N (%)	
ACEI plus ARB versus ACEI trials (n=5)												
	ACEI+ARB	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**
Sengul, 2006[20]												
Menne, 2008[19] VALERIA	0/43 (0)	1/47 (2.1)										
Mann ,2008[18] ON-TARGET												
Kanno, 2006[44]												
Mehdi, 2009[45]	1/26 (3.8)	0/27 (0.0)										
Anand, 2009[46]	362/1477 (24.5)	341/1439 (23.7)										
ACEI plus ARB versus ARB trials (n=3)												
	ACEI+ARB	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**
Sengul, 2006[20]												
Menne, 2008[19] VALERIA	0/43 (0)	0/43 (0)										
Mann, 2008 [18]ON-TARGET												
ACEI plus ARB versus ACEI or ARB (monotherapy) trials (n=1)												
	ACEI+ARB	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**
Tobe 2011[35]	520/2943	1033/5990	317/2943	654/5990								
Mann, 2008 [18]ON-TARGET	(17.7)	(17.2)	(10.8)	(11.0)								

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CVA = cerebrovascular accident

*reported for the overall participants but not for the CKD subgroup

Appendix Table C20. Clinical outcomes (outcomespart B), ACEI plus ARB versus ACEI or ARB* trials

Study	Stroke or CVA, Nonfatal n/N (%)		Stroke or CVA, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)**	
ACEI plus ARB versus ACEI trials (n=6)										
	ACEI+ARB	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**
Sengul, 2006[20]										
Menne, 2008[19] VALERIA										
Mann, 2008[18] ON TARGET										
Kanno, 2006[44]										
Mehdi, 2009[45]	1/26 (3.8)	1/27 (3.7)			2/26 (7.7)	0/27 (0.0)				
Anand, 2009[46]									499/1477 (33.8)	549/1439 (38.1)
ACEI plus ARB versus ACEI or ARB (monotherapy) trials (n=1)										
	ACEI+ARB	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**
Tobe 2011[35] Mann, 2008[18] ON-TARGET									653/2943 (22.2)	1372/5990 (22.9)

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker

*No ACE+ARB versus ARB studies reported these outcomes

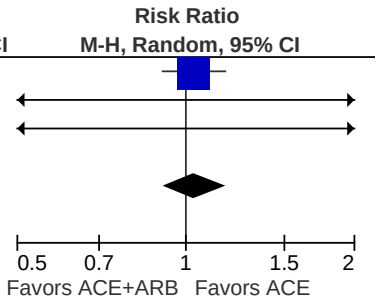
**See Composite vascular outcome definitions table

Appendix Figure C3. Forest plots for ACEI plus ARB versus ACEI trials

All-cause mortality

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2009	362	1477	341	1439	99.7%	1.03 [0.91, 1.18]
Mehdi 2009	1	26	0	27	0.2%	3.11 [0.13, 73.09]
Menne 2008	0	43	1	47	0.2%	0.36 [0.02, 8.70]
Total (95% CI)		**1546**		**1513**	**100.0%**	**1.03 [0.91, 1.18]**
Total events	363		342			

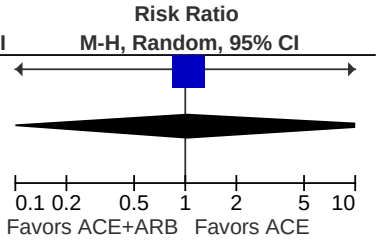
Heterogeneity: Tau² = 0.00; Chi² = 0.88, df = 2 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.52 (P = 0.61)



Stroke, nonfatal

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	1	26	1	27	100.0%	1.04 [0.07, 15.75]
Total (95% CI)		**26**		**27**	**100.0%**	**1.04 [0.07, 15.75]**
Total events	1		1			

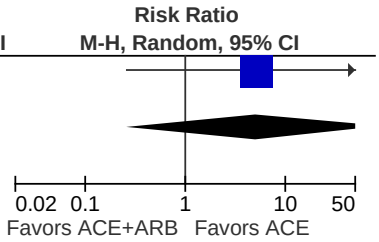
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)



Congestive heart failure, any

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	2	26	0	27	100.0%	5.19 [0.26, 103.11]
Total (95% CI)		**26**		**27**	**100.0%**	**5.19 [0.26, 103.11]**
Total events	2		0			

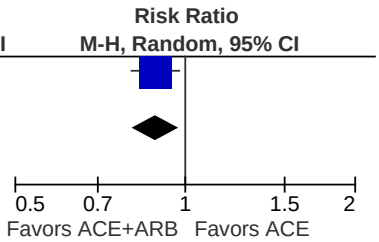
Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)



Composite vascular outcome (See Table C21 for definitions)

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Anand 2009	499	1477	549	1439	100.0%	0.89 [0.80, 0.98]
Total (95% CI)		**1477**		**1439**	**100.0%**	**0.89 [0.80, 0.98]**
Total events	499		549			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.45 (P = 0.01)

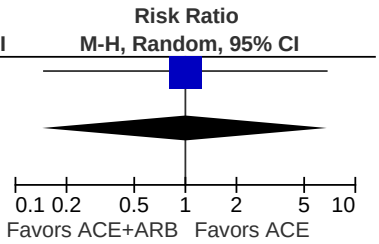


Appendix Figure C3. Forest plots for ACEI plus ARB versus ACEI trials (continued)

End-stage renal disease

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Kanno 2006	2	45	2	45	100.0%	1.00 [0.15, 6.79]
Total (95% CI)		**45**		**45**	**100.0%**	**1.00 [0.15, 6.79]**
Total events	2		2			

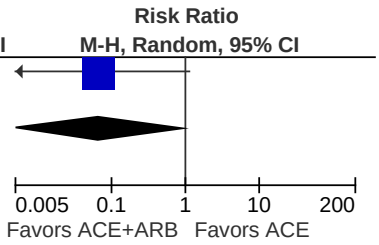
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Doubling of serum creatinine

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Kanno 2006	0	45	7	45	100.0%	0.07 [0.00, 1.13]
Total (95% CI)		**45**		**45**	**100.0%**	**0.07 [0.00, 1.13]**
Total events	0		7			

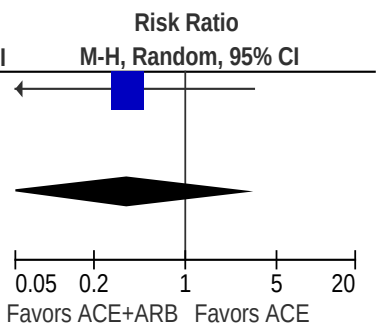
Heterogeneity: Not applicable
Test for overall effect: Z = 1.87 (P = 0.06)



Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Menne 2008	1	43	3	47	100.0%	0.36 [0.04, 3.37]
Sengul 2005	0	96	0	48		Not estimable
Total (95% CI)		**139**		**95**	**100.0%**	**0.36 [0.04, 3.37]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)



Appendix Table C21. Composite vascular outcome definitions for ACEI plus ARB versus ACEI or ARB trials

Study	Definition
Tobe 2011[35] ON-TARGET	Cardiovascular death, MI, fatal or nonfatal stroke, or hospitalization for heart failure.
Anand, 2009[46]	Death, sudden death with resuscitation, hospitalization for heart failure, or administration of intravenous inotropic or vasolilator drugs for 4 hours or more without hospitalization

ACEI = angiotensin converting enzyme; ARB = angiotensin receptor blocker

Appendix Table C22. Clinical renal outcomes (outcomes part C), ACEI plus ARB versus ACEI or ARB trials

Study	End-stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)#	
ACEI plus ARB versus ACEI trials (n=5)										
	ACEI+ARB	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**
Sengul, 2006[20]							0/96 (0)	0/48 (0)		
Menne, 2008[19] VALERIA							1/43 (2.5)	3/47 (6.4)		
Kanno, 2006[44]	2/45 (4.4)	2/45 (4.4)	0/45 (0)	7/45 (15.6)						
Mehdi, 2009[45]			**NR	**NR						
Anand, 2009[46]										
ACEI plus ARB versus ARB trials (n=3)										
			ACEI+ARB	**ARB**			**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**
Sengul, 2006[20]							0/96 (0)	0/48 (0)		
Menne, 2008[19]							1/43 (2.5)	3/43 (7.1)		
ACEI plus ARB versusACEI or ARB trials (monotherapy) (n=1)										
	ACEI+ARB	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**
Tobe 2011[35]	*Chronic*	*Chronic*	86/2943	140/5990					104/2943	173/5990
Mann, 2008[18]	*dialysis*	*dialysis*	(2.9)	(2.3)					(3.5)	(2.9)
ON-TARGET	31/2943 (1.1)	53/5990 (0.9)								

ACEI = angiotensin convertng enzyme; ARB = angiotensin receptor blocker; GFR = glomerular filtration rate

#See composite renal outcome definitions table

*Reported for the overall participants but not for the CKD subgroup

**Reported 50% increase in serum creatinine in 13/26 (50%) of ACEI+ARB group and 10/27 (37%) of ACEI group

†Had microalbuminuria at baseline; N based on back calculation using percentage with progression

Appendix Table C23. Composite renal outcome definitions for ACEI plus ARB versus ACEI or ARB trials

Study	Definition
Tobe 2011[35] ON-TARGET	Chronic dialysis or doubling of serum creatinine

ACEI = angiotensin converting enzyme; ARB = angiotensin receptor blocker

Appendix Table C24. Study withdrawals and adverse events (outcomes part D), ACEI plus ARB versus ACEI or ARB trials

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Serious Adverse Event: Any Leading to Withdrawal, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Any Specific, n/N (%)		Renal Adverse Event: Any, n/N (%)	
ACEI plus ARB versus ACEI trials (n=6)												
	ACEI+ARB	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**	**ACEI+ARB**	**ACEI**
Sengul, 2006[20]	*NR	*NR					**NR	**NR	***NR	***NR		
Menne, 2008[19] VALERIA	6/43 (14.0)	5/47 (10.6)	4/43 (9.3)	5/47 (10.6)	3/43 (7.0)	4/47 (8.5)	31/43 (72.1)	29/47 (69.7)	Hypotension: 5/43 (11.6); Hyperkalemia: 1/43 (2.3); Cough: 2/47 (4.3)§	Hypotension: 1/47 (2.1); Hyperkalemia: 1/47 (2.1); Cough: 1/43 (2.3)§		
Mann, 2008[18] ON-TARGET	#NR	#NR										
Kanno, 2006[44]	2/45 (4.4)	3/45 (6.7)	†NR	†NR	†NR	†NR	†NR	†NR				
Mehdi, 2009[45]	8/27 (29.6)	6/27 (22.2)					2/27 (7.4)	1/27 (3.7)	Heart failure: 2/27 (7.4)	Stroke: 1/27 (3.7)		
Anand, 2009[46]									Hyperkalemia: 126/1477 (8.5)	Hyperkalemia 65/1439 (4.5)		
ACEI plus ARB versus ARB trials (n=3)												
	ACEI+ARB	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**	**ACEI+ARB**	**ARB**
Sengul, 2006[20]	*NR	*NR					**NR	**NR	***NR	***NR		
Menne, 2008[19] VALERIA	6/43 (14.0)	6/43 (14.0)	4/43 (9.3)	1/43 (2.3)	3/43 (7.0)	3/43 (7.0)	31/43 (72.1)	27/43 (62.8)	Hypotension: 5/43 (11.6); Hyperkalemia: 1/43 (2.3); Cough: 2/47 (4.3)§ §	Hypotension: 4/43 (9.3); Hyperkalemia: 1/43 (2.3); Cough: 0/43 (0)§ §		
Mann, 2008[18] ON-TARGET	#NR	#NR										

Appendix Table C24. Study withdrawals and adverse events (outcomes part D), ACEI plus ARB versus ACEI or ARB trials (continued)

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Serious Adverse Event: Any Leading to Withdrawal, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Any Specific, n/N (%)		Renal Adverse Event: Any, n/N (%)	
ACEI plus ARB versus ACEI or ARB (monotherapy) trials (n=1)												
	ACEI+ARB	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**	**ACEI+ARB**	**Mono**
Sengul, 2006[20]	947/2943 (32.2)	1644/5990 (27.4)							Hypotension: 110/2943 (3.7); Cough: 114/2943 (3.9); Syncope: 6/2943 (0.2);	Hypotension: 135/5990 (2.3); Cough: 135/5990 (2.3); Syncope: 5/5990 (0.08);		

ACEI = angiotensin converting enzyme; ARB = angiotensin receptor blocker
*Reported withdrawals for original randomization groups (ACEI: 15/110 [13.6%], ARB: 12/109 [11.0%])
**Adverse events not distinguished from withdrawals
***Reported most frequent adverse events were cough (only in patients receiving lisinopril) and headache, experienced by <10% of patients; other noted side effects were nausea, stomach upset, respiratory infection, dizziness, feeling weak, gastrointestinal problems
§Other reported adverse events: vertigo (2.3% ACEI+ARB, 4.3% ACEI), dizziness (2.3% ACEI+ARB, 2.1% ACEI), headache (0% ACEI+ARB, 2.1% ACEI)
§§Other reported adverse events: vertigo (2.3% ARB), dizziness (2.3% ARB), headache (2.3% ARB)
#Reported follow-up of all but 43/25,620 (0.2%)
^Reported as "renal abnormalities"
†Reported "few" discontinuations as a result of AE and discontinuations as a result of drug-related AE
~reported for the overall participants but not for the CKD subgroup

Appendix Table C25. Overview of ACEI plus ARB versus ARB trials (n=3 trials)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Sengul, 2006[20] Turkey Funding Source: none stated	Inclusion Criteria: microalbuminuria (AER rate 30 to 300 mg/24 hour for a minimum of three consecutive occasions); aged 40 to 65 years; previously diagnosed hypertension (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), despite receiving ACEI monotherapy for ≥6 months. Exclusion Criteria: type 1 DM; BMI ≥40; secondary diabetes; alcoholism; thyroid disease; systolic BP >200 mm Hg, any nondiabetic cause of secondary HTN (including bilateral renal artery stenosis); urinary tract infection; persistent hematuria; chronic liver disease; overt carcinoma; any cardiovascular event in the previous 6 months; serum creatinine ≥ 150 mmol/L; serum potassium ≥ 5.5 mmol/L; or pregnancy.	N=219 Age (yr): 57 Gender (Male %): 37 Race/Ethnicity (%): NR BMI: 30 Systolic BP (mm Hg): 151 Diastolic BP (mm Hg): 89 Urinary AER (mg/24 h): 260 Serum creatinine (mg/dL): 1 Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 97 Total cholesterol (mg/dL): 211 LDL cholesterol (mg/dL): 135 HbA_{1c} (%): 7.9 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 37	Lisinopril 20 mg/d (n=110) Telmisartan 80 mg/d (n=109) After 24 weeks, half of the patients receiving lisinopril were randomized to receive telmisartan in addition. Similarly, half the patients initially treated with telmisartan received a combination of lisinopril plus telmisartan. The remaining patients continued to be treated with monotherapy Followup period: 1 year Study withdrawals (%): 12	Allocation Concealment: unclear Blinding: open-label Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Table C25. Overview of ACEI plus ARB versus ARB trials (n=3 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Menne, 2008[19] VALERIA Germany and Hungary Funding Source: Industry	Inclusion Criteria: microalbuminuria (urine albumin creatinine ratio for women ≥3.5 mg/ mmol/L and ≤35.0 mg/mmol and men ≥2.5 mg/ mmol/L and ≤25.0 mg/mmoL); aged 18 to 75 years; essential hypertension [defined as mean sitting diastolic BP ≥85 mmHg and <110 mm Hg]. To fulfill the criteria of microalbuminuria, two of three first morning void urines needed to be positive during the screening phase. Exclusion Criteria: primary kidney disease, renal impairment (creatinine clearance <30ml/min using the Cockroft and Gault formula; serum potassium values >5.5mmol/L; heart failure, significant arrhythmias or bradycardia; relevant valvular disease, type I DM, uncontrolled type II DM with HbA_{1c} >8.0%; history of MI; percutaneous transluminal coronary angioplasty, bypass surgery or stroke within the last 12 months prior to study inclusion; unstable angina pectoris; renal transplantation; severe hepatic disease or hepatic failure; malignant concomitant diseases or history of malignant diseases within the	N=90 (133 total with combination arm) Age (yr): 58 Gender (Male %): 69 Race/Ethnicity (%): NR BMI: 32 Systolic BP (mm Hg): 153 Diastolic BP (mm Hg): 91 Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Creatinine clearance (mg/min): 112 Urine albumin creatinine ratio (mg/ mmol): 9.4 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR HbA_{1c} (%): NR Diabetes (%): 74 History of HTN (%): 100 History of CAD “Cardiac disorders”(%): 19 History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Lisinopril 40 mg/d + valsartan 320 mg/d (n=43) Valsartan 320 mg/d (n=43) Followup period: 30 weeks Study withdrawals (%): 14	Allocation Concealment: adequate Blinding: double plus outcome assessors and data analysts Intention to Treat Analysis: no Withdrawals/Dropouts adequately described: yes

Appendix Table C25. Overview of ACEI plus ARB versus ARB trials (n=3 trials) (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	last 5 years; systemic inflammatory diseases; pregnancy or breast feeding; psychiatric disease; either history of alcohol or drug abuse or both.			
Mann, 2008[18] ONTARGET Multinational Funding Source: Industry	Inclusion Criteria: aged 55 years or older with established atherosclerotic vascular disease or with diabetes with end-organ damage. Exclusion Criteria: major renal artery stenosis, uncorrected volume or sodium depletion, a serum creatinine concentration above 265 µmol/L, and uncontrolled hypertension (>160 mm Hg systolic or >100 mm Hg diastolic).	This was a 3-arm trial of 25,620 subjects; number with CKD is not specified Estimated GFR (ml/min/1.73m^2): 51.0* Urine albumin creatinine ratio (mg/mmol): 0.81* *Patient characteristics not described for the different arms or for CKD subgroup	Ramipril 10 mg/d + telmisartan 80 mg/d (n= 8502 overall) Telmisartan 80 mg/d (n= 8542 overall) Followup period: median 4.7 years (followup is for the entire cohort) Study withdrawals (%): NR	Allocation Concealment: adequate Blinding: double Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes

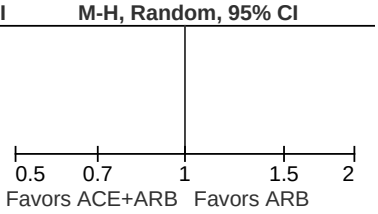
ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Figure C4. Forest plots ACEI plus ARB versus ARB trials

All-cause mortality

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Menne 2008	0	43	0	43		Not estimable
Total (95% CI)		**43**		**43**		**Not estimable**
Total events	0		0			

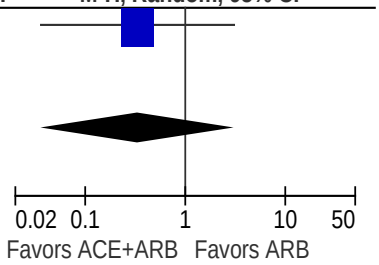
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ARB Events	ARB Total	Weight	Risk Ratio M-H, Random, 95% CI
Menne 2008	1	43	3	43	100.0%	0.33 [0.04, 3.08]
Sengul 2005	0	96	0	48		Not estimable
Total (95% CI)		**139**		**91**	**100.0%**	**0.33 [0.04, 3.08]**
Total events	1		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

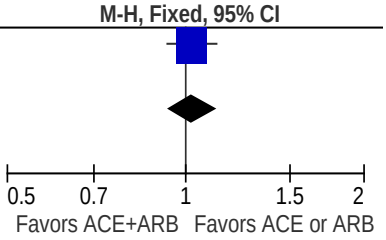


Appendix Figure C5. Forest plots ACEI plus ARB versus ACEI or ARB trial

All-cause mortality

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE or ARB Events	ACE or ARB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tobe (ONTARGET) 2011	520	2943	1033	5990	100.0%	1.02 [0.93, 1.13]
Total (95% CI)		**2943**		**5990**	**100.0%**	**1.02 [0.93, 1.13]**
Total events	520		1033			

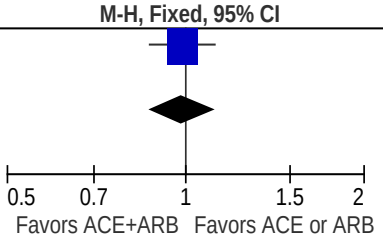
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)



Cardiovascular mortality

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE or ARB Events	ACE or ARB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tobe (ONTARGET) 2011	317	2943	654	5990	100.0%	0.99 [0.87, 1.12]
Total (95% CI)		**2943**		**5990**	**100.0%**	**0.99 [0.87, 1.12]**
Total events	317		654			

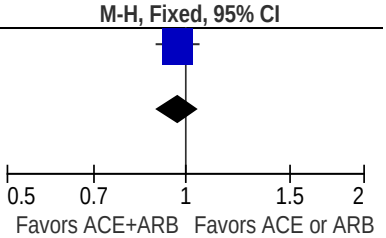
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)



Composite vascular outcome (See Table C21 for definition)

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE or ARB Events	ACE or ARB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tobe (ONTARGET) 2011	653	2943	1372	5990	100.0%	0.97 [0.89, 1.05]
Total (95% CI)		**2943**		**5990**	**100.0%**	**0.97 [0.89, 1.05]**
Total events	653		1372			

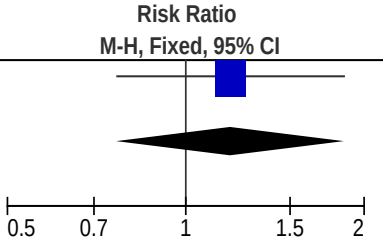
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)



End-stage renal disease (chronic dialysis)

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE or ARB Events	ACE or ARB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tobe (ONTARGET) 2011	31	2943	53	5990	100.0%	1.19 [0.77, 1.85]
Total (95% CI)		**2943**		**5990**	**100.0%**	**1.19 [0.77, 1.85]**
Total events	31		53			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.77 (P = 0.44)



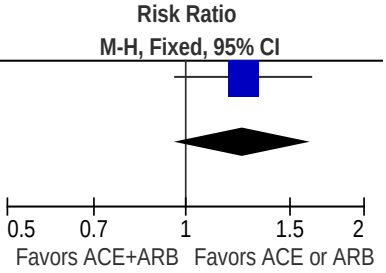
Appendix Figure C5. Forest plots ACEI plus ARB versus ACEI or ARB trial (continued)

Doubling of serum creatinine

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE or ARB Events	ACE or ARB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tobe (ONTARGET) 2011	86	2943	140	5990	100.0%	1.25 [0.96, 1.63]
Total (95% CI)		**2943**		**5990**	**100.0%**	**1.25 [0.96, 1.63]**
Total events	86		140			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.65 (P = 0.10)

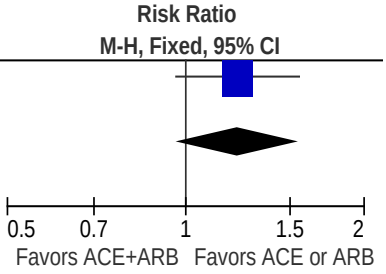


Composite renal outcome (See Table C23 for definition)

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE or ARB Events	ACE or ARB Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Tobe (ONTARGET) 2011	104	2943	173	5990	100.0%	1.22 [0.96, 1.55]
Total (95% CI)		**2943**		**5990**	**100.0%**	**1.22 [0.96, 1.55]**
Total events	104		173			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.65 (P = 0.10)



Appendix Evidence Table C26. Overview of ACEI plus ARB versus ACEI plus aldosterone antagonist trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Mehdi, 2009[45] Location United States, single-site Funding Source Government	Inclusion Criteria: Age 20 to 65; type 1 or 2 DM; seated systolic BP >130mmHg; proteinuria (24-h UACR≥300 mg/g despite treatment with ACEI or ARB for at least 3 months* Exclusion Criteria: BMI >45kg/m^2; serum creatinine >3.0mg/dl (females) or >4.0 mg/dl (males); known nonddiabetic kidney disease; serum potassium >5.5 mEq/L; hemoglobin A1c >11%; stroke or myocardial infarction within preceding 12 months; heart failure; known adverse reaction to losartan or spironolactone; anticipated need for dialysis within 12 months *Effort was made to recruit younger patients with type 2 DM as recommended by study sponsor	Baseline characteristics based on 26 in Losartan group (excluded 1 patient who withdrew prior to first dose) and 27 in spironolactone group N=53 Age (yr): 52 Gender (Male %): 49 Race/Ethnicity (%): 55% Hispanic, 28% black, 15% non-Hispanic white, 2% Native American Weight (kg): NR BMI: 32.0 Clinic Systolic BP (mm Hg): 134.0 Clinic Diastolic BP (mm Hg): 72.5 CKD stage: NR Serum creatinine (mg/dl): 1.75 Creatinine clearance (ml/min): 58.0 Albuminuria (µg/min): NR Proteinuria (g/day): NR Albumin/creatinine ratio (mg/g): 997.4 GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.5 Total cholesterol (mg/dl): 186.8 LDL cholesterol (mg/dl): 87.3 Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%):0 Peripheral arterial disease (%): NR History of MI (%): 0 in past 12 months History of MI, CABG, or PCTA (%): 7.5 History of Stroke (%): 0 in past 12 months Current smoker (%): NR History of AKI (%): NR	n= 27 to Losartan 100mg/day# n= 27 to Spironolactone 25mg/day# Followup period: 48 weeks Study withdrawals (%): 35.2 #All patients were taking Lisinopril 80 mg/day	Allocation Concealment: Unclear Blinding: Double blinded Intention to Treat Analysis (ITT): No (excluded 1 subject who withdrew prior to first losartan dose from analyses) Withdrawals/Dropouts adequately described: Yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CABG= coronary artery bypass grafting; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PTCA= Percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; TIA = transient ischemic attack; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C27. Clinical outcomes (outcomes part A), ACEI plus ARB versus ACEI plus aldosterone antagonist trial

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	ACEI+ ARB	ACEI+ Aldo Antag	ACEI+ ARB	ACEI+ Diuretic	ACEI+ ARB	ACEI+ Diuretic	ACEI+ ARB	ACEI+ Diuretic	ACEI+ ARB	ACEI+ Diuretic	ACEI+ ARB	ACEI+ Diuretic
Mehdi, 2009[45]	1/26 (3.8)	0/27			0/26 (0.0)	1/27 (3.7)					NR*	NR*

ACEI = angiotensin converting enzyme; ARB = angiotensin receptor blocker; Aldo Antag = aldosterone antagonist

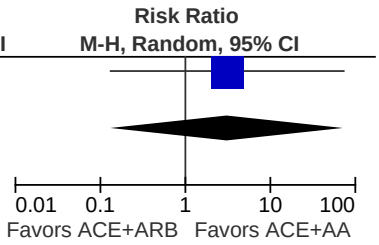
* The study reports both that hospitalizations for stroke occurred in no subjects assigned to ACEI plus ARB and two subjects assigned to ACEI plus diuretic, and that withdrawals for stroke occurred in one subject assigned to ACEI plus ARB and two subjects assigned to ACEI plus diuretic. It is unclear whether one of the reports is in error or whether there is nonoverlap between the strokes leading to hospitalization and those leading to withdrawal.

Appendix Figure C6. Forest plots for ACEI plus ARB versus ACEI plus aldosterone antagonist trial

All-cause mortality

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE+AA Events	ACE+AA Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	1	26	0	27	100.0%	3.11 [0.13, 73.09]
Total (95% CI)		**26**		**27**	**100.0%**	**3.11 [0.13, 73.09]**
Total events	1		0			

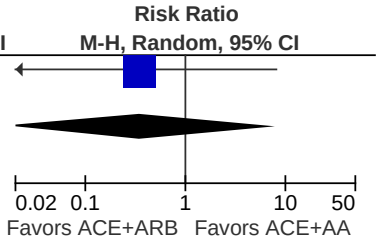
Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.48)



Myocardial infarction, any

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE+AA Events	ACE+AA Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	0	26	1	27	100.0%	0.35 [0.01, 8.12]
Total (95% CI)		**26**		**27**	**100.0%**	**0.35 [0.01, 8.12]**
Total events	0		1			

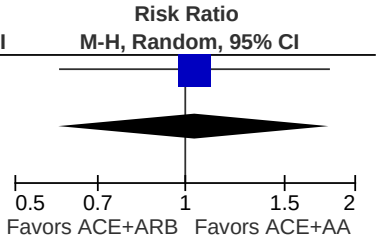
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)



Doubling of serum creatinine

Study or Subgroup	ACE+ARB Events	ACE+ARB Total	ACE+AA Events	ACE+AA Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	13	26	13	27	100.0%	1.04 [0.60, 1.80]
Total (95% CI)		**26**		**27**	**100.0%**	**1.04 [0.60, 1.80]**
Total events	13		13			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)



Appendix Table C28. Clinical renal outcomes (outcomes part C), ACEI plus ARB versus ACEI plus aldosterone antagonist trial

Study	End-Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)	
	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA
Mehdi, 2009[45]			13/26 (50.0)	13/27 (48.0)						

GFR = glomerular filtration rate; ACEI = angiotension converting enzyme; ARB = angiotensin receptor blocker: AA = aldosterone antagonist

Appendix Table C29. Study withdrawals and adverse events (outcomes part D), ACEI plus ARB versus ACEI plus aldosterone antagonist trial

Study	Study Withdrawals, Any, n/N (%)		Serious Adverse Events, Any, n/N (%)		Withdrawals Due to Adverse Events, Any, n/N (%)		Adverse Events, Any, n/N (%)		Adverse Events, Specific, n/N (%)		Renal Adverse Events, Any, n/N (%)	
	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA	ACEI+ ARB	ACEI+ AA
Mehdi, 2009[45]	9/27 (33.3)	10/27 (37.0)			2/26 (7.7)	7/27 (25.9)			0/26 (0.0)	1/27 (3.7)	Recurrent hyperkalemia: 0/26; Withdrawn due to increased SCr: 0/27	Recurrent hyperkalemia: 2/27 (7.4); Withdrawn due to increased SCr: 1/27

ACEI = angiotensin converting enzyme inhibitor; ARB = antiogensin receptor blocker; AA = aldosterone antagonist ; SCr = serum creatinine

Appendix Evidence Table C30. Overview of ACEI plus CCB versus ACEI monotherapy or CCB monotherapy trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Fogari, 2002[24] Italy Multisite Funding Source: none stated	Inclusion: microalbuminuria (UAE ≥30 and ≤300 mg/24 h in two distinct 24-hour urine collections during 7 days before enrollment); essential hypertension (sitting diastolic BP values >90 mmHg and <110 mmHg); type 2 diabetes well controlled by diet or by metformin alone or metformin plus a sulfanylurea; BMI <30 kg/m^2; serum creatinine <1.5 mg/dL. Exclusion Criteria: history of previous coronary heart disease, stroke, CHF, cancer; smoking habits; electrocardiogram showing left ventricular hypertrophy; total cholesterol values >240mg/dL; use of diuretics or beta-blockers.	N=453 randomized Baseline characteristics reported only for N=309 who were judged responders on completion of dose titration phase and did not complain of side effects. N=206 ACE+CCB vs. ACE Age (yr): 62.5 Gender (Male %): 57 Race/Ethnicity (%): NR Weight (kg): NR BMI: 27.6 Systolic BP (mm Hg): 160.3 Diastolic BP (mm Hg): 99.3 CKD stage: NR Serum creatinine (mg/dL): 1.0 Creatinine clearance (mg/min): 89.9 Albuminuria (µg/min): 97.9 Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.1 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): 0 History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): 0 History of Stroke (%): 0 Peripheral arterial disease (%): NR Current smoker (%): NR (excluded for "smoking habits" – not defined) History of AKI (%): NR N=207 ACE+CCB vs. CCB Age (yr): 62.2 Gender (Male %): 55 Race/Ethnicity (%): NR	n= 102 Fosinopril 10-30 mg/day* n=103 Amlodipine 5-15 mg/day* n=104 Amlodipine 5 to 15 mg/day + Fosinopril 10 to 30 mg/day * Followup period: 4 years Study withdrawals (%): 47% (215/453), including 144/453 (32%) in titration period and 71/309 (23%) during study period. *N=453 randomized to 3 month dose titration period with goal of DBP <90 mmHg for monotherapy groups and <85 mmHg for combined therapy group.	Allocation Concealment: Adequate Blinding: Open-label Intention to Treat Analysis: No Withdrawals/Dropouts adequately described: No

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		Weight (kg): NR BMI: 27.8 Systolic BP (mm Hg): 160.8 Diastolic BP (mm Hg): 99.4 CKD stage: NR Serum creatinine (mmol/L): 1.0 Creatinine clearance (mg/min): 89.3 Albuminuria (µg/min): 96.6 Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.0 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): 0 History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): 0 History of Stroke (%): 0 Peripheral arterial disease (%): NR Current smoker (%): NR (excluded for "smoking habits" – not defined) History of AKI (%): NR		

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C31. Clinical outcomes (outcomes part A), ACEI plus CCB versus ACEI monotherapy or CCB monotherapy trial

Study	All-Cause Mortality, n/N (%)			Cardiovascular Mortality, n/N (%)			Myocardial Infarction, Any, n/N (%)			Myocardial Infarction, Fatal, n/N (%)			Myocardial Infarction, Nonfatal, n/N (%)			Stroke, Any, n/N (%)		
	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB
Fogari, 2002[24]	2/104 (1.9)	3/102 (2.9)	4/103 (3.9)	1/104 (1.0)	2/102 (1.9)	2/103 (1.9)	1/104 (1.0)	3/102 (2.9)	4/103 (3.9)	0/104	1/102 (1.0)	2/103 (1.9)	1/104 (1.0)	2/102 (1.9)	2/103 (1.9)	1/104 (1.0)	3/102 (2.9)	2/103 (1.9)

ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker

Appendix Table C32. Clinical outcomes (outcomespart B), ACEI plus CCB versus ACEI monotherapy or CCB monotherapy trial

Study	Stroke, Nonfatal, n/N (%)			Stroke, Fatal, n/N (%)			CHF, Any, n/N (%)			CHF Hospitalization (A) or Death (B), n/N (%)			Composite Vascular Outcome, n/N (%)		
	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB	ACEI+ CCB	ACEI	CCB
Fogari, 2002[24]	1/104 (1.0)	2/102 (1.9)	2/103 (1.9)	0/104	1/102 (1.0)	0/103									

ACEI = angiotensin converting enzyme; CCB = calcium channel blocker; CHF = congestive heart failure

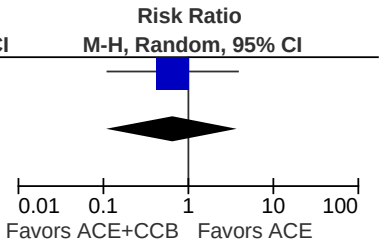
*Other no-fatal cardiovascular events (not defined): ACEI+CCB: 1/104 (1.0%), ACEI: 1/102 (1.0%), CCB: 2/103 (1.9%)

Appendix Figure C7. Forest plots for ACEI plus CCB versus ACE monotherapy trial

All-cause mortality

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	2	104	3	102	100.0%	0.65 [0.11, 3.83]
Total (95% CI)		**104**		**102**	**100.0%**	**0.65 [0.11, 3.83]**
Total events	2		3			

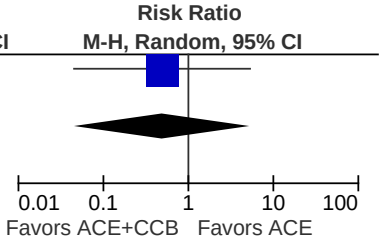
Heterogeneity: Not applicable
Test for overall effect: Z = 0.47 (P = 0.64)



Cardiovascular mortality

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	102	100.0%	0.49 [0.05, 5.32]
Total (95% CI)		**104**		**102**	**100.0%**	**0.49 [0.05, 5.32]**
Total events	1		2			

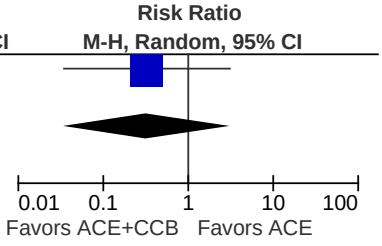
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)



Myocardial infarction, any

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	3	102	100.0%	0.33 [0.03, 3.09]
Total (95% CI)		**104**		**102**	**100.0%**	**0.33 [0.03, 3.09]**
Total events	1		3			

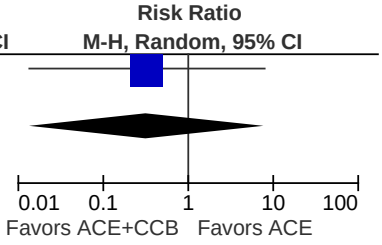
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



Myocardial infarction, fatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	0	104	1	102	100.0%	0.33 [0.01, 7.93]
Total (95% CI)		**104**		**102**	**100.0%**	**0.33 [0.01, 7.93]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

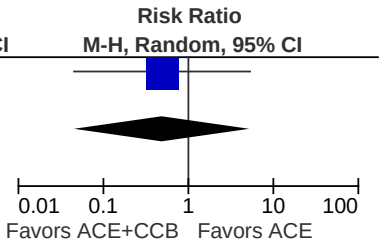


Appendix Figure C7. Forest plots for ACEI plus CCB versus ACE monotherapy trial (continued)

Myocardial infarction, nonfatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	102	100.0%	0.49 [0.05, 5.32]
Total (95% CI)		**104**		**102**	**100.0%**	**0.49 [0.05, 5.32]**
Total events	1		2			

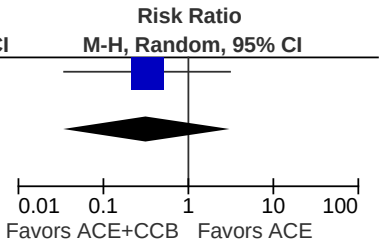
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)



Stroke, any

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	3	102	100.0%	0.33 [0.03, 3.09]
Total (95% CI)		**104**		**102**	**100.0%**	**0.33 [0.03, 3.09]**
Total events	1		3			

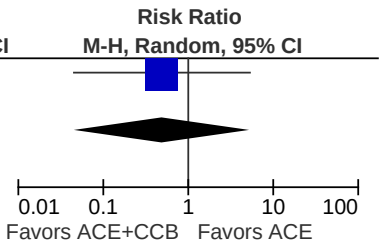
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)



Stroke, nonfatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	102	100.0%	0.49 [0.05, 5.32]
Total (95% CI)		**104**		**102**	**100.0%**	**0.49 [0.05, 5.32]**
Total events	1		2			

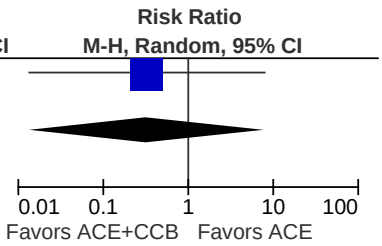
Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.56)



Stroke, fatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	ACE Events	ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	0	104	1	102	100.0%	0.33 [0.01, 7.93]
Total (95% CI)		**104**		**102**	**100.0%**	**0.33 [0.01, 7.93]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

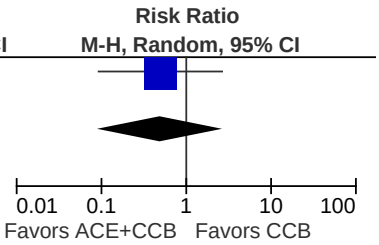


Appendix Figure C8. Forest plots for ACEI plus CCB versus CCB monotherapy trial

All-cause mortality

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	2	104	4	103	100.0%	0.50 [0.09, 2.64]
Total (95% CI)		**104**		**103**	**100.0%**	**0.50 [0.09, 2.64]**
Total events	2		4			

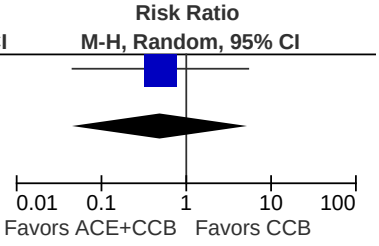
Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



Cardiovascular mortality

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	103	100.0%	0.50 [0.05, 5.38]
Total (95% CI)		**104**		**103**	**100.0%**	**0.50 [0.05, 5.38]**
Total events	1		2			

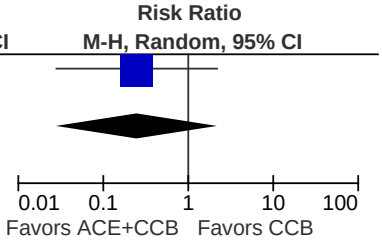
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Myocardial infarction, any

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	4	103	100.0%	0.25 [0.03, 2.18]
Total (95% CI)		**104**		**103**	**100.0%**	**0.25 [0.03, 2.18]**
Total events	1		4			

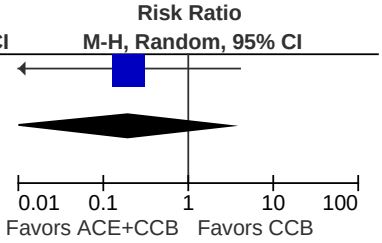
Heterogeneity: Not applicable
Test for overall effect: Z = 1.26 (P = 0.21)



Myocardial infarction, fatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	0	104	2	103	100.0%	0.20 [0.01, 4.08]
Total (95% CI)		**104**		**103**	**100.0%**	**0.20 [0.01, 4.08]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)

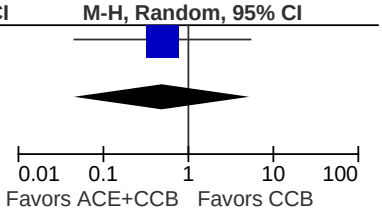


Appendix Figure C8. Forest plots for ACEI plus CCB versus CCB monotherapy trial (continued)

Myocardial infarction, nonfatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	103	100.0%	0.50 [0.05, 5.38]
Total (95% CI)		**104**		**103**	**100.0%**	**0.50 [0.05, 5.38]**
Total events	1		2			

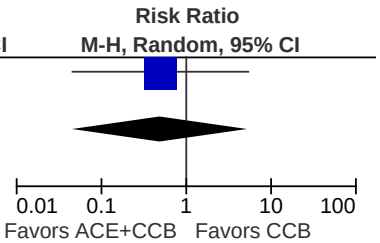
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Stroke, any

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	103	100.0%	0.50 [0.05, 5.38]
Total (95% CI)		**104**		**103**	**100.0%**	**0.50 [0.05, 5.38]**
Total events	1		2			

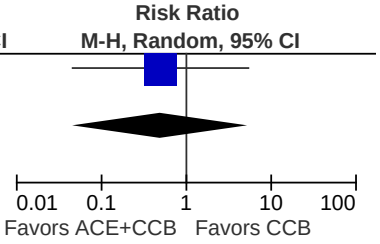
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Stroke, nonfatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	1	104	2	103	100.0%	0.50 [0.05, 5.38]
Total (95% CI)		**104**		**103**	**100.0%**	**0.50 [0.05, 5.38]**
Total events	1		2			

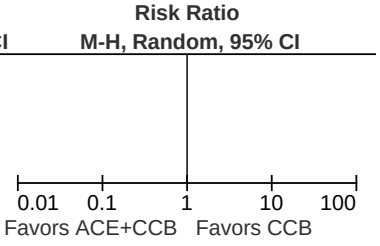
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Stroke, fatal

Study or Subgroup	ACE+CCB Events	ACE+CCB Total	CCB Events	CCB Total	Weight	Risk Ratio M-H, Random, 95% CI
Fogari 2002	0	104	0	103		Not estimable
Total (95% CI)		**104**		**103**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



Appendix Table C33. Study withdrawals and adverse events (outcomes part D), ACEI plus CCB versus ACEI monotherapy or CCB monotherapy trial

Study	Any Study Withdrawals, n/N (%)			Withdrawals Due to Serious Adverse Events, n/N (%)			Serious Adverse Events, n/N (%)			Adverse Events, Any, n/N (%)			Adverse Events, Specific, n/N (%)			‡Renal Adverse Events, n/N (%)		
	ACEI + CCB	ACEI	CCB	ACEI + CCB	ACEI	CCB	ACEI + CCB	ACEI	CCB	ACEI + CCB	ACEI	CCB	ACEI + CCB	ACEI	CCB	ACEI + CCB	ACEI	CCB
Fogari, 2002[24]	*NR	*NR	*NR	†NR	†NR	†NR							Cough: 1/104 (1.0); Edema 0/104	Cough: 2/102 (1.9) Edema 0/102	Cough: 0/103 Edema 2/103	1/104 (1.0)	2/102 (1.9)	2/103 (1.9)

ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker

*Study reported that after randomization, during dose titration phase, 144/453 subjects discontinued due to their being nonresponders or because of side effects, but their treatment group was not reported. Following dose titration, another 71/309 subjects dropped out of the study (18/104 [17.3%] ACEI+CCB, 26/102 [25.4%] ACEI, and 27/103 [26.2%] CCB).

†Study reported that of 309 completing dose titration phase, 4/103 CCB subjects, 3/102 ACEI subjects, and 2/104 ACEI+CCB subjects withdrew due to adverse events, though no data were reported on withdrawals due to serious adverse events.

‡Study reported renal adverse event of discontinuing study medication due to worsening kidney function.

Appendix Table C34. Overview of ACEI plus diuretic versus ACEI plus CCB trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Bakris, 2008[47] (GUARD) Location United States Multisite Funding Industry	Inclusion Criteria: age 21 to 85 years; type 2 diabetes; albuminuria (repeated UACR 20-500 mg/g); hypertension (mean SBP≥130 mmHg and <180 mmHg, mean DBP≥80 mmHg and <110 mmHg) Exclusion Criteria: kidney disease not caused by diabetes and/or hypertension; confirmed or suspected renal artery stenosis; cardiovascular disease event (MI, stroke, TIA, CABG, PTCA) within previous 6 months; evidence of heart failure or documented left ventricular ejection fraction <40%; type 1 diabetes or uncontrolled type 2 diabetes (hgb A1C >9.5%, serum creatinine >1.5 mg/100ml (men) or >1.3 mg/100ml (women)	N=332 Age (yr): 57.7 Gender (Male %): 65.4 Race/Ethnicity (%): 60.2% white, 26.2% black, 1.5% Asian, 12.0% other Weight: NR BMI: 35 Systolic BP (mm Hg): 150.5 Diastolic BP (mm Hg): 87.8 CKD stage: NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR Following baseline characteristics available only from n=304 subjects who completed followup (n=151 (B+HCTZ) and n=153 (B+A)): Serum creatinine (µmol/L): NR Creatinine clearance (mL/min): NR Albuminuria (g/100ml)*: 4.2 (median) Albumin/creatinine ratio (mg/g): 60.5 (median) Estimated GFR (ml/min/1.73m^2): 90.6 (median)	n=166 (ACEI/Diuretic) benazepril/HCTZ (B+HCTZ) initiated at 20/12.5 mg/day; titrated to 40/12.5 mg/day at 4 weeks if not at <130/80 mm Hg target; titrated to 40/25 mg/day at 8 weeks if not at target <130/80 mm Hg* n=166 (ACEI/CCB) benazepril/amlodipine (B+A) initiated at 20/5 mg/day; titrated to 40/5 mg at 4 weeks if not at <130/80 mm Hg target; titrated to 40/10 mg/day at 8 weeks if not at target <130/80 mm Hg* All other antihypertensive medications were discontinued during pre-randomization wash-out phase. Followup period: 12 months Study withdrawals (%): 18.7% *At 12 weeks and all subsequent visits, patients titrated to next dose if not at target BP; if at max dose (40/25 mg B+HCTZ or 40/10 mg B+A), other anti-hypertensives added (alpha blockers, beta blockers, etc.); no added ACEi, ARB, or aldosterone receptor blocker	Allocation Concealment: Adequate Blinding: Double blind Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Table C34. Overview of ACEI plus diuretic versus ACEI plus CCB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Bakris, 2010[48] Jamerson 2004[49] (ACCOMPLISH) Location Multinational, US and Europe Funding Industry	Inclusion Criteria: men and women, age ≥60 years, systolic blood pressure ≥160 mmHg or currently on antihypertensive therapy, evidence of prior MI, hospitalization for unstable angina, coronary revascularization, stroke, PAD, diabetes, left ventricular hypertrophy, renal disease (SCr >1.5 mg/dL (women) or >1.7 mg/dL (men) (NOTE: ages 55-59 years old eligible if ≥2 cardiovascular disease or target organ damage markers) Exclusion Criteria: current (within 3 months) evidence for angina pectoris; hisotry of symptomatic heart failure or evidence of LVEF<40%; myocardial infarction, acute coronary syndromes, or coronary revascularization within prior month; stroke or ischemic cerebrovascular episodes in prior 3 months; hypertension that is excessively severe, known to be refractory to treatment or known to have a secondary cause; any other condition that could interfere with effective conduct of the study	N=1,093 with CKD Age (yr): 70.9 Gender (Male %): 67.2 Race/Ethnicity (%): 77.2% white, 19.9% black, 2.8% other Weight: NR BMI: 31.3 Systolic BP (mm Hg): 145 Diastolic BP (mm Hg): 78.4 CKD stage: NR Serum creatinine (µmol/L): 139.7 Creatinine clearance (mL/min): NR Albuminuria (g/100ml): NR Albumin/creatinine ratio (mg/mmol): 28.8 Estimated GFR (ml/min/1.73m^2): 45.1 HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 58.9 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n=561 combination pill - benazepril (20 mg) plus amlodipine (5 mg) daily n=532 combination pill - benazepril (20 mg) plus hydrochlorothiazide (12.5 mg) At one month, benazepril in both groups force titrated to 40 mg; at 2 months, doses of either drug could be titrated to maximum, if needed, to reach blood pressure <140/90 mmHg (or <130/80 mmHg for patients with diabetes or chronic kidney disease); at 3 months, add-on antihypertensives (beta-blockers, alpha-blockers, clonidine, and spironolactone) were allowed; once-daily loop diuretics allowed for volume management No wash-out of previous medications Followup period: 2.9 years (terminated early because of superior efficacy of ACEI + CCB Study withdrawals (%): NA	Allocation Concealment: Adequate Blinding: Double blind Intention to Treat Analysis (ITT): Subgroup analysis Withdrawals/Dropouts adequately described: Subgroup analysis

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C35. Clinical outcomes (outcomes part A), ACEI plus diuretic versus ACEI plus CCB trials

Study	All-cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB
Bakris, 2008[47]	2/166 (1.2)	1/166 (0.6)										
Bakris, 2010[48]												

ACEI = angiotensin converting enzyme; CCB = calcium channel blocker

Appendix Table C36. Clinical outcomes (outcomes part B), ACEI plus diuretic versus ACEI plus CCB trials

Study	Stroke, Nonfatal, n/N (%)		Stroke, Fatal, n/N (%)		CHF, Any, n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome, n/N (%)	
	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB
Bakris, 2008[47]									*NR	*NR
Bakris, 2010[48]										

ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker; CHF = congestive heart failure

*Study reported discontinuation due to "cardiac disorders" in 3/166 ACEI + Diuretic subjects and in 2/166 ACEI + CCB subjects as well as due to "vascular disorders" in 2/166 ACEI + Diuretic subjects.

Appendix Table C37. Clinical renal outcomes (outcomes part C), ACEI plus diuretic versus ACEI plus CCB trials

Study	End-Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)*	
	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB
Bakris, 2008[47]							6/153 (4.0)	7/150 (4.6)		
Bakris, 2010[48]									A. 17/309** (5.5) B. 30/309 (9.7)	A. 16/335** (4.8) B. 28/335 (8.4)

ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker; GFR = glomerular filtration rate
*See Composite renal outcome definitions table
**Composite renal outcome data reported only for patients with chronic kidney disease and diabetic nephropathy

Appendix Table 38. Composite renal outcome definition, ACEI plus diuretic versus ACEI plus CCB trials

Study	Definition
Bakris 2010[48]	A. Doubling of serum creatinine concentration or end-stage renal disease (eGFR<15 mL/min/1.73m^2 or need for chronic dialysis B. Doubling of serum creatinine concentration or end-stage renal disease (eGFR<15 mL/min/1.73m^2 or need for chronic dialysis plus cardiovascular mortality

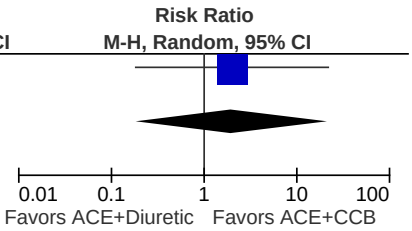
ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker; GFR = glomerular filtration rate

Appendix Figure C9. Forest plots forACEI plus diuretic versus ACEI plus CCB trials

All-cause mortality

Study or Subgroup	ACE+Diuretic Events	Total	ACE+CCB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2008	2	166	1	166	100.0%	2.00 [0.18, 21.84]
Total (95% CI)		**166**		**166**	**100.0%**	**2.00 [0.18, 21.84]**
Total events	2		1			

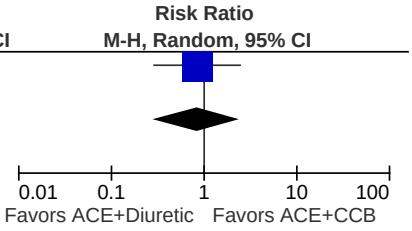
Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)



Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	ACE+Diuretic Events	Total	ACE+CCB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2008	6	153	7	150	100.0%	0.84 [0.29, 2.44]
Total (95% CI)		**153**		**150**	**100.0%**	**0.84 [0.29, 2.44]**
Total events	6		7			

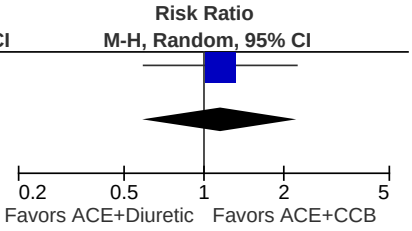
Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



Composite renal outcome A (See Table C38 for definition)

Study or Subgroup	ACE+Diuretic Events	Total	ACE+CCB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2010	17	309	16	335	100.0%	1.15 [0.59, 2.24]
Total (95% CI)		**309**		**335**	**100.0%**	**1.15 [0.59, 2.24]**
Total events	17		16			

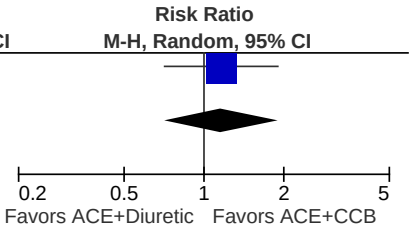
Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)



Composite renal outcome B (See Table C38 for definition)

Study or Subgroup	ACE+Diuretic Events	Total	ACE+CCB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2010	30	309	28	335	100.0%	1.16 [0.71, 1.90]
Total (95% CI)		**309**		**335**	**100.0%**	**1.16 [0.71, 1.90]**
Total events	30		28			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)



Appendix Table C39. Study withdrawals and adverse events (outcomes part D), ACEI plus diuretic versus ACEI plus CCB trials

Study	Any Study Withdrawals, n/N (%)		Withdrawals Due to Serious Adverse Events, n/N (%)		Serious Adverse Events, n/N (%)		Adverse Events, Any, n/N (%)		‡Adverse Events, Specific, n/N (%)		Renal Adverse Events, n/N (%)	
	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB	ACEI + Diuretic	ACEI + CCB
Bakris, 2008[47]	*NR	*NR	†NR	†NR					Edema: 12/166 (7.2); Cough: 17/166 (10.2); Dizzy: 11/166 (6.6)	Edema: 29/166 (17.5); Cough: 23/166 (13.9); Dizzy: 15/166 (9.0)		
Bakris, 2010[48]									Edema: 85/532 (16.0) Dizzy: 129/532 (24.2 Cough: 93/532 (17.5) Hypotension: 29/532 (5.5) Hyperk: 1/532 (0.2)	Edema: 189/561 (33.7) Dizzy: 141/561 (25.1)) Cough: 120/561 (21.4) Hypotension: 24/561 (4.3) Hyperk: 0/561 (0.0)		

ACEI = angiotensin converting enzyme inhibitor; CCB = calcium channel blocker

*Study reported 215/453 (47%) withdrawals after randomization overall, including 144/453 (32%) during dose titration period who were considered to be either nonresponders to treatment or had complained of side effects (treatment group not reported) and 71/309 (23%) during study period (36/166 [21.7%] in ACEI + Diuretic group and 26/166 [15.7%] in ACEI + CCB group).

†Study reported adverse event reasons for study medication discontinuations due to adverse events (18/166 [10.8%] for ACEI + Diuretic group and 9/166 [5.4%] for ACEI + CCB group), but did not report serious adverse events or discontinuations due to serious adverse events.

‡Study reported additional side effects by treatment group, including: fatigue (13/166 [7.8%] in each treatment group); headache (16/166 [9.6%] in ACEI + Diuretic group and 14/166 [8.4%] in ACEI + CCB group).

Appendix Table C40. Overview of ACEI plus diuretic versus ACEI monotherapy trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (Expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Mogensen, 2003[50] Country Multinational Funding Source: Industry	Inclusion: ages 40 to 75 years; type 2 diabetes; hypertension (SBP ≥140 mmHg but < 180 mmHg; DBP <110 mmHg); urinary albumin excretion rate ≥20 µg/min but <500 µg/min in at least 2 of 3 assays Exclusion: HbA1c ≥9% within 3 months before study; presumed nondiabetic kidney disease; serum creatinine ≥140 µmol/L (=1.58 mg/dL); known contraindication to ACEI or indapamide; other severe disease.	N=481 (baseline results reported for n=457 [n=233 perindopril/indapamide; n=224 enalapril] with albuminuria at baseline, who took at least one dose of treatment, and had albuminuria measured at least once under treatment) Age (yr): 58.9 Gender (Male %): 61.3 Race/Ethnicity (%): 91.0 white, 4.4 black, 0.7 Asian, 3.7 other Weight: 82.5 kg BMI: 30 Systolic BP (mm Hg): 158.4 Diastolic BP (mm Hg): 93.3 CKD stage: NR Serum creatinine (µmol/L): NR Creatinine clearance (mL/min): NR Albuminuria (µg/min): 82.1 Albumin/Creatinine ratio (mg/mmol): 8.5 HbA_{1c} (%): 7.2 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n=244 Initiated with combination of 2 mg perindopril/0.625 mg indapamide once daily, titrated to maximum of 8 mg perindopril/2.5 mg indapamide for BP target.* n= 237 Initiated with 10 mg enalapril, titrated to maximum of 40 mg enalapril for BP target* Nonstudy antihypertensive drugs were not allowed. Diabetic management left to discretion of investigator. Followup period: mean 10.7 months Study withdrawals (%): Text says 20% did not complete the study, but list of reasons for early withdrawal add to 50/244 (20.5%) for perindopril and 60/237 (25.3%) for enalapril (110/481=22.9% overall) *Dose adjustment (doubling) allowed at weeks 12, 24, or 36 if SBP ≥140 mm Hg or DBP ≥90 mm Hg based on BP permitted after week 12 (doubling of ddosage in 2 steps at 12 week intervals if SBP ≥ 140 mmHg or DBP ≥90 mmHg	Allocation Concealment: Unclear Blinding: Double Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: No

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C41. Clinical outcomes (outcomes part B), ACEI plus diuretic versus ACEI monotherapy trial

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)*	
	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI
Mogensen, 2003[50]									6/244 (2.5)	15/237 (6.3)

ACEI = angiotensin converting enzyme inhibitor; CHF = congestive heart failure
*See Composite vascular outcome definitions table

Appendix Table C42. Composite vascular outcome definitions, ACEI plus diuretic versus ACEI monotherapy trial

Study	Definition
Mogensen, 2003[50]	"Serious cardiovascular events," with serious defined as "fatal or requiring prolonged hospitalization" and cardiovascular events defined according to ICD9-1975 revision, codes 7981 (sudden death) and 390-448 (rheumatic fever with or without acute or chronic heart involvement, diseases of cardiac valves, essential hypertension, hypertensive heart or renal disease, MI, angina, chronic ischemic heart disease, cardiac aneurysm, pulmonary artery disease, pericarditis, endocarditis, myocarditis, cardiomyopathy, heart conduction disorders/dysrhythmias, heart failure, stroke, atherosclerosis, aortic aneurysm disease, peripheral arterial disease, arterial embolism/thrombosis, other disorders or the arteries/arterioles/capillaries)

ACEI = angiotensin converting enzyme; MI = myocardial infarction

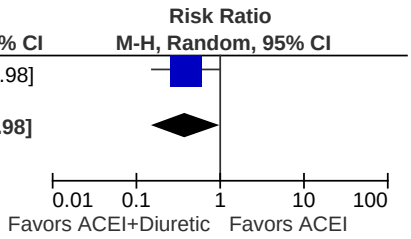
Appendix Figure C10. Forest plot for ACEI plus diuretic versus ACEI monotherapy trial

Composite vascular outcome (see Table C42 for definition)

Study or Subgroup	ACEI+Diuretic Events	Total	ACEI Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mogensen 2003	6	244	15	237	100.0%	0.39 [0.15, 0.98]
Total (95% CI)		**244**		**237**	**100.0%**	**0.39 [0.15, 0.98]**
Total events	6		15			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.99 (P = 0.05)



Appendix Table C43. Study withdrawals and adverse events (outcomes part D), ACEI plus diuretic versus ACEI monotherapy trial

Study	Any Study Withdrawals, n/N (%)		Withdrawals Due to Serious Adverse Event, n/N (%)		Serious Adverse Event: Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event, Specific, n/N (%)		Renal Adverse Event, n/N (%)	
	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI	ACEI + Diuretic	ACEI
Mogensen, 2003[50]	*50/244 (20.5)	*60/237 (25.3%)	†NR	†NR			‡NR	‡NR	HyperK: 8/244 (3.3); Cough: 9/244 (3.7)	HyperK: 13/237 (5.5); Cough: 5/237 (2.1)		

ACEI = angiotensin converting enzyme inhibitor; HyperK = hyperkalemia

* Study also reported that one patient was lost to follow-up, but didn't indicate the patient's treatment group assignment.

† Study reported withdrawal due to adverse events by treatment group, 19/244 (7.8%) for ACEI + diuretic group and 21/237 (8.8%) for ACEI group, but did not report serious adverse events or withdrawals due to serious adverse events.

‡ Study did not report adverse events overall or by treatment group, but only reported results for participants with adverse events related to drug treatment: ACEI + diuretic group 34/244 (13.9%) and ACEI group 35/237 (14.8%).

Appendix Evidence Table C44. Overview of ACEI plus diuretic versus placebo trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (Expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Lambers Heerspink 2010[51] ADVANCE Management Committee 2001[52] Country Multinational Funding Source: Industry and Government	Inclusion: age 55 years or older, diagnosed with type 2 diabetes at age 30 or older, evidence of elevated risk of cardiovascular disease (age 65 or older, diabetes diagnosed ≥ 10 years prior to entry, history of stroke or MI, hospital admission for TIA or unstable angina, coronary or peripheral revascularization, amputation secondary to vascular disease, macroalbuminuria, proliferative retinopathy or retinal photocoagulation therapy, macular edema, blindness in one eye related to diabetes, other major risk factor [current smoking, total cholesterosl >6.0 mmol/l, HDL <1.0 mmol/l, or microalbuminuria]) Exclusion: definite indication for long-term insulin therapy	N=10,640 (baseline results below are for n=2,482 with CKD stage 1 or 2 and 2,044 with CKD stage 3) Age (yr): 66.59 Gender (Male %): 52.6 Race/Ethnicity (%): NR Weight: NR BMI: 28.4 Systolic BP (mm Hg): 147.6 Diastolic BP (mm Hg): 81.0 CKD stage: subgroup analysis for CKD stages 1-3 Serum creatinine (µmol/L): NR Creatinine clearance (mL/min): NR eGFR (mL/min): 70.7 Albuminuria (µg/min): NR Albumin/Creatinine ratio (µg/mg, median): 48.1 HbA_{1c} (%): 7.7 Total cholesterol (mg/dL): NR LDL cholesterol (mmol/L): 3.2 Diabetes (%): 100 History of HTN (%): 74.6 (currently treated) Dyslipidemia (%): NR History of CAD (%): 34.7 (major macrovascular disease) History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): 12.8 History of Stroke (%): 10.8 Current smoker (%): NR History of AKI (%): NR	All subjects – 6 week run-in with 2 mg perindopril and 0.625 mg indapamide Those who were tolerant randomized to same dose or placebo; doses doubled after 3 months to 4 mg perindopril and 1.25 mg indapamide Comcomitant treatment at descretion of provider except that open-label perindopril to max of 4 mg/day was only ACEI allowed and thiazide (-like) diuretics were not permitted Followup period: mean 4.3 years Study withdrawals (%): NA	Allocation Concealment: Adequate Blinding: Double Intention to Treat Analysis (ITT): NA-subgroup analysis Withdrawals/Dropouts adequately described: NA-subgroup analysis

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HDL=high density lipoprotein cholesterol; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; TIA=transient ischemic attack; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C45. Clinical outcomes (outcomes part A), ACEI plus diuretic versus placebo trial

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke, Any, n/N (%)	
	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo
Lambers Heerspink, 2010[51]	CKD 1,2 9.2% CKD ≥3 11.6%	CKD 1,2 10.1% CKD ≥3 13.2%	CKD 1,2 4.9% CKD ≥3 6.5%	CKD 1,2 6.4% CKD ≥3 8.0%	CKD 1,2 5.6% CKD ≥3 7.3%	CKD 1,2 6.2% CKD ≥3 8.4%					CKD 1,2 4.5% CKD ≥3 5.0%	CKD 1,2 5.1% CKD ≥3 5.9%

Appendix Table C46. Clinical outcomes (outcomes part B), ACEI plus diuretic versus placebo trial

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)*	
	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo
Lambers Heerspink, 2010[51]									CKD 1,2 10.3% CKD ≥3 12.4	CKD 1,2 11.4 CKD ≥3 14.0

ACEI = angiotensin converting enzyme inhibitor; CHF = congestive heart failure
*See Composite vascular outcome definitions table

Appendix Table C47. Composite vascular outcome definition, ACEI plus diuretic versus placebo trial

Study	Definition
Lambers Heerspink 2010[51]	Cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke

ACEI = angiotensin converting enzyme inhibitor

Appendix Table C48. Clinical outcomes (outcomes part C), ACEI plus diuretic versus placebo trial

Study	End-Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)*	
	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo
Lambers Heerspink, 2010[51]									CKD 1,2 6.1% CKD ≥3 6.3%	CKD 1,2 8.5% CKD ≥3 6.7%

ACEI = angiotensin converting enzyme inhibitor; CHF = congestive heart failure
*See Composite renal outcome definitions table

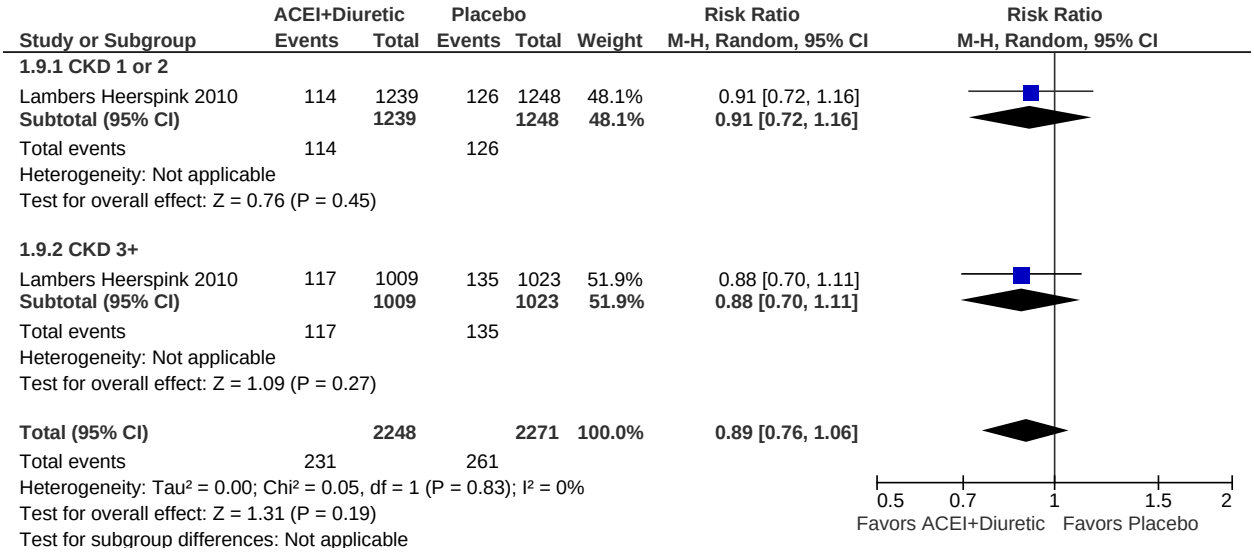
Appendix Table C49. Composite renal outcome definitions, ACEI plus diuretic versus placebo trial

Study	Definition
Lambers Heerspink 2010[51]	Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL (200 μmol/L), need for renal replacement therapy, or death due to renal illness

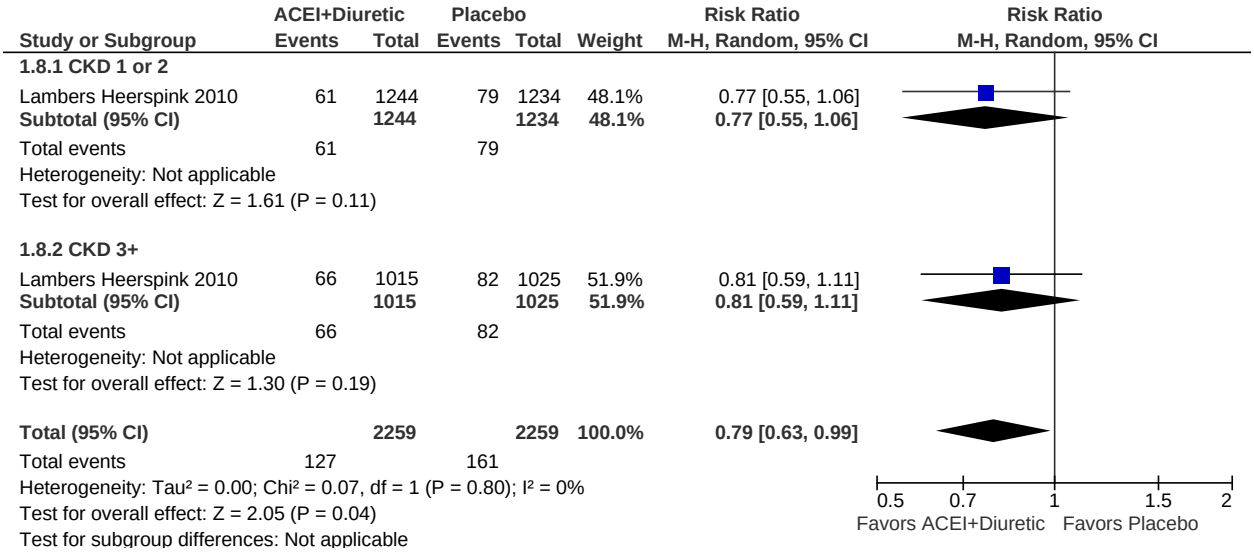
ACEI = angiotensin converting enzyme inhibitor

Appendix Figure C11. Forest plots for ACEI plus diuretic versus placebo trial

All-cause mortality



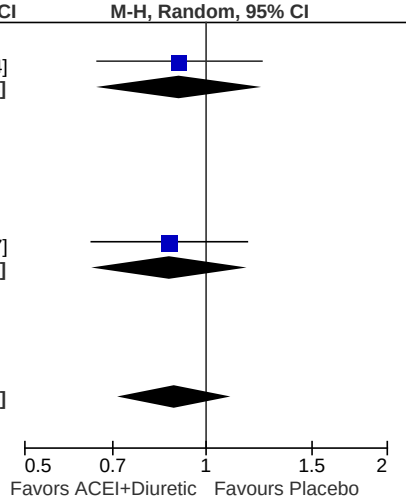
Cardiovascular mortality



Appendix Figure C11. Forest plots for ACEI plus diuretic versus placebo trial (continued)

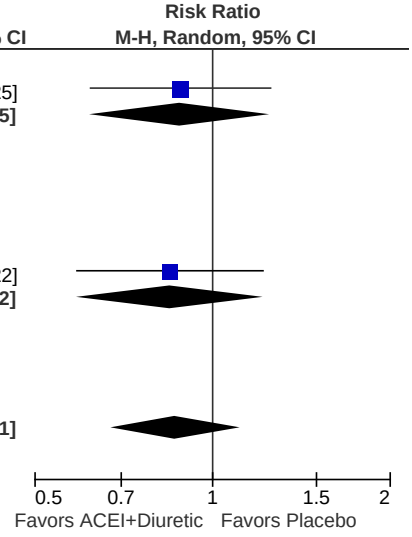
Myocardial infarction

Study or Subgroup	ACEI+Diuretic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 CKD 1 or 2						
Lambers Heerspink 2010	69	1232	77	1242	47.3%	0.90 [0.66, 1.24]
Subtotal (95% CI)		**1232**		**1242**	**47.3%**	**0.90 [0.66, 1.24]**
Total events	69		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.10.2 CKD 3+						
Lambers Heerspink 2010	74	1014	86	1024	52.7%	0.87 [0.64, 1.17]
Subtotal (95% CI)		**1014**		**1024**	**52.7%**	**0.87 [0.64, 1.17]**
Total events	74		86			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Total (95% CI)		**2246**		**2266**	**100.0%**	**0.89 [0.71, 1.10]**
Total events	143		163			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						



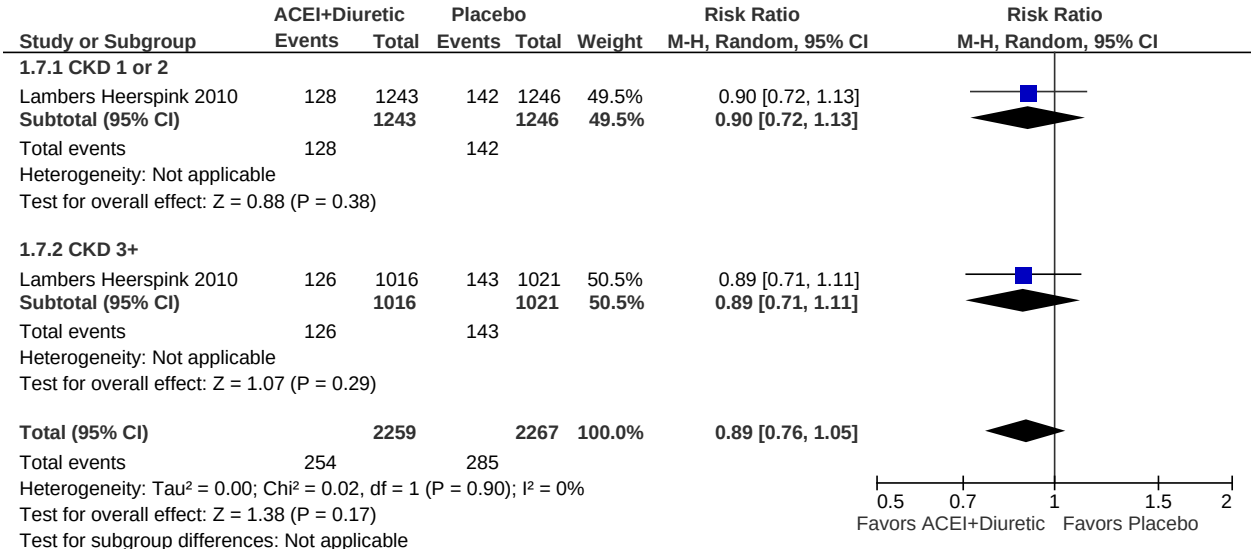
Stroke

Study or Subgroup	ACEI+Diuretic Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 CKD 1 or 2						
Lambers Heerspink 2010	56	1244	63	1235	51.7%	0.88 [0.62, 1.25]
Subtotal (95% CI)		**1244**		**1235**	**51.7%**	**0.88 [0.62, 1.25]**
Total events	56		63			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
1.11.2 CKD 3+						
Lambers Heerspink 2010	51	1021	60	1017	48.3%	0.85 [0.59, 1.22]
Subtotal (95% CI)		**1021**		**1017**	**48.3%**	**0.85 [0.59, 1.22]**
Total events	51		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**2265**		**2252**	**100.0%**	**0.86 [0.67, 1.11]**
Total events	107		123			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.13 (P = 0.26)						
Test for subgroup differences: Not applicable						

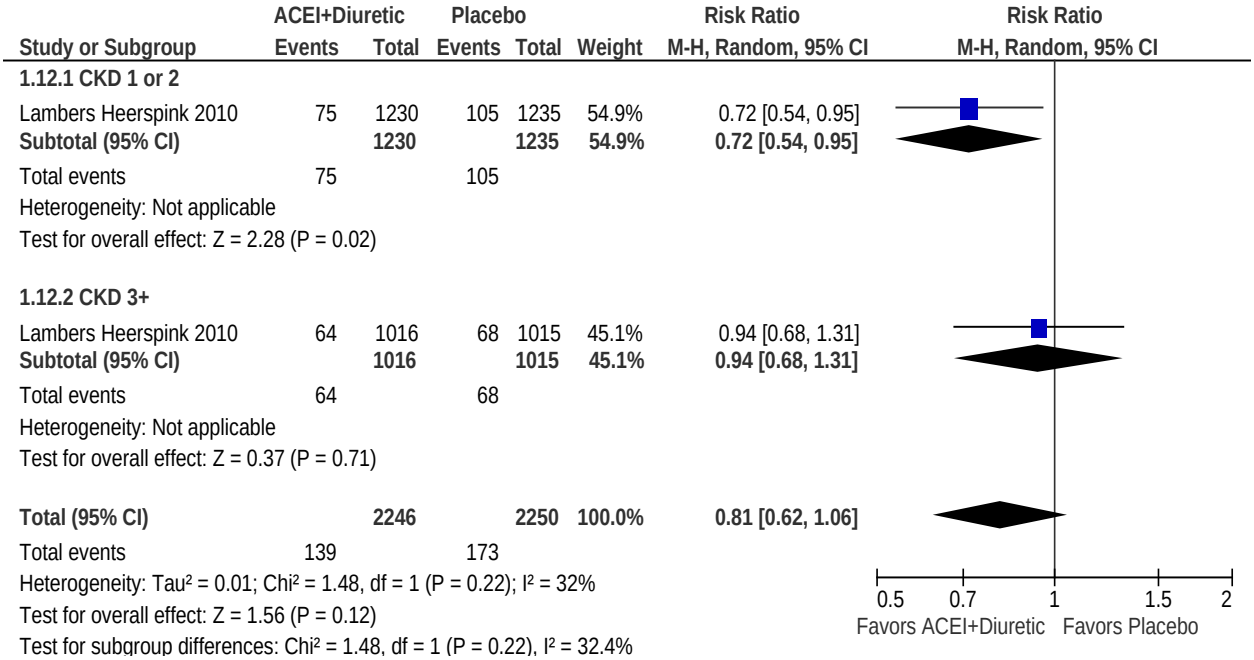


Appendix Figure C11. Forest plots for ACEI plus diuretic versus placebo trial (continued)

Composite vascular outcome (see Table C47 for definition)



Composite renal outcome (see Table C49 for definition)



Appendix Table C50. Study withdrawals and adverse events (outcomes part D), ACEI plus diuretic versus placebo trial

Study	Any Study Withdrawals, n/N (%)		Withdrawals Due to Serious Adverse Event, n/N (%)		Serious Adverse Event: Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event, Specific, n/N (%)		Renal Adverse Event, n/N (%)	
	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo	ACEI + Diuretic	Placebo
Lambers Heerspink, 2010[51]					CKD 1,2 1.4% CKD ≥3 2.2%	CKD 1,2 1.6% CKD ≥3 1.9%			Cough CKD 1,2 3.1% CKD ≥3 3.9% Hypo/Dizz CKD 1,2 0.7% CKD ≥3 1.4%	Cough CKD 1,2 1.4% CKD ≥3 1.8% Hypo/Diz z CKD 1,2 0.5% CKD ≥3 0.3%		

ACEI = angiotensin converting enzyme inhibitor, Hypo/Dizz=hypotension/dizziness; CKD = chronic kidney disease

Appendix Table C51. Overview of ARB versus ARB trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ARB versus different ARB trials				
Bakris, 2008[53] (AMADEO) Multinational (Argentina, Australia, Brazil, Canada, Mexico, New Zealand, South Korea, Taiwan, Thailand, United States) Funding Source: Industry	Inclusion: ages 21-80 years; history of type 2 diabetes mellitus; total HbA_{1c} ≤10%; serum creatinine ≤3 mg/dl (women) or ≤3.2 mg/dl (men); first-morning spot urine protein/creatinine ratio ≥700 mg/g; mean BP ≥130/80 but less than 160/110 mmHg or receiving antihypertensive(s) for hypertension Exclusion: women who were nursing, pregnant, or surgically sterile and not using effective contraception; >35% increase in serum creatinine during washout period or serum potassium level >5 mEq/l; nondiabetic renal disease; clinically significant heart disease, stroke, renal artery stenosis, hepatic dysfunction, or electrolyte imbalance; known hypersensitivity to any component of study medications; requiring chronic immunosuppressive therapy; hematuria.	N=860 Age (yr): 60.3 Gender (Male %): 62.2 Race/Ethnicity (%): 47% Caucasian, 12% black, 41% Asian, 0.1% missing Weight (kg): NR BMI: 30.0* Systolic BP (mm Hg): 143.4 Diastolic BP (mm Hg): 79.7 CKD stage: NR Serum creatinine (mg/dl): 1.55 Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Urine protein/creatinine ratio (m/g): 1991.2 Urine albumin/creatinine ratio (mg/g): 1393.7* Estimated GFR (ml/min/1.73m^2): 49.6 HbA_{1c} (%): 7.9* Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): 0 (clinically significant excluded) History of CHF (%): 0 (clinically significant excluded) Peripheral arterial disease (%): NR History of MI (%): 0 (clinically significant excluded) History of Stroke (%): 0 (clinically significant excluded) Current smoker (%): 15.6 History of AKI (%): NR *sample size <860 for these characteristics	n= 419 Telmisartan 40 mg/day for 2 weeks then 80 mg/day for 50 weeks* n= 441 Losartan 50 mg/day for 2 weeks then 100 mg/day for 50 weeks* Follow-up period: mean of 324.25 days (i.e. 10.7 months) Study withdrawals (%): 18.4 *Additional antihypertensive medications (except other ARBs, ACEIs, or direct vasodilators) allowed after forced titration period to reach BP target <130/80 mmHg	Allocation Concealment: Unclear Blinding: Double blind Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: No

Appendix Table C51. Overview of ARB versus ARB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Galle, 2008[54] Multinational (11 countries in Europe, 3 countries in Asia, South Africa) Funding Source: Industry	Inclusion: ages 30-80 years; history of type 2 diabetes mellitus; overt nephropathy (serum creatinine ≤3.0 mg/dl and proteinuria ≥900 mg/24h); hypertensive (mean BP > 130/80 mm Hg or receiving antihypertensive therapy at enrollment) Exclusion: HgbA1c >10%; premenopausal women not surgically sterile or using acceptable contraception or who were pregnant or breast feeding; recent acute cardiovascular event; congestive heart failure; receipt of metformin in patients with elevated serum creatinine levels; nondiabetic renal disease; >30% increase in serum creatinine during run-in; secondary hypertension; hepatic dysfunction; biliary obstructive disorders; renal arterial stenosis; chronic immunosuppressive therapy; history of drug or alcohol dependency; SBP >180 mmHg and/or DBP >110 mmHg on two consecutive visits during run-in	N=885 Age (yr): 61.2 Gender (Male %): 64.1 Race/Ethnicity (%): 79% white, 2% black, 19% Asian Weight: NR BMI: 30.2 Systolic BP (mm Hg): 148.1 Diastolic BP (mm Hg): 82.0 CKD stage: NR Serum creatinine (mg/dl): NR Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (g/24h): 2.78 Albumin/Creatinine ratio (mg/mmol): NR Estimated GFR (ml/min/1.73m^2): 56.6 HbA_{1c} (%): 7.8 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): 18.2 History of AKI (%): NR	n= 443 Telmisartan 40 mg/day for 2 weeks then 80 mg/day for 50 weeks* n= 442 Valsartan 80 mg/day for 2 weeks then 160 mg/day for 50 weeks* Followup period: mean of 363.5 days (1 yr) Study withdrawals (%): 19.1 *Additional antihypertensive medications (except other ARBs or ACEIs) allowed if SBP/DBP >130/80	Allocation Concealment: Unclear Blinding: Double blind Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Table C51. Overview of ARB versus ARB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ARB (higher dose) versus ARB (lower dose) trial				
Burgess, 2009[55] Canada, Multisite Funding Source: Industry	Inclusion: ages 18 to 80 years; primary glomerular disease not currently treated with any disease-specific treatment; diabetic nephropathy or hypertensive nephrosclerosis; urine protein ≥1g/d on at least 2 occasions in previous 6 months; not taking immunosuppressant drugs, corticosteroids, or nonsteroidal anti-inflammatory medications; stable hypertension (no new antihypertensive medications within 6 weeks of visit 1); if taking ACE or ARB use stable for at least 3 months before visit 1; SBP <170 and DBP <100 mm Hg with use of antihypertensive medications Exclusion: presence of known or suspected secondary hypertension including bilateral renal artery stenosis or unilateral renal artery stenosis to a solitary kidney; pregnancy; serum creatinine >300 µmol/L (=3.4 mg/dl) or eGFR <30 ml/min/1.73m^2; presence of polycystic kidney disease, systemic lupus erythematosus; polyarteritis nodosa, amyloidosis or myeloma, or serum potassium ≥ 5.5 mmol/L at baseline or on >1 occasion in 6 months before visit 1.	N=269 Age (yr): 55.3 Gender (Male %): 79.6 Race/Ethnicity (%): 83.2% white, 3.7% black, 9.3% Asian, 3.7% other Weight (kg): 91.9 BMI: 31.8 Systolic BP (mm Hg): 132.5 Diastolic BP (mm Hg): 77.4 CKD stage: NR Serum creatinine (µmol/L): 127.0 (=1.44 mg/dl) Creatinine clearance (mL/min): NR Albuminuria: NR Proteinuria (g/day): 2.83 Degree of Proteinuria: 57.3% with 1-3 g/day, 42.7% with >3 g/day Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): 52.0 HbA_{1c} (%): NR Total cholesterol: NR LDL cholesterol: NR Diabetes (%): NR History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n= 90 Candesartan 16 mg/day* n= 90 Candesartan 64 mg/day# n= 89 Candesartan 128 mg/day## Followup period: 30 weeks Study withdrawals (%): 14 *16 mg/day was highest approved antihypertensive dosage of candesartan in Canada at the time the study was initiated #dose titrated from 16 mg/day over 4 weeks ##dose titrated from 16 mg/day over 6 weeks	Allocation Concealment: Adequate Blinding: Double blind Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Table C51. Overview of ARB versus ARB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Makino, 2007[37] Location Japan Funding Source NR	Inclusion Criteria: Age 30 to 74, type 2 DM and urinary albumin-to-creatinine ratio 100-300 mg/g, serum creatinine <1.5 mg/dl (men) and <1.3 mg/dl (women). Exclusion Criteria: DM type 1, age of diabetes onset <30 years, seated systolic blood pressure (SBP)/diastolic blood pressure (DBP) >180/100 mmHg, and definable chronic kidney disease other than diabetic nephropathy	N=527 Age (yr): 61.7 Gender (Male %): NR Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 137 Diastolic BP (mm Hg): 77 Albuminuria: NR, see Inc. criteria Serum creatinine (mg/dL): NR, see Inc. criteria Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): NR History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	n= 172 to Telmisartan 40mg/day n= 168 to Telmisartan 80mg/day (plus n= 174 to placebo) period: median 1.3 +/- 0.5 years Study withdrawals (%): 2.4 % excluded from primary analysis due to suspected type 1 DM or for missing UACR measurements	Allocation Concealment Unclear Blinding: Double blinded Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Table C51. Overview of ARB versus ARB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Parving, 2001[39] IRMA-2 Location: 96 centers worldwide Funding Source Industry	Inclusion Criteria: HTN, age 30 to 70, type 2 DM, persistent microalbuminuria (UAER 20 to 200 µg/min in 2 of 3 consecutive, sterile, overnight samples), serum creatinine ≤1.5 mg/dl for men and ≤1.1 mg/dl for women. Exclusion Criteria: Nondiabetic kidney disease, cancer, life-threatening disease with death expected to occur within two years, and an indication for ACEI or ARBs.	N=590 Age (yr): 58 Gender (Male %): 68.5 Race/Ethnicity (%): White: 97.3, Non-White: 2.7 BMI: 30 Systolic BP (mm Hg): 153 Diastolic BP (mm Hg): 90 Albuminuria: 55.5 µg/min Serum creatinine (mg/dL): 1.18 Estimated GFR (ml/min/1.73m2):NR Total cholesterol (mg/dL): 224 LDL cholesterol (mg/dL): 140 Diabetes (%): 100 History of HTN (%): 100 History of CAD (%): 4.5 History of CHF (%): NR History of MI (%): 3.0 History of Stroke (%): 3.1 Peripheral arterial disease (%): 5.2 Current smoker (%): 18.6	n= 194 Irbesartan 300mg n= 195 Irbesartan 150mg (plus n= 201 placebo) Followup period: median 2 years Study withdrawals (%): 13	Allocation Concealment: Not defined Blinding: Double blind Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C52. Summary of study baseline characteristics for ARB versus ARB studies

Characteristic	Mean (range unless otherwise noted)	Number of Trials Reporting
ARB versus Different ARB (n=2)		
Total number of patients evaluated	1745 (860-885)	2
Age of subjects, years	60.8 (60.3-61.2)	2
Gender, male, %	63.2 (62.2-64.1)	2
Race/ethnicity, white, %	63.2 (47-79)	2
Race/ethnicity, black, %	6.9 (2-12)	2
Body Mass Index, kg/m^2	30.1 (30.0-30.2)	2
SBP, mmHg	145.8 (143.4-148.1)	2
DBP, mmHg	80.9 (79.7-82.0)	2
Proteinuria, g/day	2.78	1
Albuminuria, mg/day or µg/min	NR	0
Serum creatinine, mg/dL	1.55	1
Creatinine clearance, $ml/min/1.73m^2$	NR	0
Estimated GFR, $ml/min/1.73m^2$	53.2 (49.6 to 56.6)	2
History of diabetes mellitus, %	100 (both 100)	2
HbA_{1c}, %	7.85 (7.8 to 7.9)	2
History of hypertension, %	100 (both 100)	2
Coronary artery disease, %	0	1
Congestive heart failure, %	0 (both 0)	2
Myocardial infarction, %	0	1
Stroke, **%**	0	1
Current smoker, **%**	16.9 (15.6 to 18.2)	2

ARB = angiotensin receptor blocker, SBP = systolic blood pressure; DBP = diastolic blood pressure; GFR = glomerular filtration rate

Appendix Table C53. Clinical outcomes (outcomes part A), ARB versus ARB trials

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke, Any, n/N (%)	
	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control
Bakris, 2008[53]	TEL: 2/419 (0.5)*	LOS: 13/441 (2.9)										
Galle, 2008[54]	TEL: 15/428 (3.5)	VAL: 8/429 (1.9)	TEL: 8/428 (1.9)	VAL: 6/429 (1.4)	TEL: 4/428 (0.9)	VAL: 11/429 (2.6)					TEL: 11/428 (2.6)	VAL: 5/429 (1.2)
Burgess, 2009[55]	CAN 64mg/d: 0/90; CAN 128mg/d: 0/89	CAN 16mg/d: 0/90	CAN 64mg/d: 0/90; CAN 128mg/d: 0/89	CAN 16mg/d: 0/90			CAN 64mg/d: 0/90; CAN 128mg/d: 0/89	CAN 16mg/d: 0/90				
Makino, 2007[37]												
Parving, 2001[39] IRMA-2	IRB 300mg 3/194 (1.5)	IRB 150mg 0/195										

ARB = angiotensin receptor blocker; TEL = telmisartan; LOS = losartan; VAL = valsartan; CAN = candesartan; IRB = irbesartan

Appendix Table C54. Clinical outcomes (outcomes part B), ARB versus ARB trials

Study	Stroke, Nonfatal, n/N (%)		Stroke, Fatal, n/N (%)		CHF, Any, n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome, n/N (%)*	
	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control
Bakris, 2008[53]									TEL: 21/419 (5.0)	LOS: 37/441 (8.4)
Galle, 2008[54]							(A)7/428 (1.6)	(A)6/442 (1.4)	TEL: 31/428 (7.2)	VAL: 33/429 (7.7)
Burgess 2009[55]			CAN 64mg/d: 0/90; CAN 128mg/d: 0/89	CAN 16mg/d: 0/90			(B) CAN 64mg/d: 0/90; CAN 128mg/d: 0/89	(B) CAN 16mg/d: 0/90		
Makino, 2007[37]										
Parving, 2001[39] IRMA-2										

ARB = angiotensin receptor blocker; CHF = congestive heart failure; TEL = telmisartan; LOS = losartan; VAL = valsartan
*See Composite vascular outcome definitions table

Appendix Table C55. Composite vascular outcome definitions, ARB versus ARB trials

Study	Definition
Bakris, 2008[47] Ref #49	Cardiovascular morbidity (not defined) or mortality
Galle, 2008[54]	Myocardial infarction, stroke, or hospitalization for heart failure or unstable angina, coronary or peripheral revascularization

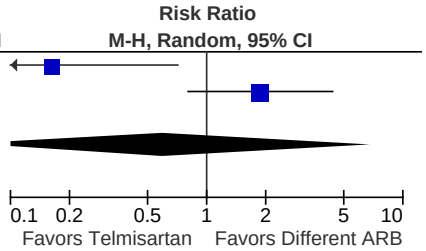
ARB = angiotensin receptor blocker

Appendix Figure C12. Forest plots for ARB versus different ARB trials

All cause mortality

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2008 Amadeo	2	419	13	441	46.9%	0.16 [0.04, 0.71]
Galle 2008	15	428	8	429	53.1%	1.88 [0.81, 4.39]
Total (95% CI)		**847**		**870**	**100.0%**	**0.59 [0.05, 6.88]**
Total events	17		21			

Heterogeneity: Tau² = 2.75; Chi² = 8.25, df = 1 (P = 0.004); I² = 88%
Test for overall effect: Z = 0.42 (P = 0.68)

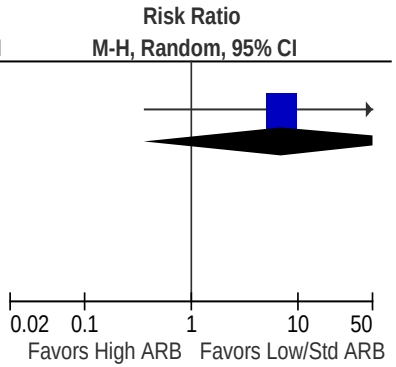


All cause mortality (high dose versus low or standard dose)

Study or Subgroup	High ARB Events	Total	Low/Std ARB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
27.2.1 Irbesartan 300 mg versus irbesartan 150 mg						
Parving (IRMA-2) 2001	3	194	0	195	100.0%	7.04 [0.37, 135.31]
Subtotal (95% CI)		**194**		**195**	**100.0%**	**7.04 [0.37, 135.31]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)

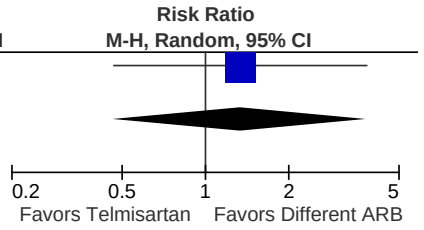
Test for subgroup differences: Not applicable



Cardiovascular mortality

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Galle 2008	8	428	6	429	100.0%	1.34 [0.47, 3.82]
Total (95% CI)		**428**		**429**	**100.0%**	**1.34 [0.47, 3.82]**
Total events	8		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)

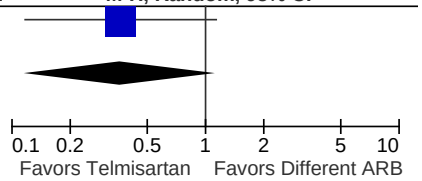


Appendix Figure C12. Forest plots for ARB versus different ARB trials (continued)

Myocardial infarction

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Galle 2008	4	428	11	429	100.0%	0.36 [0.12, 1.14]
Total (95% CI)		**428**		**429**	**100.0%**	**0.36 [0.12, 1.14]**
Total events	4		11			

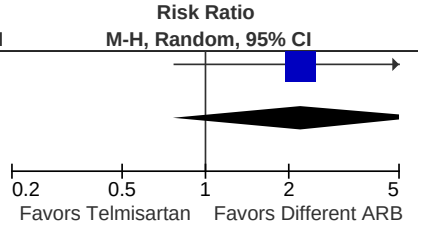
Heterogeneity: Not applicable
Test for overall effect: Z = 1.74 (P = 0.08)



Stroke

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Galle 2008	11	428	5	429	100.0%	2.21 [0.77, 6.29]
Total (95% CI)		**428**		**429**	**100.0%**	**2.21 [0.77, 6.29]**
Total events	11		5			

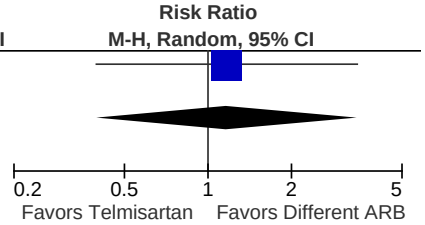
Heterogeneity: Not applicable
Test for overall effect: Z = 1.48 (P = 0.14)



Congestive heart failure, hospitalization

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Galle 2008	7	428	6	429	100.0%	1.17 [0.40, 3.45]
Total (95% CI)		**428**		**429**	**100.0%**	**1.17 [0.40, 3.45]**
Total events	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)

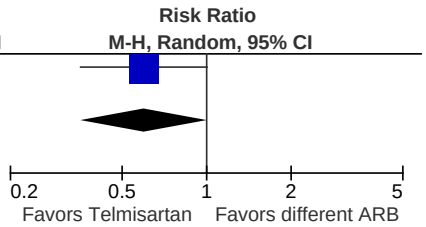


Appendix Figure C12. Forest plots for ARB versus different ARB trials (continued)

Composite vascular (outcome (see Table C55 for definition)

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2008 Amadeo	21	419	37	441	100.0%	0.60 [0.36, 1.00]
Total (95% CI)		**419**		**441**	**100.0%**	**0.60 [0.36, 1.00]**
Total events	21		37			

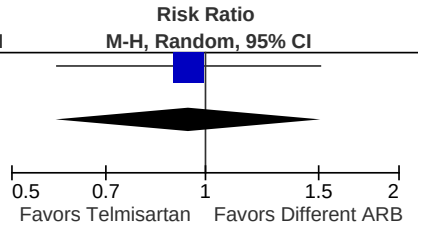
Heterogeneity: Not applicable
Test for overall effect: Z = 1.95 (P = 0.05)



Composite vascular outcome (see Table C55 for definition)

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Galle 2008	31	428	33	429	100.0%	0.94 [0.59, 1.51]
Total (95% CI)		**428**		**429**	**100.0%**	**0.94 [0.59, 1.51]**
Total events	31		33			

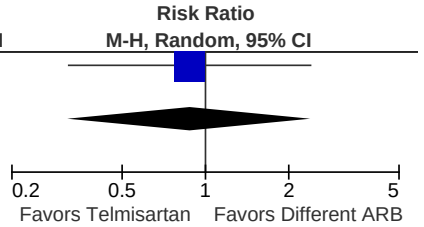
Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)



End-stage renal disease

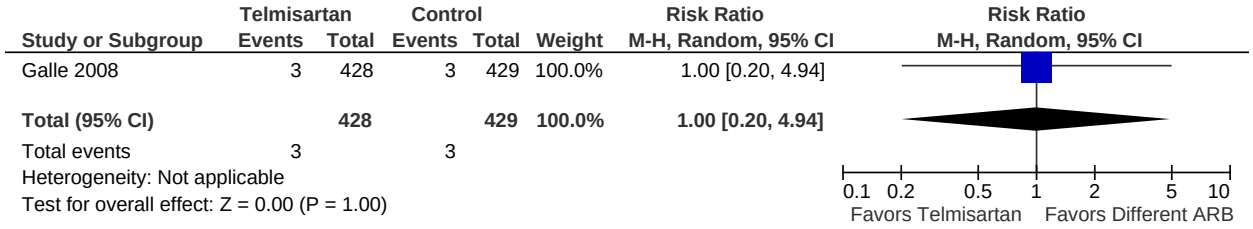
Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Galle 2008	7	428	8	429	100.0%	0.88 [0.32, 2.40]
Total (95% CI)		**428**		**429**	**100.0%**	**0.88 [0.32, 2.40]**
Total events	7		8			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)

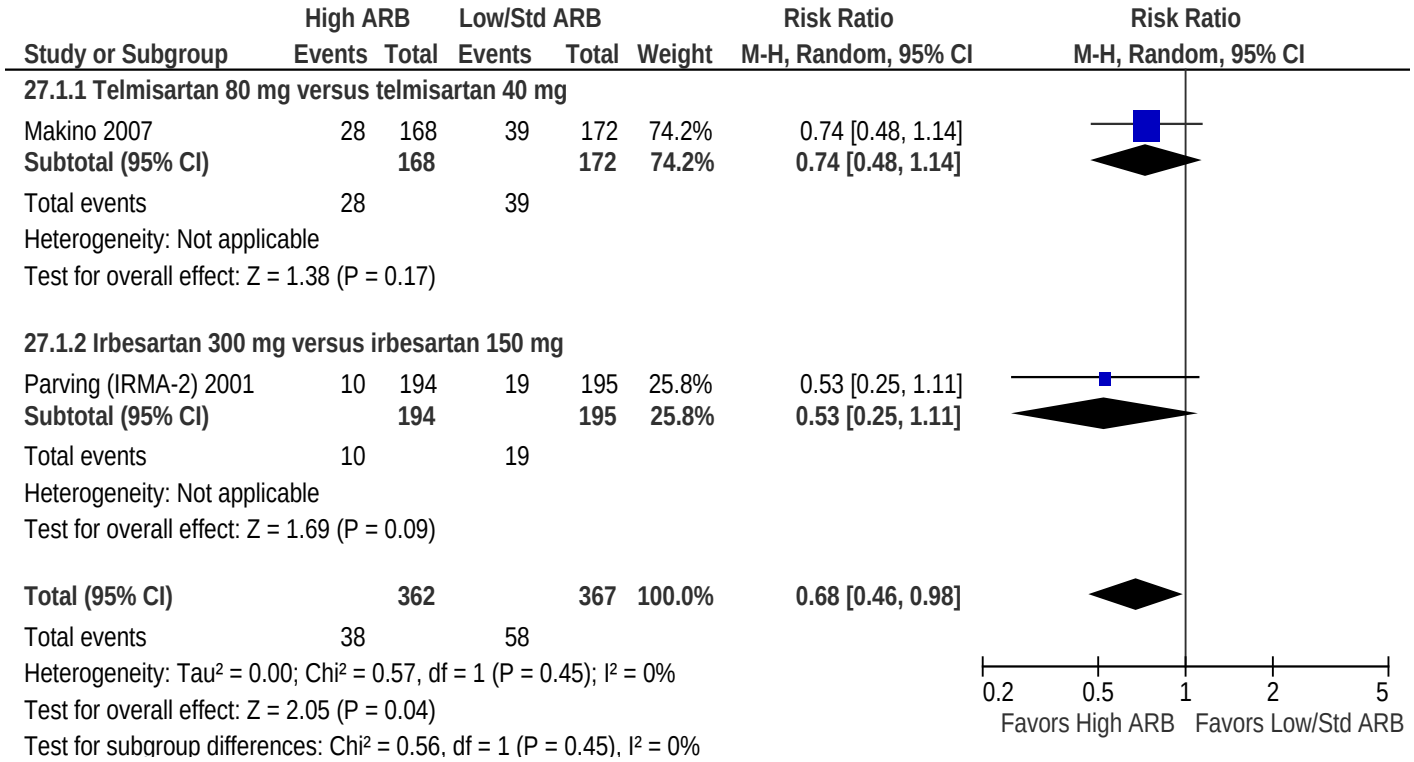


Appendix Figure C12. Forest plots for ARB versus different ARB trials (continued)

Doubling of serum creatinine



Progression from microalbuminuria to macroalbuminuria

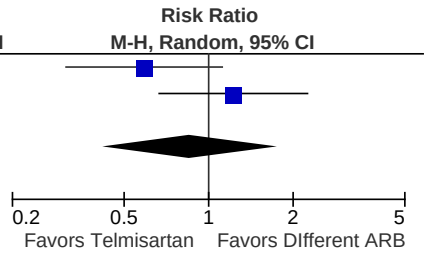


Appendix Figure C12. Forest plots for ARB versus different ARB trials (continued)

Composite renal outcome (see Table C57 for definition)

Study or Subgroup	Telmisartan Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 2008 Amadeo	14	419	25	441	49.0%	0.59 [0.31, 1.12]
Galle 2008	22	428	18	429	51.0%	1.23 [0.67, 2.25]
Total (95% CI)		**847**		**870**	**100.0%**	**0.86 [0.42, 1.75]**
Total events	36		43			

Heterogeneity: Tau² = 0.17; Chi² = 2.64, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.43 (P = 0.67)



Appendix Table C56. Clinical renal outcomes (outcomes part C), ARB versus ARB trials

Study	End-Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)*	
	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control
Bakris, 2008[53]									TEL: 14/419 (3.3)	LOS: 25/441 (5.7)
Galle, 2008[54]	TEL: 7/428 (1.6)	VAL: 8/429 (1.9)	TEL: 3/428 (0.7)	VAL: 3/429 (0.7)					TEL: 22/428 (5.1)	VAL: 18/429 (4.2)
Burgess, 2009[55]										
Makino, 2007[37]							TEL 80 mg 28/168 (16.7)*	TEL 40 mg 39/172 (22.6)*		
Parving, 2001[39] IRMA-2							IRB 300mg 10/194 (5.2)*	IRB 150mg 19/195 (9.7)		

ARB = angiotensin receptor blocker; GFR = glomerular filtration rate; TEL = telmisartan; LOS = losartan; VAL = valsartan; CAN = candesartan; IRB = irbesartan
*See Composite renal outcome definitions table

Appendix Table C57. Composite renal outcome definitions, ARB versus ARB trials

Study	Definition
Bakris, 2008[53]	Doubling of serum creatinine concentration, end-stage renal disease (need for long-term dialysis, renal transplantation, or serum creatinine ≥6 mg/dl), or death.
Galle, 2008[54]	Doubling of serum creatinine, end-stage renal disease (need for long-term dialysis, renal transplantation, or serum creatinine ≥6 mg/dl), and all-cause death

ARB = angiotensin receptor blocker

Appendix Table C58. Study withdrawals and adverse events (outcomes part D), ARB versus ARB trials

Study	Any Study Withdrawals, n/N (%)		Serious Adverse Events, Any, n/N (%)		Withdrawals Due to Serious Adverse Events, n/N (%)		Adverse Event, Any, n/N (%)		Adverse Event, Specific, n/N (%)		Renal AE	
	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control	Interven-tion	Control
Bakris, 2008[53]	TEL: 74/419 (17.7)	LOS: 99/441 (22.4)	TEL: 65/419 (15.5)	LOS: 99/441 (22.4)	TEL: 6/419 (1.4)	LOS: 6/441 (1.4)	TEL: 352/419 (84.0)	LOS: 362/441 (82.1)	*NR	*NR		
Galle, 2008[54]	TEL: 81/443 (18.3)	VAL: 88/442 (19.9)	TEL: 116/443 (26.2)	VAL: 104/442 (23.5)	TEL: 14/443 (3.2)	VAL: 9/442 (2.0)	TEL: 320/443 (72.3)	VAL: 316/442 (71.6)	TEL: HyperK: 10/443 (2.2)	VAL: HyperK: 12/429 (2.9)	TEL: "Renal & urinary disorders": 18/443 (4.0)	VAL: "Renal & urinary disorders": 17/442 (3.8)
Burgess, 2009[55]	C64: 6/90 (6.7); C128: 14/89 (15.7);	C16: 18/90 (20.0)	†NR	†NR	C64: 5/90 (5.5); C128: 8/89 (9.0)	C16: 11/90 (12.2)			C64: HyperK: 4/90 (4.4); C128: HyperK: 3/89 (3.3)	C16: HyperK: 4/90 (4.4)	Withdrawn for high SCr: C64: 0/90 C128: 2/89; Withdrawn for ARF: C64: 0/90 C128: 0/89	‡Withdrawn for high SCr: C16: 1/90 Withdrawn for ARF: C16: 1/90
Makino, 2007[37]	#NR	#NR					NR**	NR**				
Parving, 2001[39] IRMA-2	IRB 300mg 20/194 (10.3)	IRB 150mg 27/195 (13.8)	§ 60/389 (15.4)		IRB 300mg 8/194 (4.1)	IRB 150mg 18/195 (9.2)						

ARB = angiotensin receptor blocker; TEL = telmisartan; LOS = losartan; VAL = valsartan; IRB = irbesartan; C16 = candesartan 16mg/day; C64 = candesartan 64mg/day; C128 = candesartan 128mg/day; ARF = acute renal failure; SCr = serum creatinine; HyperK = hyperkalemia

*Study reported that 1.8% of entire cohort had hyperkalemia, but didn't report results by treatment group.

** Study reported that "one or more adverse event was recorded in >90% of patients in each treatment group;" no additional adverse events information was provided, including on specific types of adverse events.

†Study reported that 24 patients (8.9%) had one or more serious adverse event but didn't report this result by treatment group.

‡Study also reported that 1/90 patients in C16 treatment group was withdrawn after developing crescentic glomerulonephritis superimposed on pre-existing IgA nephropathy.

§ Study reported serious adverse events for the two ARB treatment dose groups combined only.

Appendix Evidence Table C59. Overview of ACEI plus aldosterone antagonist versus ACEI trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Mehdi, 2009[45] Location United States, Single-site Funding Source Government	Inclusion Criteria: Age 20 to 65; type 1 or 2 DM; seated systolic BP >130mmHg; proteinuria (24-h UACR≥300 mg/g despite treatment with ACEI or ARB for at least 3 months* Exclusion Criteria: BMI>45kg/m^2; serum creatinine >3.0mg/dl (females) or >4.0 mg/dl (males); known nondiabetic kidney disease; serum potassium >5.5 mEq/L; hemoglobin A1c >11%; stroke or myocardial infarction within preceding 12 months; heart failure; known adverse reaction to losartan or spironolactone; anticipated need for dialysis within 12 months *Effort was made to recruit younger patients with type 2 DM as recommended by study sponsor	N=54 Age (yr): 50.5 Gender (Male %): 46.3 Race/Ethnicity (%): 31.5% black, 53.7% Hispanic, 11.1% non-Hispanic white, 3.7% Native American Weight: NR BMI: 33 Systolic BP (mm Hg): 132 Diastolic BP (mm Hg): 73.5 CKD stage: NR Serum creatinine (mg/dL): 1.6 Creatinine clearance (mL/min): 62.2 Albuminuria: NR Urine albumin/creatinine ratio (mg/g): 1005.5 Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.8 Total cholesterol: 182.5 LDL cholesterol: 85 Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): NR History of MI/CABG/PTCA(%): 9.3 History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n= 27 to Spironolactone 12.5 mg/day for 1 week then 25mg/day† n= 27 to placebo †All patients were taking Lisinopril 80 mg/day at baseline and throughout treatment Followup period: 11.1 months Study withdrawals (%): 29.6	Allocation Concealment: Unclear Blinding: Double blinded Intention to Treat Analysis (ITT): No While the overall study analysis was not by intention-to-treat, this pertains to exclusion from analyses of a single subject randomized into the ACE plus ARB treatment group that is not the focus of this section of the report. Withdrawals/ Dropouts adequately described: No

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C60. Clinical outcomes (outcomes part A), ACEI plus aldosterone antagonist versus ACEI plus placebo trial

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo
Mehdi, 2009[45]	0/27	0/27	0/27	0/27	1/27 (3.7)	0/27	0/27	0/27	1/27 (3.7)	0/27	2/27 (7.4)	1/27 (3.7)

ACEI = angiotensin converting enzyme inhibitor; Aldo Antag = aldosterone antagonist

Appendix Table C61. Clinical outcomes (outcome part B), ACEI plus aldosterone antagonist versus ACEI plus placebo trial

Study	Stroke, Nonfatal, n/N (%)		Stroke, Fatal, n/N (%)		CHF, Any, n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome, n/N (%)	
	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo
Mehdi, 2009[45]	2/27 (7.4)	1/27 (3.7)					(A)2/27 (7.4)	(A)0/27		

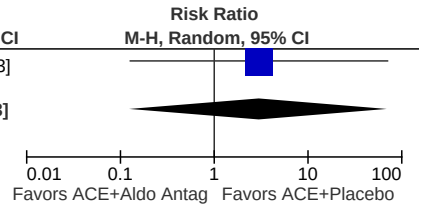
ACEI = angiotensin converting enzyme inhibitor; CHF = congestive heart failure; Aldo Antog = aldosterone antagonist

Appendix Figure C13. Forest plots for ACEI plus aldosterone antagonist versus ACEI plus placebo trial

Myocardial infarction, any

Study or Subgroup	ACE+Aldo Antag vs ACE Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	1	27	0	27	100.0%	3.00 [0.13, 70.53]
Total (95% CI)		**27**		**27**	**100.0%**	**3.00 [0.13, 70.53]**
Total events	1		0			

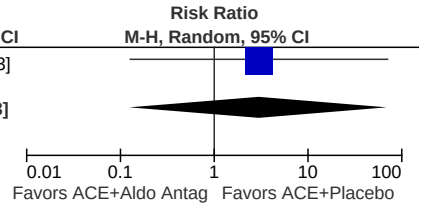
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



Myocardial infarction, nonfatal

Study or Subgroup	ACE+Aldo Antag vs ACE Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	1	27	0	27	100.0%	3.00 [0.13, 70.53]
Total (95% CI)		**27**		**27**	**100.0%**	**3.00 [0.13, 70.53]**
Total events	1		0			

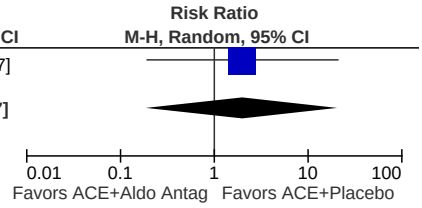
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



Stroke, any

Study or Subgroup	ACE+Aldo Antag vs ACE Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	2	27	1	27	100.0%	2.00 [0.19, 20.77]
Total (95% CI)		**27**		**27**	**100.0%**	**2.00 [0.19, 20.77]**
Total events	2		1			

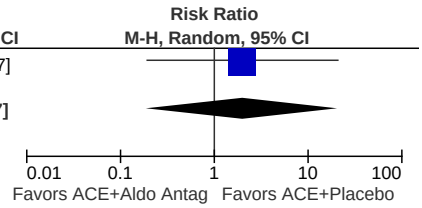
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Stroke, nonfatal

Study or Subgroup	ACE+Aldo Antag vs ACE Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	2	27	1	27	100.0%	2.00 [0.19, 20.77]
Total (95% CI)		**27**		**27**	**100.0%**	**2.00 [0.19, 20.77]**
Total events	2		1			

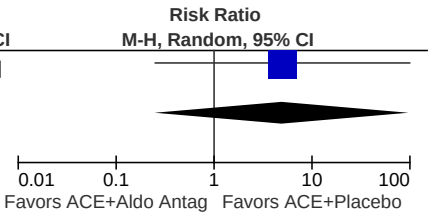
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)



Congestive heart failure, hospitalization

Study or Subgroup	ACE+Aldo Antag Events	Total	ACE+Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mehdi 2009	2	27	0	27	100.0%	5.00 [0.25, 99.51]
Total (95% CI)		**27**		**27**	**100.0%**	**5.00 [0.25, 99.51]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)



Appendix Table C62. Study withdrawals and adverse events (outcomes part D), ACEI plus aldosterone antagonist versus. ACEI plus placebo trials

Study	Any Study Withdrawals, n/N (%)		Withdrawals Due to Serious Adverse Event, n/N (%)		Serious Adverse Event: Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event, Specific, n/N (%)		Renal Adverse Event, n/N (%)	
	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo	ACEi + Aldo Antag	ACEI + Placebo	ACEI + Aldo Antag	ACEI + Placebo
Mehdi, 2009[45]	10/27 (37.0)	6/27 (22.2)	*NR	*NR					HyperK: 2/27 (7.4)	HyperK: 0/27		

ACEI = angiotensin converting enzyme inhibitor; HyperK = hyperkalemia; Aldo Antag = aldosterone antagonist

*Study reported withdrawals due to adverse events, but not specifically due to serious adverse events: ACEI + Aldo Antag (2 hyperkalemia, 2 stroke, 1 hypotension, 1 increased serum creatinine, 1 gynecomastia) and ACEI + placebo (1 stroke, 1 increased serum creatinine).

Appendix Evidence Table C63. Overview of ACE/ARB plus aldosterone antagonist versus ACE/ARB plus placebo trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
van den Meiracker, 2006[56] Location Netherlands, multiple clinic sites Funding Source None reported	Inclusion Criteria: Patients with type 2 diabetes and macroalbuminuria (24-hour urinary albumin excretion >300 mg or urinary albumin to creatinine ratio >20 mg/mmol) despite use of an ACEI inhibitor or ARB in recommended dosages for at least 1 year; ages 20 to 80 years Exclusion Criteria: Serum creatinine >265 µmol/l (i.e. >3.0 mg/dl); serum potassium >5.0 mmol/l; renal disease other than diabetic nephropathy; underlying malignant, hepatic, or gastrointestinal disease; myocardial infarction or stroke within the past 3 months; unstable angina pectoris; alcohol or drug abuse; psychological illness	N=59 Age (yr): 52.2 Gender (Male %): 66 Race/Ethnicity (%): NR Weight (kg): NR BMI: 31.0 Systolic BP (mm Hg): 147.6 Diastolic BP (mm Hg): 80.7 CKD stage: NR Serum creatinine (µmol/l): 98.2 (=1.11 mg/dl) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (g/day): NR Urine Albumin/creatinine ratio (mg/mmol): 81.0 Urine Protein/creatinine ratio (mg/mmol): 128.5 estimated GFR (ml/min/1.73m^2): 70.5 (MDRD formula) HbA_{1c} (%): 8.1 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%) NR Current smoker (%): NR History of AKI (%): NR	n=29 Spironolactone 50 mg/day* n=30 Placebo, matched tablets* Study medication added to antihypertensive medication already used by patients (71% of spironolactone group and 86% of placebo group taking an ACE inhibitor, with remainder taking an ARB) *Medication halved if potassium >5.5 mmol/l when checked 2 weeks after start; patients withdrawn if potassium >5.5 mmol/l after 2 weeks on half dose Antihypertensive medications kept constant throughout study Followup period: 1 year Study withdrawals (%): 11.9	Allocation Concealment: Adequate Blinding: Double Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

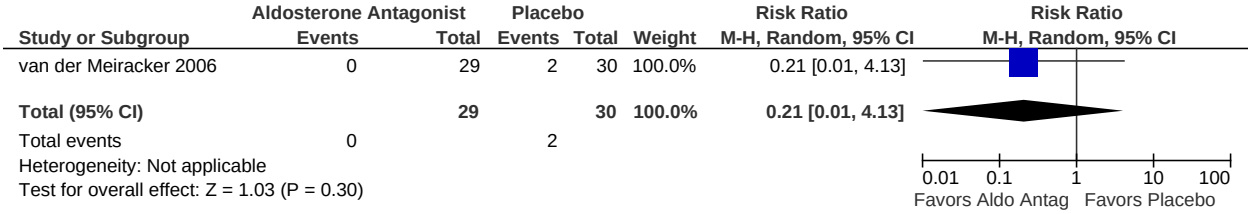
Appendix Table C64. Clinical outcomes (outcomes part A), ACEI/ARB plus aldosterone antagonist versus ACEI/ARB plus placebo trial

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial infarction, Nonfatal, n/N (%)		Stroke, Any n/N (%)	
	ACEI/ARB+ AA	ACEI/ ARB + PBO	ACEI/ARB + AA	ACEI/ ARB + PBO	ACEI/ARB + AA	ACEI/A RB + PBO	ACEI/ARB + AA	ACEI/A RB + PBO	ACEI/ARB + AA	ACEI/A RB + PBO	ACEI/ARB + AA	ACEI/A RB + PBO
van der Meiracker, 2006[56]	0/29	2/30 (6.7%)					0/29	2/30 (6.7%)				

ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker; AA = aldosterone antagonist; PBO = placebo

Appendix Figure C14. Forest plot for ACEI/ARB plus aldosterone antagonist versus ACEI/ARB plus placebo trial

All-cause mortality



Appendix Table C65. Study withdrawals and adverse events (outcomes part D), ACEI/ARB plus aldosterone antagonist versus ACEI/ARB plus placebo trial

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Study Withdrawals Due to Serious Adverse Event: Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Specific, n/N (%)		Renal Adverse Events, n/N (%)	
	ACEI/ARB + AA	ACEI/ARB + PBO	ACEI/ARB + AA	ACEI/ARB + PBO	ACEI/ARB + AA	ACEI/ARB + PBO	ACEI/ARB + AA	ACEI/ARB + PBO	ACEI/ARB + AA	ACEI/ARB + PBO	ACEI/ARB + AA	ACEI/ARB + PBO
van der Meiracker, 2006[56]	5/29 (17.2)	2/30 (6.7)							HyperK: 5/29 (17.2)	HyperK: 1/30 (3.3)		

ACEI/ARB = angiotensin converting enzyme inhibitor or angiotensin receptor blocker; AA = aldosterone antagonist; PBO = placebo

Appendix Evidence Table C66. Overview of BB versus placebo trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Cohen-Solal, 2009[57] Flather, 2005[58] SENIORS Country Europe (11 countries) Funding Source: Private Industry	Inclusion: Men and women, age ≥70 years, clinical history of chronic heart failure with at least one of the following: a) documented hospital admission in past 12 months with discharge diagnosis of CHF or b) documented LVEF ≤35% in past 6 months Exclusion: New drug therapy for CHF in the 6 weeks prior to randomization, any change in cardiovascular drug therapy in the 2 weeks prior to randomization, heart failure due primarily to uncorrected valvular heart disease, contraindication or previous intolerance to beta-blockers, current use of beta-blockers, significant hepatic or renal dysfunction, cerebrovascular accidents within the previous 3 months, on a waiting list for percutaneous coronary intervention or cardiac surgery or other major medical conditions that may have reduced survival during the period of the study	n=704 (this is subgroup with GFR ≤55.5 ml/min/1.73m2 from larger study of 2,135 patients) Age (yr): 77.4 Gender (Male %): 59.2 Race/Ethnicity (%): NR Weight (kg): NR BMI: 26.6 Systolic BP (mm Hg): 134.0 Diastolic BP (mm Hg): 78.1 CKD stage: NR Serum creatinine (umol/L): 137.8 (=1.56 mg/dL) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 43.5 HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 29.4 History of HTN (%): NR Dyslipidemia (%): 46.9 (hyperlipidemia) History of CAD (%): NR History of CHF (%): 100 Peripheral arterial disease (%): NR History of MI (%): 46.4 History of Stroke (%): NR Current smoker (%): 5.4 History of AKI (%): NR	n=348 Nebivolol, 1.25 mg once daily increased to 2.5 and 5 mg every 1-2 weeks to target of 10 mg once daily over max of 16 weeks n=356 Placebo Followup period: 21 months Study withdrawals (%): Not reported for eGFR subgroups	Allocation Concealment: adequate Blinding: double blind Intention to Treat Analysis (ITT): no (7 excluded from main analysis; additional 16 excluded from sub-group analysis due to missing basline creatinine) Withdrawals/Dropouts adequately described: unclear

Appendix Evidence Table C66. Overview of BB versus placebo trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Ghal, 2009[59] MERIT-HF Country U.S., Sweden Norway, multi-site Funding Source: NA	Inclusion: Eligible patients were men and women, aged 40-80 years, supine resting heart rate ≥68/min. who had had symptomatic heart failure (New York Heart Association [NYHA] functional class II–IV) for 3 months or more before randomization and who were receiving optimum standard therapy at enrollment (2 weeks before randomization), defined as any combination of diuretics and an ACEI. If an ACEI was not tolerated, hydralazine, long-acting nitrate, or an angiotensin-II-receptor antagonist could be used. Digitalis could also be prescribed. Other inclusion criteria were a stable clinical condition during the 2-week run-in phase between enrollment and randomization, and a left-ventricular ejection fraction of 0.40 or lower within 3 months before enrollment. Patients with ejection fraction 0.36 to 0.40 included only if their maximum walking distance was 450 m or less in a 6 min walk test. Exclusion: acute myocardial infarction or unstable angina within 28 days before randomisation; indication or contraindication for treatment with B-blockade or drugs with B-blocking properties such as amiodarone; B-blockade within 6	n=1,469 (this is subgroup with GFR ≤60 ml/min/1.73m2 from larger MERIT study of 3,991 patients) Age (yr): 68.1 Gender (Male %): 68.3 Race/Ethnicity (%): NR Weight (kg): NR BMI: 26.8 Systolic BP (mm Hg): 130.3 Diastolic BP (mm Hg): 76.7 CKD stage: NR Serum creatinine (umol/L): 134.1 (=1.52 mg/dL) Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 47.7 HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 29.3 History of HTN (%): 49.0 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 100 Peripheral arterial disease (%): NR History of MI (%): 55.3 History of Stroke (%): NR Current smoker (%): 9.7 History of AKI (%): NR	n= 735 Metoprolol CR/XL, 12.5 mg daily for NYHA III-IV pts and 25.0 mg daily for NYHA II pts, to a targeted 200 mg daily over 8 weeks n=734 Placebo Followup period: 1 year Study withdrawals (%): Not reported for CKD subgroup	Allocation Concealment: adequate Blinding: double blind Intention to Treat Analysis (ITT): yes Withdrawals/Dropouts adequately described: unclear

Appendix Evidence Table C66. Overview of BB versus placebo trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	weeks before enrollment; heart failure secondary to systemic disease or alcohol abuse; scheduled or performed heart transplantation or cardiomyoplasty, or implanted cardioversion defibrillator (expected or performed), or procedures such as coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty planned or performed in the past 4 months; atrioventricular block of the second and third degree, unless the patient had an implanted pacemaker and a spontaneous heart rate of 68 beats per min or more; unstable decompensated heart failure (pulmonary oedema, hypoperfusion) or supine systolic blood pressure lower than 100 mm Hg at enrollment; any other serious disease that might complicate management and followup according to the protocol; use of calcium antagonists such as diltiazem or verapamil; use of amiodarone within 6 months before enrollment; or poor compliance, defined as more than a 25% deviation of the number of observed compared with number of expected consumed placebo tablets during the run-in period.			

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR =

glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C67. Clinical outcomes (outcomes part A), BB versus placebo trials

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo
Cohen-Solal, 2009[57]	71/348 (20.4)	92/356 (25.8)	49/348 (14.1)	67/356 (18.8)								
Ghali, 2009[59]	63/735 (8.6)	105/734 (14.3)										

BB = beta blocker

Appendix Table C68. Clinical outcomes (outcomes part B), BB versus placebo trials

Study	Stroke, Nonfatal, n/N (%)		Stroke, Fatal, n/N (%)		CHF, Any, n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome, n/N (%)*	
	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo
Cohen-Solal, 2009[57]									129/348 (37.1)	153/356 (43.0)
Ghali, 2009[59]							(A)90/735 (12.2); (B)15/735 (2.0)	(A)147/734 (20.0); (B)36/734 (4.9)	(A)136/735 (18.5); (B)64/735 (8.7)	(A)214/734 (29.2); (B)107/734 (14.6)

CHF = congestive heart failure; BB = beta blocker

*See Composite vascular outcome definitions table

Appendix Table C69. Composite vascular outcome definitions, BB versus placebo trials

Study	Definition
Cohen-Solal, 2009[57]	All-cause mortality or cardiovascular hospital admission (time to first event)
Ghali. 2009[59]	Study defined multiple composite vascular outcomes, including: (A) all-cause mortality and CHF hospitalization;and (B) cardiac death and nonfatal MI.

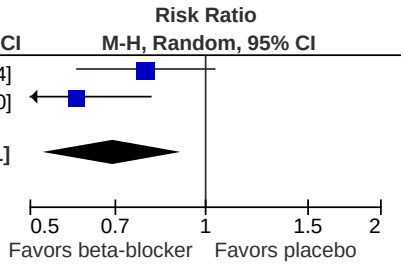
BB = beta blocker; CHF = congestive heart failure; MI = myocardial infarction

Appendix Figure C15. Forest plots for BB versus placebo trials

All-cause mortality

Study or Subgroup	Beta-blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen-Solal 2009	71	348	92	356	52.2%	0.79 [0.60, 1.04]
Ghali 2009	63	735	105	734	47.8%	0.60 [0.45, 0.80]
Total (95% CI)		**1083**		**1090**	**100.0%**	**0.69 [0.53, 0.91]**
Total events	134		197			

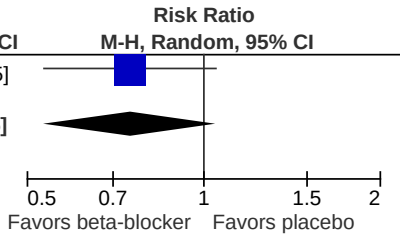
Heterogeneity: Tau² = 0.02; Chi² = 1.83, df = 1 (P = 0.18); I² = 45%
Test for overall effect: Z = 2.66 (P = 0.008)



Cardiovascular mortality

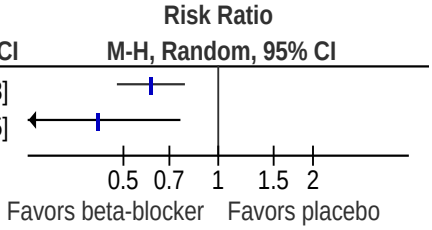
Study or Subgroup	Beta-blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen-Solal 2009	49	348	67	356	100.0%	0.75 [0.53, 1.05]
Total (95% CI)		**348**		**356**	**100.0%**	**0.75 [0.53, 1.05]**
Total events	49		67			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.68 (P = 0.09)



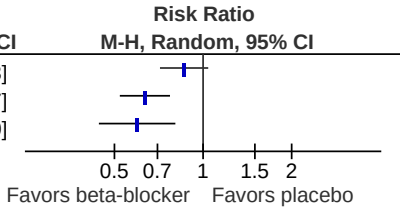
Congestive heart failure hospitalization (A) and death (B)

Study or Subgroup	Beta-blocker Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Ghali (MERIT-HF) A	90	735	147	734	0.61 [0.48, 0.78]
Ghali (MERIT-HF) B	15	735	36	734	0.42 [0.23, 0.75]



Composite vascular outcome (see Table C69 for definitions)

Study or Subgroup	Beta-blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cohen-Solal 2009	129	348	153	356		0.86 [0.72, 1.03]
Ghali (MERIT-HF) A	136	735	214	734		0.63 [0.53, 0.77]
Ghali (MERIT-HF) B	64	735	107	734		0.60 [0.45, 0.80]



Appendix Table C70. Study withdrawals and adverse events (outcomes part D), BB versus placebo trials

Study	Study Withdrawals: Any		Serious Adverse Event: Any		Serious Adverse Event: Any Leading to Withdrawal		Adverse Event: Any		Adverse Event: Other Specific		Renal Adverse Events: Any	
	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo	BB	Placebo
Cohen-Solal, 2009[57]							23/440 (5.2)	11/446 (2.5)	Hypo-tension 2/440 (0.5) Brady-cardia 10/440 (2.3) Heart failure 12/440 (2.7)	Hypo-tension 0/446 (0.0) Brady-cardia 3/446 (0.7) Heart failure 9/446 (2.0)	0/440*	0/446*
Ghali, 2009[59]							NR**	NR**				

BB = beta blocker; NR = not reported

*For safety analysis, cut point was eGFR<60 mL/min/1.73m^2 (efficacy analyis cut point was eGFR<55.5 mL/min/1.73m^2)

**Study reported rates of discontinuation of study medication due to adverse events per 100 person years but did not report data on the number of patients with any withdrawal or adverse event endpoint by treatment group. The most commonly reported adverse events leading to discontinuation of study medication were cardiac failure, fatigue, bradycardia, dizziness, and hypotension, with no data reported by treatment group.

Appendix Evidence Table C71. Overview of CCB versus placebo trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Berl, 2003[60] Lewis, 2001[40] IDNT International (North America, Latin America, Europe, United Kingdom, Israel, Australia, New Zealand, Southeast Asia) Multi-site Funding Source: Industry	Inclusion: ages 30-70; documented diagnosis of type 2 DM; hypertension (sitting SBP >135 mm Hg, sitting DBP >85 mm Hg, or documented treatment with antihypertensive agents); proteinuria (urinary protein excretion >900 mg/24h); serum creatinine between 1.0 and 3.0 mg/dL (women) and 1.2-3.0 mg/dL (men) Exclusion: none stated	N=1,136 Age (yr): 58.7 Gender (Male %): 67 Race/Ethnicity (%): 71.0% white, 14.5% African American, 5.0% Hispanic, 5.5% Asian/Pacific Islander, 4.5% other Weight (kg): NR BMI: 30.7 Systolic BP (mm Hg): 158.5 Diastolic BP (mm Hg): 87.0 CKD stage: NR Serum creatinine (mg/dL): 1.7 Creatinine clearance (mL/min): NR Albuminuria (gday): 1.9 Proteinuria (g/day): 2.9 Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 8.2 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of cardiovascular disease (%): 29.5 History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n= 567 amlodipine (titrated from 2.5 to 10 mg/day)* n= 569 placebo* Followup period: 2.5 years (mean) Study withdrawals (%): 0.5 *Antihypertensives other than ACEIs, ARBs, and CCBs used as needed; target blood pressure was SBP ≤135 mm Hg (or 10 mm Hg lower than screening value if that value was >145 mmHg) and DBP ≤85 mm Hg	Allocation Concealment: Adequate Blinding: Double blind Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C71. Overview of CCB versus placebo trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Crepaldi, 1998[10] Italy Multi-site Funding Source: None reported	Inclusion: ages 18 to 65 years; onset of insulin-dependent diabetes mellitus before age 35; insulin treatment within 3 years of diagnosis; clinical stability (HbA_{1c} <11% at entry and within 30% of value at entry during past 12 months; standing SBP from 115 to 140 mm Hg (without antihypertensives) and DBP from 75 to 90 mmHg at entry; median albumin excretion rate between 20 and 200 µg/min from 3 timed overnight urine collections within 2 weeks of entry; GFR ≥80 ml/min/1.73m^2 at randomization Exclusion: impaired renal function; serum creatinine >10% above upper limit of normal laboratory range (125 µmol/l) and median (from 3 measures) albumin excretion rate >200 µg/min at entry (after randomization); history of any nondiabetic renal disease; hematuria; evidence of clinically significant liver or hematological disease; evidence of aortic or mitral valve obstruction, arrhythmias, unstable angina, or history of myocardial infarction within the previous 3 months; clinical evidence of autonomic neuropathy; systematic malignancy; hyperkalemia (serum potassium >5.5 mmol/l at pretrial screen or entry; serum triglycerides >3.4 mmol/l or total cholesterol >6.5 mmol/l at routine pretrial check; known familiar lipid disorders; known risk of transmitting AIDS or viral hepatitis; known hypersensitivity or contraindications to ACEIs, nifedipine, or atenolol; women of child-bearing age not using medically acceptable methods of birth control (oral contraceptives were not allowed) or those planning pregnancy	N= 90 (baseline data reported for 60 patients who were not excluded during run-in phase) Age (yr): 36.6 Gender (Male %): 70 Race/Ethnicity (%): NR Weight (kg): 67.4 BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR CKD stage: NR Albumin (g/dl): 4.4 Serum creatinine (µmol/L): 85.8 (=0.97 mg/dL) Creatinine clearance (mL/min): 107.8 Albuminuria (µg/min): 80.2 Albumin/Creatinine ratio (mg/mmol): NR GFR (ml/min/1.73m^2): 111.8 HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 0 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): 58.3 History of AKI (%): NR	n= 41 10 mg nifedipine* n= 49 placebo* Followup period: 3 years Study withdrawals (%): 32.2 *If BP not controlled at 1 month after randomization (reduction of SBP and DBP by <5% of baseline), dose was doubled; if BP not controlled at 3 months (reduction of SBP and DBP by <5% of baseline and standing BP >140/90 mm HG) 50 mg/day atenolol added; if BP not controlled (standing BP >140/90 mm Hg) atenolol doubled; if BP still not adequately controlled (standing BP > 160/90 mmHg) patient withdrawn	Allocation Concealment: Unclear Blinding: Double blind Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C71. Overview of CCB versus placebo trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	during the treatment period; treatment compliance over the 4 wk placebo run in of <85%; on antihypertensive treatment			

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C72. Summary of study baseline characteristics, CCB versus placebo trials

Characteristic	Mean (range unless otherwise noted)	Number of Trials Reporting
Patients randomized, n	1226 (90-1,136)	2
Age of subjects, years	57.6 (36.6-58.7)	2
Gender, male, %	67.2 (67-70)	2
Race/ethnicity, white, %	71	1
Race/ethnicity, black, %	14.5	1
Body Mass Index	30.7	1
Weight (kg)	67.4	1
Systolic blood pressure, mmHg	158.5	1
Diastolic blood pressure, mmHg	87.0	1
Albuminuria, g/day	1.9	1
Albuminuria, µg/min	80.2	1
Proteinuria, g/day	2.9	1
Serum creatinine, mg/dL	1.7 (0.97-1.7)	2
Creatinine clearance, ml/min	107.8	1
GFR, ml/min/1.73m^2	111.8	1
History of diabetes, %	100 (both studies)	2
% HbA_{1c}	8.2	1
History of hypertension (%)	95 (0-100)	2
History of cardiovascular disease, %*	29.5	1
History of CHF, %	NR	0
Current smoker, %	58.3	1

CCB = calcium channel blocker; GFR = glomerular filtration rate, CHF = congestive heart failure

Appendix Table C73. Clinical outcomes (outcomes part A), CCB versus placebo trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial infarction, Nonfatal n/N (%)		Stroke, Any n/N (%)	
	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo
Berl, 2003[60] Lewis, 2001[40]	83/567 (14.6)	93/569 (16.3)	37/567 (6.5)	46/569 (8.1%)	27/567 (4.8)	46/569 (8.1)					15/567 (2.6)	26/569 (4.6)
Crepaldi, 1998[10]	1/41 (2.4)	0/49	1/41 (2.4)	0/49	0/41	1/49 (2.0)						

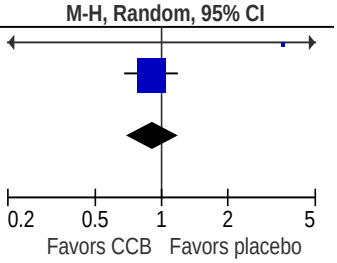
CCB = calcium channel blocker

Appendix Figure C16. Forest plots for CCB versus placebo trials

All-cause mortality

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crepaldi 1998	1	41	0	49	0.7%	3.57 [0.15, 85.39]
Lewis (IDNT) 2001	83	567	93	569	99.3%	0.90 [0.68, 1.18]
Total (95% CI)		**608**		**618**	**100.0%**	**0.90 [0.69, 1.19]**
Total events	84		93			

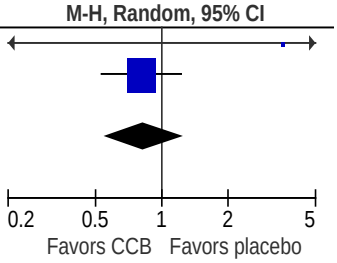
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)



Cardiovascular mortality

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crepaldi 1998	1	41	0	49	1.7%	3.57 [0.15, 85.39]
Lewis (IDNT) 2001	37	567	46	569	98.3%	0.81 [0.53, 1.22]
Total (95% CI)		**608**		**618**	**100.0%**	**0.83 [0.55, 1.25]**
Total events	38		46			

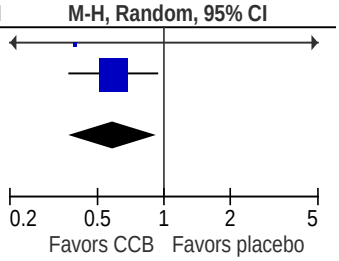
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)



Myocardial infarction

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crepaldi 1998	0	41	1	49	2.1%	0.40 [0.02, 9.49]
Lewis (IDNT) 2001	27	567	46	569	97.9%	0.59 [0.37, 0.93]
Total (95% CI)		**608**		**618**	**100.0%**	**0.58 [0.37, 0.92]**
Total events	27		47			

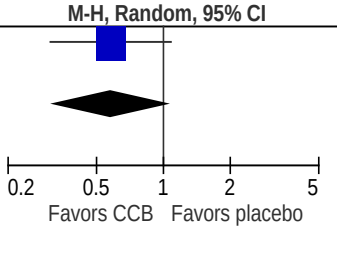
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)



Stroke

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	15	567	26	569	100.0%	0.58 [0.31, 1.08]
Total (95% CI)		**567**		**569**	**100.0%**	**0.58 [0.31, 1.08]**
Total events	15		26			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.71 (P = 0.09)

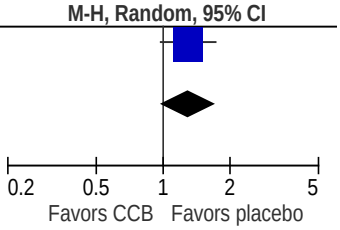


Appendix Figure C16. Forest plots for CCB versus placebo trials (continued)

Congestive heart failure

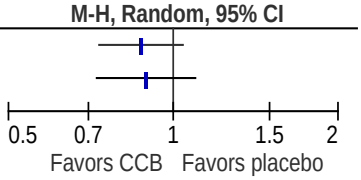
Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	93	567	72	569	100.0%	1.30 [0.97, 1.72]
Total (95% CI)		**567**		**569**	**100.0%**	**1.30 [0.97, 1.72]**
Total events	93		72			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.79 (P = 0.07)



Composite vascular outcome (see Table C75 for definitions)

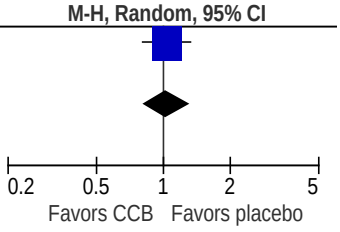
Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) A	161	567	185	569	0.87 [0.73, 1.04]
Lewis (IDNT) B	128	567	144	569	0.89 [0.72, 1.10]



End-stage renal disease

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	104	567	101	569	100.0%	1.03 [0.81, 1.32]
Total (95% CI)		**567**		**569**	**100.0%**	**1.03 [0.81, 1.32]**
Total events	104		101			

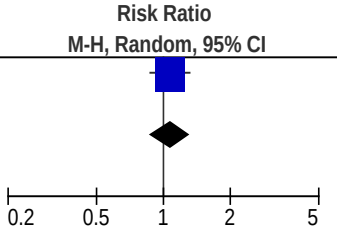
Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)



Doubling of serum creatinine

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	144	567	135	569	100.0%	1.07 [0.87, 1.31]
Total (95% CI)		**567**		**569**	**100.0%**	**1.07 [0.87, 1.31]**
Total events	144		135			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

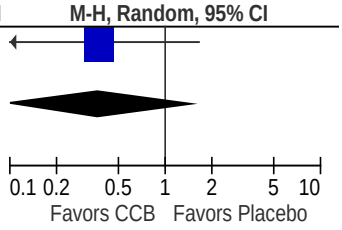


Appendix Figure C16. Forest plots for CCB versus placebo trials (continued)

Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crepaldi 1998	2	26	7	34	100.0%	0.37 [0.08, 1.65]
Total (95% CI)		**26**		**34**	**100.0%**	**0.37 [0.08, 1.65]**
Total events	2		7			

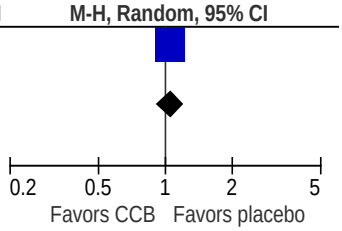
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



Composite renal outcome (see Table C77 for definitions)

Study or Subgroup	Calcium channel blocker Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lewis (IDNT) 2001	233	567	222	569	100.0%	1.05 [0.91, 1.21]
Total (95% CI)		**567**		**569**	**100.0%**	**1.05 [0.91, 1.21]**
Total events	233		222			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)



Appendix Table C74. Clinical outcomes (outcomes part B), CCB versus placebo trials

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)*	
	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo
Berl, 2003[60] Lewis, 2001[40]					93/567 (16.4)	72/569 (12.7)			(A)161/567 (28.4) (B)128/567 (22.6)	(A)185/569 (32.5) (B)144/569 (25.3)
Crepaldi, 1998[10]										

CCB = calcium channel blocker; CHF = congestive heart failure
*See Composite vascular outcome definitions table

Appendix Table C75. Composite vascular outcome definitions, CCB versus placebo trials

Study	Definition
Berl, 2003[60] Lewis, 2001[40]	Study defined two composite vascular endpoints as follows: (A) Myocardial infarction, heart failure, permanent neurologic deficit of at least 24-hour duration attributed to stroke, or unplanned (at time of randomization) coronary artery revascularization procedure (all before renal failure, death, or censorship)[60] and (B) Death from cardiovascular causes, nonfatal myocardial infarction, heart failure resulting in hospitalization, permanent neurologic deficit caused by a cerebrovascular event, or lower limb amputation above the ankle.[40]

CCB = calcium channel blocker

Appendix Table C76. Clinical renal outcomes (outcomes part C), CCB versus placebo trials

Study	End-stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)*	
	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo
Berl, 2003[60]	104/567 (18.3)	101/569 (17.8)	144/567 (25.4)	135/569 (23.7)					233/567 (41.1)	222/569 (39.0)
Lewis, 2001[40]										
Crepaldi, 1998[10]							2/26 (7.7)	7/34 (20.6)		

CCB = calcium channel blocker; GFR = glomerular filtration rate
*See Composite renal outcome definitions table

Appendix Table C77. Composite renal outcome definitions, CCB versus placebo trials

Study	Definition
Berl, 2003[60] Lewis, 2001[40]	Doubling of baseline serum creatinine concentration, onset of end-stage renal disease (initiation of dialysis, renal transplantation, or serum creatinine concentration ≥6.0 mg/dL), or death from any cause

CCB = calcium channel blocker

Appendix Table C78. Study withdrawals and adverse events (outcomes part D), CCB versus placebo trials

Study	Study Withdrawals, Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Serious Adverse Event: Any Leading to Withdrawal, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Any Specific, n/N (%)		Renal Adverse Events: Any, n/N (%)	
	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo	CCB	Placebo
Berl 2003[60] Lewis 2001[40]	2/567 (0.4)	4/569 (0.7)	*NR	*NR	†NR	†NR	†NR	†NR	HyperK: 3/567 (0.5)	HyperK: 2/569 (0.4)	‡NR	‡NR
Crepaldi 1998[10]	15/41 (36.6)	15/49 (30.6)					#NR	#NR	#NR	#NR		

CCB = calcium channel blocker; ARB = angiotensin receptor blocker; HyperK = hyperkalemia

*Study reported that 61% of participants had at least one serious adverse event but didn't report results by treatment group (note that study also included an ARB arm).

† Results were not reported for the proportion of study participants with any adverse event, or any serious adverse event leading to withdrawal, either overall or within groups. However, study reported that 51/567 (9.0%) of CCB group and 41/569 (7.2%) of placebo group discontinued treatment due to adverse event.

‡ Study reported one episode of an early increase in serum creatinine concentration suggestive of renal artery stenosis that necessitated stopping the study medication, but did not indicate in which treatment group this adverse event occurred.

During run-in period, three adverse events resulted in withdrawal from placebo group (two lower limb edema, one hyperkalemia); during randomized study, six adverse events resulted in withdrawal from placebo group (one each herpes zoster, lunge cancer, flaulence, tuberculosis, severe diabetic neuropathy, and myocardial infarction; also reported that 27% of those on CCB and 20% of those on placebo experienced side effects that did not cause withdrawal from study.

Appendix Evidence Table C79. Overview of diuretic versus placebo trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Pahor, 1998[61] Multi-center United States Funding Source: Government	Inclusion: aged 60 and above; BP inclusion criteria were a systolic BP of 160 to 219 mm Hg and a diastolic BP of less than 90 mm Hg assessed as the average of 4 measurements (2 measurements were obtained at each of the 2 baseline visits). Exclusion: a systolic BP of 220 mm Hg or higher, a recent myocardial infarction or stroke, or the presence of a major illness such as cancer, alcoholic liver disease, renal failure, insulin-treated diabetes mellitus, and depression. Participants who were receiving an antihypertensive treatment were considered potentially eligible if they had a systolic BP between 130 and 219 mm Hg and a diastolic BP of less than 85 mmHg and were free of major illnesses.	n=393 (subgroup with baseline serum creatinine above normal level [119.4-212.2 µmol/L or 1.35-2.40 mg/dL from overall cohort of 4,336) Baseline characteristics from n=393 with elevated baseline creatinine: Age (yr): 74.0 Gender (Male %): 81.4 Race/Ethnicity (%): White 76.1 Black 19.8 Asian 2.8 Weight (kg): NA BMI: 27.2 Systolic BP (mm Hg): 172 Diastolic BP (mm Hg): 77 CKD stage: NA Serum creatinine (umol/L): NR Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (mg/day): NR Albumin/creatinine ratio (mg/g): NA GFR (ml/min/1.73m^2): NA HbA_{1c} (%): NA Total cholesterol (mg/dL): NA LDL cholesterol (mg/dL): NA Diabetes (%): 11.7 History of HTN (%): 100 Dyslipidemia (%): NA History of CAD (%): NA History of CHF (%): NA Peripheral arterial disease (%): NA History of MI (%): 5.4 History of Stroke (%): 3.8 Current smoker (%): NA History of AKI (%): NA	n= 216 Initiated chlorthalidone 12.5mg/day (if goal BP not met, dose may be increased, followed by addition of atenolol, then reserpine) n=177 Placebo Treatment goal was SBP <160 mm Hg or at least 20 mm Hg reduction from baseline. Followup period: 5 years Study withdrawals (%): Not reported for elevated serum creatinine group.	Allocation concealment: adequate Blinding: double blinded (though open-label potassium supplement given to all participants with serum potassium levels <3.5 mmol/L) Intention to Treat Analysis (ITT): yes Withdrawals/Dropouts adequately described: yes (in original RCT)

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR =

glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C80. Clinical outcomes (outcomes part A), diuretic versus placebo trial

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo
Pahor, 1998[61]	37/216 (17.1)	26/177 (14.7)									14/216 (6.5)	22/177 (12.4)

Appendix Table C81. Clinical outcomes (outcomes part B), diuretic versus placebo trial

Study	Stroke, Nonfatal, n/N (%)		Stroke, Fatal, n/N (%)		CHF, Any, n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome, n/N (%)*	
	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo
Pahor, 1998[61]									(A)36/216 (16.7) (B)16/216 (7.4)	(A)47/177 (26.6); (B)21/177 (11.9)

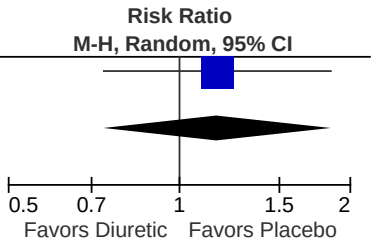
CHF = congestive heart failure
*See Composite vascular outcome definitions table

Appendix Figure C17. Forest plots for diuretic versus placebo trial

All-cause mortality

Study or Subgroup	Diuretic Events	Diuretic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Pahor 1998	37	216	26	177	100.0%	1.17 [0.74, 1.85]
Total (95% CI)		**216**		**177**	**100.0%**	**1.17 [0.74, 1.85]**
Total events	37		26			

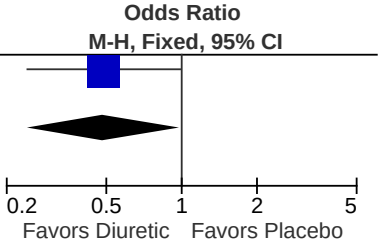
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)



Stroke, any

Study or Subgroup	Diuretic Events	Diuretic Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Pahor 1998	14	216	22	177	100.0%	0.49 [0.24, 0.99]
Total (95% CI)		**216**		**177**	**100.0%**	**0.49 [0.24, 0.99]**
Total events	14		22			

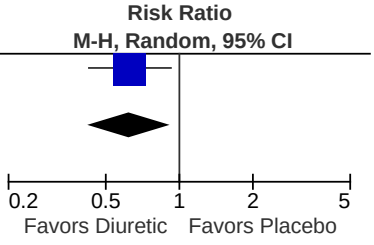
Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)



Composite vascular outcome (A) (see Table C82 for definition)

Study or Subgroup	Diuretic Events	Diuretic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Pahor 1998	36	216	47	177	100.0%	0.63 [0.43, 0.92]
Total (95% CI)		**216**		**177**	**100.0%**	**0.63 [0.43, 0.92]**
Total events	36		47			

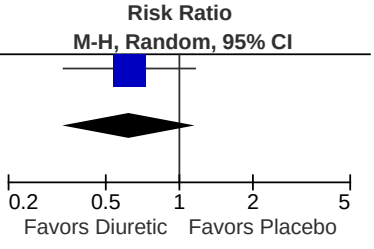
Heterogeneity: Not applicable
Test for overall effect: Z = 2.37 (P = 0.02)



Composite vascular outcome (B) (see Table C82 for definition)

Study or Subgroup	Diuretic Events	Diuretic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Pahor 1998	16	216	21	177	100.0%	0.62 [0.34, 1.16]
Total (95% CI)		**216**		**177**	**100.0%**	**0.62 [0.34, 1.16]**
Total events	16		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)



Appendix Table C82. Composite vascular outcome definitions, diuretic versus placebo trial

Study	Definition
Pahor, 1998[61]	Study defined multiple composite vascular outcomes, including: (A) "Any cardiovascular event" defined as stroke, TIA, MI, heart failure, CABG, angioplasty, aneurysm, endarterectomy, sudden death, or rapid cardiac death (within 1-24 hours of onset of severe cardiac symptoms unrelated to other known causes); and (B) "Any coronary event" defined as fatal and nonfatal coronary heart disease.

TIA = transient ischemic attack; MI = myocardial infarction; CABG = coronary artery bypass grafting

Appendix Table C83. Study withdrawals and adverse events (outcomes part D), diuretic versus placebo trial

Study	Study Withdrawals: Any		Serious Adverse Event: Any		Serious Adverse Event: Any Leading to Withdrawal		Adverse Event: Any		Adverse Event: Other Specific		Renal Adverse Events: Any	
	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo	Diuretic	Placebo
Pahor, 1998[61]												

Study did not report withdrawals or adverse events overall or by treatment group within the strata of participants with CKD (i.e. baseline serum creatinine 119.4 to 212.2 µmol/L [corresponding to 1.35 to 2.40 mg/dL]).

Appendix Evidence Table C84. Overview of ACEI versus conventional therapy without ACEI trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Cinotti, 2001[62] Country Italy, multisite Funding Source: Industry	Inclusion: ages 18-70 years; chronic renal insufficiency due to primary renoparenchymal diseases; no ACEI therapy for at least 3 months; renal insufficiency of at least 12 months with creatinine clearance between 20 and 50 ml/min/1.73m^2 with variation <30% in at least 3 determinations during past 3 months; hypertension (either nontreated DBP ≥95 mmHg or well-documented treatment with antihypertensive drugs*); proteinuria ≤1.0 g/day Exclusion: nephropathy secondary to diabetes or other systemic diseases; malignant hypertension or previous antihypertensive treatment with >2 drugs; cerebrovascular events in the last 6 months or MI in the last 3 months; heart failure, angina, or other major cardiac diseases; significant liver, hemopoietic, or endocrine pathology; concomitant therapy with steroids or immuosuppressive drugs and erythropoietin; pregnancy; lactation; serum potassium <3 mEq/l or >5.8 mEq/l; hypersensitivity or any contraindication to use of ACEI *During 3 month run-in period, patients to follow 0.8 g/kg IBW protein and 3-4 g/day salt diet. Antihypertensive agents (CCB, BB or alpha blocker) continued or added. Patients required to be "compliant" and have stable DBP ≤90 mm Hg with one or two drugs at end of run-in to proceed to randomization.	N=131 Age (yr): 50.8 Gender (Male %): 66 Race/Ethnicity (%): NR Weight (kg): 71.4 BMI: NR Systolic BP (mm Hg): 141.6 Diastolic BP (mm Hg): 85.7 CKD stage: NR Serum creatinine (mg/dL): 2.3 Creatinine clearance (mL/min): 36.3 Albuminuria (µg/min): NR Proteinuria (mg/day): 512 Albumin/creatinine ratio (mg/g): NR measured GFR (ml/min/1.73m^2): 35.8 HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): NR (no recent) History of Stroke (%): NR (no recent) Current smoker (%): NR History of AKI (%): NR	n=66 Lisinopril 5-10 mg/day or Lisinopril 10 mg/day with other antihypertensive drug (L) n=65 Conventional antihypertensive therapy (without ACEI) (C) NSAID use limited to 7 days, ASA allowed at <500 mg/d. Followup period: 22.5 months Study withdrawals (%): No information reported on study withdrawals	Allocation Concealment: Unclear Blinding: Open-label Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: No data reported on withdrawals/dropouts.

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction;

NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C85. Clinical outcomes (outcomes part A), ACEI versus conventional therapy without ACEI trial

Study	All-cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI
Cinotti, 2001[62]					0/66	1/65 (1.5)						

ACEI = angiotensin converting enzyme inhibitor

Appendix Table C86. Clinical renal outcomes (outcomes part C), ACEI versus conventional therapy without ACEI trial

Study	End-Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)*	
	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI
Cinotti, 2001[62]	2/66 (3.0)	5/65 (7.7)			3/66 (4.5)	7/65 (10.8)			5/66 (7.8)	12/65 (18.5)

ACEI = angiotensin converting enzyme inhibitor; GFR = glomerular filtration rate

*See Composite renal outcome definitions table

Appendix Table C87. Composite renal outcome definitions, ACEI versus conventional therapy without ACEI trial

Study	Definition
Cinotti, 2001[62]	Halving of GFR or need for dialysis.

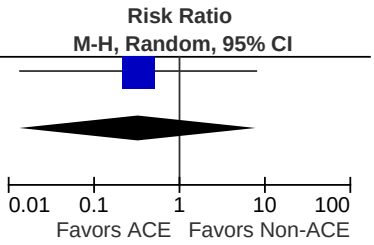
ACEI = angiotensin converting enzyme inhibitor; GFR = glomerular filtration rate

Appendix Figure C18. Forest plots for ACEI versus conventional therapy without ACEI trial

Myocardial infarction

Study or Subgroup	ACE Events	ACE Total	Non-ACE Events	Non-ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Cinotti 2001	0	66	1	65	100.0%	0.33 [0.01, 7.92]
Total (95% CI)		**66**		**65**	**100.0%**	**0.33 [0.01, 7.92]**
Total events	0		1			

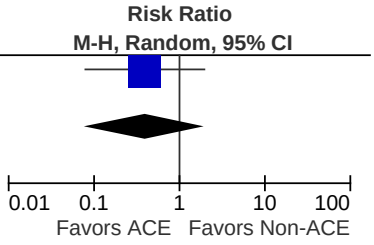
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)



End-stage renal disease

Study or Subgroup	ACE Events	ACE Total	Non-ACE Events	Non-ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Cinotti 2001	2	66	5	65	100.0%	0.39 [0.08, 1.96]
Total (95% CI)		**66**		**65**	**100.0%**	**0.39 [0.08, 1.96]**
Total events	2		5			

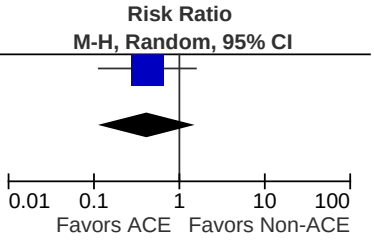
Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)



Halving of GFR

Study or Subgroup	ACE Events	ACE Total	Non-ACE Events	Non-ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Cinotti 2001	3	66	7	65	100.0%	0.42 [0.11, 1.56]
Total (95% CI)		**66**		**65**	**100.0%**	**0.42 [0.11, 1.56]**
Total events	3		7			

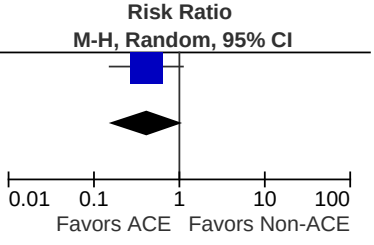
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)



Composite renal outcome (see Table C87 for definition)

Study or Subgroup	ACE Events	ACE Total	Non-ACE Events	Non-ACE Total	Weight	Risk Ratio M-H, Random, 95% CI
Cinotti 2001	5	66	12	65	100.0%	0.41 [0.15, 1.10]
Total (95% CI)		**66**		**65**	**100.0%**	**0.41 [0.15, 1.10]**
Total events	5		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)



Appendix Table C88. Study withdrawals and adverse events (outcomes part D), ACEI versus conventional therapy without ACEI trial

Study	Study Withdrawals, Any, n/N (%)		Study Withdrawals Due to Serious Adverse Events, n/N (%)		Serious Adverse Events, Any, n/N (%)		Adverse Events, Any, n/N (%)		Adverse Events, Specific, n/N (%)		Renal Adverse Events, Any, n/N (%)	
	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI	ACEI	Non-ACEI
Cinotti, 2001[62]	*NR	*NR	*NR	*NR	*NR	*NR			HyperK: 1/66 (1.5%); Uncontrolled hypotension: 1/66 (1.5%)	HyperK: 0/65; Uncontrolled hypotension: 0/65		

ACEI = angiotensin converting enzyme inhibitor

*Study did not report withdrawals, serious adverse events, or withdrawals due to serious adverse events, but did report discontinuation of treatment due to adverse events (4/66 [6.1%] in ACEI group and 3/65 [4.6%] in non-ACEI group).

Appendix Table C89. Overview of CCB versus BB trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Bakris[63] 1996 United States, Single-site Funding Source: Private (Foundation)	Inclusion: non-insulin dependent diabetes for ≥8 years; diabetic retinopathy; proteinuria ≥2.0 g/day; renal insufficiency (creatinine clearance <1.16 ml/sec [i.e. <70ml/min]); hypertension for ≥8 years; age ≥45 years Exclusion: Diastolic blood pressure >125 mm Hg on three consecutive readings during 2 week wash out period with no antihypertensive medications. Heart failure (ejection fraction ≤40%); history of poor diabetes control (blood glucose 11 mmol/l or HbA_{1c} >13%; history of difficult blood pressure control (maximum dose of ≥3 medications or diastolic blood pressure >105 mm Hg with medication); blindness, documented coronary artery disease; severe claudication (peripheral arterial disease); orthostatic hypotension (diabetic neuropathy); required intake of antiarrhythmic medications, calcium channel blockers, or angiotensin converting enzyme inhibitor; documented psychiatric disease; active urine sediment; blood glucose control by insulin therapy alone.	N=34 (CCB and BB groups) Age (yr): 62.1 Gender (Male %): 44.4 Race/Ethnicity (%): 56% black, 44% white Weight (kg): 105.6 BMI: 32.6 (calculated from given height & weight) Systolic BP (mm Hg): 158.4 Diastolic BP (mm Hg): 97.9 CKD stage: NR Serum creatinine (mmol/l): 163.8 (=1.85 mg/dL) Creatinine clearance (ml/s/1.73m^2): 1.01 (=60.6 ml/min/1.73m^2) Albuminuria (gday): NR Proteinuria (g/day): 4.36 Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 10.5 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of cardiovascular disease (%): NR History of CAD (%): 0 History of CHF (%): 0 Peripheral arterial disease (%): NR (severe claudication is excluded) History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n= 18 to either verapamil SR (n=8) or diltiazem SR (n=10)* n= 16 atenolol* Study including additional treatment arm of lisinopril (n=16) Followup period: 64 months (median) Study withdrawals (%): 11.5 *initial dose not reported; dosages titrated over two week period and then periodically throughout study to ensure similar arterial pressure control among groups; if additional blood pressure reduction needed, furosemide added (100% received furosemide by year 4); other antihypertensives (including alpha blockers and/or vasodilators) added if further blood pressure reduction needed. All patients also instructed in 90 meq/day Na and 0.8 g/kg protein and 6300 kJ ADA diet.	Allocation concealment: Unclear Blinding: Not reported Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Table C89. Overview of CCB versus BB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Wright, 2002[26] Wright, 1996[64] AASK United States Multi-site Funding Source: Government, Industry	Inclusion: self-identified African Americans; hypertension; ages 18 to 70; GFR between 20 and 65 mL/min/1.73m^2; no other identified causes of renal insufficiency Exclusion: diastolic BP <95 mm Hg; known history of diabetes mellitus (fasting glucose ≥149 mg/dL or random glucose >200 mg/dL); urinary protein to creatinine ratio >2.5; accelerated or malignant hypertension within 6 months; secondary hypertension; evidence of non-BP-related causes of chronic kidney disease; clinical congestive heart failure; specific indications for or contraindication to a study drug or study procedure.	N= 658 Age (yr): 54.8 Gender (Male %): 61.1 Race/Ethnicity (%): NR Weight (kg): NR BMI: NR Systolic BP (mm Hg): 150.0 Diastolic BP (mm Hg): 95.3 CKD stage: NR Albumin (g/dl): NR Serum creatinine (mg/dL): 2.03 Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (g/24h): 0.54 Protein/Creatinine ratio: 0.33 Urine protein/creatine ratio ≥0.22 (%): 32 GFR (ml/min/1.73m^2): 45.8 HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	n= 217 amlodipine (5 to 10 mg/day)* n= 441 metropolol (50 to 200 mg/day)* Followup period: 3 years (median, for GFR outcome)** Study withdrawals (%): 0 *if BP goal could not be achieved by randomized drug, additional open-labeled antihypertensives were added sequentially (furosemide, doxazosin, clonidine, and hydralazine or minoxidil) **amlodipine arm stopped early on recommendation of the data and safety monitoring board; patients in this arm were switched to open-label medication.	Allocation Concealment: Adequate Blinding: Participants and investigators masked to randomized drug but not BP goal; cardiovascular events classified by blinded end points committee Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes
Dahlof, 2005[65] ASCOT-BPLA Europe multi-site Funding Source: Industry	Inclusion: aged 40-79 years; untreated hypertension, SBP ≥160 mm Hg, DBP ≥100 mm Hg or both, treated hypertension with SBP ≥140 mm Hg or DBP 90 mm Hg or both; and at least 3 of the following risk factors (left ventricle hypertrophy, abnormalities on electrocardiogram, type II diabetes, PAD, previous stroke or TIA, male sex, age ≥55,	N=12,074 with "renal dysfunction" (undefined) in subgroup analysis out of 19,342 randomized overall Baseline data not presented for subgroup with renal dysfunction, though by entry criteria, the following characteristics could be determined: History of HTN (%): 100 History of MI (%): 0	n=5,893 amlodipine 5-10 mg, adding perindopril 4-8 mg as required n=6181 atenolol 50-100 mg, adding bendroflumethiazide 1.25-2.5 mg and potassium as required Followup period: 5.5 years	Allocation Concealment: adequate Blinding: Open with blinded end-point classification Intention to Treat Analysis (ITT): yes

Appendix Table C89. Overview of CCB versus BB trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL ≥6, family history of premature CHD) Exclusion: previous MI; currently treated angina; a cerebrovascular event within previous 3 months; fasting triglycerides >4.5 mmol/L; heart failure; uncontrolled arrhythmias; any clinical important hematological or biochemical abnormality on routine screening	History of CHF (%): 0	(median) (trial was stopped prematurely) Study withdrawals (%): 0.6 overall, but not reported for "renal dysfunction" subgroup	Withdrawals/Dropouts adequately described: yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PAD = peripheral arterial disease; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C90. Summary of study baseline characteristics, CCB versus BB trials

Characteristic	Mean (range unless otherwise noted)	Number of Trials Reporting
Patients randomized, n	12,766 (34-12,074)	3
Age of subjects, years	55.2 (54.8-62.1)	2
Gender, male, %	60.3 (44.4-61.1)	2
Race/ethnicity, white, %	2 (0-44)	2
Race/ethnicity, black, %	98 (56-100)	2
Body Mass Index	32.6	1
Systolic blood pressure, mmHg	150.4 (150.0-158.4)	2
Diastolic blood pressure, mmHg	95.4 (95.3-97.9)	2
Proteinuria, g/day	0.70 (0.54-4.36)	2
Serum creatinine, mg/dL	2.02 (1.85-2.03)	2
Creatinine clearance, ml/min/1.73m^2	60.6	1
GFR, ml/min/1.73m^2	45.8	1
Total cholesterol, mg/dl	NR	
LDL cholesterol, mg/dl	NR	
History of diabetes, %	4.9 (0 to 100)	2
% HbA_{1c}	10.5	1
History of hypertension (%)	100	3
History of cardiovascular disease, %*	NR	
History of CHF, %	0	3
Current smoker, %	NR	

CCB = calcium channel blocker; BB = beta blocker; GFR = glomerular filtration rate; LDL = low density lipoprotein; CHF = congestive heart failure; NR = not reported

*One study (n=34) excluded patients with history of heart failure or coronary artery disease; one study (n=12,074) excluded patients with history of MI

Appendix Table C91. Clinical outcomes (outcomes part A), CCB versus BB trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial infarction, Fatal, n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any n/N (%)	
	CCB	BB	CCB	BB	CCB	BB	CCB	BB	CCB	BB	CCB	BB
Bakris, 1996[63]	1/18 (5.6)	4/16 (25.0)	*NR	*NR			*NR	*NR				
Wright, 2002[26]; Norris 2006[27]	13/217 (6.0)	38/441 (8.6)	†NR	†NR								
Dahlof, 2005[65]												

CCB = calcium channel blocker; BB = beta blocker

* Study reported 5 (9.6%) cardiovascular deaths, 4 (7.7%) fatal myocardial infarctions, and 1 (1.9%) fatal stroke, but didn't indicate to which treatment group these patients had been assigned.

† Study did not report the number of participants with cardiovascular death, but instead the percentage of patients with cardiovascular death per patient year of followup: CCB 0.9%, BB 0.8%.

Appendix Table C92. Clinical outcomes (outcomes part B), CCB versus BB trials

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)*	
	CCB	BB	CCB	BB	CCB	BB	CCB	BB	CCB	BB
Bakris, 1996[63]			**NR	**NR						
Wright, 2002[26]									†NR	†NR
Dahlof, 2005									825/5893 (14.0)	989/6181 (16.0)

CCB = calcium channel blocker; BB = beta blocker; CHF = congestive heart failure; NR = not reported

*See Composite vascular outcome definitions table

**Study reported 1 fatal stroke (1.9%), but didn't indicate participant treatment group.

†Study did not report number of patients with composite vascular endpoint, "cardiovascular event," overall or by treatment group, but reported results as percent of patients with event per patient-year of follow-up: cardiovascular event CCB 1.7%, BB 2.9%.

Appendix Table C93. Composite vascular outcome definitions, CCB versus BB trials

Study	Definition
Wright, 2002[26]	Cardiovascular event, defined as cardiovascular mortality or first cardiovascular hospitalization.
Dahlof, 2005[65]	Study defined six composite vascular endpoints, but reported results within the subgroup of participants with "renal dysfunction" only in one of the secondary composite vascular endpoints, as follows: (A) Cardiovascular mortality, nonfatal MI (symptomatic and silent), unstable angina, chronic stable angina, life threatening arrhythmias, silent nonfatal heart failure, nonfatal stroke, peripheral arterial disease, revascularization procedures, and retinal vascular thromboses.

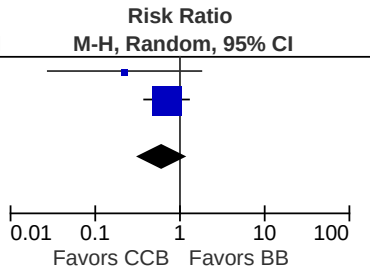
CCB = calcium channel blocker; BB = beta blocker

Appendix Figure C19. Forest plots for CCB versus BB trials

All-cause mortality

Study or Subgroup	CCB Events	CCB Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 1996	1	18	4	16	10.3%	0.22 [0.03, 1.79]
Wright 2002	13	217	38	441	89.7%	0.70 [0.38, 1.28]
Total (95% CI)		**235**		**457**	**100.0%**	**0.62 [0.31, 1.22]**
Total events	14		42			

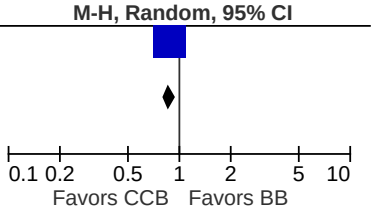
Heterogeneity: Tau² = 0.04; Chi² = 1.06, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 1.39 (P = 0.17)



Composite vascular outcome (see Table C93 for definition)

Study or Subgroup	CCB Events	CCB Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Dahlof 2005	825	5893	989	6181	100.0%	0.87 [0.80, 0.95]
Total (95% CI)		**5893**		**6181**	**100.0%**	**0.87 [0.80, 0.95]**
Total events	825		989			

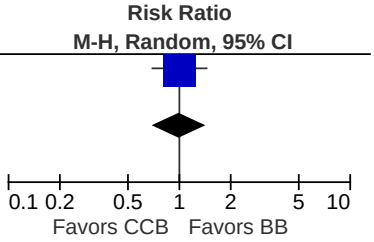
Heterogeneity: Not applicable
Test for overall effect: Z = 3.07 (P = 0.002)



End-stage renal disease

Study or Subgroup	CCB Events	CCB Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Wright 2002	36	217	73	441	100.0%	1.00 [0.70, 1.44]
Total (95% CI)		**217**		**441**	**100.0%**	**1.00 [0.70, 1.44]**
Total events	36		73			

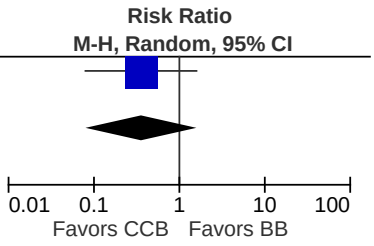
Heterogeneity: Not applicable
Test for overall effect: Z = 0.01 (P = 0.99)



Doubling of serum creatinine

Study or Subgroup	CCB Events	CCB Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Bakris 1996	2	18	5	16	100.0%	0.36 [0.08, 1.59]
Total (95% CI)		**18**		**16**	**100.0%**	**0.36 [0.08, 1.59]**
Total events	2		5			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.36 (P = 0.18)

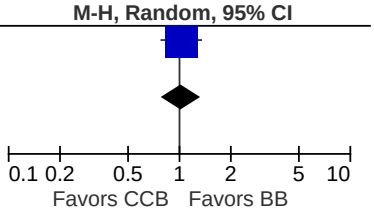


Appendix Figure C19. Forest plots for CCB versus BB trials (continued)

Composite renal outcome A (see Table C95 for definition)

Study or Subgroup	CCB Events	CCB Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Wright 2002	59	217	117	441	100.0%	1.02 [0.78, 1.34]
Total (95% CI)		**217**		**441**	**100.0%**	**1.02 [0.78, 1.34]**
Total events	59		117			

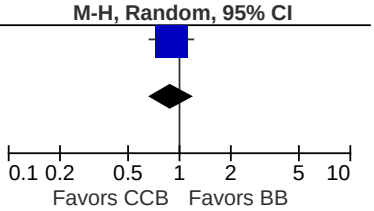
Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)



Composite renal outcome C (see Table C95 for definition)

Study or Subgroup	CCB Events	CCB Total	BB Events	BB Total	Weight	Risk Ratio M-H, Random, 95% CI
Wright 2002	49	217	111	441	100.0%	0.90 [0.67, 1.20]
Total (95% CI)		**217**		**441**	**100.0%**	**0.90 [0.67, 1.20]**
Total events	49		111			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)



Appendix Table C94. Clinical renal outcomes (outcomes part C), CCB versus BB trials

Study	End-stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome, n/N (%)*	
	CCB	BB	CCB	BB	CCB	BB	CCB	BB	CCB	BB
Bakris 1996[63]	**NR	**NR	2/18 (11.1)	5/16 (31.3)						
Wright 2002[26]	36/217 (16.6)	73/441 (16.6)							†(A)59/217 (27.2); (C)49/217 (22.5)	†(A)117/441 (26.5); (C)111/441 (25.2)
Dahlof 2005[65]										

CCB = calcium channel blocker; BB = beta blocker; GFR = glomerular filtration rate; NR = not reported

*See Composite renal outcome definitions table

**Study reported that 5/52 (9.6%) patients (includes the 18 in a separate ACEI group) started dialysis during trial, but didn't report results by treatment group.

†Study did not report number of participants with other composite renal outcomes reported, but instead reported multivariate adjusted relative risk (BB versus CCB) of these composite renal outcome events: (B) ESRD or death (RR 0.58; 95%CI, 0.40 to 0.83); and (C) ESRD or ≥50% decline in GFR (RR 0.76; 95%CI, 0.53 to 1.09).

Appendix Table C95. Composite renal outcome definitions, CCB versus BB trials

Study	Definition
Wright 2002[26]	(A) GFR event (reduction in GFR by 50% or by 25 ml/min/1.73m^2 from baseline mean) (C) ESRD or ≥50% decline in GFR

BB = beta blocker; CCB = calcium channel blocker; GFR = glomerular filtration rate; ESRD = end-stage renal disease

Appendix Table C96. Study withdrawals and adverse events (outcomes part D), CCB versus BB trials

Study	Study Withdrawals, Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Serious Adverse Event: Any Leading to Withdrawal, n/N (%)		Adverse event: Any, n/N (%)		Adverse Event: Any Specific, n/N (%)		Renal Adverse Events: Any, n/N (%)	
	CCB	BB	CCB	BB	CCB	BB	CCB	BB	CCB	BB	CCB	BB
Bakris, 1996[63]	*NR	*NR			0/18	0/16			†Pedal edema: 2/18 (11.1) Constipation: 10/18 (55.6) Impotence: 3/18 (16.7) Insomnia: 1/18 (5.6) Lethargy: 0/18	†Pedal edema: 2/16 (12.5) Constipation: 7/16 (43.8) Impotence: 9/16 (56.3) Insomnia: 6/16 (37.5) Lethargy: 13/16 (81.3)		
Wright, 2002[26]	‡0/217	‡0/441					†NR	†NR	†NR	†NR		
Dahlof, 2005[65]												

CCB = calcium channel blocker; BB = beta blocker

* 6 withdrawals, treatment group not specified

† Study reported additional participants with specific adverse events as follows: hyperkalemia (CCB 0/18, BB 1/16), dizziness (CCB 2/18, BB 3/16); headache (CCB 2/18, BB 1/16); exercise intolerance (CCB 0, BB 7); dry mouth (CCB 1, BB 13)

‡ Study reported no withdrawals in either treatment group, but also indicated that excluding deaths and dialysis, 23/217 randomized to CCB and 30/441 assigned to BB were no longer active study participants at its end.

† Study did not report the number and percentage of participants overall or by treatment group with any or specific adverse events, but instead reported as percentage of patients experiencing the adverse event per patient year of follow-up (%/pt-yr): hyperkalemia CCB 0, BB 0.2; angioedema CCB 2.3, BB 2.7; shortness of breath CCB 44.4, BB 45.8; syncope CCB 2.3, BB 6.3; dizziness CCB 46.7, BB 47.8; lightheadedness CCB 48.1, BB 47.8; edema CCB 59.8, BB 51.0; cough CCB 46.3, BB 41.5; sexual dysfunction CCB 25.7, BB 25.2.

Appendix Table C97. Overview of CCB versus diuretic trial

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Rahman 2005/2006[23,34] U.S., Canada, Puerto Rico, U.S. Virgin Islands, multi-site Funding Source: government	Inclusion: men and women 55 years or older who had stage 1 or stage 2 hypertension with at least 1 additional risk factor for coronary heart disease events. The risk factors included previous (>6 months) myocardial infarction or stroke, left ventricular hypertrophy demonstrated by electrocardiography or echocardiography, history of type 2 diabetes mellitus, current cigarette smoking, high-density lipoprotein cholesterol level of <5 mg/dL (<0.91 mmol/L), or documentation of other atherosclerotic cardiovascular disease. Exclusion: Individuals with a history of symptomatic heart failure and/or a known left ventricular ejection fraction of <35% were excluded. Participants with a serum creatinine level >2 mg/dL (176.8 µmol/L) as reported by the investigator were excluded. However, if the serum creatinine level measured at the time of randomization was found to exceed 2 mg/dL (176.8 µmol/L), these participants were maintained in the trial and followed up according to the study protocol.	n= 4,129 (Post hoc subgroup analysis within participants with GFR <60 ml/min/1.73m2 from overall study population for these treatment groups of 23,261) Age (yr): 70.8 Gender (Male %): 46.8 Race/Ethnicity (%): White non-Hispanic: 57.4 Black non-Hispanic: 25.3 White Hispanic: 11.6 Black Hispanic: 1.1 Othe:r 4.6 Weight (kg): NA BMI: 29.1 Systolic BP (mm Hg): 146.7 Diastolic BP (mm Hg): 82.5 CKD stage: NA Serum creatinine (umol/L): NA Creatinine clearance (mL/min): NA Albuminuria (µg/min): NA Proteinuria (mg/day): NA Albumin/creatinine ratio (mg/g): NA GFR (ml/min/1.73m^2): 50.3 HbA_{1c} (%): NA Total cholesterol (mmol/L): NA LDL cholesterol (mmol/L): NA Diabetes (%): 33.6 History of HTN (%): 100 Dyslipidemia (%): NA History of CAD (%): 30.2 History of CVD (%): 59.7 History of CHF (%): 0 Peripheral arterial disease (%): NA History of MI or stroke (%): 28.0 Current smoker (%): 17.6 History of AKI (%): NA	n=1,516 amlodipine 2.5, 5 and 10 mg/d n= 2,613 chlorthalidone 12.5, 12.5 (sham titration), and 25 mg/d Followup period: 4.9 yr Study withdrawals (%): Not reported for low GFR by treatment groups	Allocation Concealment:Unclear Blinding: double blind Intention-to-Treat Analysis (ITT): yes Withdrawals/Dropouts adequately described: Yes for study overall, but not specified by treatment groups

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF =

congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C98. Summary of study baseline characteristics, CCB versus diuretic trial

Characteristic	Mean (range unless otherwise noted)	Number of Trials Reporting
Patients randomized, n	4,129	1
Age of subjects, years	70.8	1
Gender, male, %	46.8	1
Race/ethnicity, white, %	69.0	1
Race/ethnicity, black, %	26.4	1
Body Mass Index	29.1	1
Systolic blood pressure, mmHg	146.7	1
Diastolic blood pressure, mmHg	82.5	1
Proteinuria, g/day	NR	
Serum creatinine, mg/dL	NR	
Creatinine clearance, ml/min/1.73m^2	NR	
GFR, ml/min/1.73m^2	50.3	1
Total cholesterol, mg/dl	NR	
LDL cholesterol, mg/dl	NR	
History of diabetes, %	33.6	1
% HbA_{1c}	NR	
History of hypertension (%)	100	1
History of cardiovascular disease, %	59.7	1
History of CHF, %	0	1
Current smoker, %	17.6	1

CCB = calcium channel blocker; NR = not reported; GFR = glomerular filtration rate; LDL = low density lipoprotein; CHF = congestive heart failure

Appendix Table C99. Clinical outcomes (outcomes part A), CCB versus diuretic trial

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal, n/N (%)		Myocardial infarction, Nonfatal, n/N (%)		Stroke, Any n/N (%)	
	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic
Rahman, 2006[34]											100/1516 (6.6)	157/2613 (6.0)

CCB = calcium channel blocker

Appendix Table C100. Clinical outcomes (outcomes part B), CCB versus diuretic trial

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)*	
	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic
Rahman, 2006[34]					174/1516 (11.5)	259/2613 (9.9)			(A)194/1516 (12.8) (B)537/1516 (35.4)	(A)318/2613 (12.2) (B)870/2613 (33.3)

CCB = calcium channel blocker; CHF = congestive heart failure
*See Composite vascular outcome definitions table

Appendix Table C101. Composite vascular outcome definitions, CCB versus diuretic trial

Study	Definition
Rahman, 2005[23]	(A) CHD, defined as nonfatal MI and fatal CHD (B) Combined CVD, defined as CHD death, nonfatal MI, coronary revascularization, hospitalized or treated angina, stroke, treated or hospitalized heart failure, and peripheral arterial disease (hospitalized or outpatient revascularization).

CCB = calcium channel blocker; CHD = coronary heart diease; CVD = cardiovascular disease; MI = myocardial infarction

Appendix Table C102. Clinical renal outcomes (outcomes part C), CCB versus diuretic trial

Study	End-stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)*	
	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic	CCB	Diuretic
Rahman, 2005[23]	Overall: 65/1516 (4.3) Diabetics: 44/506 (8.7)	Overall: 124/2613 (4.7) Diabetics: 68/881 (7.7)							**Overall: 90/1516 (5.9) Diabetics: 56/506 (11.1)	**Overall: 180/2613 (6.9)** Diabetics: 96/881 (10.9)

CCB = calcium channel blocker; GFR = glomerular filtration rate; ESRD = end-stage renal disease

*See Composite renal outcome definitions table

** Study also reported no difference in risk (RR 1.02 [95% CI, 0.90-1.15]) between treatment groups for another composite renal outcome (≥50% decline in GFR, ESRD or death), but didn't report the number of participants reaching this event overall or by treatment group.

Appendix Table C103. Composite renal outcome definitions, CCB versus diuretic trial

Study	Definition
Rahman, 2005[23]	50% or greater decline in GFR or incident end-stage renal disease (death due to kidney disease, kidney transplantation, or start of long-term renal dialysis)

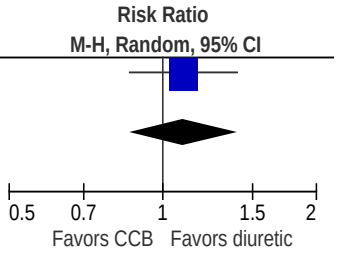
CCB = calcium channel blocker; GFR = glomerular filtration rate

Appendix Figure C20. Forest plots for CCB versus diuretic trial

Stroke

Study or Subgroup	Calcium channel blocker Events	Total	Diuretic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	100	1516	157	2613	100.0%	1.10 [0.86, 1.40]
Total (95% CI)		**1516**		**2613**	**100.0%**	**1.10 [0.86, 1.40]**
Total events	100		157			

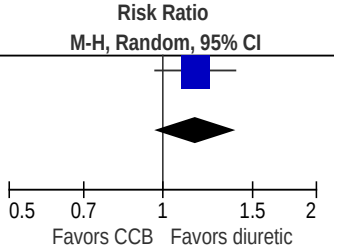
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



Heart failure

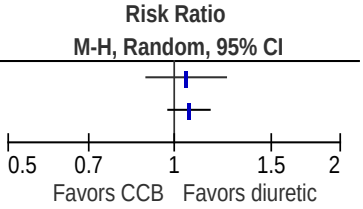
Study or Subgroup	Calcium channel blocker Events	Total	Diuretic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	174	1516	259	2613	100.0%	1.16 [0.97, 1.39]
Total (95% CI)		**1516**		**2613**	**100.0%**	**1.16 [0.97, 1.39]**
Total events	174		259			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.58 (P = 0.11)



Composite vascular outcome (see Table C101 for definition)

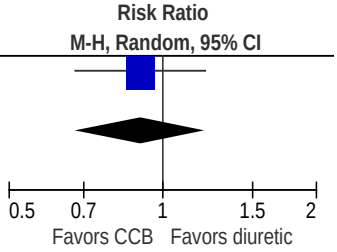
Study or Subgroup	Calcium channel blocker Events	Total	Diuretic Events	Total	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) A	194	1516	318	2613	1.05 [0.89, 1.24]
Rahman (ALLHAT) B	537	1516	870	2613	1.06 [0.98, 1.16]



End-stage renal disease

Study or Subgroup	Calcium channel blocker Events	Total	Diuretic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	65	1516	124	2613	100.0%	0.90 [0.67, 1.21]
Total (95% CI)		**1516**		**2613**	**100.0%**	**0.90 [0.67, 1.21]**
Total events	65		124			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)



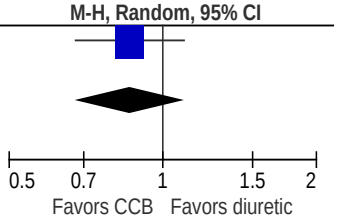
Appendix Figure C20. Forest plots for CCB versus diuretic trial (continued)

Composite renal outcome (see Table C103 for definition)

Study or Subgroup	Calcium channel blocker Events	Total	Diuretic Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rahman (ALLHAT) 2006	90	1516	180	2613	100.0%	0.86 [0.67, 1.10]
Total (95% CI)		**1516**		**2613**	**100.0%**	**0.86 [0.67, 1.10]**
Total events	90		180			

Heterogeneity: Not applicable

Test for overall effect: Z = 1.19 (P = 0.23)



Appendix Table C104. Overview of strict versus standard blood pressure control trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Blood pressure target comparison trials (n= 6)				
Ruggenenti, 2005[66] REIN-2 Multi-center Italy Industry and other (nonprofit research institute)	Inclusion Criteria: Age 18–70 years, who had nondiabetic nephropathy and persistent proteinuria (urinary protein excretion ≥1 g/24 hr for at least 3 months without evidence of urinary-tract infection or overt heart failure) and who had not received ACEI therapy for at least 6 weeks. Patients with proteinuria of 1–3 g /24 hr were included if their creatinine clearance was less than 45 mL/min per 1·73m^2; those with a proteinuria ≥3 g /24 h were included if their creatinine clearance was less than 70 mL/min per 1·73 m^2. Exclusion Criteria: Urinary tract infection, NYHA class III or IV heart failure, treatment with corticosteroids, non-steroidal anti-inflammatory drugs, or immunosuppressive drugs; acute myocardial infarction or cerebrovascular accident in the previous 6 months, severe uncontrolled hypertension, evidence or suspicion of renovascular disease, obstructive uropathy, type 1 diabetes mellitus, collagen disease, cancer, "higher" serum aminotransferase concentrations, or chronic cough, history of allergy, or poor tolerance to ACEI or dihydropyridine calcium-channel blockers; drug or alcohol abuse; pregnancy; breastfeeding; and ineffective contraception.	N= 338 (baseline characteristics reported on 335, excluding 3 subjects who never took study drugs) Age (yr): 53.8 Gender (Male %): 74.9 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 136.7 Diastolic BP (mm Hg): 84.1 MAP (mm Hg): 101.6 Proteinuria (g/day): 2.85 Serum creatinine (mg/dL): 2.7 Creatinine Clearance (ml/min/1.73m^2): 38.8 Measured GFR (ml/min/1.73m^2): 35.0 Total cholesterol (mg/dL): 217.5 LDL cholesterol (mg/dL): NR Diabetes (%): NR HgbA1C (%): NR History of HTN (%): NR History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR History of AKI (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Conventional BP control (n= 169), with target DBP <90 mm Hg, irrespective of SBP Intensified BP control (n=169), with target <130/80 mm Hg, using felodipine, initially at 5 mg/day then titrated up as needed to 10 mg/day. During pre-randomization run-in, all participants started on ramipril and uptitrated as tolerated to 5 mg/day while concomitant blood pressure medications tapered down as tolerated to keep SBP <90 mm Hg. After randomization, adjustment of concomitant BP meds (excluding ACEI, ARB, or dihydropiridine CCB other than felodipine) allowed to meet BP target/avoid hypotension. Followup period (median): 19 months Study withdrawals (%): 15.4 (52/338)	Allocation Concealment Adequate. Centrally administered randomization process. Blinding: No. Investigators and patients aware of allocation. Intention to Treat Analysis (ITT): No. Three subjects not included in analysis after randomization. Withdrawals/Dropouts adequately described: Yes

Appendix Table C104. Overview of strict versus standard blood pressure control trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Wright, 2002[26] AASK Multi-center USA Funding Source: Industry and Government	Inclusion Criteria: Self-identified African Americans with hypertension (n=1094), aged 18 to 70 yr, GFR 20 to 65 mL/min per 1.73 m^2, and no other identified causes of renal insufficiency. Exclusion Criteria: DBP 95 mm Hg, known history of diabetes mellitus (fasting glucose, ≥140 mg/dL or random glucose >200 mg/dL), urinary protein to creatinine ratio >2.5, accelerated or malignant hypertension within 6 months, secondary hypertension, evidence of non–BP-related causes of chronic kidney disease, serious systemic disease, clinical CHF, or specific indication for or contraindication to a study drug or study procedure.	N= 1094 Age (yr): 54.6 Gender (Male %): 61.2 Race/Ethnicity (%): African American 100 BMI: 30.6 Weight: 89.5 Systolic BP (mm Hg): 150.5 Diastolic BP (mm Hg): 95.5 MAP (mm Hg): 114 Proteinuria (g/24h): 0.53 Urine protein/creatinine ratio: 0.33 Serum creatinine (mg/dL): 2.0 Creatinine Clearance (ml/min/1.73m^2): NR Measured GFR (ml/min/1.73m^2): 45.6 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 HgbA1C (%): NR History of HTN (%): 100 History of CAD (%): NR History of CHF (%): 0 History of MI (%): NR Current smoker (%): NR	Target MAP 102-107 mm Hg (n=554) Target MAP ≤92 mm Hg (n=540) Study was 3x2 factorial design, including 2 target BP groups and 3 BP drug groups (amlodipine, metoprolol or ramipril). If BP target couldn't be achieved by randomized drug, additional open-label BP meds could be added. Followup period: median 3.8 yrs (median 4.1 yr in ramipril and metoprolol groups, and 3.0 yr in amlodipine group) Study withdrawals (%): Study reported 0 withdrawals, but stated that 8.1% with no GFR in their final year of followup were not "active participants" at study end.	Allocation Concealment Unclear Blinding: No, not for BP target groups Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes
Estacio 2000[67] - Study B; Schrier 2002[68] - Study A ABCD USA Industry and other	Inclusion Criteria: Study A enrolled normotensive subjects (mean DBP between 80-89 mmHg) with type 2 diabetes aged between 40 and 74 years; Study B enrolled hypertensive (DBP ≥ 90 mmHg) subjects with type 2 diabetes aged between 40 and 74 years. Subjects were to be off antihypertensive medication at the randomization visit. Exclusion Criteria: Known allergy to dihydropyridines or ACE-I, MI or CVA	Study B: N=232 of which 150 (32%) had microalbuminuria and 82 (17%) had overt albuminuria of a total study population of 470. No further baseline details provided. Study A: N=162 of which 111 (23%) had microalbuminuria and 51 (11%) had overt albuminuria of a total study population of 480. No further	Intensive blood pressure control: Study A target DBP goal 10 mmHg below baseline DBP; Study B target DBP goal of 75 mmHg Moderate blood pressure control: target DBP goal between 80-89 mmHg. Initial medications included	Allocation Concealment : unclear Blinding: Estacio described as "blinded," unclear if double-blinded; blinded end point commitee Intention to Treat Analysis (ITT): unclear Withdrawals/Dropouts

Appendix Table C104. Overview of strict versus standard blood pressure control trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	within previous six months, coronary artery bypass surgery within previous three months, unstable angina pectoris within previous six months, Class III or IV New York Heart Association classification of CHF, demonstrated absolute need for ACE-I or calcium channel blockers, were receiving hemo- or peritoneal dialysis and/or had a serum creatinine >3mg/dL.	baseline details provided.	nisoldipine or enalapril. If single study medication did not achieve target BP, open-lable antihypertensives were added. Followup period: mean 5.3 years Study withdrawals (%): No details provided for CKD subgroups.	adequately described: yes (overall) for Study B.
Lewis, 1999[69] Multi-center USA Industry	Inclusion Criteria: Previously participated in the Study of ACEI in Diabetic Nephropathy, which had randomized 409 subjects who met inclusion criteria to captopril vs. placebo as follows: age 18-40 yr, type 1 diabetes mellitus ≥7 years with onset before age 30 yr, presence of diabetic retinopathy, urinary protein excretion ≥500 mg/24 h, serum creatinine ≤2.5 mg/dL. Current study participants further had to have been receiving coded medication from the earlier study when it terminated, and current serum creatinine level had to be <4 mg/dL. Patients were not required to have a history of hypertension Exclusion Criteria: Serum creatinine >4.0 mg/dL, serum potassium ≥6.0 mEq/L, white blood cell count <2,500/muL, or a medical or psychiatric problem that precluded the patient following the protocol or taking study medication. Documented acute myocardial infarction or overt coronary artery disease. Not enrolled if investigators at their site declined to participate in the study.	N= 129 Age (yr): 37 Gender (Male %): 47.3 Race/Ethnicity (%): White 94.6 BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR MAP (mm Hg): 96.0 Proteinuria (g/24h): 1.1 Serum creatinine (mg/dL): 1.3 Creatinine Clearance (ml/min/1.73m^2): NR Measured GFR (ml/min/1.73m^2): 63.0 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 HgbA1C (%): 10.8 History of HTN (%): 77 History of CAD (%): 0 History of CHF (%): NR History of MI (%): 0 History of Stroke (%): NR History of AKI (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Target MAP ≤92 mm Hg (n=63) Target MAP 100 -107 mm Hg (n=66) Ramipril used as primary antihypertensive agent to achieve target BP goals. If needed, other BP drugs could later be used, except other ACEI or ARB. All patients to restrict dietary protein to <1 gm/kg/day, and diabetes managed “in accord with the historical treatment schedule.” Followup period: Neither mean nor median duration reported. Study reported that all subjects were followed a minimum of 2 yr, but also reported that 26% (n=33) did not complete 2 yr followup. Study withdrawals (%): 16.3	Allocation Concealment Unclear Blinding: Unclear Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: No, n=5 not accounted for.

Appendix Table C104. Overview of strict versus standard blood pressure control trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Toto, 1995[70] Multi-center USA Funding Source Government and Industry	Inclusion Criteria: Age 25 to 73 yr, with hypertensive nephrosclerosis, DBP ≥95 mm Hg, serum creatinine >1.6 mg/dl, GFR of ≤70 ml/min/1.73 m^2, long-standing hypertension, an inactive urine sediment, a urinary protein excretion rate ≤2 g/day, and no physical or biochemical evidence for a humoral-mediated cause for hypertension. Among 87 eligible patients, only those 77 "responders" whose DBP was able to be lowered to ≤80 mm Hg during 3-6 month run-in were eligible for randomization. Exclusion Criteria: Patients with diabetes mellitus, a recent history (<4 months) of malignant hypertension, stroke or myocardial infarction, acute renal failure of any cause, analgesic abuse, polycystic kidney disease, systemic lupus erythematosus, scleroderma, rapidly progressive glomerulonephritis, evidence of significant hepatic impairment (AST and ALT greater than 2.5 x normal or serum total bilirubin >1.5 mg/dl), mental incapacity, pregnancy or lactation, primary aldosteronism, renovascular hypertension, pheochromocytoma, or a serum creatinine >7.0 mg/dl	N= 77 Age (yr): 55.7 Gender (Male %): 62.3 Race/Ethnicity (%): Black 75.3, Nonblack 24.7 BMI: 28.7 Systolic BP (mm Hg): 123 Diastolic BP (mm Hg): 76 MAP (mm Hg) 92 Proteinuria (mg/day): 359 Serum creatinine (mg/dL): 2.3 Creatinine Clearance (ml/min/1.73m^2): NR Measured GFR (ml/min/1.73m^2): 37.8 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 HgbA1C (%): NR History of HTN (%): 100 History of cardiovascular disease (any of angina, MI, CHF or stroke) (%): 36.4 History of AKI (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR	Conventional target DBP 85-95 mm Hg (n=35) Strict target DBP 65-80 mm Hg (n=42) Stepped use of BP drugs during run-in to achieve DBP <80 mm Hg (diuretic; BB; hydralazine or minoxidil; clonidine, alpha-methyldopa or alpha blocker). 2x2 factorial design to strict vs. conventional BP target and to enalapril vs. placebo. Followup period (Mean): 3.4 years Study withdrawals (%): No information reported	Allocation Concealment Unclear Blinding: Double Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Unclear
Peterson, 1995[71] Klahr, 1994[72] Greene, 1993[73] MDRD (Study A) Multicenter USA Government	Inclusion Criteria: Age of 18 to 70 years; serum creatinine level of 1.2 to 7.0 mg/dL for women and 1.4 to 7.0 mg/dL for men or a creatinine clearance less than 70 mL/min • 1.73 m^2; and mean arterial pressure of 125 mm Hg or less (Study A+B). Study A had patients with GFR of 25-55 mL/min • 1.73 m^2 Dietary protein intake ≥0.9 g/kg body	N= 585 (Reported baseline characteristics differed slightly between different study reports. For characteristics reported by multiple studies, results from the most recent report were used.) Age (yr): 52 Gender (Male %): 61.0	Low target MAP (≤92 mm Hg for patients ≤60 yr old, and ≤98 mm Hg for patients ≥61 yr old) Usual target MAP (≤107 mm Hg for patients ≤60 yr old, and ≤113 mm Hg for patients ≥61 yr old)	Allocation Concealment Unclear Blinding: Unclear Intention to Treat Analysis (ITT): Unclear Withdrawals/Dropouts adequately described: Yes

Appendix Table C104. Overview of strict versus standard blood pressure control trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	weight/day. Exclusion Criteria: Diabetes requiring insulin, proteinuria of 10 g/d or more, or body weight less than 80% or more than 160% of standard body weight, Pregnancy, history of renal transplant, chronic medical conditions or doubts about compliance	Race/Ethnicity (%): White 84.6, Black 9.1, Other 6.3 BMI: 27.6 Systolic BP (mm Hg): 131 Diastolic BP (mm Hg): 81 MAP (mm Hg): 98 Proteinuria (g/day): 0.9 Serum creatinine (mg/dL): 1.9 Creatinine Clearance (ml/min/1.73m^2): 50.4 Measured GFR (ml/min/1.73m^2): 38.6 Total cholesterol (mg/dL): 221 LDL cholesterol (mg/dL): 150 Diabetes (%): NR HgbA1C (%): NR History of HTN (%): 85.3 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR History of Stroke (%): NR History of AKI (%): NR Peripheral arterial disease (%): NR Current smoker (%): 80	Followup period: Mean 2.2 yrs Study withdrawals (%): 1.9	
Shulman, 1989[74] HDFP Location United States Funding Source: Government	Inclusion Criteria: From general population subgroups of the United States. Recruited through 2 stage community based, screening program for high blood pressure in 14 U.S. communities. Adults, 30 to 69 years of age with an average home screening DBP of 95 mm Hg or above and a confirmed followup average diastolic pressure of 90 mm Hg or above. Exclusion Criteria: Only terminally ill and institutionalized persons were excluded. Treated hypertensives with	N=297 (subgroup analysis of subjects with baseline serum creatinine ≥1.7 mg/dl from overall study of N=10, 940) Age (yr): NR Gender (Male %): 68.4 Race/Ethnicity (%): White 40.4, Black 59.6 Weight: NR BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR MAP (mm Hg): NR CKD stage: NR	Stepped care (n= 5,485; of which n=159 had creatinine ≥1.7 mg/dl). Target goal DBP ≤90 mm Hg for those entering trial on BP drug treatment or with baseline DBP ≥100 mm Hg, or goal 10mm Hg DBP decrease if baseline DBP 90-99 mm Hg. Referred care (n=5,455; of which n=138 had creatinine ≥1.7 mg/dl)	Allocation Concealment Adequate Blinding: No (participants and clinic staff aware) Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: No

Appendix Table C104. Overview of strict versus standard blood pressure control trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	DBP below 95 were excluded.	Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): NR Albuminuria: NR Proteinuria (1+ proteinuria, %): 35.0 (Measured in 89.6% of patients with creatinine ≥1.7 mg/dl and 91.2% in overall study. Among HDFP subjects with creatinine <1.7 mg/dl, an additional 597/9556 = 6.2% had at least 1+ proteinuria.) Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 15.8 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Followup period: 5 yrs Study withdrawals (%): Not reported	

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C105. Summary of study baseline characteristics, strict versus standard blood pressure control trials

Characteristic	Mean (Range) (unless otherwise noted)	Number of Trials Reporting
Patients randomized, n	2,914 (77-1094)	7
Age of subjects, years	52.8 (37-55.7)	5
Gender, male, %	63.2 (47.3-74.9)	6
Race/ethnicity, white, %	35.0 (0-94.6)	4
Race/ethnicity, black, %	67.3 (9.1-100)	4
Body Mass Index	29.5 (27.6-30.6)	3
Systolic blood pressure, mmHg	141.8 (123-150.5)	4
Diastolic blood pressure, mmHg	88.9 (76-95.5)	4
Mean arterial blood pressure, mmHg	106.1 (92-114)	5
Proteinuria, g/day	1.0 (0.36-2.85)	5
Serum creatinine, mg/dL	2.0 (1.3-2.7)	5
Creatinine clearance, ml/min/1.73m^2	46.2 (38.8-50.4)	2
GFR, ml/min/1.73m^2	42.9 (35.0-63.0)	5
Total cholesterol, mg/dl	219.7 (217.5-221)	2
LDL cholesterol, mg/dl	150	1
History of diabetes, %	11.0 (0-100)	4
% HbA_{1c}	10.8	1
History of hypertension (%)	94.7 (77-100)	5
History of cardiovascular Disease, %*	36.4	1
History of CHF, %	0	1
Current smoker, %	80	1

GFR = glomerular filtration rate; LDL = low density lipoprotein; CHF = congestive heart failure

*No study reported separate prevalence of coronary artery disease, myocardial infarction or stroke. However, one study (n=77) reported that 36.4% of participants had a history of either angina, myocardial infarction, congestive heart failure, or stroke.

Appendix Table C106. Clinical outcomes (outcomes part A), strict versus standard blood pressure control trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial infarction, Nonfatal n/N (%)		Stroke, Any n/N (%)	
	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP
Ruggenenti, 2005[66] REIN-2	2/169 (1.2)	3/169 (1.8)	1/169 (0.6)	2/169 (1.2)			1/169 (0.6)	1/169 (0.6)				
Wright, 2002[26] AASK	37/540 (6.9)	43/554 (7.8)										
Schrier 2002[68] - Study A, Estacio 2000[67] - Study B ABCD												
Lewis, 1999[69]												
Toto, 1995[70]	1/42 (2.4)	0/35										
Peterson, 1995[71] Klahr, 1994[72] MDRD, Study A	†NR	†NR	†NR	†NR								
Shulman, 1989[74] HDFP	56/159 (35.2)	57/138 (41.3)	32/159 (20.1)	33/138 (23.9)								

BP = blood pressure

*Study did not report the proportion of patients with all-cause mortality or cardiovascular mortality, but instead reported only the percentage of patients experiencing these outcomes per patient year of followup (1.6 vs. 1.9% for all-cause mortality and 0.6 vs. 0.7% for cardiovascular mortality events per patient year for the strict target BP vs. control target BP groups, respectively).

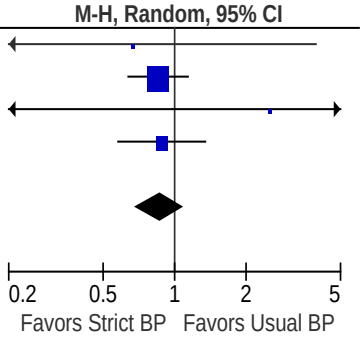
†Overall, study reported 30 deaths, including 18 cardiovascular deaths. It did not report the number of these events separately for each treatment group, though it stated that there were no significant differences in the number or causes of deaths between the two treatment groups.

Appendix Figure C21. Forest plots for strict versus standard blood pressure control trials

All-cause mortality

Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruggenenti (REIN-2) 2005	2	169	3	169	1.8%	0.67 [0.11, 3.94]
Shulman (HDFP) 1989	56	159	57	138	66.5%	0.85 [0.64, 1.14]
Toto 1995	1	42	0	35	0.6%	2.51 [0.11, 59.79]
Wright (AASK) 2002	37	540	43	554	31.2%	0.88 [0.58, 1.35]
Total (95% CI)		**910**		**896**	**100.0%**	**0.86 [0.68, 1.09]**
Total events	96		103			

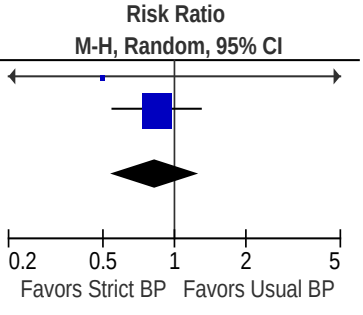
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)



Cardiovascular mortality

Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruggenenti (REIN-2) 2005	1	169	2	169	3.1%	0.50 [0.05, 5.46]
Shulman (HDFP) 1989	32	159	33	138	96.9%	0.84 [0.55, 1.29]
Total (95% CI)		**328**		**307**	**100.0%**	**0.83 [0.54, 1.26]**
Total events	33		35			

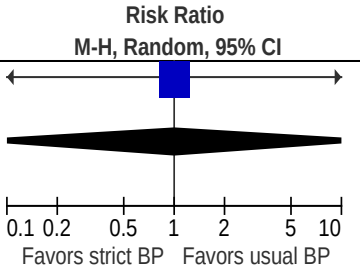
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)



Myocardial infarction, fatal

Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruggenenti (REIN-2) 2005	1	169	1	169	100.0%	1.00 [0.06, 15.86]
Total (95% CI)		**169**		**169**	**100.0%**	**1.00 [0.06, 15.86]**
Total events	1		1			

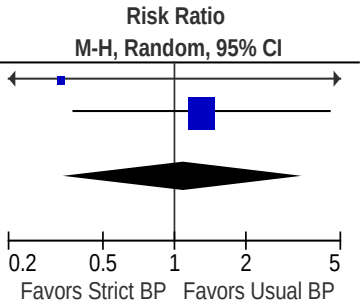
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Stroke or CVA, fatal

Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruggenenti (REIN-2) 2005	0	169	1	169	13.2%	0.33 [0.01, 8.12]
Shulman (HDFP) 1989	6	159	4	138	86.8%	1.30 [0.38, 4.52]
Total (95% CI)		**328**		**307**	**100.0%**	**1.09 [0.34, 3.47]**
Total events	6		5			

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)

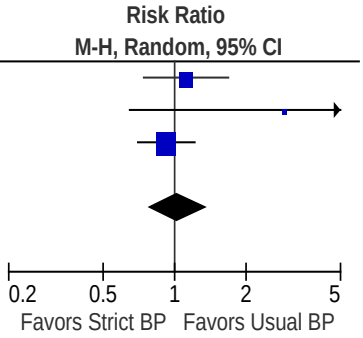


Appendix Figure C21. Forest plots for strict versus standard blood pressure control trials (continued)

End-stage renal disease

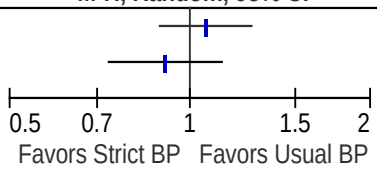
Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Weight	Risk Ratio M-H, Random, 95% CI
Ruggenenti (REIN-2) 2005	38	169	34	169	36.1%	1.12 [0.74, 1.69]
Toto 1995	7	42	2	35	3.6%	2.92 [0.65, 13.15]
Wright (AASK) 2002	81	540	90	554	60.3%	0.92 [0.70, 1.22]
Total (95% CI)		**751**		**758**	**100.0%**	**1.03 [0.77, 1.38]**
Total events	126		126			

Heterogeneity: Tau² = 0.02; Chi² = 2.55, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.21 (P = 0.84)



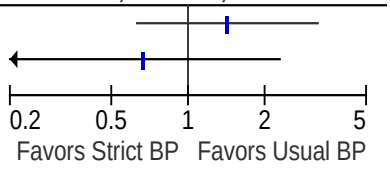
Composite renal outcome (see Table 110 for definitions)

Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Risk Ratio M-H, Random, 95% CI
Wright AASK 2002 A	173	540	167	554	1.06 [0.89, 1.27]
Wright AASK 2002 B	118	540	133	554	0.91 [0.73, 1.13]



Composite renal outcome (see Table 110 for definitions)

Study or Subgroup	Strict BP Events	Strict BP Total	Usual BP Events	Usual BP Total	Risk Ratio M-H, Random, 95% CI
Toto 1995 A	12	42	7	35	1.43 [0.63, 3.23]
Toto 1995 B	4	42	5	35	0.67 [0.19, 2.29]



Appendix Table C107. Clinical outcomes (outcomes part B), strict versus standard blood pressure control trials

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)*	
	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP
Ruggenenti, 2005[66] REIN-2			0/169	1/169 (0.6)			(A) NR; (B) 0/169	(A) NR; (B) 0/169		
Wright, 2002[26] AASK									**NR	**NR
Schrier 2002[68] - Study A, Estacio 2000[67] - Study B ABCD										
Lewis, 1999[69]										
Toto, 1995[70]										
Peterson, 1995[71] Klahr, 1994[72] MDRD, Study A										
Shulman, 1989[74] HDFP			6/159 (3.8)	4/138 (2.9)						

CHF = congestive heart failure; BP = blood pressure; NR = not reported

*See Composite vascular outcome definitions table

**Study did not report the proportion of patients with a composite vascular event (defined as cardiovascular mortality or first cardiovascular hospitalization), but instead reported only the percentage of patients experiencing a composite vascular outcome per patient year of followup (2.3 versus 2.7% per patient year for the strict versus control target blood prssure treatment groups).

Appendix Table C108. Composite vascular outcome definitions, strict versus standard blood pressure control trial

Study	Definition
Wright, 2002[26] AASK	"Cardiovascular event" defined as cardiovascular mortality or first cardiovascular hospitalization.

Appendix Table C109. Clinical renal outcomes (outcomes part C), strict versus standard blood pressure control trials

Study	End Stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)*	
	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP
Ruggenenti, 2005[66] REIN-2	38/169 (22.5)	34/169 (20.1)								
Wright, 2002[26] AASK	81/540 (15.0)	90/554 (16.2)							**(A)173/540 (32.0) (B) 118/540 (21.9) (C) NR	**(A)167/554 (30.1) (B) 133/554 (24.0) (C) NR
Estacio 2000[67] - Study B ABCD††							12/73 (16.4)	18/77 (23.4)		
Lewis, 1999[69]	†NR	†NR								
Toto, 1995[70]	7/42 (16.7)	2/35 (5.7)							(A)12/42 (28.6) (B) 4/42 (9.5)	(A) 7/35 (20.0) (B) 5/35 (14.3)
Peterson, 1995[71] Klahr, 1994[72] MDRD, StudyA	§NR	§NR			#NR	#NR				
Shulman, 1989[74] HDFP study			***NR	***NR						

GFR = glomerular filtration rate; BP = blood pressure; NR = not reported; ESRD = end stage renal disease

*See Composite renal outcome definitions table

**Study reported that 263 participants experienced the composite endpoint of (C) halving of GFR or ESRD, but did not report results for this endpoint separately for the two treatment groups.

†Study reported that 12 patients reached ESRD, but didn't report this result separately for the two treatment groups.

§Study also reported that 12 participants developed end stage renal disease, but like the Lewis study did not report this result separately for the two treatment groups.

#Study reported that 60 patients overall reached a study stopping point due to "rapidly declining glomerular filtration rate." Though study did not report this result separately for the two treatment groups, it did state that there was no significant difference between the results for the two groups.

***In 59.6% of participants with baseline creatinine $\geq$1.7 mg/dl, study reported outcome of end of follow-up serum creatinine $\geq$2.0 mg/dl and at least 25% above the baseline level (29/106 = 27.4% for strict BP group, and 19/71 = 26.8% for control target BP group).

††Schrier 2002 - Study A reported that a significantly lower percentage of patients with microalbuminuria at baseline in the intensive therapy group progressed to overt albuminuria in comparison to the moderate therapy group (p=0.028).

Appendix Table C110. Composite renal outcome definitions, strict versus standard blood pressure control trials

Study	Definition
Wright, 2002[26] AASK	Study defined three composite renal endpoints, including: (A) 50% or 25 mL/min reduction in GFR, ESRD (dialysis or transplantation), or death; (B) ESRD or death; and (C) 50% or 25 mL reduction in GFR, or ESRD
Toto, 1995[70]	Study defined two composite renal endpoints, including: (A) 50% decline in GFR, doubled serum creatinine, ESRD, or death; and (B) 50% decline in GFR or doubled serum creatinine.

GFR = glomerular filtration rate; ESRD = end stage renal disease

Appendix Table C111. Study withdrawals and adverse events (outcomes part D), strict versus standard blood pressure control trials

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any n/N (%)		Serious Adverse Event: Any Leading to Withdrawal n/N (%)		Adverse Event: Any n/N (%)		Adverse Event: Any Specific n/N (%)		Renal Adverse Events: Any, n/N (%)	
	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP
Ruggenenti, 2005[66] REIN-2	22/169 (13.0)	30/169 (17.8)	37/169 (21.9)	25/169 (14.8)	6/169 (3.6)	3/169 (1.8)			Hyperkalemia 0/169	Hyperkalemia 0/169		
Wright, 2002[26] AASK	0/540†	0/554†							‡Hyperkalemia: 0/540 Cough: 295/540 (54.6)*	‡Hyperkalemia: 4/554 (0.7) Cough: 260/554 (47.0)		
Schrier 2002[68] - Study A, Estacio 2000[67] - Study B ABCD												
Lewis, 1999[69]	§NR	§NR			§NR	§NR			Postural hypotension: 11/63 (17.5)* Edema: 4/63 (6.3)* Bronchitis: 2/63 (3.2)* Sinusitis: 3/63 (4.8)*	Postural hypotension: 4/66 (6.1) Edema: 10/66 (15.2) Bronchitis: 7/66 (10.6)* Sinusitis: 13/66 (19.7)*		
Toto, 1995[70]												
Peterson, 1995[71] MDRD, StudyA	#NR	#NR										

Appendix Table C111. Study withdrawals and adverse events (outcomes part D), strict versus standard blood pressure control trials (continued)

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any n/N (%)		Serious Adverse Event: Any Leading to Withdrawal n/N (%)		Adverse Event: Any n/N (%)		Adverse Event: Any Specific n/N (%)		Renal Adverse Events: Any, n/N (%)	
	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP	Strict Target BP	Control Target BP
Shulman, 1989[74] HDFP											**Death due to renal disease: 9/159 (5.7)	**Death due to renal disease: 12/138 (8.7)

BP = blood pressure; NR = not reported; GFR = glomerular filtration rate

*p< 0.05

†Study reported no withdrawals, but described 8.1% of subjects with no GFR measurement in the final year of follow-up (n=42/540 and 47/554 from the strict and control target treatment groups, respectively) as not active participants at study end.

‡Study reported additional specific adverse events, all of which were not statistically different in incidence between strict and control target blood pressure treatment groups, including: angioedema (3.5 vs. 5.4%), shortness of breath (48.4 vs. 45.8%), syncope (6.3 vs. 5.2%), dizziness (53.4 vs. 49.0%), lightheadedness (51.2 vs. 49.2%), edema (55.1 vs. 54.2%), and sexual dysfunction (29.6 vs. 27.1%).

§Study reported 21/129 (16.3%) withdrawals overall, including 3 withdrawals for adverse events, but didn't specify either of these outcomes by treatment group.

#Study reported 11/585 (1.9%) participants lost to followup overall, but did not report results by treatment group.

**Deaths attributed to renal disease were those with ICD codes 580-599, which includes: acute or chronic glomerulonephritis, nephrotic syndrome, acute or chronic renal failure, hydronephrosis, urolithiasis, urethritis, urethral stricture, urinary tract infection, and other disorders of the kidneys and urinary tract.

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Koya, 2009[75] (Low-Protein Diet Study Group) Japan Funding Source: Government	Inclusion Criteria: Japanese type 2 diabetics (at least 5 years duration); treated by diet or diet plus oral hypoglycemics or insulin injection; ages 30 to 70; urinary protein excretion >1g/day but <10g/day; urinary albumin excretion rate >200µg/min at least twice in 1 yr period; serum creatinine <176µmol/l; at least simple diabetic retinopathy; on normal-protein diet (1.2 g/kg/day) Exclusion Criteria: Type 1 diabetes; other renal diseases, body weight <80% of ideal; clinically significant illness such as CHF, hepatic disease, recent MI and stroke, urinary tract infection; current treatment with low protein diet (0.8 g/kg/day) and/or ACEI or ARB	N=112 Age (yr): 56.9 Gender (Male %): 58.9 Race/Ethnicity (%): NR Weight (kg): 63.4 BMI: 24.6 Systolic BP (mm Hg): 137.5 Diastolic BP (mm Hg): 77.0 CKD stage: NR Serum creatinine (mg/dL): 1.1 Creatinine clearance (mL/min): NR Albuminuria (µg/min): 507.5 Proteinuria (g/day): 1.15 Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): 62.3 (MDRD formula) HbA_{1c} (%): 7.65 Total cholesterol (mg/dL): 222.4 LDL cholesterol (mg/dL): NR Diabetes (%): 100% (by inclusion criteria) History of HTN (%): 65.8 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): 0 Peripheral arterial disease (%): NR History of MI (%): NR (no recent) History of Stroke (%): NR (no recent) Current smoker (%): NR History of AKI (%): NR	Low-protein diet (0.8 g/kg/day); n=56 Normal-protein diet (1.2 g/kg/day); n=56 All participants met with dietician every 3 months, at which time their diet was modified as necessary to achieve assigned treatment group protein intake target. Followup period: 1 to 5 years (approximately 3.5 years) Study withdrawals (%): 21.4	Allocation Concealment: Adequate (central location) Blinding: Participants and investigators were not blinded; unclear if central laboratory outcomes assessors blinded Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Dussol, 2005[76] France Funding Source: Government	Inclusion Criteria: Recruited from Endocrinology Unit of 3 hospitals; ages 18 to 75 years; type 1 or 2 diabetes; either pathologic or clinical evidence of diabetic nephropathy (diabetes duration >10 yrs, diabetic retinopathy, no evidence of other kidney or urinary tract disease); at least two microalbuminuria levels >30 mg/day (incipient nephropathy) or macroalbuminuria levels >300 mg/day (overt nephropathy)* Exclusion Criteria: absence of nephropathy; ESRD (GFR<15 mL/min); pregnancy; cachexy, body mass index >33 *Note: 87% microalbuminuria	N=63 (baseline data presented for 47 completers only) Age (yr): 57.9 Gender (Male %): 83.0 Race/Ethnicity (%): NR Weight: 79.5 kg BMI: 27.5 Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR Mean BP (mm Hg): 98.9 CKD stage: NR Serum creatinine (mg/dL): 1.1 Creatinine clearance (mL/min): NR Albuminuria (mg/d): 366 (320 for n=41 with microalbuminuria; 680 for n=6 with microalbuminuria) Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 85.7 HbA_{1c} (%): 8.1 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): 14.9 History of AKI (%): NR	Low protein diet (0.8 g/kg/day, isocaloric). Received dietician telephone call every 6 weeks to counsel and reinforce dietary instructions; n=30 Usual protein diet (no higher than 1.2 g/kg/day); n=33 All participants in both groups received either ACEI or ARB treatment at study onset and throughout diet treatment course. Followup period: 2 years Study withdrawals (%): 25.4	Allocation Concealment: Unclear Blinding: None Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes
Kopple, 1997[77] Peterson, 1995[71] Klahr, 1994[72] Greene, 1993[73] Modification of Diet in Renal Disease (MDRD) Study A only	Inclusion Criteria: age 18-70 years; serum creatinine 1.4-7.0 mg/dl (men) or 1.2-7.0 mg/dl (women) or other objective evidence of kidney disease; mean arterial pressure (MAP) ≤125 mmHg; GFR 25-55 ml/min/1.73m^2; urinary protein excretion <10g/day; protein intake >0.90g/kg/day	N=585 (end of baseline values reported where available) Age (yr): 52.6 Gender (Male %): 61.0 Race/Ethnicity (%): 84.6 white, 9.1 black, 4.3 Hispanic, 2.1 other Weight: 81.0 kg BMI: 27.6 Systolic BP (mm Hg): 131	Low protein diet (0.58g/kg/day); n=291 (140 to usual MAP, 151 to low MAP) Usual diet (1.3 g/kg/day); n=294 (145 to usual MAP, 149 to low MAP)	Allocation Concealment: Adequate Blinding: Double (for followup GFRs) Intention to Treat Analysis (ITT): Unclear

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
(GFR 25 to 55 ml/min/1.73m^2) United States Funding Source: Government	Exclusion Criteria: insulin-dependent diabetes or fasting serum glucose >200 mg/dl; dialysis; kidney transplant recipient; lactating or pregnant woman or planning to become pregnant in time frame of study; doubtful compliance; body weight <80% or >160% of standard weight; serum albumin <3.0g/dl; selected renal disorders (UTI, renal artery stenosis, branched or staghorn calculi); serious medical conditions (NYHA class 3 or 4 HF, lung disease, liver disease, GI disease, chronic systemic infection, collagen vascular disease, frequent hospitalization or disability); immunosuppressive agents (including corticosteroids in excess of replacement dosage for ≥2 months/yr); gold or penicillamine in past month; >20 tablets salicylates per week; other NSAIDS >3 times/week in past 2 months; investigational drugs; allergy to iothalamate or iodine; inability or unwilling to give consent	Diastolic BP (mm Hg): 81 Mean arterial pressure (mm Hg): 98 CKD Stage: NR Serum creatinine (mg/dL): 1.9 Creatinine clearance (ml/min/1.73m^2): 50.4 Albuminuria: NR Proteinuria (g/day/1.73m^2): 0.18 (Females), 0.35 (Males) Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 38.6 HbA_{1c} (%): NR Total cholesterol (mg/dL): 218.2 LDL cholesterol (mg/dL): 148.4 Diabetes (%): NR Diabetic nephropathy (%): 2.9 History of HTN (%): 85.3 History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): 13.7 History of AKI (%): NR	Followup period: mean 2.2 years Study withdrawals (%): 1.9% lost to followup; 14.3% reached stop point including 10% with rapidly declining GFR, 2% with renal failure and 2% with other serious medical condition NOTE: 2 x 2 factorial design with usual (MAP=107 mmHg) or low (MAP=92mmHg) goal	Withdrawals/Dropouts adequately described: Yes
D'Amico, 1994[78] Italy Funding Source: Government	Inclusion Criteria: Consecutive patients with chronic renal insufficiency attending outpatient clinic; age >18; creatinine clearance between 70 and 15 ml/min stable or moderate decline over past 3 months; no evidence of potentially reversible diseases; not affected by systemic illness (including diabetes); no nephrotic syndrome (proteinuria >3g/24h and serum albumin <2.5 g/dl); no drugs in past 6 months that	N=134 (baseline data reported for 128 completers only) Age (yr): 54 Gender (Male %): 61 Race/Ethnicity (%): NR Weight: NR BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR Mean BP (mmHg): 115 CKD stage: NR Serum creatinine (mg/dL): NR	Low protein diet (0.6 g/kg lean body weight/day) plus energy supplement of 35 kcal/kg daily; phosphate restricted to 0.26 mmol/kg; n=63 (analyzed) Control (1.0 g/kg lean body weight/day) plus 30 kcal/kg/day; phosphate restricted to 0.42 mmol/kg); n=65 (analyzed)	Allocation Concealment Unclear Blinding: None Intention to Treat Analysis (ITT): No Withdrawals/ Dropouts adequately described: No

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	might alter natural history of disease; informed consent given Exclusion Criteria: none stated	Creatinine clearance (mL/min): 33 Albuminuria: NR Proteinuria (g/24 hr): 1.5 Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 (by inclusion criteria) History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Followup period: mean of 2.3 years Study withdrawals (%): 4.5% (6 withdrew at beginning of trial – group not specified)	
Locatelli, 1991[79] Northern Italy Cooperative Study Group Italy Funding Source: Not reported	Inclusion Criteria: ages 18 to 65 years; outpatients; plasma creatinine from 1.5 (men) or 1.35 (women) to 7.0 mg/dl, GFR <60ml/min (Cockroft formula); written consent Exclusion Criteria: nephrotic syndrome (serum albumin <2.5 g/dl, proteinuria >3 g/l); ideal body weight <45 kg or >90 kg; diabetes; recent MI; acute renal failure; acute obstruction and infection of urinary tract; systemic diseases; previous gastrointestinal resection surgery; doubling of plasma creatinine during 3 month preliminary observation period	N=456 Age (yr): 48.5 Gender (Male %): 54.2 Race/Ethnicity (%): NR Weight: NR BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR CKD stage: NR Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): NR Albuminuria: NR Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 0 (by exclusion criteria) History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR	Low protein diet (0.6 g/kg ideal body weight) with energy supplement of 35 kcal/kg daily; phosphate restricted to 0.26 mmol/kg; n=230 Control (1.0 g/kg/ideal body weight) with energy supplement of 30 kcal/kg daily; phosphate restricted to 0.42 mmol/kg; n=226 Followup period: 2 years or until endpoint reached Study withdrawals (%): 15.6	Allocation Concealment Adequate Blinding: Not reported Intention to Treat Analysis (ITT): No Withdrawals/ Dropouts adequately described: Yes

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): 0 (by exclusion criteria)		
Rosman, 1989/1984[80,81] United Kingdom Funding Source: Foundation	Inclusion Criteria: nephrology outpatients who visited clinic between 1/1/82 and 4/1/84; creatinine clearance between 10 and 60 ml/min/1.73m^2 or less; no lethal disease Exclusion Criteria: lupus erythematosus, active vasculitis and Wegener's disease	N=136 in 1984 publication (reported on subjects who entered study before 1/1/1984); N=151 in 1989 publication (reported on subjects who entered study before 4/1/1984). Inclusion here only of subgroup with creatinine clearance >30 and ≤60 ml/min/1.73m^2. Baseline data reported only for a subset of participants with 18 month followup data in 1984 paper, with sample size not stated: Weight: 72 kg (low protein); 70 kg (usual) Systolic BP (mm Hg): 140 (both groups) Diastolic BP (mm Hg): 90 (both groups) Serum albumin (g/l): 42 (both groups) Creatinine excretion (mmol/l in 24 hr): 10.4 (low protein), 11.0 (usual)	Low protein diet (0.6g/kg/day); n=74 Usual diet; n=77 NOTE: all patients received a vitamin and trace element preparation Followup period: minimum of 1.5 years for 1984 publication; minimum of 3 years for 1989 publication Study withdrawals (%): 4% for n=153 with 3 years followup (1989 publication)	Allocation Concealment: Unclear Blinding: None reported Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: No
Facchini, 2003[82] United States Funding Source: Not reported	Inclusion Criteria: Type 2 diabetes referred to nephrology clinics for renal failure (GFR 15-75 ml/min) and otherwise unexplained proteinuria (350-12,000 mg/day) Exclusion Criteria: None stated	N=191 Age (yr): 59.5 Gender (Male %): 53.0 Race/Ethnicity (%): NR Weight: 78 kg reported for CR-LIPE group, 79 kg for Control (for subset of completers, number per group not reported) BMI: 28 Systolic BP (mm Hg): 156 Diastolic BP (mm Hg): 88 CKD stage: NR Serum creatinine (mg/dL): 1.84 Creatinine clearance (mL/min): NR Albuminuria: NR Proteinuria: 2,469 mg/day Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): 63.0 HbA_{1c} (%): 7.6	50% carbohydrate restricted, low-iron-available, polyphenol-enriched diet (CR-LIPE)† (suggested macronutrient composition: 35% CHO, 30% fat, 25-30% protein, 5-10% ethanol); n=100 Control (protein restricted (0.8g/kg/day) (suggested macronutrient composition: 65% CHO, 25% fat, 10% protein, 0% ethanol); n=91 Followup period: mean of 3.9 years	Allocation Concealment: Unclear ("concealed" but no details) Blinding: Study personnel blinded to aim of study; outcomes unclear Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		Total cholesterol: 5.6 mmol/l for subset of completers with fasting lipids LDL cholesterol: 3.6 mmol/l for subset of completers with fasting lipids Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Study withdrawals (%): 11 †Intended to complement angiotensin system inhibition and pharmacotherapy for glycemic and blood pressure control	
Williams, 1991[83] United Kingdom Funding Source: Foundation	Inclusion Criteria: adults <70 yrs attending 1 of 2 hospital clinics; chronic renal failure (plasma creatinine >150 µmol/l for males, >150 µmol/l for women) with evidence of deteriorating renal function on serial plasma creatinine or creatinine clearance estimations; plasma creatinine <900 µmol/l and plasma phosphate < 2 µmol/l Exclusion Criteria: patients receiving active therapy for their primary disease; proven malignancy; psychologically unstable or noncompliant; dietary protein <0.8 g/kg/day; obese patients on a reducing diet	N=98 Age (yr): 45.0 Gender (Male %): 66.3 Race/Ethnicity (%): NR Weight: 71.3 kg BMI: NR Systolic BP (mm Hg): 151 Diastolic BP (mm Hg): 90 CKD stage: NR Plasma creatinine (µmol/l): 398.1 Creatinine clearance (mL/min/1.73m^2): 26.8 Albuminuria: NR Proteinuria (g/24h): 3.15 Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): NR History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR	Dietary protein (0.6g/kg/day) and phosphate (800 mg/day) restriction; n=33 Phosphate restriction (1000 mg/day plus phosphate binders with each meal); n=30 Unrestricted (at least 0.8 g/kg/day protein); n=32 Followup period: mean 1.6 years Study withdrawals (%): 5.3 within 3 months	Allocation Concealment: Adequate Blinding: None Intention to Treat Analysis (ITT): No Withdrawals/ Dropouts adequately described: No

Appendix Table C112. Overview of low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		Current smoker (%): NR History of AKI (%): NR		
Samuelsson, 1997[84] Sweden Funding Source: Government, Foundation	Inclusion Criteria: nondiabetic primary renal disease; moderately advanced renal insufficiency (GFR 10 to 70 ml/min/1.73m^2) Exclusion Criteria: none stated	N=57 Age (yr): 51.3 Gender (Male %): 75 Race/Ethnicity (%): NR Weight (kg): 81.4 BMI: 26.2 Systolic BP (mm Hg): 136.5 Diastolic BP (mm Hg): 84.0 CKD stage: NR Serum creatinine (mg/dL): 2.4 Creatinine clearance (mL/min): NR Albuminuria: 0.95g/24 hr Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 35.5 HbA_{1c} (%): NR Total cholesterol (mg/dL): 243.6 LDL cholesterol (mg/dL): 170.2 Diabetes (%): 0 (by inclusion criteria) History of HTN (%): NR Dyslipidemia (%): unclear History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Triglyceride lowering diet (with dietary counseling), n=29 Gemfibrozil - 300mg/day increased to 300 mg twice/day after 1 month with further titration up to 450 mg twice/day at 3 months if triglyceride levels was above 1.7 mmol/l (no dietary counseling); n=28 Followup period: 1 year Study withdrawals (%): 15.8	Allocation Concealment Unclear Blinding: None Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C113. Summary of study baseline characteristics for low protein diet versus usual protein diet and other dietary intervention trials

Characteristic	Mean (Range) (unless otherwise noted)	Number of Trials Reporting
Low protein versus usual protein diet trials (n=6)		
Total number of patients evaluated	1480 (63-585)	6
Age of patients, years	51.9 (48.5-57.9)	5
Gender, male, %	59.3 (54.2-83.0)	5
Race/ethnicity, white, %	85.0	1
Body Mass Index	27.1 (24.6-27.6)	3
Patients with diabetes, %	21.4 (0-100)	4
Diabetic nephropathy trials, number of patients	159 (47-112)	2
% HbA_{1c} in patients with diabetes	7.8 (7.65-8.1)	2
Estimated or measured GFR, ml/min/1.73m^2	45.1 (38.6-85.7)	3
Serum creatinine, mg/dL	1.8 (1.1-1.9)	2
Creatinine clearance, ml/min/1.73m^2	47.3 (33-50.4)	2
Albumin excretion rate, µg/min	507.5	1
Albuminuria, mg/24 h	366.0	1
Systolic blood pressure, mm Hg	133.3 (131.0-140.0)	3
Diastolic blood pressure, mm Hg	81.9 (77.0-90.0)	3
Patients with hypertension, %	82.2 (66.1-85.3)	2
Patients with cardiovascular disease, %	NR	NR
Low protein diet versus other diets (n=2)		
Total number of patients evaluated	289 (98-191)	2
Age of patients, years	54.6 (45-59.5)	2
Gender, male, %	56.7 (52.9-64.3)	2
Race/ethnicity, white, %	NR	NR
Body Mass Index	28	1
Patients with diabetes, %	100	1
Diabetic nephropathy trials, number of patients	191	1
% HbA_{1c} in patients with diabetes	7.6	1
Estimated or measured GFR, ml/min/1.73m^2	63	1
Serum creatinine, mg/dL	1.84	1
Creatinine clearance, ml/min/1.73m^2	NR	NR
Albumin excretion rate, µg/min	NR	NR
Albuminuria, mg/24 h	NR	NR
Systolic blood pressure, mm Hg	154.3 (151-156)	2
Diastolic blood pressure, mm Hg	88.7 (88-90)	2
Patients with hypertension, %	NR	NR
Patients with cardiovascular disease, %	NR	NR
Low triglyceride diet versus gemfibrozil (n=1)		
Total number of patients evaluated	57	1
Age of patients, years	51.3	1
Gender, male (%)	75.4	1
Race/ethnicity, white (%)	NR	NR
Body Mass Index	26.2	1
Patients with diabetes (%)	0	1
Estimated or measured GFR (ml/min/1.73m^2)	35.5	1
Serum creatinine (mg/dL)	2.4	1
Creatinine clearance (ml/min/1.73m^2)	NR	NR
Albumin excretion rate (µg/min)	NR	NR
Albuminuria (mg/24 h)	950.0	1
Systolic blood pressure (mm Hg)	136.5	1
Diastolic blood pressure (mm Hg)	84	1
Patients with hypertension (%)	NR	NR
Patients with cardiovascular disease, %	NR	NR

*NR=Not reported; GFR = glomerular filtration rate

Appendix Table C114. Clinical outcomes (outcomes part A), low protein diet versus usual protein diet and other dietary intervention trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any n/N (%)	
Low protein diet versus usual protein diet trials (n=6)												
	Low Protein	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**
Koya, 2009[75]	1/47 (2.1)	1/41 (2.4)					0/47	1/41 (2.4)				
Dussol, 2005[76]												
Kopple, 1997[77] Peterson, 1995[71] Klahr, 1994[72] Greene, 1993[73] MDRD	5/291 (1.7)	10/294 (3.4)	4/291 (1.4)	5/294 (1.7)								
D'Amico, 1994[78]												
Locatelli, 1991[79]	2/230 (0.9)	3/226 (1.3)										
Rosman, 1989/1984[80,81]	4/74 (5.4)	7/77 (9.1)										
Low protein diet versus other diet trials (n=2)												
	Low Protein	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**
Facchini, 2003[82]	14/79 (17.7)	8/91 (8.8)										
Williams**, 1991[83]	†1/31 (3.0)	†Lo-Phos: 4/29 (13.3); †Control: 1/29 (3.1)										
Low triglyceride diet versus gemfibrozil (GF) trials (n=1)												
	Low TG Diet	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**
Samuelsson, 1997[84]												

GF = gemfibrozil; TG = triglyceride

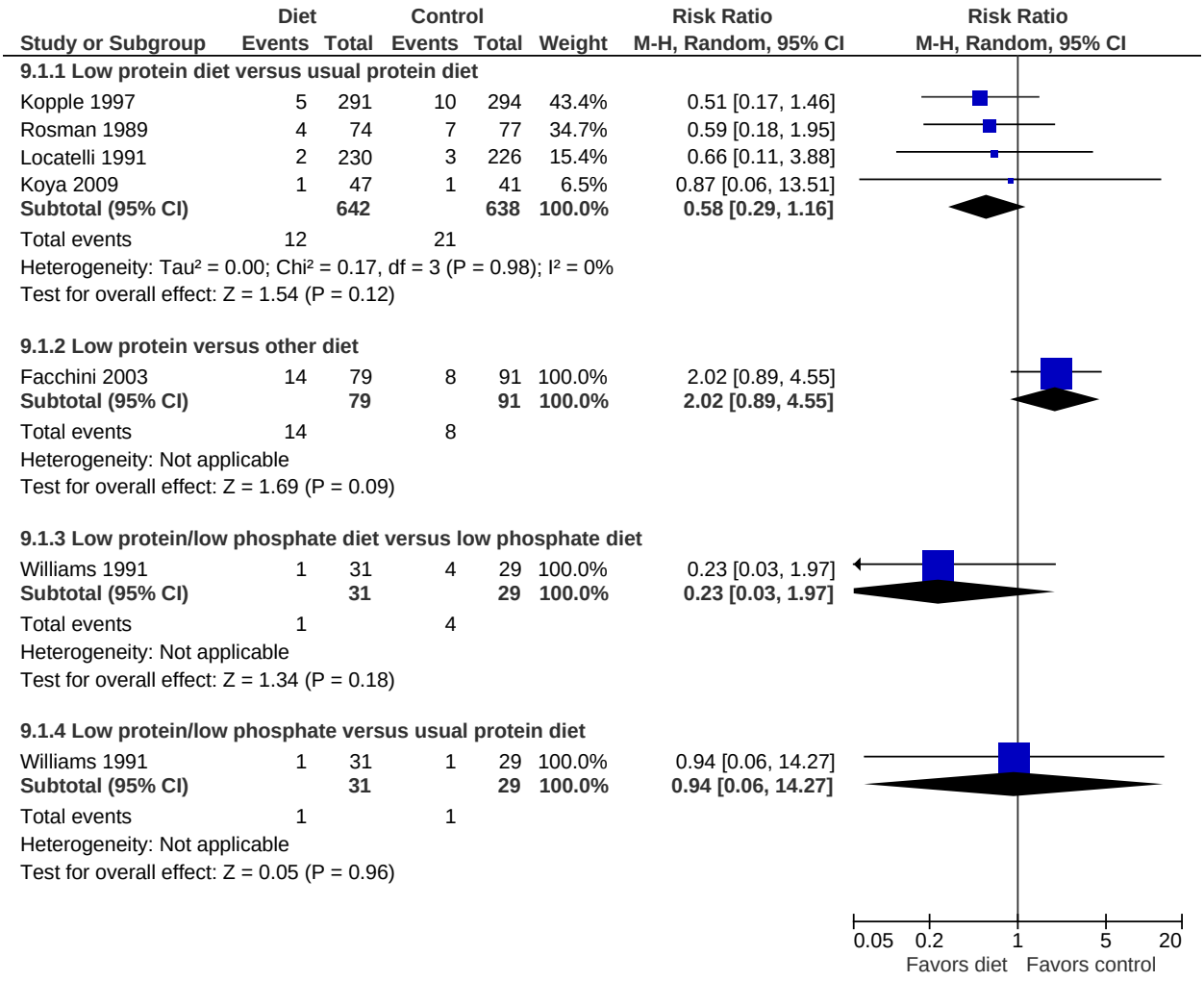
* $p < 0.05$ versus control

†Study also reported one death that occurred during the first 3 months of post-randomization followup, that they excluded from outcomes analyses, and for which they didn't report original treatment group assignment.

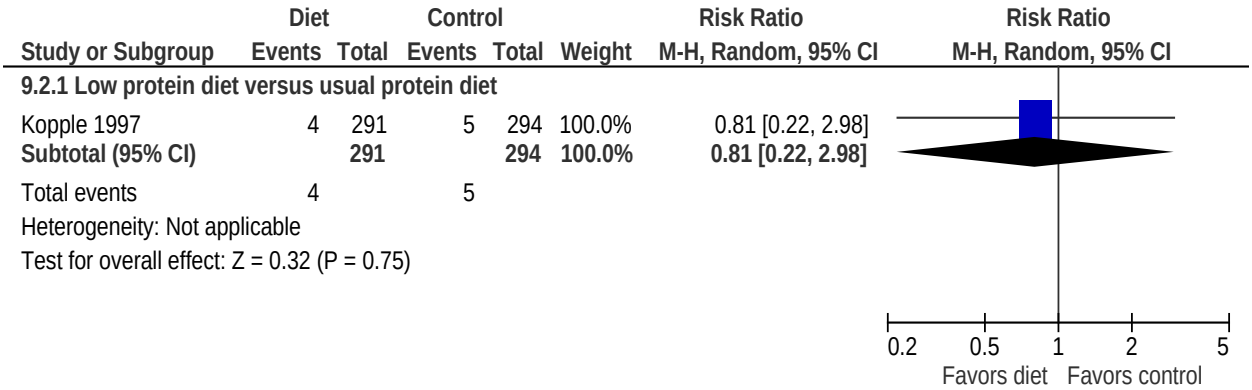
**Study compared a low protein and low phosphate diet to two different diets, a low phosphate diet, and a usual protein/usual phosphate diet.

Appendix Figure C22. Forest plots for low protein diet versus usual protein diet and other dietary intervention trials

All-cause mortality



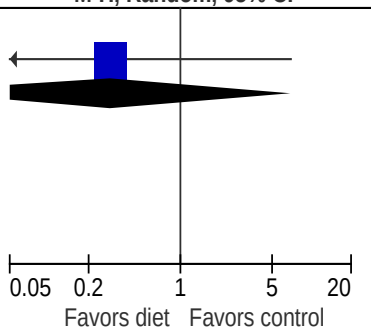
Cardiovascular mortality



Appendix Figure C22. Forest plots for low protein diet versus usual protein diet and other dietary intervention trials (continued)

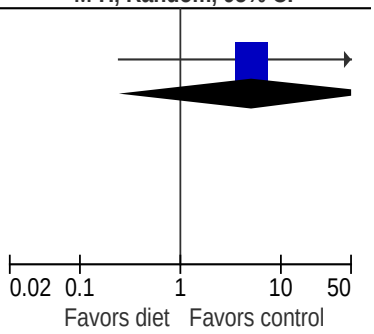
Myocardial infarction, fatal

Study or Subgroup	Diet Events	Diet Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.9.1 Low protein diet versus usual protein diet						
Koya 2009	0	47	1	41	100.0%	0.29 [0.01, 6.97]
Subtotal (95% CI)		**47**		**41**	**100.0%**	**0.29 [0.01, 6.97]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						



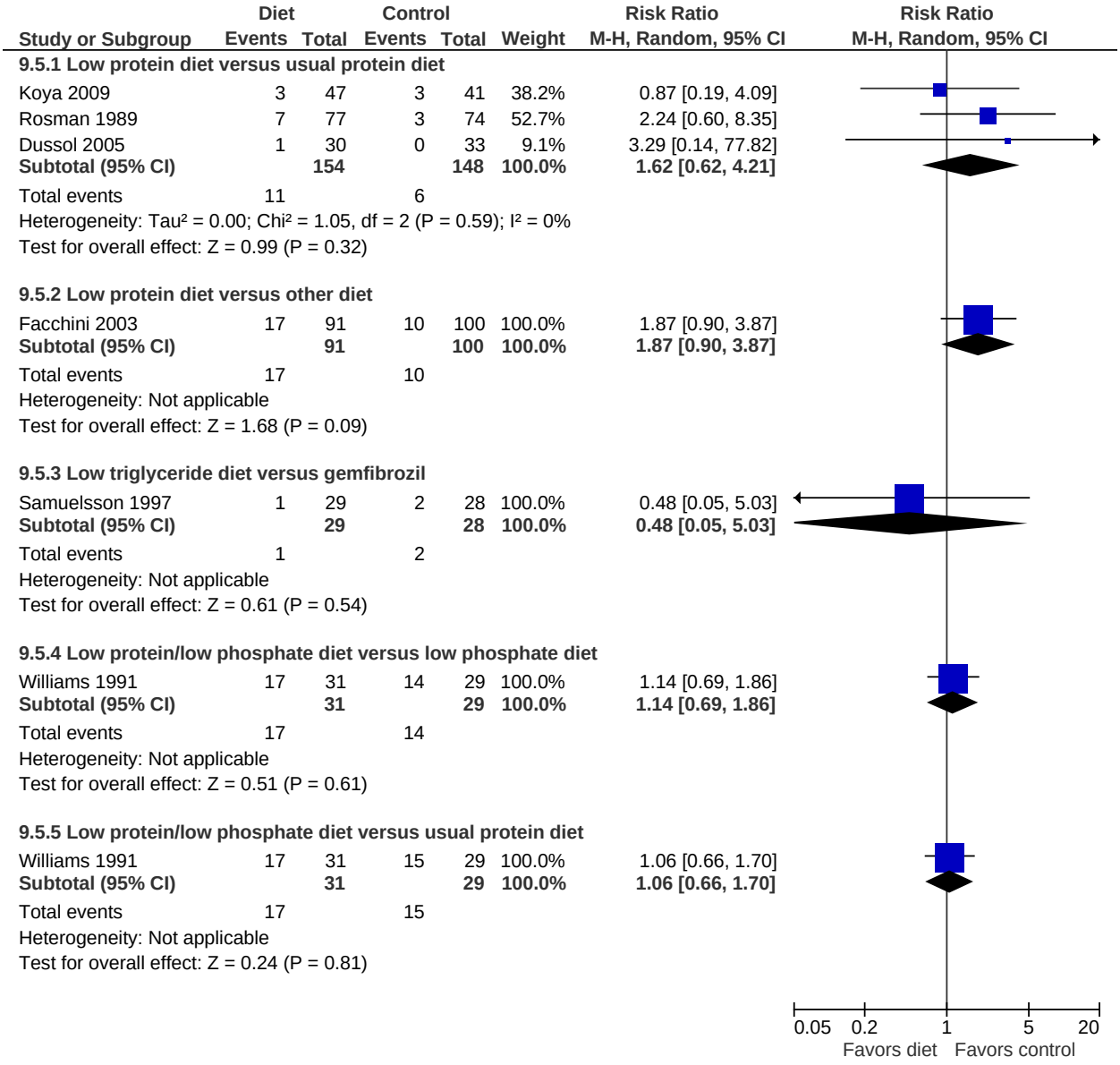
Stroke, nonfatal

Study or Subgroup	Diet Events	Diet Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.4.2 Low protein diet versus usual protein diet						
Kopple 1997	2	291	0	294	100.0%	5.05 [0.24, 104.76]
Subtotal (95% CI)		**291**		**294**	**100.0%**	**5.05 [0.24, 104.76]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						



Appendix Figure C22. Forest plots for low protein diet versus usual protein diet and other dietary intervention trials (continued)

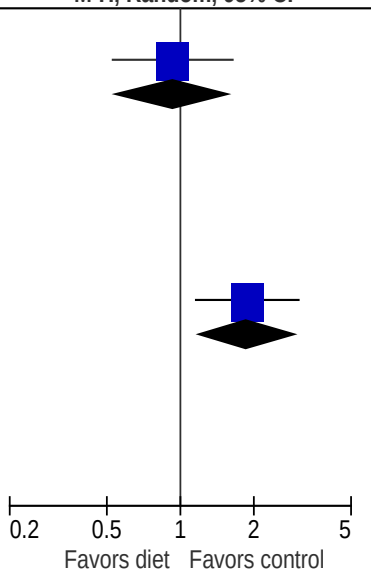
End-stage renal disease



Appendix Figure C22. Forest plots for low protein diet versus usual protein diet and other dietary intervention trials (continued)

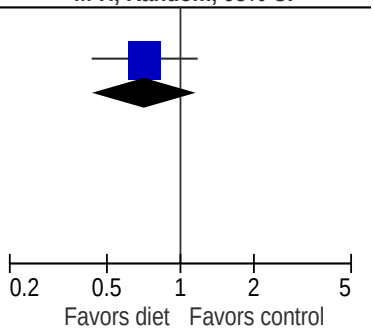
Doubling of serum creatinine

Study or Subgroup	Diet Events	Diet Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.6.1 Low protein diet versus usual protein diet						
Koya 2009	16	47	15	41	100.0%	0.93 [0.53, 1.64]
Subtotal (95% CI)		**47**		**41**	**100.0%**	**0.93 [0.53, 1.64]**
Total events	16		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
9.6.2 Low protein diet versus other diet						
Facchini 2003	31	79	19	91	100.0%	1.88 [1.16, 3.05]
Subtotal (95% CI)		**79**		**91**	**100.0%**	**1.88 [1.16, 3.05]**
Total events	31		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						



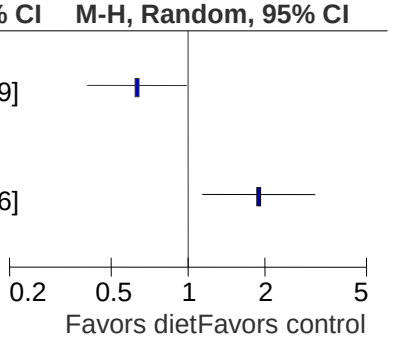
Halving of GFR

Study or Subgroup	Diet Events	Diet Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
9.7.1 Low protein diet versus usual protein diet						
D'Amico 1994	18	63	26	65	100.0%	0.71 [0.44, 1.17]
Subtotal (95% CI)		**63**		**65**	**100.0%**	**0.71 [0.44, 1.17]**
Total events	18		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						



Composite renal outcome (See Table C117 for definitions

Study or Subgroup	Diet Events	Diet Total	Control Events	Control Total	Risk Ratio M-H, Random, 95% CI
9.8.1 Low protein diet versus usual protein diet					
Locatelli 1991	27	230	42	226	0.63 [0.40, 0.99]
9.8.2 Low protein versus other diet					
Facchini 2003	31	79	18	91	1.98 [1.21, 3.26]



Appendix Table C115. Clinical outcomes (outcomes part B), low protein diet versus usual protein diet and other dietary intervention trials

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF, Any n/N (%)		CHF Hospitalization (A) or Death (B) n/N (%)		Composite Vascular Outcome n/N (%)	
Low protein diet versus usual protein diet trials (n=6)										
	Low Protein	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**
Koya, 2009[75]										
Dussol, 2005[76]										
Kopple, 1997[77] Peterson, 1995[71] Klahr, 1994[72] Green, 1993[73] MDRD	2/291 (0.7)	0/294								
D'Amico, 1994[78]										
Locatelli, 1991[79]										
Rosman, 1989/1984[80,81]										
Low protein diet versus other diet trials (n=2)										
	Low Protein	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**
Facchini, 2003[82]										
Williams, 1991[83]										
Low triglyceride diet versus GF trials (n=1)										
	Low TG Diet	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**
Samuelsson, 1997[84]										

CHF = congestive heart failure; TG = triglyceride; GF = gemfibrozil

Appendix Table C116. Clinical renal outcomes (outcomes part C), low protein diet versus usual protein diet and other dietary intervention trials

Study	End Stage Renal Disease n/N (%)		Doubling of Serum Creatinine n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome n/N (%)**	
Low protein diet versus usual protein diet trials (n=6)										
	Low Protein	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**
Koya, 2009[75]	3/47 (6.4)	3/41 (7.3)	16/47 (34.0)	15/41 (36.6)						
Dussol, 2005[76]	1/30 (3.3)	0/33								
Kopple, 1997[77] Peterson, 1995[71] Klahr, 1994[72] Greene, 1993[73] MDRD	†NR	†NR			†NR	†NR				
D'Amico, 1994[78]					‡18/63 (28.6)	‡26/65 (40.0)				
Locatelli, 1991[79]									27/230 (11.7)	42/226 (18.6)
Rosman, 1989/1984[80,81]	7/77 (9.1)	3/74 (4.1)								
Low protein diet versus other diet trials (n=2)										
	Low Protein	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**	**Low Protein**	**Other Diet**
Facchini, 2003§[82]	17/79 (21.5)	10/91 (11.0)	31/79 (39.2)	19/91 (20.9)					31/79 (39.2)	18/91 (19.8)
Williams, 1991#[83]	17/31 (54.8)	Lo-Phos: 14/29 (48.3) Control: 15/29 (51.7)								
Low triglyceride diet versus GF trials (n=1)										
	Low TG Diet	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**
Samuelsson, 1997[84]	1/29 (3.4)	2/28 (7.1)								

GFR = glomerular filtration rate; NR = not reported; TG = triglyceride; GF = gemfibrozil; Lo-Phos = low phosphate diet

*Not statistically significant versus control

**See Composite renal outcome definitions table

†Study reported that 12 participants developed end stage renal disease but did not report this result separately for the two treatment groups. Study further reported that 60 patients overall reached a study stopping point due to "rapidly declining glomerular filtration rate." Although study did not report this result separately for the two treatment groups, it did state that there was no significant difference between the results for the two groups.

‡Study reported on outcome of halving of creatinine clearance.

§Facchini study compared a low protein diet to a CR-LIPE diet (Carbohydrate Restricted, Low-Iron-available, Polyphenol-Enriched).

#Williams study compared a low protein and low phosphate diet to two different diets, a low phosphate diet, and a usual protein/usual phosphate diet.

Appendix Table C117. Composite renal outcome definitions, low protein diet versus usual protein diet and other dietary intervention trials

Study	Definition
Locatelli, 1991[79]	Dialysis or doubling of plasma creatinine concentration
Facchini, 2003[82]	Renal replacement therapy or death

Appendix Table C118. Study withdrawals and adverse events (outcomes part D), low protein diet versus usual protein diet and other dietary intervention trials

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any n/N (%)		Study Withdrawals Due to Serious Adverse Event: Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Specific n/N (%)		Renal Adverse Events n/N (%)	
Low protein diet versus usual protein diet trials (n=6)												
	Low Protein	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**	**Low Protein**	**Usual Protein**
Koya, 2009[75]	9/56 (16.1)	15/56 (26.8)										
Dussol, 2005[76]	5/30 (16.7)	7/33 (21.2)										
Kopple, 1997[77] Peterson, 1995[71] Klahr, 1994[72] Greene, 1993[73] MDRD	†NR	†NR							‡"Stop point due to serious medical condition": 6/291 (2.1); Weight loss 29%; Weight gain 25%; Hyperkalemia 10%	‡" Stop point due to serious medical condition": 6/294 (2.0); Weight loss 18%; Weight gain 40%; Hyperkalemia 17%	ARF: 1/291 (0.3)	ARF: 0/294
D'Amico, 1994[78]	§NR	§NR										
Locatelli, 1991[79]	36/230 (15.7)	35/226 (15.5)										
Rosman, 1989/1984[80,81]	3/77 (3.9)	3/74 (4.1)										
Low protein diet versus other diet trials (n=2)												
	Low Protein	**Other Diet**	**Low Protein**	**CR-LIPE Diet**	**Low Protein**	**CR-LIPE Diet**	**Low Protein**	**CR-LIPE Diet**	**Low Protein**	**CR-LIPE Diet**	**Low Protein**	**CR-LIPE Diet**
Facchini, 2003#[82]	12/91 (13.2)	9/100 (9.0)										
Williams, 1991**[83]	††NR	††NR										

Appendix Table C118. Study withdrawals and adverse events (outcomes part D), low protein diet versus usual protein diet and other dietary intervention trials (continued)

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any n/N (%)		Study Withdrawals Due to Serious Adverse Event: Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Specific n/N (%)		Renal Adverse Events n/N (%)	
Low triglyceride diet versus GF trials (n=1)												
	Low TG Diet	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**	**Low TG Diet**	**GF**
Samuelsson, 1997[84]	0/29	6/28 (21.4)							"Mild GI symptoms": 0/29	"Mild GI symptoms": 6/28 (21.4)		

NR = not reported; ARF = acute renal failure; GF = gemfibrozil; GI = gastrointestinal

*p<0.05 versus control

†Study reported that 11/585 participants overall were lost to followup, but didn't report results by treatment group.

‡Specific causes of stop points due to serious medical condition were as follows, by treatment group: Low protein diet (pregnancy (1), stroke (2), acute renal failure (1), diabetes necessitating insulin (1), and cancer (1); and Usual protein diet (diabetes necessitating insulin (3), cardiomyopathy (1), cancer (1), severe liver disease (1).

§Study reported that 6/134 (4.5%) participants withdrew overall, but didn't report results by treatment group.

#Facchini study compared a low protein diet to a CR-LIPE diet (Carbohydrate Restricted, Low-Iron-available, Polyphenol-Enriched).

**Williams study compared a low protein and low phosphate diet to two different diets, a low phosphate diet, and a usual protein/usual phosphate diet.

††Study reported that 6/95 patients were withdrawn from the trial overall but didn't report results by treatment group.

Appendix Evidence Table C119. Overview of glycemic control trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Duckworth, 2009[95] VADT Multi-center United States Funding Source: Government, Foundation, and Industry	Inclusion: Veterans with type 2 diabetes inadequately controlled on maximal doses of an oral agent or insulin therapy. Exclusion: Glycated hemoglobin <7.5%, cardiovascular event during previous 6 months, advanced congestive heart failure, severe angina, live expectancy <7 years, BMI >40, serum creatinine >1.6 mg/dL, alanine aminotransferase >3 times upper limit of normal	N=491 (subgroup analysis of subjects with baseline microalbuminuria from overall study of N=1,791) Age (yr): NR Gender (Male %): NR Race/Ethnicity (%): NR Weight (kg): NR BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR CKD stage: NR Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): NR Albuminuria (µg/min): NR Proteinuria (g/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of previous cardiovascular event (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR History of AKI (%): NR	Intensive therapy (n=251): Started on maximal doses of oral therapy*; insulin added if patients did not achieve glycated hemoglobin <6%. Subsequent changes per protocol and local assessment, though not specified. Standard therapy (n=240): Started on ½ of maximal doses of oral therapy*; insulin added if patients did not achieve glycated hemoglobin <9%. Subsequent changes per protocol and local assessment, though not specified. *Initial oral therapy was metformin plus rosiglitazone if BMI ≥27; initial therapy was glimepiride plus rosiglitazone if BMI <27 Followup period: median 5.6 years Study withdrawals (%): Reported for overall study, but not for microalbuminuria subgroup	Allocation Concealment: Adequate Blinding: No Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Evidence Table C119. Overview of glycemic control trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Microalbuminuria Collaborative Study Group, 1995[86] United Kingdom Funding Source: Government and Foundation	Inclusion Criteria: Insulin dependent diabetic patients attending 9 hospital-based diabetes centers; ages 16-60; onset of diabetes before age 39; sitting BP <160/95 mm Hg; no antihypertensive treatment; no clinical evidence of cardiovascular, peripheral vascular, or renal disease. Subjects must further have had no albuminuria on urine dipstick, but have had morning urine albumin ≥15 mg/L or albumin-creatinine ratio ≥3.5 mg/mmol, followed by overnight urine albumin excretion rate >30µg/min but <200µg/min on at least 1 of 2 samples. Exclusion Criteria: none stated	N=70 Age (yr): 37.0 Gender (Male %): 72.9 Race/Ethnicity (%): NR Weight (kg): NR BMI: 26.0 Systolic BP (mm Hg): 127.5 Diastolic BP (mm Hg): 77.5 CKD stage: NR Serum creatinine (mg/dL): 0.97 Creatinine clearance (mL/min): NR Albuminuria (µg/min): 47.9 Proteinuria (g/day): NR Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 116.7 HbA_{1c} (%): 10.1 Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): 47.1 History of AKI (%): NR	Intensive therapy (n=36): Insulin by continuous infusion or multiple daily injections; goals were glycated hemoglobin concentration ≤7.5%, fasting blood glucose 4-6 mmol/l, and 2 hr postprandial blood glucose ≤10 mmol/l. Frequent visits and medication adjustment were made as needed to achieve targets. 24 hr/day consultation available if needed. Conventional therapy (n=34): 2 daily injections of insulin (except for 9 patients who were receiving >2 doses insulin per day at baseline); Conventional education given about diet, exercise and blood glucose monitoring, but no targets set. Insulin dose and regimen was adjusted only if patients became symptomatic. No changes were made to the usual diabetic diet of any patient. BP was assessed every 3 months, and all patients were treated to keep BP <160/95. Followup period: median 5 years	Allocation Concealment: Adequate (central location) Blinding: Unclear Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
			Study withdrawals (%): 11.4	

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C120. Summary of study baseline characteristics for glycemic control trials

Characteristic	Mean (Range) (unless otherwise noted)	Number of Trials Reporting
Patients randomized, n	561 (70-491)	2
Age of subjects, years	37.0	1
Male gender, %	72.9	1
Body Mass Index, kg/m2	26.0	1
Patients with diabetic nephropathy, n	561 (70-491)	2
Serum creatinine, mg/dL	0.97	1
Estimated GFR, ml/min/1.73m^2	116.7	1
Albuminuria, µg/min	47.9	1
Systolic blood pressure, mm Hg	127.5	1
Diastolic blood pressure, mm Hg	77.5	1
History of diabetes, %	100 (100-100)	2
HbA_{1c} (%)	10.1	1
Current smokers, %	47.1	1

GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}

Appendix Table C121. Clinical outcomes (outcomes part A), glycemic control trials

Study	All-cause Mortality n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any n/N (%)	
	IT	CT	IT	CT	IT	CT	IT	CT	IT	CT	IT	CT
Duckworth, 2009[85]												
Microalbuminuria Collaborative, 1995[86]	*NR	*NR										

IT = intensive treatment; CT = conventional treatment

*Study reported 1/70 (1.4%) deaths overall, but did not report this result by treatment group. included in withdrawals

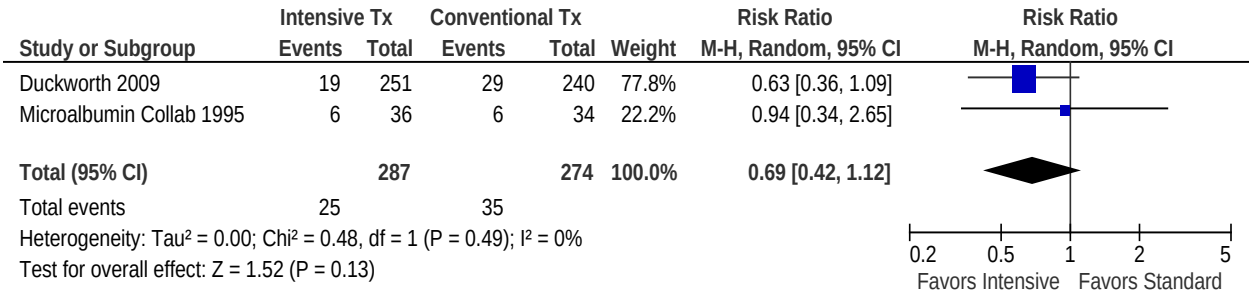
Appendix Table C122. Clinical renal outcomes (outcomes part C), glycemic control trials

Study	End Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR n/N (%)		Progression from Micro- to Macroalbuminuria n/N (%)		Composite Renal Outcome, n/N (%)	
	IT	CT	IT	CT	IT	CT	IT	CT	IT	CT
Duckworth, 2009[85]							19/251 (7.6)	29/240 (12.1)		
Microalbuminuria Collaborative, 1995[86]							6/36 (16.7)	6/34 (17.6)		

GFR = glomerular filtration rate; IT = intensive treatment; CT = conventional treatment

Appendix Figure C23. Forest plot for glycemic control trials

Progression from microalbuminuria to macroalbuminuria



Appendix Table C123. Study withdrawals and adverse events (outcomes part D), glycemic control trials

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Events: Any n/N (%)	Study Withdrawals Due to Serious Adverse Events: Any, n/N (%)		Adverse Event: Any n/N (%)		Adverse Event: Specific, n/N (%)		Renal Adverse Event: Any, n/N (%)	
	IT	CT		IT	CT	IT	CT	IT	CT	IT	CT
Duckworth, 2009[85]								Severe hypoglycemia: 5/36 (13.9); DKA: 3/36 (8.3)	Severe hypoglycemia: 5/34 (14.7); DKA: 2/34 (5.9)		
Microalbuminuria Collaborative, 1995[86]	5/36 (13.9)	3/34 (8.8)		*NR	*NR						

IT = intensive treatment; CT = conventional treatment; DKA = diabetic ketoacidosis

*Study reported 3/70 (4.3%) withdrawals due to serious adverse events overall (1 death, 1 leukemia, 1 acute renal failure), but did not report these outcomes by treatment group.

Appendix Table C124 Overview of anti-lipid trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
HMG-CoA Reductase Inhibitor versus Placebo trials (n=12)				
Kendrick, 2010[87] AFCAPS/TexCAPS United States Funding Source: Industry and other	Inclusion Criteria: Men aged 45-73 years or postmenopausal women aged 55-73 years who met the lipid entrance criteria at both 4 and 2 weeks before randomization with a <15% difference in LDL-C values between visits. Lipid entry criteria included total cholesterol 180-264 mg/dL, LDL-C 130-190 mg/dL, HDL-C ≤ 45 mg/dL for men or ≤ 47 mg/dL for women, and triglycerides ≤ 400 mg/dL. Exclusion Criteria: Clinical evidence atherosclerotic CVD, secondary hyperlipoproteinemia, nephrotic syndrome, uncontrolled HTN, and type 1 or 2 diabetes mellitus.	N=304 (Post hoc analysis in subgroup with baseline GFR < 60 ml/min/ 1.73m^2 from total of 6605 randomized). Age (yr): 62 Gender (Male %): 79 Race/Ethnicity (%): White NR, Mexican American NR, African American 1 BMI: 26 Systolic BP (mm Hg): 142 Diastolic BP (mm Hg): 79 Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): 1.4 Estimated GFR (ml/min/1.73m^2): 53 Total cholesterol (mg/dL): 222 LDL cholesterol (mg/dL): 151 Diabetes (%): 2 History of HTN (%): 35 (p<0.05 between groups) History of CAD (%): 0 History of CHF (%): NR History of MI (%): 0 PTCA (%): 0 CABG (%): 0 History of Stroke (%): NR Peripheral arterial disease (%):NR Current smoker (%): 8	Lovastatin initiated at 20 mg/d, titrated up to 40 mg/d to reach goal LDL ≤110 mg/dL (n=145) Placebo (n=159) Followup period: mean 5.1 years Study withdrawals (%): No information reported for CKD group; stated both that all had complete data and that 24% of original AFCAPS/TexCAPS participants did not have data to calculate yearly change in GFR.	Allocation Concealment: Unclear Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis (ITT): yes Withdrawals/ Dropouts adequately described: Study reported available followup data on all participants

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Ridker, 2010[88] JUPITER United States Funding Source: Industry	Inclusion Criteria: apparently healthy men over age 50 years and women over age 60 years with LDL-C <130 mg/dl at increased vascular risk due to high-sensitivity C-reactive protein (hsCRP) ≥2 mg/l. Exclusion Criteria: treatment within 6 weeks of screening with any lipid lowering therapies, current use of hormone replacement therapy, evidence of hepatic dysfunction, creatinine >2.0 mg/dl, diabetes, uncontrolled hypertension, prior malignancy, uncontrolled hypothyroidism, or a recent history of alcohol, drug abuse, or other medical condition that might compromise safety.	N=3,267 (Post hoc analysis in subgroup with baseline GFR < 60 ml/min/ 1.73m^2 from total of 17,795 randomized). Age (yr): 70 Gender (Male %): 35 Race/Ethnicity (%): White 74, Hispanic 19, African American 3 BMI: 29 Systolic BP (mm Hg): 133 Diastolic BP (mm Hg): 80 Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): 56 (51 to 58) Total cholesterol (mg/dL): 189 LDL cholesterol (mg/dL): 109 Diabetes (%): 0 History of HTN (%): NR (none with uncontrolled) History of CAD (%): NR History of CHF (%): NR History of MI (%): NR PTCA (%): NR CABG (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 8	Rosuvastatin 20 mg/d (n=1638) Placebo (n=1629) Followup period: median 1.9 years (maximum 5 years) Study withdrawals (%): No information reported for CKD group in this secondary analyses.	Allocation Concealment: adequate Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis (ITT): yes Withdrawals/ Dropouts adequately described: No information reported
Nakamura, 2009[89] MEGA Japan Funding Source: Government and industry	Inclusion Criteria: Men and postmenopausal women aged 40-70 years with total cholesterol 220-270 mg/dL and no history of CHD and/or stroke. Exclusion Criteria: Familial hypercholesterolemia, history of CVD, cancer, serum creatinine ≥1.5 mg/dL, significant liver disease, and secondary hyperlipidemia	N=2,978 (Secondary analysis in subgroup with baseline GFR 30 to 59 ml/min/ 1.73m2 from total of 7,196 patients randomized. Age (yr): 60 Gender (Male %): 24 Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): 133 Diastolic BP (mm Hg): NR Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): 53 Total cholesterol (mg/dL): 244	Pravastatin (low dose) 10-20 mg/d + Step I diet counseling (n=1471) Diet counseling (n=1,507) Followup period 5.3 years Study withdrawals (%): No information reported	Allocation Concealment: Adequate (from main paper) Blinding: open-label Intention to Treat Analysis (ITT): yes Withdrawals/ Dropouts adequately described: No information reported

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		LDL cholesterol (mg/dL): 155 Diabetes (%): 19 History of HTN (%): 46 History of CAD (%): 0 History of CHF (%): NR History of MI (%): 0 PTCA (%): 0 CABG (%): 0 History of stroke (%): 0 Peripheral arterial disease (%): NR Current smoker (%): 13		
Colhoun, 2009[90] CARDS United Kingdom and Ireland Funding Source: Industry	Inclusion Criteria: Diabetes and at least 1 of the following risk factors: (1) history of HTN, (2) retinopathy (i.e., any retinopathy, maculopathy, or prior photocoagulation), (3) microalbuminuria (urinary albumin/creatinine ratio 22 to 221 mg/g) or microalbuminuria (urinary albumin/creatinine ratio >221 mg/g), or (4) current smoking. Exclusion Criteria: History of MI, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery); creatinine concentration > 1.7 mg/dL or glycated hemoglobin (hemoglobin A1c) level >12%.	N=970 (Secondary analysis in subgroup with baseline GFR <60 ml/min/ 1.73m^2 from total of 2,838 randomized) Age (yr): 65 Gender (Male %): 48 Race/Ethnicity (%): white 96 BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR Albuminuria (% > Micro): 21 Albumin/creatinine ratio: 10 Serum creatinine (mg/dL): 1.3 Estimated GFR (ml/min/1.73m^2): 54 Total cholesterol (mg/dL): 211 LDL cholesterol (mg/dL): 120 Diabetes (%): 100 History of HTN (%): NR History of CAD (%): 0 History of CHF (%): NR History of MI (%): 0 PTCA (%): 0 CABG (%): 0 History of Stroke (%): 0 Peripheral arterial disease (%): NR Current smoker (%): NR	Atorvastatin 10 mg/d (n=482) Placebo (n=488) Followup period: median 3.9 years Study withdrawals (%): No information reported	Allocation Concealment: Adequate (from main paper) Blinding: double, end points adjudicated by blinded committee Intention to Treat Analysis (ITT): yes Withdrawals/ Dropouts adequately described: No information reported
Koren, 2009[91] Isaacsohn, 2000[92]	Inclusion Criteria: Male or female older than 18 years of age with known CHD, defined as prior acute MI, CABG, or unstable angina >3	N= 579 (Secondary analysis in subgroup with baseline GFR <60 ml/min/ 1.73m^2) from total of 2,442 randomized). Age (yr): 65	Atorvastatin, started at 10 mg/day, then titrated up to achieve LDL goal of <80 mg/dL up to maximum of	Allocation Concealment: Adequate Blinding: open-label

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
ALLIANCE United States Funding Source: Industry	months before screening, or PTCA >6 months before screening. LDL-C 110-200 mg/dL for patients on antilipid drugs or 130-250 mg/dL for patients receiving no antilipid drugs. Exclusion Criteria: Patients with chronic stable angina or awaiting revascularization procedures. Breastfeeding or pregnancy; women of childbearing age planning to become pregnant during the study or who did not practice a method of birth control acceptable to the investigator; any significant abnormalities investigator believed may compromise the patient's safety or successful completion of the study; any disease process likely to limit life to less than the duration of the study; all cancers (excluding basal cell and squamous cell skin cancers); New York Heart Association class III or IV congestive heart failure; known hypersensitivities to hydroxymethylglutaryl coenzyme A reductase inhibitors.	Gender (Male %): 77 Race/Ethnicity (%): white 88; African American 9 BMI: 29 Systolic BP (mm Hg): 137 Diastolic BP (mm Hg): 78 Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): 1.5 Estimated GFR (ml/min/1.73m^2): 51 Total cholesterol (mg/dL): 228 LDL cholesterol (mg/dL): 147 Diabetes (%): 28 History of HTN (%): NR History of CAD (%): 100 History of CHF (%): 10 History of MI (%): 62 PTCA (%): 33 CABG (%): 53 History of Stroke (%): 10 Peripheral arterial disease (%): NR Current smoker (%): 15	80 mg/day (n=286) Usual care (n=293) Followup period: median 4.5 years Study withdrawals (%): 19% (n=465/2,442) withdrawals from main study, but data not reported for CKD subgroup.	Intention to Treat Analysis (ITT): yes Withdrawals/Dropouts adequately described: No information reported.
Rahman, 2008[93] ALLHAT-LLT United States, Puerto Rico, U.S. Virgin Islands, and Canada Funding: Government and Industry	Inclusion Criteria: age ≥55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor); fasting LDL-C level of 120-189 mg/dL for those with no known CHD, or 100-129 mg/dL for those with known CHD, and fasting triglyceride levels lower than 350 mg/dL. Exclusion Criteria: currently using prescribed lipid-lowering agents or large doses (500 mg/day) of	N=1,557 (Secondary analysis in subgroup with baseline GFR < 60 ml/min/1.73m^2) from total of 10,060 randomized). Age (yr): 71 Gender (Male %): 46 Race/Ethnicity (%): white 51 , black 29, Hispanic 15 BMI: 29 Systolic BP (mm Hg): 146 Diastolic BP (mm Hg): 82 Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m2): 50	Pravastatin 40 mg/d (n=779) Usual care (n=778) Followup period: mean 4.8 years Study withdrawals (%): No information reported	Allocation Concealment: Unclear Blinding: open-label Intention to Treat Analysis (ITT): yes Withdrawals/Dropouts adequately described: No information reported

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	nonprescription niacin; were known to be intolerant of statins or to have significant liver dysfunction (serum alanine aminotransferase >100 IU/L); had other contraindications for statin therapy; or had a known secondary cause of hyperlipidemia.	Total cholesterol (mg/dL): 225 LDL cholesterol (mg/dL): 146 Diabetes, type 2 (%): 31 History of HTN (%): 100 History of CAD (%): 18 History of CHF (%): NR History of MI or Stroke (reported pooled % only): 22.0 History of coronary revascularization: 9 Peripheral arterial disease (%): NR Current smoker (%): 19		
Chonchol, 2007[94] 4S Trial Huskey, 2009[95] Scandanavia	Inclusion criteria: Men and women aged 35-70 yrs, with history of CHD (MI and/or angina), total cholesterol 212-309 mg/dL, triglycerides <221 mg/dL Exclusion criteria: Secondary hypercholesterolemia, unstable angina, planned CABG or PTCA, recent MI (recent not defined), CHF requiring treatment, hypersensitivity to HMG-CoA reductase inhibitors.	N=505 (Subgroup analysis of patients with eGFR <60 mL/min/1.73m2 performed within a post hoc analysis of patients with eGFR <75 mL/min/1.73m2 from the 4,420 with baseline creatinine measurements) from total of 4,444 participants randomized in 4S Trial. Baseline characteristics not reported for n=505 participants with eGFR <60 mL/min/1.73m2 in Chonchol paper, but are reported for n=409 participants (n=199 simvastatin, n=210 placebo) with eGFR <60 mL/min/1.73m2 in Huskey paper. Age (yr): 62.2 Gender (% male): 54 BMI (kg/m2): 25.9 Systolic BP (mm Hg): 143.1 Diastolic BP (mm Hg): 83.7 Serum creatinine (mg/dL): 1.21 Estimated GFR (mL/min/1.73m2): 54.7 Total cholesterol (mg/dL): 265 LDL cholesterol (mg/dL): 191.5 Diabetes (%): 2.7 History of HTN (%): 37.4 History of CAD (%): 100 History of CHF (%): NR History of MI (%): 77.8 PTCA or CABG (%): 7.1	Simvastatin (n=245), initiated at 20 mg/day, titrated up to 40 mg/day as needed to get total cholesterol to <200 mg/dL Placebo (n=260) Followup duration: median 5.4 years Study withdrawals (%): No data reported for eGFR<60 group	Allocation concealment: Unclear Blinding: Double blind. Outcome assessors blinded to treatment assignment Intention to treat analysis (ITT): No Withdrawals/dropouts adequately described: No data reported

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		History of Stroke (%): NR Peripheral arterial disease (%):NR Current smoker (%): 16		
Kjekshus, 2007[96] CORONA Multinational, including 19 European countries, Russia, and South Africa Funding Source: Industry	Inclusion Criteria: ≥60 years of age, chronic NYHA class II, III, or IV heart failure of ischemic cause (as reported by investigators) and an ejection fraction of no more than 40% (no more than 35% in patients in NYHA class II); investigator did not think patient needed treatment with a cholesterol-lowering drug. Exclusion Criteria: Previous statin-induced myopathy/hypersensitivity reaction; decompensated heart failure or need for inotropic therapy; MI within past 6 months; unstable angina or stroke within past 3 months; PCTA, CABG, or the implantation of a cardioverter-defibrillator or biventricular pacemaker within past 3 months or planned implantation of such a device; previous or planned heart transplantation; clinically significant, uncorrected primary valvular heart disease or malfunctioning prosthetic valve; hypertrophic cardiomyopathy; acute endomyocarditis or myocarditis, pericardial disease, or systemic disease (e.g. amyloidosis); acute or chronic liver disease; levels of alanine aminotransferase or thyrotropin >2 times the ULN range; a serum creatinine level >2.5 mg/dL; chronic muscle disease or unexplained creatine kinase level >2.5 times the ULN range; previous treatment with cyclosporine; any	N=1,635 patients with CKD (Subgroup analysis within patients with baseline GFR < 51 ml/min/1.73m^2 from among total of 5,011 randomized in CORONA study). Baseline characteristics not reported for CKD subjects only except for those identifiable from entry criteria. Age (yr): NR Gender (Male %): NR Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): NR History of HTN (%): NR History of CAD (%): 100 History of CHF (%): 100 History of MI (%): NR PTCA (%): NR CABG (%): NR History of Stroke (%): NR Peripheral arterial disease (%):NR Current smoker (%): NR	Rosuvastatin 10 mg/day (n=1,418) Placebo (n=1,432) Followup period: Median 2.7 years Study withdrawals (%): No data reported for CKD subgroup	Allocation concealment: Adequate (centralized interactive Web-based response system) Blinding: double, end points adjudicated by blinded committee Intention-to-treat analysis: yes Withdrawals/dropouts adequately described: No data reported for CKD subgroup

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	other condition that would substantially reduce life expectancy or limit compliance with the protocol; or the receipt of <80% of dispensed placebo tablets during the run-in period.			
Lemos, 2005[97] LIPS Multinational Funding Source: Industry	Inclusion Criteria: Successful completion of a first percutaneous coronary intervention (successful defined as residual stenosis <50%, no post-procedural in-hospital myocardial necrosis, repeat vascularization or death); Eligible participants had to meet at least one of the following: (1) total cholesterol level of 135 to 270 mg/dl with a fasting triglyceride level <400 mg/dl, or (2) total cholesterol level <212 mg/dl for patients whose lipids levels were measured 24 hours to 4 weeks after an episode of MI, or (3) total cholesterol level <232 mg/dl for patients who had diabetes. Exclusion Criteria: baseline serum creatinine value >1.8 mg/dl	N=310 (post hoc subgroup analysis limited to patients with creatinine clearance in the lowest quintile or <55.9 ml/min from among 1,558 subjects with complete data for creatinine clearance calculation from among 1,677 randomized participants in the LIPS study) Age (yr): 69 Gender (Male %): 67 Race/Ethnicity (%): NR BMI: 25.0 (calculated from given weight and height) Systolic BP (mm Hg): 132 Diastolic BP (mm Hg): 75 Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): 1.33 Creatinine clearance (ml/min): 47 Estimated GFR (ml/min/1.73m2): NR Total cholesterol (mg/dL): 200 LDL cholesterol (mg/dL): 131 Diabetes (%): 12 History of HTN (%): 51 History of CAD (%): 100 History of CHF (%): NR History of MI (%): 47 PTCA (%): 100 CABG (%): NR History of Stroke (%): 5 Peripheral arterial disease (%): 11 Current smoker (%): 17	Fluvastatin 40 mg twice daily (n=150) Placebo (n=160) Followup period: 3 to 4 years Study withdrawals (%): No data reported, but 100% included in endpoint analysis	Allocation Concealment: Unclear in this report Blinding: double and outcomes assessors Intention to Treat Analysis (ITT): Yes Withdrawals/ Dropouts adequately described: No data reported, but 100% included in endpoint analysis
Asselbergs, 2004[2] PREVEND IT	Inclusion Criteria: Age 28-75 years, urinary albumin concentration >10 mg/L in 1 early morning spot urine sample and urine albumin excretion	N=864 Age (yr): 51.3 Gender (Male %): 65.0 Race/Ethnicity (%): white 96.1	Pravastatin 40 mg/d (n=433) Placebo (n=431)	Allocation Concealment: Yes Blinding: double, end

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Single center Groningen, The Netherlands Funding Source: Industry and other (Foundations)	rate of 15 to 300 mg/24 hours in at least one of two 24-hour urine samples); BP <160/100 mm Hg and no use of antihypertensive medication; total cholesterol level <309 mg/dL, or <193 mg/dL in case of previous MI, and no use of lipid-lowering medication. Exclusion Criteria: creatinine clearance <60% of the normal age adjusted value; use of ACE inhibitors or ARB antagonists.	BMI: 26.4 Systolic BP (mm Hg): 130.5 Diastolic BP (mm Hg): 76.5 Albuminuria (mg/24 h): 22.8 Serum creatinine (mg/dL): 1.0 Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): 224 LDL cholesterol (mg/dL): 156 Diabetes (%): 2.6 History of HTN (%): 0 History of CAD (%): 3.3 History of CHF (%): 0 History of MI (%): 0.5 CABG or PTCA (%): 0.8 History of Stroke (%): 0.8 Peripheral arterial disease (%): 0.6 Current smoker (%): 39.9	Followup period: mean 3.8 years Study withdrawals (%): NR Study reported 199 (23.0%) withdrawals excluding deaths, but included 56 for "other medical reasons," which included but were not entirely comprised of subjects reaching study endpoints. Note: 2 x 2 factorial design with fosinopril 20 mg/day versus placebo	points adjudicated by blinded committee Intention to Treat Analysis: yes Withdrawals/Dropouts adequately described: yes
Tonelli, 2004[98] WOSCOPS/ CARE/ LIPID Multinational Funding Source: Not stated in current report	Entry Criteria: WOSCOPS studied high-risk patients who had not previously experienced an MI. Excluded baseline creatinine >1.7 mg/dL CARE and LIPID were trials of subjects with previous acute coronary syndromes and average cholesterol levels. Excluded baseline creatinine levels of >2.5 mg/dL and >4.5 mg/dL, respectively. Current report restricted to subjects with GFR 30-59.99 ml/min/1.73m2 using Cockroft-Gault formula. No further information on entry criteria provided.	N=4,491 (post hoc subject-level pooling of results in patients with GFR 30-59.99 mL/min per 1.73m2 body surface area from 19,700 subjects in three previously completed RCTs comparing pravastatin 40 mg/day to placebo, i.e. CARE, WOSCOPS and LIPID studies) Age (yr): 65.7 Gender (Male %): 81.7 Race/Ethnicity (%): NR BMI: 25.5 Systolic BP (mm Hg): 135.5 Diastolic BP (mm Hg): 79.5 Albuminuria (mg/24h): NR Serum creatinine (mg/dL): 1.4 Estimated GFR (ml/min/1.73m2, per MDRD): 55.0 Total cholesterol (mg/dL): 221.3 LDL cholesterol (mg/dL): 151.5 Diabetes (%): 9.9 History of HTN (%): 44.8 History of CAD (%): 73.7	Pravastatin 40 mg/d (n=2217) Placebo (n=2,274) Followup period: approximately 5 years Study withdrawals (%): No data reported	Allocation Concealment: Not described in current report Blinding: double and outcomes assessors Intention to Treat Analysis (ITT): unclear Withdrawals/Dropouts adequately described: Not described in current report

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		History of CHF (%): NR History of MI (%): 67.6 PTCA (%): NR CABG (%): NR History of Stroke (%): 5.3 Peripheral arterial disease (%): NR Current smoker (%): 10.3		
Tonelli, 2003[99] CARE Multicenter Funding Source: Industry	Inclusion Criteria: Men and post-menopausal women, 21-75 years, had acute MI 3-20 months before randomization, total plasma cholesterol <240 mg/dL; LDL 115-174 mg/dL; triglyceride <350 mg/dL; fasting glucose <220 mg/dL, LVEF ≥25%; no symptomatic CHF. All lipid measures collected after 4 weeks treatment with National Cholesterol Education Program Step 1 diet. Exclusion Criteria: ≥2+ proteinuria on dipstick or serum creatinine >1.5 times upper limit of normal	N= 1,711 (post hoc subgroup analysis limited to patients with creatinine clearance ≤75 mL/min from among 4,159 randomized participants in the CARE study) Age (yr): 64.3 Gender (Male %): 78.4 Race/Ethnicity (%): White 91.9, Other 8.1 BMI: NR Systolic BP (mm Hg): 131.0 Diastolic BP (mm Hg): 77.3 Proteinuria (dipstick positive, %): 31 Serum creatinine (mg/dL): 1.26 Creatinine clearance (ml/min): 61 Total cholesterol (mg/dL): 209.0 LDL cholesterol (mg/dL): 138.6 HDL cholesterol (mg/dL): 40.6 Diabetes (%): 13.9 History of HTN (%): 47.2 History of CAD (%): 100 History of CHF (%): 9.6 History of MI (%): 100 PTCA (%): NR CABG (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): 12.3	Pravastatin , 40 mg/d (n=844); Placebo (n=867) Followup Period: 4.9 years Study withdrawals (%): No participants were lost to followup and 100% were included in analyses	Allocation Concealment: Yes Blinding: double Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes
High versus Low Dose HMG-CoA Reductase Inhibitor trials (n=2)				
SEARCH, 2010[100] UK Funding Source:	Inclusion Criteria: Adults aged 18–80 years with a history of previous MI were eligible provided they Fulfilled the following criteria: either current statin use or clear indication for this treatment (and no	N=1,686 patients with CKD (Subgroup analysis within patients with baseline GFR < 60 ml/min/1.73m^2 from among total of 12,064 randomized. Baseline characteristics not reported for	Simvastatin 80 mg/d (n=820) Simvastatin 20 mg/d (n=866)	Allocation concealment: Yes (centralized telephone randomisation system) Blinding: double, end

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Industry and other	clear indication for folic acid); total cholesterol of at least 3·5 mmol/L if already on a statin or 4·5 mmol/L if not; and no clear contraindications to the study treatments. Exclusion Criteria: Predominant medical problems that could reduce compliance with long-term study treatment.	CKD subjects only except for those identifiable from entry criteria. Age (yr): NR Gender (Male %): NR Race/Ethnicity (%): NR BMI: NR Systolic BP (mm Hg): NR Diastolic BP (mm Hg): NR Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): NR History of HTN (%): NR History of CAD (%): 100 History of CHF (%): NR History of MI (%): 100 PTCA (%): NR CABG (%): NR History of Stroke (%): NR Peripheral arterial disease (%):NR Current smoker (%): NR	Followup Period: mean 6.7 years Study withdrawals (%): No data reported for CKD subgroup	points adjudicated by blinded committee Intention-to-treat analysis: yes (overall) Withdrawals/dropouts adequately described: No data reported for CKD subgroup
Shepard, 2008[101] TNT La Rosa, 2005[102] Waters, 2004[103] Multinational Funding Source: Industry	Inclusion Criteria: Men and women aged 35 to 75 years with clinically evident CHD (defined as previous myocardial infarction, previous or current angina with objective evidence of atherosclerotic CHD, or a history of coronary revascularization). LDL 130-250 mg/dL and triglycerides ≤600 mg/dL off anti-lipid drugs, with LDL <130 mg/dL after 8 week open label run-in on atorvastatin 10 mg/d. Exclusion criteria: hypersensitivity to statins; active liver disease or hepatic dysfunction defined as alanine	N=3,107 (Post hoc analysis of subjects with eGFR <60 ml/min/1.73 m^2 from among 10,003 randomized in TNT trial; 3,078 had CKD stage 3 (GFR 30-59) and 29 had CKD stage 4 (GFR 15-29) Age (yr): 65.5 Gender (Male %): 67.7 Race/Ethnicity (%): white 95.2; black 1.6, other 3.2 BMI: 28.5 Systolic BP (mm Hg): 133.0 Diastolic BP (mm Hg): 77.5 Albuminuria (mg/24 h): NR Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): 52.9 Total cholesterol (mg/dL): 175.9	Atorvastatin 10 mg/d (n=1505) Atorvastatin 80 mg/d (n=1602) Followup period: median 5 years Study withdrawals (%): 0.4	Allocation Concealment: unclear Blinding: double-blind, end points adjudicated by blinded committee Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	aminotransferase or aspartate aminotransferase >1.5 times the ULN; women who are pregnant or breastfeeding; nephrotic syndrome; uncontrolled DM; uncontrolled hypothyroidism; uncontrolled HTN (defined by the investigator) at the screening visit; a MI, coronary revascularization procedure or severe/unstable angina within 1 month of screening; any planned surgical procedure for the treatment of atherosclerosis; an ejection fraction <30%; hemodynamically important valvular disease; gastrointestinal disease limiting drug absorption or partial ileal bypass; any nonskin malignancy, malignant melanoma or other survival-limiting disease; unexplained creatine phosphokinase levels >6 times the ULN; concurrent therapy with long-term immunosuppressants; concurrent therapy with lipid-regulating drugs not specified as study treatment in the protocol; history of alcohol abuse; and participation in another clinical trial concurrently or within 30 days before screening.	LDL cholesterol (mg/dL): 96.4 Diabetes (%): 17.6 History of HTN (%): 62.7 History of CAD (%): 100 History of CHF (%): 12.2 History of MI (%): 57.5 PTCA (%): 50.4 CABG (%): 53.7 History of Stroke (%): 7.3 Peripheral arterial disease (%): 16.3 Current smoker (%): 9.0		
HMG-CoA Reductase Inhibitor versus Bile Acid Sequestrant trials (n=1)				
Tonolo, 2006[104] Single Center Funding Source: Other	Inclusion criteria: Type II diabetics with hemoglobin A1c >7% and proliferative or background retinopathy; hypertension (>130/85mm Hg) and microalbuminuria (median albumin/creatinine ratio between 30 and 300 µg/mg in three consecutive urine specimens), treated by angiotensinsin-converting enzyme	N= 86 (Baseline characteristics reported in 82 who completed study) Age (yr): 61.5 Gender (Male %): NR Race/Ethnicity (%): NR BMI: 27.5 Systolic BP (mm Hg): 131 Diastolic BP (mm Hg): 76 Albuminuria (ug/mg): 82.5	Simvastatin, 40 mg/d (n=43) cholestyramine, 30 g/d (n=43) Followup Period: 4 yr Study withdrawals (%): 4 (5%)	Allocation Concealment: Unclear Blinding: double Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
	inhibitors (5 mg ramipril or 20 mg lisinopril/day), 12.5 mg/day thiazides, and 100 mg/day atenolol in the last 3 years, with a glycemic control accomplished by 1,500 mg/day metformin with either three insulin analogs before meals or once daily long-acting insulin injection; a decrease of GFR >1 ml/min/1.73m2/year had to be observed during the 3 years before the recruitment Exclusion Criteria: NR	Serum creatinine (mg/dL): NR Estimated GFR (ml/min/1.73m^2): 90.5 Total cholesterol (mg/dL): 229 LDL cholesterol (mg/dL): 149 Diabetes (%): 100 % Hemoglobin A1C: 7.35 History of HTN (%): 100 History of CAD (%): NR History of CHF (%): NR History of MI (%): NR PTCA (%): NR CABG (%): NR History of Stroke (%): NR Peripheral arterial disease (%): NR Current smoker (%): NR		
Gemfibrozil versus Placebo/Control trials (n=2)				
Tonelli, 2004[98] VA-HIT Multi-center United States Funding source: Government and Industry	Inclusion criteria: Male veterans with coronary artery disease (previous MI, angina corroborated by objective evidence of ischemia, coronary revascularization, or angiographic evidence of stenosis >50% in 1+ major coronary arteries, age <74 yr, HDL ≤40 mg/dL, LDL ≤140 mg/dL, triglyceride ≤300 mg/dL Exclusion criteria: Serum creatinine > 2.0 mg/dL	N=470 (Subgroup analysis of patients with eGFR <60 mL/min/1.73m2 performed within a post hoc analysis of 1046 patients with creatinine clearance <75 mL/min/1.73m2 from the 2,505 with baseline creatinine measurements) from total of 2,531 participants randomized in VA-HIT Trial. Baseline characteristics not reported for n=470 participants with eGFR <60 mL/min/1.73m2 in Tonelli 2004 Kidney International paper, but are reported for n=399 participants (n=199 gemfibrozil, n=200 placebo) with eGFR <60 mL/min/1.73m2 in Tonelli 2004 Am J Kidney Disease paper: Age (yr): 67.4 Gender (% male): 100 Race (%): White 91.0 BMI (kg/m2): NR Systolic BP (mm Hg): 134.0 Diastolic BP (mm Hg): 77.2	Gemfibrozil 600 mg bid (n=242) Placebo (n=228) Followup period: 5.3 yr Study withdrawals (%): No participants were lost to followup	Allocation Concealment: Unclear Blinding: double Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Yes, because no subjects were lost to followup

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		Serum creatinine (mg/dL): NR Creatinine clearance (mL/min/1.73m2): 59.7 Estimated GFR (mL/min/1.73m2): 52.2 Total cholesterol (mg/dL): 176 LDL cholesterol (mg/dL): 111 Diabetes (%): 30.3 History of HTN (%): 67.2 History of CAD (%): 100 History of CHF (%): 10.0 History of MI (%): NR PTCA or CABG (%): NR History of Stroke (%): NR Peripheral arterial disease (%):NR Current smoker (%): 14.0		
Samuelsson, 1997[84] Single Center Sweden Funding Source Government and Foundations	Inclusion Criteria: Nondiabetic primary renal disease and moderately advanced renal insufficiency (GFR 10-70 ml/min/1.73m2) Exclusion Criteria: NR	N=57 Age (yr): 51.3 Gender (Male %): 75 Race/Ethnicity (%): NR Weight (kg): 81.4 BMI: 26.2 Systolic BP (mm Hg): 136.5 Diastolic BP (mm Hg): 84.0 CKD stage: NR Serum creatinine (mg/dL): 2.4 Creatinine clearance (mL/min): NR Albuminuria: 0.95g/24 hr Albumin/creatinine ratio (mg/g): NR GFR (ml/min/1.73m^2): 35.5 HbA_{1c} (%):NR Total cholesterol (mg/dL): 243.6 LDL cholesterol (mg/dL): 170.2 Diabetes (%): 0 (by inclusion criteria) History of HTN (%): NR Dyslipidemia (%): unclear History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): NR	Gemfibrizol initiated at 300mg/day, and could be titrated up to 450 mg twice daily (n=28) Triglyceride lowering Diet (n=29) Followup Period: 1.0 yr Study withdrawals (%): 10.5	Allocation Concealment: Unclear Blinding: Open label Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes

Appendix Table C124 Overview of anti-lipid trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
		History of AKI (%): NR		

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion; ULN = upper limit of the normal

Appendix Table C125. Summary of study baseline characteristics, anti-lipid (AL) monotherapy versus control treatment trials

Characteristic	Mean (range unless otherwise noted)	Number of Trials Reporting
HMG-CoA Reductase Inhibitors versus Placebo trials		12 studies*
Patients randomized, n	17,460 (304-4491)**	12
Age of subjects, years	65 (51-71)	10
Gender, male, %	53 (24-82)	10
Race/ethnicity, white, %	79 (51-96)	6
Body Mass Index	27 (25-29)	8
Systolic blood pressure, mm Hg	136 (131-146)	9
Diastolic blood pressure, mm Hg	80 (75-84)	8
Albuminuria, mg/24	22.8	1
Serum creatinine (mg/dL)	1.3 (1.0-1.5)	9
Estimated GFR, ml/min/1.73m^2	54 (50 to 56)	9
Creatinine Clearance, ml/min/1.73m^2	59 (4-7-61)	2
Total Cholesterol, mg/dL	220 (189-265)	10
Low Density Lipoprotein Cholesterol, mg/dL	142 (109-192)	10
Diabetes, %	17 (0-100)	10
Hypertension, %	49 (0-100)	9
Coronary Artery Disease, %	46 (0-100)	12
Congestive Heart Failure, %	39 (0-100)	4
Myocardial Infarction, %	29 (0-100)	8
Stroke, %	1 (0-10)	7
High versus Low Dose HMG-CoA Reductase Inhibitor trials		2
Patients randomized, n	4,793	2
Age of subjects, years	66	1†
Gender, male, %	68	1
Race/ethnicity, white, %	95	1
Body Mass Index	29	1
Systolic blood pressure, mm Hg	133	1
Diastolic blood pressure, mm Hg	78	1
Albuminuria, mg/24	NR	0
Serum creatinine (mg/dL)	NR	0
Estimated GFR, ml/min/1.73m^2	53	1
Creatinine Clearance, ml/min/1.73m^2	NR	0
Total Cholesterol, mg/dL	176	1
Low Density Lipoprotein Cholesterol, mg/dL	96	1
Diabetes, %	18	1
Hypertension, %	63	1
Coronary Artery Disease, %	100	2
Congestive Heart Failure, %	12	1
Myocardial Infarction, %	58	1
Stroke, %	7	1
HMG-CoA Reductase Inhibitor versus Bile Acid Sequestrant trials		1
Patients randomized, n	86	1
Age of subjects, years	62	1
Gender, male, %	NR	0
Race/ethnicity, white, %	NR	0
Body Mass Index	28	1
Systolic blood pressure, mm Hg	131	1
Diastolic blood pressure, mm Hg	76	1
Albuminuria, µg/mg	83	1
Serum creatinine (mg/dL)	NR	0
Estimated GFR, ml/min/1.73m^2	91	1
Creatinine Clearance, ml/min/1.73m^2	NR	0
Total Cholesterol, mg/dL	229	1

Appendix Table C125. Summary of study baseline characteristics, anti-lipid (AL) monotherapy versus control treatment trials (continued)

Characteristic	Mean (range unless otherwise noted)	Number of Trials Reporting
Low Density Lipoprotein Cholesterol, mg/dL	149	1
Diabetes, %	100	1
Hypertension, %	100	1
Coronary Artery Disease, %	NR	0
Congestive Heart Failure, %	NR	0
Myocardial Infarction, %	NR	0
Stroke, %	NR	0
Gemfibrozil versus Placebo/Control trials		2
Patients randomized, n	527	2
Age of subjects, years	65 (51-67)	2
Gender, male, %	97 (75-100)	2
Race/ethnicity, white, %	91	1
Body Mass Index	26	1
Systolic blood pressure, mm Hg	134 (134-137)	2
Diastolic blood pressure, mm Hg	78 (77- 84)	2
Albuminuria, mg/24 hr	950	1
Serum creatinine (mg/dL)	2.4	1
Estimated GFR, ml/min/1.73m^2	50 (36-52)	2
Creatinine Clearance, ml/min/1.73m^2	60	1
Total Cholesterol, mg/dL	184 (176-244)	2
Low Density Lipoprotein Cholesterol, mg/dL	118 (111-170)	2
Diabetes, %	27 (0-30)	2
Hypertension, %	67	1
Coronary Artery Disease, %	100	1
Congestive Heart Failure, %	10	1
Myocardial Infarction, %	NR	0
Stroke, %	NR	0

AL = anti-lipid; CKD = chronic kidney disease; NR = not recorded; GFR = glomerular filtration rate
*12 studies represent 13 individual RCTs (one study was a pooled analyses of CKD patients from 3 trials - WOSCOP/LIPID/CARE). Two studies included the CARE trial, the pooled analysis and one with only CARE patients. The CARE only study was excluded unless it provided information not available from the pooled analysis such as race/ethnicity.
**4,491 were in the pooled analysis of WOSCOP/LIPID/CARE. Otherwise, the largest single study of CKD patients was 2,978.
† Baseline characteristics for the subgroup of CKD patients were not reported in the SEARCH trial.

Appendix Table C126. Clinical outcomes (outcomes part A), AL monotherapy versus control treatment trials

Study	All-cause Mortality, n/N (%)		Cardiovascular Mortality n/N (%)		Myocardial Infarction, Any n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal n/N (%)		Stroke, Any n/N (%)	
	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control
HMG-CoA reductase inhibitors versus placebo trials (n=12)												
Kendrick, 2010[87] AFCAPS/ TexCAPS			0/145	1/159 (0.6)	2/145 (1.4)	6/159 (3.8)						
Ridker, 2010[88] JUPITER	34/1638 (2.1)*	61/1629 (3.7)							8/1638 (0.5)*	20/1629 (1.2)		
Nakamura, 2009[89] MEGA	16/1471 (2.3)*	34/1507 (4.8)									8/1471 (0.5)*	29/1507 (4.1)
Colhoun, 2009[90] CARDS	27/482 (5.6)	30/488 (6.1)									6/482 (1.2)*	15/488 (3.1)
Koren, 2009[91] ALLIANCE	47/286 (16.4)	59/293 (20.1)	17/286 (5.9)	27/293 (9.2)					17/286 (5.9)	29/293 (9.9)	11/286 (3.8)	12/293 (4.1)
Rahman, 2008[93] ALLHAT-LLT												
Chonchol, 2007[94] 4S	37/245 (15.1)	40/260 (15.4)	§NR	§NR					§NR	§NR	§NR	§NR
Kjekshus, 2007[96] CORONA												
Lemos, 2005[97] LIPS	3/150 (2.0)	3/160 (1.9)	3/150 (2.0)	3/160 (1.9)								
Asselbergs, 2004[2] PREVD	6/433 (1.4)	4/431 (0.9)	4/433 (0.9)	4/431 (0.9)							7/433 (1.6)	4/431 (0.9)
Tonelli, 2004[98] WOSCOPS/ CARE/LIPID	322/2217 (14.5)	383/2274 (16.8)										
Tonelli, 2003[99] CARE	86/844 (10.2)	111/867 (12.8)			65/844 (7.7)	90/867 (10.4)					29/844 (3.4)	46/867 (5.3)
High versus low dose HMG-CoA reductase inhibitor trials (n=2)												
	High Dose	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose	Low Dose	High Dose	Low Dose
SEARCH, 2010[100]												

Study	All-cause Mortality, n/N (%)		Cardiovascular Mortality n/N (%)	Myocardial Infarction, Any n/N (%)	Myocardial Infarction, Fatal n/N (%)	Myocardial Infarction, Nonfatal n/N (%)	Stroke, Any n/N (%)
Shepherd, 2008[101] TNT	112/1602 (7.0)	113/1505 (7.5)					
HMG-CoA reductase inhibitor versus bile acid sequestrant trials (n=1)							
Tonolo, 2006[104]				‡NR	‡NR		
Gemfibrozil versus placebo/control trials (n=2)							
Tonelli, 2004[98] VA-HIT	20/199 (10.1)	22/200 (11.0)					
Samuelsson, 1997[84]							

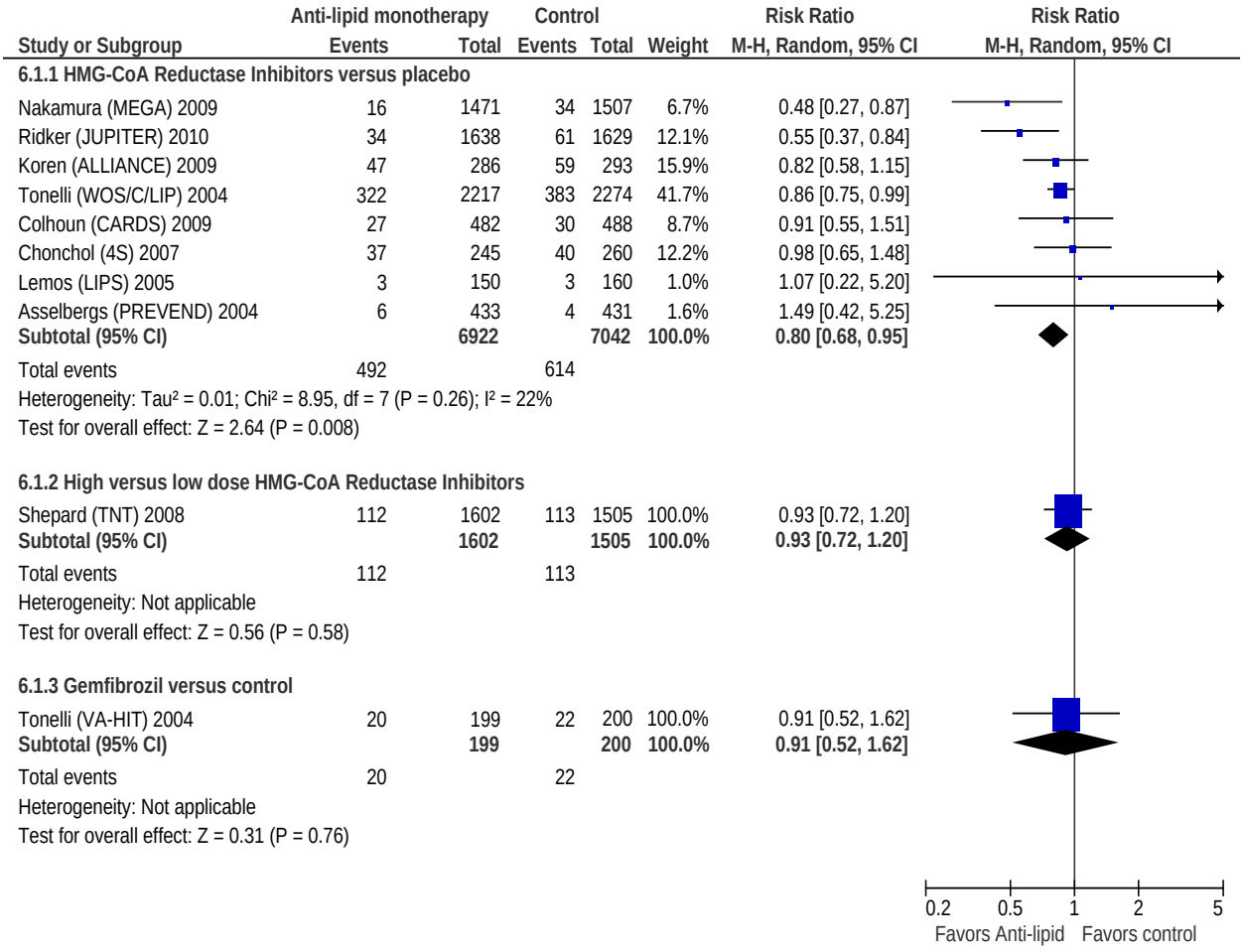
* $p<0.05$ versus control

‡Study reported that one participant had a myocardial infarction, but didn't indicate the patient's treatment group.

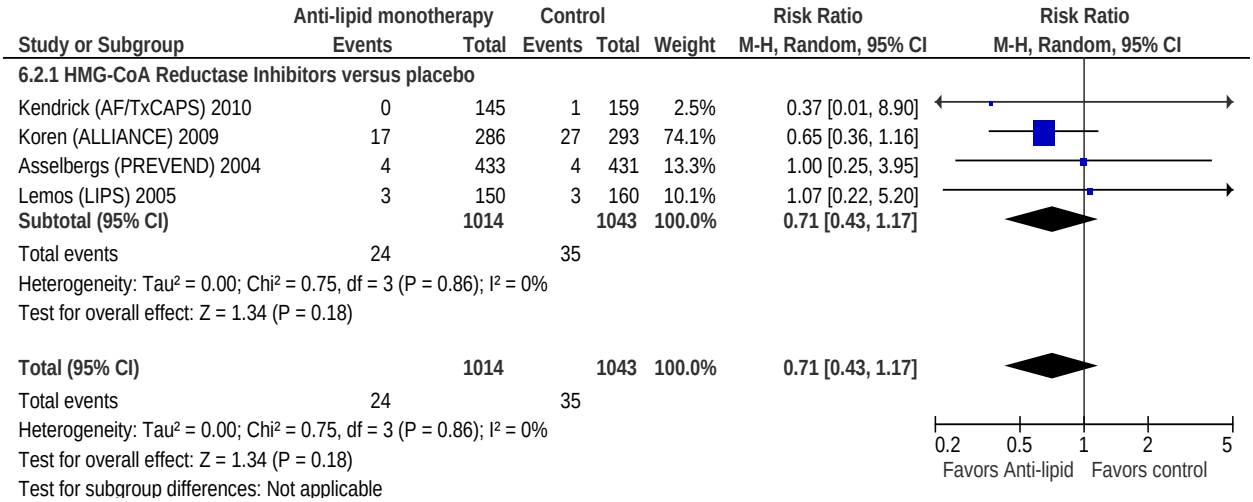
§Study did not provide the number of patients with and without the following events overall or by treatment group, but stated there was no significant difference in risk for simvastatin vs. placebo, respectively, for the following endpoints: CHD deaths (no data provided), nonfatal MI (HR 0.73, CI 0.51-1.04), and stroke (HR 1.07, CI 0.48-2.39).

Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials

All-cause mortality



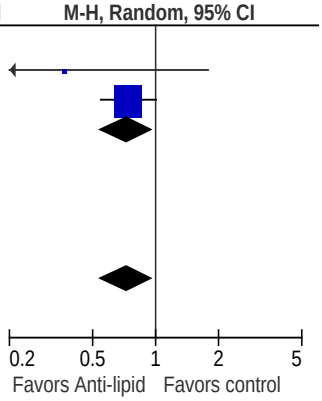
Cardiovascular mortality



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

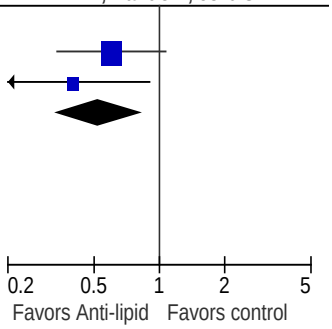
Myocardial infarction, any

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.3.1 HMG-CoA Reductase Inhibitors versus placebo						
Kendrick (AF/TxCAPS) 2010	2	145	6	159	3.6%	0.37 [0.07, 1.78]
Tonelli (CARE) 2003	65	844	90	867	96.4%	0.74 [0.55, 1.01]
Subtotal (95% CI)		**989**		**1026**	**100.0%**	**0.72 [0.54, 0.98]**
Total events	67		96			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Total (95% CI)		**989**		**1026**	**100.0%**	**0.72 [0.54, 0.98]**
Total events	67		96			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 2.12 (P = 0.03)						
Test for subgroup differences: Not applicable						



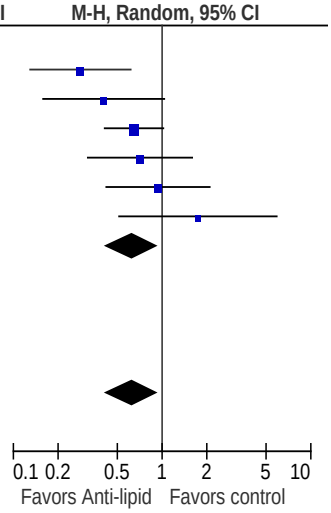
Myocardial infarction, nonfatal

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 HMG-CoA Reductase Inhibitors versus placebo						
Koren (ALLIANCE) 2009	17	286	29	293	66.8%	0.60 [0.34, 1.07]
Ridker (JUPITER) 2010	8	1638	20	1629	33.2%	0.40 [0.18, 0.90]
Subtotal (95% CI)		**1924**		**1922**	**100.0%**	**0.52 [0.33, 0.84]**
Total events	25		49			
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 1 (P = 0.42); I² = 0%						
Test for overall effect: Z = 2.69 (P = 0.007)						



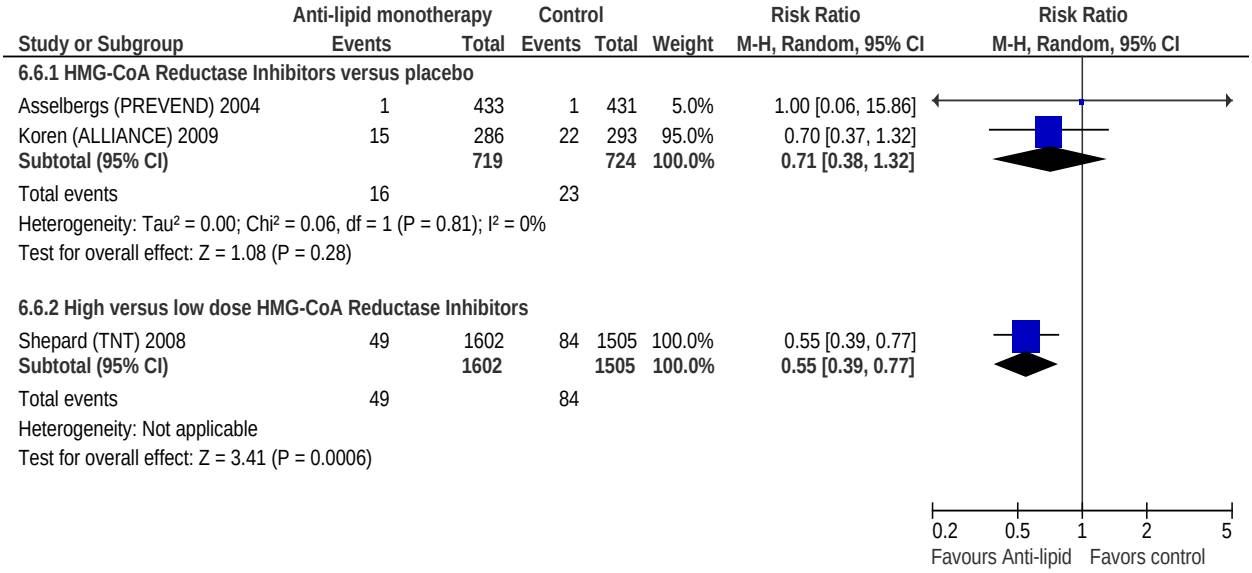
Stroke, any

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 HMG-CoA Reductase Inhibitors versus placebo						
Nakamura (MEGA) 2009	8	1471	29	1507	17.0%	0.28 [0.13, 0.62]
Colhoun (CARDS) 2009	6	482	15	488	13.4%	0.40 [0.16, 1.04]
Tonelli (CARE) 2003	29	844	46	867	27.7%	0.65 [0.41, 1.02]
Ridker (JUPITER) 2010	10	1638	14	1629	16.3%	0.71 [0.32, 1.59]
Koren (ALLIANCE) 2009	11	286	12	293	16.4%	0.94 [0.42, 2.09]
Asselbergs (PREVEND) 2004	7	433	4	431	9.2%	1.74 [0.51, 5.91]
Subtotal (95% CI)		**5154**		**5215**	**100.0%**	**0.62 [0.41, 0.95]**
Total events	71		120			
Heterogeneity: Tau² = 0.11; Chi² = 8.65, df = 5 (P = 0.12); I² = 42%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Total (95% CI)		**5154**		**5215**	**100.0%**	**0.62 [0.41, 0.95]**
Total events	71		120			
Heterogeneity: Tau² = 0.11; Chi² = 8.65, df = 5 (P = 0.12); I² = 42%						
Test for overall effect: Z = 2.20 (P = 0.03)						
Test for subgroup differences: Not applicable						



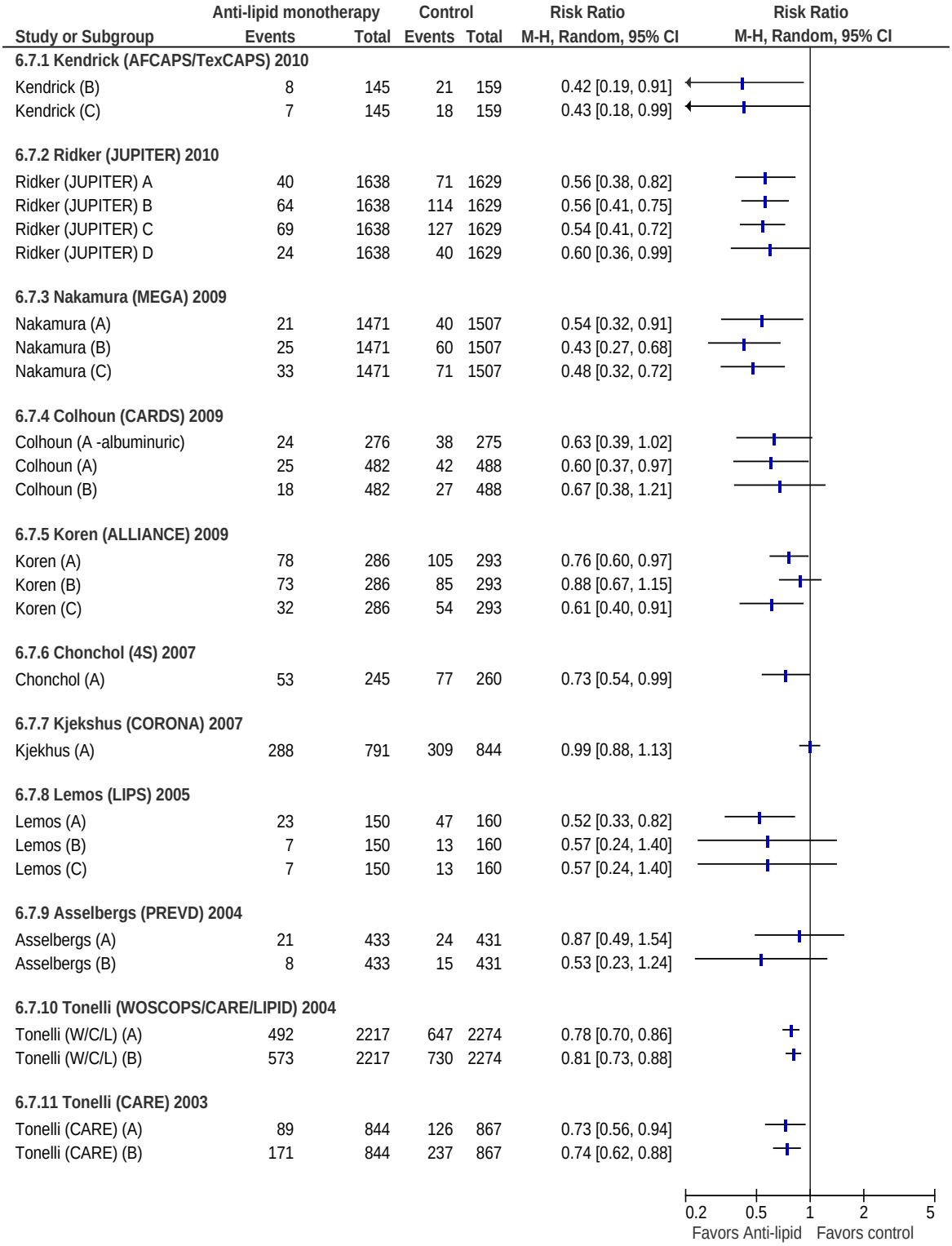
Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

Congestive heart failure, hospitalization



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

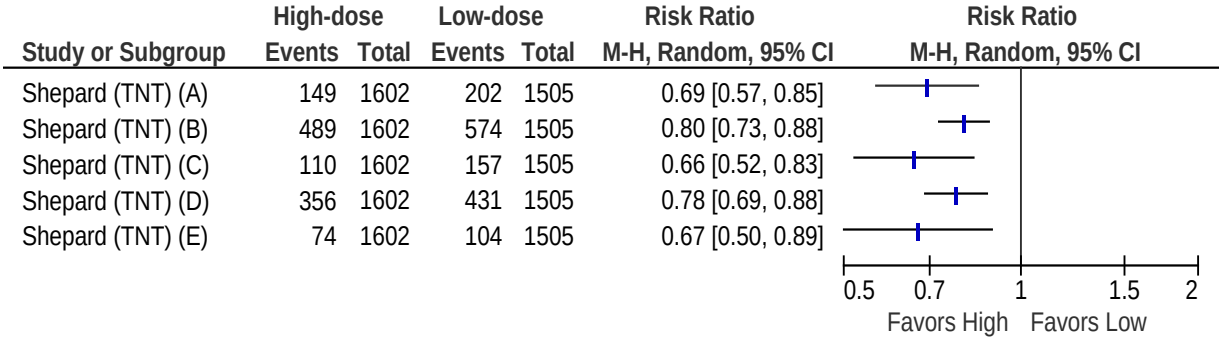
Composite vascular outcome: HMG-CoA Reductase Inhibitors versus placebo (see Table C128 for definitions)



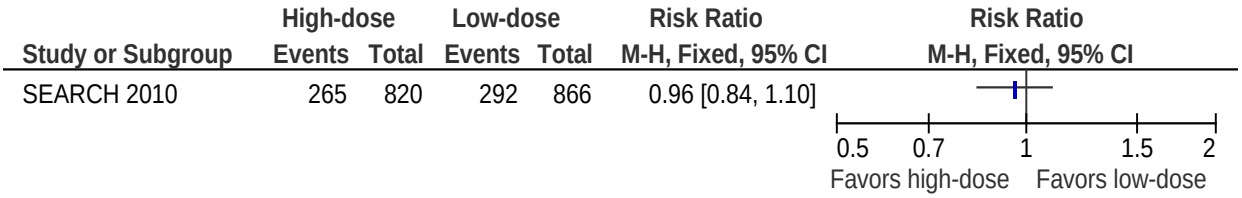
Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

Composite vascular outcome: High versus low-dose HMG-CoA Reductase Inhibitors (see Table C128 for definitions)

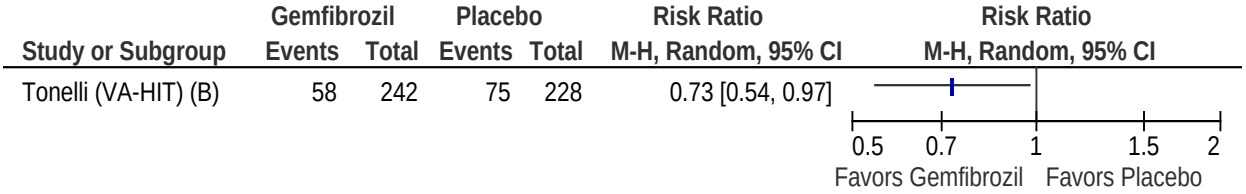
A. Atorvastatin



B. Simvastatin



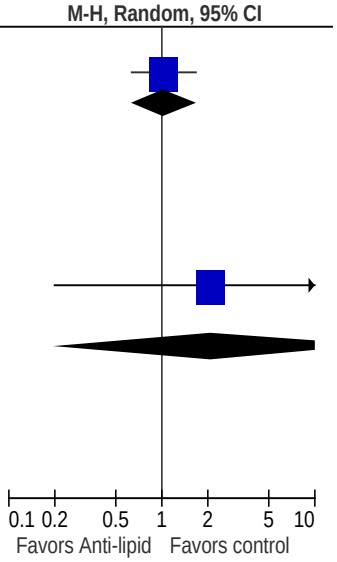
Composite vascular outcome: Gemfibrozil versus placebo (see Table C128 for definition)



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

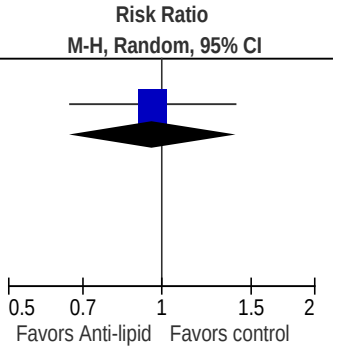
End-stage renal disease

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.11.1 HMG-CoA Reductase Inhibitors versus placebo						
Rahman (ALLHAT) 2008	32	779	31	778	100.0%	1.03 [0.64, 1.67]
Subtotal (95% CI)		**779**		**778**	**100.0%**	**1.03 [0.64, 1.67]**
Total events	32		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
6.11.2 Gemfibrozil versus control						
Samuelsson 1997	2	28	1	29	100.0%	2.07 [0.20, 21.58]
Tonelli (VA-HIT) 2004	0	199	0	200		Not estimable
Subtotal (95% CI)		**227**		**229**	**100.0%**	**2.07 [0.20, 21.58]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						



Composite renal outcome (see Table C130 for definition)

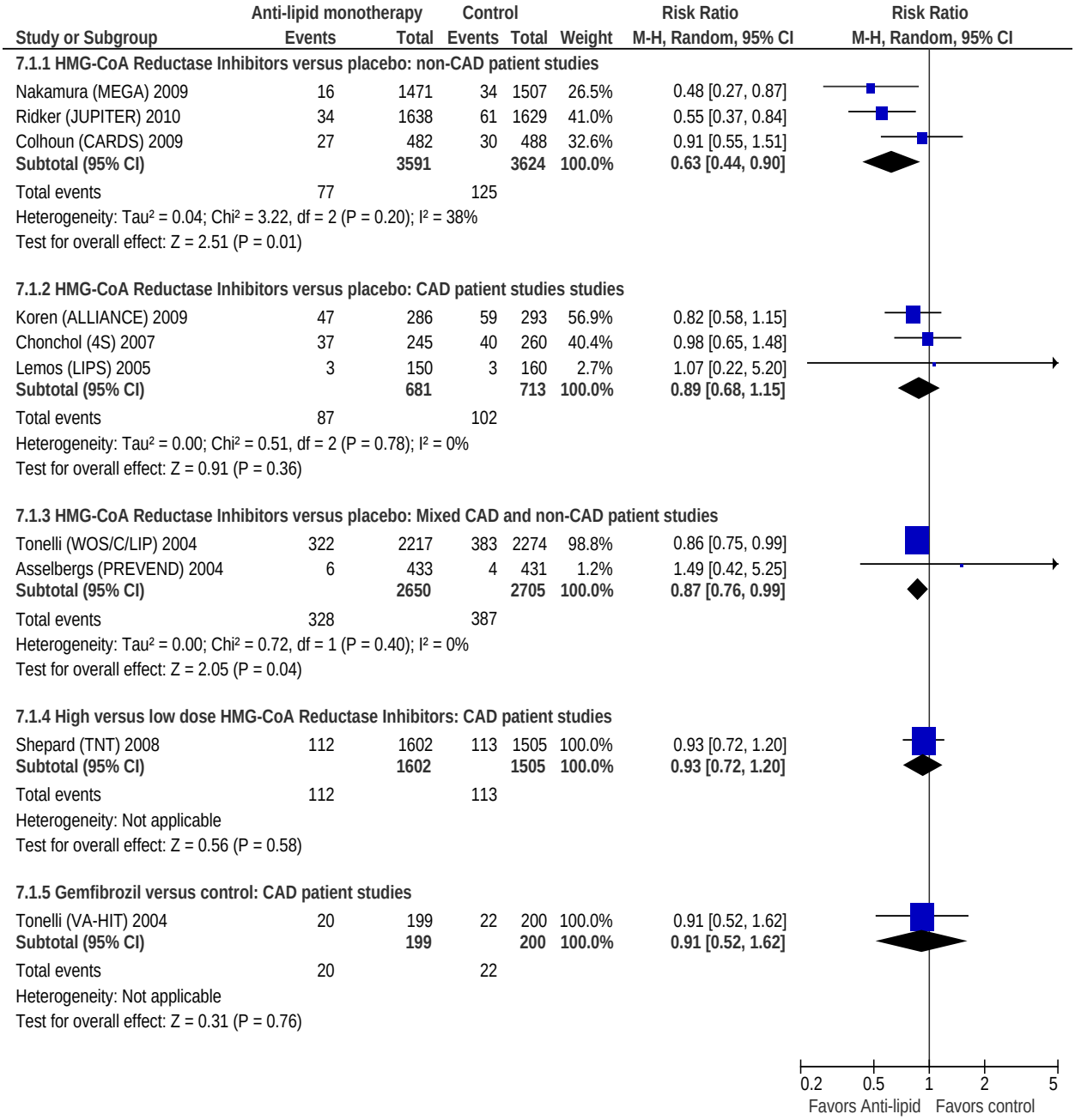
Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
6.15.2 HMG-CoA Reductase Inhibitors versus placebo						
Rahman (ALLHAT) 2008	50	779	52	778	100.0%	0.96 [0.66, 1.40]
Subtotal (95% CI)		**779**		**778**	**100.0%**	**0.96 [0.66, 1.40]**
Total events	50		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.21 (P = 0.83)						



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

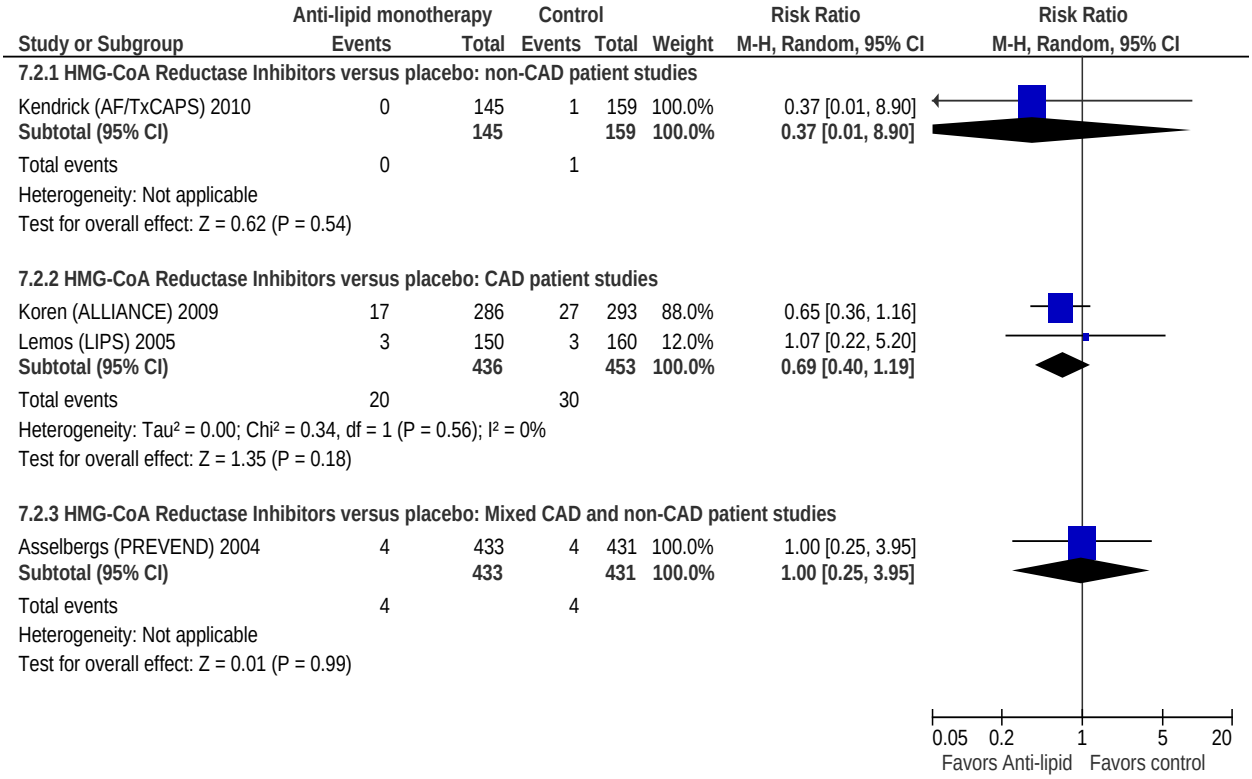
Anti-lipid monotherapy versus control: subgroup analyses

All-cause mortality

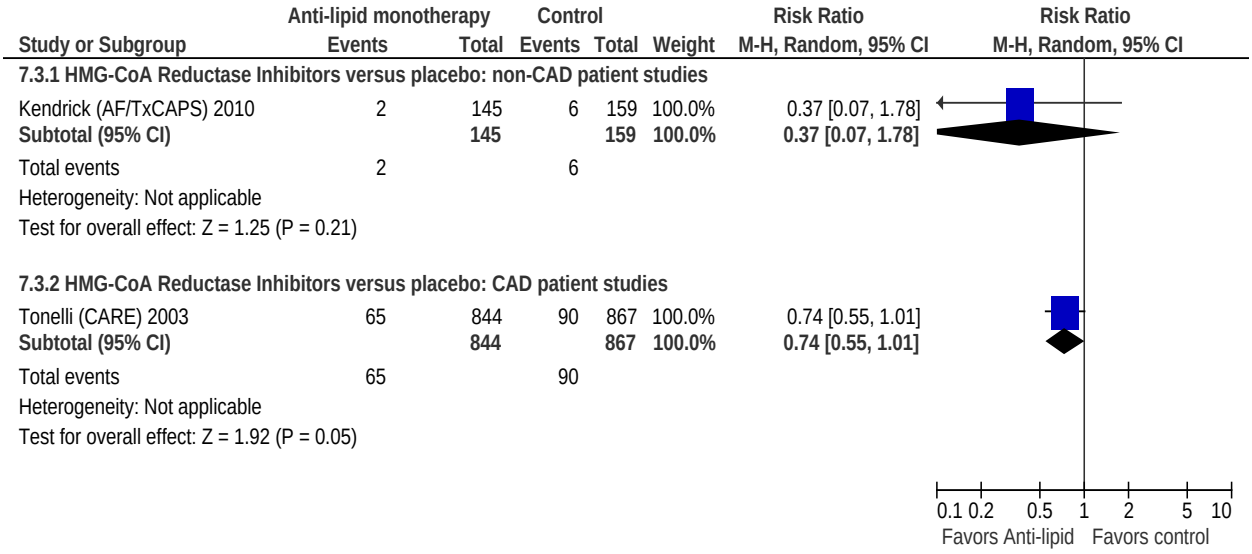


Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

Cardiovascular mortality



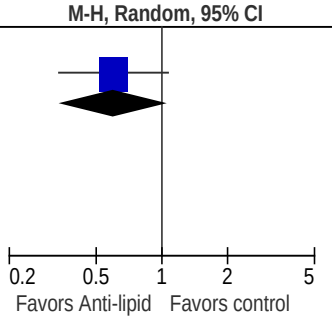
Myocardial infarction, any



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

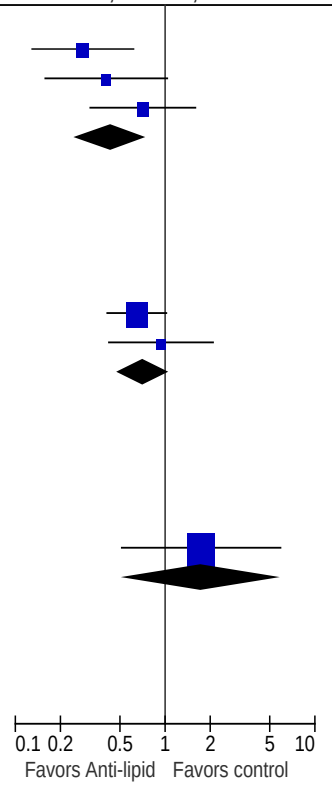
Myocardial infarction, nonfatal

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.4.1 HMG-CoA Reductase Inhibitors versus placebo: CAD patient studies						
Koren (ALLIANCE) 2009	17	286	29	293	100.0%	0.60 [0.34, 1.07]
Subtotal (95% CI)		**286**		**293**	**100.0%**	**0.60 [0.34, 1.07]**
Total events	17		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						



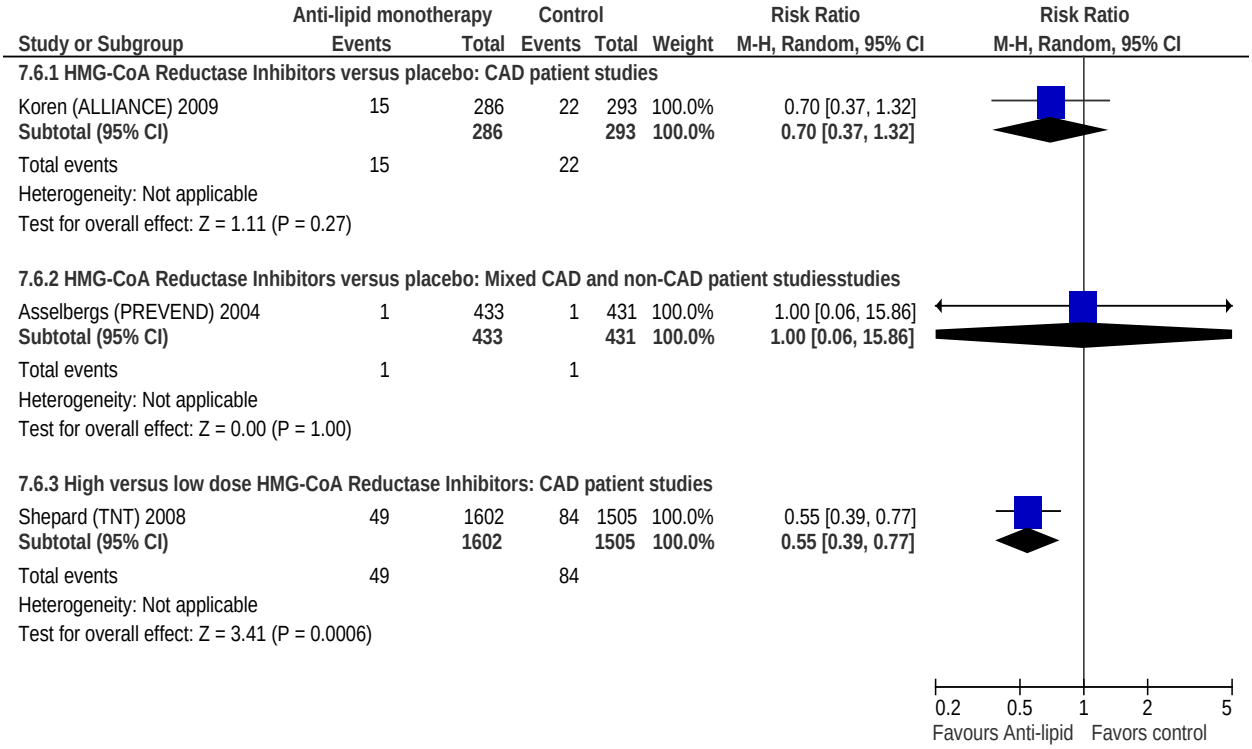
Stroke, any

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.5.1 HMG-CoA Reductase Inhibitors versus placebo: non-CAD patient studies						
Nakamura (MEGA) 2009	8	1471	29	1507	37.1%	0.28 [0.13, 0.62]
Colhoun (CARDS) 2009	6	482	15	488	27.9%	0.40 [0.16, 1.04]
Ridker (JUPITER) 2010	10	1638	14	1629	35.1%	0.71 [0.32, 1.59]
Subtotal (95% CI)		**3591**		**3624**	**100.0%**	**0.43 [0.25, 0.75]**
Total events	24		58			
Heterogeneity: Tau² = 0.06; Chi² = 2.62, df = 2 (P = 0.27); I² = 24%						
Test for overall effect: Z = 2.97 (P = 0.003)						
7.5.2 HMG-CoA Reductase Inhibitors versus placebo: CAD patient studies						
Tonelli (CARE) 2003	29	844	46	867	75.6%	0.65 [0.41, 1.02]
Koren (ALLIANCE) 2009	11	286	12	293	24.4%	0.94 [0.42, 2.09]
Subtotal (95% CI)		**1130**		**1160**	**100.0%**	**0.71 [0.48, 1.05]**
Total events	40		58			
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.70 (P = 0.09)						
7.5.3 HMG-CoA Reductase Inhibitors versus placebo: Mixed CAD and non-CAD patient studies						
Asselbergs (PREVEND) 2004	7	433	4	431	100.0%	1.74 [0.51, 5.91]
Subtotal (95% CI)		**433**		**431**	**100.0%**	**1.74 [0.51, 5.91]**
Total events	7		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.37)						

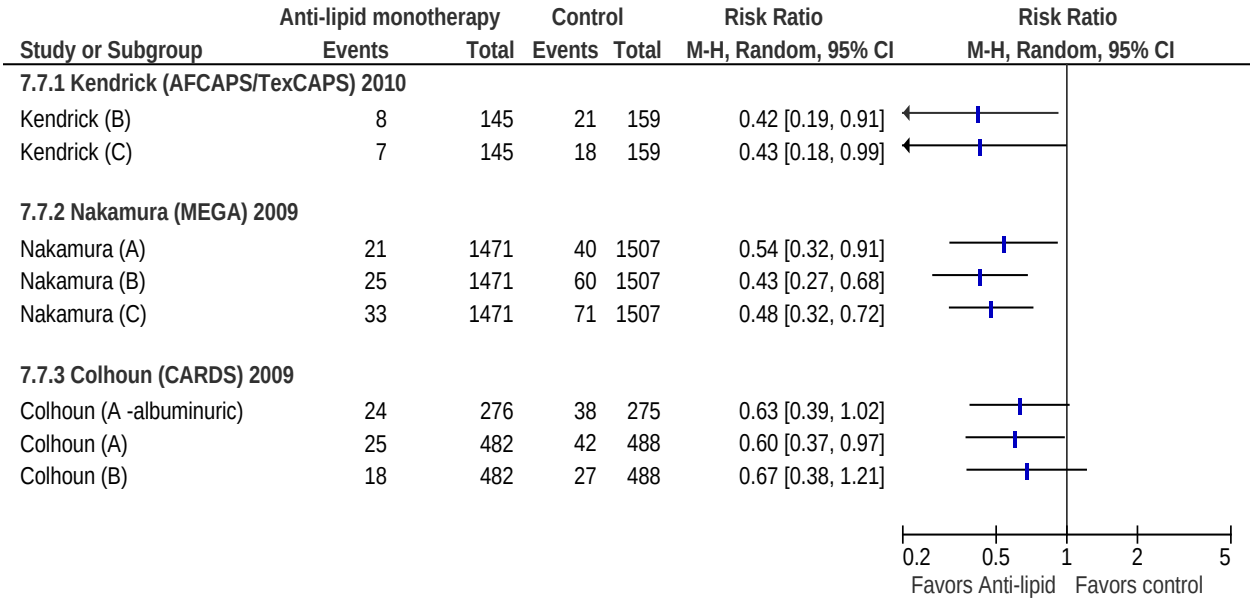


Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

Congestive heart failure, hospitalization



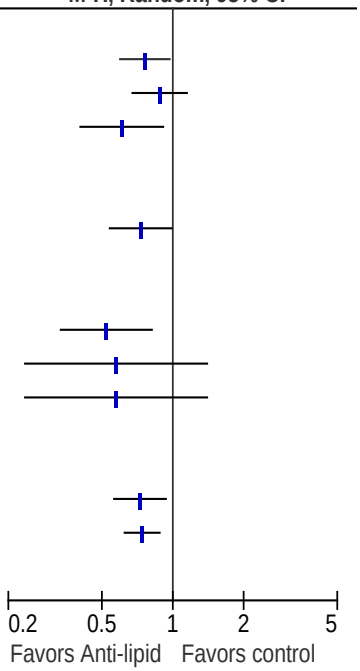
Composite vascular outcome: HMG-CoA Reductase Inhibitors versus placebo, non-CAD patient studies (see Table C128 for definition)



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

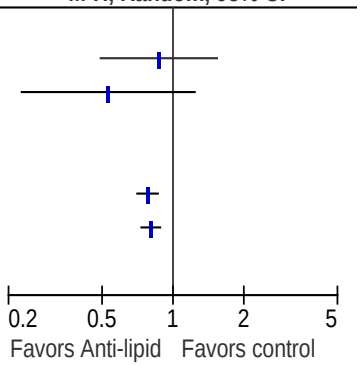
Composite vascular outcome: HMG-CoA Reductase Inhibitors versus placebo, CAD patient studies (see Table C128 for definitions)

	Anti-lipid monotherapy		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
7.8.4 Koren (ALLIANCE) 2009						
Koren (A)	78	286	105	293	0.76 [0.60, 0.97]	
Koren (B)	73	286	85	293	0.88 [0.67, 1.15]	
Koren (C)	32	286	54	293	0.61 [0.40, 0.91]	
7.8.5 Chonchol (4S) 2007						
Chonchol (A)	53	245	77	260	0.73 [0.54, 0.99]	
7.8.7 Lemos (LIPS) 2005						
Lemos (A)	23	150	47	160	0.52 [0.33, 0.82]	
Lemos (B)	7	150	13	160	0.57 [0.24, 1.40]	
Lemos (C)	7	150	13	160	0.57 [0.24, 1.40]	
7.8.10 Tonelli (CARE) 2003						
Tonelli (CARE) (A)	89	844	126	867	0.73 [0.56, 0.94]	
Tonelli (CARE) (B)	171	844	237	867	0.74 [0.62, 0.88]	



Composite vascular outcome: HMG-CoA Reductase Inhibitors versus placebo, mixed CAD and non-CAD patient studies (see Table C128 for definitions)

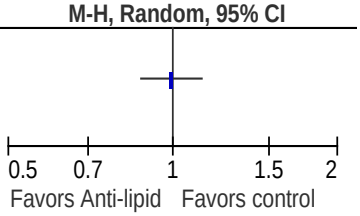
	Anti-lipid monotherapy		Control		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
7.9.8 Asselbergs (PREVD) 2004						
Asselbergs (A)	21	433	24	431	0.87 [0.49, 1.54]	
Asselbergs (B)	8	433	15	431	0.53 [0.23, 1.24]	
7.9.9 Tonelli (WOSCOPS/CARE/LIPID) 2004						
Tonelli (W/C/L) (A)	492	2217	647	2274	0.78 [0.70, 0.86]	
Tonelli (W/C/L) (B)	573	2217	730	2274	0.81 [0.73, 0.88]	



Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

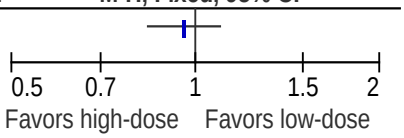
Composite vascular outcome: HMG-CoA Reductase Inhibitors versus placebo, heart failure studies (see Table C128 for definitions)

Study or Subgroup	Anti-lipid monotherapy Events	Total	Control Events	Total	Risk Ratio M-H, Random, 95% CI
7.10.6 Kjekshus (CORONA) 2007					
Kjekhus (A)	288	791	309	844	0.99 [0.88, 1.13]

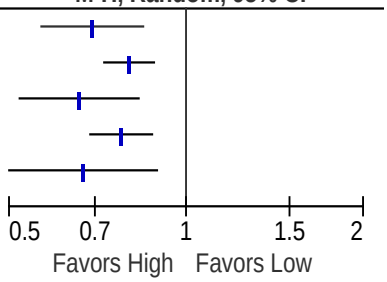


Composite vascular outcome: High versus low-dose HMG-CoA Reductase Inhibitors, CAD patient studies (See Table C128 for definitions)

Study or Subgroup	High-dose Events	Total	Low-dose Events	Total	Risk Ratio M-H, Fixed, 95% CI
SEARCH 2010	265	820	292	866	0.96 [0.84, 1.10]



Study or Subgroup	High-dose Events	Total	Low-dose Events	Total	Risk Ratio M-H, Random, 95% CI
Shepard (TNT) (A)	149	1602	202	1505	0.69 [0.57, 0.85]
Shepard (TNT) (B)	489	1602	574	1505	0.80 [0.73, 0.88]
Shepard (TNT) (C)	110	1602	157	1505	0.66 [0.52, 0.83]
Shepard (TNT) (D)	356	1602	431	1505	0.78 [0.69, 0.88]
Shepard (TNT) (E)	74	1602	104	1505	0.67 [0.50, 0.89]

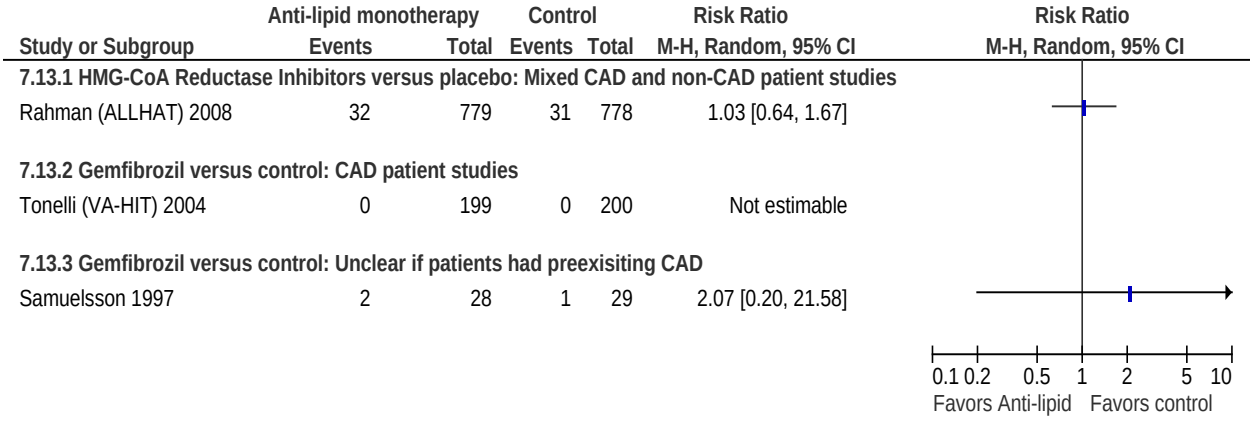


Composite vascular outcome: Gemfibrozil versus placebo, CAD patient studies (see Table C128 for definitions)

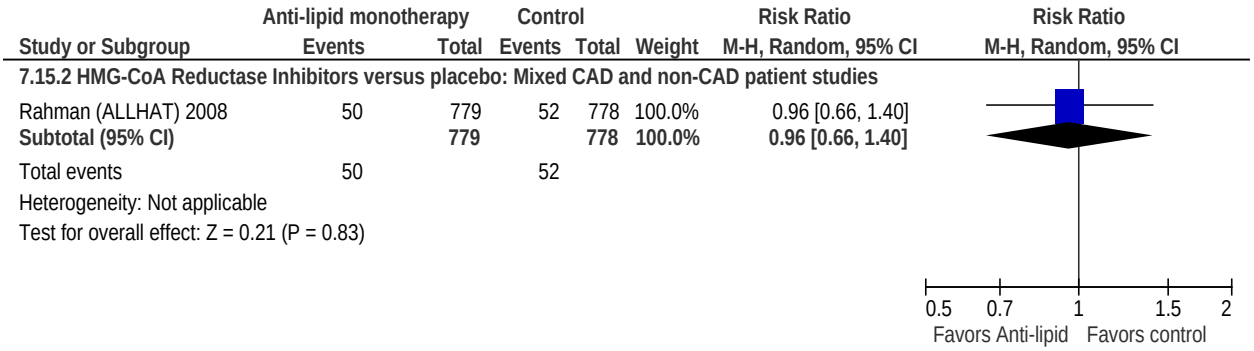
Study or Subgroup	Gemfibrozil Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Tonelli (VA-HIT) (B)	58	242	75	228	0.73 [0.54, 0.97]

Appendix Figure C24. Forest plots for anti-lipid monotherapy versus control trials (continued)

End-stage renal disease



Composite renal outcome (see Table C130 for definition)



Appendix Table C127. Clinical outcomes (outcomes part B), AL monotherapy versus control treatment trials

Study	Stroke, Nonfatal n/N (%)		Stroke, Fatal n/N (%)		CHF Hospitalization (A) or CHF Death (B), n/N (%)		Composite Vascular Outcome n/N (%)**	
	AL	Control	AL	Control	AL	Control	AL	Control
HMG-CoA reductase inhibitors versus placebo trials (n=12)								
Kendrick, 2010[87] AFCAPS/ TexCAPS							†(A) NR; (B) 8/145 (5.5)*; (C)7/145 (4.8)*	†(A) NR; (B) 21/159 (13.2); (C) 18/159 (11.3)
Ridker, 2010[88] JUPITER	10/1638 (0.6)	14/1629 (0.9)					(A) 40/1638 (2.4)* (B) 64/1638 (3.9)* (C) 69/1638 (4.2)* (D) 24/1638 (1.5)*	(A) 71/1629 (4.4) (B) 114/1629 (7.0) (C) 127/1629 (7.8) (D) 40/1629 (2.5)
Nakamura, 2009[89] MEGA							(A)21/1471 (1.2)*; (B) 25/1471 (3.7)*; (C)33/1471 (4.9)*	(A)40/1507 (5.7); (B)60/1507 (8.7); (C)71/1507 (10.3)
Colhoun, 2009[90] CARDS							§(A) Low GFR: 25/482 (5.2)*, Albuminuric: 24/276 (8.7)*; (B) Low GFR: 18/482 (3.7)	§(A) Low GFR: 42/488 (8.6)*, Albuminuric: 38/275 (13.8); (B) Low GFR: 27/488 (5.5)
Koren, 2009[91] ALLIANCE					(A): 15/286 (5.2)	(A): 22/293 (7.5)	(A)78/286 (27.3)*; (B)73/286 (25.5); (C) 32/286 (11.2)*	(A)105/293 (35.8); (B) 85/293 (29.0); (C) 54/293 (18.4)
Rahman, 2008[93] ALLHAT-LLT								
Chonchol, 2007[94] 4S							53/245 (21.6)	77/260 (29.6)
Kjekshus, 2007[96] CORONA							288/791 (15.8)	309/844 (16.3)
Lemos, 2005[97] LIPS							(A) 23/150 (15.3)*; (B) 7/150 (4.7); (C) 7/150 (4.7)	(A) 47/160 (29.4); (B) 13/160 (8.1); (C) 13/160 (8.1)
Asselbergs, 2004[2] PREVD					(A)1/433 (0.2)	(A)1/431 (0.2)	(A) 21/433 (4.8); (B) 8/433 (1.8)	(A) 24/431 (5.6); (B) 15/431 (3.5)
Tonelli, 2004[98] WOSCOPS/ CARE/ LIPID							(A)492/2217 (22.2); (B)573/2217 (25.9)	(A)647/2274 (28.5); (B)730/2274 (32.1)
Tonelli, 2003[99] CARE							(A) 89/844 (10.5)*; (B) 171/844 (20.3)*	(A)126/867(14.5); (B) 237/867 (27.0)
High versus low dose HMG-CoA reductase inhibitor trials (n=2)								
	High Dose	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**
SEARCH, 2010[100]							265/820 (32.3)	292/866 (33.7)

Study	Stroke, Nonfatal n/N (%)	Stroke, Fatal n/N (%)	CHF Hospitalization (A) or CHF Death (B), n/N (%)		Composite Vascular Outcome n/N (%)**	
Shepherd, 2008[101] TNT			(A) 49/1602 (3.1)	(A) 84/1505 (5.6)	(A)149/1602 (9.3); (B)489/1602 (30.5); (C)110/1602 (6.9)*; (D)356/1602 (22.2); (E)74/1602 (4.6)	(A)202/1505 (13.4); (B)574/1505 (38.1); (C)157/1505 (10.4); (D)431/1505 (28.6); (E)104/1505 (6.9)
HMG-CoA reductase inhibitor versus bile acid sequestrant trials (n=1)						
Tonolo, 2006[104]						
Gemfibrozil versus placebo/control trials (n=2)						
Tonelli, 2004[98] VA-HIT					58/242 (24.0)	75/228 (32.9)
Samuelsson, 1997[84]						

AL = antilipid; CHF = congestive heart failure; NR = not reported; GFR = glomerular filtration rate; MI = myocardial infarction; CABG = coronary artery bypass grafting; CHD = coronary heart disease; CKD = chronic kidney disease; CVD = cardiovascular disease

*$p < 0.05$

**See Composite vascular outcomes definition table

† Participants treated with lovastatin were reported to have an adjusted RR of 0.32 (95% CI, 0.10-1.11; $P = 0.06$) for the endpoint of "first major cardiac event," though the proportion of participants with this endpoint was not reported for either treatment group.

§ Results for composite endpoint A were reported separately for participants with CKD defined based on GFR (<60 ml/min/ 1.73m^2) and for this outcome only for participants with CKD defined based on albuminuria (urinary albumin/creatinine ratio $\geq$22 mg/g).

Appendix Table C128. Composite vascular outcome definitions, AL monotherapy versus control treatment trials

Study	Definition
HMG-CoA reductase inhibitors versus placebo trials	
Kendrick, 2010[87] AFCAPS/TexCAPS	Defined two composite vascular endpoints, as follows: (A) "First major cardiac event," which included any of unstable angina, fatal or nonfatal MI, and/or sudden cardiac death; (B) "Fatal and nonfatal cardiovascular events;" and (C) "Fatal and nonfatal coronary events."
Ridker, 2010[88] JUPITER	Study defined the primary composite endpoint as: (A) nonfatal myocardial infarction, nonfatal stroke, hospital stay for unstable angina, arterial revascularization, or confirmed cardiovascular death; (B) same as A plus any death; (C) same as A plus any death plus venous thromboembolism; (D) non-fatal myocardial infarction, nonfatal stroke, or confirmed cardiovascular death
Nakamura, 2009[89] MEGA	The primary composite endpoint was defined as: (A) the first occurrence of a CHD event, including fatal and nonfatal MI, angina pectoris, cardiac/sudden death, and coronary revascularization. Additional composite endpoints included (B) first CHD event or ischemic stroke; and (C) total CVD events, which was not defined.
Colhoun, 2009[90] CARDS	The primary composite endpoint was defined as: (A) "Major cardiovascular disease", including acute CHD event (MI, including silent MI, unstable angina, acute CHD death, or resuscitated cardiac arrest), stroke, coronary revascularization, or death. An additional composite endpoint was (B) acute CHD event as defined above.
Koren, 2009[91] ALLIANCE	Defined three composite vascular endpoints, as follows: (A) First primary cardiovascular event, including cardiac death, nonfatal MI, resuscitated cardiac arrest, cardiac revascularization, or unstable angina requiring hospitalization; (B) All-cause mortality, peripheral revascularization, hospitalization for CHF, or stroke; and (C) Nonfatal MI or cardiac death.
Chonchol, 2007[94] 4S	Study defined the primary composite vascular endpoint as: (A) Major coronary event, including coronary death, nonfatal MI, resuscitated cardiac arrest, ECG confirmed silent MI. Additional composite vascular endpoints (results not reported) were: (B) Any coronary event, including coronary death, nonfatal MI, resuscitated cardiac arrest, ECG confirmed silent MI, myocardial revascularization procedure, hospitalization for acute CHD without MI diagnosis; and (C) Death, nonfatal MI, resuscitated cardiac arrest, ECG confirmed silent MI, myocardial revascularization procedure, hospitalization for acute CHD without MI diagnosis, and hospital-verified nonfatal coronary atherosclerotic events.
Kjekshus, 2007[96] CORONA	Study defined the primary composite vascular endpoint as: (A) Cardiovascular death, nonfatal MI, or nonfatal stroke. An additional composite vascular endpoint (results not reported) was: (B) Any coronary event, which included sudden death, fatal or nonfatal MI, coronary revascularization (CABG or PCI), ventricular defibrillation by an implantable cardioverter-defibrillator, resuscitation after cardiac arrest, or hospitalization for unstable angina.
Lemos, 2005[97] LIPS	Study defined the primary composite vascular endpoint as: (A) Adverse coronary atherosclerotic events, which included cardiac death, nonfatal MI, and all surgical or percutaneous coronary interventions not caused by restenosis after an index percutaneous coronary intervention. Additional composite vascular endpoints included: (B) Cardiac death or MI; and (C) All-cause mortality or MI.
Asselbergs, 2004[2] PREVEND IT	Study defined the primary composite endpoint as: (A) Cardiovascular mortality or hospitalization for any of the following: nonfatal MI, myocardial ischemia, CHF, PVD or stroke. An additional composite endpoint was: (B) Hospitalization for nonfatal MI or myocardial ischemia.
Tonelli, 2004[98] WOSCOPS/CARE/LIPID	Study defined the primary composite vascular endpoint as: (A) Fatal CHD, nonfatal MI, or coronary revascularization. An additional composite vascular endpoint was defined as: (B) Fatal CHD, nonfatal MI, coronary revascularization, or stroke.
Tonelli, 2003[99] CARE	Study defined the primary composite vascular endpoint as: (A) Death from coronary disease (including fatal MI, sudden death, death during a coronary intervention, and death from other coronary causes) or a symptomatic nonfatal biochemically confirmed myocardial infarction. An additional composite endpoint was: (B) Major coronary events, defined as fatal coronary disease, nonfatal MI, CABG, or coronary angioplasty.

Appendix Table C128. Composite vascular outcome definitions, AL monotherapy versus control treatment trials (continued)

Study	Definition
High versus low dose HMG-CoA reductase inhibitor trials	
SEARCH, 2010[100]	Study defined the primary composite vascular endpoint as first major vascular event, including coronary death, myocardial infarction, any stroke, or any arterial revascularization.
Shepard, 2008[101] TNT	Study defined the primary composite vascular endpoint as: (A) Major cardiovascular events, which included CHD death, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, and stroke. Additional composite vascular endpoints included: (B) Any cardiovascular event (defined as CHD death, nonfatal MI, resuscitation from cardiac arrest, revascularization procedure, documented angina, stroke, TIA, CABG, or CHF hospitalization); (C) Major coronary event (defined as CHD death, nonfatal nonprocedure-related MI, or resuscitation from cardiac arrest); (D) Any coronary event (defined as CHD death, nonfatal MI, resuscitation from cardiac arrest, revascularization procedure, or documented angina); and (E) Cerebrovascular event (stroke or TIA).
Gemfibrozil versus placebo/control trials	
Tonelli, 2004[98] VA-HIT	Results reported for outcome (B): Major cardiovascular event, which included fatal CHD, nonfatal MI, and stroke. Additional composite vascular endpoint was: (A) Coronary disease death (included fatal MI, sudden death, death during a coronary intervention, and death from other coronary causes) and nonfatal MI..

AL = anti-lipid; CVA = cerebrovascular accident (i.e. stroke); HTN = hypertension; MI = myocardial infarction; PVD = peripheral vascular disease; CHD = coronary heart disease; CVD = cardiovascular disease; CHF = congestive heart failure; ECG = electrocardiogram; CABG = coronary artery bypass grafting; TIA = transient ischemic attack; PCI = percutaneous coronary intervention.

Appendix Table C129. Clinical renal outcomes (outcomes part C), AL monotherapy versus control treatment trials

Study	End Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)**	
	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control
HMG-CoA reductase inhibitors versus placebo trials (n=11)										
Kendrick, 2010[87] AFCAPS/TexCAPS										
Ridker, 2010[88] JUPITER										
Nakamura, 2009[89] MEGA										
Colhoun, 2009[90] CARDS										
Koren, 2009[91] ALLIANCE										
Rahman, 2008[93] ALLHAT	32/779 (4.1)	31/778 (4.0)							(B)50/779 (6.4)	(B)52/778 (6.7)
Chonchol, 2007[94] 4S										
Kjekshus, 2007[96] CORONA										
Lemos, 2005[97] LIPS										
Asselbergs, 2004[2] PREVD										
Tonelli, 2004[98] WOSCOPS/CARE/ LIPID										
Tonelli, 2003[99] CARE										

Appendix Table C129. Clinical renal outcomes (outcomes part C), AL monotherapy versus control treatment trials (continued)

Study	End Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro- to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)**	
High versus low dose HMG-CoA reductase inhibitor trials (n=1)										
	High Dose	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**
SEARCH, 2010[100]										
Shepherd, 2008[101] TNT										
HMG-CoA Reductase Inhibitor versus Bile Acid Sequestrant trials (n=1)										
Tonolo, 2006[104]						*†(4)	†(15)			
Gemfibrozil versus placebo/control trials (n=2)										
Tonelli, 2004[98] VA-HIT	0/199	0/200								
Samuelsson, 1997[84]	2/28 (7.1)	1/29 (3.4)								

AL = antilipid; GFR = glomerular filtration rate;

* $p < 0.05$ versus control

**See Composite renal outcome definitions table

†Study reported that conversion from microalbuminuria to overt proteinuria occurred in 4 vs. 15% in simvastatin vs. cholestyramine subjects, respectively ($p<0.01$). However, from results reported, it was not possible to determine the numerator and denominator used to derive these results for both treatment groups.

Appendix Table C130. Composite renal outcome definitions for AL monotherapy versus control treatment trials

Study	Definition
HMG-CoA Reductase Inhibitors (Statins) versus Placebo/Usual care/No treatment trials	
Rahman, 2008[93] ALLHAT-LLT	Study defined multiple composite renal outcomes, including: (A) ESRD (start of long-term dialysis, death due to kidney disease, or kidney transplantation) or ≥50% decline in GFR; and (B) ESRD or ≥50% decline in GFR.

AL = antilipid; ESRD = end stage renal disease; GFR = glomerular filtration rate

Appendix Table C131. Study withdrawals and adverse events (outcomes part D), AL monotherapy versus control treatment trials

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Study Withdrawal Due to Serious Adverse Event, Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Specific, n/N (%)		Renal Adverse Events, n/N (%)	
	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control
HMG-CoA reductase inhibitors versus placebo trials (n=11)												
Kendrick, 2010[87] AFCAPS/ TexCAPS									†Rhabdo: 0/145; CK>10x ULN: 0/159	†Rhabdo: 1/159 (0.6); CK>10x ULN: 1/159 (0.6)		
Ridker, 2010[88] JUPITER												
Nakamura‡ 2009[89] MEGA							166/1471 (11.3)	158/1507 (10.5)	AST >100IU: 18/1471 (1.2); ALT >100IU: 37/1471 (2.5); CK >500IU: 38/1471 (2.6)	AST >100IU: 17/1507 (1.1); ALT >100IU: 41/1507 (2.7); CK >500IU: 39/1507 (2.6)	sCr >4mg/dl: 0.3%	sCr >4mg/dL: 0.2%
Colhoun, 2009[90] CARDS												
Koren, 2009[91] ALLIANCE									Rhabdo 0/286; AST >3x ULN 1/286; ALT >3x ULN 1/286; CK >10xULN: 0/286	Rhabdo 0/293; AST >3x ULN NR; ALT >3x ULN NR; CK >10xULN: NR		
Rahman, 2008[93] ALLHAT-LLT												
Chonchol, 2007[94] 4S												
Kjekshus, 2007[96] CORONA												

Appendix Table C131. Study withdrawals and adverse events (outcomes part D), AL monotherapy versus control treatment trials (continued)

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any, n/N (%)		Study Withdrawal Due to Serious Adverse Event, Any, n/N (%)		Adverse Event: Any, n/N (%)		Adverse Event: Specific, n/N (%)		Renal Adverse Events, n/N (%)	
	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control	AL	Control
Lemos, 2005[97] LIPS												
Asselbergs, 2004[2] PREVD	§NR	§NR										
Tonelli, 2004[98] WOSCOPS/ CARE/ LIPID												
Tonelli, 2003[99] CARE	0/844	0/867			0/844	0/867			#Rhabdo: 0/844; CK>3x ULN: 6/844 (0.7); Abnormal LFTs: 5/844 (0.6)	#Rhabdo: 3/867 (0.3); CK>3x ULN: 3/867 (0.3); Abnormal LFTs: 5/867 (0.6)		
High versus low dose HMG-CoA reductase inhibitor trials (n=1)												
	High Dose	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**	**High Dose**	**Low Dose**
SEARCH, 2010[100]												
Shepherd, 2008[101] TNT	6/1602 (0.4)	6/1505 (0.4)			68/1602 (4.2)	29/1505 (1.9)	140/1602 (8.7)	78/1505 (5.2)	ALT or AST >3x ULN: 22/1602 (1.4); CK >10xULN: 0/1602	ALT or AST >3x ULN: 1/1505 (0.1); CK >10xULN: 0/1505	Hematuria: 58/1602 (3.6)	Hematuria: 51/1505 (3.4)
HMG-CoA reductase inhibitor versus bile acid sequestrant trials (n=1)												
Tonolo, 2006[104]	1/43 (2.3)	3/43 (7.0)					1/43 (2.3)	3/43 (7.0)	‡NR	‡NR	‡NR	‡NR
Gemfibrozil versus placebo/control trials (n=2)												
Tonelli, 2004[98] VA-HIT	0/199	0/200			0/199	0/200			**Rhabdo: 0/199; CK>3x ULN: 0/199	**Rhabdo: 0/200; CK>3x ULN: 0/200		

Appendix Table C131. Study withdrawals and adverse events (outcomes part D), AL monotherapy versus control treatment trials (continued)

Study	Study Withdrawals: Any, n/N (%)		Serious Adverse Event: Any, n/N (%)	Study Withdrawal Due to Serious Adverse Event, Any, n/N (%)	Adverse Event: Any, n/N (%)	Adverse Event: Specific, n/N (%)		Renal Adverse Events, n/N (%)
Samuelsson, 1997[84]	8/28 (28.6)	1/29 (3.4)				"Mild GI symptoms": 6/28 (21.4)	"Mild GI symptoms": 0/29	

AL = antilipid agent; Rhabdo = rhabdomyolysis; NR = not reported; AST = aspartase aminotransferase; ALT = alanine aminotransferase; LFTs = liver function tests; IU = international units; ULN = upper limit of normal; CK = creatine phosphokinase; GI = gastrointestinal; sCr = serum creatinine

*$p < 0.05$ versus control

†Study reported that increases >3 times ULN in liver function test results were rare, and incidence was similar in both treatment groups.

‡Study reported that two patients developed renal cancer, and that one patient developed a 3 to 4-fold increase of AST and ALT above baseline levels, but didn't indicate either patient's treatment group.

§Study reported total withdrawals of n = 92/433 (21.2%) and 117/431 (27.1%) in pravastatin and placebo groups, respectively. Among total withdrawals, however, the study reported those for "other medical reasons," which included but were not entirely comprised of subjects reaching study endpoints (i.e. cardiovascular mortality or hospitalization) (n = 23 and 33 for pravastatin and placebo groups, respectively.

#Study also reported the following specific adverse effects in pravastatin vs. placebo participants, respectively: depression (10/844 vs. 14/867), nondermatologic malignancy (133/844 vs. 146/867), and skin cancer (57/844 vs. 41/867, p = 0.08).

**Study also reported the following specific adverse effects in gemfibrozil vs. placebo participants, respectively: depression (4/199 vs. 7/200), nondermatologic malignancy (17/199 vs. 23/200), and skin cancer (0/199 vs. 2/200).

Appendix Evidence Table C132. Overview of intensive multicomponent intervention (INT) versus control treatment trials

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Multicomponent trials (n=4)				
Chan, 2009[105] Location China, Multi-site Funding Source Government	Inclusion Criteria: Type 2 DM and Plasma creatinine level 150-350 µmol/L, age 35-75 yrs Exclusion Criteria: Reversible cause of renal dysfunction (e.g. renal artery stenosis), malignancy or life threatening disease, nondiabetic renal disease, unstable psychiatric illness, and ≥20% difference in two consecutive plasma creatinine values within 3 months before recruitment.	N=205 Age (yr): 65 Gender (Male %): 66 Race/Ethnicity (%): NR Weight: NR BMI: 25.4 Systolic BP (mm Hg): 145 Diastolic BP (mm Hg): 74 CKD stage: NR Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): NR Albuminuria: NR Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 96 Dyslipidemia (%): NR History of CAD (%): 16 History of CHF (%): 7 Peripheral arterial disease (%): 1 History of MI (%):2 History of Stroke (%):15 Current smoker (%): NR History of AKI (%): NR	n=104 structured care (managed by multidisciplinary diabetes care team, including dietician, MD, and nurse educator, with regular lab monitoring, and treatment to target BP <130/80 mm Hg, HbA1c <7%, LDL-C <2.6 mmol/L, triglycerides <2 mmol/L, and treatment with ACEI or ARB unless develop persistent hyperkalemia or increase in baseline creatinine by >30%) n= 101 Usual care/control Followup period: median 2 years Study withdrawals (%): 2.4%	Allocation Concealment Adequate Blinding: None (i.e. open) Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: Adequate

Appendix Evidence Table C132. Overview of intensive multicomponent intervention (INT) versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Joss, 2004[106] Location: Scotland/multi-site Funding Source Other-non industry	Inclusion Criteria: Pts w/ type 2 DM and nephropathy (albuminuria >300 mg/24h, characteristic diabetic retinopathy, kidneys w/near normal morphology on ultrasound), HTN Exclusion Criteria: NR	N= 90 Age (yr): 63 Gender (Male %): 63.3 Race/Ethnicity (%):NR Weight: NR BMI (kg/m2): 30.4 Systolic BP (mm Hg): 165 Diastolic BP (mm Hg): 88 CKD stage: NR Serum creatinine (mg/dL): NR Creatinine clearance (mL/min): 55 mL/min Albuminuria: median 755 mg/24 hrs Albumin/creatinine ratio (mg/g): 78.8 mg/mmol Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): 7.9 Total cholesterol (mg/dL): 212.7 LDL cholesterol (mg/dL): NR Diabetes (%): 100 History of HTN (%): 100 Dyslipidemia (%): NR History of CAD (%): NR History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): NR Current smoker (%): 28 History of AKI (%): NR	n= 47 Intensive therapy/Project team care (Managed by multidisciplinary project care team, including dietician, MD, and nurse, with initial visits as often as every 2-3 weeks.) n= 43 Control treatment (Patients managed in their usual clinic.) Treatment goals were identical for both groups, including SBP <140 mm Hg, DBP <80 mm Hg, HbA1c <8%, sodium intake <120 mmol/day, protein intake 0.7-1 g/kg of ideal body weight per day, cholesterol <4 mmol/L or cholesterol :HDL ratio <4. Exercise was encouraged and advice was given on smoking. For both groups, BP and lab measures were collected for monitoring every 3-6 months to guide management. Followup period: median 2 years Study withdrawals (%): 3.3%	Allocation Concealment Adequate Blinding: None (i.e. open) Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Yes
Gaede, 2003/1999[107,108] STENO-2	Inclusion Criteria: Type 2 DM and microalbuminuria (defined as urinary albumin excretion rate of 30-300 mg/24hr in 4 of 6 urine samples).	N=160 Age (yr): 55.1 yrs Gender (Male %): 74 Race/Ethnicity (%): NR	n=80 Intensive care, with management by multidisciplinary Diabetes Center team, including a	Allocation Concealment Adequate Blinding: No blinding

Appendix Evidence Table C132. Overview of intensive multicomponent intervention (INT) versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Location Denmark, single site Funding Source Industry	Exclusion Criteria: Age older than 65 or younger than 40; a stimulated serum C-peptide concentration less than 600 pmol/L 6 min after IV injection of 1 mg glucagon; pancreatic insufficiency or diabetes secondary to pancreatitis; alcohol abuse; nondiabetic kidney disease; malignancy; or life threatening disease with death probable within 4 years.	Weight: NR BMI (kg/m2): 29.8 Systolic BP (mm Hg): 148 Diastolic BP (mm Hg): 86 CKD stage: NR Serum creatinine (mmol/L): 77 Creatinine clearance (mL/min): NR Albuminuria: 73.5 mg/24 hr Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): 117 HbA_{1c} (%): 8.6 Total cholesterol (mg/dL): 217 LDL cholesterol (mg/dL): 130 Diabetes (%): 100 History of HTN (%): NR Dyslipidemia (%):NR History of CAD (%): 24 (based only on ischemia on resting or stress ECG) History of CHF (%): NR Peripheral arterial disease (%): NR History of MI (%): NR History of Stroke (%): 3 Current smoker (%): 38 History of AKI (%): NR	dietician, MD, and nurse. Targeted treatment goals of SBP <140 mm Hg, DBP <85 mm Hg, HbA1c <6.5%, triglycerides <1.7 mmol/L, total cholesterol <5.0 mmol/L, HDL-cholesterol >1.1 mmol/L, aspirin for patients with known ischemia or peripheral vascular disease, ACEI regardless of blood pressure. n= 80 Standard care, with management by their regular general practitioner, who was to follow Danish diabetes management guidelines, including treatment goals of SBP <160 mm Hg, DBP <95 mm Hg, HbA1c <7.5%, triglycerides <2.2 mmol/L, total cholesterol <6.5 mmol/L, HDL-cholesterol >0.9 mmol/L, aspirin for patients with known ischemia. Followup period: median 7.8 yrs for mortality outcome, median 3.8 yrs for other outcomes Study withdrawals (%): 3.1 for longer followup period, 1.9 for shorter followup period	Intention to Treat Analysis (ITT): No Withdrawals/Dropouts adequately described: Adequate in report with 7.8 yrs followup

Appendix Evidence Table C132. Overview of intensive multicomponent intervention (INT) versus control treatment trials (continued)

Study/Region/ Funding Source	Inclusion/Exclusion Criteria	Patient Characteristics (expressed in means unless otherwise noted)	Intervention/Duration	Study Quality
Harris, 1998[109] Location USA, multi site Funding Source Other (Foundation)	Inclusion Criteria: Primary care in the general medicine practice with ≥1 physician visit in the past year, and two serum creatinine levels at least 6 months apart with estimated creatinine clearances <50 mL/min both times, and most recent serum creatinine concentration before enrollment >1.4 mg/dL. Exclusion Criteria: Living in an institution (NH or prison), inability to communicate with the research assistants, either because of a sensory or neurologic deficit or because could not speak and/or understand English.	N=437 Age (yr): 68.5 Gender (Male %): 34 Race/Ethnicity (%): African American 80.5 Weight: 172.7 lbs BMI: NR Systolic BP (mm Hg): 144 Diastolic BP (mm Hg): 83 CKD stage: NR Serum creatinine (mg/dL): 2.1 Creatinine clearance (mL/min): 34 Albuminuria: NR Albumin/creatinine ratio (mg/g): NR Estimated GFR (ml/min/1.73m^2): NR HbA_{1c} (%): NR Total cholesterol (mg/dL): NR LDL cholesterol (mg/dL): NR Diabetes (%): 43.5 History of HTN (%): 98.6 Dyslipidemia (%): NR History of CAD (%): 47.8 History of CHF (%): 40 Peripheral arterial disease (%): NR History of MI (%): 37 History of Stroke (%): 20 Current smoker (%): NR History of AKI (%): NR	n=206 Intensive case management in multidisciplinary renal clinic (nephrologist, renal nurse, renal dietician, social worker) including recommendations to patient's primary care provider to reduce use of nephrotoxic drugs, decrease dietary protein, initiate ACEI use if possible, with focus on improving medication compliance. n= 231 Standard care, with management by their regular general medicine physician. Followup period: median 5 years Study withdrawals (%): 0	Allocation Concealment Not described Blinding: No blinding Intention to Treat Analysis (ITT): Yes Withdrawals/Dropouts adequately described: No withdrawals were reported

ACEI = angiotensin converting enzyme inhibitor; ACR = albumin/creatinine ratio; AER = albumin excretion rate; AKI = acute kidney injury; ARB = angiotensin II receptor blocker; BB = bete blocker; BMI = body mass index; BP = blood pressure; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; CKD = chronic kidney disease; CV = cardiovascular; CVA = cerebrovascular accident; DBP = diastolic blood pressure; DM = diabetes mellitus; GFR = glomerular filtration rate; HbA1c = hemoglobin A1c; HTN = hypertension; INT = intensive multi-component intervention; LDL = low density lipoprotein; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NR = not reported; NSAIDS = non-steroidal anti-inflammatory drug; PVD = peripheral vascular disease; RCT = randomized controlled trial; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio; UAE = urinary albumin excretion

Appendix Table C133. Summary of study baseline characteristics for INT versus control treatment trials

Characteristic	Mean (range) *(unless otherwise noted)*	Number of Trials Reporting
INT trials		*4*
Patients randomized, n	892 (90 to 437)	4
Age of subjects, years	64.7 (55.1 to 68.5)	4
Male gender, %	51.5 (34 to 74)	4
African American Race/ethnicity, %	*80.5	1
Body Mass Index, kg/m2	27.9 (25.4 to 30.4)	3
Patients with diabetic nephropathy, n	†250 (90 to 160)	2
Serum creatinine, mg/dL	1.8 (0.9 to 2.1)	2
Estimated GFR, ml/min/1.73m^2	117	1
Creatinine clearance (mL/min)	37.6 (34 to 55)	2
Albuminuria, mg/24 hr	‡	2
Systolic blood pressure, mm Hg	147 (144 to 165)	4
Diastolic blood pressure, mm Hg	82 (74 to 88)	4
History of hypertension, %	98.0 (96 to 100)	3
HbA_{1c} (%)	8.3 (7.9 to 8.6)	2
History of CAD, %	‡34.9 (16 to 47.8)	3
History of MI, %	25.8 (2 to 37)	2
History of CHF,%	29.5 (7 to 40)	2
History of Stroke, %	15.3 (3 to 20)	3
Total cholesterol, mg/dL	215 (213 to 216.5)	2
LDL cholesterol, mg/dL	129.5	1
Current smokers, %	34.4 (28 to 38)	2

INT = Intensive Multi-Component Intervention; GFR = glomerular filtration rate; HbA_{1c} = hemoglobin A_{1c}; CAD = coronary artery disease; MI = myocardial infarction; CHF = congestive heart failure; LDL = low density lipoprotein

*This study reported data only for African American race/ethnicity, but did not report information regarding the race/ethnicity of its remaining participants.

†Two other studies included a total of 395 participants with diabetes and either impaired creatinine clearance or GFR, but did not report information on albuminuria or proteinuria. These study subjects were not counted toward the total number of patients with diabetic nephropathy.

‡Of the two studies reporting baseline albuminuria, one reported a mean of 73.5 mg/24 hours and the other a median of 755 mg/24 hours.

Appendix Table C134. Clinical outcomes (outcomes part A), INT versus control treatment trials

Study	All-Cause Mortality, n/N (%)		Cardiovascular Mortality, n/N (%)		Myocardial Infarction, Any, n/N (%)		Myocardial Infarction, Fatal n/N (%)		Myocardial Infarction, Nonfatal, n/N (%)		Stroke, Any, n/N (%)	
	INT	Control	INT	Control	INT	Control	INT	Control	INT	Control	INT	Control
INT versus control treatment trials (n=4)												
Chan, 2009[105]	8/104 (7.7)	11/101 (11.0)			4/104 (3.8)	4/101 (4.0)					*NR	*NR
Joss, 2004[106]	6/47 (12.8)	3/43 (7.0)	†4/47 (8.5)	†3/43 (7.0)	‡NR	‡NR	2/47 (4.3)	1/43 (2.3)	‡NR	‡NR	‡NR	‡NR
§Gaede, 2003/ 1999[107,108]	12/80 (15.0)	15/80 (18.8)	7/80 (8.8)	7/80 (8.8)					4/80 (5.0)	8/80 (10.0)		
Harris, 1998[109]	59/206 (28.6)	77/231 (33.3)										

INT = Intensive Multi-Component Intervention; NR = not reported

*Study reported results for composite endpoint of stroke or transient ischemic attack (2/104 in INT group vs. 3/101 in control group), but not for stroke outcome only.

†Study didn't define cardiovascular death, but these results derived from sum of participants in each group with sudden death, fatal myocardial infarction, or fatal stroke.

‡Study reported myocardial infarction, nonfatal myocardial infarction, and stroke by number of events per treatment group and not by the proportion of participants in each treatment group with one or more event.

§Study results taken from 2003 report except when data for a specific outcome only was available from the earlier 1999 report.

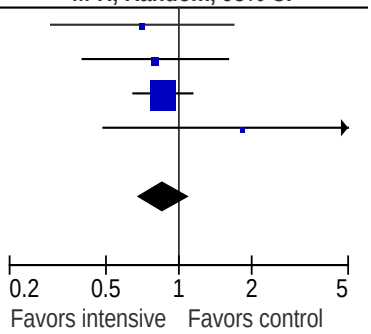
Appendix Figure C25. Forest plots for INT versus control treatment trials

All-cause mortality

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2009	8	104	11	101	8.0%	0.71 [0.30, 1.68]
Gaede 2003	12	80	15	80	12.6%	0.80 [0.40, 1.60]
Harris 1998	59	206	77	231	75.9%	0.86 [0.65, 1.14]
Joss 2004	6	47	3	43	3.5%	1.83 [0.49, 6.87]
Total (95% CI)		**437**		**455**	**100.0%**	**0.86 [0.67, 1.10]**
Total events	85		106			

Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 3 (P = 0.68); I² = 0%

Test for overall effect: Z = 1.20 (P = 0.23)

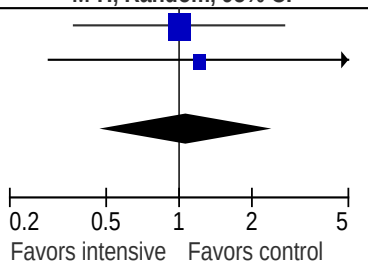


Cardiovascular mortality

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gaede 2003	7	80	7	80	67.4%	1.00 [0.37, 2.72]
Joss 2004	4	47	3	43	32.6%	1.22 [0.29, 5.14]
Total (95% CI)		**127**		**123**	**100.0%**	**1.07 [0.47, 2.43]**
Total events	11		10			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.15 (P = 0.88)

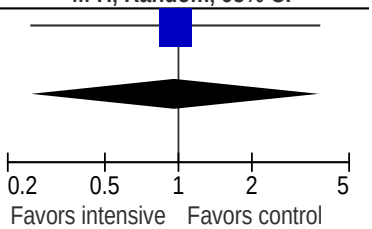


Myocardial infarction, any

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2009	4	104	4	101	100.0%	0.97 [0.25, 3.78]
Total (95% CI)		**104**		**101**	**100.0%**	**0.97 [0.25, 3.78]**
Total events	4		4			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.04 (P = 0.97)

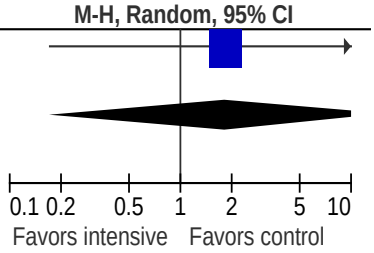


Appendix Figure C25. Forest plots for INT versus control treatment trials (continued)

Myocardial infarction, fatal

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Joss 2004	2	47	1	43	100.0%	1.83 [0.17, 19.47]
Total (95% CI)		**47**		**43**	**100.0%**	**1.83 [0.17, 19.47]**
Total events	2		1			

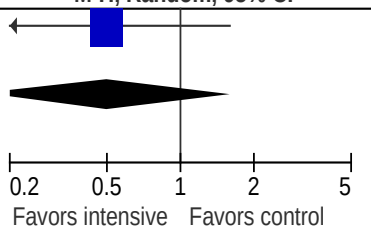
Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.62)



Myocardial infarction, nonfatal

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gaede 2003	4	80	8	80	100.0%	0.50 [0.16, 1.59]
Total (95% CI)		**80**		**80**	**100.0%**	**0.50 [0.16, 1.59]**
Total events	4		8			

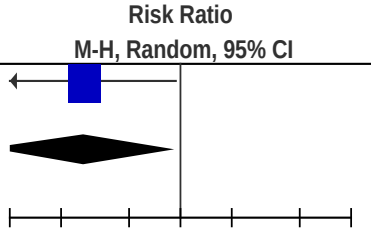
Heterogeneity: Not applicable
Test for overall effect: Z = 1.17 (P = 0.24)



Stroke, nonfatal

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gaede 2003	3	80	11	80	100.0%	0.27 [0.08, 0.94]
Total (95% CI)		**80**		**80**	**100.0%**	**0.27 [0.08, 0.94]**
Total events	3		11			

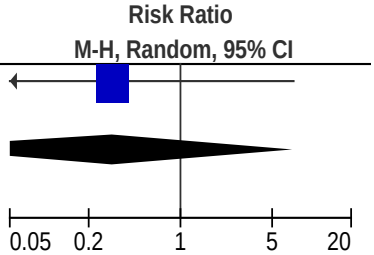
Heterogeneity: Not applicable
Test for overall effect: Z = 2.06 (P = 0.04)



Stroke, fatal

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Joss 2004	0	47	1	43	100.0%	0.31 [0.01, 7.31]
Total (95% CI)		**47**		**43**	**100.0%**	**0.31 [0.01, 7.31]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)

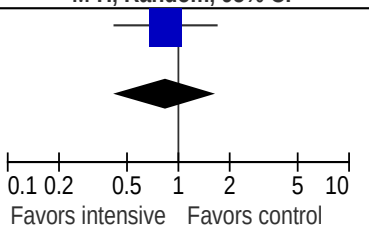


Appendix Figure C25. Forest plots for INT versus control treatment trials (continued)

Congestive heart failure, hospitalization

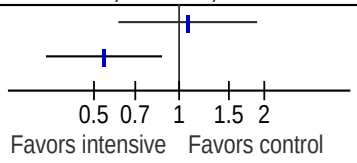
Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2009	13	104	15	101	100.0%	0.84 [0.42, 1.68]
Total (95% CI)		**104**		**101**	**100.0%**	**0.84 [0.42, 1.68]**
Total events	13		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.49 (P = 0.62)



Composite vascular outcome (see Table C136 for definitions)

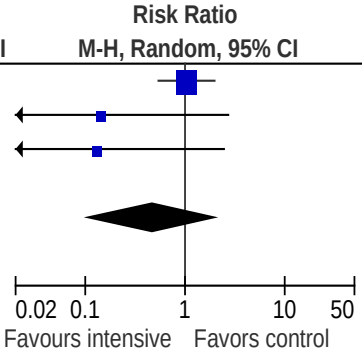
Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2009	21	104	19	101		1.07 [0.62, 1.87]
Gaede 2003	19	80	35	80		0.54 [0.34, 0.86]



End stage renal disease

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2009	16	104	15	101	60.6%	1.04 [0.54, 1.98]
Gaede 2003	0	80	3	80	19.7%	0.14 [0.01, 2.72]
Joss 2004	0	47	3	43	19.8%	0.13 [0.01, 2.46]
Total (95% CI)		**231**		**224**	**100.0%**	**0.47 [0.10, 2.20]**
Total events	16		21			

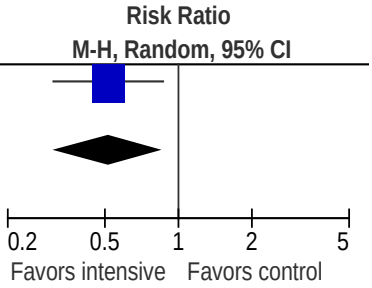
Heterogeneity: Tau² = 0.92; Chi² = 3.53, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 0.96 (P = 0.33)



Progression from microalbuminuria to macroalbuminuria

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Gaede 2003	16	80	31	80	100.0%	0.52 [0.31, 0.87]
Total (95% CI)		**80**		**80**	**100.0%**	**0.52 [0.31, 0.87]**
Total events	16		31			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.50 (P = 0.01)



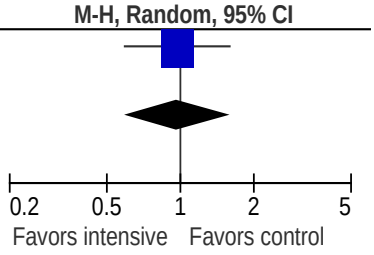
Appendix Figure C25. Forest plots for INT versus control treatment trials (continued)

Composite renal outcome (see Table C138 for definition)

Study or Subgroup	Intensive Events	Intensive Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Chan 2009	24	104	24	101	100.0%	0.97 [0.59, 1.59]
Total (95% CI)		**104**		**101**	**100.0%**	**0.97 [0.59, 1.59]**
Total events	24		24			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.12 (P = 0.91)



Appendix Table C135. Clinical outcomes (outcomes part B), INT versus control treatment trials

Study	Stroke, Nonfatal, n/N (%)		Stroke, Fatal, n/N (%)		CHF, Any, n/N (%)		CHF Hospitalization (A) or Death (B), n/N (%)		Composite Vascular Outcome, n/N (%)**	
	INT	Control	INT	Control	INT	Control	INT	Control	INT	Control
INT versus control treatment trials (n=4)										
Chan, 2009[105]							(A)13/104 (12.5) (B) NR	(A)15/101 (14.8) (B) NR	21/104 (20.2)	19/101 (18.8)
Joss, 2004[106]	†NR	†NR	0/47	1/43 (2.3)	†NR	†NR			†NR	†NR
*Gaede, 2003/1999[107,108]	3/80 (3.8)	11/80 (13.8)							(A)19/80 (23.8)	(A)35/80 (43.8)
Harris, 1998[109]										

INT = Intensive Multi-Component Intervention; CHF = congestive heart failure; NR = not reported

*Study results taken from 2003 report except when data for a specific outcome only was available from the earlier 1999 report.

**See Composite vascular outcome definitions table

†Study reported nonfatal stroke, CHF, and composite vascular outcomes by number of events per treatment group and not by the proportion of participants in each treatment group with one or more event.

Appendix Table C136. Composite vascular outcome definitions for INT versus control treatment trials

Study	Definition
INT versus control treatment trials (n=4)	
Chan, 2009[105]	"Composite cardiovascular end point" included any of the following: hospitalization for heart failure, hospitalization for angina, hospitalization for arrhythmia, MI, coronary revascularization (PTCA/CABG), other revascularization, CVA or transient ischemic attack, and lower limb amputation.
Joss, 2004[106]	"Cardiovascular events" included any of the following: sudden death, fatal and nonfatal MI, fatal and nonfatal CVA, CABG, CHF (undefined), amputation (undefined) or interventional vascular surgery.
Gaede, 2003/1999[107,108]	The primary composite endpoint was defined as (A) death from cardiovascular causes, nonfatal MI, CABG, PCI, nonfatal stroke, amputation as a result of ischemia, or surgery for peripheral atherosclerotic artery disease. Additional composite vascular endpoints were defined as: (B) All cause mortality, nonfatal MI, nonfatal CVA, CABG, PTCA, arterial revascularization to the legs, or amputation to the legs for ischemia; (C) cardiovascular mortality, nonfatal MI, nonfatal CVA, CABG, PTCA, arterial revascularization to the legs, or amputation to the legs for ischemia; and (D) nonfatal MI, nonfatal CVA, CABG, PTCA, arterial revascularization to the legs, or amputation to the legs for ischemia.

INT = Intensive Multi-Component Intervention; PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting; MI = myocardial infarction; CVA = cerebrovascular accident (i.e. stroke)

Appendix Table C137. Clinical renal outcomes (outcomes part C), INT versus control treatment trials

Study	End Stage Renal Disease, n/N (%)		Doubling of Serum Creatinine, n/N (%)		Halving of GFR, n/N (%)		Progression from Micro to Macroalbuminuria, n/N (%)		Composite Renal Outcome, n/N (%)**	
	INT	Control	INT	Control	INT	Control	INT	Control	INT	Control
Intensive Multi-Component Intervention (INT) versus Control treatment trials (n=4)										
Chan, 2009[105]	16/104 (15.4)	15/101 (14.9)							24/104 (23.1)	24/101 (23.8)
Joss, 2004[106]	0/47	3/43 (7.0)								
*Gaede, 2003/1999[107,108]	0/80	3/80 (3.8)					16/80 (20.0)	31/80 (38.8)		
Harris, 1998[109]										

INT = Intensive Multi-Component Intervention; GFR = glomerular filtration rate
*Study results taken from 2003 report except when data for a specific outcome only was available from the earlier 1999 report.
**See Composite renal outcome definitions table

Appendix Table C138. Composite renal outcome definitions for INT versus control treatment trials

Study	Definition
INT versus control treatment trials (n=4)	
Chan, 2009[105]	ESRD (defined as the need for dialysis, or plasma creatinine level $\geq$500 µmol/l) or death.

INT = Intensive Multi-Component Intervention; ESRD = end-stage renal disease

Appendix Table C139. Study withdrawals and adverse events (outcomes part D), INT versus control treatment trials

Study	Study Withdrawals: Any		Serious Adverse Event: Any		Serious Adverse Event: Any Leading to Withdrawal		Adverse Event: Any		Renal Adverse Events: Any		Adverse Event: Other Specific	
	INT	Control	INT	Control	INT	Control	INT	Control	INT	Control	INT	Control
INT versus control treatment trials (n=4)												
Chan, 2009[105]	*NR	*NR			0/104	0/101						
Joss, 2004[106]	2/47 (4.2)	1/43 (2.3)										
†Gaede, 1999/2003[107,108]	1/80 (1.3)	2/80 (2.5)	1/80 (1.3)	0/80	0/80	0/80					Hypoglycemia: Minor 42/80 (52.5), Major 5/80 (6.3)	Hypoglycemia: Minor 39/80 (48.8), Major 12/80 (15.0)
Harris, 1998[109]	0/206	0/231										

INT = Intensive Multi-Component Intervention; NR = not reported

*Study reported withdrawals only for combined treatment groups (n=5 [2.4%]), but not for each treatment group by itself.

†Study results taken from 2003 report except when data for a specific outcome only was available from the earlier 1999 report.

Table C140. Assessment of individual study quality for KQ5 and KQ6

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	WithdrawalsDescribed	Study Rating
Angiotensin converting enzyme inhibitor (ACEI) versus placebo/no treatment trials (n=17)					
Perkovic, 2007[1] PROGRESS	adequate	double*	yes	yes for overall study population**	Good
Asselbergs, 2004[2]	unclear	double*	yes	yes	Fair
Marre, 2004[3] DIABHYCAR	adequate	double*	yes	yes	Good
Katayama, 2002[4] JAPAN-IDDM	adequate	double*	no	yes	Fair
Bojestig, 2001[5]	unclear	double	yes	yes	Fair
Gerstein HOPE Trial, 2001[6]	adequate**	double*	yes	yes for overall study population**	Good
O'Hare, 2000[7] ATLANTIS	adequate	double	no	yes	Fair
Muirhead, 1999[8]	unclear	double	no	yes	Fair
Ruggenenti, 1999[9] REIN	adequate	double*	yes	yes	Good
Crepaldi, 1998[10]	unclear	double	no	yes	Fair
The GISEN Group, 1997[11]	adequate	double*	yes	yes	Good
Maschio, 1996[12]	unclear	double*	yes	yes	Fair
Trevisan, 1995[13]	unclear	double	no	yes	Fair
Laffel, 1995[14]	unclear	double	no	yes	Fair
Sano 1994[15]	unclear	no	no	yes	Fair
Lewis, 1993[16]	unclear	double*	yes	yes	Fair
Ravid, 1993[17]	unclear	double	no	yes	Fair
Angiotensin converting enzyme inhibitor (ACEI) versus angiotensin II-receptor blocker (ARB) trials (n=6)					
Mann, 2008[18] ONTARGET	adequate	double	yes	yes	Good
Menne, 2008[19] VALERIA	adequate	double*	no	yes	Fair
Sengul, 2006[20]	unclear	no	no	yes	Fair
Barnett, 2004[21] DETAIL	adequate	double	yes	yes	Good
Lacourcière, 2000[22]	unclear	double	no	yes	Fair
Muirhead, 1999[8]	unclear	double	no	yes	Fair
Angiotensin converting enzyme inhibitor (ACEI) versus Calcium channel blocker (CCB) trials (n=6)					
Rahman, 2005[23,110] ALLHAT	adequate**	double*	yes	yes for overall study population**	Good
Fogari, 2002[24]	adequate	no	no	yes	Fair
Agodoa, 2002[25] Wright, 2002[26] Norris, 2006[27] (AASK)	adequate**	double*	yes	yes	Good
Marin, 2001[28] ESPIRAL	unclear	no	yes	yes	Fair
Crepaldi, 1998[10]	unclear	double	no	yes	Fair
Zucchelli, 1995/1992[29,30]	unclear	no	yes	yes	Fair

Table C140. Assessment of individual study quality for KQ5 and KQ6 (continued)

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	WithdrawalsDescribed	Study Rating
Angiotensin converting enzyme inhibitor (ACEI) versus beta-blocker trials (n=3)					
Wright, 2002[26] Norris, 2006[27] (AASK)	adequate**	double*	yes	yes	Good
van Essen, 1997[31]	unclear	double	no	yes	Fair
Hannedouche, 1994[32]	adequate	no	yes	yes	Fair
Angiotensin converting enzyme inhibitor (ACEI) versus diuretics trials (n=2)					
Rahman, 2005[23,110] ALLHAT	adequate**	double*	yes	yes for overall study population**	Good
Marre, 2004[33]NESTOR	unclear	double	no (one subject excluded)	yes	Fair
ARB versus placebo trials (n=5)					
Tobe, 2011[35] TRANSCEND	adequate**	double*	yes	yes (for CKD patients)	Good
Makino, 2007[37]	unclear	double	no	yes	Fair
Brenner, 2001[38] RENAAL	adequate	double*	yes	yes	Good
Parving, 2001[39] IRMA-2	unclear	double	yes	yes	Fair
Lewis, 2001[40] IDNT	adequate	double*	yes	yes	Good
ARB versus CCB trials (n=4)					
Saruta, 2009[41] CASE-J	unclear	no	yes	no	Fair
Ogawa, 2007[42]	unclear	single (patient)	unclear	yes	Fair
Viberti, 2002[43] MARVAL	adequate	double	yes	yes	Good
Lewis, 2001[40] IDNT	adequate	double*	yes	yes	Good
ACEI plus ARB versus ACEI or ARB trials (n=1)					
Tobe, 2011[35] ON-TARGET	adequate**	double*	yes	yes (for CKD patients)	Good
ACEI plus ARB versus ACEI trials (n=5)					
Sengul, 2006[20]	unclear	no	no	yes	Fair
Menne, 2008[19] VALERIA	adequate	double*	no	yes	Fair
Kanno, 2006[44]	unclear	no	no	yes	Fair
Mehdi, 2009[45]	unclear	double	no (one subject excluded)	yes	Fair
Anand, 2009[46]	adequate	double	yes	yes	Good
ACEI plus ARB versus ARB trials (n=2)					
Sengul, 2006[20]	unclear	no	no	yes	Fair
Menne, 2008[19] VALERIA	adequate	double*	no	yes	Fair
ACEI plus ARB versus ACEI plus aldosterone antagonist trial					
Mehdi, 2009[45]	unclear	double	no (one subject excluded)	yes	Fair
ACEI plus CCB versus ACEI monotherapy or CCB monotherapy trial					
Fogari 2002	adequate	no	no	yes	Fair

Table C140. Assessment of individual study quality for KQ5 and KQ6 (continued)

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	WithdrawalsDescribed	Study Rating
ACEI plus diuretic versus ACEI plus CCB trials (n=2)					
Bakris, 2010[48] (ACCOMPLISH)	adequate**	double*	yes for overall study population	yes for overall study population	Good
Bakris, 2008[47] (GUARD)	adequate	double	no	yes	Fair
ACEI plus diuretic versus ACEI trial					
Mogensen, 2003[50]	unclear	double	no	no	Fair
ACEI plus diuretic versus placebo trial					
Lambers Heerspink 2010[51] ADVANCE	adequate**	double*	yes for overall study population	yes for overall study population	Good
ARB versus different ARB trials (n=2)					
Bakris, 2008[53] (AMADEO)	unclear	double	no	no	Fair
Galle, 2008[54]	unclear	double	yes	yes	Fair
ARB (high dose) versus ARB (standard dose) trials					
Burgess, 2009[55]	adequate	double	yes	yes	Good
Makino, 2007[37]	unclear	double	no	yes	Fair
Parving, 2001[39] IRMA-2	unclear	double	yes	yes	Fair
ACEI plus aldosterone antagonist versus ACEI trial					
Mehdi, 2009[45]	unclear	double	no (one subject excluded)	yes	Fair
ACEI/ARB plus aldosterone antagonist versus ACEI/ARB trial					
van den Meiracker, 2006[56]	adequate	double	no	yes	Fair
Beta blocker versus placebo trials (n=2)					
Cohen-Solal, 2009[57] Flather, 2005[58] SENIORS	adequate**	double*	no	unclear	Fair
Ghal, 2009[59] MERIT-HF	adequate	double	yes	yes	Good
CCB versus placebo trials (n=2)					
Berl, 2003[60] Lewis, 2001[40]	adequate	double	yes	yes	Good
Crepaldi, 1998[10]	unclear	double	no	yes	Fair
Diuretic versus placebo trial					
Pahor, 1998[61]	adequate	double	yes	yes	Good
ACEI versus conventional therapy without ACEI trial					
Cinotti, 2001[62]	unclear	no	yes	no	Fair
CCB versus BB trials (n=3)					
Bakris, 1996[63]	unclear	unclear	yes	yes	Fair
Wright, 2002[26] AASK	adequate**	double*	no	yes	Good
Dahlof, 2005[65]	adequate	open-label*	yes	yes	Good
CCB versus diuretic trial					
Rahman 2006 ALLHAT	adequate**	double*	yes	yes for overall study population**	Good

Table C140. Assessment of individual study quality for KQ5 and KQ6 (continued)

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	WithdrawalsDescribed	Study Rating
Strict versus standard blood pressure control trials (n=6)					
Ruggenenti, 2005[66] REIN-2	adequate	no	no, 3 subjects excluded	yes	Fair
Wright, 2002[26] AASK	adequate**	no	yes	yes	Good
Estacio 2000 - Study B ABCD	unclear	"blinded," unclear if double-blinded*	unclear	yes	Fair
Lewis, 1999[69]	unclear	unclear	yes	no	Fair
Toto, 1995[70]	unclear	double	yes	unclear	Fair
Peterson, 1995[71] Klahr, 1994[72] MDRD, Study A	unclear	unclear	yes	yes	Fair
Shulman, 1989[74] HDFP	adequate	no	no	no	Fair
Anti-lipid trials: HMG-CoA reductase inhibitor versus placebo trials (n=12)					
Kendrick, 2010[87] AFCAPS/ TexCAPS	unclear	double*	yes	yes for overall study population**	Fair
Ridker, 2010 JUPITER	adequate**	double*	yes	yes for overall study population**	Good
Nakamura, 2009[89] MEGA	adequate**	open-label	no (382 excluded from analyses)**	yes for overall study population**	Fair
Colhoun, 2009[90] CARDS	adequate**	double*	no (3 randomized patients were excluded - investigators realized they did not meet the entry criteria before they actually took their first dose of study drug)	yes for overall study population**n	Good
Koren, 2009[91] ALLIANCE	adequate	open-label	yes	yes for overall study population**	Good
Rahman, 2008[93] ALLHAT-LLT	adequate**	open-label*	no for CKD subgroups (need valid baseline eGFR); yes for overall study population	yes (for CKD patients)	Good
Chonchol, 2007[94] 4S	adequate**	double*	no (24 excluded, no serum creatinine at baseline)	partially for overall study population**	Fair
Kjekshus, 2007[96] CORONA	adequate**	double*	yes	yes	Good

Table C140. Assessment of individual study quality for KQ5 and KQ6 (continued)

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	WithdrawalsDescribed	Study Rating
Lemos, 2005[97] LIPS	unclear	double*	yes	yes for overall study population**	Fair
Asselbergs, 2004[2] PREVD	unclear	double*	yes	yes	Fair
Tonelli, 2004[98] WOSCOPS/ CARE/LIPID	adequate**	double*	yes	yes for overall study populations for CARE, LIPID; no for WOSCOPS**	Good
Tonelli, 2003[99] CARE	adequate	double*	yes	yes for overall study population**	Good
Anti-lipid trials: high versus low dose HMG-CoA reductase inhibitor trial					
SEARCH, 2010[100]	adequate	double*	yes	yes	Good
Shepherd, 2008[101] TNT	unclear	double*	no	yes (for CKD patients)	Fair
Anti-lipid trials: HMG-CoA reductase inhibitor versus bile acid sequestrant trial					
Tonolo, 2006[104]	unclear	double	yes	yes	Fair
Anti-lipid trials: Gemfibrozil versus placebo/control trials (n=2)					
Tonelli, 2004[98] VA-HIT	adequate	double*	yes	yes for overall study population**	Good
Samuelsson, 1997[84]	unclear	open-label	no	yes	Fair
Low protein diet versus usual protein diet and other dietary intervention trials (n=9)					
Koya, 2009[75]	adequate	no	no	yes	Fair
Dussol, 2005[76]	unclear	no	no	yes	Fair
Kopple, 1997[77] Peterson, 1995[71] Klahr, 1994[72] Greene, 1993[73] MDRD	adequate	double for followup GFRs	unclear	yes	Fair
D'Amico, 1994[78]	unclear	no	no	no	Fair
Locatelli, 1991[79]	adequate	unclear	no	yes	Fair
Rosman, 1989/1984[80,81]	unclear	no	no	no	Fair
Facchini, 2003[82]	unclear	study personnel blinded to aim of study	no	yes	Fair
Williams, 1991[83]	adequate	no	no	no	Fair
Samuelsson, 1997[84]	unclear	no	no	yes	Fair
Glycemic control trials (n=2)					
Duckworth, 2009[85]	adequate	open-label*	yes	yes	Good
Microalbuminuria Collaborative, 1995[86]	adequate	open-label	yes	yes	Good
Intensive multi-component intervention trials (n=4)					
Chan, 2009[105]	adequate	open-label	yes	yes	Good
Joss, 2004[106]	adequate	open-label	no	yes	Fair
Gaede, 2003/1999[107,108]	adequate	open-label	no	yes	Fair

Table C140. Assessment of individual study quality for KQ5 and KQ6 (continued)

Study ID	Allocation Concealment	Blinding	Intention to Treat Analysis	WithdrawalsDescribed	Study Rating
Harris, 1998[109]	unclear	open-label	yes	yes	Fair

*In addition, end points/clinical outcomes were adjudicated by blinded committee

** Detailed in baseline/study design or main findings manuscript. Included study was a secondary/post-hoc analysis with subgroup(s) of CKD patients.

References for Appendix C

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