Effective Health Care Program

Renal Disease
Chronic Kidney Disease, Stages 1–3

Management of Chronic Kidney Disease Stages 1–3

Focus of Research for Clinicians

A systematic review that included 110 reports of eligible studies published from January 1985 through January 2011 was undertaken to determine the potential benefits and adverse effects of screening, monitoring, and treatments for adults with chronic kidney disease (CKD) stages 1–3. CKD stages 1–3 are defined as: 1 (kidney damage with a glomerular filtration rate [GFR] >90 mL/min/1.73 m^2), 2 (kidney damage with a GFR of 60–89 mL/min/1.73 m^2), or 3 (a GFR of 30–59 mL/min/1.73 m^2, regardless of kidney damage). The systematic review excluded studies of patients with CKD stages 4 and 5. This is a summary of the systematic review meant to assist in decisionmaking along with a patient's values and preferences and should not be construed to represent clinical recommendations or guidelines. The full systematic review is available at www.effectivehealthcare.ahrq.gov/ckd.cfm.

Background Information

An estimated 11 percent of adults aged 20 or older have early (stages 1–3) CKD, and the prevalence of every stage of CKD is rising. Early stage CKD is usually asymptomatic and typically requires blood and urine testing for diagnosis. Patients with CKD are at an increased risk for mortality, cardiovascular (CV) disease, fractures, bone loss, infections, cognitive impairment, frailty, and end-stage renal disease (ESRD). CKD is most commonly due to hypertension or diabetes and is less commonly a result of primary renal disease. Typically, treatment for CKD stages 1–3 is directed at underlying conditions or CV risk factors.

Common pharmacological interventions include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, diuretics, statins, and calcium channel blockers (CCBs). Additional nonspecific therapies may include other medications and nonpharmacological interventions that target control of blood pressure, hyperglycemia, cholesterol, and obesity. The American Diabetes Association and the Kidney Disease Outcomes Quality Initiative have issued recommendations about screening for and monitoring of kidney disease.

Clinical Bottom Line: Treatment

Risk for ESRD in Patients With CKD Stages 1–3

ACEIs and ARBs

In patients with overt proteinuria, diabetes, and hypertension, ACEIs decreased the risk of ESRD by 40 percent versus placebo (ARR = 8.7%; 12% vs. 20.7%; RR = 0.60, 95% CI 0.43–0.83; 3 trials, n = 861 patients). ●●○

- ACEIs did not lower the risk of ESRD for patients with only microalbuminuria or impaired eGFR, although these studies were not powered to detect a difference.*

(Continued in next column)

ACEIs and ARBs (Continued)

ARBs reduced the relative risk of ESRD by 22 percent (ARR = 2.9%) versus placebo in trials consisting mostly of patients with overt proteinuria, most of whom had diabetes and hypertension (10% vs. 12.9%; RR = 0.78, 95% CI 0.67–0.90; n = 4,652 patients). ●●●

ESRD risk was not significantly different for these comparisons (●○○):

- ARB versus CCB
- ACEI versus CCB, beta-blocker, or diuretic
- ACEI or ARB versus ACEI plus ARB

Other Interventions

ESRD risk was not significantly different between these comparisons (●○○):

- Beta-blocker versus placebo
- CCB versus placebo
- CCB versus beta-blocker
- Statin versus a control
- Strict versus standard blood pressure control
- Low-protein diet versus usual diet
- Carbohydrate-restricted, low-iron-available, polyphenol-enriched diet versus low-protein diet

*These results were not given strength of evidence ratings.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARR = absolute risk reduction; CCB = calcium channel blocker; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; RR = relative risk; 95% CI = 95-percent confidence interval

(Continued on next page)

Strength of Evidence Scale

High:	●●●	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate:	●●○	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low:	●○○	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient:	○○○	Evidence is either unavailable or does not permit a conclusion.

Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Clinical Bottom Line: Treatment *(Continued)*

All-Cause Mortality for Patients With CKD Stages 1–3

ACEIs and ARBs

The risk for mortality was not significantly different for these comparisons:

- ACEI versus placebo ●●○
- ARB versus placebo ●●●
- ACEI versus ARB, CCB, or beta-blocker ●○○
- ARB versus CCB ●○○
- ACEI plus ARB versus ACEI ●●○
- ACEI plus ARB versus ACEI or ARB ●●○
- ACEI plus diuretic versus placebo ●○○

Subgroup Analysis

In a subgroup analysis of patients with microalbuminuria who had CV disease or diabetes with other CV risk factors, an ACEI reduced the mortality risk by 21 percent versus placebo (ARR = 2.8%; 9.3% vs. 12.1%; RR = 0.79, 95% CI 0.66–0.96; 8 trials, n = 3,440 patients). ●●○

Statins

In patients with hyperlipidemia and decreased eGFR or creatinine clearance, statins reduced the mortality risk by 20 percent versus a control (ARR = 1.6%; 7.1% vs. 8.7%; RR = 0.80, 95% CI 0.68–0.95; 8 trials, n = 13,964 patients). ●●●

- Statins also reduced the risk for MI by 28 percent (ARR = 2.6%; 6.8% vs. 9.4%; RR = 0.72, 95% CI 0.54–0.98; 2 trials, n = 2,015 patients) and for stroke by 38 percent (ARR = 0.9%; 1.4% vs. 2.3%; RR = 0.62, 95% CI 0.41–0.95; 6 trials, n = 10,369 patients) versus a control.*

High-dose versus low-dose statins had similar risks for mortality. ●○○

Beta-Blockers

A beta-blocker versus placebo reduced the mortality risk by 31 percent among patients with congestive heart failure and impaired eGFR (ARR = 5.7%; 12.4% vs. 18.1%; RR = 0.69, 95% CI 0.53–0.91; 2 trials, n = 2,173 patients). ●○○

Other Interventions

The risk for mortality was not significantly different for these comparisons (●○○):

- CCB versus placebo
- Strict versus standard blood pressure-target treatment
- Gemfibrozil versus placebo
- Low-protein diet versus usual diet
- Carbohydrate-restricted, low-iron-available, polyphenol-enriched diet versus low-protein diet

*These results were not given strength of evidence ratings.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; ARR = absolute risk reduction; CCB = calcium channel blocker; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; MI = myocardial infarction; RR = relative risk; 95% CI = 95-percent confidence interval

Clinical Bottom Line: Screening and Monitoring

Screening and Monitoring in Subpopulations

Evidence was insufficient to determine if systematic screening of high-risk adults and monitoring of patients with CKD stages 1–3 have a direct effect on clinical outcomes or adverse effects. ○○○

Indirect evidence from the treatment outcomes described above suggests that screening populations at high risk for developing CKD (patients with diabetes, hypertension, or CV disease) and monitoring patients who already have early signs of kidney disease for albuminuria and eGFR may help identify those patients with CKD stages 1–3 who might benefit from early initiation of treatment with ACEIs or ARBs and/or statins.*

Adverse Effects

Potential harms from CKD screening and monitoring may include misclassification of patients with CKD, unnecessary tests and their associated adverse effects, psychological effects of being labeled with CKD, adverse effects associated with pharmacological treatments initiated or changed following a CKD diagnosis, and possible financial and insurance ramifications of a new CKD diagnosis.*

*These results were not given strength of evidence ratings.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CV = cardiovascular; eGFR = estimated glomerular filtration rate

Conclusions

Many knowledge gaps exist; additional research is needed to increase understanding of optimal approaches to CKD screening, monitoring, and treatment.

Treatment

In patients with CKD stages 1–3 who have proteinuria, diabetes, and hypertension there is moderate- and high-strength evidence that an ACEI or an ARB will reduce their risk of ESRD. Although ACEIs reduced the risk of ESRD overall, this benefit appeared to be present only among patients with macroalbuminuria, most of whom had concomitant diabetes and hypertension. In patients with CKD stages 1–3 with only microalbuminuria or impaired eGFR, there was no evidence that ACEIs or ARBs reduced the risk of ESRD when compared with placebo; however, these studies were not powered to detect this difference. There was no increased benefit for reducing the risk of ESRD if an ACEI and an ARB were taken as combination therapy when compared with taking either an ACEI or an ARB alone. Taking an ACEI or an ARB did not reduce the risk of mortality, except when an ACEI was used for patients with microalbuminuria and CV disease or diabetes and other CV risk factors. Statins reduced the risk for mortality in patients with hyperlipidemia and impaired eGFR, and beta-blockers may reduce mortality in patients with congestive heart failure and impaired eGFR. In the included trials, many patients for whom improved outcomes were observed had a pre-existing clinical indication for the treatment studied regardless of CKD status.

(Continued on next page)

Conclusions *(Continued)*

Screening and Monitoring

Evidence is insufficient to determine if screening for or monitoring of early stage CKD improves clinical outcomes. No trials directly show a benefit for CKD screening or monitoring, and potential harms are poorly described. Indirect evidence suggests that screening and monitoring may benefit specific subgroups of patients.

Adverse Effects

Adverse effects were reported in only a few randomized clinical trials, and evidence was insufficient to permit any conclusions. The adverse events reported generally were consistent with known potential adverse effects of these treatments (e.g., hypotension with antihypertensives, cough with ACEIs, hyperkalemia with ACEIs and ARBs).

Gaps in Knowledge

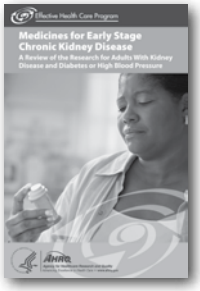
- The systematic review identified areas where clear evidence is not available:
  - Whether clinical outcomes are improved from systematic screening for CKD in patients at high risk for developing CKD (e.g., patients with diabetes, hypertension, or CV disease) or from systematic CKD monitoring for worsened kidney function or damage, especially in patients with CKD who also have hypertension, diabetes, or CV disease
  - If one-time measures of albuminuria or eGFR have the sensitivity and specificity to diagnose persistent CKD or CKD progression
  - Whether the clinical outcome benefits differ for a specific treatment between patients with recently worsened kidney function or damage (as detectable by monitoring) when compared with those who have stable CKD
  - The long-term impact of treatment on clinical outcomes
  - The impact of dietary intervention or intensification of treatment (e.g., tight vs. standard blood pressure control, high vs. standard statin dose) on clinical outcomes for patients with CKD stages 1–3

What To Discuss With Your Patients

- The presence and stage of CKD
- The risk of CKD if they have high blood pressure, CV disease, diabetes, or acute kidney disease
- The evidence about the benefits and adverse effects of treatments for CKD

Resource for Patients

Medicines for Early Stage Chronic Kidney Disease, A Review of the Research for Adults With Kidney Disease and Diabetes or High Blood Pressure is a free companion to this clinician research summary. It can help patients talk with their health care professionals about the many options for treatment. It provides information about:



- CKD and its causes and symptoms
- The role of medications in helping to protect kidney function

Ordering Information

For electronic copies of *Medicines for Early Stage Chronic Kidney Disease, A Review of the Research for Adults With Kidney Disease and Diabetes or High Blood Pressure*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/ckd.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

Source

The information in this summary is based on *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 for the Agency for Healthcare Research and Quality, January 2012. Available at www.effectivehealthcare.ahrq.gov/ckd.cfm. This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

AHRQ Pub. No. 11(13)-EHC075-3
October 2012