**NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES**
**NATIONAL INSTITUTES OF HEALTH**

# Reducing the Impact of Chronic Kidney Disease: Opportunities for Randomized Clinical Trials

**July 19 – 20, 2011**
**Natcher Conference Center, NIH Campus**
**Bethesda, MD**

**Summary Report of Talks (*Final 10-25-11*)**

## TUESDAY, JULY 19, 2011

### OPENING REMARKS AND OBJECTIVES

*Robert A. Star, M.D., Division Director, Division of Kidney, Urologic, and Hematologic Diseases (DKUH), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, MD,* and *Michael Flessner, M.D., Ph.D., Director of Inflammatory Renal Disease, DKUH, NIDDK, NIH, Bethesda, MD*

Dr. Star provided an overview of the public health importance of chronic kidney disease (CKD). In the past 5 years, we have witnessed a multitude of new scientific advances arising from large scale epidemiology and genetics studies, as well as smaller pathophysiological studies. Taken together, new mechanisms-of-actions and potential drug targets have emerged that may decrease the emergence and progression of CKD and associated cardiovascular disease. This meeting will consider therapies that are being considered by academia and Industry; discussion of novel clinical trial designs, outcomes; and careful consideration of what preliminary studies are needed before launching full scale clinical trials. It was hoped that through this meeting, the National Institutes of Health's (NIH) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) would receive expert advice from attendees in both public and private research entities and would develop an understanding of how to plan, design, and implement a large clinical trial in CKD.

Dr. Star thanked Drs. Michael Flessner and John Kusek from the NIDDK, and Drs. Glenn Chertow and Laura Dember, Co-Chairs of the Steering Committee, for bringing together an impressive list of speakers from academia, government, and private industry to assist in the meeting, with the ultimate goal of reducing the burden of chronic kidney disease.

Dr. Flessner presented the goals and objectives for the meeting and reviewed the agenda and logistics for the breakout sessions. The objectives of the meeting were to:

- Discuss critical elements of study design to optimize the conduct and impact of Phase III clinical trials in CKD, especially in diabetic neuropathy (DN).
- Identify interventions and therapies for CKD that currently are in clinical trials or are ready to be evaluated for clinical trials.

- Discuss and promote mechanisms for pathways of cooperation among academia, governments, and private industry for clinical trials.

The questions to be addressed during the plenary and breakout sessions included:

- Which interventions are most likely to have an effect on CKD outcomes? This question is important because, in these fiscal times, the NIDDK must make informed choices and implement programs that will have the greatest impact for the maximum numbers of patients. The CKD clinical trial cannot be a trial that is of marginal benefit.
- Which interventions are ready for a mainstream, major randomized controlled trial (RCT) at this time?
- Which interventions can be targeted under current budgetary constraints in a sufficiently broad population to be of clinical importance?
- Which combinations of interventions might be evaluated together in factorial designs without a major risk of interactions?

## STATE-OF-THE-ART LECTURES

**Moderator:** *Glenn Chertow, M.D., Professor of Medicine, Department of Medicine/ Nephrology, Stanford University School of Medicine, Palo Alto, CA*

### Lessons from CRIC and CKiD: Defining Risk Factors Relevant to CKD Trials

*Harold Feldman, M.D., Professor of Medicine and Epidemiology, Department of Medicine, University of Pennsylvania, Philadelphia, PA,* and *Susan Furth, M.D., Professor, Department of Pediatrics, The Children's Hospital of Philadelphia, Philadelphia, PA*

Dr. Feldman presented an overview of the Chronic Renal Insufficiency Cohort (CRIC) Study, sponsored by the NIDDK. CRIC began recruitment in 2003 and accrued 3,939 participants, with a high percentage of minority patients (42% African American and 13% Hispanic) and an equal number of men and women; participants were age 21-74 years at entry. At baseline, 50% of patients had diabetes and an average estimated glomerular filtration rate (eGFR) of 20-70 ml/min/1.73m$^2$. Medical history, physical measures, and psychometric measures also were assessed at baseline and during the study, as were blood and urine biomarkers. Primary renal outcomes include end-stage renal disease (ESRD), slope of GFR, and average GFR; adjudicated cardiovascular (CV) outcomes include myocardial infarction (MI), stroke, congestive heart failure (CHF), arrhythmia, peripheral artery disease (PAD), and death. Retention is approximately 86%.

Lessons from CRIC include the following:

- **Feasibility—**Patients across the spectrum of CKD are able to be enrolled in long-term studies, follow a demanding protocol, generate high-quality data, and sustain long periods of followup.

- **FGF23**—Fibroblast growth factor 23 (FGF23) is the earliest marker of mineral dysmetabolism in CKD, has the strongest relationship with death among other potential associations, has a strong association with elevated left ventricular mass index (LVMI), and is a very promising target for intervention.

- **25(OH) Vitamin D (25[OH]D)**—Baseline 25(OH)D levels are not associated with renal disease progression or cardiovascular disease (CVD) events, Vitamin D supplementation is rising markedly and is associated with significantly higher 25(OH)D levels, and CRIC data highlight pros and cons of a trial of vitamin D supplementation.

- **Acid-Base Balance**—Preliminary observational associations between acidosis and outcomes are inconsistent, and the rationale for intervening with alkalinizing agents cannot currently be substantiated using data from CRIC.

- **Uric Acid**—Preliminary observational associations between uric acid and outcomes are modified by level of eGFR for uncertain reasons, and the rationale for intervening for high uric acid levels currently is not well-substantiated using data from CRIC.

Dr. Furth presented information on the Chronic Kidney Disease in Children (CKiD) Study, conducted through a collaboration of the NIDDK, National Heart, Lung and Blood Institute (NHLBI), and Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Because kidney disease is not common in children (age 1-16 years), CKiD had numerous study sites and involved two cohorts: Cohort 1, from 2003-2008, enrolled children with a single GFR (sGFR) between 30 and 90 ml/min/1.73m$^2$; Cohort 2, scheduled to be conducted from 2008 until 2012, enrolled children with milder disease and an eGFR of from 45-90 ml/min/1.73m$^2$. Study goals include recruiting and retaining children with CKD; defining risk factors for CKD progression; and defining the effects of CKD progression on neurocognitive development and function, the prevalence of CVD risk factors, and growth failure. Retention is approximately 92%.

Results have been instructive in identifying opportunities for further study in clinical trials in each of the domains of the study. In the area of growth: one of the primary reasons for failure in growth among the cohorts is acidosis, a potential target for intervention. Additionally, modification of treatment for hyperphosphatemia and hypocalcemia may be an option. A study by Dr. Anthony Portale on the CKiD cohort found that FGF23 is inversely related to GFR level as seen in adults. Two other important comorbidities in children with CKD are anemia and hypertension. Approximately 40% of the cohort is anemic and more than 60% report hypertension or have elevated blood pressure at study visits. Each of these areas should be considered for intervention.

Kidney disease progression in the cohort indicates that substantial numbers of children progress to dialysis and transplant. In reviewing the effect of glomerular versus nonglomerular CKD as a reason for losing patients to followup, glomerular CKD is far more prevalent than nonglomerular CKD (66% to 39%). One of the most significant associations for increased progression in those with glomerular CKD is proteinuria. A potential target for future intervention is in children with

eGFR > 45 ml/min/1.73m$^2$ with glomerular CKD. Data show that the protein/creatinine ratio in these patients decreases more rapidly than in patients with nonglomerular CKD. Additionally, hypertension has been shown in CKiD to be associated with more rapid progression to ESRD. This is another potential target for intervention.

**Lessons from CKD Trials (AASK, RENALL, TREAT)**

*Robert Toto, M.D., Professor, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX*

The African-American Study of Kidney Disease and Hypertension (AASK) trial, the Trial to Reduce Cardiovascular Endpoints with Aranesp® Therapy (TREAT), and the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study were successful trials that changed practice and had important endpoints. The issue of surrogate markers was important in each trial, they included heterogeneous populations, and there were unanticipated findings that impacted the conduct of the trials. These are lessons to be considered for planning future CKD trials.

The AASK study was conducted in 1,093 hypertensive, nondiabetic African Americans with a GFR of 20-65 ml/min and a urine protein/creatinine ratio < 2.5. There were two levels of blood pressure (BP) control, usual and aggressive lowering. AASK was a randomized, double-blind trial with a 3 x 2 factorial design using ramipril versus metropolol versus amlodipine (2:2:1). Followup was planned for 3-4 years, and the primary renal outcome was the rate of decline in GFR; secondary renal outcomes were the composite of rapidly declining GFR, ESRD, or death from any cause. Conclusions from AASK were that achieved reductions in BP were protective for CV events in hypertensive nephrosclerosis, and that aggressive lowering of BP did not result in a significantly slower rate of decline of GFR or a significant difference in secondary endpoints. Most importantly, AASK reported that angiotensin-converting enzyme inhibitors (ACEi) were more effective than β-blockers or dihdropyridine calcium-channel blockers (CCBs) in slowing the decline in kidney function. A significant finding from AASK was that proteinuria was identified as a risk factor for CKD progression. There were pitfalls in AASK, including selection of the primary endpoint, the duration of followup may have been too short, and the heterogeneous population possibly included individuals with other kidney diseases.

The Heart Outcomes Prevention Evaluation (HOPE) Study was published during the AASK trial. HOPE, which was not a hypertension study, was a randomized, double-blind trial comparing ramipril and placebo in high-risk CV patients. Results showed that ramipril reduced CV events compared to placebo. At the same time, AASK preliminary data indicated that patients on amlodipine had a much greater rate of decline in GFR compared to those on ramipril. Based on data from the HOPE and AASK studies, the AASK Data Safety Monitoring Board (DSMB) discontinued the amlodipine arm of AASK.

The RENAAL trial was a multicenter, randomized, double-blind, placebo-controlled trial conducted in 1,213 hypertensive type 2 diabetes (T2D) patients with macroalbuminuria (i.e., > 300 mg/g). The intervention was losartan 50-100 mg/d versus placebo, plus or minus conventional antihypertensive therapies (excluding ACEi and angiotensin II receptor blocker

[ARB]), with a BP goal of < 140/90 mmHg. Followup was planned for 4 years with a composite endpoint of the doubling of serum creatinine (sCr), ESRD, and death from any cause. Conclusions from RENAAL were that losartan is renoprotective (retards progression and ESRD) in T2D patients with nephropathy beyond lowering BP and that losartan significantly reduces hospitalization for heart failure in T2D patients with nephropathy (secondary endpoint). Results indicate that losartan reduced the risk of renal disease progression compared to conventional hypertensive therapy. Lessons from RENAAL included an adequate study power for the primary composite outcome, the efficacy of losartan for slowing kidney disease progression, that similar BP control could be achieved compared to other BP medications, and the identification of proteinuria as a risk factor for CKD progression. Concerns raised by RENAAL included that there was a relatively small effect size between losartan and the control group, there was a high level of comorbidities, sCr was a soft endpoint, and there were no biopsies.

Analyses of RENAAL data indicate that albuminuria at baseline predicts ESRD in T2D patients with nephropathy. In addition, there was a difference in the rate of decline of GFR, with the losartan arm declining at a rate of approximately 1 ml/min/yr. Renal components of the composite endpoint also occurred with significantly lower frequency in the losartan group; compared with the placebo group, the incidence of doubling of sCr was reduced by 25%, and the risk of progression to ESRD was reduced by 28%.

The TREAT trial was a randomized, double-blind, placebo-controlled trial of 4,039 T2D patients with CKD (eGFR 20-60) and anemia (hemoglobin [Hb] < 11 g/dl). The intervention was darbepoetin alfa to achieve and maintain an Hb of 13 g/dL versus placebo, with "rescue therapy" if Hb was < 9.0 g/dL. Planned followup was event driven, with composite primary endpoints for CV (death, MI, myocardial ischemia, CHF, and stroke) and renal (death or ESRD) diseases. The conclusions from TREAT were that in patients with T2D, CKD, and anemia, a strategy to treat anemia with darbepoetin alfa did not reduce the primary composite endpoint, and higher stroke rates were documented. Successes included the achieved difference in Hb between the treatment and control arms, the importance of a placebo control in an erythropoiesis-stimulating agent (ESA) study, the unreliability of surrogates for efficacy and safety, and the confirmation of study power. Pitfalls were the criticism for using a placebo control in such a trial—which hurt recruitment, Hb control was higher than expected, and there was a heterogeneous population with no biopsy.

Results from two ESA trials, the Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) and the Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin Beta (CREATE) trial, were published in 2006, and neither showed benefits for CV or renal disease. In addition, there were safety concerns for higher Hb targeting. At the time, pressure was directed at TREAT investigators to stop the trial because of the results from CHOIR and CREATE. If TREAT had been stopped early, results would have shown that patients on darbepoetin alfa were doing better, which was not the case at the end of the trial. This is instructive for those planning and conducting clinical trials.

**Why Good Trials Go Bad**

*Tom Greene, Ph.D., Professor, Department of Epidemiology, University of Utah, Salt Lake City, UT*

Dr. Greene related that good trials that go "bad" do so when trials are designed with high power to produce a definitive result under the assumptions of the study design, but produce an ambiguous result due to unexpected failures in these assumptions. He stressed that an ambiguous result should not be confused with a well-conducted RCT with a definitive negative result. Negative results are an essential component of the evolution of medical knowledge, because they rule out ineffective therapies and control costs.

Common failures occur in assumptions made during trial design. The recruitment rate in a trial can be lower than expected because the patient pool is overestimated, secular trends in eligible patients are not accounted for, physicians are unwilling to randomize eligible patients, and patients may be unwilling to randomize. An example is the Focal Segmental Glomerulosclerosis Study (FSGS). The trial planned to randomize 500 patients over 26 months, but the investigators were only able to randomize 138 patients over a longer period. This reduced the statistical power of the trial so that a moderate but clinically significant effect may have gone undetected. Problems with FSGS recruitment included drug company delays, fewer than projected biopsies confirming FSGS, lack of willingness of physicians to deviate from their preferred therapies, and limitations in enthusiasm of some physicians for the trial interventions.

Unexpectedly poor adherence also can be a cause of trial failure. It leads to insufficient separation between treatment groups, and can lead to major reductions in the power of a study. For example, under the linear models for treatment effect, achieving one-half of the target separation increases the required N for achieving the same power approximately 4-fold. For example, in the Incremental Decrease in Clinical Endpoints Through Aggressive Lipid Lowering (IDEAL) trial, patients were randomized to investigate the benefits of early (eGFR of 10-14 ml/min) versus late (eGFR 5-7 ml/min) initiation of dialysis. The achieved separation in eGFR between treatment arms was substantially lower than this target, limiting statistical power.

Trials with lower-than-projected event rates may also provide lower power than projected. Lower-than-expected event rates have been noted in cardiology trials that have not factored in the reduction of CV events over time. Likewise, CKD trials will need to account for the reduction in events due to the widespread use of ACEi or ARB therapy.

Higher than projected attrition rates may lead both to loss of power and to increased risk of bias. High attrition rates can occur in almost any trial due to the unexpectedly high loss to follow-up. Also possible are unexpectedly high rates of competing events, such as the high rates of transplant in the IDEAL study or of death in some CKD studies.

Other common limitations in the interpretation of CKD clinical trials may arise from the loss of relevance of the study questions during the period of the trial; a heterogeneous patient population, including a sizable subgroup with a reduced hypothesized treatment effect; unexpected delay until the treatment benefit is seen; and the unexpected behavior of a longitudinal outcome if a slope-based analysis is used. Past violations in assumptions underlying

trials with slope-based outcomes have included a higher-than-expected variability in slopes between patients, a slower-than-expected mean slope, or a nonlinear mean trajectory.

A particularly vexing problem in slope-based CKD trials is the possibility of acute hemodynamic effects which lead to early changes in renal outcomes that may differ from the patients' long-term patient outcome. Such acute effects may lead to reduced power and can complicate the interpretation of the trial results. In general, time-to-event analyses requiring large changes in renal outcomes are less susceptible to these problems than slope-based analyses, but typically require a longer follow-up time. Whether we risk assuming no acute effects and linear mean declines for certain interventions, thereby justifying slope-based analyses with relatively short followup or time-to-event based on relatively small changes (e.g., 30% GFR or eGFR reduction) is an open question. In addition, the "robustness" of time-to-event to acute effects diminishes as the threshold defining the events is relaxed.

In summary, risk factors that can result in a "good trial going bad" include:

- "Wishful thinking" regarding recruitment.
- Failure to consider secular trends that may compromise the availability of patients or lead to reduced event rates.
- No prior demonstration of the feasibility of the intervention (or of the ability to achieve the targeted separation).
- "Gambling" on the behavior of the outcome (e.g., assuming an "optimistically" steep mean rate of decline or the absence of an acute effect).

### *Discussion*

Observational studies, such as those described above on vitamin D and uric acid, can be valuable for giving clues that could be studied in RCTs. A significant issue in RCTs is the heterogeneity of patient response to an intervention. An emerging approach is to identify responders and nonresponders when developing the study population. Heterogeneity can reduce the power assumed for a study. Examples are found in many past RCTs, such as the identification of fast- and slow-responders in CVD trials. In bicarbonate studies, there is an influence on protein level that should be considered in the design of a trial.

The issue of acute versus chronic effects of interventions is significant. Differential acute and chronic effects have been seen in trials investigating a low protein diet, a low blood pressure goal, as well as CCB, ACEi, and ARB therapies.

It was noted that patient consent in trials in children is acquired from the parent or guardian until the age of 18 years; at that time, the IRB requires that trial participants be re-consented. This is a particularly critical time because some children may not want to continue, although recent trials have been successful in keeping patients past the age of 18 years.

## CHALLENGES IN CLINICAL TRIAL DESIGN (I) – PLANNING STUDIES FOR CKD

**Moderator:** *Laura Dember, M.D., Associate Professor of Medicine, Renal Section, Boston University School of Medicine, Boston, MA*

**Selection of Study Populations: Prevention or Interventions to Slow Progression?**
*Julia Lewis, M.D., Professor of Medicine, Department of Nephrology, Vanderbilt University Medical Center, Nashville, TN*

Dr. Lewis discussed selection of study populations for CKD in people with diabetes. Diabetic nephropathy (DN) is one of the most common effects of CKD in this population. Evidence indicates that preventing microalbuminuria (MA) can prevent the outcome of ESRD. Evidence also shows that a significant subset of patients with DN but not proteinuria continues to progress to ESRD, though at a much lower rate.

A challenge for studying DN and MA is illustrated by the RoadMap Trial, which needed 262 centers to recruit 4,447 patients with the entry criteria: T2D, one CV factor (hypertension or obesity), and no ACEi/ARB use in the past 6 months. The primary outcome was the onset of MA. Significant drawbacks in conducting a trial with an outcome of MA include that MA is associated with factors other than diabetes; the urinary albumin excretion (UAE) rate may be influenced by exercise, water loading, fevers, sexual activity, etc.; UAE is difficult to measure, and serious concerns have been raised about laboratory measurement procedures; a large patient population with a long followup is even longer if on a background of ACEi/ARB; and there is uncertainty about whether UAE is clinically meaningful. Intervention studies on reversing MA also present significant challenges. In a trial of sulodexide for MA, the primary outcome was to return patients to normal MA (at least a 25% decrease) or a 50% decrease in ACR. The trial had a positive outcome, but the U.S. Food and Drug Administration (FDA) only approved sulodexide for MA if another trial was conducted with hard primary outcomes (ESRD or doubling of creatinine).

The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria–2 (IRMA-2) trial was conducted to investigate preventing MA from progressing to proteinuria. Advantages of proteinuria trials include less variability in laboratory results, and proteinuria is not influenced by exercise and some of the other factors that influence MA. The primary outcome in the IRMA 2 trial was proteinuria > 200μg/min and 30% higher than baseline. The FDA did not allow labeling for ARB for decreasing proteinuria but may reconsider this if a trial is conducted with a larger sample size. Trials for interventions to reverse proteinuria can have smaller sample sizes than trials of MA; crossover designs can reduce sample size further.

Trials on prevention of progression to ESRD include the Irbesartan in Diabetic Nephropathy Trial (IDNT), which accrued 1,715 T2D patients with hypertension, 900 mg/24hr proteinuria, sCr 1-3 in females and 1.2-3 in males. The primary outcomes were doubling of sCr or ESRD. This trial was accepted by the FDA because of the hard outcomes that were clinically meaningful. However, if this trial were conducted with a patient background of ACEi or ARB, the sample size would have to be increased by approximately 40%. A lesson from this trial is that eGFR is a better measurement of precise GFR at entry, but over longitudinal followup, eGFR actually is reflected by a change in sCr because race and gender do not change. Time-to-event

analysis is a better measure in these types of trials than average change or change in slope in GFR.

Using data from the IDNT trial, an investigation was conducted of the impact of increasing sCr in the first year of the trial to identify progression to doubling of sCr or ESRD. Data indicated that the best predictor of progression was the change in sCr from baseline to the end of the first year. It was possible to identify those who were fast progressors, and this could serve as a better surrogate outcome than proteinuria. It was suggested that a measure other than the doubling of sCr may allow trials to be completed more quickly.

***Discussion***

Change in sCr may be the same as change in GFR over time. GFR has become the standard in clinical trials, but it may be a better choice if an exact measure of renal function at baseline and followup is desired.

**Renal Outcomes for Phase III Trials**

*Lawrence Appel, M.D., M.P.H., Professor, Department of Medicine, Johns Hopkins Medical Institutions, Baltimore, MD*

AASK began in 1994 and compared three hypertensive medications (CCB, ACEi, and beta-blockers) and two levels of BP control (lower vs usual) in African-Americans with hypertensive kidney disease. The rate of decline (slope) of iothalamate GFR in ml/min/1.73m$^2$/year was the primary outcome. Subsequent analyses documented that iothalamate-based and sCr-based outcomes were not substantially different, both for slope-based analyses and time-to-event analyses. An important finding from AASK is that there was a significant reduction in proteinuria among participants in the arm with a lower BP goal compared to those in the arm with the usual BP goal, although the change in GFR was similar in both groups at 48 months.

Because it was expected that acute effects would be seen at the beginning of the treatment phase of the trial, mean GFR decline was evaluated separately in the first 3 months (acute phase) and after 3 months (chronic phase). Results indicated that the acute effects were much greater than those expected when the trial was planned. For example, it was hypothesized that the acute phase of the trial would see no increase in GFR in the CCB versus beta blocker arm; the actual effect was +4.2 ml/min.

AASK also documented the benefit of long-term follow-up in CKD trials. During the trial phase of AASK, there was no significant difference between the usual goal arm and the lower goal arm. However, during extended follow-up, the lower BP goal arm was significantly better than the usual goal arm among patients with proteinuria. This suggests that long-term followup is critical for understanding the effects of interventions in patients with CKD.

Clinical outcomes in AASK showed that of those who doubled sCr, 82% progressed to ESRD, and 9% died. Another instructive lesson was that CKD progression often is nonlinear. Unpublished results show that some have a period of stable or increasing eGFR (58%), some

have a period of fast decline (32%), some have a period of stable or increasing eGFR followed by a fast decline (5%), and some have a fast decline followed by a period of stable or increasing eGFR (3%).

Data from CRIC present an interesting store of information that could be used in designing future clinical trials. Risk factor relationships were insensitive to changes in eGFR definitions, regardless of whether halving, doubling, or another construct was used. Death was included in this analysis.

As for the future, a better understanding of kidney injury is needed, and biomarkers, other than creatinine, could be useful. For example, the kidney injury molecule-1 (KIM-1), a transmembrane tubular protein undetectable in individuals with normal kidneys, has a high expression in proximal tubule cells after ischemic or toxic kidney injury. Another suggestion is to avoid binary outcomes in study design so that of all the data can be used.

The following points summarize the presentation:

- No advantage to direct measurement of GFR.
- Proteinuria can be misleading.
- Long duration of follow-up is highly desirable.
- Slope-based analyses are problematic because acute changes in GFR have huge effects, cannot be predicted, and are difficult to interpret.
- Need to explore utility of biomarkers that reflect kidney injury.
- Opportunities for improved analysis.
- sCr-based composite outcomes remain the standard in Phase III trials.

***Discussion***

The issue of using death as an outcome is problematic in clinical trials because of the need for a safety outcome and the uncertainty of whether a death is due to the intervention. This was borne out in the AASK study, in which CVD death was not an appropriate outcome. In ESRD trials, however, investigators would want to know who died before dialysis from ESRD. Studying progression of CKD has a goal of slowing progression and improving the lives of individuals. If the lack of intervention increases mortality, this influences the results of the trial.

**Biomarkers for CKD Progression or Risk of Progression**

*Patrick Murray, M.D., Professor, Department of Medicine, University College Dublin, Catherine McAuley Centre, Dublin, Ireland*

An ongoing initiative in Europe and at the FDA was designed to evaluate the potential of cystatin C as a biomarker of acute kidney injury (AKI) related to tubular and glomerular injury due to drug interactions. Cystatin C is a better indicator of AKI than sCr for early or pre-diagnosis. Not only is cystatin C a GFR marker, but in the glomerular filtrate, it is reabsorbed in the proximal tubule and is a marker of injury there. The need to develop an approved laboratory reference

standard and clinical method for measuring cystatin C is delaying cystatin C approval; this should be resolved in the near future.

Biomarkers of progression or risk of progression must be correlated with clinical measurements that already are included as part of the assessment of CKD. For progression, an acute drop in GFR is understood to be a reasonable indicator of long-term benefit. This is seen with ACEi and ARB treatment and can be a biomarker to show which patients likely will maintain lower GFR over time. Albuminuria also is a reasonable biomarker for progression. The choice of biomarker is not critical as long as the results are reproducible.

A vast array of biomarkers is being investigated for CKD progression in the functional areas of inflammation, oxidative stress, metabolic dysfunction, endothelial dysfunction, and fibrosis, which also may be associated with CVD. None is entirely validated and ready for clinical use, mainly due to their lack of use in large clinical studies, although a few such as FGF23 may be close to this point. Examples of biomarkers that have performed well to predict progression to CKD in the Mild to Moderate Kidney Disease (MMKD) Study for GFR measured by iohexol, are asymmetric dimethylarginine (ADMA), FGF23, and apolipoprotein A-IV (apoA-IV), the naturiuretic peptides ANP, NT-proBNP, and adrenomedullin. Overall, the biomarkers with the best predictive value for CKD progression remain FGF23 and parathyroid hormone (PTH). Accumulating evidence shows that ADMA also may be a useful biomarker for progression, as well as an indicator of CVD. Biomarkers for AKI should be of interest as potential biomarkers for progression because they are associated with endothelial injury and injury to tubules. In addition, AKI is one of the contributors to CKD and high mortality. Promising AKI biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), and KIM-1, but data to date have not been conclusive.

In summary, some of the novel biomarkers can complement standard clinical tools to provide supplemental assessments of CKD progression and risk of progression. These biomarkers can be studied in clinical trials in all phases. They also may provide pathophysiologic insights and identify potential drug targets, but none of the emerging biomarkers of CKD progression is sufficiently validated to justify use as an initial enrollment or stratification criteria in CKD clinical trials.

**Effect Size and Sample Size Calculations**

*Dr. Glenn Chertow M.D., Professor of Medicine, Department of Medicine/ Nephrology, Stanford University School of Medicine, Palo Alto, CA*

A practical rule for determining effect size for a clinical trial should be based on clinical experience, integration of available data from pilot clinical trials, observational studies, other reports, and then reduced by one-half. No intervention has an 80 or 90% treatment benefit; when in doubt, choose 15 or 20%. In trial design, there must recognition of the feasibility of the study and whether it is possible to conduct a large- or small-scale trial, the possibility of recruitment challenges, and the level of financial resources that are available. Important intermediate or surrogate outcomes (non-event driven) should be identified. An example of a trial in which resources and time are modest and outcomes have been identified with access to a large study

population is a trial using a continuous measure, such as change in creatinine, albuminuria, or BP. Advantages of such a design are that all study subjects contribute to the outcome of interest, it is relatively inexpensive, it may be suitable for a relatively short-term study (e.g., 26 or 52 weeks), and it can be used to generate hypotheses and enthusiasm for studies of events. Power for such a trial could be increased by a low coefficient of variation, high precision, low variability, or normal or near normal distribution. Mean or median changes may dilute the effects at the extremes; therefore, consideration should be given to increasing/decreasing the fraction of patients by a certain percentage from baseline. A recent example of a trial that examined a continuous measure was the Bardoxolone Methyl in Patients With Chronic Kidney Disease and Type 2 Diabetes (BEAM) trial. Hazards of looking at continuous measures include confounding measures and competing risks (such as CVD in CKD trials). It may be practical to consider a hybrid rank-based method to account for unexpected events. For example, unexpected events were seen in the Frequent Hemodialysis Network (FHN) trials, such as "death-adjusted" change in left ventricular mass. This approach may be considered for CKD trials.

Power in a clinical trial is dependent on effect size and the event rate. For example, calculations based on an event size of 10% would require approximately 3,200 trial participants for 90% power; for an event size of 50%, only approximately 130 trial participants would be needed for 90% power. The same relative differences apply to event rates. This critical determination for a clinical trial must be made during the design phase. In addition, the potential impacts of unknown situations, such as a high drop-out or drop-in rates during the trial or the impact of interim analyses, must be built into the power calculations. These situations can adversely impact the meaningful results of a trial. A further important consideration is the effect on patients of participating in the trial.

Using composite outcomes is a strategy for reducing sample size by increasing event rates. Composite outcomes are defined as having occurred if any one of several components is observed, such as CKD death, dialysis, transplantation, or doubling of sCr. Each component should be clinically relevant, ascertainable without bias, sensitive to intervention, and made up of fatal and nonfatal events. Problems with composite outlines must be recognized, such as those in the Women's Health Initiative (WHI), which saw outcomes diverge in directions that were different than expected. Factorial designs also require serious consideration in determining sample size, such as whether to include two or three arms of a study. Major trials by the NIDDK (Modification of Diet in Renal Disease Study [MDRD], National Cooperative Dialysis Study [NCDS], and Hemodialysis [HEMO] Study) had 2 x 2 factorial designs, which depended on independence of the interventions.

The following points summarize the important considerations for designing clinical trials:

- A therapeutic intervention with a p-value $< 0.05$ does not necessarily imply adequate power.
- False-positive trials can wreak havoc on clinical practice.
- Be wary of post-hoc power calculations and unusually large effect estimates.
- Underpowered trials perpetuate ongoing bad practice or start new bad practice.

**Adaptive Designs to Increase Efficiency for Phase II/III Trials**

*Michael Rosenblum, Ph.D., Assistant Professor, Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

The FDA has been encouraging methodological research on the properties of adaptive designs since the publication of its Critical Path Opportunities List. Potential benefits of adaptive design include reducing the cost, duration, and number of participants in trials and giving more power to confirm effective drugs and determine which subpopulations will benefit the most. Care, however, must be taken to guarantee the correct probability of false-positive results (e.g., 0.05), minimize bias, and ensure that results are interpretable. There is no guarantee that an adaptive design will improve power--in fact it may hurt power; therefore one's design must be carefully chosen.

Examples of adaptive designs are changing the sample size, changing the probabilities of assignment to different arms of the trial, and changing the proportions of different subpopulations enrolled. If surrogates are used, they must be strong surrogates. Well-understood adaptations include adaptations to maintain study power based on blinded interim analyses of aggregate data; and group sequential methods. Less-well-understood adaptations include dose selection, response-adaptive randomization, sample size adaptation on interim-effect size estimates, enriching a subpopulation based on interim treatment-effect estimates, and endpoint selection.

It is possible to use a nonadaptive method in clinical trials by fitting a pre-specified, generalized linear model for the outcome given treatment and pre-randomization predictive variables (e.g., age, sex, race, and baseline CKD). The effect estimate should be based on the g-computation formula (not based on reading off model coefficients). This provides consistent estimates, and is robust to model misspecification, and can lead to a gain in power if the model is close to correct. See the article of Rosenblum and van der Lann, 2010, in the International Journal of Biostatistics. Modifications can be made to guarantee (asymptotically) results that are as good as or better than the standard unadjusted estimator.

**SPRINT: High-Risk CKD Subgroup Within a Larger Clinical Trial**

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The Systolic Blood Pressure Intervention Trial (SPRINT) is a multicenter, two-arm RCT co-sponsored by NIDDK, NHLBI, the National Institute on Aging (NIA), and the National Institute of Neurological Disorders and Stroke (NINDS). It plans to accrue 9,250 participants age $\geq$ 50 yrs with systolic blood pressure (SBP) $\geq$ 130 mmHg. The intervention will target SBP to either <140 mm Hg or <120 mm Hg. The follow-up period will be 4 to 6 years. The primary objective of SPRINT is to determine whether randomization to a more intensive SBP-lowering strategy is more effective than a current standard strategy in reducing the incidence of cardiovascular (CV) events, which constitute the primary outcome of SPRINT. The study also plans to include a subgroup of approximately 4,300 individuals with chronic kidney disease (CKD), based on the strong association between CKD and CV risks. This planned CKD subgroup will be further divided into two subgroups, one half with eGFRs of 45-59 ml/min/1.73m$^2$ (stage 3A) and the

other half with eGFRs of 20-44 ml/min/1.73m$^2$ (stage 3B/4A). The rationales for the inclusion of this range of eGFR are that stage 3 CKD is common, and higher stages of CKD are associated with higher CV event rates. On the other hand, including a CKD subgroup makes effect modification of the intervention more likely, and the patients with higher stage of CKD at baseline may be already too close to ESRD and chronic dialysis.

Significant proteinuria (> 1 g/d) is an exclusion criterion in SPRINT, based on the existing literature suggesting that lower SBP is associated with better renal outcomes than higher SBP in those patients. The main renal outcome measure in SPRINT is a composite of ESRD development and a 50% decline in eGFR; this measure applies specifically to the CKD subgroup. For non-CKD participants, renal outcome measures include the progression to CKD, defined as ESRD development or a 30-% decline in eGFR to values < 60 ml/min/1.73m$^2$. For the entire SPRINT cohort, incident proteinuria, defined as doubling of urinary albumin-to-creatinine from < 10 mg/g to > 10 mg/g, will be included as an additional renal outcome. It should be noted that SPRINT is not specifically powered for these renal outcomes.

***Discussion***

A potential problem of randomizing CKD patients to the SBP goal <140 mm Hg is that, if ACEI or ARB must be added for reno-protection during the follow-up period, these agent will lower the SBP further and the adherence to the standard SBP goal may not be possible. This concern is largely circumvented by the stipulation that a potential SPRINT participant must already be on the appropriate medications with blood pressure-lowering properties if there are other medical conditions for which these agents are indicated (such as ACEI/ARB for CKD or beta-blockers for coronary artery disease), before the blood pressure eligibility of that individual can be assessed at screening.

## THERAPIES IN PHASE II/PILOT STUDIES

**Moderator:** *Dr. Michael F. Flessner MD, PhD, Director of Inflammatory Renal Disease, KUH, NIDDK, NIH*

### Allopurinol

*Alessandro Doria, M.D., Ph.D., M.P.H., Principal Investigator, Sections on Genetics and Epidemiology, Joslin Diabetes Center, Boston, MA*

The number of individuals with CKD is increasing, in spite of interventions to control BP and other risk factors for renal disease. A consortium of research centers—Preventing Early Renal Function Loss (PERL) in Diabetes—was formed with the goal of finding early interventions for CKD. Prospective studies show that uric acid levels predict CKD in individuals with diabetes, with increased levels being associated with an increased risk of albuminuria and GFR loss over time. Mechanisms of kidney damage associated with increased uric acid levels include alteration of nitric oxide production, induction of pro-inflammatory cytokines, changes in intrarenal hemodynamics due to *RAS* activation, and increased oxidative stress due to xanthine oxidase hyperactivity.

Allopurinol is a xanthine oxidase inhibitor that has been on the market since 1964, has an excellent safety profile, and is effective in reducing uric acid levels. Evidence from two small clinical studies (Hong Kong and Spain) indicates that treatment with allopurinol can stop GFR loss in individuals with advanced kidney disease. Based on these findings, a double-blind, placebo-controlled, parallel group RCT is being designed in type 1 diabetes (T1D) patients with a GFR > 60 ml/min, with microalbuminuria or moderate macroalbuminuria (< 1.5g/24 hr), and serum uric acid levels ≥ 5 mg/dl. The 4-year trial will test oral allopurinol (variable dosage 100-600 mg/d), with a target serum uric acid level of 2.5-4.5 mg/dl. The primary outcome is change in GFR (clearance-based) from baseline; the secondary outcome is change in UAE rate. Questions that still need to be addressed are the advantages of a variable versus fixed dosage, and whether attention should be paid at avoiding extreme reductions in serum uric acid levels, given the inverse relationship between uric acid levels and the risk of Parkinson's disease.

**Antioxidants**

*Jonathan Himmelfarb, M.D., Kidney Research Institute Director, Professor of Medicine, Department of Medicine, Kidney Research Institute, University of Washington, Seattle, WA*

Oxidative stress is caused by an imbalance between pro-oxidants and antioxidants when the balance shifts to the pro-oxidant side of the equation. This imbalance causes tissue damage and contributes to complications in CKD. Although most data from CKD studies show that inflammation and concomitant leukocyte activation are a major etiology of increased oxidative stress in CKD, there is increasing evidence that mitochondrial dysfunction with leak of reactive oxygen intermediates is also a contributor to increased oxidative stress in CKD. In recent years, there has been some indication that there are vascular oxidative stress pathways, often triggered by stimuli such as angiotensin 2, which when activated contribute to vascular complications. These pathways may be very important in progressive loss of kidney function in CKD. Studies on plasma biomarkers of oxidative stress in CKD indicate that protein carbonyls increase and protein thiols decrease during CKD progression. Although there is heterogeneity among CKD patients, almost all studies demonstrate evidence of increased systemic oxidative stress. Many biomarkers are being investigated in CKD and ESRD. Antioxidant therapy is meant to reduce oxidative stress. The types of antioxidants being investigated include free-radical scavengers, scavengers of non-radical oxidants, compounds that inhibit the generation of oxidants, and compounds that induce the production of antioxidants. Issues for consideration in designing an antioxidant trial include the following:

- Mechanisms of antioxidant action—scavengers or cell-signaling regulators.
- Kinetics and concentrations of antioxidants and the relation to bioavailability.
- Will the antioxidant get to the right place?
- Specificity for scavenging target reactive oxygen and nitrogen species.
- Potential interactions with co-antioxidants.
- Will the antioxidant also have pro-oxidant activity in vivo?

Published literature from clinicaltrials.gov shows that more than 6,000 clinical trials have/are investigating kidney disease, with approximately 1,800 focused on CKD, and only 69 on CKD and antioxidants.

Pharmacokinetic studies of vitamin E (α-tocopherol) and N-acetyl cysteine (NAC) found altered pharmacokinetics and their metabolites to be active in CKD. A dose-estimation study to investigate coenzyme Q-10 was conducted to measure the levels of F2 isoprostanes, a marker of oxidative stress that showed that coenzyme Q-10 administration reduced oxidative stress. A randomized controlled trial of healthy lifestyle interventions in CKD patients is being conducted with NIH funding to investigate aerobic exercise versus usual exercise and caloric restriction versus usual caloric intake in a 2 x 2 factorial design. Study measures include oxidative stress biomarkers and a number of lifestyle-related factors.

Results from numerous observational studies (biomarkers) plus pilot trials in ESRD have created a plausible rationale for conducting an antioxidant trial. Questions remain on the right antioxidant agent or cocktail of active agents for the target redox reaction. Careful attention should be given to pharmacokinetics and pharmacodynamics, even if a nutriceutical is considered Generally Regarded as Safe (GRAS) by the FDA. Much more data currently are available from the dialysis population than for less severe CKD, and possible endpoints for a trial include progression of kidney disease, cardiovascular and/or infectious events, and anemia management.

***Discussion***

There is no single biomarker universally applicable for measuring oxidative stress in CKD, and similarly numerous antioxidants are currently under study. The choice depends on the hypotheses and goals of the study. In addition, many oxidative stress biomarker assays present complex sample handling issues.

**Bicarbonate**

*Michal Melamed, M.D., Assistant Professor, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY*

The Cochrane Collaboration (2007) made it clear that the evidence for correcting acidosis is very small. Possible benefits of alkali therapy in CKD are to slow the progression of the disease, preserve muscle and/or bone, and improve insulin sensitivity. Evidence from basic science research, particularly some animal models, suggests that kidney function improves when alkali increases.

Observational studies and RCTs also have shown the positive effect of alkali in CKD. A study of 5,000 patients in the Bronx, NY, found that patients with lower bicarbonate levels were at greater risk for progression of CKD; approximately 50% of these patients had lower eGFR. Similar findings have been seen in other cohorts: higher serum bicarbonate levels within the normal range are associated with better survival and renal outcomes in African Americans, long-term outcomes in CKD, mortality in patients with nondialysis-dependent CKD, and predialysis

risk of mortality and hospitalization in the Dialysis Outcomes and Practice Patterns Study (DOPPS).

A small RCT of 129 patients in England found a separation in bicarbonate levels. ESRD incidence was reduced in patients who had bicarbonate therapy, and improvements also were seen in serum albumin and protein intake levels. Another RCT of 120 patients with baseline EGFR 60-90 ml/min/1.73m2 found that cystatin C, creatinine and urine albumin levels were lower after 5 years of randomization to alkali therapy. There was no difference in blood pressure and higher potassium excretion in the alkali group. A non-randomized trial of 59 patients who had Stage III or IV CKD showed better secondary outcomes (lower endothelin-1, TGF-beta urinary levels) in the alkali group.

A dose-ranging study of sodium bicarbonate supplements in preparation for a clinical trial found that GFR levels increased linearly with increasing dose of serum bicarbonate. Regarding toxicity, sodium bicarbonate supplements had no notable effect on weight or BP, although there was a risk of hypokalemia, which is not particularly adverse in CKD patients.

In summary, some studies, including animal models, observational data, and small RCTs, provide evidence that bicarbonate therapy offers renal protection. The safety profile is acceptable. Adverse effects potentially exist regarding BP, volume overload, and hypokalemia.

***Discussion***

Long-term patient compliance presents a challenge because of the bad taste of the agent. Unfortunately, sodium bicarbonate is not available in a more palatable form. This is particularly difficult in treating some pediatric patients for whom bicarbonate materials must be given nearly every 6 hours to maintain adequate alkali levels. In one RCT that stipulated a low daily dose, approximately 10% of patients could not tolerate the dose. Sodium citrate is exceptionally foul tasting.

Possible adverse effects are related to the deposition of calcium phosphate. Although vascular calcification is a theoretical risk, data are not available to confirm this. The hope is that improving the health of the bone would result in calcium entering the bone and not the vascular system.

**Non-Pharmacologic Therapies: Glucose Control, Weight Loss, and Sodium Restriction**
*William Mitch, M.D., Director, Nephrology, Department of Medicine, Baylor College of Medicine, Houston, TX*

Dietary factors must be considered when designing therapies for patients with CKD. This requirement is necessary because metabolic and physiologic responses to dietary factors can influence the outcome, leading to faulty interpretations of results from a clinical trial. For example, hyperuricemia is associated with hypertension, kidney damage and gout, and the risk of hyperuricemia rises sharply when the amounts of meat/fish in the diet are increased. Since lowering uric acid levels reportedly blocks the development of hypertension in children and may even slow the loss of kidney function in patients with CKD, changes in the diet should be

documented and evaluated during clinical trials to improve the outcome of patients with CKD. Other uremic toxins such as indoxyl sulfate can change metabolism in patients with CKD. Indoxyl sulfate accumulates when the diet contains high protein content so changes in the diet could raise or lower indoxyl sulfate and obscure responses to the therapeutic intervention. There are other physiologic responses related to changes in the diet that affect the measurement of GFR. In the MDRD trial, those assigned to low protein diets experienced a decrease in GFR initially and it was concluded that this represented a hemodynamic response rather than evidence of kidney damage. In other investigations it was found that an excess of dietary protein raises the GFR at least temporarily. Thus, there are physiologic responses to changes in the diet that can interfere with the interpretation of how drugs or other strategies influence the progression of CKD. Finally, the diet can influence the progression of renal insufficiency. In those patients participating in the MDRD who also adhered to dietary protein restriction for 1 year, the rate of loss of their GFR was significantly slowed.

Changes in protein intake affect other responses that are characteristic of CKD. A high protein diet increases phosphate accumulation but decreases serum bicarbonate levels. Both responses have been implicated as mediators of progressive loss of kidney function. Besides influences on the kidney, excess phosphate intake causes bone disease. The presence of metabolic acidosis causes loss of muscle mass in normal children and adults as well as patients with CKD. Besides the disabilities associated with loss of muscle mass, there could be a change creatinine metabolism. Clinical investigations of children, normal adults and patients with CKD including dialysis treatment have demonstrated that correcting metabolic acidosis will improve protein stores and other markers of nutritional safety. Not surprisingly, results from the MDRD trial indicate that after one year, hyperphosphatemia and metabolic acidosis are both suppressed in patients who reduced their dietary protein over a year of observation. In summary, ignoring the influence of changes in the diet could interfere with the interpretation of results obtained during a clinical trial.

Other dietary factors that can influence the outcome of clinical trials are salt intake and the degree of diabetes control. A high salt diet is associated with aggravation of hypertension and since hypertension can affect the function of many organs, dietary salt must be considered in designing trials to improve the health of CKD patients. Dietary salt must also be considered in trials directed at slowing the loss of kidney function in patients with CKD. For example, the degree of hypertension in diabetic patients participating in the RENAAL Study was initially difficult to control. However, their regimen did not concentrate on restricting salt intake and when control was emphasized, patients in the RENAAL Study achieved improvements in the degree of hypertension. Strict blood glucose control has also been shown to be beneficial: in the Diabetes Control and Complications Trial (DCCT) of patients with type I diabetes as well as participants in the UK Prospective Diabetes Study (UKPDS) of patients with type 2 diabetes, tight glucose control was associated with improved outcomes and a reduction in the risks of developing complications of CKD.

***Discussion***

Fortunately, the amount of protein and salt in the diet can be effectively estimated from 24 h collections of urine. First, the intake of dietary protein can be calculated from the steady-state excretion of urea nitrogen. Specifically, dietary protein is calculated by adding the 24 h urine

urea nitrogen excreted plus 0.31 g nitrogen/kg/day (the amount of non-urea nitrogen excreted per day). When this sum is multiplied by 6.25, the nitrogen is converted to the daily amount of protein in the diet. This calculation can identify when the dietary protein has been changed. Secondly, the 24 hour excretion of sodium is the best estimate of dietary salt. Not only can changes in dietary salt be documented but it can be compared to changes in blood pressure. In trials of diabetic patients, blood glucose or hemoglobin A1c should be measured; the latter is the more accurate estimate of glucose control.

In summary, testing strategies aimed at reducing the progression of CKD should include a monitoring of dietary factors. Ignoring dietary factors will complicate interpretation of the results and importantly, if the diet does change, the diet can be adjusted to limit its influence on the outcome. Obviously, knowledge of the diet and changes in it is especially important when multi-therapy strategies based on both lifestyle and pharmacologic interventions are being designed.

When analyzing the impact of various types of protein in the diet, a critical factor to be considered is the absorption of different types of protein. Animal proteins are more completely absorbed than are plant proteins. If patients ingest equal amounts of plant or animal protein there could be different metabolic or functional responses based on how much of the protein is absorbed rather than the amount of plant or animal protein. There are reports concluding that dietary soy protein is less harmful to the kidney compared to non-soy proteins. However, this conclusion is complicated because of differences in absorption of the various proteins. There also is the complication of determining if hormonal factors (i.e., phytoestrogens) present in soy protein products influence metabolism or kidney function.

***Pentoxifylline***

Robert Perkins, M.D., Clinical Investigator and Nephrologist, Center for Health Research, Geisinger Medical Center, Danville, PA

Pentoxyfylline (PTX) has been marketed in the United States and Europe since 1972 and is indicated for the treatment of claudication associated with PAD. PTX is an orally active phosphodiesterase inhibitor and has dose-dependent hemorheologic effects, reducing blood viscosity and increasing tissue oxygen levels. It also has renal anti-inflammatory and antifibrotic activity, which are of particular interest for CKD treatment. PTX treatment has been shown to inhibit collagen expression in rat kidney fibroblasts and inhibit α-smooth muscle actin expression in rat kidney tubular epithelial cells.

PTX, having been marketed for four decades, has extensive safety and tolerance data available. In rare cases, hypotension, cholecystitis, and leucopenia have been associated with the drug; however no causal relationships have been established. In Phase II clinical trials, the most common PTX side effects were angina (0.3%), belching (0.6%), nausea (2.2%), and vomiting (1.2%).

To date, 19 clinical trials have used PTX to treat diabetic and/or nondiabetic kidney disease. In about one-half of the studies, the patients also were treated with ACEi or ARB. All of the PTX CKD studies completed to date were small, had short follow-up times, and examined surrogate outcomes (proteinuria, slope of eGFR, and/or markers of inflammation). A review and meta-analysis of 10 PTX studies with a total of 476 patients with diabetic kidney disease, using proteinuria levels as the primary outcome, was published in 2008. This meta-analysis showed a statistically significant reduction in proteinuria with PTX treatment. Three trials performed since this meta-analysis indicate improvements in the rate of decline of kidney function, as measured by eGFR, with PTX treatment.

In summary, PTX is an inexpensive, well-tolerated drug with an excellent safety profile. It is active against a novel therapeutic target and would complement current standard care for CKD. It has broad therapeutic potential in diabetic and nondiabetic as well as early- and late-stage CKD. In addition, there are promising clinical trial results using surrogate outcomes.

**Pirfenidone**

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Pathological features in diabetic nephropathy include changes in large glomeruli and podocytes, increasing proteinuria, matrix expansion, and decreases in GFR. These are areas that science can address to positively impact diabetic- and obesity-related kidney disease. Various pathways are involved in the process of diminishing kidney function. The anti-inflammatory and antifibrotic agent pirfenidone has shown promise in this area in both animal and human studies. Db/db mice, administered pirfenidone for 4 weeks after onset of expansion of the mesangial matrix, had a significant reduction in expansion and had reduced expression of type-I collagen, type-IV collagen, and fibronectin. A proteomic analysis of gene expression in the db/db mice indicated that 21 genes related to mRNA translation were the key pathway regulated by pirfenidone. Further studies showed that pirfenidone dephosphorylated the elongation factor eIF4E, which may be the major mechanism for its benefit. It remains to be seen if this can be replicated in human studies.

Recent clinical studies in people include an open label study in patients with refractory FSGS; pirfenidone slowed the rate of CKD progression by 25%. In a Phase III trial in Japan, it was reported that pirfenidone benefited patients with idiopathic pulmonary fibrosis (IPF), and the drug was approved for IPF in Japan. One of two Phase III trials in the United States and Europe reported significant improvement in pulmonary function; pirfenidone is approved in Europe (2011) for IPF but was not approved by the FDA in 2010.

A randomized, double-blind, placebo-controlled exploratory trial to evaluate pirfenidone versus placebo was conducted in 77 patients with T1D and T2D with impaired eGFR < 80 ml/min on existing ACEi or ARB therapy or ACEi and ARB therapy. Participants were randomized to 1,200 mg/d or 2,400 mg/d pirfenidone, or to placebo, and must have had a history of overt proteinuria; the primary endpoint was a change in eGFR from baseline to 12 months during the

study. Of the patients who completed the study, none were significantly different at baseline. Reports of results indicate that patients randomized to 1,200 mg/d pirfenidone had improved eGFR at 12 months and no change in proteinuria or urine TGFβ levels. Biomarkers were measured but although they were correlated with eGFR, none of them predicted the outcome of eGFR during the study. A correlation of interest was that a higher albumin level at baseline correlated with better outcomes in those taking pirfenidone.

Further studies, both animal and human, are needed to identify new biomarkers of outcome. Studies on urinary exosome and metabolomics could identify patients who can benefit from pirfenidone. Of interest, a Phase II study with pirfenidone at 1,200 mg/d should be considered, with measurements of absolute GFR at baseline and yearly. Such a study could include both blood and urine biomarkers, with tissue biopsy and urine exosome analysis.

***Discussion***

Ethics always are an issue when conducting a study that requires biopsy, although biopsies are completed in many kidney trials, such as AASK and IDNT.

The fact that 1,200 mg/d was beneficial and 2,400 mg/d was not is confounding. It could be that there were increased side effects (e.g., gastrointestinal) in the higher-dose group, but the data show that it was not as beneficial. It may or may not have been a biphasic response.

**Mineralocorticoid Receptor Blockers**

*Robert Toto, M.D., Professor, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX*

Mineralocorticoid receptor blockade (MRB) has been shown in clinical trials of CVD to improve outcomes, including death, in heart failure. In CKD trials, MRBs have been shown to improve surrogate outcomes in CKD (lowering BP and proteinuria) but can cause hyperkalemia. No long-term outcome trials have been conducted in the CKD population. For many years, the hormone aldosterone has been the focus of mineralocortocoid study; the resulting findings are positive for BP and sodium/potassium balance, but deleterious effects on the kidney, heart, and vasculature that can cause an increase in stroke, heart failure, and renal failure have been observed. Aldosterone also has been shown in animal models to overcome the proteinuria-lowering effects of ARB treatment; the same results occur for glomerular sclerosis in a model of chronic renal failure.

To date there have been no CV-outcome studies using MRBs in patients with CKD or in studies of kidney disease progression using MRBs in patients with CKD. The MRB spironolactone has been shown in multiple small RCTs (parallel and cross-over) and non-RCTs in patients on ACEi or ARB therapy to reduce proteinuria from 20 to 50%.

An NIDDK-sponsored study was conducted to determine whether the ARB losartan or spironolactone provided better renal protection than an ACEi-based regimen alone in patients with CKD. This placebo-controlled, double-blind RCT found UAE suppression, the primary study outcome, by the either losartan or spironolactone, but no significant differences in 24-hour

BP among placebo or the treatments. Spironolactone performed better than losartan regarding UAE suppression, although potassium was higher than in the losartan or placebo group. This indicates that there should be concern about hyperkalemia if a trial of spironolactone is considered. This also was a concern in findings from the Randomized Aldactone Evaluation Study (RALES).

***Discussion***

In the NIDDK-sponsored study, plasma aldosterone was measured and, as expected, was found to be higher in the spironolactone group; however, it was not measured during the period when potassium levels were high. Other measures were taken to try to explain the hyperkalemia, but nothing definitively explained the rise in potassium; it may be dietary, a factor that was not controlled for in the trial.

Concerns about the dose of spironolactone included the short half-life of the drug, but the 25-mg dose was what had been used in primary outcomes trials. It may be possible to use a lower dose or a divided dose.

The trial was designed to have BP as an independent variable, and it appears that strategy was successful because the results showed no discernable differences in BP among the treatment groups or placebo group. Many of the patients were taking other antihypertensive drugs in addition to the study drugs.

**Vitamin D/Phosphate Binding/Dietary Intervention**
*Geoffrey Block, M.D., Director of Clinical Research, Denver Nephrology, Denver, CO*

Over the past decade, mineral metabolism studies have accrued indicating the need for a CKD-Metabolic Bone Disease (MBD) intervention trial. An original study igniting interest in mineral metabolism observed the relationship between serum phosphorus and calcium levels and the relative risk of death in patients on hemodialysis. Both DaVita, Inc., and Fresenius Medical Care Holdings, Inc., found a startling consistency with patients having the lowest serum phosphorus levels achieving the best outcomes, whereas patients with the highest serum phosphorus levels were at higher risk of death. Coincident with that finding, Giachelli et al. reported that phosphorus, at levels regularly observed in ESRD patients, induced vascular calcification. Observational studies following these seminal works found a survival benefit of roughly 20% in dialysis patients receiving active vitamin D.

Mineral metabolism and vitamin D both are related to hard clinical outcomes, and FGF-23 links phosphorus and vitamin D disorders. FGF-23 elevation, independent of phosphorus, is likely to exert a biological effect yielding collateral damage (e.g., left ventricular hypertrophy). An analysis of data on patients from the CRIC study found that as CKD progresses, FGF-23 levels increase. In patients with a GFR of < 50 ml/min./1.73 $m^2$, 75-90% had high FGF-23. In early CKD progression, FGF-23 levels rise, likely explaining calcitriol (1,25-dihydroxycholecalciferol [$1,25(OH)_2D$]) reduction. Indeed, starting in patients with a GFR of 43 ml/min./1.73 $m^2$ and 3.7 mg/dL phosphorus, those in the highest quartile of FGF-23 had a four-fold increased mortality risk; FGF-23 was a better predictor of outcome than either eGFR albuminuria. This was not seen

in PTH or fractional excretion of phosphorus (FEP), suggesting direct FGF-23 toxicity. Furthermore, at any eGFR > 30 ml/min/1.73m$^2$, FGF-23 was a strong independent predictor of progressive loss of kidney function.

Observationally, patients with high levels of phosphorus are at higher risk for death. Intervention is currently advised to begin when patients have phosphorus levels at 4.6 mg/dL; however most nephrologists do not begin intervention until mean values of 5.2 mg/dL. Data from the very large ARIC study suggest that these values are much higher than the suitable phosphorus level that this study implies (~ 3.5-4.0 mg/dL) with regard to stroke and all-cause mortality. In terms of public health, at a GFR of 30-44 ml/min./1.73 m$^2$, there is a marked and unexplained increase in cardiovascular events and death. A reasonable explanation is a risk relationship between P and FGF-23, linked by calcitriol metabolism.

Dr. Block recently conducted a phosphate normalization trial (PNT) pilot study, from which data are not yet available, to examine if active phosphate-binder treatments lower serum phosphorus over a 9-month period. The randomized trial enrolled patients with a 20-45 GFR range and serum phosphorus > 3.5 and ≤ 6.0 mg/dL. Using titrated doses, a change in serum phosphorus from baseline was the primary endpoint; secondary endpoints assessed were PTH, FGF-23, calcitriol, urine phosphorus, bone density, vascular imaging, and pulse wave velocity.

Animal studies and observational data are clear and convincing that there is an increased risk associated with high phosphorus levels, FGF-23, and reductions in calcitriol. However, to date no human randomized trials have been conducted using a phosphate load reducing strategy to observe clinical outcomes. Such studies are needed to inform this emerging public health issue.

**WEDNESDAY, JULY 20, 2011**

**GOVERNMENT-ACADEMIC-INDUSTRY PARTNERSHIPS**
**Moderator:** *Dr. Michael F. Flessner MD, PhD, Director of Inflammatory Renal Disease, KUH, NIDDK, NIH*

**Regulatory Issues: FDA Viewpoint**
Clinical Trials in Chronic Kidney Disease- a Regulatory Perspective
*Aliza Thompson, M.D., Medical Officer, Division of Cardiovascular and Renal Products, U.S. Food and Drug Administration, Silver Spring, MD*

**Disclaimer: The views expressed in this talk represent Dr. Thompson's opinions and do not necessarily represent the views of the FDA.**

Prior to approval, drugs must be shown to meet the statutory standards for safety and effectiveness. There needs to be substantial evidence of effectiveness from adequate and well-controlled studies, and the effect that is shown must be clinically meaningful. Clinically meaningful endpoints are often described as endpoints that reflect how a patient "feels, functions or survives". In addition, surrogate endpoints (biomarkers intended to substitute for a clinical efficacy endpoint) can be used to establish the efficacy of a novel therapeutic agent. Surrogate endpoints are expected to predict the treatment's effect on the clinical outcome of interest.

Some observations can be made about surrogates and their use in drug development:

- With regard to establishing the effectiveness of a therapy, there is a hierarchy of endpoints. Showing effects on mortality or end-stage renal disease provides the most convincing evidence of efficacy; showing an effect on a surrogate endpoint is clearly less compelling.
- There is less tolerance for risk in development programs that use surrogate markers.
- There is a high evidentiary standard for surrogate endpoints because of the potential harm to public health should the surrogate fail to predict the treatment's effect on clinical outcomes.

The term chronic kidney disease (CKD) encompasses an array of kidney diseases. Endpoints and other aspects of the design of drug development programs in CKD should be tailored to the particular kidney disease(s) being treated as well as the perceived toxicities and benefits of the drug. In general, accepted endpoints in clinical trials of CKD have included progression to ESRD (including need for chronic dialysis, transplantation or GFR < 15), death, and a marked loss of renal function (i.e., a "doubling of serum creatinine"). Other important clinical outcomes associated with CKD (e.g., cardiovascular events) could also be used as endpoints in drug development programs.

There has been a great deal of interest in albuminuria/proteinuria and lesser changes than a doubling in serum creatinine as endpoints for establishing the effectiveness of novel agents for CKD. FDA is actively exploring data that address the relationship between given changes in renal function/creatinine over defined periods of time and ESRD at various time points thereafter. Albuminuria and proteinuria also have been investigated as candidate surrogate

endpoints for the purpose of drug approval, but, for the most part, have not been accepted. It may be reasonable to consider changes in albuminuria/proteinuria as a basis for accelerated approval in certain types of kidney diseases and under certain settings/conditions. Accelerated approval is used for serious and/or life-threatening diseases; under this pathway, approval can be based on a surrogate that is *reasonably likely to predict* a drug's benefit. Development programs then complete studies confirming the clinical benefit in the post-marketing setting.

Biomarkers like creatinine and albuminuria/proteinuria are used as indicators of the underlying disease process/injury. However, changes in these biomarkers can also occur for a variety of other reasons (e.g., because of hemodynamic effects of drugs, effects on tubular secretion). Particularly for drugs that exhibit early effects on such a biomarker, it is important to understand if these effects on the biomarker persist (if at all or to any extent) over a reasonable time frame after the drug is withdrawn; this may have implications for the design of the drug development program and acceptable endpoints for establishing efficacy.

Biomarkers play other important roles in drug development. Biomarkers can be used in enrichment study designs to select patients who are more likely to progress to the clinical outcome of interest over the course of the trial (hence shortening the duration of the trial and lessening its size). Biomarkers can be used to identify likely "responders" during a run-in phase of a trial in which all subjects receive treatment with the study drug; only those subjects who show a response to the treatment in the run-in phase (as defined by a change in the biomarker) would be randomized to the second phase of the trial. Biomarkers can also be used to help determine what dose(s) or dosing regimen(s) will likely provide the best balance of safety and efficacy.

A drug's safety must be established prior to approval. A drug's toxicities are viewed in the context of its established benefits in the intended population. Compared to effectiveness, safety is often less robustly assessed by development programs; hence, the approach to assessing a drug's potential toxicities is different from the approach taken when assessing a drug's effectiveness. In drawing conclusions about a drug's safety, it is important to consider not only what safety signals are seen in a development program but also how well studies were designed (and conducted) to capture potential toxicities and what particular risks and level of risk the development program can exclude.

An FDA Guidance describes the Agency's current thinking on a topic and can be a good resource. Guidance documents are located on the FDA website at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. Some guidance documents to consider include the following:

- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf

- Adaptive Design Clinical Trials for Drugs and Biologics http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM201790.pdf

- Qualification Process for Drug Development Tools
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

***Discussion:***

The optimal timeframe for assessing off-treatment effects on a biomarker is not clear and is likely drug specific. At a minimum, the drug should probably be out of the system.

The use of biopsies to establish the effectiveness of novel therapies for CKD merits further discussion. There are some challenges- in many kidney diseases, biopsies (or repeat biopsies) are not routinely performed; the small number of samples taken during the biopsy may not accurately capture the underling pathology (thus introducing noise in the measurement); one also has to consider how to define a clinically important change in the biopsy finding.

Further work is needed to establish novel biomarkers of kidney function as surrogate endpoints for drug approval. Data that are often considered include the following: whether or not the biomarker is on the causal pathway of the disease, observational analyses showing a relationship between the biomarker and outcome of interest, and data from intervention trials showing that the biomarker reliably predicts the treatment's effect on the clinical outcome of interest.

Under certain circumstances a single study can be used to establish the efficacy of a drug. It is difficult to define a specific p-value that must be achieved in that study. The finding must be sufficiently compelling and consideration is also given to other factors such as the consistency of findings across important study subgroups and endpoints. The FDA guidance titled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" addresses these and other considerations.

**Public – Private Partnerships/Collaborative Opportunities/An NIH View**
*Dr. Flessner (Presented slide presentation in the absence of Drs. Barbara Mittleman and April Franks)*

Public-private partnerships are mandated by Congress, are included in the missions of each of the 27 NIH Institutes and Centers (NIH ICs), and inform research choices and partnership decisions. To assist this effort, the Private Public Partnership (PPP) Program, located in the Office of the Director of the NIH (ppp.od.nih.gov**)**, was established in 2005 as an outgrowth of the NIH Roadmap initiative. Although each NIH IC is mandated to implement a partnership program, there is no requirement that they implement one through the PPP Program, which simply is a resource available to all NIH ICs. The reason the Program is valuable is that it complements and leverages Federal resources, produces synergy in research across the country, and offers new opportunities to respond quickly to changing research goals, especially in the drug development arena.

The ICs can partnership with academia, the FDA, other NIH ICs, and private industry as long as the process is: science-driven; fair; inclusive; transparent; compliant with Federal law, regulation, and policy; and is a priority to the agency involved. A hallmark of the partnership relationship is that working together (e.g., with a foundation) enables shared decision-making and governance. However, the Federal Government may not delegate its authority in areas such as resource allocation and grants and contracts policy and regulation; in areas controlled by the Federal Advisory Committee Act; or in contraindications of the Bayh-Dole Act that governs the rights of federally funded invention intellectual property (IP) rights.

For a partnership to succeed there must be a value for each partner. The partners need to: arrive at shared and acceptable business practices for each partnership, including shared goals and objectives; share understanding of the task and requirements; establish a common culture; and adopt open and transparent communication and problem-solving approaches. Issues of funding, products, IP relationships and rights, and privacy and integrity should be agreed upon before establishing a partnership.

To determine if a partnership is needed, first steps include identifying knowledge gaps, areas needing improvement, and stakeholders. If the needs cannot be met by current programs and initiatives, a partnership may be the answer. In CKD, areas that could be considered for partnerships include developing new tools, science, approaches, targets, compounds, trials, devices, and diagnostics.

Examples of current NIH partnerships include the following:

- Biomarkers Consortium (NIH, FNIH, FDA, Pharma), www.biomarkersconsortium.org
- Alzheimer Disease Neuroimaging Initiative (ADNI), http://www.adni-info.org
- Genetic Association Information Network (GAIN), http://www.genome.gov/19518664

***Discussion***

The partnership process is ideal for preclinical development programs, such as for biomarkers for investigation of clinical toxicity (e.g., biomarkers for AKI). This is a way for industry to work collaboratively with the NIH. The NIH Foundation is an example of an honest broker between the NIH and industry to develop partnerships in clinical or preclinical investigations. The examples given above have been successful in bringing together interested parties working on common problems, such as development of better endpoints for clinical studies.

**Intellectual Property – An NIDDK View**

*Anna Amar, Acting Deputy Director, Office of Technology Transfer and Development, NIDDK, NIH, Bethesda, MD*

The NIH's mission is to improve public health. We do this through our clinicians and scientists working on the NIH campuses (intramural) and through providing funding to other institutions through grants and contracts (extramural). NIH funds extramural research because this helps others to succeed in developing novel medical breakthroughs which will lead to the public having new options for health care needs.

NIDDK has an extramural component that funds clinical trial networks usually through Cooperative Agreements, which is a collaborative grant mechanism which includes substantial NIDDK staff involvement. The goal of these grants is to support and stimulate a clinical area of interest to the institute by working in partnership with the grantee. Grantee recipient investigators have joint responsibility for: planning, directing, and patient recruitment, as well as following regulatory and NIH requirements that are defined in the Terms and Conditions of the award. Usually the grantees form a network of sites to allow for greater patient recruitment, and the network together with NIDDK form a steering committee to coordinate activities.

The steering committee frequently works with industry partners (e.g. pharmaceutical companies) to study products of interest to improve health in a field of interest. It is job of my office to assist in the collaboration between NIDDK and Industry by drawing up transactional agreements that will clarify the roles and obligations of both parties. The agreement mechanisms tend to be either a:

- **Confidentiality Disclosure Agreement (CDA)** - to cover exploratory discussions and the exchange of proprietary information between the NIDDK and potential collaborators,
- **Clinical Trial Agreement (CTA)** - to establish terms and conditions for use of proprietary drugs or devices and sharing of research data and publications with the collaborator, or a
- **Cooperative Research and Development Agreement (CRADA)**, which, in addition to the above, also permits the NIDDK to accept funding for the collaboration from an industry collaborator and to offer them an option to a license to anything invented by NIDDK during the trial.

A number of the considerations contained in the CTA and/or CRADA were discussed:

- **New inventions:** protection for collaborators and outlines ownership for new inventions, although by law, the Government must retain internal use rights. The Government also retains march-in-rights to protect the taxpayers' investment; however the NIH has never made use of this right.
- **The Bayh-Dole Act:** states that grant recipient institutions may retain ownership of inventions their employees create under U.S. Federal funding mechanisms. The NIH cannot require the clinical networks to assign their inventions; however, the grantees usually are willing to sign a separate agreement directly with the collaborator to license or assign any IP related to the trial. Generally, the sites are universities that do not have extra money to pay to patent an improvement to a technology that already is well protected.

- **The Freedom of Information Act (FOIA):** may require the Government to release information to outside entities (5 USC § 552). There is an exemption for information that concerns trade secrets and commercial or financial information that is privileged or confidential. CRADA-related data are protected by law for 5 years (15 USC § 3710a[c][7][A]). If information can be shown to be patentable, it is protected until a patent application is filed (35 USC § 205).
- **Confidentiality:** information provided to the NIH will be protected if marked; oral disclosures should be summarized for maximum protection. PIs cannot sign agreements to bind their institutes but they can acknowledge the agreement. All Federal employees are bound by 18 USC § 1905 of the Federal Code, which provides criminal penalties for disclosing confidential information.
- **Data and publications:** access and use is provided to both parties. Publications are an area of focus for the NIH, will agree to collaborator's review of disclosures before release, and will agree to remove confidential information or to delay publication while patent applications are filed.

Take home message: there is much to be gained from partnering with the NIH if you are able to exercise a bit of flexibility to allow NIH to work within the laws, regulations and policies by which it is bound.

## ONGOING INDUSTRY TRIALS/RESEARCH AND DEVELOPMENT

**Moderator:** *David Warnock, M.D., Hilda B. Anderson Endowed Chair in Nephrology, Department of Medicine/Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL*

### Bardoxolone: BEACON Trial

*Paul K. Audhya M.D., M.B.A., Vice President of Development and Chief Medical Officer, Reata Pharmaceuticals, Inc.,* and *Colin Meyer, M.D., M.B.A., Vice President of Product Development, Reata Pharmaceuticals, Inc., Irving, TX*

Previous studies have identified the association between inflammation and CKD progression, with various pathways involved. Nrf2 knockout mouse models have been investigated to test the usefulness of bardoxolone methyl (BM), an antioxidant inflammation modulator (AIM), for inhibiting inflammation and CKD progression. BM binds to Keap1 and activates transcription factor Nrf2, which suppresses inflammation through NFκB. A 52-week dose-ranging study conducted by Reatta Pharmaceuticals showed that treatment with bardoxolone methyl in patients with moderate to severe CKD and T2D improved measures of kidney function relative to placebo.

The Bardoxolone Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes (BEACON) trial, the first multinational trial evaluating the effect of bardoxolone methyl treatment on clinical outcomes, will randomize 1,600 to 2,200 patients with T2D and Stage 4 CKD to either 20 mg bardoxolone methyl or placebo. Randomization will be stratified by the

enrolling site. To participate, patients must be at least 18 years of age, have an eGFR of 15 to < 30 ml/min/1.73m$^2$, and be taking a stable dose of an ACE inhibitor and/or ARB or have a documented medical contraindication if not on either. Exclusion criteria include evidence of nondiabetic renal disease, recently active cardiovascular disease, history of kidney transplant, and recent kidney injury or acute dialysis.

The primary endpoint is the time to the first event of ESRD (need for chronic dialysis or kidney transplantation) or CV death. Secondary endpoints are: (1) change in eGFR; (2) time to first hospitalization for heart failure; and (3) time to first event of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or cardiovascular death. A blinded Events Adjudication Committee will adjudicate all potential events for the composite endpoints. Safety analyses will include evaluation of adverse events and monitoring of other safety parameters at all study visits.

BEACON will test whether the large, sustained improvements in kidney function noted in previous trials of bardoxolone methyl translate into a delay in the progression to ESRD or CV death.

***Discussion***

Proteinuria was tracked with the eGFR in the BEAM study, and the change in creatinine was approximately a 0.3 mg/dL decrease from a baseline mean of approximately 2.0 mg/dL.

The use of ESRD as a hard endpoint may be a problem because the definition of ESRD is based on eGFR meeting a specific level (i.e, 10 ml/min/1.73m$^2$). This is a problem in many CKD clinical trials, because there may be a misinterpretation of the acute phase that would put a person on dialysis. Symptomatology of the patient is problematic if hard endpoints are used.

Inflammatory markers and blood sugar in the BEAM study were assessed, but this was not presented.

**CTP-499, a First-in-Class Clinical Development Candidate for Diabetic Nephropathy**
*James Shipley, M.D., Chief Medical Officer, Concert Pharmaceuticals, Inc., Lexington, MA*

CTP-499 is a first-in-class deuterated analog of 1-((S)-5-hydroxyhexyl)-3,7-dimethylxanthine (HDX), an active metabolite of pentoxifylline (PTX). Concert Pharmaceuticals applied its deuterium chemistry to produce CTP-499 as a novel compound having a unique and favorable metabolic profile. CTP-499 has a pleiotropic mechanism of action with anti-inflammatory, anti-fibrotic, and anti-oxidant properties that are similar to HDX and believed to be predominantly responsible for the beneficial effects that were observed in small clinical studies of PTX in CKD patients. Combined with standard-of-care renin-angiotensin modulation, CTP-499 has the potential to further delay the progression of CKD. CTP-499 significantly and dose-dependently inhibits TNFα and MCP-1 secretion induced by lipopolysaccharide in human blood. IFNγ secretion induced by anti-CD3 antibodies in human blood, hyperglycemia-induced TGF-β and

CTGF expression in human mesangial cells, and oxidative burst induced by fMLP in human neutrophils.

A Phase I single-ascending dose study to evaluate the safety, tolerability, and pharmacokinetics (PK) of a controlled-release (CR) single dose of 600, 1,200, 1,800, and 2,400 mg has demonstrated that doses in excess of the anticipated clinically relevant single dose were well tolerated. The CR formulation provides the potential for once-a-day dosing. Based on the outcomes from Phase I single dose studies, Concert is advancing CTP-499 into a Multiple Dose Safety and Tolerability Study in patients with Stage 3 CKD, which will be followed by a Phase II Efficacy and Safety Study in CKD/diabetic nephropathy. Both studies will include assessments of PK, as well as blood and urine biomarkers of safety and/or efficacy.

The CTP-499 Phase II Efficacy and Safety Study is expected to include 170 patients with CKD associated with T2D, randomized equally to active treatment or placebo. T2D nephropathy patients will have Stage 2-3 CKD with macro-albuminuria and be receiving effective doses of ACEi/ARBs. CTP-499 will be given at a 600-mg dose twice daily, or placebo. The study will include a blood pressure stabilization run-in followed by 24 weeks of double-blind treatment. The primary endpoint will be change in urine albumin-creatinine ratio (UACR) from pretreatment baseline to post-treatment using a longitudinal model. Changes in blood and urine biomarkers of the anti-inflammatory, anti-oxidant, and anti-fibrotic actions of CTP-499 will be assessed.

***Discussion***

CTP-499 has the same metabolites as PTX. *In vitro* preclinical data exist and will be available for presentation in a few months. As for efficacy, the deuteration does not change the biological property efficacy but does change the PTX metabolic pathway. The benefit of this approach is that it delivers more of the agent, thus having a greater effect.

**ACE-011 in Renal Anemia/Bone Disease**

*William Smith, M.D., Director of Clinical Research and Development, Inflammation and Immunology, Celgene Corporation, Warren, NJ*

Sotatercept (ACE-011), developed by Celgene Corporation, targets activin A, a member of the transforming growth factor-beta (TGF-β) superfamily. Activin A promotes osteoclast differentiation through synergy with RANKL, which is necessary for osteoclast formation. Based on animal studies in rats, the activin A receptor was chosen as a target for investigation as a novel agent for renal anemia and bone disease. Thus, ACE-011 was developed as an activin receptor IIA (ActR-IIA) fusion protein.

A Phase I study of ACE-011 was conducted in 31 postmenopausal women (age 49 to 81 years) who received various doses of ACE- 011 (at least one dose) or placebo. The study showed a dose-dependent increase in red cell hematological parameters (e.g., RBC number, Hb, Hct). Results indicated that ACE-011 promotes new bone formation, and the change in total hip bone mineral density from baseline is dose-related; an increase in Hb levels also was dose-related.

A Phase IIA, multicenter, randomized, single-dose, double-blind, placebo-controlled study followed by a multiple-dose, double-blind, double-dummy, active-controlled, iterative dose study is ongoing. We will evaluate the pharmacokinetics, safety, efficacy, tolerability, and pharmacodynamics of ACE-011 for the correction of anemia in subjects with ESRD on hemodialysis. A goal is to find ESA responders to take part in the study. The first part of the study will involve a single dose of ACE-011 to investigate the PK and effect on the increase in Hb. The second part of the study will determine safety, tolerability and effect on hemoglobin in a multidose study. Exploratory objectives include the effect on bone turnover, quality, and quantity.

***Discussion***

In response to a question: there is some weak inhibitory activity of ACE-011 on myostatin, but it is less than activin A. Another related compound, ACE-031, is being studied in muscular dystrophy. There is a potential for an effect on muscle metabolism with ACE-031.

**Atrasentan for Diabetic Nephropathy**

*Dennis Andress, M.D., Senior Medical Director, Research and Development, Abbott Laboratories, Abbott Park, IL*

In the 1980s, the endothelin receptor endothelin-1 (ET-1) was identified in endothelia**l** cells. Diabetes is associated with elevated blood and kidney levels of ET-1 and enhanced renal expression of the endothelin A receptor (ETAR). Preclinical studies in diabetic models indicate that ETAR overactivity contributes directly to podocyte and mesangial cell dysfunction and antagonists of ETAR attenuate proteinuria and glomerulosclerosis, particularly in combination with renin-angiotensin system (RAS) inhibitors. In a mouse model, **A**trasentan, a small molecule being developed by the Abbott pharmaceutical compan**y,** was determined to be a highly selective antagonist of the ETAR; **A**trasentan subsequently has shown recent promise in patients with diabetic nephropathy.

A Phase IIa study of 89 patients with diabetic nephropathy evaluated the efficacy of Atrasentan (0.25, 0.75 and 1.75 mg) to reduce urinary albumin to creatinine ratio (UACR) over an 8 week treatment period. The results indicated that UACR was significantly reduced (30-40%) below baseline for the 0.75 mg and 1.75 mg compared to placebo. The side effect profile was favorable with a low incidence of mild to moderate peripheral edema. Confirmatory dose-ranging studies are ongoing to validate efficacy and safety findings in patients who are on maximum doses of RAS inhibitors, the results of which are expected to be available in 2012. The results of this study will allow for optimal dose selection for the planned Phase III pivotal trial of hard renal outcomes and long-term safety evaluation.

***Discussion***

Phase II results indicate that low doses of Atrasentan substantially reduce urinary albumin excretion in diabetic patients when added to conventional RAS inhibitor therapy, with minimal

concern for fluid retention. The excellent safety profile observed in this study provides rationale for pursuing a long-term Phase III clinical trial with Atrasentan to establish its potential efficacy in delaying the progression of chronic kidney disease.

**AST-120/EPPIC Program**

*Alan Glicklich, M.D., Senior Medical Director, Mitsubishi Tanabe Pharma Development, America, Inc., Warren, NJ*

Uremic toxins (retained uremic metabolites) are a potential cause of oxidative stress and inflammation in CKD. A substantial number of uremic toxins associated with CKD and CKD progression are generated by microbial metabolism in the intestines. Two of the best-characterized uremic toxins are indoxyl sulfate and p-cresylsulfate. Studies have shown that there is an inverse relationship between levels of eGFR and levels of indoxyl sulfate or p-cresylsulfate. Indoxyl sulfate levels also have been inversely associated with CV mortality and overall mortality. Indoxyl sulfate appears to cause renal tubular damage through oxidative stress and to promote tubulointerstitial fibrosis, glomerular sclerosis, and progression of CKD by stimulating the expression of fibrosis-related genes.

AST-120 is an orally administered adsorbent without evidence of systemic absorption. It is composed of black spherical carbon particles approximately 0.2-0.4 mm in diameter. The clinical utility of AST-120 is believed to reside in its ability to adsorb uremic toxins in the gastrointestinal tract, thereby reducing systemic absorption of uremic toxins and related contributions to the CKD disease process. AST-120 has been approved and used in Japan since 1991. A Phase II trial in the United States has been conducted to evaluate the effect(s) of three doses of AST-120 compared with placebo, on the change from baseline in serum indoxyl sulfate levels. Results indicated that AST-120 reduced levels of indoxyl sulfate in a dose-related manner. Phase III studies of AST-120 for the prevention of CKD progression are ongoing in North America, Latin America, and Europe. The program consists of two similar clinical trials being conducted at about 240 study centers worldwide. EPPIC-1 (A Study of AST-120 for Evaluating Prevention of Progression In Chronic Kidney Disease) and EPPIC-2 (A Study of AST-120 for Evaluating Prevention of Progression in Chronic Kidney Disease Including Assessment of Quality of Life) are randomized, double-blind, placebo-controlled studies that will determine the effects of AST-120 added to standard-of-care therapy on renal outcomes in moderate to severe CKD. The primary objective of the studies is to show whether AST-120 added to standard-of-care therapy in patients with moderate to severe CKD will decrease the risk for developing a component of a triple composite endpoint (initiation of dialysis therapy, kidney transplantation, or doubling of sCr level) compared with placebo.

***Discussion***

There is some concern that drugs such as AST-120 could adsorb other compounds, such as prescription drugs, but in these studies AST-120 is given at least an hour before or after other medications to circumvent this problem. AST-120 does bind with creatinine, but in the Phase II trials, excretion levels did not significantly change when comparing the treatment arm to placebo.

**ALTITUDE Trial**

*Marc Pfeffer, M.D., Dzau Professor of Medicine, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA*

Physicians have been using pharmacologic inhibition of the renin angiotensin system (RAS) with either angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) to improve the prognosis of patients with cardiovascular and renal diseases. The clinical efficacy of RAS inhibitors is particularly established in patients with type 2 diabetes. Aliskiren, a novel direct renin inhibitor which blocks the RAS cascade at the initial step, is an effective antihypertensive agent and has been shown to reduce urinary protein excretion in subjects with type 2 diabetes and nephropathy who were already receiving background RAS inhibition. ALTITUDE (ALiskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints) is an randomized, double-blind, placebo-controlled, international trial, which is directly testing whether this alteration in an important surrogate outcome marker would be translated into improvements in clinical outcomes. The ALTITUDE investigators from 36 countries have completed the randomization of 8606 high risk (macro-albuminuria, micro-albuminuria with reduced eGFR, or history of prior CV disease) type II diabetic patients already receiving either an ACEI or ARB to either 300 mg of Aliskiren or placebo. The primary endpoint of the trial is to determine whether the composite outcome of cardiovascular death, resuscitated sudden death, nonfatal myocardial infarction, nonfatal stroke, unplanned hospitalization for heart failure, end-stage renal disease or renal death or doubling of baseline serum creatinine concentration would be reduced by the addition of Aliskiren to conventional therapies including standard RAS inhibitors. The trial is designed as event driven (1620 unique patient primary endpoints) to provide 90% power to detect 15% risk reduction by randomization to Aliskiren. Clinicaltrials.gov, NCT00549757

**Development of Acthar for Treatment of Diabetic Nephropathy**

*David Young, Ph.D., Pharm.D., Chief Scientific Officer, Research and Development, Questcor Pharmaceuticals, Inc., Ellicott City, MD*

H.P. Acthar Gel, a highly purified sterile preparation of the adrenocorticotropic hormone (ACTH), is FDA-approved to induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or of that due to lupus erythematosus. Acthar is produced from porcine pituitary and first was approved by the FDA in 1952. It has a positive safety profile and is most often prescribed on-label for multiple sclerosis flares and infantile spasms; it is prescribed less often on-label for Idiopathic Nephrotic Syndrome (e.g., membranous nephropathy). Acthar works through the melanocortin receptors to produce anti-inflammatory and immunomodulation effects. Acthar has a direct protective effect on the kidney, and also has indirect kidney immunomodulation effects, as well as effects on the central nervous system, each of which can impact the kidney.

A 2010 pilot study by Tumlin et al. was a randomized, open-label, prospective trial that examined the safety and efficacy of Acthar on proteinuria and progression of kidney dysfunction in patients with diabetic nephropathy and nephrotic range proteinuria. A total of 15 diabetic

patients with nephrotic range proteinuria despite ACEI/ARB therapy were enrolled and randomized to daily subcutaneous injections of Acthar (16 or 32 units) for 6 months. These patients were staged at CKD 3b to 4 and were receiving ACEi or ARB. Proteinuria was significantly reduced and kidney function stabilized over 6 months. Acthar gel (16 units daily) induced a complete or partial response in 60% (68% mean) of patients with nephrotic range diabetic nephropathy. Using ESRD as an outcome measure, 40% of controls (not treated with Acthar but most on ACEi or ARB) progressed to ESRD, whereas none of the participants on Acthar progressed to ESRD. Mean change in eGFR at 6 months was approximately 6% for those receiving Acthar and 45% for the untreated cohort; no patients on Acthar and 45% of the untreated cohorts doubled SCr or had ESRD at 7 months.

A Phase II randomized, placebo-controlled trial in diabetic nephropathy patients will begin soon to test the potential safety and efficacy of Acthar in this population. Endpoints for the trial include percent change in eGFR at 24 weeks comparing medium and high doses of Acthar to placebo. If eGFR is significantly different, the endpoint will be the percent of patients who double creatinine or have ESRD within 24 weeks after randomization comparing medium to high doses of Acthar versus placebo.

***Discussion***

Conducting the study of Acthar in a population with diabetics is more complicated than conducting it in a population of non-diabetics. In fact, there are ongoing studies of Acthar in non-diabetics.

The ACTH component of Acthar can raise cortisol levels, which can impact inflammation. However, there are other melanocortin peptides that do not impact cortisol.

By the FDA's definition, Acthar is a biologic but is reviewed through CDER at the FDA. The production process has been approved by the FDA, and FDA requirements will ensure that batches produced meet exacting standards.

**Industry Panel Discussion: Speaker Panel and Moderator**

The panel accepted questions from the audience, some directed at one speaker and some directed at the panel as a whole. The following is a general summary of the questions and answers.

- Industry can work with academia, public institutions, or other companies in many areas of research, depending on the scope, infrastructure, and efficiency of potential collaborations. Smaller companies are more likely to collaborate.
- The standard-of-care for T2D includes inhibition of the RAS. This causes problems for designing clinical trials for CKD because adjustments must be made to ensure that all participants have equivalent blood pressure before beginning the trial. Some trials have a run-in phase to maximize RAS inhibition, but concerns have been raised about secondary effects such as hypotension and effects on the kidney. In the CHARM study on congestive heart failure, the FDA was concerned that 96% of participants had maxed out on ACEi or

ARB and ultimately would not accept this situation. In addition, some patients experience adverse effects from ACEi or ARB.

- Comments were made regarding a potential spironolactone trial that the NHLBI is conducting, known as the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial. TOPCAT is a multicenter, international, randomized, double-blind, placebo-controlled trial of the aldosterone antagonist spironolactone in 3,515 adults with heart failure and a left ventricular ejection fraction of at least 45%, recruited from more than 200 clinical centers. The primary endpoint is a composite of cardiovascular mortality, aborted cardiac arrest, or hospitalization for the management of heart failure. Secondary endpoints include all-cause mortality, new onset of diabetes mellitus or atrial fibrillation, and quality of life. (See http://www.topcatstudy.com.)
- It is clear that the collection of data before beginning a trial will result in benefits at the end. It is not uncommon for investigators get involved in a trial and then wish they had added a parameter or outcome that would be significant by the end of the trial. It was noted that other countries may be more attuned to this issue.
- A biorepository for CKD samples from previous and future clinical trials is sorely needed. At this time, samples are collected and kept in different repositories using different standards. The question was raised as to whether there are standardized storage protocols that could be applied across institutions/industries. The NIDDK has a biorepository and will store samples provided by investigators with collaborations with the NIDDK. It is possible to have samples stored from non-NIDDK trials through the NIH Foundation. In addition, there is a White Paper that discusses storage and other issues, and the NIDDK is committed to sharing these resources with investigators who have good ideas.
- A great need exists for new, validated biomarkers for use in CKD clinical studies, especially in the area of prognostic and predictive biomarkers. Although much has been accomplished in this area to date, this field is ripe for new discoveries that could address some of the most pressing questions regarding CKD. The NIDDK also has a biomarker consortium project that supports programs for diabetes and digestive and kidney diseases.
- The issue of a blood pressure goal has a great impact in kidney diseases and clinical trials. Goals for patients with kidney disease and diabetes are lower (by Joint National Commission [JNC] VII guidelines) than for people without kidney disease or diabetes. This can become an exclusion criterion in clinical trials for CKD, but it must be remembered that CKD trials are not blood pressure trials. Blood pressure generally is a stratification issue for analyzing clinical trial data.
- Quality of life (QOL) and patient-reported outcomes (PRO), though included in some clinical trials, could be raised as an issue for future trials. QOL and PRO are included in many trials, such as the Neptune Study, but few of the tools are validated and they do not have the same importance as hard endpoint outcomes. This does not mean that QOL and PRO are not important; in fact, the FDA has been including these factors in its approval decision process.

At the end of the discussion period, the question was raised as to how the NIDDK could assist future CKD research. Since so much research is being conducted in various public and private settings, the NIDDK can help coordinate through its grants and contracts and also in areas that are receiving attention in the larger scientific community. The following are potential areas mentioned in which the NIDDK could provide leadership in CKD research.

- Pathophysiology of CKD in areas not already under the focus of researchers in public or private research institutions/companies.
- Biomarker research.
- Assistance with FDA regulations regarding subpart H.
- Identifying issues related to safety in the life-cycle of a drug.
- Small companies need resources to conduct state-of-the-science research in areas that cannot be handled within the company. These areas can include technologies or basic research.
- Small companies do not have the resources to participate in regulatory trailblazing regarding endpoints.
- Global studies are needed in CKD; these cannot be conducted by many private companies, especially those developing cutting-edge compounds for CKD treatment or prevention.

In conclusion, Dr. Star thanked the participants for a successful meeting. We hoped that the interactions would spur research and clinical trials in CKD – both from NIH and Industry.