National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Workshop on Focused Opportunities for Clinical Research in Kidney Disease

January 29–30, 2007
Bethesda Marriott Pooks Hill
Bethesda, Maryland

Meeting Summary

I. Welcome and Opening Remarks

Welcome
Griffin Rodgers, M.D., Acting Director, NIDDK

Dr. Rodgers welcomed all attendees for their participation at the workshop. He noted that, despite the financially difficult times in which the budget is expected to remain flat for several years, it is important to continue kidney research; chronic kidney disease (CKD), for example, currently results in $20 billion in Medicare expenditures. The NIDDK has been asked by Congress to come up with preemptive, preventive, and cost-effective treatment strategies for kidney disease. There are opportunities that will arise during the next several years for new clinical studies, and the NIDDK has sponsored this workshop to hear ideas from the extramural community for potential studies. Dr. Rodgers thanked participants for their attendance, requested their active contribution to the meeting, and encouraged everyone to continue to advocate for basic research with their patients and with Congress.

Introductions and Opening Remarks
Robert A. Star, M.D., Acting Director, Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK

Dr. Star thanked Dr. Rodgers for setting the meeting priorities and focuses and thanked participants for attending. The NIDDK is accountable to Congress and the American people to provide ideas for studies that have a profound impact on public health. This workshop has been held to help the NIDDK identify focused opportunities for clinical research in kidney disease.

Following a brief introduction by participants, Dr. Star provided an overview of the workshop topics and explained the agenda. Medicare costs related to CKD, *diabetes mellitus* (referred to hereafter as diabetes), and congestive heart failure (CHF) are three times what have been expected. To demonstrate this point, Dr. Star noted that; a study from the United States Renal Data System (USRDS) for the Centers for Medicare and Medicaid Services (CMS) showed that, in 2002, 19 percent of Medicare expenditures were for CKD and 7.8 percent went for the treatment of end stage renal disease (ESRD).

To prepare for this meeting, the NIDDK developed a Kidney Disease Interaction Map that illustrated the relationships among CKD, acute kidney injury (AKI), and ESRD dialysis and

transplant, as well as with cardiovascular diseases (CVD), diabetes, obesity, and issues surrounding access. The public health problem is one of mortality: the number of patients is increasing, and the mortality rate remains high. There has been a recent appreciation of the role that AKI plays in CKD.

The NIDDK core missions to assist with public health problems are to:

- Maintain a vigorous investigator-initiated research portfolio;
- Foster exceptional research training and mentoring opportunities;
- Preserve a stable pool of talented new investigators;
- Support pivotal clinical studies and trials; and
- Ensure knowledge dissemination through outreach and communications.

During the time of the budget doubling, the NIDDK supported a number of large kidney studies through the U01 mechanism. Listed below are nine studies scheduled to end between Fiscal Year (FY) 2007 and FY 2009:

- African American Study of Kidney Disease and Hypertension (AASK)
- Family Investigation of Nephropathy of Diabetes (FIND)
- Acute Renal Failure Trial Network (ATN) Dialysis study
- Dialysis Access Clinical Trials Consortium (DAC)
- Frequent Hemodialysis Network (FHN)
- Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT),
- Focal Segmental Glomerulosclerosis (FSGS)
- Randomized Intervention for Children With Vesicoureteral Reflux (RIVUR)
- Chronic Kidney Disease in Children Prospective Cohort Study (CKiD)
- Chronic Renal Insufficiency Cohort (CRIC)

The NIDDK is seeking concepts for meritorious trials to follow these closing trials. The FY 2007 budget remains unknown, but planning has begun for FY 2008 and FY 2009. In light of this, the goal of the workshop is to identify the top 5 to 10 most promising, compelling, and feasible opportunities that address the question, "What research is needed next to most reduce the morbidity and mortality of kidney disease?"

Participants were asked to consider the following criteria in their discussions:

- Compelling problem that addresses a profound public health issue in adults or children;
- Large potential economic impact;
- Catalytic project that surmounts a current translational barrier;
- Answerable, and feasible to start in 1-3 years; and
- Will not be addressed by others, or by standard R01/R21 mechanisms.

Dr. Star explained the agenda for the workshop and following presentations, instructed participants to divide into three groups to discuss: AKI (acute kidney injury); CKD (including diabetic nephropathy and heritable renal disease); or ESRD (including dialysis access and

chronic allograft nephropathy). The breakout discussion groups would listen to nominations, identify broad clinical and public health questions and scientific barriers, decide on the two or three most compelling questions, and discuss feasible next steps for each question. Each group would report their discussions to the plenary session in the late afternoon. Day 2 would continue with the breakout discussion groups discussing the top two or three most compelling questions in detail, and presenting to the plenary session several draft proposals for the NIDDK to consider. If the groups wished to present more concepts, they were asked to prioritize them.

The participants were also encouraged to consider the types of studies, such as clinical research and trials and translational tools; and whether the studies encouraged collaborations, such as with the NHLBI, Veterans Administration (VA), or DoD. The centers, networks, and individual R01/R21 studies would not be discussed.

II. Acute Kidney Injury

A. Plenary Presentation

Bruce Molitoris, M.D., Director, Nephrology Department, Professor of Medicine, Indiana University School of Medicine; Paul M. Palevsky, M.D., Chief, Renal Section, Veterans Administration Pittsburgh Healthcare System, Professor of Medicine, University of Pittsburgh School of Medicine

Drs. Molitoris and Palevsky described the current state of AKI and renal replacement therapy (RRT). The number of hospitalizations with a diagnosis of acute renal failure (ARF) has increased dramatically during the past 20 years, from 35,000 in 1979 to more than 650,000 in 2002, an annual rate of increase of more than 13 percent. This has occurred despite a slight decline in total hospitalizations. The overall hospital discharge mortality rate has remained fairly stable during the past 20 years at about 2.5 percent; of those patients who died in the hospital, however, an increasing percentage, from 1.5 to 15% have a code of ARF.

AKI is a serious problem. Even a small increase in serum creatinine is associated with higher mortality ("a little dab will undo you"). In addition, it is an accelerant for the progression of CKD and can initiate CKD. There are two key challenges in the AKI field: (1) The identification of at-risk patients for AKI is an essential component of patient evaluation and prevention of AKI. Improvements to this identification involve clinical factors, biomarkers for risk, minimizing risk factors, close surveillance of at-risk patients, and preventative therapy. (2) The surveillance of all patients, especially high-risk patients, for AKI is an essential component of patient management, yet little progress in this critical area has occurred.

The AKI Conceptual Model identifies four components: antecedents (normal kidney and increased risked); intermediate stage (damage); AKI (decreased glomerular filtration [GFR] and kidney failure); and outcomes (death).

The AKI Therapeutic Model describes an improved treatment of AKI patients. The first steps identify and stratify at-risk patients and minimize risk factors. Drugs that could prevent AKI could be considered, followed by enhanced surveillance. Early diagnosis and stratification by

risk with enhanced surveillance methodologies, may lead to effective drug therapy and ultimately, improved outcomes. This in turn will minimize the development of CKD and more importantly the progression of existing CKD to ESRD.

Ongoing trials evaluating the management of RRT are making some progress, but many questions remain unanswered. Key questions that still need to be answered include timing of initiation of RRT (is earlier better?), selection of modality and dosing of therapy. Several recent studies comparing intermittent to continuous therapies have not found a survival benefit associated with modality of RRT. Two large multicenter trials of dosing of therapy are ongoing.

Plenary Discussion

The next few years in AKI research likely will yield candidate structural and functional biomarkers allowing for improvements in surveillance, and further identification of risk factors.

The issue of prevention in AKI was discussed. There is a problem in identifying those with high risk to AKI: The greatest number of adverse events occurred in low-risk populations, although the risk for an individual event in this population is smaller. The risk factors for AKI present an emerging area for study. In addition, there are only limited post-hospital long-term follow-up studies of patients who had AKI.

A suggestion was made that new markers identified for the kidney in general could assist with the identification of AKI risk factors. This would require measurement of true GFR in populations with normal and altered kidney function.

B. Working Group Discussions

Drs. Molitoris and Palevsky chaired the AKI breakout session. The working group participants then introduced themselves and noted any possible conflicts of interest.

General Discussion

Early diagnosis of AKI, and stratification by level of injury, is critical. Structural and functional markers and early diagnostic data are needed for a therapeutic study and would benefit a preventative study.

The Acute Kidney Injury Network (AKIN) Conceptual Model was presented, with an overlay of CKD. Interventions occur at all three points: increased risk, AKI, and renal failure.

A question was raised as to whether AKI has a different outcome in the presence or absence of injury. There has been no functional definition of pre-renal azotemia (i.e., AKI with no damage).

A discussion focused on what is meant by "AKI" and how it relates to outcomes. The critical care approach was discussed at a recent meeting in Vancouver. There are confounding variables, such as when the kidney functions normally but there are AKI symptoms. A suggestion was

made that there is a need for a study looking at "early goal directed therapy" in patients with early stage AKI, analogous to the study by Rivers, et al of early goal directed therapy in sepsis.

Study of the natural progression of AKI was discussed, including how to refine risk estimates in the AKI population and whether AKI is the outcome or the exposure. To quantify risk, a multidimensional series of markers is needed. Clinical trials using early interventions are also needed.

A study design should consider primary and secondary prevention. It also should look at various therapies, including those that are targeted or supportive, as well as dialysis. A focus on damage (particularly the loss of physiological functions) is important, and other risk factors will need to be defined.

A distinction was drawn between clinical settings in which patients are at increased risk, but do not have a predictable inciting event (e.g., sepsis) and the development of AKI after a predictable discrete event (e.g., cardiovascular surgery). The paradigm of radiocontrast nephropathy was discussed, particularly in relation to identifying a definable and timed event.

Participants agreed on the need to develop markers to determine both the onset of AKI and predict the clinical trajectory. The working group favored a study that would inform therapy in those cases where a high-risk patient has a "clear" event. Biomarkers will inform studies looking at creatinine.

A question was raised as to whether there was a benefit to interventions at later stages of AKI, particularly drawing from data from animal studies. It was noted that prevention (as conducted by animal studies) is a different question from the clinical setting, which focuses either on the prevention or mitigation of human renal injury. Agents, for instance, may work in humans for a longer period of time. In addition, an increase in creatinine does not necessarily result from tubular injury.

There are two distinct groups to study: those patients with pre-existing kidney problems (CKD) and those persons with de novo kidney injury (AKI). A study could examine the correlation between the rise in creatinine and decrease in the GFR.

Targeted populations could include those persons receiving high-risk procedures and high-risk patients. Studies are needed to validate biomarkers and to develop new biomarkers. Existing cohorts have not done this, although six or seven biomarkers have been defined. Short- and long-term outcomes (mortality, renal failure, and others) need to be studied.

A participant asked whether an intervention could be included in natural history studies. Other participants noted that this is a good idea and it could be done, but it would pose many challenges, especially with followup.

A number of problems facing AKI research concern timely diagnosis and biomarker validation: it is unknown ahead of time when an injury will occur and it is unknown how to identify the patients. The trigger point must be defined from observation to determine how to define the

research project. Assessment of biomarkers requires that labs have to be blinded with respect to patient AKI status. Patients who do not develop the disease of interest would need to be included in the study protocol.

Opportunities in the National Institutes of Health (NIH) (such as NHLBI studies) that could be plugged into should be identified. A proposed multicenter trial of early goal directed therapy in sepsis based on the Rivers protocol that has been funded by the NIGMS was suggested as a potential trial.

Potential AKI Project Areas

The working group identified the following potential AKI project areas:

- Diagnose AKI onset in a timely fashion.
- Determine the natural history of AKI, including its interface with CKD in terms of short- and long-term history. Understand how the decrease in the GFR relates to outcomes, such as non-renal organ failure, mortality, and subsequent CKD. Discover the progression (clinical course) and predictors for patients with an early insult, with the objective of identifying the high-risk patient.
- Identify and validate clinically useful biomarkers. A second phase study following a biomarker study could focus on therapy/intervention.
- Studies need to be developed evaluating AKI in settings of both timed (predetermined) interventions and "untimed" insults. Timed studies refer to interventions that definitely are linked to AKI, such as cardiovascular surgery (e.g. CABG) and radiocontrast administration. Untimed studies refer to AKI that cannot be linked to a predetermined intervention, such as sepsis.
- Specific settings of AKI associated with a defined insult that was discussed included radiocontrast nephropathy and AKI following cardiovascular surgery. It was pointed out that the Cleveland Clinic risk stratification for AKI after cardiac surgery is significantly driven by the patient's baseline renal function (GFR). It was also noted that although the rate of AKI was high (20-25%) in the highest risk group, the majority of episodes of AKI occurred in lower-risk patients. A contrast study probably would not be conducted at an academic center.
- Compare animal studies to human studies to determine where data exist. Examine various species to determine systemic effects.
- Define a study population, such as an intensive care unit (ICU) population that could be broken into 10 basic groups by injury (e.g., sepsis). The population could be characterized upfront, and protocol-driven input could be included.

Four additional areas of interest are:

- The usefulness of gathering economic data in an AKI study. This would almost certainly have to be done within the Medicare population, or a population linked to some other administrative data base.
- Novel approaches (in addition to biomarkers), such as imaging, that need to be addressed. There is 3-dimensional imaging of the heart; this could be done for the kidney. The role of edema could be determined for the kidney. It was asked whether PET CT is coming out with

- Nephrotoxicity (and biomarkers for screening) is an interest for the FDA, particularly with the monitoring of drugs for nephrotoxicity in patients. The FDA apparently is looking for a partner in this arena.
- The nephrology focus looks at the effect of drugs on the kidney and raises patient safety issues. The other side of the issue is the use of antibiotics, and whether a drug dosage is effective. Drug metabolism in AKI involves less or decreased renal clearance, changed hepatic metabolism, and RRT. A suggestion was that drugs should be screened for their effect on inflammation. Such a study could be funded collaboratively.

Plenary Discussion

Participants asked about special populations at high risk for AKI and the natural history of AKI. CRIC and CKiD might be able to assist with a study of the history, and the NHLBI might present opportunities for collaboration.

Two longitudinal cohort (i.e., phased) studies could be considered; they could focus on the predictable and early ICU cases. The timing of dialysis also could be studied.

A discussion focused on the elderly population and Part D Medicare coverage in relation to AKI and CKD. It would be helpful if safe dosage data were available for the general population. The NIH could conduct feasibility studies regarding drugs and safety.

The extent of dialysis ("how much is enough") may provide clues into determining the optimal timing for inception and occurrences. A better understanding of AKI progression is needed.

A participant suggested that AKI researchers look at what investigators in other fields have done. A comment was offered regarding the difference of the oversight currently provided by institutional review boards (IRBs) as compared to past oversight practices and the implications that this has on study feasibility.

Day 2: Refinement of AKI Project Areas

There was general enthusiasm based on biologic and scientific perspectives for the inclusion of pediatric patients in studies. AKI in children appears to be increasing. Fifty percent die in the ICU and the other 50 percent are re-admitted into chronic care within 5 years. Biomarkers function differently in children than in adults.

The AKI field needs biomarker guidance for risk, diagnosis, prognosis, and treatment. The working group focused on concepts that would address these four areas.

A participant commented that a stronger public health argument is needed in the AKI research arena—specifically, reduced AKI leads to reduced CKD and ESRD. A better knowledge base is needed, but it would be helpful to move the discussions of AKI into the framework of CKD and ESRD. AKI rates have increased much faster than either CKD or ESRD.

Participants suggested the following as potential clinical trial topics:

- Two special populations to study could be those who do not have AKI but are categorized as high risk, and those who have AKI and require treatment. No one perfect biomarker will emerge, so it will be important to work with multiple biomarkers in conjunction with measurement of serum creatinine and urine output. A study focused on prevention or mitigation of AKI could involve a defined injury cohort and innovative therapy. Potential settings would include high-risk patients undergoing iodinated radiocontrast administration and patients undergoing cardiovascular surgery. It was noted that the number of cardiovascular surgeries has decreased for adults but is rising significantly in the pediatric population.
- A study focused on primary prevention (with secondary surgery) could be based on a number of drug compounds. A limitation likely would be the current decrease in surgeries and only one insult. This could involve timed and untimed insults.
- Phases of AKI (pre, early, and established) could be studied in relation to cardiovascular surgery and sepsis. A panel of markers could be incorporated, and additional markers could be sought.
- An AKI study that informs on inflammation could be helpful. It would require validated biomarkers and contrast events.
- A timed insult that assesses biomarker development could be considered. This could be analogous to developing a "troponin" for the kidney.
- A study could develop a biomarker base for diagnosis and prognosis to better understand AKI's natural history. It could involve cardiovascular surgery patients and be designed as subsets to pilot interventions that correlate with clinical data. An alternative is to perform multiple Phase 2 subsets that look for signals, interactions, and interventions for biomarkers. The endurance would be a minimum of 1 year with an optimal time of 5 years. It would involve a phased therapeutic arm, and perhaps include NAG and is widely available.
- An additional concept is to use a timed event and a simple endpoint. For example, a trial could start with a cardiovascular event and collect serial samples. The focus could last for 60 days. A test panel could be conducted to handle safety issues surrounding agents. The working group expressed enthusiasm for a sepsis study, as more research is needed in this area.

C. Potential AKI Clinical Trials Recommended to the NIDDK: Presentation to the Plenary

There are several overarching ideas that the working group considered in developing the following potential clinical trials. AKI is a growing public health priority in adults and children; it includes high morbidity and mortality rates and often involves a rise in creatinine. AKI is frequent among hospitalized patients and impacts the incidence and progression of CKD to ESRD. There currently are no NIH studies targeted to the prevention, early diagnosis, or treatment of AKI. Current biomarkers should be considered as actionable clinical tools. A repository/database should be maintained for future R01 studies. A framework is needed for therapeutic interventions, and protocol-based strategies are needed. There also should be testing of multiple drugs/compounds.

1. AKI: Observational cohort with embedded interventions, with (a) timed injury (e.g., cardiovascular surgery) and (b) untimed injury (e.g., sepsis)

Objective and Design: The goal is to identify lead compounds in phase 2 trials to take to eventual phase 3 trials. This likely will involve multiple compounds or drugs in a rapidly changing field. Different compounds will be based on current pathophysiological principles of AKI. The studies would be based on CKD/AKI epidemiology. Current biomarkers would be used to help with the identification of risk/stratification; diagnosis; prognosis and severity, particularly as related to the timing of RRT; and treatment.

Objectives: 1) To characterize the early natural history of AKI by prospectively following populations with defined exposures associated with high-risk of development of AKI including both prospectively planned exposures (e.g., cardiovascular surgery, radiocontrast exposure) and "unplanned" exposures; 2) To develop a repository of biological samples for validation of current candidate biomarkers and identification and validation of novel biomarkers for early diagnosis and prognostic stratification of AKI; 3) To facilitate testing of candidate compounds for prevention and or treatment of AKI in phase 2 trials to identify most promising agents for phase 3 trials.

Design: Observational cohort with embedded interventions in subsets of patients

Enrollment: Inclusion of children is highly supported.

2. AKI: Protocol-driven treatment of established AKI

Objectives: 1) to define optimal non-dialytic management of early AKI, following the paradigm of early goal directed therapy; 2) to compare "early" as compared to "late" initiation of RRT; 3) to validate the use of candidate biomarkers for early diagnosis and prognosis of clinical course of AKI.

Design: Protocol-driven nondialytic management would include volume, hemodynamic, and pharmacological management. It would compare early versus late and include CKI/AKI epidemiology. It would involve the implementation of current biomarkers that require validation from multiple centers.

Enrollment: Inclusion of children is highly supported.

3. Other Areas of Importance in AKI Research

Although the working group noted that special settings for AKI research include those listed below, they did not develop concepts for potential trials.

- Cardiac-Renal AKI
- Liver-Renal AKI

An additional issue is the importance of sepsis studies (e.g., the RIVUR study) to further the sample acquisition and validation of biomarkers to AKI.

Plenary Session Discussion

The hypothesis underlying the protocol-driven sepsis study (Study #2) was that the treatment for AKI is diverse. There is an opportunity and need to conduct research in the sepsis area, and samples can be collected at the same time as sepsis tests/treatment. It was noted that the AKI practice is not advancing even though the field might be. A protocol-driven study is doable; the FACT trial was mentioned as an example of this.

III. Chronic Kidney Disease (+ diabetic and hereditary nephropathy)

A. Plenary Presentation

Tom Hostetter, M.D., Albert Einstein College of Medicine; Harold I. Feldman, M.D., Associate Professor of Medicine and Epidemiology, Center for Clinical Epidemiology and Biostatistics; and Susan Furth, M.D., Ph.D., Johns Hopkins University

The Status of CKD. Dr. Hostetter described the status of CKD in the United States. An eGFR between 15 and 59 has a prevalence rate in adults of approximately 4 percent and did not change in samples from 1988 to 1994 and 1999 to 2000. The ESRD incidence has reached a stagnant level, and its incidence due to diabetes in whites under age 40 years has declined; however, large racial differences exist in ESRD incidence. Although these results are welcome, there is no reason for complacency because the number of patients reaching dialysis, the increasing risk of cardiovascular diseases (CVD) in patients with CKD, and the increased fraction of CKD and dialysis patients who are elderly or in minority groups continues to be unacceptably high.

In addition, the awareness of people with CKD is low, and testing of those at risk is low. The application of secondary preventive measures is low. Although the reporting of eGFR is increasing, the screening tools remain GFR estimates and albuminuria. Blood pressure prescription, Angiotensin Converting Enzyme inhibitor (ACEi), Angiotensin Receptor Blocker (ARBs), and glycemic control are the only proven secondary prevention measures. For people with eGFR under 60, the ability to predict the course of CKD progression to ESRD, development of a CVD event, or a benign course is poor. Finally, defining the transition to ESRD remains haphazard.

There has been some improvement and stabilization of the problem of CKD/ESRD, but few advances have been made in more than a decade in the understanding of variations among individual/groups, screening approaches, or predictive tools or therapy.

Better tests and strategies to apply therapies these are needed, as well as an improved understanding of group and individual variation in the course of CKD. New therapies and effective means of assessing their efficacy, as well as better means of implementing current best practices for testing and therapy, are needed.

Chronic Renal Insufficiency Cohort Study. Dr. Feldman provided an overview of the CRIC study, which aims to examine the patterns of and risk factors for chronic renal insufficiency (CRI) and CVD among patients with CRI. They also aim to develop predictive models that will identify high-risk subgroups, and potential etiological factors for future treatment trials of therapies. The goal is to reduce the burden of advanced CKD and its associated cardiovascular morbidity.

CRIC studies address five hypothesis clusters:

- Non-traditional risk factors are associated with both the progression of CRI and the development of ESRD;
- Non-traditional risk factors are associated with CVD events and progression of CVD in the setting of CKD;
- Risk factors for CRI progression and CVD in the setting of CRI vary by demographics and the status of diabetes;
- Complications of CRI diminish the quality of life (QOL), impair functional status, and increase health resource utilization; and
- The progression of CRI estimated by serum creatinine may yield biased estimates of CRI progression.

As of January 2007, CRIC has funded 16 ancillary studies. Cohort studies address a number of scientific content domains, including vascular and myocardial functions, blood pressure, genetics and pharmacogenetics, measurement and level of renal function, metabolism, inflammation, thrombosis pathways, and cytokines. CRIC also addresses how race/ethnicity, socioeconomic status, health behaviors, access to care, environment, QOL, functional status, and health services affect CKD and its complications.

CRIC began in October 2001 and is scheduled to operate until June 2009. Seven clinical centers throughout the U.S. work with a Scientific and Data Coordinating Center to conduct research. The study data include: sociodemographic information and health care resource utilization measures; physical and renal measures; comorbidity; and cardiovascular, biochemical, and hematological measures. Study outcomes focus on subclinical evidence of progressive CVD and discrete CVD events, such as ischemic heart disease (IHD), CHF, stroke, and peripheral vascular disease (PVD). Renal disease outcomes include reductions in the GFR and elevations in level of proteinuria and discrete clinically relevant renal failure "events." Dr. Feldman also described CRIC's enrollment data and early outcomes.

Chronic Kidney Disease in Children Study. Dr. Furth provided an overview of the CKiD study. It was designed as a 5-year observational cohort study with a recruitment goal of 540 children. CKiD has reached 75 percent of its enrollment goal as of mid-January 2007. Its goals are to define risk factors for CKD progression and the effects of CKD progression on neurocognitive development/function, the prevalence of CVD risk factors, and growth failure. Dr. Furth described CKiD's scientific domains and key measures; clinical characteristics; and the annual GFR decline gleaned from preliminary study data.

Plenary Discussion

Longitudinal data remain important for CRIC, but true progression rates remain to be determined.

Data on the loss of GFR are sparse, but the range for existing data is broad and mostly in the negative range.

Dr. Star asked participants to consider the following questions about CRIC: What questions beyond those provided should CRIC attempt to answer? What study should follow CRIC, or should CRIC be extended?

A discussion ensued about the critical therapeutic opportunities for pharmaceutical companies moving forward with new drugs. The question of how useful expensive new drugs are in comparison with standard therapies was raised.

Other chronic organ injury research is using a combination of biomarkers and imaging tools. The tools provide surrogate endpoints to define organ injury to obtain regulatory approval for drugs. This approach could be adopted by CRIC.

The relationship between the NIH and the pharmaceutical industry was discussed. Dr. Star mentioned that Barbara Mittleman, Office of Science Policy Analysis, Office of the Director, NIH, works hard to make such interactive studies much easier to create. The pharmaceutical industry feels like it "owns nephrology" (i.e., has excessive influence) and is surprised that the academic community would like to access its databases. Obtaining the right drug dose and prescribing it to patients is a central goal for treating CKD patients. The FDA's activity with the pharmaceutical industry regarding preclinical studies could help reach a consensus regarding the use of markers.

B. Working Group Discussions

Chair: William (Bill) E. Mitch, M.D., F.A.S.N., F.A.H.A., Gordon A. Cain Chair in Nephrology, Director of Nephrology, Professor of Medicine, Baylor College of Medicine

Dr. Mitch noted that the group was charged with identifying one or more proposals that the NIDDK could undertake in a reasonable period of time. Several ongoing studies will be completed soon, leading to available funds for research and clinical investigation. There also is room for improvement in the treatment of patients with CKD. It would be good to identify projects that could make a big impact on this population.

Dr. Mitch asked group members to identify project scientific areas during the first part of the session. During the next phase, participants would be asked to identify specific projects. The final phase of the group process would involve reaching a consensus on project ideas to send forward to the NIDDK.

Day 1: General Discussion

There was general support for the CRIC study and a recommendation that its coverage should be expanded to include a more diverse population.

Large trials are very expensive, and efforts should be made to optimize their total scientific outcome and utility (e.g., by storing serum and urine).

The cost/benefits of a variety of screening activities should be explored to determine whether an intensive approach to identify people with undetected CKD could yield benefits above the costs involved.

There is insufficient information on the burden of CKD in terms of cost; from a societal perspective, resources should be matched to address the burden of CKD. This idea perhaps could be studied as an add-on to CRIC or as a stand-alone study.

Potential CKD Project Areas

The working group identified the following potential CKD project areas:

- Developing a multidimensional approach to identifying people at risk for morbid outcomes. This might involve a panel of measurements that could detect change over time.
- Estimating the GFR in an accurate, cost-effective manner; identifying changes in the GFR; emphasizing how changes in GFR occur in older adults.
- Identifying good predictors of CKD progression.
- Defining, across the spectrum of impaired renal function, which of the classical therapies (e.g., blood pressure management) is effective.
- Studying the interface between CKD and CVD more aggressively to develop
- interventional studies.
- Developing more sensitive markers of early stages of CKD.
- Inhibiting CKD progression (e.g., a clinical trial that compares the implementation of optimal therapies with newly developed drugs, etc., to keep costs reasonable).
- Optimizing the use of information contained in the large genetic banks that are available.
- Identifying people at high risk for CKD, treating blood pressure at two different levels, and ascertaining the outcomes.
- Identifying kidney diseases in earlier stages across the age spectrum to enable earlier identification of high-risk groups and allow earlier intervention; identifying the most important treatable early signs of kidney disease.
- Focusing on screening at-risk subgroups, including children from diabetic families and
- obese children.
- Exploring interventions that allow patients to live longer via a large project (perhaps a joint effort between the NHLBI and the NIDDK could be undertaken with mortality as one outcome).
- Improving imaging to advance the knowledge of CKD and its progression.
- Revising ways in which care is delivered (e.g., identifying people at highest risk of progression, cost-effective workup procedures, computer-delivered interventions).

- Examining causes versus progression (e.g., environmental factors such as viruses or environmental toxins that are not yet identified).
- Examining agents that can slow CKD progression; studying many drugs at the same time and identifying those that seem to have the greatest potential.
- Maximizing the use of electronic health databases by developing a communication plan so that recommendations are passed quickly to primary care providers.
- Instituting a large, joint trial between the NIDDK and the NHLBI to study systolic blood pressures of 140 versus 120 and examine CVD and appropriate renal endpoints.
- Exploring patterns of blood pressure, especially with regard to elevated nocturnal blood pressure despite medication (non-dippers).

Refinement of Potential CKD Project Areas

The working group further refined their ideas and offered specific protocols that might be considered for implementation. These are to:

- Identify the genetic associations with the presence of renal disease using available data.
- Study the inhibition of CKD progression by implementing standard versus optimal therapies and determining which patients need the optimal therapies, as opposed to applying such therapies to all patients.
- Explore novel pathogenetic links between CKD and CVD to identify those with a high likelihood of becoming a therapeutic intervention.
- Identify patients with earlier stages of CKD by improving the estimating equation and improving the ability to estimate kidney function at milder stages of disease. Issues such as changing body size, etc., might be applicable to the elderly population as well.
- Examine CKiD study results that may be translatable to clinical trials, such as the progression and treatment of anemia in CKD.
- Identify and screen high-risk groups (e.g., hypertension, family history of diabetes, or obesity) of adolescents and children, collect the information in a database to be used as a resource for potential biomarkers, disease progression, and therapeutic interventions for CKD, and develop appropriate transition mechanisms that target both pediatric and
- adult populations.
- Effectively identify (including with novel imaging) and treat patients at earlier stages of CKD using three arms: optimized treatment at a research center, optimized treatment through a primary physician, and optimized treatment at a research center with
- innovative therapy.
- Identify patients, vigorously control for blood pressure, etc., and randomize those still showing significant proteinuria to a design with therapeutic choices. In discussion, it was noted that such a scenario could be used to screen drugs to determine which drug might warrant further study.
- Using existing data, study biomarkers directed at becoming predictors of CKD progression in longitudinal treatment cohort studies and assess (using stored specimens) the responsiveness of the biomarkers to treatment. Use available data to ascertain whether the biomarkers' responses to treatment in past trials match the responses of hard endpoints to those same

treatments. This will provide information on biomarkers that could provide benefits in therapy monitoring and selection.

- Use unselected populations to develop better, more precise estimates of kidney function. New markers and imaging modalities are needed to make better estimates.
- Develop a potential sequence of studies to test the reduction of nocturnal blood pressure and its effects on CKD and CVD. Phase 1 would be a pilot to test reducing nocturnal blood pressure (perhaps by altering the schedule for administering medications) and could be done efficiently at the end of the African American Study of Kidney Disease (AASK) Cohort Study, phase 2 would be an intermediate outcome trial, and phase 3 would be a clinical outcome trial. Phases 2 and 3 might involve participants in addition to those in the
- AASK Trial.
- Examine the effects of preventing acidosis in progressive renal disease. In discussion, it was noted that this could be done simply and inexpensively and would be nontoxic. Such a study is well suited to be a factorial in another study. The United Kingdom (U.K.) food industry was encouraged to lower the salt content of various foods; this had a beneficial effect in the U.K. and should be considered in the United States, as well.

Day 2: General Discussion

Research on pediatric CKD is lacking. Three suggestions for advancing research in this area were made:

- Create a pediatric arm for one of the potential trials (SPRINT, nondiabetic CKD and blood pressure).
- Include pediatric patients in the trial aimed at developing new ways to estimate the GFR and detect kidney disease at a younger age. It is difficult to detect kidney dysfunction in children because body cell mass measurements are based on height, which is inaccurate in obese children. The CKiD trial attempts to address this issue.
- Because children with CKD represent a small population, creating a platform or network of patients who can be quickly informed of and/or recruited to trials on pediatric kidney disease would be useful. It is not the charge of this meeting to develop networks, but because the field of pediatric nephrology has unique needs, this activity should be considered. Networks also represent an opportunity to identify new investigators. The Pediatric Oncology Network could be used as a template for a pediatric nephrology network.

Creating networks also would be advantageous for adult CKD research. Currently, patients are lost at the end of the trial, and must be recruited again for new trials. This means a delay in starting trials, especially because the population of CKD patients eligible for or interested in trials is small. Moreover, the response to solicitations to participate in trials is generally low. Creating a network or pipeline would help consolidate information that will help in the design and development of future trials.

There was discussion of research into genetic factors being used as a modifier of asymptomatic kidney disease or primary glomerular disease. But, there is no network to allow collection of DNA so addressing the problem would be difficult. Samples from at least 1,000 to 5,000 individuals would be needed for a proper genetics study.

This group stated its support of CRIC and CKiD and does not intend that the trials proposed here replace these ongoing studies of CKD.

Developing a better definition of what causes death in certain patients (i.e., why patients with CVD and kidney disease die) would be an appropriate issue for the group developing trials for ESRD.

Addressing CKD issues means impacting public health issues. A renal equivalent to the Diabetes Prevention Project, in which a limited number of interventions to prevent CKD are tested for efficacy and ease/success of implementation, would be useful. A significant challenge to decreasing the burden of kidney disease is health care delivery.

Plenary Discussion

Enthusiasm was expressed for the continuation of the CRIC and CKiD studies. A participant asked whether CRIC could be supplemented by private funds.

C. Potential CKD Clinical Trials Recommended to the NIDDK: Presentation to the Plenary

The group suggested five concepts for potential clinical trials related to CKD.

1. Anti-fibrosis Rx (exploratory phase II trials with novel design for efficacy) (48 votes)

Objective: This study would examine the efficacy of new drugs (anti-fibrotic or cytoprotective agents with no or limited phase 2 data in CKD patients and little enthusiasm from the pharmaceutical industry for further development) to slow progressive loss of GFR/function. Agents approved for non-renal indications and those with investigative new drug (IND) status could be included. One issue will be cooperation from pharmaceutical companies that will want their drugs tested in a population that is most likely to have a good response.

Population: This study would include patients with diabetic and non-diabetic CKD, with an eGFR between 30 and 60, and exclude those with relapsing/remitting immunologic diseases. Dividing the population into diabetic and non-diabetic CKD patients might still result in heterogeneity within a diagnostic category. However, a benefit to heterogeneity is that the results might be more broadly applicable. Fibrogenesis is a final common path in renal disease, but primary pathophysiology is unique and depends on virulence and location. However, dividing patients further by entry classification could yield too many small trials. Some participants noted that when the GFR falls below 60, diseases appear to follow a similar path. Changing the initiating process would likely not predict response to therapy.

Endpoints: Endpoints include proteinuria (primary), iGFR decline (at 0 and 12 months), and biomarkers (urine TGFb, urine col1 and col4 peptides, tubular markers). A subset of patients could undergo kidney biopsies. However, if the disease is focal, two biopsies (pre- and post-

treatment) may be insufficient to assess the effect. Collecting samples for gene array testing also could be considered.

Design: The quantitative outcome of the trial would be remission induction. The best drug should be at least 15 percent better than the runner up with 90 percent confidence. Another option is to design the trial to rule out the worst drugs. In the event all tested drugs "tie," this could indicate that there are many different drugs that offer a benefit. For a trial with placebo and 5 drugs, 50 to 75 patients per arm would be needed. This is possible, albeit challenging, if diabetic and nondiabetic patients are enrolled.

2. Systolic blood pressure control—SPRINT Trial with the NHLBI (38 votes)

Objectives: Determine whether treating systolic blood pressure (SBP) to a lower goal (<120 mm Hg) than currently recommended (<140 mm Hg) reduces CVD (+/- renal) morbidity/mortality in nondiabetic persons with one or more risk factors.

Rationale: SBP is associated with major CVD events and ESRD. A large proportion of blood pressure-associated CVD and ESRD risk has not been addressed (trial evidence is inconsistent or lacking, and therapeutic inertia and other health care delivery issues have hindered progress). A recent meta-analysis favors more blood pressure reduction. There was a nonsignificant trend toward benefit in diabetics, but a nonsignificant trend toward harm in non-diabetics. Lower systolic blood pressure is better for healthy populations, but this may not apply to patients with CVD.

Design: SPRINT is a 2-armed randomized controlled trial (RCT) comparing two drug therapies (thiazide or ACE/ARB) used to reduce SBP to below 140 or to below 120 mm Hg.

Eligibility: Men and women older than 55 with SBP above 130 mm Hg, with at least one additional CVD risk factor, nondiabetic, no prior stroke. Sample patients with an eGFR less than 60 plus low to moderate albumin/creatinine ratio.

Design: A sample size of 7,500 is needed for 90 percent power to detect a 20 percent effect. A sample size of 3,500 in the CKD stratum is needed for 90 percent power to detect a 25 percent effect.

3. AASK non-dipping—feasibility trial with development if positive (45 votes)

Rationale: High nocturnal blood pressure is associated with poor outcomes. The AASK Study is an ongoing trial with a high event rate, so recruitment issues can be avoided because data collection is complete in June 2007. Subsequently, some of the study participants can be transitioned to a pilot study to determine if nocturnal blood pressure can be lowered. Currently, the trial has approximately 500 patients, and approximately 120 would be needed for the pilot study. The patients in this study are loyal and probably would enroll in the new study.

Logistics: A therapy that can decrease nocturnal blood pressure must be identified. Also, there are questions concerning whether sufficient participants can be recruited de novo to participate in second and third stages of the trial (clinical outcome study with events).

4. Bicarbonate—feasibility trial with development if positive (53 votes)

Rationale: Bicarbonate therapy attacks three problems: 1) preservation of muscle mass and function in patients with CKD, 2) alleviation of bone disease in CKD patients, and 3) slowing of progression of CKD. Bicarbonate is nontoxic, may have a minor effect on blood pressure, and is cheap. There is no industry support for this therapy; therefore, the NIH will have to sponsor studies to test its efficacy. Animal data on bicarbonate are plausible, but not conclusive. A caveat to this trial is that a recent Cochrane review of metabolic acidosis in CKD found no evidence, in adults or children, that decreasing acidosis hinders CKD progression.

Design: Small, prospective, randomized controlled trial with 65 patients in two groups to test if bicarbonate limits progression better than ACEi.

5. CKD Epidemiology: Development of renal functional measurements (beyond serum creatinine and albuminuria) plus genetics and imaging (41 votes)

Rationale: New measures to monitor CKD are needed.

Design:

1. Recruit a population-based multi-ethnic group of participants with a measured GFR. Identify new filtration markers, markers of kidney damage, body composition, nutrition, and inflammation. Conduct a proteomic screen for new markers of CKD and validate the markers in existing populations.

2. Measure the GFR in existing population-based investigations (for example, a stratified random sample from the Framingham Heart Study). Correlate the GFR with past and existing measures and relate the GFR to future risk of events (such as CKD, CVD, or other events). Include imaging and functional response to stressors in subgroups.

3. Pool the data from new (unselected) and existing (selected) populations measured with the GFR for increased power, application of state-of-the-art statistical methodology, and sharing with the scientific community.

4. Apply the state-of-the-art markers developed in Aim 1 and identified in the literature regarding NHANES 1988-94 and 2003-2009 and make the data publicly available within 6 months.

Plenary Discussion

A question was asked about the non-dipping with regard to blood pressure. Despite the control of blood pressure, the AASK study found limited benefits in terms of doubling of serum

creatinine or death. The proposed concept focuses on reversing the night-time blood pressure to create normal "dipping." It is unknown what causes the pathologic pattern associated with "non-dipping."

A nocturnal blood pressure study could be accomplished in three phases: 1) switch to daily dosage; 2) conduct an outcome study; and 3) conduct a formal clinical outcome study.

Regarding antifibrosis treatment, the goal would be to select a few drugs that seem most promising. This would not be a formal RCT, but would include a reasonable evaluation of efficacy, in which drugs could be ranked in order of effect or identifying those with no benefit. If type 1 errors were ignored, the sample size could be reduced.

A participant requested clarification on the SBP concept. The response was that the method of estimating the GFR is not ideal. There are three or four other markers available in addition to cystatin. The GFR could be measured by a "gold standard" method to supplement biomarkers. This study would involve several hundred patients and be based on ethnicities.

IV. End Stage Renal Disease (+ Access and Chronic Allograft)

A. Plenary Presentation

Allan Collins, M.D., F.A.C.P, Director, Chronic Disease Research Group, Minneapolis Medical Research Foundation, Professor of Medicine, University of Minnesota

Dr. Collins provided an overall picture of ESRD based on data from the USRDS 2006 ADR. He described the growth, incidence, prevalence counts, and rates of the ESRD population. In addition to the new dialysis population starting each year, there are returning transplant patients. The study also looked at mortality patterns from incident patients, the patterns from the first year versus later years, and peritoneal dialysis (PD) compared to hemodialysis (HD). In 2004, the prevalent population had reached 472,000 with estimated total ESRD expenditures of $32 billion. The actual growth is within -0.5 to -0.9 percent of the conservative estimates. The ESRD program costs now accounts for 6.8 percent of the Medicare program. Incidence counts are lower.

He shared data concerning adjusted incidence rates, including primary diagnosis such as diabetes and age. One of the studies concluded that the more conservative population-based incidence rates may be less representative of the potential progress that has been made in treating diabetes and reducing complications such as ESRD. Regarding trends in ESRD death rates and survival, the study looked at incident-based interval death rates and comparisons in 5-year survival rates of the HD, PD, and therapy populations, including first-year HD death rates. The incident-based death rates for the ESRD population have declined. First-year death rates are flat across all age, gender, race and causes of ESRD. For HD, the first year mortality rates have been unchanged for 11 years, but death rates for Years 2-5 have decreased. Death rates are down across all years for PD. Additionally, fewer patients are entering PD, suggesting there is greater selection bias.

Mortality issues that should be addressed include: the first-year death rates on HD; the apparent selection bias for PD; no RCTs compare HD and PD (or home frequent HD versus PD); transitional death rates on PD may be secondary to changing CVD event rates over time; cardiovascular disease progression and PD membrane changes may be secondary to the dextrose solutions; no large-scale RCTs compare glycemic sparing therapy on PD versus HD, or home HD.

He provided current data about clinical aspects of care, which should encompass: guidelines and targets across the spectrum of care; dialysis adequacy (e.g., the time on treatment FHD study); anemia treatment (over shooting of Hb levels in incident patients may increase the risk of death); diabetes and cardiovascular care; and vaccinations. He also shared the new data from the USRDS on bio-chemicals from tests focusing on HbA1c and four lipid profiles (TC, LDL, HDL, and TG).

Dr. Collins concluded with the ESRD mortality dilemma and RCTs. The National Cooperative Dialysis Study (NCDS) in the late 1970s indicated that longer time on dialysis and a lower TAC urea were predictors of the outcome. The Kt/V was developed from the observational re-analysis of the NCDS, not an RCT. The Hemodialysis study (HEMO) study showed little difference in outcomes based on a higher KT/V and high flux membranes. The Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) study showed no difference in outcomes with more PD therapy. Anemia correction to normal Hb levels has shown neutral or adverse impact on mortality. The 4-D Statin trial showed a neutral impact on mortality, and the Sevalemer trial showed no impact on mortality. There are two possible explanations: (1) nothing makes a difference once a patient reaches ESRD, or (2) everything makes a difference, particularly in the first year.

Plenary Discussion

One participant cautioned that the dialysis checks are important, but patients still must be encouraged to have cholesterol and other tests performed.

There is a potential for a large study using reverse epidemiology (i.e., an observational trial), as the population has been understudied; however, it will not be easy or simple.

A combination study that looked at Years 2-5 of survival was suggested. Regarding CVD death rates, it was noted that there is a clear connection between the use of catheters and the diabetic death rate, but the results from clinical trials often are different than observational data.

Softer endpoints, such as smell, appetite, sleep disturbance, and other QOL elements, could be used to develop quantitative data.

The critical issue in dialysis is that how patients die, including those at home or those who have "sudden death," needs to be labeled in a more meaningful way for ESRD research. The NIDDK, the NHLBI, and the National Heart Association have an active interest in coordinating their studies.

Inflammatory events play a role with higher risk patients, particularly with early mortality and the young.

A question was raised about the use of reverse epidemiology to warn against confounding bias. ESRD is a complex disease. A single intervention likely would have only a small impact. ESRD involves a select population that should not be compared with the general population. Better data are needed to inform trials.

B. Working Group Discussions

Alan Kliger, M.D., Chairman, Department of Medicine, Hospital of St. Raphael

Dr. Kliger chaired the ESRD breakout session. He reviewed the charge to the ESRD breakout group and stated that they will be looking at potential clinical trials for ESRD through discussion of potential clinical trials submitted by the meeting planning group. He commented that it may be more beneficial to think of trials with multiple interventions because single intervention trials may not be as useful for this population. Before addressing individual trials, a discussion ensued on the strategies that need to be addressed in planning for future trials.

The overall goal of an ESRD trial should focus on decreasing morbidity and mortality of ESRD patients. Health services research tells us that if the goal is to reduce mortality, the trial should be powered to show results in decreasing end organ disease rather than targeting specific risk factors. For example, targeting cholesterol through statin therapy does not result in reduction of disease; it is becoming clear that other types of lipids may secure a better outcome.

The fastest growing ESRD population is those who have received kidney transplants, with approximately 90 percent of transplant patients progressing to ESRD. Another aspect that needs consideration is the decreasing NIH budget. If a new trial is to be proposed with statistical power needed for this study (approximately 1,000 patients), there would be a high cost (approximately $10-15 million per year), although a trial in these patients could have an enormous public health benefit.

Issues related to proposing a trial in the ESRD population include the following:

- The trial would have to be multifactorial, although this would demand stricter inclusion criteria, which may reduce the possibility of accruing enough patients to power statistical outcomes.
- Most kidney patients are on multiple drugs, and finding enough patients not taking drugs that may interfere with the interventions would be challenging.
- There is a need for a trial that includes children and adults and that is expanded to international research centers for additional patient accrual.

Dr. Kliger asked that the session continue with the presentation of suggested trials. These should be discussed with the goal of coming to agreement on a few trials that could be proposed to the NIDDK. It is not so important to come away with a fully designed trial as it is to develop a concept for a trial that can be more fully developed after the meeting. The submitted trials were

conducted by asking a clinical question and describing how the question could be addressed in a clinical study.

Potential ESRD Clinical Trials

The following highlights focus on discussion of individual submitted clinical questions and the type of trial suggested for answering each question. Descriptions of the trials were included in the meeting materials and will not be described in detail here other than in the discussion and opinions of the breakout participants.

1. How can we improve cardiac outcomes in the general hemodialysis population?

This 2 x 2 factorial intervention trial would target end-organ effects with cardiac mortality as the major outcome. Suggestions regarding the proposed design include disqualification of those with past myocardial infarction (MI), and those taking specific drugs (e.g., aspirin and statins). This trial would have problems obtaining IRB approval because of the use of placebo with statins, and it would be difficult to randomize.

2. Is atherosclerotic coronary artery disease (CAD) a common cause of CV events in dialysis patients?

This observational trial addresses an important question: Why do dialysis patients die of MI? Data indicate that 44 percent of dialysis patients have AD, but have no symptoms. Other studies have observed this, but there are no followup studies to explain why this is so. A problem is that there are small numbers of deaths from AD in this population (less than 300 in 5 years). The CRIC study, which soon will have results, may be able to partially answer this question. Data from Kaiser show that CVD is associated with CKD approximately 40-60 percent of the time, but do not explain why. The proposed study may not have results for many years.

3. What are the optimal blood pressures in hemodialysis patients?

This observational study is possible, but blood pressure may not be the best measure; 24-hour ambulatory blood pressure measures may be more useful. This would not be a large study, and could be conducted pre- and post-dialysis to gain more insight. There is some interest in understanding "dippers" versus "non-dippers". There was discussion of designing this study around heart failure patients, and randomization should be considered to show delivery of care is important in blood pressure control. It also may be beneficial to combine this observation study with an intervention trial of blood pressure-lowering drugs such as ACE inhibitors, beta-blockers, or aldosterone antagonists. There was an unpublished Japanese study that indicated that lowering blood pressure decreased mortality.

4. Multiple studies on pediatric kidney disease. These will be addressed *in toto*.

These studies address the need for more knowledge about pediatric kidney disease. The clinical questions are:

A. The development of CVD in children with CKD and ESRD.
B. Determination of dialysis adequacy in pediatrics.
C. The utilization of recombinant human erythropoietin (EPO) and recombinant human growth factor hormone (GH) is poor in patients with CKD/ESRD.
D. The optimal target hemoglobin for children on dialysis and post-renal transplantation.
E. The relationship between medication non-adherence and transplant outcome in the adolescent population.
F. Quality of life of pediatric patients with ESRD and following kidney transplantation.
G. The transition of pediatric ESRD patients from pediatric to adult care.

There is a great need to study ESRD in the pediatric population, although the lack of evidence in almost every proposed study would contribute to the difficulty in designing a trial. The prevalence of atherosclerosis is low in children, which also makes a study for this condition difficult.

For the EPO study, it is known that the prevalence of anemia is significant in this population, and studies of GH have not determined what a target hemoglobin level should be. It was suggested that an observational trial in GH would be small but beneficial to address some of these questions.

For study D, there are only about 1,400 patients in the United States and all of them would be needed for the study. Currently, there is little data available on this topic, and it seems important to conduct such a study. This would have a public health benefit, but it may have to be a cross-age study to accrue enough patients. There was a lot of interest in finding answers to the question posed.

For the study of adherence among pediatric patients (study E), it was noted that mortality of pediatric transplant patients has not changed in the past 5 years, even though new allograft drugs have been developed for transplantation. Parents are a large part of the adherence equation among pediatric patients. There is a need to know why 10 to 15 percent of pediatric patients still have rejection of the transplant.

For questions F and G, there is little data available to design a trial for these topics, and neither meets the criteria as a large public health issue. These should be handled as educational issues in a potential lifestyle study.

5. Does dyslipidemia contribute to CV events in dialysis patients?

There have been some studies (e.g., CHOICE, SHARP, and AURORA) that may have lipid data that might be assessed before designing this trial. It is difficult to imagine how this could be translated to care. It would have to be a large observational trial, with a possible small intervention trial included. Enough data is available to indicate that statins are not an appropriate intervention in dialysis patients.

6. Does aldosterone antagonism decrease CV events and mortality in ESRD patients?

There are data in this area on non-ESRD patients. There would need to be a pilot study before a larger study could be planned. Existing data in ESRD patients come from small trials, which have not definitively answered this question.

7. Does screening for coronary artery disease (CAD) reduce major adverse cardiac events (MACE) in candidates for kidney transplantation?

This could be an RCT that would build on similar smaller studies (e.g., VA study) that have shown screening leads to unnecessary revascularization procedures in asymptomatic patients that may cause more harm than good. It is thought that surgeons would not want to participate because some randomized study participants would not have the full work-up before surgery, although it was noted that preliminary talks with surgeons indicate they may be interested. It was noted that lawyers would have a problem with this study, as would the IRB, although CMS may find it intriguing.

8. Impact of vascular calcification on survival and CV events in ESRD patients.

This trial investigates maintaining vitamin D and parathyroid hormone (PTH) levels within a target range, and its impact on survival. This may be similar to the EVOLVE trial, but would address a major public health issue because of the benefits already shown for maintaining levels of vitamin D in CV patients. This would have to be an RCT with comparisons to usual care. Data show that 70 percent of kidney patients have less than optimal levels of vitamin D. It was not determined what level of PTH to use. There was a lot of interest in this trial idea; an advantage would be that the trial could be stopped if benefits are shown before the scheduled end of the trial.

9. How are we to increase AV fistula prevalence and decrease catheter use?

The core issue is that we do not understand fistula maturation; if we did, we could improve current therapy and help design future interventional trials. An observational trial could answer some of these questions. A further question would be to determine predictors of fistula failure. This would be a very costly trial ($150−350 million), but of great public health importance. Expertise of fistula surgery is an issue that could be addressed first through educational programs. The NIDDK DAC program may have answers to some of the questions.

10. Can beta blockade and an RAS inhibitor decrease mortality and CV events in ESRD patients?

This study would have to be large with possible pharmaceutical involvement. A pilot study could be conducted before the larger trial. The trial would address the cause of mortality in ESRD patients.

Other Suggestions

After formal presentation and discussion of submitted clinical trial ideas, a discussion of proposed trials not submitted was held. The following ideas were proposed:

1. Leverage the USRDS database to answer some of the questions posed in submitted trials.
2. Devise and test computer programs to determine variables in trials. Define the correct level of delivery of care (e.g., for dosing and vitamin A).
3. Outcomes in heart studies could include mortality, but there is a need for quality-of-life measures. There also are questions about antioxidants and other issues of nutrition and dysmetabolism that should be addressed in trials. There are ongoing intervention trials addressing nutrition and metabolism in ESRD patients, but results are not published. It would be possible to conduct a quality-of-life trial that included mortality as an outcome. A problem with investigating nutritional components is the need to go beyond a 2 x 2 factorial design, which is not recommended in any of the proposed trials.
4. Obesity is an issue that should be studied in transplant patients.
5. There still is the question of whether glucose control is of importance in ESRD patients. It is difficult to investigate glycemic control in these patients because of the complicated relationship with other markers. CRIC is collecting glycemic data but it is not one of the interventions.

Discussion of the Trials to Recommend

Dr. Kliger instructed the breakout participants to focus on trials that should be recommended to the NIDDK. He requested that they look at four to five potential trials, and think about combining some aspects of different trials to include in a single trial. It would be appropriate to recommend at least two trials in special populations. Discussion highlights are described below.

After 15 years of research, there is little information on pediatric GH or on the impact of transplantation on growth and cognition. There are approximately 6,000−7,000 pediatric ESRD patients each year, enough to conduct a trial.

A study in allograft patients should be recommended because followup outcomes data are not available. This could be combined with a CVD risk screening RCT.

An intervention trial to investigate reducing morbidity and mortality in dialysis patients is needed. The trial could include comparisons of ACE inhibitors, beta-blockers, aldosterone antagonists, or vitamin D agonists in a 2 x 2 factorial design. Risk factors should be assessed in this trial. The consensus was that anything more than a 2 x 2 factorial design should not be considered. Some participants thought that a trial using β-blockers would not be new enough to be considered innovative.

There is a need for an observational trial investigating early mortality in dialysis patients. Approximately 24 percent of new dialysis patients die during the first year, and the first 90 days may be the critical time when increases in mortality occur. This increased mortality occurs across all age and race groups. The trial could consider potassium monitoring, possibly through implantable monitors, although it is unclear if the information gathered would be useful for answering the question. This is a critical care issue and it was recommended that USRDS put this data element in their data collection system. It also is important to have data on the causes for dialysis in these patients.

We still do not know the appropriate time to begin dialysis. Earlier may be beneficial, but there are no data on this. There is a study in New Zealand that is addressing this issue, but data is not yet available.

There needs to be better modeling in ESRD. Contrary to the United States view on urea kinetics, internationally, it is viewed as the wrong measure to use. Other countries are moving to measures of β2-microglobulin, phosphates, volume modeling, and other markers of kidney function to benefit clinical decisions. There have been no RCTs on this topic.

Plenary Discussion

Issues surrounding blood pressure were discussed. It was pointed out that the optimal blood pressure level is unknown. Additionally, blood pressure is taken pre- and post-dialysis, but not during dialysis and is not compared with non-ESRD patients.

The issue of bias was discussed. There is a significant amount of data on dialysis but very little careful observational study data.

There was interest and enthusiasm in several concepts, including: solutes beyond urea; and, a reduction in morbidity and mortality, particularly to reduce the high death rate in Year 1.

The sequence of catheter and defibrillator placement was discussed. The frequency of infections due to catheters was noted.

C. Potential ESRD Clinical Trials Recommended to the NIDDK: Presentation to the Plenary Session

1. RCT: BB + RAS inhibition in CVD

Rationale: This concept targets CHF, CAD, sudden death ambulatory blood pressures, and vintage, associated variables. In cardiac diseases in dialysis patients, targets of beta-blockers and RAS blockade (regardless of underlying risk factors) include: left ventricular hypertrophy (LVH) and CHF, obstructive CAD, arrhythmia, and sudden death. Physiological rationales include increased sympathetic activities in HD patients. Moreover, RAS inhibition in HD patients decreases pulse pressure, helps with the regression of LVH, decreases myocardial fibrosis, decreases inflammation and oxidative stress, and decreases sympathetic activity.

2. RCT: Calcimimetics versus vitamin D: techniques to reduce calcium/phosphorus product and optimize vitamin D use to reduce vascular calcification and CVD

Designs: Regarding vascular access, an observational study could focus on the reasons for poor maturation of AVF, and an RCT could aim to decrease infection from catheters.

The working group encouraged the NIH to fund this study.

3. Determinants of fistula maturation observational study

Rationale: Fistulas are associated with lower morbidity, mortality, and cost; a 10 percent increase in fistulas should lower annual costs for HD patient care by $350 million. In addition, 25 to 50 percent of fistulas fail to mature and the etiology is unknown. The maturation failure increases catheter prevalence.

Design: A prospective, multicenter observational study will elucidate the etiology of fistula maturation failure, establish early predictors of maturation failure, and enable early intervention.

Enrollment and Duration: 600 patients, 6 to 9 sites, 3 years total.

4. Transplantation

Designs: As an RCT, a study could evaluate pre-treatment CVD. An observational study could be designed to develop a CRIC-like database and DeKAF add-on.

5. Observational trial: mortality/morbidity in the first 90 Days of dialysis

Design: This concept considers the use of catheters, AKI, interventions, complications, and the effect of co-morbid conditions on mortality through a medical records review. It could draw on the work of USRDS Special Studies. It could consider the following: the relationship of blood pressure level to LVH and CVD, incorporating other CVD risk factors; Ca/P product; fluid status; arrhythmia; and anemia. This could also incorporate diabetes and glycemic control, as well as examine measures of dialysis delivery.

Other—Pediatrics

The working group noted the importance of ESRD research in pediatrics, although it did not develop or refine a study concept. It was suggested that an RCT could study adherence or look at neurocognitive functions (GH, ESA).

Plenary Discussion

A discussion ensued about the fistula data and that the source should be cellular or hematic. The identification of the modes of failure will result in sustainability.

A participant suggested that one could look at some specific populations and learn from looking backwards. Another attendee, however, noted that to make inferences, one has to select a survivorship group and this can result in drawing false inferences, albeit there are ways to avoid bias.

The study of the beta-blocker, particularly in the hypertension field, was recommended as a practical, large trial. The approach could be to "attack" what is known, as nothing has been shown to work. This combination likely is the best of what currently exists and can have the best

possible effect in the short-term. It is doable and fairly inexpensive. This study has both primary and secondary outcomes, including dialysis and measures of QOL and functional status.

A participant wondered why diabetes was not included among the recommended concepts, noting that it could serve as a confounder. The working group responded, agreeing that it was important, but pointed out that other issues held greater priority or promise.

Regarding the calcification trial, the working group urged the NIDDK to conduct an independent study on the issue.

V. Final Comments

Robert A. Star, M.D., Acting Director, Division of Kidney, Urologic, and Hematologic Diseases (KUH), NIDDK

Dr. Star thanked all attendees for their assistance in providing NIDDK excellent advice. The NIDDK staff listened carefully to the discussions, and will work internally to develop some of these ideas. Additional meetings also may be held for further input.