Opening Words for CJASN

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Opening words for CJASN! We are pleased to participate in the inauguration of this new journal for clinical research on kidney disease. Fostering the clinical research enterprise in nephrology is a major focus of the activities of the Kidney, Urology, and Hematology Division of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) through its National Kidney Disease Education Program and a rapidly growing portfolio of clinical and translational grants on kidney disease. We therefore enthusiastically welcome this new forum for examination of this work. The inaugural issue of CJASN is a cause for celebration of the strengths of clinical research in our discipline and for assessment of the challenges that it faces ahead.

Clinical research begins with observations, either by investigators at the bench or by clinicians at the bedside. The bidirectional flow of observations—bench to bedside, bedside to bench—is critical for the genesis of new ideas. The evolution of clinical research as a rigorous scientific discipline has benefited from the growing recognition that clinical researchers require a period of specialized training in investigative methods. As a result, we have seen the emergence in the past 10 yr or so of a new cohort of superbly trained renal clinical investigators who have been encouraged, at least in part, by new National Institutes of Health (NIH) mechanisms to support careers and training in clinical investigation, such as the K23, the K24, and other training awards. The development of a new journal that focuses on renal clinical research is a logical consequence of this growing clinical renal research community, whose work this journal will highlight, promoting further progress in research methods, study designs, and analytic tools for clinical research in nephrology.

Observational Studies: Databases and Cohorts

Clearly one of the strengths of our discipline is the vigorous renal epidemiology community. A major stimulus has been the rich vein of information about end-stage disease that comes from the Center for Medicare Services through the United States Renal Data System (USRDS) and comparable data sets from other international registries. Extensive expertise in mining of these data has grown up around the USRDS, which has provided a training ground for kidney disease epidemiologists. Other important resources for renal “number crunching” have come from National Health and Nutrition Examination Survey, the Nurses Health Study, other cohort studies, and renal clinical trial data sets. The NIH is currently engaged in establishing two cohorts of individuals with chronic renal disease, CRIC (the Chronic Renal Insufficiency Cohort Study) (1) and CKiD (Chronic Kidney Disease in Children), which we are confident will provide important new data resources and scientific contributions. We have also recently entered into a partnership with the National Heart, Lung, and Blood Institute to encourage studies of renal outcomes using the rich cohort study populations that are maintained by that institute (www.nhlbi.nih.gov).

Despite the impressive strengths of renal epidemiology, the evidence base for many of the important clinical questions that nephrologists face remains inadequate. The golden currency for evidence-based medicine is, of course, the adequately powered, randomized, clinical trial. Why are there not more trials? We certainly have no shortage of important problems that need to be addressed. Despite the infrequent development of new drugs specifically for renal indications, largely because of the time and sample size requirements for phase III trials, there are countless important questions founded on a strong biologic rationale regarding the diagnosis, prognosis, and treatment of renal diseases. Nonetheless, clinical trials are long and expensive to conduct and do not always yield definitive answers. A few comments on contributing factors follow.

Outcome Measures

We consider better methods to measure the progression of chronic kidney disease, especially in the early stages, to be one of nephrology’s most pressing unmet needs. A promising new drug that is developed to prevent the progression of kidney disease would face a long and arduous set of hurdles as a result of limitations in many of our measures of disease progression. We need strategies to reduce the barriers to conducting this important type of investigation. Many of the problems that are encountered in the design of renal clinical trials are a consequence of shortcomings of the available outcome measures and a limited range of established analytic strategies for use of composite outcomes. Risky interventions ultimately will need to establish their benefit in large-scale phase III trials using hard outcome measures, such as time to onset of renal replacement...
therapy. However, we need strategies to prioritize which treatments deserve these major research investments. We often rely on GFR, but GFR-based outcomes necessitate large trials: The substantial day-to-day variability in GFR in the same patient, the magnitude of measurement errors, and the relatively modest yearly decline in GFR in most patients with progressive kidney disease all contribute to the problem. Directly measured GFR (i.e., inulin or iothalamate clearance) imposes substantial burden and cost, without reducing intrasubject variability. Use of a prespecified decrement in estimated GFR or a doubling in serum creatinine reduces subject burden, and there is some evidence that use of cystatin may help somewhat in the “close to normal” range, a subject of active current investigation (2).

Better measures of GFR would not solve all of our problems, however. The most important limitation of GFR-based outcome measures is that the magnitude of changes in GFR, especially in the close-to-normal range, does not necessarily reflect changes in clinical outcomes. Pathology may progress without a decrement in GFR, and an increase in GFR may not indicate amelioration of disease. Two major NIDDK trials, AASK and Modification of Diet in Renal Disease (MDRD), were bedeviled by interpretation problems because two of the interventions, the calcium channel blocker in AASK (3) and the higher protein diet in MDRD (4), actually increased GFR, at least transiently, in many patients while worsening other measures of renal prognosis.

So what are the alternatives? Pathology-based outcome measures clearly are valuable, but methods for morphometric assessment or semiquantitative scoring have to be validated very carefully, and the variability has to be established on a subject population similar to the study population. Ideally, there should be evidence that correlates the biopsy findings with direct measures of renal outcomes. Some encouraging progress has been made with such approaches (e.g., [5,6]), but wider use of biopsy-based methods for renal trials is likely to be limited by the significant costs, major subject burden, and the small but significant risk associated with repeat biopsies. Quantitative measures of urinary protein excretion need to be incorporated more effectively into renal trial methods. Protein excretion is established as an outcome measure in certain states, for example prevention of microalbuminuria in individuals with diabetes (7) or remission of nephrotic syndrome (8,9). However, there is no effective consensus on how to use measures of protein excretion in other clinical research settings. For example, take the problem of assessing early diabetic kidney disease. There is increasing evidence that neither low GFR nor the presence of microalbuminuria alone completely predicts renal risk (10,11). It is possible that early disease could be assessed better by a composite measure that incorporates GFR estimation and repeat measures of albumin-to-creatinine ratio. There are promising innovative approaches on the horizon that we hope will be examined in these pages. Proteomic methods may provide surrogates or at least biomarkers of progressive disease. Imaging methods also need more attention. The CRISP consortium is making substantial progress in use of MRI to measure the growth of the cystic kidney (12), progress that may facilitate trials in this disease. An interesting and understudied area is the use of imaging methods to assess interstitial fibrosis and scarring. Collagen deposition and/or scarring has established prognostic significance on renal biopsy, especially in the setting of allograft nephropathy (13). As well, all nephrologists are aware of the increased ultrasound echogenicity of the end-stage kidney, but whether scarring and fibrosis can be measured noninvasively early in disease is uncertain but of substantial interest.

**Patients**

We hope the somewhat mundane but absolutely critical problems of patient recruitment will not be neglected in the pages of this journal. Patient recruitment into trials is never easy, and there is no “one size fits all” strategy. It is important that each study group be tailored to the problem and the intervention being studied. For example, studies of acute renal failure need the involvement of intensivists and studies of dialysis vascular access need the participation of vascular surgeons. Increasingly, cancer and cardiovascular trials are using community practitioners, an approach that deserves attention in the renal community, and may be of particular value in studies of early disease.

There are also a number of important issues in deciding on the patient population for trials, and, again, careful preliminary assessment of the best population to study can very much strengthen trial design. The best trials are built on strong epidemiology: It is important to know the demographics of those most burdened by disease, to have well-grounded estimates of likely event rates, and to be able to make educated guesses about the population who might benefit most. The USRDS has been an invaluable resource for trial design in ESRD; although we lack comparable data sets for chronic kidney disease, a number of resources are becoming available, including the CRIC cohort study (1).

**ClinicalTrials.gov and CJASN**

We very much welcome the willingness of the Editorial Board of CJASN to highlight NIH-sponsored trials in these pages and to provide information about ongoing trials that are recruiting. We hope that this will be a regular feature and that both the progress of existing trials and debate on the best topics for future trials become regular topics for this new journal. We also hope that CJASN will be a forum for broader discussion of trials by all sponsors, private and public sector. Clearly much important work on treatment of kidney disease is sponsored by the pharmaceutical industry, but the challenges discussed here have been the focus of only limited private-sector investment. One hope for this new journal is that, by contributing to improvements in renal clinical trial methods, it can help to increase pharmaceutical interest, so there is much work to be done and clearly an important role to be played by CJASN! We wish Godspeed to this new enterprise.
References


