Diagnostic and therapeutic approaches to AKI secondary to ischemia, sepsis, and nephrotoxins are receiving increasing attention as the effects of AKI on hospitalization, morbidity, and mortality and on the acceleration of CKD progression to ESRD are becoming better illuminated. Numerous studies have delineated the high mortality risk in patients with AKI, especially in patients with sepsis or trauma and in patients undergoing cardiovascular surgery (1). The National Institutes of Health (NIH) has promoted interest in developing diagnostic and therapeutic approaches to AKI through scientific meetings and clinical programs. In September 2000, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored the following meeting: “Design Issues for Clinical Trials in Acute Renal Failure,” in which experts in nephrology and other disciplines (e.g., critical care medicine, neonatology, clinical trials methodology, and biostatistics) with a wide array of scientific and clinical expertise considered investigative strategies to overcome barriers to improving outcomes in AKI (2). Meeting participants identified several complex issues in moving drug targets to trials, as well as scientific opportunities for future research. Consideration was given to the multifactorial nature of the disease processes, the heterogeneity of patient populations, the severity of clinical disease and comorbid conditions, the existence of multiple overlapping outcome measures, and the inadequacy of clinical trial design. No best clinical trial design was identified because potentially preventable AKI (e.g., after contrast administration or cardiac surgery) is relatively uncommon in the general population and is often mild, whereas severe AKI in septic or intensive care unit patients is characterized by clinical heterogeneity and is less predictable. The ensuing decade witnessed an intense focus on the following: translating fundamental biologic discoveries into informative biomarkers of AKI and novel drug targets; using clinical and epidemiologic studies to assess and quantify new clinical disease definitions, risk scores, and clinically relevant outcomes; conceptualization of new trial designs; and establishing repositories for clinical data and specimens. During this period, the annual number of articles on ARF or AKI in PubMed increased dramatically (Figure 1).

Several professional groups, including the Acute Dialysis Quality Initiative, the Acute Kidney Injury Network, and the American Society of Nephrology’s AKI Advisory Group, worked to promote and accelerate translational studies. The clinical interest in and understanding of the importance of AKI has spread from nephrologists and basic scientists to critical care physicians, cardiologists, and industry scientists. Indeed, AKI has been identified as a worldwide area of clinical need and opportunity. Whereas epidemiologic studies have quantified the incidence of AKI in as many as 60% of critically ill patients (1), other studies have emphasized the importance of AKI in non-critically ill populations (3). For example, in one recent study, as many as one-fourth of patients with nonsevere community-acquired pneumonia developed AKI (3). Observations from administrative databases that a substantial proportion of patients who have AKI do not fully recover renal function, and may require permanent renal replacement therapy, have had an important effect on the global epidemiology of CKD and ESRD (4,5).

Numerous observational studies have confirmed these initial findings (6–8) and have raised the awareness of AKI at World Kidney Day, emphasizing the complex bidirectional interactions between AKI and CKD (9). Future long-term human and animal studies on the natural history of AKI are awaited and may demonstrate a causal relationship between AKI and CKD/ESRD. Attention must now also be centered on the prevention of AKI and the treatment of established AKI to minimize the severity of injury, which correlates with morbidity and mortality (10). The clinical observations delineated above have led to a renewed interest in AKI by academia and industry, which have identified reducing the morbidity and mortality of AKI and CKD as major and growing unmet clinical needs with substantial therapeutic potential. Translating existing basic science AKI knowledge regarding cellular involvement/injury, pathophysiology, and therapeutic targets into clinically preventive and therapeutic agents is now a primary goal for many academic scientists and multidisciplinary academic programs. This newfound excitement and commitment to translation of emerging knowledge into clinically important tools (e.g., disease definitions, risk scores, and biomarkers) and therapies (e.g., drugs and devices) stems from investigator passion for improving patient care. Industry–academic partnerships have evolved to fuel scientific and clinical opportunities that may address important clinical needs.

Over 10 years have passed since the 2000 NIDDK conference. In response to growing interest and clinical
needs, the NIDDK convened a two-day conference “Clinical Trials in AKI: Current Opportunities and Barriers” in December 2010, with the goal of having a broad discussion about contemporary scientific opportunities and barriers to implementation of clinical trials in AKI. The conference involved NIH scientists and staff, academic scientists and clinicians engaged in AKI research and patient care, US Food and Drug Administration (FDA) representatives, and industry leaders. The first day focused on lessons learned from previous trials and challenges in clinical trial design. Clinical trial leaders from non-nephrology disciplines presented their experiences and views on lessons learned from ophthalmologic studies (Dr. Frederick Ferris, National Eye Institute), pharmaceutical company rheumatology clinical trials (Dr. Zeb Horowitz, Celgene Corporation), critical care trials (Dr. Taylor Thompson, Massachusetts General Hospital), clinical trials in patients with sepsis (Dr. William Macias, Eli Lilly and Company), and considerations regarding why supposedly well designed trials fail (Dr. John Lachin, George Washington University). A FDA representative (Dr. Aliza Thompson) presented new “fit for purpose constructs” for qualification of biomarkers for specific purposes (surveillance, diagnosis, risk assessment, outcome prediction, therapeutic efficacy, etc.). These presentations were complemented by breakout sessions focused on critical areas including patient selection, development of tenable end points, qualification of biomarkers, and consideration of sample size. On the second day, participants were divided into groups to discuss and design trials aimed at primary prevention and therapy of established AKI. At an industry round table, representatives from a range of entities, including small biotechnology to large pharmaceutical companies, gave seven presentations on topics including work on small molecules that might ameliorate the course of AKI and medical devices to improve the care of AKI patients.

The accompanying three articles based on the deliberations of the conference workgroups cover overarching methodological issues affecting AKI study design, as well as specific considerations for trials of AKI prevention and for trials of interventions in special populations with established AKI (e.g., septic or intensive care unit patients). There was a rich mutual exchange among the different groups represented. The aim of the meeting participants is that the information contained in these articles will be useful as the field progresses toward effective surveillance, diagnostic, and therapeutic approaches to minimize the occurrence and severity of AKI and to improve patient outcomes.

Disclosures
None.

References

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