Chronic Kidney Disease and the Public Health
Gaps in Evidence From Intervventional Trials

Jonathan Himmelfarb, MD

In recent years, chronic kidney disease has received increased attention as a leading public health problem.1 The kidney disease burden, measured in terms of prevalence, associated economic costs, and morbidity, is substantial and increasing. In the United States, more than 400,000 individuals have end-stage renal disease (ESRD),2 for which life can be sustained only with renal replacement therapy such as dialysis or kidney transplantation. In a recent population-based study of US residents 45 years and older, 9.5% had a first-degree relative with ESRD.3 It is estimated that by 2015, more than 700,000 individuals in the United States will have ESRD, and more than 107,000 ESRD-related deaths will occur annually.2 Cardiovascular mortality in patients with ESRD is 10- to 20-fold higher than in the general population and is the leading cause of death.4 Mortality rates for patients with ESRD have shown only modest improvement over the past 2 decades.

The prevalence of individuals with chronic kidney disease (CKD) at less severe stages (not requiring renal replacement therapy) has been estimated at 11% of the adult US population, or approximately 19.2 million individuals.1 There is a robust but poorly understood association between the severity of CKD and increased risks of cardiovascular events and death.4 For example, in a large community-based sample,5 the adjusted hazard ratio for death and cardiovascular events from 1998 to 2005, 80% excluded patients with ESRD and 75% excluded patients with known CKD. The baseline level of kidney function should be apparent. This is robustly associated with the extent of CKD and increased risks of cardiovascular events and death.4 For example, in a large community-based sample,5 the adjusted hazard ratio for death and cardiovascular events from 1998 to 2005, 80% excluded patients with ESRD and 75% excluded patients with known CKD. The baseline level of kidney function should be apparent.

Where Are the Intervventional Trials?

Kidney disease research has been rich in epidemiologic studies derived from large registries and databases, particularly with reference to the ESRD population. In 1988, the United States Renal Data System registry was established to collect and analyze information on the incidence, prevalence, morbidity, and mortality of ESRD. Analyses of data from the registry have helped shape health care delivery and policy for the ESRD population. Numerous additional data sets from population surveys and longitudinal cohort studies have expanded the capability for epidemiologic investigation focused on kidney diseases.6 Observations derived from epidemiologic studies in patients with CKD and ESRD provide insight into associated complications and have generated multiple hypotheses regarding interventions that may attenuate related morbidity and mortality.

However, the richness of epidemiologic investigation in nephrology has been counterbalanced by a distinct paucity of interventional trials. The Cochrane Renal Group reported that the number of randomized clinical trials published in nephrology from 1966 to 2002 was fewer than all other specialties of internal medicine and that the proportion of all citations in the literature that are randomized clinical trials in nephrology (1.15%) is the third lowest of the 13 medical specialties examined.7 Even when an intervention question is addressed (eg, the research question is about the relationship between the patient, exposure to a treatment, and an outcome of interest), the randomized clinical trial study design is used in nephrology in less than 50% of published reports.7 These data are particularly compelling because patients with ESRD comprise easily tracked, circumscribed populations having frequent longitudinal medical follow-up with a relatively small cadre of practicing nephrologists. Patients with ESRD should be relatively easy to locate and enroll in relevant and appropriate interventional trials. Given the high mortality for such patients and little improvement in outcomes over the past 2 decades, the need for a greater sense of urgency to find demonstrably effective treatments should be apparent.

In addition to the lack of interventional trials directed specifically at kidney disease, patients with renal disease have been underrepresented in many major cardiovascular trials. In an analysis of 86 large clinical trials evaluating coronary artery disease therapies from 1998 to 2005, 80% excluded patients with ESRD and 75% excluded patients with known CKD. The baseline level of kidney function for study participants was reported in only 7% of these trials.8 In a similar analysis of 153 controlled trials of interventions for congestive heart failure and myocardial infarction, patients with kidney disease were excluded in 56%. Only 5% reported the proportion of enrolled patients with...
kidney disease and only 10% reported baseline levels of kidney function.9 Thus, even though patients with CKD experience an extraordinarily high rate of cardiovascular complications, current guidelines for practice recommendations must of necessity be extrapolated from studies in other patient populations.

Large clinical trials are inordinately expensive and the current clinical trials enterprise is frequently inefficient. Moreover, complex regulations add major costs and delays before results are obtained. Between design and execution lie many potential pitfalls that can invalidate trial results. Even well-designed, sufficiently powered, and well-executed studies are rarely definitive and often lead to further controversy. Highly cited studies are frequently followed by publication of contradictory data.10 Yet despite these difficulties, few would argue with the contention that randomized clinical trials of high methodological quality are essential for providing the highest standard of evidence in support of clinical practice recommendations, for the simple reason that randomized clinical trials are the best design to provide unconfounded estimates of the effects of interventions on patient outcomes. Even from the perspective of return on investment, publicly funded interventional trials have been shown to be ultimately highly cost-effective.11

Clinical Practice Guidelines and Performance Measures: What Standard of Evidence?
The starkness of the lack of evidence from clinical trials is illustrated by the consideration that since the birth of the Medicare ESRD Program in 1972, there has not been a single well-powered randomized clinical trial that has clearly demonstrated a mortality benefit for any intervention in the population receiving dialysis. Yet despite the lack of convincing evidence from randomized clinical trials, there have been robust efforts to create evidence-based clinical practice guidelines for the management of kidney disease, led by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative. Although numerous observers have emphasized that clinical practice guidelines should not be translated into clinical performance measures in the absence of high-grade evidence supporting a relationship between the intervention and outcome, this is precisely what has transpired in the management of ESRD. The Balanced Budget Act of 1997 directed Medicare to report on the quality of care for patients receiving dialysis.12 The resulting ESRD Clinical Performance Measures Project (an outgrowth of the previously existing ESRD Core Indicators Project) has defined performance measures for in-center adult and pediatric patients receiving hemodialysis and for adult patients receiving peritoneal dialysis.

While the goals of the ESRD Clinical Performance Measures Project are laudable, and there is evidence that attainment of project goals may be associated with improved outcomes among patients receiving long-term hemodialysis,13 overall results with respect to morbidity and mortality improvements are modest. Short-term (≤ 3 years of dialysis) mortality rates are improving; however, long-term mortality rates (for patients surviving ≥ 5 years while receiving dialysis) are actually increasing over time.12

Overreliance on observational data for determining clinical practice guidelines and clinical performance measures in the field of nephrology while interventional trial data are lacking has had several deleterious consequences. It has contributed to a sense of complacency in the care of patients with kidney disease. The current Centers for Medicare & Medicaid Services clinical performance measures for patients receiving dialysis are largely related to processes of care such as adequacy of dialysis dose, target hemoglobin level, and target serum albumin level.12 Although observational studies demonstrate a graded relationship between these variables and morbidity and mortality, this may simply be due to bias, because patients who are at increased risk of adverse outcomes are also at risk to not attain interventional targets. A cogent example of this phenomenon occurred in the HEMO study,14 a randomized clinical trial comparing outcomes of patients receiving hemodialysis who were assigned to a high dose of urea clearance compared with a standard dose. The primary intention-to-treat analysis demonstrated no benefit based on dialysis dose; however, an as-treated analysis of the same data revealed an association of delivered dose of dialysis with mortality, a phenomenon referred to as “dose-targeting bias.”15

Although process-of-care measures are emphasized in the health care quality movement today, Porter and Teisberg16 have argued recently that basing quality and performance measures on anything other than tangibly improved patient outcomes will be ineffective. The contention of Porter and Teisberg appears to be true, at least with respect to clinical performance measures in dialysis. While there has been steady nationwide improvement in achievement of many clinical performance measure targets during the past decade, this has not translated into substantive improvements in the overall demographic- and comorbidity-adjusted hospitalization rates or mortality rates for the population receiving dialysis. Furthermore, implementing clinical practice guidelines that are not supported by compelling trial data may be associated with high costs, as has recently been demonstrated for bone metabolism guidelines for patients with CKD.17

A second problem with basing clinical practice guidelines on evidence standards short of interventional trial data is that such guidelines may actually serve as an impediment to performing those randomized clinical trials that could provide the sought-after higher standard of evidence. Pharmaceutical companies and even the National Institutes of Health (NIH) may be reluctant to invest large sums of money to “prove” what has already been implemented into standard clinical practice. Furthermore, clinical investigators and

©2007 American Medical Association. All rights reserved.

(Reprinted) JAMA, June 20, 2007—Vol 297, No. 23 2631
COMMENTARIES

institutional review boards may balk at study designs in which the control group is not being treated according to practice guideline standards, even if these guidelines are opinion-based. Trial recruitment may be further slowed as use of a therapy becomes highly prevalent within the target population despite lack of evidence of efficacy.

A third deleterious consequence of basing clinical practice guidelines and performance measures largely on observational data rather than on interventional trials is that great consternation and turmoil may occur when interventional trials are subsequently performed and the results do not support already existing practice guidelines and performance measures. Several such examples have occurred in nephrology. Practice guidelines and performance measures in adequacy of peritoneal dialysis were largely derived from observational study data and advocated prescribing peritoneal dialysis on the basis of the amount of cleared urea and creatinine. Previously, peritoneal dialysis had been prescribed empirically on the basis of the number of daily exchanges and volume of dialysate. After these guidelines and performance measures were promulgated, the ADEMEX (Adequacy of Peritoneal Dialysis in Mexico) Trial compared a peritoneal dialysis prescription based on solute clearance with a simple empirical prescription based on 4 daily dialyses, and the results demonstrated no significant differences in patient survival despite a large difference in peritoneal clearance. It has been speculated that overly arduous and complex guidelines for peritoneal dialysis adequacy may have contributed to the decline in use of this technique in the United States.

A great deal of attention is being paid to results of the CHOIR and CREATE studies, 2 randomized clinical trials in which patients with CKD were randomized to achieve different target hemoglobin concentrations with the use of erythropoietic-stimulating agents. The results of these trials have been viewed by some as inconsistent with current clinical practice guidelines for management of anemia in kidney disease. This has created great upheaval within the field of nephrology and has stimulated complex interactions between the US Food and Drug Administration, the Centers for Medicare & Medicaid Services, and Congress. More timely interventional trials might have prevented much of the current upheaval.

Increasing Clinical Trials in Kidney Disease

Collective action will be required to increase the foundation of evidence from outcome-based clinical trials in kidney disease. To be effective, a systematic approach will likely require aligning the NIH, industry, and medical payers including the Centers for Medicare & Medicaid Services. Due to the expense of large randomized clinical trials, public-private partnerships should be emphasized. As a first step, a concerted effort should be made to analyze and remove perceived and real barriers to conducting clinical trials in the outpatient dialysis setting. Setting target enrollments in the dialysis and kidney transplant populations for interventional trials with cardiovascular event rates, hospitalization rates, and mortality as key end points will be required to create a sense of urgency and eliminate complacency.

Patients with CKD should be overrepresented, rather than underrepresented, in large cardiovascular trials. Considering that patients with kidney disease have proportionately higher event rates, the inclusion of more patients with kidney disease will help ensure that trials do not become underpowered due to lower observed than expected event rates. Since the ultimate goal of intervention trials is to find therapies that are effective when applied to a broadly defined patient population, including patients with kidney disease in controlled studies may tighten the linkage between efficacy and effectiveness.

The NIH has recently increased its portfolio of clinical trials in the population with CKD and ESRD. The NIH should continue to take the initiative in evaluating conventional and novel therapeutics targeted at cardiovascular risk associated with kidney disease, including convening study sections for mechanistic R01 applications focused on the problems encountered by patients with advanced CKD and ESRD. Although NIH budgets are tight, consideration should be given to developing a durable clinical trials network focused on outcome-based interventional trials for the population with advanced CKD and ESRD. Such a network, particularly if integrated with a public-private therapeutics discovery process under the auspices of the NIH, would have the capability of facilitating a series of important trials in this patient population.

Financial Disclosures: Dr Himmelfarb reports receiving research support for interventional trials in the CKD and ESRD population from the National Heart, Lung, and Blood Institute and the National Institute of Diabetes, Digestive, and Kidney Diseases of the National Institutes of Health, and has received a research grant from Fresenius Medical Care of North America. Dr Himmelfarb is chair of the Public Policy Board of the American Society of Nephrology.

Disclaimer: The opinions expressed are solely those of the author and do not represent the views of the American Society of Nephrology.

REFERENCES

The Locality Rule and the Physician’s Dilemma
Local Medical Practices vs the National Standard of Care

Michelle Huckaby Lewis, MD, JD
John K. Gohagan, PhD
Daniel J. Merenstein, MD

The purpose of medical malpractice law is to protect patients from substandard medical care and to compensate them for injuries sustained as a result of substandard care. Each medical malpractice case serves an additional function by further delineating the medical care that is legally acceptable in a particular field. Although medical school training, medical licensing requirements, and board certification requirements are based on national standards, many states rely on local practice standards to determine the applicable standard of care in medical malpractice lawsuits. Jurisdictions that maintain local practice standards may inhibit the incorporation of scientific progress into practice standards. In addition, adherence to the locality rule can create uncertainty for physicians when they must choose between following local practice standards and national, evidence-based standards for care.

How the Legal Standard of Care Is Determined
When a physician assumes care of a patient, he or she undertakes a legal duty to abide by a certain standard of care. The traditional standard of care for physicians is to exercise “the degree of care and skill that a physician or surgeon of the same medical specialty would use under similar circumstances.”¹ This legal standard, however, is not defined uniformly throughout the United States. Traditionally, US courts have allowed the medical profession to set its own standards of care by defining the standards according to medical custom. Expert witness testimony is usually necessary to provide evidence of this custom (97% of medical malpractice cases involve expert medical testimony, with an average of 5 witnesses per trial).²

In states that maintain a custom-based standard, the role of the jury in a malpractice case is to decide whether the physician’s actions were consistent with what other physicians customarily do under similar circumstances.³ In theory, the customary standard is based on empirical evidence, but expert witnesses are unlikely to know how other physicians practice. Instead, these expert witnesses are likely to base their testimony on what they would have done under similar circumstances.⁴,⁵

Some state courts have taken a normative approach in defining the standard of care. In these states, the legal standard is what a reasonable physician would have done under similar circumstances.²,⁶

Author Affiliations: Robert Wood Johnson Clinical Scholars Program, Johns Hopkins School of Medicine, Baltimore, Md (Dr Lewis); Greenwall Fellowship Program in Bioethics and Health Policy, Johns Hopkins Berman Institute of Bioethics, Baltimore, Md, and Georgetown University, Washington, DC (Dr Lewis); Division of Cancer Prevention, National Cancer Institute, US National Institutes of Health, Bethesda, Md (Dr Gohagan); and Department of Family Medicine, Georgetown University, Washington, DC (Dr Merenstein).

Corresponding Author: Michelle Huckaby Lewis, MD, JD, Greenwall Fellowship Program in Bioethics and Health Policy, Johns Hopkins Berman Institute of Bioethics, 100 N Charles St, Suite 740, Baltimore, MD 21201 (michellelewismd@yahoo.com).

©2007 American Medical Association. All rights reserved.