For those of us who are practicing nephrologists, acute kidney injury (AKI) is the most common reason for in-hospital consultation requested by our non-nephrology colleagues. Most of our diagnostic and interventional efforts are concentrated on the period when serum creatinine level is increasing. If the patient survives the episode of AKI and serum creatinine level is decreasing, we often “sign off.” Furthermore, patients seen by a nephrology consultant are by definition a subset of patients with AKI in the hospital; some patients have only small increases in serum creatinine level or recover kidney function easily, and thus nephrology consultation is not obtained. Thus, for a variety of reasons, even very experienced nephrologists may not be familiar with the long-term natural history of AKI.

This issue of the *American Journal of Kidney Diseases* includes a meta-analysis by Coca et al regarding the long-term risk of adverse outcomes after AKI, summarizing the literature from 1985 to 2007. The investigators included all studies of survivors of AKI with at least a 6-month follow-up period and examined outcomes of mortality and the subsequent development of cardiovascular disease or chronic kidney disease (CKD). The large amount of effort required to complete this meta-analysis using state-of-the-art techniques is laudable and is obvious from reading the article. This report is very timely given the recent surge of interest in the long-term consequences of AKI. Their meta-analysis concludes that even mild AKI is associated with adverse long-term consequences in terms of mortality, cardiovascular disease, and other outcomes.

We believe there are several points worth making about this important article.

The necessity of a uniform definition of AKI is made clear by this meta-analysis. It is not possible to make a comparison across studies if there is heterogeneity in what different investigators consider AKI. In this regard, the initial efforts to develop consensus definitions for AKI by the Acute Dialysis Quality Initiative (RIFLE classification system) and, more recently, the Acute Kidney Injury Network (AKIN definition and staging system) are most welcome (Table 1).

Next, it is striking that after screening more than 3,000 citations and analyzing in detail 49 studies that contained a total of 47,017 participants, Coca et al concluded that “the relative risk for CKD and ESRD [end-stage renal disease] after AKI was unattainable due to lack of follow-up of appropriate non-AKI controls” (our emphasis). This limitation points to a weakness of many of the published studies: that many were designed as case series. A much stronger study design would be a cohort study, which compares future outcomes between exposed (those who experienced AKI) and unexposed groups (those who did not experience AKI). The meta-analysis by Coca et al highlights the need for more epidemiological research in this area. To help fill this major gap in knowledge, the National Institutes of Health recently sponsored an Acute Kidney Injury Natural History Consortium to directly address this issue (http://grants.nih.gov/grants/guide/rfa-files/RFA-DK-07-009.html). There also are a number of investigative teams examining this question by using different data sources, many of which presented preliminary results at the recent 2008 American Society of Nephrology Meeting in Philadelphia, PA.

Finally, careful reading of this meta-analysis shows several major methodological challenges in AKI epidemiological research that will need to be addressed in the coming years. We mention the 3 most important ones in our opinion.

First, there is fundamental tension with the way AKI currently is defined. AKI implies structural injury to the kidney parenchyma, but currently is defined as a functional decrease in kidney function ascertained from an increasing serum creatinine level (or decrease in urine output; Table 1). However, different causes of an...
acute decrease in kidney function may reflect different types of underlying injury, which are likely to be associated with different outcomes. For example, a much invoked pathophysiological mechanism for increased risk of CKD after AKI is irreversible structural damage sustained during the AKI episode.\textsuperscript{15,16} Thus, it would seem improbable that a 0.5-mg/dL acute increase in serum creatinine level caused by decreased kidney perfusion would have the same impact on the subsequent risk of CKD as a 0.5-mg/dL increase in serum creatinine level caused by acute tubular necrosis. Similarly, a decrease in urine output to less than 0.5 mL/kg for 6 hours may not reflect the same degree of underlying kidney injury as a 50% increase in serum creatinine level from baseline or a 0.3-mg/dL absolute increase in serum creatinine level, although these are all considered stage I AKI according to the AKIN classification system (Table 1). Although there are no agreed-on diagnostic criteria for the different causes of AKI,\textsuperscript{17} there clearly is a spectrum of disease ranging from rapidly reversible cases (eg, by restoration of intravascular volume) to irreversible ones (eg, caused by acute cortical necrosis). This problem may be exacerbated by the trend to use smaller and smaller changes in serum creatinine level to define AKI because these are more and more likely to reflect hemodynamic changes. Novel biomarkers hold the promise of distinguishing different causes of AKI in the future and might provide a solution to this conundrum.

Second, there currently is no consensus definition of what constitutes “baseline kidney function” before an AKI episode. In the published literature, baseline kidney function has been assumed to be the lowest serum creatinine level observed during the hospitalization,\textsuperscript{18} the minimum of the first 3 inpatient serum creatinine readings,\textsuperscript{10} serum creatinine measured immediately before surgery,\textsuperscript{20} or simply whatever prehospital or nadir serum creatinine value was available to the investigators.\textsuperscript{21} This obviously is problematic if one wishes to determine exactly how different the post-AKI serum creatinine measurement(s) are from the baseline measurement(s). Notably, although the AKIN definition mentioned the concept of a baseline kidney function, it is silent about how this is to be defined. The Acute Dialysis Quality Initiative RIFLE definition proposed using the Modification of Diet in Renal Disease (MDRD) Study equation to estimate baseline serum creatinine level based on the assumption that pre-AKI glomerular filtration rate was 75 mL/min/1.73 m\textsuperscript{2} in situations when this information is unavailable.\textsuperscript{2} This approach is unsatisfactory when the main research question is to compare levels of kidney function before and after an episode of AKI.

Some investigators recently have advocated using preadmission outpatient serum creatinine values to define baseline kidney function, arguing that this strategy presents the best chances of evaluating steady-state level of kidney function in the absence of an acute illness.\textsuperscript{22} For patients who experience AKI, serum creatinine level on admission may already be increased as a result of the illness that precipitated the acute hospitalization. More empiric research is necessary to help determine whether this is the optimal approach under different circumstances. A limitation of this approach is that it will restrict analyses to those with (recent) outpatient serum creatinine data, who may or may not be representative of the population at large. Decreases in serum creatinine levels (compared with recent outpatient values) during hospitalization are not infre-
quently observed. Whether this is caused by fluid resuscitation and hemodilution, unmasking of preexisting AKI, acute decrease in creatinine production, or some combination thereof is unclear.

Third, the possibility that any observed association between AKI and future adverse events is caused by confounding by severity of baseline kidney function has not been sufficiently emphasized. In other words, AKI is associated with adverse outcomes because those who experience AKI have more severe preexisting CKD than those who did not experience AKI, and severity of CKD, not AKI, is the true reason for the increased mortality and cardiovascular disease observed after AKI. Confounding is a major concern because CKD is a very strong risk factor for AKI and baseline CKD is a strong risk factor for cardiovascular disease, death, and progression to more severe stages of CKD. The magnitude of the effect of the former has not been quantified until recently. Compared with patients with an estimated glomerular filtration rate of 60 mL/min/1.73 m^2 or greater, the relative risk of dialysis-requiring AKI in those with an estimated glomerular filtration rate of 15 to 29 mL/min/1.73 m^2 is about 20, an unusually strong association.22 Residual confounding can be an important problem because this very large effect size may hinder determining the true impact of AKI on future risk of adverse outcomes if the latter increases risk by only 50% or 100% (ie, relative risk, ~1.5 to 2.0, which is still very important clinically).

There are clues in the current literature that there is indeed bias arising from residual confounding by baseline differences in CKD severity (or other risk factors for AKI such as diabetes mellitus or advanced age which are also risk factors for future adverse events). In 1 study summarized by Coca et al,1 patients who underwent elective abdominal aortic aneurysm surgery were divided into those with no worsening of Cockcroft-Gault estimated creatinine clearance after surgery, temporary worsening (by > 10% at day 1 or 2, then complete recovery within 10% of preoperative value at day 3), and persistent worsening.23 The reported adjusted hazard ratio for death up to 10 years after surgery was very similar for the temporary and persistent worsening groups (1.5 [95% confidence interval, 1.2 to 1.9] versus 1.7 [95% confidence interval, 1.3 to 2.3]). In another study of elderly patients who experienced acute myocardial infarction (published after the meta-analysis cut-off date), seemingly minimal changes in serum creatinine level (0.1 mg/dL) were associated with an increased risk of subsequent kidney failure by as much as 45%, even after adjustment for numerous covariates.24 These data raise the concern that small or very temporary “bumps” in serum creatinine are simply markers for comorbid conditions, which are incompletely adjusted for in epidemiological studies and not truly in the causal pathway.

In conclusion, the meta-analysis by Coca et al1 provides a substantial contribution to the literature by summarizing the state of the science at an important junction in the evolution of the field. It also highlights several critical methodological issues that need to be considered. Addressing these methodological challenges and making concerted efforts to achieve consensus for definitions, including a definition of baseline kidney function, will propel research in this field to a higher level.

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ACKNOWLEDGEMENTS

Support: The authors’ work is supported by National Institutes of Health (NIH) grants T32DK007219, R01DK67126, and U01DK82223, as well as grant KL2RR024130 from the National Center for Research Resources, a component of the NIH and NIH Roadmap for Medical Research.

Financial Disclosure: None.

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