AKI: Not Just a Short-Term Problem?

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AKI is a common syndrome, with a population-based incidence estimated to have grown from 3000 to >5000 episodes per million person-years during the past 2 decades in the United States (1). The immediate prognostic implications of AKI are well established and include prolonged hospitalization, the need for acute RRT, and high mortality. The increasing incidence of AKI, coupled with the fact that adjusted hospital mortality has decreased by approximately 60% among patients with the condition, has increased the number of individuals discharged from the hospital after experiencing an episode of AKI. This has raised questions as to whether AKI may have long-term health implications. Although most survivors of AKI have partial or complete recovery of kidney function by the time of hospital discharge (2), several recent observational studies examining the long-term course of AKI suggest that outcomes can encompass a spectrum that includes progressive loss of kidney function, CKD, and ESRD (3). This suggests that individuals who survive an episode of AKI may also be at risk of downstream complications of CKD, including cardiovascular events and late mortality.

In this issue of *CJASN*, Chawla *et al.* compare subsequent mortality, cardiovascular, and kidney outcomes between individuals hospitalized with myocardial infarction (MI), AKI, and the combination of MI and AKI (4). They studied 36,980 patients hospitalized in the US Department of Veterans Affairs with primary discharge diagnoses of AKI or MI, mean baseline eGFR≥45 ml/min per 1.73 m^2, and serum creatinine measurements both before and during admission. Using combinations of *International Classification of Diseases Ninth Revision-Clinical Modification* codes for MI and AKI, augmented with serum creatinine measures to define AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) definition, three groups of interest were identified: (*1*) a group with a primary diagnosis of MI without an increase in serum creatinine indicating AKI, (*2*) a group with a primary diagnosis code for AKI and an increase in serum creatinine indicating AKI, and (*3*) a group with a primary diagnosis of MI and an increase in serum creatinine indicating AKI. This study focused on several composite outcomes that have been proposed for clinical trials in AKI, including the composite of major adverse kidney events (defined as chronic dialysis, a 25% decline in eGFR, or death), major adverse cardiac events (defined as a subsequent admission for stroke, MI, or congestive heart failure), and major adverse renal cardiovascular events (a composite of all of these events), over a median follow-up of 1.4 years after hospital admission.

The investigators compared outcomes with a reference group with MI alone and noted that those with a primary diagnosis of AKI had a 37% increase in the relative risk of a composite major adverse renal or cardiovascular event, whereas those with MI and serum creatinine changes of AKI had a 92% increase. Further examination of the components of this composite showed that individuals with MI accompanied by serum creatinine changes indicative of AKI were at higher risks of death, the composite of cardiovascular events, and the composite of kidney events, than individuals with MI without AKI. This provides new information about the association between AKI and the risk of subsequent cardiovascular events after an MI, extending the findings of other large observational studies and a meta-analysis that reported that AKI, even when defined by small changes in serum creatinine, is associated with long-term risks of mortality and ESRD in similar settings (5–7).

In further comparisons made with individuals with MI alone, those with a primary diagnosis of AKI were at a higher risk of death and the composite of major adverse kidney events, but were at a lower risk of subsequent major adverse cardiovascular events. Although these comparisons highlight the prognostic importance of a group with AKI relative to a well characterized condition (MI), the implications of these comparisons are more challenging to interpret. Individuals with established coronary artery disease are among the highest-risk groups for subsequent cardiovascular events; thus, it is perhaps not surprising that individuals with a primary diagnosis of AKI were at lower risk of subsequent cardiovascular events over the follow-up period than those who had been recently hospitalized for MI. Furthermore, the etiology and severity of AKI can be heterogeneous, and the use of *International Classification of Diseases Ninth Revision-Clinical Modification* codes (which are highly specific but not particularly sensitive) (8) to select participants with a primary diagnosis of AKI preferentially enriches this group with individuals with more severe AKI, confirmed by the observation that 49% had KDIGO stage 3 AKI in the study. Comparisons of outcomes between individuals with primary diagnoses of MI and AKI should thus be interpreted with some caution, recognizing that these may be generalizable only to individuals with the most severe forms of AKI.

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The risks of cardiovascular and kidney events in the study by Chawla *et al.* are characterized using composite outcomes, selected based on the rationale that they have been proposed for use as endpoints in clinical trials. Such outcomes are frequently used in trials because they increase statistical efficiency, leading to higher event rates and thus enabling smaller sample sizes or shorter follow-up. However, such measures can make the interpretation of results challenging. In this study, one component of the composite outcome called major adverse kidney events was a 25% decrease in eGFR. This contributes to several limitations in the interpretation of the composite outcome. Not surprisingly, a 25% decrease in eGFR occurred much more frequently than chronic dialysis, a kidney endpoint of unquestionable clinical significance. Furthermore, the ascertainment of a 25% decline in eGFR is such that it may not represent actual progression to CKD in many participants, but rather an episode of potentially reversible AKI. Finally, even if the decrease in eGFR was reflective of chronic disease, it can be influenced by regression to the mean because the cohort was selected based on high baseline eGFR.

Another limitation of the "super-composite outcome" known as major adverse renal or cardiovascular events, a merger of the major adverse kidney and major adverse cardiovascular composite endpoints, arose because the component outcomes did not all move in line with each other. Although the composite of major cardiovascular and renal events as a whole appeared to be significantly associated with AKI in the study, the risks of death and the composite of adverse kidney events associated with a diagnosis of AKI were higher, yet the risks of cardiovascular events were lower compared with individuals with MI alone. This finding illustrates how composite outcomes can obscure associations with the individual components (9). Risk factors for cardiovascular and kidney outcomes may be vastly different, so a merger of major adverse kidney and cardiovascular events may not be appropriate. For large observational studies such as this, more refined characterization of the risks of each of the component outcomes could prove more helpful to characterize the prognosis of AKI and inform the development of appropriate outcomes for future trials.

Although observational studies of this nature cannot establish that AKI causes subsequent adverse cardiovascular and renal events, this study does reinforce a growing body of literature on the long-term prognostic importance of AKI. For patients who have had an MI, there is a relative abundance of high-quality evidence for secondary prevention strategies for cardiovascular disease to apply to this high-risk group, including lifestyle modification and pharmacotherapy, most effectively delivered through structured cardiac rehabilitation programs (10). However, for patients who have had an episode of AKI, there are no established interventions known to mitigate the risk of CKD and its attendant consequences, including cardiovascular events, progression to ESRD, and mortality. Identifying individuals at high risk of subsequent adverse outcomes is a critical step toward designing and evaluating interventions to prevent disease progression and complications. Interventions based on strategies to enhance longitudinal care and increase the uptake of therapies that slow progression of CKD and reduce cardiovascular risk could provide a means to improve these outcomes of AKI, but will warrant evaluation in future trials before widespread use.

Disclosures

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