Kidney Disease, Hospitalized Hypertension, and Cardiovascular Events: Cause or Consequence?

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In this issue of *Circulation*, Szczech et al report selected results from the Studying the Treatment of Acute Hypertension (STAT) registry, a recently completed observational study whose goal is “to improve the understanding of the clinical condition of acute, severe hypertension . . . managed in a critical care setting and treated with intravenous antihypertensive therapy.” The STAT registry is sponsored by the Medicines Company, a publically traded entity focused on “advancing the treatment of critical care patients through the delivery of innovative, cost-effective medicines to the worldwide hospital marketplace.” The stated goal of the analyses presented was to “define the risk among patients with acute severe hypertension and acute kidney injury (AKI), and the risk associated with both AKI and chronic kidney disease (CKD) on cardiovascular outcomes and mortality.” Although the extensive array of analyses presented by Szczech et al highlights an important area of investigation, readers should be circumspect about the conclusions reached.

Before proceeding to the study results, we must carefully consider the authors’ definitions. The authors define CKD as an estimated glomerular filtration rate (eGFR) <90 mL/min/1.73m², calculated using the 4-variable Modification of Diet in Renal Disease study equation, designating CKD in nearly 4 of every 5 STAT registry enrollees. Although some have advocated that eGFR in the range of 60 to 89 mL/min/1.73m² represents mild CKD, several studies have demonstrated that the Modification of Diet in Renal Disease study equation often underestimates true GFR above the range of 25 to 55 mL/min/1.73m², the population from which the original equation was derived. Moreover, even liberal definitions of CKD require a chronic element (eg, reduced eGFR for 3 or more months). The authors define baseline kidney function using single serum creatinine determinations up to 12 months before admission (“where available”), which could be particularly problematic if the serum creatinine concentration were not in steady state in the setting of acute illness. Thus, misclassification of CKD by errors inherent in the Modification of Diet in Renal Disease study equation and single rather than multiple values indicating the persistence of impaired kidney function probably yielded a sizeable overestimate in CKD prevalence. Such an error may have diminished the apparent risk associated with CKD and inflated the risk associated with AKI.

Adding insult to injury (pun intended), the authors employ a definition of AKI that also maximizes its prevalence by calculating change in eGFR from “baseline” to “nadir” without considering the length of hospitalization or the number of serum creatinine determinations. Thus, if a 70-year-old white woman were admitted with a serum creatinine concentration of 1.0 mg/dL (corresponding to an eGFR of 55 mL/min/1.73m² defined as “moderate CKD”) and had subsequent serum creatinine concentrations of 1.0, 1.0, 1.0, 0.9, 1.0, 1.3, and 1.0 mg/dL (with the nadir eGFR calculated at 40 mL/min/1.73m²), the relative change in eGFR (15 divided by 55, or 27%) would be classified as AKI (“risk” by the risk, injury, failure, loss, end-stage renal disease criteria). In this example, the patient probably had neither CKD nor AKI but was misclassified as having both, rendering true estimates of risk uninterpretable.

The STAT registry designated enrollees as having acute, severe hypertension managed in emergency or critical care settings. However, the reader is unable to determine whether hypertension was truly acute or chronic. Overall, 89% of the study sample had a history of hypertension, including 94% and 98% of those with advanced and end-stage kidney disease, respectively. Indeed, the cohort may be better defined as hypertension requiring intervention (probably owing to some untoward clinical manifestation), rather than “acute” and “severe.”

Much is made of AKI in this article. The authors are indeed correct that small changes in serum creatinine have been associated with adverse outcomes in other settings, although the incidence of clinically relevant AKI in this study was relatively low. Despite the severity of hypertension, only 122 (8%) developed “injury” using the definition of a relative change in eGFR ≥50% adopted by proponents of the risk, injury, failure, loss, end-stage renal disease criteria. Moreover, only when considering left ventricular dysfunction and moderate to severe bleeding was there a significant difference with a “dose response” by AKI stage.

Although the authors acknowledge some of the limitations of their work, others should be highlighted to help place the results in a proper context. The authors failed to provide sufficient detail about in-hospital testing. For example, how was acute left ventricular dysfunction evaluated? Were echocardiograms routinely performed for the purpose of research? The authors also failed to note whether cardiac and cerebrovascular events were evaluated routinely or by protocol. If all
enrollees were not screened for subarachnoid hemorrhage (because in all likelihood imaging was ordered in response to signs and/or symptoms), the incidence estimates, which suggest a paradoxically higher risk with better kidney function, could simply reflect the threshold for testing rather than the true incidence because the denominator is unknown. The authors’ contention that a critical mass of functioning nephrons “compensates” or somehow otherwise protects an individual from target organ injury is appealing to nephrologists but is not supported by facts.

So what facts can be gleaned from the article by Szczech et al? First, in the setting of severe hypertension, a decline in kidney function in-hospital is more common in persons with underlying CKD, as has been shown in other settings.6,7 Second, currently available renal diagnostic studies (ie, serum creatinine or derivations thereof) are neither sufficiently specific nor sensitive to guide therapy or reliably predict outcomes. Finally, determining whether kidney disease is a cause or consequence of severe hypertension and understanding the mechanism(s) linking kidney disease to cardiovascular disease are likely to be exceptionally worthwhile pursuits at both the bench and the bedside.

**References**


**Disclosures**

None.

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