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Is There One Best Way to Define AKI?

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Acute kidney injury (AKI) has been repeatedly shown to be associated with adverse outcomes in both inpatient and outpatient settings, with even small elevations in serum creatinine associated with subsequent risk of cardiovascular disease (CVD) and mortality (1–3). Accurate ascertainment of AKI is then fundamental to determine whether a more stringent blood pressure (BP) goal may have an unintended consequence of higher rates of AKI. Approaches to AKI ascertainment that leverage serum creatinine measurements from the electronic health record (EHR) may be more sensitive than traditional billing-based methods, allowing for greater precision and less bias in randomized clinical trials that use AKI as an outcome.

To this end, the recent secondary analysis of the SPRINT trial (4) by Drawz *et al.* (5) had two objectives. First, the authors aimed to evaluate the treatment effect of intensive BP lowering on AKI, on the basis of three definitions of AKI: (*1*) serious adverse events (SAE) adjudication on the basis of inpatient diagnosis codes and review of admission and discharge notes, as in the primary SPRINT analysis; (*2*) an increase of ≥50% or ≥0.3 mg/dl in inpatient EHR serum creatinine values compared with baseline outpatient values; or (*3*) an increase of ≥50% in outpatient serum creatinine using both serum creatinine measurements collected through the clinical trial protocol and the EHR. For both inpatient and outpatient EHR-based definitions, baseline serum creatinine was defined as the most recent creatinine measured as part of the trial follow-up. Second, the authors examined the association of each of these definitions of AKI with subsequent development of the primary SPRINT outcomes of cardiovascular events (fatal or nonfatal myocardial infarction, stroke, or heart failure; unstable angina; or death attributable to CVD) and mortality.

Utilizing linked EHR data from 47 out of 102 clinical sites representing 3644 SPRINT participants, the authors found that both inpatient and outpatient EHR laboratory-based definitions of AKI identified more than double the number of events (342 and 416 events, respectively) compared with the trial's SAE adjudication (156 events). Intensive BP lowering treatment significantly elevated the risk of SAE adjudicated inpatient AKI (hazard ratio [HR]=1.51; 95% confidence interval [CI], 1.09 to 2.08) and creatinine-based outpatient AKI (HR=1.40; 95% CI, 1.15 to 1.7); there was a more modest, although not statistically significant, effect on creatinine-based inpatient AKI (HR=1.2; 95% CI, 0.97 to 1.48). The majority of AKI cases in either EHR-based definition were mild, and most patients had quick resolution of their AKI. All three definitions of AKI were associated with higher mortality, with creatinine-based inpatient AKI having the strongest association (HR=5.54; 95% CI, 3.94 to 7.8). In contrast, only creatinine-based inpatient AKI was significantly associated with a greater risk of CVD (HR=1.74; 95% CI, 1.15 to 2.64).

This study highlights the difficulties in ascertaining AKI as a study outcome. As the authors note, an AKI definition on the basis of SAEs may be biased in an open-label study, where providers may be sensitive to the risk of AKI for a given treatment group and therefore more likely to mention it in admission and discharge notes. The authors note that the creatinine-based inpatient AKI definition found relatively more additional events in the standard versus intensive group, suggesting that this phenomenon may have been present in SPRINT. In addition, AKI on the basis of SAEs has previously been shown to have poor sensitivity (<20%) compared with AKI defined by inpatient creatinine values (6). Conversely, in an outpatient setting, there may be bias in why serum creatinine is measured in the first place.

In this study, EHR-based definitions identified many more AKI events compared with the SAE-based definition, and most patients with outpatient AKI regained kidney function within 12 months, defined as returning to within 30% of their pre-AKI SPRINT value. One might wonder, then, whether the additional AKI events identified with EHR data represent meaningful kidney dysfunction with long-term effects. In fact, AKI identified from inpatient creatinine values had a stronger association with mortality than SAE-based AKI and was also significantly associated with incident CVD. Although the association of AKI with CVD and mortality has been shown repeatedly and is not in itself novel, it underscores the fact that traditional methods of ascertaining AKI from SAEs miss events that may carry real risk for long-term clinical outcomes.

The authors suggest that future studies of implementation of intensive BP control would be beneficial because certain forms of intensive control might carry different risks of AKI. However, from the results of the current work, it is unclear whether reducing AKI in this setting would directly reduce subsequent morbidity and mortality. The strong association of AKI with mortality shown here may simply be a "stress

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test" of a person's overall and cardiovascular fitness to acute changes in BP. Development of mild AKI resultant from changes in BP may identify patients at higher risk of poor long-term outcomes, with the mortality benefits of intensive BP lowering occurring independently of an AKI pathway. Given the clear overall benefit shown in SPRINT, an intensive BP management strategy is here to stay; however, it seems relevant to study whether the risk of AKI is modifiable within the intensive BP management strategy.

The findings of Drawz and colleagues also have implications for the design and analysis of future studies. First, the results argue for incorporating EHR ascertained AKI into the design of large and/or pragmatic clinical trials. The authors note in their discussion that in evaluating the effect of intensive BP control in an open-label trial, providers may have been more likely to identify and mention AKI in their admission and discharge notes, from which SAEs were ascertained. In contrast, leveraging EHR data to define AKI may minimize this bias. More broadly, the prospect of incorporating EHR data into clinical trial outcome definition is appealing because of improvements in efficiency. However, this needs to be balanced with issues of ascertainment bias, in that clinicians may measure serum creatinine values more often in patients at higher risk of AKI. Thus, the ascertainment of the outcome may be different in populations with differing baseline risk. Clinical settings in which this bias may be limited include maintenance dialysis centers, in which routine vital sign measurements and laboratory values are less likely to be subject to ascertainment bias. Second, EHR-based definitions of AKI are likely to identify more events that are associated with risk of clinically meaningful outcomes. Trials that utilize this method for ascertainment can be smaller compared with studies that use SAE-defined AKI, with the same power to detect clinically meaningful treatment effects. Finally, similar approaches could be used to abstract data to examine related outcomes such as eGFR trajectory over time, which is often used as a surrogate outcome in clinical trials.

In summary, the EHR offers the prospect of a more sensitive and less biased method of ascertaining AKI in large clinical trials. Drawz and colleagues have shown the feasibility of implementing EHR-based AKI definitions in this secondary analysis of the SPRINT trial, which should promote and guide the use of this type of ascertainment in the design of future trials that have AKI as an outcome.

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Author Contributions

Both authors were responsible for conceptualization, wrote the original draft of the manuscript, and reviewed and edited the manuscript.

References

1. Ikizler TA, Parikh CR, Himmelfarb J, Chinchilli VM, Liu KD, Coca SG, Garg AX, Hsu CY, Siew ED, Wurfel MM, Ware LB, Faulkner GB, Tan TC, Kaufman JS, Kimmel PL, Go AS; ASSESS-AKI Study Investigators: A prospective cohort study of acute kidney injury and kidney outcomes, cardiovascular events, and death. *Kidney Int* 99: 456–465, 2021 https://doi.org/10.1016/j.kint.2020.06.032
2. Heung M, Steffick DE, Zivin K, Gillespie BW, Banerjee T, Hsu CY, Powe NR, Pavkov ME, Williams DE, Saran R, Shahinian VB; Centers for Disease Control and Prevention CKD Surveillance Team: Acute kidney injury recovery pattern and subsequent risk of CKD: An analysis of Veterans Health Administration data. *Am J Kidney Dis* 67: 742–752, 2016 https://doi.org/10.1053/j.ajkd.2015.10.019
3. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR: Long-term risk of mortality and other adverse outcomes after acute kidney injury: A systematic review and meta-analysis. *Am J Kidney Dis* 53: 961–973, 2009 https://doi.org/10.1053/j.ajkd.2008.11.034
4. Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT; SPRINT Research Group: A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 373: 2103–2116, 2015 https://doi.org/10.1056/NEJMoa1511939
5. Drawz P, Rai N, Lenoir K, Suarez M, Powell J, Raj D, Beddhu S, Agarwal A, Soman S, Whelton P, Lash J, Rahbari-Oskoui F, Dobre M, Parkulo M, Rocco M, McWilliams A, Dwyer J, Thomas G, Rahman M, Oparil S, Horwitz E, Pajewski N, Ishani A: Effect of intensive hypertension treatment on acute kidney injury and subsequent cardiovascular disease and mortality. *Kidney360* 3: 1253–1262 10.34067/KID.0001572022
6. Grams ME, Waikar SS, MacMahon B, Whelton S, Ballew SH, Coresh J: Performance and limitations of administrative data in the identification of AKI. *Clin J Am Soc Nephrol* 9: 682–689, 2014 https://doi.org/10.2215/CJN.07650713

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See related article, "Effect of Intensive versus Standard BP Control on AKI and Subsequent Cardiovascular Outcomes and Mortality: Findings from the SPRINT EHR Study," on pages 1253–1262.