Blood Pressure Control, Acute Kidney Injury, and Cardiovascular Events: Separating the Chaff from the Wheat

George Thomas^a Jesse D. Schold^{b, c}

^aGlickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH, USA; ^bDepartment of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA; ^cCenter for Populations Health Research, Cleveland Clinic, Cleveland, OH, USA

Hypertension is a strong independent risk factor for cardiovascular disease, with observational studies demonstrating a continuous positive linear relationship between blood pressure (BP) and cardiovascular risk. The Systolic Blood Pressure Intervention Trial (SPRINT) was designed to answer the question: “In patients with increased cardiovascular risk, including chronic kidney disease (CKD) but without diabetes or stroke, does a systolic blood pressure (SBP) goal of less than 120 mm Hg reduce adverse clinical events more than the SBP goal of less than 140 mm Hg?”

SPRINT was a randomized, controlled, open-label trial; and participants in the study had to be at least 50 years old, with a SBP of 130–180 mm Hg, and had to have at least one cardiovascular risk factor, which included clinical or subclinical cardiovascular disease (other than stroke), CKD defined as estimated glomerular filtration rate of 20 to less than 60 mL/min/1.73 m², Framingham risk score of 15% or more, or age 75 years or older. Major exclusion criteria included diabetes, stroke, polycystic kidney disease, CKD with estimated glomerular filtration rate less than 20 mL/min/1.73 m², and proteinuria more

than 1 g/day. Participants were randomized to an “intensive group” (SBP less than 120 mm Hg) or to a “standard group” (SBP less than 140 mm Hg). At a median follow-up of 3.2 years, the primary outcome (composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute decompensated heart failure, or cardiovascular mortality) event rate was significantly lower in the intensive group compared to standard group (1.6 vs. 2.1% per year, hazard ratio [95% CI] 0.75 [0.64–0.89], *p* < 0.0001). Adverse events including hypotension and acute kidney injury (AKI) were more common in the intensive group [1].

In this issue of the journal, Dieter et al. [2] present a post hoc observational study investigating the relationship between AKI events, fatal and nonfatal cardiovascular events, and all-cause death among patients enrolled in SPRINT. The data included only unadjudicated investigator reported AKI events, which were provided as part of a SPRINT data analysis challenge. Modified KDIGO criteria were used to define AKI, incorporating only serum creatinine since urine output was not consistently recorded in the SPRINT trial.

The primary findings of the study indicated AKI occurred in 4.4% of the intensive group compared to 2.6% of the standard group. Additionally, those who experienced AKI had 50% higher risk of cardiovascular events and 2-fold increase in risk of death from any cause, after controlling for age, sex, race, baseline SBP, body mass index, number of antihypertensive medications, cardiovascular disease and CKD status, hypotensive episodes, and treatment assignment. Thus, the authors conclude that intensive treatment of BP independently raised the risk of AKI, which consequentially increased risks of major cardiovascular events and death.

While the paper raises a very important issue that practicing clinicians should be aware of regarding monitoring kidney function closely when more intensive BP goal is targeted, there is an apparent discordance with the primary results of the overall SPRINT study, which clearly demonstrated cardiovascular benefits with more intensive BP control. As such, there are important considerations for attempting to reconcile findings and the risks and benefits of intensive BP control.

A principal issue placing findings in proper context is that SPRINT was not designed to determine the effect of AKI on cardiovascular events and death. Thus, the findings of the present secondary analysis must be considered with the caveats and appropriate interpretations of retrospective analyses subject to confounding and conclusions describing associations without causal inferences. Second, the absolute rate of investigator-reported (unadjudicated) AKI was small. An analysis by Rocco et al. [3], using adjudicated AKI events, also reported low absolute rates of AKI – in 3.8% of the intensive group and 2.3% of standard group, with most AKI events classified as stage 1 (mild), and complete resolution of AKI seen in 90% of the events in the intensive group. Thus, both the overall impact and absolute differences between groups depicted in current findings are modest as compared to inferences applicable to the entire SPRINT population. Lastly, the most common reasons for AKI depicted in the analysis by Rocco et al. [3] were dehydration or intravascular volume depletion, followed by hypotension. As such, it is very likely that AKI is related to hemodynamic effects rather than intrinsic renal injury, and a study examining biomarkers of kidney injury appears to corroborate these mechanisms [4]. This observation was further corroborated by an analysis from findings in the ACCORD trial as well [5]. Finally, long-term follow-up is not available to ascertain the more definitive potential benefits of intensive BP control on kidney outcomes in

SPRINT. However, an independent analysis of changes in serum creatinine using SPRINT criteria for the ACCORD trial showed a cardiovascular benefit with up to a 30% rise in serum creatinine after 8 years of follow-up [6, 7].

While the paucity of AKI events and reported resolution of most events lessens some concern in SPRINT, prior studies have shown that AKI has the potential to cause significant morbidity, and as reported in this study, an increased risk for cardiovascular events and death [8, 9]. However, many of these studies were in hospitalized patients with chronic illnesses. The current study highlights the trade-off between the potential benefits and adverse events when deciding on a BP control strategy, and the authors appropriately draw attention to the need for close monitoring for potential adverse events.

“Real world” follow-up of patients may be notably distinct from a study environment where there is stricter adherence to study protocols with built-in safety checks. The technique of BP measurement should also be noted – SPRINT followed a strict protocol of BP measurement with an automated device, checking sitting BP 3 times at 1-min intervals after 5 min of rest, with the patient alone in the room and without an observer present at many of the sites. This technique may be not be followed in usual practice, which could lead to misdiagnosis and unnecessary intensification of medical regimens to achieve BP targets, resulting in adverse events including AKI due to hypotension.

The new hypertension guidelines recommend a target BP goal of less than 130/80 mm Hg in most patients rather than the SPRINT target of less than 120 systolic – perhaps recognizing that the SPRINT BP measurement protocol may not be universally followed.

Cumulatively, the results of this study should not be interpreted to infer that intensive BP control should be avoided in SPRINT-like patients; rather, it emphasizes the need for careful monitoring such that adverse events can be avoided or better managed. If there is a decline in renal function with attempted intensive BP control, clinicians should be vigilant about potential cardiovascular events, integrating a team management approach that includes internists, cardiologists, and nephrologists to individualize patient care that is effective, efficient, and safe. Future studies that can elucidate populations that may be applicable for personalized therapeutic BP-control regimens based on individual risk factors and personal preferences may be critical to continue to improve both cardiovascular and renal health and minimize potential complications.

References

- 1 Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, et al.; SPRINT Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. *N Engl J Med*. 2015 Nov;373(22):2103–16.
- 2 Dieter BP, Daratha KB, McPherson SM, Short R, Alicic RZ, Tuttle KR. Association of Acute Kidney Injury with Cardiovascular Events and Death in Systolic Blood Pressure Intervention Trial. *Am J Nephrol*. 2019;49:359–67.
- 3 Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, et al.; SPRINT Research Group. Effects of Intensive Blood Pressure Treatment on Acute Kidney Injury Events in the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis*. 2018 Mar;71(3):352–61.
- 4 Zhang WR, Craven TE, Malhotra R, Cheung AK, Chonchol M, Drawz P, et al.; SPRINT Research Group. Kidney Damage Biomarkers and Incident Chronic Kidney Disease During Blood Pressure Reduction: A Case-Control Study. *Ann Intern Med*. 2018 Nov;169(9):610–8.
- 5 Nadkarni GN, Chauhan K, Rao V, Ix JH, Shlipak MG, Parikh CR, et al. Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury: Findings From the ACCORD Trial Study Participants. *Am J Kidney Dis*. 2019 Jan;73(1):31–8.
- 6 Collard D, Brouwer TF, Peters RJ, Vogt L, van den Born BH. Creatinine Rise During Blood Pressure Therapy and the Risk of Adverse Clinical Outcomes in Patients With Type 2 Diabetes Mellitus. *Hypertension*. 2018 Dec;72(6):1337–44.
- 7 Bakris GL, Agarwal R. Creatinine Bump Following Antihypertensive Therapy. *Hypertension*. 2018 Dec;72(6):1274–6.
- 8 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*. 2009 Jun;53(6):961–73.
- 9 Odotayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, et al. AKI and Long-Term Risk for Cardiovascular Events and Mortality. *J Am Soc Nephrol*. 2017 Jan;28(1):377–87.