In the Wake of Systolic Blood Pressure Intervention Trial: New Targets for Improving Hypertension Management in Chronic Kidney Disease?

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Abstract

Systolic Blood Pressure Intervention Trial (SPRINT) was a multicenter randomized controlled trial showing the significant benefit of intensive reduction of blood pressure to a target of 120 mm Hg in individuals with hypertension and elevated cardiovascular risk. Because SPRINT includes the largest cohort of adults with chronic kidney disease (CKD) to be prospectively studied in a hypertension intervention trial, it has particular relevance to the field of nephrology. Here, we review the findings of SPRINT and assess their potential impact on guidelines for treatment of hypertension in patients with CKD. We believe that the data from SPRINT will support a recommendation for lowering blood pressure targets to 120 mm Hg in a substantial segment of adults with CKD.

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Hypertension is one of the most common disorders of humankind, and the kidney has a prominent role as both a cause and target of elevated blood pressure [1]. Proportional associations between blood pressure and cardiovascular risk [2], along with prospective benefits of lowering blood pressure to improve cardiovascular outcomes [3] have been well-established in epidemiological studies

and clinical trials. Such observations have fueled decades of research focused on developing better approaches for preventing and treating hypertension. While much progress has been made over the years in identifying a range of effective blood pressure lowering therapies, a critical clinical question has persisted: “how low should blood pressure be reduced to provide optimal protection against end-organ damage?” A definitive answer to this question would have a profound impact on public health considering that millions of people worldwide die annually from heart disease, stroke, and kidney disease, for which hypertension is a major contributor [4].

The burden of hypertension and cardiovascular disease in chronic kidney disease (CKD) is particularly striking. Compared to the general population, hypertension is 2–3 times more prevalent in CKD [5]. Kidney disease is also independently associated with cardiovascular disease and death, with substantially higher risk occurring in more advanced stages of disease [6]. Furthermore, individuals with CKD are more likely to die from a cardiovascular event than to develop end-stage renal disease [7, 8]. Therefore, reducing cardiovascular risk in CKD is arguably the major clinical challenge facing the field of nephrology today. In this regard, the Systolic Blood Pressure Intervention Trial (SPRINT), a landmark trial testing whether intensively lowering blood pressure improves cardiovascular outcomes, provides important new findings relevant to individuals with kidney disease [9].

SPRINT was a randomized, controlled trial testing whether reducing the systolic blood pressure (SBP) to a target of 120 mm Hg would diminish cardiovascular events compared to the accepted standard of 140 mm Hg [9]. The trial enrolled a total of 9,361 adults aged ≥ 50 years with SBP ≥ 130 mm Hg and evidence of increased cardiovascular risk. While SPRINT was primarily designed to define blood pressure targets in adults at risk for cardiovascular events, 2,646 adults with CKD were enrolled, comprising 28% of the entire cohort and exceeding the number of combined participants enrolled in the 3 previous major trials designed to evaluate different blood pressure targets on kidney function in patients with CKD: Modification of Diet in Renal Disease [10], African American Study of Kidney Disease and Hypertension [11], and Ramipril Efficacy In Nephropathy [12]. Thus, SPRINT comprises the largest prospective cohort of individuals with CKD studied in a randomized, prospective trial testing optimal levels of blood pressure control.

In SPRINT, separation of blood pressure was successfully achieved between the treatment groups. Mean SBP in the intensive treatment group was reduced by 15 mm Hg, compared to the standard therapy (121 vs. 136 mm Hg). Remarkably, the mean number of anti-hypertensive medications used to achieve this separation was only 2.8 in the intensive group compared to 1.8 in the standard group. The primary outcome in SPRINT was a composite of myocardial infarction, acute coronary syndrome, stroke, decompensated heart failure, and cardiovascular-related death. The study was terminated prematurely after the data and safety monitoring board found evidence of benefit in the group subjected to intensive treatment. Specifically, the event rate of the primary composite outcome was significantly lower for those who received intensive therapy (1.65% per year) compared to standard therapy (2.19% per year), representing a 25% reduction in relative risk. Furthermore, these results were consistent across pre-specified clinical subgroups including age, sex, race, tertiles of SBP, history of cardiovascular disease, and importantly in the context of this review, history of CKD. With the stipulation that some CKD subgroups were excluded from participation, including individuals with estimated glomerular filtration rate (eGFR) < 20 mL/min/1.73 m², proteinuria ≥ 1 g/day, diabetes, and polycystic kidney disease, findings from SPRINT indicate that intensive blood pressure lowering can improve cardiovascular outcomes for individuals with CKD.

Previous observational studies suggested the existence of a so-called “U-curve” relationship between blood pressure and CV risk across populations of individuals with

CKD, where risk was paradoxically increased in individuals with lower blood pressure ranges [13–15]. Such studies had raised concerns that lowering the blood pressure even below 140 mm Hg might actually cause harm in patients with kidney disease. However, causal relationships cannot be established through observational studies and it was suggested that low blood pressure might actually be a surrogate for failing health or other comorbidities impacting risk. SPRINT now provides level 1 evidence indicating that aggressive lowering of blood pressure improves cardiovascular risk in a selected population with CKD.

It should be noted that blood pressure measurements in SPRINT were carried out using an automated measurement system after the patient had been seated quietly and unattended for 5 min [16]. The aim of this approach was to achieve more precise measurements, avoiding the potentially confounding issue of “white coat” hypertension, but with the proviso that blood pressure values obtained through this method may be systematically lower than conventional office measurements. Thus, while SPRINT has clearly demonstrated the benefits of intensive blood pressure lowering, questions have been raised about translation of data from the clinical trial into specific numerical targets to be safely implemented in the real world [17]. This issue will likely be clarified as more data emerge from SPRINT, including information on subsets of participants who underwent ambulatory blood pressure monitoring. On the other hand, it could be argued that measurement with automated devices after resting should be adopted as the standard method for determining blood pressure in the outpatient setting.

Pre-specified secondary kidney outcomes were also assessed in SPRINT. Among participants with CKD at baseline, there was no significant difference between the intensive and standard treatment groups in the relatively small number of participants with a decline in eGFR of $\geq 50\%$ (0.8 vs. 0.8%), incident albuminuria (9.3 vs. 11.8%), incident end-stage renal disease requiring dialysis (0.5 vs. 0.8%), incident kidney transplant (0 vs. 0%), or a composite of each of these outcomes (1.1 vs. 1.1%). A caveat here is that the number of kidney outcomes in SPRINT was relatively small, likely because individuals with proteinuria, a major risk factor for progressive CKD, were excluded from the trial. Thus, in patients with CKD, there was no detectable benefit of intensive blood pressure lowering on CKD progression, but also no evidence of harm.

In contrast, for the subgroup with normal kidney function, intensive therapy was associated with a significantly higher incidence of eGFR decline, defined as $\geq 30\%$ reduction in eGFR to a value < 60 mL/min/1.73 m² (3.8 vs. 1.1%

with standard therapy). Irrespective of CKD status, intensive therapy was also associated with a significantly higher incidence of acute kidney injury compared to standard therapy (4.4 vs. 2.6%, $p < 0.001$). The mechanisms underlying this preponderance of adverse kidney events are not clear. In SPRINT, the standard for assessing deterioration in kidney function among individuals without CKD was a 30% decline in eGFR, compared to 50% in individuals with CKD. This less stringent threshold may account for the higher rate of events observed for this subgroup. Furthermore, renin-angiotensin-aldosterone inhibitors were used more frequently in the intensive therapy group, which may have contributed to the overall decline in eGFR as well as the higher incidence of acute kidney injury. Despite these adverse kidney events, intensive therapy reduced the cardiovascular end points for individuals whether CKD was present or not (hazard ratio 0.7 and 0.8, respectively; p for interaction = 0.36), suggesting that the benefits of intensive therapy may outweigh the risks. Nonetheless, additional time and follow-up will be required to determine whether there will be longer term impact on kidney health and mortality.

SPRINT clearly provides strong evidence that lowering SBP to a goal of 120 mm Hg compared to current targets of 140 mm Hg improves cardiovascular outcomes in adults with increased cardiovascular risk. This also seems to hold true for individuals with CKD. However, since diabetics were excluded from SPRINT, the trial does not provide guidance on optimal targets for blood pressure in diabetes, a powerful cardiovascular risk factor and major cause of progressive CKD. This issue was addressed in a previous trial, ACCORD, a prospective randomized clinical trial with many similarities to SPRINT, testing in diabetics whether lowering blood pressure to 120 mm Hg compared to 140 mm Hg would improve cardiovascular outcomes [18]. Although a significant difference in lowering of blood pressure was achieved in the intensively treated group with a magnitude very similar to SPRINT (15 mm Hg reduction in SBP), there was no significant benefit in cardiovascular outcomes. While eGFR was lower with intensive blood pressure lowering (75 vs. 81 mL/min/1.73 m²; $p < 0.001$), frequency of macroalbuminuria was reduced (6.6 vs. 8.7%, $p = 0.009$), but, as in SPRINT, there was no beneficial effect on the progression to end-stage renal disease (2.5 vs. 2.4%). In retrospect, because of an unexpectedly low frequency of cardiovascular events in ACCORD, it has been suggested that it was underpowered, with 4,733 participants compared to 9,361 in SPRINT. Nonetheless, at this point, there is no firm evidence supporting blood pressure targets below current recommendations of

140/90 mm Hg for persons with diabetes in reducing cardiovascular risk or kidney disease progression.

In summary, SPRINT is truly a landmark trial in hypertension therapy that will surely impact blood pressure guidelines, suggesting an optimal target of 120 mm Hg for therapy in adults with hypertension and increased risk for cardiovascular disease. The findings from SPRINT suggest this target should also apply to individuals with CKD, with the exception of those with proteinuria, diabetes, or polycystic kidney disease [19] where benefits of more intensive blood pressure lowering have not yet been clearly established. While blood pressure reduction in SPRINT reduced the cardiovascular risk in CKD, there was no significant effect on kidney disease progression albeit in a cohort with low rates of kidney outcomes. The intensive blood pressure target was achieved with, on average, one additional anti-hypertensive drug, suggesting that achieving the lower goal is feasible without undue patient or financial burden. However, this was at the cost of some adverse effects including higher rates of acute kidney injury for all participants and greater eGFR decline in participants who entered the trial with normal kidney function. The long-term consequences of these apparent adverse kidney effects are not yet clear. Certainly the risks and benefits of intensive blood pressure reduction will be further clarified as additional analyses of the SPRINT data come to light. If intensive therapy is implemented, clinicians should monitor patients carefully and be prepared to de-escalate treatment in the event of symptomatic hypotension or other adverse events. But for now, the findings from SPRINT suggest that intensive blood pressure reduction to a systolic goal of 120 mm Hg will attenuate cardiovascular risk in a large segment of patients with CKD.

Disclosure Statement

The authors have no conflicts of interest to declare.

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