SPS3 Evidence Supports Intensive Blood Pressure Control

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Interest in identifying the most appropriate targets for systolic blood pressure (SBP) lowering to reduce cardiovascular events in persons with hypertension has been piqued by the widely publicized results of the Systolic Blood Pressure Intervention Trial (SPRINT).1,2 SPRINT found overwhelming benefit (25% reduction in the primary composite outcome of myocardial infarction [MI], acute coronary syndrome not resulting in MI, stroke, acute decompensated heart failure, or death from cardiovascular causes) and 27% reduction in all-cause mortality among participants randomly assigned to a SBP target of <120 mm Hg (intensive treatment) in comparison with <140 mm Hg (standard treatment). In contrast, serious adverse events, including acute kidney injury or acute renal failure that contributed to hospitalizations or emergency department visits were significantly more common in the intensive treatment group (4.4% versus 2.6%, hazard ratio, 1.71; P<0.001). Among those who did not have chronic kidney disease (CKD) at baseline, incident CKD, defined as a decrease in estimated glomerular filtration rate (eGFR) of ≥30% to a level of <60 mL·min⁻¹·1.73 m⁻² occurred more frequently in the intensive treatment group (1.21%/y versus 0.35%/y). Among those with CKD at baseline, few reached the primary renal end point of decrease in eGFR ≥50% or end-stage renal disease (ESRD). Incident albuminuria, another measure of kidney damage, did not differ between treatment groups. The investigators concluded that available data provide no evidence of substantial permanent kidney injury associated with the lower SBP goal in SPRINT, but that the possibility of such adverse outcomes cannot be excluded and that longer follow-up data that include more clinical outcomes and analyses of rates of fall in eGFR are needed to address this important issue.

A recent post hoc analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) trial in this issue of *Circulation* examined the effect of reducing SBP to a lower (<130 mm Hg) versus higher (130–149 mm Hg) target on kidney function in 2610 persons with a recent history of symptomatic ischemic lacunar stroke (a population excluded from SPRINT) and preserved kidney function (mean eGFR 80 mL·min⁻¹·1.73 m⁻²).3 Achieved SBP was 127 mm Hg in the lower-target group and 137 mm Hg in the higher-target group. The primary outcome of SPS3 was reduction in all stroke, including ischemic stroke and intracranial hemorrhages.4,5 Overall, there were statistically nonsignificant reductions in stroke and in the composite outcome of stroke, MI, or vascular death in the lower-target group, leading the investigators to conclude that targeting a SBP of <130 mm Hg is likely to be beneficial in most patients with recent lacunar stroke.5

The primary kidney outcomes of SPS3 were annualized eGFR change and rapid kidney function decline, defined as a reduction in eGFR of ≥30% from baseline. Incident CKD during the study period was defined as eGFR <60 mL·min⁻¹·1.73 m⁻² plus a decline of ≥30% among persons with eGFR > 60 mL·min⁻¹·1.73 m⁻² at baseline, consistent with SPRINT.1,3 Within the first year of treatment, reductions in eGFR were ≥2 mL·min⁻¹·1.73 m⁻² greater in the lower-target group, and more participants in the lower-target group (313 or 24%) than in the higher-target group (247 or 19%) had rapid kidney function decline. Intensive blood pressure (BP) lowering resulted in greater reductions in eGFR in subgroups of particular interest, including older (>65 years of age) persons and those with diabetes mellitus. Only the subgroup with CKD (eGFR<60 mL·min⁻¹·1.73 m⁻²) at baseline did not show a decline in kidney function, reflected in the slowing of reduction in eGFR, with intensive treatment. Rapid kidney function decline in the first year was associated with greater risk for stroke and for a composite outcome of death, major vascular events, MI or stroke in the higher-target group (hazard ratio, 1.62; confidence interval, 1.05–2.51), but not in the lower-target group (hazard ratio, 0.83; confidence interval, 0.51–1.35), Ρ=0.03. Rates of eGFR decline and rapid kidney function decline did not differ between treatment arms after the first year.

The ≥30% decline in eGFR, used as an index of kidney function decline in SPS3 and in participants without CKD at baseline in SPRINT, has been validated as a predictor of adverse cardiovascular events, death, and ESRD based on meta-analyses of data from observational studies and randomized, controlled trials of CKD progression.6–9 An individual meta-analysis of data from ≥1.7 million persons with CKD in 35 cohorts within the CKD Prognosis Consortium demonstrated a strong relationship between decline in eGFR over 2 years of follow-up and ESRD or all-cause mortality.4,9 A 30% decline in eGFR was associated with a 5-fold increased risk of ESRD and a 2-fold increased risk of death. Furthermore, an analysis of clinical trials that tested various interventions, including intensive versus usual BP control, renin-angiotensin system blockade versus control, renin-angiotensin system blockade versus calcium channel blocker, low-protein versus usual-protein diet, and immunosuppressive versus other therapy in patients with CKD showed that a 30% decline in
eGFR over a 1- to 3-year period was strongly and consistently (across different causes of CKD and different interventions to slow its progression) associated with ESRD.7–9 These analyses, undertaken in conjunction with a workshop, “GFR Declines as an End point for Clinical Trials in CKD,” sponsored by the National Kidney Foundation and the US Food and Drug Administration, resulted in the recommendation that an eGFR decline of 30% (with stronger evidence for a 40% decline) could be a useful surrogate end point for progression to ESRD in future clinical trials of CKD.7 The report cautioned that the recommendation does not apply to interventions that produce transient reductions in eGFR and that least 2 to 3 years of follow-up are needed to allow for adequate evaluation of benefits and harms of any intervention that reduces eGFR.

A major question raised by the findings of SPS3 is why the greater reductions in eGFR seen in the presence of more intensive BP lowering were associated with decreases in stroke and cardiovascular events, whereas lesser reductions in eGFR in the presence of an average 11 mm Hg higher SBP in the higher-target group were associated with increases in these outcomes. One possible explanation is that intensive BP lowering, particularly with renin-angiotensin system blockers and diuretics, as often prescribed in SPS3, could lead to renal hypoperfusion because of a combination of hypotension and volume depletion in patients with microvascular disease, including those with a history of lacunar stroke. Glomerular hypoperfusion in this setting is a hemodynamic effect that leads to decreases in eGFR that are reversible, generally not progressive over time, and rarely result in long-term changes in kidney structure or ESRD.10–14 In fact, the acute fall in eGFR that follows the initiation or intensification of BP-lowering treatment has been shown to be inversely related to long-term kidney function decline.11–13 Intensive BP lowering as seen in the lower-target groups in SPS3 and SPRINT protects against macrovascular disease and structural kidney damage and reduces the risk of future cardiovascular events. In contrast, among persons in the higher-target groups in SPS3 and SPRINT, the protective effects of BP lowering against macrovascular disease and cardiovascular events were not maximized, and it is unlikely that BP levels were low enough to result in renal hypoperfusion, so the reductions in eGFR that occurred in these participants likely reflect structural kidney damage and true progression in CKD.

Two recent systematic reviews and meta-analyses have reinforced the conclusion that more intensive BP-lowering strategies are associated with greater reductions in major cardiovascular and renal events and little apparent harm.15,16 The first of these included 19 trials (including SPS3 and Action to Control Cardiovascular Risk in Diabetes [ACCORD], but not SPRINT) that randomly assigned 44 989 participants to more intensive versus less intensive BP-lowering treatment.15 Achieved BPs were 133/76 mm Hg in the more intensive group and 140/81 mm Hg in the less intensive group, and 2496 major cardiovascular events were reported. Significant reductions in major cardiovascular events, MI, stroke, progression of albuminuria and retinopathy (for patients with diabetes mellitus), but not ESRD, heart failure, or death occurred in the more intensive treatment group. These reductions were consistent across patient subgroups (with the exception of those with CKD at baseline) and types of intervention. The benefits were greatest in patients at high risk because of vascular disease, kidney disease, or diabetes mellitus. Although adverse events were not reported consistently across trials, there was a statistically nonsignificant increase in serious adverse events associated with BP lowering in the intensive group (1.2%/y versus 0.9%/y).

The second meta-analysis of 123 studies with 613 815 participants also included trials of antihypertensive drugs for conditions other than hypertension: 14 of these, including both SPS3 and SPRINT, compared lower versus higher BP targets.16 The main finding was that risk reductions for all outcomes were proportional to the BP reductions achieved, such that a 10 mm Hg reduction in SBP was associated with statistically significant and clinical meaningful reductions in all cardiovascular disease outcomes and death, with the exception of renal failure, for which there was a statistically nonsignificant risk reduction (relative risk, 0.95; 0.84–1.07; P = 0.09). The benefits of BP lowering were seen across baseline SBP levels (range, <130 to ≥160 mm Hg) and all antihypertensive drugs classes, with the exception of β-blockers. The finding from SPS3 that intensive BP lowering protects patients with recent lacunar stroke from subsequent clinical events, even in the face of rapid kidney function decline, adds to the rapidly accumulating evidence in support of lower SBP targets, and provides reassurance for clinicians caring for this high-risk patient population.

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References


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