Published in final edited form as:

Circulation. 2016 February 9; 133(6): 552–554. doi:10.1161/CIRCULATIONAHA.116.021125.

SPS3 Evidence Supports Intensive Blood Pressure Control

Suzanne Oparil, MD

Vascular Biology and Hypertension Program, Division of Cardiovascular Disease, Department of Medicine, The University of Alabama at Birmingham, Birmingham, AL

Keywords

eGFR; ESRD; Editorial; stroke; hypertension; kidney; hypertension; high blood pressure; hypertension; low blood pressure

Journal Subject Terms

High Blood Pressure; Clinical Studies; Cardiovascular Disease; Meta Analysis

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 randomized to a SBP target of < 120 mm Hg (intensive treatment) compared to < 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% vs. 2.6%, HR 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) ≥ 30% to a level of < 60 mL/min/1.73 m^2 occurred more frequently in the intensive treatment group (1.21% vs. 0.35%/yr). Among those with CKD at baseline, few reached the primary renal endpoint 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

Address for Correspondence: Suzanne Oparil, MD, Vascular Biology and Hypertension Program, The University of Alabama at Birmingham, 1720 2nd Avenue South, ZRB 1034, Birmingham, AL 35294-0007, Phone: 205-934-2580, Fax: 205-975-5119, soparil@uabmc.edu.

Disclosures: Dr. Oparil reports that she has received research grant funding from NIH/NHLBI Sponsor: Brigham and Women's Hospital, Center for CVD Prevention, AstraZeneca, Bayer, Medtronic, Merck and Co, Novartis; educational grant funding from Arbor Pharmaceuticals, LLC; and has received consulting/other fees from Amgen (Onyx – Subsidiary), AstraZeneca, Bayer, Boehringer-Ingelheim, GlaxoSmithKline, Forest Laboratories, Inc., Medtronic; and served as Co-chair (2007-2013) for "Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC 8), Co-Chair, (JAMA 311(5):507-520, 2014).

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) vs. higher (130–149 mm Hg) target on kidney function in 2,610 persons with a recent history of symptomatic ischemic lacunar stroke (a population excluded from SPRINT) and preserved kidney function (mean eGFR 80 mL/min/1.73 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 non-significant 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 launar stroke[5].

The primary kidney outcomes of SPS3 were annualized eGFR change and rapid kidney function decline, defined as a reduction in eGFR ≥ 30% from baseline. Incident CKD during the study period was defined as eGFR < 60 ml/min/1.73m^2 plus a decline ≥ 30% among persons with eGFR > 60 mL/min/1.73 m^2 at baseline, consistent with SPRINT[1,3]. Within the first year of treatment, reductions in eGFR were ~ 2 mL/min/1.73 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 BP-lowering resulted in greater reductions in eGFR in subgroups of particular interest, including older (> age 65) persons and those with diabetes. Only the subgroup with CKD (eGFR<60ml/min/1.73m2) at baseline failed to show a decline in kidney function, reflected in 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 (HR 1.62, CI 1.05–2.51), but not in the lower-target group (HR 0.83, CI 0.51–1.35), P=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 nearly 1.7 milion 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[6]. A 30% decline in eGFR was associated with a 5-fold increased risk of ESRD and a 2-fold increased risk of death. Further, an analysis of clinical trials that tested various interventions, including intensive vs. usual BP control, renin-angiotensin system (RAS) blockade vs. control, RAS blockade vs calcium channel blocker, low-protein vs usual-protein diet, and immunosuppressive vs other therapy in patients with CKD showed that a 30% decline in eGFR over a 1–3 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 Endpoint 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 endpoint 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 2–3 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 RAS blockers and diuretics, as often prescribed in SPS3, could lead to renal hypoperfusion due to 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[10–16]. In fact, the acute fall in eGFR that follows initiation or intensification of BP-lowering treatment has been shown to be inversely related with 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 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 GFR 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 ACCORD, but not SPRINT) that randomized 44,989 participants to more intensive vs. 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 2,496 major cardiovascular events were reported. Significant reductions in major cardiovascular events, MI, stroke, progression of albuminuria and retinopathy (for patients with diabetes), 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 due to vascular disease, kidney disease or diabetes. While 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%/year vs. 0.9%/year).

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 vs. 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 (RR 0.95 (0.84–1.07) P=0.09. The benefits of BP-lowering were seen across baseline SBP levels (range < 130 – ≥160 mm Hg) and with all antihypertensive drugs classes except 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 the high-risk patient population.

References

1. 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 Study Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015; 373:2103–2116. [PubMed: 26551272]
2. Ambrosius WT, Sink KM, Foy CG, Berlowitz DR, Cheung AK, Cushman WC, Fine LJ, Goff DC Jr, Johnson KC, Killeen AA, Lewis CE, Oparil S, Reboussin DM, Rocco MV, Snyder JK, Williamson JD, Wright JT Jr, Whelton PK. SPRINT Study Research Group. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials. 2014; 11:532–546. [PubMed: 24902920]
3. Peralta CA, McClure LA, Scherzer R, Odden MC, White CL, Shlipak M, Benavente O, Pergola P. Intensive vs. Usual blood pressure control and kidney function decline among persons with prior lacunar stroke- a post-hoc analysis of the SPS3 randomized trial. Circulation. 2016; 133:XX–XXX.
4. Benavente OR, White CL, Pearce L, Pergola P, Roldan A, Benavente MF, Coffey C, McClure LA, Szychowski JM, Conwit R, Heberling PA, Howard G, Bazan C, Vidal-Pergola G, Talbert R, Hart RG. SPS3 Investigators. The secondary prevention of small subcortical strokes (SPS3) study. Int J Stroke. 2011; 6:164–175. [PubMed: 21371282]
5. Benavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, Pergola PE, Szychowski JM. SPS3 Study Group. Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. Lancet. 2013; 382:507–515. [PubMed: 23726159]
6. Coresh J, Turin TC, Matsushita K, Sang Y, Ballew SH, Appel LJ, Arima H, Chadban SJ, Cirillo M, Djurdjev O, Green JA, Heine GH, Inker LA, Irie F, Ishani A, Ix JH, Kovesdy CP, Marks A, Ohkubo T, Shalev V, Shankar A, Wen CP, de Jong PE, Iseki K, Stengel B, Gansevoort RT, Levey AS. CKD Prognosis Consortium. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. JAMA. 2014; 311:2518–2531. [PubMed: 24892770]
7. Levey AS, Inker LA, Matsushita K, Greene T, Willis K, Lewis E, de Zeeuw D, Cheung AK, Coresh J. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014; 64:821–835. [PubMed: 25441437]
8. Inker LA, Lambers Heerspink HJ, Mondal H, Schmid CH, Tighiouart H, Noubary F, Coresh J, Greene T, Levey AS. GFR decline as an alternative end point to kidney failure in clinical trials: a meta-analysis of treatment effects from 37 randomized trials. Am J Kidney Dis. 2014; 64:848–859. [PubMed: 25441438]
9. Lambers Heerspink HJ, Tighiouart H, Sang Y, Ballew S, Mondal H, Matsushita K, Coresh J, Levey AS, Inker LA. GFR decline and subsequent risk of established kidney outcomes: a meta-analysis of 37 randomized controlled trials. Am J Kidney Dis. 2014; 64:860–866. [PubMed: 25441439]
10. Apperloo AJ, de Zeeuw D, de Jong PE. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney Int. 1997; 51:793–797. [PubMed: 9067912]

11. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med. 2000; 160:685–693. [PubMed: 10724055]
12. Bidani AK, Griffin KA. Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension. 2004; 44:595–601. [PubMed: 15452024]
13. Holtkamp FA, de Zeeuw D, Thomas MC, Cooper ME, de Graeff PA, Hillege HJ, Parving HH, Brenner BM, Shahinfar S, Lambers Heerspink HJ. An acute fall in estimated glomerular filtration rate during treatment with losartan predicts a slower decrease in long-term renal function. Kidney Int. 2011; 80:282–287. [PubMed: 21451458]
14. Bidani AK, Polichnowski AJ, Loutzenhiser R, Griffin KA. Renal microvascular dysfunction, hypertension and CKD progression. Curr Opin Nephrol Hypertens. 2013; 22:1–9. [PubMed: 23132368]
15. Xie X, Atkins E, Lv J, Bennett A, Neal B, Ninomiya T, Woodward M, MacMahon S, Turnbull F, Hillis GS, Chalmers J, Mant J, Salam A, Rahimi K, Perkovic V, Rodgers A. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: updated systematic review and meta-analysis. Lancet. 2015 Nov 7. pii: S0140-6736(15)00805-3. [Epub ahead of print]. doi: 10.1016/S0140-6736(15)00805-3
16. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2015 Dec 23. pii: S0140-6736(15)01225-8. [Epub ahead of print]. doi: 10.1016/S0140-6736(15)01225-8