# Effect of Intensive Versus Usual Blood Pressure Control on Kidney Function Among Individuals With Prior Lacunar Stroke

## A Post Hoc Analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) Randomized Trial

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***Background***—The effect of intensive blood pressure (BP) lowering on kidney function among individuals with established cerebrovascular disease and preserved estimated glomerular filtration rate (eGFR) is not established.

***Methods and Results***—Among 2610 participants randomized to a lower (<130 mm Hg) versus higher (130–149 mm Hg) systolic BP target with repeated measures of serum creatinine, we evaluated differences by study arm in annualized eGFR decline and rapid decline (eGFR decline >30%) using linear mixed models and logistic regression, respectively. We assessed associations of both treatment and kidney function decline with stroke, major vascular events, and the composite of stroke, death, major vascular events, or myocardial infarction using multivariable Cox regression, separately and jointly including a test for interaction. Analyses were conducted by treatment arm. Mean age was 63±11 years; 949 participants (36%) were diabetic; and mean eGFR was 80±19 mL·min$^{-1}$·1.73 m$^{-2}$. At 9 months, achieved systolic BP was 137±15 versus 127±14 mm Hg in the higher versus lower BP group, and differences were maintained throughout follow-up (mean, 3.2 years). Compared with the higher target, the lower BP target had a −0.50–mL·min$^{-1}$·1.73 m$^{-2}$ per year (95% confidence interval [CI], −0.79 to −0.21) faster eGFR decline. Differences were most pronounced during the first year (−2.1 mL·min$^{-1}$·1.73 m$^{-2}$; 95% CI, −0.97 to −3.2), whereas rates of eGFR decline did not differ after year 1 (−0.095; 95% CI, −0.47 to 0.23). A total of 313 patients (24%) in the lower BP group had rapid kidney function decline compared with 247 (19%) in the higher BP group (odds ratio, 1.4; 95% CI, 1.1–1.6). Differences in rapid decline by treatment arm were apparent in the first year (odds ratio, 1.4; 95% CI, 1.1–1.8) but were not significant after year 1 (odds ratio, 1.0; 95% CI, 0.73–1.4). Rapid decline was associated with higher risk for stroke, major vascular events, and composite after full adjustment among individuals randomized to the higher BP target (stroke hazard ratio, 1.93; 95% CI, 1.15–3.21) but not the lower BP arm (stroke hazard ratio, 0.93; 95% CI, 0.50–1.75; all *P* for interaction <0.06).

***Conclusions***—In patients with prior lacunar stroke and relatively preserved kidney function, intensive BP lowering was associated with a greater likelihood of rapid kidney function decline. Differences were observed primarily during the first year of antihypertensive treatment. Rapid kidney function decline was not associated with increased risk for clinical events among those undergoing intensive BP lowering.

***Clinical Trial Registration***—URL: http://www.clinicalTrials.gov. Unique identifier: NCT00059306.

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Management of hypertension remains the mainstay of treatment in chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) <60 mL·min$^{-1}$·1.73 m$^{-2}$ or the presence of proteinuria.[1] However, the optimal blood pressure (BP) level to attenuate CKD progression remains an issue of active debate. Observational data show a graded association of higher BP levels with progression to end-stage renal disease (ESRD), but the BP threshold for the observed higher risk is variable.[2–4] Data from randomized trials among individuals with established

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CKD have not consistently shown benefit from achieving BP to targets <140/90 mm Hg, particularly among those without proteinuria.[5–9]

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Less is known about the effect of higher versus more intensive BP lowering on changes in kidney function among individuals with preserved eGFR (>60 mL·min$^{-1}$·1.73 m$^{-2}$). Some studies among diabetics have suggested that intensive BP lowering may reduce the level of proteinuria, but it may not attenuate progression of disease.[10–13] On the other hand, it is also possible that intensive BP lowering may accelerate kidney function decline, particularly in patients with established vascular disease and little or no proteinuria.[14] The Systolic Blood Pressure Intervention Trial (SPRINT) showed that although more intensive BP lowering resulted in lower rates of cardiovascular events and death compared with the usual target, aggressive BP treatment led to higher rates of kidney function decline among participants without CKD.[15] Understanding the potential renal effects of intensive BP lowering is especially pressing among individuals at high cardiovascular risk (ie, patients with atherosclerotic disease, those with prior stroke, and the elderly) because the optimal systolic BP (SBP) goal for cardiovascular protection in these individuals remains an issue of active debate.[16–18] Given the longer life expectancy rates, understanding the effects of intensive versus usual BP lowering on kidney function change is important in addressing the increasingly high morbidity from renal disease in elders and individuals at high cardiovascular risk.

The Secondary Prevention of Small Subcortical Strokes (SPS3) study compared the effectiveness of a lower SBP (<130 mm Hg) with a higher target (130–149 mm Hg) to reduce recurrent stroke among patients with a history of lacunar stroke. The lower BP target did not significantly reduce the risk of stroke or the composite outcome of stroke, myocardial infarction, or vascular death.[19] In this report, we examined the effects of intensive versus usual BP lowering on renal outcomes among these individuals with largely preserved kidney function.

## Methods

### Participants

SPS3 was a randomized, multicenter, clinical trial designed to evaluate the effectiveness of 2 antiplatelet treatments (aspirin versus aspirin plus clopidogrel) and 2 target levels of SBP in preventing strokes among patients with previous lacunar stroke. Details of the study design have previously been published.[20] Briefly, individuals in North America, Latin America, and Spain ≥ 30 years of age with a recent symptomatic lacunar stroke were randomized in a 2-by-2 factorial design to the antiplatelet intervention (double-blind) and to a lower SBP target of <130 mm Hg or higher target (130–149 mm Hg) at least 2 weeks after the qualifying stroke. The SBP intervention used the Prospective Randomized Open, Blinded End-Point (PROBE) design. Individuals were excluded if they had a disabling stroke, a hemorrhagic stroke, or a cortical ischemic stroke. In addition, individuals were excluded if they had advanced kidney disease, defined as an eGFR <40 mL·min$^{-1}$·1.73 m$^{-2}$. For these analyses, we included all SPS3 participants who had at least 2 measures of serum creatinine during the study period. A total of 3020 SPS3 participants entered SPS3. We excluded 410 participants who had only 1 measure of serum creatinine, for a final sample size of 2610 individuals. All participants signed informed consent, and the trial was approved by the appropriate institutional review board.

### BP Targets

Participants were randomly assigned to a higher SBP target (130–149 mm Hg) or a lower target (<130 mm Hg). Relevant to this study, there was no washout period of antihypertension medication. As previously described, patients were seen monthly until their BP target was achieved and then quarterly for BP measures and medication adjustment. If participants randomized to the higher target were below target, antihypertensive medications were discontinued or reduced unless their use was indicated for other reasons. BP was measured with the Colin 8800C automated device, and management was overseen by a physician at each study site. The physician prescribed antihypertensive medication from the available study formulary, which included at least 1 drug of the major classes, and medications were provided to participants. Classes or doses of medications were not managed per protocol. All participants were followed up to a common end-study date. For these analyses, we consider year 5 the end of this study because of the very low number of participants with >5 years of follow-up renal measures.

### Kidney Function Measures

Kidney function was measured by serum creatinine among all participants at yearly intervals until the end of the study. Serum creatinine was measured at each study site. The eGFR was estimated with the Chronic Kidney Disease Epidemiology Collaboration equation.[21] For these analyses, there were 2 primary kidney outcomes: annualized eGFR change and rapid kidney function decline. Rapid decline was defined as a reduction in eGFR of ≥30% from baseline. This definition is recommended as a valid surrogate outcome for kidney disease trials, and it is a strong predictor of adverse cardiovascular events, death, and ESRD.[22–24] In sensitivity analyses, we defined rapid decline as ≥40% because this outcome has been shown to have even stronger associations with ESRD,[22,23] and we examined rates of incident CKD during the entire study period, defined as eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$ plus a decline of ≥30% among individuals with eGFR >60 mL·min$^{-1}$·1.73 m$^{-2}$ at baseline, consistent with SPRINT.[15]

### Clinical Outcomes

Trial outcomes were adjudicated by a committee blinded to treatment arm, as has been previously described in detail.[20] For these analyses, we define 3 clinical outcomes: the SPS3 primary outcome of any stroke (ischemic or hemorrhagic confirmed by neuroimaging), the secondary end point of need for hospitalization owing to a major vascular event (MVE), and a composite outcome of stroke, death, MVE, or myocardial infarction. Myocardial infarction was defined on the basis of clinical history, ECG changes, and cardiac enzymes.

### Analyses

We first compared baseline characteristics of 2610 SPS3 participants by study arm and by baseline eGFR. We then evaluated BP levels and use of each major medication class (angiotensin-converting enzyme inhibitor [ACEI]/angiotensin receptor blocker [ARB], diuretic, calcium channel blocker, and β-blocker) in the higher and lower BP study arms over the study period. We then compared annualized eGFR decline in the higher and lower BP groups using linear mixed models with random intercepts. We used smoothing splines to pictorially depict eGFR decline over the study period by treatment arm. We compared differences up to 5 years of follow-up. We also stratified our results by study period (baseline to year 1 versus year 1 to the end of the study) to determine whether any observed differences were seen in short- and long-term renal function changes.[25] We further examined whether any differences in eGFR decline by study arm differed by age (>65 or <65 years), diabetic status, or the presence of CKD (eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$). In sensitivity analyses, we stratified at eGFR <90 or ≥90 mL·min$^{-1}$·1.73 m$^{-2}$ to ensure consistency of our findings across baseline eGFR levels. Then, we estimated the

proportion of patients with rapid decline by study arm. We compared odds of rapid decline by usual versus intensive BP treatment using logistic regression. In these analyses, we present comparisons for the entire study and by study period as above. These analyses followed intention-to-treat principles.

Next, we were interested in understanding the clinical relevance of rapid decline. Thus, we first evaluated whether kidney function loss could explain the trial null findings. Specifically, on the basis of the intention-to-treat principles, we used Cox regression models to compare time to event for the clinical outcomes by treatment arm. We then adjusted for eGFR slope or rapid decline in year 1 separately and determined the importance on the treatment effect. In a second step, we used an observational design. We estimated the association of baseline characteristics and achieved SBP (defined as mean SBP at 6 and 9 months) with rapid kidney function decline using multivariable logistic regression. Our final objective was to compare the associations of rapid kidney function decline in the first year with the clinical outcomes of stroke, MVE, and the composite outcome (death, MVE, myocardial infarction, or stroke). We used Cox proportional hazards regression models adjusted for treatment arm and then additionally adjusted for age, sex, ethnicity, smoking, diabetes mellitus, hypertension, use of an ACEI/ARB, baseline SBP, and baseline eGFR. We included tests of the interaction between rapid decline and treatment arm to determine whether the effects of kidney decline on the clinical outcomes differed by intensive versus usual BP treatment, and we repeated the analyses stratified by treatment arm.

All analyses were performed with SAS versions 9.2 and 9.4.

## Results

Among 2610 participants included in these analyses, a total of 2041 (78%) had ≥3 creatinine measures over a mean follow-up of 3.2 years (range, 1–5 years). At baseline, the mean age was 63.4±10.7 years, 384 participants (15%) were black, 854 (33%) were Hispanic, 949 (36%) were diabetic, and 2339 (90%) had hypertension. The mean eGFR was 80±18.5 mL·min$^{-1}$·1.73 m$^{-2}$, and 410 (16%) had an eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$ at the time of randomization. There were no significant differences in baseline characteristics by study arm except for a higher proportion of men in the higher target group (Table 1). Individuals with lower eGFR at baseline were more likely to be older, hypertensive, and a current user of an ACEI, an ARB, or a diuretic (Table I in the online-only Data Supplement).

Of the initial 3020 SPS3 participants, 410 were excluded from these analyses because of loss to follow-up or an event (and thus no follow up creatinine measures); the proportion excluded did not differ by treatment arm (11.7% versus 11.2%). When those who were excluded were compared with participants in these analyses, there were no significant differences in baseline age, sex, body mass index, diabetes mellitus,

**Table 1. Characteristics of SPS3 Participants by Treatment Group at Baseline**

| | Overall (n=2610) | Higher BP, Usual (n=1309) | Lower BP, Intensive (n=1301) | *P* Value |
|---|---|---|---|---|
| Age, y | 63 (11) | 64 (11) | 63 (11) | 0.34 |
| Male, n (%) | 1655 (63) | 862 (66) | 793 (61) | 0.01 |
| Race, n (%) | | | | |
| Non-Hispanic white | 1300 (50) | 641 (49) | 659 (51) | 0.75 |
| Black | 413 (16) | 205 (16) | 208 (16) | |
| Hispanic | 834 (32) | 430 (33) | 404 (31) | |
| Other/multiple | 63 (2) | 33 (3) | 30 (2) | |
| Region, n (%) | | | | |
| North America | 1672 (64) | 835 (64) | 837 (64) | 0.87 |
| Latin America | 647 (25) | 330 (25) | 317 (24) | |
| Spain | 291 (11) | 144 (11) | 147 (11) | |
| Smoking, n (%) | | | | |
| Current | 506 (19) | 255 (19) | 251 (19) | |
| Past | 1069 (41) | 525 (40) | 544 (42) | |
| Never | 1035 (40) | 529 (40) | 506 (39) | 0.65 |
| BMI, kg/m$^2$ | 29 (7) | 29 (8) | 29 (6) | 0.27 |
| Diabetes mellitus, n (%) | 950 (36) | 469 (36) | 481 (37) | 0.54 |
| Hypertension, n (%) | 2337 (90) | 1176 (90) | 1161 (89) | 0.62 |
| SBP at baseline, mm Hg | 143 (19) | 144 (19) | 142 (18) | 0.10 |
| SBP at 3 mo, mm Hg | 133 (16) | 137 (15) | 130 (15) | <0.0001 |
| SBP at 9 mo, mm Hg | 132 (15) | 137 (15) | 127 (14) | <0.0001 |
| eGFR, mL·min$^{-1}$·1.73 m$^{-2}$ | 80 (19) | 80 (18) | 80 (19) | 0.59 |
| eGFR category at baseline, n (%) | | | | |
| <60 mL·min$^{-1}$·1.73 m$^{-2}$ | 410 (16) | 195 (15) | 215 (17) | 0.25 |
| >60 mL·min$^{-1}$·1.73 m$^{-2}$ | 2198 (84) | 1113 (85) | 1085 (83) | |

Data are presented as mean (SD) when appropriate. Two individuals were missing creatinine data at baseline but had at least 2 values at follow-up. BMI indicates body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; and SPS3, Secondary Prevention of Small Subcortical Strokes.

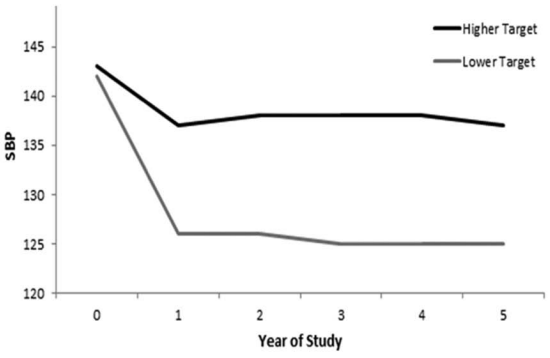
hypertension, history of transient ischemic attack, eGFR, SBP, or use of an ACEI/ARB. Excluded participants were more likely to come from Spain (18% versus 11%), and they were less likely to be Hispanic (21% versus 33%) or to use thiazide diuretic at baseline (30% versus 51%). There were no differences in the characteristics of individuals who discontinued the study by treatment arm (all $P>0.1$).

## BP and Antihypertensive Treatment in SPS3

BP levels were reduced in both treatment arms over the study period compared with baseline. At 9 months, the achieved SBP was 137±15 mm Hg and achieved diastolic BP was 76±10 mm Hg among participants randomized to the higher BP target. The achieved SBP was 127±14 mm Hg and diastolic BP was 70±9 mm Hg among those randomized to the lower BP group. Approximately 72% of participants in the intensive arm had achieved the SBP target at 9 months. As previously reported, differences were maintained to the end of the study.[19] Relative to the higher BP arm, use of ACEIs or ARBs, diuretics, and calcium channel blockers was similarly increased by ≈20% among those in the lower BP arm (Figure 1).

## Intensive Versus Usual BP Target and Kidney Function Decline

Among all participants, the mean eGFR decline was −3.2±8.6 mL·min$^{-1}$·1.73 m$^{-2}$ per year during follow-up. Overall, there was a pronounced eGFR decline during the first year of the study in both groups, followed by a steady decline in eGFR from year 1 to the end of the study (Figure 2). Compared with those in usual BP target group, individuals in the intensive BP target had −0.50–mL·min$^{-1}$·1.73 m$^{-2}$ per year (95% confidence interval [CI], −0.79 to −0.21) faster eGFR decline overall. In analyses stratified by study period, in the first year, individuals in the lower BP group had a 2.1–mL·min$^{-1}$·1.73 m$^{-2}$ (95% CI, 0.97–3.2) faster decline compared with those in the higher target group ($P$=0.0002). The differences in eGFR decline between BP treatment arms were not statistically significant when only changes from year 1 to the end of the study were considered (Figure 2). Findings were not materially different by age or diabetic status. However, differences in eGFR decline by treatment arm were not observed among individuals with eGFR <60 mL·min$^{-1}$·1.73 m$^{-2}$ at baseline ($P$ for interaction=0.04; Figure I in the online-only Data Supplement).




| | | | | | | |
|---|---|---|---|---|---|---|
| High Target (N) | 1309 | 1283 | 1034 | 800 | 598 | 388 |
| Lower Target (N) | 1301 | 1268 | 1030 | 812 | 614 | 419 |
| **Percentage of Persons on Medication** | | | | | | |
| **ACE/ARB** | | | | | | |
| High Target | 67 | 63 | 62 | 62 | 62 | 64 |
| Lower Target | 67 | 81 | 81 | 81 | 81 | 81 |
| **Diuretic** | | | | | | |
| High Target | 37 | 49 | 49 | 52 | 51 | 51 |
| Lower Target | 36 | 67 | 70 | 73 | 69 | 71 |
| **CCB** | | | | | | |
| High Target | 25 | 30 | 29 | 27 | 30 | 32 |
| Lower Target | 25 | 43 | 48 | 45 | 46 | 51 |
| **BB** | | | | | | |
| High Target | 23 | 25 | 26 | 25 | 27 | 32 |
| Lower Target | 25 | 31 | 33 | 35 | 35 | 40 |
| **Total # of Meds** | | | | | | |
| High Target | 1.7 | 1.8 | 1.8 | 1.8 | 1.9 | 2.0 |
| Lower Target | 1.7 | 2.4 | 2.5 | 2.6 | 2.6 | 2.8 |

**Figure 1.** Blood pressure level and use of each antihypertensive class in the Secondary Prevention of Small Subcortical Strokes (SPS3) study: systolic blood pressure (SBP) vs year of study.

A total of 313 individuals (24%) in the lower BP group had rapid kidney function decline compared with 247 (19%) in the usual BP arm (odds ratio [OR], 1.4; 95% CI, 1.1–1.6). There were no differences in these estimates when we stratified by baseline eGFR ≥90 or < 90 mL·min$^{-1}$·1.73 m$^{-2}$. For example, among individuals with eGFR ≥90 mL·min$^{-1}$·1.73 m$^{-2}$, the OR comparing the lower and higher BP target groups was 1.4 (95% CI, 1.0–2.0); it was 1.3 (95% CI, 1.1–1.7) among individuals with eGFR <90 mL·min$^{-1}$·1.73 m$^{-2}$. We found that differences in rapid decline by treatment arm were apparent in the first year but were not statistically significant after year 1 (Table 2). When we defined rapid decline as ≥40%, the OR for rapid decline was 1.3 (95% CI, 1.01–1.7) during follow-up. Among individuals with preserved eGFR at randomization, 14% in the intensive BP arm had incident CKD compared with 11% in the usual treatment arm (OR, 1.41; 95% CI, 1.09–1.82) over the study period.

After adjustment for treatment arm, characteristics associated with rapid decline included older age, current smoking, diabetes mellitus, higher SBP, use of β-blockers, and use of an ACEI/ARB (Table II in the online-only Data Supplement). Higher achieved SBP was associated with rapid decline in the higher target arm (OR, 1.3; 95% CI, 1.1–1.6), but the association was not statistically significant in the lower BP arm (OR, 1.1; 95% CI, 0.9–1.3; $P$ for interaction=0.07).

## Kidney Function Decline and Study Outcomes

We estimated the association of lower versus higher BP target with stroke, MVE, or the composite outcome (death, MVE, myocardial infarction, or stroke) before and after adjustment for eGFR decline (slope) or rapid decline at year 1. In unadjusted models, the HR for intensive compared with usual treatment was 0.84 for stroke (95% CI, 0.65–1.09), 0.87 for MVE (95% CI, 0.69–1.10), and 0.91 for the composite outcome (95% CI, 0.75–1.12). Adjustment for eGFR decline increased the strength of the point estimates only slightly, but they did not become statistically significant. Specifically, in models that controlled for rapid decline in year 1, the HR for intensive versus usual treatment was 0.81 for stroke (95% CI, 0.62–1.05), 0.83 for MVE (95% CI, 0.65–1.06), and 0.89 for the composite outcome (95% CI, 0.72–1.09).

Finally, we evaluated the association of rapid decline in year 1 with each clinical outcome separately. We found that the association of rapid decline with outcomes varied by treatment arm. Specifically, among those randomized to the higher target group, participants with rapid decline during the first year had an ≈2-fold risk for stroke, MVE, and

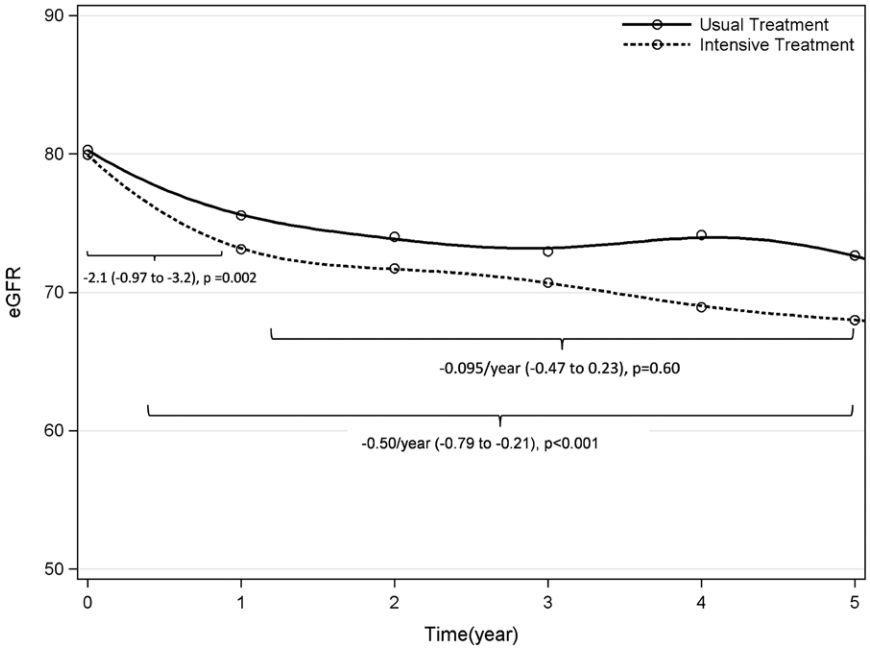



**Figure 2.** The effect of usual vs intensive blood pressure lowering on kidney function change (mL·min$^{-1}$·1.73 m$^{-2}$ per year) in the Secondary Prevention of Small Subcortical Strokes (SPS3) study: estimated glomerular filtration rate (eGFR) vs time (years).

the composite outcome compared with no rapid decline. Associations remained significant after adjustment for potential confounders. In contrast, rapid decline did not appear to be associated with increased risk for stroke, MVE, or the composite outcome among participants randomized to the lower BP target (Table 3).

## Discussion

We showed that among individuals with prior lacunar stroke who had a mean age of 63±11 years and relatively preserved kidney function, compared with treating to a higher SBP target (130–149 mm Hg), treating to a lower SBP target (<130 mm Hg) was associated with a greater reduction in eGFR and a higher risk of having rapid kidney function decline during follow-up. We found that differences in kidney function loss were observed primarily during the first year of antihypertensive treatment intensification. In longer follow-up, kidney function did not improve in the lower BP target group but rather continued to decline in parallel with the higher BP group. Rapid kidney function decline during the first year was associated with a higher risk of stroke, MVEs, and the composite outcome only among individuals randomized to the higher target group. Rapid kidney function decline was not associated with higher risk for the clinical end points among individuals randomized to the lower BP arm.

**Table 2. Rapid Kidney Function Decline Among SPS3 Participants Randomized to Higher (130–149 mm Hg) Versus Lower (<130 mm Hg) SBP Target: Intention-to-Treat Analysis**

| | Higher SBP | Lower SBP |
|---|---|---|
| Overall study period (n=2610) | | |
| Rapid decline, n (%) | 247 (19) | 313 (24) |
| OR for lower vs higher (95% CI) | Referent | 1.4 (1.1–1.6) |
| Baseline to year 1 (n=2489) | | |
| Rapid decline, n (%) | 101 (8) | 133 (11) |
| OR for lower vs higher (95% CI) | Referent | 1.4 (1.1–1.8) |
| From year 1 to 5 (n=2085) | | |
| Rapid decline, n (%) | 83 (8) | 83 (8) |
| OR for lower vs higher (95% CI) | Referent | 1.0 (0.73–1.4) |

OR compares the effect of a higher versus a lower BP target on rapid kidney function decline, defined as estimated glomerular filtration rate decline of ≥30% from baseline to any annual follow-up visit. Analyses are presented over the entire follow-up (overall) and stratified by study period. For analyses of baseline to year 1, rapid decline is assessed from baseline to 12 months. For analyses of year 1 to the end of the study, rapid decline is assessed from year 1 to any yearly follow-up visit. CI indicates confidence interval; OR, odds ratio; SBP, systolic blood pressure; and SPS3, Secondary Prevention of Small Subcortical Strokes.

The optimal BP target remains one of the most critical issues in the management of patients with hypertension and high cardiovascular risk. Placebo-controlled, randomized trials have examined SBP goals of <160 mm Hg[26] or <150 mm Hg,[27] and the recommendations on lowering SBP beyond 140 mm Hg remain conflicting.[28–30] Recently, SPRINT showed lower rates of death and cardiovascular events with more intensive BP lowering in individuals at high cardiovascular risk but without a history of stroke or diabetes mellitus.[15] Among patients with diabetes mellitus, there was no difference in clinical outcomes among individuals randomized to lower versus usual BP targets in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial.[31] Whether there may be renal benefit or harm from more intensive BP lowering in individuals at high cardiovascular risk without established CKD remains less clear. In a meta-analysis of antihypertensive treatment trials conducted in the 1970s to 1990s, which were designed with higher BP targets and before the widespread use of ACEIs/ARBs, treatment was not associated with a reduction in the incidence of renal dysfunction.[32] The Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) showed faster rates of kidney function decline among individuals treated with dual ACEI/ARB therapy compared with either alone, but whether this was attributable to lower achieved

**Table 3. Association of Rapid Kidney Function Decline at Year 1 With Clinical End Points in SPS3 by Treatment Arm**

| | Higher Target | | | Lower Target | | | *P* for Interaction Between Treatment and Decline |
|---|---|---|---|---|---|---|---|
| | Rate per 1000 patient-y | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) | Rate per 1000 patient-y | Unadjusted HR (95% CI) | Adjusted* HR (95% CI) | |
| All stroke | | | | | | | |
| No rapid decline year 1 | 24.1 | Referent | Referent | 21.5 | Referent | Referent | |
| Rapid decline year 1 | 51.6 | 2.13 (1.29–3.52) | 1.93 (1.15–3.21) | 21.4 | 0.99 (0.53–1.86) | 0.93 (0.50–1.75) | 0.06 |
| MVE | | | | | | | |
| No rapid decline year 1 | 30.1 | Referent | Referent | 27.5 | Referent | Referent | |
| Rapid decline year 1 | 58.6 | 1.95 (1.22–3.13) | 1.76 (1.09–2.85) | 25.4 | 0.92 (0.52–1.63) | 0.86 (0.48–1.53) | 0.05 |
| Composite (death, MVE, MI, or stroke) | | | | | | | |
| No rapid decline year 1 | 39.2 | Referent | Referent | 38.0 | Referent | Referent | |
| Rapid decline year 1 | 70.3 | 1.84 (1.20–2.82) | 1.62 (1.05–2.51) | 35.2 | 0.90 (0.55–1.47) | 0.83 (0.51–1.35) | 0.03 |

HRs and 95% CIs are from Cox proportional hazard regression models. Rapid kidney function decline is defined as estimated glomerular filtration rate decline or ≥30% from baseline to year 1. CI indicates confidence interval; HR, hazard ratio; MVE, major vascular event; and SPS3, Secondary Prevention of Small Subcortical Strokes.

*Adjusted for age, sex, ethnicity, smoking, diabetes mellitus, hypertension, use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, baseline systolic blood pressure, and baseline estimated glomerular filtration rate.

BP is unclear.[14] Both SPRINT and ACCORD have reported higher rates of kidney function decline with intensification of antihypertensive therapy.[15,31] In the setting of established CKD, randomized trials show a benefit from lower BP levels only among individuals with proteinuria,[5–7,9] and SPRINT did not show a difference in CKD progression to ESRD by study arm.[15] Our study suggests that among individuals with cerebrovascular disease and relatively preserved eGFR, intensive BP lowering results in the expected sharper eGFR decline in the first year but is not followed by recovery or eventual renal benefit during the study period. Our findings that SPS3 participants in the lower BP arm had increased use of most of the antihypertensive medication classes make it less likely that the renal function decline is attributable to 1 class alone but rather to the BP lowering from a combination of the drugs.

We also found that rapid kidney function decline was associated with an increased risk for stroke, MVEs, and the composite outcome among individuals randomized to the higher BP but not the lower BP target. The reasons for these observed differences are not certain. One possibility is that more intensive lowering of BP may have some benefit in reducing the likelihood of the SPS3 clinical outcomes, which offsets the higher cardiovascular risk associated with kidney dysfunction. In this scenario, intensive BP lowering in individuals with existing small-vessel disease may be cardioprotective, but it could also result in renal hypoperfusion owing to decreased effective circulating volume, overdiuresis, or an intrinsic impairment in adequate renal autoregulation; concomitant use of inhibitors of the renin-angiotensin system or diuretics may exacerbate this risk.[33] In our study, adjustment for rapid kidney function decline did not substantially alter the comparisons of higher versus lower BP target with risk of clinical outcomes in SPS3. A second possibility is that the physiological mechanisms leading to rapid kidney function decline differ by study arm. That is, among individuals randomized to the lower BP target, eGFR loss represents a hemodynamic phenomenon that may be reversible and does not increase future cardiovascular risk. In contrast, among those in the higher BP target group, kidney function decline may represent true kidney disease progression, perhaps as a result of persistent BP levels above the threshold needed for nephroprotection.[34,35] A hemodynamic renal effect with intensive BP lowering is supported by previous clinical trial data in individuals with established CKD that show a sharp, immediate reduction in eGFR when BP is lowered, followed by eventual renal protection among individuals with proteinuria.[5,6,25,36] In the setting of ACEI use, some experts have suggested that an initial reduction in eGFR typically occurs early (within weeks), followed by stabilization (within months) and eventual attenuation of renal function loss.[33] Hemodynamic effects on renal function with calcium channel blockers have also been suggested.[37] However, in a recent meta-analysis of 37 trials among individuals with kidney disease of various causes, rapid decline was strongly associated with a higher risk for ESRD.[24] Taken together, our findings suggest that the clinical significance of rapid kidney function decline may vary on the basis of whether the eGFR change is observed in the setting of active, aggressive BP lowering. Given the results of SPRINT, many patients may find their antihypertensive treatment intensified in the near future. Our findings are especially important in this context because patients may have their therapy deintensified as a result of concerns about increases in creatinine levels in the setting of BP lowering. Future studies are required to understand whether changes in renal function during intensification of antihypertensive therapy are associated with electrolyte disturbances, patient-centered outcomes, resource use, and clinical events.

In addition to the randomized design, this study has other strengths. SPS3 maintained a significant difference in SBP between arms throughout the study period, which allows examination of a sustained lower BP level. Because the overall trial was null, differences in renal function decline are less likely influenced by bias owing to differential loss to follow-up. The clinical outcomes used were adjudicated by blinded reviewers. We must also note important limitations. The study was not designed or powered to detect differences in incident

CKD or ESRD. However, rapid decline is considered an appropriate surrogate renal outcome for clinical trials. SPS3 did not measure serum creatinine repeatedly during the first year. Although we are unable to assess short-term changes in eGFR, intensification of antihypertensive medications in SPS3 happened early in the first year (first 3 months), with most individuals achieving BP control within 6 months. Nonetheless, the renal function measure at year 1 allows ample time for the eGFR stabilization described in other studies.[25,38,39] Although SPS3 had a relatively short follow-up time, it is consistent with the follow-up times of other studies that have suggested renal protection with intensive BP lowering in individuals with proteinuria.[25] We are unable to ascertain whether rapid decline in the usual arm is reversible because this would require withdrawal of medication. Whether there is renal benefit eventually from lower BP targets requires longer follow-up. Although creatinine values were not specifically calibrated by the study, we expect variations to be randomly allocated by study arm. We were unable to study the effect of intensive BP lowering among individuals with significant proteinuria. Because SPS3 was not enriched for kidney disease, it is likely that the overall prevalence of significant proteinuria was low.

## Conclusions

We found that in this population of individuals with an average age of 63±11 years with previous lacunar stroke and relatively preserved kidney function, intensive BP lowering was associated with somewhat greater eGFR drop. This difference was most pronounced during the first year, and we found no evidence for renal protection over the follow-up period. The clinical significance of rapid kidney function decline varied by treatment arm; it was associated with increased risk of clinical outcomes only among patients in the higher target group. Rapid decline was not associated with higher risk for clinical events among patients undergoing intensive BP lowering.

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## Disclosures

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## CLINICAL PERSPECTIVE

The effect of intensive blood pressure lowering on kidney function among individuals at high cardiovascular risk with relatively preserved kidney function has been unclear. Among participants in the Secondary Prevention of Small Subcortical Strokes (SPS3) randomized trial with prior lacunar stroke, we found that individuals undergoing active, intensive BP lowering had faster rates of kidney function decline compared with individuals undergoing usual treatment to established goals. In the intensive treatment group, rapid kidney function decline was not associated with a higher risk for stroke, death, or major vascular events. In contrast, among individuals undergoing usual antihypertensive treatment, rapid decline was associated with a higher risk for all outcomes, as has been observed in many prior observational studies. Taken together, our findings could guide clinicians to understand that decline in kidney function is common and expected among patients undergoing intensive blood pressure lowering. In this specific setting, kidney function decline does not appear to pose significant clinical risk for adverse cardiovascular outcomes. Further studies are needed to understand whether rapid kidney function decline in the setting of intensive BP lowering is associated with end-stage renal disease in longer follow-up.

# Effect of Intensive Versus Usual Blood Pressure Control on Kidney Function Among Individuals With Prior Lacunar Stroke: A Post Hoc Analysis of the Secondary Prevention of Small Subcortical Strokes (SPS3) Randomized Trial

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**SUPPLEMENTAL MATERIAL**

**Supplemental Table 1. Characteristics of SPS3 Participants by eGFR (in ml/min/1.73m$^2$) level at baseline**

| Characteristic | Overall | eGFR >90 | eGFR 60-90 | eGFR <60 |
|---|---|---|---|---|
| N | 2610 | 867 | 1331 | 410 |
| Age | 63.4 (10.7) | 58.0 (8.2) | 65.0 (10.4) | 69.9 (10.9) |
| Male Gender | 1655 (63%) | 570 (66%) | 849 (64%) | 236 (58%) |
| Race | | | | |
| Non-Hispanic | | | | |
| White | 1298 (50%) | 377 (43%) | 704 (53%) | 217 (53%) |
| Black | 384 (15%) | 149 (17%) | 181 (14%) | 54 (13%) |
| Hispanic | 854 (33%) | 325 (37%) | 405 (30%) | 124 (30%) |
| Other/mixed | 75 (3%) | 17 (2%) | 43 (3%) | 15 (4%) |
| Region | | | | |
| North America | 1674 (64%) | 546 (63%) | 872 (65%) | 256 (62%) |
| Latin America | 647 (25%) | 217 (25%) | 326 (25%) | 104 (25%) |
| Spain | 290 (11%) | 105 (12%) | 135 (10%) | 50 (12%) |
| Smoking | | | | |
| Never | 1035 (40%) | 322 (37%) | 539 (40%) | 174 (42%) |
| Current | 507 (19%) | 240 (28%) | 216 (16%) | 51 (12%) |
| Past | 1069 (41%) | 306 (35%) | 578 (43%) | 185 (45%) |
| BMI | 29.1 (7.0) | 29.7 (8.7) | 28.9 (5.9) | 28.6 (5.8) |
| Diabetes | 949 (36%) | 371 (43%) | 423 (32%) | 155 (38%) |
| Baseline HTN | 2339 (90%) | 744 (86%) | 1207 (91%) | 388 (95%) |
| ARB Use | 428 (16%) | 102 (12%) | 242 (18%) | 84 (20%) |

| | | | | |
|---|---|---|---|---|
| (baseline) | | | | |
| ACE Use | | | | |
| (baseline) | 1375 (53%) | 471 (54%) | 693 (52%) | 211 (51%) |
| CCB (baseline) | 665 (26%) | 161 (19%) | 368 (28%) | 136 (33%) |
| BB (baseline) | 641 (25%) | 169 (19%) | 332 (25%) | 140 (34%) |
| Diuretic (baseline) | 951 (36%) | 271 (31%) | 492 (37%) | 188 (46%) |
| Other (baseline) | 177 (7%) | 42 (5%) | 90 (7%) | 45 (11%) |
| ARB (year 1) | 704 (27%) | 210 (25%) | 352 (27%) | 142 (35%) |
| ACE (year 1) | 1201 (47%) | 411 (48%) | 624 (48%) | 166 (41%) |
| CCB (year 1) | 938 (37%) | 253 (30%) | 503 (38%) | 182 (45%) |
| BB (year 1) | 716 (28%) | 193 (23%) | 381 (29%) | 142 (35%) |
| Diuretic (year 1) | 1488 (58%) | 458 (54%) | 776 (59%) | 254 (63%) |
| Other (year 1) | 252 (10%) | 52 (6%) | 131 (10%) | 69 (17%) |
| History of TIA | 146 (6%) | 50 (6%) | 63 (5%) | 33 (8%) |
| SBP (mmHg) | | | | |
| Baseline | 143 (19) | 140 (17) | 143 (19) | 146 (20) |
| 3 month | 133 (16) | 132 (15) | 134 (16) | 136 (17) |
| 9 month | 132 (15) | 131 (14) | 132 (15) | 133 (15) |
| eGFR | | | | |
| ml/min/1.73m$^2$ | 80 (18.5) | 100 (7.7) | 76 (8.4) | 51 (7.1) |

BMI=body mass index, ACE= angiotensin converting enzyme inhibitor, ARB= angiotensin receptor blocker, CCB= calcium channel blocker, BB= beta blocker, TIA= history of transient ischemic attack, SBP=systolic blood pressure

2 persons are missing creatinine data at baseline, but have at least two values at follow-up (are included in overall)

**Supplemental Table 2. The Association of Selected Characteristics, Achieved SBP and Baseline Use of Anti-Hypertensive Medication Classes with Rapid Kidney Function Decline Among SPS3 Participants (n=2520)**

| Characteristic | Adjusted*<br>OR (95%CI) |
|---|---|
| Age (per 11 years) | 1.2 (1.0, 1.3) |
| Achieved SBP<br>(per SD increase) | 1.2 (1.1, 1.3) |
| ACE or ARB | 1.3 (1.0, 1.7) |
| ACE and ARB | 1.1 (0.4, 2.8) |
| Diuretic | 1.1 (0.9, 1.4) |
| CCB | 1.2 (1.0, 1.6) |
| Beta Blocker | 1.6 (1.2, 2.0) |
| Diabetes | 2.1 (1.7, 2.6) |
| Current Smoking (vs. never) | 1.4 (1.0, 1.9) |
| eGFR (ml/min/1.73m$^2$) | 1.1 (0.9, 1.2) |

*Adjusted for treatment arm (in overall), age, gender, race/ethnicity, smoking, diabetes, history of TIA, region, BMI, baseline use of ACE, ARB, diuretic, calcium channel blocker, beta blocker (each adjusted for use of the other classes), baseline eGFR. ACE or ARB= use of one (vs. none), ACE and ARB means use of both (vs. none)

**Supplemental Figure 1. The Effect of Usual vs. Intensive BP Lowering and Kidney Function Decline by Age, Diabetes and Chronic Kidney Disease Status at Baseline**

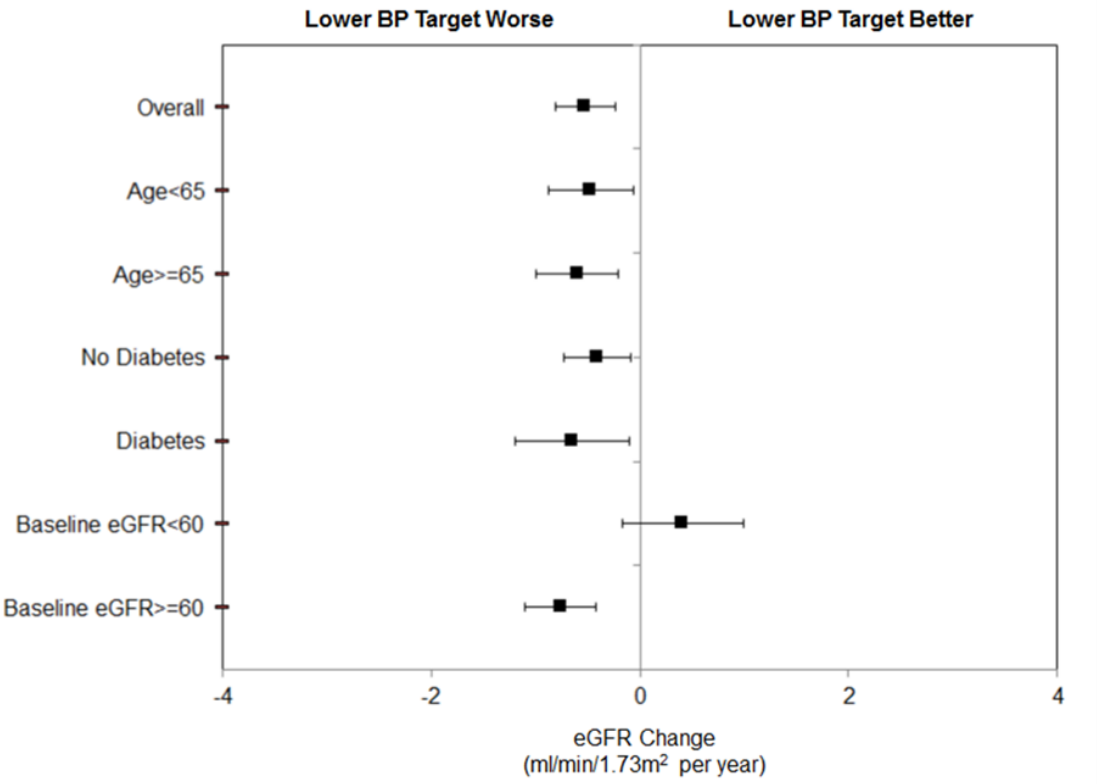


**Figure Legend:** Estimates represent eGFR in ml/min/1.73m$^2$ per year from the linear mixed model