ORIGINAL RESEARCH

Effect of Baseline Kidney Function on the Risk of Recurrent Stroke and on Effects of Intensive Blood Pressure Control in Patients With Previous Lacunar Stroke: A Post Hoc Analysis of the SPS3 Trial (Secondary Prevention of Small Subcortical Strokes)

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Background—We conducted a post hoc analysis of the SPS3 (Secondary Prevention of Small Subcortical Strokes) Trial to examine the association of chronic kidney disease (CKD) with *recurrent* stroke, and to assess whether baseline renal function modifies the effects of intensive systolic blood pressure control in patients with previous stroke.

Methods and Results—A total of 3020 patients with recent magnetic resonance imaging–defined symptomatic lacunar infarctions were randomized to a systolic blood pressure target of <130 mm Hg versus 130 to 149 mm Hg. Predefined primary outcomes were (all-recurrent) stroke and a composite of stroke, acute myocardial infarction, or all-cause death; secondary outcomes were acute myocardial infarction, all-cause death, and intracerebral hemorrhage individually. Among 3017 patients with baseline estimated glomerular filtration rate measurements, we evaluated, using Cox proportional hazards models, the association of CKD with recurrent stroke and effects of the blood pressure targets on outcomes using baseline estimated glomerular filtration rate both as a categorical and linear variable. Regardless of the randomized treatment, CKD at baseline was significantly associated with an increased risk of the primary cardiovascular composite outcome (hazard ratio, 1.7; 95% CI, 1.4–2.1), and all-recurrent stroke (1.5; 1.1–2.0). However, the effects of the lower systolic blood pressure intervention on the primary outcome were not influenced by baseline CKD status (*P* for interaction=0.62).

Conclusions—CKD increases the risk of recurrent stroke by 50% in patients with previous lacunar stroke. We found no definitive evidence that renal dysfunction modifies the effects of systolic blood pressure control in patients with previous stroke. Conclusive evidence for this will require adequately powered studies with moderate-to-advanced CKD.

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Key Words: high blood pressure • hypertension • lacunar stroke • renal function

Hypertension and chronic kidney disease (CKD) are interrelated global public health problems and both independently increase the risk of stroke.[1,2] In the United States, more than one-third of the population has hypertension[3,4] and around 15% of the population has CKD.[5] Both hypertension and CKD could cause or result from each other,[6] and because of this inter-related pathophysiology, hypertension, CKD, and a history of previous stroke often coexist in patients.[7] However, optimal blood pressure (BP) targets in patients with previous stroke, especially in those with CKD, are unclear.

The SPRINT (Systolic Blood Pressure Intervention) trial reported cardiovascular benefits of an intensive systolic blood

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Clinical Perspective

What Is New?

- We know that chronic kidney disease (CKD) increases risk of stroke; however, whether CKD increases risk of *recurrent* stroke has been relatively unclear.
- This study shows that CKD is associated with an independent 50% increase in risk for *recurrent* stroke in patients with previous lacunar stroke.
- We found no evidence that baseline estimated glomerular filtration rate modifies the effects of blood pressure control in patients with previous stroke.

What Are the Clinical Implications?

- Clinicians taking care of patients with previous stroke should be aware that the presence of CKD in these patients substantially increases risk of *recurrent* stroke.
- Providers should take measures to reduce risk and have a low threshold for suspicion for *recurrent* stroke in patients with previous stroke and CKD.
- We found no evidence that baseline renal function should prompt clinicians to modify BP goals in patients with previous stroke.

pressure (SBP) target of <120 mm Hg versus the standard SBP target of <140 mm Hg in high-risk nondiabetic patients.[8] This landmark trial has resulted in a wider acceptance of intensive SBP targets. The 2017 American College of Cardiology/American Heart Association BP guidelines recommend a target SBP goal of <130 mm Hg for most patients, including for patients with previous stroke.[3,9]

Observational data, however, suggest that CKD may attenuate the beneficial effects of intensive SBP control.[10] Randomized controlled trials (RCTs) have also not confirmed a cardiovascular benefit from intensive BP control in patients with CKD.[11] A post hoc analysis of SPRINT found that in the subset of participants with moderate-to-advanced CKD (defined as estimated glomerular filtration rate [eGFR] of <45 mL/min/1.73 m^2), intensive SBP control provided little[3] or no cardiovascular benefit, suggesting that CKD attenuates the benefits of intensive SBP control.[12] SPRINT excluded patients with a history of stroke, and it remains unknown how renal dysfunction modifies the effects of intensive SBP control in patients with previous stroke.

The SPS3 (Secondary Prevention of Small Subcortical Strokes) trial[1,2] was a National Institutes of Health–sponsored RCT that examined the cardiovascular effects of a lower SBP target of <130 mm Hg versus a higher target of 130 to 149 mm Hg in patients with recent magnetic resonance imaging–defined lacunar stroke. This RCT found a *significant* reduction in hemorrhagic stroke with the lower SBP target and a *nonsignificant* reduction in all (recurrent) stroke, disabling or fatal stroke, and the cardiovascular composite outcome of myocardial infarction (MI) or vascular death.[2]

It is also important to note that although CKD is an established risk factor for stroke,[13–16] the association between CKD and risk of *recurrent* stroke is less clear.[16] We conducted a post hoc analysis of the SPS3 trial to examine (1) the association of CKD with recurrent stroke and (2) whether baseline eGFR modifies the effects of intensive SBP control in patients with previous stroke.

Methods

The SPS3 Trial data reported here are available to the public and were provided to us by the National Institute of Health–National Institute of Neurological Disorders and Stroke upon request.

Design and Participants

Details of the SPS3 study design have been previously published.[1,2] Briefly, SPS3 was a randomized, multicenter clinical trial that enrolled 3020 participants from 81 centers in North America, Latin America, and Spain. Eligible patients were at least 30 years old and had a recent (at least 2 weeks, but within 180 days) symptomatic lacunar stroke confirmed by magnetic resonance imaging. Individuals were excluded if they had a cortical or large (>2 cm) subcortical stroke, a disabling stroke, a hemorrhagic stroke, or if they had advanced kidney disease, defined as an eGFR <40 mL/min/1.73 m^2 at screening. Participants were randomized to a lower SBP target of <130 mm Hg or higher target of 130 to 149 mm Hg using the prospective, randomized, open, blinded end-point design.[1] All participants signed informed consent, and the appropriate institutional review board approved the trial.[1,2]

For this post hoc analysis, we obtained de-identified data from the SPS3 trial from the National Institute of Neurological Disorders and Stroke data repository. The institutional review board at the University of Utah granted exemption from institutional review board oversight given that this was a secondary analysis of de-identified data. We only included the SPS3 participants who had a measure of serum creatinine at study baseline. Of the 3020 participants who entered SPS3, we excluded 3 participants who had missing measures of serum creatinine at baseline, for a final sample size of 3017 individuals.

BP Targets and Management

As noted above, participants were randomly assigned to a higher SBP target of 130 to 149 mm Hg or a lower target of <130 mm Hg. A study physician at each study site oversaw

BP management. Patients were allowed to continue their antihypertensive medications. Patients were seen monthly until their BP target was achieved and then quarterly for BP measures and medication adjustment. Patients were provided the antihypertensive medications through a study formulary, which included at least 1 drug from each of the major classes. Other details have been reported previously.[2]

Study Measurements

BP was measured using the Colin 8800C automated device, according to a detailed protocol based on the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines.[17] BP was determined by the average of the 3 BP readings separated by at least 2 minutes in the seated position. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate eGFR.[18] Sociodemographic and medical history data were collected at baseline. Clinical and laboratory data were obtained at baseline and every 3 months. Other details have been outlined previously.[2]

Clinical Outcomes

A committee blinded to treatment arm adjudicated the outcomes, which have been previously described in detail.[1] The primary end point of the SPS3 trial was reduction in all stroke. For our analyses, in addition to all recurrent stroke, we defined an additional primary outcome as the composite of all recurrent stroke or acute MI or all-cause death. The secondary outcomes for our study were acute MI, all-cause death, and intracerebral hemorrhage.

Statistical Analysis

Our first objective was to assess the associations of CKD, defined as eGFR <60 mL/min/1.73 m^2 at baseline with the primary and secondary outcomes. We used Cox proportional hazards regression models adjusted for treatment arm and then additionally adjusted for age, sex, study sites, baseline diabetes mellitus, hypertension, coronary artery disease, use of statin, use of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, and SBP. We tested proportional hazards assumptions using log-log against survival plots and Schoenfeld residuals. If multiple events of the same type occurred, we calculated the time to event as the time to first event. We censored data for patients with no events at the end of study participation or death, whichever occurred first. Our second objective was to evaluate the consistency of the effects of lower BP control on the outcomes between eGFR strata. We computed hazard ratios (HRs) and 95% CIs by 2 eGFR strata (<60 and ≥60 mL/min/1.73 m^2) for primary and secondary outcomes. In addition, we investigated the possibility of interaction by fitting a Cox regression for the primary and secondary outcomes with main effects for the SBP intervention and each 10 mL/min/1.73 m^2 increase in baseline eGFR, plus the interaction term between the SBP intervention and each 10 mL/min/1.73 m^2 increase in baseline eGFR. The *P* value for the interaction term <0.1 is showing potential evidence of effect modification. In sensitivity analyses, we examined the effects of lower BP control across 4 eGFR strata (<45, 45 to <60, 60 to <90, and ≥90 mL/min/1.73 m^2). We conducted all analyses with the intention-to-treat approach and with 2-sided tests at the 5% level of significance using R software (version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Mean age for the 3017 participants was 62.8±10.8 years, 37.1% were female, 16.3% were black, 33.2% were diabetic, 75.0% were hypertensive, and the mean eGFR at baseline was 80.5±19.0 mL/min/1.73 m^2. Mean baseline SBP was 143.0±18.8, and diastolic BP was 78.3±10.6 mm Hg. Mean baseline eGFRs in the <60 and ≥60 mL/min/1.73 m^2 subgroups were 51.0±7.0 and 86.0±15.0 mL/min/1.73 m^2, respectively. Even though patients with <40 mL/min/1.73 m^2 were excluded at screening, we found that 41 participants had an eGFR of <40 mL/min/1.73 m^2 at baseline (using the CKD-EPI equation). Baseline characteristics for the whole cohort and by the 2 baseline eGFR subgroups are summarized in Table 1 and by the 4 eGFR subgroups are summarized in Table S1. In general, participants with lower baseline eGFR tended to be older, have a higher baseline SBP, and more likely to be hypertensive at baseline.

Achieved BPs

Mean achieved SBPs at 1 year in the lower and higher SBP arms were 126.9 and 137.9 mm Hg, respectively, and for the <60 and ≥60 mL/min/1.73 m^2 eGFR subgroups were 135.0 and 132.0 mm Hg, respectively. Boxplots displaying the medians and 25th and 75th percentiles of the achieved SBP and diastolic BP at 1-year follow-up by 2 baseline eGFR subgroups for participants in the lower and higher SBP target groups are presented in Figure 1 and by 4 baseline eGFR subgroups are presented in Figure S1. The achieved SBP was significantly higher among participants in the eGFR <60 mL/min/1.73 m^2 compared with eGFR ≥60 mL/min/1.73 m^2

Table 1. Baseline Characteristics of the Secondary Prevention of Small Subcortical Strokes Trial Participants According to Treatment Arms and 2 Baseline eGFR Subgroups (n=3017)

	Baseline eGFR Subgroups				
	<60 mL/min/1.73 m^2		≥60 mL/min/1.73 m^2		
	Higher-Target Group (n=227)	Lower-Target Group (n=247)	Higher-Target Group (n=1290)	Lower-Target Group (n=1253)	All
Age, mean (SD), y	69.4 (10.9)	69.3 (11.4)	61.7 (10.4)	61.5 (10.1)	62.8 (10.8)
Female, N (%)	91 (40.1)	125 (50.6)	438 (34.0)	464 (37.0)	1118 (37.1)
Race/ethnicity, N (%)					
Non-Hispanic white	128 (56.4)	134 (54.3)	630 (48.8)	638 (50.9)	1530 (50.7)
Black	36 (15.9)	33 (13.4)	215 (16.7)	208 (16.6)	492 (16.3)
Hispanic	56 (24.7)	73 (29.6)	412 (30.3)	380 (30.3)	921 (30.5)
Other/multiple	7 (3.1)	7 (2.8)	33 (2.6)	27 (2.2)	74 (2.5)
Region, N (%)					
North America	134 (59.0)	164 (66.4)	848 (65.7)	812 (64.8)	1958 (64.9)
Latin America	55 (24.2)	57 (23.1)	297 (23)	285 (22.7)	694 (23.0)
Spain	38 (16.7)	26 (10.5)	145 (11.2)	156 (12.5)	365 (12.1)
SBP, mean (SD), mm Hg	146.8 (21.0)	147.3 (21.0)	143.0 (18.7)	141.5 (17.8)	143.0 (18.8)
DBP, mean (SD), mm Hg	77.9 (11.6)	76.9 (11.1)	79.2 (10.6)	77.8 (10.3)	78.4 (10.6)
History of CAD, N (%)	29 (12.8)	28 (11.3)	109 (8.4)	86 (6.9)	252 (8.4)
History of CHF, N (%)	3 (1.3)	7 (2.8)	10 (1.0)	12 (1.0)	32 (1.1)
Diabetes mellitus, N (%)	74 (32.6)	93 (37.7)	425 (32.9)	409 (32.6)	1001 (33.2)
Hypertension, N (%)	196 (86.3)	218 (88.3)	939 (72.8)	909 (72.5)	2262 (75.0)
eGFR, mean (SD), mL/min/1.73 m^2	50.9 (7.1)	51.1 (6.9)	85.9 (14.9)	86.0 (15.1)	80.5 (19.0)
Total cholesterol, mean (SD), mg/dL	174.0 (56.8)	175.1 (52.4)	177.3 (57.6)	175.7 (55.7)	176.2 (56.3)
Smoking, N (%)					
Current	32 (14.1)	27 (10.9)	275 (21.3)	282 (22.5)	616 (20.4)
Past	100 (44.1)	113 (45.7)	498 (38.6)	495 (39.5)	1206 (40.0)
Never	95 (41.9)	107 (43.4)	517 (40.1)	476 (38.0)	1195 (39.6)
Plasma glucose, mean (SD), mg/dL	118.9 (45.1)	127.6 (60.7)	126.9 (55.8)	125.0 (54.6)	125.6 (55.0)
Statin use, N (%)	152 (67.0)	175 (70.9)	890 (69.0)	862 (68.8)	2079 (68.9)
Aspirin use, N (%)	130 (57.3)	129 (52.2)	731 (56.7)	707 (56.4)	1697 (56.3)
BMI, mean (SD), kg/m^2	28.8 (5.9)	28.3 (5.5)	29.3 (7.7)	29.1 (6.2)	29.1 (6.8)
No. of antihypertensive drugs, mean (SD)	1.9 (1.2)	2.0 (1.2)	1.6 (1.1)	1.5 (1.1)	1.6 (1.1)

Values for categorical variables are presented as number (percentage); values for continuous variables, as mean (SD). BMI indicates body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure.

within both the lower-target group (130.0±17.1 versus 126.3±13.2 mm Hg; P=0.003) and higher-target group (140.5±14.8 versus 137.4±14.4 mm Hg; P=0.01).

Clinical Outcomes

Association of baseline CKD with outcomes

During the median follow-up period of 3.7 years, there were total 474 primary outcome events (the composite of all recurrent stroke or acute MI or all-cause death). In the subgroup *with* CKD (baseline eGFR of <60 mL/min/1.73 m^2) at baseline (N=474), 113 (23.8%) primary outcome events occurred, of which 58 (12.2%), 11 (2.3%), and 44 (9.3%) were recurrent stroke, acute MI, and all-cause death, respectively. In the subgroup *without* CKD (eGFR ≥60 mL/min/1.73 m^2) at baseline (N=2543), 361 (14.2%) primary outcome events occurred, of which 213 (8.4%), 52 (2%), and 96 (3.8%) were recurrent stroke, acute MI, and

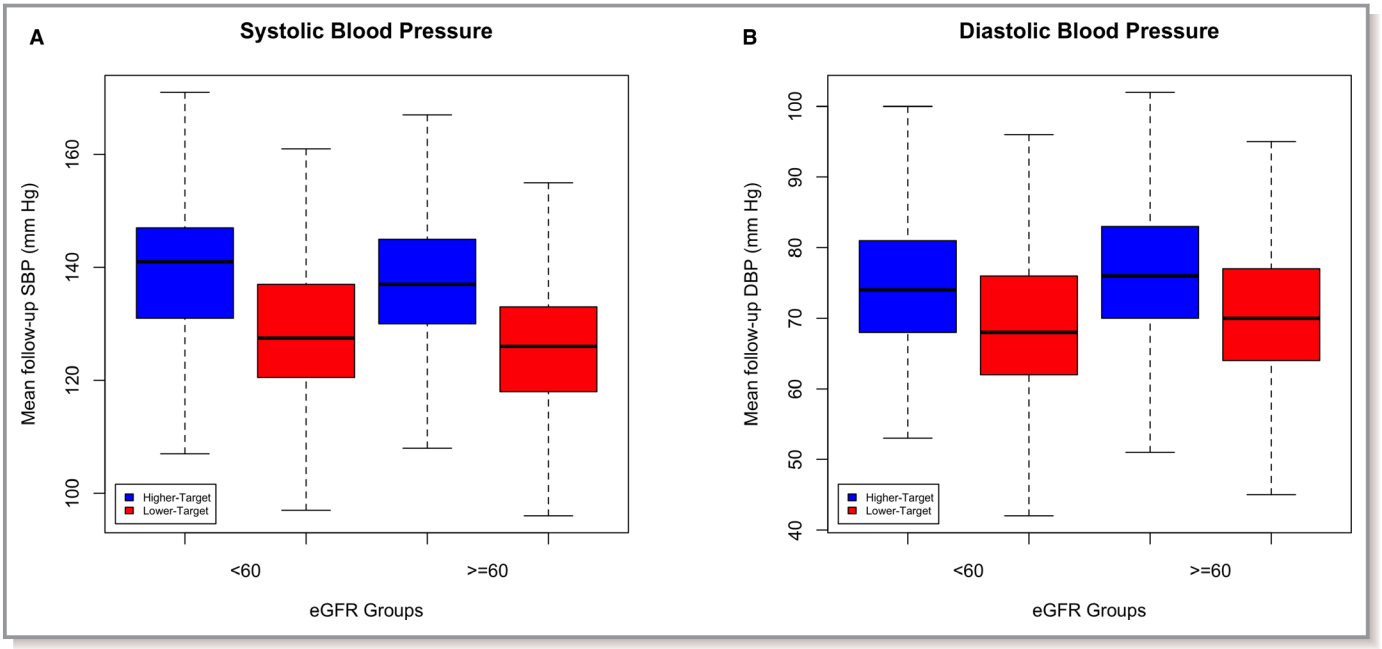

Figure 1. Achieved blood pressures by randomized SBP intervention and 2 baseline eGFR subgroups. Boxplots display the median, 25th, and 75th percentiles of the patients' follow-up values at 1 year for systolic blood pressure (SBP; **A**) and diastolic blood pressure (DBP; **B**) by randomized SBP intervention and two baseline eGFR groups. One hundred twenty-three of 3017 subjects (4.1%; 68 in the higher-target group and 55 in the lower-target group) had missing blood pressure measurements at 1 year and were not included. eGFR indicates estimated glomerular filtration rate.

all-cause death, respectively. CKD at baseline was associated with a significant 40% increase in risk for the composite outcome (HR, 1.4; 95% CI, 1.1–1.7) and with a significant 50% increase in risk for all recurrent stroke (HR, 1.5; 95% CI, 1.1–2.0; Table 2). Nevertheless, differences in risk for secondary outcomes of acute MI, all-cause death, and intracerebral hemorrhage were not significant between subgroups with and without baseline CKD. Figure 2 shows the cumulative incidence of the primary composite outcome and all recurrent stroke in patients with versus without CKD at baseline, respectively.

Modification of effects of the SBP intervention on the outcomes by baseline eGFR

When stratified by 2 baseline eGFR strata, <60 and ≥60 mL/min/1.73 m^2 (CKD and non-CKD), the HR for the primary composite outcome was 0.98 (95% CI, 0.67–1.41) within the CKD group and 0.86 (95% CI, 0.70–1.06)

Table 2. Association Between Baseline CKD (eGFR <60 mL/min/1.73 m^2) and Risk of Primary and Secondary Outcomes (Regardless of the SBP Intervention)

	Baseline eGFR Subgroups							
	<60 mL/min/1.73 m^2 (n=474)		≥60 mL/min/1.73 m^2 (n=2543)		Unadjusted		Adjusted*	
Outcome	Events N (%)	Incidence (95% CI) Per 100 PY	Events N (%)	Incidence (95% CI) Per 100 PY	HR (95% CI)	*P* Value	aHR (95% CI)	*P* Value
Stroke, MI, or death	113 (23.8)	6.6 (5.5, 8.0)	361 (14.2)	3.9 (3.5, 4.4)	1.7 (1.4, 2.1)	1.4E-6	1.4 (1.1, 1.7)	4.4E-3
Stroke	58 (12.2)	3.4 (2.6, 4.4)	213 (8.4)	2.3 (2.0, 2.7)	1.5 (1.1, 2.0)	0.01	1.5 (1.1, 2.0)	0.01
Acute MI	11 (2.3)	0.6 (0.4, 1.2)	52 (2.0)	0.6 (0.4, 0.7)	1.1 (0.6, 2.2)	0.70	1.0 (0.5, 1.9)	0.92
All-cause death	44 (9.3)	2.6 (1.9, 3.5)	96 (3.8)	1.0 (0.9, 1.3)	2.5 (1.7, 3.5)	8.3E-7	1.4 (0.9, 2.0)	0.10
IC hemorrhage	7 (1.5)	0.4 (0.2, 0.9)	15 (0.6)	0.2 (0.1, 0.3)	2.5 (1.0, 6.2)	0.04	1.8 (0.7, 4.8)	0.22

aHR indicates adjusted hazard ratio; CKD, chronic kidney disease; HR, hazard ratio; IC hemorrhage, intracerebral hemorrhage; MI, myocardial infarction; PY, person-years.
*Adjusted for age, sex, treatment assignment, study sites, and baseline diabetes mellitus, hypertension, statin use, angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker use, systolic blood pressure, and history of coronary artery disease.

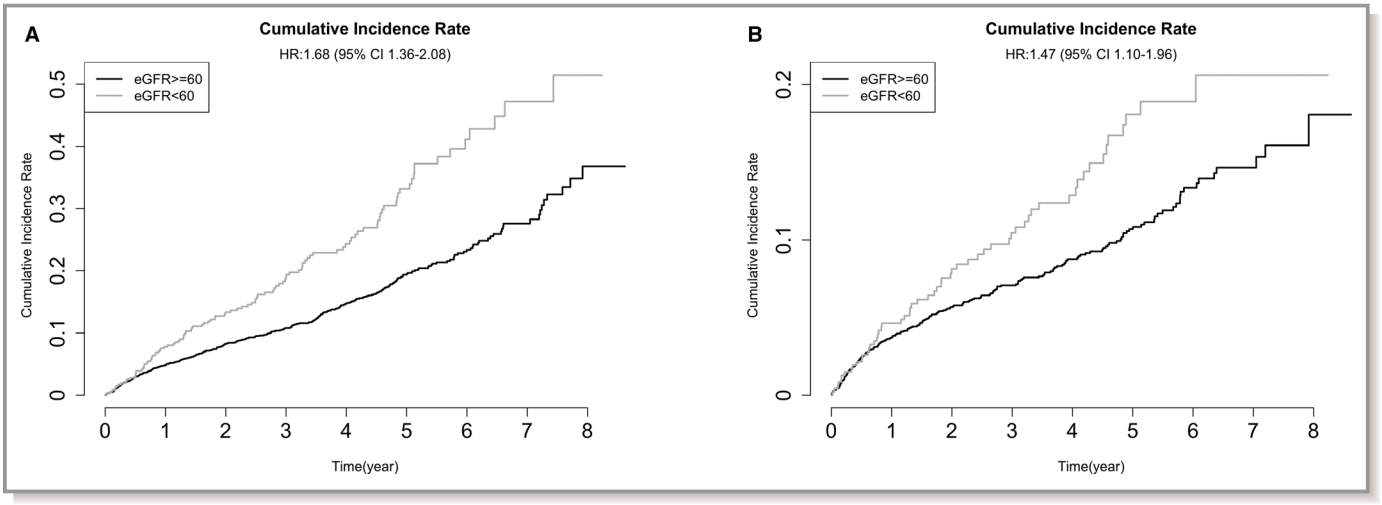

Figure 2. Cumulative incidence of the composite outcome and all recurrent stroke for those with and without CKD. **A**, Composite outcome. **B**, All recurrent stroke. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate HR, hazard ratio.

within the non-CKD group (*P* interaction=0.57; Figure 3). Furthermore, there was no evidence of an interaction between SBP intervention and baseline CKD for any of the outcomes, including the primary composite outcome, all recurrent stroke, all-cause death, acute MI, or intracerebral hemorrhage events (Figure 3).

We further examined the consistency of the SBP intervention effect on the primary and secondary outcomes across 4 strata of baseline eGFR (<45, 45 to <60, 60 to <90, and ≥90-mL/min/1.73 m^2). The beneficial effect of lower-target SBP intervention on all-cause death was attenuated with increase of eGFR (*P* interaction=0.04), whereas eGFR did not modify the effect on the primary composite outcome (*P* interaction=0.66), all recurrent stroke (*P* interaction=0.22), acute MI (*P* interaction=0.47), or intracerebral hemorrhage (*P* interaction=0.33; Figure S2).

Outcome	Lower-target N(%)	Higher-target N(%)	Hazard Ratio (95% CI)	P*
Composite CV				**0.57**
eGFR<60	59(24%)	54 (24%)	0.98 (0.67,1.41)	
eGFR>=60	167(13%)	194 (15%)	0.86 (0.70,1.06)	
All Recurrent Stroke				**0.22**
eGFR<60	32(13%)	26(11%)	1.10 (0.65,1.84)	
eGFR>=60	92(7%)	121(9%)	0.77 (0.58,1.01)	
Acute MI				**0.37**
eGFR<60	7(3%)	4(2%)	1.57 (0.46,5.38)	
eGFR>=60	24(2%)	28(2%)	0.86 (0.50,1.48)	
All-cause Death				**0.25**
eGFR<60	20(8%)	24(11%)	0.74 (0.41,1.35)	
eGFR>=60	51(4%)	45(3%)	1.13 (0.76,1.69)	
IC Hemorrhage				**0.98**
eGFR<60	2(1%)	5(2%)	0.36 (0.07,1.86)	
eGFR>=60	4(0%)	11(1%)	0.37 (0.11,1.16)	

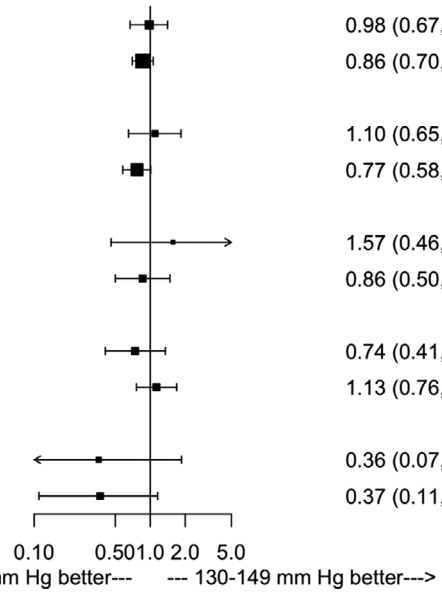

Figure 3. Forest plots with hazard ratios for the effect of SBP intervention on the events of primary and secondary outcomes by 2 baseline eGFR subgroups. *The interaction test for each outcome compared HRs below and above eGFR value of 60 mL/min/1.73 m^2. Composite CV indicates composite cardiovascular outcome; HR, hazard ratio; IC hemorrhage, intracerebral hemorrhage; MI, myocardial infarction; SBP, systolic blood pressure.

After adjustment for the linear form of baseline eGFR (each 10 mL/min/1.73 m^2 increase), intensive SBP control remained beneficial for the primary and secondary outcomes when compared with standard SBP control, with no significant modification by baseline eGFR on this effect (Table 3). The HR of intracerebral hemorrhage remained significantly reduced (HR, 0.37; 95% CI, 0.14–0.93; *P*=0.04) with adjustment for baseline eGFR. There was no evidence of interaction between SBP intervention and linear form of baseline eGFR for the primary composite outcome (*P* interaction=0.62), all recurrent stroke (*P* interaction=0.78), acute MI (*P* interaction=0.42), all-cause death (*P* interaction=0.16), or intracerebral hemorrhage (*P* interaction=0.30; Table 3).

Discussion

We found that in patients with well-defined previous lacunar stroke, baseline eGFR of <60 mL/min (versus ≥60 mL/min) was significantly associated with an increased risk of all recurrent stroke and the composite outcome of stroke, acute MI or all-cause death. Risk of recurrent stroke increased by 50% (and by 40% for the composite outcome) in patients with baseline CKD (eGFR <60 mL/min/1.73 m^2) versus those without CKD even after adjusting* (*Adjusted for age, gender, treatment assignment, study sites and baseline diabetes mellitus, hypertension, statin use, ACE inhibitor or ARB use, systolic blood pressure, and history of coronary artery disease.) for other baseline variables. However, we found no evidence that baseline eGFR significantly modifies the effects of lower SBP target (<130 mm Hg) on either recurrent stroke or the composite outcome, or on any of the secondary outcomes of acute MI, all-cause death, or intracerebral hemorrhage.

This post hoc analysis of SPS3 is the first to report a clear association between CKD and *recurrent* stroke in patients with confirmed and well-defined previous lacunar stroke. Several previous studies show that renal dysfunction increases risk of cardiovascular events, and incident stroke,[19–21] but do not show clear associations of renal dysfunction with recurrent stroke. This may be because there are few RCTs that have enrolled patients with a well-characterized history of previous stroke. The SPS3 trial, however, included patients with well-characterized magnetic resonance imaging–defined lacunar infarctions that occurred within 6 months before entry to the trial and thus presented an opportunity for accurately defining the association of CKD with recurrent stroke. In the previous RCTs that enrolled patients with previous stroke (PROGRESS [Perindopril pROtection aGainst REcurrent Stroke Study][22] and PRoFESS [Prevention Regimen for Effectively Avoiding Second Strokes][23] trials), previous stroke was not as well defined as in the SPS3 trial; nevertheless, post hoc analyses of these trials[24,25] did report increased risk of recurrent stroke with baseline CKD. Our study clarifies and defines the independent association of CKD with a 50% increase in risk of recurrent stroke in patients with a history of well-defined previous lacunar stroke. A widely cited meta-analysis by Lee et al published in 2010 found that an eGFR of <60 mL/min/1.73 m^2 is associated with a 43% higher risk of primary incident stroke.[16] Our results show a similar increase in risk of *recurrent* stroke in patients with an eGFR of <60 mL/min/1.73 m^2.

This study is also the first to report whether baseline kidney function modifies the effects of BP control in patients with previous stroke. Although greater absolute risks magnify treatment benefits, previous data suggest that CKD attenuates the benefits of intensive BP control.[10,12] However, no such data

Table 3. Effects of the SBP Intervention, Baseline eGFR, and the Linear Interaction Between the SBP Intervention and Baseline eGFR for the Primary and Secondary Outcomes

	Model 1*				Model 2†	
	Lower-Target vs Higher-Target		Change in Each 10 mL/min/1.73 m^2 Increase in Baseline eGFR		Interaction Term (Change in Lower-Target vs Higher-Target HR for Each 10 mL/min/1.73 m^2 Increase in Baseline eGFR	
	HR (95% CI)	*P* Values	HR (95% CI)	*P* Values	HR (95% CI)	*P* Values
Stroke, MI, or death	0.89 (0.75, 1.07)	0.22	0.89 (0.85, 0.93)	7.7E-7	1.02 (0.93, 1.13)	0.62
Stroke	0.83 (0.66, 1.06)	0.14	0.95 (0.89, 1.01)	0.12	1.02 (0.90, 1.16)	0.78
Acute MI	0.95 (0.58, 1.56)	0.84	0.92 (0.81, 1.05)	0.22	0.90 (0.69, 1.17)	0.42
Death (all-cause)	0.98 (0.71, 1.37)	0.93	0.76 (0.69, 0.83)	1.7E-9	1.14 (0.95, 1.36)	0.16
Intracerebral hemorrhage	0.37 (0.14, 0.93)	0.04	0.76 (0.61, 0.96)	0.02	0.76 (0.45, 1.29)	0.30

eGFR indicates estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure.

*The second to fifth columns under model 1 display the results of Cox regression analyses relating the primary and secondary outcomes to the randomized SBP intervention (HRs in the second column) and to the level of baseline eGFR at each increase of 10 mL/min/1.73 m^2 (HRs in the fourth column).

†The sixth and seventh columns display the proportional change in the HR comparing the intensive and standard SBP interventions for each 10 mL/min/1.73 m^2 increase in baseline eGFR under model 2, which includes main effects for the randomized SBP intervention and linear form of baseline eGFR, plus linear interactions between the randomized SBP intervention and baseline eGFR. The linear interactions were evaluated by likelihood ratio tests.

existed for patients with previous stroke. A cohort study of US veterans with prevalent CKD (eGFR of <60 mL/min/1.73 m²) suggested increased mortality when treated to an SBP of <120 mm Hg versus 120 to 139 mm Hg.[26] A secondary analysis of 2 community-based, longitudinal studies (ARIC[27] [Atherosclerosis Risk in Communities Study] and Cardiovascular Health Study[28]) including data from 20 358 individuals showed an increased risk of stroke with an SBP of <120 mm Hg in patients with CKD (eGFR <60 mL/min/1.73 m^2), but not in those without CKD.[29]

The SPRINT trial did show cardiovascular benefits of intensive SBP control (<120 versus <140 mm Hg), but was not designed to assess whether CKD modified the effects of SBP control. Post-hoc analyses of SPRINT report conflicting results. Benefits of intensive SBP control were observed to persist in patients with CKD when baseline eGFR was used as a dichotomous variable (<60 versus ≥60 mL/min/1.73 m^2).[8,30] However, another post hoc analysis of SPRINT suggested that in the subset of participants with moderate-to-advanced CKD (defined as eGFR of <45 mL/min/1.73 m^2), intensive SBP control provided little or no cardiovascular benefit.[12] Given that SPRINT excluded patients with a history of stroke, these analyses could not examine how renal dysfunction may modify the effects of intensive SBP control in patients with previous stroke. Another large BP target trial, the Action to Control Cardiovascular Risk in Type 2 Diabetes (ACCORD) trial, looked at the effects of similar SBP targets (<120 versus <140 mm Hg); however, it had a relatively small proportion (9%) of participants with baseline CKD and a poorly defined cohort of participants with previous stroke.[31] In contrast, all participants of SPS3 had previous stroke, and almost 16% had baseline CKD; thus, a post hoc analysis of SPS3 data presented an opportunity for assessing how renal dysfunction may modify the effects of intensive SBP control in patients with previous stroke.

It is also important to point out that elucidation of optimal BP targets in patients with previous stroke and CKD is important. Hypertension is the most prevalent risk factor for cardiovascular disease and stroke.[32] BP is an important determinant of cardiovascular disease,[33] and lowering of BP prevents initial[33,34] and recurrent[22,35,36] stroke. Lacunar or small subcortical strokes account for around 25% of all ischemic strokes and may have a stronger association with hypertension than other types of strokes.[37]

As noted above, we did not find any evidence that baseline CKD or eGFR modified the effects of lower (<130 mm Hg) versus higher (130–149 mm Hg) SBP targets in patients with previous lacunar stroke. This may be either because eGFR does not modify the effects of SBP control in patients with previous stroke or because our study lacked power to detect small effects. The number of participants with low eGFR was relatively low (474 with <60 versus 2543 with ≥60 mL/min/1.73 m²), and that was the main limitation of our study. Given that it is possible that attenuation of the benefits of SBP control is observed only with moderate-to-advanced CKD,[12] we also assessed the effects of SBP intervention across 4 baseline eGFR strata (<45, 45 to <60, 60 to <90, and ≥90 mL/min/1.73 m^2). This helped to assess possible effects of more-advanced CKD, but reduced the number of participants in each eGFR strata, further limiting the statistical power. Using these 4 categorical strata, we found a borderline significant interaction with all-cause death, but not with any other outcome. This could be because of the small sample size for the eGFR <45 mL/min/1.73 m^2 category; categorizing continuous variables like eGFR may impair the statistical power to detect meaningful differences.

In addition to having relatively few participants with CKD, especially moderate-to-advanced CKD, our study had some other limitations. The SPS3 trial evaluated recurrent stroke only in patients with previous lacunar stroke; thus, the results may not be generalizable to other types of stroke. In addition, the SPS3 trial had lower than anticipated event rates. The post hoc nature of our analyses could only detect association, not causality. On the other hand, our study had certain strengths. Magnetic resonance imaging confirmation and characterization of previous lacunar stroke ensured homogeneity of the study population, unlike any previous study. The SPS3 was a well-designed and well-conducted trial, and we studied effects of contemporaneously relevant SBP targets of <130 mm Hg (the target SBP recommended by the 2017 American College of Cardiology/American Heart Association guidelines for patients with previous stroke) versus a higher target of 130 to 149 mm Hg.

In conclusion, we found an independent 50% increase in risk for *recurrent* stroke in patients with CKD (eGFR <60 mL/min/1.73 m^2). Clinicians treating patients with previous stroke should be aware of this increased risk with CKD, take measures to reduce the risk of recurrent stroke, and have a low threshold for clinical suspicion for recurrent stroke in patients with CKD. It remains possible that renal dysfunction modifies the effects of BP control in patients with previous stroke, but we found no definitive evidence of that. We need large-scale BP target trials for those with moderate-to-advanced CKD.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline data for the four eGFR subgroups.

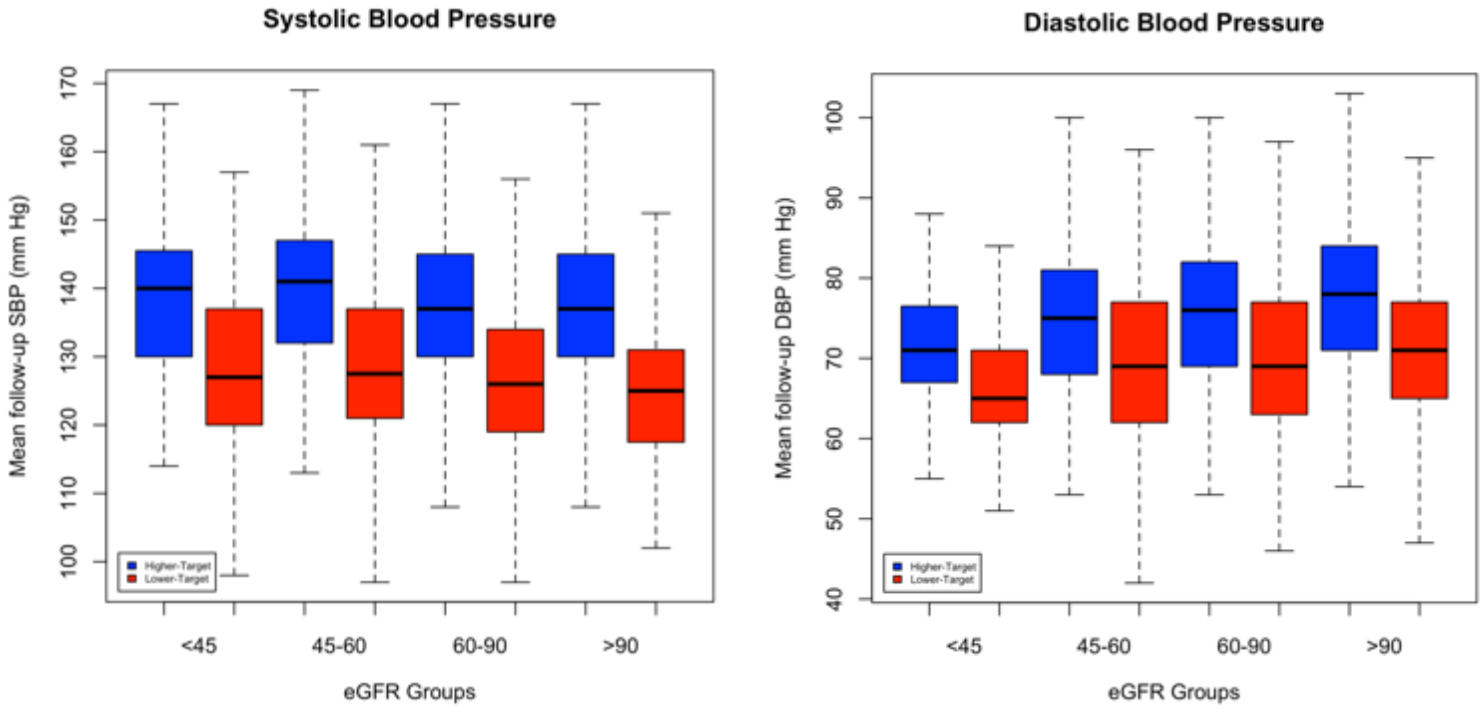
	Baseline eGFR subgroups							
	< 45 mL/min/1.73 m²		45 - < 60 mL/min/1.73 m²		60 - < 90 mL/min/1.73 m²		≥ 90 mL/min/1.73 m²	
SBP target intervention (mm Hg)	**Higher 130-149**	**Lower <130**	**Higher 130-149**	**Lower <130**	**Higher 130-149**	**Lower <130**	**Higher 130-149**	**Lower <130**
N (number)	49	46	178	201	773	750	517	503
Age, mean (SD), year	69.10 (11.62)	70.24 (11.04)	69.44 (10.68)	69.07 (11.49)	64.91 (10.23)	64.13 (10.64)	56.88 (8.59)	57.45 (7.72)
Female, N (%)	19 (38.78)	24 (52.17)	72 (40.45)	101 (50.25)	264 (34.15)	283 (37.73)	174 (33.66)	181 (35.98)
Race/ethnicity, N (%)								
Non-Hispanic white	25 (51.02)	24 (52.17)	103 (57.87)	110 (54.73)	408 (52.78)	404 (53.87)	222 (42.94)	234 (46.52)
Black	12 (24.49)	5 (10.87)	24 (13.48)	28 (13.93)	111 (14.369)	112 (14.93)	104 (20.12)	96 (19.09)
Hispanic	8 (16.33)	14 (30.43)	48 (26.97)	59 (29.35)	231 (29.88)	216 (28.80)	181 (35.01)	164 (32.60)
Other/multiple	4 (8.16)	3 (6.52)	3 (1.69)	4 (11.76)	23 (2.98)	18 (2.40)	10 (1.93)	9 (1.79)
Region, N (%)								
North America	34 (69.39)	31 (67.39)	100 (56.18)	133 (66.17)	512 (66.24)	487 (64.93)	336 (64.99)	325 (64.61)
Latin America	8 (16.33)	12 (26.09)	47 (26.40)	45 (22.39)	174 (22.51)	173 (23.07)	123 (23.79)	112 (22.27)
Spain	7 (14.29)	3 (6.52)	31 (17.42)	23 (11.44)	87 (11.25)	90 (12.00)	58 (11.22)	66 (13.12)
SBP, mean (SD), mmHg	144.65 (21.00)	142.96 (18.63)	147.44 (20.97)	148.32 (21.47)	144.47 (19.09)	142.36(18.45)	140.79 (17.97)	140.18 (16.74)
DBP, mean (SD), mmHg	76.35 (12.59)	73.63 (10.71)	78.33 (11.29)	77.64 (11.11)	79.24 (11.09)	77.35 (10.48)	79.22 (9.96)	78.48 (9.97)
History of CAD, N (%)	6 (12.24)	7 (15.22)	23 (12.92)	21 (10.45)	75 (9.70)	57 (7.60)	34 (6.58)	29 (5.77)
History of CHF, N (%)	2 (4.08)	1 (2.17)	1 (0.56)	6 (2.99)	7 (0.91)	7 (0.93)	3 (0.58)	5 (0.99)
Diabetes Mellitus, N (%)	18 (36.73)	20 (43.48)	56 (31.46)	73 (36.32)	234 (30.27)	217 (28.93)	191 (36.94)	192 (38.17)
Hypertension, N (%)	45 (91.84)	41 (89.13)	151 (84.83)	177 (88.06)	598 (77.36)	567 (75.60)	341 (65.96)	342 (67.99)
eGFR, mean (SD), mL/min/1.73m2	40.04 (4.47)	39.71 (4.04)	53.92 (4.15)	53.65 (4.31)	75.95 (8.35)	75.83 (8.43)	100.89 (8.64)	101.25 (8.68)
Total cholesterol, mean (SD), mg/dL	171.52 (68.01)	186.21 (55.50)	174.65 (53.53)	172.54 (51.41)	173.11 (57.29)	174.11 (55.54)	183.49 (57.61)	177.99 (55.81)
Smoking, N (%)								

Current	9 (18.37)	2 (4.35)	23 (12.92)	25 (12.44)	123 (15.91)	132 (17.60)	152 (29.40)	150 (29.82)
Past	24 (48.98)	18 (39.13)	76 (42.70)	95 (47.26)	331 (42.82)	314 (41.87)	167 (32.30)	181 (35.98)
Never	16 (32.65)	26 (56.52)	79 (44.38)	81 (40.30)	319 (52.12)	304 (40.53)	198 (38.30)	172 (34.19)
Plasma glucose, mean (SD), mg/dL	117.81 (42.26)	132.54 (68.44)	119.21 (45.93)	126.43 (58.86)	122.85 (52.00)	120.59 (48.71)	132.99 (60.65)	131.62 (61.74)
Statin use, N (%)	34 (69.39)	37 (80.43)	118 (66.29)	138 (68.66)	523 (67.66)	503 (67.07)	367 (70.99)	359 (71.37)
Aspirin use, N (%)	26 (53.06)	25 (54.35)	104 (58.43)	104 (51.74)	431 (55.76)	407 (54.27)	300 (58.03)	300 (59.64)
BMI, mean (SD), kg/m2	29.22 (7.19)	27.79 (5.56)	28.72 (5.44)	28.48 (5.51)	28.83 (5.91)	28.91 (6.14)	29.98 (9.83)	29.33 (6.31)
No. of antihypertensive drugs, mean (SD)	2.3 (1.34)	2.00 (0.94)	1.81 (1.11)	2.03 (1.21)	1.66 (1.15)	1.64 (1.11)	1.42 (1.12)	1.41 (1.06)
Alcohol, N (%)	11 (22.45)	8 (17.39)	38 (21.35)	48 (23.88)	237 (30.66)	213 (28.40)	138 (26.69)	154 (30.62)

Values for categorical variables are presented as number (percentage); values for continuous variables, as mean (standard).

eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure, CAD, coronary artery disease; CHF, congestive heart failure.

Figure S1. Achieved blood pressures by randomized SBP intervention and four baseline eGFR subgroups.

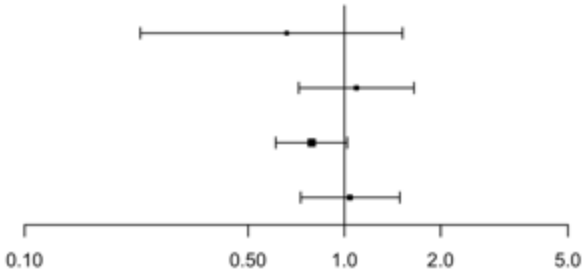


The boxplots display the median, 25th and 75th percentiles of the patients' follow-up values at 1-year for systolic blood pressure (SBP; A), diastolic blood pressure (DBP; B) by randomized SBP intervention and four baseline eGFR groups. 123 of 3017 subjects (4.1%) (68 in the higher-target group and 55 in the lower-target group) had missing blood pressure measurements at 1-year and were not included.

Figure S2. Forest plots with hazard ratios for the effect of SBP intervention on the events of primary and secondary outcomes by four eGFR subgroups.

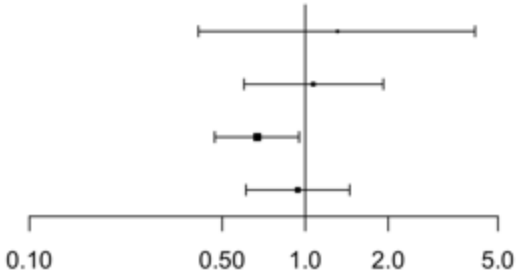
A. Composite

Composite CV	EventRates Lower	EventRates Higher	HR (95% CI)	P*
				0.66
eGFR<45	10 (22%)	13 (27%)	0.66 (0.29, 1.52)	
45-60	49 (24%)	41 (23%)	1.09 (0.72, 1.65)	
60-90	104 (14%)	136 (18%)	0.79 (0.61, 1.02)	
eGFR>90	63 (13%)	58 (11%)	1.04 (0.73, 1.49)	



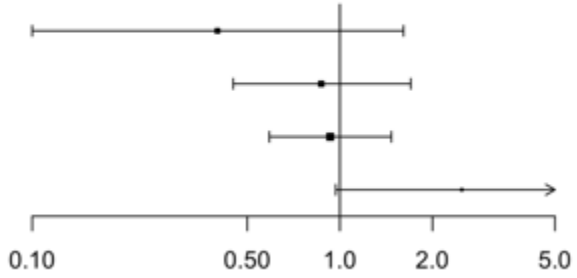
B. Stroke

All Recurrent Stroke	EventRates Lower	EventRates Higher	HR (95% CI)	P*
				0.22
eGFR<45	7 (15%)	5 (10%)	1.31 (0.41, 4.13)	
45-60	25 (12%)	21 (12%)	1.07 (0.60, 1.92)	
60-90	51 (7%)	79 (10%)	0.67 (0.47, 0.95)	
eGFR>90	41 (8%)	42 (8%)	0.94 (0.61, 1.45)	



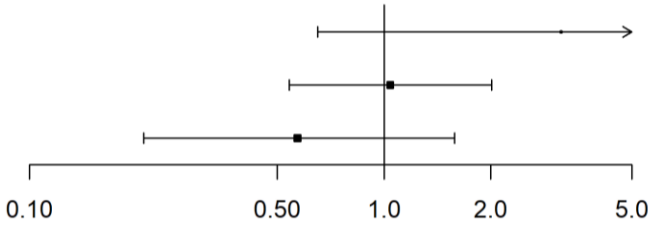
C. Death

All Cause Death	EventRates Lower	EventRates Higher	HR (95% CI)	P*
				0.04
eGFR<45	3 (7%)	6 (12%)	0.40 (0.10, 1.61)	
45-60	17 (8%)	18 (10%)	0.87 (0.45, 1.70)	
60-90	35 (5%)	39 (5%)	0.93 (0.59, 1.47)	
eGFR>90	16 (3%)	6 (1%)	2.49 (0.97, 6.37)	



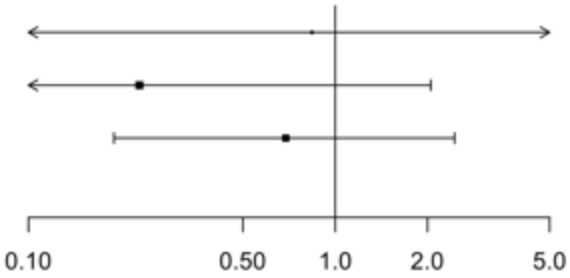
D. Acute MI

Acute MI	EventRates Lower	EventRates Higher	HR (95% CI)	P*
				0.47
eGFR<45	0 (0%)	2 (4%)	NA	
45-60	7 (3%)	2 (1%)	3.15 (0.65, 15.14)	
60-90	18 (2%)	18 (2%)	1.04 (0.54, 2.01)	
eGFR>90	10 (2%)	10 (2%)	0.57 (0.21, 1.58)	



E. IC Hemorrhage

IC Hemorrhage	EventRates Lower	EventRates Higher	HR (95% CI)	P*
				0.33
eGFR<45	1 (2%)	1 (2%)	0.84 (0.05, 13.52)	
45-60	1 (0%)	4 (2%)	0.23 (0.03, 2.05)	
60-90	4 (1%)	6 (1%)	0.69 (0.19, 2.45)	
eGFR>90	0 (0%)	5 (1%)	NA	



*The interaction test for each outcome compared HRs between the four baseline eGFR groups.
Composite CV, composite cardiovascular outcome; MI, myocardial infarction; IC Hemorrhage, intracerebral hemorrhage; HR, hazard ratio; CI, confidence interval.