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ACHIEVED BLOOD PRESSURE AND OUTCOMES IN THE SECONDARY PREVENTION OF SMALL SUBCORTICAL STROKES TRIAL

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Abstract

Studies suggest a J-shaped association between blood pressure and cardiovascular events in the setting of intensive systolic blood pressure control; whether there is a similar association with stroke remains less well established. The Secondary Prevention of Small Subcortical Strokes was a randomized trial to evaluate higher (130-149 mmHg) vs. lower (<130 mmHg) systolic blood pressure targets (ClinicalTrials.gov NCT 00059306) in participants with recent lacunar infarcts. We evaluated the association of mean achieved blood pressure, 6 months after randomization, and recurrent stroke, major vascular events, and all-cause mortality. After a mean follow up of 3.7 years, there was a J-shaped association between achieved blood pressure and outcomes; the lowest risk was at approximately124 and 67 mmHg systolic and diastolic, respectively. For example, above a systolic blood pressure of 124 mmHg, one standard deviation higher (11.1 mmHg) was associated with increased mortality (adjusted hazard ratio: 1.9; 95% confidence interval: 1.4, 2.7), whereas below this level, this relationship was inverted (0.29; 0.10, 0.79), p<0.001 for interaction. Above a diastolic blood pressure of 67 mmHg, a one standard deviation higher (8.2 mmHg) was associated with an increased risk of stroke (2.2; 1.4, 3.6), whereas below this level, the association was in the opposite direction (0.34; 0.13, 0.89), p=0.02 for interaction. The lowest risk of all events occurred at a nadir of approximately 120-128 mmHg systolic and 65-70 mmHg diastolic.

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CONFLICT OF INTEREST:
None of the authors have any conflicts of interest to disclose.

Future studies should evaluate the impact of excessive blood pressure reduction, especially in older populations with pre-existing vascular disease.

Keywords

aged; antihypertensive agents; blood pressure; stroke; secondary prevention

INTRODUCTION

Recent guidelines for the treatment of high blood pressure (BP) recommend lowering BP to a specified target, with no mention of a lower limit above which pressure should be maintained.[1, 2] Whether a lower level for BP is also associated with increased risk of adverse events is uncertain. The majority of the literature points toward the presence of a J-shaped association between BP and cardiovascular events, whereby there is an increased risk of events at both high and low BP levels. [3, 4] Whether a similar J-shaped relationship exists between BP and risk of stroke is more tenuous.[5] Additionally, some observational studies have suggested that low diastolic BP (DBP) in combination with high systolic BP (SBP), is associated with cardiovascular outcomes [6-8]. Whether the association between low DBP and increased risk of outcomes is independent of SBP is unclear.

There are limited data on achieved BP in the setting of treatment for stroke prevention, although the existing data suggest a linear relationship between BP and stroke outcomes. [5] A limitation of prior literature is that most data come from observational studies or randomized trials that were designed for a composite cardiovascular outcome, and not specifically to evaluate stroke. Low BP may result in inadequate cerebral blood flow due to decreased perfusion pressure.[5] This may be exaggerated in persons with pre-existing cerebrovascular disease, although no prior randomized trials of blood pressure lowering have evaluated the association of low BP and stroke in the setting of secondary prevention.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial was a randomized study comparing higher (130-149 mmHg) versus lower (<130 mmHg) SBP targets among individuals with recent lacunar infarcts.[9] Investigators demonstrated a non-significant reduction in both stroke and a composite outcome of myocardial infarction and vascular death in the lower target group compared with the higher target group. In this study, we compared the association between achieved SBP and DBP with the primary outcome of recurrent stroke, as well as major vascular events, and all-cause mortality. We examined each of the BP parameters both individually and in combination to determine the level of achieved BP associated with the lowest risk of stroke, major vascular events, and death.

METHODS

Study Population

SPS3 was a randomized, multi-center clinical trial designed to evaluate the effectiveness of two antiplatelet treatments in a blinded fashion (aspirin vs. aspirin plus clopidogrel) and two target levels of SBP (open label) for secondary stroke prevention in participants with recent lacunar infarcts. Details of the study design have been previously published.[10] Briefly,

persons in North America, Latin America and Spain, aged 30 years or older with a recent symptomatic MRI-determined lacunar infarct were randomized in a 2-by-2 factorial design to the antiplatelet intervention and to an intensive SBP target of <130 mmHg or usual target of 130-149 mmHg. Participants were enrolled between two weeks and 180 days after the qualifying event. Detailed inclusion and exclusion criteria are reported elsewhere. [10] All patients signed an informed consent and the protocol was approved by each local Institutional Review Board. This study is registered with ClinicalTrials.gov, number NCT 00059306.

Blood Pressure Management and Measurement

Patients were randomly assigned to one of two SBP targets, irrespective of DBP. Randomization was stratified by clinical center and according to baseline hypertension status (hypertensive vs. normotensive), using a permuted-block design. Since the goal was to achieve a target systolic BP, randomization was not blinded (open-label) and there was no washout period. All major classes of antihypertensive medicines were available to use, with an algorithm based on JNC 7 guidelines developed and distributed to sites.[11, 12] BP was measured in the sitting position and in the same arm following a strict validated protocol as described previously.[10] BP was measured using an automated BP machine (Colin 8800C, Omron, San Antonio, TX, USA), provided to each clinical center. Achieved BP was calculated as the mean BP from all trial readings taken after the first six months of follow-up; only those participants with two or more BP measures after this time interval are included in the present study (n=2,748 of 3,020). Participants with less than six months of follow-up were excluded from this analysis.

Outcomes

The primary endpoint was all recurrent stroke. Ischemic stroke was clinically defined as a focal neurological deficit persisting for longer than 24 h, with an absence of hemorrhage confirmed by neuroimaging. Major vascular events, a secondary outcome, included acute myocardial infarction (defined by standard criteria, i.e. compatible clinical history with changes on ECG or in cardiac enzyme concentrations), or need for acute admission to hospital for a major vascular event. Death was classified as vascular, non-vascular, or unknown. All outcomes were ascertained by a site examiner blinded to BP treatment group assignment and confirmed by a central adjudication committee that was blinded to treatment assignment.

Statistical Analysis

Several investigations of BP and outcomes in older adults have demonstrated non-linear associations; therefore, we used a data-guided approach to identify the relationship between achieved BP and outcomes. To identify the point of lowest risk of events, we began by fitting restricted cubic spline models with 5 knots (5th, 25th, 50th, 75th, 95th percentiles) of achieved SBP and DBP and all recurrent stroke. Based on these splines, we stratified participants based on dichotomized SBP and DBP above or below the point of lowest risk for each component (determined to be 124 and 67 mmHg, respectively). We stratified into two groups in order to preserve sample size within the strata.

Baseline characteristics of participants stratified by high (≥124 mmHg) and low (<124 mmHg) achieved SBP were summarized in Table 1, and compared using ANOVA or chi-square tests as appropriate.

We next fit a series of multivariable Cox proportional hazard models to evaluate the independent association of achieved SBP and DBP (per SD higher BP) with outcomes; participants were censored at the time of event or last follow-up. Since the relationship of BP and outcomes appeared J-shaped, we stratified all models based on the cutpoints identified above. The first model included age, sex, ethnicity, region, smoking, alcohol use, BMI, baseline SBP, baseline DBP, history of hypertension, diabetes, heart disease, and prior stroke/TIA. The second model added number of medications at baseline, number of medications at 1 year follow-up, and randomization group. Finally, the third model added achieved SBP (linear and quadratic term) in the models with DBP as the primary predictor, and vice versa in the models with SBP as the primary predictor.

We tested for effect modification in all models of the primary outcome of interest (all stroke) by including an interaction term between achieved SBP and DBP and age and randomization group, as well between achieved SBP and both achieved and baseline DBP, and vice versa.

RESULTS

After a mean follow-up of 3.7 (SD 2.0) years, participants in the higher-target BP randomization group achieved a mean SBP of 137 (SD 9.2) mmHg and DBP of 75.3 (SD 7.9) mmHg, compared with a SBP of 126 (SD 9.9) mmHg and DBP of 69.4 (SD 7.5) mmHg in the lower target group. The spline plots demonstrated a J-shaped association of achieved SBP and DBP with stroke (Figure 1). The lowest risk of stroke occurred at approximately 124 mmHg systolic and 67 mmHg diastolic; 27% and 26% of participants achieved BPs below these levels, respectively (Figure 2).

Participants with high achieved SBP had a different racial/ethnic distribution compared with those with lower achieved SBP. Additionally, those with high achieved SBP and were more likely to be from the U.S., and have higher BMI, and baseline SBP and DBP.(Table 1) Additionally, these participants had a higher prevalence of hypertension, diabetes, and ischemic heart disease, and were more likely to be on all classes of antihypertensive medications compared with persons with low achieved SBP. Finally, participants with high achieved SBP were also more likely to be on more antihypertensive medications after 1 year, specifically calcium-channel blockers, beta-blockers, and other non-thiazide, non-ACE-inhibitor/ARB medications; not surprisingly participants in this group were more likely to be in the higher-target SBP randomization group and had fewer visits.

The associations between SBP and all stroke, ischemic stroke, major vascular events, and mortality differed above and below 124 mmHg; p for interaction all <0.05. (Table 2) Above SBP of 124 mmHg, higher SBP was associated with an increased risk of all stroke, ischemic stroke, major vascular events and mortality. (Table 2) In contrast, below SBP of 124 mmHg, the associations were inverted; higher pressure was associated with lower risk. These

patterns were consistent after multivariable adjustment, although the association between SBP and ischemic stroke was attenuated in the SBP ≥124 mmHg group. The associations with ischemic stroke and major vascular events were further attenuated after the inclusion of DBP. The J-shaped association between SBP and mortality remained strong even after adjustment for DBP.

We observed a similar pattern of association between DBP and outcomes. (Table 3) Above DBP of 67 mmHg, higher DBP was associated with an increased risk of all stroke, ischemic stroke, and major vascular events. In contrast, below DBP of 67 mmHg, the associations were significantly different and in the opposite direction. Higher DBP was associated with increased mortality above 67 mmHg, although this association was attenuated after adjustment for SBP. The association between DBP and all stroke, ischemic stroke, and major vascular events both above and below 67 mmHg were robust against adjustment for covariates and SBP.

There were no significant interactions between achieved SBP and DBP and age, randomization group, baseline SBP and DBP, and achieved SBP and DBP.

DISCUSSION

In this observational analysis of the SPS3 trial, there was a J-shaped association between achieved SBP and DBP and stroke, vascular events, and mortality. The lowest risk of events was at approximately 120-128 mmHg systolic and 65-70 mmHg diastolic; above these levels, higher SBP and DBP were associated with an increased risk of events. In contrast, below this level we observed inverted associations; higher pressures were associated with a lower risk of events. Achieved DBP appeared to be more important compared with SBP for ischemic stroke and major vascular events; however, achieved SBP had a stronger association with all-cause mortality.

The present study fills a gap in knowledge regarding the association of achieved BP and outcomes; no previous investigation has studied a population with symptomatic lacunar infarcts. The majority of previous literature has reported a J-shaped association between BP and cardiovascular events, and a linear association with stroke outcomes. In a post-hoc analysis of 22,576 patients with hypertension and coronary artery disease enrolled in the International Verapamil-Trandoloapril Study (INVEST), the association between both SBP and DBP and a composite cardiovascular outcome was J-shaped; although the J-shape was not apparent for stroke outcomes alone.[4] A meta-analysis from the Individual Data ANalysis of Antihypertensive intervention (INDANA) database reported a J-shaped association of both diastolic and systolic BP with mortality; this association was only present for CVD mortality in the treatment group.[13] In the Treating to New Targets (TNT) trial, which enrolled over 10,000 participants with a history of coronary artery disease, the mortality rate was the lowest at a BP of 146/81 mmHg.[14] A nonlinear J-shaped association was found for SBP and vascular events, but not stroke. In a pooled analysis of the European Carotid Surgery Trial, the North American Carotid Endarterectomy Trial, and the United Kingdom Transient Ischaemic Attack Aspirin Trial, investigators found evidence of a J-shaped association of blood pressure and recurrent stroke among participants with bilateral carotid

stenosis, suggesting that participants with advanced carotid disease may be more susceptible to stroke risk at lower blood pressure.[15]

An important strength of the present study is that the BP lowering was primarily due to medication, which allows us to distinguish the effect from observational studies in which low BP may be due to comorbid conditions, such as heart failure. However, the mechanisms mediating the associations of low BP with poor outcomes remains to be determined. Diastolic arteriolar tone appears to be an important determinant of cardiovascular risk. Some investigators have argued that low DBP may have a negative effect on coronary events because the heart is perfused during diastole; these effects may be accentuated in patients with pre-existing coronary artery disease.[4] Similarly, we theorize that low BP could result in inadequate perfusion of the brain in persons with pre-existing small vessel disease, leading to stroke thus leading to a cerebral infarct. The strong association of both low and high systolic blood pressure with mortality suggests that both extremes of blood pressure are associated with severe events. Finally, there are challenges with accurate measurement of BP in older adults, including the presence of pseudohypertension, postprandial hypertension, and cuff artifact[16-18], which could have contributed to some overtreatment of older adults who have normal intra-arterial BP or low diastolic blood pressure.

Although this is the first study to investigate a J-shaped association of achieved BP and outcomes in the setting of intensive BP lowering for secondary prevention, this study also has limitations which must be considered. The primary limitation of the present study is that it is a post-hoc analysis of a randomized trial. Although achieved BP was highly influenced by pharmacotherapy, there were other factors that impacted achieved SBP and DBP. We adjusted for a large number of potential confounders, but residual and unmeasured confounding may remain. Subclinical cardiovascular disease could affect both BP and risk of events. Second, the mechanism explaining a J-shaped association of BP and outcomes remains uncertain. Future studies designed to better understand the physiologic effects of low BP may better describe the mediating pathways.

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PERSPECTIVES

In summary, the lowest risk of events occurred at a nadir of approximately 120-128 mmHg systolic and 65-70 mmHg diastolic. The present study highlights the need to evaluate the impact of excessive BP reduction in persons treated with antihypertensives. This may be more important in older patients with pre-existing vascular disease, or those who are vulnerable to adverse effects of hypotension.

NOVELTY AND SIGNIFICANCE

What Is New?

In a trial of blood pressure control in participants with a history of lacunar stroke, there was a J-shaped association between blood pressure and stroke, vascular events, and mortality.

What Is Relevant?

The present study suggests the need to evaluate whether a lower bound for blood pressure reduction should be considered for prevention of cerebrovascular events.

Summary

In the SPS3 trial of systolic blood pressure lowering in participants with a history of lacunar stroke, the lowest risk of events was at approximately 120-128 mmHg systolic blood pressure and 65-70 mmHg diastolic blood pressure; above these levels, higher blood pressures were associated with an increased risk of events. In contrast, below this level we observed inverted associations; higher pressures were associated with a lower risk of events.

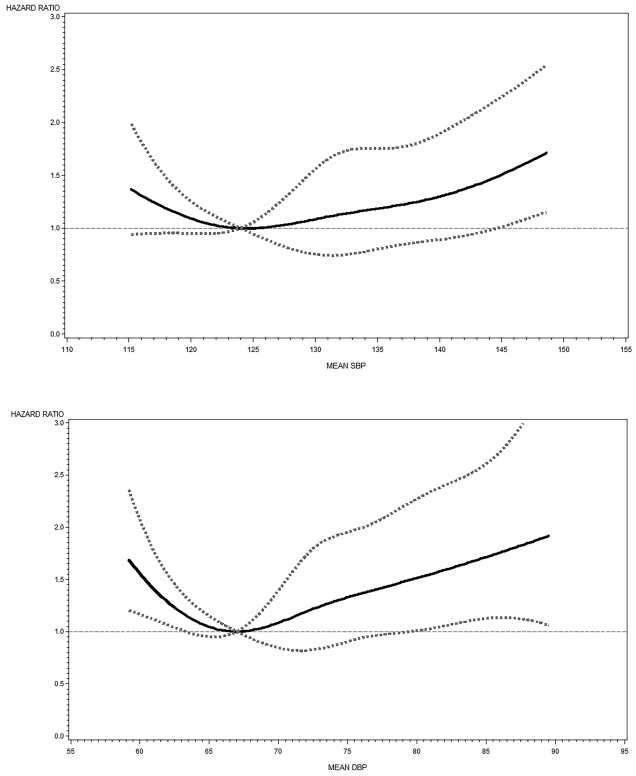

FIGURE 1.

Non-linear association between mean achieved SBP (top) and DBP (bottom) and all stroke; dotted lines = 95% confidence interval

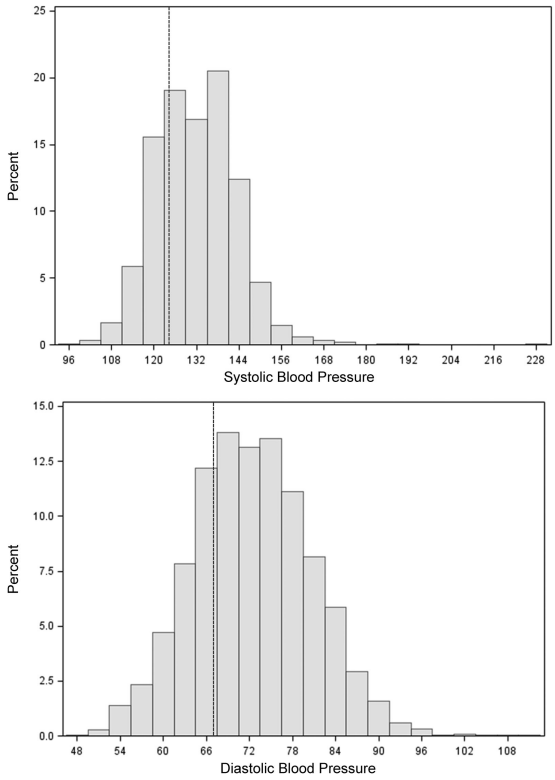

FIGURE 2.

Histogram of systolic (top) and diastolic (bottom) blood pressure; dotted lines at 124 mmHg systolic and 67 mmHg diastolic

TABLE 1

Characteristics of Participants by Mean Achieved SBP

Characteristic	N	Low SBP (<124 mmHg) (n=747)	High SBP (≥124 mmHg) (n=2000)	p-value
		N (%) or Mean (SD)		
Demographics				
Age (years)	2747	63.8 (10.5)	63.2 (10.7)	0.17
Male	2747	462 (62%)	1278 (64%)	0.33
Race/Ethnicity	2747			<0.0001
White		371 (50%)	1017 (51%)	
Black		75 (10%)	356 (18%)	
Hispanic		290 (39%)	570 (29%)	
Other/mixed		11 (1%)	57 (3%)	
Region	2747			<0.0001
US		336 (45%)	1147 (57%)	
Canada		67 (9%)	200 (10%)	
Latin America		249 (33%)	413 (21%)	
Spain		96 (13%)	240 (12%)	
Health Behaviors				
Smoking	2747			0.45
Current		134 (18%)	400 (20%)	
Past		308 (41%)	816 (41%)	
Never		305 (41%)	784 (39%)	
Regular Alcohol Use	2747	87 (12%)	275 (14%)	0.14
Physiologic Measures				
BMI (kg/m^2)	2746	28.5 (5.9)	29.3 (7.3)	0.002
Baseline SBP (mmHg)	2747	135 (17)	146 (18)	<0.0001
Baseline DBP (mmHg)	2747	75 (9.9)	80 (10.6)	<0.0001
Health History				
Hypertension	2747	479 (64%)	1567 (78%)	<0.0001
Diabetes	2747	231 (31%)	750 (38%)	0.001
Ischemic Heart Disease	2747	55 (7%)	221 (11%)	0.003
Stroke/TIA	2742	93 (12%)	302 (15%0	0.07
Baseline Medication Use				
# Antihypertensive Medications	2747	1.3 (1.0)	1.8 (1.2)	<0.0001
Thiazides	2559	170 (24%)	715 (38%)	<0.0001
ACE Inhibitors/ARB Use	2747	464 (62%)	1383 (69%)	0.0005
Calcium-channel blockers	2747	120 (16%)	572 (29%)	<0.0001
Beta-blockers	2747	125 (17%)	529 (26%)	<0.0001
Others	2747	37 (5%)	149 (7%)	0.02
Statins	2747	506 (68%)	1390 (70%)	0.38

Characteristic	N	Low SBP (<124 mmHg) (n=747)	High SBP (≥124 mmHg) (n=2000)	p-value
		N (%) or Mean (SD)		
Medications at 1 Year*				
# Antihypertensive	2539	1.8 (1.3)	2.2 (1.4)	<0.0001
Medications				
Thiazides	2530	347 (49%)	957 (53%)	0.09
ACE Inhibitors/ARBs	2539	506 (68%)	1312 (66%)	0.29
Calcium-channel blockers	2539	204 (29%)	713 (39%)	<0.0001
Beta-blockers	2539	143 (20%)	548(30%)	<0.0001
Others	2539	41 (6%)	204 (11%)	<0.0001
Statins	2539	475 (67%)	1218 (67%)	0.92
Number of Visits	2747	14.0 (7.4)	13.0 (7.7)	0.002
Higher-Target BP Group	2747	113 (15%)	1270 (64%)	<0.0001

TABLE 2

Association of Achieved SBP and Outcomes

Model	SBP < 124 mmHg (N=747)	SBP ≥124 mmHg (N=2000)	p-value for interaction
	HR per SD* Higher SBP (95% CI)		
All Stroke			
# of events	45	130	
Model 1†	0.44 (0.21, 0.93)	1.3 (1.1, 1.7)	0.005
Model 2†	0.40 (0.19, 0.84)	1.3 (0.97, 1.7)	0.005
Model 3†	0.43 (0.17, 1.1)	1.1 (0.76, 1.6)	0.02
Ischemic Stroke			
# of events	38	110	
Model 1†	0.43 (0.19, 0.99)	1.4 (1.1, 1.7)	0.01
Model 2†	0.38 (0.17, 0.87)	1.3 (0.92, 1.7)	0.01
Model 3†	0.41 (0.15, 1.1)	1.0 (0.70, 1.6)	0.03
Major Vascular Events			
# of events	53	178	
Model 1†	0.45 (0.22, 0.90)	1.4 (1.2, 1.7)	0.001
Model 2†	0.41 (0.20, 0.84)	1.4 (1.1, 1.8)	0.0008
Model 3†	0.53 (0.22, 1.3)	1.1 (0.84, 1.5)	0.005
Death			
# of events	38	119	
Model 1†	0.45 (0.20, 1.0)	1.5 (1.2, 1.8)	0.001
Model 2†	0.40 (0.17, 0.93)	1.9 (1.5, 2.4)	<0.001
Model 3†	0.29 (0.10, 0.79)	1.9 (1.4, 2.7)	<0.001

*11.1 mmHg

†Model 1 includes age, sex, ethnicity, region, smoking, alcohol use, BMI, baseline SBP, baseline DBP, history of hypertension, diabetes, heart disease, or prior stroke/TIA; Model 2 adds number of medications at baseline and number of medications at 1 year follow-up, and randomization group, Model 3 adds achieved DBP (linear and quadratic term)

TABLE 3

Association of Achieved DBP and Outcomes

Model	DBP < 67 mmHg (N=726)	DBP ≥67 mmHg (N=2016)	
	HR per SD* Higher DBP (95% CI)		
All Stroke			
# of events	52	123	
Model 1†	0.43 (0.22, 0.84)	1.8 (1.3, 2.3)	0.001
Model 2†	0.35 (0.17, 0.73)	1.7 (1.2, 2.3)	0.002
Model 3†	0.37 (0.16, 0.84)	2.1 (1.3, 3.3)	0.005
Ischemic Stroke			
# of events	43	105	
Model 1†	0.42 (0.20, 0.89)	1.8 (1.3, 2.4)	0.007
Model 2†	0.34 (0.15, 0.77)	1.7 (1.2, 2.4)	0.01
Model 3†	0.34 (0.13, 0.89)	2.2 (1.4, 3.6)	0.02
Major Vascular Events			
# of events	66	165	
Model 1†	0.47 (0.26, 0.87)	1.9 (1.5, 2.3)	<0.001
Model 2†	0.39 (0.21, 0.75)	1.9 (1.4, 2.5)	0.001
Model 3†	0.42 (0.20, 0.89)	2.0 (1.4, 3.0)	0.004
Death			
# of events	58	99	
Model 1†	0.85 (0.45, 1.6)	1.5 (1.1, 2.1)	0.18
Model 2†	1.1 (0.55, 2.3)	1.7 (1.2, 2.5)	0.64
Model 3†	1.6 (0.72, 3.6)	0.85 (0.51, 1.4)	0.89

*8.2 mmHg

†Model 1 includes age, sex, ethnicity, region, smoking, alcohol use, BMI, baseline SBP, baseline DBP, history of hypertension, diabetes, heart disease, or prior stroke/TIA; Model 2 adds number of medications at baseline and number of medications at 1 year follow-up, and randomization group, Model 3 adds achieved SBP (linear and quadratic term)