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Predictors of lowering SBP to assigned targets at 12 months in the Secondary Prevention of Small Subcortical Strokes study

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Abstract

Objective—Lowering blood pressure for secondary stroke prevention remains a challenge. These analyses were conducted to identify factors predicting achievement of SBP targets in the Secondary Prevention of Small Subcortical Strokes (SPS3) study.

Methods—SPS3 is a randomized trial assigning patients with lacunar stroke to two targets of SBP control (130–149 mmHg or <130 mmHg). Logistic regression models were used to identify patient and SPS3 site characteristics predictive of lowering SBP to target at the 12-month study visit.

Results—Of those above target at baseline ($n = 1041$), 69% were within their assigned target at 12 months. In the model with baseline characteristics only, those receiving treatment for hypertension at baseline were 68% less likely to achieve target [odds ratio (OR) = 0.32; 95% confidence interval (CI) = 0.17–0.60], whereas those of Hispanic ethnicity were 1.49 times more likely (95% CI = 1.09–2.03) to achieve SBP target. When clinical site characteristics were added to the model, only treated hypertension at baseline remained significant. In addition, management

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Conflicts of interest

No financial or potential financial conflicts of interest relevant to this research.

at a larger site (OR = 1.51; 95% CI = 1.03–2.20), SBP in target at 6 months (OR = 2.39; 95% CI = 1.79–3.19), and medication adherence (OR = 2.73; 95% CI = 1.51–4.95) were positively associated with achieving target SBP. Missed appointments (OR = 0.55; 95% CI = 0.41–0.73) were negatively associated with lowering SBP to target at 12 months.

Conclusion—These results demonstrate that it is feasible to achieve targets of SBP control in this multiethnic stroke cohort across multiple sites and countries. The results highlight the important variables reflecting clinical site management.

Keywords

blood pressure control; hypertension; lacunar stroke; predictors; Secondary Prevention of Small Subcortical Strokes Study; stroke

INTRODUCTION

Hypertension is the most prevalent and modifiable risk factor for stroke irrespective of subtype [1,2] but particularly for strokes caused by cerebral small vessel disease [3,4]. Observational studies and randomized trials have consistently demonstrated that a reduction in SBP of 10 mmHg is associated with at least a 30% reduction in the risk of stroke [5,6]. The magnitude of benefit is larger in patients with prior lacunar and hemorrhagic strokes [7,8]. These factors highlight the importance of blood pressure control in this population. Despite the clear association between hypertension and stroke, successful control of blood pressure poststroke is still suboptimal [9]. It is important to identify factors that might preclude the ability to adequately lower blood pressure to a predetermined level of control in this population.

Previous studies of hypertension control have outlined factors associated with blood pressure control. These factors have included SBP rather than DBP targets, presence of comorbid conditions (diabetes, renal insufficiency), sex, race, number of drugs required, a lack of awareness of hypertension, advanced age, and adherence [9–14]. Of note is the lack of consistency among studies regarding predictors of blood pressure control, perhaps related in part to the different patient populations and to differences in study designs.

The Secondary Prevention of Small Subcortical Strokes (SPS3) study is an ongoing National Institutes of Health sponsored multicenter international trial evaluating two targets of SBP control and antiplatelet treatment in patients with prior lacunar stroke [15]. The objectives of these analyses were to identify baseline characteristics of SPS3 participants that are predictive of lowering SBP to the assigned target at 12 months after entry into the trial; and to identify characteristics of SPS3 clinical sites and management of blood pressure that are associated with lowering SBP to the assigned target at 12 months, adjusted for baseline characteristics.

METHODS

Secondary Prevention of Small Subcortical Strokes trial

The rationale and design of SPS3 have been presented elsewhere [15]. Briefly, the SPS3 target population was patients with recent (within 6 months) MRI-proven lacunar stroke with no evidence of cortical stroke and without significant ipsilateral carotid stenosis and a major cardioembolic source. Patients were recruited from clinical centers in United States, Canada, Mexico, Ecuador, Peru, Chile, Argentina, and Spain. All patients were randomized, in a factorial design, to one of two SBP management groups: an ‘intensive’ group (target SBP <130 mmHg) or a ‘usual’ group (target SBP of 130–149 mmHg), and simultaneously to an antiplatelet intervention (aspirin 325 mg daily or aspirin 325 mg daily and clopidogrel

75 mg daily). It was hypothesized that 'intensive' management of SBP will result in fewer recurrent strokes and a decreased rate of cognitive decline. Recruitment began in March 2003 and was completed in April 2011. Patients were followed, on average, for 4 years with all participants followed to a common end date (April 2012). Sufficient power to detect an effect of blood pressure lowering was predicated on a mean difference of at least 10 mmHg systolic between the two treatment groups. This underscores the importance of identifying factors that predict the ability of participants to achieve target SBP in both the 'intensive' and the 'usual' groups. The SPS3 study was approved by the institutional review boards of all participating centers and all patients provided written informed consent.

Study sample

By SPS3 study design, there were no lower or upper exclusions for baseline SBP; thus, some participants were already within their assigned target or below target (those assigned to the 130–149 mmHg) at baseline and these participants were excluded from the current sample. As the aim of these analyses was to examine the predictors of lowering SBP into the randomly assigned target at 12 months, only those participants who were above their assigned targets at entry to the trial and who were seen at 12 months were included in the present study.

Secondary Prevention of Small Subcortical Strokes blood pressure protocol

Blood pressure was measured according to a detailed protocol [15,16] based on Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) guidelines [17], and all site personnel received instruction on the protocol prior to initiating the trial. Sites were provided with the Colin 8800C, an automated oscillometric electronic device for blood pressure measurement, which meets the Association for the Advancement of Medical Instrumentation standards [16,18].

Prior to randomization, blood pressure was measured at two separate clinic visits to determine hypertension status prior to trial entry. Randomization was stratified by blood pressure status with both normotensive and hypertensive patients being assigned to one of the two SBP management groups. Participant blood pressure was managed locally at each clinical center by a physician with expertise in blood pressure management. A recommended algorithm, based on JNC-VII guidelines [17], was provided to all sites to assist with blood pressure management (access algorithm at <http://www.sps3.org>). The algorithm advocates titration of dose as well as addition of agents using a step-wise approach, monitoring carefully for specific side effects of agents or due to lowering of the blood pressure. By protocol, patients assigned to the 130–149 mmHg group who were on antihypertensive medication with SBP below target were to have medication dose reduced or discontinued in order to achieve the assigned target, unless there was a clinical contraindication. Antihypertensive drugs prescribed to participants for reasons other than blood pressure control (e.g. β -blockers after myocardial infarction, angiotensin-converting enzyme inhibitors for diabetic nephropathy) were not discontinued in order to achieve the assigned blood pressure target. Drugs to increase blood pressure were not administered to achieve the 130–149 mmHg target for those participants whose SBP was less than 130 mmHg on no blood pressure lowering medications. Normotensive patients at study entry who became hypertensive during follow-up were managed according to their assigned blood pressure target.

Patients were seen at least monthly for adjustment of antihypertensive medications to achieve the assigned target blood pressure. Once the SBP was in the assigned target range at two consecutive visits, the participant continued with quarterly follow-ups. To maximize adherence, blood pressure medications were provided free of charge to participants as

deemed appropriate by the site hypertension expert. One or two drugs from each of the major classes of antihypertensive medications and additional medications on a case-by-case basis were available.

Measurement of predictors

Demographics variables including lifestyle variables associated with hypertension, comorbid conditions, medications, and variables related to the clinical site and the patient's participation were examined as potential predictors of achieving blood pressure target. Lifestyle variables included smoking status, alcohol consumption, and exercise. The presence of comorbid conditions including obesity (BMI >30 versus ≤30), depression (measured by the Patient Health Questionnaire-9 [19]), renal function (measured by the glomerular filtration rate), diabetes (based on self-report or if prescribed antidiabetic medications within the initial 3 months of study entry), and coronary artery disease (defined as present if the patient reported a definite history of myocardial infarction, angina, or revascularization procedure) were assessed for their potential impact on achieving blood pressure target. Baseline blood pressure, treated or untreated hypertension at entry to the study, and the presence of isolated systolic hypertension were also examined as potential predictors of achieving target SBP.

Variables related to the management of blood pressure included the number and class of antihypertensive medications at the 12-month follow-up and the presence of orthostatic hypotension (defined as SBP drop >20 mmHg from sitting to the standing position or reported symptoms of lightheadedness) at the 12-month follow-up. Site characteristics included the number of study participants at the clinical site at the time of the analyses (<20 versus ≥20), geographic location of clinical site (United States versus all other sites), and the ability to manage patient into target by 6 months (the average time to lower SBP into target). Adherence to medications (four-item self-report scale) and to study appointments and status in the blood pressure arm of the trial were included as predictors. Patients who refused to have their blood pressure managed into their assigned target by the study team or missed multiple visits so the team was unable to manage their blood pressure were designated as inactive, although they could be reactivated if the situation reversed.

Measurement of outcome at 12 months

In the SPS3 study, patients in the 'usual' group with SBP less than 130 mmHg were considered out of target and required withdrawal of medication, if not contraindicated, to allow SBP to increase to a level 130 mmHg or more. As these analyses were concerned with predictors of lowering SBP into the assigned targets, patients were considered 'in target' if the average SBP of three sitting measurements obtained at 12 months was less than 150 mmHg for the 'usual' group and less than 130 mmHg for the 'intensive' group. Patients assigned to the 'usual' group with SBP less than 130 mmHg were classified as 'in target'.

Statistical analyses

The analyses proceeded in two stages. The first analysis was concerned with examining characteristics of the study participant associated with achieving the assigned target including demographic and lifestyle factors, comorbid conditions, and the severity of hypertension at study entry. The second analysis examined the impact of SPS3 interventions to lower blood pressure, adjusted for the baseline characteristics.

Univariate logistic regression models were used to examine the relationship between the baseline potential predictors and whether or not a participant was in target at the 12-month clinic visit. Each model included the predictor, an indicator variable for the SBP target group, and a term capturing the interaction between the predictor and the SBP target group.

The interaction term assessed the possibility of a differential predictor effect between the two SBP target groups. Predictor effects were examined separately in the two SBP treatment groups in the presence of a significant interaction. The common effect of the predictor was reported in the absence of a significant interaction.

Two separate logistic regression models were fitted to investigate independent predictors of achieving SBP under the upper target limit. The first parsimonious regression model included patient baseline predictors of lowering to target at the 12-month follow-up. All potential predictors were considered in a multivariable analysis using backwards selection. All significant interaction terms identified at the univariate level were also included in the 'full model.' After fitting the full model, the least significant term (identified by the largest *P* value greater than 0.05) was removed. A subsequent model was fit without the term. The process was repeated until no additional terms could be removed. In the second analysis, the independent effect of the variables reflecting SPS3 blood pressure management was examined. All baseline characteristics included in the parsimonious baseline model were permanently included in the model as covariates. Backward selection was again used to determine the most parsimonious model.

Frequencies (percentages) and means (SDs) are presented for categorical and quantitative descriptive statistics, respectively. Estimated predictor effects obtained from logistic regression models are presented as odds ratios and 95% confidence intervals. All tests of significance were two-sided and evaluated at a 0.05 level of significance. SAS version 9.2 (SAS Institute Inc, Cary, North Carolina, USA) was used for all statistical analyses.

RESULTS

There were 1041 participants as of July 2010, whose SBP was above target at study entry and who had completed the 12-month follow-up (see Figure 1). Table 1 summarizes the characteristics of the study sample along with the univariate models of lowering SBP to the assigned target at 12 months. The mean age was 63 years at study entry with 61% men. This sample that included only those above their assigned target at study entry was 17% African American and 44% Hispanic individuals, owing to high recruiting sites in Latin America and including sites in the United States, which serve Hispanic communities. Although over one-third of the sample was diabetic and 38% were obese, only 7.6% reported a history of ischemic heart disease. Their average blood pressure at baseline was 155/83 with 91% of the sample reporting antihypertensive treatment at study entry. The majority of patients were taking at least one antihypertensive medication with around 53% taking two or more agents. The most common classification was an angiotensin-converting enzyme inhibitor (56.4%) followed by a diuretic (38.1%; data not shown).

At the 6-month follow-up, 67.2% were within their assigned target, 63.4% in the 'intensive' group and 75.8% in the 'usual' group. The average SBP in the 'intensive' group was 129 (± 14.4) mmHg and in the 'usual' group was 142.7 (± 13.9) mmHg. This was sustained at the 12-month follow-up with 69% overall in target, 64.8% in the 'intensive' group and 78.2% in the 'usual' group. The average SBP in the 'intensive' group was 128.2 (± 14.2) mmHg and 142.8 (± 15.0) mmHg in the 'usual' group.

Baseline predictors of lowering SBP to assigned target at 12 months

The initial multivariable model examined the predictive value of patient characteristics at study entry for achieving assigned target at the 12-month follow-up. As can be seen in Table 2, those who were classified as Hispanic at baseline were significantly more likely to be in target at 12 months than those classified as white (reference group; OR = 1.49; 95% CI = 1.11–2.02). Treated hypertension was also a significant risk factor for achieving target at 12

months with participants who were receiving antihypertensive medications at study entry much less likely (OR = 0.31; 95% CI = 0.17–0.59) to be in target compared to those who were not receiving antihypertensive medication at study entry.

Secondary Prevention of Small Subcortical Strokes clinical site predictors of lowering SBP to assigned target at 12 months

The contribution of variables related to the SPS3 clinical site management of SBP toward achieving assigned target at 12 months, adjusted for both race and treated hypertension at baseline, can be seen in Table 3. Although baseline treatment for hypertension remained a significant independent predictor (OR = 0.31; 95% CI = 0.16–0.59), Hispanic ethnicity was no longer significant. Those participants who missed appointments were significantly less likely to achieve target than those who attended all study appointments (OR = 0.55; 95% CI = 0.41–0.73). Participants who were managed at larger sites (≥ 20 enrolled participants) were 1.51 times more likely to have blood pressure lowered to target at 12 months compared to those managed at smaller recruiting sites. Participants whose SBP was lowered to the assigned target at the 6-month visit were over two times more likely to be in target at the 12-month visit than those whose SBP was not in target at the 6-month follow-up (OR = 2.39; 95% CI = 1.79–3.19). Finally, those who reported adherence with antihypertensive medications at 12 months were significantly more likely to be in target compared to nonadherent participants (OR = 2.73; 95% CI = 1.51–4.95).

DISCUSSION

These analyses provide several important observations related to blood pressure control in patients with established cerebrovascular disease within the context of an international clinical trial. The results are particularly important, as several studies have shown that lacunar strokes and intracerebral hemorrhage (presumed to have a similar mechanism) have a greater response to blood pressure lowering than other stroke subtypes [7,8]. Most importantly, the findings from this study demonstrate that good blood pressure control can be achieved and this control can be sustained over time. After 6 months of follow-up, almost 70% of participants who were above their assigned target at study entry had achieved target and this control was sustained at the 12-month follow-up. It is important to note that this control rate has been achieved in a sample, which includes a high proportion of diabetics (38%) and African-Americans (17%), subgroups generally believed to be more difficult to control. Further, the effect of the predictor variables did not vary by target group. Although we may be underpowered to detect significant interactions, the lack of interactions may suggest that the effects of predictor variables including treated blood pressure at baseline and adherence to medications and appointments on lowering SBP to target are not different whether we are lowering SBP to less than 130 or less than 150 mmHg.

The aim of this study was to examine predictors of lowering SBP to assigned target at the 12-month follow-up. The initial model was restricted to patient baseline characteristics. Several studies have examined the role of demographic and clinical characteristics in achieving blood pressure control [10–12,20]. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported that better blood pressure control was associated with male sex and the presence of arteriosclerotic cardiovascular disease. Worse control was associated with increasing age, lower initial SBP, and the presence of diabetes, obesity, or renal failure (serum creatinine ≥ 1.5 mg/dl) [10]. The Losartan Intervention for Endpoint (LIFE) study found that previous blood pressure treatment and diabetes were associated with a reduced odds of achieving the LIFE Study target blood pressure of less than 140/90 mmHg [20]. Interestingly, comorbid conditions including diabetes and obesity were not significant risk factors for achieving SBP target in the current study. In the model that included only baseline characteristics, however,

Hispanic participants were significantly more likely to be in target compared to white participants. A recent report examining hypertension treatment and control rates using National Health and Nutrition Examination Survey (NHANES) 1999–2008 data reported lower control rates in Hispanics versus white individuals and recommended that to improve control, Hispanic individuals need to be screened and referred for treatment [21]. The higher percentage of Hispanics in this nested sample of those above target at study entry compared to the ethnicity breakdown in the overall SPS3 study may reflect access to care problems that were ameliorated by participation in the trial. This is consistent with findings from the ALLHAT Trial wherein Hispanic participants were less likely to be controlled at enrollment but within 6–12 months of follow-up, a greater proportion of Hispanics were in target compared with non-Hispanics [22]. The ALLHAT investigators concluded that blood pressure control can be achieved in all patients with equal access to care and the provision of medications at no cost.

Achieving the assigned SBP target at the 6-month follow-up was strongly associated with being in target at the 12 month follow-up visit and underscores the importance of treating to the SBP goal in a timely manner [23]. Investigators for the Valsartan Antihypertensive Long Term Use Evaluation (VALUE) study reported that there was little improvement in blood pressure control that occurred past the 6th month of the study, with good control rates persisting at 2 years (60.5%) [13,24]. Perhaps more importantly, the enhanced efficacy of the amlodipine arm in achieving goal blood pressure early in the trial was associated with better longitudinal outcomes [24,25]. As with the VALUE, most major hypertension treatment trials reported in the past 15 years have demonstrated that the most significant improvements in blood pressure occur in the initial 6 months of study participation with little improvement thereafter [20,26–30]. The only major trial that demonstrated significant improvement in blood pressure control beyond the initial 6 months of the study was the ALLHAT Trial [10]. Blood pressure control (<140/90 mmHg) increased from 55% at 12 months to 66% at 60 months into the study. The reason for continued improvement was attributed to the use of multiple antihypertensive medications currently available today and to the use of tracking and feedback systems to monitor patient progress. Oliveria *et al.* [31] surveyed physicians of hypertensive patients and reported that pharmacological therapy was initiated or changed at only 38% of visits despite documented hypertension for at least 6 months before the patient's most recent visit. The most frequent reason for failure to initiate or intensify therapy was related to satisfaction with the blood pressure value. Within the context of the SPS3 trial, as has been found elsewhere [10,23,32,33], it is most likely that the regular access to care combined with management to a specific target is critical for controlling blood pressure. SPS3 does not mandate the medications to be used but rather sites are provided with a variety of tools to assist with achieving target blood pressure including an algorithm to guide management, a formulary of medications that can be provided to patients free of charge based on need, and regular feedback regarding site performance.

The size of the clinical site was a significant predictor with patients being treated at larger sites (>20 enrolled patients) about 1.5 times more likely to achieve target. Number of enrolled participants may reflect familiarity with the protocol and experience in lowering blood pressure to target in a timely manner. As has been reported with other conditions, increased exposure (volume) to a condition is associated with better outcomes [34]. Adherence to anti-hypertensive medications and study appointments, which may also reflect the experience of the clinical site in their interactions with study participants, were independent predictors of achieving target. As has been previously observed [35–37], patients who reported adherence to their study medications at the 12-month follow-up were almost three times as likely to be in target as nonadherent patients.

A limitation of the analyses as conducted here relates to the definition of 'in target'. This was based on the in-clinic measurement at 12 months and as such reflects one averaged measurement rather than measurements from several clinic visits to define the achievement of target. This may result in some measurement error. However, as it could be in either direction it should not substantially change the results but may decrease their precision.

Results based on NHANES 1999–2008 data reported lower hypertension control rates in those 60 years or older [21]. Age was not associated with achieving good control in this study and this is particularly important in this cohort of stroke survivors related to the relationship between advancing age and increased incidence of stroke. Furthermore, our results suggest that the biologically important variables including diabetes, African–American ethnicity, and obesity that have, in many settings, contributed to the difficulty in achieving blood pressure control, can be overcome with quality care, which includes both access to care and the provision of effective interventions.

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References

1. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991; 265:3255–3264. [PubMed: 2046107]
2. Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP. Systolic blood pressure, arterial rigidity, and risk of stroke: the Framingham Study. *JAMA*. 1981; 245:1225–1229. [PubMed: 7206111]
3. Kubo M, Kiyohara Y, Ninomiya T, Tanizaki Y, Yonemoto K, Doi Y, et al. Decreasing incidence of lacunar vs other types of cerebral infarction in a Japanese population. *Neurology*. 2006; 66:1539–1544. [PubMed: 16717214]
4. Tanizaki Y, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, Shinohara N, et al. Incidence and risk factors for subtypes of cerebral infarction in a general population. The Hisayama Study. *Stroke*. 2000; 31:2616–2622. [PubMed: 11062284]
5. Collins R, Peto R, MacMahon S, Hebert P, Fiebach NH, Eberlein KA, et al. Blood pressure, stroke and coronary heart disease. Part 2, short-term reductions in blood pressure: overview of randomized drug trials in their epidemiological context. *Lancet*. 1990; 335:827–838. [PubMed: 1969567]
6. MacMahon S, Peto R, Cutler J, Collins R, Sorlie P, Neaton J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet*. 1990; 335:765–774. [PubMed: 1969518]
7. Chapman N, Huxley R, Anderson C, Boussier MG, Chalmers J, Colman S, et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS Trial. *Stroke*. 2004; 35:116–121. [PubMed: 14671247]
8. Perry HM Jr, Davis BR, Price TR, Applegate WB, Fields WS, Guralnik JM, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 2000; 284:465–471. [PubMed: 10904510]
9. Qureshi AI, Suri MFK, Guterman LR, Hopkins LN. Ineffective secondary prevention in survivors of cardiovascular events in the US population: report from the Third National Health and Nutrition Examination Survey. *Arch Intern Med*. 2001; 161:1621–1628. [PubMed: 11434794]

10. Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, et al. Success and predictors of blood pressure control in diverse North American settings: the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *J Clin Hypertens*. 2002; 4:393–404.
11. Duggirala MK, Cuddihy RM, Cuddihy M-T, Naessens JM, Cha SS, Mandrekar JN, et al. Predictors of blood pressure control in patients with diabetes and hypertension seen in primary care clinics. *Am J Hypertens*. 2005; 18:833–838. [PubMed: 15925744]
12. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. *N Engl J Med*. 2001; 345:479–486. [PubMed: 11519501]
13. Julius S, Kjeldsen SE, Brunner H, Hansson L, Platt F, Ekman S, et al. VALUE trial: Long-term blood pressure trends in 13 449 patients with hypertension and high cardiovascular risk. *Am J Hypertens*. 2003; 16:544–548. [PubMed: 12850387]
14. Kjeldsen SE, Dahlof B, Devereux RB, Julius S, de Faire U, Fyhrquist F, et al. Lowering of blood pressure and predictors of response in patients with left ventricular hypertrophy: the LIFE study. *Am J Hypertens*. 2000; 13:899–906. [PubMed: 10950398]
15. Benavente OR, White CL, Pearce L, Pergola P, Roldan A, Benavente M-F, et al. The Secondary Prevention of Small Subcortical Strokes (SPS3) study. *Int J Stroke*. 2011; 6:164–175. [PubMed: 21371282]
16. Pergola PE, White CL, Graves JW, Coffey CS, Tonarelli SB, Hart RG, et al. Reliability and validity of blood pressure measurement in the Secondary Prevention of Small Subcortical Strokes study. *Blood Press Monitoring*. 2007; 12:1–8.
17. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JLJ, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003; 289:2560–2571. [PubMed: 12748199]
18. Ling J, Ohara Y, Orime Y, Noon GP, Takatani S. Clinical evaluation of the oscillometric blood pressure monitor in adults and children based on the 1992 AAMI SP-10 standards. *J Clin Monit*. 1995; 11:123–130. [PubMed: 7760085]
19. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *JAMA*. 1999; 282:1737–1744. [PubMed: 10568646]
20. Lindholm LH, Ibsen H, Dahlof B, Devereux RB, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002; 359:1004. [PubMed: 11937179]
21. Egan BM, Zhao Y, Axon RN. US Trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA*. 2010; 303:2043–2050. [PubMed: 20501926]
22. Margolis KL, Piller LB, Ford CE, Henriquez MA, Cushman WC, Einhorn PT, et al. Blood pressure control in Hispanics in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension*. 2007; 50:854–861. [PubMed: 17846352]
23. Cushman WC, Basile J. Achieving blood pressure goals: why aren't we? *J Clin Hypertens*. 2006; 8:865–872.
24. Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004; 363:2022–2031. [PubMed: 15207952]
25. Weber MA, Julius S, Kjeldsen SE, Brunner HR, Ekman S, Hansson L, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet*. 2004; 363:2049–2051. [PubMed: 15207957]
26. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005; 366:895–906. [PubMed: 16154016]
27. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the

- Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998; 351:1755–1762. [PubMed: 9635947]
28. Pepine CJ, Handberg EM, Cooper-DeHoff RM, Marks RG, Kowey P, Messerli FH, et al. A calcium antagonist vs a noncalcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003; 290:2805–2816. [PubMed: 14657064]
 29. Wing LMH, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GLR, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003; 348:583–592. [PubMed: 12584366]
 30. Wright JT Jr, Agodoa L, Contreras G, Greene T, Douglas JG, Lash J, et al. Successful blood pressure control in the African American Study of Kidney Disease and Hypertension. *Arch Intern Med*. 2002; 162:1636–1643. [PubMed: 12123409]
 31. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM. Physician-related barriers to the effective management of uncontrolled hypertension. *Arch Intern Med*. 2002; 162:413–420. [PubMed: 11863473]
 32. Fagard RH, Van Den Enden M, Leeman M, Warling X. Survey on treatment of hypertension and implementation of World Health Organization/International Society of Hypertension risk stratification in primary care in Belgium. *J Hypertens*. 2002; 20:1297–1302. [PubMed: 12131525]
 33. Godwin M, Birtwhistle R, Seguin R, Lam M, Casson I, Delva D, et al. Effectiveness of a protocol-based strategy for achieving better blood pressure control in general practice. *Family Pract*. 2010; 27:55–61.
 34. Corsino L, Yancy WS, Samsa GP, Dolor RJ, Pollak KI, Lin PH, et al. Physician characteristics as predictors of blood pressure control in patients enrolled in the Hypertension Improvement Project (HIP). *J Clin Hypertens*. 2011; 13:106–111.
 35. Fung V, Huang J, Brand R, Newhouse JP, Hsu J. Hypertension treatment in a medicare population: adherence and systolic blood pressure control. *Clin Therapeut*. 2007; 29:972–984.
 36. Lindholm LH. The problem of uncontrolled hypertension. *J Hum Hypertens*. 2002; 16:S3–S8. [PubMed: 12140722]
 37. Mant J, McManus RJ. Does it matter whether patients take their antihypertensive medication as prescribed? The complex relationship between adherence and blood pressure control. *J Hum Hypertens*. 2006; 20:551–553. [PubMed: 16710290]

Abbreviation

SPS3 Secondary Prevention of Small Subcortical Strokes Study

FIGURE 1.

Flow of study participants. *, 533 were 'in target' at both the 6-month and 12-month visits (331 in the 'intensive' group and 202 in the 'usual' group). 'In target': SBP below upper limit of the randomly assigned target group ('intensive' group <130 mmHg; 'usual' group <150 mmHg).

TABLE 1

Baseline characteristics of Secondary Prevention of Small Subcortical Strokes participants above target at trial entry

	<i>n</i> = 1041	Univariate model of achieving 12-month target OR (95% CI)
Mean age (SD) at entry	63.3 (10.6)	1.00 (0.77–1.30) ^a
Male sex	631 (60.6%)	1.20 (0.92–1.57)
Ethnicity		
White	390 (37.5%)	Ref
African-American	175 (16.8%)	0.87 (0.60–1.26)
Hispanic	454 (43.6%)	1.49 (1.11–2.01)
Other	22 (2.1%)	0.61 (0.26–1.46)
Smoking status		
Never	424 (40.7%)	Ref
Former	427 (41.0%)	1.13 (0.84–1.50)
Current	190 (18.3%)	1.27 (0.88–1.86)
Alcohol (more than 7 drinks/week)	123 (11.8%)	0.82 (0.55–1.21)
Mean days exercising per week (SD)	3.0 (2.9)	1.02 (0.98–1.07)
BMI >30	399 (38.3%)	0.86 (0.66–1.12)
Depression (diagnosed in first 3 months)	130 (12.5%)	
130–149 target group		0.89 (0.46–1.70)
<130 target group		1.46 (0.89–2.38)
Mean GFR (SD)	82.2 (23.5)	1.00 (1.00–1.01)
Diabetes (diagnosed in first 3 months)	390 (37.5%)	0.78 (0.60–1.02)
Ischemic heart disease	79 (7.6%)	0.91 (0.56–1.48)
Mean blood pressure (SD) at study entry	155/83 (17/10)	0.92 (0.85–0.99) ^b
Treated hypertension at study entry	949 (91.2%)	0.31 (0.17–0.57)
Isolated systolic hypertension	594 (57.1%)	0.76 (0.58–1.00)

CI, confidence interval; GFR, glomerular filtration rate; OR, odds ratio.

^a OR for age ≥ 65 at baseline.

^b OR per a 10mmHg increase in SBP at baseline.

TABLE 2

Baseline predictors of achieving SBP target at 12 months

Predictor	Adjusted OR (95% CI)
Ethnicity	
White	Ref
African-American	0.91 (0.62–1.32)
Hispanic	1.49 (1.11–2.02)
Other	0.61 (0.26–1.46)
Treated hypertension at baseline	0.31 (0.17–0.59)

CI, confidence interval; OR, odds ratio.

TABLE 3

Baseline and clinical site predictors of achieving SBP target at 12 months

Predictor	Adjusted OR (95% CI) ^a
Treated hypertension at baseline	0.31 (0.16–0.59)
Missed appointments during first 12 months	0.55 (0.41–0.73)
Large site	1.51 (1.03–2.20)
SBP in target at 6 months	2.39 (1.79–3.19)
Medication adherence at 12-month follow-up	2.73 (1.51–4.95)

^a Adjusted for ethnicity.