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Effects of Blood Pressure Targets in Patients with Recent Lacunar Stroke

The SPS3 Investigators

Abstract

BACKGROUND—Lowering blood pressure (BP) prevents stroke, however optimal target levels of blood reduction to prevent stroke recurrence are lacking. We hypothesized that targeting systolic BP of <130 mmHg would reduce stroke recurrence in patients with recent lacunar stroke.

METHODS—The Secondary Prevention of Small Subcortical Strokes (SPS3) was a multi-center international trial, involving 3020 patients with recent symptomatic MRI-defined lacunar infarcts randomized to two target levels of systolic BP: a) higher group 130–149 mm Hg vs. b) lower group <130 mm Hg, and followed for a mean of 3.7 years. The primary outcome was all recurrent stroke (including ischemic strokes and intracranial hemorrhages). The study is registered, NCT 00059306.

FINDINGS—Mean participant age was 63 years; after 1 year mean systolic BP was 138 mm Hg (95% CI 137 to 139) in the higher group and 127 mm Hg (95% CI, 126 to 128) in the lower group. At last study visit, the difference in systolic BP between groups averaged 11 mm Hg (±SD 16). The annualized rate of recurrent stroke in the higher target group was 2.77% (n=152) compared with 2.25% (n=125) in the lower target group (HR 0.81, 95% CI 0.64, 1.03, p-value 0.08). Similar trends were observed for reductions in disabling/fatal stroke (HR 0.81, 95%CI 0.53, 1.23, p-value 0.32) and in the composite outcome of stroke, myocardial infarct or vascular death (HR 0.84, 95%CI 0.68,1.01, p-value 0.10). Intracerebral hemorrhage was reduced by 63% in those assigned to the lower target group (HR 0.37 95% CI, 0.14, 0.89, p-value 0.03). Serious complications of BP lowering were in frequent, and not significantly different in frequency between groups.

INTERPRETATION—In patients with recent lacunar stroke, targeting asystolic BP of< 130 mm Hg did not significantly reduce all stroke, but markedly reduced intracerebral hemorrhage. The lower target was safe and well tolerated.

INTRODUCTION

Hypertension is the single most powerful and prevalent risk factor for stroke, particularly for stroke associated with cerebral small vessel disease. Blood pressure (BP) reduction is the most effective intervention to prevent stroke.[1–3]

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Small subcortical brain infarcts, commonly known as lacunar strokes, comprise about 25% of ischemic strokes.[4, 5] Most result from intrinsic disease of the small penetrating arteries. Despite their frequency and importance, no previous randomized trials have focused on secondary prevention of stroke in patients with MRI-defined lacunar stroke. Optimal target levels of BP control to prevent stroke recurrence in patients with cerebral small artery disease are lacking.[6]

The SPS3 trial tested two randomized interventions in a 2-by-2 factorial design in patients with recent symptomatic MRI-confirmed lacunar stroke: clopidogrel and aspirin vs. aspirin alone and two target levels of systolic BP. The results of the antiplatelet component have been published previously.[7] The results of the BP target component are presented here.

METHODS

Details of the rationale, study design and participant characteristics of SPS3 have been described elsewhere.[8, 9] In brief, SPS3 was a randomized, multicenter clinical trial conducted in 81 clinical centers in North America, Latin America, and Spain. Patients aged 30 years or older with a recent (≤180 days) symptomatic lacunar stroke who were without surgically-amenable ipsilateral carotid artery stenosis or major-risk cardioembolic sources were eligible and randomized, in a 2-by-2 factorial design, to both the antiplatelet intervention (double-blind) and to one of two target levels of systolic BP control; higher(130–149 mmHg) vs. lower (<130 mmHg). The blood pressure trial was open label using the PROBE study design.[10] To avoid BP lowering in proximity to an acute stroke, participants were randomized at least two weeks after the qualifying stroke. Participants with a clinical lacunar syndrome were required to meet MRI criteria. Main exclusion criteria included disabling stroke (modified Rankin Scale ≥4), previous intracranial hemorrhage (excluding traumatic), or cortical ischemic stroke.[7, 8] Participation required written informed consent and approval by local human research subjects committees. Randomization assignments, stratified by clinical center and baseline hypertensive status, were generated using a permuted-block design (variable block size) and protected from previewing.

Blood pressure management

Both normotensive and hypertensive patients were eligible for SPS3. Hypertension status was determined at study entry by BP measurements done at two consecutive visits prior to randomization. BP was measured three times at each visit, and the average of these three measurements was used to determine hypertensive status; BP medications were not discontinued.[8, 11]. Patients were classified as hypertensive if either or both were present: i) average BP from the two consecutive SPS3 visits was ≥140 mmHg systolic or ≥90 mmHg diastolic; ii) definite history of hypertension prior to the qualifying stroke and on antihypertensive medication at the time of visit. Following randomization, all patients were seen at least monthly for the first three months and on a quarterly basis there after for measurement of BP and adjustment of medications to reach assigned target. Participants who were not within their assigned target were seen at least monthly for blood pressure measurement and medication adjustments until their blood pressure was within the assigned target for two consecutive visits, after which they continued with the quarterly schedule. If at any subsequent quarterly visit their systolic blood pressure fell outside their assigned target, they returned for a blood pressure visit within one month. If that measurement was within the assigned target, they resumed the quarterly schedule. Sites were provided with an automated electronic device, the Colin 8800C.[11] Blood pressure management was overseen at the clinical sites by a physician with special expertise in blood pressure control. If patients assigned to the higher target (130–149 mmHg) group were below target and on blood pressure lowering medications, the protocol required that antihypertensive medications be discontinued or their dose reduced unless prescribed for reasons other than blood pressure

control. Those who were below target in the higher group and on no antihypertensive medications continued to be followed quarterly and if their systolic blood pressure increased, they were managed according their originally assigned target. Patients were designated “inactive” if they or their primary care physicians refused to have their blood pressure titrated to their assigned target per protocol. Patients were designated “failure to achieve assigned target” in the event of medical reasons that their blood pressure could not be managed into their assigned target or for patients who suffered intolerable side-effects of anti-hypertensive drugs, despite trying multiple agents. All participants were followed to a common end-study date, irrespective of active/inactive status or failing to achieve their target.

Antihypertensive medications were provided to study participants as prescribed by their local study physician. The medications available in the study formulary included at least one drug from major classes of antihypertensive medications, obtained and distributed by the Cooperative Studies Program Clinical Research Coordinating Center, Drug Distribution Center in Albuquerque, NM.

Outcome Events

Ischemic stroke was clinically defined as a focal neurological deficit persisting for greater than 24 hours, with absence of hemorrhage documented by neuro-imaging. Intracranial hemorrhages included intracerebral, subdural/epidural and subarachnoid locations as defined by neuro-imaging. Disabling strokes were those with modified Rankin scores of ≥3 assessed after 3 to 6 months due to recurrent stroke. Strokes were counted as fatal if death occurred within 30 days or if death after 30 days was attributable to the stroke. Secondary outcomes included acute myocardial infarct, defined by standard criteria consisting of a compatible clinical history combined with ECG and/or cardiac enzyme changes and requiring acute hospitalization and death was classified as vascular, non-vascular, or unknown. Safety outcomes were serious complications of hypotension and those related to the use of BP medications.

All reported efficacy outcomes were confirmed by a central adjudication committee that was unaware of treatment assignment.

Sample size estimates and statistical analysis

The initial sample size of 2500 patients was calculated assuming an average follow-up of three years, an estimated 3-year recurrent stroke rate of 21%, a 25% relative risk reduction in stroke by intensive BP control, a type I error of 0.05, and a 90% power. Sample size re-estimation, performed midway through the trial to assess power based on the currently observed overall event rate in the study, resulted in an increase in the sample size from 2500 to 3000 patients. Details of the sample size estimation were described elsewhere.[12]

We hypothesized that assignment to the lower target systolic BP would result in a reduction in stroke recurrence (the combination of ischemic strokes and all intracranial hemorrhages, including subdural hematomas). In addition, there were two pre-specified subgroup analyses: a) excluding participants who did not meet criteria for hypertension at entry, i.e. those who had systolic BP of <130mmHg while not taking BP lowering medications. These patients were randomized, but they were not treated with antihypertensive medications unless BP exceeded the assigned target range during follow-up; and b) censoring follow-up for the initial 6 months following randomization justified by maximal separation of the achieved BP requiring an average of 6 months of medication titration. Participants, who did not die or withdraw from the study during the first 6 months irrespective of whether or not they had an event during this time, were included.

The primary analyses used standard time-to-event methods with each treatment arm assessed using the log-rank test and Cox proportional hazards models to compute hazard ratios. Time to event was computed as time to first event if multiple events of the same type occurred, and for the composite endpoint of stroke, myocardial infarction, or vascular death. Patients not experiencing events were censored at the time of termination of study participation or death. The proportional hazards assumption was verified by assessing the interaction between time and the BP intervention group. Interactions between covariates and blood pressure intervention group were evaluated with the use of Cox models to determine if effect of intervention differed by specific subgroups. All analyses were based on the intention-to-treat principle.

The trial was monitored by an independent data and safety monitoring committee selected by the sponsor.

RESULTS

Between 2003 and 2011, 3020 participants were entered from North America (n=1960; 65%), Latin America (n=694; 23%) and Spain (n=366; 12%) and followed for a mean of 3.7 (range 0–8.6; ±SD 2) years(Supplementary materials. Figure 1). The mean participant age was 63 (±SD11) years, 63% were men, and history of hypertension, diabetes, and current tobacco smoking were present in 75%, 37% and 20%, respectively(Table 1). The median time from qualifying stroke to randomization was 62 days. At study entry, the average systolic BP was 144mm Hg (95%, CI143 to 145) in the higher group and 142 mm Hg (95%, CI 141 to 143) in the lower group with the same mean number of BP medications used by both groups (1.7, ±SD1.2). Of 3020 participants, 314 were normotensive at entry.

Permanent discontinuation of BP therapy occurred in17% of the higher group participants and 16% of the lower group (p=0.20). Three percent of participants were lost to follow-up, with an additional number ending follow-up early for other reasons (8% withdrew consent, 5% site closure, 0.4% physician request, 2% other reasons).

Blood pressure management

At one year of follow up the achieved average systolic BPs were 138 mm Hg (95%, CI 137 to 139) and 127 mm Hg (95% CI, 126 to 128) for the higher and lower groups respectively with 75% of the higher group and 65% of the lower being in assigned target range. At the last study visit, the average systolic BP difference between the two groups was 11 mm Hg (±SD 16)(Figure 1). Those assigned to the lower target averaged a greater number of antihypertensive drugs (Table 1). The mean number of medications during the course of the study averaged 1.8 for the higher target vs. 2.4 for the lower target. (Figure 1).

Outcomes

During follow-up, 277 first recurrent strokes occurred. Of first recurrent strokes, 86% (n=243) were ischemic and 14% (n=34) were intracranial hemorrhages. The annualized rate of recurrent stroke among those assigned to the higher target was 2.77% as compared with 2.25% in the lower target group (HR 0.81, 95% CI 0.64, 1.03 p-value 0.08) (Table 2, Figure 2). There was no heterogeneity of treatment effect on the primary outcome according to age, sex, or among the pre-specified subgroups (Figure 3). Non-significant trends of similar magnitude for higher vs. lower target BP were seen for disabling/fatal stroke (HR 0.81, 95%CI 0.53, 1.23 p-value 0.32) and for the composite outcome of stroke, myocardial infarct or vascular death (HR 0.84, 95%CI 0.68,1.01 p-value 0.10) The risk of intracerebral hemorrhage was significantly lower in those assigned to the lower target group (6 vs. 16

events) (HR 0.37 95% CI; 0.15, 0.95 p-value 0.03), while mortality rates were nearly identical. (Table 2).

Subgroup analysis restricted to the 2706 participants classified as hypertensive at study entry showed a 20% reduction in recurrent stroke(HR 0.80, 95% CI 0.62, 1.02, p-value 0.07) (Figure 4). Censoring the first 6 months of follow up in all participants showed a nearly identical hazard ratio for recurrent stroke(HR 0.81, 95% CI 0.62, 1.06). BP lowering offered similar effects on stroke recurrence irrespective of stroke sub-type. The effect on lacunar infarcts, comprising 71% of the recurrent ischemic strokes was a 13% reduction (HR 0.87 (95% CI: 0.62, 1.22 p-value 0.41). There was no interaction between the antiplatelet and BP target interventions (p-value 0.46)

Adverse events

Serious complications of BP lowering were infrequent (<2%) but more often seen among those assigned to the lower target (23 vs. 15 events) (HR 1.53, 95% CI 0.80–2.93) (Table 3). Syncope was the most common (0.5% vs. 0.8% among those assigned lower vs. higher targets, respectively, p-value 0.14), but did not result in permanent sequelae. Neither association was statistically significant. Symptoms potentially related to BP reduction reported at each follow up were similar in both groups (Table 3).

DISCUSSION

Lowering systolic BP to a target of <130mmHg in patients with recent lacunar stroke resulted in statistically non-significant trends toward reductions in all stroke, disabling/fatal stroke, and major vascular events. These effects were of clinically important magnitude, and assignment to the lower target was associated with few serious side-effects. The relative effects of assignment to the lower target were consistent among major participant subgroups, including subjects with diabetes mellitus, Hispanics, and regardless of systolic BP at entry (Figure 3). Excluding patients who were normotensive at entry (10% of participants), recurrent stroke was reduced by 20% (p-value 0.07) among those assigned to the lower BP target relative to those in the higher BP target group (Figure 4).

It is a general construct that “lower is better” for chronic BP management after stroke, but optimal clinical practice requires that benefit and disutility associated with specific targets be defined. Results of PROGRESS showed that lowering BP in stroke survivors was associated with an important reduction of 28% in stroke recurrence. The mean achieved systolic BP at the end of the study was 138 mmHg, but the optimal target of BP control was not established.[2] Similar to the recent ACCORD trial,[13] the SPS3 trial explored the efficacy and safety of targeting systolic BPs below 130 mmHg and, uniquely, in patients with MRI-defined lacunar stroke attributed to small vessel disease.

The results of the SPS3 BP target trial are best considered in the context of prior trials of long-term BP lowering in patients with prior brain ischemia[1–3, 14–19](Supplementary material Table 1). While SPS3 tested target levels (not specific antihypertensive agents) and explored BP lowering in patients with well-defined ischemic stroke subtype, the magnitude of the reduction in stroke observed in SPS3, although not statistically significant, is strongly supported by these previous trials testing BP lowering after stroke.[1–3]

The trial protocol was based on achieving the assigned target of systolic BP, and the use of specific antihypertensive agents was not specified. Those assigned to the lower target used an average of 2.4 antihypertensive medications, with a different distribution of medication categories between groups (Table 1). The mean achieved difference of systolic BP over the course of the trial was 11mmHg; based on previous studies, it was anticipated that this

difference would result in about a 30% reduction in recurrent stroke. The observed reduction of 19% (95% CI −3, 36%) was smaller than the hypothesized 25%. This could be due to chance or the specific patient population tested.[2, 20] While the confidence interval for the observed 19% reduction (95% CI −3% to 36%) includes the hypothesized 25% reduction, it also spans 0% and thus is not statistically significant. Intracerebral hemorrhage was reduced by 63%, consistent with the known sensitivity of this stroke subtype to strict blood pressure control. [15] The intracerebral hemorrhage results indicate that the NNT to prevent one intracerebral hemorrhage at four years (about the average follow-up in SPS3) is 175.

The SPS3 blood pressure trial had limitations. First, the observed stroke rate was about 50% of anticipated. The relatively low stroke recurrence rate is similar to that seen in recent trials for prevention of recurrent stroke; this may be the result of good blood pressure control in both treatment arms, the frequent use of statins, and high adherence to antiplatelet therapy.[21–23] Second, the assignment to BP targets was not blinded which could potentially have introduced bias. However stroke endpoints were confirmed by a blinded central adjudication committee, as commonly done in large hypertension trials.[24] Third, while the study tested treatment targets and not the effect of specific blood pressure agents, it would be difficult to exclude if any of the results are due to mechanisms beyond the effects of lowering BP. Finally, not all patients reached their assigned target at any point during follow-up (4.6% in the higher and 4.9% in the lower group), similar to what was observed in other trials testing blood pressure targets and reflecting clinical realities of blood pressure management.[13, 24] A major strength of the SPS3 trial is that BP lowering was tested in a well-defined and homogenous cohort of stroke patients.

In conclusion, the results of the SPS3 BP trial, although not showing a statistically significant reduction, are congruent with findings of prior trials of BP lowering after stroke and support a treatment target of systolic BP <130mmHg for most patients with recent lacunar stroke. Whether these results from a cohort with recent lacunar strokes due mainly to cerebral small vessel disease apply to patients with strokes from other mechanisms requires additional trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Peru, 1 site(n =186)

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Ecuador, 1site(n=171

Hospital-Clínica-Kennedy, Guayaquil: Oscardel Brutto, MD, Rocio Santibáñez, MD, Joffre Lara, MD, Mauricio Zambrano (171)

Mexico, 4 sites (n = 165)

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Chile,2 sites(n =127)

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Argentina, 5sites(n =45)

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Spain, 10sites(n =366)

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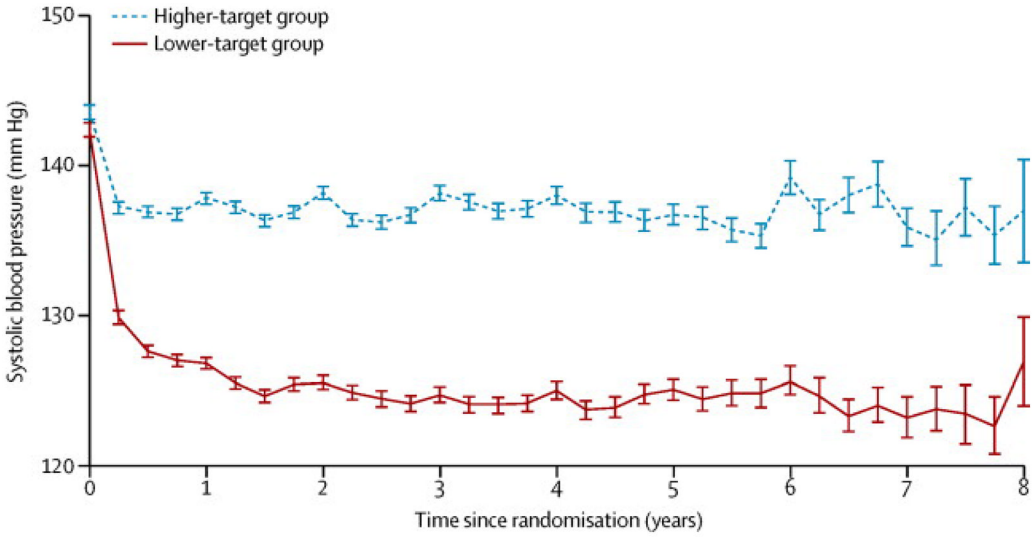

Figure 1.
Systolic blood pressure by treatment group.

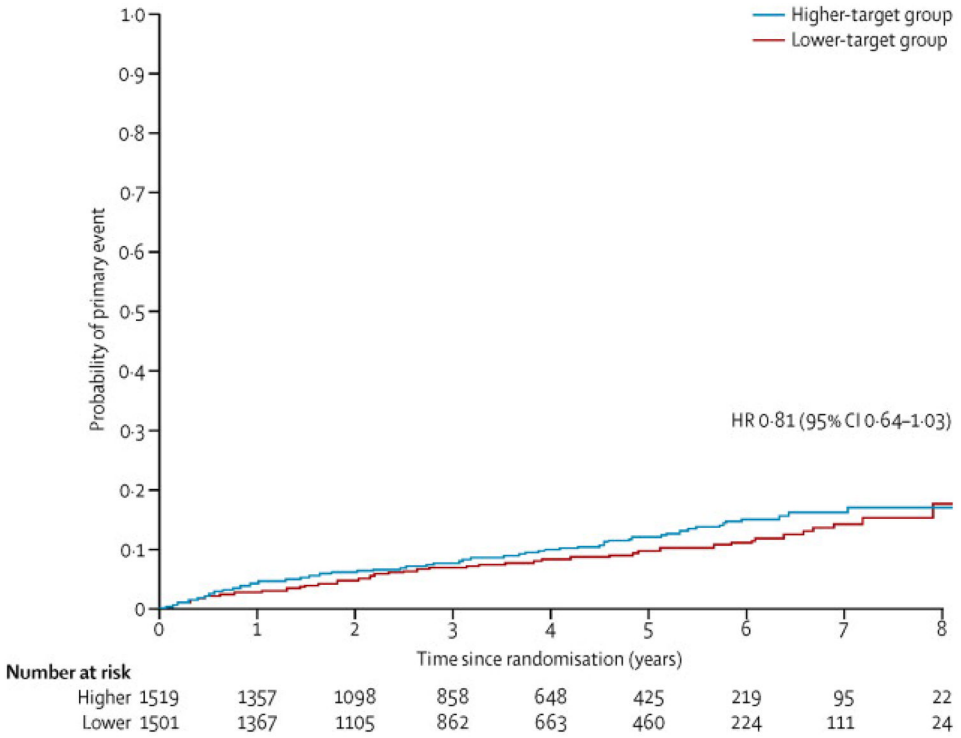

Figure 2.
Probability of patients experiencing a primary event by time after randomization. Primary events were all recurrent strokes, myocardial infarction, or vascular death. HR=hazard ratio.

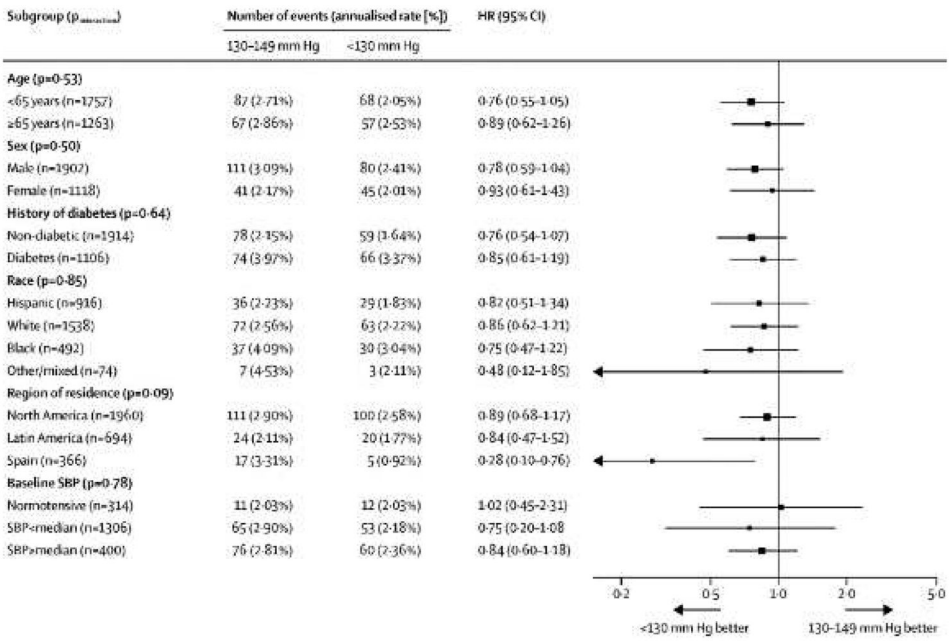

Figure 3.
Primary outcome assessed by demographic and clinical subgroups. HR=hazard ratio. SBP=systolic blood pressure.

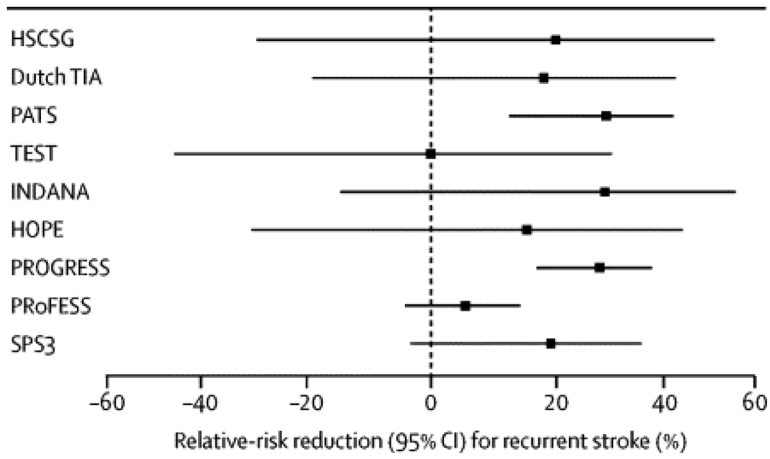

Figure 4.
Randomised trials of long-term blood-pressure lowering for secondary stroke prevention.

Table 1

Patient characteristics

	Higher Target 130–149 mmHg (N=1519)	Lower Target ≤130 mmHg (N=1501)
Mean age, years	63 (11)	63 (11)
Men, %	65	61
Blood pressure at entry, mean		
-Systolic	144 (19)	142 (19)
-Diastolic	79 (11)	78 (10)
Body-mass index	29 (8)	29 (6)
History of hypertension, %	75	75
Diabetes, %	36	37
Ischemic heart disease, %	11	10
Prior clinical stroke or TIA, %	14	16
Current tobacco smoker, %	20	21
Qualifying event		
- ischemic stroke, %	99	98
- TIA, %	1	2
Ethnicity/Race		
-White, %	50	52
- Hispanic, %	31	30
- Black, %	17	16
- Other, %	3	2
Region		
- North America, %	65	65
- Latin America, %	23	23
- Spain, %	12	12
Anti-hypertensive medications at study entry		
Mean number	17 (1.2)	1.7 (1.2)
Anti-hypertensive medications at 1 yr^^		
Mean number	1.8 (1.4)	2.4 (1.3)

	Higher Target 130–149 mmHg (N=1519)	Lower Target ≤130 mmHg (N=1501)
-thiazides, %	43	58
-ACEI/ARB, %	63	80
-Calcium Channel Blockers, %	30	43
-Beta blockers, %	25	31
-Other, %	9	11
Anti-hypertensive medication @ last visit**		
Mean number	1.8 (1.4)	2.4 (1.4)
-thiazides, %	38	54
-ACEI/ARB, %	60	78
-Calcium Channel Blockers, %	39	43
-Beta blockers, %	28	35
-Other, %	11	14
Statins during follow up, %	84	85

^^** At one year mean number and all categories p<0.0001, except beta blockers (p=0.0008), and other, p=0.051. At last visit: mean number and all categories p<0.0001, except other p=0.042.

Table 2

Primary Outcomes

	Higher Target (n=1519)		Lower Target (n=1501)		HR (95% CI)	*p* value
	N	**Rate (%/pt-yr)**	**N**	**Rate (%/pt-yr)**		
All stroke (ischemic & hemorrhage)	152	2.77	125	2.25	0.81 (0.64, 1.03)	0.08
- ischemic stroke/unknown*	131	2.4	112	2.0	0.84 (0.66, 1.09)	0.19
- intracranial hemorrhage	21**	0.38	13^^	0.23	0.61 (0.31, 1.22)	0.16
- intracerebral	16	0.29	6	0.11	0.37 (0.15,095)	0.03
- subdural/epidural	5	0.091	6	0.11	1.18 (0.36,3.88)	0.78
- other	2	0.036	4	0.072	1.97 (0.36, 10.74)	0.43
Disabling/fatal stroke*	49	0.89	40	0.72	0.81 (0.53, 1.23)	0.32
Myocardial infarct	40	0.70	36	0.62	0.88 (0.56, 1.39)	0.59
Major vascular events**	188	3.46	160	2.91	0.84 (0.68, 1.04)	0.10
Deaths (all)	101	1.74	106	1.80	1.03 (0.79, 1.35)	0.82
-Vascular death	41	0.70	36	0.61	0.86 (0.55, 1.35)	0.52
-Non-vascular	35	0.60	40	0.68	1.12 (0.71, 1.76)	0.62
-Uncertain	25	0.43	30	0.51	1.18 (0.69, 2.00)	0.55

** 1 classified as both intracerebral and other; 1 classified as both intracerebral and subdural/epidural

^^ 1 classified as both intracerebral and subdural/epidural; 2 classified as both intracerebral and other

Table 3

Safety outcomes

	Higher Target (N =1519)		Lower Target (N =1501)		HR (95%CI)	*p* value
	N	**Rate (%/pt-yr)**	**N**	**Rate (%/pt-yr)**		
Serious complications of hypotension	15	0.26	23	0.40	1.53 (0.80, 2.93)	0.20
-orthostatic syncope	5	0.087	11	0.19	2.18 (0.76, 6.27)	0.14
-stroke associated with hypotension	1	0.017	2	0.034	2.00 (0.18, 22.09)	0.57
-MI associated with hypotension	0	N/A	0	N/A	N/A	N/A
-fall with injury secondary to hypotension	0	0.00	3	0.052	N/A	N/A
-other	11	0.19	9	0.15	0.82 (0.34, 1.97)	0.65
Serious complications related to antihypertensive medications	0	0.00	1*	0.017	N/A	N/A
Side effects related to blood pressure management (ever reported), %	**N**	**%**	**N**	**%**	**OR (95% CI)**	***p* value**
-unsteadiness when standing	355	24	375	26	1.09 (0.92, 1.29)	0.31
-blurred vision when standing	103	7	85	6	0.82 (0.61, 1.11)	0.19
-dizziness when standing up	304	21	324	22	1.10 (0.92, 1.31)	0.30
-lightheadedness when standing	236	16	222	15	0.94 (0.77, 1.15)	0.54
-palpitations when standing	24	0.41	21	0.36	0.86 (0.48, 1.55)	0.62

* Bradycardia requiring hospitalization.