Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial

*The SPS3 Study Group**

Summary

Background Lowering of blood pressure prevents stroke but optimum target levels to prevent recurrent stroke are unknown. We investigated the effects of different blood-pressure targets on the rate of recurrent stroke in patients with recent lacunar stroke.

Methods In this randomised open-label trial, eligible patients lived in North America, Latin America, and Spain and had recent, MRI-defined symptomatic lacunar infarctions. Patients were recruited between March, 2003, and April, 2011, and randomly assigned, according to a two-by-two multifactorial design, to a systolic-blood-pressure target of 130–149 mm Hg or less than 130 mm Hg. The primary endpoint was reduction in all stroke (including ischaemic strokes and intracranial haemorrhages). Analysis was done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT 00059306.

Findings 3020 enrolled patients, 1519 in the higher-target group and 1501 in the lower-target group, were followed up for a mean of 3·7 (SD 2·0) years. Mean age was 63 (SD 11) years. After 1 year, mean systolic blood pressure was 138 mm Hg (95% CI 137–139) in the higher-target group and 127 mm Hg (95% CI 126–128) in the lower-target group. Non-significant rate reductions were seen for all stroke (hazard ratio 0·81, 95% CI 0·64–1·03, p=0·08), disabling or fatal stroke (0·81, 0·53–1·23, p=0·32), and the composite outcome of myocardial infarction or vascular death (0·84, 0·68–1·04, p=0·32) with the lower target. The rate of intracerebral haemorrhage was reduced significantly (0·37, 0·15–0·95, p=0·03). Treatment-related serious adverse events were infrequent.

Interpretation Although the reduction in stroke was not significant, our results support that in patients with recent lacunar stroke, the use of a systolic-blood-pressure target of less than 130 mm Hg is likely to be beneficial.

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Introduction

Hypertension is the most relevant and prevalent risk factor for stroke, particularly for stroke associated with cerebral small-vessel disease. Reduction in blood pressure is the most effective intervention to prevent stroke.[1–3]

Small subcortical brain infarcts, commonly known as lacunar strokes, comprise about 25% of ischaemic strokes.[4,5] Most result from disease of the small penetrating arteries. Despite the frequency and importance of these strokes, randomised trials have not focused on prevention of recurrent stroke in patients with MRI-defined lacunar stroke. Whether there are optimum blood-pressure targets to prevent stroke recurrence in patients with cerebral small-artery disease is unknown.[6]

In the Secondary Prevention of Small Subcortical Strokes (SPS3) trial we tested two interventions in patients with recent, symptomatic, MRI-confirmed lacunar stroke: two antiplatelet regimens and two target ranges of systolic blood pressure. The results of the antiplatelet component have been published previously.[7] We present here the results of the blood-pressure component of the trial, in which we tested the hypothesis that assignment to a lower target range for systolic blood pressure would lessen the rate of stroke recurrence compared with a higher target range.

Methods

Patients

Details of the rationale, study design, and characteristics of the participants in SPS3 have been described elsewhere.[8,9] Briefly, SPS3 was a randomised, multicentre, clinical trial undertaken in 81 centres in North America, Latin America, and Spain between March, 2003, and April, 2011. Eligible patients were aged 30 years or older, were normotensive or hypertensive, had had a recent (within 180 days), symptomatic, MRI-confirmed lacunar stroke, and were without surgically amenable ipsilateral carotid artery stenosis or high-risk cardioembolic sources. Main exclusion criteria included disabling stroke (modified Rankin score of 4 or higher), previous intracranial haemorrhage from non-traumatic causes, or cortical ischaemic stroke.[7,8] Participation required written informed consent and approval was provided by local ethics committees for human research.

Randomisation and masking

Patients were randomised, according to a two-by-two factorial design, to two blood-pressure-control groups with targets of 130–149 mm Hg or less than 130 mm Hg.[10] Treatment was open label. To avoid lowering of blood pressure soon after an acute stroke, participants were randomised at least 2 weeks after the index stroke.

Randomisation was stratified by clinical centre and baseline hypertensive status. The schedule was computer generated with a permuted-block design (variable block size). Treatment assignments were stored electronically on the study servers at the SPS3 statistical centre, University of Alabama at Birmingham, AL, USA, as well as locally for each study site on an SPS3-designated computer. Upon patients' eligibility being established, study coordinators ransomised patients via their data entry systems.

	Higher-target group (n=1519)	Lower-target group (n=1501)
Age (years)	63 (10·8)	63 (10·7)
Men	990 (65%)	912 (61%)
Blood pressure at entry (mm Hg)		
Systolic	144 (19)	142 (19)
Diastolic	79 (11)	78 (10)
Body-mass index (kg/m²)	29·2 (7·5)	29·0 (6·1)
History of hypertension	1137 (75%)	1127 (75%)
Diabetes mellitus	553 (36%)	553 (37%)
Ischaemic heart disease	173 (11%)	144 (10%)
Previous clinical stroke or TIA	211 (14%)	237 (16%)
Current tobacco smoker	308 (20%)	309 (21%)
Qualifying event		
Ischaemic stroke	1506 (99%)	1473 (98%)
TIA	13 (1%)	28 (2%)
Ethnic origin		
White	760 (50%)	778 (52%)
Hispanic	468 (31%)	448 (30%)
Black	251 (17%)	241 (16%)
Other	40 (3%)	34 (2%)
Region		
North America	987 (65%)	976 (65%)
Latin America	352 (23%)	342 (23%)
Spain	183 (12%)	183 (12%)
Number of antihypertensive medications at study entry	1·7 (1·2)	1·7 (1·2)
Mean number of antihypertensive medications at 1 year*	1·8 (1·4)	2·4 (1·3)
Types of antihypertensive medications at 1 year†		
Thiazides	576 (43%)	774 (58%)
ACE inhibitor/ARB	835 (63%)	1064 (80%)
Calcium-channel blockers	398 (30%)	571 (43%)
β blockers	333 (25%)	408 (31%)
Other	117 (9%)	146 (11%)
Mean number of antihypertensive medication at last visit‡	1·8 (1·4)	2·4 (1·4)
Types of antihypertensive medications at last visit§		
Thiazides	569 (38%)	804 (54%)
ACE inhibitor/ARB	894 (60%)	1156 (78%)
Calcium-channel blockers	438 (39%)	637 (43%)
β blockers	424 (28%)	521 (35%)
Other	168 (11%)	204 (14%)
Statins used during follow-up	1248 (84%)	1254 (85%)

Data are mean (SD) or number (%). TIA=transient ischaemic attack. ACE=angiotensin-converting enzyme. ARB=antiotensin-II-receptor blocker. *Difference between groups p<0·0001. †Difference between groups p<0·0001 for all types, except β blockers (p=0·0008) and other (p=0·051). ‡Difference between groups p<0·0001. §Difference between groups p<0·0001 for all types, except other (p=0·042).

***Table 1*: Patients' characteristics**

Management of blood pressure

Baseline hypertensive status was determined by measurement of blood pressure taken at two consecutive visits before randomisation. Patients taking medications to control blood pressure were allowed to continue doing so. Blood pressure was measured three times at every visit and the average measurement was used to decide hypertensive status.[8–11] Patients were classified as being hypertensive if either or both of the following features were noted: average systolic blood pressure 140 mm Hg or higher or diastolic blood pressure 90 mm Hg or higher on two consecutive visits, and confirmed history of hypertension before the index stroke and taking antihypertensive medication at the time of visit. After randomisation, if patients had blood pressures outside the assigned target range, they were initially seen at least monthly for measurement of blood pressure and adjustment of medications. Patients whose blood pressure was in the relevant range for two consecutive visits were seen every 3 months. If at any point during the study a patient's systolic blood pressure was outside the assigned target range, he or she was asked to return within 1 month.

All study sites were provided with automated Colin Press-Mate BP-8800C sphygmomanometers (Colin Medical Instruments, San Antonio, TX, USA).[11] Blood-pressure management was overseen at each site by a physician with special expertise in blood-pressure control. If systolic blood pressure in patients assigned to the higher-target group (130–149 mm Hg) dropped to below the lower limit of the target range, the protocol required that patients taking antihypertensive medications stop taking them or have the doses reduced, unless prescribed for reasons other than blood pressure control; patients taking no antihypertensive medications continued to be followed up every 3 months. If systolic blood pressure increased to within the target range, patients were managed according to their originally assigned target. If patients or primary-care physicians refused to titrate blood pressure to the assigned target range per protocol, patients were classified as inactive. Patients whose blood pressure could not be kept within the assigned target range for medical reasons or because of intolerable side-effects of antihypertensive drugs after trying different agents were classified as failure to achieve assigned target. All participants were followed up to a common end-of-study date, irrespective of activity status.

Antihypertensive medications were prescribed by the local study physician and supplied via the study formularies. At least one drug from each of the major classes of

antihypertensive medications was available. They were obtained and distributed to study centres by the Veterans Administration Cooperative Studies Program Clinical Research Coordinating Center, Drug Distribution Center, Albuquerque, NM, USA.

Statistical analysis

The primary endpoint was reduction in all stroke. Ischaemic stroke was clinically defined as a focal neurological deficit persisting for longer than 24 h, with an absence of haemorrhage confirmed by neuroimaging. Intracranial haemorrhages included intracerebral, subdural or epidural, and subarachnoid locations defined by neuroimaging. Disabling strokes were classified as those with modified Rankin scores of 3 or higher after 3–6 months. Strokes were deemed fatal if death occurred within 30 days or if death after 30 days could be attributed to the stroke. Secondary endpoints were reductions in acute myocardial infarction, defined by standard criteria (compatible clinical history with changes on ECG or in cardiac enzyme concentrations), need for acute admission to hospital for a major vascular event, and death, classified as vascular, non-vascular, or unknown. All reported efficacy outcomes were confirmed by a central adjudication committee that was unaware of treatment assignment. Safety outcomes were serious adverse events related to hypotension and blood-pressure management. The trial was monitored by an independent data and safety monitoring committee selected by the sponsor.

The initial sample size of 2500 patients was calculated assuming an average follow-up of 3 years, an estimated 3-year recurrent stroke rate of 21%, a 25% relative-risk reduction in stroke by intensive control of blood pressure, a type I error of $\alpha=0{\cdot}05$, and 90% power. Sample-size estimation was reassessed midway through the trial to check the power of the study on the basis of the observed overall event rate. This assessment resulted in the final sample size being increased from 2500 to 3000 patients.[12]

We did two prespecified subgroup analyses. The first was in patients who were hypertensive at baseline. Thus, we excluded from this analysis patients who were non-hypertensive at baseline (systolic blood pressure lower than 130 mm Hg without taking antihypertensive medications) and who received no antihypertensive therapy during the study unless blood pressure exceeded the assigned target range during follow-up. The second included data after censoring at 6 months of follow-up. This analysis was undertaken because the maximum separation of the baseline and achieved blood pressures requires an average of 6 months of medication titration. All 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 in this subgroup. We also assessed outcomes in various demographic and clinical subgroups.

We did standard time-to-event analyses of the primary endpoint with the log-rank test and used Cox's proportional hazards models to compute hazard ratios (HRs) and 95% CIs in each treatment group. If multiple events of the same type occurred, time to event was calculated as time to first event. Data for patients with no

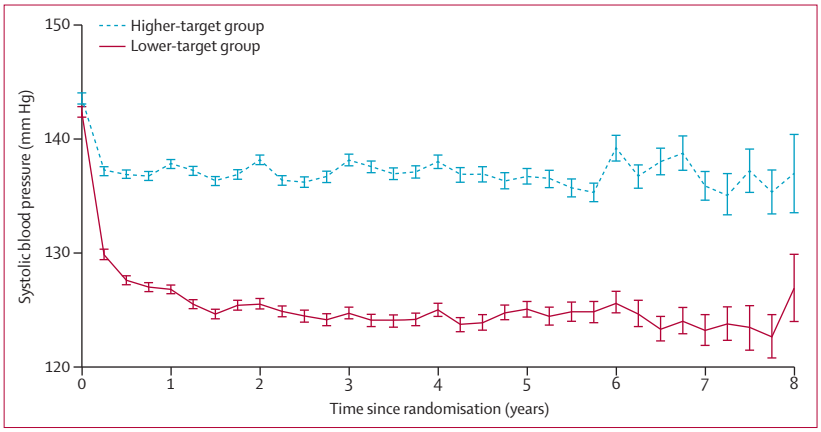

Figure 1: **Systolic blood pressure by treatment group**

	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
Stroke						
All stroke	152	2·77%	125	2·25%	0·81 (0·64–1·03)	0·08
Ischaemic stroke or unknown	131	2·4%	112	2·0%	0·84 (0·66–1·09)	0·19
Intracranial haemorrhage						
All	21*	0·38%	13†	0·23%	0·61 (0·31–1·22)	0·16
Intracerebral	16	0·29%	6	0·11%	0·37 (0·15–0·95)	0·03
Subdural or 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 or fatal stroke‡	49	0·89%	40	0·72%	0·81 (0·53–1·23)	0·32
Myocardial infarction	40	0·70%	36	0·62%	0·88 (0·56–1·39)	0·59
Major vascular event*	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

*One classified as both intracerebral and other, and one as both intracerebral and subdural or epidural. †One classified as intracerebral and subdural or epidural, and two as both intracerebral and other. ‡Disabling strokes classified as modified Rankin score 3 or higher after 3–6 months.

Table 2: **Primary and secondary outcomes**

events were censored at the end of study participation or death, whichever occurred first. The proportional hazards assumption was verified by assessment of the interaction between time and blood-pressure-intervention group, and we used Cox's models to investigate whether the effect of intervention differed by specific subgroups. Odds ratios and 95% CIs were computed by logistic regression for orthostatic symptoms, as these were measured as whether or not the patient had at least one symptom during the follow-up period All analyses were based on the intention-to-treat principle and were done with SAS (version 9.2). The study is registered with ClinicalTrials.gov, number NCT00059306.

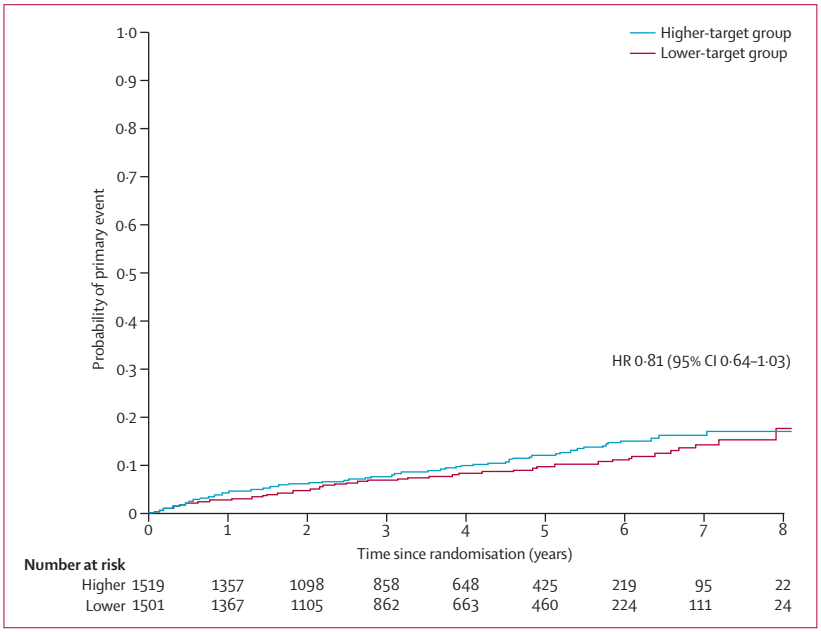

***Figure 2*: Probability of patients experiencing a primary event by time after randomisation**
Primary events were all recurrent strokes, myocardial infarction, or vascular death. HR=hazard ratio.

Role of the funding source

The sponsor of the study participated in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

3020 participants were enrolled from North America (n=1960 [65%]), Latin America (n=694 [23%]), and Spain (n=366 [12%]) and were followed up for a mean of 3·7 (range 0–8·6, SD 2·0) years (appendix p 1). Baseline characteristics did not differ substantially between target groups (table 1). The median time from qualifying stroke to randomisation was 62 days. Blood-pressure therapy was permanently discontinued in similar numbers of

Subgroup ($p_{interaction}$)	Number of events (annualised rate [%])		HR (95% CI)
	130–149 mm Hg	<130 mm Hg	
Age (p=0·53)			
<65 years (n=1757)	87 (2·71%)	68 (2·05%)	0·76 (0·55–1·05)
≥65 years (n=1263)	67 (2·86%)	57 (2·53%)	0·89 (0·62–1·26)
Sex (p=0·50)			
Male (n=1902)	111 (3·09%)	80 (2·41%)	0·78 (0·59–1·04)
Female (n=1118)	41 (2·17%)	45 (2·01%)	0·93 (0·61–1·43)
History of diabetes (p=0·64)			
Non-diabetic (n=1914)	78 (2·15%)	59 (1·64%)	0·76 (0·54–1·07)
Diabetes (n=1106)	74 (3·97%)	66 (3·37%)	0·85 (0·61–1·19)
Race (p=0·85)			
Hispanic (n=916)	36 (2·23%)	29 (1·83%)	0·82 (0·51–1·34)
White (n=1538)	72 (2·56%)	63 (2·22%)	0·86 (0·62–1·21)
Black (n=492)	37 (4·09%)	30 (3·04%)	0·75 (0·47–1·22)
Other/mixed (n=74)	7 (4·53%)	3 (2·11%)	0·48 (0·12–1·85)
Region of residence (p=0·09)			
North America (n=1960)	111 (2·90%)	100 (2·58%)	0·89 (0·68–1·17)
Latin America (n=694)	24 (2·11%)	20 (1·77%)	0·84 (0·47–1·52)
Spain (n=366)	17 (3·31%)	5 (0·92%)	0·28 (0·10–0·76)
Baseline SBP (p=0·78)			
Normotensive (n=314)	11 (2·03%)	12 (2·03%)	1·02 (0·45–2·31)
SBP<median (n=1306)	65 (2·90%)	53 (2·18%)	0·75 (0·20–1·08
SBP≥median (n=400)	76 (2·81%)	60 (2·36%)	0·84 (0·60–1·18)

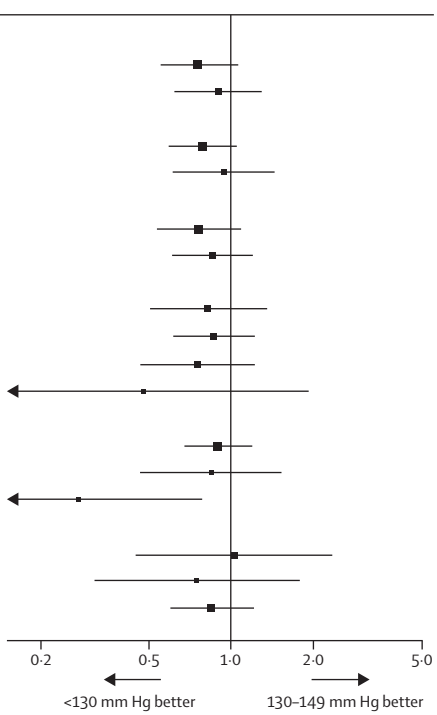

***Figure 3*: Primary outcome assessed by demographic and clinical subgroups**
HR=hazard ratio. SBP=systolic blood pressure.

patients in the higher-target and lower-target groups (258 [17%] *vs* 240 [16%]). 90 (3%) participants were lost to follow-up and an additional 465 (15%) ended follow-up early for the following reasons: withdrawn consent (n=242), site closure (n=151), physician request (n=12), and other reasons (n=60).

At 1 year of follow up, the achieved average systolic blood pressures were 138 mm Hg (95% CI 137–139) in the higher-target group and 127 mm Hg (126–128) in the lower-target group, with 1139 (75%) and 976 (65%), respectively, having blood pressures within the assigned target ranges. At the last study visit, the mean difference in systolic blood pressures between the two groups was 11 mm Hg (SD 16, figure 1, appendix p 2). At 1 year, patients in the lower-target group had received a greater mean number of antihypertensive drugs than had those in the higher-target group (table 1).

During follow-up, 277 first recurrent strokes occurred. Of these, 243 (86%) were ischaemic (of which 173 [71%] were recurrent lacunar strokes) and 34 (14%) were intracranial haemorrhages. The annualised rate of recurrent stroke among those assigned to the higher-target group was 2·77%, as compared with 2·25% in the lower-target group (hazard ratio 0·81, 95% CI 0·64–1·03; p=0·08; table 2, figure 2). A similar result was seen for disabling or fatal stroke (table 2). The rate of intracerebral haemorrhage was significantly reduced in the lower-target group, whereas mortality was nearly identical (table 2). A 13% reduction in the rate of recurrent lacunar strokes was seen in the lower-target group (HR 0·87, 95% CI 0·62–1·22, p=0·41). There was no heterogeneity in treatment effect on the primary outcome in any of the demographic or clinical subgroups (figure 3).

In the prespecified subgroup analysis restricted to the 2706 participants classified as hypertensive at study entry, a 20% reduction in recurrent stroke was seen in the lower-target group (appendix p 3). Censoring of the first 6 months of follow-up in all participants showed a nearly identical rate reduction for recurrent stroke (appendix p 3).

Although few serious adverse events related to hypotension were noted, they were more frequent in the lower-target group than in the higher-target group, but not significantly so (table 3). Syncope was the most frequent event but did not result in permanent sequelae. Symptoms potentially related to blood-pressure management were similar in the two groups (table 4).

	Higher-target group (n=1519)		Lower-target group (n=1501)		Hazard ratio (95% CI)	p value
	Number of patients	Rate (% per patient-year)	Number of patients	Rate (% per patient-year)		
All	15	0·26	23	0·40	1·53 (0·80–2·93)	0·20
Orthostatic syncope	5	0·09	11	0·19	2·18 (0·76–6·27)	0·14
Stroke associated with hypotension	1	0·02	2	0·03	2·00 (0·18–22·09)	0·57
Myocardial infarction	0	0	0	0	NA	NA
Fall with injury	0	0	3	0·052	NA	NA
Other	11	0·19	9	0·15	0·82 (0·34–1·97)	0·65

NA=not applicable.

Table 3: **Serious adverse events related to hypotension**

	Higher-target group (n=1519)	Lower-target group (n=1501)	Odds ratio (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
Light-headedness when standing	236 (16%)	222 (15%)	0·94 (0·77–1·15)	0·54
Palpitations when standing	24 (0·4%)	21 (0·4%)	0·86 (0·48–1·55)	0·62

Table 4: **Side-effects potentially related to blood-pressure management**

Discussion

Lowering of systolic blood pressure to a target of less than 130 mm Hg in patients with recent lacunar stroke resulted in non-significant reductions in all stroke, disabling or fatal stroke, and major vascular events, and a significant reduction in intracerebral stroke. These effects were associated with few serious side-effects, and were consistent across major subgroups, including patients with diabetes and Hispanic patients, and irrespective of blood pressure at study entry. Exclusion of normotensive patients at entry showed a reduction in the rate of recurrent stroke of 20% in the lower–target group, although this reduction was not significant. Blood-pressure lowering offered a similar effect on stroke recurrence irrespective of stroke subtype (table 5, figure 4).

That lower is better is a general construct for chronic blood-pressure management after stroke, but optimum clinical practice requires that benefits and risks associated with specific targets be defined. The PROGRESS trial[2] showed that lowering of blood pressure in stroke survivors was associated with a reduction of 28% in stroke recurrence. The mean achieved systolic blood pressure at the end of the study was 138 mm Hg, but the optimum target for blood-pressure control was not established. Similarly to the ACCORD trial,[19] we explored the efficacy and safety of setting systolic-blood-pressure targets lower than 130 mm Hg, but our assessment was extended to patients with MRI-defined lacunar stroke attributed to small-vessel disease.

Our results are best viewed in the context of previous trials of long-term lowering of blood pressure in patients who have had brain ischaemia (table 5, figure 4).[1–3,13–17,20] We tested target blood pressure rather than specific antihypertensive agents and explored effects in patients with well defined ischaemic-stroke subtypes. Although the magnitude of the reduction in rate was not significant, the findings are strongly supported by those of previous trials.[1–3]

See Online for appendix

	Intervention	Population (mean follow-up)	Number of patients	Achieved systolic blood pressure (difference between treated patients and controls [mm Hg])	Relative risk reduction for recurrent stroke (95% CI)
HSCSG (1974)[13]	Deserpidine, thiazide	Heterogeneous stroke, uncertain ischaemic (96%) *vs* ICH (2·3 years)	452	~167 *vs* ~142 (25)	20%† (–29 to 51)
Dutch TIA (1993)[14]	Atenolol	All causes of TIA (34%) or ischaemic stroke (2·6 years)	1473	~155 *vs* ~149 (6)	18% (–19 to 43)
PATS (1995)[15]	Indapamide	Heterogeneous, including TIA (12%) and ICH (14%; 2·0 years)	5665	149 *vs* 144 (5)	29% (12 to 41)
TEST (1995)[16]	Atenolol	Heterogeneous ischaemic stroke (2·3 years)	720	161 *vs* 157 (4)	0% (–45 to 30)
INDANA (1997)[1]	Multiple	Subgroups with previous stroke from five hypertension trials (NR)	519	NR	29% (–14 to 56)
HOPE (2000)[17]‡	Ramipril	Heterogeneous (NR)	1013	~151 *vs* ~141 (10)	15% (–30 to 44)
PROGRESS (2001)[2]	Perindopril, indapamide	Heterogeneous, including TIA (22%) and ICH (11%; 3·9 years)§	6105	~144 *vs* ~135 (9)	28% (17 to 38)
PRoFESS (2008)[15]	Telmisartan	All causes of ischaemic stroke, including small-artery disease (52%; 2·5 years)	20322	~141 *vs* ~137 (4)	5% (–4 to 14)
SPS3 (2013)	Target systolic-blood-pressure levels*	MRI-proven recent lacunar infarction (3·6 years)	3020	138 *vs* 127 (11)	19% (–3 to 36)

ICH=intracerebral haemorrhage. TIA=transient ischemic attack. NR=not reported. *No trials other than SPS3 tested target blood-pressure levels, although the MOSES trial compared eprosartan with nitrendipine in stroke survivors, but only a small difference (1·5 mm Hg) was achieved in systolic blood pressure in a small number of participants and, therefore, did not reliably characterise blood-pressure effects.[18] †Relative-risk reduction computed as 1–odds ratio because not reported in publication. ‡HOPE results for patients with previous stroke or TIA are presented in figure 2a of Rashid and colleagues,[3] but are otherwise unpublished.§Analysis restricted to patients with ischaemic stroke as the qualifying events showed a 26% (95% CI 12–36) reduction in subsequent strokes.[2]

Table 5*: Randomised trials of long-term blood-pressure lowering in patients with stroke or TIA

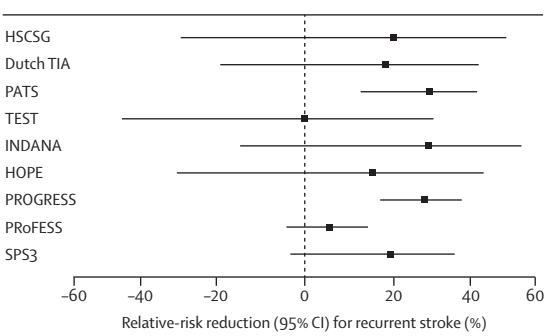

***Figure 4*: Randomised trials of long-term blood-pressure lowering for secondary stroke prevention**

The trial protocol was based on the assigned target of systolic blood pressure being achieved and, therefore, we did not require specific antihypertensive agents to be used. Patients assigned to the lower-target group used an average of 2·4 antihypertensive medications and the distribution of medication categories differed from that in the higher-target group (table 1). The mean difference in systolic blood pressure at the end of the trial was 11 mm Hg. On the basis of previous studies, this difference should have resulted in about a 30% reduction in recurrent stroke. The observed reduction of 19% (95% CI –3 to 36), however, was smaller even than the hypothesised 25%. This finding could be due to chance or the specific population of patients assessed.[2,21] The 95% CI for the 19% reduction does include the hypothesised 25% reduction, but it also spans zero and, therefore, is not significant. The rate of intracerebral haemorrhage was reduced by 63% in the lower-target group, which is consistent with the known sensitivity of this stroke subtype to strict blood-pressure control.[14] This result indicates that the number needed to treat to prevent one intracerebral haemorrhage at 4 years (roughly the average follow-up in SPS3) would be 175.

The SPS3 trial had limitations. First, the observed rate of recurrent stroke was much lower than that anticipated. This low rate is similar to that seen in other trials that have assessed prevention of recurrent stroke.[22–24] It might, therefore, be the result of good blood-pressure control in both treatment groups, the frequent use of statins, and high adherence to antiplatelet therapy. Second, the assignment to blood-pressure targets was not masked, which could have potentially introduced bias. Stroke endpoints were, however, confirmed by a central adjudication committee that was unaware of patients' group allocations, as is frequently done in large hypertension trials.[25] Third, we tested treatment targets and not the effect of specific blood-pressure agents. Finally, some patients did not achieve blood pressures within the target ranges at any point during follow-up (70 [4·6%] in the higher-target group and 74 [4·9%] in the lower-target group). These proportions, however, are similar to those reported in other trials of blood-pressure targets and, therefore, probably reflect the clinical realities of blood-pressure management.[19,25] An important strength of the SPS3

Panel: Research in context

Systematic review

We searched PubMed and Cochrane Library for randomised clinical trials of secondary stroke prevention with blood-pressure reduction as an intervention, published before April, 2013, in all languages. We used the search terms "blood pressure", "reduction", hypertension", "secondary", "stroke", "prevention", and "clinical trial". Eight randomised clinical trials[2,13–18] and one pooled analysis[1] were identified. Aggregate results showed consistently that reduced blood pressure in stroke survivors lessened the risk of stroke recurrence.

Interpretation

We assessed blood-pressure targets in survivors of MRI-defined lacunar stroke. A reduced rate of all stroke was observed in patients with a target systolic blood pressure lower than 130 mm Hg compared with a target of 130–149 mm Hg, but this difference was not significant. The intervention was safe and well tolerated. Interpreted in the context of previous randomised, controlled trials of blood-pressure lowering after stroke, our results suggest that management of systolic to levels lower than 130 mm Hg is likely to reduce the risk of recurrent stroke in patients with recent lacunar stroke.

trial is that blood-pressure lowering was tested in a well defined and homogeneous cohort of stroke patients.

In conclusion, although our results do not show a significant reduction in the rate of recurrent stroke, the findings are congruent with those of previous trials of blood-pressure lowering after stroke and support a treatment target of less than 130 mm Hg systolic blood pressure for most patients with recent lacunar stroke (panel). As our study cohort comprised patients with recent lacunar strokes due mainly to cerebral small-vessel disease, whether our findings are applicable to patients with strokes from other mechanisms warrants additional research.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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