Published in final edited form as:

Lancet Neurol. 2014 December ; 13(12): 1177–1185. doi:10.1016/S1474-4422(14)70224-8.

Effects of long-term blood pressure lowering and dual antiplatelet therapy on cognition in patients with recent lacunar stroke: Secondary Prevention of Small Subcortical Strokes (SPS3) trial The SPS3 Investigators*

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Abstract

Background—The primary outcome results for the Secondary Prevention of Small Subcortical Strokes (SPS3) trial suggested that a lower target blood pressure may be beneficial (19% nonsignificant reduction) for reducing risk of recurrent stroke but that addition of clopidogrel to aspirin was not. Whether blood pressure (BP) reduction and dual antiplatelet therapy affect changes in cognition over time in patients with cerebral small vessel disease is unclear.

Methods—Pre-specified secondary endpoint analyses of the SPS3 trial involving 3020 patients, mean age 63 years, with recent symptomatic lacunar infarcts randomized 1:1 to two target levels of systolic BP (130–149 mm Hg vs. <130 mm Hg, open-label) and 1:1 to once-daily antiplatelet therapy (75 mg clopidogrel plus 325 mg aspirin vs. 325 mg aspirin alone, double-blind) during 2003–2011 at 81 centers. The primary cognitive outcome was change in Cognitive Abilities Screening Instrument (CASI) during follow-up. Patients were tested annually (median 3 years of follow-up, maximum 5) during which the mean difference in systolic BP averaged 11 mmHg between the two target (138 mm Hg vs 127 mm Hg at 1 year). This study is registered with ClinicalTrials.gov, number NCT 00059306.

Findings—The 2916 participants with CASI scores at study entry are included in the analysis. Mean (SD) changes in CASI z-scores from study entry to assessment at years 1 (n=2699), 2 (n=2251), 3 (n=1785), 4 (n=1134) and 5 (n=803) were 0.11 (0.84), 0.15 (0.85), 0.15 (0.97), 0.19 (1.0), and 0.16 (1.2), respectively. Changes in CASI z-scores over time did not differ between

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Contributions.

All authors contributed to design of the cognitive component of the SPS3 trial. The initial draft of the manuscript was prepared by L. Pearce and L. McClure, who provided statistical input. The remaining coauthors all participated in data collection and critical revision of the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest.

assigned antiplatelet groups ($p=0.9$) or between assigned blood pressure control groups ($p=0.5$). There was no interaction between assigned antiplatelet groups and assigned blood pressure control groups and change over time. ($p=0.2$)

Interpretation—Cognitive function is not influenced by short-term treatment with dual antiplatelet therapy or blood pressure reduction in relatively young patients with recent lacunar stroke. Future studies of the effects of blood pressure reduction on cognition should focus on patients with higher rates of cognitive decline.

Introduction

Hypertension and stroke are well-established risk factors for cognitive impairment and vascular dementia¹⁻⁵. Lacunar strokes are a common cause of cognitive impairment^{1,6}. Lowering blood pressure reduces stroke⁷⁻⁹, therefore, it is plausible that effective control of blood pressure in lacunar stroke patients could result in reduction of cognitive impairment. Results of clinical trials testing blood pressure lowering to reduce dementia and/or cognitive decline in stroke patients^{10,11} and in those without cerebrovascular disease¹²⁻¹⁴ have been conflicting. Similarly, data supporting the role of anti-thrombotic therapies in preventing cognitive decline are lacking^{15,16}.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial tested two interventions for prevention of recurrent stroke in patients with lacunar strokes: dual vs. single agent antiplatelet therapy, and lower vs. higher blood pressure targets. Risk of recurrent stroke was not reduced with the addition of clopidogrel to aspirin, and the antiplatelet trial was stopped 8 months before scheduled end date due to increased mortality in the dual antiplatelet arm, whereas lower blood pressure target was associated with reduced stroke recurrence by a non-significant 19% ($p=0.08$) and reduced intracerebral hemorrhage by 63% ($p=0.03$), with no safety concerns^{8,19}. Here we report the effect of each of these interventions on the pre-specified secondary endpoint of change in cognition over time as measured by the Cognitive Abilities Screening Instrument (CASI) during a median follow-up of 3 years.

Methods

Study Design

Study rationale, design, participant characteristics, and the primary outcomes results of SPS3 have been previously reported^{8,17-20}. In brief, SPS3 was a randomized clinical trial conducted in 81 clinical centers in North America, Latin America, and Spain from March 2003 to May 2012 (enrollment period 2003-2011). Eligible participants had a recent (within 6 months) lacunar stroke documented on MRI and were without major-risk cardioembolic source, ipsilateral carotid stenosis $\geq 50\%$ (in hemispheric infarct cases), or evidence of prior cortical stroke. Persons with moderate-severe disability were ineligible (modified Rankin score above 3) as were those with an age- and education-adjusted Mini-Mental Status Exam (MMSE) score < 24 . Participation required written informed consent and study protocol approval by the human research subjects committee at each study center.

Randomisation and Masking

Participants were simultaneously randomized in a 2-by-2 factorial design to both an antiplatelet intervention (1:1, double-blind, aspirin + placebo vs. aspirin + clopidogrel) and to a target level of systolic blood pressure control (1:1, open-label, “lower”, <130 mm Hg vs. “higher”, 130-149 mmHg). Randomization assignments (permuted block design of variable size, stratified by clinical centre and hypertension status) were unavailable for preview and stored electronically at each clinical center and at the SPS3 Statistical Center.

Study Conduct

Participants were seen at least every 3 months for blood pressure measurement and medication adjustment, antiplatelet medication dispensing, and event detection¹⁸. Adherence to assigned antiplatelet therapy was estimated as 94%, with permanent discontinuation of assigned antiplatelet therapy in 30% of those given clopidogrel plus aspirin (e.g. dual antiplatelet therapy) and 27% of aspirin alone¹⁹. After 1 year the mean systolic blood pressure was 138 mm Hg in the higher target group and 127 mm Hg in the lower target group, with a mean difference of 11 mm Hg persisting during subsequent follow-up⁸.

Outcomes

Neuropsychological testing was done at study entry and annually during the first 5 years of each participant's follow-up. SPS3 participants were enrolled over a rolling period and followed for a minimum of 1 year to a common termination date so the number of annual neuropsychological assessments per patient varied between 1 and 5. The neuropsychological testing battery for SPS3 included a broad range of tests, and administration procedures and has been previously described (Supplemental table 1)¹. Briefly, the CASI, a measure of global cognition and assessing attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgment, was the primary measure for assessing cognition in SPS3²¹. A score for the MMSE can be estimated from the CASI, but it is lengthier and has a wider measurement range of 0-100²². For this analysis, raw scores at each assessment were converted to z-scores reflecting performance in standard deviations above (+) or below (-) an expected average for a non-stroke population using available published normative data with reference to age, education, region, and language of testing¹. Other tests, covering the domains of episodic memory, attention, visuo-construction, and motor dexterity, included: the California Verbal Learning Test short and long delay cued, free recall tests, and discriminability; the WAIS-III Block Design, Symbol Search, and Digit Span tests; the Controlled Oral Word Association test; the Grooved Pegboard test; and the Clox test, with raw scores converted to z-scores similarly²³⁻²⁷. (Supplemental table 1) Tests were administered by certified examiners in the language spoken by the participant (English, Spanish, French)¹. Parallel test forms were not available and/or not used.

Mild cognitive impairment (definition derived post-hoc) was defined psychometrically at entry and annually on the basis of test scores^{1,28}. Status was defined as no cognitive impairment if no definite impairment was present in any cognitive domain; mild cognitive impairment - single amnesic type if there was definite impairment on at least two of the

memory (California Verbal Learning Test) scores, with non-memory scores normal; mild cognitive impairment - multidomain if there was definite impairment on at least two memory test scores, and definite impairment on at least two non-memory test scores (Block Design, Symbol Search, Controlled Oral Word Association, and Digit Span, and/or definite impairment on the Clox test if > 8 years education); and mild cognitive impairment - nonamnestic if there was definite impairment on at least two non-memory test scores only. Definite impairment was defined as a z-score -1.5 , i.e. 1.5 standard deviations below the mean. Scores from neither the Cognitive Abilities Screening Assessment nor the Grooved Pegboard test were part of the definition of mild cognitive impairment^{28,29}.

Statistical Analysis

Analyses were performed under the intention to treat principle. All participants with neuropsychological testing at study entry are included in these analyses. Any neuropsychological testing results following a recurrent clinical stroke were excluded. Participant characteristics at study entry were described by antiplatelet groups and blood pressure groups separately as means and standard deviations or frequencies and percents, as appropriate. Means and standard deviations (SD), as well as medians and interquartile (IQR) ranges, were computed for the CASI z-score as well as other tests, at study entry and at each annual visit. The distributions of these assessments at each time point were assessed for normality and found to be approximately normally distributed with the exception of the Grooved Pegboard test.

Linear mixed models were used to compare changes in the CASI z-score and other tests over time between the different groups, allowing for correlation within each participant's measures over time, as well as allowing for varying numbers of observed cognitive assessments. Several covariance structures were compared, and that with the lowest Akaike's Information Criteria (AIC) was chosen for modeling. For all situations, the Toeplitz covariance structure was chosen. For the Grooved Pegboard test, for which the distribution of the assessments was not normally distributed, a linear mixed model was performed on the ranks of the scores³⁰. We examined linearity of the effect of time and determined that participants experienced the largest change from baseline to year 1 and that subsequent changes over time were much smaller. Thus, time was not modeled continuously, but rather was considered as a nominal variable.

To test whether changes over time differed between treatment groups, we were primarily interested in three different tests: the three-way interaction between antiplatelet arm, blood pressure arm and time, and the two way interactions between each of the antiplatelet arm and the blood pressure arm and time. Because of the large number of cognitive assessments considered and because there were 3 tests of interest for each, it was determined *a priori* that an alpha level of 0.01 would be used to determine statistical significance.

The primary analysis compared changes over time in the CASI z- score by treatment groups. Due to safety concerns, follow-up was terminated in the antiplatelet arm in August, 2011 whereas follow-up for the blood pressure arm continued through April, 2012^{8,19}. Testing done during this 8 month period was initially excluded from analyses, but results were

unchanged when the 1086 assessments from this interval when antiplatelet therapy was not supervised by the trial investigators were subsequently included, so we present results based on all available data. Incidence of mild cognitive impairment was compared between treatment groups using a log-rank test, whereas the prevalence of mild cognitive impairment at the last observed visit was compared between treatment groups using a chi-square test of association. These analyses involving mild cognitive impairment were not pre-specified.

Role of the funding source

The sponsor of the study participated in study design, data collection, data analysis and data interpretation. All members of the Writing Committee for this manuscript had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Results

Of the 3020 SPS3 participants, 2916 had the CASI administered at study entry. We were unable to administer standardized testing in 104 participants for several reasons (i.e. lack of availability of tests in participant's native language ($n = 56$), participant's refusal, and unavailability of a certified examiner). The 3% (104) of SPS3 participants without testing were similar in vascular risk profile to those with testing except they were more often of other or mixed races (33 (32%) vs. 41 (1%), $p < 0.001$). (data not shown) Of the 2916 participants included in these analyses, 1632 (56%) were English-speaking participants from US or Canada, 109 (4%) were French-speaking from Canada, and 693 (24%), 362 (12%), 120 (4%) were Spanish-speaking participants from Latin America, Spain, and the US respectively. Among the 2916 participants, 535 (18%) had results from 1 annual testing during follow-up, 488 (17%) had results from 2 testings, 426 (15%) from 3, 381 (13%) from 4, and 718 (25%) from 5; 368 (13%) participants had results for testing at study entry only. Seventy-four percent of the 2916 did not terminate study participation early and had the CASI assessment done at their last annual visit.

Participant demographics and characteristics by assigned treatment groups are presented in Table 1. Average age of participants at study entry was 63 (SD 11) years, with 1828 (63%) male, and hypertension, diabetes, and prior stroke present in 2179 (75%), 1070 (37%), and 158 (10%) of participants, respectively. 1943 (67%) participants had a modified Rankin score of 0-1 at study entry.

Median (IQR) time from qualifying stroke to baseline neuropsychological testing was 62 (37-102) days. Average time from study enrollment to last neuropsychological testing was 2.8 (SD 1.8) years and did not differ between assigned antiplatelet treatment ($p=0.3987$) or blood pressure control ($p=0.3443$) groups; median time was 3 years (1.0-4.9).

CASI z-scores improved slightly from assessment at study entry to each of years 1 to 5. (Figure 1, Table 2) Only the mean change of 0.11 (SD 0.84) from study entry to year 1 was statistically significant. The changes over time in CASI z-scores were not significantly different between assigned antiplatelet groups ($p=0.8579$) or between assigned blood pressure control groups ($p=0.5198$), and there was no significant interaction between

assigned antiplatelet and assigned blood pressure control group with respect to the changes over time ($p=0.1965$). (Figure 1) These results were not different after adjusting for age, sex, region of enrollment, and education ($p = 0.8576$ for assigned antiplatelet, $p = 0.4931$ for assigned blood pressure control, and $p = 0.1877$ for interaction). Results were similar for analyses done with raw CASI scores and when the 431 assessments among 180 patients done post-recurrent stroke were included. (data not shown) Changes in CASI z-score over time also did not differ between antiplatelet treatment groups or blood pressure control groups or in subgroups defined by age, native language and region of enrollment, by above or below median baseline CASI z-score, by mild cognitive impairment status at entry, or by history of prior subcortical stroke. (Table 3) Changes over time also did not differ between antiplatelet groups or blood pressure control groups in subgroups defined by additional old small subcortical infarcts on MRI or frequency and severity of white matter hyperintensities on MRI. (Table 3)

Average z-scores for other tests were also lower at study entry with minimal change during follow-up. (Supplemental Table 3a) Changes over time were not significantly different between antiplatelet groups or blood pressure target groups, and results were similar when adjusted for age, sex, region of enrollment, and education. (Supplemental Table 3b)

Of the 2916 participants with a CASI at study entry, 2890 had adequate testing to determine mild cognitive impairment at study entry. (At study entry and during follow-up, participants sometimes completed the CASI but did not agree to complete the entire remaining SPS3 neuropsychological battery.) There were 1586 participants without mild cognitive impairment at study entry, with 1413 of these having at least one follow-up assessment with complete testing. Of those 1413, 376 developed mild cognitive impairment in the absence of a stroke during the study: 87 amnesic, 268 non-amnesic, and 21 multi-domain. Incidence of mild cognitive impairment did not differ by treatment group for either the antiplatelet arm (9.7%/year in the combination group, vs. 9.9%/year in the aspirin group, $p=0.7043$) or blood pressure arm (10.0%/year for the lower BP arm, vs. 9.5%/year for the higher BP arm, $p=0.5549$), and there was no interaction between treatment groups ($p=0.8394$). (Figure 2) Of the 1304 participants with mild cognitive impairment at study entry, 50% (511) of the 1013 with complete testing on at least one follow-up assessment did not meet criteria at some point during the follow-up period, and this did not differ between either the antiplatelet group (247 (49%) in the combination group, vs. 264 (52%) in the aspirin group, $p=0.4897$) or the blood pressure group (246 (49%) in the lower BP arm, vs. 265 (52%) in the higher BP arm, $p=0.2327$). At most recent testing 1041 (39%) met the criteria for mild cognitive impairment, and this did not differ between the antiplatelet groups (515 (49%) in the combination group, vs. 526 (51%) in the aspirin group, $p=0.4753$) or the blood pressure groups (506 (49%) in the lower BP arm, vs. 535 (51%) in the higher BP arm, $p=0.4179$).

Discussion

The results of the SPS3 study, with a well characterized lacunar stroke population and detailed cognitive assessments, provide the most reliable evidence of the effects of dual antiplatelet therapy with clopidogrel plus aspirin vs. single antiplatelet therapy with aspirin alone and lower (<130 mmHg systolic) vs. higher (130-149 mmHg systolic) blood pressure

targeted cognition in patients with cerebral small vessel disease. While almost half of the cohort had mild cognitive impairment at study entry,¹ further decline beyond age-expected changes over a median follow-up of three years was not evident. In addition there was no difference in the changes over time between dual vs. single antiplatelet therapy or lower vs. higher blood pressure target control, nor were there differences in changes over time between treatment groups by subgroups defined by age, native language and region of enrollment, by above or below median CASI z-score, by mild cognitive impairment status at entry, or by history of prior subcortical stroke. These data suggest that for lacunar stroke patients in the presence of good blood pressure control and an antiplatelet regimen, changes in cognition outside of a subsequent stroke are minimal in the short term.

About 25% (376 of 1413) of the SPS3 participants without mild cognitive impairment at study entry were defined to have mild cognitive impairment in the absence of a stroke during the study, and about 50% (511 of 1013) of those defined at entry did not meet criteria at some time during the study. This observation suggests that the non-CASI test scores used to define mild cognitive impairment within an individual rose and fell above the thresholds for defining mild cognitive impairment during the study.

That similar numbers acquired and lost mild cognitive impairment during the study is consistent with the minimal overall changes in CASI observed. The 25% is lower than the 37% (95% CI 23 to 53) of cognitively intact lacunar stroke patients (n = 275) reported to develop mild cognitive impairment or dementia after a first or recurrent stroke in a recent systematic review article⁶. Limitations of these data include small sample sizes, short follow-up, lack of uniform definition of stroke subtype, and variability on definition of cognitive impairment and time from stroke to test administration. Hospital and population-based studies report the prevalence of dementia post-stroke to be 10% with up to a third of patients developing dementia after multiple recurrent strokes³. However, unlike patients included in those studies, SPS3 patients all had small subcortical infarcts, were younger, and did not have significant cognitive impairment at study entry (patients with MMSE > 2 standard deviations below the mean for age and education, the generally accepted cutoff for mild dementia, were excluded from SPS3.) As well, we excluded cognitive data obtained after a recurrent stroke during follow-up. A limitation of our results is that we did not collect data on incidence of dementia.

Two other randomized trials reported the effects of blood pressure control on reducing cognitive decline in patients with prior stroke^{10,11} (see Research in Context). One of the trials¹⁰ enrolled more than 50% of participants with presumed small vessel disease though the cognitive outcome was not reported separately for this stroke subtype. In contrast, SPS3 was comprised solely of well-characterized lacunar stroke patients. As well, rather than testing specific blood pressure agents, SPS3 tested blood pressure targets. Lastly, the neuropsychological assessment used in SPS3 was more extensive.

Other trials involving patients primarily without cerebrovascular disease have tested blood pressure lowering to reduce cognitive decline¹²⁻¹⁴. In the ONTARGET trial, 21% of participants (n=9954) had a history of stroke with a similar proportion in the TRANSCEND trial (2427)¹². Neither trial reported blood pressure control affecting cognitive function. Only

the Syst-Eur trial with 4% of participants having a history of stroke reported an effect on cognition in patients assigned to active treatment (nitendipine $\pm$ enalapril $\pm$ HCTZ) versus matching placebo. While there was no change in MMSE by treatment group, the number of patients developing dementia was reduced by 50% with very few outcomes (21 vs 11, $p = 0.05$) and 23 cases attributed to Alzheimer's disease¹³.

Lack of decline in cognition regardless of assigned treatment group in SPS3 may be due to the stringent control of risk factors during the trial, as suggested by the recurrent stroke rate being about half that expected¹⁹. The mean systolic blood pressure at study entry in SPS3 was 143 mmHg, noticeably lower than that reported in other cohorts, and the difference in achieved blood pressures between the lower vs higher systolic blood pressure targets was 11 mmHg,⁸ larger than for most other randomized trials involving blood pressure change. It is also possible that the effect of blood pressure lowering on cognitive decline is less at lower baseline pressures. All participants were on an antiplatelet regimen with an estimated 94% adherence by pill count¹⁹, and statin use was prevalent. Observational data suggest secondary prevention mitigates cognitive decline¹⁵. The median length of three years of follow up in SPS3 also may be too short to detect differences in treatment effects between groups as elevated blood pressure needs to be present at least 5-15 years before the development of cognitive impairment^{5,31,32}. Finally, SPS3 tested only blood pressure targets as intervention; therefore an agent specific effect on cognition beyond lowering of blood pressure cannot be excluded.

The role of antiplatelet agents to prevent cognitive impairment remains unclear, and SPS3 appears to be the first randomized trial testing dual antiplatelet therapy versus aspirin monotherapy in stroke patients and examining cognitive outcomes³³. The PROFESS study also tested dual antiplatelet therapy regimen (aspirin plus dipyridamole vs. monotherapy (clopidogrel alone)) and did not find a difference in changes in cognition between the groups¹⁰.

The Cognitive Abilities Screening Instrument (CASI) used for this pre-specified secondary analysis in SPS3 is a well-known instrument for measuring global cognition. While validated in multiple languages and used in numerous studies³⁴, it has potential limitations. Though the CASI is less susceptible to a ceiling effect than the MMSE,^{22,35} we did observe a significant number of participants with perfect scores on the CASI, suggestive of a ceiling effect. That said, our observed mean z-score at study entry was below 0 (the expected mean for an unimpaired population), and the results for dual vs. mono antiplatelet and higher vs. lower blood pressure control were not different for those with versus those without mild cognitive impairment at study entry. The slight improvement of z-scores from study entry to the year 1 assessment may be the result of incomplete recovery from the qualifying stroke at study entry or possibly a practice effect of using the same test form at each assessment. However, results from the other tests, each measuring different domains, were similar to those from the CASI. At any specific time point, given that we had over 1400 patients in each antiplatelet (or blood pressure target) arm, and assuming a 2-sided t-test with alpha of 0.01, we had 90% power to detect a difference of 0.1 standard deviations between the antiplatelet (or blood pressure target) arms. The CASI findings are further supported by domain-specific scores of memory, attention, visuo-construction, and motor skills, which show a similar

change pattern over time, with no differences between treatment groups. Because the SPS3 neuropsychological battery covered cognitive domains vulnerable to lacunar stroke and small vessel cerebrovascular disease^{1,36}, we think it is unlikely but cannot rule out that a more comprehensive neuropsychological battery would have detected group differences.

A major limitation of this study is non-random missing data. The 26% of participants with incomplete testing, i.e. those who terminated SPS3 early or who did not complete cognitive testing at their last completed follow-up, were more educated and more frequently had mild cognitive impairment at study entry. (Supplemental tables 2a and 2b) The effect of this bias is difficult to quantitate. Numbers of patients not completing testing were similar between antiplatelet or blood pressure control groups. (Figure 2), and, those who did not complete testing were no more likely to have a recurrent stroke than those who did (suggesting to us that although we did censor at the time of a stroke event, this had little impact on our results). We also censored follow-up at death and did not impute scores, and though there was a higher rate of death in the combination therapy group, this likely had little impact given the relatively few deaths observed overall in the study. Additional caveats are the relatively young mean age of the trial cohort (63 years-old at entry) and the minimal cognitive decline observed during follow-up.

In summary, in a population of patients with well-characterized recent lacunar strokes, we did not observe further decline in cognitive function beyond age-expected changes over a median follow-up of about three years in the absence of recurrent stroke. In addition, we did not detect a clinically important difference in the changes over time between clopidogrel plus aspirin vs. aspirin antiplatelet therapy or lower vs. higher blood pressure targets.

Panel: Research in context

Systematic review

We searched PubMed and Cochrane Library for randomized clinical trials with cognitive function as outcome in patients with stroke or TIA that tested blood pressure reduction and/or antiplatelet therapy as interventions, published before August 2014, in all languages. We used the research terms “cognition”, “cognitive function”, “dementia” combined with “stroke”, “TIA”, “blood pressure”, “reduction”, “prevention”, “hypertension”, “aspirin”, “clopidogrel”, “secondary”, and with “clinical trial”. Two clinical trials were identified; both used the MiniMental Status Exam (MMSE) to measure cognition. The PROGRESS trial tested blood pressure lowering in a broad range of patients (n=6105) for secondary stroke prevention; cognitive decline was defined as a decrease in 3 points on the MMSE, and dementia was clinically defined.⁽¹¹⁾ Mean follow-up was 3.9 years, and the average achieved systolic blood pressure in the active treatment group was 138 mmHg with a difference of 9 mmHg between the groups. Cognitive decline, and the composite outcomes of dementia were only reduced when patients with recurrent clinical stroke were included. However, there was no evidence for a reduction in either dementia or cognitive decline in the absence of recurrent stroke¹¹. The PROFESS trial randomized 20,332 patients with prior ischemic stroke in a factorial design to a dual antiplatelet regimen of aspirin plus dipyridamole or monotherapy with clopidogrel, and either telmisartan or placebo with a follow up of 2.4 years. Mean reduction in systolic blood pressure with telmisartan was 8 mm

Hg to 136 compared with 3 mm Hg in the placebo group to 141 (mean difference -5 mmHg). The results for cognitive function, assessed with the MMSE one month after randomization and at the penultimate visit with no censorship at time of recurrent stroke, showed no significant differences in the median MMSE scores, the percent of MMSE with scores of ≥ 24 points, the percent of patients dropping 3 points in MMSE, or the number of demented patients among the groups ¹⁰.

Interpretation

The SPS3 trial results confirm the results of two previous trials of secondary stroke prevention that, in aggregate, show no effects of blood pressure lowering or dual antiplatelet therapy on cognition during 2-4 years of mean follow-up, adding novel information specific for this stroke cohort with cerebral small vessel disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: National Institute of Neurological Disorders and Stroke (United States)(U01 NS38529-04A1)

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Figure 1.

Average (standard deviation) Cognitive Abilities Screening Instrument (CASI)z-scores over time by assigned antiplatelet treatment and assigned blood pressure control group. Higher scores indicate better performance.

Figure 2.
Cumulative incidence of mild cognitive impairment by assigned treatments in 1413 participants without mild cognitive impairment at study entry.

Table 1

Participant characteristics by assigned antiplatelet and blood pressure control groups (n=2916).

	Assigned Antiplatelet Therapy		Assigned Systolic Blood Pressure Target	
	aspirin + clopidogrel	aspirin + placebo	lower < 130 mmHg	higher 130-149 mmHg
n	1468	1448	1452	1464
Age, mean (SD)	63.5 (10.8)	63.1 (10.7)	63.2 (10.7)	63.4 (10.8)
Female, %	557 (38%)	531 (37%)	574 (40%)	514 (35%)
Education, %				
0-8 yrs	391 (27%)	374 (26%)	388 (27%)	377 (26%)
9-12 yrs	527 (36%)	578 (40%)	543 (37%)	562 (38%)
> 12 yrs	550 (37%)	496 (34%)	521 (36%)	525 (36%)
Race/ethnicity, %				
White, not Hispanic	751 (51%)	745 (51%)	754 (52%)	742 (51%)
Hispanic	454 (31%)	452 (31%)	445 (31%)	461 (31%)
Black	237 (16%)	236 (16%)	233 (16%)	240 (16%)
Other or multiracial	26 (2%)	15 (1%)	20 (1%)	21 (1%)
Medical history:				
Diabetes, %	524 (36%)	546 (38%)	536 (37%)	534 (36%)
Hypertension, %	1107 (75%)	1072 (74%)	1085 (75%)	1094 (75%)
Ischemic heart disease, %	157 (11%)	150 (10%)	140 (10%)	167 (11%)
Lacunar stroke, %	154 (11%)	146 (10%)	154 (11%)	146 (10%)
Subcortical TIA, %	80 (5%)	78 (5%)	92 (6%)	66 (5%)
Days from index event to neuropsychological testing, mean (SD)	78 (50)	74 (51)	76 (50)	76 (52)
Modified Rankin stroke disability score, %				
0	230 (16%)	209 (14%)	234 (16%)	205 (14%)
1	763 (52%)	741 (51%)	744 (51%)	760 (52%)
2	348 (24%)	368 (25%)	338 (23%)	378 (26%)

	Assigned Antiplatelet Therapy		Assigned Systolic Blood Pressure Target	
	aspirin + clopidogrel	aspirin + placebo	lower < 130 mmHg	higher 130-149 mmHg
3	127 (9%)	130 (9%)	136 (9%)	121 (8%)
Barthel index score 95, %	1173 (80%)	1148 (79%)	1151 (79%)	1170 (80%)
Mild cognitive impairment, %	649 (45%)	654 (46%)	634 (44%)	669 (46%)
Additional small subcortical infarcts on MRI, %	573 (40%)	553 (39%)	547 (39%)	579 (41%)
White matter lesions (ARWMC score), %				
None/Mild (0-4)	709 (49%)	728 (51%)	738 (52%)	699 (49%)
Moderate (5-8)	407 (28%)	397 (28%)	402 (28%)	402 (28%)
Severe(9+)	327 (23%)	298 (21%)	290 (20%)	335 (23%)

Table 2

CASI Z-Scores by time of assessment

Time of assessment	# of assessments expected [^]	# (%) of assessments done	Mean CASI z-score at study entry, mean (SD)	Change in CASI z-score from study entry, mean (SD)
Study entry	2916	--	−0.59 (1.4)	--
1 year	2699	2486 (92%)	−0.52 (1.4)	0.11 (0.84)
2 year	2251	1974 (88%)	−0.50 (1.4)	0.15 (0.85)
3 year	1785	1531 (86%)	−0.50 (1.4)	0.15 (0.97)
4 year	1373	1144 (83%)	−0.48 (1.4)	0.19 (1.01)
5 year	982	807 (89%)	−0.50 (1.4)	0.16 (1.18)

[^] An assessment was expected annually if the participant was alive, without recurrent stroke, and had not terminated the study. Note that study enrollment was done on a rolling basis, so that not all participants had the same amount of follow-up through study closure.

Table 3

Statistical significance for models evaluating change in CASI z-score over time by assigned treatments for various subgroups. AP/BP Combination* Time is the three-way interaction between antiplatelet arm, blood pressure arm and time; AP*Time and BP*Time are the two way interactions between the antiplatelet arm and time, and the blood pressure arm and time. Lack of statistical significance ($p > 0.01$) indicates no difference in change over time between treatment arms within a subgroup.

	AP/BP Combination*Time	AP*Time	BP*Time
Age at study entry, years			
< 65 (n = 752)	0.2396	0.9895	0.2920
65-74 (n = 1689)	0.8943	0.9619	0.7312
75 (n = 475)	0.2419	0.0568	0.5734
Region of enrollment and language spoken			
US and Canada, English-speaking (n=1632)	0.0499	0.5619	0.2176
US and Canada, Spanish-speaking (n=120)	0.3717	0.2143	0.8732
Canada, French-speaking (n=109)	0.7814	0.6040	0.7872
Latin America (n=693)	0.8418	0.4005	0.7583
Spain (n=362)	0.8979	0.6596	0.7894
CASI z-score at study entry			
At or below median z-score (n=1457)	0.1709	0.9426	0.4606
Above median z-score (n=1459)	0.8213	0.4859	0.6311
Mild cognitive impairment at study entry*			
No mild cognitive impairment (n=1586)	0.8628	0.6653	0.7056
Mild cognitive impairment (n=1303)	0.3902	0.8568	0.6359
Prior lacunar stroke			
No prior stroke (n=2611)	0.1200	0.8351	0.6560
Prior stroke (n=300)	0.5870	0.1237	0.5191
Additional small subcortical infarcts on MRI			
Single (n=1710)	0.1344	0.5260	0.2983
Multiple (n=1126)	0.3354	0.8473	0.1306
White matter hyperintensities, ARWMC score			
0-4 (n=1437)	0.0149	0.6806	0.2727
5-8(n=804)	0.7070	0.6790	0.2434
9+ (n=625)	0.9422	0.7876	0.8317

Abbreviations: ARWMC= Age-Related White Matter Changes