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Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial

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Conflicts of interest

All other authors declare that they have no conflicts of interest.

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Summary

Background—Early results of the Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis trial showed that, by 30 days, 33 (14.7%) of 224 patients in the stenting group and 13 (5.8%) of 227 patients in the medical group had died or had a stroke (percentages are product limit estimates), but provided insufficient data to establish whether stenting offered any longer-term benefit. Here we report the long-term outcome of patients in this trial.

Methods—We randomly assigned (1:1, stratified by centre with randomly permuted block sizes) 451 patients with recent transient ischaemic attack or stroke related to 70–99% stenosis of a major intracranial artery to aggressive medical management (antiplatelet therapy, intensive management of vascular risk factors, and a lifestyle-modification programme) or aggressive medical management plus stenting with the Wingspan stent. The primary endpoint was any of the following: stroke or death within 30 days after enrolment, ischaemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularisation procedure of the qualifying lesion during follow-up. Primary endpoint analysis of between-group differences with log-rank test was by intention to treat. This study is registered with [ClinicalTrials.gov](https://www.clinicaltrials.gov), number NCT 00576693.

Findings—During a median follow-up of 32.4 months, 34 (15%) of 227 patients in the medical group and 52 (23%) of 224 patients in the stenting group had a primary endpoint event. The cumulative probability of the primary endpoints was smaller in the medical group versus the percutaneous transluminal angioplasty and stenting (PTAS) group ($p=0.0252$). Beyond 30 days, 21 (10%) of 210 patients in the medical group and 19 (10%) of 191 patients in the stenting group had a primary endpoint. The absolute differences in the primary endpoint rates between the two groups were 7.1% at year 1 (95% CI 0.2 to 13.8%; $p=0.0428$), 6.5% at year 2 (−0.5 to 13.5%; $p=0.07$) and 9.0% at year 3 (1.5 to 16.5%; $p=0.0193$). The occurrence of the following adverse events was higher in the PTAS group than in the medical group: any stroke (59 [26%] of 224 patients vs 42 [19%] of 227 patients; $p=0.0468$) and major haemorrhage (29 [13%] of 224 patients vs 10 [4%] of 227 patients; $p=0.0009$).

Interpretation—The early benefit of aggressive medical management over stenting with the Wingspan stent for high-risk patients with intracranial stenosis persists over extended follow-up. Our findings lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

Introduction

Intracranial atherosclerosis is a common cause of stroke and is associated with a high risk of recurrent stroke, especially in patients with a recent stroke or transient ischaemic attack and severe arterial stenosis.^{1–4} The Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial was designed to assess whether percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical treatment is more effective than aggressive medical treatment alone in high-risk patients with this disease.⁵ Enrolment in SAMMPRIS began on Nov 25, 2008, but was stopped for safety concerns on April 5, 2011, because the 30-day rate of stroke and death was higher in the PTAS group.⁶

When enrolment was stopped, fewer than half the 451 patients had been followed up for longer than 1 year.⁶ Since then, patients in both treatment groups have been followed up for 2 more years to establish whether the early benefit in the medical group would persist over longer follow-up, or whether the medical group would have a high incidence of late strokes that would eliminate the early efficacy gap between the two groups. In this Article, we report the final results of the SAMMPRIS trial.

Methods

Patients and study design

The trial design and early results are available elsewhere.^{5–7} SAMMPRIS was a randomised, superiority, multi-centre, clinical trial funded by the National Institute of Neurological Disorders and Stroke (NINDS). The US Food and Drug Administration (FDA) issued an Investigational Device Exemption to do the study with the Wingspan stent system (Stryker Neurovascular, Fremont, CA, USA; formerly Boston Scientific Neurovascular),⁸ which had been approved under a Humanitarian Device Exemption in 2005 for patients with 50–99% intracranial stenosis who are refractory to medical treatment.⁹ Eligible patients were 30–80 years old and had non-disabling stroke or transient ischaemic attack within 30 days before enrolment that was attributed to 70–99% atherosclerotic stenosis of a major intracranial artery verified by catheter angiography.¹⁰ Exclusion criteria included tandem extracranial or intracranial stenosis (70–99%) proximal or distal to the target intracranial stenosis, intraluminal thrombus proximal to or at the target lesion, progressive neurological signs within 24 h before enrolment, any haemorrhagic infarct within 14 days before enrolment, non-atherosclerotic causes of intracranial stenosis, and the presence of a cardiac source of embolus. Other eligibility criteria are provided in the study protocol. All patients gave written informed consent to participate. Institutional review boards at all 50 participating sites in the USA approved the study protocol.

Randomisation and masking

We used a one-to-one ratio to randomly allocate patients to treatment, stratifying by centre. The randomisation sequence was produced at the Statistical Coordinating Center (Department of Biostatistics and Bioinformatics, Emory University, GA, USA), using a pseudo-random number generator with randomly permuted block sizes.⁵ The study participants, coordinators, and primary neurologists were not masked to treatment assignment but a second site neurologist was masked to assess patients with mild stroke

endpoints. All potential neurological, cardiac, and haemorrhagic endpoints were adjudicated by independent panels of neurologists and cardiologists who were masked to treatment.

Treatments

Details of the implementation of aggressive medical management have been reported elsewhere.⁷ Briefly, with the exception of the peri-procedural antithrombotic treatment in the PTAS group, medical management was identical in both groups throughout the entire follow-up period. Treatment consisted of aspirin (325 mg per day) for the duration of follow-up, clopidogrel (75 mg per day) for 90 days after enrolment, management of the primary risk factors (systolic blood pressure [SBP] and low-density lipoprotein cholesterol [LDL-C]), targeting SBP lower than 140 mm Hg (<130 mm Hg if diabetic) and LDL-C lower than 1.81 mmol/L, and management of secondary risk factors (diabetes, non-high-density lipoprotein cholesterol, smoking, weight, exercise) with the help of a lifestyle modification programme.¹¹ We provided aspirin, clopidogrel, one drug from each major class of antihypertensive agents, and rosuvastatin. The lifestyle modification programme was delivered by a coach who contacted the patients by telephone every 2 weeks for the first 3 months after enrolment and then monthly. The programme included baseline assessment of risk factors, formulating an action plan (with a focus on exercise, correct nutrition, weight management, and tobacco smoking cessation), and follow-up counselling sessions to help patients acquire the skills, motivation, and support needed to implement and adhere to their individualised action plan. Written health education materials were also provided to the study patients.

PTAS was done by neurointerventionists who were credentialed to participate in the trial based on review of 20 consecutive intracranial angioplasty and stenting cases, at least three of which must have used the Wingspan system. Details on the credentialing process, monitoring of PTAS performance during the trial, and peri-procedure outcomes according to previous operator experience are available elsewhere.^{5,12} A 600 mg dose of clopidogrel was given to patients 6–24 h before PTAS if they had not been taking clopidogrel 75 mg daily for the previous 5 days. Intravenous heparin was used during the procedure to maintain an activated clotting time of 250–300 s. Other details of the procedure and post-PTAS care are provided in the study protocol.

Duration of follow-up and outcomes

The original plan was to follow patients up for a maximum of 3 years and a minimum of 1 year, but when enrolment in the trial was stopped a decision was made by the Executive Committee (MIC, CPD, MJL, DF, TNT, LSJ, JM, and BFL), NINDS, and the data and safety monitoring board to extend the follow-up of all patients to a common termination date 2 years after the last patient was enrolled.

We assessed patients at study entry, 4 days, 30 days, and then every 4 months. All follow-up visits were in person unless the patient could not return for the visit, in which case telephone follow-up was done. Every in-person visit included blood pressure measurement, an examination by the study neurologist, and management of the patient's risk factors. The schedule for doing laboratory tests, the National Institute of Health Stroke (NIH) stroke scale, the modified Rankin scale, and the Barthel index are provided in the study protocol. Telephone follow-up was done by the site coordinator and included assessment of the patient's functional abilities and mobility using the Barthel index and modified Rankin scale, and establishing whether the patient had any adverse events. If so, we obtained the patient's medical records for those events for review.

Patients with a suspected stroke underwent brain MRI or CT and were assessed by the primary site neurologist. Patients who had events that were potentially difficult to classify (a transient ischaemic attack lasting >1 h or mild ischaemic stroke [an increase in the patient's NIH stroke scale of <4 from study entry]) were assessed by a second site neurologist who was masked to treatment. Both neurologists' assessments were sent for central adjudication.

The primary endpoint was any of the following: any stroke or death within 30 days after enrolment, ischaemic stroke in the territory of the qualifying artery beyond 30 days of enrolment, or any stroke or death within 30 days after a revascularisation procedure of the qualifying lesion during follow-up (ie, stenting of a patient in the medical group or angioplasty for symptomatic restenosis in a patient in the PTAS group). We defined ischaemic stroke as a new focal neurological deficit of sudden onset, lasting for at least 24 h, that was not associated with a haemorrhage on brain CT or MRI. We categorised ischaemic strokes as either in or out of the territory of the qualifying artery. We defined symptomatic brain haemorrhage as parenchymal, subarachnoid, or intraventricular haemorrhage detected by CT or MRI that was associated with new neurological signs or symptoms lasting 24 h or more or a seizure.

Statistical methods

The study was originally designed to detect a 35% relative risk reduction in the primary endpoint with PTAS compared with a projected rate in the medical group of 24.7% at 2 years.^{5,6} This rate was based on the outcome of patients with recent symptoms and 70–99% intracranial arterial stenosis who participated in the WASID trial¹³ and incorporated a proposed 15% relative risk reduction with aggressive medical management. With this effect size, probability of type I error of 0.05, power of 0.80, 5% crossover rate from the medical to the PTAS group, and 2% loss to follow-up, the intended sample size based on a two-sided log-rank test was 382 patients per group.

The log-rank test was used to compare the treatment groups for the primary and secondary endpoints. Cumulative probabilities based on estimates of the primary endpoint from the Kaplan-Meier curves at specific timepoints (years 1, 2, and 3) were compared between the treatment groups with a Z test. We investigated longitudinal differences in risk factors between the treatment groups using generalised estimating equation regression models with an exchangeable correlation structure. Subgroup analyses for prespecified baseline factors were done by fitting a Cox proportional hazards regression model that included treatment, a treatment by time interaction (because the proportional hazards assumption for the treatment was not met), the factor, and the treatment by factor interaction (the p value for which is reported in this paper). All analyses were done by intention to treat. All reported p values are two-sided without adjustment for multiple testing.

We did three prespecified sensitivity analyses to generate data for patients withdrawing or becoming lost to follow-up. First, all patients lost to follow-up or withdrawn were considered to have had a primary endpoint at last contact. Second, only patients in the PTAS group were considered to have had a primary endpoint at last contact. Third, only patients in the medical group were considered to have had a primary endpoint at last contact. Additionally, we used a simulation approach (appendix) in which a hazard rate per month for the primary endpoint was estimated for each treatment group from available data for all patients with patients lost to follow-up or withdrawn censored at their last study visit. For each patient lost to follow-up or withdrawn, we randomly determined whether a primary endpoint occurred for each study month according to the hazard rate. If a simulated primary endpoint did not occur in any month, the patient was censored at the longest possible follow-up time. The simulated data for patients lost to follow-up or withdrawn were combined with the actual data for the remaining patients and the p value for the log-rank test comparing the

treatment groups and the probabilities of a primary endpoint by 2 years were computed. The process was repeated 10 000 times. We used SAS (version 9.3) for all statistical analyses.

Role of the funding source

The Executive Committee designed the study and oversaw trial activities. A representative of the study sponsor was on the Executive Committee of the trial (LSJ) and participated in oversight of the trial. Industry partners supplied the stents and rosuvastatin for study patients and supplemental funding for third-party monitoring and auditing of sites, but did not participate in the design, conduct, data analysis, or reporting of the trial. CPD, MIC, and MJL had full access to the study data and had final responsibility to submit for publication.

Results

Between Nov 25, 2008, and March 31, 2011, we randomly assigned 451 patients to treatment: 227 to the medical group and 224 to the PTAS group (figure 1). Baseline characteristics were much the same between the two groups (table 1). The median duration of follow-up in all patients was 32.4 months (IQR 24.2–40.5; range 0 months to 52.6 months). A larger proportion of patients in the medical group were lost to follow-up or withdrew consent than in the PTAS group (24 [11%] of 227 vs 10 [5%] of 224; $p=0.0193$). Most withdrawals in both groups occurred after 1 year of follow-up (appendix).

The percentages of patients who achieved SBP and LDL-C targets and the mean SBP and LDL-C values at various stages of follow-up in both groups are shown in figure 2 and table 2. Data for the secondary risk factors are shown in the appendix. In these analyses, we detected no statistically significant between-group difference over time for any risk factors when analysed in terms of either the actual values or the percentage of patients in target range.

Throughout the trial, primary endpoint events occurred more often in the PTAS group than in the medical group (table 3, figure 3). The occurrence of primary endpoints in the medical group versus PTAS group was 5.8% versus 14.7% at day 30 ($p=0.0016$), 12.6% versus 19.7% at year 1 ($p=0.0428$), 14.1% versus 20.6% at year 2 ($p=0.07$), and 14.9% versus 23.9% at year 3 ($p=0.0193$). Beyond 30 days of enrolment, 10% of patients in each group had a primary endpoint event (21 of 210 patients in the medical group and 19 of 191 patients in the PTAS group; appendix). Beyond 1 year of enrolment, six (3%) of 185 patients in the medical group and eight (5%) of 175 patients in the PTAS group had a primary endpoint event.

The results of all sensitivity analyses are provided in the appendix. The worst case scenario for the medical group in which only patients in the medical group who withdrew or were lost to follow-up were assigned primary endpoints at last contact still resulted in the probability of a primary endpoint being numerically higher in the PTAS group, although not statistically significantly higher. In the simulation analysis, none of the 10 000 repetitions resulted in the probability of a primary endpoint being less common in the PTAS group than in the medical group.

Table 3 shows the secondary endpoints and other major adverse events in each group (additional details on all events in appendix). The rates of any stroke ($p=0.0468$) and any major haemorrhage ($p=0.0009$) were statistically significantly lower in the medical group than they were in the PTAS group.

Results of subgroup analyses for pre-specified baseline factors with rates of the primary endpoint at 2 years for the medical and PTAS groups are shown in table 4. We detected no interaction with treatment for any of the factors.

Discussion

The early benefit of aggressive medical treatment compared with PTAS in high-risk patients with intracranial arterial stenosis persisted over a median duration of 32.4 months of follow-up in this trial. Although we cannot rule out the possibility that longer follow-up would have shown less benefit from medical treatment alone, we think this possibility is unlikely because there was no suggestion that the efficacy gap between the two groups narrowed over time—the absolute risk reduction from medical treatment was 8.9% at 30 days and 9.0% at 3 years. These data imply that even if the 30-day rate of stroke and death had been as low as anticipated in the PTAS group (ie, similar to the 30-day rate of 5.8% in the medical group), PTAS would still not have provided any long-term benefit over medical treatment alone because the anticipated benefit of PTAS over medical treatment beyond the peri-procedural period did not occur. This finding was mainly because the primary endpoint rate in the medical group (14.1% at 2 years) was much lower than was projected (24.7% at 2 years).

The much lower rate of stroke in the medical group in SAMMPRIS compared with patients in WASID who had similar entrance criteria,^{4,13,14} is probably explained by differences in medical treatment in these trials. Patients in WASID were treated with usual risk factor management and either aspirin or warfarin, whereas patients in SAMMPRIS were treated with intensive risk factor management and combined aspirin and clopidogrel for 90 days followed by aspirin alone. In SAMMPRIS, SBP lower than 140 mm Hg and LDL-C lower than 1.81 mmol/L were attained in 34% (SBP) and 24% (LDL-C) of patients at enrolment and in 70% and 62% of patients at 1 year (figure 2), whereas in WASID these same risk factor levels were attained in 49% and 6% of patients at enrolment and in 50% and 12% of patients at 1 year (the LDL-C target in WASID was <2.59 mmol/L, which was achieved in 42% of patients at 1 year).¹⁵ At 30 days after enrolment, when the benefits of intensive risk factor management would be expected to be limited, the stroke or death rate in the medical group in SAMMPRIS (5.8%) was almost half the rate of that in those patients in WASID with similar entrance criteria (10.7%).¹⁴ This finding suggests that dual antiplatelet therapy could have played an important part in lowering the early risk of stroke in the medical group of SAMMPRIS. Findings from two other trials have also shown that dual antiplatelet therapy can be more effective than aspirin alone in recently symptomatic patients with intracranial stenosis¹⁶ or at high risk of harbouring intracranial stenosis.¹⁷

Concerns have been raised that the medical management used in SAMMPRIS is not real-world practice and that the early success in controlling risk factors would not be sustained over long-term follow-up.¹⁸ However, all the essential elements of medical management in SAMMPRIS (dual antiplatelet therapy, intensive management of blood pressure and LDL-C, and the lifestyle programme) can be incorporated into clinical practice. Blood pressure and LDL-C were managed by study coordinators and neurologists who followed the study's risk factor management algorithms. These algorithms are available elsewhere⁷ and could easily be used in practice. Provision of a lifestyle management programme to patients with stroke is not yet routine care. However, an American Heart Association Presidential Advisory committee recommended that third-party payers should cover the costs of evidence-based lifestyle programmes for secondary prevention.¹⁹ Concern regarding the durability of risk factor control in SAMMPRIS should be allayed by the data showing continued improvement in patients achieving targets for both primary (figure 2) and most secondary risk factors (appendix) over a median follow-up of 32.4 months.

In our pre-specified subgroup analyses, we did not identify any subgroup that benefited from PTAS compared with medical treatment (table 4). The subgroup with a qualifying event while taking antithrombotic treatment constitutes the type of patients treated with Wingspan under the original Humanitarian Device Exemption in clinical practice. These patients had a worse outcome in the PTAS group compared with the medical group in SAMMPRIS (table 4). After publication of the early SAMMPRIS results,⁶ the FDA narrowed the Humanitarian Device Exemption criteria for use of the Wingspan stent to patients with 70–99% stenosis who have had two or more strokes despite aggressive medical management, and whose last stroke occurred more than 7 days ago.²⁰ We cannot provide specific data for this small subgroup of patients (data for medical management at the time of a stroke before the qualifying stroke were not collected), but the closest surrogate is shown in the last variable in table 4. Although this subgroup seems to be at very high risk of stroke on aggressive medical management, there was a similarly high rate of stroke in this subgroup treated with PTAS. Therefore, there are no data suggesting that PTAS with the Wingspan stent is more effective than medical treatment for any subgroup of patients with intracranial stenosis. However, if other endovascular techniques, such as angioplasty alone,^{21,22} can substantially lower the risk of the most frequent types of peri-procedural strokes that occurred in SAMMPRIS (ie, perforator stroke in the region of stent deployment, subarachnoid haemorrhage, and parenchymal brain haemorrhage related to reperfusion),^{23,24} further randomised trials assessing these techniques in high-risk patients might be needed.

This study has some limitations. Because only one of the treatment groups underwent stenting, the trial could not be double masked. However, we tried to make the assessment of potential endpoints as unbiased as possible by making sure that a second site neurologist who was masked to treatment also assessed patients with potential mild stroke endpoints because these are the events that are most difficult to judge and subject to potential bias. Although we selected and credentialled experienced neurointerventionists to participate in this trial, it is possible that the high rate of peri-procedural stroke in SAMMPRIS in part reflects the fact that intracranial stenting is still an uncommon procedure compared with coronary stenting, and that the complication rates of intracranial stenting will decrease with more experience. However, the challenge is to obtain this clinical experience without putting patients at excessive risk. Additionally, even if the peri-procedural risk could be reduced substantially, it is unlikely to be lowered to the level needed for intracranial stenting to be more effective than aggressive medical management because of the inherent risk of the procedure.

The final results of SAMMPRIS show that aggressive medical treatment is superior to PTAS with the Wingspan system at both early and later phases of follow-up (panel). Although aggressive medical management seems to have substantially lowered the risk of stroke in these patients compared with historical controls managed with usual medical management, there are still subgroups of patients at high risk of stroke on aggressive medical treatment. Future research should focus on the development of new treatments to lower the risk of stroke in these high-risk patients. In this regard, it is interesting that the risk of stroke in the territory of a stenotic artery beyond 1 year of follow-up was very low in the medical group in SAMMPRIS, as was the case in WASID.^{4,13} A lower risk of stroke over time has also been shown in patients with symptomatic atherosclerotic stenosis (70–99%) of an extracranial internal carotid artery.²⁵ One possible explanation for these findings is that the common pathophysiological mechanisms of recurrent stroke in patients with atherosclerotic intracranial or extracranial stenosis (artery-to-artery embolism and distal hypoperfusion)^{26–28} become attenuated over time. This might be related to stabilisation of vulnerable plaque²⁹ and improvement in collateral blood flow,³⁰ in which case new treatments that accelerate these reparative processes could become important components of the treatment of these high-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Panel: Research in context**Systematic review**

This study (SAMMPRIS) is the first randomised trial to compare aggressive medical management alone with aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS) with the Wingspan stent system in patients with atherosclerotic intracranial arterial stenosis. Wingspan is the only stent approved by the FDA (under a humanitarian device exemption) for use in patients with atherosclerotic intracranial arterial stenosis. We know that SAMMPRIS is the first randomised trial to assess the Wingspan stent from participating in an FDA panel meeting (March 23, 2012; Washington, DC, USA) on the Wingspan stent after the early results of SAMMPRIS had been published. We also searched Medline, the Cochrane Central Register of Controlled Trials, the Internet Stroke Trials Center Registry, and ClinicalTrials.gov from 2005 (when Wingspan was approved by the FDA) for publications in English and identified no other completed randomised trials using the Wingspan stent. We did our last search on Sept 15, 2013. Before SAMMPRIS began, three single-arm multicentre studies provided limited pilot data for the safety and potential efficacy of the Wingspan stent in patients with intracranial arterial stenosis and set the stage for the SAMMPRIS trial.

Interpretation

The final results of SAMMPRIS show that aggressive medical treatment is superior to PTAS with the Wingspan stent in patients with recent transient ischaemic attack or stroke (within past 30 days) attributed to 70–99% atherosclerotic intracranial arterial stenosis. PTAS was inferior because of the high risk of peri-procedural stroke and because there was no benefit from PTAS beyond the peri-procedural period. Other key findings in the study were as follows. First, high success rates at achieving target levels for vascular risk factors, particularly the primary risk factors (systolic blood pressure and low-density lipoprotein cholesterol) throughout the duration of the trial (median follow-up 32.4 months) using the study's risk factor protocols. This, in combination with the use of aspirin and clopidogrel for 90 days followed by aspirin alone, probably contributed to the much lower than expected risk of stroke in the medical group. Second, that the risk of stroke beyond 1 year in medically treated patients with severe intracranial arterial stenosis is low. And third, there was no suggestion that any subgroup of patients benefited from PTAS compared with medical management alone. Overall, these results lend support to the use of aggressive medical management rather than PTAS with the Wingspan system in high-risk patients with atherosclerotic intracranial arterial stenosis.

Figure 1. Trial profile

PTAS=percutaneous transluminal angioplasty and stenting. *Months after enrolment when PTAS was done: 0·1, 0·9, 2·2, 2·6, 3·2, 3·8, 6·5, 8·2, 14·1. †See appendix for length of follow-up for these patients.

Figure 2. Patients achieving target systolic blood pressure (A) and low-density lipoprotein cholesterol (B) throughout the trial
 (A) Target systolic blood pressure was <140 mm Hg (<130 mm Hg if diabetic). (B) Target low-density lipoprotein was <1.81 mmol/L. PTAS=percutaneous transluminal angioplasty and stenting.

Figure 3. Cumulative probability of a primary endpoint by treatment
PTAS=percutaneous transluminal angioplasty and stenting.

Table 1

Baseline characteristics

	Medical group (N=227)	PTAS group (N=224)
Age in years	59.5 (11.8)	61.0 (10.7)
Men	145 (64%)	127 (57%)
Ethnic origin (self-reported)		
Black	49 (22%)	55 (25%)
White	162 (71%)	160 (71%)
Other	16 (7%)	9 (4%)
History of hypertension	203 (89%)	200 (89%)
History of lipid disorder	202 (89%)	195 (87%)
Smoking		
Never	78 (34%)	90 (40%)*
Previously	80 (35%)	79 (35%)*
Currently	69 (30%)	54 (24%)*
Diabetes [†]	103 (45%)	105 (47%)
Systolic blood pressure (mm Hg)	146.8 (21.8)	143.9 (20.6)
Low-density lipoprotein cholesterol (mmol/L)	2.53 (0.95)	2.49 (0.99)
High-density lipoprotein cholesterol (mmol/L)	1.00 (0.26)	0.98 (0.27)
Non-high-density lipoprotein cholesterol (mmol/L)	3.02 (1.04)	3.01 (1.14)
Glycosylated haemoglobin in patients with diabetes [‡]	8.2 (2.3)	7.8 (2.1)
Body-mass index (kg/m ²)	30.7 (6.3)	30.3 (6.2)
History of coronary artery disease	59 (26%)	47 (21%)
History of stroke (not qualifying event)	58 (26%)	60 (27%)
Qualifying event		
Stroke	152 (67%)	142 (63%)
Transient ischaemic attack	75 (33%)	82 (37%)
On antithrombotic therapy at qualifying event	140 (62%)	144 (64%)
Days from qualifying event to randomisation (median [IQR])	7 (4–19)	7 (4–16)
Symptomatic qualifying artery		
Internal carotid artery	49 (22%)	45 (20%)
Middle cerebral artery	105 (46%)	92 (41%)

	Medical group (N=227)	PTAS group (N=224)
Vertebral artery	22 (10%)	38 (17%)
Basilar artery	51 (22%)	49 (22%)
Percent stenosis of symptomatic qualifying artery [§]	81 (7)	80 (7)
Categories of percent stenosis of symptomatic qualifying artery [§]		
70–79%	102 (45%)	107/223 (48%)
80–89%	97 (43%)	92/223 (41%)
90–99%	28 (12%)	24/223 (11%)

Data are mean (SD) or n (%), unless otherwise stated. PTAS=percutaneous transluminal angioplasty and stenting.

* Data for one patient missing, so denominator is 223.

[†] Diabetic at baseline if history of diabetes or if haemoglobin A_{1c} ≥ 6.5%.

[‡] For this analysis, baseline haemoglobin A_{1c} values for any patient with a history of diabetes, new diagnosis of diabetes during follow-up, or haemoglobin A_{1c} ≥ 6.5% at any time in the study were included.

[§] According to reading of angiogram by site interventionist.

Table 2

Primary risk factors according to treatment and visit

	Low-density lipoprotein cholesterol (mmol/L)				Systolic blood pressure (mm Hg)			
	Medical group		PTAS group		Medical group		PTAS group	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	226	2.53 (0.95)	220	2.49 (0.99)	227	146.8 (21.8)	220	143.9 (20.6)
30 days	215	1.85 (0.69)	210	2.01 (0.73)	216	140.8 (21.7)	213	138.8 (20.0)
4 months	193	1.84 (0.67)	186	1.96 (1.03)	198	134.2 (17.0)	186	133.1 (15.8)
1 year	138	1.75 (0.71)	138	1.79 (0.76)	172	132.1 (16.1)	172	129.5 (17.4)
2 years	95	1.61 (0.58)	100	1.74 (0.80)	149	129.1 (14.1)	153	130.0 (15.4)
3 years	39	1.74 (0.66)	45	1.74 (0.79)	88	128.7 (16.3)	86	126.7 (14.2)

For low-density lipoprotein cholesterol at years 1, 2, and 3, we used the value that was closest to the designated timepoint within a window of 4 months before or after the timepoint. For systolic blood pressure, the value that was closest to the designated timepoint within a window of 2 months before or after the timepoint was used. PTAS=percutaneous transluminal angioplasty and stenting.

Table 3
Comparison of treatment groups for the primary endpoint, secondary endpoints, and other major adverse events

	Medical group (N=227)		PTAS group (N=224)		p value	
	Patients with event	Probability at 1 year	Probability at 2 years	Patients with event		Probability at 1 year
Primary endpoint	34 (15%)	12.6% (8.9%–17.8%)	14.1% (10.1%–19.4%)	52 (23%)	19.7% (15.0%–25.5%)	20.6% (15.9%–26.5%)
Any stroke or death	51 (23%)	17.5% (13.1%–23.2%)	19.8% (15.1%–25.6%)	64 (29%)	22.8% (17.8%–28.9%)	24.1% (19.1%–30.3%)
Any death [†]	13 (6%)	4.0% (2.0%–7.8%)	4.5% (2.4%–8.5%)	13 (6%)	4.0% (2.1%–8.0%)	4.6% (2.4%–8.7%)
Any stroke	42 (19%)	14.9% (10.8%–20.3%)	17.2% (12.9%–22.9%)	59 (26%)	21.9% (17.0%–27.9%)	23.3% (18.3%–29.4%)
Disabling or fatal stroke [‡]	18 (8%)	6.7% (4.0%–11.1%)	7.8% (4.8%–12.4%)	21 (9%)	9.1% (5.9%–13.8%)	10.1% (6.7%–15.1%)
Myocardial infarction	9 (4%)	3.4% (1.6%–7.1%)	3.4% (1.6%–7.1%)	5 (2%)	2.1% (0.8%–5.5%)	2.7% (1.1%–6.4%)
Major non-stroke haemorrhage [§]	9 (4%)	1.9% (0.7%–5.1%)	3.0% (1.4%–6.7%)	16 (7%)	4.4% (2.3%–8.3%)	7.9% (4.8%–12.7%)
Any major haemorrhage [¶]	10 (4%)	2.4% (1.0%–5.7%)	3.5% (1.7%–7.2%)	29 (13%)	9.8% (6.5%–14.6%)	13.1% (9.1%–18.5%)

Data are n (%) or probability (95% CI). PTAS=percutaneous transluminal angioplasty and stenting.

* The p value is for comparison of time-to-event curves for the two treatment groups for each of the specified adverse events, calculated with the log-rank test.

† Causes of death in the medical group=brain haemorrhage (n=1), ischaemic stroke (n=1), myocardial infarction (n=2); one had an ischaemic stroke in the territory 17 days before but the immediate cause of death was myocardial infarction), cardiac arrest after coronary artery bypass surgery (n=1), sudden cardiac death (n=1), and non-vascular death (n=7); causes of death in the PTAS group=brain haemorrhage (n=4), ischaemic stroke (n=2), sudden cardiac death (n=2), and non-vascular death (n=5).

‡ Disability was based on the post-stroke assessment closest to 90 days after a patient's stroke (a disabling stroke was defined as any of the following: modified Rankin of 4, Barthel index of 80, composite National Institutes of Health (NIH) stroke scale of 7), NIH stroke scale of 3 for motor examination of arm or leg, NIH stroke scale of 2 for best language, NIH stroke scale of 3 for visual category—ie, cortical blindness: a stroke was considered fatal for this analysis if death occurred within 30 days or if stroke was the adjudicated cause of death.

§ Any subdural or epidural haemorrhage or a systemic haemorrhage requiring any of the following: admission to hospital, blood transfusion, or surgery.

¶ Any intracranial haemorrhage or a systemic haemorrhage requiring any of the following: admission to hospital, blood transfusion, or surgery; one patient in the PTAS group had both a symptomatic brain haemorrhage and a major non-stroke haemorrhage.

Table 4

Comparison of treatment groups for the primary endpoint in pre-specified subgroups

	Medical group		PTAS group		p value [‡]
	n	Probability [*] by 2 years	n	Probability [*] by 2 years	
Age (median)					0.75
<60 years	119	12%	107	16%	
60 years	108	17%	117	25%	
Gender					0.40
Male	145	11%	127	18%	
Female	82	20%	97	24%	
Symptomatic artery					0.63
ICA	49	23%	45	29%	
MCA	105	13%	92	14%	
Vertebral	22	10%	38	21%	
Basilar	51	10%	49	25%	
Qualifying event					0.12
TIA	75	7%	82	21%	
Stroke	152	18%	142	21%	
Days from qualifying event to enrolment (median)					0.55
7	115	13%	115	23%	
>7	112	15%	109	18%	
Old infarct in the territory of symptomatic artery [‡]					0.35
No	147	9%	146	16%	
Yes	75	23%	69	28%	
On antithrombotic at time of qualifying event					0.68
No	87	12%	80	19%	
Yes	140	16%	144	22%	

	Medical group		PTAS group		p value [†]
	n	Probability by 2 years [*]	n	Probability by 2 years [*]	
Old infarct in territory and stroke as qualifying event while on antithrombotic treatment					0.21
No	186	10%	185	17%	
Yes	36	35%	30	33%	

ICA=intracranial carotid artery. MCA=middle cerebral artery. PTAS=percutaneous transluminal angioplasty and stenting. TIA=transient ischaemic attack.

^{*} The product-limit estimate of the cumulative probability of a primary endpoint by 2 years after enrolment.

[†] p value for the interaction of treatment and the factor from a Cox proportional hazards model that included treatment, treatment by time interaction, factor, and treatment by factor interaction.

[‡] As assessed by brain imaging after qualifying event.