

**Stenting for symptomatic vertebral artery stenosis: a preplanned pooled individual patient data analysis**

Prof Hugh S Markus FMed Sci, Eric L Harshfield PhD, Annette Compter MD Wilhelm Kuker MD, Prof L Jaap Kappelle MD, Andrew Clifton FRCR, Bartvan der Worp MD, Prof Peter Rothwell FMed Sci, Ale Algra MD.

Vertebral Stenosis Trialists' Collaboration

Funding

None.

## **Abstract**

### **Background**

Symptomatic vertebral artery stenosis is associated with a high risk of recurrent stroke, with higher risks for intracranial than for extracranial stenosis. Vertebral artery stenosis can be treated with stenting with good technical results, but whether it results in improved clinical outcome is uncertain. We aimed to compare vertebral stenting with medical treatment for symptomatic vertebral stenosis.

### **Methods**

We did a preplanned pooled individual patient data analysis of three completed randomised controlled trials comparing stenting with medical treatment in patients with symptomatic vertebral stenosis. The primary outcome was any fatal or non-fatal stroke. Analyses were performed for vertebral stenosis at any location and separately for extracranial and intracranial stenoses. Data from the intention-to-treat analysis were used for all studies. We estimated hazard ratios (HRs) with 95% CIs using Cox proportional-hazards regression models stratified by trial.

### **Findings**

Data were from 354 individuals from three trials, including 179 patients from VIST (148 with extracranial stenosis and 31 with intracranial stenosis), 115 patients from VAST (96 with extracranial stenosis and 19 with intracranial stenosis), and 60 patients with intracranial stenosis from SAMMPRIS (no patients had extracranial stenosis). Across all trials, 168 participants (46 with intracranial stenosis and 122 with extracranial stenosis) were randomly assigned to medical treatment and 186 to stenting (64 with intracranial stenosis and 122 with extracranial stenosis). In the stenting group, the frequency of periprocedural stroke or death was higher for intracranial stenosis than for extracranial stenosis (ten (16%) of 64 patients vs one (1%) of 121 patients;  $p<0.0001$ ). During 1036 person-years of follow-up, the hazard ratio (HR) for any stroke in the stenting group compared with the medical treatment group was 0.81% CI 0.45–1.44;  $p=0.47$ ). For extracranial stenosis alone the HR was 0.63 (95% CI 0.27–1.46) and for intracranial stenosis alone it was 1.06 (0.46–2.42;  $p_{\text{interaction}}=0.395$ ).

## Interpretation

Stenting for vertebral stenosis has a much higher risk for intracranial, compared with extracranial, stenosis. This pooled analysis did not show evidence of a benefit for stroke prevention for either treatment. There was no evidence of benefit of stenting for intracranial stenosis. Stenting for extracranial stenosis might be beneficial, but further larger trials are required to determine the treatment effect in this subgroup.

## Introduction

About 20% of all acute ischaemic strokes are in the posterior (or vertebrobasilar) circulation.<sup>1</sup> In about a quarter of these strokes, the underlying pathophysiological mechanism is stenosis of the vertebral or basilar arteries.<sup>1</sup> Symptomatic vertebral stenosis is associated with a substantially increased risk of recurrent stroke, particularly in the first few weeks after symptoms occur.<sup>2</sup> It has been suggested that vertebral artery stenting might reduce this risk. Several trials in the past 8 years have examined this question, although all have been essentially phase 2 trials without a sufficient sample size to definitively determine whether stenting is better than medical therapy.

Interpretation of trial data is complicated by the differing natural history, and safety of stenting, for extracranial versus intracranial vertebral stenosis. Natural history studies have shown that intracranial stenosis is associated with a higher risk of early recurrent stroke,<sup>2</sup> but it has also been associated with increased periprocedural stroke risk with stenting.<sup>3</sup> By contrast, extracranial stenosis is associated with a lower but still elevated early recurrent stroke risk,<sup>2</sup> and a lower risk of periprocedural stroke with stenting.<sup>3, 4</sup> Therefore, it is possible that the benefits of vertebral stenting differ for extracranial and intracranial vertebral stenoses.

Studies in symptomatic carotid stenosis have shown that the benefit of intervention with revascularisation is highest in patients treated within the first 2 weeks after symptoms occur.<sup>5</sup> The temporal profile of increased stroke risk after symptomatic vertebral stenosis is very similar to that seen for carotid stenosis,<sup>2</sup> and therefore it is possible that a similar enhanced benefit in patients treated soon after symptoms occur might also apply to vertebral stenosis. The results of the Vertebral Artery Ischaemia Stenting Trial (VIST)<sup>6</sup> supported this hypothesis, although it was inadequately powered to definitively answer this question because it was terminated early by the funder because of low recruitment.

## **Research in context**

### **Evidence before this study**

Vertebral stenting has been widely used to treat symptomatic vertebral stenosis, but whether it reduces the frequency of recurrent stroke is uncertain. Randomised controlled trials comparing stenting with medical treatment were identified in the scientific literature. We searched PubMed for research articles published in English between database inception and Jan 27, 2018, using the search terms “vertebral artery AND stenting AND clinical trial”. We identified three trials of stenting versus medical therapy that included patients with symptomatic vertebral stenosis, from which original participant data could be obtained. This included data from 354 individuals with 1036 person-years of follow-up.

### **Added value of this study**

Our analysis showed that the periprocedural risk of stroke and death was much higher for patients with intracranial compared with extracranial stenosis (16% vs 1%). There was no significant difference between either stenting or medical therapy alone in stroke prevention. There was no suggestion of any potential benefit for intracranial stenosis. For extracranial stenosis, larger studies are required to determine whether there could be a benefit for stenting.

### **Implications of all the available evidence**

Data from current randomised controlled trials comparing medical treatment alone with stenting as treatment for symptomatic vertebral stenosis show no evidence that either option is superior. Stenting of intracranial vertebral stenosis is associated with a high perioperative stroke risk and is unlikely to be of benefit unless technological advances resulting in a lower stroke risk are developed. Stenting of extracranial stenosis is associated with a low perioperative stroke risk; further larger trials are required to determine whether it might confer benefit over medical therapy.

We aimed to determine whether vertebral stenting is more effective than medical treatment for symptomatic vertebral stenosis using individual patient data pooled from vertebral artery stenting trials published so far. Because of the potentially different treatment benefits in extracranial versus intracranial stenosis, we also aimed to do a preplanned analysis in each subgroup. Additionally, we aimed to evaluate whether the benefit of stenting was increased for patients recruited within 14 days of last symptoms.

## Methods

### Overview

Randomised controlled trials comparing stenting with medical treatment were identified in the scientific literature. We searched PubMed for research articles published between database inception and Jan 27, 2018, using the search terms “vertebral artery AND stenting AND clinical trial”. 45 papers were identified, which included three trials. References and reviews were also searched, identifying two further trials. Five trials were identified: VIST,<sup>6</sup> the Vertebral Artery Stenting Trial (VAST),<sup>7</sup> the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial,<sup>8</sup> the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial,<sup>9</sup> and the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS).<sup>10</sup>

VIST and VAST included patients with both extracranial and intracranial stenosis. SAMMPRIS included patients with intracranial stenosis only, at various arterial locations. VISSIT randomised 112 patients with symptomatic intracranial stenosis in any artery, including the intracranial vertebral artery. The publication did not specify the number of patients with vertebral stenosis and the trial investigators did not respond to emails enquiring about the number of vertebral artery cases and a data access request. Therefore, results of VISSIT could not be included in this analysis. CAVATAS recruited only 16 patients with vertebral stenosis; however, the primary intervention in the majority of cases was angioplasty rather than stenting, and patients were treated in the 1990s with a different generation of interventional devices and different medical regimens. For these reasons, CAVATAS was not included in the pooled analysis.

Individual patient data for VIST and VAST were obtained from the trial investigators, and individual patient data for SAMMPRIS were obtained from the US National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) clinical trial data portal. All three trials recruited patients with recent stroke or transient ischaemic attack, and in all three trials patients gave informed written consent and the protocol was approved by the relevant ethics committee. Recruitment took place from November, 2008, to April, 2011, for SAMMPRIS, January, 2008, to April, 2013, for VAST, and October, 2008, to February, 2015, for VIST.

## **Data analysis**

Data from the intention-to-treat analysis were used for all studies. The data from each trial were cleaned and harmonised to facilitate pooling across studies. We estimated hazard ratios (HRs) with 95% CIs using Cox proportional-hazards regression models stratified by trial to compare outcomes in the stenting versus medical treatment groups. Each patient accumulated follow-up time from their date of randomisation until the date of first event of each type, death, withdrawal, or loss of follow-up. Kaplan-Meier survival analysis was used to construct time-to-event curves, and the log-rank test was used to compare the cumulative number of events between groups. We also tested for interaction between the stenosis site and treatment group. The primary outcome was any fatal or non-fatal stroke during follow-up. We also examined secondary outcomes for posterior circulation stroke, any stroke or transient ischaemic attack, stroke or death, and periprocedural stroke or death, which was defined as stroke or death within 30 days of randomisation. Analyses were performed for vertebral stenosis at any location and separately for extracranial and intracranial stenoses.

As a sensitivity analysis, we also repeated all analyses within the subset of the patients who were recruited within 14 days of symptom onset. Analyses were conducted using R, version 3.4.4, and Stata, version 15.1, with two-sided p values and a significance level of  $p < 0.05$ .

## **Role of the funding source**

There was no funding source for this study.

## **Results**

We analysed individual participant data from 354 individuals who were at risk of vertebral stenosis for 1036 person-years. The study population consisted of 179 patients from VIST (148 with extracranial stenosis and 31 with intracranial stenosis), 115 patients from VAST (96 with extracranial stenosis and 19 with intracranial stenosis), and 60 patients with intracranial stenosis from SAMMPRIS (no patients with extracranial stenosis were enrolled in this trial; figure 1; appendix). 168 participants (46 with intracranial stenosis and 122 with extracranial stenosis) were randomly assigned to medical treatment and 186 to stenting (64 with intracranial stenosis and 122 with extracranial stenosis). The mean age was 66 years (SD 10), and 282 (80%) participants were male (table 1).

Mean time from last symptoms (transient ischaemic attack or stroke) to randomisation was 9.8 days (SD 7.4) in SAMMPRIS, 36.4 days (34.6) in VAST, and 36.0 days (40.8) in VIST.

The overall median follow-up time was 36.5 months (IQR 24.2–49.4). The number of events for each outcome overall and by trial is shown in table 2. 23 (12%) of 186 patients in the stenting group and 24 (14%) of 168 patients in the medical treatment group had a stroke (HR 0.81, 95% CI 0.45–1.44). For extracranial stenosis alone the HR was 0.63 (95% CI 0.27–1.46), and for intracranial stenosis alone it was 1.06 (0.46–2.42; pinteraction=0.395 for the interaction of vertebral stenosis site with treatment group).

Kaplan-Meier survival curves show an initial high early stroke risk with stenting, largely reflecting a high periprocedural stroke or death risk in intracranial stenosis (figure 2). The 30-day periprocedural stroke or death frequency in the stenting group was one (1%) of 121 patients with extracranial stenosis, and ten (16%) of 64 patients with intracranial stenosis ( $\chi^2=16.3921$ ;  $p<0.0001$ ; figure 3).

Results for stroke and transient ischaemic attack are shown in table 3 and figure 4. None of the analyses of secondary outcomes was statistically significant (table 3; appendix).

161 (46%) of 354 patients had a qualifying event that occurred within 14 days of randomisation. Analyses of the primary outcome within this subset of patients are shown in the appendix, again for all stenosis and for extracranial and intracranial stenosis alone. The HRs were 0.65 (95% CI 0.31–1.39) for all stenoses, 0.56 (0.17–1.87) for extracranial stenosis, and 0.72 (0.27–1.90) for intracranial stenosis (pinteraction=0.77).

The risk of stroke during follow-up in each group was nine (7%) of 122 patients in the extracranial stenting group versus 14 (11%) of 122 patients in the extracranial medical treatment group, and 14 (22%) of 64 patients in the intracranial stenting group and ten (22%) of 46 patients in the intracranial medical treatment group.

## Discussion

This pooled analysis of individual patient data from completed vertebral artery stenting trials did not show evidence of a benefit for either stenting or medical treatment in symptomatic vertebral stenosis. Consistent with previous data, this study confirmed a significantly higher periprocedural risk from intracranial than from extracranial vertebral artery stenting.<sup>3</sup> There was no evidence of benefit of either strategy for intracranial stenosis, although CIs around our effect estimates were wide. By contrast, we observed some evidence of benefit for stenting for extracranial stenosis, but this was not statistically significant.

Symptomatic intracranial stenosis has been associated with a high risk of early recurrent stroke.<sup>2</sup> However, SAMMPRIS and VISSIT, both of which included patients with intracranial stenosis at a variety of locations in both the anterior and posterior circulations, reported that medical treatment was more effective than stenting, and that stenting was associated with a high risk of periprocedural stroke. SAMMPRIS instituted an intense medical antiplatelet treatment and intense treatment of cardiovascular risk factors as well as lifestyle prevention measures. This intervention was associated with a lower-than-expected recurrent stroke risk in the medical treatment group. It is possible that the higher risk from stenting in intracranial stenosis might relate both to the much thinner wall of intracranial vessels leading to increased rupture risk and also to the fact that perforating arteries arise from the intracranial vessels and that these arteries could be damaged during stenting. The results of our pooled analysis showed no evidence of any difference in outcome between intracranial vertebral stenosis treated with either medical treatment or stenting.

Stenting for extracranial vertebral stenosis has been associated with a much lower periprocedural stroke risk than has intracranial stenosis.<sup>3, 4</sup> Large series have found this risk to be in the order of 1%.<sup>4</sup> The results of our pooled analysis were consistent with this low risk. However, natural history studies have shown that although the risk of stroke with medical treatment alone is increased with extracranial stenosis, the absolute risk is lower than with intracranial stenosis.<sup>2</sup> Our pooled analysis showed no significant benefit for either stenting or medical treatment alone in this patient group. However, since the HR of any stroke for stenting was 0.63 (95% CI 0.27–1.46), our analysis is consistent with either substantial benefit or harm from stenting, and larger trials than those completed so far are required to determine the benefit of stenting in extracranial stenosis.

To determine the feasibility of further studies in extracranial and intracranial vertebral stenosis, we determined the sample sizes required for a trial to show a difference between the two treatments using estimates of benefit from our current analysis. We used the risk of stroke during follow-up in each group, with power of 0.8 and significance of 0.05, and the ClinCalc online calculator to show that to detect a statistically significant benefit of stenting over medical treatment for patients with intracranial stenosis, a trial with more than 2 million participants would be needed.

The risk of stroke after symptomatic minor stroke and transient ischaemic attack in carotid stenosis is highest in the first 2 weeks, and rapidly reduces after this time.<sup>5</sup> Natural history data from vertebral stenosis suggest a similar temporal profile.<sup>2</sup> A secondary analysis of the carotid endarterectomy trials showed that the benefit of surgery was much greater in



participants who were randomised within 2 weeks of symptoms.<sup>5</sup> For this reason, we performed a secondary analysis limited to patients with symptomatic vertebral stenosis who were randomised within 2 weeks of symptoms. The results of this analysis were similar to the overall analysis, again with a HR of 0.72 for intracranial stenosis and a HR of 0.56 for extracranial stenosis.

Strengths of our analysis are that we were able to include individual patient data, allowing comprehensive assessment of benefits in the overall population and within subgroups. However, it also has some limitations. We were unable to determine how many patients in the VISSIT trial had vertebral stenosis or obtain data on these patients. However, if the proportion of patients with vertebral stenosis is similar to that seen in SAMMPRIS, we estimate that only about 20 of the 112 patients would have had vertebral stenosis and therefore inclusion of these data is unlikely to have had a major effect on our results. Notably, the overall results from VISSIT were similar to those from SAMMPRIS. A potential limitation is the variety of medical therapy used in the different trials. Unlike in SAMMPRIS, in which dual antiplatelet therapy and statins were mandated in the protocol, not all patients in VIST and VAST were on dual antiplatelet therapy with aspirin and clopidogrel, which has been suggested to be more effective at preventing embolisation in large-artery stroke<sup>11</sup> and recurrent events after stroke and transient ischaemic attack.<sup>12, 13</sup> In VIST, the proportion of patients on dual antiplatelet treatment at 1 month was 33% in the medical treatment group and 57% in the stenting group.<sup>6</sup> However, the use of statin treatment at 1 month follow-up (98% in the medical group and 94% in the stenting group) and antihypertensive treatment (80% in the medical group and 78% in the stenting group) was high in both treatment groups in VIST. A further limitation is that even with inclusion of data from three studies, the analysis was relatively underpowered, partly because of premature termination of the VIST trial by the funder because of slow recruitment.

Other considerations in interpretation and generalisability of the results are that SAMMPRIS included a high proportion of African Americans, whereas VIST and VAST had a predominantly white population, and that 80% of the participants in the pooled analysis were male. Furthermore, in VIST, patient selection was based on non-invasive angiographic imaging and in 23 of 91 patients randomly assigned to stenting there was no stenosis, defined as a stenosis of 50% or greater, at angiography performed before stenting, which could have led to an underestimation of the risk associated with stenting. An additional consideration is that these studies examined stenting for first occurrence of stroke or transient ischaemic attack. It has been suggested that recurrent stroke or transient ischaemic attack refractory to medical treatment might represent an indication for stenting,

and it has been frequently performed for this indication, but we were unable to answer this question with this dataset.

In conclusion, this pooled individual patient analysis of data from all available vertebral stenting trials provides the most comprehensive analysis currently possible of the effectiveness of vertebral stenting versus medical treatment in patients with recently symptomatic vertebral stenosis. We found no evidence of a difference between treatment approaches in preventing recurrent stroke. For intracranial stenosis, the periprocedural risk of stenting was high, and there was no evidence of overall benefit on longer-term follow-up. On the basis of these data, further trials are unlikely to alter this conclusion unless the safety of intracranial stenting can be improved considerably. By contrast, stenting for symptomatic extracranial stenosis might be beneficial, but further larger trials than those used in this analysis are required to determine the effect of the intervention more reliably.

## **Contributors**

HSM and AA conceived the research idea and designed the study. EH, AA, and HSM did the analysis and drafted the paper. HSM, ACo, WK, LJK, ACI, HBvdW, PR, and AA contributed data. All authors reviewed the final manuscript.

## **Vertebral Stenosis Trialists' Collaboration**

Ale Algra, Neil Baldwin, Marcus Bradley, Stefan Brew, Andrew Clifton, Annette Compter, Robert Crossley, Anand Dixit, Hedley Emsley, Ian Ford, Peter Gaines, Anil Gholkhar, Anthony Goddard, Timothy Hampton, Ahamad Hassan, Nick Higgins, L Jaap Kappelle, Wilhelm Kuker, Susanna C Larsson, Ralf-Bjoern Lindert, T Hauw Lo, Jeremy Madigan, Hugh S Markus, Willem P Th M Mali, Frans L Moll, Barry Moynihan, Hans Nahser, Sanjeev Nayak, Maneesh Patel, Bartlomiej Piechowski-Jozwiak, Senthil Raghunathan, Christine Roffe, Peter Rothwell, Wouter J Schonewille, Ursula G Schulz, Alakendu Sekhar, Pankaj Sharma, H Bart van der Worp, Jan Albert Vos, David Werring, Siddhartha Wuppalapati.

## **Declaration of interests**

HSM reports grants from the UK National Institute for Health Research Health Technology Assessment and personal fees from BIBA Publishing, outside the submitted work. HBvdW

reports personal fees from Boehringer Ingelheim and Bayer, outside the submitted work. PR reports personal fees from Bayer and Bristol-Myers Squibb, outside the submitted work. All other authors declare no competing interests.

## **Acknowledgments**

HSM is supported by a UK National Institute for Health Research Senior Investigator award. His research is supported by infrastructural support from the Cambridge University Hospital Trust, National Institute for Health Research Biomedical Research Centre. EH's salary is supported by the CoSTREAM project, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement number 667375. PR is supported by the National Institute for Health Research Biomedical Research Centre, Oxford, and by the Wellcome Trust.

## References

1. HS Markus, HB van der Worp, PM Rothwell. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. *Lancet Neurol*, 12 (2013), pp. 989-998.
2. G Gulli, L Marquardt, PM Rothwell, HS Markus. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: pooled data analysis from prospective studies. *Stroke*, 44 (2013), pp. 598-604.
3. O Eberhardt, T Naegle, S Raygrotzki, M Weller, U Ernemann. Stenting of vertebrobasilar arteries in symptomatic atherosclerotic disease and acute occlusion: case series and review of the literature *J Vasc Surg*, 43 (2006), pp. 1145-1154.
4. AN Stayman, RG Nogueira, R Gupta. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. *Stroke*, 42 (2011), pp. 2212-2216.
5. PM Rothwell, M Eliasziw, SA Gutnikov, et al. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. *Lancet*, 361 (2003), pp. 107-116.
6. HS Markus, SC Larsson, W Kuker, VIST Investigators. Stenting for symptomatic vertebral artery stenosis: the Vertebral Artery Ischaemia Stenting Trial. *Neurology*, 89 (2017), pp. 1229-1236.
7. A Compter, HB van der Worp, WJ Schonewille, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. *Lancet Neurol*, 14 (2015), pp. 606-614.
8. MI Chimowitz, MJ Lynn, CP Derdeyn, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*, 365 (2011), pp. 993-1003.
9. OO Zaidat, BF Fitzsimmons, BK Woodward, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. *JAMA*, 313 (2015), pp. 1240-1248.
10. LJ Coward, DJ McCabe, J Ederle, et al. Long-term outcome after angioplasty and stenting for symptomatic vertebral artery stenosis compared with medical treatment in the

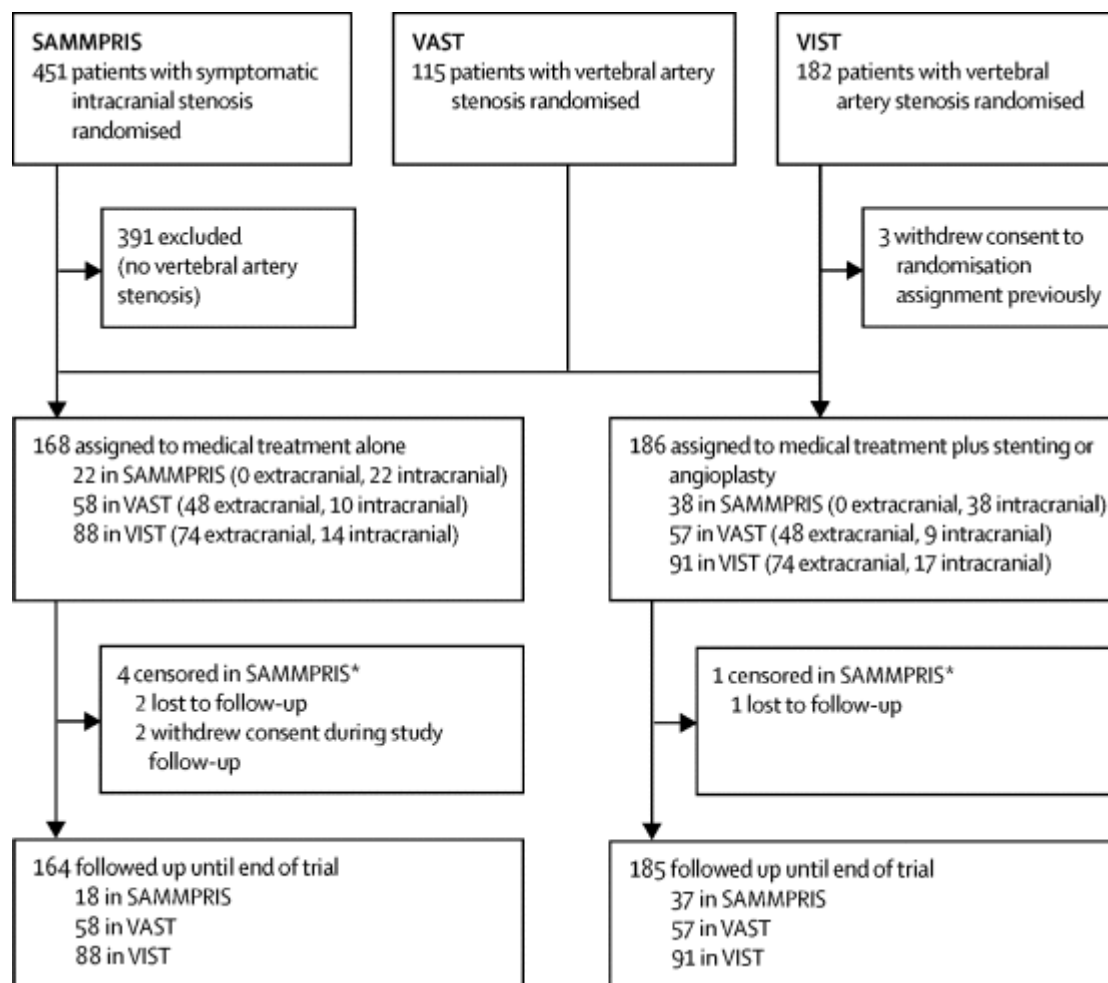
Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomized trial. *Stroke*, 38 (2007), pp. 1526-1530

11. HS Markus, DW Droste, M Kaps, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation*, 111 (2005), pp. 2233-2240.

12. Y Wang, Y Wang, X Zhao, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*, 369 (2013), pp. 11-19.

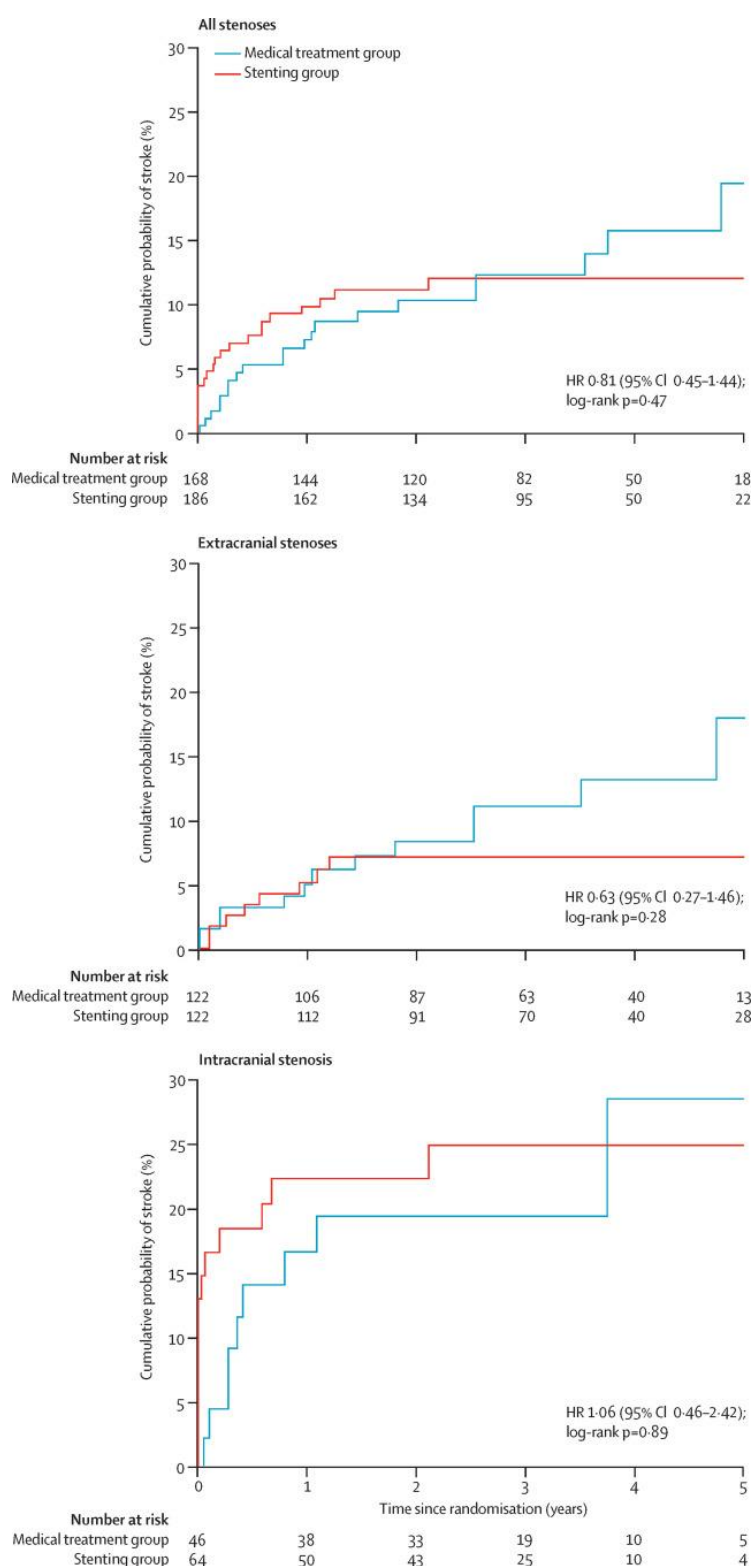
13. SC Johnston, JD Easton, M Farrant, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*, 379 (2018), pp. 215-225.

**Figure 1. Study profile**



SAMMPRIS=Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis. VAST=Vertebral Artery Stenting Trial. VIST=Vertebral Artery Ischaemia Stenting Trial. \*Patients who withdrew consent or were lost to follow-up were censored at date of last contact for time-to-event analyses.

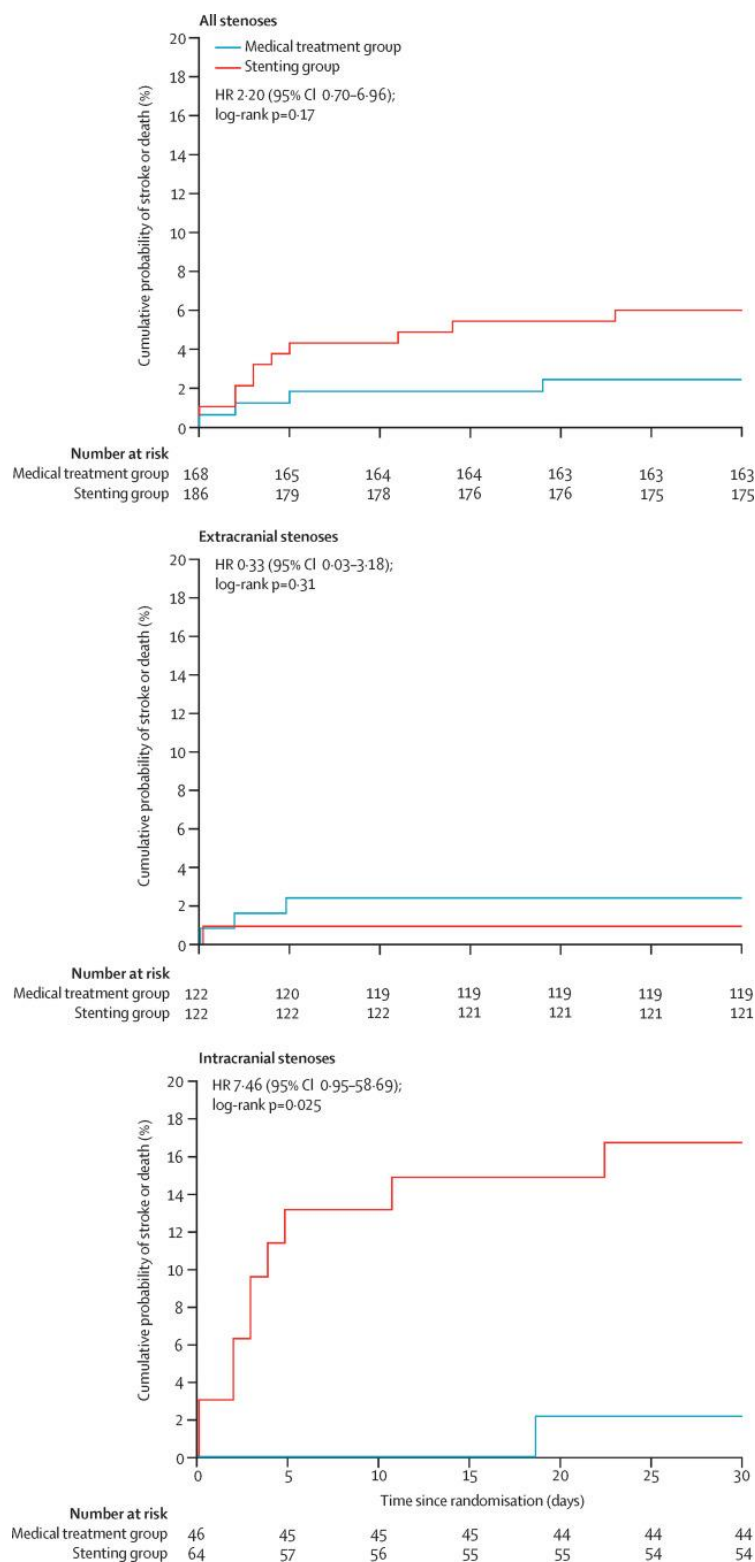
**Figure 2.** Kaplan-Meier plots for cumulative probability of any stroke



SAMMPRIS was excluded from analysis of extracranial stenosis because there were no patients in SAMMPRIS with extracranial stenosis. HR=hazard ratio. SAMMPRIS=Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.

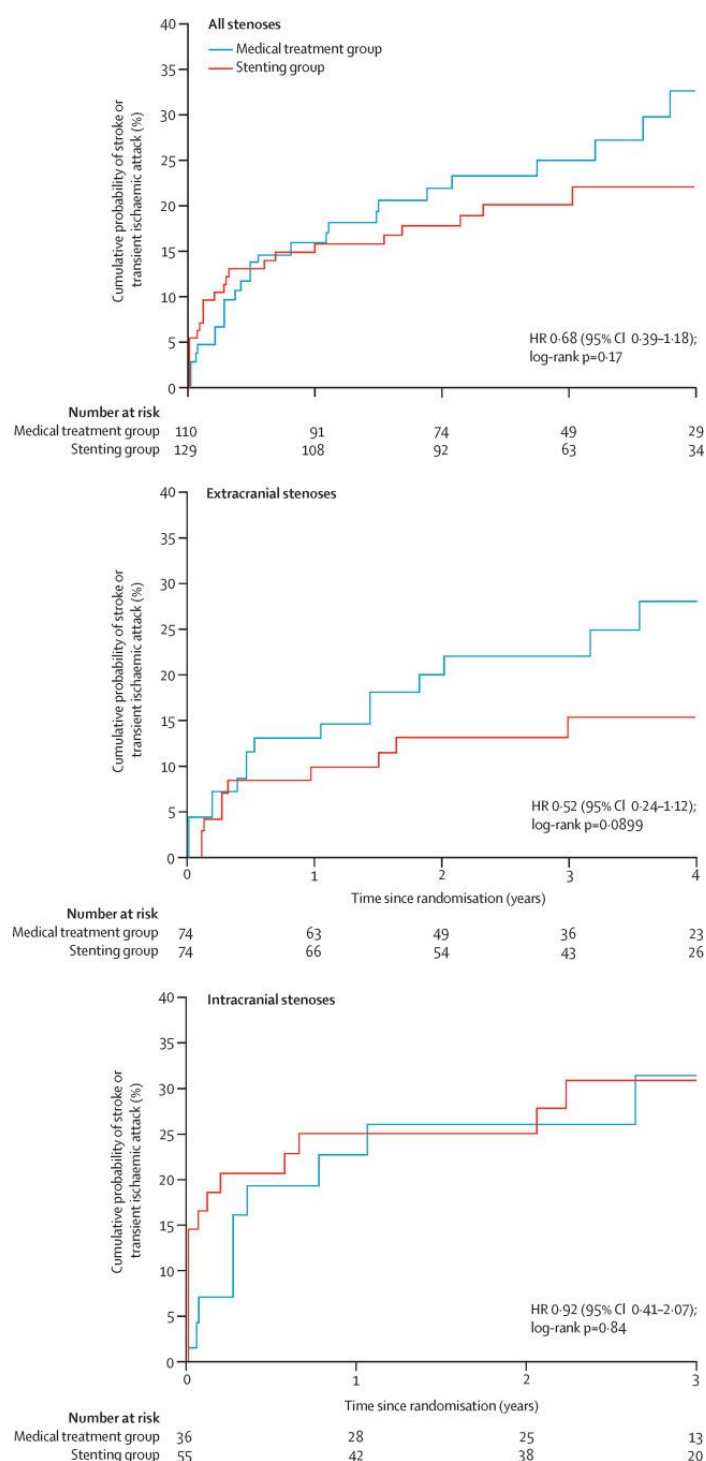
**Figure 3.** Kaplan-Meier plots for cumulative probability of periprocedural stroke or death

SAMMPRIS was excluded from analysis of extracranial stenosis because there were no patients in SAMMPRIS with extracranial stenosis. HR=hazard ratio. SAMMPRIS=Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis.





**Figure 4.** Kaplan-Meier plots for cumulative probability of stroke or transient ischaemic attack by territory



VAST was excluded from all analyses of stroke or transient ischaemic attack because data on the outcome transient ischaemic attack were unavailable for VAST. Additionally, SAMMPRIS was excluded from analysis of extracranial stenosis because there were no patients in SAMMPRIS with extracranial stenosis.

**Table 1.** Summary of baseline characteristics by trial and treatment group

	Age, years	Male sex	Hypertension	Systolic blood pressure, mm Hg	Diabetes	Current smokers	Median follow-up, months
<b>Overall</b>							
SAMMPRIS (n=60)	64 (9)	49 (82%)	37 (63%)	146 (19)	25 (42%)	18 (30%)	32.8 (25.1– 41.1)
VAST (n=115)	65 (10)	85 (74%)	78 (68%)	NA	19 (17%)	33 (29%)	36.4 (15.5– 48.7)
VIST (n=179)	67 (10)	148 (83%)	126 (70%)	143 (60)	39 (22%)	43 (24%)	42.2 (25.6– 56.3)
Total (n=354)	66 (10)	282 (80%)	241 (68%)	144 (52)	83 (23%)	94 (27%)	36.5 (24.2– 49.4)
<b>Medical treatment group</b>							
SAMMPRIS (n=22)	64 (8)	18 (82%)	17 (77%)	149 (17)	7 (32%)	11 (50%)	34.3 (28.9– 41.1)
VAST (n=58)	65 (10)	43 (74%)	38 (66%)	NA	12 (21%)	14 (24%)	36.2 (12.8– 48.9)
VIST (n=88)	67 (10)	75 (85%)	60 (68%)	148 (83)	19 (22%)	25 (28%)	42.5 (23.4– 56.4)
Total (n=168)	66 (10)	136 (81%)	115 (68%)	148 (74)	38 (23%)	50 (30%)	37.1 (23.2– 50.4)
<b>Stenting group</b>							
SAMMPRIS (n=38)	64 (10)	31 (82%)	20 (54%)	144 (20)	18 (47%)	7 (18%)	30.8 (25.1– 39.1)
VAST (n=57)	65 (10)	42 (74%)	40 (70%)	NA	7 (12%)	19 (34%)	36.4 (23.2– 48.6)
VIST (n=91)	68 (9)	73 (80%)	66 (73%)	138 (19)	20 (22%)	18 (20%)	41.6 (27.0– 56.1)
Total (n=186)	66 (10)	146 (78%)	126 (68%)	140 (20)	45 (24%)	44 (24%)	36.4 (24.3– 49.0)

Data are mean (SD), n (%), or median (IQR). NA=not available. SAMMPRIS=Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis. VAST=Vertebral Artery Stenting Trial. VIST=Vertebral Artery Ischaemia Stenting Trial.

**Table 2.** Summary of outcomes by trial and stenosis site

	Transient ischaemic attack	Any stroke	Ischaemic stroke	Haemorrhagic stroke	Posterior circulation stroke	Death	Any stroke or transient ischaemic attack	Any stroke or death	Any stroke or death within 30 days
<b>Overall</b>									
SAMMPRIS (n=60)	4 (7%)	14 (23%)	11 (18%)	3 (5%)	9 (15%)	6 (10%)	18 (30%)	16 (27%)	7 (12%)
VAST (n=115)	NA	16 (14%)	14 (12%)	1 (1%)	9 (8%)	4 (3%)	NA	18 (16%)	4 (3%)
VIST (n=179)	19 (11%)	17 (9%)	15 (8%)	0 (0%)	12 (7%)	17 (9%)	34 (19%)	30 (17%)	4 (2%)
Total (n=354)	23 (6%)	47 (13%)	40 (11%)	4 (1%)	30 (8%)	27 (8%)	52 (15%)	64 (18%)	15 (4%)
<b>Extracranial</b>									
VAST (n=96)	NA	12 (13%)	11 (11%)	1 (1%)	7 (7%)	2 (2%)	NA	14 (15%)	2 (2%)
VIST (n=148)	18 (12%)	11 (7%)	11 (7%)	0 (0%)	6 (4%)	13 (9%)	28 (19%)	22 (15%)	2 (1%)
Total (n=244)	18 (7%)	23 (9%)	22 (9%)	1 (0%)	13 (5%)	15 (6%)	28 (11%)	36 (15%)	4 (2%)
<b>Intracranial</b>									
SAMMPRIS (n=60)	4 (7%)	14 (23%)	11 (18%)	3 (5%)	9 (15%)	6 (10%)	18 (30%)	16 (27%)	7 (12%)
VAST (n=19)	NA	4 (21%)	3 (16%)	0 (0%)	2 (11%)	2 (11%)	NA	4 (21%)	2 (11%)
VIST (n=31)	1 (3%)	6 (19%)	4 (13%)	0 (0%)	6 (19%)	4 (13%)	6 (19%)	8 (26%)	2 (6%)
Total (n=110)	5 (5%)	24 (22%)	18 (16%)	3 (3%)	17 (15%)	12 (11%)	24 (22%)	28 (25%)	11 (10%)

Data are number of events (%). All patients in SAMMPRIS had intracranial stenosis. VAST did not provide data on transient ischaemic attack outcomes so they were excluded from all analyses of transient ischaemic attack and stroke or transient ischaemic attack. NA=not available. SAMMPRIS=Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis. VAST=Vertebral Artery Stenting Trial. VIST=Vertebral Artery Ischaemia Stenting Trial.

**Table 3.** Results of survival analyses: overall and by symptomatic artery

	Events (%)	Hazard ratio (95% CI)
<b>Any stroke</b>		
All patients (n=354)	47 (13%)	0.81 (0.45–1.44)
Extracranial (n=244)	23 (9%)	0.63 (0.27–1.46)
Intracranial (n=110)	24 (22%)	1.06 (0.46–2.42)
<b>Posterior circulation stroke</b>		
All patients (n=354)	30 (8%)	0.82 (0.40–1.70)
Extracranial (n=244)	13 (5%)	0.84 (0.28–2.49)
Intracranial (n=110)	17 (15%)	0.83 (0.31–2.19)
<b>Any stroke or transient ischaemic attack</b>		
All patients (n=239)	52 (22%)	0.68 (0.39–1.18)
Extracranial (n=148)	28 (19%)	0.52 (0.24–1.12)
Intracranial (n=91)	24 (26%)	0.92 (0.41–2.07)
<b>Any stroke or death</b>		
All patients (n=354)	64 (18%)	0.81 (0.49–1.33)
Extracranial (n=244)	36 (15%)	0.70 (0.36–1.35)
Intracranial (n=110)	28 (25%)	1.01 (0.47–2.16)
<b>Any stroke or death within 30 days of randomisation</b>		
All patients (n=354)	15 (4%)	2.20 (0.70–6.96)
Extracranial (n=244)	4 (2%)	0.33 (0.03–3.18)
Intracranial (n=91)	11 (10%)	7.46 (0.95–58.69)

VAST did not provide data on transient ischaemic attack outcomes so they were excluded from all analyses of transient ischaemic attack and stroke or transient ischaemic attack. VAST=Vertebral Artery Stenting Trial.