Stenting for Symptomatic Vertebral Artery Stenosis: Pooled Individual Patient Data analysis of VIST, VAST and SAMMPRIS

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Abstract (number of words: 295)

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 outcome is uncertain. We performed an individual patient pooled analysis of completed randomised controlled trials comparing vertebral stenting with medical treatment for symptomatic vertebral stenosis.

Methods

We analysed individual participant data from 354 individuals from three trials, including 179 patients from VIST (148 extracranial, 31 intracranial), 115 patients from VAST (96 extracranial, 19 intracranial), and 60 intracranial patients from SAMMPRIS (no extracranial). The primary outcome was any fatal or nonfatal stroke. Cox regression analysis was performed stratified by trial.

Findings

168 subjects (46 intracranial; 122 extracranial) were randomised to medical treatment and 186 to stenting (64 intracranial; 122 extracranial). In those randomised to stenting, the periprocedural stroke or death rate was higher for intracranial stenosis than for extracranial stenosis (10/64(15.6%) v 1/121(0.8%), p=0.00005). During 1,036 years of follow-up, the hazard ratio (HR) for any stroke in the stenting compared with the medical arm was 0.81 (95% confidence interval [CI] 0.45-1.44). For extracranial stenosis alone it was 0.63 (0.27-1.46), and for intracranial stenosis alone 1.06 (0.46-2.42). For patients randomised within 14 days of last symptoms HRs for any stroke were: all 0.65 (0.31-1.39), extracranial 0.56 (0.17-1.87), and intracranial 0.72 (0.27-1.90).

Interpretation

Stenting for vertebral stenosis has a much higher risk for intracranial, compared with extracranial, stenosis. This pooled analysis did not show a statistically significant benefit on preventing stroke 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 whether there is benefit in this subgroup.

Research in context

<u>Evidence before this study</u>

Vertebral stenting has been widely used to treat symptomatic vertebral stenosis, but it is uncertain as to whether it reduces recurrent stroke rate. Randomised controlled trials comparing stenting with medical treatment were identified in the literature. A PubMed search was performed on 27th January 2018 using the search terms "vertebral artery AND stenting AND clinical trial". We identified 3 trials of stenting versus medical therapy which included patients with symptomatic vertebral stenosis from which original participant data could be obtained. This included data from 354 individuals with 1,036 person-years of follow-up.

<u>Added value of this study</u>

Analysis showed that the peri-procedural risk of stroke and death was much higher for intracranial compared with extracranial stenosis (15.5 v 0.8%). There was no significant difference between either stenting or medical therapy alone in treatment in preventing stroke. 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.

<u>Implications of all the available evidence</u>

Data from current randomised controlled trials, comparing medical treatment alone with stenting, for symptomatic vertebral stenosis shows no evidence that either treatment 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 may confer benefit over medical therapy

Introduction

20% of all acute ischaemic strokes are in the posterior (or vertebrobasilar) circulation.(1) In about a quarter of these the underlying pathophysiological mechanism is stenosis of the vertebral or basilar arteries.(1) Symptomatic vertebral stenosis is associated with a markedly increased risk of recurrent stroke, particularly in the first few weeks following symptoms.(2) It has been suggested that vertebral artery stenting may reduce this risk. A number of recent trials have examined this question, although all have been essentially phase 2 trials without 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 intracranial stenosis is associated with a higher risk of early recurrent stroke,(2) but it has also been associated with a higher periprocedural stroke risk with stenting.(3) In contrast, extracranial stenosis is associated with a lower but still elevated early recurrent stroke risk,(2) and a lower risk of periprocedural stroke.(3,4) Therefore, it is possible that the benefits of vertebral stenting differ for extracranial and intracranial vertebral stenosis.

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

To determine whether vertebral stenting is more effective than medical treatment for symptomatic vertebral stenosis we performed an individual patient data pooled analysis of the vertebral artery stenting trials published to date. Because of the potential different treatment benefits in extracranial versus intracranial stenosis we also performed a pre-planned analysis in each subgroup. Additionally, we determined whether the benefit of stenting was increased for patients recruited within 14 days of last symptoms.

Methods

Randomised control trials comparing stenting with medical treatment were identified in the literature. A PubMed search was performed on 27th January 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. In total five trials were identified: the Vertebral artery Ischaemia Stenting Trial (VIST)(6); the Vertebral Artery Stenting Trial (VAST) (7); the Stenting and Aggressive Medical Management for the Prevention of Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial (8); the Vitesse Intracranial Stent Study for Ischaemic Stroke Therapy (VISSIT)(9); and the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS). (10)

VIST and VAST included patients with both extracranial and intracranial stenosis. SAMMPRIS included patients with intracranial stenosis only at a variety of arterial locations: 60 participants were recruited for symptomatic vertebral stenosis. VISSIT randomised 112 patients with symptomatic intracranial stenosis in any artery, including the intracranial vertebral artery. The trial publication did not specify the number 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 National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke (NINDS) clinical trial data portal (https://clinicaltrials.gov/ct2/show/NCT00576693).

Statistical analysis

Data from the intention to treat analysis was used for all studies. The data from each trial were cleaned and harmonised to facilitate pooling across studies. We estimated hazard ratios with 95% confidence intervals using Cox proportional-hazards regression models stratified by trial to compare outcomes in the stenting versus medical treatment arms. 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 arm. 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 TIA, 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 stenosis. 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 (R Core Team) and Stata version 15.1 (StataCorp) with two-sided *P*-values and a significance level of *P* < 0.05.

Results

We analysed individual participant data from 354 individuals from three trials who were at risk for a total of 1,036 person-years. The study population consisted of 179 patients from VIST (148 extracranial stenosis, 31 intracranial), 115 patients from VAST (96 extracranial, 19 intracranial), and 60 patients with intracranial stenosis from SAMMPRIS (no patients with extracranial stenosis were enrolled in this trial) (Figure 1, Supplementary Figure 1 and Supplementary Table 1). The mean (SD) age was 66 (10) years and 282 (80%) participants were male. A summary of other baseline characteristics by trial and treatment group is shown in Table 1.

Mean (SD) time from last symptoms (TIA or stroke) to randomisation was 9.8 (7.4) days in SAMMPRIS, 36.4 (34.6) in VAST, and 36.0 (40.8) in VIST. The median follow-up time was 36.5 months (5th–95th percentile: 3.4–64.2 months). The number of events for each outcome overall and by trial is shown in Table 2. Twenty-three (12.4%) of the 186 patients allocated to stenting and 24 (14.3%) of the 168 medically treated patients had a stroke. The resulting hazard ratio (HR) was 0.81 (95% confidence interval (CI) 0.45-1.44). For extracranial stenosis alone the HR was 0.63 (0.27-1.46), and for intracranial stenosis alone 1.06 (0.46-2.42). The *P*-value for the interaction of vertebral stenosis site with treatment arm was 0.395.

Kaplan-Meier survival curves for the primary outcome are shown in Figure 2 for all stenoses (Figure 2a), extracranial stenosis (Figure 2b), and intracranial (Figure 2c). These show an initial high early stroke risk with stenting, largely reflecting a high periprocedural stroke or death risk in intracranial stenosis. The 30 day periprocedural stroke or death rate in those

patients randomised to stenting was 1/121(0.8%) for extracranial stenosis, and 10/64(15.6%) for intracranial stenosis (chi-squared=16.3921; p<0.0001) (Figure 3).

Results for stroke and TIA are shown in Table 3 and Figure 4. Results from the analyses of the other secondary outcomes are shown in Table 3 and Supplementary Figures 2-3. None of the analyses of secondary outcomes were statistically significant.

Nearly half (n=161, 46%) of the 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 Supplementary Tables 2-4 and in Supplementary Figures 4-6, again for all stenosis and for extracranial and intracranial stenosis alone. The HRs were: 0.65 (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; interaction *P*-value = 0.77.

Discussion

This pooled analysis of individual patient data from completed vertebral artery stenting trials did not show a statistically significant benefit for either interventional or medical treatment in symptomatic vertebral stenosis. Consistent with previous data it confirmed a significantly higher periprocedural risk from intracranial compared with extracranial vertebral artery stenting.(3) Because of these different risks and benefits between intracranial and extracranial stenting we performed separate analyses for extracranial and intracranial stenoses. There was no evidence of benefit of either strategy for intracranial stenosis although confidence intervals around our effect estimates were wide. In contrast, we observed a trend towards benefit of stenting for extracranial stenosis, but this was not statistically significant and there was no significant interaction between the site of stenosis and longer-term outcome.

Symptomatic intracranial stenosis has been associated with a high risk of early recurrent stroke. However, both SAMMPRIS and VISSIT, which both 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 was associated with a lower-than-expected recurrent stroke risk in the medical treatment arm. It is possible that the higher risk from stenting in intracranial stenosis may 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

8

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. Large series have found this to be in the order of 1%.(4) The results of our pooled analysis were consistent with this low risk. However, natural history studies have shown that while the risk of stroke on medical treatment alone is increased with extracranial stenosis, the absolute risk is lower than with intracranial stenosis.(2) Our pooled analysis showed no significant benefit for either stenting or medical treatment alone in this patient group. However, since the hazard ratio 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 are required to determine the benefit for 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 (extracranial stenting arm 9/122 (7.38%), medical arm 14/122 (11.48%)), and intracranial, stenting arm 14/64 (21.88%)and medical arm 10/46 (21.74%), with power of 0.8 and significance of 0.05 and the ClinCalc online calculator (https://clincalc.com/stats/samplesize.aspx) The sample size required for to demonstrate an effect in extracranial stenosis would be 1592, but for intracranial stenosis would be 2731606.

The risk of stroke after symptomatic minor stroke and TIA in carotid stenosis is highest in the first two weeks, and rapidly reduces after this time.(5) Natural history data from vertebral stenosis suggests a similar temporal profile.(2) A secondary analysis of the carotid endarterectomy trials showed that the benefit of surgery was much greater in those participants randomised within two weeks of symptoms(5). For this reason we performed a secondary analysis limited to those patients with symptomatic vertebral stenosis randomised within two weeks of symptoms. The results of this was similar to the overall analysis, again with a hazard ratio of any stroke of close to unity 0.72 for intracranial stenosis and a hazard ratio 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 a number of 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 proportions of patients with vertebral stenosis are similar to that seen in SAMMPRIS we would 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. In SAMMPRIS patients in the medical arm received intensive protocolised treatment. In VIST and VAST intensive medical therapy was recommended but not mandated. 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 (11) and recurrent events after stroke and TIA.(12,13) In VIST the proportion on dual antiplatelet treatment at one month was 33% in the medical treatment arm and 57% in the stenting arm.(6) However, the use of statin treatment at one month follow-up (medical group 98%, stenting group 94%) and antihypertensive treatment (medical group 80%, stenting group 78%) 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; this partly resulted from premature termination of the VIST trial by the funder due to slow recruitment.

Other considerations in interpretation and generalisability of the results are that SAMMPRIS included a high proportion of African Americans, while VIST and VAST had a predominantly white population, and that 80% of the participants in the pooled analysis were male, with only 20% female. Furthermore, in VIST patient selection was based on non-invasive angiographic imaging and in 23 of 91 patients randomised to stenting there was no stenosis >50% stenosis at angiography performed prior to stenting. This could have led to an under-estimation of the risk associated with stenting. An additional consideration is that these studies examined stenting for usually first occurrence of first stroke or TIA. It has been suggested that recurrent stroke or TIA 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 in 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 statistically significant difference between either treatment 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. Based on these data further trials are unlikely to alter this conclusion unless the safety of intracranial stenting can be markedly improved. In contrast, stenting for symptomatic extracranial stenosis might be

beneficial, but further larger trials are required to determine the effect of the intervention more reliably.

References

1. Markus HS, van der Worp HB, Rothwell PM. Posterior circulation ischaemic stroke and transient ischaemic attack: diagnosis, investigation, and secondary prevention. Lancet Neurol. 2013;12: 989–98.

2. Gulli G, Marquardt L, Rothwell PM, Markus HS. Stroke risk after posterior circulation stroke/transient ischemic attack and its relationship to site of vertebrobasilar stenosis: pooled data analysis from prospective studies. Stroke 2013; 44:598-604.

3. Eberhardt O, Naegele T, Raygrotzki S, Weller M, Ernemann U. Stenting of vertebrobasilar arteries in symptomatic atherosclerotic disease and acute occlusion: case series and review of the literature. J Vasc Surg 2006; 43: 1145–54.

4. Stayman AN, Nogueira RG, Gupta R. A systematic review of stenting and angioplasty of symptomatic extracranial vertebral artery stenosis. Stroke 2011; 42: 2212–16.

5. Rothwell PM, Eliasziw M, Gutnikov SA, et al, for the Carotid Endarterectomy Trialists' Collaboration. Analysis of pooled data from the randomised controlled trials of endarterectomy for symptomatic carotid stenosis. Lancet 2003; 361: 107–16.

6. Markus HS, Larsson SC, Kuker W; VIST Investigators. Stenting for symptomatic vertebral artery stenosis: The Vertebral Artery Ischaemia Stenting Trial. Neurology 2017; 89:1229-1236.

7. Compter A, van der Worp HB, Schonewille WJ, et al. Stenting versus medical treatment in patients with symptomatic vertebral artery stenosis: a randomised open-label phase 2 trial. Lancet Neurol 2015; 14:606-614.

8. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med 2011; 365:993–1003.

9. Zaidat OO, Fitzsimmons BF, Woodward BK, 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 2015; 313:1240–1248.

10. Coward LJ, McCabe DJ, Ederle J, 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 2007; 1526-1530.

11. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. 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. 2005;111:2233-40.

12. Wang Y, Wang Y, Zhao X et l. CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013;369:11-9.

13. Johnston SC, Easton JD, Farrant M, et al and the POINT Investigators. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med. 2018;379:215-225.

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Author Contributions

HSM and AA conceived the research idea and designed the study. EH, AA and HSM performed the analysis and drafted the paper. HSM, A Compter, WK, LJK, A Clifton, HBW, PR and AA contributed data. All authors reviewed the final manuscript.

Declaration of Interests

Data access

The data used in this analysis is available to other researchers via the following link: XXXXXXXX (link to be filled in when access arranged with University of Cambridge data repository)

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Table 1 Summary of baseline characteristics by trial and treatment group

Trial (Treatment group)	N	Age (yrs) at baseline mean (SD)	Male sex n (%)	Hypertension at baseline n (%)	SBP (mm Hg) at baseline mean (SD)	Diabetes mellitus at baseline n (%)	Current smokers n (%)	Median follow-up (months) (5th & 95th percentiles)
Overall								
SAMMPRIS	60	64 (9)	49 (82)	37 (63)	146 (19)	25 (42)	18 (30)	32.8 (0.1 to 47.0)
VAST	115	65 (10)	85 (74)	78 (68)	-	19 (17)	33 (29)	36.4 (11.5 to 60.7)
VIST	179	67 (10)	148 (83)	126 (70)	143 (60)	39 (22)	43 (24)	42.2 (3.4 to 71.4)
Total	**354**	**66 (10)**	**282 (80)**	**241 (68)**	**144 (52)**	**83 (23)**	**94 (27)**	**36.5 (3.4 to 64.2)**
Medical treatment group								
SAMMPRIS	22	64 (8)	18 (82)	17 (77)	149 (17)	7 (32)	11 (50)	34.3 (3.3 to 43.6)
VAST	58	65 (10)	43 (74)	38 (66)	-	12 (21)	14 (24)	36.2 (10.8 to 60.5)
VIST	88	67 (10)	75 (85)	60 (68)	148 (83)	19 (22)	25 (28)	42.5 (3.4 to 69.5)
Total	**168**	**66 (10)**	**136 (81)**	**115 (68)**	**148 (74)**	**38 (23)**	**50 (30)**	**37.1 (4.9 to 63.3)**
Stenting/angioplasty treatment group								
SAMMPRIS	38	64 (10)	31 (82)	20 (54)	144 (20)	18 (47)	7 (18)	30.8 (0.1 to 48.0)
VAST	57	65 (10)	42 (74)	40 (70)	-	7 (12)	19 (34)	36.4 (12.0 to 61.3)
VIST	91	68 (9)	73 (80)	66 (73)	138 (19)	20 (22)	18 (20)	41.6 (3.6 to 71.4)
Total	**186**	**66 (10)**	**146 (78)**	**126 (68)**	**140 (20)**	**45 (24)**	**44 (24)**	**36.4 (1.5 to 65.8)**

SBP, systolic blood pressure; SD standard deviation

Table 2. Summary of outcomes by trial and stenosis site

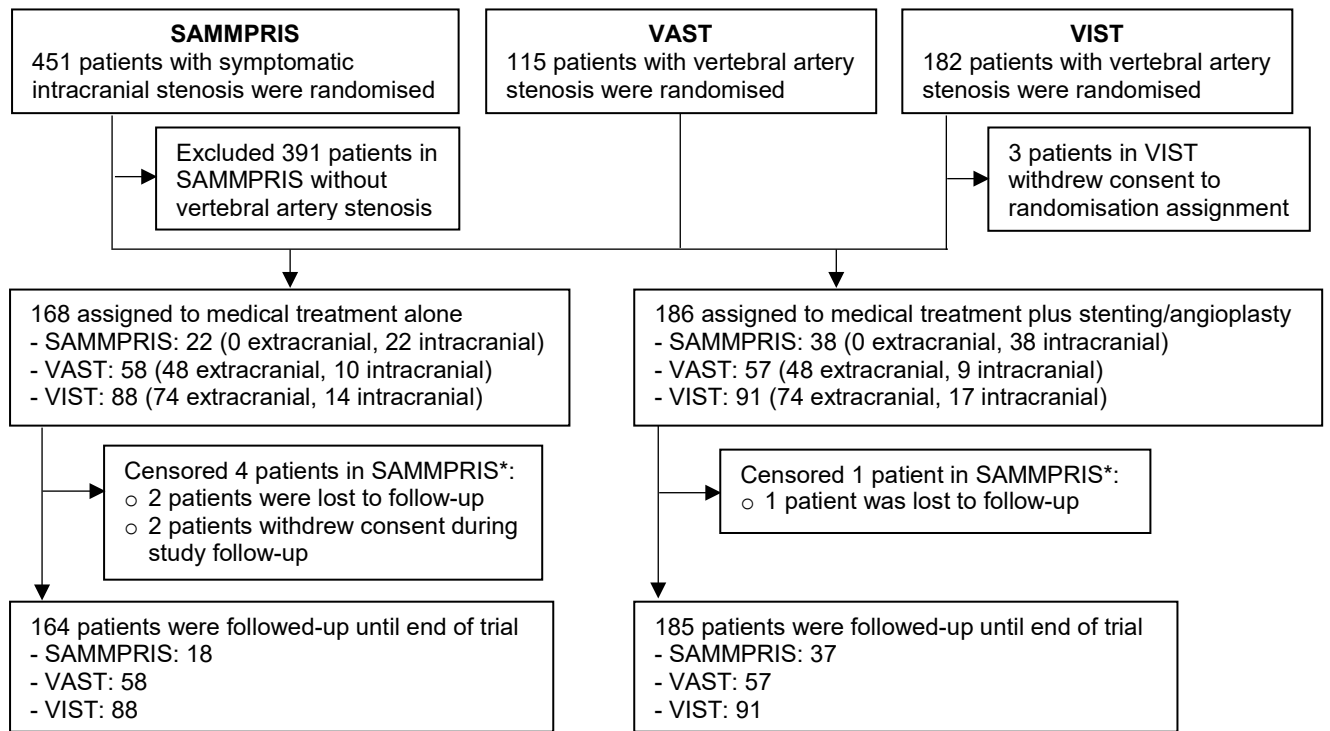| Trial (Stenosis site)	N	TIA	Any stroke	Ischaemic stroke	Haemorrhagic stroke	Posterior circulation stroke	Death	Any stroke or TIA	Any stroke or death	Any stroke or death within 30 days
Overall										
SAMMPRIS	60	4 (7%)	14 (23%)	11 (18%)	3 (5%)	9 (15%)	6 (10%)	18 (30%)	16 (27%)	7 (12%)
VAST	115	NA	16 (14%)	14 (12%)	1 (1%)	9 (8%)	4 (3%)	NA	18 (16%)	4 (3%)
VIST	179	19 (11%)	17 (9%)	15 (8%)	0 (0%)	12 (7%)	17 (9%)	34 (19%)	30 (17%)	4 (2%)
Total	**354**	**23 (6%)**	**47 (13%)**	**40 (11%)**	**4 (1%)**	**30 (8%)**	**27 (8%)**	**52 (15%)**	**64 (18%)**	**15 (4%)**
Extracranial										
SAMMPRIS	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
VAST	96	NA	12 (13%)	11 (11%)	1 (1%)	7 (7%)	2 (2%)	NA	14 (15%)	2 (2%)
VIST	148	18 (12%)	11 (7%)	11 (7%)	0 (0%)	6 (4%)	13 (9%)	28 (19%)	22 (15%)	2 (1%)
Total	**244**	**18 (7%)**	**23 (9%)**	**22 (9%)**	**1 (0%)**	**13 (5%)**	**15 (6%)**	**28 (11%)**	**36 (15%)**	**4 (2%)**
Intracranial										
SAMMPRIS	60	4 (7%)	14 (23%)	11 (18%)	3 (5%)	9 (15%)	6 (10%)	18 (30%)	16 (27%)	7 (12%)
VAST	19	NA	4 (21%)	3 (16%)	0 (0%)	2 (11%)	2 (11%)	NA	4 (21%)	2 (11%)
VIST	31	1 (3%)	6 (19%)	4 (13%)	0 (0%)	6 (19%)	4 (13%)	6 (19%)	8 (26%)	2 (6%)
Total	**110**	**5 (5%)**	**24 (22%)**	**18 (16%)**	**3 (3%)**	**17 (15%)**	**12 (11%)**	**24 (22%)**	**28 (25%)**	**11 (10%)**

Note: All cases in SAMMPRIS had intracranial stenosis. VAST did not provide data on TIA outcomes so they were excluded from all analyses of TIA and stroke or TIA. NA, not available

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

	N	No. of events (%)	HR (95% CI)
Any stroke			
All patients	354	47 (13%)	0.81 (0.45-1.44)
Extracranial	244	23 (9%)	0.63 (0.27-1.46)
Intracranial	110	24 (22%)	1.06 (0.46-2.42)
Posterior circulation stroke			
All patients	354	30 (8%)	0.82 (0.40-1.70)
Extracranial	244	13 (5%)	0.84 (0.28-2.49)
Intracranial	110	17 (15%)	0.83 (0.31-2.19)
Any stroke or TIA			
All patients	239	52 (22%)	0.68 (0.39-1.18)
Extracranial	148	28 (19%)	0.52 (0.24-1.12)
Intracranial	91	24 (26%)	0.92 (0.41-2.07)
Any stroke or death			
All patients	354	64 (18%)	0.81 (0.49-1.33)
Extracranial	244	36 (15%)	0.70 (0.36-1.35)
Intracranial	110	28 (25%)	1.01 (0.47-2.16)
Any stroke or death within 30 days of randomisation			
All patients	354	15 (4%)	2.20 (0.70-6.96)
Extracranial	244	4 (2%)	0.33 (0.03-3.18)
Intracranial	110	11 (10%)	7.46 (0.95-58.69)

VAST did not provide data on TIA outcomes so they were excluded from all analyses of TIA and stroke or TIA.

Figure 1. CONSORT flow diagram

SAMMPRIS	VAST	VIST
451 patients with symptomatic intracranial stenosis were randomised	115 patients with vertebral artery stenosis were randomised	182 patients with vertebral artery stenosis were randomised

Excluded 391 patients in SAMMPRIS without vertebral artery stenosis

3 patients in VIST withdrew consent to randomisation assignment

168 assigned to medical treatment alone
- SAMMPRIS: 22 (0 extracranial, 22 intracranial)
- VAST: 58 (48 extracranial, 10 intracranial)
- VIST: 88 (74 extracranial, 14 intracranial)

186 assigned to medical treatment plus stenting/angioplasty
- SAMMPRIS: 38 (0 extracranial, 38 intracranial)
- VAST: 57 (48 extracranial, 9 intracranial)
- VIST: 91 (74 extracranial, 17 intracranial)

Censored 4 patients in SAMMPRIS*:
o 2 patients were lost to follow-up
o 2 patients withdrew consent during study follow-up

Censored 1 patient in SAMMPRIS*:
o 1 patient was lost to follow-up

164 patients were followed-up until end of trial
- SAMMPRIS: 18
- VAST: 58
- VIST: 88

185 patients were followed-up until end of trial
- SAMMPRIS: 37
- VAST: 57
- VIST: 91

*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 survival curves for cumulative probability of any stroke

(a) All stenoses, (b) Extracranial stenosis, (c) Intracranial stenosis. Note: SAMMPRIS was excluded from analysis of extracranial stenosis as there were no patients in SAMMPRIS with extracranial stenosis.
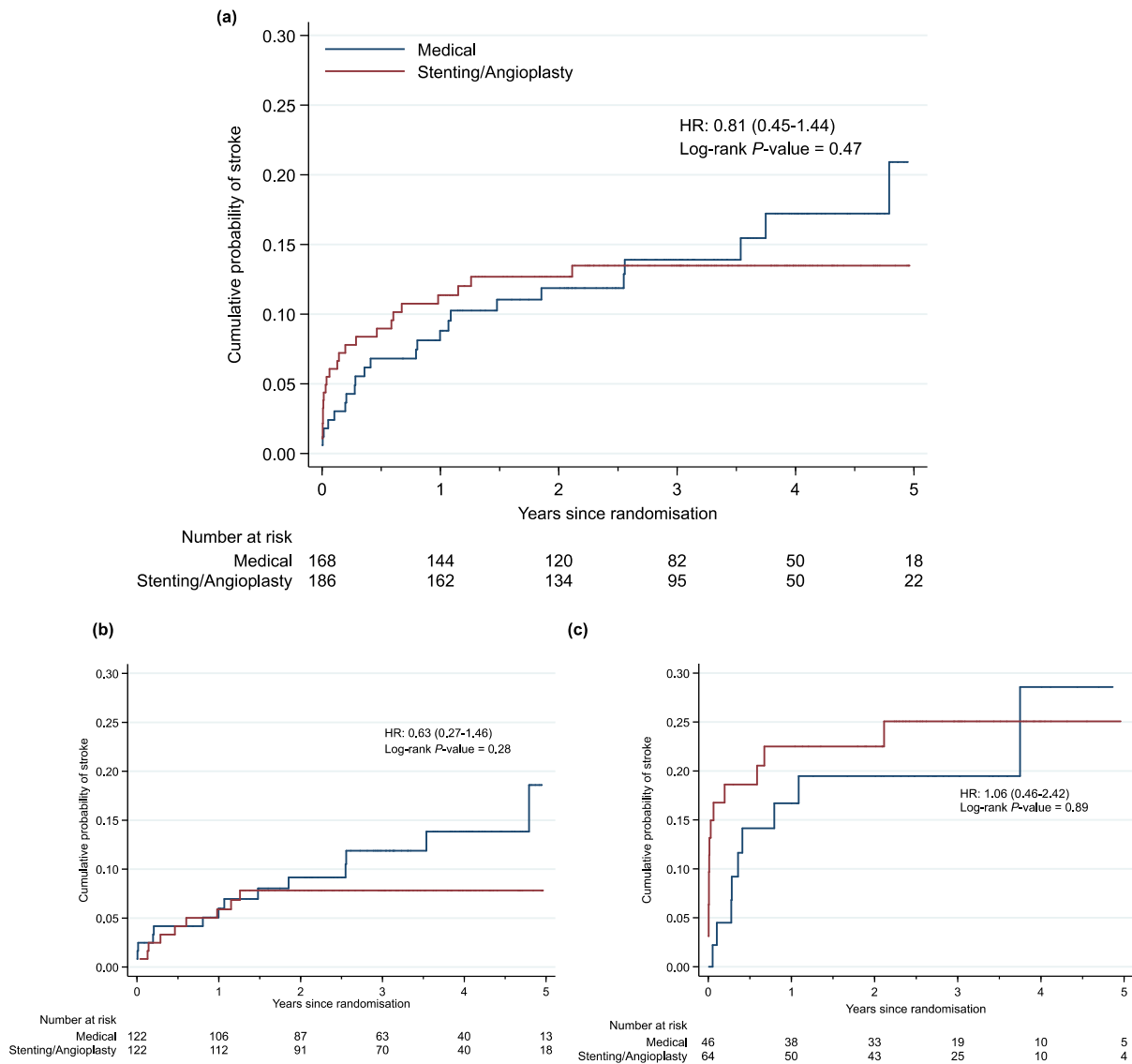
Figure 3. Kaplan-Meier survival curves for cumulative probability of periprocedural stroke or death

(a) All stenoses, (b) Extracranial stenosis, (c) Intracranial stenosis. Note: SAMMPRIS was excluded from analysis of extracranial stenosis as there were no patients in SAMMPRIS with extracranial stenosis.
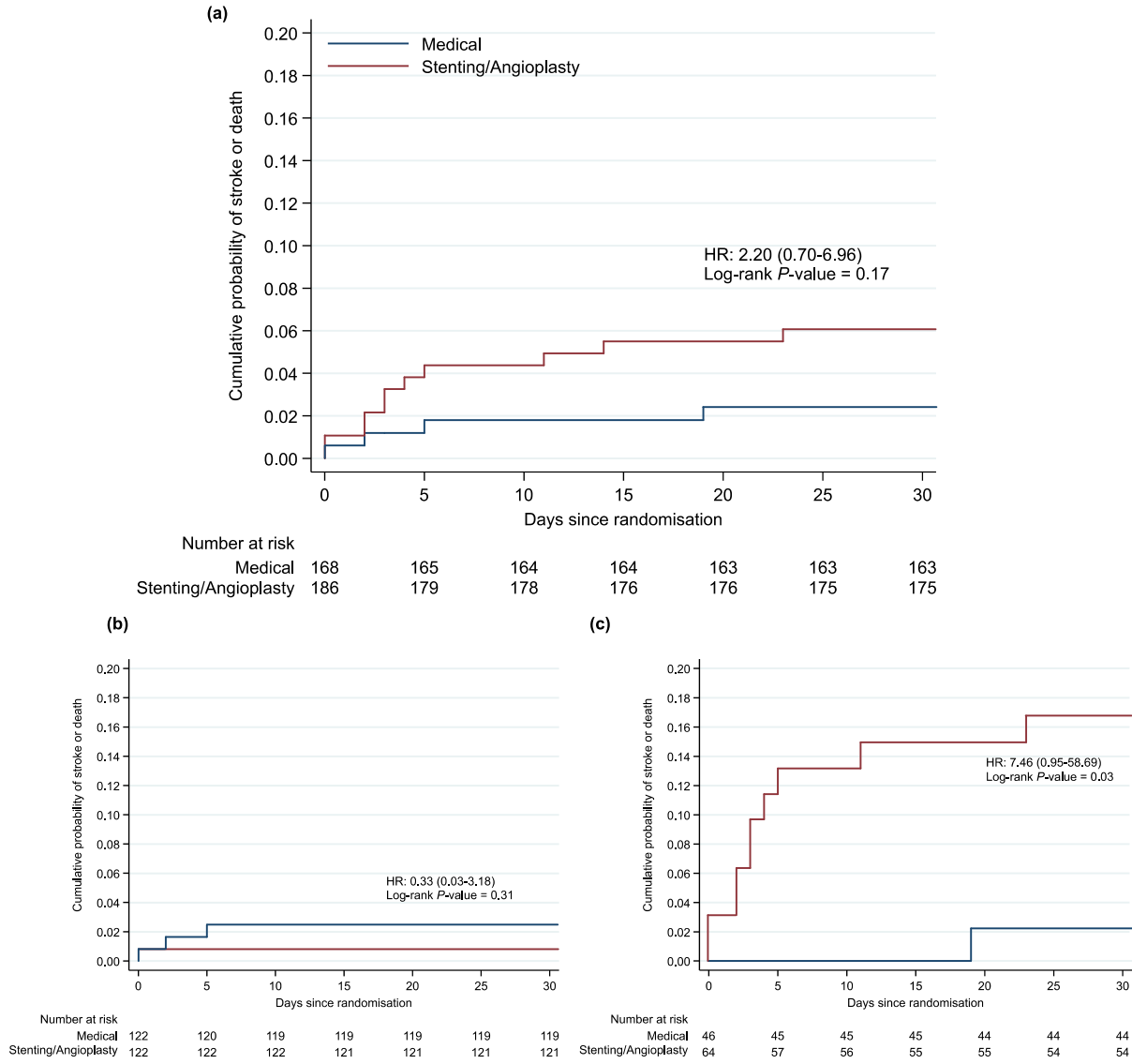
Figure 4. Kaplan-Meier survival curves for cumulative probability of stroke or TIA by territory

(a) All stenoses, (b) Extracranial stenosis, (c) Intracranial stenosis. Note: VAST was excluded from all analyses of stroke or TIA because data on the outcome TIA were unavailable for VAST. Additionally, SAMMPRIS was excluded from analysis of extracranial stenosis as there were no patients in SAMMPRIS with extracranial stenosis.