SVN Stroke and Vascular Neurology

Stenting for intracranial stenosis: potential future for the prevention of disabling or fatal stroke

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To cite: Yu W, Jiang W-J. Stenting for intracranial stenosis: potential future for the prevention of disabling or fatal stroke. *Stroke and Vascular Neurology* 2018;**3**: e000158. doi:10.1136/svn-2018-000158

Received 29 March 2018
Revised 20 May 2018
Accepted 24 May 2018
Published Online First
18 June 2018

Check for updates

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ABSTRACT

Intracranial stenosis is a common cause of ischaemic strokes, in particular, in the Asian, African and Hispanic populations. The randomised multicentre study Stenting and Aggressive Medical Management for the Prevention of Recurrent stroke in Intracranial Stenosis (SAMMPRIS) showed 14.7% risk of stroke or death in the stenting group versus 5.8% in the medical group at 30 days, and 23% in the stenting group versus 15% in the medical group at a median follow-up of 32.4 months. The results demonstrated superiority of medical management over stenting and have almost put the intracranial stenting to rest in recent years. Of note, 16 patients (7.1%) in the stenting group had disabling or fatal stroke within 30 days mostly due to periprocedural complications as compared with 4 patients (1.8%) in the medical group. In contrast, 5 patients (2.2%) in the stenting group and 14 patients (6.2%) in the medical group had a disabling or fatal stroke beyond 30 days, indicating significant benefit of stenting if periprocedural complications can be reduced. Recently, the results of the Chinese Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis trial and the Wingspan Stent System Post Market Surveillance Study (WEAVE trial) showed 2%–2.7% periprocedural complications. It is time to evaluate the role of intracranial stenting for the prevention of disabling or fatal stroke.

INTRODUCTION

Stroke is a leading cause of adult disability.[1] Intracranial stenosis is the narrowing of major intracranial arteries due to the build-up of atherosclerotic plaque.[2 3] It is probably the most common cause of stroke worldwide.[2–4] It is more common in the Asian, African and Hispanic populations.[4–8] The incidence is as high as 30%–50% among Chinese population.[8] The standard medical therapy for patients with intracranial stenosis includes the use of antithrombotics, statins, antihypertensives and risk factor controls.[9]

The risk of recurrent stroke in patients with high-grade intracranial stenosis is significant despite medical therapy.[10–13] Among patients with a haemodynamically significant stenosis, 60.7% had a recurrent stroke or TIA in the territory of the stenotic artery.[13] In the double-blind, randomised multicentre Warfarin–Aspirin Symptomatic Intracranial Disease trial that compared the efficacy of warfarin (target international normalized ratio (INR) 2–3) with that of aspirin (1300 mg daily) in symptomatic intracranial stenosis of 50%–99%, the primary end point (ischaemic stroke, intracranial haemorrhage or vascular death not caused by ischaemic stroke) occurred in 22.1% in the aspirin group and 21.8% in warfarin group.[14] The cumulative probability of the recurrent ischaemic stroke in the territory of the stenosed artery was 12% at 1 year and 15% at 2 years in the aspirin group. This trial also revealed that warfarin was associated with higher rates of mortality and major haemorrhage. Patients with symptomatic high-grade stenosis (≥70%) were at higher risk of the lesion-related ischaemic stroke.[15]

HISTORY OF ANGIOPLASTY AND STENTING FOR INTRACRANIAL STENOSIS

Cerebral balloon angioplasty was initially performed for two patients with medically refractory basilar artery stenosis in 1980.[16] Since then, case reports and retrospective series described the techniques and feasibility of angioplasty for intracranial stenosis.[17–19] However, angioplasty was associated with significant risk of intimal dissection, thrombosis, recoiling and vessel rupture.[18 19] In 1999, Connors and Wojak proposed slow inflation and undersizing of the balloons to reduce the risk of complications.[20] In a large single-centre retrospective study with a total of 120 patients, primary angioplasty was found to be associated with a 5.8% periprocedural stroke and death.[21] At a mean 42.3-month follow-up, the annual stroke rate was 3.2% in the territory of treated vessel and 4.4% for all strokes. In a recent multicentre retrospective study of 74 patients, the 30-day stroke/death rate was 5% and the 3-month stroke or death rate was 8.5%.[22]

In 1996, Feldman *et al* successfully used Coronary Palmaz-Schatz stent for the treatment of intracranial carotid stenosis.[23] The

Table 1 Periprocedural complications and outcome of intracranial stenting

Studies	Design	Number of cases	Type of stents	Mean ages	Mean or median follow-up (months)	30-day stroke or death (%)	Stroke or death beyond 30 days (%)
Gomez *et al* 2005[25]	Retrospective	12	Coronary stent	62.6	5.9	16.7	8.3
Mori *et al* 2000[27]	Retrospective	10	Coronary stent	68	11	0	
Levy *et al* 2001[28]	Retrospective	11	Coronary stent	63	4	36.3	
Jiang *et al* 2004[34]	Retrospective	40	Coronary stent		10	10	
SSYLVIA study investigators 2004[35]	Multicentre prospective	43	Neurolink	63.6	6	9.3	4.7
Yu *et al* 2005[36]	Retrospective	18	Coronary stent	69	26.7	11.8	5.6
Chow *et al* 2005[37]	Retrospective	39	Coronary stent		13	28.2	
Kim *et al* 2005[38]	Retrospective	17	Coronary stent	64	17	12	5.9
Qureshi *et al* 2006[39]	Retrospective	18	Drug-eluting stent	57.8	14.3	5.6	5.6
Fiorella *et al* 2007[40]	Retrospective	44	Coronary stent	64.8	43.5	26.1	2.3
Jiang *et al* 2007[41]	Retrospective	213	Coronary or Apollo	52.8	26	4.7	3.4
Kurre *et al* 2010[42]	Multicentre registry	243	Not reported			7	8.2
Bose *et al* 2007[43]	Prospective, multicentre	45	Wingspan	66	13	4.5	4.6
Fiorella *et al* 2007[44]	Retrospective	78	Wingspan	63.6	9	6.1	
Zaidat *et al* 2008[45]	Multicentre registry	129	Wingspan	64.2	5.8	9.6	3.1
Wolfe *et al* 2009[46]	Retrospective	51	Wingspan	63	14.6	8	2
Jiang *et al* 2010[47]	Prospective, single centre	100	Wingspan	53.2	21.4	5	4
Fiorella *et al* 2011[48]	Multicentre registry	158	Wingspan	62.7	14.2		8.2

patient had chronic transient ischaemic attacks (TIAs) due to severe stenosis of the intracranial carotid artery and failed treatment with both antiplatelet and anticoagulant therapy. The use of stent led to better angiographic result than angioplasty alone and clinical improvement. A few groups subsequently investigated the feasibility and safety of stenting for intracranial stenosis.[24–30] In a small single-centre study, stenting was shown to have lower rates of residual stenosis than angioplasty.[31] However, there was no difference in restenosis at 12 months or stroke/death-free survival at 2 years.

The rigid coronary stent was associated with up to 30% risk of procedure-related complications (table 1).[26 30] In a small case series, staged stent placement or placement of undersized stents were shown to reduce risk of periprocedural complication.[32 33]

In 2004, Jiang *et al* developed a lesion location, morphology and access classification to predict the technical success and outcome of intracranial stenting.[34]

Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA trial) was the first multicentre, non-randomised, prospective feasibility study that evaluated the balloon-expandable Neurolink stent system (Guidant, Indianapolis, IN, USA) for patients with symptomatic stenosis of ≥50.[35] In the 43 patients with intracranial stenosis, the rate of stroke was 9.3% within 30 days and 4.7% between 30 days and 1 year. In 2005, Yu *et al* reported the long-term outcome of stenting for symptomatic basilar artery stenosis.[36] Although periprocedural complication rate was high at 17.8%, the risk of stroke at a mean 26.7-month follow-up was 5.6%.

Table 1 lists the rates of periprocedural complications and outcome of the pivotal case series and multicentre studies with at least 10 patients. Although most studies vary widely in inclusion criteria, severity of stenosis, medical therapy, type of stents and duration of follow-up, the rate of 30-day stroke or death was lower in studies published after 2007. The rate of stroke or death beyond 30 days was very low (2%–8.3%) and relatively consistent among various studies. These findings suggested potential long-term benefit of intracranial stenting.[34–47] The beneficial effect of intracranial stenting appears to hinge on the risk of periprocedural complications.[47]

Wingspan stent for intracranial arterial stenosis

The balloon-expandable coronary stent has limited flexibility and requires high inflation pressure for deployment in the fragile intracranial vessels.[26–29] There were also risks of shearing the stent off the balloon while navigating to the target lesion and difficulty in sizing the stent accurately for vessels of different diameters across the target lesion.

In 2005, the Food and Drug Administration approved the Wingspan stent system (Boston Scientific, Fremont, CA, USA) under the Humanitarian Device Exemption programme for patients with symptomatic intracranial stenosis >50% who are refractory to medical treatment.[43] Wingspan stent is a self-expanding intracranial stent composed of nitinol with similar trackability but at least twice the radial outward strength of the Neuroform III stent (Boston Scientific). The use of this system involves submaximal inflation of an angioplasty balloon (Gateway balloon), followed by deployment of the stent. In the initial study of 45 patients with >50% stenosis, the 30-day ipsilateral stroke and death rate was 4.5% and 6-month ipsilateral stroke and death rate was 7%.[43] A few uncontrolled studies have further evaluated the safety and short-term outcome of the Wingspan stents.[44–48] The periprocedural rates of complications were 5%–9.6%.[45–47] The National Institutes of Health registry had the highest rate of 30-day stroke or death at 9.6% partly due to inclusion of large numbers of patients with vertebrobasilar stenosis (41%) and a much higher complication rate at the low-volume centres (17.2%), as compared with the high-volume centre (6.8%).[45]

RANDOMISED TRIALS ON INTRACRANIAL STENTING

Results of SAMPPRIS trial

The Stenting and Aggressive Medical Management for the Prevention of Recurrent stroke in Intracranial Stenosis (SAMMPRIS) trial is a randomised controlled trial comparing aggressive medical management to aggressive medical management plus Wingspan stenting in patients with symptomatic high-grade intracranial stenosis.[49 50] Aggressive medical management included aspirin 325 mg/day for the entire follow-up, clopidogrel 75 mg/day for the first 90 days, intensive management of vascular risk factors to keep systolic blood pressure (SBP) <140 mm Hg (<130 mm Hg if diabetic) and low-density lipoprotein (LDL) <70 mg/dL, and a lifestyle modification programme.[51]

The SAMMPRIS trial started to enrol patients in November 2008 and was stopped early on 5 April 2011 by the data safety monitoring board after 451 patients had been enrolled at 50 participating sites in the USA. The interim data analysis showed a higher-than-expected rate of periprocedural events at 30 days in the stenting group (14.7%) as compared with 5.8% in the medical group (p=0.002) and a lower-than-expected rate of stroke in the medical group (table 2).[49] During a median follow-up of 32.4 months, there were 34 (15%) primary endpoint events in the medical group and 52 (23%) in the stenting group. The absolute differences in the primary endpoints between the two groups were 8.9% at 30 days and 9.0% at year 3.[50] The outcome from stenting is worse than the medical management alone due to higher-than-expected rate of periprocedural complications. Of note, significantly more patients in the medical group withdrew or lost to follow-up.

Results of VISSIT trial

One limitation of the self-expanding Wingspan stent was over-the-wire exchange after balloon angioplasty for the stent deployment, resulting in increased risk of haemorrhagic and embolic stroke from dissection or wire perforation. In contrast, a balloon-mounted stent only needs to cross the lesion once for simultaneous angioplasty and stent placement.

The results of the first randomised trial using a balloon mounted intracranial stent (VISSIT) were reported in 2015. The VISSIT trial had similar eligibility criteria to the SAMMPRIS trial.[52] The medical management in both groups also included aspirin and clopidogrel for 90 days after enrolment followed by aspirin alone, and risk factor management targeting SBP <140 mm Hg and LDL <100 mg/dL. Some study sites in China and Europe were among the six highest enrolling centres in the trial.

Enrolment in VISSIT was stopped early after 112 patients were randomised due to a higher-than-expected rate of stroke in the stenting group and a lower-than-expected rate of stroke in the medical group. The 30-day primary safety endpoint occurred in more patients in the stent group than the medical group (24.1% vs 9.4%, p=0.05) (table 2). Intracranial haemorrhage within 30 days was also much higher in the stent group than in the medical group (8.6% vs 0%, p=0.6). More patients in the stent group had stroke or TIAs at 1 year as compared with medical group (36.2% vs 15.1%, p=0.02). These results

Table 2 Results of the two randomised trials on intracranial stenting

	Symptomatic disease	Number of patients	30-day events	Long-term events beyond 30 days	Withdrew	Lost to follow-up
SAMMPRIS	70%–99% stenosis			32.4 months		
Stenting group		224	33 (14.7%)	52 (23%)	3 (1.3%)	7 (3.1%)
Medical group		227	13 (5.8%)	34 (15%)	13 (5.7%)	11 (4.8%)
VISSIT	70%–99% stenosis			12 months		
Stenting group		59	14 (23.7%)	21 (36.2%)	3 (5.1%)	1 (1.7%)
Medical group		53	5 (9.4%)	8 (15.1%)	3 (5.7%)	6 (11.3%)

do not support the use of a balloon-expandable stent for stroke prevention.

LIMITATIONS OF THE SAMMPRIS AND VISSIT TRIALS

The sample size of the VISSIT trial was too small when it was stopped early. We will focus the discussion on the possible limitations of the SAMMPRIS trial. The aggressive medical therapy in the SAMMPRIS trial included free medications (rosuvastatin and antihypertensives), regular phone calls by a case manager; regular checks and targets for physical exercise, weight, blood pressure, LDL and glycated haemoglobin levels. It sets a very high standard for medical management.[49 51]

In contrast, the stenting protocols were suboptimal. The credentialling requirement for participation in the study was minimal: operator experience of at least 20 stent or angioplasty cases including a minimum of 3 Wingspan cases.[49 51] The procedure may be performed under general or local anaesthesia. After the procedure, the patients may be monitored in the intensive care or step-down unit, with measurement of blood pressure at least every 2 hours, and treatment of SBP >150. Patients who had not been on clopidogrel 75 mg per day for 5 days before stenting were given 600 mg loading dose between 6 and 24 hours before the procedure.[49] The procedure was performed at a median of 9 days after the qualifying event.[53]

Of the 224 patients in the stenting group, 213 patients underwent angioplasty alone (n=5) or angioplasty and stenting (n=208) by 63 interventionists at 48 study sites. Average enrolment was 1.36 patients per year per centre. In the 12 highest enrolling centres, the average enrolment was less than four patients per year.

There were four periprocedural subarachnoid haemorrhages (SAHs) and six intracerebral haemorrhages (ICHs) with four fatalities. Such complications are usually the results of arterial dissection and/or cerebral hyperperfusion.[54] Limited operator experience, a 600 mg clopidogrel loading dose, higher dose of heparin use, relaxed periprocedural monitoring and BP management were the most likely contributing factors. Preoperative clopidgrel loading (600 mg) in combination with high procedural activated clotting time (>300 s) was associated with risk of parenchymal haemorrhage.[53] Lower enrolling sites were also found to have higher rates of haemorrhagic stroke (9.8% at sites enrolling <12 patients vs 2.7% at sites enrolling >12 patients).[55]

In addition, all patients were enrolled based on lesion severity (77%–99% stenosis) without consideration of stroke mechanism, collaterals or brain perfusion. In patients with subcortical stroke, stenting may occlude perforators and increase the risk of recurrent stroke. This may explain why 15 of the 19 periprocedural ischaemic strokes were perforator stroke.[56] Exclusion of these patients or using a smaller balloon to dilate the lesion followed by stent deployment may decrease periprocedural complication.[57–59]

Table 3 Rates of disabling or fatal stroke and withdrawal or lost to follow-up

SAMMPRIS trial	Disabling or fatal stroke within 30 days	Disabling or fatal stroke beyond 30 days	Rate of withdrawal or lost to follow-up
Medical group (n=227)	4 (1.8%)	14 (6.2%)	24 (10.5%)
Stenting group (n=224)	14 (6.2%)	5 (2.2%)	10 (4.4%)

DISABLING OR FATAL STROKE AS PRIMARY ENDPOINT

Minor or moderate strokes portend good long-term functional recovery. The primary goal of intracranial stenting should be the prevention of disabling or fatal stroke rather than any TIA or stroke. As shown in table 3, significantly more patients (14, 6.2%) in the medical group of the SAMMPRIS trial had a disabling or fatal stroke than in the stenting group (5, 2.2%) beyond 30 days, indicating significant benefit of stenting for the prevention of severe stroke beyond 30 days. In addition, more patients (10.5%) withdrew or were lost to follow-up in the medical group than in the stenting group (4.5%) ($p<0.05$). Given that most of the patients were lost or withdrawn after 30 days in study, the probability of disabling or fatal strokes in the medical group is likely much higher than the stenting group if all patients had long-term follow-up. It appears that if the risk of periprocedrual complications is lower, intracranial stenting may significantly reduce the risk of disabling or fatal stroke at long-term follow-up.

STRATEGIES FOR REDUCING PERIPROCEDURAL COMPLICATIONS

Intracranial stenosis is not a homogeneous disease. It causes ischaemic strokes by one or more of the following mechanisms: perfusion failure, artery-to-artery thromboembolism, occlusion at the origin of perforators or occlusion at the site of the stenosis due to plaque rupture, intraplaque haemorrhage or plaque growth. CT or MR angiography and perfusion study may identify stenosis-related perfusion deficit and collaterals. High-resolution MRI delineates the morphology of lesion, non-atherosclerotic lesion and anatomical relation of the plaque with the ostia of the major branch artery.[59] It may guide us to minimise the risk of 'snow-ploughing', or forceful displacement of atheromatous material into branch-vessel ostia.[60]

Procedure-related complications are diverse, including SAH, ICH, target-lesion thrombosis, perforator stroke, embolic stroke and vessel dissection. The majority of adverse events occur within the first weeks of the procedure. The periprocedural complication rate is higher in the posterior circulation than in the anterior circulation due to tortuous and small vessels.[47 61 62]

A 600 mg clopidogrel loading and high dose of intravenous heparin infusion during the procedure should be avoided to minimise haemorrhagic complications.

Intracranial arteries are more tortuous and the target lesions are located more distally from the orifice of the guiding catheter. Assembly of a floppy-tipped microwire and a microcatheter should be used to navigate the tortuous vessel and to traverse the target lesion under the guidance of biplane roadmaps. Cerebral arteries have invisible small perforators that supply blood to functional areas of the brain or the brain stem. Injury to a small artery from microwire manipulation may cause significant neurological deficit. A tiny deformation of the microwire tip often results in the trapping of the tip within the orifice of small perforator or the plaque of the arterial wall. It is essential to slightly withdraw the microwire to redirect the tip.

The primary principles of intracranial stenting with Gateway balloon and Wingspan stent are as follows: (1) the microwire and guiding catheter should be placed at an appropriate position to support the delivery of stent system. (2) Selection of the stent size is based on the adjacent normal vessel diameter. Fully expanded stent diameter is 0.5 mm to 1.0 mm greater than the adjacent normal vessel diameter. The deployed stent should cover the length of the stenotic lesion and at least 3 mm normal vessel on either side of the lesion. (3) Due to thin vessel well, submaximal angioplasty with slow inflation should be applied in intracranial vasculature to avoid dissection and rupture. (4) Continuous heparinised saline flush is essential to minimise the risk of thrombosis.

Neurointerventionists should be proficient in neuroanatomy and minimise potential injury to the eloquent area of the brain. For instance, the microwire should be placed in the lower division of MCA or its temporo-occipital branch during the treatment of M1 lesion to prevent injury to the upper division. For basilar artery stenosis, it is preferable to place the microwire in the P4 segment of posterior cerebral artery (PCA) because distal PCA thrombosis or supratentorium bleeding is often less severe than proximal PCA occlusion or infratentorium bleeding.

Cerebral arteries are suspended in cerebrospinal fluids tethered by branching arteries and small perforators. The stent delivery system-induced straightening of target vessel may cause the shift or deformation of the perforators, resulting in rupture of perforators and catastrophic ICH or SAH.[58] Even with the flexible Wingspan stent delivery system, extreme caution should be exercised to minimise the shift of major arteries and the avulsion of perforators.

Real-time haemodynamic monitoring and aggressive blood pressure control may reduce the risk of hyperperfusion injury.[54]

RESULTS OF RECENT PIVOTAL STUDIES

Chinese multicentre registry of intracranial stenting

Recently, Miao and his collaborators reported the results of the first multicentre, prospective, endovascular registry for symptomatic intracranial stenosis in China.[63 64] The strength of this registry were rigorous patient selection criteria and well-defined study protocol, including lesion parameters, hypoperfusion from high-grade stenosis (70%–99%) and stenting at least 3 weeks after qualifying event. Interventionists had the freedom to use the balloon-mounted stent or pre-dilated self-expanding stent per lesion characteristics and operator experience. Medical management was similar to that of the SAMMPRIS trial. Patients were treated with dual antiplatelet for 90 days plus risk factor management, including goals of SBP <140 (<130 mm Hg if patient had diabetes), LDL <70 mg/dL and a lifestyle modification programme. An independent neurologist evaluated patients for stroke or death within 1 month after the procedure. The study enrolled 300 patients from September 2013 to January 2015 and showed a 4.3% rate of stroke, TIA or death within 30 days. The periprocedural event rate was within the CIs (5.8% (3.4 to 9.7)) of the medical arm's primary endpoint at 30 days in the SAMMPRIS trial.[49] The probability of primary outcome at 1 year was 8.1% (95% CI 5.3% to 11.7%).[64]

Wingspan Stent System Post Market Surveillance Study (WEAVE trial)

The WEAVE trial is a U.S. Food and Drug Administration-mandated prospective post-market surveillance study evaluating the periprocedural complications from Wingspan stenting.[65] The on-label indications include (1) ≥70% intracranial stenosis due to atherosclerotic disease; (2) evidence of two prior strokes in the target artery territory, with at least one of the events occurring while receiving medications to control individual risk factors and at least one antithrombotic agent; (3) stenting ≥7 days following the recent qualifying event. One hundred fifty patients were enrolled for the study. The primary endpoints were periprocedural stroke or death within 72 hours of the stenting procedure. Patient outcomes were assessed by an independent stroke neurologist at 96±24 hours for subjects discharged home within 64 hours post-procedure. The mean stenosis was 83.3% with target artery break down as follows: 38.7% middle cerebral artery (MCA), 25.8% internal carotid artery (ICA), 13.5% basilar artery and 21.3% vertebral or vertebrobasilar junction. Of the 150 patients, 4 patients (2.7%) had a primary event (stroke or death) within 72 hours. The results demonstrate that refined patient selection criteria and study protocol can minimise the periprocedural risk of intracranial stenting.

China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS trial)

The CASSISS trial is a prospective multicentre trial conducted at high-volume centres with a track record of low complication rates in China.[66 67] It recruits patients with a recent TIA or stroke caused by 70%–99% stenosis of a major intracranial artery. Patients with stroke related to perforator occlusion is excluded. For credentialling and quality control, the CASSISS was divided into two

stages: the lead-in phase and randomised phase. The lead-in phase recruited 100 consecutive patients for Wingspan stent placement from July 2013 to February 2014 at 13 sites. The technical success rate of stent deployment with residual stenosis less than 50% was 100%. The 30-day stroke or death rate was 2%.[66] The randomised phase started in March 2014 and enrolled 380 patients to best medical therapy alone or medical therapy plus stenting (1:1) at eight sites. The primary endpoints were any stroke or death within 30 days after enrolment, or stroke in the territory of the target lesion beyond 30 days. The recruitment was complete in November 2017.[67] Patients will be followed for at least 3 years.

FUTURE PERSPECTIVES

Given significant rates of disabling or fatal stroke beyond 30 days in the medial arm of the SAMMPRIS trial and the ideal low complication rates demonstrated by the well-designed Chinese multicentre registry, WEAVE Trial and CASSISS Trial,[50 63–67] it is time to propose a new trial using disabling or fatal stroke as primary efficacy endpoint and inviting only high-volume centres with a track record of less than 3% complication rates to participate. For patients with two prior strokes from high-grade intracranial stenosis despite maximal medical therapy, it is reasonable to consider stenting at established high-volume centres in the setting of registry or clinical trial. Intracranial stenting at low-volume centres or centres with known high complication rate should not be sanctioned.

CONCLUSION

The SAMMPRIS trial demonstrates superiority of medical management over stenting due to high risk of periprocedural complications in the stenting group. Recent studies have shown that critical evaluation of stroke mechanisms, careful patient selection, stenting ≥7 days after the qualifying event by experienced operators and optimal periprocedural management are associated with much lower risk of periprocedural complications at 2%–4.3%. Given much lower rate of disabling or fatal stroke in the stenting group than in the medical group beyond 30 days in the SAMMPRIS trial, it is time to evaluate intracranial stenting for the prevention of disabling or fatal stroke.

Contributors WY contributed to the conception, drafting, revision and final approval of the version to be published. W-JJ contributed to the conception, drafting and critical revision of important intellectual content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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