MEDICAL PRACTICE

Angioplasty and stenting for intracranial atherosclerotic stenosis: position statement of the Hong Kong Society of Interventional and Therapeutic Neuroradiology

CME

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As a means of preventing secondary ischaemic stroke, angioplasty and stenting are considered potentially beneficial for patients with severe intracranial atherosclerotic stenosis. However, the role of stenting has been challenged since the publication of the first randomised controlled trial on Stenting versus Aggressive Medical Management for Preventing Recurrent stroke in Intracranial arterial Stenosis (SAMMPRIS). This indicated that aggressive medical management was superior to stenting using Wingspan to prevent recurrent stroke, because stenting has a high peri-procedural stroke and death rate. In this paper, we review the management of intracranial atherosclerosis, revisit the skepticism on stenting, and state our position on the topic in the form of recommendations. These are based on the prevalence of the disease in Hong Kong, the high risk of recurrent stroke despite medical therapy in the presence of haemodynamic intracranial stenosis without sufficient collaterals, an analysis of the weak points of SAMMPRIS, and results of clinical studies in Hong Kong.

Key words
Cerebral angiography; Intracranial arteriosclerosis; Risk factors; Stents

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Intracranial atherosclerotic stenosis and its treatment

Intracranial atherosclerotic stenosis is responsible for approximately 8 to 10% and up to 33% of ischaemic strokes in the United States and Asia, respectively.[1-3] In patients with intracranial atherosclerosis, the annual stroke risk from all causes is estimated to be 3.6% to more than 13% annually.[4-11]

Current medical management of intracranial stenosis basically depends on anti-thrombotics to prevent thromboembolic events (over the short term), and reduction of risk factors to prevent disease progression (over the long term). Aspirin, clopidogrel, heparin, and warfarin are used alone or in combination to prevent thromboembolism; whereas, statin therapy is the mainstay for preventing disease progression. However, in a large prospective study it was found that high-grade intracranial stenosis (70-99%) is associated with a high risk of recurrent stroke, despite such medical treatments.[12] In more than 20% of patients, a recurrent ischaemic event in the same vascular territory may occur within 1 year of the index stroke.[12,13] Therefore, with high-grade intracranial stenosis, adjunctive treatment appears warranted. When the degree of vascular stenosis is severe (>70%) in the presence of symptomatic carotid disease, vascular reconstruction is of substantial benefit in preventing ischaemic stroke.[14] However, surgical endarterectomy is technically not feasible for intracranial vessels such as the intracranial part of the internal carotid artery and the middle cerebral artery (MCA). Although extracranial to intracranial (EC/IC) bypass has been attempted to improve circulation to the brain, it proved ineffective in reducing the stroke rate. This was the inference from a prospective randomised controlled multi-centre trial of over 1300 symptomatic patients, with MCA stenosis, which showed worse outcomes following EC/IC bypass than after medically treated controls.[8] Another randomised controlled trial involved 195 patients with symptomatic atherosclerotic internal carotid artery occlusion and haemodynamic cerebral ischaemia.[15] After 2 years, EC/IC bypass surgery plus medical therapy was not associated with a reduced risk of recurrent ipsilateral ischaemic stroke when compared to medical therapy alone.

The scientific basis for intracranial angioplasty and stenting as a therapeutic option can be found in the recent literature.[12,16,17] A matched comparison between medically treated patients in the Warfarin Aspirin Symptomatic Intracranial Disease study and stent-treated patients in the National Institutes of Health intracranial stent registry concluded that stent placement might offer benefit in patients with 70 to 99% stenosis.[18]

顱內動脈粥樣硬化狹窄的血管成形術和支架置入術：香港腦神經介入放射及治療醫學會的立場聲明

血管成形術和支架置入術被認為對患有嚴重顱內動脈粥樣硬化狹窄的病人有幫助，因這些技術可以防止患者出現繼發性缺血性中風。然而，自從首個有關顱內動脈狹窄的隨機對照研究（SAMMPRIS）比較支架置入術及積極的藥物治療發表以後，支架置入術的作用受到質疑。這是由於SAMMPRIS結果顯示支架置入術有較高的圍手術期中風和死亡率，因此與利用Wingspan的支架置入術比較，積極的藥物治療更能防止中風復發。香港腦神經介入放射及治療醫學會回顧了顱內動脈粥樣硬化的治療方法，並重新審視對支架置入術的各種疑問後，申明學會的立場及提出建議。這些立場及建議是建基於顱內動脈粥樣硬化在香港的較高患病率、在影響血流動力的顱內動脈狹窄和缺乏足夠補償血管的情況下雖然有藥物治療但仍有高中風復發的風險、分析SAMMPRIS研究的弱點，以及香港臨床研究結果。

The Wingspan stenting system

The Wingspan stent system is the first and most widely used self-expanding stent designed to treat intracranial atherosclerotic stenosis (Stryker Medical, Michigan, US).[19] This Food and Drug Administration–approved and literature-supported off-label system comprises a self-expanding nitinol stent preloaded in a delivery catheter, to be used with a separately packaged Gateway PTA balloon catheter (Boston Scientific Corporation, US). Clopidogrel (75 mg orally per day for 3 days before the procedure or 225 mg orally a day before treatment) and aspirin (300 or 325 mg orally per day for 3 days before the procedure or 300 to 650 mg orally on the day before treatment) are given. A bolus of intravenous heparin is given before the procedure to increase and maintain a prolonged activated clotting time. After predilation of the stenosis with the balloon catheter, the stent is deployed across the lesion. Selection of stent size is based on the native diameter of the target vessel (the fully expanded stent diameter should be 0.5 to 1.0 mm greater than the labelled diameter) and when deployed should extend at least 3 mm on either side of the stenotic lesion. The stent delivery catheter is a 3.5-F, coaxial, over-the-wire catheter with segments of varying stiffness and a nominal working length of 135 mm. The recommended Gateway balloon diameter (when inflated at the nominal pressure of 6 atm) occupies 80% of the native vessel diameter. Undersizing of the balloon is intended to restrict barotrauma to the plaque while minimising intimal damage to the native parent vessel. Following stenting, clopidogrel (75 mg daily by mouth) for 30 days and aspirin (300 or 325 mg daily by mouth) are prescribed for life.[19-24]

Wingspan stenting as a treatment for intracranial atherosclerosis

The clinical and angiographic peri-procedure outcomes of the initial studies on Wingspan stenting for intracranial atherosclerosis are shown in the Table.[19-21] In these studies, rates of major peri-procedural complications (stroke or death) ensuing in the first 30 days varied from 4.5% to 9.6%.[19-21] The Wingspan study by Bose et al[19] enrolled highly selected patients and achieved the lowest rates of peri-procedural stroke or death (4.5%). The studies by Fiorella et al[20] and Zaidat et al[21] represented reports of the same United States multicentre study at two different stages, and showed that the peri-procedural stroke or death rate increased from 6.1% (when the patient number was 78) to 9.6% (when the patient number was 129). Published data in the current literature on in-stent restenosis (ISR) following treatment with Wingspan for intracranial atherosclerosis basically came from the same multicentre study group.[22-24] The frequency of ISR in this series was 32% (41/127) overall, and included 28% (36/127) with partial ISR and 4% (5/127) with complete stent occlusion; 15 (37%) of these 41 patients were symptomatic.[22] In that study, the mean follow-up time to imaging was only 8.5 months. Notably, ISR was associated with (i) younger age, namely 14/31 (45%) in those aged ≤55 years versus 15/62 (24%) in persons >55 years, and (ii) lesions located at the internal carotid artery (14/32, 44%) versus other locations (15/61, 25%).[23] In that study, five cases of complete occlusion had been excluded from ISR analysis.

TABLE. Peri-procedure clinical outcomes of Wingspan stenting for intracranial atherosclerotic stenosis[19-21]

Study	No. of patients	Patient age in years (mean ± 2SD*)	Degree of stenosis (%)	Stenosis after treatment (%)	Technical success rate (%)	Ipsilateral stroke or death rate at 30 day (%)
Bose et al,[19] 2007	45	66	74.9 ± 9.8	31.9 ± 13.6	100	4.5
Fiorella et al,[20] 2007	78	63.6	74.6 ± 13.9	27.2 ± 16.7	98.8	6.1
Zaidat et al,[21] 2008	129	64.2 ± 12.4	82 ± 9	20 ± 16	96.7	9.6

* SD denotes standard deviation

Controversy regarding medical treatment and Wingspan stenting

Since the publication of the first randomised controlled trial on stenting versus aggressive medical therapy for intracranial arterial stenosis (Stenting versus Aggressive Medical Management for Preventing Recurrent stroke in Intracranial arterial Stenosis (SAMMPRIS),[25] the clinical value of angioplasty and stenting in the prevention of recurrent stroke in patients with intracranial atherosclerotic stenosis is no longer eagerly appreciated. The safety of stenting as revealed by its high peri-procedural stroke and death rate has been a key concern. The results indicated that aggressive medical management was superior to stenting (using Wingspan) in preventing recurrent stroke. In SAMMPRIS, the peri-procedural stroke or death rate within 30 days of Wingspan stenting (14.7%) was unacceptably high and substantially higher than the rates reported in early studies (4.5 to 9.6%).[19-21] The authors of SAMMPRIS attributed the high rate of peri-procedural complications to inclusion of patients with recent symptoms with increased risk of distal embolism during stenting.[26,27] Nevertheless, the high proportion with symptomatic brain haemorrhage (30.3%) among all events resulting in stroke or death within 30 days indicated that haemorrhagic complications related to technical aspects of the stenting procedure might have been causative and warranted further study. The SAMMPRIS authors also argued that the high rate of peri-procedural complications was not due to inexperience of the operators.[25] However, as 30% (10/33) of the peri-procedural strokes were due to symptomatic brain haemorrhage, procedure-related haemorrhagic complications cannot be discounted, and may be consistent with technical factors leading to unsatisfactory outcomes of stent deployment in the large number of participating centres in this study. The importance of the learning curve for intracranial stenting has drawn considerable attention. Notably, a multivariate analysis has shown that (i) any stroke or death within 30 days of stenting, or (ii) a stroke in the territory of the stented artery beyond 30 days, were associated with procedures carried out at low enrolment sites (<10 patients each) versus sites with higher enrolment rates.[28] Based on unpublished data of the first author (SCHY) involving 95 patients treated in a local centre, procedure-related fatal haemorrhagic complications occurred in the 66th patient, indicating that a long learning curve is necessary for this procedure. In the SAMMPRIS study, the 12 highest-enrolling sites enrolled half the patients in the stenting group (n=112); on average 9.3 patients were enrolled in each of these sites. Based on our local centre experience, the caseload in these 'high-enrolment' sites in SAMMPRIS clearly did not meet our criteria for the necessary learning curve period. This could explain why the peri-procedural stroke rate in the SAMMPRIS study did not decline over the course of the enrolment period and did not differ significantly between high- and low-enrolling sites.

Given such a background, it is important to take a closer look at the evidence revealed in the SAMMPRIS trial, before we abandon stenting for reasons of safety. Moreover, the trial's published results were limited to 1 year of follow-up, and we are yet to see longer-term outcome data to evaluate whether stenting provides benefits for preventing stroke.

Other considerations and local experience on Wingspan stenting

Because intracranial atherosclerosis is much more common among Asians than westerners, doctors in Hong Kong see more patients with haemodynamic strokes or transient ischaemic attacks (TIAs) refractory to medical therapy. We manage patients with haemodynamic intracranial stenosis without sufficient collaterals that have the highest risk of recurrent stroke or TIA, despite medical therapy.[29,30] For these patients with features that are unique to our region, Wingspan stenting may offer a chance of protection from disabling stroke. A study from Hong Kong by Yu et al[31] showed that the peri-procedural complication rate may be much lower (5%, 3/57) when the procedure is performed in a centre with a high caseload and a consistent team of operators. The same study group also reported that although MCAs are relatively more peripheral, of smaller calibre, and technically more challenging and risky for angioplasty and stenting, there was no significant difference in terms of procedural safety, patient outcomes, and restenosis rates than in those with stenoses located at other sites. This suggests that the clinical applicability of Wingspan stenting is not limited by the location of the intracranial stenosis.[32] These authors reported that Wingspan stenting even for high-grade MCA stenoses did not pose a major risk of occlusion to perforators.[33] Since the primary purpose of intracranial stenting is to widen and maintain the widened lumen of stenotic vessels, ISR is an important concern during the follow-up. Yet in another Hong Kong study, using digital subtraction angiography (DSA) and an established assessment methodology,[22,23] the incidence of ISR at the 1-year follow-up was 17% (11/66).[34] This was lower than the ISR rates reported in other studies. All 11 cases of ISR were asymptomatic. Luminal gain beyond the baseline diameter occurred in 36 (55%) of the lesions. It was also suggested that age is probably unrelated to ISR. Moreover, lesions located at the internal carotid artery are probably less prone to ISR. All these findings were at variance from those reported in previous studies from the West.[22-24]

We learned from these local studies that the safety and treatment outcomes of Wingspan stenting in terms of peri-procedural complications and restenosis rates were in fact more promising in Hong Kong, compared to the West. Therefore doctors in Hong Kong should not be overwhelmed by suboptimal results of Wingspan stenting reported from the West and should not abandon the treatment because of such findings.

Recommendations

Angioplasty and stenting with Wingspan should be considered for patients with intracranial stenosis of ≥70%, presenting with a recurrent ischaemic stroke or TIA, despite medical therapy; with the ischaemic strokes of minor degree and cerebral function that is potentially salvageable, as inferred from a National Institute of Health Stroke Scale score of ≤8 and a baseline modified Rankin Scale score of ≤3, with stenosis confirmed by DSA. Moreover, the stenosis location had to correspond to the vascular territory consistent with the ischaemic event, and with a vessel diameter immediately adjacent to the stenosis of ≥2 mm, and a stenosis length of ≤14 mm. Written informed consent from the patient is necessary.

Wingspan stenting should be contra-indicated for patients with ischaemic strokes of non-atherosclerotic aetiology, such as cardiogenic embolism, Moyamoya disease or other vasculitis. It is also contra-indicated if patients have a medical contra-indication to anti-platelet therapy, or a sizable cerebral infarct (>1/3 MCA territory) at risk of haemorrhagic transformation. Concurrent intracranial pathology—such as tumour, arteriovenous malformation, or aneurysm—also constitute contra-indications.

Finally, Wingspan stenting should be performed in centres with experienced operators and a consistent team.

Declaration

No conflicts of interest were declared by the authors.

References

1. Sacco RL, Kargman DE, Gu Q, Zamanillo MC. Race-ethnicity and determinants of intracranial atherosclerotic cerebral infarction. The Northern Manhattan Stroke Study. Stroke 1995;26:14-20.
2. Broderick J, Brott T, Kothari R, et al. The Greater Cincinnati/Northern Kentucky Stroke Study: preliminary first-ever and total incidence rates of stroke among blacks. Stroke 1998;29:415-21.
3. Wong KS, Huang YN, Gao S, Lam WW, Chan YL, Kay R. Intracranial stenosis in Chinese patients with acute stroke. Neurology 1998;50:812-3.
4. Bogousslavsky J, Barnett HJ, Fox AJ, Hachinski VC, Taylor W. Atherosclerotic disease of the middle cerebral artery. Stroke 1986;17:1112-20.
5. Chimowitz MI, Kokkinos J, Strong J, et al. The Warfarin-Aspirin symptomatic intracranial disease study. Neurology 1995;45:1488-93.
6. Thijs VN, Albers GW. Symptomatic intracranial atherosclerosis: outcome of patients who fail antithrombotic therapy. Neurology 2000;55:490-7.
7. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352:1305-16.
8. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. The EC/IC Bypass Study Group. N Engl J Med 1985;313:1191-200.
9. Rundek T, Elkind MS, Chen X, Boden-Albala B, Paik MC, Sacco RL. Increased early stroke recurrence among patients with extracranial and intracranial atherosclerosis: the Northern Manhattan Stroke Study [abstract]. Neurology 1998;50(Suppl 4):A75.
10. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Stroke 1998;29:1389-92.
11. Caplan LR. Advances in stroke research: basic science, treatment, and clinical trial outcomes. Rev Neurol Dis 2004;2:91-4.
12. Kasner SE, Chimowitz MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. Circulation 2006;113:555-63.
13. Wong KS, Li H. Long-term mortality and recurrent stroke risk among Chinese stroke patients with predominant intracranial atherosclerosis. Stroke 2003;34:2361-6.
14. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis: North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998;339:1415-25.
15. Powers WJ, Clarke WR, Grubb RL Jr, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the Carotid Occlusion Surgery Study randomized trial. JAMA 2011;306:1983-92.
16. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. Stroke 2008;39:2396-9.
17. Meyers PM, Schumacher HC, Higashida RT, et al. Indications for the performance of intracranial endovascular neurointerventional procedures: a scientific statement from the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Interdisciplinary Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation 2009;119:2235-49.
18. Qureshi AI, Feldmann E, Gomez CR, et al. Consensus conference on intracranial atherosclerotic disease: rationale, methodology, and results. J Neuroimaging 2009;19(Suppl 1):1S-10S.
19. Bose A, Hartmann M, Henkes H, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial

atherosclerotic stenoses: the Wingspan study. Stroke 2007;38:1531-7.
20. Fiorella D, Levy EI, Turk AS, et al. US multicenter experience with the wingspan stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke 2007;38:881-7.
21. Zaidat OO, Klucznik R, Alexander MJ, et al. The NIH registry on use of the Wingspan stent for symptomatic 70-99% intracranial arterial stenosis. Neurology 2008;70:1518-24.
22. Albuquerque FC, Levy EI, Turk AS, et al. Angiographic patterns of Wingspan in-stent restenosis. Neurosurgery 2008;63:23-8.
23. Turk AS, Levy EI, Albuquerque FC, et al. Influence of patient age and stenosis location on wingspan in-stent restenosis. AJNR Am J Neuroradiol 2008;29:23-7.
24. Levy EI, Turk AS, Albuquerque FC, et al. Wingspan in-stent restenosis and thrombosis: incidence, clinical presentation, and management. Neurosurgery 2007;61:644-51.
25. 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.
26. Gray WA, Yadav JS, Verta P, et al. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. Catheter Cardiovasc Interv 2007;70:1025-33.
27. Topakian R, Strasak AM, Sonnberger M, et al. Timing of stenting of symptomatic carotid stenosis is predictive of 30-day outcome. Eur J Neurol 2007;14:672-8.
28. Nahab F, Lynn MJ, Kasner SE, et al. Risk factors associated with major cerebrovascular complications after intracranial stenting. Neurology 2009;72:2014-9.
29. Derdeyn CP, Videen TO, Yundt KD, et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain 2002;125:595-607.
30. Mazighi M, Tanasescu R, Ducrocq X, et al. Prospective study of symptomatic atherothrombotic intracranial stenoses: the GESICA study. Neurology 2006;66:1187-91.
31. Yu SC, Leung TW, Hung EH, Lee KT, Wong LK. Angioplasty and stenting for intracranial atherosclerotic stenosis with nitinol stent: factors affecting technical success and patient safety. Neurosurgery 2012;70(1 Suppl Operative):104S-113S.
32. Yu CH, Leung WH, Lee KT, Hui JW, Wong LK. Angioplasty and stenting of atherosclerotic middle cerebral arteries with Wingspan: evaluation of clinical outcome, restenosis, and procedure outcome. AJNR Am J Neuroradiol 2011;32:753-8.
33. Leung TW, Yu SC, Lam WW, Chan AY, Lau AY, Wong LK. Would self-expanding stent occlude middle cerebral artery perforators? Stroke 2009;40:1910-2.
34. Yu CH, Leung WH, Hung HY, Lee KT, Wong KS. Angioplasty and stenting of intracranial atherosclerosis with Wingspan system: factors affecting one-year restenosis in a single center of 66 cases. Proceedings of the Radiological Society of North America (RSNA) 97th Scientific Assembly and Annual Meeting. 2011 Nov 27-Dec 2. US Chicago.