
J. W. Osbun, M.D.


L. J. Kim, M.D.

INTERNAL CAROTID ARTERY STENTING FOR INTRACRANIAL ATHEROSCLEROSIS

Joshua W. Osbun, M.D.; Louis J. Kim, M.D.
University of Washington, Seattle, Washington

Abstract

Intracranial atherosclerotic disease is a significant cause of stroke in the United States. Much like coronary atherosclerosis, this disease leads to arterial stenosis secondary to the buildup of lipid-based plaques in intracranial vessels. Ischemic stroke may occur following thromboembolic events near the site of stenosis or from watershed ischemia secondary to cerebral hypoperfusion. While this disease has been treated with intracranial angioplasty and stenting and cerebrovascular bypass surgery, the current literature supports aggressive medical management with dual antiplatelet therapy, treatment of comorbidities such as hypertension, diabetes, and hyperlipidemia, and lifestyle modification. Intracranial angioplasty and stenting is reserved for cases of medical failure.

Introduction

Nearly 1 million strokes occur in the United States each year, and approximately 10% to 15% of these can be attributed to intracranial atherosclerotic disease (ICAD).[1] ICAD is a common cause of stenosis in the intracranial internal carotid artery (ICA) vasculature.[2,3] It also causes ischemic stroke secondary to cerebral blood flow limitations and thromboembolic complications resulting from stenosis and atheroma formation in diseased intracranial blood vessels. Atherosclerosis may develop along the course of the internal carotid artery and in its major branches after bifurcating into the middle and anterior cerebral artery. Likewise, ICAD also can affect the posterior circulation of the brain through plaque formation in the vertebral arteries, basilar artery, and posterior cerebral arteries. While ICAD tends to develop in patients with comorbidities such as hypertension, hypercholesterolemia, diabetes, and a history of smoking, certain ethnic populations seem to be predisposed as well, including Asians, African-Americans, and Hispanics.

Intracranial stenting as treatment for ICAD has been a topic of recent intense debate in the stroke, neurosurgical, and interventional neuroradiology literature.[4-8] While dual antiplatelet therapy has been a mainstay of treatment for symptomatic patients, the use of balloon angioplasty with or without stent placement has undergone a recent paradigm shift—mainly in light of data from the Stenting versus Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS).[9] This study is the only prospective randomized trial regarding the use of balloon angioplasty and stenting as treatment of ICAD. The study placed all enrolled patients with symptomatic ICAD on dual antiplatelet therapy with aspirin and clopidogrel; it then randomized patients to medical therapy alone or to medical therapy plus angioplasty and stenting with the Wingspan® Stent System and Gateway® PTA Balloon Catheter (Stryker Neurovascular, Freemont, CA). The trial was prematurely halted due to significantly increased rates of stroke and complications in the angioplasty and stenting arm, and the results have prompted many practitioners to opt for medical therapy in lieu of angioplasty and stenting for treating ICAD. Angioplasty with or without stenting remains a viable option in patients that fail medical therapy, and this evolving technique continues to be evaluated in ongoing clinical trials.[10]

Currently, aggressive medical management with dual antiplatelet agents is the mainstay of treatment for ICAD, and despite results of the SAMMPRIS trial, there are certain clinical scenarios in which intracranial stenting is a viable treatment option. In this review, we will discuss the pathophysiology of intracranial atherosclerotic disease and its potential treatment with medical therapies, lifestyle modification, and situation-specific use of intracranial stents and cerebrovascular bypass surgery.

Pathophysiology and Diagnosis of Intracranial Atherosclerotic Disease

In the strictest sense, intracranial arterial stenosis is intraluminal narrowing of an intracranial vessel. This can occur from atherosclerosis, infection, radiation exposure, or inflammatory conditions that cause vasculitis, or it can be idiopathic in cases such as Moyamoya disease.[2,3,11] The most common of these causes is atherosclerosis. The development of ICAD shares many of the same risk factors as coronary atherosclerosis. Certainly specific ethnic groups such as individuals of African, Hispanic, and Asian decent are genetically predisposed.[12] Lifestyle factors such as diet, exercise, and smoking play an important role, as do medical conditions such as hyperlipidemia, hypertension, and diabetes. Intraluminal narrowing of major intracranial vessels such as the internal carotid and basilar arteries—as well as secondary branches such as the anterior, middle, and posterior cerebral arteries—can place the patient in a state of cerebral hypoperfusion. Stroke in these patients occurs from thromboembolic events at the site of stenosis, leading to wedge-shaped infarcts in a specific arterial distribution, or from chronic hypoperfusion and ischemia in watershed areas.

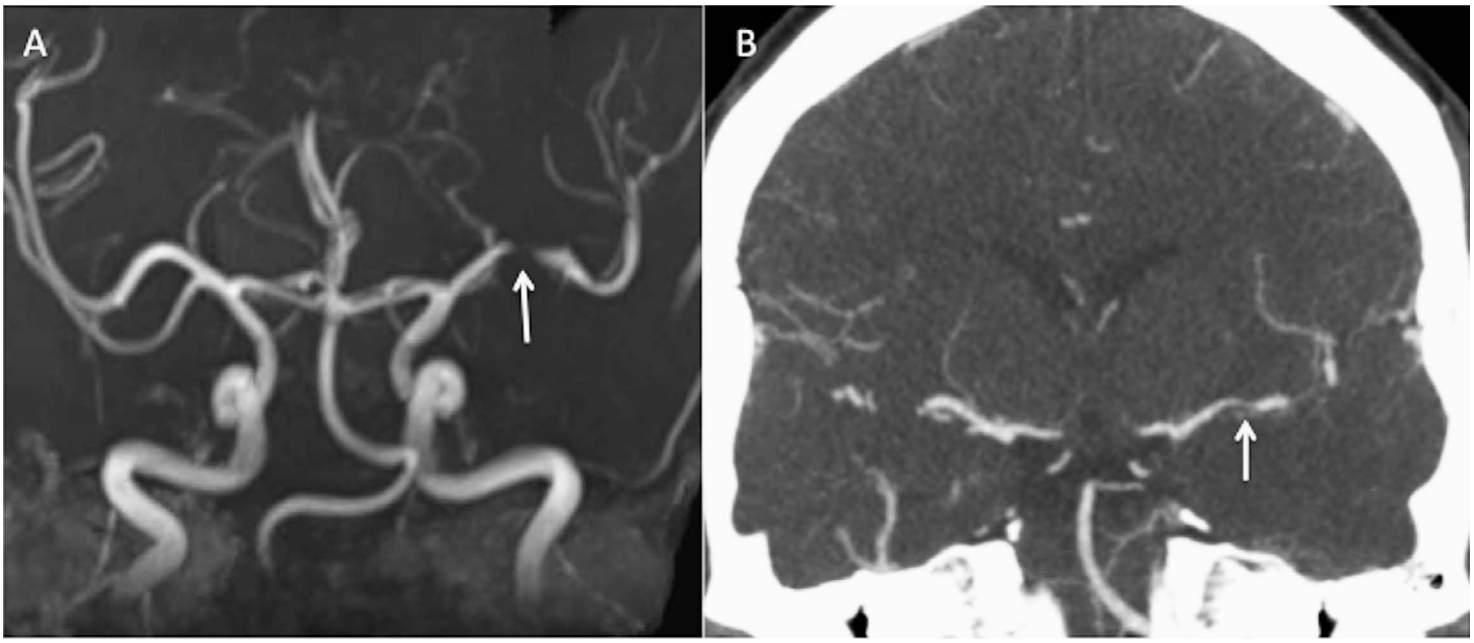

Figure 1. A 60-year-old male who presented with recurrent left hemisphere transient ischemic attacks. (A) Magnetic resonance angiography (MRA) demonstrating left middle cerebral artery (MCA) stenosis (arrow). (B) Computed tomography angiography from the same patient demonstrating left MCA stenosis (arrow).

Most patients with ICAD will present either with transient ischemic attacks (TIAs) or ischemic stroke. Magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are routinely used for rapid diagnosis of both hemorrhagic and ischemic stroke and generate high-resolution, 3-dimensional images of arterial anatomy (Figure 1). Some patients undergo vascular imaging for a host of other indications, and ICAD is diagnosed incidentally. Nonetheless, these two noninvasive imaging modalities have become the mainstay for screening and diagnosis of ICAD. While formal catheter-based cerebral angiography remains the gold standard in imaging, it comes with the cost of an invasive imaging test and rare but potential complications such as embolic stroke, vertebral and carotid artery dissection, and hematoma at the site of arterial access in the femoral artery. Transcranial Doppler ultrasound (TCD) can be used to follow disease progression or treatment efficacy by assessing blood flow velocities in intracranial vessels as an indirect measure of cerebral perfusion, thereby serving as a rapid and noninvasive imaging test. TCD also is valuable in detecting ongoing microembolic events in the intracranial vasculature.[13]

Treatment of Intracranial Atherosclerotic Disease

Antithrombotic Therapy

Early reports on the treatment of ICAD suggested that patients could benefit from antithrombotic therapy with warfarin,[14] which is frequently used to prevent stroke from cardiogenic emboli, such as in patients with atrial fibrillation. Other studies have suggested that warfarin has no benefit over aspirin in preventing noncardiogenic sources of stroke.[15] Such controversy led to the Warfarin versus Aspirin for Symptomatic Intracranial Disease (WASID) study,[16] which, as the name implies, attempted to compare warfarin to aspirin as treatment for patients with symptomatic intracranial stenosis.[16] Patients with angiographically confirmed ICAD, including 50% to 99% stenosis of a major intracranial artery, were randomized in equal numbers to treatment with either aspirin (1300 mg/day) or warfarin (target international normalized ratio of 2-3) in a double-blind trial. Patients met inclusion criteria of nondisabling stroke or transient ischemic attack within 90 days prior to randomization. The primary end point was ischemic stroke, brain hemorrhage, or death from a vascular cause. While the two groups were equivalent in terms of preventing recurrent stroke, the warfarin group had significantly higher rates of bleeding complications and death during the follow-up period. The study concluded that aspirin should be used for primary stroke prevention in ICAD. While not end points of the study, the investigators also suggested that blood pressure and serum lipid level were two modifiable risk factors that may prevent recurrent stroke in the setting of ICAD.

In addition to WASID demonstrating evidence favoring antiplatelet therapy with aspirin over warfarin, studies such as Clopidogrel plus Aspirin for Infarction Reduction (CLAIR)[17] and Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS)[13] have supported the use of dual antiplatelet therapy. Both trials demonstrated that combination therapy of clopidogrel and aspirin led to fewer recurrent strokes in patients with recent first-time event and arterial stenosis. CARESS focused on extracranial carotid artery stenosis and was an adjunctive study to trials on carotid endarterectomy such as ACAS and NASCET.[18,19] However, its results can be easily extrapolated to suggest a benefit for dual antiplatelet therapy for stenosis of downstream intracranial vessels.

Perhaps the most compelling evidence for the use of dual antiplatelet therapy is from the SAMMPRIS Trial, which placed patients with symptomatic ICAD on aspirin (325 mg/day) and clopidogrel (75 mg/day) with or without angioplasty and stenting of the narrowed intracranial vessel. The trial planned to enroll 764 patients but was stopped after enrolling 451 patients (59% of target) due to the significantly higher complication rate in the stenting arm compared to those who underwent medical therapy alone. In the stenting arm, 14.7% of patients suffered a stroke within 30 days of treatment compared to only 5.8% (P = .002) in the medical therapy group. The 5.8% rate of 30-day recurrent stroke

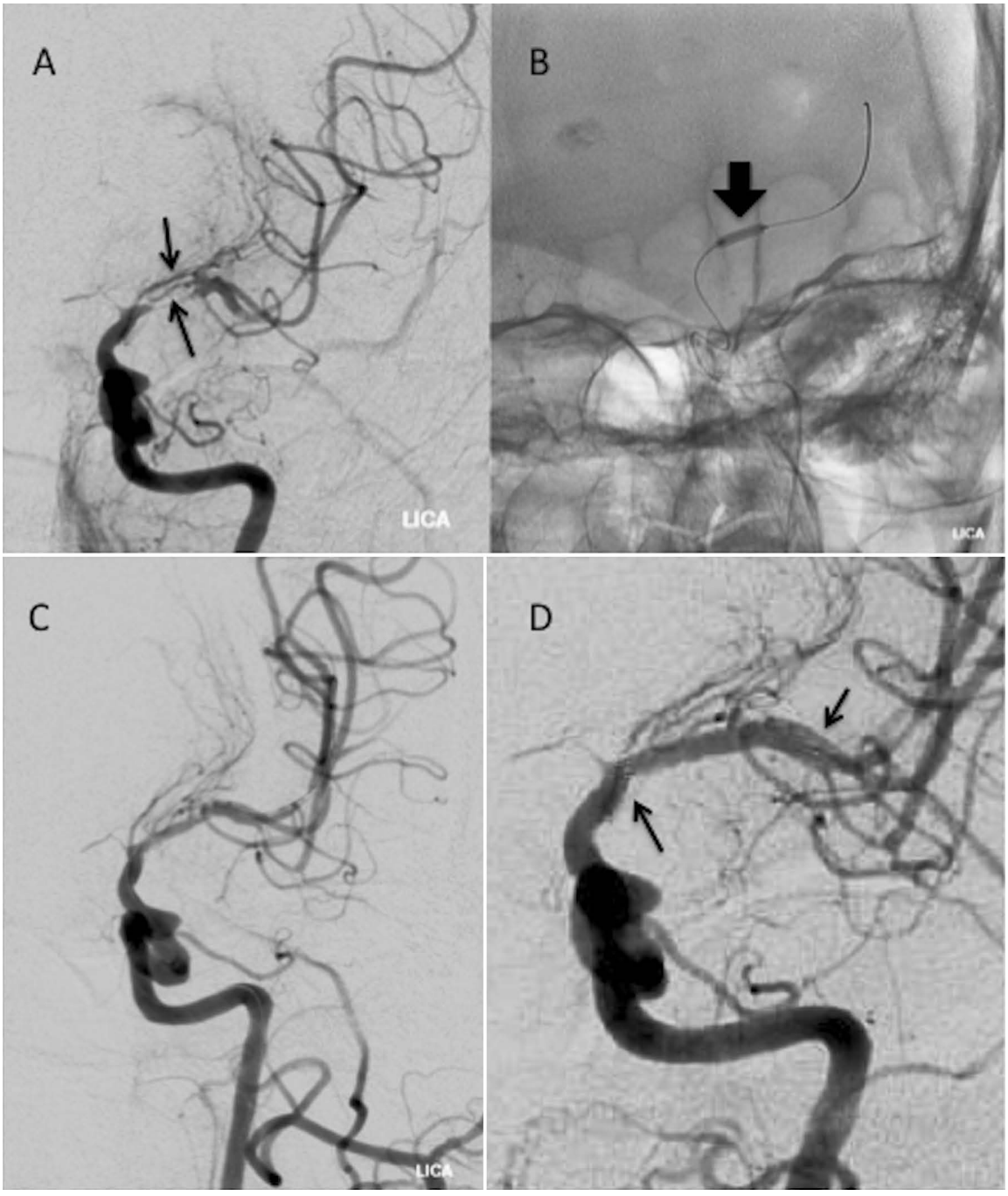

Figure 2. An 81-year-old man with a history of remote left middle cerebral artery (MCA) distribution stroke who presented with left hemisphere transient ischemic attacks despite treatment with aspirin and clopidogrel. (A) Cerebral angiogram with anterior-posterior (AP) view of left internal carotid artery (ICA) injection demonstrating severe left ICA stenosis (arrows). (B) Spot fluoroscopy image demonstrating balloon inflation (large arrow) during percutaneous balloon angioplasty of the left MCA. (C) AP view of left ICA injection status post percutaneous balloon angioplasty demonstrating marked improvement of left MCA stenosis. (D) Final post-treatment AP view of left ICA injection after Wingspan stent placement. The proximal and distal stent tines are marked by the arrows.

on dual antiplatelet therapy is comparable to a rate of 10.7% of aspirin alone in the WASID study, which had the same inclusion criteria. Such level 1 evidence has made a strong argument for dual antiplatelet therapy and aggressive medical management with systolic blood pressure reduction to less than 140 mm Hg and target LDL levels less than 181 mmol/L as first-line treatment for ICAD.

Intracranial Stenting and Balloon Angioplasty

Stenting has been a popular treatment for intracranial stenosis, particularly with the advent of the Wingspan® Stent System as an endovascular tool (Figure 2). As with the placement of any bare metal stent, intracranial stents require dual antiplatelet therapy during the stent endothelialization period. It stands to reason that treating the areas of stenosis in the intracranial circulation with angioplasty and stenting, thereby improving vessel caliber in the stenotic segment, should be more beneficial than medical therapy alone. Theoretically, angioplasty and stenting should increase blood flow and decrease the incidence of watershed infarcts secondary to chronic cerebral ischemia due to hypoperfusion. Early reports of stenting for ICAD showed promise to this end,[20-23] and bare metal stents, balloon mounted stents,[24,25] and drug-eluting stents[26-29] have been evaluated for this purpose.

The SAMMPRIS Trial has received a great deal of attention in the literature because it demonstrated compelling evidence that best medical management alone is still superior to angioplasty and stenting—with the angioplasty/stenting group having a 14.7% stroke rate at 30 days compared to 5.8% in the aggressive medical

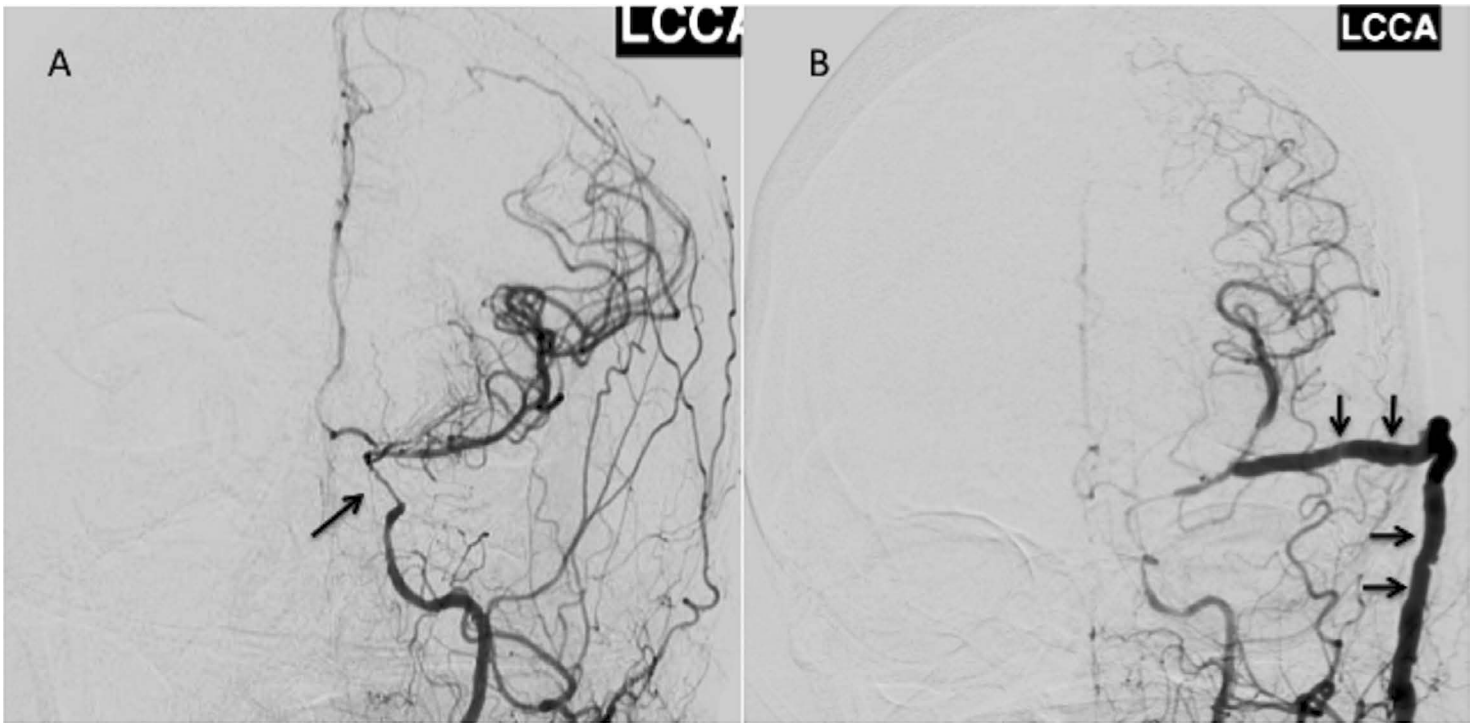

Figure 3. A 53-year-old woman who presented with terminal left internal carotid artery (ICA) stenosis and multiple recurrent strokes and transient ischemic attacks. After failure of medical management with aspirin and clopidogrel, the patient underwent Wingspan stenting of the terminal ICA, which was complicated by in-stent restenosis that was ultimately refractory to percutaneous angioplasty. (A) Cerebral angiogram of left common carotid artery, anterior-posterior view, demonstrating area of terminal ICA stenosis (arrow) after restenosis of Wingspan stent. (B) Cerebral angiogram of the left common carotid artery (CCA) after left CCA to left MCA bypass using a saphenous vein graft (graft demarcated by arrows).

management group. The study has been criticized for a number of factors, including potential inexperience of the interventionalist performing the procedure and a relatively brief initial follow-up period being unable to yield long-term results that may confer more of a benefit to intervention.[30] Long-term follow-up of the patients who were enrolled prior to the trial's discontinuation has demonstrated no difference between the two arms in terms of recurrent stroke rate and mortality at 3 years.[9] In addition, most of the trial's procedural complications that led to early stroke or intracranial hemorrhage occurred in patients treated by the most experienced interventionalists (those who had performed ten or more stents compared to the minimum of three required for study participation). With the study now complete after long-term follow-up, the current paradigm is continued aggressive medical management in patients with ICAD, with stenting performed only in situations of medical failure.

After the results of the SAMMPRIS trial were reported, the U.S. Food and Drug Administration issued a bulletin narrowing the indications for use of the Wingspan® Stenting System for intracranial stenosis.[31] Current indications are for patients between 22 and 80 years of age with 70% to 99% intracranial stenosis. Patients must have had at least two strokes related to intracranial stenosis despite maximal medical management and must be at least 7 days removed from the most recent stroke. Patients who meet these criteria are eligible for angioplasty and stenting. A new trial, the Post Market Surveillance Study of Wingspan Stenting System (WEAVE),[10] has begun enrolling patients with this indication to determine if a narrowed scope of use confers a benefit on recurrent stroke after maximal medical management.

The results have called for a reappraisal and redesign of stents for intracranial use.[6,7,32,33] Device manufacturers and scientists will have to reevaluate stent design and develop new products with superior safety and efficacy profiles. Many have called for different materials to be used and suggested potential drug-eluting models that have thus far been used with varying success worldwide.

Cerebrovascular Bypass

Cerebrovascular bypass for intracranial stenosis involves anastomosis of an extracranial vessel, such as the superficial temporal artery (STA), to an intracranial vessel, such as the middle cerebral artery (MCA), in an attempt to bypass stenotic arterial segments or augment blood flow to a hypoperfused hemisphere. Other techniques such as high-flow bypass using donor vessels (e.g., the radial artery or saphenous vein) and anastomosing the cervical carotid artery to the intracranial carotid or MCA have also been used (Figure 3). Cerebral hypoperfusion can be diagnosed with CT perfusion studies in which blood flow is measured on CT or with single positron emission spectroscopy (SPECT). Cerebral perfusion can be compared between hemispheres or before and after vasodilatory challenge with an agent such as acetazolamide. In cases of ICAD with perfusion-limiting stenosis, bypass surgery can potentially prevent recurrent stroke by augmenting blood flow to the affected hemisphere.

Cerebrovascular bypass has largely fallen out of favor compared to best medical management. Trials such as the Extracranial-Intracranial (EC-IC) bypass trial in the 1980s demonstrated no benefit of bypass grafts.[34] The study was wrought with design flaws and criticisms, and a new attempt to demonstrate the utility of cerebrovascular bypass and address criticisms of the prior study was made with the modern Carotid Occlusion Surgery Study (COSS)[35] trial. This trial also failed to demonstrate any benefit of EC-IC bypass for preventing recurrent

stroke in ICAD and demonstrated a much higher complication profile for surgery than aggressive medical management. Much like with angioplasty and stenting, however, patients who have suffered recurrent stroke despite medical management and who have evidence of decreased cerebral perfusion may benefit from bypass surgery.

Conclusion

Intracranial atherosclerotic disease accounts for at least 10% of all strokes in the United States and perhaps an even larger percentage in certain populations around the world. Balloon angioplasty and stenting have been used as primary treatment for this disease, but randomized controlled trials have demonstrated aggressive medical management to be the superior therapy. Treatment should focus on initiating dual antiplatelet therapy with aspirin and clopidogrel, reducing LDL with statin drugs, and controlling hypertension. Lifestyle modifications such as weight loss, exercise, diet control, and cessation of smoking are also paramount in treating and reducing stroke risk. In cases of clear medical failure and recurrent stroke, angioplasty and stenting remain viable treatment options. Future stent design is aimed at reducing 30-day stroke and procedural complication rates while providing clear patient benefit compared to medical therapy alone.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Funding/Support: Dr. Kim is a shareholder in SPI Surgical, Inc., and a consultant for Aesculap, Inc., and MicroVention, Inc.

Keywords: intracranial atherosclerosis, intracranial stent, stroke

References

1. Flaherty ML, Flemming KD, McClelland R, Jorgensen NW, Brown RD Jr. Population-based study of symptomatic internal carotid artery occlusion: incidence and long-term follow-up. Stroke. 2004 Aug;35(8):e349-52.
2. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol. 2013 Nov;12(11):1106-14.
3. Qureshi AI, Caplan LR. Intracranial atherosclerosis. Lancet. 2014 Mar 15;383(9921):984-98.
4. Ding D. Effect of SAMMPRIS on endovascular interventions for intracranial atherosclerosis. Clinical Neurol Neurosurg. 2014 May;120:145.
5. Fiorella D, Turan TN, Derdeyn CP, Chimowitz MI. Current status of the management of symptomatic intracranial atherosclerotic disease: the rationale for a randomized trial of medical therapy and intracranial stenting. J Neurointerv Surg. 2009 Jul;1(1):35-9.
6. Marks MP. Is there a future for endovascular treatment of intracranial atherosclerotic disease after Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS)? Stroke. 2012 Feb;43(2):580-4.
7. Qureshi AI, Al-Senani FM, Husain S, Janjua NA, Lanzino G, Lavados PM, et al. Intracranial angioplasty and stent placement after stenting and aggressive medical management for preventing recurrent stroke in intracranial stenosis (SAMMPRIS) trial: present state and future considerations. J Neuroimaging. 2012 Jan;22(1):1-13.
8. Turan TN, Cotsonis G, Lynn MJ, Wooley RH, Swanson S, Williams JE, et al. Intracranial stenosis: impact of randomized trials on treatment preferences of US neurologists and neurointerventionists. Cerebrovasc Dis. 2014;37(3):203-11.
9. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014 Jan 25;383(9914):333-41.
10. ClinicalTrials.gov [Internet]. Bethesda, MD: U.S. National Institutes of Health; c2014. Postmarket Surveillance Study of the Wingspan Stent System (WEAVE). 2014 Apr [cited 2014 Aug 18]. Available from; http://clinicaltrials.gov/show/NCT02034058.
11. Carvalho M, Oliveira A, Azevedo E, Bastos-Leite AJ. Intracranial arterial stenosis. J Stroke Cerebrovasc Dis. 2014 Apr;23(4):599-609.
12. Kim JS, Nah HW, Park SM, Kim SK, Cho KH, Lee J, et al. Risk factors and stroke mechanisms in atherosclerotic stroke: intracranial compared with extracranial and anterior compared with posterior circulation disease. Stroke. 2012 Dec;43(12):3313-8.
13. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, 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. 2005 May 3;111(17):2233-40.
14. Millikan CH, Siekert RG, Shick RM. Studies in cerebrovascular disease. III. The use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. Proc Staff Meet Mayo Clin. 1955 Mar 23;30(6):116-26.
15. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001 Nov 15;345(20):1444-51.
16. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med. 2005 Mar 31;352(13):1305-16.
17. Wang X, Lin WH, Zhao YD, Chen XY, Leung TW, Chen C, et al. The effectiveness of dual antiplatelet treatment in acute ischemic stroke patients with intracranial arterial stenosis: a subgroup analysis of CLAIR study. Int J Stroke. 2013 Dec;8(8):663-8.
18. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA. 1995 May 10;273(18):1421-8.
19. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med. 1991 Aug 15;325(7):445-53.
20. Siddiq F, Vazquez G, Memon MZ, Suri MF, Taylor RA, Wojak JC, et al. Comparison of primary angioplasty with stent placement for treating symptomatic intracranial atherosclerotic diseases: a multicenter study. Stroke. 2008 Sep;39(9):2505-10.
21. Siddiq F, Memon MZ, Vazquez G, Safdar A, Qureshi AI. Comparison between primary angioplasty and stent placement for symptomatic intracranial atherosclerotic disease: meta-analysis of case series. Neurosurgery. 2009 Dec;65(6):1024-33; discussion 1033-4.
22. Gomez CR, Misra VK, Liu MW, Wadlington VR, Terry JB, Tulyapronchote R, et al. Elective stenting of symptomatic basilar artery stenosis. Stroke. 2000 Jan;31(1):95-9.
23. Gomez CR, Misra VK, Campbell MS, Soto RD. Elective stenting of symptomatic middle cerebral artery stenosis. AJNR Am J Neuroradiol. 2000 May;21(5):971-3.

24. Mocco J, Darkhabani Z, Levy EI. Pharos neurovascular intracranial stent: elective use for a symptomatic stenosis refractory to medical therapy. Catheter Cardiovasc Interv. 2009 Oct 1;74(4):642-6.
25. Kessler IM, Mounayer C, Piotin M, Spelle L, Vanzin JR, Moret J. The use of balloon-expandable stents in the management of intracranial arterial diseases: a 5-year single-center experience. AJNR Am J Neuroradiol. 2005 Oct;26(9):2342-8.
26. Natarajan SK, Ogilvy CS, Hopkins LN, Siddiqui AH, Levy EI. Initial experience with an everolimus-eluting, second-generation drug-eluting stent for treatment of intracranial atherosclerosis. J Neurointerv Surg. 2010 Jun;2(2):104-9.
27. Fields JD, Petersen BD, Lutsep HL, Nesbit GM, Liu KC, Dogan A, et al. Drug eluting stents for symptomatic intracranial and vertebral artery stenosis. Interv Neuroradiol. 2011 Jun;17(2):241-7.
28. Lee JH, Jo SM, Jo KD, Kim MK, Lee SY, You SH. Comparison of Drug-eluting Coronary Stents, Bare Coronary Stents and Self-expanding Stents in Angioplasty of Middle Cerebral Artery Stenoses. J Cerebrovasc Endovasc Neurosurg. 2013 Jun;15(2):85-95.
29. Park S, Lee DG, Chung WJ, Lee DH, Suh DC. Long-term Outcomes of Drug-eluting Stents in Symptomatic Intracranial Stenosis. Neurointervention. 2013 Feb;8(1):9-14.
30. Chen S, Hanel RA. The final SAMMPRIS results: a review. World Neurosurg. 2014 Apr 24. [Epub ahead of print]
31. U.S. Food and Drug Administration [Internet]. Silver Spring, MD: U.S. Department of Health and Human Services; c2014. FDA revises safety information and limits use of Stryker Wingspan brain stent system; 2012 Aug 8 [cited 2014 Aug 18]. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm314845.htm
32. Miao Z, Song L, Liebeskind DS, Liu L, Ma N, Wang Y, et al. Outcomes of tailored angioplasty and/or stenting for symptomatic intracranial atherosclerosis: a prospective cohort study after SAMMPRIS. J Neurointerv Surg. 2014 Apr 23.
33. Nahab F, Kingston C, Frankel MR, Dion JE, Cawley CM, Mitchell B, et al. Early aggressive medical management for patients with symptomatic intracranial stenosis. J Stroke Cerebrovasc Dis. 2013 Jan;22(1):87-91.
34. 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 Nov 7;313(19):1191-200.
35. Grubb RL Jr, Powers WJ, Clarke WR, Videen TO, Adams HP Jr, Derdeyn CP; Carotid Occlusion Surgery Study Investigators. Surgical results of the Carotid Occlusion Surgery Study. J Neurosurg. 2013 Jan;118(1):25-33.