

Intracranial atherosclerosis update for neurointerventionalists

Michael J Alexander ,¹ Wengui Yu ²

¹Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California, USA
²Neurology, University of California Irvine, Irvine, California, USA

Correspondence to

Dr Michael J Alexander, Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA; michael.alexander@cshs.org

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ABSTRACT

The management of intracranial atherosclerotic disease (ICAD) has been evolving with advanced imaging, refinements of best medical treatment, and the development of endovascular options. There has been a significant increase in the use of endovascular therapy for symptomatic ICAD in the USA over the past 6 years. The rationale for this review is to update neurointerventionalists in these areas so that evidence-based decisions can be considered when counseling potential patients regarding their risks, benefits, and potential complications. The landmark SAMMPRIS trial demonstrated superiority of aggressive medical management (AMM) over intracranial stenting as an initial treatment. However, the risk of disabling or fatal stroke remains high in patients presenting with stroke treated with AMM. Recent studies showed a significantly lower rate of periprocedural complications from intracranial stenting. Patients who have failed medical treatment may therefore benefit from intracranial stenting, particularly in those with hemodynamic compromise and large vessel embolic stroke. Drug coated angioplasty balloons and drug eluting stents may potentially reduce the risk of in-stent re-stenosis. Large vessel occlusion (LVO) due to underlying ICAD is seen in a subset of thrombectomy-eligible patients. The use of stenting as a rescue therapy in LVO thrombectomy has also shown promising early results.

INTRODUCTION

The management of intracranial atherosclerotic disease (ICAD) has been evolving with advanced imaging, refinements of best medical treatment, and the development of endovascular options. There has been a significant increase in the use of endovascular therapy for symptomatic ICAD in the USA over the most recent 6 years of data in the National Inpatient Sample (NIS) database.¹ The number of stenting procedures for ICAD in 2020 was five-fold higher than the number of stenting procedures performed in 2014. The rationale for this review is to update neurointerventionalists in these areas so that evidence-based decisions can be considered when counseling potential patients regarding their risks, benefits, and potential complications. We will review imaging options of digital subtraction angiography (DSA), CT angiography (CTA), CT perfusion (CTP), high-resolution MR vessel wall imaging (HR-VWI), quantitative MR angiography (qMRA), optical coherence tomography (OCT), intravascular ultrasound (IVUS), and fractional

flow reserve (FFR) assessment and how these may impact management decisions.

The seminal studies of medical treatment for ICAD will be reviewed with respect to patient subgroups and how these are influencing ongoing medical therapy trials. We will analyze endovascular considerations, including patient selection, timing of procedure, medical treatment issues, and periprocedural management. We will review the options of angioplasty alone versus angioplasty with stenting, and discuss options of balloon types (standard vs drug-coated) and stents (bare metal, polymer-coated, and drug-eluting; balloon expandable vs self-expanding, open cell vs closed cell design). Finally, we will review preliminary data on the use of rescue stenting or performing angioplasty and/or stenting for failed thrombectomy in patients with large vessel occlusive acute ischemic stroke (AIS) with underlying ICAD.

DIAGNOSIS OF ICAD

DSA is the gold standard for assessing the severity of stenosis in ICAD and angiographic collaterals. However, DSA alone does not assess cholesterol plaque characteristics, circumferential nature of plaque, and potential inflammatory changes of intracranial arterial stenosis.

MR intracranial vascular imaging is a valuable non-invasive diagnostic tool, but the sensitivity depends on the type of MR imaging. Time of flight (TOF) MRA typically has less sensitivity than other modalities. In highly stenotic lesions, there is an overestimation of stenosis in TOF due to loss of local blood flow signal intensity and the dephasing effect causing magnetization artifacts.² Contrast enhanced MRA has shown better sensitivity in determining stenosis in higher grade lesions. HR-VWI with contrast and post-processing analysis may lend more insight into inflammation, intraplaque rupture, and differentiation of other causes of intracranial artery narrowing such as arterial dissection, moyamoya, vasculitis, and other pathologies.³ Additionally, there are some data to suggest that ICAD features such as concentric plaque and high degree of plaque enhancement on pre-intervention HR-VWI may be predictive of delayed in-stent stenosis.⁴ Quantitative MRA has been used in VERITAS and other studies to determine flow in individual large vessels, but does not directly assess tissue perfusion or pial collateral vessel blood flow.⁵ It appears less reliable in the posterior circulation and has not been of proven universal utility thus far.

CTA and CTP have been used for assessment of ICAD and AIS from large vessel occlusion (LVO).



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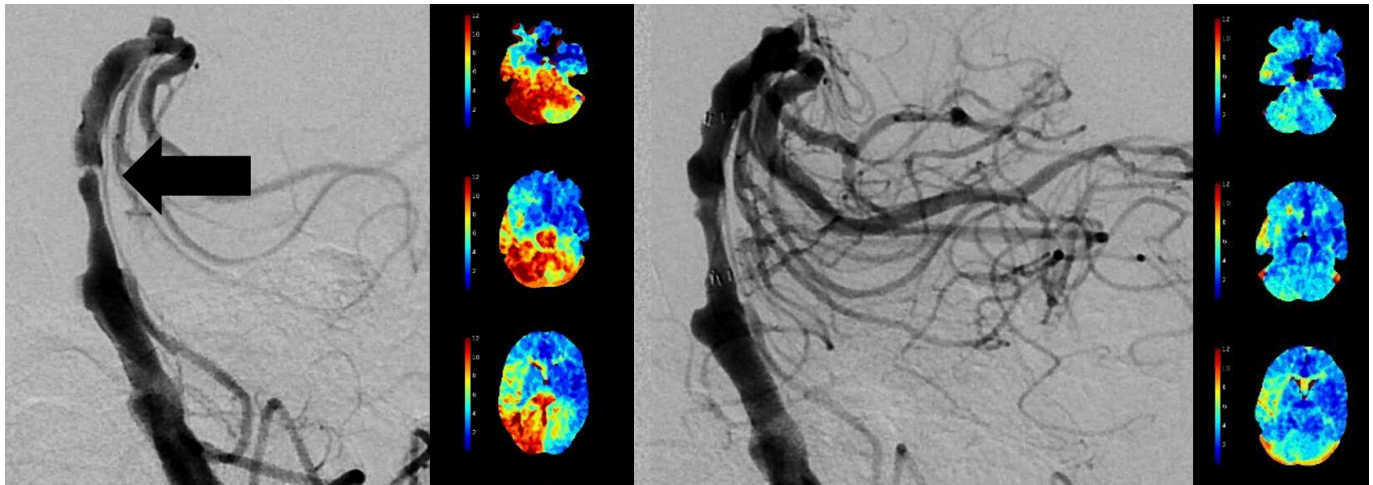


Figure 1 Left panel: Lateral vertebral artery angiogram of patient with severe basilar artery stenosis (arrow) with multiple ischemic strokes despite aggressive medical therapy. Initial CT perfusion (CTP) showed a large area of posterior fossa and right posterior cerebral artery hypoperfusion with markedly elevated time to peak (Tmax). Right panel: Post-stenting lateral angiogram showed improved luminal diameter with improved distal flow and CTP with normalization of Tmax.

The studies are easily obtainable at most centers and are non-invasive. CTA has high sensitivity and specificity for detecting >50% stenosis of large intracranial artery segments. However, the artifact from highly calcified lesions may lead to inaccurate stenosis analysis. CTP is a dynamic contrast-enhanced study developed for the analysis of the infarct core and ischemic penumbra by assessing cerebral blood flow, mean transition time, and cerebral blood volume. This combination gives both percentage stenosis and semiquantitative regional tissue perfusion, and there has been some correlation between elevated time to peak (Tmax) on CTP and recurrent stroke risk from ICAD in the anterior circulation. DeHavenon *et al* found that the primary predictor of recurrent ischemic stroke in patients with anterior circulation ICAD was hypoperfusion, defined as ≥ 15 mL volume with Tmax delay >6 s by CTP imaging.⁶ The parameters for posterior circulation ischemia have traditionally been less well defined. However, a recent study by Edwards *et al* has proposed a regional increase in mean transition time of $>145\%$ and delay time of >1 s on CTP as benchmarks for ischemic penumbra.⁷ Figure 1 shows a patient with severe symptomatic basilar artery stenosis with recurrent strokes and markedly elevated Tmax, and normalization of the CTP following angioplasty and stenting.

During DSA, intravascular imaging such as OCT and IVUS may be performed to assess the luminal wall and characteristics of the atherosclerotic plaque.⁸ Similarly, FFR measurement has been described in the cerebral circulation using a pressure sensor monitoring wire proximal and distal to the stenotic ICAD lesion to assess pressure gradient and blood flow compromise.⁹ How this would be used to affect intracranial stenting decisions has not been well studied. These intravascular methods of imaging can help characterize plaque or flow differential but have not gained widespread use to date, and it is unclear if their use will change decision-making patterns for stenting.

MEDICAL TREATMENT IN ICAD

Medical treatment is the mainstay in the management of ICAD, and optimizing medical care may reduce risk for an asymptomatic plaque to become symptomatic, and reduce the risk of recurrent stroke once a patient is symptomatic. Briefly, medical treatment consists of cessation of smoking, optimizing the patient's lipid profile, controlling hypertension, managing

diabetes or pre-diabetes, taking appropriate antithrombotic medication, optimizing body mass index (BMI), and exercising. Current guidelines are largely based on the SAMMPRIS trial¹⁰ and support goals of low-density lipoprotein cholesterol <70 mg/dL and systolic blood pressure <140 .

For asymptomatic ICAD, a single antiplatelet agent, typically aspirin, is recommended. However, for symptomatic ICAD, dual antiplatelet therapy (DAPT) is currently recommended for a minimum of 3 months, followed by resuming single antiplatelet therapy. Prolonged DAPT use may lower the risk of stroke but slightly increase the risk of major hemorrhage. In a post-SAMMPRIS survey of stroke neurologists and neurointerventionists, almost equal numbers of respondents recommended DAPT for 3 months (45%) and indefinitely (44%).¹¹

It has been reported that approximately 15% or more of the US population are resistant to clopidogrel and 5% are resistant to aspirin.^{12, 13} Clopidogrel is a prodrug that requires metabolic conversion in the liver to transition to its active form, and patients with CYP2C19 genetic polymorphisms cannot process the drug.^{13, 14} Likewise, other factors, such as very high BMI, may cause subtherapeutic antiplatelet activity.¹⁵ Ticagrelor is a P2Y12 inhibitor that does not require metabolic activation, and cilostazol inhibits phosphodiesterase and platelet aggregation. Both can be alternatives to clopidogrel in patients with CYP2C19 variations with drug resistance. Common benchmarks for antiplatelet therapy by Accumetrics VerifyNow measurement include P2Y12 inhibition in the 80–237 range (20–80% inhibition) and aspirin reactivity units (ARU) <550 .¹²

CAPTIVA is a prospective, randomized, currently enrolling trial comparing medical regimens of clopidogrel and aspirin, ticagrelor and aspirin, and low-dose rivaroxaban and aspirin in patients with ICAD to determine the optimal antithrombotic combination therapy. The study is enrolling patients with 70–99% atherosclerotic stenosis in a major intracranial artery within 30 days of presenting with an associated stroke (NCT05047172). The trial includes a wide range of clinical presentations, so subgroup analysis will be important in analyzing the results of this study.

	Hemodynamic compromise	Embolic	Perforator stroke alone	TIA alone	In-situ thrombosis with LVO
Stenting	+++	++	+	+	++
Medical therapy	+	+++	++	+++	+

Figure 2 Clinical presentations of intracranial atherosclerotic disease (ICAD) and the success of their management in prior clinical trials: hemodynamic compromise, embolic, perforator stroke alone, transient ischemic attack (TIA), and large vessel occlusion (LVO) from in situ thrombosis of an underlying ICAD stenosis.

CLINICAL PRESENTATION OF ICAD

Currently, there is no indication for endovascular therapy of asymptomatic ICAD, no matter the severity of stenosis. Therefore, we will confine the discussion to patients with symptomatic ICAD. The clinical presentation for high-grade stenosis in ICAD is variable, and the outcome in each of these subgroups is dependent on their management. Percent stenosis is only one factor to consider in symptomatic ICAD. There are five primary presentations, shown in figure 2.

Hemodynamic compromise occurs with severe stenosis and compromised collaterals. This presentation is most likely to benefit from revascularization strategies, since medical treatment does not improve perfusion. The GESICA study¹⁶ reported a very high recurrent stroke rate in patients who presented with hemodynamic compromise due to severe ICAD. With a 23.4-month mean follow-up, patients with hemodynamic compromise from ICAD had a 60.7% rate of recurrent stroke and transient ischemic attack (TIA). Similarly, the subgroup analysis by Wabnitz *et al*¹⁷ of the SAMMPRIS data showed that patients who presented with a borderzone stroke and were treated with aggressive medical management (AMM) had a 21.2% risk of recurrent stroke at 1 year. Patients who presented with a borderzone stroke and evidence of poor collaterals had a 37% rate of stroke or death at 1 year on AMM. This analysis also showed a long-term 4-year difference between AMM and AMM plus stenting in patients presenting with borderzone strokes. At 4 years post-enrollment, the risk of stroke or death was 28% in the AMM cohort and 18% in the stenting cohort, representing an absolute risk reduction of stroke or death in the stenting group of 10% and relative risk reduction of 36%. These data support the concept that patients with severe stenosis who present with stroke and hemodynamic compromise may benefit from stenting.

Patients with embolic stroke in the absence of cardiac or a proximal carotid etiology and severe intracranial artery stenosis may benefit both from medical treatment and stenting. With embolic stroke there may be components of both emboli from a ruptured plaque and hemodynamic compromise, as in watershed infarcts. Medical treatment obviates some of the risk of emboli from a thrombogenic ruptured plaque and stenting may improve perfusion to reduce recurrent stroke. In the SAMMPRIS trial

subgroup analysis, patients with middle cerebral artery core infarct had an 8.5% risk of recurrent stroke at 1 year.¹⁷

Patients who present with perforator stroke alone referable to a large vessel ICAD lesion have narrowing or occlusion of the proximal perforator from atherosclerotic disease. This typically occurs in the M1 segment with the lenticulostriate perforators or in the upper segment of the basilar artery with the pontine perforators. Endovascular intervention, whether it is angioplasty alone or angioplasty with stenting, has a high risk for further perforator stroke due to the snow plow effect from the angioplasty procedure. In the stenting arm of SAMMPRIS, perforator stroke was the most common post-procedural ischemic stroke.¹³ The protocol for the subsequent WEAVE trial took these data into consideration by employing suboptimal dilation of the ICAD lesion with the angioplasty balloon to only 60–70% of the normal luminal diameter, as opposed to the typical goal of 80–90% dilation.¹⁸ This change of practice, in addition to other protocol differences, resulted in a lower periprocedural stroke rate with stenting in the WEAVE trial compared with SAMMPRIS. However, medical treatment alone in patients presenting with perforator stroke still has a relatively high recurrent stroke rate of 13.3% at 1 year, as seen in the analysis by Wabnitz *et al*.¹⁷

Patients who present with TIA alone and no evidence of stroke have been included in many interventional studies over the years. However, there are no data to suggest that stenting patients who present with TIA alone is of clinical benefit. Data from the WASID¹⁹ and SAMMPRIS²⁰ studies show very low rates of subsequent stroke and death with medical treatment in patients who presented with TIA. The 2-year stroke and death rate for medical treatment in patients presenting with TIA in the SAMMPRIS study was 7% for an average annual stroke rate of 3.5% per year.²⁰ Endovascular therapy is unlikely to be superior to AMM in patients who present with TIA only.

Finally, patients may present with AIS from LVO due to in situ thrombosis of a severely stenotic ICAD lesion. Following thrombectomy, with either a stent retriever or aspiration alone, an underlying severely atherosclerotic stenotic lesion may be diagnosed. The artery may re-occlude immediately and rescue angioplasty or angioplasty and stenting may be necessary for revascularization.²¹

RATIONALE FOR CURRENT ICAD STENTING CRITERIA

There are some basic guidelines for endovascular intervention with stenting in patients with ICAD. These include general functional status such as modified Rankin Scale (mRS) score of ≥ 3 , age 22–80, and general medical health to undergo an interventional procedure.²² There are several specific criteria that are used for determination of whether a patient is a candidate for intracranial stenting.

Patients with 70% or greater stenosis in an artery that is 2 mm or larger may be candidates for stenting. The WASID study showed that the 1-year stroke and death rate for patients with 50–69% stenosis was 8% and the 1-year stroke and death rate with medical treatment was 18% for patients with 70–99% stenosis.¹⁹ Therefore, patients with 50–69% stenosis should be managed with medical therapy even if they presented with a stroke.

The second criterion is that patients should present with a stroke. Patients who are asymptomatic or who present with TIA only have a lower recurrent stroke rate with medical treatment. Derdeyn *et al* reported a 2-year stroke and death rate of 7% with medical treatment in patients presenting with TIA compared with 18% in patients presenting with stroke.²⁰

The next criterion is that patients should have failed medical treatment. Currently, stenting is approved as a salvage therapy. Since most patients with ICAD also have either coronary or peripheral vascular disease, most symptomatic ICAD patients are already on aspirin or some type of antithrombotic. Approximately 67% of patients in the SAMMPRIS trial had already failed medical treatment when they presented with a stroke.²⁰ However, patients not previously on antithrombotic therapy should be placed on antiplatelet therapy and risk factor management.

Current evidence also indicates that patients be stented >7 days following their index stroke event. The NIH Wingspan registry,²³ SAMMPRIS,²⁰ and the WEAVE¹⁸ registry data indicate that patients have worse periprocedural outcomes if treated within the first few days following their stroke (figure 3). In SAMMPRIS, the cohort of patients enrolled 7 days or less from their qualifying event had a higher stroke and death rate at 2 years in the stenting group compared with AMM alone (23% vs 13%). In contrast, patients who were enrolled >7 days after their qualifying event had similar stroke and death rates at 2 years (15% in AAM vs 18% in stenting). Although several of the stenting studies from Asia for ICAD have very low periprocedural complication rates after waiting 3–4 weeks from the index event, many patients have a recurrent ischemic event while waiting this length of time, so the higher risk patients may have

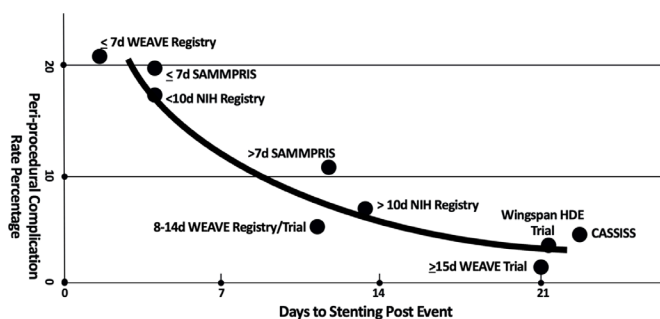


Figure 3 Evaluation of periprocedural complication rate with stenting for intracranial atherosclerotic disease based on time to treatment from index event, showing high complication rates with stenting in the first few days, which diminishes with time.

been filtered out by that late time period. It appears that the optimum time for intervention is 1–2 weeks post-stroke.¹⁸ For patients with crescendo ischemic events from severe hypoperfusion that cannot be mitigated with midodrine and fludrocortisone, earlier revascularization may be warranted prior to the 1-week interval.

It is unclear if the increased risk of stenting in the early time window is due to inflammatory changes from a hot or a recently ruptured plaque that is still thrombogenic, or whether this reflects the patients are subtherapeutic on their antiplatelet regimen. With the addition of a foreign body such as a stent, either scenario could lead to a higher periprocedural event rate. Recent loading or initiation of DAPT, or a combination of these factors, may contribute to a subtherapeutic effect resulting in periprocedural thrombotic events.¹⁴ Regardless of the etiology, multiple studies have shown that the time to treatment impacts periprocedural adverse events (figure 3).

The final general criterion by FDA guidelines for Wingspan treatment is that patients have had two strokes to be considered a candidate for intracranial stenting. There are no data to support this recommendation, and there is no precedent for this in other areas such as carotid artery stenting or coronary artery stenting. No trial until the WEAVE trial required two strokes for enrollment. In fact, most trials enrolled patients with TIA alone. In a post hoc analysis of the SAMMPRIS trial results, Yu and Jiang showed that patients who developed a delayed stroke on medical treatment had more severe and disabling strokes than those who were stented (6.2% in the medical group vs 2.2% in the stenting group).²⁴ Therefore, waiting for a second stroke on medical therapy may no longer qualify a patient for stenting because of severe disability or death. This FDA criterion has the least scientific data to support it as an indication for stenting.

Improvements in endovascular technology have also made angioplasty and stenting for ICAD much more straightforward and safer than the SAMMPRIS trial era. Flexible and easy-to-navigate distal access intermediate guide catheters allow catheter access just proximal to stenotic lesions. Double lumen microcatheters, with one lumen for balloon insufflation and one lumen to deliver the stent, such as Neurospeed and Fastunnel microcatheters, obviate the need for difficult to control exchange wires. These advancements reduce the potential for periprocedural complications.

SCIENTIFIC APPROACH TO PATIENT SELECTION AND MANAGEMENT

Proper patient selection is key in any surgical or interventional treatment. In the case of endovascular treatment of symptomatic ICAD, the evidence indicates we should exclude patients with TIA alone and patients with perforator infarcts only. Patient should be medically stable and generally meet on-label criteria to be considered for stenting.

Best medical treatment guidelines include the paradigm of AMM outlined in the SAMMPRIS trial. However, in intervention, we should avoid last minute loading doses of clopidogrel and aspirin, particularly on the interventional table. This often will result in subtherapeutic values, as pharmacokinetics indicates a clopidogrel load may take 12–24 hours to become therapeutic.¹² Loading a patient on the table may have higher risk for periprocedural thromboembolic complications. Close blood pressure control, both during and after the procedure, are key to avoiding periprocedural complications such as reperfusion hemorrhage.

Standardizing training of neurointerventionalists may reduce procedural complications. This includes safe technique, including

using a biplane roadmap to ensure the microwire is not entering perforators, suboptimal dilation of the balloon in perforator-rich areas such as the M1 segment of the middle cerebral artery or the pontine segment of the basilar artery, and ensuring that the intervention is beyond the 7-day interval. These general guidelines were followed in the FDA-mandated WEAVE trial, which demonstrated a 2.6% periprocedural stroke and death rate. In comparison, these guidelines were not followed in the SAMMPRIS trial and its periprocedural complication rate was 14.7%.

ANALYSIS OF POST-SAMMPRIS STENT TRIALS USING SELF-EXPANDING STENT

The WEAVE trial¹⁸ was an FDA-mandated post-market US study to evaluate the safety of the Wingspan stent in which 100% of patients were stented according to the FDA on-label designation. This was the largest on-label stenting trial for a self-expanding stent performed to date with 152 patients. With best practice guidelines and training of interventionists, there was a 2.6% periprocedural stroke and death rate. This was lower than the FDA safety benchmark, and the study was stopped at an early interim analysis based on the safety profile of the data. The WOVEN trial²⁵ was the longitudinal follow-up of the WEAVE trial patients, and demonstrated a 1-year total stroke and death rate of 8.5%. These were prospective trials with consecutive on-label patient enrollment and had independent neurologist adjudication of clinical outcomes. The median time to stenting from stroke in the trial was 13 days and the mode time to stenting was 8 days. Since all of the patients in the trial presented with stroke and met the study protocol, this is the most homogeneous group of patients in any stenting trial to date. Following the results of the WEAVE and WOVEN trials and the post hoc analysis of the SAMMPRIS data analyzing patients with watershed infarcts, the American Heart Association/American Stroke Association (AHA/ASA) changed the guidelines for recommending stenting for ICAD from a Class 3 (no benefit, should not be performed) to a Class 2b recommendation (benefit, weak evidence, may be considered).²⁶

The CASSISS trial²⁷ was a randomized trial evaluating medical treatment versus stenting in China. The primary outcome of stroke and death at 1 year was 8.0% in the stenting group and 7.2% in the medical treatment group, which represented no significant difference. This study has been criticized for a very high representation in enrollment of patients presenting with TIA alone (49%).²⁸ This percentage of patients with TIA was higher than in the SAMMPRIS study, where 33% of the patients presented with TIA alone. Given the natural history with medical treatment of patients presenting with TIA, it is expected that patients in the TIA group would have a lower stroke and death rate. Figure 4 shows the expected outcomes at 1 year of various clinical presentations and a comparison with clinical trial results. It is clear that a higher percentage of patients enrolled in a trial with TIA only will have better results with medical treatment, but studies with a higher enrollment of patients with stroke presentation, particularly borderzone strokes, will result in medical treatment appearing less effective.

The WICAD trial²⁹ was a post-market single-arm study in Japan evaluating angioplasty for symptomatic ICAD and Wingspan stenting as a rescue therapy following angioplasty for post-angioplasty dissection, artery recoil, or inadequate dilation. The study showed a 1-year stroke and death rate in the stenting group of 9.2%. These results are similar to the 1-year follow-up in the WOVEN and CASSISS studies, which showed 1-year event rates of 8.5% and 8.0%, respectively.

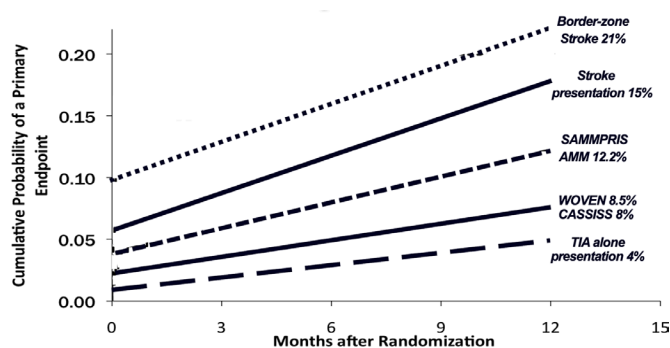


Figure 4 Projected stroke and death event rate at 1 year based on historical controls stratified by clinical presentation. Trials enrolling a high percentage of patients with transient ischemic attack (TIA) alone would be expected to demonstrate better 1-year outcomes with medical treatment.

ALTERNATIVE INTERVENTIONAL STRATEGIES

Angioplasty alone has been performed in the setting of symptomatic ICAD. The benefit of this strategy is that there is no stent implant and, theoretically, fewer periprocedural thrombotic complications. Angioplasty alone, however, has problems of arterial recoil, leading to immediate re-stenosis or arterial dissection. The WICAD trial²⁹ evaluated stenting as a salvage treatment for angioplasty alone when there was evidence of dissection, recoil, or short-term re-stenosis. Dissection or microdissection with angioplasty was the most common reason for stenting at 46.5% in a cohort of 301 patients. A total of 33.9% of the patients were enrolled in the stenting study due to post-angioplasty artery recoil or short-term re-stenosis. The WICAD publication does not indicate the incidence of these events within the total number of angioplasties performed at the participating centers. Angioplasty may be of benefit in lesions which are not amenable to stenting such as arteries smaller than 2 mm, or high-grade Mori lesions such as long segment stenoses or tightly angled ICAD lesions.

Angioplasty with a drug coated balloon (DCB) impregnates antiproliferative compounds such as paclitaxel or sirolimus into the arterial wall to decrease the risk of re-stenosis from endothelial proliferation. A few small studies using a DCB alone in ICAD have not shown impressive results due to a wide range of periprocedural complication rates. Zhang *et al* treated 42 patients with the Sequent DCB with a 2.6% complication rate and 2.6% re-stenosis rate.³⁰ Wang *et al* treated 35 patients with the Sequent DCB with a 11.4% complication rate and 8.3% re-stenosis rate.³¹ Remonda *et al* treated 33 patients with either the Neuro Elutax or Sequent DCB and had a 6% periprocedural complication rate with a 15% re-stenosis rate. However, there were four recurrent strokes within 7 months for an overall stroke rate of 18.2% in less than a year following DCB angioplasty.³² In a larger review of 240 patients, Li *et al*³³ have shown even better delayed re-stenosis rates with DCB (5.7%), but a not insignificant periprocedural complication rate (5.9%).

Stenting with bare metal balloon-mounted stents has been performed for decades with coronary stents. The first dedicated intracranial stent for ICAD, the NeuroLink stent, was a balloon-mounted bare metal stent similar to coronary stents. While long sheaths and intermediate catheters can be placed high in the neurovascular circulation to make the stiffer balloon-mounted stents easier to navigate to the ICAD lesion, these types of stents do have some issues. Balloon-mounted neurovascular stents such as the Apollo stent are not tapered so, in tapered arteries

or bifurcations, the stent does not appose the inner wall well or a portion of the artery is dilated above its normal diameter. This may lead to arterial rupture. Balloon-mounted stents are straight and stiffer than self-expanding stents, so are only useful in straight arterial segments. Finally, balloon-mounted stents can only be delivered by inflating the balloon to its nominal diameter or higher. So, one cannot underdilate in perforator-rich areas. This increases the risk of perforator occlusion in M1 and upper basilar artery segments. Furthermore, in a randomized trial by Jia *et al*,³⁴ balloon-mounted bare metal stents had a 30.2% 1-year re-stenosis rate and a 1-year stroke and death rate of 12.2%, which was not superior to recent Wingspan studies. Early results evaluating surface modifications of bare metal stents, such as fibrin polymer and heparin coating such as the CREDO Heal stent, have shown promise in reducing stent thrombogenicity but more thorough studies with long-term follow-up are pending (NCT05345483).

Stenting with self-expanding stents designed for treating wide-neck aneurysms has been studied with mixed results. These types of stents have lower radial force than ICAD stents so have less positive remodeling potential than ICAD stents.³⁵ While open cell aneurysm stents are easy to deliver, some results suggest high re-stenosis rates likely related to the weak stent structure. Closed cell design aneurysm stents are also easy to deliver, but they tend to ovalize around tight angles and cannot be used if there is a potential for Y-stent or sequential Y-angioplasty of an ICAD bifurcation lesion. The aneurysm stents (Neuroform, Enterprise, LVIS, Acclino, Atlas and Solitaire) have been proposed as alternative stents for ICAD in some studies, but the majority of these studies are retrospective, with self-reported clinical outcomes, and delay in stenting for ≥ 3 weeks post-event. They have not been studied with the same degree of rigor as the Wingspan ICAD stent. Sun *et al*³⁶ reported a review of 557 patients in the literature treated with the Enterprise stent for ICAD and found a periprocedural stroke and death rate of 7.4% and delayed event rate of 3.2% for a total 1-year event rate of 10.6%. Although they conclude that the delayed re-stenosis rate (10.1%) was lower than historical Wingspan controls, the clinic outcomes were not superior to the major post-SAMMPRIS studies.

Stenting with drug-eluting balloon-mounted stents (DES) may help reduce the re-stenosis rate seen with bare metal stents but has some of the same issues as bare metal balloon mounted stents. Jia *et al*³⁴ studied 132 patients treated with the NOVA stent, the first neurovascular DES, in a prospective randomized controlled trial and found a periprocedural stroke and death rate of 7.6% and a total 1-year stroke and death rate of 8.4% with a 1-year re-stenosis rate of 9.5%. So, although the re-stenosis rate was lower than most self-expanding stent studies, the 1-year stroke and death rate was similar to the WOVEN, CASSISS, and WICAD trials using the Wingspan stent. A multicenter single-arm study evaluating the Resolute Onyx stent in 132 patients showed a 30-day stroke and death rate of 3%, but did not have long-term follow-up.³⁷ Similar reports have shown favorable long-term re-stenosis rates, but further prospective controlled studies are warranted.

Stenting with drug-eluting self-expanding stents for the intracranial arteries seems attractive, in that there is a potential decrease in re-stenosis and delayed stroke and the stents can conform to the tapered and angled neurovasculature. One of the problems in developing a drug-eluting self-expanding stent for neurovascular use is that prior technologies for coating the stents with antiproliferative drugs resulted in relatively high particle release not felt to be safe as a permanent neurovascular implant. Newer nanothin spray film coatings or drug loaded nanoparticle

coatings may hold promise for future use.³⁸ There is currently an ongoing trial in China evaluating the safety and efficacy of the Neurovita DES, the first drug-eluting self-expanding stent designed for ICAD (NCT05217459).

MANAGING PATIENTS WITH LVO AND ICAD

Currently, there is no FDA-approved treatment for the management of underlying severe ICAD stenosis in patients with AIS and LVO. Likewise, there are currently no AHA/ASA recommendations regarding the treatment of underlying stenosis in LVO. There are published case series and some controlled cohort studies that may give us some guidance.

Ni *et al* reported a series of 47 patients treated with angioplasty plus tirofiban as a first-line treatment after failed mechanical thrombectomy.³⁹ This was a retrospective study with no control group. They reported that 41 patients (87.2%) had successful revascularization with angioplasty alone, with the remaining six patients requiring stenting. An additional seven patients underwent stenting 1–2 months later for severe residual stenosis. At follow-up, they noted a good functional outcome in 26/47 patients (55.3%).

Li *et al*²¹ published a multicenter experience in which they studied 184 patients with severe stenosis from ICAD identified at the time of thrombectomy for AIS. A total of 64 patients had rescue angioplasty and stenting and 120 had no additional intervention. Better functional outcomes (mRS 0–2) were seen in the rescue stenting group (51.6%) than in patients with no adjuvant rescue stenting (35.0%, $p=0.02$). The use of postprocedural tirofiban was higher in the rescue stenting group, however, so this may have had a significant impact on the clinical outcomes.

Swaid *et al* performed a retrospective analysis of patients with LVO and underlying ICAD and compared patients who had stenting as a bailout measure with those who did not.⁴⁰ With stenting, 82.4% of patients had favorable revascularization with no increase in postprocedural complications. Patient outcomes in delayed clinical follow-up at 3 months were better in the stenting group than in the thrombectomy alone group (39.2% vs 12%, $p=0.01$).

Interestingly, rescue stenting has not been associated with higher symptomatic cerebral hemorrhages compared with non-revascularization, despite the postprocedural DAPT. There is a not insignificant risk of stent thrombosis in rescue stenting but, even with this risk, patients have shown better clinical outcomes compared with leaving the artery occluded or severely stenotic post-thrombectomy. A study of the NIS database indicates that the use of rescue stenting has increased fivefold over the past 6 years in the USA with the increase in the number of thrombectomies for AIS.¹

CONCLUSIONS

Medical treatment is the mainstay of most cases of ICAD, whether asymptomatic or symptomatic. However, for patients who have failed medical treatment, endovascular revascularization can be performed with a low risk in most subgroups. Patients with hemodynamic compromise and large vessel emboli presentation appear to have the most potential benefit for intracranial artery stenting. The primary long-term risk for these patients post-stenting is in-stent re-stenosis. The use of DCB and DES has demonstrated lower re-stenosis rates, but shown mixed results regarding periprocedural complications. Currently, there are no FDA-approved DCB or DES devices for ICAD. The use of stenting as a rescue therapy in LVO thrombectomy has also shown promising early results. The investigation of this option

in failed revascularization during thrombectomy may be beneficial to patients with AIS.

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ORCID iDs

Michael J Alexander <http://orcid.org/0000-0003-0280-809X>

Wengui Yu <http://orcid.org/0000-0003-1664-3580>

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