Intracranial Atherosclerotic Disease
Current Concepts in Medical and Surgical Management

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Abstract

Purpose of the Review
This article reviews the current concepts in intracranial atherosclerotic disease (ICAD) as a common etiology of ischemic stroke; pathophysiologic mechanisms of ischemic stroke; diagnostic evaluation; and therapeutic modalities, including maximal medical therapy (MMT), percutaneous transluminal angioplasty and stenting (PTAS), and bypass surgery.

Recent Findings
Data from recent studies demonstrate that proper patient selection and timing of procedure and standardized PTAS techniques by experienced operators resulted in acceptably low periprocedural adverse events for patients who failed MMT.

Summary
ICAD is a common cause of ischemic stroke. Complex pathology and high rates of recurrent and disabling ischemic strokes despite currently available treatments make ICAD the most challenging to treat of all ischemic stroke etiologies. Randomized trials previously showed that MMT, which involves the use of combinations of antiplatelet medications, targeted control of hypertension and serum low-density lipoprotein cholesterol, and adequate management of body weight through lifestyle modification, was superior to PTAS in decreasing rates of recurrent ischemic strokes from symptomatic ICAD. MMT performed better than expected, while periprocedural complications were significantly higher than expected in PTAS. Meanwhile, high rates of recurrent ischemic stroke despite MMT remain a great challenge. New clinical evidence continues to emerge on a safer application of PTAS, which is currently offered to a subset of patients who present with recurrent ischemic strokes despite MMT.
Intracranial atherosclerotic disease (ICAD) commonly involves the basilar artery, internal carotid arteries, middle cerebral arteries, intracranial vertebral arteries, posterior cerebral arteries, and anterior cerebral arteries in decreasing frequency. Ischemic stroke rates related to ICAD remain high despite maximal medical therapy (MMT), although MMT has improved over the years and significantly decreases recurrent stroke risk. The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, which enrolled patients between 1999 and 2003 and compared aspirin and warfarin for the treatment of symptomatic ICAD, found a 23% annual risk of stroke in a subgroup of patients who presented with ischemic stroke due to ≥70% stenosis. A similar group of patients who were given MMT in the Stenting Versus Aggressive Medical Management Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial had only half of that risk (12.6%) per year. SAMMPRIS, which was prematurely stopped in 2011, also found that MMT was superior to MMT plus percutaneous transluminal angioplasty and stenting (PTAS), a finding driven mainly by unusually high rates (14.7%) of periprocedural stroke/death associated with PTAS. Using stringent patient selection criteria, proper timing of stenting, and application of standardized stenting techniques and protocols, the Wingspan Stent System Post Market Surveillance (WEAVE) study reported in 2019 only a 2.6% risk of periprocedural stroke/death. A 1-year follow-up of most of the WEAVE cohort was assessed by the Wingspan One-Year Vascular Events and Neurologic Outcomes (WOVEN) trial, which in June 2020 reported a relatively low (8.5%) rate of stroke and death.

**Pathology**

An early autopsy report of 200 consecutive patients (newborn–80 years of age) observed lipid streaks or spots as the earliest evidence of atherosclerosis in cerebral arteries. These findings were noted to begin in the fourth decade of life in cerebral arteries, ~2 decades after they were observed in coronary arteries. Another postmortem study of 334 patients found intimal necrosis to be an earlier event in atherosclerotic involvement of cerebral arteries, predating the development of fatty streaks and fibromuscular plaques, which are secondary phenomena. Intimal thickening and proliferative changes of the basement membrane and adventitia were more prevalent than fatty infiltrations in cerebral arteries. More defined fibrous plaques and complicated lesions that consist of calcifications and plaque rupture were observed with advanced age (after the fifth decade) and limited to proximal segments of basilar, vertebral, and internal carotid arteries, and necrotic and hemorrhagic changes were generally less common in cerebral arteries.

**Epidemiology**

ICAD is the most common cause of ischemic stroke worldwide, mainly due to its high prevalence in Asian patients. Symptomatic ICAD was observed in as many as 50% of Chinese patients hospitalized for cerebral ischemic events. Higher rates of ICAD are also observed in Black and Hispanic patients compared to White patients. While the reasons for the disproportionately high prevalence of ICAD in Asian, Black, and Hispanic patients remain uncertain, genetic predispositions and higher rates of uncontrolled hypertension, hyperlipidemia, and diabetes appear to play significant roles.

**Mechanism of Stroke**

Various ICAD-related mechanisms of stroke are described in literature and summarized in Figures 1–5. Artery-to-artery embolism with infarcts distal to the stenotic vessel (Figure 1) was the most common mechanism of stroke in intracranial...
arterial stenosis (59.7%), followed by local branch occlusion (Figure 2) involving ≥1 perforators (14.9%), in situ thrombo-occlusion (13.7%) (Figure 3), hemodynamic impairment with linear border-zone infarcts (0.9%) (Figure 4), and mixed mechanisms (10.8%) (Figure 5), in a 1,000-patient prospective multicenter MRI based study in Korea. Another study found that isolated hypoperfusion (35.3%) and a mixed mechanism of artery-to-artery embolism and hypoperfusion (37.3%) were both common and ischemic lesion patterns on MRI suggested to be the underlying mechanism of stroke. Isolated infarct in a penetrating artery distribution is due to local branch occlusion from parent artery ICAD. Cortical and subcortical territorial infarctions are from either artery-to-artery embolism or parent artery in situ thrombo-occlusion. Linear (chain-like) (Figure 4) internal border-zone or wedge-shaped external border-zone infarcts are likely from hemodynamic impairment (hypoperfusion). Mixed mechanisms can lead to combinations of ischemic lesion patterns. Concurrent atherosclerotic stenosis of intracranial and extracranial arteries was common (43% of 251 patients) in a study and led to mainly hemodynamic and artery-to-artery embolism–attributable strokes. Compared with extracranial stenosis, hemodynamic strokes were more common in ICAD.

Clinical Course
Symptomatic ICAD is associated with a high risk of recurrent ischemia. Early progression of clinical deficits and new ischemic changes on imaging are common with ICAD. In a study, 32% of those who presented with recurrent ischemia while on aggressive medical management had progressive or crescendo strokes. About 25% of patients developed clinical recurrence with corresponding diffusion-weighted lesions on MRI within 1 week after the index stroke, and 14% of patients with subcortical ischemia had progressive neurologic deficits within a median of 2 days. Patients with mixed mechanism of artery-to-artery embolism and hypoperfusion, multiple infarcts (diffusion-weighted imaging lesions on MRI), and diffuse atherosclerosis on angiography were more likely to have early recurrent strokes (Figure 2).

The 30-day and 1-year recurrent stroke or death rates in WASID were 10.7% and 25%, respectively. The corresponding rates in the medical management group of SAMMPRIS were 5.8% and 12.6%, respectively. While WASID randomized patients with nondisabling stroke/TIA to either warfarin (with target international normalized ratio of 2.0–3.0) or aspirin 1,300 mg/d with standard management of vascular risk factors for both treatment groups, SAMMPRIS applied MMT. MMT in SAMMPRIS was defined as dual antiplatelet therapy (DAPT) with aspirin 325 mg/d and clopidogrel 75 mg/d for 90 days after enrollment, management of primary risk factors (systolic blood pressure <140 mm Hg, <130 mm Hg for those with diabetes; low-density lipoprotein cholesterol [LDL-C] <70 mg/dL or 1.81 mmol/L), and management of secondary risk factors (diabetes, elevated non–high-density lipoprotein cholesterol...

Figure 1 Artery-to-Artery Embolism With Cortical Infarction

(A) A 65-year-old Hispanic man presented with recurrent right arm weakness and aphasia. Focal left middle cerebral artery (MCA) (M1 segment) stenosis on CT angiography (white arrow in B) and digital subtraction angiography (DSA) (black arrowhead in D). Delayed left MCA cortical flow on CT perfusion (CTP) (C) and DSA (yellow circle and ellipse in E and F, anteroposterior and lateral arteriograms, respectively). Patient also had right anterior cerebral artery stenosis with corresponding flow impairment on CTP.
levels, smoking, excess weight, and insufficient exercise) with the help of a lifestyle modification program. DAPT in SAMMPRIS likely played a significant role in cutting the early recurrent stroke risk by nearly in half.

Long-term recurrent stroke risk and cognitive decline related to focal or diffuse cerebral infarcts or white matter degeneration from hypoperfusion or hypometabolism are well documented in previous reports. Dementia; impaired executive function; slowness of memory, information processing, and motor function; amnesia; and depression were identified. The burden of white matter hyperintensities in patients with acute ischemic stroke was significantly higher with intracranial stenosis compared with extracranial atherosclerotic stenosis or no intracranial stenosis. There was a dose-response relationship between the number of intracranial stenotic lesions and white matter hyperintensities. A post hoc analysis of SAMMPRIS observed an overall improvement in cognitive function in patients assigned to both treatment groups.

Figure 2 Local Branch Occlusion With Multiple Brainstem Infarcts

(A–D) An 81-year-old White woman who despite maximal medical therapy experienced 3 strokes involving the brainstem and right occipital lobe over a 3-month period presented with right-sided weakness and severe dysarthria during her third stroke. Diffuse basilar artery stenosis on anteroposterior (E) and lateral (F) left vertebral arteriograms. (G and H) Anteroposterior and lateral left vertebral arteriograms after treatment of basilar stenosis with submaximal angioplasty and 2 overlapping Wingspan stents. Patient was discharged to rehabilitation with baseline clinical examination.
Diagnostic Evaluation

CT angiography (CTA) and magnetic resonance angiography (MRA) are routinely used for initial evaluation of ICAD. In a study that examined 672 vessel segments, CTA had a significantly higher sensitivity (98% vs 70%) and positive predictive value (93% vs 65%) than 3-dimensional time-of-flight MRA for intracranial stenosis. The negative predictive value of CTA was also superior to that of MRA, 100% vs 87%. CTA accurately ruled out severe stenosis (70%–99%) and may eliminate the need for digital subtraction angiography (DSA) in many patients with ICAD. CT and magnetic resonance perfusion studies can demonstrate cortical flow impairment related to severe ICAD, typically in the acute stroke setting (Figures 1 and 7).

An important advantage of DSA over CTA or MRA is in the assessment of collateral flow, which is very useful for selecting patients who are candidates for endovascular revascularization. Extent of collateral circulation was an independent predictor of subsequent stroke in the territory of both severe (70%–99%) and moderate (50%–69%) symptomatic arterial stenoses. More extensive collaterals significantly reduced the risk of subsequent stroke.

The diagnostic accuracy of color-coded transcranial Doppler (TCD) was compared with that of DSA in a study, which found sensitivity, specificity, positive predictive value, and negative predictive value of 73%, 83%, 79%, and 77%, respectively. Generally more reliable in the anterior circulation, power motion–mode TCD has been shown to have higher accuracy owing to its contiguous and overlapping gates. Flow velocity changes detected on TCD during vasomotor reactivity (VMR) testing correlate with cerebral blood volume changes. VMR refers to the vasodilatory capacity of cerebral arteries and arterioles to vasomotor stimuli such as an increased blood level of carbon dioxide (via breath holding or inhalation) or IV acetazolamide. Corresponding to chronic compensatory vasodilatation, VMR is expected to be lower or impaired in patients with ICAD.

High-resolution MRI helps to discern vessel wall and plaque characteristics with prognostic and therapeutic implications and complements luminal imaging modalities such as CTA,
MRA, and DSA. In a study that looked at 516 arteries of the circle of Willis in 43 patients who received both DSA and 3-dimensional high-resolution MRI within a month, 3-dimensional high-resolution MRI showed better diagnostic accuracy, sensitivity, and positive predictive value; a comparable degree of stenosis; and statistically higher luminal diameter compared with DSA.27

High-resolution vessel wall MRI (HRvwMRI) directly images the submillimeter arterial wall by suppressing blood signal and shows plaque morphology and enhancement patterns with high special resolution.28 Typically, ICAD on HRvwMRI appears to be eccentric and less often circumferential, often with discrete plaque commonly leading to positive remodeling or unchanged diameter of the wall rather than negative remodeling. Ma et al.29 described the association of negative remodeling and perforator stroke after basilar artery stenting. If plaque is symptomatic with recent emboli (hot plaque), the degree of enhancement that diminishes over months has been demonstrated.30 T1-, T2-, or proton density–weighted sequences without and with (to see enhancement) gadolinium are commonly used in HRvwMRI.

Medical Treatment

MMT is recommended for the treatment of ischemic stroke or TIA attributable to ICAD31 and is widely adopted among clinicians with some differences in practice such as duration of antiplatelet therapy.32 MMT for SAMMPRIS eligible patients (TIA or stroke within 30 days due to 70%–99% stenosis) includes the combination of aspirin 325 mg daily and Plavix 75 mg daily for 90 days, systolic blood pressure <140 mm Hg (130 mm Hg for those with diabetes), LDL-C <70 mg/dL, maintenance of hemoglobin A1c <7%, body mass index <25 kg/m² (if body mass index was 25–27 kg/m²) or 10% weight loss if body mass index was >27 kg/m², cessation of cigarette smoking, and moderate-intensity exercise at least 3 times per week.3 The same approach is recommended for patients with TIA or stroke due to moderate stenosis (50%–69%) with aspirin monotherapy; however, short-term (21–30 days) DAPT followed by aspirin monotherapy is also used as an alternative. Randomized trials on patients with non-cardioembolic ischemic stroke/TIA showed benefit of DAPT to be concentrated in the first month after the ischemic event while its hemorrhagic risk remained constant.33,34 It is important to note that currently there is no Level 1 evidence for DAPT over monotherapy and that the optimal duration of DAPT is unknown. Another important caveat with regard to antiplatelet management of ICAD is that some of the studies discussed below were not specifically targeting ICAD.

Antiplatelets

While aspirin alone for treatment of symptomatic ICAD was found to be associated with high rates of recurrent stroke in WASID, concurrent studies35,36 suggested potential benefit from combining antiplatelet agents. The Trial for Cilostazol in Symptomatic Intracranial Arterial Stenosis (TOSS)35 showed lower rates of stenosis progression as measured by MRA in patients assigned to cilostazol 200 mg and aspirin 100 mg compared with patients who took only aspirin 100 mg, supporting the vasodilating and antiplatelet properties of
cilostazol, but benefit in stroke prevention was not explored. The TOSS-2 trial, which randomly assigned 457 patients into cilostazol-aspirin vs clopidogrel-aspirin groups with symptomatic middle cerebral artery or basilar artery stenoses, found no difference in preventing both disease progression or new ischemic lesions on MRA and MRI, respectively, at the 7-months follow-up.

More recent studies that included patients with non-cardioembolic stroke etiologies such as ICAD showed the early benefit of DAPT over monotherapy. In 2013, the Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) trial, which compared clopidogrel and aspirin for the first 21 days followed by clopidogrel alone for 90 days with aspirin alone for 90 days, reported that clopidogrel-aspirin treatment lowered subsequent stroke risk (8.2% vs 11.7%, hazard ratio [HR] 0.68, 95% confidence interval [CI] 0.57–0.81; p < 0.001). However, a subgroup analysis of CHANCE in 2015 that looked at the relative efficacy and safety of the 2 treatment groups among patients with and without ICAD found no significant beneficial effects of DAPT over aspirin alone for both groups of patients, even though there was a significantly higher rate of recurrent stroke in patients with ICAD than those without. Small sample size, fewer outcome events, and potential selection bias were mentioned as limitations of this analysis. The Platelet-Oriented Inhibition in New TIA and Minor Stroke (POINT) trial, which was conducted from 2010 to 2017, showed that the combination of aspirin and clopidogrel lowered the risk of recurrent major ischemic events (5% vs 6.5%, HR 0.75, 95% CI 0.59–0.95) and increased the risk of major hemorrhage (0.9% vs 0.4%, HR 2.32, 95% CI 1.10–4.87) compared with aspirin alone at 90 days. The benefit of DAPT is likely the highest during the first few days after stroke when the hazard curves for recurrent stroke were observed to be steep in both POINT and CHANCE. The early benefit was also demonstrated in the Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolization in Patients With Acute Symptomatic Cerebral or Carotid Stenosis (CLAIR) study, in which 93 of the 100 patients had cerebral stenosis, and in its subsequent subgroup analysis of only the patients with ICAD, in which a clopidogrel-aspirin treatment significantly reduced microembolic signals detected by TCD on days 2 and 7 compared with aspirin alone.

Figure 5 Mixed Mechanisms of Strokes With Internal and External Border-Zone and Cortical Infarcts

A 69-year-old White woman presented with recurrent left-sided weakness. Right internal carotid artery arteriogram with distal right middle cerebral artery, M1 segment stenosis shown with white arrowheads in anteroposterior (C) and lateral (D) views, White arrows in anteroposterior (E) and lateral (F) views show images after submaximal angioplasty and Wingspan stenting.
The randomized Acute Stroke or Transient Ischemic Attack With Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial found that ticagrelor was not superior to aspirin, with the rates of recurrent stroke within 90 days being 5.8% and 6.7% respectively (HR 0.87, 95% CI 0.76–1.00). A subgroup analysis of SOCRATES suggested that ticagrelor might be more effective than aspirin when stroke/TIA was associated with ipsilateral atherosclerotic stenosis. Ticagrelor plus aspirin could be used as an alternative to Plavix plus aspirin in patients with Plavix resistance (carriers of CYP19 loss-of-function alleles). The Acute Stroke or Transient Ischemic Attack Treated With Ticagrelor and Aspirin for Prevention of Stroke and Death (THALES) trial compared ticagrelor-aspirin with placebo-aspirin in patients with mild to moderate ischemic stroke (NIH Stroke Scale score ≤5) or high-risk TIA. Similar to POINT, THALES results, which were published in July 2020, showed that the risk of stroke or death (composite primary outcome) was lower in the ticagrelor-aspirin group than in the placebo-aspirin group (5.5% vs 6.6%, HR 0.83, 95% CI, 0.71–0.96; p = 0.02), but the incidence of overall disability was similar between the 2 groups, and the risk of severe hemorrhage was higher in the ticagrelor-aspirin group.

Anticoagulation

Anticoagulation is currently not recommended for stroke prevention from ICAD. The randomized Fraxiparin in Stroke Study for the Treatment of Ischemic Stroke (FISS-tris) assigned patients with stroke with large artery occlusive disease (300 of 353 had intracranial large artery occlusive disease) to either subcutaneous nadroparin calcium (a low-molecular-weight heparin with anti–factor Xa activity) or aspirin given for 10 days followed aspirin for 6 months for all patients in both groups and found no significant difference in good outcomes (Barthel index ≥85). A follow-up subgroup analysis of FISS-tris hinted at some benefit of low-molecular-weight heparin in elderly patients (age >68), previous antiplatelet nonusers, and those with posterior circulation stenosis.

Warfarin offered no benefit over aspirin both in the WASID and European/Australian Stroke Prevention in Reversible Ischemia (ESPRIT) trials. WASID compared warfarin (for target international normalized ratio of 2–3) with aspirin 1,300 mg/d in stroke or TIA attributable to 50% to 99% intracranial stenosis and found no difference (21.8% vs 21.1%) in the composite end point of ischemic stroke, brain hemorrhage, or vascular death, while the ischemic stroke risk in the territory of the stenotic artery was high for both groups at 12.1% vs 15%, respectively, during a mean follow-up of 1.8 years. Similarly, ESPRIT compared warfarin (for target international normalized ratio of 2–3) and lower-dose aspirin (30–325 mg per day) and showed 19% vs 18% in primary end points over a mean follow-up of 4.6 years. The potential benefit in ICAD of the newer non–vitamin K oral anticoagulants alone or in combination with antiplatelet agents needs further investigation.

Risk Factor Management

Data are limited on the optimal blood pressure target for stroke prevention from all causes of stroke, including ICAD. It is recommended to maintain a blood pressure target of <140/90 mm Hg and considered safe to decrease blood pressure.
within 48 to 72 hours after an acute stroke if patients are neurologically stable. A post hoc analysis of patients from the WASID trial showed that systolic blood pressure $\geq 140$ mm Hg was associated with increased risk of stroke, myocardial infarction, and vascular death (HR 1.79, 95% CI 1.27–2.52; $p = 0.0009$). Similarly, a post hoc analysis of SAMMPRIS showed that well-controlled systolic blood pressure ($< 140$ mm Hg) was associated with fewer vascular events.47

Guidelines recommend statins with intensive lipid-lowering effects with target LDL-C $\leq 100$ mg/dL for patients with stroke or TIA due to atherosclerotic disease.31 A lower target of LDL-C $< 70$ mg/dL is often used in patients with stroke because the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial found a significant reduction in stroke risk in patients who achieved LDL-C $< 70$ mg/dL (atorvastatin 80 mg daily group) compared with those with LDL-C $> 100$ mg/dL (placebo group). In WASID, only 7% of patients who had mean LDL-C $< 70$ mg/dL (10% of total cohort) had the primary endpoint (stroke/vascular death/myocardial infarction) compared to 23% of patients with LDL-C $\geq 70$ mg/dL.48 A post hoc analysis of SAMMPRIS also showed a trend toward benefit with LDL-C $< 70$ mg/dL.47

Hyperglycemia in acute ischemic stroke is associated with worse outcomes. The Stroke Hyperglycemia Insulin Network Effort trial found no difference in 90-day favorable outcome between intensive (80–130 mg/dL) and standard (80–179 mg/dL) treatment groups of adult patients with ischemic stroke with hyperglycemia.49 The intensive group had higher rates of hypoglycemia and other adverse events. Hemoglobin A1c $< 7\%$ is recommended as a marker for long-term control of diabetes.

**Intracranial Angioplasty and Stenting**

Intracranial angioplasty or stenting (Figure 6) has not been shown to be safer and more effective than medical management in randomized trials, even as the rates of recurrent ICAD-related disabling strokes remain high despite MMT. The 2 multicenter randomized trials5,50 that are completed thus far were terminated prematurely due to unacceptably high periprocedural adverse events in the angioplasty and stenting cohorts. A single-center randomized trial that compared angioplasty and stenting with medical management in Chinese patients with $\geq 70\%$ stenosis of the middle cerebral artery found no difference in the rates of ipsilateral stroke/TIA or death (19.4% vs 17.6%) at 1 year.51

The Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT),50 which was conducted between January 2009 and June 2012, randomly assigned patients with symptomatic intracranial stenosis ($\geq 70\%$) to either Vitesse balloon-expandable stent plus medical therapy or medical therapy alone. The trial was discontinued early after enrolling 112 (45%) of the planned 250 patients. The 30-day primary safety outcome (a composite of any stroke, death, or intracranial hemorrhage) rates for stent vs medical group were 24% vs 9%; the rates for 1-year primary outcome (a composite or stroke and hard TIA in the same territory) were 36% vs 15%.

SAMMPRIS randomized patients with TIA or stroke within 30 days of symptoms related to 70% to 99% stenosis of a major intracranial artery to either aggressive medical management alone or aggressive medical management plus angioplasty and stenting with the Wingspan self-expanding stent system. Enrollment was terminated after 451 (59%) of the originally planned 764 patients were enrolled. The risks of stroke or death in the stenting group vs the medical group were 14.7% vs 5.8% at 30 days, 19.7% vs 12.6% at 1 year, and 23.9% vs 14.9% at 3 years.52 The persistent efficacy gap was due largely to the 30-day outcomes differences.

Periprocedural stroke/death rates in SAMMPRIS and VISSIT were significantly higher than previously reported rates (range 2.2%–6.2%) from clinical trials, including the Wingspan study and the NIH registry for the use of the Wingspan stent for symptomatic 70% to 99% intracranial arterial stenosis, which led to Food and Drug Administration approval of the Wingspan stent (Stryker, Kalamazoo, MI) in 2005. Twenty-five of the 33 early strokes/deaths occurring within the first day of stenting in SAMMPRIS indicate suboptimal combination of patient selection and stenting technique. After SAMMPRIS, the Food and Drug Administration mandated a postmarket surveillance trial (WEAVE) to assess periprocedural safety of the Wingspan stent in treatment of symptomatic ICAD.

WEAVE, the largest on-label multicenter prospective trial of the Wingspan stent for ICAD so far, was also terminated early after an interim analysis of 152 (39%) of the planned 389 patients found only a 2.6% rate of periprocedural stroke, bleeding, or death within 72 hours of the procedure, lower than the 4% periprocedural safety benchmark. On-label criteria included 70% to 99% stenosis, $\geq 2$ strokes in the vascular territory of the stenotic artery (with at least 1 stroke while on medical therapy), and stenting by experienced interventionalists $\geq 8$ days after the qualifying stroke.

The China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis (CASSISS), which started enrolling patients in March 2014, is an ongoing multicenter randomized trial with strict patient and interventionalist selection criteria and procedures to be performed no earlier than 3 weeks after the qualifying stroke. The lead-in phase of CASSISS recruited 100 patients and found a 2% stroke or death rate at 1 month.54

**Future Direction for PTAS**

Given the great performance of MMT in SAMMPRIS, future randomized trials of PTAS will likely focus on patients who...
failed MMT. Proper patient selection, adequate operator experience and standardized practice, and ongoing improvement in balloon and stent technology and delivery systems will likely offer additional safety and long-term efficacy of PTAS in this vulnerable group of patients.

**Patient Selection**

Stenosis with evidence of hypoperfusion or embolism is more likely to benefit from PTAS as opposed to perforator occlusion–related ischemia. PTAS to treat perforator occlusion–related ischemia could lead to a snow-plowing effect and occlusion of more perforators, leading to new strokes. If PTAS is necessary, submaximal angioplasty should be performed to treat stenosis near perforators. Submaximal angioplasty (60%–80% of normal parent artery diameter) and stenting near perforators may have contributed to the lower rates of perforator occlusion–related strokes observed in WEAVE compared with SAMMPRIS (0.7% vs 5.8%). Besides stroke subtypes, MRI can identify vessel wall remodeling patterns, which could help in selecting eligible patients for stenting. Patients with poor collaterals on angiography and stable plaque might benefit from PTAS.

A 69-year-old Hispanic woman presented with recurrent left-sided weakness and left homonymous hemianopia. Previously placed Wingspan stent spanning from distal basilar to the P1 segment of the right posterior cerebral artery (PCA) had severe in-stent restenosis (white arrow in A). Right PCA territory perfusion deficit on CT perfusion (B). Angioplasty of Wingspan performed with 2.25 × 15-mm Gateway. The more distal P2 stenosis treated with 2 × 8-mm Resolute Onyx balloon-mounted stent, which was advanced past the Wingspan stent (C–H). Arrowhead in image D shows 5F Sofia (Microvention Inc, Aliso Viejo, CA) advanced to the proximal P1 segment inside the Wingspan stent to support delivery of Resolute Onyx stent to the P2 segment.
Timing of Stenting

Stenting early (within 7 days of stroke) likely increases stroke/hemorrhage risk and should be avoided if possible. Recent stroke is likely an indicator for unstable plaque (hot plaque) that may rupture and lead to distal embolic stroke during angioplasty and stenting. Early reperfusion could also increase the risk of reperfusion hemorrhage from weakened and leaky capillaries from blood-brain barrier disruption in the acute stroke bed, compounded by the early combination of antiplatelet and procedural IV heparin. A loading dose of clopidogrel 600 mg (which was allowed in SAMMPRIS) and procedural IV heparin (with activated clotting time >300 seconds) increased the risk of intraparenchymal hemorrhage. In SAMMPRIS, half of stent placements were done ≤7 days after the qualifying ischemic event, while all patients in WEAVE were stented ≥8 days later (median time to stenting 22 days). CASSISS does not enroll patients within 3 weeks of stroke.

Hemodynamic augmentation (permissive hypertension, euvoolemia) and medications such as midodrine and fludrocortisone can be used to stabilize patients with recurrent/fluctuating symptoms within the first 7 days.

Operator Experience

It is not surprising that experience in intracranial stenting was associated with lower periprocedural adverse events. The mean Wingspan case experience for each interventionalist in WEAVE was 37 cases, and those with >50 Wingspan cases had 0% periprocedural complications. CASSISS required 30 intracranial stentings for ICAD per site for 3 consecutive years. In SAMMPRIS, the median case volume for interventionalists was 10 before they were allowed to enroll patients. VISSIT also allowed only 10 cases of stenting experience (either in ICAD or stent-assisted aneurysm treatment), which, compounded with the unfavorable stent design with only a 54% rate of proper deployment, likely contributed to the high periprocedural morbidity and mortality.

Proper patient selection and optimal technique by experienced interventionalists in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) 2 registry, the first national carotid stenting registry running along with the ongoing CREST 2 trial, resulted in a 2% 30-day stroke/death rate, a significant reduction compared with the 7.2% rate in the original CREST trial.

Stent/Balloon Technology

Newer-generation lower-profile stents (Figure 7) can be placed intracranially with relative ease in a single-step delivery technique. This technique avoids multiple wire exchanges and decreases the risk of wire perforation and subarachnoid hemorrhage. Highly trackable distal access support catheters can be navigated through tortuous intracranial arteries close to the stenosis (Figure 7D) and help deliver the stents relatively easily. Drug-eluting stents (Figure 8) could decrease restenosis rates, which are as high as 25% to 30% for ICAD. Symptomatic restenosis is one of the major causes of non-procedural stroke. Future research is needed to evaluate safety and efficacy of bioactive balloons, absorbable stents, disease-modifying agents, and robotics technology in intracranial stenting.

Direct and Indirect Surgical Revascularization

Extracranial-intracranial (EC-IC) bypass is a direct surgical anastomosis through a small craniotomy of the superficial...
temporal artery with distal branches of the middle cerebral artery (MCA) (EC-IC bypass). The EC-IC Bypass Study included 1,377 patients with recent hemispheric strokes, retinal infarction, or TIA who had atherosclerotic stenosis or occlusion of ipsilateral internal carotid artery (extracranial and intracranial) or MCA who were randomized into EC-IC bypass combined with aspirin vs aspirin alone and found no benefit of EC-IC bypass in decreasing rate of ipsilateral stroke or death. In particular, patients with severe MCA stenosis ≥70% (n = 109) who underwent bypass surgery had significantly higher rates of stroke compared with the medical management group (44% vs 23.7%).

Indirect revascularization surgeries include encephaloduroarteriosynangiosis (EDAS) and encephalomyosynangiosis. A retrospective review included 36 patients with intracranial atherosclerotic steno-occlusive disease who had ischemic symptoms despite intensive medical management and underwent EDAS. That review found that EDAS increased collateral circulation to territory at risk of ischemia, and 2 (6%) patients had strokes over a median follow-up of 22 months. A phase II trial (Surgical Indirect Revascularization for Symptomatic Intracranial Arterial Stenosis) on 52 patients who had failed medical treatment and underwent EDAS plus intensive medical management showed a 9.6% rate of stroke/death within 30 days of surgery or stroke in the target artery territory at 1 year. The authors concluded that a phase Ib/III trial is justified because the above rate is >10% lower than the 20% event rate observed in SAMMPRIS for the subgroup of patients receiving MMT who had poor collaterals.

Mechanical Thrombectomy in ICAD

Underlying ICAD was identified in up to 34% of patients who underwent mechanical thrombectomy (MT) for large vessel occlusion in 1 study, and 64% of those met criteria for rescue therapy with angioplasty and stenting. While MT is safe in patients with ICAD (compared with those without ICAD), it is unclear which initial MT technique is more effective. There is no consensus among neurointerventionalists on the “go-to” approach for first-pass success in MT, and this includes MT on patients with underlying ICAD. Generally, neurointerventionalists use MT devices and techniques that work best in their hands considering their experience, patient factors, and thrombus characteristics on imaging. If underlying ICAD is suspected on the basis of history and preprocedural imaging, some neurointerventionalists believe that stent-retrievers are most likely to be effective in extracting the thrombus, in addition to their benefit in outlining the extent and severity of the underlying stenosis, which may be judged from the degree of expansion of stent-retrieves during deployment. Moreover, flow patterns and vessel caliber distal to the stenosis/occlusion can be studied while the stent-retriever is still deployed for a few minutes, during which rescue therapy (angioplasty and/or stenting) can be planned if needed. Other neurointerventionalists prefer using large-bore distal access reperfusion catheters as the first approach to removing/debulking the superimposed thrombus and restoring flow without passing the stenotic segment with wires and catheters and plan for rescue therapy as needed. There seems to be a consensus that rescue therapy is indicated only if there is significant delay in antegrade flow or if reocclusion occurs after successful MT.

Conclusion

ICAD is a common vascular disease with high rates of recurrent ischemic strokes. While MMT significantly decreases the rates of recurrent stroke, safer and effective endovascular and open surgical revascularization treatment alternatives are needed for patients who fail MMT.

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Appendix Authors

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<tr>
<th>Name</th>
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<tr>
<td>Wondwossen G. Tekle, MD</td>
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<td>Ameer E. Hassan, DO</td>
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<td>Made critical revisions to the manuscript</td>
</tr>
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</table>

References

Intracranial Atherosclerotic Disease: Current Concepts in Medical and Surgical Management
Wondwossen G. Tekle and Ameer E. Hassan
Neurology 2021;97;S145-S157
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