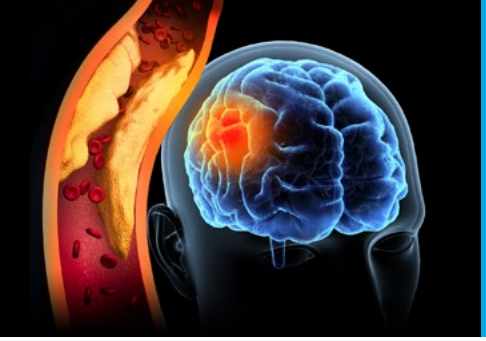

AAN Summary of Practice Advisory for **Clinicians**

Stroke Prevention in Symptomatic Large Artery Intracranial Atherosclerosis Practice Advisory

This is a summary of the American Academy of *Neurology*'s (AAN's) "Stroke Prevention in Symptomatic Large Artery Intracranial Atherosclerosis Practice Advisory," which was published in *Neurology*® online on March, 21, 2022, and appears in the March 22, 2022, print issue.

Please refer to the full guideline at AAN.com/guidelines for the full systematic review of the evidence as well as descriptions of the processes for classifying evidence, deriving conclusions, and making recommendations.

Diagnosis

Recommendation 1

Rationale

Symptomatic intracranial atherosclerotic arterial stenosis (s-ICAS) is one of the most common causes of stroke worldwide, responsible for 10%–50% of strokes depending on racial and ethnic factors,[1,2,3] and can coexist with other stroke etiologies such as extracranial atherosclerosis or atrial fibrillation.[4,5] There is no diagnostic gold standard for diagnosing s-ICAS and various noninvasive and invasive techniques (e.g., magnetic resonance angiography [MRA], CT angiography, transcranial Doppler [TCD], and catheter cerebral angiography) are used with varying sensitivity and specificity.[6,7] Intracranial artery luminal stenosis may be due to a variety of vasculopathies and atherosclerosis may be differentiated clinically in most cases.[8] It is important to identify s-ICAS as the etiology of stroke to optimize secondary prevention strategies. Expeditious evaluation is reasonable as the highest risk of recurrent stroke is soon after the incident event.

Level	Recommendation
Level B	Clinicians should utilize diagnostic modalities to diagnose s-ICAS and distinguish it from other intracranial vasculopathies if the results would be expected to change management or provide important prognostic information.

Antithrombotic Medication Therapy

Recommendations 2, 3, and 4

Rationale

The Warfarin-Aspirin Symptomatic Intracranial Disease trial (WASID) showed that in patients with s-ICAS, aspirin 650 mg twice daily was safer and as effective as warfarin for preventing the combined endpoint of stroke, intracerebral hemorrhage, and vascular death. While the optimal aspirin dose for s-ICAS has not been determined, patients in the medical arm of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS) were treated with aspirin alone 325 mg/day after the first 90 days. Other antiplatelet agents used for stroke prevention (e.g., ticagrelor or combination dipyridamole and aspirin) and other doses of aspirin have not been specifically studied in s-ICAS. The safety and efficacy of novel oral anticoagulants for prevention of stroke in s-ICAS are not established. Similarly, the safety and efficacy of adding aspirin to anticoagulation in patients with s-ICAS that require anticoagulation for another condition (e.g., atrial fibrillation) have not been established. However, given that warfarin was equally effective as aspirin for stroke prevention in WASID, the utility of adding aspirin to warfarin does not seem warranted in light of bleeding concerns.

Combination short-term clopidogrel and aspirin use in s-ICAS was not directly supported by this systematic review but is supported by related evidence.[9,10] The Clopidogrel Plus Aspirin versus Aspirin Alone for Reducing Embolisation in Patients with Acute Symptomatic Cerebral or Carotid Artery Stenosis trial (CLAIR) showed that patients randomized to clopidogrel plus aspirin had significantly decreased microemboli in the territory of the stenotic artery when compared with aspirin alone.[11] When combined with the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis trial (CARESS), a similar study of patients with carotid atherosclerosis, patients treated with clopidogrel and aspirin had a significant reduction in recurrent stroke compared with patients treated with aspirin monotherapy.[12] Additionally, s-ICAS patients in the Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events trial (CHANCE) who were randomized to clopidogrel and aspirin had a numerically lower rate of stroke at 90 days compared with those on aspirin alone, albeit not statistically significant. Additional support for combined short-term clopidogrel and aspirin comes from analyses comparing patients in the medical arm of SAMMPRIS treated with 90 days of clopidogrel plus aspirin who had a lower primary endpoint rate compared with similar patients from WASID treated with aspirin alone at 1 month (5.8% vs 10.5%) and 6 months (8.9% vs 17.9%).[13,14] This analysis of WASID patients who met SAMMPRIS entry criteria was adjusted for confounding factors and still showed almost double the risk of stroke in the WASID patients, despite the higher burden of poor prognostic features in the SAMMPRIS patients. The optimal duration of combined clopidogrel and aspirin in s-ICAS has not been tested in randomized controlled trials (RCTs) and remains unknown, but the high rate of stroke beyond the first few months on aspirin alone in the medical arm of SAMMPRIS suggests further study is needed to determine if extending clopidogrel use beyond 3 months is warranted.

Trials of cilostazol combined with other antiplatelet agents for stroke prevention in s-ICAS have had mixed results. The Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis (TOSS) and TOSS-2 trials found cilostazol plus aspirin was not better for stroke prevention than aspirin alone or clopidogrel plus aspirin. However, the Cilostazol-aspirin Therapy Against Recurrent Stroke with Intracranial Artery Stenosis

Study (CATHARSIS) did demonstrate that cilostazol plus aspirin prevented the combined secondary endpoint of all vascular events and new silent brain infarcts when compared with aspirin alone.[15] Subgroup analysis of patients with s-ICAS in the Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS) study (which included heterogeneous causes of stroke) showed a lower rate of stroke when randomized to cilostazol plus either aspirin or clopidogrel compared with those on aspirin or clopidogrel alone. Generalizability of these cilostazol studies is limited in that they were conducted in a primarily Asian population and low-dose aspirin (≤150 mg/d) was used.

Level	Recommendation
Level B	Clinicians should recommend aspirin 325 mg/d over warfarin for long-term prevention of stroke and death in patients with s-ICAS.
Level B	Clinicians should recommend adding clopidogrel 75mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with severe (70%–99%) s-ICAS who have low risk of hemorrhagic transformation of ischemic stroke.
Level C	Clinicians may recommend adding cilostazol 200 mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with s-ICAS and low risk of hemorrhagic complications as an alternative to clopidogrel or in Asian patients.

Lipid and Hypertension Vascular Risk Factor Modification

Recommendations 5 and 6

Rationale

Support for the management of vascular risk factors in patients with s-ICAS comes from prespecified, post-hoc analyses of s-ICAS clinical trials and other clinical practice guidelines for patients with stroke and vascular disease. Evidence for the use of high-intensity statins in patients with symptomatic atherosclerotic disease is well established and is applicable to patients with s-ICAS.[16] In addition, a lower rate of cerebrovascular events was seen in s-ICAS patients randomized to high-intensity statin therapy compared with other dosages.[17] A target LDL <70 mg/dL among patients with stroke and atherosclerotic disease was found to reduce major cardiovascular events compared with patients with a target LDL <100 mg/dL.[18] Post-hoc analyses from WASID and SAMMPRIS also show lower rates of vascular events with lower LDLs in s-ICAS. The use of other lipid lowering agents (e.g., PCSK9 inhibitors or omega-3) has not been specifically studied in s-ICAS but may be supported by studies of symptomatic atherosclerotic disease.[19]

Historically, there was concern for targeting normal BP in the setting of an intracranial stenosis resulting in hypoperfusion and contrasting concern for worsening atherosclerosis due to uncontrolled hypertension.[20] Analyses from WASID, SAMMPRIS, and the CICAS registry have demonstrated that among clinically stable patients with s-ICAS, a mean systolic blood pressure (SBP) <140 mm Hg during follow-up was associated with a lower risk of stroke and vascular events, even in patients with posterior circulation or severe stenosis.[21,22,23] While the current American Heart Association guideline-recommended target of SBP <130 mm Hg has not been studied in patients with s-ICAS, an RCT of s-ICAS patients comparing SBPs <120 mm Hg vs <140 mm Hg found that the more intensive group (which had a mean SBP of 124.6 mm Hg) had a higher rate of new ischemic lesions on imaging and larger stroke volume than the standard group.[24,25] Some subgroups of s-ICAS patients may be at higher risk of stroke with lower BPs, including those with hemodynamic impairment[26,27] or those with a large reduction in BP from baseline.

Level	Recommendation
Level B	Clinicians should recommend high-intensity statin therapy to achieve a goal LDL <70 mg/dL in patients with s-ICAS to reduce the risk of recurrent stroke and vascular events.
Level B	Clinicians should recommend a long-term blood pressure target of <140/90 mm Hg in clinically stable patients with s-ICAS to reduce the risk of recurrent stroke and vascular events.

Physical Activity

Recommendation 7

Rationale

In the general population, moderate physical activity reduces incidence of stroke.[28] Among patients with s-ICAS, a post-hoc analysis of SAMMPRIS showed that not performing moderate physical activity at least 3–5 times per week was associated with a higher risk of recurrent stroke and vascular events (odds ratio [OR] 6.7, 95% CI 2.5–18.1).

Level	Recommendation
Level B	Clinicians should recommend at least moderate physical activity in patients with s-ICAS who are safely capable of exercise to reduce the risk of recurrent stroke and vascular events.

Other Modifiable Vascular Risk Factors

Recommendation 8

Rationale

Benefits on morbidity and mortality from maintaining a healthy lifestyle and management of other vascular risk factors are well established for patients with atherosclerotic disease and are applicable to patients with s-ICAS.[29]

Level	Recommendation
Level A	Clinicians must recommend treatment of other modifiable vascular risk factors in patients with s-ICAS to reduce the risk of recurrent stroke and vascular events.

Bilateral Arm Ischemic Preconditioning

Recommendation 9

Rationale

Based on 2 RCTs done in patients with s-ICAS, 5 cycles of bilateral arm ischemic preconditioning (BAIPC) twice daily appears to reduce the risk of recurrent stroke and death. However, the evidence is derived from only 2 centers in China, the studies had small sample sizes, and the studies were not blinded. These methodical issues limit conclusions about efficacy in a multi-ethnic population. While the risk of the procedure appears low, the BAIPC device does not have approval for use in the United States, limiting its application. These methodological issues limit confidence in conclusions about efficacy and there are no data in a multi-ethnic population.

Level	Recommendation
N/A	The authors could not achieve consensus on a recommendation for BAIPC in patients with s-ICAS.

Endovascular and Surgical Therapy

Recommendations 10 through 13

Rationale

Percutaneous Transluminal Angioplasty and Stenting

Recommendations related to percutaneous transluminal angioplasty and stenting (PTAS) are informed by several randomized trials that showed no benefit of PTAS (with either self-expanding or balloon mounted stents) over medical therapy. Three RCTs have shown a higher rate of periprocedural cerebrovascular events and death from PTAS and no benefit of stroke prevention during follow-up compared with medical therapy in patients with s-ICAS.

Single-arm, uncontrolled registries assessing subpopulations of patients with s-ICAS, including "medical failures" (i.e., stroke or TIA while on antithrombotic medications) or those with progressive neurological symptoms, have reported conflicting rates of periprocedural complications.[30,31] In a Food and Drug Administration (FDA)-mandated post-market surveillance study of the Wingspan stent, the stroke or death rate was 23.9% within 72 hours among those who did not meet criteria for FDA-approved use, many of whom had not failed medical therapy or were treated recently after stroke.[32,33] In post-hoc analyses of RCTs, no studied subgroups have been shown to benefit from PTAS, including those with intracranial vertebral segment location or those taking antithrombotic medications at the time of the initial cerebrovascular event. PTAS has not been systematically compared with medical therapy in patients with moderate (50%–69%) s-ICAS, but the low risk of stroke in these patients and the high risk of periprocedural complications, which do not depend on severity of stenosis, makes PTAS unwarranted.[34,35]

Angioplasty alone

In light of safety issues related to PTAS, balloon angioplasty alone (i.e., without placement of an intracranial stent) has been considered a possible alternative for endovascular therapy.[36] However, no RCTs have compared angioplasty alone with medical therapy for stroke prevention in patients with s-ICAS. A systematic review and meta-analysis of 25 studies of angioplasty alone compared event rates in patients treated with angioplasty to events in the SAMMPRIS medical group and found no benefit of angioplasty due to the high periprocedural morbidity and mortality.[37] Balloon angioplasty alone may be performed with a submaximal staged approach, which may have a lower rate of morbidity and mortality.[38]

Optimal stroke prevention for patients with s-ICAS who have recurrent strokes despite antiplatelet therapy and intensive treatment of risk factors is unknown. However, given the lack of efficacy data, the use of PTAS or angioplasty alone for stroke prevention in any subpopulation of patients with s-ICAS is investigational.[39,40,41]

Level	Recommendation
Level B	Clinicians should NOT recommend PTAS as the initial treatment for stroke prevention in patients with severe (70%–99%) s-ICAS.
Level B	Clinicians should NOT recommend PTAS for stroke prevention in patients with moderate (50%–69%) s-ICAS.
Level B	Clinicians should NOT routinely recommend angioplasty alone for stroke prevention in patients with s-ICAS outside clinical trials.
Level B	Clinicians should counsel patients about the risks of PTAS and alternative treatments if one of these procedures is being contemplated.

Surgical Treatment

Recommendations 14 and 15

Rationale

Direct bypass

Recommendations related to the use of direct surgical bypass for stroke prevention in patients with s-ICAS are informed by 1 RCT. The extracranial to intracranial (EC/IC) bypass trial included patients with s-ICAS and found that bypass was not associated with a decrease in recurrent stroke and death as compared with medical therapy alone. For subgroups with severe MCA stenosis or occlusion, there was an increased risk of recurrent stroke or death with direct bypass. Similar to the EC/IC bypass study, the Carotid Occlusion Surgery Study (COSS), which studied patients with symptomatic internal carotid artery (ICA) occlusion, found that direct bypass increases the risk of stroke and death predominantly due to early peri-procedural complications.[42] For patients with posterior circulation vertebral artery disease, a single-center case series reported that surgical revascularization decreased recurrent stroke and death as compared with medical therapy alone, but no RCTs have been performed to establish efficacy and the procedure is considered investigational.[43,44]

Indirect bypass

In patients with anterior circulation s-ICAS, indirect bypass with encephaloduroarteriosynangiosis (EDAS) is an emerging investigational surgery for stroke prevention.[45,46,47,48,49] A small initial study of indirect

revascularization without standardized medical management showed a high rate of recurrent stroke in patients with s-ICAS.[50] Four non-randomized studies, including 2 small case series,[51,52] 1 single-center prospective study,[53] and 1 2-center prospective trial with independent outcomes assessment[54] suggested that there may be benefit of EDAS over medical therapy when applied with standardized medical treatment. Well-designed and well-conducted randomized trials have not been completed.

Level	Recommendation
Level B	Clinicians should NOT recommend direct bypass for stroke prevention in patients with s-ICAS.
Level A	Clinicians must NOT routinely recommend indirect surgical revascularization for stroke prevention in patients with s-ICAS outside clinical trials.

This practice guideline was endorsed by the American Heart Association/American Stroke Association, the Society of Vascular and Interventional Neurology, and the Neurocritical Care Society.

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