SPECIAL ARTICLE Level of Recommendation

Stroke Prevention in Symptomatic Large Artery Intracranial Atherosclerosis Practice Advisory

Report of the AAN Guideline Subcommittee

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Abstract

Background and Objectives

To review treatments for reducing the risk of recurrent stroke or death in patients with symptomatic intracranial atherosclerotic arterial stenosis (sICAS).

Methods

The development of this practice advisory followed the process outlined in the American Academy of Neurology *Clinical Practice Guideline Process Manual, 2011 Edition,* as amended. The systematic review included studies through November 2020. Recommendations were based on evidence, related evidence, principles of care, and inferences.

Major Recommendations

Clinicians should recommend aspirin 325 mg/d for long-term prevention of stroke and death and should recommend adding clopidogrel 75 mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with severe (70%–99%) sICAS who have low risk of hemorrhagic transformation. Clinicians should recommend high-intensity statin therapy to achieve a goal low-density lipoprotein cholesterol level <70 mg/dL, a long-term blood pressure target of <140/90 mm Hg, at least moderate physical activity, and treatment of other modifiable vascular risk factors for patients with sICAS. Clinicians should not recommend percutaneous transluminal angioplasty and stenting for stroke prevention in patients with moderate (50%–69%) sICAS or as the initial treatment for stroke prevention in patients with severe sICAS. Clinicians should not routinely recommend angioplasty alone or indirect bypass for stroke prevention in patients with sICAS outside clinical trials. Clinicians should not recommend direct bypass for stroke prevention in patients with sICAS. Clinicians should counsel patients about the risks of percutaneous transluminal angioplasty and stenting and alternative treatments if one of these procedures is being contemplated.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AAN = American Academy of Neurology; **AMM** = aggressive medical management; **BAIPC** = bilateral arm ischemic preconditioning; **BP** = blood pressure; **DAPT** = dual antiplatelet therapy; **EC/IC** = extracranial to intracranial; **EDAS** = encephaloduroarteriosynangiosis; **FDA** = Food and Drug Administration; **LDL** = low-density lipoprotein; **LMWH** = low molecular weight heparin; **LOF** = loss of function; **MCA** = middle cerebral artery; **OR** = odds ratio; **PTAS** = percutaneous transluminal angioplasty and stenting; **RCT** = randomized controlled trial; **RD** = risk difference; **SAMMPRIS** = Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; **SBP** = systolic blood pressure; **sICAS** = symptomatic intracranial atherosclerotic arterial stenosis; **WASID** = Warfarin–Aspirin Symptomatic Intracranial Disease.

Symptomatic intracranial atherosclerotic arterial stenosis (sICAS) is one of the most common causes of stroke worldwide and is associated with a high risk of recurrent stroke.[1-4] The global burden of stroke associated with sICAS is expected to rise as the population ages and as Asian, Black, and Hispanic populations, which have a higher prevalence of sICAS, increase, as major contributors to global population growth.[5]

Over the past 2 decades, evidence has accumulated informing the treatment of sICAS, with 2 general approaches emerging: (1) aggressive medical management (AMM) with dual antiplatelet therapy (DAPT) plus intensive control of vascular risk factors and (2) medical therapy plus endovascular procedures. Given the high risk of recurrent stroke reported in many studies,[6,7] clinical trials also focused on identifying and quantifying modifiable and nonmodifiable risk factors that may place patients at a particularly high risk of recurrent stroke. Knowledge of predictors of recurrent stroke is crucial for risk stratification, effect modification, and identifying therapeutic targets in future clinical trials.

This practice advisory seeks to answer the following clinical questions:

1. For patients with a history of sICAS, which medical therapies, as compared with no therapy or an alternative therapy, reduce the risk of recurrent stroke/death or increase the risk of major hemorrhage (therapeutic scheme)?
   a. Anticoagulation vs antiplatelet therapy
   b. Specific antiplatelet therapy regimens vs alternative regimens
   c. Antihypertensive agents or blood pressure (BP) control targets
   d. Statin therapy or lipid targets
   e. Ischemic preconditioning
2. For patients with a history of sICAS, do endovascular or extracranial to intracranial (EC/IC) bypass procedures, as compared with no procedure, reduce the risk of recurrent stroke or death (therapeutic scheme)?
3. For patients with a history of sICAS, what modifiable and nonmodifiable risk factors predict an increased risk of recurrent stroke or death (prognostic scheme)?
   a. Degree of stenosis
   b. Length of stenosis
   c. Tandem lesions
   d. Vascular bed
   e. Degree of collateral circulation
   f. Demographics including sex, race, and ethnicity of patient
   g. Medical comorbidities
   h. Time from index event
   i. Physical activity level
   j. Lack of use of aggressive medical therapy

This article is a summary of the key findings of the practice advisory. The complete practice advisory, including evidence tables, is available at aan.com/Guidelines/home/GuidelineDetail/1067.

Description of the Analytic Process

This practice advisory follows the 2011 edition of the American Academy of Neurology's (AAN) guideline development process manual.[8] In September 2014, a multidisciplinary panel was recruited to develop the protocol for this practice advisory. The authors include content experts (T.N.T., L.B.G., M.I.C., A.C., A.J.F., J.G.L., M.J.S., A.B.S., L.R.W., O.O.Z., R.S.S., N.R.G, T.N.N., A.A.R.), a methodology expert (G.S.G.), and Guidelines Subcommittee members (J.J.F., S.R.M.). All authors were required to submit the AAN's relationship disclosure forms and copies of their curriculum vitae, which were reviewed by panel leadership. The full author panel was solely responsible for final decisions about the design, analysis, and reporting of this practice advisory, which was submitted for approval to the Guidelines Subcommittee.

Inclusion and exclusion criteria for article selection were chosen to be rated for risk of bias on the basis of a priori criteria. Consistent with prior AAN stroke-related guidelines, the primary outcome of interest was recurrent stroke or recurrent stroke and death. sICAS is defined as TIA or ischemic stroke attributed to 50%–99% atherosclerotic stenosis of a major intracranial artery. Therapeutic clinical trials of sICAS were primarily limited to stenosis of the middle cerebral, intracranial carotid, basilar, and vertebral arteries.

For therapeutic questions, only studies that randomly allocated patients with sICAS to different treatment groups and followed patients to compare their subsequent risks of recurrent stroke or death were included in the systematic review

and intention-to-treat analyses were used to inform conclusions. The author panel determined a priori that the effect measure used would be risk differences (RDs), with a change of 5% considered clinically meaningful. Generic inverse variance random effects meta-analytic models were used to pool effect sizes as we expected substantive heterogeneity based on patient selection, time from qualifying event, medical management, duration of follow-up, or inclusion and exclusion criteria. For the primary analysis, we utilized studies with the lowest risk of bias and greatest generalizability to inform conclusions.

For the prognostic question, only cohort studies or case-control studies that compared recurrent stroke risk in patients with sICAS with and without a putative risk factor were included in the systematic review. The author panel determined a priori that the primary effect measure used would be the odds ratio (OR), and if no OR was reported or calculable, the hazard ratio would be considered equivalent to the risk ratio and would be used to estimate the OR.[9-11] An increased risk ratio of 0.5 (i.e., OR >1.5) was considered clinically meaningful. When determining risk of bias in prognostic studies, we did not downgrade a study's contribution if baseline risk factors were ascertained prior to the determination of the outcome.

Confidence in the evidence was anchored by the number and class of studies included in the synthesis. Generalizability and study precision were also considered, but studies were not downgraded for generalizability based on race or ethnicity. Evidence was downgraded when the CI for a statistically insignificant effect measure included a clinically meaningful effect (e.g., an OR >1.5) indicating poor precision. Evidence was not downgraded for imprecision when CIs around effect measures were consistent with statistical significance but contained values of uncertain clinical importance (e.g., an OR of 1.05); however, the evidence could not be upgraded. All CIs were presented transparently for individual interpretation and use in the modified Delphi process. Confidence in the evidence was downgraded by 2 levels for imprecision. Confidence in the evidence was only downgraded by 1 level in indirect studies with good precision. The magnitude of effect was considered when upgrading the confidence in evidence supported by studies with direct evidence and low risk of bias (Class I evidence).

The overall confidence in the evidence was determined using a modified Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[8,12,13] Recommendations were derived by the author panel utilizing an iterative modified Delphi process after considering the evidence strength, risks and benefits, cost, availability, and patient preference variations.

Analysis of Evidence

The panel searched the MEDLINE, Cochrane, and Science Citation Index databases from database inception to February 2016 for relevant peer-reviewed articles that met inclusion criteria. The panelists reviewed the titles and abstracts of 2,325 articles for relevance, which resulted in 505 obtained for full-text review. Independent review of the 505 articles by 2 panel members resulted in 45 articles for inclusion in the analysis and evidence rating. An updated literature search following the same process was conducted in November 2020, yielding 1,233 articles. Of the reviewed abstracts, 54 were identified for full-text review and 11 new articles were ultimately selected to inform conclusions.

1a. For patients with a history of sICAS, does anticoagulation, as compared with antiplatelet therapy, reduce the risk of recurrent stroke or death?

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of warfarin, as compared with aspirin, in reducing the recurrent risk of stroke or death (RD –0.3%, 95% CI –7.2% to 6.5%; very low confidence in the evidence, 1 Class I trial,[7] confidence downgraded due to imprecision).

For patients with sICAS, it is likely that warfarin, as compared with aspirin, increases the risk of major hemorrhage (RD 5.1%, 95% CI 1.2%–9.1%) and death (RD 5.4%, 95% CI 1.2%–9.8%). This conclusion is based on 1 Class I trial[7] and confidence in the evidence is moderate.

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of short-term nadroparin calcium (low molecular weight heparin [LMWH]), as compared with aspirin, for reducing the composite of early neurologic decline and recurrent stroke (RD 0.2%, 95% CI –6.3% to 6.5%) or death (RD 0.4%, 95% CI –4.5% to 5.2%; very low confidence in the evidence, 1 Class I study,[14] confidence downgraded due to imprecision and indirectness).

For patients with sICAS, there is insufficient evidence to support or refute the effect of short-term nadroparin calcium (LMWH), as compared with aspirin, on hemorrhagic adverse events (RD 4.7%, 95% CI –3.3% to 10.3%; very low confidence in the evidence, 1 Class I study,[14] confidence downgraded due to imprecision and indirectness).

1b. For patients with a history of sICAS, do specific antiplatelet therapy regimens, as compared with alternative antithrombotic regimens, reduce the risk of recurrent stroke or death?

Cilostazol Regimens

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of cilostazol plus aspirin or clopidogrel (DAPT), as compared with monotherapy (aspirin or clopidogrel), for reducing the risk of recurrent stroke or death (RD –3%, 95% CI –8% to 3%; I^2 = 57%; very low confidence in the evidence, 1 Class I study[15] and 1 Class II study,[16] confidence downgraded for insufficient precision). The risk of serious hemorrhagic complications is likely not

different between DAPT with cilostazol compared with monotherapy (RD 0%, 95% CI –1% to 0%; I^2 = 0%; moderate confidence in the evidence, 1 Class I study[15] and 1 Class II study[16]).

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of DAPT with cilostazol plus aspirin, as compared with clopidogrel plus aspirin, in reducing recurrent stroke or death (RD 1.7%, 95% CI –2.4% to 5.7%; very low confidence in the evidence, 1 Class 1 study,[17] confidence downgraded due to imprecision). DAPT with cilostazol plus aspirin is likely not associated with any difference in hemorrhagic complications compared with clopidogrel plus aspirin (RD –1.8%, 95% CI –4.9% to 0.8%; moderate confidence in the evidence, 1 Class I study[17]).

DAPT With Aspirin and Clopidogrel Regimens

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of DAPT with clopidogrel plus aspirin, compared with aspirin monotherapy, initiated soon after high-risk TIA or stroke in reducing the risk of recurrent stroke or death (RD –3%, 95% CI –7% to 1%; I^2 = 0%; very low confidence in the evidence, 1 Class I study[18] and 1 Class II study,[19] confidence downgraded due to imprecision and indirectness).

For patients with sICAS, it is possible that short-term DAPT with clopidogrel plus aspirin does not increase the risk of hemorrhagic complications compared with aspirin monotherapy in patients with TIA or minor stroke (RD –1%, 95% CI –2% to 1%; I^2 = 7%; low confidence in the evidence, 1 Class I study[20] and 1 Class II study,[19] confidence downgraded due to indirectness).

1c. For patients with a history of sICAS, which antihypertensive agents or BP control targets, as compared with alternative agents or targets, reduce the risk of recurrent stroke or death?

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of intensive vs modest BP control in reducing the risk of recurrent stroke or death (RD 0%, 95% CI –8.5% to 7.2%; very low confidence in the evidence, 1 Class IV study[21] with insufficient precision).

1d. For patients with a history of sICAS, do statin therapy or lipid targets, as compared with alternative management, reduce the risk of recurrent stroke or death?

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of any statin therapy or other lipid-lowering regimens in reducing the recurrent risk of stroke or death (very low confidence in the evidence, 2 Class IV studies[22,23]).

1e. For patients with a history of sICAS, does ischemic preconditioning, as compared with sham therapy, reduce the risk of recurrent stroke or death?

In patients with sICAS, bilateral arm ischemic preconditioning (BAIPC) is likely effective in reducing the risk of recurrent stroke (RD –15%, 95% CI –27% to –2%; I^2 = 0%; moderate confidence in the evidence, 2 Class II studies[24,25]).

2a. For patients with a history of sICAS, do EC/IC bypass procedures, as compared with no procedure, reduce the risk of recurrent stroke or death?

For patients with symptomatic severe middle cerebral artery (MCA) stenosis, EC/IC direct bypass, as compared with medical therapy alone, is highly likely to increase the risk of recurrent stroke or death (RD 20.3%, 95% CI 2.5%–36.7%; high confidence in the evidence, 1 Class I study,[26] confidence upgraded due to magnitude of effect).

2b. For patients with a history of sICAS, do endovascular procedures, as compared with no procedure, reduce the risk of recurrent stroke or death?

For patients with recent TIA or nondisabling stroke attributed to sICAS, it is highly likely that percutaneous transluminal angioplasty and stenting (PTAS) plus AMM, compared with AMM alone, increases the early risk of recurrent stroke and death (RD 13%, 95% CI 3%–24%; I^2 = 59%; high confidence in the evidence, 2 Class I studies[27-29] with large magnitude of effect).

For patients with recent TIA or nondisabling stroke attributed to sICAS, it is possible that PTAS plus AMM, compared with AMM alone, does not reduce the long-term risk of recurrent stroke or death (RD 3%, 95% CI –3% to 8%; I^2 = 86%; low confidence in the evidence, 2 Class I studies,[27-29] confidence downgraded due to imprecision).

3. For patients with a history of sICAS, what modifiable and nonmodifiable risk factors predict an increased risk of recurrent stroke or death?

Evidence supporting factors that did or did not predict an increased risk of recurrent stroke or death is summarized in Table 1.

Practice Recommendations

Diagnosis

Rationale for Recommendation 1

sICAS is one of the most common causes of stroke worldwide, responsible for 10%–50% of strokes depending on racial and ethnic factors,[2,4,30] and can coexist with other stroke etiologies such as extracranial atherosclerosis or atrial fibrillation.[31,32] There is no diagnostic gold standard for diagnosing sICAS and various noninvasive and invasive techniques (e.g., magnetic resonance angiography, CT angiography, transcranial Doppler, and catheter cerebral angiography) are used with varying sensitivity and specificity.[33,34] Intracranial artery

Table 1 Predictors of Recurrent Stroke or Death in Patients With Symptomatic Intracranial Atherosclerotic Arterial Stenosis

Increased Risk	No Increased Risk	Point Estimate	Confidence
Risk factor control during follow-up[a]			
SBP (out of target)[e18]		1.7	High
Mean arterial pressure (out of target)[36]		2.8	Moderate
Diastolic blood pressure (out of target)[40]		2.2	Moderate
Strict BP control plus low distal flow status[e11]		6.2	Low
TC (out of target)[36]		2.1	Moderate
TC/HDL ratio (out of target)[36]		1.9	Moderate
	Non-HDL cholesterol (out of target)[36,e18]	1.4	Low
	LDL cholesterol (out of target)[36,e18]	1.3	Low
Physical activity (out of target)[e18]		6.7	High
Alcohol use (out of target)[36]		1.8	Moderate
Hemoglobin A1c (out of target)[e18]		2.3	Moderate
Modifiable risk factors at baseline[b]			
	SBP[e9,e19]	1.3	Low
	Diastolic BP (lower)[e20]	0.9	Moderate
	Hypertension (no history)[6,e9]	0.9	Low
	HDL cholesterol[e9, e19]	1.0	Low
Glucose >200 mg/dL[e9,e19]		2.0	Moderate
History of diabetes[6,e9,e21]		1.6	Moderate
Elevated triglycerides[e22]		1.6	Moderate
	Physical activity (less active)[6,e9]	1.1	Low
	Body mass index[6,e9]	1.4	Low
	Smoker[6,e9]	1.0	Low
	History of coronary artery disease[6,e20]	0.95	Low
	Failure of antithrombotic therapy[e9,e23]	1.0	Low
Nonmodifiable risk factors at baseline[c]			
Misery perfusion (SPECT)[e32]		31.5	High
Impaired flow (vs complete)[e12]		5.9	Low
Qualifying infarct = borderzone[e12]		3.1	Low
Low distal flow status on quantitative magnetic resonance angiography[e11]		3.4	Low
>70% stenosis (vs 50%–69%)[6, e33]		2.0	High
	Anterior vs posterior circulation[6,e9,e33]	1.0	High
NIH Stroke Scale >1[6,e9]		1.8	High
Stroke as QE[6,e9]		0.6	High
Old infarcts[e9,e19]		3.3	Moderate
Time from QE <17 d[6]		0.6	Moderate

Continued

Table 1 Predictors of Recurrent Stroke or Death in Patients With Symptomatic Intracranial Atherosclerotic Arterial Stenosis *(continued)*

Increased Risk	No Increased Risk	Point Estimate	Confidence
Qualifying infarct = borderzone plus impaired collaterals[e12]		6.9	Low
Sex (female)[6,e9]		0.6	High
	Age (lower ref group)[6,e9]	1.1	Low
	Non-White vs White[6,e9]	1.2	Low

Abbreviations: BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; QE = qualifying event; SBP = systolic blood pressure; TC = total cholesterol.
[a] The evidence is insufficient to support or refute that failure to achieve a body mass index target and smoking cessation predicts an increased risk of recurrent stroke.[e18]
[b] There is insufficient evidence to support or refute the following modifiable risk factors in predicting an increased risk of recurrent stroke: baseline HbA1c,[e24] baseline TC, history of peripheral vascular disease,[e25] history of dyslipidemia,[6,e11,e24-e27] baseline LDL cholesterol,[e9,e24,e25] elevated lipoprotein (a),[e28] metabolic syndrome,[e22] alcohol use,[6,e11,e25,e26] high-sensitivity C-reactive protein,[e29,e30] and a positive myocardial SPECT scan.[e31]
[c] The evidence is insufficient to support or refute the following nonmodifiable risk factors in predicting an increased risk of recurrent stroke: history of stroke,[e20,e21,e25] history of TIA,[6] time from QE (when dichotomized at <7 d),[e9] concomitant small vessel disease,[e34,e35] concomitant intracranial atherosclerotic arterial stenosis,[e26,e35] not being on a statin (at baseline of WASID or SAMMPRIS),[e20] baseline modified Rankin Scale score ≥1,[e20] percent stenosis of >80% vs 70%–79%,[e20] length of stenosis,[6] white blood cell count of >7,200,[e19] neutrophil count,[e36] progression of stenosis on magnetic resonance angiography,[e37] increased oxygen extraction fraction asymmetry (PET scan),[e32] and hypoperfusion patterns on imaging.[e27]

luminal stenosis may be due to a variety of vasculopathies and atherosclerosis may be differentiated clinically in most cases.[5] It is important to identify sICAS 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.

Recommendation 1 Statement

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

Antithrombotic Medication Therapy

Rationale for Recommendations 2, 3, and 4

The WASID trial (Warfarin–Aspirin Symptomatic Intracranial Disease) showed that in patients with sICAS, aspirin 650 mg twice daily was safer and as effective as warfarin for preventing the combined endpoint of stroke, intracerebral hemorrhage, and vascular death. Whereas the optimal aspirin dose for sICAS has not been determined, patients in the medical arm of the SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) were treated with aspirin alone 325 mg/d 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 sICAS. The safety and efficacy of novel oral anticoagulants for prevention of stroke in sICAS are not established. Similarly, the safety and efficacy of adding aspirin to anticoagulation in patients with sICAS who 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 sICAS was not directly supported by this systematic review but is supported by related evidence.[19,35] The CLAIR study (Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolisation in Patients With Acute Symptomatic Cerebral or Carotid Artery Stenosis) showed that patients randomized to clopidogrel plus aspirin had significantly decreased microemboli in the territory of the stenotic artery when compared with aspirin alone.[19] When combined with the CARESS trial (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis), 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.[35] In addition, patients with sICAS in the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) 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, 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%).[27,36] 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 sICAS 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 the SAMMPRIS trial suggests further study is needed to determine whether extending clopidogrel use beyond 3 months is warranted.

Trials of cilostazol combined with other antiplatelet agents for stroke prevention in sICAS have had mixed results. TOSS (Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis) and TOSS-2 found cilostazol plus aspirin was not better for stroke prevention than aspirin alone or clopidogrel plus aspirin. However, the CATHARSIS study (Cilostazol-Aspirin Therapy Against Recurrent Stroke with Intracranial Artery Stenosis) demonstrated that cilostazol plus aspirin prevented the combined secondary endpoint of all vascular events and new silent brain infarcts when compared with aspirin alone. A subgroup analysis of patients with sICAS in CSPS (Cilostazol Stroke Prevention Study for Antiplatelet Combination), 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.

Recommendation 2 Statement

Clinicians should recommend aspirin 325 mg/d over warfarin for long-term prevention of stroke and death in patients with sICAS (Level B).

Recommendation 3 Statement

Clinicians should recommend adding clopidogrel 75 mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with severe (70%–99%) sICAS who have low risk of hemorrhagic transformation of ischemic stroke (Level B).

Recommendation 4 Statement

Clinicians may recommend adding cilostazol 200 mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with sICAS and low risk of hemorrhagic complications as an alternative to clopidogrel or in Asian patients (Level C).

Lipid and Hypertension Vascular Risk Factor Modification

Rationale for Recommendations 5 and 6

Support for the management of vascular risk factors in patients with sICAS comes from prespecified, post hoc analyses of sICAS 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 sICAS.[37] In addition, a lower rate of cerebrovascular events was seen in patients with sICAS randomized to high-intensity statin therapy compared with other dosages. A target low-density lipoprotein (LDL) level <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.[38] Post hoc analyses from WASID and SAMMPRIS also show lower rates of vascular events with lower LDLs in sICAS. The use of other lipid-lowering agents (e.g., PCSK9 inhibitors or omega-3) has not been specifically studied in sICAS but may be supported by studies of symptomatic atherosclerotic disease.[37]

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.[39] Analyses from WASID, SAMMPRIS, and the CICAS registry (Chinese Intracranial Atherosclerosis) have demonstrated that among clinically stable patients with sICAS, a mean systolic BP (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.[e18,40,41] Although the current American Heart Association guideline–recommended target of SBP <130 mm Hg has not been studied in patients with sICAS, an RCT of patients with sICAS 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.[21,42] Some subgroups of patients with sICAS may be at higher risk of stroke with lower BPs, including those with hemodynamic impairment[43,44] or those with a large reduction in BP from baseline.

Recommendation 5 Statement

Clinicians should recommend high-intensity statin therapy to achieve a goal LDL <70 mg/dL in patients with sICAS to reduce the risk of recurrent stroke and vascular events (Level B).

Recommendation 6 Statement

Clinicians should recommend a long-term BP target of <140/90 mm Hg in clinically stable patients with sICAS to reduce the risk of recurrent stroke and vascular events (Level B).

Physical Activity

Rationale for Recommendation 7

In the general population, moderate physical activity reduces incidence of stroke.[45] Among patients with sICAS, 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 (OR 6.7, 95% CI 2.5–18.1).[e18]

Recommendation 7 Statement

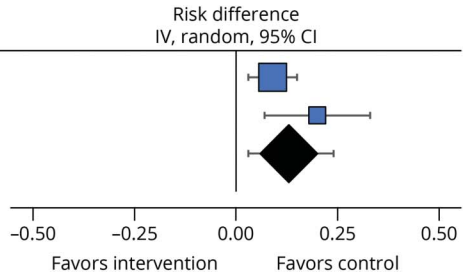
Clinicians should recommend at least moderate physical activity in patients with sICAS who are safely capable of exercise to reduce the risk of recurrent stroke and vascular events (Level B).

Figure 1 Summary Estimate of the Effects of PTAS + AMM Compared to AMM Alone on 30-Day Risk of Recurrent Stroke or Death

Study	PTAS + medical Events	PTAS + medical Total	Medical Events	Medical Total	Weight (%)	Risk difference IV, random, 95% CI
SAMMPRIS	33	224	13	227	64.0	0.09 (0.03, 0.15)
VISSIT	15	58	3	53	36.0	0.20 (0.07, 0.33)
Total (95% CI)		**282**		**280**	**100.0**	**0.13 (0.03, 0.24)**
Total events	48		16			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.45$; df = 1 ($p = 0.12$); $I^2 = 59\%$

Tests for overall effect: $z = 2.43$ ($p = 0.02$)



AMM = aggressive medical management; PTAS = percutaneous transluminal angioplasty and stenting; SAMMPRIS = Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; VISSIT = Vitesse Intracranial Stent Study for Ischemic Therapy

Other Modifiable Vascular Risk Factors

Rationale for Recommendation 8

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 sICAS.[46]

Recommendation 8 Statement

Clinicians must recommend treatment of other modifiable vascular risk factors in patients with sICAS to reduce the risk of recurrent stroke and vascular events (Level A).

Bilateral Arm Ischemic Preconditioning

Rationale for Recommendation 9

Based on 2 RCTs done in patients with sICAS, 5 cycles of 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 methodologic issues limit conclusions about efficacy in a multiethnic population. Whereas the risk of the procedure appears low, the BAIPC device does not have approval for use in the United States, limiting its application. These methodologic issues limit confidence in conclusions about efficacy and there are no data in a multiethnic population.

Recommendation 9 Statement

The authors could not achieve consensus on a recommendation for BAIPC in patients with sICAS.

Endovascular and Surgical Therapy

Rationale for Recommendations 10–13

Percutaneous Transluminal Angioplasty and Stenting

Recommendations related to 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 sICAS.

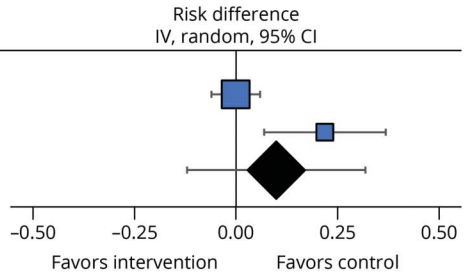
Single-arm, uncontrolled registries assessing subpopulations of patients with sICAS, including medical failures (i.e., stroke or TIA while on antithrombotic medications) or those with progressive neurologic symptoms, have reported conflicting rates of periprocedural complications.[47,48] In a Food and Drug Administration (FDA)–mandated postmarket 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-

Figure 2 Summary Estimate of the Effects of PTAS + AMM Compared to AMM Alone on Recurrent Stroke or Death Beyond 30 Days

Study	PTAS + medical Events	PTAS + medical Total	Medical Events	Medical Total	Weight (%)	Risk difference IV, random, 95% CI
SAMMPRIS	19	191	21	210	55.1	−0.00 (−0.06, 0.06)
VISSIT	10	38	2	48	44.9	0.22 (0.07, 0.37)
Total (95% CI)		**229**		**258**	**100.0**	**0.10 (−0.12, 0.32)**
Total events	29		23			

Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 7.21$; df = 1 ($p = 0.007$); $I^2 = 86\%$

Tests for overall effect: $z = 0.90$ ($p = 0.37$)



AMM = aggressive medical management; PTAS = percutaneous transluminal angioplasty and stenting; SAMMPRIS = Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; VISSIT = Vitesse Intracranial Stent Study for Ischemic Therapy

approved use, many of whom had not failed medical therapy or were treated recently after stroke.[49,50] 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%) sICAS, 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.[7,51]

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.[52] However, no RCTs have compared angioplasty alone with medical therapy for stroke prevention in patients with sICAS. 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 high periprocedural morbidity and mortality.[53] Balloon angioplasty alone may be performed with a submaximal staged approach, which may have a lower rate of morbidity and mortality.[54]

Optimal stroke prevention for patients with sICAS 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 sICAS is investigational.[52-54]

Recommendation 10 Statement

Clinicians should not recommend PTAS as the initial treatment for stroke prevention in patients with severe (70%–99%) sICAS (Level B) (Figures 1 and 2).

Recommendation 11 Statement

Clinicians should not recommend PTAS for stroke prevention in patients with moderate (50%–69%) sICAS (Level B).

Recommendation 12 Statement

Clinicians should not routinely recommend angioplasty alone for stroke prevention in patients with sICAS outside clinical trials (Level B).

Recommendation 13 Statement

Clinicians should counsel patients about the risks of PTAS and alternative treatments if one of these procedures is being contemplated (Level B).

Surgical Treatment

Rationale for Recommendations 14 and 15

Direct Bypass

Recommendations related to the use of direct surgical bypass for stroke prevention in patients with sICAS are informed by 1 RCT. The EC/IC bypass trial included patients with sICAS 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, COSS (Carotid Occlusion Surgery Study), which studied patients with symptomatic ICA occlusion, found that direct bypass increases the risk of stroke and death predominantly due to early periprocedural complications.[55] 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.[56,57]

Indirect Bypass

In patients with anterior circulation sICAS, indirect bypass with encephaloduroarteriosynangiosis (EDAS) is an emerging investigational surgery for stroke prevention.[58-60,e1,e2] A small initial study of indirect revascularization without standardized medical management showed a high rate of recurrent stroke in patients with sICAS.[59] Four nonrandomized studies, including 2 small case series,[58,e1] 1 single-center prospective study,[e2] and 1 two-center prospective trial with independent outcomes assessment,[e3] 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.

Recommendation 14 Statement

Clinicians should not recommend direct bypass for stroke prevention in patients with sICAS (Level B).

Recommendation 15 Statement

Clinicians must not routinely recommend indirect surgical revascularization for stroke prevention in patients with sICAS outside clinical trials (Level A).

Suggestions for Future Research

Medical Research

Randomized trials are needed to optimize type and duration of antithrombotic therapy for patients with sICAS. The most promising candidate therapies for future studies are combinations of antithrombotic therapy that have been shown in prior trials to reduce the risk of stroke in patients with (1) large artery cerebrovascular disease (ticagrelor plus aspirin),[e4] (2) coronary or peripheral vascular disease (low dose factor Xa inhibitor plus aspirin),[e5] and (3) stroke (cilostazol plus aspirin or clopidogrel).[15] Novel factor XIa inhibitors alone or in combination with aspirin and clopidogrel are being evaluated in Phase II stroke prevention trials and could also be considered for future trials in patients with sICAS. Because clopidogrel is a prodrug that may be ineffective in patients who carry genetic single-nucleotide loss-of-function (LOF)

polymorphisms for the CYP2C19 cytochrome P450 enzyme necessary to metabolize clopidogrel to its active form,[e6] trials that include clopidogrel should determine the effect of CYP2C19 LOF allele carrier status on clinical outcomes.

Randomized therapeutic trials of patients with sICAS should incorporate intensive risk factor management in all arms, including the intraoperative and perioperative periods for surgical and endovascular interventions. Consideration should be given to encouraging lifestyle management including exercise, stopping smoking, and weight reduction,[e7] the use of a PCKS9 inhibitor in patients with raised LDL despite a maximum tolerated dose of a statin,[37] and icosapent ethyl for patients with elevated triglycerides.[e8]

Endovascular and Surgical Research

Phase I and II trials are needed to develop safe and durable endovascular treatments (e.g., submaximal balloon angioplasty alone[52] or new intracranial stents) that could subsequently be compared with AMM in high-risk sICAS. Randomized controlled clinical trials (Phase III) are needed to compare surgical treatments (e.g., EDAS)[e1] with AMM in these patients.

Other Areas of Future Research

Adequately powered studies are needed to validate clinical,[e9] genetic (e.g., ring finger protein 213 variant),[e10] and imaging biomarkers[e11-e14] that identify high-risk patients with sICAS for enrollment in future therapeutic trials. Other promising novel therapeutic approaches that should be considered for evaluation are ischemic preconditioning,[e15] continuous positive airway pressure in patients with sleep apnea, and anti-inflammatory agents such as colchicine or canakinumab.[e16,e17]

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Appendix *(continued)*

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Mary Dolan O'Brien, MLIS	American Academy of Neurology, Minneapolis, MN	Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content
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Additional references e1–e37 available in the supplemental document, links.lww.com/WNL/B803