Stroke Prevention in Symptomatic Large Artery Intracranial Atherosclerosis Practice Advisory

Report of the Guidelines Subcommittee of the AAN

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M. Schneck has served on the editorial board of the *Journal of Stroke and Cerebrovascular Disease* and *Frontiers in Neurology* and owns mutual funds that include health retail business stock. An immediate family member of Dr. Schneck has received personal compensation for serving as an employee of HistoGeneX. Dr. Schneck has received personal compensation in the range of $500-$4,999 for serving on a scientific advisory board or DSMB for HLT. Dr. Schneck has received personal compensation in the range of $10,000-$49,999 for serving as an expert witness for miscellaneous legal firms. Dr. Schneck's institution has received research support from the NIH.

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M. Dolan O'Brien is an employee of the American Academy of Neurology.

H. Silsbee is an employee of the American Academy of Neurology.

J. Fletcher has nothing to disclose.

GLOSSARY

AAN: American Academy of Neurology
AMM: aggressive medical management
BAIPC: bilateral arm ischemic preconditioning
BMI: body mass index
CATHARSIS: Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis study
CHANCE: Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events trial
CI: confidence interval
COI: conflict of interest
CSPS: Cilostazol Stroke Prevention Study for Antiplatelet Combination
CV: curriculum vitae
DAPT: dual antiplatelet therapy
DBP: diastolic blood pressure
DWI: diffusion-weighted imaging
EC/IC: extracranial to intracranial
EDAS: encephaloduroarteriosynangiosis
FDA: Food and Drug Administration
FISS-tris: Fraxiparin in Stroke Study for the Treatment of Ischemic Stroke
GRADE: Grading of Recommendations Assessment, Development and Evaluation
GS: Guideline Subcommittee
HbA1c: hemoglobin A1c
HDL-C: high-density lipoprotein cholesterol
HR: hazard ratio
hs-CRP: high-sensitivity C-reactive protein
IAT: intensive-dose atorvastatin therapy
ICH: intracerebral hemorrhage
INR: international normalized ratio
LAT: low-dose atorvastatin therapy

LDL-C: low-density lipoprotein cholesterol

LMWH: low molecular weight heparin

LOF: loss-of-function

MAP: mean arterial pressure

MCA: middle cerebral artery

MCAO: middle cerebral artery occlusion

MI: myocardial infarction

MRA: magnetic resonance angiography

mRS: modified Rankin Scale

NIHSS: National Institutes of Health Stroke Scale

OEF: oxygen extraction fraction

OR: odds ratio

POR: pooled odds ratio

PTAS: percutaneous transluminal angioplasty and stenting

PVD: peripheral vascular disease

QE: qualifying event

QMRA: quantitative magnetic resonance angiography

RCT: randomized controlled trial

RD: risk difference

SAMMPRIS: Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis

SAT: standard-dose atorvastatin therapy

SBP: systolic blood pressure

SVD: small vessel disease

s-ICAS: symptomatic intracranial atherosclerotic arterial stenosis

TC: total cholesterol

TCD: transcranial Doppler

TIA: transient ischemic attack

TOSS: Trial of cilOstazol in Symptomatic intracranial arterial Stenosis

VISSIT: Vitesse Intracranial Stent Study for Ischemic Stroke Therapy

WASID: Warfarin–Aspirin Symptomatic Intracranial Disease trial

WBC: white blood cell

INTRODUCTION

Symptomatic intracranial atherosclerotic arterial stenosis (s-ICAS) is one of the most common causes of stroke worldwide and is associated with a high risk of recurrent stroke.[1, 2, 3, 4] The global burden of stroke associated with s-ICAS is expected to rise as the population ages and as Asian, Black, and Hispanic populations, which have a higher prevalence of s-ICAS, increase as major contributors to global population growth.[5]

Over the last 2 decades, evidence has accumulated informing the treatment of s-ICAS with 2 general approaches emerging: aggressive medical management (AMM) with dual antiplatelet therapy (DAPT) plus intensive control of vascular risk factors, and 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 non-modifiable 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.

Because of the impact of s-ICAS, this practice advisory seeks to answer the following clinical questions:

1) For patients with a history of s-ICAS, which medical therapies, as compared with no therapy or an alternative therapy, reduce the risk of recurrent stroke or death (therapeutic scheme)?
    a. Anticoagulation vs antiplatelet therapy
    b. Specific antiplatelet therapy regimens vs alternative regimens
    c. Antihypertensive agents or blood pressure control targets
    d. Statin therapy or lipid targets
    e. Ischemic preconditioning
2) For patients with a history of s-ICAS, 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 s-ICAS, what modifiable and non-modifiable risk factors predict an increased risk of recurrent stroke or death (prognostic scheme)?

    a. degree of stenosis
    b. length of stenosis
    c. the presence of tandem lesions
    d. vascular bed
    e. degree of collateral circulation
    f. demographics including sex, race, or ethnicity of patient
    g. medical co-morbidities
    h. time from index event
    i. lack of use of maximal medical therapy

DESCRIPTION OF THE ANALYTIC PROCESS

This practice advisory follows the 2011 edition of the AAN's guideline development process manual.[8] In September 2014, a multidisciplinary panel of authors 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 (GS) 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 (CV). The panel leadership, consisting of the lead author (T.N.T.), the AAN methodologist (G.S.G.), the AAN staff persons (M.D.O., H.S.), and GS leadership reviewed the relationship disclosure forms and CVs for financial and intellectual conflicts of interest (COI). These documents were used to exclude both those individuals with a clear financial conflict and those whose profession and intellectual bias would negatively affect the credibility of the review. As required by the AAN, a majority (at least 51 percent) of the members (G.S.G., M.I.C., A.C., A.J.F., N.R.G., J.G.L., T.N.N., R.S.S., M.J.S., A.A.R., J.J.F.) of the development panel, and the lead author (T.N.T.), are free of COI relevant to the subject matter of this practice advisory. Five of the 17 development panel members were determined to have COI, but the COI were judged to be of insufficient importance to preclude them from authorship (L.B.G., S.R.M., A.B.S., L.R.W., O.O.Z.). All authors determined to have COI did not review or rate the evidence. These

individuals were used in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. The panel members with COI were allowed to participate in the recommendation development process. The full author panel was solely responsible for the final decisions about the design, analysis, and reporting of the systematic review and practice advisory, which was submitted for approval to the GS.

Inclusion and exclusion criteria for article selection was chosen to be rated for risk of bias on the basis of a priori criteria. Because the scope of this practice advisory spans both prognostic and therapeutic questions, both prognostic and therapeutic evidence schemes were used to rate the evidence, as indicated throughout the manuscript. For therapeutic questions, only studies that randomly allocated patients with s-ICAS to different treatment groups and followed patients to compare their subsequent risks of recurrent stroke or death were included in the systematic review. For the prognostic question, only cohort studies or case-control studies that compared recurrent stroke risk in patients with s-ICAS with and without a putative risk factor were included in the systematic review. We did not assess for transient ischemic attacks (TIAs) as the reliability of that diagnosis is low.[9] The aim of the prognostic question was to identify modifiable and non-modifiable risk factors that predict an increased risk of recurrent stroke or death. Although other important vascular endpoints (myocardial infarction [MI], angina, hospitalization, claudication, and peripheral vascular disease [PVD]) may be affected by risk factor control, the main objective of this practice guideline is to assess their effect on stroke prevention, with less weight on other vascular endpoints. Hence, only studies in which the risk of recurrent stroke and death could be extracted were used to inform conclusions. Studies reporting a composite of vascular endpoints (e.g., TIA, MI, and vascular death) were discussed but not used to inform conclusions unless recurrent stroke and death could be separately extracted. Studies reporting only composite endpoints were excluded from analysis. Additionally, the aim of the prognostic question was to identify risk factors that predicted an increased risk of recurrent stroke among the broad population of patients with s-ICAS. Hence for the prognostic questions, we excluded studies if the endpoints were assessed following percutaneous transluminal angioplasty or percutaneous transluminal angioplasty and stenting (PTAS) in all or part of the cohort. We also excluded studies of laboratory risk factors that are not readily available in

routine practice. Review articles, studies of animals, editorials, and studies that involved fewer than 20 patients were excluded. Studies that assessed only lacunar stroke, lipohyalinosis, small vessel stroke, or small artery occlusion were also excluded. Referenced studies consisting of subgroups from larger trials were rated for classification based on the parent study, were identified as a subgroup study, and the confidence in the evidence (risk of bias) was downgraded as appropriate due to reduced precision and directness.

Consistent with prior AAN stroke-related guidelines, the primary outcome of interest was recurrent stroke or recurrent stroke and death. For the therapeutic question, because only randomized controlled trials (RCTs) were included, risk differences (RDs) were used to describe the outcomes of individual studies to allow for ease of clinical interpretation. A change in risk of 5% was considered clinically important. For the prognostic questions, odds ratios (OR) were used as the primary measure of effect to describe the difference in risk between those with and without a potential risk factor. This was chosen as it was either the most reported or most calculable measure among studies of various study designs. During evidence synthesis, if no OR was reported or calculable, the hazard ratio (HR) was considered equivalent to the risk ratio and was used to estimate the OR.[10, 11, 12] An increased risk ratio of 0.5 (i.e., OR > 1.5) was considered clinically important. 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, when knowledge of the risk factor would not have likely introduced systematic bias. To minimize bias due to cross-overs, we relied on intention-to-treat analyses of included studies to inform conclusions. Because we anticipated substantive heterogeneity, we defaulted to generic inverse variance random effects meta-analytic models to pool effect sizes. Random effects models were most appropriate as we expected substantive heterogeneity based on patient selection, time from qualifying event (QE), 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 (see the evidence synthesis tables in appendix 4).

Confidence in the evidence (measuring internal validity) was anchored by the number and class of studies included in the synthesis. Evidence syntheses based on multiple Class I studies were

anchored to high confidence; those based solely on 1 Class I study or multiple Class II studies were anchored to moderate confidence; those based solely on 1 Class II study or multiple Class III studies were anchored to low confidence; and those based solely on 1 Class III study or multiple Class IV studies were anchored to very low confidence. Hence, confidence in the evidence syntheses including multiple studies of different risk-of-bias classes was anchored to the study with the highest risk of bias (i.e., lowest class level). Generalizability (directness or indirectness) and study precision (inadequately or adequately powered) were additional factors considered when downgrading our confidence in the available evidence. Studies were not downgraded for generalizability based on race or ethnicity. Specifically, we did not downgrade for generalizability for studies of East Asian populations, but instead we considered this in voting on recommendations during the modified Delphi process. Evidence was downgraded when the confidence interval (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, 13, 14] 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 (see appendix 3 for search strategies). The initial search yielded 2,325 articles. The

panelists reviewed the article titles and abstracts for potential relevance. Of the reviewed abstracts, 505 were identified as potentially relevant and their corresponding articles were obtained for full-text review. Each of the 505 articles was reviewed by 2 panel members working independently of each other. The panelists selected 51 articles for inclusion in the analysis, including 1 article providing extended follow up from a previously published trial. All 51 articles were selected for evidence rating and, after determining that 6 articles discussed cardiovascular outcomes without the ability to extract separate data on recurrent stroke and death, 45 were used to inform conclusions. An updated literature search was conducted in November 2020 yielding 1,233 articles. Of the reviewed abstracts, 54 were identified for full-text review and 13 new articles were selected for evidence rating with 11 new articles used to inform conclusions.

1a) For patients with a history of s-ICAS, does anticoagulation, as compared with antiplatelet therapy, reduce the risk of recurrent stroke or death?

Two Class I studies were identified that informed conclusions on anticoagulation vs antiplatelet therapy.[7, 15] One study was determined to have limited generalizability (indirectness) due to 15% of the enrolled patients not having isolated ICAS and only enrolling patients within 48 hours of the QE.[15]

The Warfarin–Aspirin Symptomatic Intracranial Disease trial (WASID) (Class I) was an investigator-initiated, National Institute of Neurological Disorders and Stroke–sponsored, prospective, randomized, placebo-controlled double-blind study conducted at 59 sites in North America.[7] The trial included 569 patients randomized within 90 days following a TIA or non-disabling stroke that was attributed to 50%–99% stenosis of a major intracranial vessel. Patients in the intervention arm received warfarin with a target international normalized ratio (INR) of 2–3 and patients in the control arm received aspirin 650 mg twice daily. The primary intention-to-treat efficacy endpoint was a composite of recurrent ischemic stroke, brain hemorrhage, or vascular death not from stroke. WASID was terminated prematurely due to safety concerns in participants assigned to the warfarin group. Baseline characteristics were well balanced between groups and patients in the intervention arm achieved an INR in the target range for 63% of the maintenance period. At a mean follow up of 1.8 years, the primary endpoint occurred in 21.8%

(63/289) of patients in the intervention arm compared with 22.1% (62/280) of controls with an RD of -0.34% (95% CI -7.2% to 6.5%). Warfarin, relative to aspirin, was associated with a higher risk of major hemorrhage (8.3% vs 3.2%; RD 5.1%, 95% CI 1.2%–9.1%) and death (9.7% vs 4.3%; RD 5.4%, 95% CI 1.2%–9.8%).

The Fraxiparin in Stroke Study for the Treatment of Ischemic Stroke (FISS-tris) (Class I) was a randomized, controlled, blinded outcome assessment trial conducted in China enrolling patients with large artery occlusive disease within 48 hours after a non-severe stroke.[15] Overall, 97% of patients had intracranial atherosclerosis with 85% of the cohort having intracranial atherosclerosis alone and 12% having intracranial and extracranial atherosclerosis. Patients were randomized to receive either nadroparin calcium 3800 anti-factor Xa IU/0·4 mL (low molecular weight heparin [LMWH]) subcutaneously twice daily or aspirin 160 mg once daily for 10 days. After the initial period, all received aspirin 80–300 mg once daily for 6 months. Six-month survival with good functional outcome occurred in 73% (131/180) of the patients in the LMWH group compared with 69% (119/173) in the aspirin group (RD 4%, 95% CI -5.5% to 13.4%). The composite of early neurological deterioration by day 9 or recurrent stroke by 6 months occurred in 10% (18/180) of patients in the LMWH group compared with 9.8% (17/173) in the aspirin group (RD 0.2%, 95% CI -6.3% to 6.5%). Six-month mortality was 5% (9/180) in the LMWH arm compared with 4.6% (8/173) in the aspirin arm (RD 0.4%, 95% CI -4.5% to 5.2%). Similarly, no difference was found in hemorrhagic adverse events, which occurred in 13.3% (24/180) of patients in the LMWH group compared with 8.7% (15/173) in the aspirin group (RD 4.7%, 95% CI -3.3% to 10.3%).

Because of the differences in study design and agents, we chose not to pool the efficacy and safety effect sizes in WASID and FISS-tris.

Conclusions

1. For patients with s-ICAS, 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, 1 Class I trial, confidence in evidence downgraded due to imprecision)

2. For patients with s-ICAS, 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%). (Moderate confidence, 1 Class I study)
3. For patients with s-ICAS there is insufficient evidence to support or refute the effectiveness of short-term nadroparin calcium (LMWH), as compared with aspirin, for reducing the composite of early neurological 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, 1 Class I study, confidence in evidence downgraded due to imprecision and indirectness)
4. For patients with s-ICAS 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, 1 Class I study, confidence in evidence downgraded due to imprecision and indirectness)

1b) For patients with a history of s-ICAS, do specific antiplatelet therapy regimens, as compared with alternative regimens, reduce the risk of recurrent stroke or death?

Cilostazol Regimens

Two Class I studies, 1 Class II study, and 1 Class IV study were identified that evaluated DAPT with cilostazol, compared with other regimens, in reducing the risk of recurrent stroke and death.[16, 17, 18, 19] All studies were determined to have good generalizability. The Trial of cilOstazol in Symptomatic intracranial arterial Stenosis (TOSS) (Class II) investigated the efficacy and safety of cilostazol for prevention of progression of acute symptomatic intracranial atherosclerosis.[16] The prospective RCT enrolled 135 patients from South Korea within 2 weeks of ischemic stroke attributed to middle cerebral artery (MCA) or basilar artery stenosis. Patients were randomized to DAPT with cilostazol (100 mg twice daily) plus aspirin (100 mg daily) or aspirin monotherapy (100 mg daily). Progression of symptomatic stenosis based on magnetic resonance angiography (MRA) after 6 months was assessed. Study drop-out occurred in a high portion of patients (29.9% in the intervention arm and 20.6% in the control arm). Progression of symptomatic stenosis in the cilostazol group (6.7% [3/45]) was significantly lower than that in the aspirin monotherapy group (28.8% [15/52]) with an RD of -22.2% (95% CI -36.3% to -6.8%). There was 1 unexplained death in each study arm and no recurrent cerebrovascular events

during the study period. Hence, the risk of stroke or death was 2.2% (1/45) in the intervention arm compared with 1.9% (1/52) in the control arm with an RD of 0.3% (95% CI -8.1% to 9.8%). No major bleeding was reported in either group (RD 0%, 95% CI -6.9% to 7.9%).

The Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis study (CATHARSIS) (Class IV) was a multicenter, prospective, open labeled, RCT that enrolled patients in Japan. The aim of the study was to compare the effect of cilostazol plus aspirin vs aspirin alone on the progression of intracranial atherosclerosis and recurrent stroke.[17] Patients were enrolled within a range of 2 weeks to 6 months after a QE of an ischemic stroke attributed to >50% stenosis of a major intracranial artery. There was no difference in the primary outcome of progression of intracranial arterial stenosis in the intervention arm (8.4%, 7/83) compared with the control arm (5.0%, 4/80) with an RD of 3.4% (95% CI -4.9% to 12%) at median follow-up of 762 days. The percent of patients who had clinical or radiographic strokes during the 2 years of follow up was 9.6% (8/83) in the intervention arm and 17.5% (14/80) in the control arm with an RD of -7.9% (95% CI -18.7% to 2.8%). Outcome assessment was adjudicated by raters unmasked to treatment assignment. The risk of serious hemorrhagic complications was 4.8% (4/83) in the intervention arm compared with 3.8% (3/80) in the control arm with an RD of 1.1% (95% CI -6.3% to 8.4%).

The Cilostazol Stroke Prevention Study for Antiplatelet Combination (CSPS) (Class I) was designed to test the hypothesis that a combination of cilostazol and aspirin or clopidogrel reduces recurrence of ischemic stroke without increasing the bleeding risk compared with aspirin or clopidogrel alone.[18] The trial enrolled patients in Japan between 8 and 180 days after a noncardioembolic ischemic stroke. Key inclusion criteria included documented ≥50% stenosis of an intracranial or extracranial cervicocephalic artery or ≥2 high-risk features (i.e., age >65, hypertension, diabetes, chronic kidney disease, PVD, history of prior stroke, heart disease, or smoking). The median time from QE to enrollment was 25 days. The primary efficacy outcome was the first recurrence of symptomatic ischemic stroke. Secondary efficacy outcomes included any stroke, TIA, death, and other vascular events. Safety outcomes included severe or life-threatening bleeding. Eighty-one percent of participants were followed for at least 6 months. The trial was stopped early due to slow enrollment after a median of 1.4 years of follow-up, at which

time the primary efficacy outcome occurred in 3% (29/932) of the intervention group and 7% (64/947) of the control group with an RD of -3.7% (95% CI -5.7% to -1.7%). In the subgroup of patients with intracranial atherosclerosis, 4% (11/275) of patients in the intervention group and 9.2% (25/272) of patients in the control group had a primary outcome with an RD of -5.2% (95% CI -9.6% to -1%). Severe or life-threatening bleeding occurred in 1% (8/910) of the intervention group and 1% (13/921) of the control group with an RD of -0.5% (95% CI -1.6% to 0.5%).

The Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis II (TOSS-2) study (Class I) was a prospective, randomized, double-blind controlled trial enrolling 457 patients at multiple centers in East Asia within 14 days following minor (median NIH Stroke Scale [NIHSS] score of 3 at the time of QE) ischemic stroke attributed to MCA M1 or basilar artery stenosis.[19] Patients with symptomatic intracranial atherosclerosis were all treated with aspirin 75–100 mg daily and randomized to receive either combination therapy with cilostazol 100 mg twice a day or clopidogrel 75 mg daily. The primary outcome was progression of intracranial atherosclerosis on MRA, which occurred in 9.9% (20/202) of patients in the cilostazol group and 15.5% (32/207) in the clopidogrel group with an RD of -5.6% (95% CI -12.7% to 1%). During 7 months of follow-up, the composite of recurrent stroke and vascular death occurred in 5.2% (12/232) of patients in the cilostazol group and 3.6% (8/225) in the clopidogrel group with an RD of 1.7% (95% CI -2.4% to 5.7%). No difference was seen in major hemorrhagic complications, which occurred in 0.9% (2/232) of patients in the cilostazol group compared with 2.7% (6/225) in the clopidogrel group with an RD of -1.8% (95% CI -4.9% to 0.8%).

An inverse variance random effect model was used to pool effect sizes and generate a summary estimate for DAPT with cilostazol compared with monotherapy in CSPS and TOSS. Dual antiplatelet therapy with cilostazol compared with monotherapy resulted in a summary estimate RD of -3% (95% CI -8% to 3%; $I^2 = 57\%$) for reducing the risk of recurrent stroke, indicating significant uncertainty due to imprecision. The summary estimate of the RD in hemorrhagic complications was 0% (95% CI -1% to 0%; $I^2 = 0\%$), which indicated no difference in bleeding risks between regimens.

Conclusions

5. For patients with s-ICAS, 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, 1 Class I study and 1 Class II study 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, 1 Class I study and 1 Class II study)
6. For patients with s-ICAS, there is insufficient evidence to support or refute the effectiveness of DAPT with cilostazol plus aspirin, as compared with clopidogrel plus aspirin alone, in reducing recurrent stroke or death (RD 1.7%, 95% CI -2.4% to 5.7%). (Very low confidence, 1 Class 1 study, confidence in evidence downgraded due to imprecision) DAPT with cilostazol plus aspirin is likely not associated with any difference in hemorrhagic complications compared with clopidogrel plus aspirin alone (RD -1.8%, 95% CI -4.9% to 0.8%). (Moderate confidence, 1 Class 1 study)

DAPT with Aspirin and Clopidogrel Regimens

One Class I study and 1 Class II study informed conclusions on DAPT with aspirin and clopidogrel, compared with aspirin monotherapy, in reducing the risk of recurrent stroke and death.[20, 21] Both studies were determined to have limited generalizability due to only enrolling patients within 24 hours of the QE[20] or only enrolling patients with microembolic signals and isolated extracranial disease (no s-ICAS).[21]

The Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events trial (CHANCE) (Class I) evaluated risk of recurrent stroke with DAPT, compared with aspirin alone, among Chinese patients presenting with acute minor noncardioembolic stroke or TIA.[22] Patients with high-risk TIA or minor stroke within 24 hours of the QE were randomized to receive DAPT (clopidogrel/aspirin) or single antiplatelet (placebo plus aspirin) therapy for 21 days followed by single antiplatelet therapy through 90 days. A subgroup analysis of the CHANCE trial evaluated the effect of DAPT on recurrent stroke risk in patients with >50% stenosis of an intracranial

artery.[20] Although patients with intracranial atherosclerosis had a higher risk of recurrent stroke than those without (12.5% vs 5.4%), there was no significant treatment effect. In the cohort of patients with intracranial atherosclerosis, 11.3% (26/231) in the intervention group and 13.6% (34/250) in the control group had a recurrent stroke by 90 days with an RD of 2.3% (95% CI -8.3% to 3.7%). There were no hemorrhagic strokes or death from any cause during the 90-day follow-up period. Severe or moderate bleeding occurred in 0% (0/231) of the intervention group and 0.4% (1/250) of the control group with an RD of -0.4% (95% CI -2.2% to 1.3%). Multiple subgroup analyses of CHANCE have been undertaken in patients with s-ICAS suggesting a possible benefit to DAPT in subgroups of patients with non-elevated hs-CRP or non-elevated Lp-PLA2 activity, however this requires further study.[23, 24]

The Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR) study (Class II) was an investigator-initiated, multicenter, randomized trial with blinded outcome assessment that recruited patients from Asia within 7 days of a QE of TIA or stroke.[21] The primary aim was to assess whether combination therapy with clopidogrel and aspirin was more effective than aspirin monotherapy in preventing transcranial Doppler (TCD)–detected microembolic signals among patients with cerebral or carotid >50% arterial stenosis and microembolic signals at baseline. Overall, 95% of the cohort had an intracranial arterial stenosis. The primary outcome (continued microembolic signals on day 2) occurred in 31% (14/45) of patients in the intervention arm and 54% (27/50) in the control arm with an RD of -22.9% (95% CI -40.3% to -3%). Despite the persistence of a reduction in microembolic signals detected by TCD on day 7 in the intervention group, there was no difference in new diffusion-weighted imaging (DWI) lesions on MRI by day 7 or any reduction in early recurrent stroke. The risk of recurrent stroke by day 7 was 0% (0/46) in the intervention arm and 3.8% (2/52) in the control arm with an RD of -3.8% (95% CI -13% to 4.4%). No serious hemorrhages occurred in either group (RD 0%, 95% CI -6.8% to 7.7%). In summary, this study demonstrated DAPT reduced asymptomatic microembolic signals on TCD but had no effect on the occurrence of new DWI lesions or early recurrent stroke, although the study was underpowered to evaluate the effect of treatment on clinical events and lacks generalizability due to patient selection and inadequate follow-up.

Because of significant study heterogeneity, an IV random effect model was used to generate a summary estimate of the RD of DAPT with clopidogrel plus aspirin soon after high-risk TIA or stroke, compared with monotherapy, in reducing the risk of recurrent stroke (CHANCE and CLAIR). The summary estimate could not exclude a potentially meaningful effect (RD -3%, 95% CI -7% to 1%; $I^2 = 0\%$) as the CI included the possibility of a clinically meaningful reduction in stroke risk. Hemorrhage complications were not higher with DAPT with clopidogrel plus aspirin compared with monotherapy (RD -1%, 95% CI -2% to 1%; $I^2 = 7\%$).

Conclusions

7. For patients with s-ICAS, 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, 1 Class I study and 1 Class II study, confidence downgraded due to imprecision and indirectness)
8. For patients with s-ICAS, it is possible that short term DAPT 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, 1 Class I study, 1 Class II study, evidence downgraded due to indirectness)

1c) For patients with a history of s-ICAS, which antihypertensive agents or blood pressure control targets, as compared with alternative agents or targets, reduce the risk of recurrent stroke or death?

One multicenter Class IV study (outcome assessor not masked to treatment arm) conducted at 10 centers in South Korea randomly allocated patients to receive either intensive blood pressure control (defined as a systolic blood pressure [SBP] goal of <120 mm Hg) or modest blood pressure control (SBP goal of <140 mm Hg) following ischemic stroke attributed to >50% stenosis of the intracranial ICA or MCA.[25] The risk of recurrent stroke or death was not different between groups, with occurrences in 1.7% (1/59) of the intensive group and 1.9% (1/52) of the modest group (RD of stroke or death 0.23%, 95% CI -8.5% to 7.2%). No relevant studies were found addressing specific antihypertensive agents that met criteria for inclusion.

Conclusion

9. For patients with s-ICAS, there is insufficient evidence to support or refute the effectiveness of intensive vs modest blood pressure control in reducing the risk of recurrent stroke or death (RD 0%, 95% CI -8.5% to 7.2%). (Very low confidence, 1 Class IV study with insufficient precision)

1d) For patients with a history of s-ICAS, does statin therapy or lipid targets, as compared with alternative management, reduce the risk of recurrent stroke or death?

Two Class IV studies from a single center cohort in China, describe outcomes following randomization of a cohort of 120 patients with s-ICAS to 1 of 3 treatment arms: low-dose atorvastatin therapy (LAT, 10 mg/d), standard-dose atorvastatin therapy (SAT, 20 mg/d), and intensive-dose atorvastatin therapy (IAT, 40 mg/d).[23, 26] After 52 weeks of treatment, serum lipid profiles improved in all patients, but no difference in rates of stroke and death was observed. No relevant studies were found addressing lipid targets or alternative management that met criteria for inclusion.

Conclusion

10. For patients with s-ICAS, 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, 2 Class IV studies)

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

Two Class II prospective randomized clinical trials evaluated the use of brief repetitive bilateral arm ischemic preconditioning (BAIPC) following TIA or ischemic stroke.[27, 28] Both studies were

done in Chinese patient populations but otherwise determined to have good generalizability to the broad patient population of s-ICAS.

In the initial study, the investigators enrolled patients <80 years old within 30 days of a QE attributed to >50% stenosis of an intracranial artery. Subsequently, the investigators enrolled patients aged 80–95 years within 7 days of a QE attributed to >70% stenosis of an intracranial artery. The BAIPC treatment consisted of 5 cycles of bilateral upper limb ischemia using a patented device similar to a blood pressure cuff inflated to 200 mm Hg, for 5 minutes followed by reperfusion for another 5 minutes, performed twice a day. The control group underwent a similar process twice daily in a sham procedure without the ischemia/reperfusion cycle. In the patients aged 80–95 years, after 180 days of follow up, the percent of patients with recurrent stroke in the affected vascular territory was no different in the intervention group (6.7%, 2/30) compared with the control group (17.8%, 5/28) with an RD of -11.2% (95% CI -29.6% to 6.5%). The composite occurrence of TIA and recurrent stroke occurred less frequently in the BAIPC group (13.3%, 4/30) compared with the sham group (35.7%, 10/28) with an RD of -22.4% (95% CI -42.5% to -0.2%). The study also demonstrated that BAIPC resulted in a reduction in plasma inflammatory markers and platelet aggregation with increased endogenous fibrinolytic activity. In the patients aged <80 years, the incidence of recurrent stroke with positive brain imaging at 90 days was lower in the BAIPC group (5%, 2/38) compared with the sham group (23.3%, 7/30) with an RD of -18.1% (95% CI -36.1% to -1.4%). This effect was sustained at 300 days of follow-up with 7.9% (3/38) of patients in the BAIPC group and 26.7% (8/30) of participants in the sham treatment group having a recurrent stroke (RD -18.8%, 95% CI -37.3% to -0.8%). The study also reported favorable benefits of BAIPC on multiple secondary endpoints including a reduction in recurrent TIAs, improvement in functional recovery times, and improved brain perfusion (measured by SPECT scan at days 90 and 300) as well as improvement in TCD peak systolic velocities over time at the site of arterial stenosis.

Because of the difference in ages and inclusion criteria, including the percent stenosis of the affected intracranial artery, we used an IV random effect model to provide a summary estimate of the mean RD of BAIPC compared with the sham treatment among patients with s-ICAS.

Patients randomized to the intervention arm had a reduced risk of stroke compared with those randomized to the sham treatment with an RD of -15% (95% CI -27% to -2%; $I^2 = 0\%$).

Conclusion

11. In patients with s-ICAS, BAIPC is likely effective in reducing the risk of recurrent stroke (RD -15%, 95% CI -27% to -2%; $I^2 = 0\%$). (Moderate confidence, 2 Class II studies)

2a) **For patients with a history of s-ICAS, do EC/IC bypass procedures, as compared with no procedure, reduce the risk of recurrent stroke or death?**

One Class I study with good generalizability was identified that informed the conclusion on EC/IC bypass. The EC/IC bypass trial (Class I) was a prospective RCT enrolling 1377 patients within 90 days of a TIA or non-disabling stroke with the aim of determining whether anastomosis of the superficial temporal artery to the MCA would lower the risk of recurrent stroke or death compared with medical therapy in patients with symptomatic occlusion or severe stenosis of an ipsilateral cervicocephalic carotid artery.[29] Patients in the study were followed for a mean of 55.8 months during which time the procedure not only failed to prevent stroke, but was associated with a numerically higher 30-day risk of fatal and non-fatal stroke. For the subgroup of patients with severe MCA stenosis or occlusion, 29.2% (38/130) in the surgical group and 23.1% (32/138) of patients in the medical group had a fatal or non-fatal stroke with an RD of 6% (95% CI -4.5% to 16.5%). For those with severe MCA stenosis, 44% (22/50) in the surgical group and 23.7% (14/59) in the medical group had a primary event with an RD of 20.3% (95% CI 2.5%–36.7%).

Conclusion

12. For patients with symptomatic severe 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, 1 Class I study, confidence in evidence upgraded due to magnitude of effect)

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

Three Class I, 2 Class II, and 1 Class IV study were identified that informed the conclusions on endovascular procedures in patients with s-ICAS. Three studies were determined to have limited generalizability due to enrolling patients with only vertebral artery stenosis[30, 31] or due to enrollment remote (mean of 7 months) from QE.[32]

The NIH-supported Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS) (Class I) randomized 451 patients within 30 days of a TIA or non-disabling stroke attributed to 70% to 99% diameter stenosis of a major intracranial artery to AMM alone, or AMM in addition to PTAS.[33, 34] Enrollment was stopped after an interim analysis due to safety concerns regarding the risk of periprocedural stroke or death in the PTAS group and because futility analyses indicated that there was virtually no chance that a benefit from PTAS would be found. The 30-day stroke or death risk was 14.7% (33/224; 12.5% non-fatal stroke, 2.2% stroke-related death) in the PTAS arm and 5.7% (13/227; 5.3% non-fatal stroke, 0.4% non-stroke related death) in the AMM arm with an RD of 9% (95% CI 3.4%–14.7%). At a mean follow up of 11.9 months, 20.5% (46/224) in the PTAS arm and 11.5% (26/227) in the AMM arm had a primary outcome with an RD of 9% (95% CI 2.3%–15.8%). The majority of strokes in the PTAS arm (75%) occurred within 1 day of the procedure and 30% were symptomatic brain hemorrhage. After enrollment was stopped, the oversight committee decided to follow up with all patients for the 2 years following the last patient's enrollment. The cumulative probability of the primary outcome was greater in the PTAS arm than the AMM arm throughout follow up. During a median follow-up period of 32.4 months, 23% (52/224) of patients in the PTAS arm and 15% (34/227) of patients in the AMM arm had a primary endpoint event with an RD of 8.2% (95% CI 1%–15.4%). The risk of any stroke (26%, 59/224 PTAS vs 19%, 43/227 AMM; RD 7.4%, 95% CI -0.34% to 15%) and any major hemorrhage (13%, 29/224 PTAS vs 4%, 10/227 AMM; RD 8.5%, 95% CI 3.4%–14%) was also higher in the PTAS arm. Beyond 30 days, the risk of the primary endpoint was similar in both arms. In summary, the final results of SAMMPRIS showed that AMM is superior to PTAS in patients with recent TIA or stroke attributed to 70%–99% atherosclerotic intracranial arterial

stenosis. This was attributed to the high periprocedural risk of stroke and no benefit of PTAS beyond the periprocedural period.

An exploratory analysis of SAMMPRIS data was undertaken to determine if stenting might be helpful in specific patient subgroups.[35] Seven predefined subgroups (age, sex, symptomatic artery, QE [TIA or stroke], days to enrollment [<7 days], old infarct in territory, and anti-thrombotic therapy at QE) and 9 post hoc subgroups (race, hypertension, lipid disorder, diabetes, smoking, symptomatic circulation [anterior or posterior], percent stenosis [<80%], proton pump inhibitor usage, hypo-perfusion symptoms at QE) were evaluated to determine if any subgroup might benefit from PTAS compared with AMM. No significant interaction with treatment was found in any subgroup. For the vast majority of variables, the observed 2-year event rates were higher with PTAS compared with AMM.

As with SAMMPRIS, the industry-funded Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) (Class I) randomized patients with a recent stroke or TIA attributed to 70%–99% stenosis of a major intracranial artery (or 50%–99% stenosis tandem lesions) to medical management alone or medical management plus PTAS within 30 days of a QE.[36] The VISSIT stenting procedure differed from SAMMPRIS by use of a balloon-expandable stent rather than a self-expanding stent. Following the results of SAMMPRIS, the sponsor of VISSIT halted the trial for an unplanned safety analysis after enrolling 112 of the intended 250 participants. The risk of stroke in the territory of the stenotic artery within 1 year was higher in the intervention arm 34.5% (20/58) than in the medical arm 9.4% (5/53) with an RD of 25.1% (95% CI 9.7%–38.9%). The study's primary endpoint was a composite of stroke in the territory of the stenotic artery or a "hard" TIA. A hard TIA was defined as a transient episode of neurological dysfunction caused by focal brain or retinal ischemia that lasts for at least 10 minutes but resolves within 24 hours. Specifically, the patient should present with focal weakness or language disturbance (other than isolated slurred speech), transient monocular blindness, or required assistance when walking. The primary endpoint was also higher in the intervention arm (36.2%, 21/58) than in the medical arm (15.1%, 8/53) with an RD of 21.2% (95% CI 4.8%–35.9%). The 30-day primary safety endpoint occurred more frequently in the intervention arm (24.1%, 14/58) compared with the medical arm (9.4%, 5/53) with an RD of 14.7% (95% CI

0.5%–28.2%). Stroke or death risk by day 30 occurred in 25.9% (15/58) of patients in the PTAS arm and 5.7% (3/53) in the medical arm with an RD of 20% (95% CI 6.6%–33.3%). Three deaths occurred in the PTAS arm (2 intracerebral hemorrhages [ICH] and 1 acute ischemic stroke).

One single-center Class II prospective, randomized, controlled trial compared the efficacy and safety of PTAS with the efficacy and safety of medical management for symptomatic MCA stenosis in a Chinese population.[32] Seventy patients were randomized to PTAS plus medical management or to medical management alone following TIA or stroke attributed to a >70% MCA stenosis. QE occurred at a median of 7 months from enrollment limiting generalizability to those with recent stroke or TIA. The primary outcome was a composite of recurrent ipsilateral stroke, TIA, or death within 1 year. At a median follow-up of 10 months, 13 patients achieved the endpoint consisting of 2 recurrent strokes and 11 TIAs in the territory of the affected artery. The 30-day risk of stroke or death in the intervention arm was significantly lower than in SAMMPRIS or VISSIT at 2.8%, possibly reflecting the interval between QE to enrollment. There was no difference in risk of recurrent stroke or TIA between the medical arm (19.4%, 7/36) and the stenting arm (17.6%, 6/34) (RD 1.8%, 95% CI -16.8% to 19.9%). One recurrent stroke occurred in the stenting arm (2.8%, 1/36) and 1 occurred in the medical arm (2.9%, 1/34) (RD -0.2%, 95% CI -12.4% to 11.5%).

Vertebral Artery Stenting Trial (VAST) was a Class I prospective, open-label, blinded outcome trial that randomized patients with >50% stenosis of a symptomatic vertebral artery to either PTAS plus medical management or medical management alone.[31] Patients were enrolled from 7 hospitals in the Netherlands within 6 months of a TIA or minor ischemic stroke. The trial used a pragmatic design that allowed for the choice of stent to be determined by the interventional surgeon. All patients allocated to stenting received clopidogrel 75 mg daily in addition to aspirin, or a vitamin K antagonist, starting 5 days or more before the procedure (or a clopidogrel load of 300 mg prior to procedure) and continuing for more than 30 days afterwards. All patients received the best medical treatment as determined by the treating neurologist. The pre-specified primary outcome was the composite of vascular death, MI, or any stroke within 30 days after the start of treatment. After the death of 1 patient from a complication of stenting, the trial executive

committee suspended enrollment. The trial was subsequently terminated by the investigators. The primary outcome occurred in 5% (3/57) of patients in the PTAS group and 2% (1/58) of the medical group at 30 days with an RD of 3.5% (95% CI -4.6% to 12.8%). When follow-up was completed at a median of 3 years, the composite outcome occurred in 19% (11/57) of patients in the PTAS group 17% (10/58) of the medical (RD 2.1%, 95% CI -12.2% to 16.3%). Any stroke in the territory of the stenotic artery at 30 days occurred in 5% (3/57) of patients in the PTAS group and 2% (1/58) of the medical group (RD 3.5%, 95% CI -4.6% to 12.8%). After complete follow-up, 12% (7/57) of patients in the PTAS group and 7% (4/58) of the medical group (RD 5.4%, 95% CI -6% to 17.1%) had a stroke in the territory of the symptomatic vertebral artery. Nineteen patients (16.5%) in the cohort had s-ICAS (V4 stenosis). The authors reported the 30-day composite outcome for this subgroup, which occurred in 22.2% (2/9) of the PTAS group and 0% (0/10) of the medical group (RD 22.2%, 95% CI -9.8% to 54.7%). Because no patient in either group had an MI within 30 days, this composite outcome represented the 30-day risk of stroke or death. The study was underpowered and demonstrated a low risk of recurrent vertebrobasilar stroke in the medical group, likely due to including patients with predominantly extracranial stenosis (compared with s-ICAS).

Vertebral Artery Ischaemia Stenting Trial (VIST) was a Class II prospective, open-label, blinded-outcome trial that randomized patients with $\geq$50% stenosis of a symptomatic vertebral artery to either PTAS plus medical management or medical management alone.[30] Patients were enrolled from 14 hospitals in the United Kingdom within 6 months (or 3 months after the first 100 patients were enrolled) following TIA or non-disabling stroke. Similar to VAST, the trial had a pragmatic design that allowed for various stent types determined by the interventional surgeon but did not mandate best medical care. The primary endpoint was fatal or non-fatal stroke in any arterial territory (including periprocedural stroke) during follow-up. Because of slow recruitment and lack of continued funding, recruitment was stopped after 182 of the planned 540 participants were enrolled. Follow-up was a minimum of once per year for each participant. Only 17% of the cohort had s-ICAS (V4) and neither the 30-day risk of any stroke nor the long-term risk of stroke in the territory of the stenotic artery were reported. At a median follow-up of 3.5 years, 5.5% (5/91) in the PTAS group and 13.6% (12/88) in the medical group had a fatal or non-fatal stroke with an RD of -8.1% (95% CI -17.4% to 0.7%). For patients with

s-ICAS (V4), the long-term risk of fatal or non-fatal stroke (in any territory) was 11.8% (2/17) in the PTAS group and 28.6% (4/14) in the medical group with an RD of -16.8% (95% CI -44.2% to 11.4%). Of the 91 participants randomized to stenting, the procedure was not performed in 30 (33.0%), predominantly due to 76.7% (23/30) of the group having <50% stenosis on digital subtraction angiography. This, in addition to the shorter time between QE and randomization in the stenting group, and the low enrollment of patients with s-ICAS, downgraded the confidence in the evidence.

In a single center (Class IV) trial investigators randomized 50 patients with "refractory ICAS" attributed to 70%–99% stenosis of a major intracranial artery to PTAS (with a balloon mounted stent) plus medical management versus medical management alone. Allocation concealment was not reported, potentially relevant baseline characteristics were imbalanced between treatment arms, and outcome adjudication was unmasked. Participants were randomized >1 month from QE, must have been on maximal medical therapy to be included in the trial, and 66% of participants had at least 2 previous strokes. The median age of participants in the intervention arm was 58.4 (+/- 6.8) years and in the medical arm was 60 (+/- 7.2) years. Only 24% of participants had anterior circulation s-ICAS and 24% had a lacunar stroke as the QE. The primary endpoint was recurrent large artery stroke at 90 days and secondary endpoints included change in NIHSS, mRS, clinical improvement, lacunar stroke, mortality, and TCD parameters. Recurrent stroke in the territory of the stenotic artery occurred in 16% (4/25) of the intervention arm compared to 56% (14/25) in the medical management arm (RD -48%, 95% CI -66.5% to -21%). The authors also reported improvement in 6-month functional outcome and vessel imaging status. The trial was limited in generalizability due to including only patients with "refractory s-ICAS", patients with lacunar infarcts as QE and predominantly posterior circulation ICAS.

We used a random effect IV model to obtain a summary estimate of the RD of any stroke or death among patients with recent TIA or non-disabling stroke randomized to the intervention arm, compared with the control arm, in SAMMPRIS and VISSIT. When comparing PTAS plus medical management to medical management alone, the summary estimate of the 30-day stroke or death RD was 13% (95% CI 3%–24%; $I^2 = 59\%$; figure 1) demonstrating a significantly

increased risk with PTAS. Adding data from the VAST trial (which was downgraded due to indirectness) did not significantly change the summary estimate of 30-day stroke or death (RD 13%, 95% CI 5%–22%; I^2 = 34%). When evaluating the risk of recurrent stroke in the territory of the stenotic vessel beyond 30 days, we used a random effect IV model to obtain a summary estimate using data from SAMMPRIS and VISSIT. When comparing PTAS plus medical management to medical management alone, the summary estimate of the risk beyond 30 days demonstrated an increased risk of 3%; however, the CI indicated poor precision (95% CI -3% to 8%; figure 2).

Figure 1: Summary estimate of the effects of PTAS + AMM compared to AMM alone on 30-day risk of recurrent stroke or death

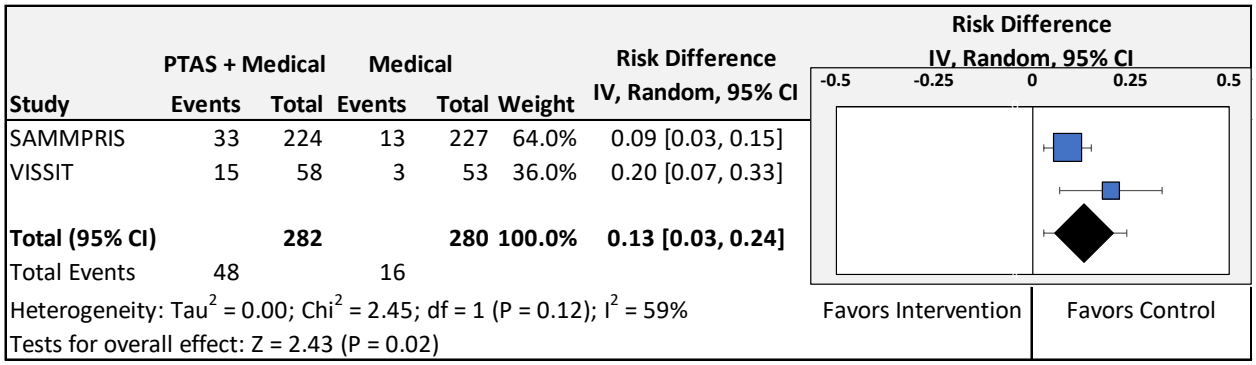
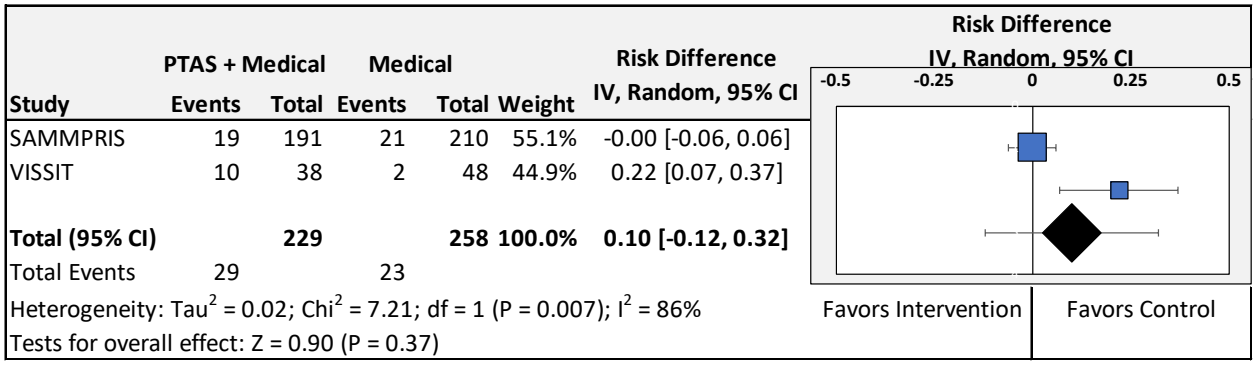


Figure 2: Summary estimate of the effects of PTAS + AMM compared to AMM alone on recurrent stroke or death beyond 30 days



Conclusion

13. For patients with recent TIA or non-disabling stroke attributed to s-ICAS, it is highly likely that PTAS plus medical management, compared with medical management alone, increases the early risk of recurrent stroke and death (RD 13%, 95% CI 3%–24%; I^2 = 59%). (High confidence, 2 Class I studies with large magnitude of effect)
14. For patients with recent TIA or non-disabling stroke attributed to s-ICAS, it is possible that PTAS plus medical management, compared with medical management 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, 2 Class I studies, confidence downgraded due to imprecision)

3) For patients with a history of s-ICAS, what modifiable and non-modifiable risk factors predict an increased risk of recurrent stroke or death?

For the prognostic questions, studies evaluating "attainment of risk factor control" were discussed separately from studies of baseline risk factors. The aim of evaluating risk factor control in these studies was to provide stronger pragmatic evidence in the pathway between risk factor control and recurrent stroke. Similarly, studies of baseline modifiable risk factors predicting recurrent stroke or death were discussed separately from studies of non-modifiable risk factors. Modifiable risk factors are potential targets for future therapeutic trials whereas knowledge of non-modifiable risk factors is crucial for risk stratification and potential effect modification in future therapeutic studies. The main findings of the prognostic studies are summarized in the table on page 47.

Risk factor control

Four Class I studies were identified that informed conclusions on risk factor control and recurrent stroke or death in patients with s-ICAS.[37, 38, 39, 40] One of the studies was a subgroup analysis comprising patients enrolled in the medical arm of SAMMPRIS.[39] All studies were deemed to have good generalizability to the broad patient population with s-ICAS except the Vertebrobasilar Flow Evaluation and Risk of Transient Ischemic Attack and Stroke study (VERiTAS).[40] VERiTAS included patients with ICAS primarily due to basilar disease or, less often, bilateral V4 stenosis, however 10% of participants had isolated extracranial stenosis.

Risk factor control after symptom onset

One Class I study that included WASID participants was identified relevant to the conclusion for being "out of target" for total cholesterol (TC) or TC / high-density lipoprotein cholesterol (HDL-C) ratio.[37]

Two Class I studies that included WASID participants and those in the medical arm of SAMMPRIS were identified relevant to the conclusion on being "out of target" for low-density lipoprotein cholesterol (LDL-C).[37, 39] To improve precision, a generic IV meta-analytic model was used to generate a pooled odds ratio (POR) of 1.3 (95% CI 0.8–2.1; $I^2 = 0\%$).

One Class I study that included WASID participants was identified relevant to the conclusion on being out of target for TC.[37]

Two Class I studies that included WASID participants and those in the medical arm of SAMMPRIS were identified relevant to the conclusion on being out of target for non-HDL-C.[37, 39] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.4 (95% CI 0.8–2.5; $I^2 = 0\%$).

One Class I study that included WASID participants was identified relevant to the conclusion on being "out of target" for mean arterial pressure (MAP).[37]

One Class I cohort study that included WASID participants was identified relevant to the conclusion on being out of target for diastolic blood pressure (DBP).[38]

Three Class I studies that included WASID participants and SAMMPRIS participants were identified relevant to the conclusion on being "out of target" for SBP.[37, 38, 39] Two studies reported different measures of effect sizes from the same cohort (WASID).[37, 38] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.7 (95% CI 1.2–2.4; $I^2 = 0\%$) for being out of target for SBP using ORs from each cohort.

One Class I study (VERiTAS) was identified relevant to the conclusion on strict control of SBP and DBP in patients with and without low distal blood flow.[40]

One Class I study using participants in the medical arm of SAMMPRIS was identified relevant to the conclusion for being out of target for body mass index (BMI).[39]

One Class I cohort study that included WASID participants was identified relevant to the conclusion for alcohol use.[37]

One Class I study that included participants in the medical arm of SAMMPRIS was identified relevant to the conclusion for being out of target for hemoglobin A1c (HbA1c).[39]

One Class I study that included participants in the medical arm of SAMMPRIS was identified relevant to the conclusion for being out of target for smoking cessation.[39]

One Class I study that included participants in the medical arm of SAMMPRIS was identified relevant to the conclusion for being out of target for physical activity.[39]

Conclusions

1. For patients with s-ICAS it is *highly likely* that failure to achieve risk factor control of SBP (POR 1.7, 95% CI 1.2–2.4; $I^2 = 0\%$) and physical activity (OR 6.7, 95% CI 2.5–18.1) predicts an increased risk of recurrent stroke. (High confidence, 2 Class I studies supporting evidence for SBP; 1 Class I study supporting physical activity, upgraded for magnitude of effect)
2. For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for TC/HDL-C ratio (HR 1.9, 95% CI 1.2–2.9), TC (HR 2.1, 95% CI 1.4–3.1), MAP (HR 2.8, 95% CI 1.7–3.0), DBP (OR 2.2, 95% CI 1.1–4.6), HbA1c (OR 2.3, 95% CI 1.0–5.0), and absent alcohol use (HR 1.8, 95% CI 1.2–2.6) predicts an increased risk of recurrent stroke. (Moderate confidence, 1 Class I study supporting each risk factor)
3. For patients with s-ICAS and co-existing low distal flow status on quantitative magnetic resonance angiography (QMRA), it is *possible* that strict blood pressure control (i.e., "in target" for SBP <140 and DBP <90 mm Hg) may increase the risk of recurrent stroke or death (OR 6.2, 95% CI 1.5–27). (Low confidence, 1 Class I, indirect study)
4. For patients with s-ICAS it is *possible* that failure to achieve risk factor control (being out of target) for LDL-C (POR 1.3, 95% CI 0.8–2.1; $I^2 = 0\%$) and non-HDL-C (POR 1.4, 95% CI 0.8–2.5; $I^2 = 0\%$), does not predict an increased risk of recurrent stroke. (Low confidence, 2 Class I studies, confidence downgraded for imprecision)

5. The evidence is insufficient to support or refute that failure to achieve risk factor control for BMI (OR 0.9, 95% CI 0.4–2.1) and smoking cessation (OR 0.5, 95% CI 0.3–1.3) predicts an increased risk of recurrent stroke. (Very low confidence, 1 Class I study with confidence downgraded for imprecision supporting smoking cessation and BMI)

Modifiable risk factors

Sixteen studies were identified that informed conclusions on the effect of baseline modifiable risk factors on the risk of recurrent stroke or death.[6, 23, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54] Six studies were subgroup analyses of Class I studies comprising patients from SAMMPRIS, WASID, or CHANCE.[42, 46, 49, 51, 52] Eight studies were determined to have some limited generalizability (indirectness) for the following reasons: the percentage of patients with only TIA as the QE,[46] the percentage of patients with symptomatic middle cerebral artery occlusion (MCAO), not stenosis,[47] having a small cohort of patients who received angiogram for possible intervention,[44] only enrolling patients without known coronary artery disease, enrolling patients long after the QE,[41] enrolling patients only within 24 hours,[23] inclusion of patients with only posterior circulation stenosis (10% extracranial, otherwise basilar or bilateral V4),[43] inclusion of only patients with anterior circulation stenosis who did not get PTAS[54] and for limited follow-up.[53]

Five studies (4 Class I, 1 Class II) that enrolled patients from 3 cohorts (WASID, the medical arm of SAMMPRIS, and a retrospective cohort study) were identified relevant to the conclusion on failure of antithrombotic therapy.[6, 42, 44, 48, 49] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.0 (95% CI 0.5–1.9; $I^2 = 0\%$) for failure of antithrombotic therapy from the 2 direct Class I cohort studies reporting the ORs from WASID and the medical arm of SAMMPRIS.

Eight studies (4 Class I, 4 Class II) that enrolled patients from 5 cohorts (WASID, SAMMPRIS, VERiTAS, and 2 single-center cohorts) were identified relevant to the conclusion on history of coronary artery disease and recurrent stroke.[6, 42, 43, 44, 46, 47, 54, 53] To improve precision, a generic IV meta-analytic model was used to generate a POR of 0.95 (95% CI 0.6–1.4; $I^2 = 0\%$) using

effect measures from the WASID and SAMMPRIS cohorts, which had the lowest risk of bias and most direct evidence.

Two Class II studies were identified relevant to the conclusion on baseline HbA1c.[53, 54] One study reported the difference in HbA1c between those with and without recurrent stroke allowing the ability to calculate the OR for recurrent stroke in those with HbA1c dichotomized at 7.9 (OR 0.8, 95% CI 0.3–2.3).

Two Class I studies that enrolled patients with TIA as the QE from WASID and participants from the medical arm of SAMMPRIS were identified relevant to the conclusion on baseline glucose (>200 mg/dL).[46, 49] To improve precision, a generic IV meta-analytic model was used to generate a POR of 2.0 (95% CI 1.2–3.5; $I^2 = 0\%$).

Ten studies (5 Class I, 5 Class II) that included participants from 8 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 2 prospective multicenter cohorts, and 3 single-center cohorts) were identified relevant to the conclusion on history of diabetes predicting recurrent stroke or death.[6, 42, 43 44, 46, 47, 49, 50, 53, 54] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.6 (95% CI 1.2–2.2; $I^2 = 0\%$) using the 3 studies with the least bias, most providing direct evidence.[6, 49, 50]

Seven studies (3 Class I, 4 Class II) from 6 cohorts (WASID, medical arm of SAMMPRIS, a 2-center cohort, and 3 single-center cohorts) were identified relevant to the conclusion on history of hypertension predicting recurrent stroke or death.[6, 42, 44, 47, 49, 53, 54] To improve precision, a generic IV meta-analytic model was used to generate a POR of 0.9 (95% CI 0.5–1.5; $I^2 = 0\%$) using effect measures from WASID and the medical arm of SAMMPRIS.

Five studies (3 Class I, 2 Class II) from 4 cohorts (patients with TIA as QE from WASID, medical arm of SAMMPRIS, and 1 2-center and 1 single-center cohort) were identified relevant to the conclusion on elevated SBP predicting recurrent stroke or death.[42, 44, 46, 49, 54] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.3 (95% CI 0.5–3.5; $I^2 = 0\%$) using effect measures from WASID and the medical arm of SAMMPRIS.

Two Class I and 1 Class II study from 3 cohorts (the medical arm of SAMMPRIS from patients with TIA as QE for WASID and a 2-center cohort from China), were identified relevant to the

conclusion on elevated DBP predicting recurrent stroke or death.[42, 46, 54] One study dichotomized elevated DBP at >90 mm Hg, while the other modeled DBP as a continuous variable. The conclusion was based on the medical arm of SAMMPRIS, which gave the most direct, precise evidence (OR 0.9, 95% CI 0.8–1.2).

Six studies (2 Class I, 4 Class II) from 6 cohorts (WASID, VERiTAS, 3 single-center cohorts, and 1 cohort from 2 centers in China) were identified relevant to the conclusion on history of dyslipidemia predicting recurrent stroke or death.[6, 43, 44, 47, 53, 54] To improve precision, because there was only 1 Class I direct, imprecise study, we used a generic IV meta-analytic model to generate a POR of 1.2 (95% CI 0.8–1.8; $I^2 = 0\%$) using all 6 cohorts.

One Class II study from a single-center cohort was identified relevant to the conclusion on TC predicting recurrent stroke or death with an OR of 16.5 (95% CI 2.5–104.6).[44]

Three Class I studies and 1 Class II study enrolling patients from 3 cohorts (WASID, the medical arm of SAMMPRIS, and a 2-center cohort from China) were identified relevant to the conclusion on baseline HDL-C predicting recurrent stroke or death.[42, 45, 49, 54] Two studies modeled HDL-C as a categorical variable and 1 study modeled it as a continuous variable. To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.0 (95% CI 0.7–1.5; $I^2 = 0\%$) using the ORs from WASID and the medical arm of SAMMPRIS.

Five studies (2 Class I and 3 Class II) that included participants from 4 cohorts (medical arm of SAMMPRIS, 2 single-center cohorts, and a 2-center cohort) were identified relevant to the conclusion on baseline LDL-C predicting recurrent stroke or death.[42, 44, 49, 53, 54] To improve precision, because there was only 1 Class I direct, imprecise study, we used a generic IV meta-analytic model to generate a POR of 1.6 (95% CI 0.8–3.1; $I^2 = 16\%$) using the ORs from 3 cohorts that dichotomized LDL-C.

One Class I and 1 Class II study (patients enrolled in WASID and a 2-center cohort from China) were identified relevant to the conclusion on baseline triglycerides predicting recurrent stroke or death with an OR of 1.6 (95% CI 1.0–2.5).[45, 54]

One Class I study using patients enrolled in the medical arm of SAMMPRIS was identified relevant to the conclusion on lipoprotein(a) predicting recurrent stroke or death.[52]

One Class II single-center cohort study was identified relevant to the conclusion on history of PVD predicting recurrent stroke or death with an OR of 1.03 (95% CI 0.5–2.1).[44]

Five Class I studies from 3 cohorts (WASID, medical arm of SAMMPRIS, and VERiTAS) were identified relevant to the conclusion on BMI predicting recurrent stroke or death.[6, 42, 43, 45, 49] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.4 (95% CI 0.9–2.1; $I^2 = 0\%$) using effect measures from WASID and the medical arm of SAMMPRIS.

One Class I study that included WASID participants was identified relevant to the conclusion on metabolic syndrome predicting the recurrent risk of stroke or death (HR 1.5; 95% CI 0.96–2.4).[45]

Four Class I studies that included participants from 3 cohorts (WASID, medical arm of SAMMPRIS, and VERiTAS) were identified relevant to the conclusion on baseline physical activity predicting recurrent stroke or death.[6, 42, 43, 49] Each study used a different definition of baseline physical activity. To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.1 (95% CI 0.7–1.9; $I^2 = 56\%$) using the ORs from WASID and the medical arm of SAMMPRIS (which had direct, Class I evidence).

Eight studies (4 Class I, 4 Class II) that included participants from 7 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 1 2-center cohort, and 3 single-center cohorts) were identified relevant to the conclusion on smoking predicting recurrent stroke or death.[6, 42, 43, 44, 47, 49] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.0 (95% CI 0.7–1.6; $I^2 = 0\%$) using ORs from WASID and the medical arm of SAMMPRIS (which had the lowest risk of bias and most direct evidence).

Four studies (2 Class I, 2 Class II) including participants from 4 cohorts (WASID, VERiTAS, and 2 single-center cohorts) were identified relevant to the conclusion on alcohol use predicting recurrent stroke or death.[6, 43, 44, 47] Because there was only 1 imprecise Class I, direct study we used a generic IV meta-analytic model to generate a POR of 0.8 (95% CI 0.5–1.2; $I^2 = 0\%$) using measures of effect sizes from all 4 cohorts.

One Class I study and 1 Class II study that included SAMMPRIS and CHANCE participants were identified relevant to the conclusion on elevated high-sensitivity C-reactive protein (hs-CRP) predicting recurrent stroke or death (HR 1.8, 95% CI 0.96–3.4).[51, 55]

One Class I, prospective, single-center study was identified relevant to the conclusion on a positive myocardial SPECT scan predicting recurrent stroke or death (OR 3.4, 95% CI 0.8–12.9).[41]

Conclusions

6. For patients with s-ICAS it is *likely* that the modifiable risk factors of baseline glucose levels >200 mg/dL (POR 2.0, 95% CI 1.2–3.5; $I^2 = 0\%$), a history of diabetes (POR 1.6, 95% CI 1.1–2.2; $I^2 = 0\%$), and elevated triglycerides (>150 mg/dL) (OR 1.6, 95% CI 1.0–2.5) predict an increased risk of recurrent stroke or death. (Moderate confidence, 2 Class I studies supporting glucose, confidence downgraded due to indirectness; 2 Class I studies and 1 Class II study supporting diabetes; 1 Class I study supporting triglycerides)
7. For patients with s-ICAS it is *likely* that the modifiable risk factor of baseline DBP does not predict an increased risk of recurrent stroke or death (OR 0.9, 95% CI 0.7–1.4). (Moderate confidence, 1 Class I study)
8. For patients with s-ICAS it is *possible* that the following modifiable risk factors do not predict an increased risk of recurrent stroke or death: failure of antithrombotic therapy (POR 1.0, 95% CI 0.5–1.9; $I^2 = 0\%$), history of coronary artery disease (POR 0.95, 95% CI 0.6–1.4; $I^2 = 0\%$), history of hypertension (POR 0.9, 95% CI 0.5–1.5; $I^2 = 0\%$), baseline SBP (>140–144 mm Hg) (POR 1.3, 95% CI 0.5–3.5; $I^2 = 0\%$), baseline HDL-C (POR 1.0, 95% CI 0.7–1.5; $I^2 = 0\%$), elevated BMI (POR 1.4, 95% CI 0.9–2.1; $I^2 = 0\%$), baseline physical activity (POR 1.1, 95% CI 0.7–1.9; $I^2 = 56\%$), and smoking (POR 1.0, 95% CI 0.7–1.6; $I^2 = 0\%$). (Low confidence, 2 Class I studies downgraded for imprecision supporting failure of antithrombotic therapy, coranary artery disease, hypertension, baseline HDL-C, baseline BMI, baseline physical activity, and smoking; 2 Class I studies downgraded for indirectness and imprecision supporting SBP)
9. There is insufficient evidence to support or refute the following modifiable risk factors in predicting an increased risk of recurrent stroke: Baseline HbA1 (OR 0.8, 95% CI 0.3–2.3), baseline TC (OR 16.5, 95% CI 2.5–104.6), a history of PVD (OR 0.6, 95% CI 0.1–6.0), baseline DBP (OR 0.9, 95% CI 0.8–1.2), a history of dyslipidemia (POR 1.2, 95% CI 0.8–1.8; $I^2 = 0\%$), baseline LDL-C (POR 1.6, 95% CI 0.8–3.1; $I^2 = 16\%$), elevated

lipoprotein (a) (OR 1.03, 95% CI 0.5–2.1), metabolic syndrome (HR 1.5, 95% CI 0.96–2.4), alcohol use (POR 0.8, 95% CI 0.5–1.2; $I^2 = 0\%$), hs-CRP (HR 1.8, 95% CI 0.96–3.4), and a positive Myocardial SPECT scan (OR 3.4, 95% CI 0.8–12.9). (Very low confidence, 2 Class I and 4 Class studies supporting history of dyslipidemia and alcohol use, confidence downgraded for imprecision and indirectness; 1 Class I study supporting lipoprotein(a), hs-CRP, and metabolic syndrome, confidence in the evidence downgraded due to imprecision; 1 Class I and 2 Class II studies supporting baseline LDL-C, confidence in the evidence downgraded due to indirectness; 1 Class I study supporting Myocardial SPECT, confidence in the evidence downgraded due to indirectness and imprecision; 1 Class II indirect study supporting baseline TC and HbA1c; 1 Class 2 study supporting history of PVD, confidence in the evidence downgraded due to indirectness)

Non-modifiable risk factors

Twenty-two studies were identified that informed conclusions on non-modifiable risk factors predicting the risk of recurrent stroke or death in patients with s-ICAS.[6, 42, 43, 44, 46, 47, 49, 50, 53, 54, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67] Eleven studies were subgroup analyses of either Class I or Class II studies comprising patients enrolled in WASID, SAMMPRIS, CHANCE, and/or VERiTAS.[6, 42, 43, 46, 49, 58, 59, 64, 65, 66, 67] Twelve studies were determined to have some limited generalizability (indirectness) for the following reasons: a high percentage of patients with only TIA as QE,[46] a high percentage of patients with only symptomatic MCAO with concomitant ICAS,[47] a small cohort of patients who received an angiogram for possible intervention,[44] comparing only basilar with MCA occlusion,[61] including only posterior circulation stenosis,[56] only isolated MCA stenosis,[57] including patients with only posterior circulation stenosis, including some with extracranial disease,[43] enrolling only patients early after TIA or a minor stroke,[65, 66, 67] enrolling only anterior circulation stenosis while excluding 20% due to opting for PTAS, inclusion of only patients with anterior circulation stenosis who did not get PTAS[54] and for limited follow-up.[53]

Ten studies (5 Class I, 5 Class II) that included participants from 6 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 3 single-center cohorts, and 2 multicenter cohorts) were identified relevant to the conclusion on age predicting recurrent stroke or death.[6, 42, 43, 44, 46, 47, 49,

[53, 54, 56] Age was modeled as a dichotomized variable in some studies and as a continuous variable (yearly or by decade) in others. None of the direct Class I studies demonstrated a significant association between age and recurrent stroke or death. To improve precision, a generic IV meta-analytic model was used to generate a POR of 0.9 (95% CI 0.6–1.4; I^2 = 0%) using measures of effect size from WASID and the medical arm of SAMMPRIS (which had the lowest risk of bias, most direct evidence, and age modeled as a dichotomous variable).

Seven studies (5 Class 1, 2 Class II) that included participants from 5 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 1 single-center, and 1 2-center cohort) were identified relevant to the conclusion on race predicting recurrent risk of stroke or death[6, 42, 43, 49, 53, 54, 59] One analysis demonstrated a borderline increased risk of any recurrent ischemic stroke in Black participants as compared with White participants with an HR of 1.6 (95% CI 1.01–2.6). However, no analysis demonstrated a significantly increased risk of recurrent stroke in the territory of the stenotic artery or in the composite of stroke and death. To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.2 (95% CI 0.8–1.8; I^2 = 0%) using the ORs from WASID and the medical arm of SAMMPRIS.

Eight studies (5 Class I, 3 Class II) that included participants from 6 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 2 single-center, and one 2-center cohort) were identified relevant to the conclusion on sex (male vs female) predicting recurrent stroke or death.[6, 42, 43, 46, 47, 49, 53, 54] To improve precision, a generic IV meta-analytic model was used to generate a POR of 0.6 (95% CI 0.4–0.8; I^2 = 0%) using measures of effect size from WASID and the medical arm of SAMMPRIS (which had the lowest risk of bias and most direct evidence).

Seven studies (3 Class I, 4 Class II) that included participants from 6 cohorts (WASID, medical arm of SAMMPRIS, 1 prospective multicenter cohort, 2 single-center, and 1 2-center cohort) were identified relevant to the conclusion on history of stroke predicting recurrent stroke or death.[6, 42, 44, 46, 50, 53, 54] Because only 1 Class I, direct but imprecise study including participants from both WASID and SAMMPRIS was identified,[42] we used a generic IV meta-analytic model to generate a POR of 1.2 (95% CI 0.8–1.7; I^2 = 5%) using measures of effect sizes that also included the 2 Class II studies reporting recurrent stroke.

One Class I study that included WASID participants was identified relevant to the conclusion on history of TIA predicting recurrent stroke or death with an OR of 0.8 (95% CI 0.4–1.4).[6]

Three Class I and 2 Class II studies (participants from WASID, those in the medical arm of SAMMPRIS, a subgroup of CHANCE, and a 2-center cohort) were identified relevant to the conclusion on prior infarcts on imaging predicting recurrent stroke or death.[42, 46, 49, 53, 54, 65] All 3 studies demonstrated this risk factor to be a significant predictor of recurrent stroke. To improve precision, a generic IV meta-analytic model was used to generate a POR of 3.3 (95% CI 1.7–6.2; $I^2 = 0\%$) using the OR from WASID and the medical arm of SAMMPRIS.

Two Class II studies comprised of participants from the medical arm of SAMMPRIS were identified relevant to the conclusion on the presence of concomitant small vessel disease (SVD) predicting the recurrent risk of stroke with an OR of 2.0 (95% CI 0.7–5.1).[64, 67]

Two Class II studies, a single-center cohort and subgroup of CHANCE, were identified relevant to the conclusion on the presence of concomitant asymptomatic ICAS predicting recurrent stroke or death.[47, 67] To improve precision, a generic IV meta-analytic model was used to generate a POR of 2.2 (95% CI 0.8–6.1; I^2=70%).

Two Class I and 1 Class II study (comprised of participants from the medical arm of SAMMPRIS, WASID patients meeting SAMMPRIS inclusion criteria, and 1 single-center cohort), were identified relevant to the conclusion on statin therapy (at trial enrollment) predicting recurrent stroke or death.[42, 49, 53] The combined cohort from the Class I study with better precision was used to support the conclusion (OR 1.3, 95% CI 0.8–2.1).

Four studies (3 Class I, 1 Class II) that included participants from WASID and those in the medical arm of SAMMPRIS as well as a single-center cohort, were identified relevant to the conclusion on NIHSS predicting recurrent stroke or death.[6, 42, 49, 53] To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.8 (95% CI 1.1–3.0; $I^2 = 26\%$) using the ORs from the Class I cohorts.

Two Class I studies that included participants from WASID and those that were “WASID-like” from the medical arm of SAMMPRIS were identified relevant to the conclusion on modified Rankin Scale (mRS) score predicting recurrent stroke or death.[42, 49] Precision was determined

from the report by Chaturvedi, et al., which combined both cohorts resulting in improved precision (OR 1.3, 95% CI 0.8–2.3).

Ten studies (7 Class I studies, 3 Class II studies) that included participants from 8 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 3 additional multicenter cohorts, and 2 single-center cohorts) were identified relevant to the conclusion on vascular distribution predicting recurrent stroke or death.[6, 42, 43, 44, 46, 49, 53 57, 60, 61] No study reported a significant association between vascular distributions and recurrent stroke; however, estimates from all the studies were imprecise. To improve precision, a generic IV meta-analytic model was used to generate a POR of 1.0 (95% CI 0.7–1.4; I^2 = 15%) comparing the risk of recurrent stroke between those with a QE in the anterior circulation and those with a OE in the posterior circulation. The OR from the 3 Class I studies (WASID, medical arm SAMMPRIS, and 1 prospective multicenter cohort) providing direct evidence was utilized in the analysis.[6, 49, 60]

Six studies (5 Class I, 1 Class II) that included participants from 4 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, and 1 single-center cohort) were identified relevant to the conclusion on the QE (TIA vs stroke) predicting recurrent stroke or death.[6, 42, 43, 44, 46, 49] To improve precision, a generic IV meta-analytic model was used to generate a POR of 0.6 (95% CI 0.3–0.95; I^2 = 24%) using measures of effect size from WASID and the medical arm of SAMMPRIS (which had the lowest risk of bias and most direct evidence).

Five Class I studies that included participants from 3 cohorts (WASID, medical arm of SAMMPRIS, and VERiTAS) were identified relevant to the conclusion on time from the QE predicting recurrent stroke or death.[6, 42, 43, 46, 49] Given the differences in secondary prevention and various ways the studies modeled the outcome variable, we choose not to generate a pooled summary estimate but report the individual point estimates in the conclusions and evidence tables.

Four studies (2 Class I, 2 Class II) that included participants from 4 cohorts (medical arm of SAMMPRIS, VERiTAS, 1 single-center cohort, and 1 2-center cohort) were identified relevant to the conclusion on the effect of hemodynamic markers for predicting recurrent stroke.[43, 54, 58, 63] Various imaging correlates (markers) of hemodynamic status were utilized, so it was not

appropriate to pool the results into one effect size and CI. We report the individual point estimates in the conclusions and evidence tables.

Nine studies (6 Class I, 3 Class II) that included participants from 7 cohorts (WASID, medical arm of SAMMPRIS, VERiTAS, 2 multicenter, and 2 single-center cohorts) were identified relevant to the conclusion on severity of stenosis predicting recurrent stroke or death.[6, 42, 43, 44, 46, 49, 53, 54, 60] Two studies[46, 60] provided direct Class I evidence informing the conclusion on percent stenosis (>70% vs 50%–69%) predicting recurrent stroke. To improve precision, a generic IV meta-analytic model was used to generate a POR of 2.0 (95% CI 1.4–3.0; $I^2 = 0\%$) using ORs from these studies. One study that combined results from WASID and SAMMPRIS allowed comparison of having a 70%–79% stenosis vs ≥80% stenosis in predicting recurrent stroke or death.[42]

One Class I study that included participants from WASID was identified relevant to the conclusion on length of stenosis predicting recurrent stroke or death with an OR of 1.0 (95% CI 0.6–1.7).[6]

One Class I study that included participants from WASID with a QE of TIA only was identified relevant to the conclusion on white blood cell (WBC) count predicting recurrent stroke or death with an OR of 1.5 (95% CI 0.5–4.3).[46]

One Class II study that included participants from CHANCE was identified relevant to the conclusion on neutrophil count predicting recurrent stroke or death with an OR of 0.7 (95% CI 0.4–1.2).[66]

One Class I single-center study was identified relevant to the conclusion on progression of stenosis predicting recurrent stroke or death with an OR of 1.0 (95% CI 0.2–4.9).[62]

Conclusions

10. For patients with s-ICAS, it is *highly likely* that the following non-modifiable risk factors predict an increased risk of recurrent stroke or death; sex (male vs female) (POR 0.6, 95% CI 0.4–0.8; $I^2 = 0\%$), baseline NIHSS score >1 (POR 1.8, 95% CI 1.1–3.0; $I^2 = 26\%$), percent stenosis ≥70% vs 50%–69% (POR 2.0, 95% CI 1.4–3.0; $I^2 = 0\%$), QE of TIA vs stroke (POR 0.6, 95% CI 0.3–0.95; $I^2 = 24\%$) and presence of misery perfusion

on a PET scan (OR 31.5, 95% CI 3.7–288.4). (High confidence, 2 Class II studies supporting sex, NIHSS, percent stenosis, and QE; 1 Class I study supporting misery perfusion, upgraded for magnitude of effect)

11. For patients with s-ICAS, it is *likely* that the non-modifiable risk factors of old infarcts on imaging (POR 3.3, 95% CI 1.7–6.2; $I^2 = 0\%$), and time from QE of <17 days (OR 1.7, 95% CI 1.1–2.5) predict an increased risk of recurrent stroke or death. (Moderate confidence, 2 Class I studies supporting old infarcts, confidence in the evidence downgraded for indirectness; 1 Class I study supporting time from QE)
12. For patients with s-ICAS it is *possible* that the following non-modifiable risk factors predict an increased risk of recurrent stroke or death: qualifying infarct borderzone (vs not) (OR 3.1, 95% CI 1.04–9.0), qualifying infarct borderzone plus impaired collaterals (vs not) (OR 6.9, 95% CI 2.0–23.2), impaired flow (vs complete flow) (OR 5.9, 95% CI 1.3–25.1) and low distal flow status on QMRA (in posterior circulation stroke) (OR 3.4, 95% CI 1.1–10.5). (Low confidence, 1 Class II study supporting qualifying infarcts, collaterals, and impaired flow; 1 Class I indirect study supporting QMRA)
13. For patients with s-ICAS, it is *highly likely* that anterior (vs posterior) vascular distribution does *not* predict an increased risk of recurrent stroke (POR 1.0, 95% CI 0.7–1.4; $I^2 = 15\%$). (High confidence, 3 Class I studies)
14. For patients with s-ICAS it is *possible* that the non-modifiable risk factors of age (POR 0.9, 95% CI 0.6–1.4; $I^2 = 51\%$) and race (non-White vs White for the outcome of stroke in the territory of stenotic artery) (POR 1.2, 95% CI 0.7–2.2; $I^2 = 0\%$) do *not* predict an increased risk of recurrent stroke or death. (2 Class I studies supporting age and race, confidence in the evidence downgraded for imprecision)
15. The evidence is insufficient to support or refute the following non-modifiable risk factors in predicting an increased risk of recurrent stroke: history of stroke (POR 1.5, 95% CI 0.8–2.7; $I^2 = 44\%$), history of TIA (OR 0.8, 95% CI 0.4–1.4); time from QE (when dichotomized at <7 days) (OR 1.0, 95% CI 0.5–2.1), concomitant SVD (OR 2.0, 95% CI 0.7–5.1), concomitant ICAS (POR 2.2, 95% CI 0.8–6.1), not being on a statin (at baseline of WASID or SAMMPRIS) (OR 1.3, 95% CI 0.3–2.1), baseline mRS score $\geq$1 (OR 1.3, 95% CI 0.8–2.3), percent stenosis of >80% vs 70%–79% (POR 1.0, 95% CI 0.8–1.4; $I^2 = 0\%$), length of stenosis (OR 1.0, 95% CI 0.6–1.7), WBC count of >7200 (OR 1.5, 95% CI

0.5–4.3), neutrophil count (OR 0.7, 95% CI 0.4–1.2), progression of stenosis on MRA (OR 1.0, 95% CI 0.2–4.9), increased oxygen extraction fraction (OEF) asymmetry (PET scan) (OR 2.3, 95% CI 0.3–15) and hypoperfusion patterns on imaging (artery to artery embolism + hypoperfusion [OR 3.8, 95% CI 1.3–10.9]; any hypoperfusion [OR 6.4, 95% CI 0.98–38.9]). (Very low confidence, 1 Class I and 2 Class II studies supporting history of stroke, confidence in the evidence downgraded for indirectness and insufficient precision; 1 Class I study supporting history of TIA, statin therapy, and mRS score, confidence in the evidence downgraded due to imprecision; 3 Class 1 studies supporting percent stenosis, confidence in the evidence downgraded for indirectness and imprecision; 1 Class 1 study supporting time from QE, increased OEF asymmetry, length of stenosis, and MRA progression, confidence in the evidence downgraded due to imprecision; 1 Class I supporting WBC, confidence in the evidence downgraded due to indirectness and imprecision; 1 Class II study supporting neutrophil count, and concomitant SVD both downgraded due to imprecision; 2 Class II, indirect studies supporting concomitant ICAS downgraded due to imprecision; 1 indirect Class II study downgraded for imprecision supporting hypoperfusion patterns)

Table: Predictors of Recurrent Stroke or Death in patients with s-ICAS

Risk Factor Control During Follow-up			
Increased Risk	No Increased Risk	Point Estimate	Confidence
SBP (out of target)		1.7	High
MAP (out of target)		2.8	Moderate
DBP (out of target)		2.2	Moderate
Strict BP control plus low distal flow status		6.2	Low
TC (out of target)		2.1	Moderate
TC/HDL ratio (out of target)		1.9	Moderate

	Non-HDL-C (out of target)	1.4	Low
	LDL-C (out of target)	1.3	Low
Physical activity (out of target)		6.7	High
Alcohol use (out of target)		1.8	Moderate
HbA1C (out of target)		2.3	Moderate
Modifiable Risk Factors at Baseline			
Increased Risk	No Increased Risk	Point Estimate	Confidence
	SBP	1.3	Low
	Diastolic BP (lower)	0.9	Moderate
	Hypertension (no history)	0.9	Low
	HDL-C	1.0	Low
Glucose >200 mg/dL		2.0	Moderate
History of diabetes		1.6	Moderate
Elevated triglycerides		1.6	Moderate
	Physical activity (less active)	1.1	Low
	BMI	1.4	Low
	Smoker	1.0	Low
	History of coronary artery disease	0.95	Low
	Failure of anti-thrombotic therapy	1.0	Low
Non-Modifiable Risk Factors at Baseline			

Increased Risk	No Increased Risk	Point Estimate	Confidence
Misery perfusion (SPECT)		31.5	High
Impaired flow (vs complete)		5.9	Low
Qualifying infarct = borderzone		3.1	Low
Low distal flow status on QMRA		3.4	Low
>70% stenosis (vs 50%–69%)		2.0	High
	Anterior vs posterior circulation	1.0	High
NIHSS >1		1.8	High
Stroke as QE		0.6	High
Old infarcts		3.3	Moderate
Time from QE <17 days		0.6	Moderate
Qualifying infarct = borderzone plus impaired collaterals		6.9	Low
Sex (female)		0.6	High
	Age (lower ref. group)	1.1	Low
	Non-White vs White	1.2	Low

PRACTICE RECOMMENDATIONS

Diagnosis

Recommendation 1 rationale

Symptomatic intracranial atherosclerotic arterial stenosis is one of the most common causes of stroke worldwide, responsible for 10%–50% of strokes depending on racial and ethnic factors,[2, 4, 68] and can coexist with other stroke etiologies such as extracranial atherosclerosis or atrial fibrillation.[69, 70] There is no diagnostic gold standard for diagnosing s-ICAS and various noninvasive and invasive techniques (e.g., MRA, CT angiography, TCD, and catheter cerebral

angiography) are used with varying sensitivity and specificity.[71, 72] Intracranial artery 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 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.

Recommendation 1 statement

1) 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 (Level B).

Antithrombotic Medication Therapy

Rationale for recommendations 2, 3, and 4

WASID showed that in patients with s-ICAS, aspirin 650 mg twice a day was safer and as effective as warfarin for preventing the combined endpoint of stroke, ICH, and vascular death. While the optimal aspirin dose for s-ICAS has not been determined, patients in the medical arm of the SAMMPRIS trial 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 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.[21, 73] The CLAIR trial showed that patients randomized to clopidogrel plus aspirin had significantly decreased microemboli in the

territory of the stenotic artery when compared with aspirin alone.[21] When combined with the CARESS trial, which was 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.[73] In addition, patients with s-ICAS in the CHANCE trial 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%).[33, 37] 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 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 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 TOSS and TOSS-2 trials found cilostazol plus aspirin was not better for stroke prevention than aspirin alone or clopidogrel plus aspirin. However, 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. Subgroup analysis of patients with s-ICAS in CSPS, 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 statements 2, 3, and 4

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

3) 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 and low risk of hemorrhagic transformation (Level B).

4) 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 (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 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.[74] In addition, a lower rate of cerebrovascular events was seen in s-ICAS patients randomized to high-intensity statin therapy compared with other dosages.[26] 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.[75] 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.[74]

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.[76] Analyses from WASID, SAMMPRIS, and the Chinese Intracranial Atherosclerosis registry (CICAS) have demonstrated that among clinically stable patients with s-

ICAS, a mean 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.[38, 70, 77] 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.[25, 78] Some subgroups of s-ICAS patients may be at higher risk of stroke with lower BPs, including those with hemodynamic impairment [40, 79] or those with a large reduction in BP from baseline.

Recommendation statements 5 and 6

5) 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).

6) 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 (Level B).

Physical Activity

Rationale for recommendation 7

In the general population, moderate physical activity reduces incidence of stroke.[80] 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 (OR 6.7, 95% CI 2.5–18.1).[39]

Recommendation statement 7

7) 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 (Level B).

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 s-ICAS.[81]

Recommendation statement 8

8) 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 (Level A).

Bilateral Arm Ischemic Preconditioning

Rationale for recommendation 9

Based on 2 RCTs done in patients with s-ICAS, 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. 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 methodologic issues limit confidence in conclusions about efficacy and there are no data in a multiethnic population.

Recommendation statement 9

9) The writing group could not achieve consensus on a recommendation for BAIPC in patients with s-ICAS.

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 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 neurologic symptoms, have reported conflicting rates of periprocedural complications.[82, 83] 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.[84, 85] 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.[7, 86]

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 endovascular therapy.[87] 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.[88] Balloon angioplasty alone may be performed with a submaximal staged approach, which may have a lower rate of morbidity and mortality.[89]

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 the purpose of stroke prevention in any subpopulation of patients with s-ICAS is investigational.[87, 88, 89]

Recommendation statements 10–13

10) Clinicians should NOT recommend PTAS as the *initial* treatment for stroke prevention in patients with severe (70%–99%) s-ICAS (Level B).

11) Clinicians should NOT recommend PTAS for stroke prevention in patients with moderate (50%–69%) s-ICAS (Level B).

12) Clinicians should NOT routinely recommend angioplasty alone for stroke prevention in patients with s-ICAS outside clinical trials (Level B).

13) 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 s-ICAS are informed by 1 RCT. The 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 COSS trial, which studied patients with symptomatic ICA occlusion, found that direct bypass increases the risk of stroke and death predominantly due to early periprocedural complications.[90] 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.[91, 92]

Indirect bypass

In patients with anterior circulation s-ICAS, indirect bypass with encephaloduroarteriosynangiosis (EDAS) is an emerging investigational surgery for stroke prevention.[93, 94, 95, 96, 97] A small initial study of indirect revascularization without standardized medical management showed a high rate of recurrent stroke in patients with s-ICAS.[94] Four non-randomized studies, including 2 small case series, [93, 96] 1 single-center prospective study,[97] and 1 two-center prospective trial with independent outcomes assessment,[98] 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 statements 14 and 15

14) Clinicians should NOT recommend direct bypass for stroke prevention in patients with s-ICAS (Level B).

15) Clinicians must NOT routinely recommend indirect surgical revascularization for stroke prevention in patients with s-ICAS 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 s-ICAS. The most promising candidates for these studies are combinations of antithrombotic therapy that have been shown to reduce the risk of stroke in patients with: 1) large artery cerebrovascular disease (ticagrelor plus aspirin),[99] 2) coronary or peripheral vascular disease (low dose factor Xa inhibitor plus aspirin),[100] and 3) stroke (cilostazol plus aspirin or clopidogrel).[18] Additionally, 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 s-ICAS. Since 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,[101] trials that include clopidogrel should determine the impact of CYP2C19 LOF allele carrier status on clinical outcomes.

Randomized therapeutic trials of patients with s-ICAS should incorporate intensive risk-factor management in all arms of these trials, 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,[102] the use of a PCKS9 inhibitor in subjects with raised LDL despite a maximum tolerated dose of a statin,[74] and icosapent ethyl for patients with elevated triglycerides.[103]

Endovascular and Surgical Research

Phase I and II trials are needed to develop safe and durable endovascular treatments (e.g., sub-maximal balloon angioplasty alone,[87] or new intracranial stents) that could subsequently be compared with optimal medical management in high-risk patients with s-ICAS. Randomized controlled clinical trials (Phase III) are needed to compare surgical treatments (e.g., EDAS)[96] with optimal medical management in high-risk patients with s-ICAS.

Other Areas of Future Research

Adequately-powered studies are needed to validate clinical,[49] genetic (e.g., ring finger protein 213 variant[104]), and imaging biomarkers[43, 58, 105, 106] that identify high-risk subjects with s-ICAS for enrollment in future therapeutic trials. Other promising novel therapeutic approaches that should be considered for evaluation in randomized trials of patients with s-ICAS are ischemic preconditioning,[107] continuous positive airway pressure in subjects with sleep apnea, and anti-inflammatory agents such as colchicine or canakinumab.[108, 109]

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CONFLICT OF INTEREST

The American Academy of Neurology is committed to producing independent, critical, and truthful clinical practice guidelines (CPGs). Significant efforts are made to minimize the potential for conflicts of interest to influence the recommendations of this CPG. To the extent possible, the AAN keeps separate those who have a financial stake in the success or failure of the products appraised in the CPGs and the developers of the guidelines. Conflict of interest forms were obtained from all authors and reviewed by an oversight committee prior to project initiation. AAN limits the participation of authors with substantial conflicts of interest. The AAN forbids commercial participation in, or funding of, guideline projects. Drafts of the guideline have been reviewed by at least three AAN committees, a network of neurologists, *Neurology* peer reviewers, and representatives from related fields. The AAN Guideline Author Conflict of

Interest Policy can be viewed at www.aan.com. For complete information on this process, access the 2011 AAN process manual.[8]

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APPENDICES

Appendix 1. AAN Guidelines Subcommittee mission

The mission of the Guidelines Subcommittee is to develop, disseminate, and implement evidence-based systematic reviews and clinical practice guidelines related to the causation, diagnosis, treatment, and prognosis of neurologic disorders.

The Guidelines Subcommittee is committed to using the most rigorous methods available within its budget, in collaboration with other available AAN resources, to most efficiently accomplish this mission.

Appendix 2. AAN Guidelines Subcommittee members 2021-2023

Alexander Rae-Grant, MD (Chair), John J. Halperin, MD (Vice-Chair), Matthew Bradford Bevers, MD, Lori L. Billinghurst, MD, Kelsey Cacic, MD, James Dorman, MD, Wendy S. Edlund, MD, Brittany Jade Farro, MSPAS, PA-C, Gary S. Gronseth, MD, FAAN, Le Hua, MD, Koto Ishida, MD, Mark Douglas Johnson, MD, Charles Kassardjian, MD, Mark Robert Keezer, MD, PhD, K.H. Vincent Lau, MD, Mia T. Minen, MD, Alison M. Pack, MD, Sonja Potrebic, MD, PhD, James J. Reese, Jr., MD, MPH, Vishwanath Sagi, MD, Navdeep Sangha, MD, Nicolaos Scarmeas, MD, Niranjan N. Singh, MD, Sarah Tanveer, Benjamin D. Tolchin, MD, Shawniqua T. Williams Roberson, MD, Shuhan Zhu, MD

Appendix 3. Complete search strategy

Search Disclaimer:

Results of database searches are subject to limitations of the database(s) searched. It is the responsibility of the requestor to determine the accuracy, validity, and interpretation of the search results. While the staff of HealthSearch makes every effort to ensure that the information gathered is accurate and up-to-date, HealthSearch disclaims any warranties of any kind, expressed, implied, or statutory regarding the accuracy or completeness of the information or its fitness for a particular purpose. HealthSearch provides information from public sources both in electronic and print formats and does not guarantee its accuracy, completeness, or reliability.

The information provided is only for the use of the Client and no liability is accepted by HealthSearch to third parties.

PRISMA Initial Results: total number of results before duplicates removed

Database [Platform] Searches run Nov 24, 2020. *Results limited to Feb 2016 to current, where possible.*	**Results**
MEDLINE(R) ALL 1946 to November 23, 2020 [Ovid]	1,025
Cochrane Central Register of Controlled Trials 2014 to Present [Ovid]	137
Cochrane Database of Systematic Reviews 2005 to Present [Ovid]	56
TOTAL	**1,218**

PRISMA Initial Results: Duplicates removed

Database [Platform] Searches run Nov 24, 2020. *Results limited to Feb 2016 to current, where possible.*	**Results**
MEDLINE(R) ALL 1946 to November 23, 2020 [Ovid]	1,024
Cochrane Central Register of Controlled Trials 2014 to Present [Ovid]	65
Cochrane Database of Systematic Reviews 2005 to Present [Ovid]	55
TOTAL	**1,144**

MEDLINE(R) ALL 1946 to November 23, 2020

Search Strategy:

#	Searches	Results

1	clinical trial.mp. or clinical trial.pt. or random*.mp. or tu.xs.	5858535
2	exp Intracranial Arteriosclerosis/	11056
3	intracranial.mp.	169687
4	arteriosclerosis.mp.	71177
5	3 and 4	6810
6	intracranial arteriosclerosis.mp.	6148
7	intracranial.mp.	169687
8	atherosclerosis.mp.	129427
9	7 and 8	3151
10	intracranial atherosclerosis.mp.	669
11	intracranial.mp.	169687
12	intracranially.mp.	1857
13	Constriction, Pathologic/	30774
14	constriction.mp.	60618
15	pathologic.mp.	224610
16	pathologic constriction.mp.	6
17	stenosis.mp.	199370
18	(11 or 12) and (13 or 14) and (15 or 16 or 17)	1266
19	exp Intracranial Arterial Diseases/	63932

20	intracranial.mp.	169687
21	arterial.mp.	415754
22	diseases.mp.	3126051
23	20 and 21 and 22	4158
24	intracranial arterial diseases.mp.	371
25	intracranial.mp.	169687
26	arterial.mp.	415754
27	disease.mp.	4472102
28	25 and 26 and 27	3959
29	intracranial arterial disease.mp.	33
30	2 or 5 or 6 or 9 or 10 or 18 or 19 or 23 or 24 or 28 or 29	69158
31	1 and 30 [Base set]	16218
32	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	41198
33	"hydroxymethylglutaryl coa".mp.	34420
34	reductase.mp.	132350
35	inhibitors.mp.	1221340
36	33 and 34 and 35	30851
37	hydroxymethylglutaryl-coa reductase inhibitors.mp.	30505
38	statins.mp.	29275

39	32 or 36 or 37 or 38	52695
40	31 and 39 [Statins]	209
41	extracranial.mp.	14399
42	intracranial.mp.	169687
43	bypass.mp.	157985
44	41 and 42 and 43	1155
45	31 and 44 [EC-IC Bypass]	160
46	exp Platelet Aggregation Inhibitors/	124859
47	platelet.mp.	244799
48	aggregation.mp.	183733
49	inhibitors.mp.	1221340
50	47 and 48 and 49	43026
51	platelet aggregation inhibitors.mp.	37278
52	antiplatelet.mp.	27928
53	agents.mp.	2527726
54	52 and 53	9706
55	antiplatelet agents.mp.	4973
56	exp Aspirin/	45276
57	aspirin.mp.	68026

58	Clopidogrel/	9092
59	clopidogrel.mp.	14737
60	46 or 50 or 51 or 54 or 55 or 56 or 57 or 58 or 59	153991
61	31 and 60 [Antiplatelets]	1237
62	exp Stents/	78870
63	stents.mp.	89509
64	stent.mp.	75669
65	62 or 63 or 64	110495
66	31 and 65 [Stents]	1445
67	exp Anticoagulants/	223325
68	anticoagulants.mp.	88964
69	exp Warfarin/	19692
70	warfarin.mp.	30787
71	67 or 68 or 69 or 70	239078
72	31 and 71 [Anticoagulation]	996
73	40 or 45 or 61 or 66 or 72	3275
74	limit 73 to ed=20160201-20201124	1018
75	(("2016*" or "2017*" or "2018*" or "2019*" or "2020*") not "201601*").dt.	6140206
76	73 and 75	826

77	74 or 76 [All Topics Update]	1025

Cochrane Central Register of Controlled Trials 2014 to Present

Search Strategy:

#	Searches	Results
1	exp Intracranial Arteriosclerosis/	444
2	intracranial.mp.	7816
3	arteriosclerosis.mp.	1986
4	2 and 3	201
5	intracranial arteriosclerosis.mp.	178
6	intracranial.mp.	7816
7	atherosclerosis.mp.	10196
8	6 and 7	241
9	intracranial atherosclerosis.mp.	90
10	intracranial.mp.	7816
11	intracranially.mp.	20
12	Constriction, Pathologic/	792
13	constriction.mp.	1959
14	pathologic.mp.	6627
15	pathologic constriction.mp.	1

16	stenosis.mp.	13183
17	(10 or 11) and (12 or 13) and (14 or 15 or 16)	59
18	exp Intracranial Arterial Diseases/	1157
19	intracranial.mp.	7816
20	arterial.mp.	48670
21	diseases.mp.	107826
22	19 and 20 and 21	135
23	intracranial arterial diseases.mp.	14
24	intracranial.mp.	7816
25	arterial.mp.	48670
26	disease.mp.	392019
27	24 and 25 and 26	290
28	intracranial arterial disease.mp.	2
29	1 or 4 or 5 or 8 or 9 or 17 or 18 or 22 or 23 or 27 or 28 [Base set]	1644
30	exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/	5348
31	"hydroxymethylglutaryl coa".mp.	3555
32	reductase.mp.	8248
33	inhibitors.mp.	51036
34	31 and 32 and 33	3514

35	hydroxymethylglutaryl-coa reductase inhibitors.mp.	3502
36	statins.mp.	5858
37	30 or 34 or 35 or 36	9420
38	29 and 37 [Statins]	32
39	extracranial.mp.	862
40	intracranial.mp.	7816
41	bypass.mp.	21396
42	39 and 40 and 41	78
43	29 and 42 [EC-IC Bypass]	22
44	exp Platelet Aggregation Inhibitors/	11035
45	platelet.mp.	25567
46	aggregation.mp.	8227
47	inhibitors.mp.	51036
48	45 and 46 and 47	4240
49	platelet aggregation inhibitors.mp.	3931
50	antiplatelet.mp.	6168
51	agents.mp.	157165
52	50 and 51	1245
53	antiplatelet agents.mp.	684

54	exp Aspirin/	5868
55	aspirin.mp.	14311
56	Clopidogrel/	2029
57	clopidogrel.mp.	5976
58	44 or 48 or 49 or 52 or 53 or 54 or 55 or 56 or 57	21952
59	29 and 58 [Antiplatelets]	183
60	exp Stents/	4182
61	stents.mp.	8251
62	stent.mp.	13844
63	60 or 61 or 62	15361
64	29 and 63 [Stents]	145
65	exp Anticoagulants/	10661
66	anticoagulants.mp.	6426
67	exp Warfarin/	1686
68	warfarin.mp.	5270
69	65 or 66 or 67 or 68	15726
70	29 and 69 [Anticoagulation]	85
71	38 or 43 or 59 or 64 or 70	374
72	limit 71 to yr="2016 -Current"	137

Cochrane Database of Systematic Reviews 2005 to Present

Search Strategy:

#	Searches	Results
1	intracranial.mp.	663
2	arteriosclerosis.mp.	81
3	1 and 2	16
4	intracranial arteriosclerosis.mp.	5
5	intracranial.mp.	663
6	atherosclerosis.mp.	262
7	5 and 6	41
8	intracranial atherosclerosis.mp.	2
9	intracranial.mp.	663
10	intracranially.mp.	2
11	constriction.mp.	129
12	pathologic.mp.	232
13	pathologic constriction.mp.	2
14	stenosis.mp.	374
15	(9 or 10) and 11 and (12 or 13 or 14)	9
16	intracranial.mp.	663
17	arterial.mp.	1322

18	diseases.mp.	4628
19	16 and 17 and 18	220
20	intracranial arterial diseases.mp.	150
21	("cerebral arterial diseases" or cadasil or "cerebral amyloid angiopathy" or "anterior cerebral artery infarction" or "middle cerebral artery infarction" or "posterior cerebral artery infarction" or "moyamoya disease" or "intracranial aneurysm").mp.	143
22	intracranial.mp.	663
23	arterial.mp.	1322
24	disease.mp.	8035
25	22 and 23 and 24	293
26	intracranial arterial disease.mp.	2
27	3 or 4 or 7 or 8 or 15 or 19 or 20 or 21 or 25 or 26 [Base Set]	335
28	"hydroxymethylglutaryl coa".mp.	41
29	(atorvastatin or lovastatin or meglutol or pravastatin or rosuvastatin calcium or simvastatin).mp.	98
30	reductase.mp.	154
31	inhibitors.mp.	1699
32	(28 or 29) and 30 and 31	49
33	statins.mp.	190
34	32 or 33	192

35	27 and 34 [Statins]	14
36	extracranial.mp.	89
37	intracranial.mp.	663
38	bypass.mp.	462
39	36 and 37 and 38	14
40	27 and 39 [EC-IC Bypass]	13
41	platelet.mp.	646
42	aggregation.mp.	381
43	inhibitors.mp.	1699
44	41 and 42 and 43	125
45	platelet aggregation inhibitors.mp.	63
46	(abciximab or alprostadil or aspirin or cilostazol or dipyridamole or disintegrins or epoprostenol or eptifibatide or iloprost or ketanserin or milrinone or pentoxifylline or "prasugrel hydrochloride" or resveratrol or "s-nitrosoglutathione" or "s-nitrosothiols" or sevoflurane or ticagrelor or ticlopidine or tirofiban or trapidil).mp.	732
47	antiplatelet.mp.	273
48	agents.mp.	4822
49	47 and 48	217
50	antiplatelet agents.mp.	117
51	aspirin.mp.	546

52	clopidogrel.mp.	88
53	44 or 45 or 46 or 49 or 50 or 51 or 52	824
54	27 and 53 [Antiplatelets]	114
55	stents.mp.	145
56	stent.mp.	210
57	55 or 56	240
58	27 and 57 [Stents]	27
59	anticoagulants.mp.	276
60	("4-hydroxycoumarins" or abciximab or acenocoumarol or ancrod or becaplermin or "blood coagulation factor inhibitors" or citric acid or dalteparin or "dermatan sulfate" or dextrans or dicumarol or "edetic acid" or enoxaparin or ethyl biscoumacetate or "fibrin fibrinogen degradation products" or gabexate or heparin or heparinoids or nadroparin or "pentosan sulfuric polyester" or phenindione or phenprocoumon or "protein c" or "protein s" or "sodium citrate" or tinzaparin or "beta 2-glycoprotein I").mp.	437
61	warfarin.mp.	192
62	59 or 60 or 61	571
63	27 and 62 [Anticoagulation]	104
64	35 or 40 or 54 or 58 or 63 [All topics update]	159
65	limit 64 to last 4 years	56

Web of Science search

#	Search	# of Results
1.	TS=clinical trial OR TS=random*	2,328,188
2.	TS=Intracranial arteriosclerosis	166
3.	TS=vascular dementia	16,742
4.	TS=Intracranial atherosclerosis	2,397
5.	TS=intracranial arterial disease*	2,622
6.	TS=cerebral arterial disease*	7,760
7.	TS=cadasil	1,849
8.	TS=cerebral amyloid angiopathy	4,634
9.	TS=familial cerebral amyloid angiopathy	316
10.	TS=anterior cerebral artery infarction	1620
11.	TS=middle cerebral artery infarction	7,621
12.	TS=posterior cerebral artery infarction	1,418
13.	TS=moyamoya disease	4,464
14.	TS=Intracranial* AND TS=constriction AND TS=(pathologic OR stenosis)	16
15.	2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14	44,456
16.	**1 and 15 [Base set]**	4,748
17.	TS=Hydroxymethylglutaryl-CoA Reductase Inhibitors	660
18.	TS=atorvastatin	16,569
19.	TS=lovastatin	6,714
20.	TS=meglutol	3
21.	TS=pravastatin	9,066
22.	TS=rosuvastatin calcium	312
23.	TS=simvastatin	16,851
24.	TS=statins	312
25.	17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24	59,134
26.	**16 AND 25 [Statins]**	139

27.	TS=extracranial	13,023
28.	TS=intracranial	122,084
29.	TS=bypass	187,426
30.	27 AND 28 AND 29	1,398
31.	**16 AND 30 [EC-IC Bypass]**	71
32.	TS=Platelet Aggregation Inhibitors	9,541
33.	TS=abciximab	3,790
34.	TS=alprostadil	932
35.	TS=aspirin	64,957
36.	TS=cilostazol	2,414
37.	TS=clopidogrel	20,256
38.	TS=dipyridamole	8,804
39.	TS=disintegrins	710
40.	TS=epoprostenol	2,298
41.	TS=eptifibatide	1,349
42.	TS=iloprost	3,626
43.	TS=ketanserin	4,118
44.	TS=milrinone	2,784
45.	TS=pentoxifylline	6,053
46.	TS=prasugrel hydrochloride	50
47.	TS=resveratrol	22,234
48.	TS=s-nitrosoglutathione	2,163
49.	TS=s-nitrosothiols	2,118
50.	TS=sevoflurane	11,936
51.	TS=ticagrelor	3,944
52.	TS=ticlopidin	55
53.	TS=tirofiban	1,778
54.	TS=trapidil	323
55.	TS=antiplatelet agents	8,935

56.	32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55	157,543
57.	**16 OR 56 [Antiplatelets]**	336
58.	TS=Stent*	137,547
59.	**16 AND 58 [Stents]**	340
60.	TS=anticoagulants	69,463
61.	TS=4-hydroxycoumarins	449
62.	TS=abciximab	3,790
63.	TS=acenocoumarol	1,104
64.	TS=ancrod	426
65.	TS=becaplermin	216
66.	TS=blood coagulation factor inhibitors	5,783
67.	TS=citric acid	34,869
68.	TS=dalteparin	1,527
69.	TS=dermatan sulfate	4,314
70.	TS=dextrans	41,453
71.	TS=dicumarol	826
72.	TS=edetic acid	110
73.	TS=enoxaparin	7,618
74.	TS=ethyl biscoumacetate	24
75.	TS=fibrin fibrinogen degradation products	1,401
76.	TS=gabexate	604
77.	TS=heparin	93,292
78.	TS=heparinoids	385
79.	TS=nadroparin	491
80.	TS=pentosan sulfuric polyester	14
81.	TS=phenindione	140
82.	TS=phenprocoumon	1,030
83.	TS=”protein C”	30,470

84.	TS=”protein S”	18,235
85.	TS=sodium citrate	8,357
86.	TS=tinzaparin	607
87.	TS=warfarin	35,385
88.	TS=beta 2-glycoprotein	3,997
89.	TS=antithrombin*	17,796
90.	TS=dabigatran	8,299
91.	TS=hirudins	4,103
92.	TS=factor xa inhibitors	7,107
93.	TS=warfarin	35,385
94.	60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93	315,977
95.	**16 AND 94 [Anticoagulation]**	272
96.	**26 OR 31 OR 57 OR 59 OR 95 [all topics update]**	927
97.	**Limit to 1/1/16-present**	323

Appendix 4. Evidence synthesis tables

Therapeutics

Table 1. Anticoagulation vs Antiplatelet

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Chimowitz 2005	I	PRCT (WASID)	Warfarin vs aspirin	**Stroke or Vascular Death**
				RD -0.3% (-7.2% to 6.5%)
				Major Hemorrhage
				RD 5.1% (1.2% to 9.1%)

				All Causes of Death
				RD 5.4% (1.2% to 9.8%)
Conclusions: 1. For patients with s-ICAS, 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, 1 Class I trial, confidence in evidence downgraded due to imprecision) 2. For patients with s-ICAS, 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%). (Moderate confidence, 1 Class I study)				
Wang 2007	I	PRCT (FISS-tris)	Nadroparin calcium vs aspirin	**Early Deterioration (day 9) or Recurrent Stroke by 6 months**
				RD 0.2% (-6.3% to 6.5%)
				Hemorrhagic Complications
				RD 3.5% (-3.3% to 10.3%)
				Mortality by 6 Months
				RD 0.4% (-4.5% to 5.2%)
Conclusions: 1. For patients with s-ICAS there is insufficient evidence to support or refute the effectiveness of short-term nadroparin calcium (LMWH), as compared with aspirin, for reducing the composite of early neurological 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, 1 Class I study, confidence in evidence downgraded due to imprecision and indirectness)				

2. For patients with s-ICAS 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, 1 Class I study, confidence in evidence downgraded due to imprecision and indirectness)

Table 2. Dual Antiplatelet Therapy

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Toyoda 2019	I	PRCT (CSPS Subgroup)	Cilostazol (+ aspirin or clopidogrel) vs aspirin or clopidogrel monotherapy	**Recurrent Ischemic Stroke/Death**
				RD -5.2% (-9.6% to -1%)
Kwon 2005	II	PRCT (TOSS)	Cilostazol + aspirin versus aspirin monotherapy	RD 0.3% (-8.1% to 9.8%)
				Pooled RD -3% (-8% to 3%); I^2=57%)
Conclusion: For patients with s-ICAS, 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, 1 Class I study and 1 Class II study downgraded for insufficient precision)				
Toyoda 2019	I	PRCT (CSPS Subgroup)	Cilostazol (+ aspirin or clopidogrel) vs aspirin or clopidogrel monotherapy	**Severe or Life-Threatening Bleeding**
				RD 0.5% (-1.6% to 0.5%)

Kwon 2005	II	PRCT (TOSS)	Cilostazol + aspirin versus aspirin monotherapy	RD 0% (-6.9% to 7.9%)
				Pooled RD 0% (-1% to 0%; I^2=0%)
Conclusion: 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, 1 Class I study and 1 Class II study)				
Uchiyama-2015	IV	PRCT (CATHARSIS)	Cilostazol + aspirin versus aspirin monotherapy	**Clinical or Radiographic Strokes**
				RD -7.9% (-18.7% to 2.8%)
				Serious Hemorrhagic Complications
				RD 1.1% (-6.3% to 8.4%)

Table 3. DAPT with Cilostazol vs DAPT with Clopidogrel

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Kwon-2011	I	PRCT (TOSS-2)	Cilostazol + aspirin versus aspirin + clopidogrel	**Recurrent Stroke or Vascular Death**

				RD 1.7% (-2.4% to 5.7%)
				Major Hemorrhagic Complications
				RD -1.8% (-4.9% to 0.8%)
Conclusion: For patients with s-ICAS, there is insufficient evidence to support or refute the effectiveness of DAPT with cilostazol plus aspirin, as compared with clopidogrel plus aspirin alone, in reducing recurrent stroke or death (RD 1.7%, 95% CI -2.4% to 5.7%). (Very low confidence, 1 Class 1 study, confidence in evidence downgraded due to imprecision) DAPT with cilostazol plus aspirin is likely not associated with any difference in hemorrhagic complications compared with clopidogrel plus aspirin alone (RD -1.8%, 95% CI -4.9% to 0.8%). (Moderate confidence, 1 Class 1 study)				

Table 4. DAPT with Clopidogrel vs Aspirin Monotherapy

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Liu 2015	I	PRCT (Subgroup of CHANCE)	Clopidogrel + aspirin versus aspirin monotherapy	**Recurrent Stroke**
				RD -2.3% (-8.3% to 3.7%)
Wong-2010	II	PRCT (CLAIR)	Clopidogrel + aspirin versus aspirin monotherapy	RD -3.8% (-13% to 4.4%)
				Pooled RD -3% (-7% to 1%); I^2=0%)
Conclusion: For patients with s-ICAS, 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, 1 Class I study and 1 Class II study, confidence downgraded due to imprecision and indirectness)				
Liu-2015	I	PRCT (Subgroup of CHANCE)	Clopidogrel + aspirin versus aspirin monotherapy	**Bleeding Complications**
				RD -0.4% (-2.2% to 1.3%)
Wong-2010	II	PRCT (CLAIR)	Clopidogrel + aspirin versus aspirin monotherapy	RD 0% (-6.8% to 7.7%)
				Pooled RD -1% (-2 to 1%; I^2=7%)
Conclusion (confidence): For patients with s-ICAS, it is possible that short term DAPT 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, 1 Class I study, 1 Class II study, evidence downgraded due to indirectness)				

Table 5. DAPT with Ticagrelor vs Aspirin Monotherapy

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Amarenco-2020	I	PRCT (subgroup THALES)	Ticagrelor + aspirin versus aspirin monotherapy	Recurrent Stroke/Death
				RD -5% (-8.1% to -0.96%)
				Severe Bleeding

				RD 0.1% (-0.4 to 0.7%)

Table 6. Blood Pressure Control

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Park-2018	IV	PRCT (Multicenter)	Intensive versus modest BP control	Recurrent Stroke/Death
				RD 0% (-8.5% to 7.2%)
Conclusion: For patients with s-ICAS, there is insufficient evidence to support or refute the effectiveness of intensive versus modest blood pressure control in reducing the risk of recurrent stroke or death (RD 0%, 95% CI -8.5% to 7.2%). (Very low confidence, 1 Class IV study with insufficient precision)				

Table 7. Statin/Lipid Therapy

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Zhou-2018	IV	Single Center PRCT	Intensive versus standard/low dose Atorvastatin (cerebral infarction)	**"Cerebral Infarction or Events"**
				RD -5.3% (-14% to 6.6%)
Zhou-2014	IV	Single Center PRCT	Intensive versus standard/low dose Atorvastatin (cerebrovascular events)	RD 20.9% (4.2%–37.1%)

Table 8. Ischemic Preconditioning

Study	Class	Cohort	Intervention	RD (95% CI)
Meng-2012	II	PRCT, 2 Center Trial	Bilateral arm ischemic preconditioning	**Recurrent Stroke**
				RD -18.8% (-37.3% to - 0.8%)
Meng-2015	II	Single Center PRCT	Bilateral arm ischemic preconditioning (in age 80–95)	RD -11.2% (-29.6% to 6.5%)
				Pooled RD -15% (-27% to -2%; I^2=0%)
Conclusion (confidence): In patients with s-ICAS, BAIPC is likely effective in reducing the risk of recurrent stroke (RD -15%, 95% CI -27% to -2%; I^2 = 0%). (Moderate confidence, 2 Class II studies)				

Table 9. EC/IC Bypass (vs Medical Therapy Alone)

Study	Class	Cohort	Intervention	RD (95% CI)
EC/IC Bypass Study-1985	I	PRCT	EC/IC bypass for MCA stenosis group	**Fatal or Non-fatal Stroke**
				RD 20.3% (2.5%–36.7%)
Conclusion: For patients with symptomatic severe 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, 1 Class I study, confidence in evidence upgraded due to magnitude of effect)				
EC/IC Bypass Study-1985	I	PRCT	EC/IC bypass (MCA stenosis + occlusion)	RD 6% (-4.5% to 16.5%)

Table 10. PTAS vs Aggressive Medical Management

Study	**Class**	**Cohort**	**Intervention**	**RD (95% CI)**
Derdeyn-2014	I	PRCT (SAMMPRIS)	PTAS vs AMM	**30 Day Stroke and Death**
				RD -0.3% (-7.2% to 6.5%)
Zaidat-2015	I	PRCT (VISSIT)	PTAS vs AMM	RD 20% (6.6%–33.3%)
				Pooled RD 13% (3%–24%; I^2=59%)
Conclusion: For patients with recent TIA or non-disabling stroke attributed to s-ICAS, it is highly likely that PTAS plus medical management, compared with medical management alone, increases the early risk of recurrent stroke and death (RD 13%, 95% CI 3%–24%; I^2 = 59%). (High confidence, 2 Class I studies with large magnitude of effect)				
Compter-2016	I	PRCT (VAST Subgroup)	PTAS vs AMM	**30 Day Stroke and Death**
				RD 22.2% (-9.8% to 54.7%)
				Pooled RD (all 3 studies) RD 13% (5%–22%; I^2=34%)
Adding data from the VAST trial (which was downgraded due to indirectness) did not significantly change the summary estimate of 30-day stroke or death (RD 13%, 95% CI 5%–22%; I^2 = 34%).				
				Beyond 30 days

Derdeyn-2014	I	PRCT (SAMMPRIS)	PTAS vs AMM	RD 0% (-6% to 6%)
Zaidat-2015	I	PRCT (VISSIT)	PTAS vs AMM	RD 22.5% (7.2.%–38.1%)
				Pooled RD 10% (-12% to 32%; I^2=86%)
Miao-2012	II	Single center PRCT	PTAS vs AMM	**Long Term risk of study primary outcome**
				RD -0.2% (-12.4% to 11.5%)
Markus-2017	II	PRCT (VIST Subgroup)	PTAS vs AMM	RD -16.8% (-44.2% to 11.4%)
Nassef-2020	IV	PRCT	PTAS vs AMM	RD -48% (-66.5% to -21%)

Risk Factor Control

Table 11. Total Cholesterol/HDL Ratio

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Chaturvedi 2007	I	Prospective cohort (WASID)	Out of target (total cholesterol / HDL ratio >4.4)	Recurrent stroke	HR 1.9 (1.2–2.9)
Conclusion: For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for TC/HDL-C ratio (HR 1.9, 95% CI 1.2–2.9). (Moderate confidence, 1 Class I study)					

Table 12. LDL-C

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Chaturvedi-2007	I	Prospective cohort (WASID)	Out of target LDL-C (<100)	Any recurrent ischemic stroke	OR 1. 3 (0.8–2.1)
Turan-2017	I	Prospective cohort (Medical arm of SAMMPRIS)	Out of target LDL-C (<70)	Any recurrent ischemic stroke by 3 years	OR 1.7 (0.8–3.5)
					POR 1.3 (0.8–2.1) (I^2=0%)
Conclusion (confidence): For patients with s-ICAS it is *possible* that failure to achieve risk factor control (being out of target) for LDL-C (POR 1.3, 95% CI 0.8–2.1; I^2 = 0%) and non-HDL-C (POR 1.4, 95% CI 0.8–2.5; I^2 = 0%), does not predict an increased risk of recurrent stroke. (Low confidence, 2 Class I studies, confidence downgraded for imprecision)					

Table 13. Total Cholesterol

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**

Chaturvedi-2007	I	Prospective cohort (WASID)	Out of target total cholesterol ≥200	Any recurrent ischemic stroke	HR 2.1 (1.4–3.1)
Conclusion: For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for TC (HR 2.1, 95% CI 1.4–3.1) predicts an increased risk of recurrent stroke. (Moderate confidence, 1 Class I study)					

Table 14. Non-HDL-C

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Turan-2017	I	Prospective cohort (Medical arm of SAMMPRIS)	Out of target non-HDL-C (>100)	Any recurrent stroke by 3 years	OR 1.4 (0.7–2.9)
Chaturvedi-2007	I	Prospective cohort (WASID)	Out of target non-HDL-C (>130)	Any recurrent ischemic stroke	OR 1.4 (0.9–6.3)
					POR 1.4 (0.8–2.5) (I^2=0%)
Conclusion (confidence): For patients with s-ICAS it is *possible* that failure to achieve risk factor control (being out of target) for non-HDL-C (POR 1.4, 95% CI 0.8–2.5; I^2 = 0%), does not predict an increased risk					

of recurrent stroke. (Low confidence, 2 Class I studies, confidence downgraded for imprecision)

Table 15. MAP

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Chaturvedi-2007	I	Prospective cohort (WASID)	Out of target MAP ≥106	Any recurrent ischemic stroke	HR 2.8 (1.7–3.0)
Conclusion (confidence): For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for MAP (HR 2.8, 95% CI 1.7–3.0) predicts an increased risk of recurrent stroke. (Moderate confidence, 1 Class I study supporting each risk factor)					

Table 16. DBP

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Turan-2007	I	Prospective cohort (WASID)	Out of target (DBP ≥90)	Recurrent ischemic stroke	OR 2.2 (1.1–4.6)
Conclusion (confidence): For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for DBP (OR 2.2, 95% CI 1.1–4.6) predicts an increased risk of recurrent stroke. (Moderate confidence, 1 Class I study)					

Turan-2007	I	Prospective cohort (WASID)	Out of target (DBP ≥90)	Recurrent ischemic stroke in territory	OR 2.5 (1.1–5.4)

Table 17. SBP

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Turan-2017	I	Prospective Cohort (Medical arm of SAMMPRIS)	Out of target (≥140 or 130 (for DM)	Any recurrent ischemic stroke by 3 years	OR 1.6 (0.8–3.2)
Turan-2007	I	Prospective cohort (WASID)	Out of target (≥140)	Any recurrent ischemic stroke	OR 1.7 (1.08–2.5)
					POR 1.7 (1.2–2.4) (I^2=0%)
Conclusion: For patients with s-ICAS it is *highly likely* that failure to achieve risk factor control of SBP (POR 1.7, 95% CI 1.2–2.4; I^2 = 0%) predicts an increased risk of recurrent stroke. (High confidence, 2 Class I studies)					
Chaturvedi-2007	I	Prospective cohort (WASID)	Out of target (≥140)	Any recurrent ischemic stroke	HR 1.6 (1.1–2.4)

Turan-2007	I	Prospective cohort (WASID)	SBP ≥160 (vs less)	Recurrent ischemic stroke in territory	OR 4.1 (2.2–7.7)
Turan-2007	I	Prospective cohort (WASID)	SBP ≥160 (vs less)	Any recurrent Ischemic stroke	OR 3.8 (2.1–7.0)

Table. 18. SBP or DBP

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS) with only low distal flow	In target (SBP < 140 and DBP < 90) + low distal blood flow	Recurrent fatal/non-fatal VB ischemic stroke	OR 6.2 (1.5–27)
Conclusion: For patients with s-ICAS and co-existing low distal flow status on quantitative magnetic resonance angiography (QMRA), it is *possible* that strict blood pressure control (i.e., "in target" for SBP <140 and DBP <90 mm Hg) may increase the risk of recurrent stroke or death (OR 6.2, 95% CI 1.5–27). (Low confidence, 1 Class I, indirect study)					
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	In target (SBP <140 and DBP < 90)	Recurrent fatal/non-fatal VB ischemic stroke	OR 2.2 (0.5–8.6)

Table 19. BMI

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Turan-2017	I	Prospective cohort (Medical arm of SAMMPRIS)	Out of target BMI	Any recurrent stroke by 3 years	OR 0.9 (0.4–2.1)
Conclusion: The evidence is insufficient to support or refute that failure to achieve risk factor control for BMI (OR 0.9, 95% CI 0.4–2.1) predicts an increased risk of recurrent stroke. (Very low confidence, 1 Class I study with confidence downgraded for imprecision)					

Table 20. Alcohol Use

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Chaturvedi-2007	I	Prospective cohort (WASID)	Out of target (no alcohol use)	Any recurrent ischemic stroke	HR 1.8 (1.2–2.6)
Conclusion (confidence): For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for no alcohol use (HR 1.8, 95% CI 1.2–2.6) predicts an increased risk of recurrent stroke. (Moderate confidence, 1 Class I study)					

Table 21. HbA1c

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Turan-2017	I	Prospective cohort (Medical arm of SAMMPRIS)	≥7	Any recurrent stroke by 3 years	OR 2.3 (1.0–5.0)
Conclusion: For patients with s-ICAS it is *likely* that failure to achieve risk factor control (i.e., being out of target) for HbA1c (OR 2.3, 95% CI 1.0–5.0) predicts an increased risk of recurrent stroke. (Moderate confidence, 1 Class I study)					

Table 22. Smoking

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Turan-2017	I	Prospective cohort (Medical arm of SAMMPRIS)	Smoking cessation	Any recurrent stroke by 3 years	OR 0.5 (0.3–1.3)
Conclusion: The evidence is insufficient to support or refute that failure to achieve risk factor control for smoking cessation (OR 0.5, 95% CI 0.3–1.3) predicts an increased risk of recurrent stroke. (Very low confidence, 1 Class I study with confidence downgraded for imprecision)					

Table 23. Physical Activity

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Turan-2017	I	Prospective cohort (Medical arm of SAMMPRIS)	"Out of target"	Any ischemic stroke by year 3	OR 6.7 (2.5–18.1)
Conclusion: For patients with s-ICAS it is *highly likely* that failure to achieve risk factor control for physical activity (OR 6.7, 95% CI 2.5–18.1) predicts an increased risk of recurrent stroke. (High confidence, 1 Class I study, upgraded for magnitude of effect)					

Modifiable Risk Factors

Table 24. Failure of Antithrombotic Therapy

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	On therapy vs off	SAMMPRIS	OR 1.0 (0.5–2.1)
Turan-2009	I	Prospective cohort (WASID)	On therapy vs off	Stroke in territory	OR 1.0 (0.6–1.5)
					POR 1.0 (0.5–1.9) (I^2=0%)

Conclusion: For patients with s-ICAS it is *possible* that the failure of antithrombotic therapy (POR 1.0, 95% CI 0.5–1.9; I^2 = 0%) does not predict an increased risk of recurrent stroke or death. (Low confidence, 2 Class I studies downgraded for imprecision)					
Kasner-2006	I	Prospective cohort (WASID)	On therapy vs off	Recurrent stroke in territory at follow up	OR 0.9 (0.6–1.5)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID (SAMMPRIS Like)	On therapy vs off	SAMMPRIS	HR 0.9 (0.6–1.4)
Kozak-2011	II	Retrospective Cohort	On therapy vs off	Recurrent stroke	OR 0.5 (0.1–2.5)
Turan-2009	I	Prospective cohort (WASID)	On therapy vs off	Any stroke or vascular death	OR 0.9 (0.6–1.4)

Table 25. CAD

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	CAD	Recurrent stroke in territory at follow up	OR 1.0 (0.6–1.8)

Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID (SAMMPRIS Like)	CAD	SAMMPRIS	OR 0.9 (0.6–1.5)
					POR 0.95 (0.6–1.4) (I^2=0%)
Conclusion (confidence): For patients with s-ICAS it is *possible* that history of coronary artery disease does not predict an increased risk of recurrent stroke or death (POR 0.95, 95% CI 0.6–1.4; I^2 = 0%). (Low confidence, 2 Class I studies downgraded for imprecision)					
Kozak-2011	II	Retrospective cohort (single center)	CAD	Recurrent stroke	OR 2.9 (0.3–27.5)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	CAD	Recurrent stroke/death	HR 1.9 (0.9–4.0)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	CAD	Recurrent stroke in territory by 90 days	OR 1.1 (0.4–3.4)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	CAD	Recurrent fatal/non-fatal ischemic stroke	HR 10.5 (1.5–71.3)

Sangha-2017	II	Prospective single center cohort	CAD	Recurrent stroke in territory at 30 days	OR 1.2 (0.4–3.7)
Feng-2019	II	Retrospective 2 center cohort	CAD	Recurrent stroke in territory at one year	OR 1.6 (0.2–11.7)

Table 26. Glucose

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	>200 mg/dl	Recurrent stroke 90 days in territory	OR 2.0 (1.1–3.7)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	>200 mg/dl	SAMMPRIS	OR 2.3 (0.8–6.9)
					POR 2.0 (1.2–3.5) (I^2=0%)
Conclusion: For patients with s-ICAS it is *likely* that baseline glucose levels >200 mg/dL (POR 2.0, 95% CI 1.2–3.5; I^2 = 0%) predict an increased risk of recurrent stroke or death. (Moderate confidence, 2 Class I studies confidence downgraded due to indirectness)					

Table 27. Baseline Hemoglobin A1c

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Sangha-2017	II	Prospective single center cohort	HbA1c >7.9	Recurrent stroke in territory at 30 days	OR 0.8 (0.3–2.3)
Conclusion (confidence): There is insufficient evidence to support or refute baseline HbA1 (OR 0.8, 95% CI 0.3–2.3) predicting an increased risk of recurrent stroke. (Very low confidence, 1 Class II indirect study supporting baseline HbA1c)					
Feng-2019	II	Retrospective 2 center cohort	Mean for recurrent stroke vs no recurrent stroke	Recurrent stroke in territory at one year	RMD 0.5 (-0.2 to 1.2)

Table 28. Diabetes

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Kasner-2006	I	Prospective cohort (WASID)	DM	Recurrent stroke in territory at follow up	OR 1.6 (1.0–2.6)

Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	DM	SAMMPRIS	OR 1.9 (0.90–3.9)
Weber-2010	II	Prospective cohort	DM	Recurrent stroke	OR 1.5 (0.9-3-4.3)
					POR 1.6 (1.2–2.2) (I^2=0%)
Conclusion (confidence): For patients with s-ICAS it is *likely* that a history of diabetes (POR 1.6, 95% CI 1.1–2.2; I^2 = 0%) predicts an increased risk of recurrent stroke or death. (Moderate confidence, 2 Class I studies and 1 Class II study)					
Kozak-2011	II	Retrospective cohort (single center)	DM	Recurrent stroke	OR 0.8 (0.2–3.6)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	DM	Recurrent stroke /Death	HR 3.6 (1.9–7.0)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID [SAMMPRIS Like])	DM	SAMMPRIS	HR 2.0 (1.2–3.2)

Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	DM	Recurrent stroke in territory at 90 days	OR 0.9 (0.3–2.7)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	DM	Recurrent fatal/non-fatal ischemic stroke	HR 9.6 (1.7–55.8)
Sangha-2017	II	Prospective single center cohort	DM	Recurrent stroke in territory at 30 days	OR 0.4 (0.2–1.1)
Feng-2019	II	Retrospective 2 center cohort	DM	Recurrent stroke in territory at one year	OR 1.2 (0.5–3.4)

Table 29. Hypertension

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	HTN	Recurrent stroke in territory at follow up	OR 1.0 (0.5–2.0)
Waters-2016	I	Prospective cohort (Medical arm SAMMPRIS)	HTN	SAMMPRIS	OR 0.6 (0.2–1.7)

					POR 0.9 (0.5–1.5) (I^2=0%)
Conclusion: For patients with s-ICAS it is *possible* that a history of hypertension (POR 0.9, 95% CI 0.5–1.5; I^2 = 0%) does not predict an increased risk of recurrent stroke or death. (Low confidence, 2 Class I studies downgraded for imprecision)					
Kozak-2011	II	Retrospective cohort (single center)	HTN	Recurrent stroke	OR 9.2 (0.7–104.7)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	HTN	Recurrent stroke/death	HR 3.7 (1.5–9.0)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID [SAMMPRIS Like])	HTN	SAMMPRIS	HR 1.0 (0.5–1.9)
Sangha-2017	II	Prospective single center cohort	HTN	Recurrent stroke in territory at 30 days	OR 0.9 (0.3–2.8)
Feng-2019	II	Retrospective 2 center cohort	HTN	Recurrent stroke in territory at one year	OR 4.4 (1.03–18.1)

Table 30. Baseline Systolic Blood Pressure

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	SBP ≥140	Recurrent stroke in territory at 90 days	OR 1.3 (0.5–3.7)
Waters-2016	I	Prospective cohort (Medical arm of SAMMPRIS)	SBP ≥144	SAMMPRIS	OR 0.6 (0.3–1.2)
					POR 1.3 (0.5–3.5) (I^2=0%)
Conclusion: For patients with s-ICAS it is *possible* that baseline SBP (>140–144 mm Hg) does not predict an increased risk of recurrent stroke or death (POR 1.3, 95% CI 0.5–3.5; I^2 = 0%). (Low confidence, 2 Class I studies downgraded for indirectness and imprecision)					
Kozak-2011	II	Retrospective cohort (single center)	SBP ≥140	Recurrent stroke	OR 0.2 (0.03–0.8)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID [SAMMPRIS Like])	Per 10-unit increase	SAMMPRIS	HR 1.0 (0.9–1.1)

Feng-2019	II	Retrospective 2 center cohort	Mean for recurrent stroke vs no recurrent stroke	Recurrent stroke in territory at one year	RMD -1 (-11.8 to 9.8)

Table 31. Baseline Diastolic Blood Pressure

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID (SAMMPRIS Like)	Per 10-unit increase	SAMMPRIS	OR 0.9 (0.8–1.2)
Conclusion: For patients with s-ICAS it is *likely* that the modifiable risk factor of baseline DBP does not predict an increased risk of recurrent stroke or death (OR 0.9, 95% CI 0.7–1.4). (Moderate confidence, 1 Class I study)					
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	>90 mmHg	Recurrent stroke in territory at 90 days	OR 1.3 (0.2–8.6)
Feng-2019	II	Retrospective 2 center cohort	Mean for recurrent stroke vs no recurrent stroke	Recurrent stroke in territory at one year	RMD -4 (-11.5 to 3.5)

Table 32. Dyslipidemia

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Kasner-2006	I	Prospective cohort (WASID)	DLP	Recurrent stroke in territory at follow up	OR 0.9 (0.5–1.5)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	DLP	Recurrent stroke/death	HR 1.7 (0.6–5.1)
Kozak-2011	II	Retrospective cohort (single center)	DLP	Recurrent stroke	OR 2.5 (0.4–13.8)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	DLP	Recurrent fatal/non-fatal ischemic stroke	HR 1.0 (0.2–4.6)
Sangha-2017	II	Prospective single center cohort	DLP	Recurrent stroke in territory at 30 days	OR 3.1 (0.5–19.3)

Feng-2019	II	Retrospective 2 center cohort	DLP	Recurrent stroke in territory at one year	OR 1.3 (0.262) (0.5–3.6)
					POR 1.2 (0.8–1.8) (I^2=0%)
Conclusion (confidence): There is insufficient evidence to support or refute a history of dyslipidemia predicting an increased risk of recurrent stroke (POR 1.2, 95% CI 0.8–1.8; I^2 = 0%), (Very low confidence, 2 Class I and 4 Class II studies, confidence downgraded for imprecision and indirectness)					

Table 33. Total Cholesterol

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kozak-2011	II	Retrospective cohort (single center)	>200 mg/dl	Recurrent stroke	OR 16.5 (2.5–104.6)
Conclusion: There is insufficient evidence to support or refute the following modifiable risk factors in predicting an increased risk of recurrent stroke: baseline TC (OR 16.5, 95% CI 2.5–104.6). (Very low confidence, 1 Class II indirect study, confidence in the evidence downgraded due to indirectness)					

Table 34. Baseline HDL-C

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Ovbiagele-2006	I	Prospective cohort (WASID)	HDL-C <40 male or <50 female	Recurrent ischemic stroke	OR 1.1 (0.7–1.7)
Waters-2016	I	Prospective cohort (Medical arm of SAMMPRIS)	HDL-C <36.3	SAMMPRIS	OR 0.8 (0.4–1.7)
					POR 1.0 (0.7–1.5) (I^2=0%)
Conclusion: For patients with s-ICAS it is *possible* that baseline HDL-C (POR 1.0, 95% CI 0.7–1.5; I^2 = 0%) does not predict an increased risk of recurrent stroke or death. (Low confidence, 2 Class I studies downgraded for imprecision)					
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS + WASID [SAMMPRIS Like])	Per 10-unit increase	SAMMPRIS	HR 1.06 (0.9–1.3)
Feng-2019	II	Retrospective 2 center cohort	Baseline mean HDL-C in those with	Recurrent stroke in territory at one year	RMD -3.8 (-10.8 to 3.2)

			recurrent stroke vs not		

Table 35. Baseline LDL-C

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Waters-2016	I	Prospective cohort (Medical arm of SAMMPRIS)	LDL-C ≥90	SAMMPRIS	OR 1.2 (0.6–2.4)
Kozak-2011	II	Retrospective cohort (single center)	LDL-C ≥90	Recurrent stroke	OR 10.2 (0.8–117.0)
Sangha-2017	II	Prospective single center cohort	LDL-C >100	Recurrent stroke in territory at 30 days	OR 2.0 (0.7–5.3)
					POR 1.6 (0.8–3.1) (I^2=16%)
Comment:					

There is insufficient evidence to support or refute baseline LDL-C predicting an increased risk of recurrent stroke (POR 1.6, 95% CI 0.8–3.1; I^2 = 16%). (Very low confidence, 1 Class I and 2 Class II studies confidence in the evidence downgraded due to indirectness)					
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID (SAMMPRIS Like)	Per 10-unit increase	SAMMPRIS	HR 1.0 (0.98–1.1)
Feng-2019	II	Retrospective 2 center cohort	Mean + recurrent stroke vs no stroke	Recurrent stroke in territory at one year	RMD -23.3 (-46.7 to 0.3)

Table 36. Triglycerides

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Ovbiagele-2006	I	Prospective cohort (WASID)	>150 mg/dl	Recurrent ischemic stroke	OR 1.6 (1.0–2.5)
Conclusion: For patients with s-ICAS it is *likely* that elevated triglycerides (>150 mg/dL) predicts an increased risk of recurrent stroke or death (OR 1.6, 95% CI 1.0–2.5). (Moderate confidence, 1 Class I study)					

Feng-2019	II	Retrospective 2 center cohort	Mean + recurrent stroke vs no stroke	Recurrent stroke in territory at one year	RMD-17.1 (-48.4 to 13.1)

Table 37. Lipoprotein (a)

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Pawar-2014	I	Prospective cohort (Medical arm of SAMMPRIS)	Elevated Lipoprotein (a)	Any ischemic stroke	OR 1.03 (0.5–2.1)
Conclusion: There is insufficient evidence to support or refute elevated lipoprotein (a) predicting an increased risk of recurrent stroke (OR 1.03, 95% CI 0.5–2.1). (Very low confidence, 1 Class I study, confidence in the evidence downgraded due to imprecision;)					

Table 38. Peripheral Vascular Disease

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kozak-2011	II	Retrospective cohort (single center)	PVD	Recurrent stroke	OR 0.6 (0.1–6.0)

Conclusion:

There is insufficient evidence to support or refute a history of PVD predicting an increased risk of recurrent stroke (OR 0.6, 95% CI 0.1–6.0). (Very low confidence, 1 Class II study, confidence in the evidence downgraded due to indirectness)

Table 39. BMI

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	≥25	Recurrent stroke in territory at follow up	OR 1.3 (0.8–2.5)
Waters-2016	I	Prospective cohort (Medical arm of SAMMPRIS)	≥29	SAMPPRIS	OR 1.5 (0.7–3.1)
					POR 1.4 (0.9–2.1) (I^2=0%)

Conclusion:

For patients with s-ICAS it is *possible* that elevated BMI does not predict an increased risk of recurrent stroke or death (POR 1.4, 95% CI 0.9–2.1; I^2 = 0%). (Low confidence, 2 Class I studies downgraded for imprecision)

Table 40. Metabolic syndrome

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Ovbiagele-2006	I	Prospective cohort (WASID)	Metabolic syndrome	Recurrent ischemic stroke	HR 1.5 (0.96–2.4)
Conclusion: There is insufficient evidence to support or refute metabolic syndrome predicting an increased risk of recurrent stroke (HR 1.5, 95% CI 0.96–2.4). (Very low confidence, 1 Class I study, confidence in the evidence downgraded due to imprecision)					

Table 41. Baseline Physical Activity

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Kasner-2006	I	Prospective cohort (WASID)	Sedentary	Recurrent stroke in territory at follow up	OR 0.9 (0.5–1.6)
Waters-2016	I	Prospective cohort (Medical arm of SAMMPRIS)	"Out of target"	SAMMPRIS	OR 2.1 (0.8–5.2)

					POR 1.1 (0.7–1.9) (I^2=56%)
Conclusion: For patients with s-ICAS it is *possible* that baseline physical activity does not predict an increased risk of recurrent stroke or death (POR 1.1, 95% CI 0.7–1.9; I^2 = 56%). (Low confidence, 2 Class I studies downgraded for imprecision)					
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID [SAMMPRIS Like])	"Out of target"	SAMMPRIS	HR 1.3 (0.7–2.2)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	> 1 time per week	Recurrent fatal/non-fatal ischemic stroke	HR 16.6 (1.7–200)

Table 42. Smoking

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	Smoker	Recurrent stroke in territory at follow up	OR 0.9 (0.5–1.5)

Waters-2016	I	Prospective cohort (Medical arm of SAMMPRIS)	Smoker	SAMMPRIS	OR 1.3 (0.6–2.8)
					POR 1.0 (0.7–1.6) (I^2=0%)
Conclusion: For patients with s-ICAS it is *possible* that smoking does not predict an increased risk of recurrent stroke or death (POR 1.0, 95% CI 0.7–1.6; I^2 = 0%). (Low confidence, 2 Class I studies downgraded for imprecision)					
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	Smoker	Recurrent stroke/death	HR 1.07 (0.94–1.2)
Koazk-2011	II	Retrospective cohort (single center)	Smoker	Recurrent stroke	OR 1.3 (0.3–6.1)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS +WASID (SAMMPRIS Like)	Smoker	SAMMPRIS	HR 0.8 (0.5–1.4)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	Smoker	Recurrent fatal/non-fatal ischemic stroke	HR 0.9 (0.2–3.4)

Sangha-2017	II	Prospective single center cohort	Smoker	Recurrent stroke in territory at 30 days	OR 0.5 (0.1–1.9)
Feng-2019	II	Retrospective 2 center cohort	Smoker	Recurrent stroke in territory at one year	OR 0.4 (0.1–1.2)

Table 43. Alcohol Use

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	Alcohol use	Recurrent stroke in territory at follow up	OR 0.8 (0.6–1.5)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	Alcohol use	Recurrent fatal/non-fatal ischemic stroke	OR 0.6 (0.3–1.7)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	Alcohol use	Recurrent stroke/death	OR 1.0 (0.4–2.1)

Kozak-2011	II	Retrospective cohort (single center)	Alcohol use	Recurrent stroke	OR 1.3 (0.1–15.3)
					POR 0.8 (0.5–1.2) (I^2=0%)
Conclusion (confidence): There is insufficient evidence to support or refute alcohol use predicting an increased risk of recurrent stroke (POR 0.8, 95% CI 0.5–1.2; I^2 = 0%). (Very low confidence, 2 Class I and 2 Class II studies, confidence downgraded for imprecision and indirectness;)					

Table 44. CRP

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Frankel-2014	I	Prospective cohort (SAMMPRIS)	Elevated hsCRP	Recurrent any ischemic stroke	HR 1.8 (0.96–3.44)
Conclusion: There is insufficient evidence to support or refute hs-CRP predicting an increased risk of recurrent stroke (HR 1.8, 95% CI 0.96–3.4). (Very low confidence, 1 Class I study, confidence in the evidence downgraded due to imprecision)					

Li-2018	II	Prospective cohort (subgroup of CHANCE)	Elevated hsCRP	Recurrent any stroke	OR 1.1 (0.6–2.1)

Table 45. Myocardial Spect

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Candel-Riera-2007	I	Prospective single center cohort	+ Myocardial spect	Recurrent stroke	OR 3.6 (0.7–17.1)
Candel-Riera-2007	I	Prospective single center cohort	+ Myocardial spect	Recurrent stroke /death	OR 3.4 (0.8–12.9)
Conclusion: There is insufficient evidence to support or refute a positive Myocardial SPECT scan predicting an increased risk of recurrent stroke (OR 3.4, 95% CI 0.8–12.9). (1 Class I study supporting Myocardial SPECT, confidence in the evidence downgraded due to indirectness and imprecision)					

Non-modifiable Risk Factors

Table 46. Age

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**

Kasner-2006	I	Prospective cohort (WASID)	≥64	Recurrent stroke in territory at follow up	OR 0.8 (0.6–1.3)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	≥60	SAMMPRIS	OR 1.3 (0.6–2.7)
					POR 0.9 (0.6–1.4) (I^2=0%)
Conclusion: For patients with s-ICAS it is *possible* that age (POR 0.9, 95% CI 0.6–1.4; I^2 = 51%) does *not* predict an increased risk of recurrent stroke or death. (2 Class I studies, confidence in the evidence downgraded for imprecision)					
Kozak-2011	II	Retrospective cohort (single center)	≥60	Recurrent stroke	OR 0.9 (0.2–4.1)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	≥60	Recurrent stroke 90 days in territory	OR 1.3 (0.4–4.1)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS	Smoker	SAMMPRIS	HR 0.8 (0.5–1.4)

		+WASID [SAMMPRIS Like])			
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	Increasing age per 10 years	SAMMPRIS	HR 1.0 (0.8–1.2)
Qureshi-2003	II	Retrospective cohort (4 US centers)	Increasing age per year	Recurrent stroke/death	HR 1.05 (1.0–1.1)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	Increasing age per year	Recurrent stroke/death	HR 1.01 (0.9–1.1)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	Increasing age per year	Recurrent fatal/non-fatal ischemic stroke	HR 0.80 (0.70–0.91)
Sangha-2017	II	Prospective single center cohort	Increasing age per year	Recurrent stroke in territory at 30 days	OR 0.6 (0.3–1.5) / RMD -2.9 (-8 to 2.2)
Feng-2019	II	Retrospective 2 center cohort	Mean age stroke vs no stroke	Recurrent stroke in territory at one year	RMD -1 (-5.7 to 2.7)

Table 47. Race

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	Non-White vs White	SAMMPRIS	OR 1.2 (0.6–2.7)
Kasner-2006	I	Prospective cohort (WASID)	Non-White vs White	Recurrent stroke in territory at follow up	OR 1.2 (0.7–1.9)
					POR 1.2 (0.8–1.8) (I^2=0%)
Conclusion: For patients with s-ICAS it is *possible* that race (non-White vs White for the outcome of stroke in the territory of stenotic artery) (POR 1.2, 95% CI 0.7–2.2; I^2 = 0%) does *not* predict an increased risk of recurrent stroke or death. (2 Class I studies, confidence in the evidence downgraded for imprecision)					
Waddy-2009	I	Prospective cohort (WASID)	Black vs White	Stroke in territory	HR 1.3 (0.5–3.2)

Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	Black vs White	SAMMPRIS	HR 1.4 (0.8–2.3)
Waddy-2009	I	Prospective cohort (WASID)	Black vs White	Recurrent any stroke/death	HR 1.4 (0.9–2.1)
Waddy-2009	I	Prospective cohort (WASID)	Black vs White	Ischemic Stroke	HR 1.6 (1.01–2.6)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	Black vs non-black	Recurrent fatal/non-fatal ischemic stroke	HR 2.4 (0.7–8.4)
Sangha-2017	II	Prospective single center cohort	Non-White vs White	Recurrent stroke in territory at 30 days	OR 1.2 (0.4–3.1)
Feng-2019	II	Retrospective 2 center cohort	Non-White vs White	Recurrent stroke in territory at one year	OR 0.9 (0.3–2.8)

Table 48. Gender

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Kasner-2006	I	Prospective cohort (WASID)	Male vs female	Recurrent stroke in territory at follow up	OR 0.6 (0.4–1.0)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	Male vs Female	SAMMPRIS	OR 0.5 (0.3–1.1)
					POR 0.6 (0.4–0.8) (I^2=0%)
Conclusion: For patients with s-ICAS, it is *highly likely* that sex (male vs female) (POR 0.6, 95% CI 0.4–0.8; I^2 = 0%) predicts an increased risk of recurrent stroke or death. (High confidence, 2 Class II studies upgraded for magnitude of effect)					
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	Male vs Female	Recurrent stroke /Death	HR 0.6 (0.1–6.1)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	Male vs female	Recurrent stroke in territory at 9 0days	OR 0.7 (0.3–2.1)

Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	Male vs Female	SAMMPRIS	HR 0.5 (0.3–0.8)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	Male vs female	Recurrent fatal/non-fatal ischemic stroke	HR 0.5 (0.1–1.5)
Sangha-2017	II	Prospective single center cohort	Male vs female	Recurrent stroke in territory at 30 days	OR 2.6 (0.9–7.3)
Feng-2019	II	Retrospective 2 center cohort	Male vs female	Recurrent stroke in territory at one year	OR 0.5 (0.2–1.2)

Table 49. History of Stroke (Cerebrovascular Disease)

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	History of stroke	SAMMPRIS	OR 1.1 (0.7–1.9)

Weber-2010	II	Prospective multicenter Cohort	History of stoke	Recurrent Stroke	OR 1.4 (0.8–2.5)
Kozak-2011	II	Retrospective cohort (single center)	History of stroke	Recurrent stroke	OR 0.2 (0.01–2.1)
					POR 1.2 (0.8–1.7) (I^2=5%)
Conclusion: The evidence is insufficient to support or refute history of stroke predicting an increased risk of recurrent stroke (POR 1.5, 95% CI 0.8–2.7; I^2 = 44%). (Very low confidence, 1 Class I and 2 Class II studies supporting, confidence in the evidence downgraded for indirectness and insufficient precision)					
Kasner-2006	I	Prospective cohort (WASID)	History of stroke	Recurrent stroke in territory at follow up	OR 0.8 (0.4–1.4)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	History of stroke	Recurrent stroke in territory by 90 days	OR 1.4 (0.5–4.2)

Sangha-2017	II	Prospective single center cohort	History stroke/TIA	Recurrent stroke in territory at 30 days	OR 0.8 (0.3–2.0)
Feng-2019	II	Retrospective 2 center cohort	History stroke/TIA	Recurrent stroke in territory at one year	OR 3.6 (1.1–11.7)

Table 50. History of TIA (Cerebrovascular Disease)

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	History of TIA	Recurrent stroke in territory at follow up	OR 0.8 (0.4–1.4)
Conclusion: The evidence is insufficient to support or refute history of TIA predicting an increased risk of recurrent stroke (OR 0.8, 95% CI 0.4–1.4). (Very low confidence, 1 Class I study, confidence in the evidence downgraded due to imprecision)					

Table 51. Old Infarcts (Cerebrovascular Disease)

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**

Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	Old infarcts	Recurrent stroke in territory by 90 days	OR 5.0 (1.5–16.7)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	Old infarcts	SAMMPRIS	OR 2.8 (1.3–5.8)
					POR 3.3 (1.7–6.2) (I^2=0%)
Conclusion: For patients with s-ICAS, it is *likely* that old infarcts on imaging predict an increased risk of recurrent stroke or death (POR 3.3, 95% CI 1.7–6.2; I^2 = 0%). (Moderate confidence, 2 Class I studies supporting old infarcts, confidence in the evidence downgraded for indirectness)					
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	Old infarcts	SAMMPRIS	HR 1.8 (1.1–2.9)
Pan-2017	II	Prospective cohort (subgroup of CHANCE)	Multiple baseline infarcts	Any recurrent ischemic stroke	OR 2.2 (1.3–3.8)
Pan-2017	II	Prospective cohort (subgroup of CHANCE)	Any baseline infarct	Any recurrent ischemic stroke	OR 5.5 (1.7–16.7)

Sangha-2017	II	Prospective single center cohort	Any previous in territory	Recurrent stroke in territory at 30 days	OR 1.3 (0.5–3.4)

Table 52. Small Vessel Disease (Cerebrovascular Disease)

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kwon-2016	II	Prospective cohort (medical arm SAMMPRIS)	SVD	Any recurrent ischemic stroke in territory	OR 2.0 (0.7–5.1)
Conclusion: The evidence is insufficient to support or refute concomitant SVD predicting an increased risk of recurrent stroke (OR 2.0, 95% CI 0.7–5.1). (Very low confidence, 1 Class II study, downgraded due to imprecision)					
Kwon-2016	II	Prospective cohort (medical arm SAMMPRIS)	SVD	Any recurrent ischemic stroke	OR 2.2 (0.9–5.2)
Chen-2020	II	Prospective cohort (subgroup of CHANCE)	SVD	Recurrent Stroke at 90 days	OR 0.7 (0.4–1.4)

Table 53. Concomitant asymptomatic ICAS

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Tian-2015	II	Single center cohort (China) with MCAO + concomitant ICAS	Present	Recurrent stroke/death	OR 4.0 (1.5–10.4)
Chen-2020	II	Prospective cohort (subgroup of CHANCE)	>1 ICAS vs one	Recurrent Stroke at 90 days	OR 1.4 (0.8–2.4)
					POR 2.2 (0.8–6.1)
Conclusion: The evidence is insufficient to support or refute concomitant ICAS predicting an increased risk of recurrent stroke (POR 2.2, 95% CI 0.8–6.1). (2 Class II, indirect studies, downgraded due to imprecision)					

Table 54. Statin Therapy

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and	No statin	SAMMPRIS	OR 1.3 (0.8–2.1)

		WASID [SAMMPRIS like])			
Conclusion: The evidence is insufficient to support or refute not being on a statin (at baseline of WASID or SAMMPRIS) predicting an increased risk of recurrent stroke (OR 1.3, 95% CI 0.3–2.1). (Very low confidence, 1 Class I study, confidence in the evidence downgraded due to imprecision)					
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	No statin	SAMMPRIS	OR 2.8 (1.2–6.7)
Sangha-2017	II	Prospective single center cohort	No statin	Recurrent stroke in territory at 30 days	OR 1.4 (0.6–5.0)

Table 55. NIH Stroke Scale

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	NIHSS >1	Recurrent stroke in territory at follow up	OR 2.2 (1.4–3.6)

Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	NIHSS >1	SAMPPRIS	OR 1.3 (0.6–2.7)
					POR 1.8 (1.1–3.0) (I^2=26%)
Conclusion: For patients with s-ICAS, it is *highly likely* that the following non-modifiable risk factors predict an increased risk of recurrent stroke or death; baseline NIHSS score >1 (POR 1.8, 95% CI 1.1–3.0; I^2 = 26%). (High confidence, 2 Class I studies)					
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	NIHSS >1	SAMPPRIS	HR 1.9 (1.2–3.1)
Sangha-2017	II	Prospective single center cohort	NIHSS >1	Recurrent stroke in territory at 30 days	OR 1.1 (0.4–3.1)

Table 56. Modified Rankin Scale

Study	**Class**	**Cohort+**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**

Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	≥1	SAMMPRIS	OR 1.3 (0.8–2.3)
Conclusion: The evidence is insufficient to support or refute baseline mRS score ≥1 predicting an increased risk of recurrent stroke (OR 1.3, 95% CI 0.8–2.3). (Very low confidence, 1 Class I study, confidence in the evidence downgraded due to imprecision)					
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	≥1	SAMMPRIS	OR 2.2 (0.9–5.4)

Table 57. Vascular Distribution

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	Anterior (vs posterior)	Recurrent stroke in territory at follow up	OR 1.1 (0.6–1.7)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	Anterior (vs posterior)	SAMMPRIS	OR 1.4 (0.6–3.1)

Wang-2014	I	Prospective multicenter Chinese cohort	Anterior (vs posterior)	Recurrent stroke	OR 0.7 (0.4–1.2)
					POR 1.0 (0.7–1.4) (I^2=15%)
Conclusion: For patients with s-ICAS, it is *highly likely* that anterior (vs posterior) vascular distribution does *not* predict an increased risk of recurrent stroke (POR 1.0, 95% CI 0.7–1.4; I^2 = 15%). (High confidence, 3 Class I studies)					
Kozak-2011	II	Retrospective cohort (single center)	Anterior (vs posterior)	Recurrent stroke	OR 0.4 (0.1–1.8)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	Anterior (vs posterior)	Recurrent stroke in territory by 90 days	OR 0.9 (0.3–2.9)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	Anterior (vs posterior)	SAMMPRIS	HR 1.3 (0.8–2.0)
Tsai-2005	II	Single center MCA stenosis	MCA Origin vs not	Recurrent ischemic stroke	OR 0.5 (0.1–1.7)

Tsai-2005	II		M1 vs not	Recurrent ischemic stroke	OR 1.9 (0.4–8.6)
Tsai-2005	II		M2 vs not	Recurrent ischemic stroke	OR 2.0 (0.4–11.9)
Weimer-2006	I	Prospective multicenter cohort	Basilar vs M1 occlusion only	Recurrent stroke/death	OR 1.1 (0.3–3.4)
Amin-Hanjani-2016	I	Cohort from VERiTAS	Basilar vs non-basilar (in VB disease)	Recurrent VB fatal/non-fatal ischemic stroke	HR 1.2 (0.3–4.5)
Sangha-2017	II	Prospective single center cohort	VBI vs other	Recurrent stroke in territory at 30 days	OR 0.6 (0.2–2.0)

Table 58. Qualifying Event

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**

Kasner-2006	I	Prospective cohort (WASID)	TIA vs stroke	Recurrent stroke in territory at follow up	OR 0.7 (0.4–1.2)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	TIA vs stroke	SAMMPRIS	OR 0.4 (0.12–0.9)
					POR 0.6 (0.3–0.95) (I^2=24%)
Conclusion: For patients with s-ICAS, it is *highly likely* that QE of TIA vs stroke predicts an increased risk of recurrent stroke or death (POR 0.6, 95% CI 0.3–0.95; I^2 = 24%). (High confidence, 2 Class II studies)					
Kozak-2011	II	Retrospective cohort (single center)	TIA vs stroke	Recurrent stroke	OR 0.4 (0.1–1.9)
Ovbiagele-2008	I	Prospective cohort (WASID)	TIA vs stroke	Recurrent stroke in territory by 90 days	OR 1.5 (0.7–3.3)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and	TIA vs stroke	SAMMPRIS	HR 0.5 (0.3–0.8)

		WASID [SAMMPRIS like])			
Amin-Hanjani-2016	I	Cohort from VERiTAS	TIA vs stroke	Recurrent VB fatal/non-fatal ischemic stroke	HR 1.0 (4.3–0.3)

Table 59. Time from Qualifying Event

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	>17 days	Recurrent stroke in territory at follow up	OR 0.6 (0.4–0.9)
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	>7 days	SAMMPRIS	OR 1.0 (0.5–2.1)
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	>17 days	Recurrent stroke in territory by 90 days	OR 0.6 (0.2–1.8)

Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	Per 1-day increases	SAMMPRIS	HR 0.9 (0.6–1.2)
Amin-Hanjani-2016	I	Prospective cohort (VERiTAS)	<21 days	Recurrent fatal/non-fatal ischemic stroke	HR 3.8 (0.8–18.0)

Table 60. Hemodynamic Markers

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Wabnitz-2019	II	Prospective cohort (medical arm SAMMPRIS)	Qualifying infarct borderzone (vs not)	Ischemic stroke in the territory of the stenotic artery after enrollment	OR 3.1 (1.04–9.0)
Conclusion: For patients with s-ICAS it is *possible* that qualifying infarct borderzone (vs not) predicts an increased risk of recurrent stroke or death (OR 3.1, 95% CI 1.04–9.0). (Low confidence, 1 Class II study)					
Wabnitz-2019	II	Prospective cohort (medical arm SAMMPRIS)	Qualifying infarct borderzone + impaired collaterals (vs not)	Ischemic stroke in the territory of the stenotic artery after enrollment	OR 6.9 (2.0–23.2)

Conclusion: For patients with s-ICAS it is *possible* that qualifying infarct borderzone plus impaired collaterals (vs not) predicts an increased risk of recurrent stroke or death (OR 6.9, 95% CI 2.0–23.2). (Low confidence, 1 Class II study)					
Wabnitz-2019	II	Prospective cohort (medical arm SAMMPRIS)	Impaired flow (vs complete)	Ischemic stroke in the territory of the stenotic artery after enrollment.	OR 5.9 (1.3–25.1)
Conclusion: For patients with s-ICAS it is *possible* that impaired flow (vs complete flow) predicts an increased risk of recurrent stroke or death (OR 5.9, 95% CI 1.3–25.1). (Low confidence, 1 Class II study)					
Yamauchi-2012	I	Single center prospective cohort	Misery Perfusion (Pet Scan)	Recurrent Ischemic Stroke	OR 31.5 (3.7–288.4)
Conclusion: For patients with s-ICAS, it is *highly likely* that presence of misery perfusion on a PET scan predicts an increased risk of recurrent stroke or death (OR 31.5, 95% CI 3.7–288.4). (High confidence, 1 Class I study, upgraded for magnitude of effect)					
Yamauchi-2012	I	Single center prospective cohort	Increase OEF asymmetry (Pet Scan)	Recurrent Ischemic Stroke	OR 2.3 (0.3–15)

Conclusion:

The evidence is insufficient to support or refute increased oxygen extraction fraction (OEF) asymmetry (PET scan) predicting an increased risk of recurrent stroke (OR 2.3, 95% CI 0.3–15). (Very low confidence, 1 Class 1 study, confidence in the evidence downgraded due to imprecision)

Amin-Hanjani-2016	I	Cohort from VERiTAS	Low distal flow status on QMRA	Recurrent VB fatal/non-fatal ischemic stroke	OR 3.4 (1.1–10.5)

Conclusion:

For patients with s-ICAS it is *possible* that low distal flow status on QMRA (in posterior circulation stroke) predict an increased risk of recurrent stroke or death (OR 3.4, 95% CI 1.1–10.5). (Low confidence, 1 Class I indirect study)

Feng-2019	II	Cohort 2 China centers	Mixed artery/artery embolism and hypoperfusion	Recurrent stroke in same territory	OR 3.8 (1.3–10.9)

Conclusion:

The evidence is insufficient to support or refute artery to artery embolism + hypoperfusion patterns on imaging predicts an increased risk of recurrent stroke (OR 3.8, 95% CI 1.3–10.9). (Very low confidence, 1 indirect Class II study downgraded for imprecision)

Feng-2019	II		Any hypoperfusion	Recurrent stroke in same territory	OR 6.4 (0.98–38.9)

Conclusion:

The evidence is insufficient to support or refute any hypoperfusion patterns on imaging predicting an increased risk of recurrent stroke (OR 6.4, 95% CI 0.98–38.9). (Very low confidence, 1 indirect Class II study downgraded for imprecision)

Table 61. Severity of Stenosis

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	≥70% (vs 50%–69%)	Recurrent stroke in territory at follow up	OR 2.2 (1.4–3.6)
Wang-2014	I	Multicenter prospective cohort	≥70% (vs 50%–69%)	Recurrent stroke	OR 1.8 (0.99–3.3)
					POR ≥70% (vs 50%–69%) 2.0 (1.4–3.0) (I^2=0%)
Conclusion: For patients with s-ICAS, it is *highly likely* that percent stenosis ≥70% vs 50%–69% predicts an increased risk of recurrent stroke or death (POR 2.0, 95% CI 1.4–3.0; I^2 = 0%). (High confidence, 2 Class I studies)					

Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	≥70% (vs 50%–69%)	Recurrent stroke in territory at 90 days	OR 2.2 (0.7–6.7)
Amin-Hanjani-2016	I	Cohort from VERiTAS	≥70% vs (50%–69%)	Recurrent VB fatal/non-fatal ischemic stroke	OR 0.8 (0.4–1.9)
Sangha-2017	II	Prospective single center cohort	≥70% (vs 50%–69%)	Recurrent stroke in territory at 30 days	OR 1.9 (0.6–6.1)
Feng-2019	II	Retrospective 2 center cohort	≥70% (vs 50%–69%)	Recurrent stroke in territory at one year	OR 2.0 (0.7–5.7)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	80–89% (vs 70%–79%)	SAMMPRIS	OR 1.0 (0.7–1.6)
Chaturvedi-2015	I	Prospective cohort (medical arm SAMMPRIS and WASID [SAMMPRIS like])	90–99% (vs 70%–79%)	SAMMPRIS	OR 1.0 (0.6–1.9)

					POR ≥80% (vs 70%–79%) 1.0 (0.8–1.4) (I^2=0%)
Conclusion: The evidence is insufficient to support or refute percent stenosis of >80% vs 70%–79% predicting an increased risk of recurrent stroke (POR 1.0, 95% CI 0.8–1.4; I^2 = 0%). (Very low confidence, 3 Class 1 studies, confidence in the evidence downgraded for indirectness and imprecision)					
Waters-2016	I	Prospective cohort (medical arm SAMMPRIS)	≥80% (vs 70%–79%)	SAMMPRIS	OR 1.9 (0.9-4.0)
Kozak-2011	II	Retrospective cohort (single center)	≥80% (vs 50%–79%)	Recurrent stroke	OR 10.5 (1.8–65.4)

Table 62. Length of Stenosis

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Kasner-2006	I	Prospective cohort (WASID)	>2.5 ratio vs less	Recurrent stroke in territory at follow up	OR 1.0 (0.6–1.7)

Conclusion (confidence): The evidence is insufficient to support or refute length of stenosis predicting an increased risk of recurrent stroke (OR 1.0, 95% CI 0.6–1.7). (Very low confidence, 1 Class 1 study, confidence in the evidence downgraded due to imprecision)

Table 63. White Blood Cell Count

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Ovbiagele-2008	I	Prospective cohort (WASID [QE=TIA only])	>7200	Recurrent stroke in territory by 90 days	OR 1.5 (0.5–4.3)
Conclusion: The evidence is insufficient to support or refute WBC count of >7200 predicting an increased risk of recurrent stroke (OR 1.5, 95% CI 0.5–4.3). (Very low confidence, 1 Class I supporting WBC, confidence in the evidence downgraded due to indirectness and imprecision)					

Table 64. Neutrophil Level

Study	**Class**	**Cohort**	**Risk Factor**	**Endpoint**	**Point Estimate (95% CI)**
Zhu-2018	II	Prospective cohort (subgroup of CHANCE)	Lower vs higher level	Recurrent stroke (any)	OR 0.7 (0.4–1.2)

Conclusion: The evidence is insufficient to support or refute neutrophil count predicting an increased risk of recurrent stroke (OR 0.7, 95% CI 0.4–1.2). (Very low confidence, 1 Class II study downgraded due to imprecision)

Table 65. Progression of Stenosis

Study	Class	Cohort	Risk Factor	Endpoint	Point Estimate (95% CI)
Tan-2009	I	Prospective single center cohort	MRA stationary or progression vs regression at a mean of 10.6 months	Recurrent stroke	OR 1.0 (0.2–4.9)
Conclusion: The evidence is insufficient to support or refute progression of stenosis on MRA predicting an increased risk of recurrent stroke (OR 1.0, 95% CI 0.2–4.9). (Very low confidence, 1 Class 1 study, confidence in the evidence downgraded due to imprecision)					

Appendix 5. Narrative Description of Prognostic Studies

RISK FACTOR CONTROL

In a Class I study evaluating the relationship between control of vascular risk factors and vascular events in patients with s-ICAS, the authors analyzed data from 569 patients from the WASID study database.[37] Vascular and lifestyle risk factors were averaged from baseline through the course of the trial using cutoff levels defining good control. Patients who smoked or consumed alcohol at baseline or at any follow-up visit were categorized as having the risk factor. The primary endpoint was a composite of ischemic stroke, myocardial infarction, or vascular death; however, the analysis was repeated with any ischemic stroke alone as an endpoint. Poor risk factor control ("out of target") was defined as having an SBP >140 mm Hg, MAP >106 mm

Hg, TC >200 mg/dL, LDL-C >100 mg/dL, HDL-C <40 mg/dL, TC/HDL-C ratio ≥4.4, HbA1c >7%, non-HDL-C >130 mg/dL, any current smoking, and no current consumption of alcohol. Risk factors were managed by the local principal investigator in association with the patient's primary care physician. National guidelines addressing treatment of risk factors were periodically sent to local sites in addition to reminders on the importance of risk factor modification. From baseline until the year-2 follow-up, there was not a significant improvement in blood pressure control. Although there were improvements in TC and LCL-C, only 10% achieved an LDL-C <70 mg/dL. Multivariable analysis showed poor control (out of target) of SBP (HR 1.79, 95% CI 1.27–2.52), TC (HR 1.44, 95% CI 1.004–2.07), and no alcohol consumption (HR 1.69, 95% CI 1.21–2.39) were associated with an increased risk of stroke, myocardial infarction, or vascular death. For the outcome of recurrent stroke, the authors did not provide data on number of events dichotomized by risk factor status; however, the HR and P values for "significant" predictors were provided, allowing for calculation of 95% CI.[PMID: 21824904] Patients were more likely to have a recurrent ischemic stroke if, during follow-up, they had poor risk factor control (out of target) SBP (HR 1.63, 95% CI 1.1–2.4), MAP (HR 2.83, 95% CI 1.7–3.0), TC (HR 2.06, 95% CI 1.4–3.1), LDL-C (HR 1.72, 95% CI 1.05–2.8), non-HDL-C (HR 1.94, 95% CI 1.2–25.3), TC/HDL-C ratio (HR 1.89, 95% CI 1.2–2.9), and no alcohol consumption (HR 1.78, 95% CI 1.2–2.6). Multivariable analysis showed that poor control (out of target) SBP (HR 1.58, 95% CI 1.07–2.32), TC (HR 1.95, 95% CI 1.29–2.97), and no alcohol consumption (HR 1.76, 95% CI 1.19–2.59) were the most important predictors of recurrent ischemic stroke.

In a separate analysis of patients enrolled in WASID (Class I), the risk of any recurrent stroke or any recurrent stroke in the territory of the stenotic vessel was evaluated stratified by average SBP and DBP during follow up.[38] Different than in Chaturvedi et al., risk factor control was evaluated by ordinal categorization of participants according to recommendations from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[110] Ischemic stroke risk increased with increasing mean SBP and DBP on univariate analysis and adjusted analyses, largely driven by patients in the highest blood pressure group. Subgroup analyses demonstrated that in those with >70% stenosis, increasing DBP but not SBP increased the risk of stroke; however, in no subgroup did lower blood pressure increase

the risk of recurrent stroke by either endpoint. Using data provided by the authors, the risk of recurrent ischemic stroke was 42.9% (21/49) in those with SBP >160 mm Hg (highest quartile) compared to 16.4% (85/518) in those with average SBP <160 mm Hg (OR 3.8, 95% CI 2.1–7.0). The risk of recurrent stroke in the territory of the stenotic artery was 34.7% (17/49) in those with SBP >160 mm Hg compared to 11.6% (60/518) in those with an average SBP <160 mm Hg (OR 4.1, 95% CI 2.2–7.7). The risk of recurrent ischemic stroke was 32.3% (11/34) in those with DBP >90 mm Hg compared to 17.8% (95/533) in those with DBP <90 mm Hg (OR 2.2, 95% CI 1.06–4.6). The risk of recurrent stroke in the territory of the stenotic artery was 26.5% (9/34) in those with DBP >90 mm Hg compared to 12.8% (68/533) in those with DBP <90 mm Hg (OR 2.5, 95% CI, 1.1–5.4). If a cut point of SBP >140 mm Hg as "out of target" was used, the risk of recurrent ischemic stroke was 22.7% (61/269) in those out of target compared to 15% (45/300) in those "in-target" (OR 1.7, 95% CI 1.08–2.5). In summary, in patients with intracranial stenosis, higher blood pressure was associated with increased risk of ischemic stroke and stroke in the territory of the stenotic vessel.

In a prespecified subgroup analysis of the Class I SAMMPRIS trial, the relationship between modifiable risk factor control and recurrent vascular events in patients allocated to the medical arm was investigated.[39] Participants were randomized a median of 7 days after the QE, and all were managed with an intensive risk factor management protocol that included multiple strategies to maximize attainment of risk factor targets. These included SBP (<140 mm Hg or <130 mm Hg if diabetic), LDL-C <70 mg/dL, non-HDL-C <100 mg/dL, HbA1c <7.0% (if diabetic), smoking cessation, weight management (BMI <25 kg/m2 or 10% reduction in weight if initial BMI >27 kg/m2) and physical activity (PACE score of 4–8). Adjustments were made to the lipid-lowering medications based on the LDL-C results. In addition to risk factor management, aggressive medical therapy consisted of aspirin 325 mg/d during the entire follow-up period (mean follow-up of approximately 32 months) and clopidogrel 75 mg/d for 90 days after enrollment. Risk factor control was dichotomized as "in target" or "out of target" by averaging values from baseline until the time of the vascular event (for patients having these events), 3 years of follow-up, or at the end of the study (if no events). The percentage of patients "in target" was 53% for SBP, 47% for LDL-C, 60% for non-HDL-C, 42% for HbA1c, 65% for smoking cessation, 19% for weight management, and 44% for physical activity. Although

absolute events were not reported, the risk of having a primary outcome event (composite of any ischemic stroke, MI, or vascular death) was significantly increased in patients who were "out of target" for physical activity (OR 5.4, 95% CI 2.4–12.1) and SBP (OR 2.1, 95% CI 1.2–4.0). Only physical activity (expressed as being "in target") remained significant in the adjusted analysis (OR 0.6, 95% CI 0.4–0.8). When repeating the analysis for an endpoint of ischemic stroke alone, only being "out of target" for physical activity (OR 6.7, 95% CI 2.5–18.1) was associated with an increased risk of recurrent stroke. Being "out of target" for LDL-C, SBP, smoking cessation, non-HDL-C, BMI, and HbA1c were not significantly associated with the endpoint. Although the control of these other risk factors did not significantly reduce recurrent stroke risk in this analysis, this may have been due to inadequate statistical power, because risk factor values were averaged over the duration of follow-up, or because of collinearity of risk factors.

To evaluate the effect of hemodynamics on stroke risk in the posterior circulation, the NINDS funded VERiTAS trial prospectively followed patients with symptomatic atherosclerotic vertebrobasilar steno-occlusive disease and utilized QMRA to evaluate large vessel flow.[40, 43] Eligible patients were within 60 days of a QE and had a >50% stenosis of the symptomatic vertebrobasilar artery. Patients with solely unilateral vertebral artery stenosis or occlusion were excluded due to the preponderance of normal flow. The cohort consisted of 72 patients, of whom all but 65 (90%) had stenoses located in the intracranial circulation with 70% involving the basilar artery. Participants had a QMRA within 14 days of enrollment and were classified as having a low or normal distal flow status. The primary endpoint for the study was fatal and non-fatal recurrent ischemic stroke in the vertebrobasilar territory. Central determination of QMRA distal flow status was performed and outcomes were adjudicated by raters who were masked to the participant's distal flow status. Although control of hypertension has been advocated to reduce the risk of recurrent stroke in patients with s-ICAS based on the increased risk found in patients in WASID and SAMMPRIS who failed to meet target blood pressure goals, concern remained for patients with proven hemodynamic compromise.

A secondary analysis of VERiTAS (Class I) was performed to evaluate the association between BP control and recurrent fatal or non-fatal ischemic stroke among patients with low distal flow on QMRA.[40] Participants were followed for a minimum of 12 months and a maximum of 24

months. BP was measured at baseline and at each 6-month visit and was averaged over the study period. Participants were considered "out of target" if either the average SBP or DBP was >140/90 mm Hg. The risk of the primary outcome was 17.9% (7/39) in those "in target" compared to 9% (3/33) in those out of target (OR 2.2, 95% CI 0.5–8.6). In the subgroup of participants with low distal flow status on QMRA, the risk of the primary outcome was 40% (4/10) in those in target compared to 9.7% (6/62) in those out of target (OR 6.2, 95% CI 1.5–27). This suggests, contrary to the broad category of patients with s-ICAS, that strict BP control in those with compromised hemodynamic flow may be harmful. However, the study has important limitations in generalizability because the patient population consisted predominantly of those with basilar steno-occlusive disease and also included a small number or patients with only extracranial disease.

In another prospective cohort study (Class I), investigators enrolled patients with a first ever TIA or stroke due to MCA stenosis (diagnosed by TCD and confirmed with MR or conventional angiography) with the aim of determining factors associated with the progression of stenosis on serial TCDs.[111] Clinical and radiographic predictors included TCDs, age, sex, smoking status, diabetes mellitus (DM), coronary artery disease (CAD), dyslipidemia (DLP), QE, claudication, location of stroke on MRI, severity of stenosis, co-existing intracranial stenosis and normal extracranial internal carotid artery The primary outcome was TCD progression and secondary outcomes included ipsilateral cerebrovascular events (stroke or TIA) and the composite of any major vascular event (any stroke, MI, angina, claudication, and sudden death). During a median follow-up of 27 months, the occurrence of any major vascular event was 61.5% (8/13) for TCD progression compared to 18.5% (5/27) for those who did not progress (OR 7.0, 95% 1.7–29.4). Recurrent stroke or TIA occurred in 46.2% (6/13) in those with TCD progression compared to 7.4% (2/27) in those without progression (OR 10.7, 95% CI 1.9–57.4). The risk of recurrent stroke alone, or stroke or death was not reported.

BASELINE RISK FACTORS

In a retrospective cohort (Class II) study comprising patients from 4 centers in the U.S., investigators evaluated the natural history of patients diagnosed with symptomatic vertebrobasilar stenosis.[56] Patients were included following TIA or stroke attributable to >50%

stenosis of the intracranial portions of the vertebral or the basilar artery. The primary outcome was time to recurrent stroke or death. The mean follow-up period was 15 months. The stroke-free survival rate was 86% at 12 months (95% CI 76%–92%) and 81% at 24 months (95% CI 69%–89%). The Cox proportional HR revealed that increasing age (HR 1.05, 95% CI 1.00–1.09) decreased stroke-free survival. Measures of association were not reported for other predictors which did not have significant association with recurrent stroke or death.

In a Class II, retrospective, single-center study conducted in Taiwan, investigators evaluated multiple baseline demographic, radiographic, and presenting features among patients with a first-ever stroke due to isolated symptomatic stenosis of the MCA.[57] Forty-nine patients were enrolled an average of 2 days following a QE. Variables were entered as predictors of poor outcome (a composite of recurrent stroke, death, and Barthel Index <12 at 1 year). Separate data were reported for the outcome of recurrent stroke alone at a mean follow up of 25.6 months based on location of MCA stenosis. The risk of recurrent stroke of MCA origin compared to a M1 or M2 was 22.2% (8/36) vs 38.5% (5/13) with an OR of 0.5 (95% CI 0.1–1.7). The risk for recurrent stroke with M1 stenosis vs MCA origin/M2 was 37.5% (3/8) vs 24.4% (10/41) with an OR of 1.9 (95% CI 0.4–8.6). The risk for recurrent stroke for M2 stenosis vs MCA origin/M1 was 40% (2/5) vs 25% (11/44) with an OR of 2.0 (95% CI 0.4–11.9). The study may have been inadequately powered for many of the predictor variables as CIs did not exclude clinically meaningful associations.

A Class I study of participants enrolled in the WASID trial evaluated the prevalence and prognosis of metabolic syndrome among individuals with s-ICAS.[45] A modified definition of metabolic syndrome was used and multiple components of the syndrome and other predictors were included. The primary outcome was the composite of any ischemic stroke, MI, or vascular death. The secondary outcome was ischemic stroke alone. During a mean follow-up period of 1.8 years, time to the first ischemic stroke, MI, or vascular death was shorter among patients with metabolic syndrome with an HR of 1.6 (95% CI 1.1–2.4). The presence of metabolic syndrome was also associated with an increased risk of ischemic stroke with an HR of 1.7 (95% CI 1.1–2.6). Adjusted analysis when controlling for glucose metabolism and hypertension showed that metabolic syndrome was not significant for the combined outcome (HR 1.4, 95% CI 0.9–2.1) or

for the occurrence of ischemic stroke alone (HR 1.5, 95% CI 0.96–2.4) after correction for glucose metabolism. Events for individual components of metabolic syndrome were reported for the outcome of recurrent stroke. Elevated triglycerides (>150 mg/dL) and glucose levels (>200 mg/dL) were associated with recurrent stroke, whereas BMI and HDL-C levels were not. Inclusion of metabolic syndrome may not provide additional predictive accuracy for vascular outcomes beyond the effect of individual component factors for patients with intracranial stenosis.

A prespecified aim of WASID (Class I) was to identify patients at highest risk for stroke in the territory of the stenotic artery who would be a target group for subsequent trials.[6] WASID enrolled 569 patients with TIA or non-disabling ischemic stroke due to 50%–99% stenosis of a major intracranial artery. Median time from QE to randomization was 17 days, and the mean follow-up time was 1.8 years. The primary outcome was recurrent ischemic stroke in the territory of the symptomatic intracranial stenosis. The risk of recurrent stroke was 10% (29/281) for time from QE >17 days compared to 17% (48/288) for those <17 days from the QE (OR 0.6, 95% CI 0.4–0.9). The risk of recurrent stroke was 19% (40/206) in those with >70% stenosis compared to 10% (35/355) in those with 50%–69% stenosis (OR 2.2, 95% CI 1.4–3.6). The risk of the primary outcome was 20% (40/204) for those with NIHSS >1 compared to 10% (36/364) in those with NIHSS <1 (OR 2.2, 95% CI 1.4–3.6). There was an increased risk of recurrent stroke that was just below statistical significance in those with a history of diabetes, those with a BMI >25kg/m2, and in women, possibly due to the study being underpowered. Age, race, alcohol use, smoking status, activity level, QE (TIA vs stroke), vascular distribution, length of stenosis (>2.5 ratio vs less), failure of anti-thrombotic therapy, history of ischemic stroke, TIA, coronary artery disease (CAD), hypertension, and DLP were not associated with recurrent stroke.

A Class I, multicenter prospective cohort study conducted in Germany recruited consecutive patients in 2000–2002 within 24 hours after a TIA or stroke.[61] The aim was to describe the distribution of vascular disease and associated risk of recurrent stroke and death up to 1 year after the index event. Overall, 272 patients (6.5%) with symptomatic 50%–99% ICAS were identified. Although multiple comparisons were made between those with ICAS and those without, the only risk factor among the subgroup of ICAS patients reporting the recurrent risk of

stroke or death was the subgroup with MCA (M1) compared to basilar occlusion. The risk of recurrent stroke between day 4 and 1 year was 9% (4/48) for basilar occlusion as compared to 8% (12/153) for MCA occlusion (OR 1.1, 95% CI 0.3–3.4).

In a Class I, prospective cohort study, the prognostic value of myocardial perfusion gated SPECT was evaluated in patients with s-ICAS and no known coronary artery disease.[41] Seventy-two consecutive patients with their first ever TIA or stroke attributable to s-ICAS underwent a stress myocardial perfusion–gated SPECT. Patients were enrolled 3–6 months after the QE, which may limit generalizability to those with a recent stroke or TIA attributable to s-ICAS. During an average follow-up of 15.2 months, the risk of stroke was 17.1% (6/35) in patients with a positive myocardial perfusion gated SPECT scan compared to 5.4% (2/37) in patients with a negative myocardial perfusion gated SPECT scan (OR 3.6, 95% CI 0.7–17.1). The risk of stroke and death was 22.9% (8/35) in patients with a positive myocardial perfusion gated SPECT scan compared to 8.1% (3/37) in patients with a negative myocardial perfusion gated SPECT scan (OR 3.4, 95% CI 0.8–12.9).

Using data from patients enrolled in WASID (Class I), investigators evaluated the early (within 90 days) risk of ischemic stroke in the territory of a stenotic intracranial artery after TIA as compared to stroke.[46] Among the cohort of patients with TIA, investigators also identified clinical and imaging predictors of recurrent stroke in the territory of the stenotic artery during the first 90 days. Of 569 patients enrolled in the WASID Study Group trial, 222 had TIA alone, 241 had stroke alone, and 106 had stroke combined with TIA as their QE. The median time from the QE to randomization was 17 days, and the mean follow-up was 1.9 years. Interestingly, the 90-day risk of ischemic stroke in the arterial territory was 6.9% (15/222) after TIA alone vs 4.7% (11/214) after stroke alone (OR 1.5, 0.7–3.3). The finding of a higher risk of recurrent stroke after TIA vs stroke is inconsistent with other analyses of WASID or SAMMPRIS.[6, 42, 49] This is likely due to the exclusion of patients with stroke combined with TIA as the QE and the relatively short-term follow-up period. In a subgroup analysis of patients with TIA alone, the risk of recurrent stroke in the territory of the stenotic artery by 90 days was only elevated for the predictor of infarction on imaging, with 16.7% (8/48) having a recurrent stroke compared to 3.8% (4/104) of those without infarction on imaging (OR 5.0, 95% CI 1.5–16.7). Male sex, age,

SBP >140 mm Hg, DBP >90 mm Hg, history of ischemic stroke, diabetes, CAD, WBC >7,200, anterior (vs posterior) location, >70% stenosis, and time from QE >17 days did not have significant associations with recurrent stroke; however, CIs were wide, suggesting the study may have been inadequately powered.

A prospective, single-center observation study (Class I) conducted in China enrolled patients within 3-months of stroke or TIA to observe the effect of atorvastatin on the progression of ICAS and explore the factors associated with atherosclerosis regression and the rate of recurrent stroke.[62] The study enrolled 40 stroke patients with MCA and/or basilar artery stenosis and elevated lipids. All patients were given atorvastatin 40mg daily and were observed for the primary outcome of progression of ICAS. At the end of the study, 23 (58%) patients had regressed ICAS, 15 (38%) patients had stationary ICAS, and 2 (4%) patients progressed ICAS, as determined by blinded review of MRAs at 6 months. At a mean follow up of 10.6 months, recurrent stroke occurred in 17.6% (3/17) of patients with progressed or stationery MRA findings compared with 17.4% (4/23) of those with regression of ICAS (OR 1.0, 95% CI 0.2–4.9).

A prospective cohort study (Class I) of patients enrolled in WASID evaluated racial differences in recurrent stroke between Black patients (N=174) and non-Hispanic White patients (N=331).[59] Participants self-identified their race and ethnicity as well as many other descriptive variables. Study endpoints were: (1) the composite of ischemic stroke, brain hemorrhage or vascular death (stroke or death); (2) ischemic stroke alone; or (3) stroke in the territory of the symptomatic artery. There was no significant difference in randomization to warfarin or aspirin between Black and White patients (52% of Black and 51% of White patients). Event rates at 2 years for Black patients were 28.2% with stroke or death outcomes, 25.3% with any stroke, and 17.2% with stroke in the territory of the stenotic vessel. The event rates for White patients were 18.6%, 15.8%, and 12.6% respectively. Black patients were more likely than White patients to have any stroke or death (HR 1.49, 95% CI 1.01–2.2) or ischemic stroke alone (HR 1.62, 95% CI 1.08–2.5). When stroke in the territory of the symptomatic artery was evaluated, there was no difference between Black and White patients (HR 1.30, 95% CI 0.53–3.2). Adjusted models were reported for the 2 primary outcomes. No significant difference was found between Black and White patients in instances of any stroke or death (HR 1.35, 95% CI 0.87–2.11), but there

was an increased risk of any stroke in Black patients (HR 1.62, 95% CI 1.00–2.63). The CIs suggest the study may have been inadequately powered leading to some decreased confidence in clinically meaningful differences between groups.

A Class I prospective cohort study of patients enrolled in WASID sought to determine if patients with intracranial stenosis who have a TIA or stroke while on antithrombotic therapy are at particularly high risk for recurrent stroke.[48] Patients self-reported whether they were on (N=299) or off (N=269) antithrombotic therapy at time of the QE. The primary endpoint was a composite of any stroke or vascular death and the secondary endpoint was stroke in the territory of the stenotic artery. The risk of any recurrent stroke or death was 21% (64/299) in patients on therapy compared to 23% (61/269) in those off therapy (OR 0.9, 95% CI 0.6–1.4). The risk of any recurrent stroke in the territory of the stenotic artery was 13% (39/299) in patients on therapy compared to 14% (38/269) in those off therapy (OR 1.0, 95% CI 0.6–1.5). Hence, failure of antithrombotic failure was not found to increase the risk of recurrent stroke.

A Class II prospective cohort study enrolling patient from September 2002 to December 2006 at 19 centers in Germany investigated the risk of recurrent of stroke in patients with s-ICAS.[50] A total of 304 consecutive patients with acute ischemic stroke or TIA due to 50%–99% ICAS were prospectively evaluated; however, only 201 patients (68.1%) were available for follow-up. The overall cumulative recurrent stroke rate after admission was 17.9% (95% CI 13.4–23.5) for the first year and 23.3% (95% CI 17.8–29.8) over 3 years. Only the point estimates and CIs for the risk factors of diabetes (HR 2.41, 95% CI 1.33–4.33) and previous stroke (HR 2.11, 95% CI 1.14–3.91) for predicting recurrent stroke were provided. No point estimates or events per risk factor were reported for non-significant factors.

A Class II, retrospective descriptive study at 2 centers in the U.S. evaluated the risk of early recurrent stroke in a cohort of patients with symptomatic >50% intracranial stenosis in whom intracranial angioplasty and stent placement were considered, but initially deferred.[44] The main finding was that among the 25 patients who were maintained on medical management, 14 (56%) were readmitted with recurrent ischemic events in the distribution of the target artery within a median of 28 days (range 1–243 days); however, time from QE to enrollment was not provided.

Patient-level data was provided allowing calculation of the risk of recurrent stroke dichotomized by various risk factors; however, the study was inadequately powered. The recurrent risk of stroke was increased among patients with stenosis >80% with a risk of 78% (7/9) in those with higher stenosis compared to 25% (4/16) in those with less severe stenosis (OR 10.5, 95% CI 1.8–65.4). No increased risk of recurrent stroke was found for history of diabetes, hypertension, dyslipidemia, CAD, PVD, previous stroke, smokers, alcohol users, failure of antithrombotic therapy, type of QE, SBP (>140 mm Hg), total cholesterol (>200 mg/dL), LDL-C (>90 mg/dL), or anterior (vs posterior) circulation. The study was inadequately powered and lacks generalizability because the cohort consisted only of patients who received an angiogram for consideration of an intervention and because some risk factors were assessed at time of deferred intervention (not at the time of the QE).

A Class I, prospective cohort study conducted in Japan studied 165 non-disabled patients with symptomatic atherosclerotic internal carotid artery or middle cerebral artery occlusive disease who underwent positron emission tomography from 1999 to 2008.[63] The purpose of this study was to determine whether misery perfusion is a predictor of subsequent stroke despite recent improvements in medical treatment for secondary prevention. Eighty-eight (53%) patients had s-ICAS, of whom 69 where managed medically (as compared to EC/IC bypass). Misery perfusion was defined as decreased cerebral blood flow, increased oxygen extraction fraction, and decreased ratio of cerebral blood flow to blood volume in the hemisphere supplied by the stenosed artery. All patients were followed for 2 years, or until stroke recurrence or death. In the 69 medically treated patients, 50% (2/4) with misery perfusion compared to 3% (2/65) without had a recurrent ischemic stroke (OR 31.5, 95% CI 3.7–288.4). Recurrent stroke occurred in 9.1% (2/22) of patients with increased OEF asymmetry compared with 4.3% (2/47) of those without (OR 2.3, 95% CI 0.3–15).

In a prospective cohort study of 226 patients from the medical arm of the Class I SAMMPRIS trial, investigators sought to determine the association between baseline lipoprotein(a) (Lp(a)) levels and the risk of vascular events during follow-up.[52] High Lp(a) was defined as >65 mg/dL in Black patients and >35 mg/dL in patients in all other racial categories. The primary outcome was any recurrent ischemic stroke. Overall, 18.5% (17/92) of patients with high Lp(a) levels had

an ischemic stroke during follow-up compared 17.9% (24/134) of patients with normal Lp(a) levels (OR 1.03, 95% CI 0.5–2.1). Although prior studies have suggested a pathogenic contribution of high Lp(a) to the development of ICAS, these results did not find an association between high Lp(a) and increased risk of recurrent stroke in patients with s-ICAS.

The Chinese Intracranial Atherosclerosis study (CICAS) (Class I) was a prospective, multicenter study enrolling consecutive patients from 22 Chinese hospitals <7 days after an ischemic stroke or TIA.[60] Patients with cardioembolic stroke were excluded and all patients underwent MRA with measurement of the diameter of the main intracranial arteries with ICAS as defined as having a ≥50% diameter reduction. The cohort was followed for 12 months for the outcome of recurrent stroke. Of 2864 patients, 1074 (37.5%) patients had intracranial lesions stenoses, 261 (9.1%) had both intracranial and extracranial stenoses, 141 (4.9%) had only extracranial stenoses, and 1388 (48.5%) had no significant occlusive disease. Multiple predictors were assessed for the risk of recurrent stroke among the entire cohort; however, the only information reported for recurrent stroke in the subgroup of patients with s-ICAS was severity and location of intracranial stenosis. The risk of recurrent stroke in patients with ≥70% stenosis compared to 50%–69% stenosis was 6.7% (67/995) vs 3.8% (13/340) with an OR of 1.8 (95% CI 0.99–3.3). The risk of recurrent stroke was 4.3% (29/670) in patients with an anterior circulation stenosis compared to 6.3% (21/334) in patients with posterior circulation stenosis (OR 0.7, 95% CI 0.4–1.2).

The Biomarkers of Ischemic Outcomes in Symptomatic Intracranial Stenosis (BIOSIS) study preliminary results reported whether serum biomarkers of inflammation and the number of circulating progenitor cells in participants with symptomatic intracranial stenosis are independent predictors of ischemic stroke.[51] Using blood samples from a subgroup of patients in the Class I SAMMPRIS trial, levels of inflammatory biomarkers (plasminogen activator inhibitor-1 (PAI-1), E-selectin, hs-CRP, and LpPLA2) and progenitor cells were analyzed for the pre-specified outcomes of interest: stroke in the territory of the symptomatic stenotic artery and any ischemic stroke. There were 451 patients with baseline blood samples and the median follow-up period was 32.4 months. In participants randomized to medical treatment only, dichotomized biomarker values (determined by using the median as the cut-point) revealed a trend between elevated

levels of PAI-1 (HR 1.85, 95% CI 0.95–3.62), hs-CRP (HR 1.82, 95% CI 0.96–3.44), and any ischemic stroke. None of the other inflammatory markers were associated with clinical outcomes. Low levels of progenitor cells enumerated revealed a trend toward association with ischemic stroke in the territory of the symptomatic stenotic artery for the treatment groups combined (HR 1.56, 95% CI 0.93–2.63).

A single-center Chinese cohort study (Class II) included 232 patients followed prospectively following a qualifying stroke or TIA attributed to MCA occlusion.[47] Patients must have survived >1 month from QE and have had at least one other vascular risk factor. The aim of the study was to evaluate the effect of concomitant intracranial arterial stenosis (≥50%) in at least one other vessel on recurrent risk of any stroke or death. The risk of recurrent stroke or death was 20.3% (30/148) in patients with concomitant ICAS compared to 6% (5/84) in patients with MCA occlusion without concomitant ICAS (OR 4.0, 95% CI1.5–10.4). For other predictors, events per group were not reported, but Cox-regression was used to calculate the risk for recurrent stroke or death. A history of hypertension (HR 3.7, 95% CI 1.5–9.0) or diabetes (HR 3.6, 95% CI 1.9–7.0) predicted the risk of recurrent stroke or death. No associations were found for age, gender, dyslipidemia, alcohol use, or smoking. Because this was a single-center Chinese cohort of only patients with their first-ever stroke due to MCA occlusion, it has limited generalizability to the broad cohort of symptomatic ICAS patients.

The rate of the primary endpoint in the medical group in SAMMPRIS was much lower than predicted from the preceding WASID trial. To investigate if patient characteristics vs more aggressive medical care explained this difference, investigators compared all 227 patients randomized to the medical arm of SAMMPRIS with the 143 participants in WASID who met similar enrollment criteria to those in SAMMPRIS.[42] The outcome for this analysis was the SAMMPRIS primary endpoint. After adjustment for confounding baseline characteristics, WASID patients had an almost 2-fold higher risk of the SAMMPRIS primary endpoint, which supported the hypothesis that the lower rate of the primary endpoint in the medical arm of SAMMPRIS compared with WASID patients was a result of the AMM used in SAMMPRIS. In addition, using the combined set of patients from WASID and SAMMPRIS, the authors evaluated the relationship between baseline characteristics and the SAMMPRIS primary

endpoint by reporting the bivariate HR for each predictor using the subgroups from both Class 1 studies. The HR for meeting the SAMMPRIS endpoint was significant for history of diabetes (HR 2.0, 95% CI 1.2–3.2), women (HR 2.0, 95% CI 1.2–3.2), not using a statin at enrollment (HR 1.8, 95% CI 1.1–2.9), modified Rankin score ≥1 (HR 1.8, 95% CI 1.0–3.3), NIH Stroke Scale score >1 (HR 1.9, 95% CI 1.2–3.1), and prior infarcts in the territory of the symptomatic artery (HR 1.8, 95% CI 1.1–2.9). No increased risk of having the endpoint was found for race, age, history of hypertension, smoking status, CAD, ischemic stroke as the QE, physical activity out of target, type of QE, failure of antithrombotic therapy, time from QE to randomization, anterior circulation (vs posterior), percent stenosis of symptomatic artery (by 10% increases), SBP, DBP, BMI, LDL-C, or HDL-C. The study may have been inadequately powered for many of the predictor variables as CIs could not exclude clinically meaningful associations.

To evaluate the effect of hemodynamics on stroke risk in the posterior circulation, VERiTAS (Class I) enrolled patients with a vertebrobasilar stenosis using the criteria listed previously and prospectively determined the risk of recurrent stroke.[43] At a median follow up of 23 months, the primary endpoint occurred in 28% (5/18) of patients with low distal flow status and 9% (5/54) of patients with normal distal flow status (OR 3.8, 95% CI 0.9–14.4). On adjusted analysis, the HR for low distal flow compared to normal was 11.6 (95% CI 1.9–71). Additionally, on adjusted analysis, age (year) (HR 0.80, 95% CI 0.70–0.91), history of CAD (HR 10.5, 95% CI 1.5–71.3), history of DM (HR 9.6, 95% CI 1.7–55.8), and physical activity <1 time/week (HR 16.6, 95% CI 1.7–200) were each associated with the primary endpoint. Gender, race, QE, prior stroke or TIA, time from QE to enrollment, DLP, smoking, alcohol use, BMI, stenosis severity ≥70%, and involvement of the basilar artery were not significant predictors of the primary outcome.

In a Class II study comprised of a subset of participants enrolled in the medical arm of SAMMPRIS (previously described), investigators evaluated if the presence of SVD) was associated with recurrent stroke.[64] Magnetic resonance imaging was performed in 66% (149/227) of participants in the medical arm and SVD was centrally adjudicated when an old lacunar infarct (grade 2–3 on the Fazekas scale) or ≥ 1 microbleed was detected. The primary outcomes were any recurrent ischemic stroke and any ischemic stroke in the territory of the stenotic artery during follow-up. Any ischemic stroke occurred in 23.7% (18/76) of participants with SVD

compared to 12.2% (9/73) of those without SVD (OR 2.21, 95% CI 0.93–5.2). Any ischemic stroke in the territory of the stenotic artery occurred in 17.1% (13/76) of those with SVD compared to 9.6% (7/73) of those without SVD (OR 1.95%, 95% CI 0.74–5.1).

In a subgroup analysis from SAMMPRIS (Class I), investigators used patients in the medical arm to evaluate baseline features associated with a high risk for the primary SAMMPRIS endpoint.[49] The risk of the primary endpoint was 24% (18/75) for those with a prior infarct in the territory of the symptomatic artery compared to 10.2% (15/147) for those with no previous infarct (OR 2.8, 95% CI 1.3–5.8). The risk of the primary endpoint was 8% (6/75) for QE as TIA compared to 18.4% (28/152) for stroke (OR 0.4, 95% CI 0.2–0.9). The risk of the primary endpoint was 29% (9/31) for those who were not on statin therapy at the time of enrollment compared to 12.8% (25/196) for those on statin therapy (OR 2.8, 95% CI 1.2–6.7). For the following predictors, no significant association was found between the risk factor and the endpoint: time from QE >7 days, failure of antithrombotic, age (>60), non-White (compared to White), men, glucose >200 mg/dL, diabetics, BMI (>29), history of hypertension, NIHSS >1, anterior circulation (compared to posterior), out of target for baseline physical activity, mRS >1, smokers, >80% stenosis, SBP >144 mm Hg, HDL-C >36.3 mg/dL, and LDL-C >90 mg/dL. However, the study was inadequately powered for many variables.

In a Class II prospective study involving patients with s-ICAS identified from a single academic medical center, investigators compared the 30-day risk of ischemic stroke in the territory of a stenotic artery based on various baseline risk factors.[53] Follow-up was available for 77.9% of patients and the risk of recurrent stroke for the cohort was high at 20.2%. Age, gender, ethnicity, diabetes, hypertension, HbA1c, LDL level, smoker, previous infarct, dyslipidemia, CAD, statin therapy, NIHSS score, vertebrobasilar location, and severity of stenosis were all evaluated as predictors of recurrent stroke. No risk factor accurately predicted recurrent stroke. However, the study had limited precision and decreased generalizability due to only following patients for 30 days, and changes in AMM occurred during the study period.

In a Class II subgroup study of the previously described CHANCE trial, investigators evaluated the relationship between number of infarctions and recurrent stroke at 90 days in the subgroup of

patients with s-ICAS who had MRI scans at the time of enrollment.[65] Only a minority of patients enrolled in the trial had MRI scans at admission and, in total, 481 patients with ICAS were identified. The primary outcome was any recurrent ischemic stroke at 90 days. The risk of recurrent stroke in patients with ICAS and multiple infarctions was 18% (33/183) compared to 9.1% (27/298) in those without (OR 2.2, 95% CI 1.3–3.8). Participants with any infarction (multiple or single) had a 14.8% (57/384) risk of recurrent stroke compared to 3.1% (3/97) in those without any baseline infarction (OR 5.5, 95% CI 1.7-16.7). The findings are limited due to the small percentage of patients who had received MRI scans and the early enrollment after only TIA or minor stroke.

In another subgroup analysis of the CHANCE trial (Class II) investigators assessed the association between neutrophil counts and recurrent stroke in participants with s-ICAS.[66] Only 8.8% of participants (457/5170) had both intracranial vascular imaging and neutrophil count measured, limiting validity of the subgroup analysis. The risk of recurrent stroke in those with a "lower" neutrophil level (<4.3 x 109 per L) was 10.2% (20/196) compared to 14.6% (38/261) in those with a "higher" neutrophil level (OR 0.67, 95% CI 0.38–1.19). The generalizability of the results is limited by inclusion criteria and the size of the subgroup.

In the previously described CHANCE trial, the authors undertook a subgroup analysis (Class II) evaluating the effect of hsCRP on recurrent among stroke the cohort of patients with ICAS.[55] The hsCRP level was dichotomized as elevated (i.e., high risk >3mg/L) or non-elevated and was performed in 74% of eligible patients. The risk of recurrent stroke was 13.2% (19/144) among those with elevated levels compared to 12.1% (26/214) among those with non-elevated levels (OR 1.1, 95% CI 0.6–2.1). The generalizability of the results is limited given the levels were drawn at 24 hours following randomization (+/- 12 hours), early after TIA or minor stroke, and prognostic accuracy may be modified by the chosen antiplatelet regimen.

In a cohort study (Class II) conducted at 2 centers in China, authors prospectively followed 153 patients within 7 days after an acute ischemic stroke attributed to 50%–99% ICAS in anterior circulation.[54] Researchers retrospectively adjudicated the stroke mechanism as: (1) parent artery atherosclerosis occluding penetrating artery, (2) artery-artery embolism, (3) hypoperfusion

(borderzone infarcts), and (4) mixed mechanisms, and reported excellent inter-rater agreement on classification. These stroke mechanisms were correlated with features of the patients at baseline and recurrent ischemic stroke in the same territory by 1 year was the primary outcome. The most common stroke mechanisms were a mixed mechanism of artery-artery embolism plus hypoperfusion (37.3%) and isolated hypoperfusion (35.3%). Thirty-one patients received PTAS and were excluded from analysis of predictors of recurrent stroke. Among the 122 patients who were treated medically, 13.9% (17/122) had a recurrent stroke in the territory of the stenotic artery by 1 year. When stratified by initial stroke mechanism, 1 recurrent stroke occurred in the artery-artery embolism group, 5 in the hypoperfusion group, and 11 in the patients with initial stroke due to the mixed mechanism of artery-artery embolism plus hypoperfusion. No recurrent strokes occurred in patients with the initial stroke mechanism due to parent artery atherosclerosis occluding a penetrating artery. Due to the small numbers, the authors compared the probability of the primary outcome in those with the mixed mechanism of artery-artery embolism plus hypoperfusion (24.4%, 11/45) with the probability in those with other initial mechanisms (7.8%, 6/77) (OR 3.8, 95% CI 1.3–10.9). The risk of recurrent stroke in those with any hypoperfusion was 17.6% (16/91) compared to 3.2% (1/31) in those without (OR 6.4, 95% CI 0.98–38.9). The authors also reported the risk of recurrent stroke based on other baseline risk factors. The risk of recurrent stroke was 18.5% (15/81) in those with a history of hypertension compared to 4.9% (2/41) in those without (OR 4.4, 95% CI 1.03–18.1). The risk of recurrent stroke was 31.3% (5/16) in those with previous history of stroke or TIA compared to 11.3% in those without (OR 3.6, 95% CI 1.1–11.7). Other risk factors did not demonstrate significant associations with the primary outcome. The studies generalizability was limited given 20% of the cohort was excluded from analysis due to receiving PTAS and only the patients' anterior circulation ICAS were included in the study.

Another post hoc subgroup analysis of SAMMPRIS (Class II) evaluated hemodynamic markers in the anterior circulation as predictors of recurrent stroke with the aim of determining the association between borderzone infarct pattern and impaired collateral flow at the time of the QE on rates of recurrent stroke.[58] The analysis was restricted to patients in the medical arm whose baseline brain imaging showed an acute infarct distal to a stenosis of an intracranial carotid artery or MCA. The outcome of interest was ischemic stroke in the territory of the stenotic artery

after enrollment (median 32.7 months of follow-up). Infarcts were adjudicated as involving primarily internal or cortical borderzone territories as compared non-borderzone infarcts (core middle cerebral artery territory or perforator territories). Collateral flow was defined according to the American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology scale and reported as impaired (grade 0–3) or complete collaterals (grade 4). Outcome was determined without knowledge of hemodynamic status. The risk of recurrent stroke was 26.4% (14/53) in those with borderzone infarcts compared to 10.4% (5/48) in those with non-borderzone infarcts (OR 3.1, 95% CI 1.04–9.0). The risk of recurrent stroke was 27.1% (13/48) in those with impaired collateral flow compared to 5.9% (2/34) in those with complete collateral flow (OR 5.9, 95% CI 1.3–25.1). In patients with borderzone infarcts and impaired collaterals, the risk of recurrent stroke was 36.7% (11/30) compared to 7.7% (4/52) in the control group (OR 6.9, 95% CI 2.0–23.2).

In another subgroup analysis of CHANCE (Class II) comprising 11.2% (460/4125) of patients enrolled, investigators evaluated the role of cerebral small vessel disease (CSVD) and concomitant ICAS on recurrent stroke.[67] The subgroup analysis included patients who received intracranial vascular imaging, and the primary outcome was recurrent stroke at 3 months (no intracranial hemorrhages occurred). The presence of severe CSVD was associated with a 9.9% (15/152) risk of recurrent stroke compared to a 13% (40/308) risk in those with no or slight CSVD (OR 0.7, 95% CI 0.4–1.4). The presence of >1 ICAS segment was associated with a recurrent stroke risk of 13.8% (29/210) compared to 10.4% (26/250) in those with only one ICAS segment (OR 1.4, 95% CI 0.8–2.4). The study was limited by the small proportion of patients who underwent intracranial imaging, enrolling only patients with minor stroke or TIA early after the index event, and that antiplatelet therapy regimens may have confounded the results.

A Class II retrospective cohort study identified patients from the Stanford stroke database with s-ICAS with the aim of evaluating the natural history of those failing antithrombotic therapy.[112] The endpoint was a composite of recurrent stroke and TIA, which occurred in 62.5% (5/8) of those failing antithrombotic therapy compared to 47.7% (21/44) not initially failing therapy (OR 1.8, 95% CI 0.5–8.0). The rates of recurrent of stroke and death were not provided separately.

The effect of other risk factors on prognostic accuracy for presenting as an antithrombotic failure were evaluated; however, the study did not compare the risk of recurrent stroke for other predictors.

A Class I, single-center prospective study conducted in China enrolled 114 consecutive patients with s-ICAS and MCA stenosis to evaluate the clinical significance of micro embolic signals (MES) detected on TCD within 3 days from QE.[113] The signals on a digital audio recording were analyzed by an independent observer who was masked to all other data. The number of MES during the 30-minute recording was noted. All patients were followed for the occurrence of recurrent stroke or TIA related to the index MCA territory. In patients with MES, 24% (6/25) had a recurrent stroke or TIA compared to 6.7% (6/89) of those without microembolic signals (OR 4.4, 95% CI 1.3–14.6). However, recurrent stroke or death risks were not separately reported and 25% of patients included did have initial symptoms attributable to the stenotic MCA, limiting generalizability of the results.

A prospective multicenter observational study conducted in France (GESICA) (Class II) evaluated the recurrent risk of stroke in 102 patients with s-ICAS within 6 months of a non-disabling stroke or TIA.[114] The following baseline demographics were prospectively collected: hemodynamic stenosis (positional symptoms), sex, diabetes, hypertension, hypercholesterolemia, anticoagulant and antiplatelet therapy regimens, vascular distribution, and presence of coexisting stenosis. Angiograms were retrospectively reviewed and recurrent stroke risk assessed with a median follow up of 23.4 months. During the study period, 38.2% of patients had a recurrent stroke or TIA. The only variable associated with recurrent stroke or TIA was hemodynamic stenosis; recurrent stroke or TIA occurred in 60.7% (17/28) of patients with hemodynamic stenosis compared to 32% (24/74) without (OR 3.2, 95% CI 1.3–7.9). However, separate data on recurrent stroke or death without the composite including TIA was not reported.

A Class I, prospective single-center trial conducted in Spain enrolled 71 patients with first-ever TIA or ischemic stroke attributable to an intracranial stenosis to determine the prognostic significance of serum hs-CRP.[115] Patients were followed for 1 year. Endpoint events included ischemic stroke or TIA attributable to intracranial stenosis, ischemic stroke or TIA unrelated to

intracranial stenosis, and coronary ischemic events and sudden death Using an hsCRP level of 1.41 mg/dL as the cut-off point, hs-CRP level was an independent predictor of further major vascular events (HR 7.14, 95% CI 1.77–28.73). Using the same cut-off point, hs-CRP level also was an independent predictor or recurrent TIA or stroke in the territory of the stenotic artery (HR 30.67, 95% CI 3.6 –255). Stroke or stroke or death alone were not reported, and the patients were enrolled a minimum of 3 months after the QE which may limit generalizability.

In a prospective cohort study conducted in Spain, investigators evaluated the association of a composite of major vascular events (TIA, stroke, or MI) and progression of ICAS on TCD with a variety of pro-inflammatory markers and raised concentrations of endogenous fibrinolysis inhibitors.[115] Although the authors found a strong association with these surrogate markers and composite of vascular events, individual events of recurrent stroke or stroke and death were not reported separately. Using the same patient population in a subsequent study (Class I), the authors aimed to prospectively investigate the relationship between the CRP gene C1444T polymorphism and the risk of recurrent ischemic events.[115] The risk of the composite primary outcome (stroke, TIA, MI, angina, or vascular death) was 35% (14/40) in those with the CRP gene C1444T allele compared to 11.4% (4/35) in those without the allele (OR 4.2, 95% CI 1.3–13.5). The risk of recurrent stroke or TIA was 25% (10/40) in those with the CRP gene C1444T allele compared to 8.6% (3/35) in those without the allele (OR 3.6, 95% CI 0.9–13.1). Events for recurrent stroke or stroke and death alone were not separately reported.

In a Class I, single-center prospective cohort of patients with TIA or stroke attributed to ICAS, investigators evaluated the ankle-brachial index and serum inflammatory markers as predictors of recurrent cerebrovascular events.[116] After a median follow-up of 22.4 months, having a new cerebrovascular event was associated with an ankle brachial index <0.8 in 28.6% (10/35) of patients compared to 8.1% (3/38) of patients with an index >0.8 (OR 4.7, 95% CI 1.2–17.4); however, recurrent stroke or stroke and death was not reported. Additionally, patients were enrolled >3 months after the QE which limits generalizability.

In a Class I prospective cohort study from a single center in China, investigators evaluated multiple risk factors in predicting recurrent stroke in patients they adjudicated to have s-ICAS.[117]

The mean age was 63.5 years (+/-11.5 years) and 85.2% (121/142) of patients completed follow-up. The authors included patients with mild (0%–39%) stenosis and only patients who refused or had unfavorable anatomy for intracranial stent placement. The primary and secondary outcomes included TIA, MI, and acute angina. Recurrent stroke was not reported separately. After an average follow-up of 15.2 months, the authors found only diabetes and severity of stenosis predicted recurrent ischemic events. The study is limited by not reporting separately on recurrent stroke and has decreased generalizability due to the patient population enrolled.

Appendix 6. Rationale of factors considered in developing the practice recommendations

In this appendix, *EVID* refers to evidence systematically reviewed; *RELA* to strong evidence derived from related conditions; *PRIN* to axiomatic principles of care; and *INFER* to inferences made from one or more statements in the recommendation rationale.

In the tables that follow, consensus is considered to have been reached if 80% or more of the guideline panel agree on the strength of a given domain. For nonpremise domains, intensity of shading corresponds to the number of panel members who were in agreement (shading of greater intensity indicates a larger number of panel members who reached agreement). The strength of the recommendation is anchored to the strength of the inference. The recommendation strength can be downgraded for any modifier; it can be upgraded only by one level for a moderate to large benefit relative to harm. In addition, domains include the premises and factors on which the recommendations are based.

Diagnosis

Recommendation 1 rationale

S-ICAS is one of the most common causes of stroke worldwide, responsible for 10%–50% of strokes depending on racial and ethnic factors,[2, 4, 68] and can coexist with other stroke etiologies such as extracranial atherosclerosis or atrial fibrillation [EVID, RELA].[69, 70] There is no diagnostic gold standard for diagnosing s-ICAS and various noninvasive and invasive techniques (e.g., MRA, CT angiography, TCD, and catheter cerebral angiography) are used with varying sensitivity and specificity [RELA].[71, 72] Intracranial artery luminal stenosis may be due to a variety of vasculopathies and atherosclerosis may be differentiated clinically in most cases

[RELA].[5] It is important to identify s-ICAS as the etiology of stroke to optimize secondary prevention strategies [PRIN, INF]. Expeditious evaluation is reasonable as the highest risk of recurrent stroke is soon after the incident event [EVID].

Recommendation 1 statement

1) 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 (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 0	Benefit > harm 1	Benefit >> harm 7	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 13	Critically important 3	Yes
Variation in preferences	Large 0	Moderate 1	Modest 6	Minimal 9	Yes
Feasible	Rarely 0	Occasionally 1	Usually 12	Always 3	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 12	Small 3	Yes
Strength of recommendation	R/U	C	B	A	

Antithrombotic Medication Therapy

Rationale for recommendations 2, 3, and 4

WASID showed that in patients with s-ICAS, aspirin 650 mg twice a day was safer and as effective as warfarin for preventing the combined endpoint of stroke, ICH, and vascular death [EVID]. While the optimal aspirin dose for s-ICAS has not been determined, patients in the medical arm of the SAMMPRIS trial were treated with aspirin alone 325 mg/d after the first 90 days [EVID]. 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 [EVID]. The safety and efficacy of novel oral anticoagulants for prevention of stroke in s-ICAS are not established [EVID]. 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 [EVID]. 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 [EVID].

Combination short-term clopidogrel and aspirin use in s-ICAS was not directly supported by this systematic review but is supported by related evidence [EVID, RELA].[21, 73] The CLAIR trial showed that patients randomized to clopidogrel plus aspirin had significantly decreased microemboli in the territory of the stenotic artery when compared with aspirin alone [RELA].[21] When combined with the CARESS trial, 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 [RELA].[73] In addition, s-ICAS patients in the CHANCE trial 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 [EVID]. 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%) [EVID, RELA].[33, 37] 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 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 if extending clopidogrel use beyond 3 months is warranted [EVID/PRIN].

Trials of cilostazol combined with other antiplatelet agents for stroke prevention in s-ICAS have had mixed results [EVID]. The TOSS and TOSS-2 trials found cilostazol plus aspirin was not better for stroke prevention than aspirin alone or clopidogrel plus aspirin [EVID]. However, 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 [EVID]. Subgroup analysis of patients with s-ICAS in the CSPS trial, 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 [EVID]. 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 [EVID].

Recommendation statements 2, 3, and 4

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 9	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 7	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 2	Always 14	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 11	Yes
Strength of recommendation	R/U	C	B	A	

3) 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 and low risk of hemorrhagic transformation (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 2	Benefit >> harm 6	Benefit >>> harm 7	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 10	Critically important 4	Yes
Variation in preferences	Large 0	Moderate 1	Modest 8	Minimal 6	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 9	Small 6	Yes
Strength of recommendation	R/U	C	B	A	

4) 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 (Level C).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 7	Benefit >> harm 5	Benefit >>> harm 2	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 4	Very important 8	Critically important 2	Yes
Variation in preferences	Large 0	Moderate 5	Modest 7	Minimal 2	Yes
Feasible	Rarely 0	Occasionally 2	Usually 8	Always 4	Yes
Cost relative to net benefit	Very large 0	Large 3	Moderate 9	Small 2	Yes
Strength of recommendation	R/U	C	B	A	

Lipid and Hypertension Vascular Risk Factor Modification

Rationale for recommendations 5 and 6

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 [EVID, PRIN]. 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 [RELA].[74] In addition, a lower rate of cerebrovascular events was seen in s-ICAS patients randomized to high-intensity statin therapy compared with other dosages [EVID].[26] 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 [RELA].[75] Post-hoc analyses from WASID and SAMMPRIS also show lower rates of vascular events with lower LDLs in s-ICAS [EVID]. 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 [EVID, RELA].[74]

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 [RELA].[76] Analyses from WASID, SAMMPRIS, and the CICAS registry have demonstrated that among clinically stable patients with s-ICAS, a mean 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 [EVID, RELA].[38, 70, 77] 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 [EVID, RELA].[78] Some subgroups of patients with s-ICAS may be at higher risk of stroke with lower BPs, including those with hemodynamic impairment[40, 79] or those with a large reduction in BP from baseline [EVID, RELA].

Recommendation statements 5 and 6

5) 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 stroke and vascular events (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 1	Benefit >> harm 6	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 1	Very important 9	Critically important 5	Yes
Variation in preferences	Large 0	Moderate 3	Modest 8	Minimal 4	Yes
Feasible	Rarely 0	Occasionally 0	Usually 5	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 9	Small 5	Yes
Strength of recommendation	R/U	C	B	A	

6) 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 stroke and vascular events (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 7	Benefit >>> harm 8	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 7	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 0	Modest 10	Minimal 5	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 6	Small 9	Yes
Strength of recommendation	R/U	C	B	A	

Physical Activity

Rationale for recommendation 7

In the general population, moderate physical activity reduces incidents of stroke [RELA].[80] 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 (OR 6.7, 95% CI 2.5–18.1) [EVID].

Recommendation statement 7

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 7	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 11	Yes
Feasible	Rarely 0	Occasionally 0	Usually 1	Always 14	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

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 s-ICAS [PRIN].

Recommendation statement 8

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 3	Critically important 12	Yes
Variation in preferences	Large 0	Moderate 1	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 0	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 5	Small 10	Yes
Strength of recommendation	R/U	C	B	A	

Bilateral Ischemic Preconditioning

Rationale for recommendation 9

Based on 2 RCTs done in patients with s-ICAS, 5 cycles of BAIPC twice daily appears to reduce the risk of recurrent stroke and death [EVID]. 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 multiethnic population [EVID]. While the risk of the procedure appears low, the BAIPC device does not have approval for use in the United States, limiting its application [EVID]. These methodologic issues limit confidence in conclusions about efficacy and there are no data in a multi-ethnic population.

Recommendation statement 9

9) The writing group could not achieve consensus on a recommendation for BAIPC in patients with s-ICAS.

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	No
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	No
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low 10	Moderate	High	
Benefit relative to harm	Harm ≥ benefit 2	Benefit > harm 5	Benefit >> harm 6	Benefit >>> harm 1	No
Importance of outcomes	Not important or unknown 2	Mildly Important 5	Very important 5	Critically important 2	No
Variation in preferences	Large 4	Moderate 9	Modest 1	Minimal 0	Yes
Feasible	Rarely 6	Occasionally 7	Usually 1	Always 0	Yes
Cost relative to net benefit	Very large 0	Large 4	Moderate 10	Small 0	Yes
Strength of recommendation	R/U	C	B	A	

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 [EVID]. 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 [EVID].

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 neurologic symptoms, have reported conflicting rates of periprocedural complications [RELA].[82, 83] In an 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[RELA].[84, 85] 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 [EVID]. 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 [EVID, RELA].[7, 86]

Angioplasty alone

In light of safety issues related to PTAS, balloon angioplasty alone has been considered a possible alternative endovascular therapy [RELA].[87] However, no RCTs have compared angioplasty alone with medical therapy for stroke prevention in patients with s-ICAS [EVID]. 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 [EVID, RELA].[88] Balloon angioplasty alone may be performed with a submaximal staged approach, which may have a lower rate of morbidity and mortality [RELA, EVID].[89]

Optimal stroke prevention for patients with s-ICAS who have recurrent strokes despite antiplatelet therapy and intensive treatment of risk factors is unknown [EVID]. However, given the lack of efficacy data, the use of PTAS or angioplasty alone for the purpose of stroke prevention in any subpopulation of patients with s-ICAS is investigational [EVID, RELA].[87, 88, 89]

Recommendation statements 10–13

10) Clinicians should NOT recommend PTAS as the initial treatment for stroke prevention in patients with severe (70%–99%) s-ICAS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 10	Yes
Variation in preferences	Large 1	Moderate 1	Modest 4	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 14	Yes
Strength of recommendation	R/U	C	B	A	

11) Clinicians should NOT recommend PTAS for stroke prevention in patients with moderate (50%–69%) s-ICAS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 3	Benefit >>> harm 13	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 5	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 1	Usually 3	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 15	Yes
Strength of recommendation	R/U	C	B	A	

12) Clinicians should NOT routinely recommend angioplasty alone for stroke prevention in patients with s-ICAS outside clinical trials (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 5	Benefit >>> harm 11	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 2	Modest 6	Minimal 8	Yes
Feasible	Rarely 0	Occasionally 2	Usually 4	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 2	Small 14	Yes
Strength of recommendation	R/U	C	B	A	

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

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm > benefit 1	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 12	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 8	Yes
Variation in preferences	Large 0	Moderate 2	Modest 2	Minimal 10	Yes
Feasible	Rarely 0	Occasionally 2	Usually 2	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 0	Small 13	Yes
Strength of recommendation	R/U	C	B	A	

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 s-ICAS are informed by 1 RCT [EVID]. The 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 sub-groups with severe MCA stenosis or occlusion, there was an increased risk of recurrent stroke or death with direct bypass [EVID]. Similar to the EC/IC bypass study, the COSS trial, which studied patients with symptomatic ICA occlusion, found that direct bypass increases the risk of stroke and death predominantly due to early periprocedural complications [RELA].[90] 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 [RELA].[91, 92]

Indirect bypass

In patients with anterior circulation s-ICAS, indirect bypass with encephaloduroarteriosynangiosis (EDAS) is an emerging investigational surgery for stroke prevention [RELA].[93, 94, 95, 96, 97] A small initial study of indirect revascularization without standardized medical management showed a high rate of recurrent stroke in patients with s-ICAS [RELA].[94] Four non-randomized studies, including 2 small case series,[93, 96] 1 single-center prospective study,[97] and 1 two-center prospective trial with independent outcomes assessment,[98] 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 [RELA].

Recommendation statements 14 and 15

14) Clinicians should NOT recommend direct bypass for stroke prevention in patients with s-ICAS (Level B).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate 10	High	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 15	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 5	Critically important 11	Yes
Variation in preferences	Large 0	Moderate 1	Modest 2	Minimal 13	Yes
Feasible	Rarely 0	Occasionally 3	Usually 1	Always 12	Yes
Cost relative to net benefit	Very large 0	Large 0	Moderate 1	Small 15	Yes
Strength of recommendation	R/U	C	B	A	

15) Clinicians must NOT routinely recommend indirect surgical revascularization for stroke prevention in patients with s-ICAS outside clinical trials (Level A).

Domain	Rating				Consensus
Rationale is logical	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Evidence statements are accurate	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Axioms are true	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Related evidence is strong and applicable	< 50%	50% to < 80%	80% to < 100%	100%	Yes
Internal inferences logically follow	< 50%	50% to < 80%	80% to < 100%	100%	N/A
Confidence in inferences and evidence	Very low	Low	Moderate	High 10	
Benefit relative to harm	Harm ≥ benefit 0	Benefit > harm 0	Benefit >> harm 1	Benefit >>> harm 14	Yes
Importance of outcomes	Not important or unknown 0	Mildly Important 0	Very important 6	Critically important 9	Yes
Variation in preferences	Large 0	Moderate 0	Modest 2	Minimal 13	Yes
Feasible	Rarely 0	Occasionally 3	Usually 2	Always 10	Yes
Cost relative to net benefit	Very large 0	Large 1	Moderate 0	Small 14	Yes
Strength of recommendation	R/U	C	B	A	