Stroke Prevention in Symptomatic Large Artery Intracranial Atherosclerosis Practice Advisory

Report of the AAN Guideline Subcommittee

Tanya N. Turan, MD, MSCR, Osama O. Zaidat, MD, Gary S. Gronseth, MD, Marc I. Chimowitz, MBChB, Antonio Culebras, MD, Anthony J. Furlan, MD, Larry B. Goldstein, MD, Nestor R. Gonzalez, MD, Julius G. Latorre, MD, MPH, Steven R. Messé, MD, Thanh N. Nguyen, MD, Rajbeer S. Sangha, MD, Michael J. Schneck, MD, MBA, Aneesh B. Singhal, MD, Lawrence R. Wechsler, MD, Alejandro A. Rabinstein, MD, Mary Dolan O’Brien, MLIS, Heather Silsbee, and Jeffrey J. Fletcher, MD, MSc

Neurology® 2022;98:486-498. doi:10.1212/WNL.000000000000200030

Abstract

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

Methods

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

1. For patients with a history of sICAS, which medical therapies, as compared with no therapy or an alternative therapy, reduce the risk of recurrent stroke/death or increase the risk of major hemorrhage (therapeutic scheme)?
   a. Anticoagulation vs antiplatelet therapy
   b. Specific antiplatelet therapy regimens vs alternative regimens
   c. Antihypertensive agents or blood pressure (BP) control targets
   d. Statin therapy or lipid targets
   e. Ischemic preconditioning

2. For patients with a history of sICAS, do endovascular or extracranial to intracranial (EC/IC) bypass procedures, as compared with no procedure, reduce the risk of recurrent stroke or death (therapeutic scheme)?

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

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

For therapeutic questions, only studies that randomly allocated patients with sICAS to different treatment groups and followed patients to compare their subsequent risks of recurrent stroke or death were included in the systematic review.
and intention-to-treat analyses were used to inform conclusions. The author panel determined a priori that the effect measure used would be risk differences (RDs), with a change of 5% considered clinically meaningful. Generic inverse variance random effects meta-analytic models were used to pool effect sizes as we expected substantive heterogeneity based on patient selection, time from qualifying event, medical management, duration of follow-up, or inclusion and exclusion criteria. For the primary analysis, we utilized studies with the lowest risk of bias and greatest generalizability to inform conclusions.

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

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

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

Analysis of Evidence

The panel searched the MEDLINE, Cochrane, and Science Citation Index databases from database inception to February 2016 for relevant peer-reviewed articles that met inclusion criteria. The panels reviewed the titles and abstracts of 2,325 articles for relevance, which resulted in 505 obtained for full-text review. Independent review of the 505 articles by 2 panel members resulted in 45 articles for inclusion in the analysis and evidence rating. An updated literature search following the same process was conducted in November 2020, yielding 1,233 articles. Of the reviewed abstracts, 34 were identified for full-text review and 11 new articles were ultimately selected to inform conclusions.

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

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of warfarin, as compared with aspirin, in reducing the recurrent risk of stroke or death (RD –0.3%, 95% CI –0.8% to 0.2%; very low confidence in the evidence, 1 Class I trial, confidence downgraded due to imprecision).

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

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

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

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

Cilostazol Regimens

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of cilostazol plus aspirin or clopidogrel (DAFT), as compared with monotherapy (aspirin or clopidogrel), for reducing the risk of recurrent stroke or death (RD –3%, 95% CI –8% to 3%; I² = 57%; very low confidence in the evidence, 1 Class I study and 1 Class II study, confidence downgraded for insufficient precision). The risk of serious hemorrhagic complications is likely not
different between DAPT with cilostazol compared with monotherapy (RD 0%, 95% CI −1% to 0%; I² = 0%; moderate confidence in the evidence, 1 Class I study15 and 1 Class II study16).

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of DAPT with cilostazol plus aspirin, as compared with clopidogrel plus aspirin, in reducing recurrent stroke or death (RD 1.7%, 95% CI −2.4% to 5.7%; very low confidence in the evidence, 1 Class I study17, confidence downgraded due to imprecision). DAPT with cilostazol plus aspirin is likely not associated with any difference in hemorrhagic complications compared with clopidogrel plus aspirin (RD −1.8%, 95% CI −4.9% to 0.8%; moderate confidence in the evidence, 1 Class I study17).

**DAPT With Aspirin and Clopidogrel Regimens**

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of DAPT with clopidogrel plus aspirin, compared with aspirin monotherapy, initiated soon after high-risk TIA or stroke in reducing the risk of recurrent stroke or death (RD −3%, 95% CI −7% to 1%; I² = 0%; very low confidence in the evidence, 1 Class I study17 and 1 Class II study19, confidence downgraded due to imprecision and indirectness).

For patients with sICAS, it is possible that short-term DAPT with clopidogrel plus aspirin does not increase the risk of hemorrhagic complications compared with aspirin monotherapy in patients with TIA or minor stroke (RD −1%, 95% CI −2% to 1%; I² = 7%; low confidence in the evidence, 1 Class I study20 and 1 Class II study19, confidence downgraded due to indirectness).

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

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of intensive vs modest BP control in reducing the risk of recurrent stroke or death (RD 0%, 95% CI −8.5% to 7.2%; very low confidence in the evidence, 1 Class IV study21 with insufficient precision).

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

For patients with sICAS, there is insufficient evidence to support or refute the effectiveness of any statin therapy or other lipid-lowering regimens in reducing the recurrent risk of stroke or death (very low confidence in the evidence, 2 Class IV studies22,23).

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

In patients with sICAS, bilateral arm ischemic preconditioning (BAIPC) is likely effective in reducing the risk of recurrent stroke (RD −15%, 95% CI −27% to −2%; I² = 0%; moderate confidence in the evidence, 2 Class II studies24,25).

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

For patients with symptomatic severe middle cerebral artery (MCA) stenosis, EC/IC direct bypass, as compared with medical therapy alone, is highly likely to increase the risk of recurrent stroke or death (RD 20.3%, 95% CI 2.5%–36.7%; high confidence in the evidence, 1 Class I study26, confidence upgraded due to magnitude of effect).

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

For patients with recent TIA or nondisabling stroke attributed to sICAS, it is highly likely that percutaneous transluminal angioplasty and stenting (PTAS) plus AMM, compared with AMM alone, increases the early risk of recurrent stroke and death (RD 13%, 95% CI 3%–24%; I² = 59%; high confidence in the evidence, 2 Class I studies27–29 with large magnitude of effect).

For patients with recent TIA or nondisabling stroke attributed to sICAS, it is possible that PTAS plus AMM, compared with AMM alone, does not reduce the long-term risk of recurrent stroke or death (RD 3%, 95% CI −3% to 8%; I² = 86%; low confidence in the evidence, 2 Class I studies27–29 confidence downgraded due to imprecision).

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

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

**Practice Recommendations**

**Diagnosis**

**Rationale for Recommendation 1**

sICAS is one of the most common causes of stroke worldwide, responsible for 10%–50% of strokes depending on racial and ethnic factors3–30 and can coexist with other stroke etiologies such as extracranial atherosclerosis or atrial fibrillation.31,32 There is no diagnostic gold standard for diagnosing sICAS and various noninvasive and invasive techniques (e.g., magnetic resonance angiography, CT angiography, transcranial Doppler, and catheter cerebral angiography) are used with varying sensitivity and specificity.33,34 Intracranial artery
Table 1 Predictors of Recurrent Stroke or Death in Patients With Symptomatic Intracranial Atherosclerotic Arterial Stenosis

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>No Increased Risk</th>
<th>Point Estimate</th>
<th>Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor control during follow-up</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (out of target)&lt;sup&gt;18&lt;/sup&gt;</td>
<td></td>
<td>1.7</td>
<td>High</td>
</tr>
<tr>
<td>Mean arterial pressure (out of target)&lt;sup&gt;36&lt;/sup&gt;</td>
<td></td>
<td>2.8</td>
<td>Moderate</td>
</tr>
<tr>
<td>Diastolic blood pressure (out of target)&lt;sup&gt;40&lt;/sup&gt;</td>
<td></td>
<td>2.2</td>
<td>Moderate</td>
</tr>
<tr>
<td>Strict BP control plus low distal flow status&lt;sup&gt;11&lt;/sup&gt;</td>
<td></td>
<td>6.2</td>
<td>Low</td>
</tr>
<tr>
<td>TC (out of target)&lt;sup&gt;36&lt;/sup&gt;</td>
<td></td>
<td>2.1</td>
<td>Moderate</td>
</tr>
<tr>
<td>TC/HDL ratio (out of target)&lt;sup&gt;36&lt;/sup&gt;</td>
<td></td>
<td>1.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Non-HDL cholesterol (out of target)&lt;sup&gt;36,18&lt;/sup&gt;</td>
<td></td>
<td>1.4</td>
<td>Low</td>
</tr>
<tr>
<td>LDL cholesterol (out of target)&lt;sup&gt;36,18&lt;/sup&gt;</td>
<td></td>
<td>1.3</td>
<td>Low</td>
</tr>
<tr>
<td>Physical activity (out of target)&lt;sup&gt;18&lt;/sup&gt;</td>
<td></td>
<td>6.7</td>
<td>High</td>
</tr>
<tr>
<td>Alcohol use (out of target)&lt;sup&gt;36&lt;/sup&gt;</td>
<td></td>
<td>1.8</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hemoglobin A1c (out of target)&lt;sup&gt;18&lt;/sup&gt;</td>
<td></td>
<td>2.3</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Modifiable risk factors at baseline</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e19&lt;/sup&gt;</td>
<td></td>
<td>1.3</td>
<td>Low</td>
</tr>
<tr>
<td>Diastolic BP (lower)&lt;sup&gt;e20&lt;/sup&gt;</td>
<td></td>
<td>0.9</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hypertension (no history)&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e9&lt;/sup&gt;</td>
<td></td>
<td>0.9</td>
<td>Low</td>
</tr>
<tr>
<td>HDL cholesterol&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e19&lt;/sup&gt;</td>
<td></td>
<td>1.0</td>
<td>Low</td>
</tr>
<tr>
<td>Glucose &gt;200 mg/dL&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e19&lt;/sup&gt;</td>
<td></td>
<td>2.0</td>
<td>Moderate</td>
</tr>
<tr>
<td>History of diabetes&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e21&lt;/sup&gt;</td>
<td></td>
<td>1.6</td>
<td>Moderate</td>
</tr>
<tr>
<td>Elevated triglycerides&lt;sup&gt;e22&lt;/sup&gt;</td>
<td></td>
<td>1.6</td>
<td>Moderate</td>
</tr>
<tr>
<td>Physical activity (less active)&lt;sup&gt;e9&lt;/sup&gt;</td>
<td></td>
<td>1.1</td>
<td>Low</td>
</tr>
<tr>
<td>Body mass index&lt;sup&gt;e9&lt;/sup&gt;</td>
<td></td>
<td>1.4</td>
<td>Low</td>
</tr>
<tr>
<td>Smoker&lt;sup&gt;e9&lt;/sup&gt;</td>
<td></td>
<td>1.0</td>
<td>Low</td>
</tr>
<tr>
<td>History of coronary artery disease&lt;sup&gt;e6&lt;/sup&gt;&lt;sup&gt;,e20&lt;/sup&gt;</td>
<td></td>
<td>0.95</td>
<td>Low</td>
</tr>
<tr>
<td>Failure of antithrombotic therapy&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e23&lt;/sup&gt;</td>
<td></td>
<td>1.0</td>
<td>Low</td>
</tr>
<tr>
<td><strong>Nonmodifiable risk factors at baseline</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misery perfusion (SPECT)&lt;sup&gt;e32&lt;/sup&gt;</td>
<td></td>
<td>31.5</td>
<td>High</td>
</tr>
<tr>
<td>Impaired flow (vs complete)&lt;sup&gt;e12&lt;/sup&gt;</td>
<td></td>
<td>5.9</td>
<td>Low</td>
</tr>
<tr>
<td>Qualifying infarct = borderzone&lt;sup&gt;e12&lt;/sup&gt;</td>
<td></td>
<td>3.1</td>
<td>Low</td>
</tr>
<tr>
<td>Low distal flow status on quantitative magnetic resonance angiography&lt;sup&gt;e11&lt;/sup&gt;</td>
<td></td>
<td>3.4</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;70% stenosis (vs 50%–69%)&lt;sup&gt;e33&lt;/sup&gt;</td>
<td></td>
<td>2.0</td>
<td>High</td>
</tr>
<tr>
<td>Anterior vs posterior circulation&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e33&lt;/sup&gt;</td>
<td></td>
<td>1.0</td>
<td>High</td>
</tr>
<tr>
<td>NIH Stroke Scale &gt;1&lt;sup&gt;e9&lt;/sup&gt;</td>
<td></td>
<td>1.8</td>
<td>High</td>
</tr>
<tr>
<td>Stroke as QE&lt;sup&gt;e9&lt;/sup&gt;</td>
<td></td>
<td>0.6</td>
<td>High</td>
</tr>
<tr>
<td>Old infarcts&lt;sup&gt;e9&lt;/sup&gt;&lt;sup&gt;,e19&lt;/sup&gt;</td>
<td></td>
<td>3.3</td>
<td>Moderate</td>
</tr>
<tr>
<td>Time from QE &lt;17 d&lt;sup&gt;6&lt;/sup&gt;</td>
<td></td>
<td>0.6</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Continued
luminal stenosis may be due to a variety of vasculopathies and atherosclerosis may be differentiated clinically in most cases.\textsuperscript{5} It is important to identify sICAS as the etiology of stroke to optimize secondary prevention strategies. Expedient evaluation is reasonable as the highest risk of recurrent stroke is soon after the incident event.

**Recommendation 1 Statement**

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

**Antithrombotic Medication Therapy**

**Rationale for Recommendations 2, 3, and 4**

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

Combination short-term clopidogrel and aspirin use in sICAS was not directly supported by this systematic review but is supported by related evidence.\textsuperscript{19,35} The CLAIR study (Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolisation in Patients With Acute Symptomatic Cerebral or Carotid Artery Stenosis) showed that patients randomized to clopidogrel plus aspirin had significantly decreased microemboli in the territory of the stenotic artery when compared with aspirin alone.\textsuperscript{19} When combined with the CARESS trial (Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis), a similar study of patients with carotid atherosclerosis, patients treated with clopidogrel and aspirin had a significant reduction in recurrent stroke compared with patients treated with aspirin monotherapy.\textsuperscript{35} In addition, patients with sICAS in the CHANCE trial (Clopidogrel in High-Risk Patients With Acute Non-disabling Cerebrovascular Events) who were randomized to clopidogrel and aspirin had a numerically lower rate of stroke at 90 days compared with those on aspirin alone, albeit not statistically significant. Additional support for combined short-term clopidogrel and aspirin comes from analyses comparing patients in the medical arm of SAMMPRIS treated with 90 days of clopidogrel plus aspirin, who had a lower primary endpoint rate, with similar patients from WASID treated with aspirin alone at 1 month (5.8% vs 10.5%) and 6 months (8.9% vs 17.9%).\textsuperscript{27,36} This analysis of WASID patients who met SAMMPRIS entry criteria was adjusted for confounding factors and still showed almost double the risk of stroke in the WASID patients, despite the higher burden of poor prognostic features in the SAMMPRIS patients. The optimal duration of combined clopidogrel and aspirin in sICAS has not been tested in randomized controlled trials.

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

<table>
<thead>
<tr>
<th>Increased Risk</th>
<th>No Increased Risk</th>
<th>Point Estimate</th>
<th>Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qualifying infarct = borderzone plus impaired collaterals\textsuperscript{a}\textsuperscript{12}</td>
<td></td>
<td>6.9</td>
<td>Low</td>
</tr>
<tr>
<td>Sex (female)\textsuperscript{a}\textsuperscript{9}</td>
<td></td>
<td>0.6</td>
<td>High</td>
</tr>
<tr>
<td>Age (lower ref group)\textsuperscript{a}\textsuperscript{9}</td>
<td></td>
<td>1.1</td>
<td>Low</td>
</tr>
<tr>
<td>Non-White vs White\textsuperscript{a}\textsuperscript{9}</td>
<td></td>
<td>1.2</td>
<td>Low</td>
</tr>
</tbody>
</table>

Abbreviations: BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; QE = qualifying event; SBP = systolic blood pressure; TC = total cholesterol.

\textsuperscript{a}The evidence is insufficient to support or refute that failure to achieve a body mass index target and smoking cessation predicts an increased risk of recurrent stroke.\textsuperscript{18}

\textsuperscript{b}There is insufficient evidence to support or refute the following modifiable risk factors in predicting an increased risk of recurrent stroke: baseline HbA1c,\textsuperscript{e24}\textsuperscript{e26} baseline TC, history of peripheral vascular disease,\textsuperscript{e25} history of dyslipidemia,\textsuperscript{e11,e24-e27} baseline LDL cholesterol,\textsuperscript{e24,e25} elevated lipoprotein (a),\textsuperscript{e20,23} metabolic syndrome,\textsuperscript{e22} alcohol use,\textsuperscript{e4,e11,e25,e26} high-sensitivity C-reactive protein,\textsuperscript{e29,e30} and a positive myocardial SPECT scan.\textsuperscript{e31}

\textsuperscript{c}The evidence is insufficient to support or refute the following nonmodifiable risk factors in predicting an increased risk of recurrent stroke: history of stroke,\textsuperscript{e26,e31} history of TIA,\textsuperscript{e20,e21,e25} history of peripheral vascular disease,\textsuperscript{e25} progression of stenosis on magnetic resonance angiography,\textsuperscript{e37} increased oxygen extraction fraction asymmetry (PET scan),\textsuperscript{e34} and hypoperfusion patterns on imaging.\textsuperscript{e37}
Trials of cilostazol combined with other antiplatelet agents for stroke prevention in sICAS have had mixed results. TOSS (Trial of Cilostazol in Symptomatic Intracranial Arterial Stenosis) and TOSS-2 found cilostazol plus aspirin was not better for stroke prevention than aspirin alone or clopidogrel plus aspirin. However, the CATHARSIS study (Cilostazol-Aspirin Therapy Against Recurrent Stroke with Intracranial Artery Stenosis) demonstrated that cilostazol plus aspirin prevented the combined secondary endpoint of all vascular events and new silent brain infarcts when compared with aspirin alone. A subgroup analysis of patients with sICAS in CSPS (Cilostazol Stroke Prevention Study for Antiplatelet Combination), which included heterogeneous causes of stroke, showed a lower rate of stroke when randomized to cilostazol plus either aspirin or clopidogrel compared with those on aspirin or clopidogrel alone. Generalizability of these cilostazol studies is limited in that they were conducted in a primarily Asian population and low-dose aspirin (≤150 mg/d) was used.

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

**Recommendation 3 Statement**
Clinicians should recommend adding clopidogrel 75 mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with severe (70%–99%) sICAS who have low risk of hemorrhagic transformation of ischemic stroke (Level B).

**Recommendation 4 Statement**
Clinicians may recommend adding cilostazol 200 mg/d to aspirin for up to 90 days to further reduce stroke risk in patients with sICAS and low risk of hemorrhagic complications as an alternative to clopidogrel or in Asian patients (Level C).

**Lipid and Hypertension Vascular Risk Factor Modification**

**Rationale for Recommendations 5 and 6**
Support for the management of vascular risk factors in patients with sICAS comes from prespecified, post hoc analyses of sICAS clinical trials and other clinical practice guidelines for patients with stroke and vascular disease. Evidence for the use of high-intensity statins in patients with symptomatic atherosclerotic disease is well established and is applicable to patients with sICAS. In addition, a lower rate of cerebrovascular events was seen in patients with sICAS randomized to high-intensity statin therapy compared with other dosages. A target low-density lipoprotein (LDL) level <70 mg/dL among patients with stroke and atherosclerotic disease was found to reduce major cardiovascular events compared with patients with a target LDL <100 mg/dL. Post hoc analyses from WASID and SAMMPRIS also show lower rates of vascular events with lower LDLs in sICAS. The use of other lipid-lowering agents (e.g., PCSK9 inhibitors or omega-3) has not been specifically studied in sICAS but may be supported by studies of symptomatic atherosclerotic disease.

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. Analyses from WASID, SAMMPRIS, and the CICAS registry (Chinese Intracranial Atherosclerosis) have demonstrated that among clinically stable patients with sICAS, a mean systolic BP (SBP) <140 mm Hg during follow-up was associated with a lower risk of stroke and vascular events, even in patients with posterior circulation or severe stenosis.

Although the current American Heart Association guideline–recommended target of SBP <130 mm Hg has not been studied in patients with sICAS, an RCT of patients with sICAS comparing SBPs <120 mm Hg vs <140 mm Hg found that the more intensive group (which had a mean SBP of 124.6 mm Hg) had a higher rate of new ischemic lesions on imaging and larger stroke volume than the standard group. Some subgroups of patients with sICAS may be at higher risk of stroke with lower BPs, including those with hemodynamic impairment or those with a large reduction in BP from baseline.

**Recommendation 5 Statement**
Clinicians should recommend high-intensity statin therapy to achieve a goal LDL <70 mg/dL in patients with sICAS to reduce the risk of recurrent stroke and vascular events (Level B).

**Recommendation 6 Statement**
Clinicians should recommend a long-term BP target of <140/90 mm Hg in clinically stable patients with sICAS to reduce the risk of recurrent stroke and vascular events (Level B).

**Physical Activity**

**Rationale for Recommendation 7**
In the general population, moderate physical activity reduces incidence of stroke. Among patients with sICAS, a post hoc analysis of SAMMPRIS showed that not performing moderate physical activity at least 3–5 times per week was associated with a higher risk of recurrent stroke and vascular events (OR 6.7, 95% CI 2.5–18.1).

**Recommendation 7 Statement**
Clinicians should recommend at least moderate physical activity in patients with sICAS who are safely capable of exercise to reduce the risk of recurrent stroke and vascular events (Level B).
Other Modifiable Vascular Risk Factors

Rationale for Recommendation 8
Benefits on morbidity and mortality from maintaining a healthy lifestyle and management of other vascular risk factors are well established for patients with atherosclerotic disease and are applicable to patients with sICAS.46

Recommendation 8 Statement
Clinicians must recommend treatment of other modifiable vascular risk factors in patients with sICAS to reduce the risk of recurrent stroke and vascular events (Level A).

Bilateral Arm Ischemic Preconditioning

Rationale for Recommendation 9
Based on 2 RCTs done in patients with sICAS, 5 cycles of BAIPC twice daily appears to reduce the risk of recurrent stroke and death. However, the evidence is derived from only 2 centers in China, the studies had small sample sizes, and the studies were not blinded. These methodologic issues limit conclusions about efficacy in a multiethnic population. Whereas the risk of the procedure appears low, the BAIPC device does not have approval for use in the United States, limiting its application. These methodologic issues limit confidence in conclusions about efficacy and there are no data in a multiethnic population.

Recommendation 9 Statement
The authors could not achieve consensus on a recommendation for BAIPC in patients with sICAS.

Endovascular and Surgical Therapy

Rationale for Recommendations 10-13
Percutaneous Transluminal Angioplasty and Stenting
Recommendations related to PTAS are informed by several randomized trials that showed no benefit of PTAS (with either self-expanding or balloon-mounted stents) over medical therapy. Three RCTs have shown a higher rate of periprocedural cerebrovascular events and death from PTAS and no benefit of stroke prevention during follow-up compared with medical therapy in patients with sICAS.

Single-arm, uncontrolled registries assessing subpopulations of patients with sICAS, including medical failures (i.e., stroke or TIA while on antithrombotic medications) or those with progressive neurologic symptoms, have reported conflicting rates of periprocedural complications.47,48 In a Food and Drug Administration (FDA)–mandated postmarket surveillance study of the Wingspan stent, the stroke or death rate was 23.9% within 72 hours among those who did not meet criteria for FDA-
approved use, many of whom had not failed medical therapy or were treated recently after stroke.\textsuperscript{49,50} In post hoc analyses of RCTs, no studied subgroups have been shown to benefit from PTAS, including those with intracranial vertebral segment location or those taking antithrombotic medications at the time of the initial cerebrovascular event. PTAS has not been systematically compared with medical therapy in patients with moderate (50\%-69\%) sICAS, but the low risk of stroke in these patients and the high risk of periprocedural complications, which do not depend on severity of stenosis, makes PTAS unwarranted.\textsuperscript{51} 

**Angioplasty Alone**

In light of safety issues related to PTAS, balloon angioplasty alone (i.e., without placement of an intracranial stent) has been considered a possible alternative for endovascular therapy.\textsuperscript{52} However, no RCTs have compared angioplasty alone with medical therapy for stroke prevention in patients with sICAS. A systematic review and meta-analysis of 25 studies of angioplasty alone compared event rates in patients treated with angioplasty to events in the SAMMPRIS medical group and found no benefit of angioplasty due to high periprocedural morbidity and mortality.\textsuperscript{53} Balloon angioplasty alone may be performed with a submaximal staged approach, which may have a lower rate of morbidity and mortality.\textsuperscript{54} 

Optimal stroke prevention for patients with sICAS who have recurrent strokes despite antplatelet therapy and intensive treatment of risk factors is unknown. However, given the lack of efficacy data, the use of PTAS or angioplasty alone for stroke prevention in any subpopulation of patients with sICAS is investigational.\textsuperscript{52-54} 

**Recommendation 10 Statement**

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

**Recommendation 11 Statement**

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

**Recommendation 12 Statement**

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

**Recommendation 13 Statement**

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

**Surgical Treatment**

**Rationale for Recommendations 14 and 15**

**Direct Bypass**

Recommendations related to the use of direct surgical bypass for stroke prevention in patients with sICAS are informed by 1 RCT. The EC/IC bypass trial included patients with sICAS and found that bypass was not associated with a decrease in recurrent stroke and death as compared with medical therapy alone. For subgroups with severe MCA stenosis or occlusion, there was an increased risk of recurrent stroke or death with direct bypass. Similar to the EC/IC bypass study, COSS (Carotid Occlusion Surgery Study), which studied patients with symptomatic ICA occlusion, found that direct bypass increases the risk of stroke and death predominantly due to early periprocedural complications.\textsuperscript{55} For patients with posterior circulation vertebral artery disease, a single-center case series reported that surgical revascularization decreased recurrent stroke and death as compared with medical therapy alone, but no RCTs have been performed to establish efficacy and the procedure is considered investigational.\textsuperscript{56,57}

**Indirect Bypass**

In patients with anterior circulation sICAS, indirect bypass with encephaloduroarteriosynangiosis (EDAS) is an emerging investigational surgery for stroke prevention.\textsuperscript{58-60,e1,e2} A small initial study of indirect revascularization without standardized medical management showed a high rate of recurrent stroke in patients with sICAS.\textsuperscript{59} Four nonrandomized studies, including 2 small case series,\textsuperscript{58,e1} 1 single-center prospective study,\textsuperscript{e2} and 1 two-center prospective trial with independent outcomes assessment,\textsuperscript{63} suggested that there may be benefit of EDAS over medical therapy when applied with standardized medical treatment. Well-designed and well-conducted randomized trials have not been completed.

**Recommendation 14 Statement**

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

**Recommendation 15 Statement**

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

**Suggestions for Future Research**

**Medical Research**

Randomized trials are needed to optimize type and duration of antithrombotic therapy for patients with sICAS. The most promising candidate therapies for future studies are combinations of antithrombotic therapy that have been shown in prior trials to reduce the risk of stroke in patients with (1) large artery cerebrovascular disease (ticagrelor plus aspirin),\textsuperscript{64} (2) coronary or peripheral vascular disease (low dose factor Xa inhibitor plus aspirin),\textsuperscript{65} and (3) stroke (cilostazol plus aspirin or clopidogrel).\textsuperscript{15} Novel factor Xa inhibitors alone or in combination with aspirin and clopidogrel are being evaluated in Phase II stroke prevention trials and could also be considered for future trials in patients with sICAS. Because clopidogrel is a prodrug that may be ineffective in patients who carry genetic single-nucleotide loss-of-function (LOF)
polymorphisms for the CYP2C19 cytochrome P450 enzyme necessary to metabolize clopidogrel to its active form, trials that include clopidogrel should determine the effect of CYP2C19 LOF allele carrier status on clinical outcomes.

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

**Endovascular and Surgical Research**

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

**Other Areas of Future Research**

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

**Disclaimer**

Clinical practice guidelines, practice advisories, systematic reviews, and other guidance published by the American Academy of Neurology (AAN) and its affiliates are assessments of current scientific and clinical information provided as an educational service. The information (1) should not be considered inclusive of all proper treatments, despite of care, or as a statement of the standard of care; (2) is not continually updated and may not reflect the most recent evidence (new evidence may emerge between the time information is developed and when it is published or read); (3) addresses only the question(s) specifically identified; (4) does not mandate any particular course of medical care; and (5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an “as is” basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

**Conflict of Interest**

The American Academy of Neurology (AAN) 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 3 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 aan.com. For complete information on this process, access the 2011 AAN process manual.

**Acknowledgment**

The authors thank former AAN staﬀ members Thomas S.D. Getchius and Shannon A. Merrill, MLIS, for their assistance during the guideline development process.

**Study Funding**

This practice advisory was developed with ﬁnancial support from the AAN. Authors who have served as AAN subcommittee members (S.R.M., J.J.F., G.S.G.) or who are or were AAN staﬀ (M.D.O., H.S.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

**Disclosure**

T. Turan has received research support from the NIH for the SAMMPRIS, CREST 2, SE-CoAST StrokeNet RCC, and CHAMPION studies, as well as for serving on the event adjudication committee for the VERITAS clinical trial; has received personal compensation in the range of $10,000–$49,999 for serving as a blinded clinical events adjudicator for Pfizer and Boehringer Ingelheim; has received personal compensation in the range of $500–$4,999 for serving as a blinded clinical events adjudicator for trials unrelated to intracranial stenosis for W.L. Gore & Associates; and has received publishing royalties from a publication relating to health care. O. Zaidat has received personal compensation for consulting work unrelated to intracranial atherosclerosis and research support from Stryker, Cerenovous, Penumbra, and Medtronic; is the co-chair of the endovascular committee for the NIH StakeNet, the co-editor in chief for the Endovascular and Interventional Neurology section of Frontiers
in Neurology, and a past president of the Society of Vascular and Interventional Neurology; and is a founder of Galaxy Therapeutics, Inc. G. Gronseth has received personal compensation in the range of $0–$499 for serving as an editor, associate editor, or editorial advisory board member for Brain & Life and has received personal compensation in the range of $10,000–$49,999 for serving as an associate editor of Neurology®; and has received personal compensation in the range of $0–$499 for serving as an evidence-based medicine consultant for the AAN Guidelines Subcommittee. M. Chinomwotz has received product support from Stryker Neurovascular, AstraZeneca, Bayer AG, and Bristol Myers Squibb for the NIH-funded SAMMPRIS and WASID trials; has received personal fees from Gore, Medtronic, Merck & Co., Parexel, and NoNO Inc. for participating as a member of a data and safety monitoring board or stroke adjudicator in clinical trials unrelated to intracranial stenosis; has received funding from the NIH for the SAMMPRIS and WASID trials and the NIH Wingspan registry; has received personal compensation in the range of $500–$4,999 for serving on a scientific advisory or data safety monitoring board for NoNO Inc.; and his institution has received research support from the NIH. A. Culebras has served on UpToDate and MedLink Neurology editorial boards. A. Furlan has nothing to disclose. L. Goldstein has served on scientific advisory boards for Daichi Sankyo and Merz; has received funding for travel from Pfizer, Daiichi Sankyo, and the National Lipid Association to attend scientific meetings to discuss SPARCL studies; has received publishing royalties from UpToDate, Henry Stewart Publications, and Wiley; has received research support from St. Jude Medical, Inc., for the RESPECT trial, from Nexstim for the NICHE trial, and from the NIH; has received intellectual property interests from a publication relating to health care; and his institution has received research support from the NIH; has received compensation for consulting work from Nestlé, Artemida, Roche, Abbott, and Shire; has received compensation for participating in a data safety monitoring board from Artemida and Roche; and he has received an honorarium from the American Heart Association (AHA). N. Gonzalez has received research support from the NIH and the AHA. J. Latorre has nothing to disclose. S. Messé has received funding for travel from the AAN; has received publishing royalties from articles written for UpToDate, including articles about antiplatelets for secondary stroke prevention, carotid disease and surgery, and patent foramen ovale (PFO) and stroke; has received personal compensation from the Yale Cardiovascular Research Group for serving on clinical event committees for trials of embolic protection during valve replacement and a registry of left atrial appendage occluder placement; has received research support from W.L. Gore & Associates for a PFO closure study and a study of proximal aortic repair, from Novartis for a study of medication to reduce inflammation after intracerebral hemorrhage, from Biogen for a study of a medication to reduce edema from malignant infarction, and from the NIH for a study examining an embolic protection in aortic valve replacement, a cohort study examining renal insufficiency, and a study of sleep apnea treatment after acute stroke; and is a co-founder of and has equity in Neuralert Technologies, a company developing monitors to detect in-hospital stroke. T. Nguyen serves as editor of Frontiers in Neurology; has received compensation as a consultant for Avanix; and has received research support from Medtronic and the Society of Vascular and Interventional Neurology. R. Sangha has nothing to disclose. M. Schneck has served on the editorial boards of the Journal of Stroke and Cerebrovascular Disease and Frontiers in Neurology and owns mutual funds that include health retail business stock; has received personal compensation in the range of $500–$4,999 for serving on a scientific advisory or data safety monitoring board for HLTM; has received personal compensation in the range of $10,000–$49,999 for serving as an expert witness for miscellaneous legal firms; an immediate family member has received personal compensation for serving as an employee of Histogenix; and his institution has received research support from the NIH. A. Singhal has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Omnia, Deck Therapeutics, Proneurotech, MedLink, and UpToDate; and has served as an expert in legal cases, holds stock and/or stock options in Biogen and Zafgen, and has received research support from the NIH. A. N. Turan has served as a consultant for the NIH StrokeNet, site PI of the ARCADIA trial, and the National Stroke Prevention and Antithrombotic Therapy clinical event committee. M. Brien is an employee of the American Academy of Neurology. J. Fletcher has nothing to disclose. Go to Neurology.org/N for full disclosures.

Publication History
Received by Neurology August 10, 2021. Accepted in final form January 3, 2022.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanya N. Turan, MD, MSCR</td>
<td>Department of Neurology, Medical University of South Carolina, Charleston</td>
<td>Design or conceptualization of the study, major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
</tbody>
</table>
## Appendix (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osama Zaidat, MD</td>
<td>Department of Neurology, Mercy Health, Toledo, OH</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Gary S. Gronseth, MD</td>
<td>Department of Neurology, University of Kansas, Kansas City, MO</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Marc I. Chimowitz, MBChB</td>
<td>Department of Neurology, Medical University of South Carolina, Charleston</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Antonio Culebras, MD</td>
<td>Department of Neurology, SUNY Upstate Medical University, Syracuse, NY</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Anthony J. Furlan, MD</td>
<td>Department of Neurology, Cleveland Medical Center, OH</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Larry B. Goldstein, MD</td>
<td>Department of Neurology, University of Kentucky, Lexington</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Nestor R. Gonzalez, MD</td>
<td>Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, CA</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Julius G. Latorre, MD, MPH</td>
<td>Department of Neurology, SUNY Upstate Medical University, Syracuse, NY</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Steven R. Messé, MD</td>
<td>Department of Neurology, University of Pennsylvania, Philadelphia</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Thanh N. Nguyen, MD</td>
<td>Department of Neurology, Radiology, Boston Medical Center, MA</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Rajbeer S. Sangha, MD</td>
<td>Department of Neurology, University of Alabama, Birmingham</td>
<td>Major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Michael J. Schneck, MD, MBA</td>
<td>Department of Neurosurgery, Loyola University Chicago, Maywood, IL</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Aneesh B. Singhal, MD</td>
<td>Department of Neurology, Massachusetts General Hospital, Boston</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Lawrence R. Wechsler, MD</td>
<td>Department of Neurology, University of Pennsylvania, Philadelphia</td>
<td>Analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
<tr>
<td>Alejandro A. Rabinstein, MD</td>
<td>Department of Neurology, Mayo Clinic, Rochester, MN</td>
<td>Major role in the acquisition of data, analysis or interpretation of the data, drafting or revising the manuscript for intellectual content</td>
</tr>
</tbody>
</table>

## References

9. Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ. 2014;348:g7430.

Additional references e1–e37 available in the supplemental document, links.hww.com/WNL/B803

Quality Improvement: Start Small to Make Big Changes

You deliver excellent patient care, but there is always room for improvement. In health care, quality improvement (QI) is the framework used to systematically improve the ways care is delivered to patients. Learn how to increase desired health outcomes. Browse AAN resources to help you drive change at AAN.com/Practice/Quality.