Protocol for proposed guideline project: Prevention of Stroke in Patients with Symptomatic Large Vessel Intracranial Atherosclerotic Disease

Proposal of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on April 22, 2015. All comments submitted during the 30-day public comment period in which this protocol is posted will be reviewed and addressed by the author panel members. Although all comments will be considered, author panel members will not specifically respond to individual comments online.

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This practice advisory protocol was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members (S.M., J.F.) were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.

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Tanya Turan has received research support from the BI 1356, 10773 Clinical Trial Event Adjudication Committee, from the W.L. Gore and Associates events committee, and from the NIH for SAMMPRIS, CREST 2, and CHIASM clinical trials, as well as for serving on the event adjudication committee for the Veritas clinical trial.

Garry S. Gronseth has been serving on the *Neurology Now*, Editorial advisory board from its inception to present, has been serving as an associate editor for *Neurology* from 2013 to present. He receives financial compensation from the American Academy of Neurology for providing methodology services.

Marc Chimowitz has received research support from Stryker Neurovascular, Astra Zeneca, W.L. Gore and Associates DSMB related to PFO closure trial, and from the NIH for SAMMPRIS, CREST 2, and CHIASM clinical trials.

Antonio Culebras has served on UpToDate, Henry Stewart, and *Neurology Medreviews* journal editorial boards; has received publishing royalties from Informa Healthcare and Cambridge University Press; holds stock in Clinical Stroke Research, Inc., which is a fund deposit revenue
generated by the Sleep Center and the EEG laboratory at Community General Hospital in Syracuse.

Anthony J. Furlan reports no disclosures.

Dr. Larry B. Goldstein has served on scientific advisory boards for Daiichi 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, and Wiley; has received research support from St. Jude’s (RESPECT Trial site), Nexstim (NICHE Trial site), and the National Institutes of Health (NIH).

Julius G. Latorre has received honoraria for a grand rounds presentation at Strong Memorial Hospital and has received research support for investigator-initiated research on near-infrared spectroscopy.

Steven R. Messé has served on a Glaxo Smith Kline scientific advisory board as a consultant for development of a study examining a neuroprotectant in high-risk surgery; has received funding for travel from the American Academy of Neurology (AAN), GlaxoSmithKline, and W.L. Gore and Associates; has received publishing royalties from articles written for UpToDate, including an article about antiplatelets for secondary stroke prevention and PFO and stroke; has received support from W.L. Gore and Associates for a PFO closure study, from GlaxoSmithKline for a study examining a neuroprotectant in high-risk surgery, and from the NIH for a study examining an embolic protection in aortic valve replacement, a cohort study examining renal insufficiency, and a study examining neurologic outcomes of aortic valve surgery.

Rajbeer Sangha reports no disclosures.

Michael Schneck has served on the editorial board of the Journal of Stroke and Cerebrovascular Disease and Frontiers in Neurology; is an employee of Loyola University of Chicago; has served as an expert in legal cases; and owns mutual funds that include health retail business stock.

Aneesh Singhal has received honoraria from the AAN; Medlink, Inc.; and Sun Pharma, Inc.; has received research support from Pfizer, Biogen-Idec, and the NIH National Institute of Neurological Disorders and Stroke; and has held stock in Biogen-Idec, and currently holds stock in Vertex Pharmaceuticals.
Lawrence R. Wechsler has served on Lundbeck and San Bio scientific advisory boards; has served on the Dias Data, Safety, and Monitoring Board and the Biogen-Idec Steering Committee (ACT 1); and holds stock in SilkRoad Medical.

Osama Zaidat reports no disclosures.

Thomas S.D. Getchius has received financial compensation for travel for speaking at the University of Louisville mTBI conference; has been serving as the vice-chair of the Council of Medical Specialty Societies Clinical Practice Guideline Component Group from November 2013 to present, and has received research support from the CDC as a grant for muscular dystrophy guideline development, dissemination, and implementation.

Shannon A. Merillat reports no relevant disclosures.

Jeffrey J. Fletcher reports no disclosures.
GUIDELINE PROJECT PROTOCOL

Guideline project development plan

This proposed project will be developed in accordance with the processes described in the AAN clinical practice guideline development process manual 2011 (as amended). The authors of this guideline project intend to develop a practice advisory based upon the systematic review developed. The Guideline Development, Dissemination, and Implementation subcommittee (GDDI) will determine if the systematic review will inform an evidence-based guideline or a practice advisory. This protocol will be posted for public comment, and a limited search of the grey literature will be performed. Patient representatives will not be included on the panel.

Guideline project timeline

The tentative timeline for development of the systematic review is as follows:

Panel formation: Completed May 30, 2015

Protocol posted for public comment: July 13, 2015 to August 13, 2015

Literature search: Completed by September 1, 2015

Panel review of abstracts: Completed by November 1, 2015

Review of full articles, data extraction, and development of evidence tables: March 1, 2016

Systematic review draft posted for public comment: September 2016

First Draft of the systematic review: Completed and presented to GDDI by November 1, 2016

Composition of the author panel

In September 2014, a multidisciplinary panel consisting of 14 AAN physician members was recruited to develop this practice advisory protocol. The physicians included content experts
(T.T., L.G., M.C., A.C., A.F., J.L., M.S., A.S., L.W., O.Z., R.S.), a methodology expert (G.G.),
and Guideline Development, Dissemination, and Implementation (GDDI) Committee members
(J.F., S.M.). The physicians were required to submit online conflict of interest (COI) forms and
copies of their curriculum vitae (CV). The panel leadership, consisting of the lead author (T.T.),
the AAN methodologist (G.G.), and the AAN staff persons (T.G., S.M.), reviewed the COI
forms and CVs for financial and intellectual COI. These documents were specifically screened to
exclude both those individuals with a clear financial conflict and those whose profession and
intellectual bias would diminish the credibility of the review in the eyes of the intended users. In
accordance with AAN policy, the lead author (T.T.) has no COIs. Four of the 14 authors were
determined to have COI, but the COI were judged to be not significant enough to preclude them
from authorship (L.G., S.M., A.S., L.W.). All authors determined to have COIs will not be
permitted to review or rate the evidence. These individuals will be 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. Panel members with COIs will
be allowed to participate in the recommendation development process. The panel was
recommended to the AAN GDDI leadership, who reviewed the author panel constitution and the
panel leadership’s COI Forms, and provided final approval. This panel will be solely responsible
for the final decisions about the design, analysis, and reporting of the proposed systematic review
and proposed subsequent practice advisory, which will then submitted for approval to the AAN
GDDI.

23  Introduction to proposed guideline project topic
Atherosclerotic intracranial arterial stenosis is one of the most common causes of stroke worldwide and is associated with a high risk of recurrent stroke.\textsuperscript{1-4} Despite the development of proper medical treatment, the risk of recurrent stroke is as high as 23% in one year if the patient has suffered a TIA or a stroke and has severe stenosis of more than 70%.\textsuperscript{5,6} Two forms of treatment have emerged: aggressive medical therapy with a combination of aspirin and clopidogrel plus intensive control of risk factors, and medical therapy plus endovascular procedures.

**Rationale for this proposed guideline project**

A variety of interventions intended to prevent stroke, which are intuitive from a pathophysiologic perspective, have not proven to be of benefit when evaluated in well-designed and carefully conducted clinical trials. This is the case for intracranial stenting as employed for secondary stroke prevention in intracranial arterial stenosis. The National Institutes of Health (NIH)–supported Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial randomized 451 patients with a recent stroke or TIA associated with a 70% to 99% diameter stenosis of a major intracranial artery to medical therapy alone, or medical therapy in addition to percutaneous transluminal angioplasty and stenting (PTAS). The primary intention-to-treat analysis endpoint was stroke or death within 30 days after enrollment or after a revascularization procedure for the qualifying lesion during the follow-up period, or stroke in the territory of the qualifying artery beyond 30 days.\textsuperscript{7} SAMMPRIS was stopped before the intended enrollment target because of a higher event rate with PTAS. The 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the medical management group (nonfatal stroke, 5.3%; non–stroke-
related death, 0.4%) (risk difference [RD] 8.9%; 95% confidence interval [CI] 3.5%–14.5%). In long-term follow-up, occurrence of primary endpoints in the medical group vs the PTAS group was 12.6% vs 19.7% at one year and at a median follow-up of 32.4 months was 14.9% vs 23.2% (RD 8.1%; 95% CI 1.0%–15.5%).

As with SAMMPRIS, the industry-funded Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT) trial randomized patients with a recent stroke or TIA attributed to 70% to 99% stenosis (or 50%–99% stenosis tandem lesions) of a major intracranial artery to aggressive medical therapy alone or medical therapy plus PTAS. The VISSIT trial study design differed from SAMMPRIS by use of a balloon-expandable stent (PHAROS Vitesse neurovascular stent system) in place of a self-expanding stent (wing-span). The primary intention-to-treat analysis endpoint was the composite of any stroke or TIA within 1 year in the same territory as the qualifying event. Following the results of SAMMPRIS, the sponsor of the VISSIT trial prematurely halted the trial for an unplanned safety analysis after enrolling 112 of the intended 250 patients. The 30-day risk of stroke, TIA, or death occurred more frequently in the PTAS group (24.1%) than in the medical group (9.4%) (RD 14.7%; 95% CI 1.2%–28.2%). At 1 year the primary outcome occurred in 36.2% of the PTAS group and 15.1% of the medical group, confirming the benefit of aggressive medical therapy (RD 21.2%; 95% CI 5.4%–36.8%). The recently published vertebral artery stenting (VAST) trial also found PTAS was associated with a higher-than-expected risk of major periprocedural vascular complications and that the risk of recurrent vertebrobasilar stroke under best medical treatment alone was lower than predicted. The VAST study was designed as a randomized, controlled safety and feasibility trial in patients with symptomatic vertebrobasilar ischemia in order to inform sample size and necessity for a
phase III trial. Although the majority of the 115 patients randomized had symptomatic lesions in the extracranial vertebral arteries, 16% of target lesions were located in the intracranial vertebral arteries.\(^\text{10}\)

Recent trials have confirmed the benefit of aggressive medical management over PTAS in patients with symptomatic large vessel intracranial atherosclerosis and that this benefit was driven by a higher early-event rate and no benefit beyond the periprocedural period in the PTAS group. Conventional medical management was associated with a lower risk of stroke or death than in historical controls, suggesting intensive risk factor management and dual antiplatelet therapy may be the preferred treatment for severe intracranial atherosclerosis.\(^\text{5, 6, 8, 9}\) Indeed, studies of early (< 24 hours from onset) initiation of dual antiplatelet therapy in patient populations with a high prevalence of intracranial atherosclerosis may support this therapy.\(^\text{11, 12}\) The recently completed Cilostazol-Aspirin Therapy against Recurrent Stroke with Intracranial Artery Stenosis (CATHARSIS) trial also may support further evaluation of dual antiplatelet therapy in patients with recent ischemia (2 weeks to 6 months) attributed to intracranial atherosclerosis.\(^\text{13}\)

Despite the results of SAMMPRIS and VISSIT, there are those who believe the data support modification but not discontinuation of the approach to intracranial angioplasty or stenting, or both, and that subsets of patients should be investigated further.\(^\text{14}\) However, an exploratory analysis of the periprocedural strokes in SAMMPRIS found that they had multiple causes (most commonly perforator occlusions) and risk factors, and that restricting the procedure to those with a lower predicted complication risk would limit its use to a very small subset of patients.\(^\text{15}\)
Likewise, a subgroup analysis of SAMMPRIS failed to support the hypothesis that PTAS may be beneficial in patients who were on antithrombotic therapy at the time of their qualifying events.\textsuperscript{16} Although there are no data demonstrating that intracranial stenting prevents strokes, with the available data reflecting a higher stroke or death rate as compared with medical therapy alone, some centers continue to perform this procedure. Nevertheless, many centers employ aggressive medical therapy alone for the treatment of symptomatic intracranial arterial stenosis.

Clinical questions

For patients with a clinical diagnosis of cerebral ischemia, the diagnosis of symptomatic intracranial atherosclerosis is largely assumptive. Although a formal systematic review under a diagnostic scheme is beyond the scope of a practice advisory, a summary of the inclusion criteria for major studies will be reviewed to help place the practice advisory questions into the appropriate clinical context.

Certain patient characteristics may predict an increased risk of recurrent stroke after a stroke related to intracranial atherosclerosis.

This practice advisory seeks to answer the following clinical questions:

1) For patients with a history of symptomatic intracranial atherosclerosis, what factors (degree of stenosis, length of stenosis, vascular bed, imaging modalities, sex of patient, race/ethnicity of patient, time from initiating event, whether patient on maximal medical therapy) predict an increased risk of recurrent stroke? [Prognostic scheme]
Medical, endovascular, and surgical procedures are used to prevent recurrent stroke after a stroke related to intracranial atherosclerosis. No comprehensive evidence-based guideline exists to guide management and future research in patients with symptomatic intracranial atherosclerosis.

2) For patients with a history of symptomatic intracranial atherosclerosis, which medical therapies, as compared with no therapy or an alternative therapy, reduce the risk of recurrent stroke? [Therapeutic scheme]

   a. Antithrombotics
   i. Antiplatelet therapy vs anticoagulation
   ii. Single antiplatelet therapy vs dual antiplatelet therapy

   b. Antihypertensives

   c. Statins

   d. Other risk factor modifications such as glycemic control and lifestyle modifications (weight reduction, nutrition, physical activity, smoking cessation, and treatment of sleep apnea) will be discussed in the clinical context section if there is a paucity of data specifically concerning recurrent stroke due to intracranial atherosclerosis.

3) For patients with a history of symptomatic intracranial atherosclerosis, do endovascular or extracranial/intracranial bypass procedures, as compared with no procedure or an alternative procedure, reduce the risk of recurrent stroke? [Therapeutic scheme]

Types of participants/population

Patients with a history of stroke or TIA attributed to stenosis of a large intracranial artery.
Types of intervention
All pharmacologic, nonpharmacologic, surgical, and endovascular interventions aimed at improving outcomes important to patients will be included.

Comparison group
Patients with a history of stroke or TIA attributed to atherosclerotic stenosis of a large intracranial artery not receiving the intervention of interest (therapeutic question) or without the risk factor of interest (prognostic question).

Types of outcome measures
Patient-centered outcomes will be included. These include stroke, TIA, death, myocardial infarction, functional outcomes, or quality of life. Surrogate outcomes such as vascular imaging or microembolic detection will not be included.

Rationale for the clinical questions
There are currently no guidelines that specifically address prevention of stroke in patients with stroke related to intracranial atherosclerosis despite the worldwide burden of stroke and high risk of recurrent stroke. An evidence-based practice guideline may help the practicing clinician navigate the available treatment choices and highlight areas where data are lacking. The need for developing new and effective treatments for patients with symptomatic intracranial stenosis cannot be ignored. Such a guideline would help evaluate the state of the current evidence,
highlight whether one treatment is best supported, identify related risks, and reveal whether additional trials are needed.

Terms and databases to be used in the literature search

**Key text words and index words for the condition**
- Atherosclerotic intracranial arterial stenosis; large artery intracranial occlusive disease;
- intracranial atherosclerosis; intracranial stenosis; intracranial atherosclerotic disease; acute stroke; stroke; transient ischemic attack

**Key text words and index words for the intervention**
- Secondary prevention; treatment; diagnosis; percutaneous transluminal angioplasty and stenting;
- transluminal angioplasty

**Database to be searched**
- Medline, Cochrane, and Science Citation Index. Grey literature search sources will be limited to clinicaltrials.gov and the Cochrane registry. Because this is a practice advisory with a narrow focus including patient-centered outcome, the grey literature is expected only to inform future research.

**Years to be searched**
- Published through July 1st 2015

**Study screening and selection criteria: inclusion and exclusion criteria for article selection**
- Studies will be chosen to be rated for risk of bias on the basis of criteria established a priori. For therapeutic questions, only studies that randomly allocated patients with symptomatic
intracranial stenosis to different treatment groups and followed patients to compare their
subsequent risks of recurrent stroke will be included in the systematic review. For the prognostic
question, only cohort studies or case-control studies that compare recurrent stroke risk (or odds)
in patients with symptomatic intracranial stenosis with and without a putative risk factor will be
included in the systematic review. Review articles, studies of animals, editorials, and studies that
involved fewer than 20 patients will be excluded. Studies that assessed only “lacunar stroke,”
“lipohyalinosis,” “small vessel stroke,” or “small artery occlusion” will also be excluded.
DISCLAIMER

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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.¹⁷