Evidence-based review of primary and secondary ischemic stroke prevention in adults: a neurosurgical perspective

SUNIL MANJILA, M.D.,1 TONY MASRI, M.D.,2 TANZILA SHAMS, M.D.,2 SHAKEEL A. CHOWDHRY, M.D.,1 CATHY SILA, M.D.,2 AND WARREN R. SELMAN, M.D.1

Departments of 1Neurological Surgery and 2Neurology, The Neurological Institute, University Hospitals Case Medical Center, Cleveland, Ohio

In this paper, the authors’ aim is to provide an evidence-based review of primary and secondary ischemic stroke prevention guidelines covering most of the common risk factors and stroke etiologies for the practicing neurosurgeon. The key to stroke prevention is in the identification and treatment of the major risk factors for stroke. These include hypertension, heart disease, diabetes mellitus, dyslipidemia, and tobacco smoking. An updated approach to secondary prevention of stroke in the setting of intracranial and extracranial large vessel atherosclerosis and cardioembolism is provided along with a brief overview of pertinent clinical trials. Novel pharmacological options for prevention of cardioembolic strokes, such as new alternatives to warfarin, are addressed with recommendations for interruption of therapy for elective surgical procedures. In addition, the authors have reviewed the anticoagulation guidelines and the risk of thromboembolic complications of such therapies in the perioperative period, which is an invaluable piece of information for neurosurgeons. Less common etiologies such as arterial dissections and patent foramen ovale are also briefly discussed. Finally, the authors have outlined the quality measures in the Medicare Physician Quality Reporting System and essential guidelines for Primary Stroke Center certification, which have implications for day-to-day neurosurgical practice. (DOI: 10.3171/2011.2.FOCUS1164)

KEY WORDS • evidence-based study • stroke prevention • clinical trial • CHADS2 • Physician Quality Reporting System

Across the world, stroke is considered the second leading cause of death, responsible for 4.4 million (9%) of the total 50.5 million deaths each year. According to the US National Center for Health Statistics, stroke mortality has improved, and it is now the fourth leading cause of death behind heart disease, cancer, and chronic respiratory diseases but remains the leading cause of disability among adults in the US.63 Each year, about 55,000 more women than men have a stroke among a total of 795,000 strokes occurring each year, or about 1 stroke every 40 seconds. The prevalence of stroke in people 20 years of age and older is around 2.9% across the US population. The direct and indirect costs associated with stroke for 2010 are projected to total $7.3 billion.63 Likewise, the prevalence of asymptomatic carotid artery stenosis greater than 50% is approximately 5%–9% in patients 65 years of age and older, which amounts to 1.3–2.4 million patients, more among men than women.31,49 Symptomatic carotid artery stenosis with TIA occurs in 4.9 million patients, 36% of whom have moderate to severe stenosis.40,66 In 2010, a new definition for TIA was introduced as a transient episode of focal neurological signs and symptoms not resulting in evidence of brain injury on neuroimages. This reflects the fact that many transient episodes lasting hours are associated with evidence of tissue infarction on imaging (CT or MR imaging) and are actually a stroke. As the best treatment of stroke is preventing the stroke, this article focuses on the evidence-based guidelines for primary and secondary ischemic stroke prevention with key messages important to the practicing neurosurgeon.

Why is an Understanding of Ischemic Stroke Subtypes Important?

For patients who have had a TIA or ischemic stroke, understanding the underlying mechanism is critical in developing an appropriate management plan. There are many classification schemes but the best is the TOAST criteria, which was developed for the Trial of ORG 10172 in Acute Stroke Treatment. ORG 10172 was an antithrombin tested

Abbreviations used in this paper: CAS = carotid artery stenting; CEA = carotid endarterectomy; CHD = coronary heart disease; EC-IC = extracranial-intracranial; HR = hazard ratio; ICA = internal carotid artery; INR = international normalized ratio; MCA = middle cerebral artery; MI = myocardial infarction; PFO = patent foramen ovale; PQRS = Physician Quality Reporting System; PSC = Primary Stroke Center; TIA = transient ischemic attack.
for the treatment of acute stroke. The trial, evaluating low-molecular-weight heparin for acute ischemic stroke, was negative, but the classification scheme has stood the test of time. The 5 major subtypes are as follows: large artery atherosclerosis, including large artery thrombosis and artery-to-artery embolism; cardioembolism; lacunar small artery occlusion; stroke of other determined cause or determined etiology; and stroke of undetermined cause due either to an inadequate evaluation or more than one cause being identified by risk factor profiles, clinical features, and results of diagnostic tests (Table 1).

**Large Artery Atherosclerosis**

Patients with TIA or ischemic stroke due to large artery atherosclerosis affecting the cervicocephalic or intracranial vessels represent approximately 15% of all patients with TIA/strokes but are at highest risk for early stroke progression or recurrent ischemic stroke and are also at high risk for vascular death, largely due to cardiovascular disease. Treatment options for stroke prevention include aggressive medical management, revascularization surgeries, and endovascular revascularization with angioplasty and stenting.

**Carotid Revascularization Procedures.** Introduced in 1953, CEA has been established by multiple randomized clinical trials as the superior option for stroke prevention for many patients with symptomatic carotid artery stenosis (Table 2). The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Stenosis Trial (ECST) are the landmark studies that demonstrated the superior efficacy of CEA with medical therapy over medical therapy alone in patients with severe symptomatic carotid artery stenosis. After only 2 years of follow-up, the risk of ipsilateral stroke and stroke or death in patients with 70%–99% carotid artery stenosis was significantly reduced from 26%–32.3% in patients with medical therapy alone to 9%–15.8% in patients receiving both CEA and medical therapy. The risk of perioperative stroke (within 30 days of surgery) or death was 5.8%–6.7% for combined CEA and medical therapy versus 2.5%–3.3% for medical therapy alone. A lesser degree of benefit was seen for patients with 50%–69% stenosis, but this was statistically significant at 5 years of follow-up.

For asymptomatic carotid artery stenosis, the trial results are less concordant. For selected patients with significant (> 60%–80%) carotid artery stenosis, CEA can reduce the risk of perioperative stroke over medical therapy alone, but patient selection is crucial. Data from the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) reported that over the ensuing 5 years, the risk of a periprocedural stroke and death was reduced by half, from 11%–11.7% with medical therapy alone to 5.1%–6.4% with early CEA. As the benefits of surgery are influenced by periprocedural risks, endarterectomy is recommended when the procedure can be performed with a perioperative risk of less than 6% for symptomatic patients and less than 3% for asymptomatic patients.

Emerging in 1994, CAS offers an alternative treatment for highly selected patients with carotid artery stenosis. Several randomized trials of CAS, such as the Carotid and Vertebral Transluminal Angioplasty Study (CAVATAS)—CEA, Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S), and Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE), have not demonstrated superiority or noninferiority over CEA for patients eligible for both procedures. However, some patients are not candidates for CEA, and for them CAS still fills an important role. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) Trial is notable for introducing several unique aspects including focusing on high-risk patients, requiring the use of an emboli-protection device, adding major adverse cardiac events to the primary end point of stroke and death, and requiring a triumvirate of a surgeon, stenting proceduralist, and neurologist to agree on patient selection. Protected CAS was noninferior to CEA for patients with either ≤ 50% symptomatic or ≥ 80% asymptomatic carotid artery stenosis, but there was a significant reduction in secondary end points of associated cranial nerve palsy, revascularizations, and length of hospital stay, which were lower among the endovascular cohort. However, these data are specific to high-risk medical and surgical patients and did not address low-to-moderate risk patients. The EVA-3S trial was prematurely terminated due to safety concerns and a futility analysis. The SPACE study was also prematurely terminated after a futility analysis but identified a significant increased risk with CAS of complications in patients older than 68 years and a higher rate of in-stent restenosis as defined by ultrasonography.

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) offers the most recent and comprehensive assessment of stenting versus endarterectomy.

### TABLE 1: Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td>requires &gt;50% stenosis or occlusion of ipsilateral cervicocephalic or intracranial artery, CE excluded, infarcts usually &gt;1.5 cm</td>
</tr>
<tr>
<td>CE</td>
<td>infarcts usually &gt;1.5 cm, LAA excluded; high risk: AF, prosthetic heart valve, clot, recent MI, infective endocarditis, dilated cardiomyopathy; possible: PFO, atrial septal aneurysm, mitral valve prolapse, low ejection fraction</td>
</tr>
<tr>
<td>lacunar infarct</td>
<td>traditional syndrome, infarct &lt;1.5 cm, CE &amp; LAA excluded, usually in the setting of risk factors such as hypertension &amp; DM</td>
</tr>
<tr>
<td>other determined etiology</td>
<td>dissection, other vasculopathy, infection, hematological, drugs; CE &amp; LAA excluded</td>
</tr>
<tr>
<td>undetermined etiology</td>
<td>no cause identified (cryptogenic) or evaluation incomplete; uncertain w/ multiple potential causes identified</td>
</tr>
</tbody>
</table>

* AF = atrial fibrillation; CE = cardiac embolism; DM = diabetes mellitus; LAA = large artery atherosclerosis.
TABLE 2: Summary of randomized controlled trials of surgical or endovascular interventions with best medical therapy in patients with carotid artery stenosis*

<table>
<thead>
<tr>
<th>Study &amp; Year</th>
<th>No. of Pts</th>
<th>% CA Stenosis</th>
<th>Symptomatic vs Asymptomatic</th>
<th>Study Results</th>
<th>Benefit From Surgical or Endo Intervention w/ Best Medical Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET, 1991</td>
<td>659</td>
<td>70–99 symptomatic</td>
<td>stenosis 70–99% showed most significant reduction in ipsilat stroke risk; ipsilat stroke risk significantly decreased in pts w/ 50–69% stenosis undergoing CEA; no benefit in pts w/ &lt;50% stenosis</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>ECST, 1998</td>
<td>858</td>
<td>50–69 symptomatic</td>
<td>11.6% benefit from op after 3 yrs in pts w/ stenosis &gt;80% (w/ variations in age &amp; sex)</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>VACSP, 1991</td>
<td>504</td>
<td>50–99 symptomatic</td>
<td>at 11.9 mos mean FU, there was significant reduction in stroke or crescendo TIA in pts undergoing CEA (7.7%) compared w/ nonsurgical pts (19.4%); benefits were more pronounced in stenosis &gt;70%</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>ACAS, 1995</td>
<td>1662</td>
<td>60–99 asymptomatic</td>
<td>aggregate risk for ipsilat stroke, any periop stroke, or death was estimated to be 5.1% for surgical pts &amp; 11.0% for pts treated medically</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>ACST, 2008</td>
<td>3120</td>
<td>60–99 asymptomatic</td>
<td>comparing all pts randomized to immediate CEA vs all patients randomized to deferral, net 5-yr stroke risks were 6.4% vs 11.8% for all &amp; 3.5% vs 6.1% for fatal or disabling strokes and 2.1% vs 4.2% for only fatal strokes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>CAVATAS, 2001</td>
<td>504</td>
<td>50–99 symptomatic</td>
<td>w/in 30 days of treatment (randomly assigned to endovascular vs surgical), there were more minor strokes that lasted &lt;7 days in the endovascular group, but the no. of other strokes in any territory or death was the same; more CN palsies in the endarterectomy group than in the endovascular group; more pts had stroke during FU in the endovascular group than in the surgical group, but the rate of ipsilat non-periop stroke was low in both groups &amp; none of the differences in the stroke outcome measures was significant</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>SAPPHIRE, 2004</td>
<td>334</td>
<td>50–99 both</td>
<td>at 36 mos the incidence of stroke was virtually identical for both CAS &amp; CEA, indicating that CAS is not inferior to CEA; 3-yr incidence of stroke across the CAS treatment group members had only an average increase of 4.0% over the 30-day stroke rate</td>
<td>noninferior</td>
<td>noninferior</td>
</tr>
<tr>
<td>SPACE, 2008</td>
<td>1200</td>
<td>50–99 symptomatic</td>
<td>in contrast to CEA the periprocedural risk of the CAS cohort seems to be dependent upon the timing of intervention, having a higher risk w/ early treatment; hence, for pts w/ symptomatic CA stenosis that can be treated early, CEA seems to be the safer method, most likely due to plaque stabilization</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>EVA-3S, 2006</td>
<td>527</td>
<td>60–99 symptomatic</td>
<td>30-day risk of stroke or mortality was significantly increased in the stenting group compared w/ the endarterectomy group; stenting showed a significantly lower risk for CN injury &amp; a beneficial trend for systemic complications but a much higher risk for major or local complications &amp; TIA</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>ICSS, 2010</td>
<td>1713</td>
<td>50–99 symptomatic</td>
<td>incidence of stroke, death, or procedural MI was 8.5% in the stenting group compared w/ 5.2% in the endarterectomy group; risks of any stroke &amp; all-cause death were higher in the stenting group than in the endarterectomy group</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>CREST, 2010</td>
<td>2502</td>
<td>50–99 both</td>
<td>among pts w/ symptomatic or asymptomatic carotid stenosis, the risk of the composite primary outcome of stroke, MI, or death did not differ significantly in the group undergoing CAS and the group undergoing CEA; during the periprocedural period, there was a higher risk of stroke w/ stenting &amp; a higher risk of MI w/ endarterectomy</td>
<td>equivalent</td>
<td>equivalent</td>
</tr>
<tr>
<td>COSS, 2011</td>
<td>191</td>
<td>symptomatic ICA occlusion</td>
<td>early termination after futility analysis of 139 pts after 2-yr FU; despite excellent graft patency &amp; improved cerebral hemo-dynamics, EC-IC bypass surgery failed to provide an overall benefit on 2-yr stroke recurrences due to the much better than expected recurrence rate in the nonsurgical group</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

* CA = carotid artery; CN = cranial nerve; Endo = endovascular; FU = follow-up; Pts = patients. Studies are as follows: ACAS = Asymptomatic Carotid Atherosclerosis Study; ACST = Asymptomatic Carotid Surgery Trial; CAVATAS = Carotid and Vertebral Transluminal Angioplasty Study; COSS = Carotid Occlusion Surgery Study; CREST = Carotid Revascularization Endarterectomy vs Stenting Trial; ECST = European Carotid Surgery Trial; EVA-3S = Endarterectomy Versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis; ICSS (CAVATAS-2) = International Carotid Stenting Study; NASCET = North American Symptomatic Carotid Endarterectomy Trial; SAPPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; SPACE = Stent-protected Percutaneous Angioplasty of the Carotid vs. Endarterectomy; VACSP = Veterans Affairs Cooperative Studies Program.
for treatment of carotid artery stenosis. Comprising more than 2500 individuals with symptomatic and asymptomatic extracranial carotid stenosis and over 108 centers in the US and Canada, the primary endpoint studied was the composite of any stroke, MI, or death during the periprocedural period or ipsilateral stroke within 4 years after randomization. Over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary endpoint between the stenting and endarterectomy cohorts (7.2% and 6.8%, respectively; HR with stenting 1.11 [95% CI 0.81–1.51; p = 0.51]). There was no discernible treatment effect with regard to the primary endpoint according to symptomatic status (p = 0.84) or sex (p = 0.34), but the 4-year rate of stroke or death was 6.4% with stenting and 4.7% with endarterectomy (HR 1.50; p = 0.03). In contrast, the rates among symptomatic patients were 8.0% and 6.4% (HR 1.37; p = 0.14), and the rates among asymptomatic patients were 4.5% and 2.7% (HR 1.86; p = 0.07), respectively. After this initial period, the rates of ipsilateral stroke with CAS and CEA were nonsignificant (2.0% and 2.4%, respectively; p = 0.85). In general, outcomes were slightly better after CAS in patients younger than 70 years old and better after CEA for patients older than 70 years old. The risks of stroke and death were found to be significantly higher for CAS versus CEA in symptomatic patients (6.0% vs 3.2%; HR 1.89, 95% CI 1.11–3.21) but not for asymptomatic patients (2.5% vs 1.4%; HR 1.88, 95% CI 0.79–4.42). However, the rate of periprocedural MI was higher in CEA versus CAS (1.1% vs 2.3%, p = 0.032).

In the ICSS (International Carotid Stenting Study), 1713 patients were enrolled and randomized from 50 mostly European academic centers for the study, allowing a variety of stents and emboli-protection devices in 72% of CAS-treated patients, possibly more accurately reflecting the practice in the broader medical community. The mean time intervals from the most recent time-to-treatment were 35 days for CAS and 40 days for CEA. The main safety end points (stroke, death, or procedural MI at 120 days) was 8.5% and 5.2% for CAS and CEA, respectively (HR 1.69; p = 0.006) At 30 days, the incidence of disabling stroke was the same in both groups (17%), but the incidence of fatal and nondisabling stroke was significantly higher in CAS-treated patients. Seventy-four percent of CAS-treated patients and 44% of CEA-treated patients had periprocedural strokes that occurred on the day of the procedure. Whether most strokes in the CAS-treated patients were intraintral cerebral hemodynamics, limiting the utility of the analysis. Powers and colleagues designed the carotid occlusion surgery study (COSS), which sought to randomize patients with symptomatic carotid artery occlusion, demonstrated neither superiority nor inferiority of EC-IC bypass when compared with medical therapy alone.

The meta-analysis included 2 randomized controlled trials (EC-IC bypass trial and JET) and 19 nonrandom studies with a total of 2591 patients. No benefit with regard to stroke or death and dependency was found, although a trend toward benefit for surgery with regard to ischemic stroke was noted in a meta-analysis of the 2 randomized controlled trials. However, the majority of studies included patients without evaluation of their cerebral hemodynamics, limiting the utility of the analysis. Powers and colleagues designed the carotid occlusion surgery study (COSS), which sought to randomize patients with symptomatic carotid artery occlusion defined by recent stroke and evidence of hemodynamic insufficiency by 15 O PET. Based on the St. Louis Carotid Occlusion Study, a stroke rate of 40% was expected in the medical arm at 2 years. An anticipated stroke rate of 24% 2 years was expected in the surgical arm. The first patient was enrolled in 2002. With 372 randomized
diabetes.56,57 than 75 years, history of heart failure, hypertension, and prior TIA or stroke; other risk factors include age older important risk factor for stroke with atrial fibrillation is ber is bound to increase as the population ages. The most claim for approximately 20% of ischemic strokes as well as a common medical comorbidity with elderly neurosurgical patients.

Cardiac Embolism. The classic causes of cardiac embolism include atrial fibrillation, valvular heart disease, heart failure, and recent myocardial infarction and account for approximately 20% of ischemic strokes as well as a common medical comorbidity with elderly neurosurgical patients.

Atrial Fibrillation. The projected figures might actually be larger since some patients initially diagnosed as cryptogenic will be determined to have paroxysmal atrial fibrillation at a follow-up medical evaluation or after an extended period of portable cardiac monitoring. Atrial fibrillation is the most common arrhythmia in the elderly, claiming well over 2 million American lives. This number is bound to increase as the population ages. The most important risk factor for stroke with atrial fibrillation is prior TIA or stroke; other risk factors include age older than 75 years, history of heart failure, hypertension, and diabetes.56,57 For the majority of patients with atrial fibrillation, anticoagulation therapy is the standard of care. Multiple randomized studies have proven the superiority of anticoagulation with warfarin for preventing stroke with an overall relative risk reduction of 68%, from 4.5% in patients with placebo or aspirin compared with 1.4% in treated patients.58 The ideal INR for these patients is 2.5 with a therapeutic range from 2.0 to 3.0. There is no evidence to support increasing the target INR because patients who have suffered a stroke have better outcomes while in the therapeutic range.

In early clinical trials, warfarin therapy was generally found to be safe with an annual major bleeding risk of 1.4% compared with 1% for placebo or aspirin. Many patients and doctors are opposed to long-term warfarin therapy, largely fueled by the fear of bleeding or requirements for monitoring. As an alternative to long-term warfarin therapy for atrial fibrillation, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE A) study reported a reduction in stroke risk with aspirin plus clopidogrel at 2.4% compared with 3.3% with aspirin alone in patients refusing or thought to be too high risk for anticoagulation therapy.1 However, major bleeding was significantly greater (2% vs 1.3%) and similar to the bleeding risk with warfarin in other studies.1

Other anticoagulants are emerging as an alternative to warfarin therapy. Dabigatran, a direct thrombin inhibitor, was the first to receive FDA approval in September 2010. The Randomized Evaluation of Long-Term Anticoagulation Therapy (RELY) trial randomized 18,113 patients with nonvalvular atrial fibrillation and determined that the 150 mg twice daily dose of dabigatran was superior and the 110 mg twice daily dose of dabigatran was noninferior to standard warfarin therapy in the prevention of stroke (including hemorrhagic stroke) and systemic embolism. The risk of major bleeding was similar to that of warfarin at the higher dosage but less than that for warfarin at the lower dosage, and the rates of hemorrhagic stroke were

Table 3: Overview of the completed EC-IC bypass trials*

<table>
<thead>
<tr>
<th>Study &amp; Year</th>
<th>Hypothesis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC/IC Bypass Study, 1985</td>
<td>to determine whether anastomosis of STA-MCA decreases the rate of stroke &amp; stroke-related death among pts w/ symptomatic disease of the ICA &amp; MCA</td>
<td>nonfatal &amp; fatal stroke occurred more frequently &amp; earlier in pts who underwent op; patients w/ severe MCA stenosis &amp; those w/ persistence of ischemic symptoms after ICA occlusion fared substantially worse in the surgical group</td>
</tr>
<tr>
<td>St. Louis Carotid Occlusion Study, 1998</td>
<td>evaluates prognostic abilities of hemodynamic factors for pts w/ CA occlusion</td>
<td>ipsilateral stroke rate at 2 yrs in asymptomatic pts had a lower frequency of hemodynamic abnormalities compared w/ similar symptomatic pts w/ baseline risk factors</td>
</tr>
<tr>
<td>Cost-effectiveness Analysis of Therapy for Symptomatic Carotid Occlusion, 2002</td>
<td>PET screening before selective EC-IC vs medical treatment</td>
<td>PET screening of the cohort followed by EC-IC bypass yielded 23.2 additional QALYs (at $20,000/QALY) compared w/ medical treatment alone</td>
</tr>
<tr>
<td>JET-1, 2006</td>
<td>Stage II hemodynamic compromise improves w/ bypass</td>
<td>EC-IC bypass surgery significantly reduced the frequency of recurrent stroke for pts w/ Stage II ischemia compared w/ strict medical therapy</td>
</tr>
<tr>
<td>JET-1 subanalysis</td>
<td>EC-IC bypass changes brain volume &amp; hemodynamics</td>
<td>EC-IC bypass increased the affected/unaffected % regional cerebral blood flow ratio</td>
</tr>
<tr>
<td>COSS, 2003</td>
<td>to determine whether surgical STA-to-MCA anastomoses in conjunction w/ the best medical therapy can reduce the incidence of ipsilateral ischemic stroke by ≥40% in pts w/ symptomatic ICA occlusion</td>
<td>study concluded on June 24, 2010, based on futility analysis of 139 pts who had completed a 2-yr FU; despite well patent grafts &amp; improved cerebral hemodynamics, EC-IC bypass surgery did not provide an overall benefit in terms of 2-yr ischemic stroke recurrence</td>
</tr>
</tbody>
</table>

* JET-1 = Japanese EC-IC Bypass Trial; QALY = quality-adjusted life year; STA = superficial temporal artery.
lower with dabigatran (0.10%–0.12% per year) compared with warfarin (0.38% per year).\textsuperscript{16} Dabigatran is an attractive alternative to warfarin since it is not impacted by diet or drug interactions and requires no laboratory monitoring. However, the lack of routine laboratory monitoring is a blessing and a curse because its anticoagulant effect is not accurately reflected in routine laboratory studies such as the prothrombin time and the activated partial thromboplastin time and requires a validated thrombin time. Although short acting and requiring twice-a-day dosing, it accumulates in patients with renal failure and has no specific antidote for reversal of effect. The interconversion of warfarin, dabigatran, and heparin are performed at our institution based on the guidelines listed in Table 4.

On the horizon are several oral factor Xa inhibitors including rivaroxaban and apixaban. These agents will also be attractive alternatives to warfarin in terms of limited drug interactions and reduced bleeding risk, but they also have no routine laboratory assay or antidote.

Interrupting Anticoagulation Therapy and Risk of Thromboembolism. Deciding to interrupt anticoagulation therapy to perform an invasive procedure or surgery can be difficult. The risk of a thromboembolic event during interruption of therapy is often a factor that weighs heavily on that decision and should be guided by an understanding of patient-specific factors to stratify risk as high, moderate, or low (Table 5).\textsuperscript{18} A more difficult situation from a neurosurgical standpoint is the treatment of patients with intracranial or intraspinal hemorrhage who have underlying conditions requiring anticoagulation, such as mechanical heart valves or chronic atrial fibrillation. In the acute setting of intracranial, subdural, or subarachnoid hemorrhages, the current practice is to discontinue all anticoagulants and antiplatelets for 1–2 weeks; however, in cases at high risk for ischemic stroke, warfarin is restarted after 7–10 days of hemorrhage due to compelling indications. Factors that would allow resuming anticoagulation in such patients include a hypertension-related hemorrhage (given that the blood pressure is well controlled), the need for secondary prevention, atrial fibrillation with a high CHADS2 score, the presence of a mechanical valve, or a hypercoagulable state. On the other hand, if there is any evidence of cerebral angiopathy or microhemorrhages on gradient echo MR imaging or if primary prevention is only sought in the setting of atrial fibrillation with a low CHADS2 score, then anticoagulation should not be resumed immediately.

Small Artery Occlusion and Lacunar Infarcts

Small artery occlusion can present in a wide variety of lacunar syndromes. Patients in these cases do not have any evidence of cortical involvement. Imaging usually reveals a brainstem or subcortical hemispheric infarct smaller than 1.5 cm.\textsuperscript{2,42} Such lesions occur most frequently in the putamen, basis pontis, thalamus, posterior limb of the internal capsule, and caudate nucleus. The etiology of these lacunar infarcts is attributed to hypertension, hyperlipidemia, diabetes mellitus, tobacco smoking, or a combination of these risk factors in addition to other less frequently emphasized (or addressed) risk factors such as alcohol consumption, obesity and physical inactivity, metabolic syndrome, obstructive sleep apnea, and restless leg syndrome. It is thought that these risk factors are directly or indirectly responsible for inflicting detrimental structural changes to small penetrating arteries through arterial hypertension. These changes commonly involve fibrinoid angiopathy, lipohyalinosis, and mircoraneurysm formation.\textsuperscript{4} Other sources of cerebral ischemia such as large-vessel atherosclerosis or cardioembolism are absent. Hypertension and diabetes mellitus play a major role in small vessel ischemic disease. In fact, lacunar disease is rarely found at autopsy without a history of diabetes or hypertension.\textsuperscript{11}

Other Determined Causes

Arterial Dissections. Carotid and vertebral artery dissections are relatively common causes of TIA and stroke, particularly among young patients, either due to head and neck trauma or occurring spontaneously.\textsuperscript{44,60} Connective tissue disorders are known risk factors for spontaneous dissection, including fibromuscular dysplasia, Marfan syndrome, Ehlers-Danlos syndrome (Type IV), and osteogenesis imperfecta. Currently, there is no substantial available medical treatment for the aforesaid conditions. Computed tomography angiography or MR imaging and MR angiography with fat saturation protocols are used to diagnose extracranial dissection, and conventional angiography is the gold standard for the diagnosis of intracranial dissection.

Although most ischemic strokes due to dissection are a result of early thromboembolism, a minority are attributed to hemodynamic compromise.\textsuperscript{16} Rather infrequently, these dissections can lead to formation of a dissecting aneurysm, which can also serve as a nidus of thrombus formation. Posterior fossa dissections can result in fatal subarachnoid hemorrhage, as well as cerebellar infarction.\textsuperscript{48} The treatment paradigm for dissections generally includes anticoagulation therapy, antiplatelet therapy, angioplasty with or without stenting, or conservative obser-

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>converting from warfarin to dabigatran etexilate</td>
<td>discontinue warfarin &amp; start dabigatran etexilate when the INR is below 2</td>
</tr>
<tr>
<td>converting from dabigatran etexilate to warfarin</td>
<td>starting time of warfarin is based on creatinine clearance (CrCL) as follows:</td>
</tr>
<tr>
<td></td>
<td>CrCL &gt;50 ml/min: start warfarin 3 days before discontinuing dabigatran etexilate;</td>
</tr>
<tr>
<td></td>
<td>CrCL 31–50 ml/min: start warfarin 2 days before discontinuing dabigatran etexilate;</td>
</tr>
<tr>
<td></td>
<td>CrCL 15–30 ml/min: start warfarin 1 day before discontinuing dabigatran etexilate</td>
</tr>
<tr>
<td>converting from intravenous heparin to dabigatran etexilate</td>
<td>start dabigatran etexilate at the time of intravenous heparin discontinuation</td>
</tr>
</tbody>
</table>

S. Manjila et al.
Review of primary and secondary ischemic stroke prevention

TABLE 5: Periprocedural risk stratification for surgical or invasive procedures in patients needing anticoagulation: CHADS2 score*

<table>
<thead>
<tr>
<th>Risk Stratum</th>
<th>Mechanical Heart Valve</th>
<th>Embolic Stroke</th>
<th>AF</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>recent (within 6 mos) stroke or TIA; older (caged-ball or tilting disc) aortic valve prosthesis; any mitral valve prosthesis</td>
<td>recent stroke (within 3 mos)</td>
<td>CHADS2 score of 5 or 6; recent (within 3 mos) stroke or TIA; rheumatic valvular heart disease</td>
<td>recent (within 3 mos) VTE; severe thrombophilia (e.g., deficiency of protein C)</td>
</tr>
<tr>
<td>moderate</td>
<td>bileaflet aortic valve prosthesis &amp; 1 of the following: congestive heart failure, hypertension, age &gt;75 yrs, diabetes, AF, or prior stroke or TIA</td>
<td>Hx of stroke (&gt;3 but &lt;6 mos prior)</td>
<td>CHADS2 score of 3 or 4</td>
<td>VTE within past 3–12 mos; nonsevere thrombophilic conditions; recurrent VTE; active cancer (treated within 6 mos or palliative)</td>
</tr>
<tr>
<td>low</td>
<td>bileaflet aortic valve prosthesis w/o AF &amp; no other risk factors for stroke</td>
<td>Hx of stroke (26 mos prior)</td>
<td>CHADS2 score of 0–2 (&amp; no prior stroke or TIA)</td>
<td>single VTE occurred &gt;12 mos ago &amp; no other risk factors</td>
</tr>
</tbody>
</table>

* Data were obtained from the study by DeLoughery. The CHADS2 score is calculated as follows: congestive heart failure (1 point), hypertension (1 point), age older than 75 years (1 point), diabetes (1 point), and stroke (2 points). Abbreviation: VTE = venous thromboembolism.

The relative efficacy of antiplatelet therapy compared with anticoagulation is unknown for patients with ischemic stroke or TIA and extracranial carotid or vertebral arterial dissection. For patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite optimal medical therapy, endovascular therapy (stenting) may be considered. Patients with stroke or TIA and extracranial carotid or vertebral arterial dissection who are not candidates for endovascular therapy or in whom it has failed may be considered for surgical treatment.

**Patent Foramen Ovale.** A PFO is an embryonic defect in the interatrial septum that allows right to left passage of emboli. Although thrombus is rarely detected within the heart, it is a presumed cause, supported mostly by its higher frequency in patients with cryptogenic stroke, particularly those younger than 55 years, compared with the 15%–25% prevalence in the adult population. Although endovascular device closure of the PFO has gained considerable interest, the recently completed CLOSURE study did not support superiority of the Starflex endovascular PFO closure device compared with medical therapy alone for stroke prevention. Antiplalet therapy remains the treatment of choice for patients with ischemic stroke (along with optional anticoagulation therapy), and other trials of PFO closure devices are ongoing. The presence of a PFO can pose a unique challenge for neurosurgical patients during operations performed in the sitting position. The risk of venous air embolism is reported to be 23%–45% and can be associated with paradoxical cerebral embolism in up to 14% of patients.

**Current Treatment for Stroke From Noncardioembolic, Atherosclerotic Source or Unidentified Cause**

For patients who suffered a noncardioembolic stroke or a TIA, the strongest evidence supports antiplatelet therapy as a first of line of treatment to prevent future strokes. Initial antiplatelet therapy can be in the form of aspirin (50–
325 mg), clopidogrel 75 mg monotherapy, or a combination or aspirin 25 mg with extended-release dipyridamole 200 mg twice daily depending on each patient’s underlying conditions, limiting allergies, and tolerance. There are no good data on patients in whom aspirin therapy has failed, and although many physicians use this opportunity to increase the dosage of aspirin, switch to an alternative antiplatelet therapy, or switch to anticoagulation, there are no data to support these practices. Alternative antiplatelet therapies are available for CHD, such as prasugrel, a third generation of thienopyridine. However, it is not indicated in patients with a history of TIA or strokes because of the increased risk of intracranial bleeding. Studies evaluating lower doses are ongoing.

Risk Factor Identification and Management for Primary and Secondary Stroke Prevention

Hypertension

Hypertension is the single most important risk factor for stroke due to its impact on ischemic and hemorrhagic stroke and its prevalence in the population; therefore, blood pressure measurement should be a routine part of any patient interaction. Around 72 million Americans suffer from hypertension, defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg with normal blood pressure lower than 120/80 mm Hg. There is a clear and graded association between elevated blood pressure and stroke risk starting at a systolic blood pressure of 115 mm Hg. Meta-analysis of randomized controlled trials has shown that lowering of blood pressure decreases the risk of stroke, defined as a systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg to a normal blood pressure lower than 120/80 mm Hg. This reduction in systolic blood pressure reduces the risk of stroke by 22%, and the reduction in diastolic blood pressure reduces the risk of stroke by 16%.

Dyslipidemia

Epidemiological studies have long established a strong correlation between abnormal cholesterol levels in blood and CHD, which is also present for atherosclerotic stroke subtypes. Meta-analysis of more than 90,000 patients included in statin trials showed that the larger the reduction in low-density lipoprotein cholesterol (LDL-C), the greater the reduction in all stroke subtypes (both ischemic and hemorrhagic). The Stroke Prevention by Aggressive Reduction Levels (SPARCL) study of 4731 TIA or stroke patients without a history of CHD supports the use of intensive statin therapy for secondary stroke prevention. High-dose atorvastatin (80 mg daily) significantly reduced the risk of stroke from 13.1% to 11.2%; the 18% relative risk reduction means that 258 patients must be treated to prevent 1 recurrent stroke over the course of 1 year. Guidelines recommend statin therapy with intensive lipid-lowering effects for patients with ischemic stroke or TIA who have an LDL (low-density lipoprotein) cholesterol ≥ 100 mg/dl and, if accompanied by known CHD, the target in these patients should be either a 50% reduction in LDL or an LDL lower than 70 mg/dl. If these patients suffer from low HDL (high-density lipoprotein) cholesterol (≤ 40 mg/dl), they may be considered for treatment with niacin or gemfibrozil.

Diabetes

The prevalence of diabetes is estimated at about 8% in the US. Among patients who suffered an ischemic stroke, the prevalence of diabetes increases to as high as 33%. Diabetic patients who suffer a stroke are also at an increased risk of morbidity and mortality in comparison with nondiabetic stroke patients. In addition, diabetes is an independent risk factor for recurrent strokes; it has been estimated to be the culprit in 9.1% of recurrent strokes. Criteria that support the diagnosis of diabetes mellitus are a fasting glucose ≥ 126 mg/dl, hemoglobin A1C ≥ 6.5%, or a random fasting glucose higher than 200 mg/dl. In addition, an A1C higher than 7% is indicative of poor control of hyperglycemia. Several randomized clinical trials of intensive glucose management in persons with diabetes who had a history of cardiovascular disease, stroke, or other risk factors could not demonstrate a reduction in cardiovascular events and deaths in the tight glycemic control group. However, tight control of hypertension and dyslipidemia is associated with a significant reduction in all vascular events. An ongoing trial at the National Institutes of Health, the Insulin Resistance Intervention after Stroke (IRIS) trial is currently evaluating whether treatment with the insulin sensitizer pioglitazone will reduce secondary stroke or MI.

Unhealthy Lifestyles: Tobacco Abuse, Excessive Alcohol Intake, and Physical Inactivity

In addition, promoting smoking cessation, encouraging regular physical activity, and limiting alcohol intake are proven to be indispensable in secondary stroke prevention. Counseling stroke patients on the importance of smoking cessation and prescribing oral cessation medications are all effective measures for helping smokers quit. It is recommended that patients who have had ischemic stroke or TIA who are able to engage in physical activity do so regularly. Beneficial physical activity is defined as at least 30 minutes of moderate intensity physical exercise that is vigorous enough to cause sweating or an increase in heart rate as often as 1–3 times a week.

Joint Commission and Primary Stroke Center Certification

Many US hospitals lack the necessary infrastructure and organization required to triage and treat patients with stroke quickly and efficiently, and do not deliver adequate stroke care. Even though a 2003 statewide assessment of hospital-based stroke care and prevention in North Carolina demonstrated that many hospitals had improved in key elements necessary to provide care over the 5-year study, the data indicate that the hospitals were still lack-
Review of primary and secondary ischemic stroke prevention

In a number of areas, including the use of a tissue plasminogen activator protocol (54%), the availability of a neurologist (30%) or interventional radiologist (9%) at all times, use of stroke care maps (30%), presence of a stroke unit (19%) and a stroke team (16%), and a sufficient community awareness program (27%). While this evidence supports a growth in infrastructure, there is room for improvement.

In 2005, the Brain Attack Coalition published recommendations for the establishment of comprehensive stroke centers. A PSC stabilizes and treats acute stroke patients, providing initial acute care.63 Primary Stroke Centers are able to appropriately use tissue plasminogen activator and other acute therapies such as stabilization of vital functions, provision of neuroimaging procedures, and management of intracranial pressure and blood pressure. Comprehensive stroke centers treat patients at all needed levels of care, even in cases of the most complex strokes. They offer specialized diagnostics and other interventions, including tertiary care centers, and have the infrastructure and personnel necessary for highly technical procedures. Based on patient needs and the hospital's capabilities, they either admit patients or transfer them to a comprehensive stroke center. As of January 2006, there were 174 PSCs certified by the Joint Commission on Accreditation of Healthcare Organizations in the US.3

According to the Joint Commission and recommendations from Brain Attack Coalition’s task force, specific standards for PSC certification include the following elements: standardize methods of delivering the recommendations established by the Brain Attack Coalition’s task force, support a patient’s self-management activities, tailor treatment and intervention to individual needs, standardize performance measures data to improve treatment plans, demonstrate compliance with clinical practice guidelines, and promote the flow of patient information across settings and providers while protecting patient rights, security, and privacy.5 Effective January 1, 2010, PSCs must collect and report data on National Inpatient Hospital Quality measures for stroke, which include venous thromboembolism prophylaxis, discharge of patients on a regimen of antithrombotic therapy, anticoagulation therapy for atrial fibrillation/flutter, thrombolytic therapy, and antithrombotic therapy by end of hospital Day 2.3

Through standardizing care and strict compliance with a universal set of measures nationwide, hospitals and providers are able to provide improved quality of stroke management, increased efficiency of patient care, reduced mortality and morbidity, reduced costs to the health care system, and improved patient satisfaction.

**Physician Quality Reporting System in Stroke Management**

To participate in the 2011 PQRS, eligible professionals may choose to report information on individual quality measures or on a group of measures. Professionals who meet the criteria for satisfactory submission of quality measures and submit data via one of the reporting mechanisms during a 2011 reporting period will qualify to earn a PQRS payment equal to 1.0% of their total estimated Medicare Part B Physician Fee Schedule allowed charges for covered professional services furnished during that same reporting period.

To qualify to earn a PQRS incentive payment, eligible professionals must meet specified criteria for satisfactory reporting during the applicable reporting period. Given the broad array of specialties and settings in which eligible professionals practice, Centers for Medicare and Medicaid Services has designed the PQRS program in a manner that gives eligible professionals flexibility in determining how best to integrate PQRS quality measures reporting into their practice work flows. Practitioners participating in stroke management already engage in the following measures: deep venous thrombosis prophylaxis for stroke or intracranial hemorrhage, discharging patients on antiplatelet therapy, screening for dysphagia in the acute setting, prescribing anticoagulation for atrial fibrillation, and providing rehabilitation services (Table 6). Also, management options such as CEA, the use of an arterial patch graft during conventional CEA, and thrombolytic therapy are easily reportable measures included in the PQRS program.14 Providers have already incorporated the above as standards of best practice within stroke care. The PQRS incentive program simply offers providers a financial incentive to aid in standardizing patient care and therefore improve the quality of practice across various institutions.

**Conclusions**

We have provided a comprehensive update on the evi-

---

**TABLE 6: Highlighted 2011 PQRS Measure Specifications for Reporting of Individual Measures: role of stroke prevention**

<table>
<thead>
<tr>
<th>Measure No.</th>
<th>Measure Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>31</td>
<td>Stroke and Stroke Rehabilitation: Deep Vein Prophylaxis (DVP) for Ischemic Stroke or Intracranial Hemorrhage</td>
</tr>
<tr>
<td>32</td>
<td>Stroke and Stroke Rehabilitation: Discharged on Antiplatelet Therapy</td>
</tr>
<tr>
<td>33</td>
<td>Stroke and Stroke Rehabilitation: Anticoagulant Therapy Prescribed for Atrial Fibrillation at Discharge</td>
</tr>
<tr>
<td>35</td>
<td>Stroke and Stroke Rehabilitation: Screening for Dysphagia</td>
</tr>
<tr>
<td>36</td>
<td>Stroke and Stroke Rehabilitation: Consideration of Rehabilitation Services</td>
</tr>
<tr>
<td>158</td>
<td>Carotid Endarterectomy: Use of Patch During Conventional Carotid Endarterectomy</td>
</tr>
<tr>
<td>187</td>
<td>Stroke and Stroke Rehabilitation: Thrombolytic Therapy</td>
</tr>
</tbody>
</table>

dence-based guidelines for primary and secondary stroke prevention including risk factor management. Common neurosurgical issues such as perioperative adjustment of anticoagulation, management of atrial fibrillation, and incorporating the CHADS scoring method are discussed along with new pharmacological options for prevention of cardioembolic strokes. The new reporting incentives in the changing medical reimbursement scene and hence the mandatory guidelines for PSC certification may have a much greater impact on the contemporary vascular neurosurgical practice.

Disclosure

Dr. Sila is a consultant for Abbott Vascular and Hoffman-La Roche.

Author contributions to the study and manuscript preparation include the following. Conception and design: Selman, Manjila, Masri, Chowdhry, Sila. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Statistical analysis: Masri. Administrative/technical/material support: Selman, Masri, Sila. Study supervision: Selman, Sila.

References

25. Engelst SR, Lyser PA, Kirsch EC, Steck AJ: Long-term fol-
Review of primary and secondary ischemic stroke prevention


Neurosurg Focus / Volume 30 / June 2011


Address correspondence to: Warren R. Selman, M.D., Department of Neurological Surgery, The Neurological Institute, University Hospitals Case Medical Center, 11100 Euclid Avenue, HAN 5042, Cleveland, Ohio 44106. email: Warren.Selman@UHhospitals.org.