Medical management of intracranial atherosclerosis: Current state of the art

CATHY A. SILA, MD

Noncardioembolic ischemic stroke accounts for at least 60% of all strokes due to atherothrombosis or thromboembolism involving the large cervicocephalic vessels, the medium intracranial vessels, or the small perforating vessels. In the intracranial vasculature, the proposed mechanisms of an acute vascular event include plaque rupture and thrombotic occlusion or thromboembolism due to platelet adhesion/activation/aggregation and subsequent cross-linking with fibrin. Theoretically, both antiplatelet and oral anticoagulant therapies should be effective in preventing these events.

However, most clinical trials assessing the efficacy of antithrombotic therapies have focused on the index event (such as transient ischemic attack [TIA], reversible ischemic neurologic deficit, minor or moderate stroke) or the involved vascular territory (carotid vs vertebrobasilar) as a starting point without much analysis beyond excluding those subtypes that require anticoagulation (atrial fibrillation, recent myocardial infarction [MI], prosthetic valve) or that require surgical therapy (severe symptomatic carotid stenosis). As a result, the most frequently cited clinical trials, including most of the aspirin trials, the Ticlopidine-Aspirin Stroke Study (TASS), the European Stroke Prevention Study (ESPS-2), and the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, do not allow for subset analyses devoted to patients with intracranial atherosclerosis. Without adequate identification of stroke subtypes or knowledge of the differences in stroke subtype mix among the studies, it is also impossible to make meaningful indirect efficacy comparisons among the various antithrombotic therapy trials. These factors are largely responsible for the ongoing controversy regarding optimal therapy for patients with cerebrovascular disease due to causes other than atrial fibrillation or carotid stenosis.

From the Cerebrovascular Center, Section of Stroke and Neurologic Intensive Care, Department of Neurology, The Cleveland Clinic Foundation, Cleveland, Ohio.

Address: Cathy A. Sila, MD, Associate Medical Director, Cerebrovascular Center, Department of Neurology, The Cleveland Clinic Foundation, 9500 Euclid Avenue, S91, Cleveland, OH 44195.

ASPIRIN AND OTHER ANTIPLATELETS

Aspirin remains the standard preventive therapy for most patients at risk for stroke. Its initial US Food and Drug Administration approval in 1980 specified its use in men with TIAs "due to fibrin platelet emboli" based on a trial that used 1,300 mg daily, although current recommendations favor 50 to 325 mg daily. Meta-analyses of trials in patients with cerebrovascular disease showed that aspirin at dosages of 75 to 325 mg/day reduced the combined end point of stroke, MI, or vascular death by 25%, but its major effect comes from its 22% reduction of nonfatal stroke, which is the most common recurrent event in this population. Subgroup analyses (based on fewer than 400 events) in 25 trials showed no significant differences in reduction of vascular events between doses of 75 to 150 mg (26%), 160 to 325 mg (28%), or 500 to 1,500 mg, and the lower doses currently in use are primarily favored for their lower rates of gastrointestinal side effects and hemorrhage.

In the **Extracranial-Intracranial (EC/IC) Bypass Study**, patients with carotid occlusion, intracranial carotid/siphon stenosis, or middle cerebral artery stenosis received best medical care with or without the addition of bypass surgery. The antiplatelet therapy chosen was aspirin 1,300 mg/day. Although patients randomized to surgery had more and earlier recurrent and fatal strokes **(Table 1)**, patients in the medical arm also experienced a high rate of stroke (about 10% per patient-year).

TABLE 1
Rates of fatal and nonfatal stroke in the EC/IC Bypass Study, by site of stenosis and type of therapy

	Stroke incidence		
	Medical therapy	Surgical therapy	*P* value
MCA stenosis ≥ 70%	14/59 (24%)	22/50* (44%)	<.05
ICA stenosis ≥ 70%	26/72 (36%)	29/77 (38%)	NS

*14% converted from stenosis to occlusion on postoperative angiography.
MCA = middle cerebral artery; ICA = internal carotid artery.

ESPS-2. The combination of aspirin and dipyridamole has been studied in five clinical trials, but none specifically assessed patients for intracranial disease. The early trials did not reveal an additional benefit of combination therapy over high-dose aspirin alone (doses of 900 to 1,300 mg daily). ESPS-2 compared aspirin 25 mg twice daily, modified-release dipyridamole 200 mg twice daily, their combination, and placebo. Primary end points were stroke and stroke or death. Compared with placebo, the relative reduction in stroke risk was 18% with low-dose aspirin alone, 16% with dipyridamole alone, and 37% with the combination, suggesting an additive effect. The combination was 23% better than low-dose aspirin alone in preventing stroke, supporting a synergistic effect with combination antiplatelet therapy.

In **TASS**, ticlopidine 250 mg twice daily reduced the risk of recurrent stroke in patients with noncardioembolic TIA and minor stroke by a significant 19% compared with high-dose aspirin (650 mg twice daily). Although angiography was commonly performed in patients with carotid symptoms, only data regarding extracranial carotid stenosis were presented.

In **the CAPRIE trial**, clopidogrel 75 mg daily significantly reduced the relative risk of the combined end point of stroke, MI, or vascular death by 9% over aspirin 325 mg daily in 19,185 patients with a recent stroke or MI or with symptomatic peripheral vascular disease. There was no significant difference for the stroke cohort of more than 6,000 patients, although the analyses were not powered to specifically address subsets. Intracranial stenosis was not addressed in the CAPRIE trial and is also not addressed in the ongoing MATCH trial comparing clopidogrel 75 mg daily plus aspirin 325 mg daily with clopidogrel 75 mg daily alone.

■ WARFARIN VS ASPIRIN

Hemorrhagic risks and a lack of randomized trials limited the use of warfarin in stroke prevention until contemporary atrial fibrillation trials demonstrated an acceptable risk with modern therapeutic ranges and careful international normalized ratio (INR) monitoring. However, patients with cerebrovascular disease may have higher rates of anticoagulation-associated intracranial hemorrhage, as suggested by comparing the higher complication rates at INRs of 3.0 to 4.5 for patients with primary cerebrovascular disease in the SPIRIT trial.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) compared warfarin (INR initially targeted to 1.4 to 2.8 and later to 2 to 3) with aspirin 325 mg daily in patients with minor to moderate stroke who were followed for 2 years. The primary end point was recurrent stroke or death. Information was prospectively collected on stroke mechanism, and intracranial atherosclerosis was largely supported by magnetic resonance angiography and transcranial Doppler ultrasonography, which has limitations in sensitivity/specificity in the diagnosis of intracranial stenosis. Stroke subtype at entry included 56% lacunar stroke and 12% large-artery stenosis/occlusion, which included an unknown proportion of patients with intracranial stenosis. The 11% benefit in favor of aspirin was not statistically significant for the group or the subset with large-artery disease. Rates of major hemorrhage were low, at 1.92% per year with aspirin and 1.2% per year with warfarin, but patients with hypertension and a National Institutes of Health Stroke Scale score greater than 5 fared worse on warfarin. One fourth of patients had failed to respond to aspirin on entry. Although the overall 2-year recurrent stroke or death rate was significantly higher for these patients who had failed aspirin than for those who were naïve to aspirin (21.4% vs 13.8%), the fate of these aspirin nonresponders was not improved by switching to warfarin.

Retrospective, nonrandomized pilot data obtained by the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group suggested that warfarin reduced the risk of stroke and vascular death (primarily nonfatal stroke) by 50% (95% confidence interval, 23% to 86%) compared

with aspirin despite a 1.8% per patient-year risk of major hemorrhage. Stroke risk varied with the location and severity of intracranial stenosis, with the greatest risk seen in those patients with severe intracranial vertebrobasilar stenosis **(Table 2)**.

Prospective WASID findings

The major goal of WASID, a 5-year NINDS-supported prospective, randomized, double-blind, multicenter trial, was to compare warfarin (INR of 2 to 3) with aspirin (1,300 mg/day) for preventing stroke (ischemic and hemorrhagic) and vascular death in 403 patients with symptomatic, angiographically documented, 50% or greater stenosis of a major intracranial artery. (Sample size was based on stroke and vascular death rates of 33%/3 years in the aspirin group vs 22%/3 years in the warfarin group, an α of 0.05, a β of 0.80, a 24% withdrawal-of-therapy rate, and a 1% dropout rate). The study's aims were:

- To determine whether warfarin or aspirin is more effective for patients with symptomatic intracranial arterial stenosis
- To identify patients whose rate of ischemic stroke in the territory of the stenotic intracranial artery on best medical therapy is sufficiently high (ie, > 6% per year) to justify a subsequent trial comparing intracranial angioplasty with best medical therapy.

The trial was halted by its performance, safety, and monitoring board in August 2003 because of patient safety concerns. Data will be presented at the American Stroke Association's International Stroke Conference in February 2004.

TABLE 2
Incidence of clinical outcomes in the WASID retrospective study

	Warfarin (n = 88) (%/yr)	Aspirin (n = 63) (%/yr)
Stroke	3.6	10.4
Fatal MI or sudden death	3.0	4.2
Major hemorrhage	1.8	0
Same-territory stroke, 50%–69% stenosis	1.6	5.4
Same-territory stroke, 70%–99% stenosis	3.8	7.2
Same-territory stroke, severe vertebrobasilar stenosis	8.2	15.1

■ SELECT BIBLIOGRAPHY

The EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. N Engl J Med 1985; 313:1191–1200.

Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study Group. N Engl J Med 1989; 321:501–507.

Chimowitz MI, Kokkinos J, Strong J, et al. The Warfarin-Aspirin Symptomatic Intracranial Disease Study. Neurology 1995; 45:1488–1493.

Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143:1–13.

CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348:1329–1339.

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Study Group. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. Stroke 1998; 29:1389–1392.

Benesch CG, Chimowitz MI, for the WASID Investigators. Best treatment for intracranial stenosis? 50 years of uncertainty. Neurology 2000; 55:465–466.

Thijs VN, Albers GW. Symptomatic intracranial atherosclerosis. Outcome of patients who fail antithrombotic therapy. Neurology 2000; 55:490–497.

Mohr JP, Thompson JLP, Lazar RM, et al, for the Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001; 345:1444–1451.

Torn M, Algra A, Rosendaal FR. Oral anticoagulation for cerebral ischemia of arterial origin: high initial bleeding risk (SPIRIT). Neurology 2001; 57:1993–1999.

The Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) Trial Investigators. Design, progress, and challenges of a double-blind trial of warfarin versus aspirin for symptomatic intracranial arterial stenosis. Neuroepidemiology 2003; 22:106–117.