Carotid Atherosclerosis
Medical Management

Combination therapy may hold promise in the treatment of carotid disease.

BY SEEMANT CHATURVEDI, MD

Medical therapy remains a critical aspect of carotid stenosis management, and the clinician in 2004 must be aware of recent developments in the field. These developments include the advantage of newer antiplatelet agents compared to aspirin, the demonstrated value of statins, and the recognized benefits of lowering blood pressure. The application of these elements in a multimodality cocktail holds promise for reducing the vascular event rate in patients with carotid stenosis.

TODAY'S THERAPEUTIC OPTIONS

The multicenter carotid endarterectomy (CEA) trials of the last 2 decades were landmark studies. Studies such as the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and Asymptomatic Carotid Atherosclerosis Study (ACAS) clarified the risk/benefit ratio of CEA for medium-risk patients.[1,2] However, these trials were launched in the late 1980s, and medical progress marches forward—in the area of medical management of carotid atherosclerosis, several developments have occurred since the 1980s, and optimal medical therapy has changed.

ANTIPLATELET THERAPY

Antiplatelet therapy is recommended for secondary prevention in most patients after an ischemic stroke or TIA. There are three main options currently: aspirin, clopidogrel, and aspirin plus dipyridamole. These medications interfere with platelet aggregation, thus inhibiting the formation of thrombi and emboli that lead to vessel occlusion.

Aspirin

Aspirin remains the most widely used antiplatelet agent in the secondary prevention of ischemic stroke. It is the oldest, most studied, and most economical of these agents. Recently, the FDA made a recommendation of 50 mg/d to 325 mg/d after several trials had shown that low-dose aspirin is at least as effective as high-dose aspirin (Table 1). Currently, many physicians recommend a daily dose of 325 mg or less for prevention of stroke; aspirin has been associated with a 22% risk reduction for stroke.[3]

Clopidogrel

Clopidogrel is a thienopyridine derivative. The efficacy of clopidogrel was established in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study.[4] CAPRIE was a randomized, blinded, multicenter trial that included three groups of patients: those with recent ischemic stroke, recent MI, and symptomatic peripheral vascular disease. Patients were assigned to either clopidogrel (75 mg/d) or aspirin (325 mg/d). In 19,185 patients, it was found that there was an 8.7% relative risk reduction in favor of clopidogrel (95% CI, 0.3 to 16.5; P=.043), and an absolute risk reduction of 0.5%. An on-treatment analysis showed a relative risk reduction of 9.4%. The inclusion of major hemorrhages along with the primary endpoint led to a relative risk reduction with clopidogrel of 9.5% (95% CI, 1.2 to 18.5).

For patients undergoing carotid stenting, aspirin plus clopidogrel is frequently used as a standard antithrombotic regimen. Cases of fatal carotid stent thrombosis

COVER STORY

TABLE 1. MAJOR ANTITHROMBOTIC PREVENTION TRIALS FOR STROKE/TIA

Trials	Drugs	N	Dose (mg)	Enrollment Time After TIA or Stroke		Follow-Up Time (Months)	Primary Outcome	Results
SALT[15]	ASA vs placebo	1,360	75	1-4 months		32	Stroke, MI, or vascular death	18%; RR 0.82 95% CI 0.67-0.99
Dutch TIA[16] 1991	Aspirin	3,131	30 vs 283			30	Stroke, MI, or vascular death	Frequency of death 14.7% (30 mg) vs 15.2 (283 mg)
ESPS II 1996	Dipyridamole, ASA + dipyridamole placebo	6,602	ASA 50 vs dipyridamole 400	Within 3 months		24	Stroke or death together	Stroke risk: ASA, 18% (P=.013) Dipyridamole, 16% (P=.039) ASA+dipyridamole, 37% ($P \leq .001$)
ACE[17]	Aspirin	2,849	81, 325, 650, 1,300	Before surgery		3	Stroke, MI, or death	6.2% vs 8.4% (P=.03) in favor of low-dose group
TASS	ASA vs ticlopidine	3,069	Ticlopidine 500 vs ASA 1,300	Within 3 months		24 to 72	Death or stroke	Ticlopidine: 12% relative risk reduction (95% CI 2 to 26%). Event rate: ASA 19%, Ticl 17%
CATS[18]	Ticlopidine vs placebo	1,072	500	1 to 4 months		Up to 36	Stroke, MI, or vascular death	Ticlopidine: 30.2% relative risk reduction (95% CI 7.5 to 48.3%).
CAPRIE	Clopidogrel vs aspirin	19,185	Clopidogrel 75 vs ASA 325	Within 6 months		12 to 36	Stroke, MI, or vascular death	Clopidogrel 8.7% relative risk reduction (95% CI 0.3-16.5, P=.043)
WARRS	Warfarin vs aspirin	2,206	Warfarin (INR 1.4 to 2.8) vs ASA 325	Within 30 days		24	Stroke or death	Reached in 17.8% patients on warfarin and 16% on aspirin. Hazard ratio: warfarin to aspirin, 1.13 (95% CI 0.92-1.32)

have been reported in patients not treated with the aspirin plus clopidogrel combination.[5] In most patients, however, the addition of aspirin to clopidogrel has not been demonstrated to be of conclusive benefit. The recent Management of Atherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischemic stroke (MATCH) trial, in which high-risk patients with TIA or stroke were treated with either clopidogrel alone or aspirin plus clopidogrel found only a nonsignificant 6.4% relative risk reduction with the addition of aspirin. On the other hand, a recent study using transcranial Doppler in patients with symptomatic carotid stenosis found a reduced number of microemboli to the brain when clopidogrel was added to aspirin. The effectiveness of this combination needs to be studied further; it is possible that combination therapy will still prove to be of value for patients with symptomatic carotid stenosis.

Dipyridamole and Aspirin

The combination of aspirin, a cyclo-oxygenase inhibitor, and dipyridamole, a cyclic nucleotide phosphodiesterase inhibitor, theoretically offers a pharmacologic advantage over each of these agents alone. The European Stroke Prevention Study II (ESPS-II) study was a multicenter, randomized, blinded, placebo-controlled study in 6,602 patients with a preceding TIA or ischemic stroke.[6] Patients were allocated to the following treatments: aspirin, 25 mg bid; extended-release dipyridamole, 200 mg bid; aspirin, 25 mg, plus extended-release dipyridamole, 200 mg bid; and placebo. The primary endpoint was recurrent stroke (fatal and nonfatal). The results of the study were intriguing. Both aspirin and extended-release dipyridamole were independently effective at reducing stroke risk (18% and 16% reductions, respectively). The combined agent had a 23% risk reduction over aspirin alone. This was the first demonstration in a primary stroke population that two antiplatelet agents with differing mechanisms of action were more effective than one medication alone.

The most common side effects of extended-release dipyridamole-containing preparations were headache and gastrointestinal disturbance. The aspirin group had an increase in bleeding, although the addition of dipyridamole did not lead to an inordinate increase in the bleeding events (ESPS-II bleeding: 135 bleeding events with aspirin, 144 bleeding events with aspirin plus dipyridamole; P=NS).

Because there are now agents that have been proven to be more effective than aspirin, the question arises as to when the newer agents should be used as first-line therapy. In my opinion, some of the patient types described in Table 2 would benefit from the newer medications and/or combination antiplatelet treatment. There are no rigorous data to support these recommendations as of yet, but the basic concept is that high-risk patients deserve maximal antiplatelet treatment. The most recent American College of Chest Physicians statement also commented that clopidogrel and aspirin/extended release dipyridamole, in addition to aspirin, were reasonable first-line therapy choices.[7]

ORAL ANTICOAGULANTS

Secondary Prevention of Cardioembolic Stroke

Anticoagulants, such as heparin and warfarin, have a narrow therapeutic window and a highly variable dose-response, cause serious bleeding, and need close laboratory monitoring for their anticoagulant effects. The erratic anticoagulant effect of warfarins is not fully understood, but the likely explanations include variability in the affinity of warfarin for its hepatic receptor, changes in vitamin K content of the diet, fluctuations in bioavailability, concomitant use of interacting drugs, inappropriate dosage adjustment, and poor compliance.

For patients who do not have atrial fibrillation or high-risk sources of cardioembolism, warfarin is not recommended for long-term stroke prevention. The Warfarin Aspirin Recurrent Stroke Study (WARSS) was a large, multicenter trial, which compared aspirin 325 mg/d with warfarin (INR 1.4-2.8) in patients with noncardioembolic stroke and no planned carotid endarterectomy.[8] This trial did not show any difference between aspirin and warfarin in the prevention of stroke or death (there was a 11% trend in favor of aspirin) or in the rate of major hemorrhage. The rates of major hemorrhage were low (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the aspirin group). In view of these data, anticoagulation is difficult to justify in patients with noncardioembolic stroke and with the stroke subtypes seen in the WARSS trial.

Another recent trial in patients with atherosclerotic cerebrovascular disease, the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial, failed to show an advantage for warfarin compared to aspirin. This further reinforced the concept that antiplatelet therapy is preferred for patients with carotid stenosis.

STATINS

In the last decade, there has been increased enthusiasm regarding the potential role of lipid-lowering treatment for stroke prevention. In randomized trials of patients with coronary artery disease, HMG CoA reductase inhibitors (or statins) have been shown to reduce the incidence of stroke. These agents reduce total cholesterol and low-density lipoprotein and slightly increase high-density lipoprotein levels. Other mechanisms of action include their effects on endothelial cells, macrophages, platelets, smooth muscle cells, and endothelial nitric oxide synthesis.

Based on observations from studies involving patients with coronary heart disease, the FDA has approved the use of pravastatin and simvastatin for stroke prevention in patients with CHD. In a study that evaluated patients with heart disease and total cholesterol levels of 155 to 271 mg/dL, pravastatin treatment was associated with a 19% risk reduction in nonhemorrhagic stroke.[9]

There are ongoing trials evaluating the role of statins in patients with a TIA or minor stroke. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial is studying the efficacy of atorvastatin 80 mg per day in patients with previous stroke or transient ischemic attack (TIA) in the reduction of the primary endpoint of fatal or nonfatal stroke. This study is evaluating only patients with no known history of coronary artery disease. The results of this study will add important information on the use of statins in recurrent stroke prevention.

In people who do not have established CHD, it would be reasonable to follow the guidelines of the Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). The guidelines include a target LDL goal of <100 mg/dL in persons with CHD and CHD risk equivalents.[10] The CHD risk equivalents are diseases that have a 10-year risk for CHD >20%, such as symptomatic carotid artery disease, diabetes mellitus, and multiple risk factors. In my opinion, these guidelines are too narrowly focused, and it would be prudent to vigorously treat hyperlipidemia in other populations at risk for stroke, including those with asymptomatic carotid stenosis and those patients with symptomatic intracranial disease (eg, basilar artery narrowing). It remains to be seen whether patients with stroke or TIA due to other mechanisms, such as small vessel disease, will benefit from statin treatment.

The recent demonstration that high-dose treatment with atorvastatin arrested coronary plaque progression has significant implications for carotid stenosis as well.[11] This finding suggests that we may be undertreating patients with carotid stenosis and perhaps more aggressive LDL reduction (such as <70 mg/dL) will be recommended in the future.

Finally, it is important to remember that the majority of patients in previous CEA trials such as NASCET were not aggressively treated for hyperlipidemia. In NASCET, only approximately 15% of patients were on lipid-lowering agents.[2] Currently, one could argue that all patients with symptomatic or asymptomatic carotid stenosis (and without overt contraindications) should be on a statin. Increased use of statins could narrow the modest benefit seen for CEA in symptomatic patients with 50% to 69% stenosis and asymptomatic patients with 60% to 99% stenosis.

ANGIOTENSIN-CONVERTING ENZYME (ACE)-INHIBITORS/BLOOD PRESSURE LOWERING

Two recent clinical trials have led to increased interest in the use of ACE-Inhibitors (ACE-Is) for stroke prevention. The Heart Outcomes and Prevention Evaluation (HOPE) Study, was a double-blind, randomized trial that compared ramipril (10 mg/d) and vitamin E in 9,297 high-risk vascular disease patients.[12] It included patients with established vascular disease or diabetes mellitus and an additional risk factor. Eleven percent of the enrolled patients had a history of stroke or TIA. There were reductions of 32% for all types of stroke and 61% for fatal stroke. Blood pressure lowering was reported as only 3/2 mm Hg over the course of the study. This strongly suggested that the benefit was not due to reduction of blood pressure alone, and that ramipril had an intrinsic vasculoprotective effect. The FDA subsequently approved the use of ramipril for the prevention of vascular events in patients with established vascular disease, including stroke.

TABLE 2. POTENTIAL CANDIDATES FOR NEWER ANTIPLATELET AGENTS

- Moderate/severe intracranial/extracranial stenosis
- Minor cardioembolic sources
- Atrial fibrillation but not a good warfarin candidate
- Extensive microvascular ischemic change
- Recurrent symptoms on aspirin

Another study that highlighted the tangible benefits of blood pressure lowering was the Perindopril Protection Against Recurrent Stroke Study (PROGRESS).[13] This was a double-blind, placebo-controlled, randomized trial of treatment with the ACE-I perindopril and the diuretic indapamide. Perindopril-based therapy was well tolerated for the primary endpoint of total recurrent stroke, with a 28% risk reduction for all patients (P<.0001) and a 43% risk reduction for those on combination therapy. In patients treated with perindopril alone, there was a nonsignificant 5% reduction in stroke, leaving the possibility that most of the benefit occurred due to the diuretic. Other endpoints that included major vascular events (26%; P<.001), nonfatal myocardial infarction, dementia, and cognitive decline were also lowered with the perindopril-based regimen. Both the HOPE and PROGRESS studies found that nonhypertensive patients had benefit, suggesting that ACE-Is may be useful in these patients. Therefore, blood pressure lowering should be an important component of the treatment regimen for patients with carotid stenosis.

EVOLVING TRENDS

On the basis of the material discussed previously, an evolving approach is to use multimodality treatment in attempts at stroke prevention. As has been outlined, the

use of newer antiplatelet agents, increased use of statins, and ACE-I treatment will likely lower the rate of stroke in patients with carotid stenosis.

For patients with carotid stenosis, there are several issues that will need clarification in the coming years. These issues include defining the optimal LDL target and the optimal blood pressure target. Whether combination antiplatelet therapy should be used routinely in carotid stenosis patients is also uncertain. Finally, studies comparing "intensive medical therapy" versus CEA or carotid stenting would be of great interest.[14] ■

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