Antithrombotic Therapy in Stroke Prevention and Treatment: A Review

Marilyn M. Rymer
Saint Luke's Hospital Stroke Center, Kansas City, Missouri

Abstract. Current knowledge of antithrombotic therapy based on controlled clinical trials has revolutionized the way clinicians approach stroke prevention and treatment. This review article addresses the pathogenesis of stroke and summarizes information from clinical trials regarding the use of antiplatelet agents, heparin, warfarin (particularly in nonvalvular atrial fibrillation), and thrombolytics in stroke prevention and treatment.

Key Words. anticoagulant, stroke, tPA, atrial fibrillation

Stroke is now the most preventable of all catastrophic conditions. After decades of relatively slow progress in the prevention and treatment of stroke, significantly improved approaches to prevention and treatment have been developed and are being studied. This review summarizes the opportunities for improved outcome in patients at risk for cerebrovascular disease.

Stroke is the third leading cause of death in the United States, accounting for 150,000 deaths per year. More than half a million new strokes occur each year, leading to a prevalence of greater than 2,000,000 stroke survivors. Stroke is the leading cause of adult disability, often more feared than death by elderly adults [1]. The most common diagnosis of patients discharged from hospitals to nursing homes is stroke. In addition to the human toll, strokes in the United States cost an estimated $30 billion in 1993, $17 billion in direct costs and $13 billion in indirect costs. Prevention or reversal of stroke could save an estimated $60,000 per episode in health care costs and lost productivity.

Stroke Pathogenesis

The majority of strokes are ischemic. (This review will not deal with hemorrhagic stroke, which accounts for 17% of all strokes.) About 30% of all ischemic strokes result from atherothrombosis in extracranial and larger intracranial vessels, another 20%–25% are cardioembolic, usually secondary to atrial fibrillation or myocardial infarction. The remaining approximately 50% are lacunar strokes, due to small-vessel disease, often associated with long-standing hypertension, diabetes, and/or smoking. The portion of brain tissue that is solely dependent on the blocked artery for oxygen and glucose is referred to as the core of the stroke. The area around the core, the penumbra, contains cells that are injured as a result of the ischemia but may receive some blood supply from collateral vessels. Many neuroprotective agents are being tested to improve the outcome of cell viability in the penumbra.

Antiplatelet Therapy

Antiplatelet drugs discourage the buildup of thrombus on surfaces or in spaces where platelet aggregation is likely, such as the surface of an atherosclerotic plaque or artificial valve or in the left heart of a patient with atrial fibrillation. Three antiplatelet drugs are currently available for prescription or over-the-counter use: aspirin, dipyrimadol, and ticlopidine. [2] Some trials with clopidogrel have been completed and shown some efficacy, but it has not been approved for prescription use.

Numerous trials have looked at the role of aspirin in stroke and transient ischemic attack (TIA) prevention. [3] In 1994, the Antiplatelet Trialists Collaborative Group demonstrated that aspirin can reduce the risk of nonfatal stroke by about 25%, based on 145 randomized trials and 100,000 patients (three fourths of them high-risk patients). It is equally effective in men and women. Doses varying from 75 to 1300 mg have been studied. At present there is no compelling evidence allowing a decision about whether a high or low dose is more efficacious. In view of the slightly lower incidence of side effects with lower doses and the possibility of increased patient compliance, many authors recommend 325 mg as an initial dose. Efficacy in some of the etiologic subgroups of stroke, such as intrinsic atherosclerosis and lacunar infarction, is uncertain [4].

Aspirin is being studied in the two largest stroke trials ever initiated. The International Stroke Trial (IST) is looking at the benefit of starting heparin or aspirin as soon as a stroke has occurred. There appears to be (final data are pending) an advantage to starting aspirin as soon as a stroke has occurred to prevent secondary events. The Chinese Acute Stroke Trial (CAST), which also involves a large patient population,
concluded that starting aspirin immediately after stroke versus waiting up to 48 hours after stroke avoids, in the first month, about 10 deaths or nonfatal strokes per 1000 patients who have already had a stroke. In other words, this regimen would prevent about 10,000 stroke events for every million patients treated.

Dipyridamole, another antiplatelet agent, may provide additional protection from stroke when combined with aspirin. The European Stroke Prevention Study 2 (ESPSP2) demonstrated, in its report published in 1996, that in patients treated with dipyridamole plus aspirin there was a 38.1% reduction in all strokes compared with placebo. Thus, combination therapy confers a significant additional benefit over aspirin alone. Previous studies of dipyridamole had not demonstrated a beneficial effect, but the number of nonfatal strokes in those studies was quite small. Practitioners will have to weigh the potential benefit of adding dipyridamole to aspirin against the increased cost and complexity of therapy.

Two multicenter controlled clinical trials examined the role of ticlopidine in stroke prevention [3,6]. The CATS trial compared ticlopidine with placebo in 1053 patients who had a recent stroke. The patients were followed for 3 years. There was a 30% reduction in nonfatal stroke, nonfatal MI, and vascular deaths from any cause in the group treated with ticlopidine. The TASS trial studied 3069 patients who had had TIA or stroke and compared 1300 mg of aspirin with 500 mg of ticlopidine. The follow-up ranged from 2 to 6 years. There was a 12% reduction in the occurrence of nonfatal stroke or death in the ticlopidine group and a 21% reduction in fatal and nonfatal strokes in the aspirin group. The benefit of ticlopidine over aspirin has to be weighed against other considerations. If 100 patients with TIA or small stroke were treated with ticlopidine for 2 years, there would be three fewer strokes and two fewer severe gastrointestinal complications. However, 10 patients would have significant diarrhea, 5 would develop rash, and 1 would develop neutropenia.

The bid dosing and need for WBC monitoring, as well as the expense of ticlopidine, all have to be considered in choosing the regimen for secondary prevention. The American Heart Association made the following recommendation: “Considering the slight benefit of ticlopidine compared to its increased cost, the incidence of side effects, and the need for hematologic monitoring, the committee of the AHA considered aspirin appropriate initial antiplatelet therapy in most cases. Ticlopidine is a useful alternative, particularly in patients who cannot take aspirin or who have continued symptoms despite aspirin therapy.” In view of the recent ESPSP2 report, dipyridamole may be a competitor for ticlopidine.

Clopidogrel, a novel antiplatelet agent related chemically to ticlopidine, is being studied in a multicenter trial called the CAPRIE study. Some portions of the study are still in progress. The study compares the efficacy and safety of 75 mg of clopidogrel with 325 mg of aspirin. All vascular events, including MI, stroke, and death, are endpoints. Preliminary data indicate an advantage of clopidogrel over ASA of a 10% risk reduction, similar to ticlopidine. A study of clopidogrel plus ASA versus clopidogrel alone has not yet been done.

Most of the data on antiplatelet therapy addresses the issue of secondary prevention in a documented at-risk population. Some of the aspirin trials, however, clearly demonstrate effective primary prevention of stroke and MI. If there are no contraindications, recommending patients over the age of 50 to use one 325 mg aspirin per day seems quite reasonable. There is a growing list of options for secondary prevention, which allows for individual recommendations, depending on the patients particular circumstances.

**Anticoagulant Therapy**

**Heparin**

Heparin is widely prescribed without the benefit of good data to indicate its usefulness. We now have very good controlled clinical trial results with regard to the use of warfarin in certain conditions. Low-molecular-weight heparin may be a new star on the horizon for cerebrovascular disease.

Heparin is widely prescribed for secondary stroke prevention or in the setting of stroke-in-evolution. It is likely considered the standard of treatment for such conditions, but without the benefit of evidence to support its use. What practitioner would hesitate to order heparin in a patient with new onset of atrial fibrillation and transient ischemic attack (TIA)? It is thought to prevent clot propagation and recurrent embolization. Although this widespread practice is based on clinical experience, the lack of data leads to a variation in the use of IV heparin. There is debate over the use of a bolus dose, the route of administration, and whether the weight-based nomogram is safe in all patients.

Heparin alone or in combination with aspirin is being tested in the International Stroke Trial (IST). A preliminary report summarized experience with 20,000 patients enrolled within 24 hours of a stroke. Patients were randomized to 325 mg of aspirin or to subcutaneous heparin at 25,000 or 10,000 units daily. Endpoints were death at 14 days or neurological function at 6 months. There was no difference in the death rate at 14 days in any of the groups. Recurrent ischemic events decreased in both heparin groups as compared with aspirin, but the benefit was offset by the incidence of symptomatic significant cerebral hemorrhage. There was no net benefit in the heparin groups. No advantage was associated with the higher dose heparin compared with the lower dose, and the higher dose carried with it increased morbidity from hemorrhage.

The American Heart Association has evaluated the data on heparin and concluded that “the data about safety and efficacy are insufficient and conflicting.