Update on Antiplatelet Therapy for Stroke Prevention

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The high rates of mortality and long-term disability associated with ischemic stroke, coupled with its prevalence, necessitate good, long-term preventive strategies. Risk-factor management is effective for individuals with preclinical and clinical cerebrovascular disease. Patients suffering from a transient ischemic attack or stroke are particularly vulnerable to subsequent stroke. Most of these individuals are candidates for antiplatelet treatment to prevent a recurrence. Available antiplatelet therapies include aspirin, ticlopidine, and clopidogrel. The combination of low-dose aspirin plus extended-release dipyridamole has been shown to offer safe, effective antiplatelet therapy for appropriate patients. In the second European Stroke Prevention Study, the combination was found to be significantly more effective than either drug alone, at the cost of relatively few treatment-related adverse effects. This combination is currently recommended as one of the first-line treatments for stroke prevention after first transient ischemic attack or stroke.

Stroke has a tremendous impact on public health. It is the third leading cause of death and the leading cause of substantial disability in the United States. Recent epidemiologic studies estimate that more than 700,000 strokes occur each year. Despite recent advances in immediate stroke treatment, prevention is still by far the best method for reducing stroke morbidity. Many risk factors for stroke have been identified, and many of these can be modified to reduce risk. Even individuals who have experienced a transient ischemic attack (TIA) or ischemic stroke, and are thus at high risk of subsequent stroke, may reduce their risk with appropriate management.

Antiplatelet agents, which interfere with thrombus formation by platelets in diseased or damaged blood vessels, are indicated for most patients after a first TIA or stroke to reduce the risk of subsequent stroke. Aspirin, ticlopidine, clopidogrel, and dipyridamole are antiplatelet therapies that are effective after TIA or stroke. Until recently, the appropriate dose of aspirin and the value of added dipyridamole were controversial. Based on recent evidence, the Food and Drug Administration and the American College of Chest Physicians (ACCP) now support the use of low-dose aspirin (50 to 325 mg daily) alone and in combination with extended-release dipyridamole for secondary stroke prevention. The clinical evidence behind these guidelines is reviewed.

Risk of Stroke After a First TIA or Stroke

Stroke risk is low among healthy persons but increases as an individual ages and/or develops risk factors for stroke. After a TIA or stroke, the risk of stroke is high, particularly within the first 30 days, and remains elevated over time. Estimates indicate that as many as 40% of those who survive a first TIA or stroke will have a subsequent stroke within 5 years.

Risk-factor modification is an effective way to reduce stroke risk, regardless of the stage of cerebrovascular disease. Numerous risk factors for first stroke have been identified, and all but a few are modi-
fiable (Table 1). Among the modifiable risk factors, hypertension is probably the most important. Nearly 60% of the US population has hypertension, and estimates suggest that almost half of all strokes could be prevented with adequate blood pressure control. Reduction in blood cholesterol levels and control of blood glucose may also reduce the risk of first stroke. Atrial fibrillation greatly increases stroke risk; this condition is relatively rare among young persons but becomes increasingly prevalent with age. Anticoagulant treatment with warfarin ("statin" drugs), and antihypertensive agents (diuretics, angiotensin-converting enzyme inhibitors, β-blockers, calcium channel blockers, and α-blockers). The surgical treatment is carotid endarterectomy; and lifestyle changes include smoking cessation, moderation in alcohol consumption, appropriate physical activity, and weight reduction. This list is continually expanding as our understanding of the underlying causes of stroke increases.

**EFFICACY OF ANTIPLATELET AGENTS IN CLINICAL TRIALS**

Numerous trials have examined the efficacy of antiplatelet treatment, primarily with aspirin, for prevention of vascular events. Many of these trials were small and inconclusive on their own. However, the Antiplatelet Trialists’ Collaboration (APTC) involved a meta-analysis to determine the effect of antiplatelet therapy (with any agent) in various populations at risk for vascular events. Based on 17 trials, the findings of the APTC were that antiplatelet treatment reduced the odds of nonfatal stroke, nonfatal MI, or vascular death by 22% in persons with a history of TIA or stroke. Overall, the benefits of antiplatelet therapy were evident in both men and women, young and old, those with hypertension and those without, and those with diabetes and those without.

Another meta-analysis by Algra and van Gijn, which was restricted to aspirin therapy in patients with cerebrovascular disease, found that aspirin reduced the odds of stroke, MI, or vascular death by 16%. A similar 15% overall relative risk reduction for stroke was found by Johnson et al in an additional meta-analysis of aspirin trials in patients with cerebrovascular disease. In the absence of a definitive single trial establishing the optimal aspirin dose for preventing stroke and other vascular events among persons with prior TIA or stroke, each of these 2 meta-analyses also evaluated the benefits of different aspirin doses. Algra and van Gijn concluded that aspirin reduces the risk of stroke, MI, or vascular death by about 13% at any dose between 50 and 1300 mg daily. Johnson et al also found no dose relationship for the effects of aspirin within this dose range. Two trials that directly compared high and low doses found no significant difference in efficacy; however, gastrointestinal adverse effects were less prevalent with low-dose aspirin. Most recently, the ASA (acetylsalicylic acid) and Carotid Endarterectomy (ACE) trial in North America directly compared low (81 or 325 mg daily) and high (650 or 1300 mg daily) aspirin doses in 2804 patients who underwent carotid endarterectomy because of symptomatic or asymptomatic carotid stenosis. During the study, patients who received low-dose aspirin experienced fewer vascular events than those who received high-dose aspirin; these differences were statistically significant for stroke, MI, or death at 3 months after carotid endarterectomy. The ACE study results support the idea that low-dose aspirin may be preferable to high doses.

Ticlopidine is another antiplatelet agent that has been evaluated in 2 large, randomized, controlled trials involving patients with cerebrovascular disease. Compared with placebo, ticlopidine (500 mg daily) significantly reduced the risk of stroke, MI, or vascular death.
by 23% (P=.02) after 2 years (N=1072).\textsuperscript{20} Compared with aspirin (1300 mg daily), ticlopidine provided a 12% reduction (P=.05) in the risk of stroke or death, and a 21% reduction (P=.02) in the risk of fatal or nonfatal stroke at 3 years among 3069 patients with TIA or minor stroke.\textsuperscript{21} The frequency of adverse effects (primarily diarrhea and rash) and the risk of neutropenia, thrombocytopenia, and thrombocytopenic thrombotic purpura have limited the use of this drug.\textsuperscript{21,22}

Clopidogrel, a relative of ticlopidine, was compared with aspirin (75 mg daily and 325 mg daily) in a single trial, which enrolled 19185 patients with atherosclerotic vascular disease manifested in 1 of 3 ways: prior MI, prior stroke, or peripheral vascular disease.\textsuperscript{23} After an average of 1.91 years of follow-up, the annual incidence of stroke, MI, or vascular death was 5.83% in the aspirin group and 5.32% in the clopidogrel group, providing a statistically significant 8.7% (P=.05) relative risk reduction with clopidogrel. Among patients with prior stroke, there was a nonsignificant reduction in the incidence of these vascular outcomes from 7.71% with aspirin to 7.15% with clopidogrel. Clopidogrel demonstrated a safety profile comparable with that of aspirin.

The combination of aspirin plus dipyridamole has been compared with aspirin alone for stroke prevention in patients with cerebrovascular disease in several clinical trials.\textsuperscript{1,24-26} Nonetheless, the second European Stroke Prevention Study (ESPS-2) can be considered as distinct from the earlier trials for 2 reasons. First, studies comparing the aspirin/dipyridamole combination with aspirin alone before ESPS-2 were small (the largest included 890 patients divided into 3 groups), limiting the statistical power of those studies to detect treatment differences. An additional larger trial, the European Stroke Prevention Study (ESPS-1; N=2500 divided into 2 groups), lacked an aspirin-only treatment arm, preventing any determination of the contributions of each drug to the observed benefit.\textsuperscript{27}

The second factor distinguishing ESPS-2 from early trials is drug dose. Prior studies using high-dose aspirin found no additional benefit of the combination over aspirin alone. However, evidence from preclinical studies suggests that high doses of aspirin may actually interfere with the action of dipyridamole. Results of experiments using a hamster model of thrombosis show that dipyridamole combined with aspirin in ratios of about 10:1 or higher effectively inhibit thrombus formation, whereas a ratio of 1:1 has little effect.\textsuperscript{28-29} In contrast to earlier studies, ESPS-2 evaluated a relatively high dose of extended-release dipyridamole combined with low-dose aspirin in a final dose ratio of 8:1. This specific dose combination produced an additive inhibitory effect on platelet aggregation compared with placebo and either drug alone in a randomized, double-blind human ex vivo study involving 4 groups of 24 healthy volunteers.\textsuperscript{30} The study evaluated inhibition of platelet aggregation in whole blood under flow conditions on a cultured subendothelial matrix after 4 days of treatment, compared with baseline values. The platelet inhibitory effects of the aspirin/extended-release dipyridamole combination were significantly greater than those of aspirin alone, both for total aggregation and for the formation of large aggregates in particular.\textsuperscript{30}

**EVIDENCE FOR EFFICACY OF LOW-DOSE ASPIRIN AND EXTENDED-RELEASE DIPYRIDAMOLE: THE ESPS-2 TRIAL**

The ESPS-2 trial is the largest to evaluate antiplatelet agents for stroke prevention in patients with prior TIA or stroke.\textsuperscript{1} The study randomized 6602 patients into 1 of 4 treatment groups: low-dose aspirin (25 mg twice daily) alone, extended-release dipyridamole (200 mg twice daily) alone, aspirin and extended-release dipyridamole combined (same doses), or placebo. Patients were observed for 2 years to determine the effects of these drugs on the incidence of stroke and death from any cause.

At the end of the study, each of the active treatments significantly reduced the risk of stroke (Table 2).\textsuperscript{1} The 18% risk reduction observed with low-dose aspirin alone was comparable with the benefit observed in earlier studies of low-dose aspirin in stroke patients.\textsuperscript{31} However, ESPS-2 was the first study to show an independent statistically significant reduction in stroke risk with extended-release dipyridamole alone, which is an important finding for patients who are intolerant of low-dose aspirin. The combination of aspirin and extended-release dipyridamole was twice as effective for stroke prevention as either drug alone, indicating an additive benefit. Because of its size and factorial design, this study was able to show a statistically significant benefit of this particular combination of low-dose aspirin and extended-release dipyridamole over aspirin alone.

A good safety assessment is essential with medications for stroke prevention, as they must be administered for extended periods—potentially many years. Low-dose aspirin and extended-release dipyridamole were each well tolerated in ESPS-2. Long clinical experience with both aspirin and dipyridamole had already revealed certain adverse effects to be expected with these drugs (Table 3); the ESPS-2...
investigators monitored extensively for these and for any additional events. The quality of the safety assessment was evident from the overall incidence of adverse effects among patients treated with placebo, which was comparable with that among patients in the other treatment groups (Table 3). As expected, aspirin was associated with an increased risk of bleeding events and dipyridamole with a higher incidence of headaches and gastrointestinal events (primarily diarrhea). Most of these were mild.

NEW PRESCRIBING HABITS ARE RECOMMENDED

In response to the preponderance of evidence favoring low-dose aspirin for stroke prevention, the Food and Drug Administration has issued new professional labeling for aspirin indicating that the appropriate dose for stroke prevention after TIA or stroke is 30 to 325 mg daily. Similarly, the ACCP has issued new guidelines recommending low-dose aspirin (50 to 325 mg daily) as a first-line preventive treatment after noncardioembolic TIA or stroke. Aspirin has been the mainstay of antiplatelet therapy, but recent years have seen an increase in the number of available options. The growing armamentarium includes aspirin, ticlopidine, clopidogrel, and dipyridamole. The ACCP evaluated the other antiplatelet agents and, based on the results of the ESPS-2 trial, also recommends the combination of dipyridamole and aspirin bid may be more effective than clopidogrel and has a similarly favorable adverse effect profile.*

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Table 3. Percentage of Patients Reporting at Least 1 Adverse Effect in ESPS-2*