New Developments in Secondary Stroke Prevention: Impact of the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) on Clinical Management

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Secondary stroke prevention is an important goal of poststroke patient treatment. Various pharmacologic approaches have been advocated, but the relative efficacy and safety of these regimens has remained the subject of much debate. Recently released data from the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) indicated that combination therapy with aspirin and extended-release dipyridamole was more effective than aspirin monotherapy, and probably more effective than anticoagulants, for the prevention of cerebrovascular events after a stroke or transient ischemic attack. When viewed in light of results of earlier trials, these findings confirmed that combination aspirin plus extended-release dipyridamole therapy improved outcomes in these patients and is a recommended option for poststroke patient treatment. **Key Words:** Antiplatelets—aspirin—stroke—dipyridamole—secondary stroke prevention.

Individuals who have had a stroke are at increased risk for a number of adverse vascular outcomes, the most common of which is recurrent stroke.[1-4] It has been estimated that more than three fourths of all secondary vascular events among survivors of stroke are recurrent strokes.[3] The risk for recurrent stroke is greatest within the first several months after an initial event[5] but persists in the long term.[1,4,5] Five-year cumulative stroke recurrence rates (after atherothrombotic brain infarction) in the 26-year Framingham Heart Disease Epidemiology Study (N = 5209) were 24% in women and 42% in men.[1] In the 10-year Perth Community Stroke Study,[5] 9% of patients who had a first acute stroke experienced a recurrent stroke within the first 6 months of the initial event. For years 1 through 10 poststroke, the recurrent stroke rate approximated 4% annually.

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The American Heart Association/American Stroke Association Council on Stroke, the American College of Chest Physicians, and the National Stroke Association recommend that antiplatelet agents be used first line to prevent secondary stroke in patients who have experienced noncardioembolic stroke or transient ischemic attack (TIA).[6-8] Although all 3 groups recommend aspirin (50–325 mg/d), combination aspirin plus extended-release dipyridamole (ER-DP), or clopidogrel for stroke prevention, the most recent of these guidelines recommend the use of combination aspirin plus ER-DP as the first-choice option.[6,8] Clopidogrel provides a useful alternative in patients that have an aspirin allergy or intolerance to the other antiplatelet agents; it may be used as an alternative first-line stroke prevention therapy.[6–8] As a group, the antiplatelet agents are associated with a 28% reduction in the risk for nonfatal strokes and a 16% reduction in fatal strokes among patients with diseases or conditions that place them at high risk for vascular events.[9] More specifically, in the subgroup of patients with a history of stroke or TIA, they significantly ($P < .05$) reduce the risk for nonfatal stroke (25 fewer per 1000 patients), nonfatal myocardial infarction (MI) (6 fewer per 1000 patients), vascular death (7 fewer per 1000 patients), and all-cause mortality (15 fewer per 1000 patients).[9]

Aspirin is perhaps the most widely studied of the antiplatelet agents; however, its clinical role in the pre-

vention of secondary stroke remains incompletely understood. Results of the Antithrombotic Trialists' Collaboration meta-analysis demonstrated that, in patients considered at risk for vascular outcomes, aspirin (<75–1500 mg/d) reduced the risk of secondary vascular events (combined end point of stroke, MI, or vascular death) approximately 23% relative to placebo.[9] However, results of a separate analysis in which just those patients who entered the studies as a result of stroke or TIA were included demonstrated less benefit (risk reduction for secondary vascular events, 13% relative to placebo).[10] Whereas the studies included in these analyses used a wide range of doses, specific dose comparisons performed in the minor stroke/TIA population (300 *v* 1200 mg/d and 30 *v* 283 mg/d) have demonstrated that low doses are as effective as high doses in preventing secondary vascular events.[11,12] For the specific end point of stroke in patients with TIA/stroke, aspirin (25 mg twice daily) reduced the risk 18% relative to placebo ($P = .013$) in the second European Stroke Prevention Study (ESPS-2).[13] Based on these data and the desire to avoid any dose-related increase in gastrointestinal toxicity, the use of lower aspirin doses (50–325 mg/d) is currently advocated.[7]

The addition of ER-DP to daily aspirin therapy was shown in ESPS-2 to provide patients who experienced stroke with greater protection against recurrent stroke than aspirin alone.[13] Patients with a recent (within 3 months) history of stroke or TIA (N = 6602) were randomized to receive aspirin (25 mg twice daily), ER-DP (200 mg twice daily), the combination of both agents, or placebo, and were followed up for 2 years. Fewer recurrent strokes occurred in the combination group (2-year rate, 9.9%) than in the aspirin monotherapy group (12.9%), the ER-DP monotherapy group (13.2%), or the placebo group (15.8%). All active treatments were associated with significant reduction in stroke risk relative to placebo (relative risk reduction [RRR], 37.0%, 18.1%, and 16.3%, respectively; $P < .05$ for all comparisons *v* placebo), and combination therapy was significantly more effective than monotherapy with either agent (RRR 23.1% *v* aspirin monotherapy [$P = .006$] and RRR 24.7% *v* ER-DP monotherapy [$P = .002$]). When all outcome events were considered (e.g., stroke, death, TIA, MI, ischemic events, and other vascular events), combination aspirin plus ER-DP therapy was nearly two times more effective than aspirin or ER-DP alone.[13] The relative benefits of combination therapy versus aspirin monotherapy on secondary stroke were greatest for the subgroup of patients with a stroke or TIA before the qualifying event (RRR 44.6%).[14]

The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT)

Results of the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) confirm that the combination of aspirin plus ER-DP is more effective than aspirin alone in the prevention of recurrent vascular events after a stroke or TIA and is probably more efficacious than anticoagulants. ESPRIT was an independent (academic-supported), 8-year, international, multicenter, randomized, open-label trial designed to compare the efficacy and safety of antithrombotic therapies for the secondary prevention of serious vascular complications in patients after nondisabling cerebral ischemia of presumed arterial origin.[15] To be eligible for participation, patients must have experienced a TIA or minor ischemic stroke (≤grade 3 on the modified Rankin scale) within the previous 6 months. The primary analysis was based on the intent-to-treat population; outcome events were also presented for the on-treatment analysis.

Patients were randomized to receive aspirin alone (30–325 mg/d), combination aspirin (30–325 mg/d) plus dipyridamole (400 mg/d) therapy, or oral anticoagulation (international normalized ratio [INR] 2.0–3.0) as part of one of 3 schemes and followed up for at least 1 year.[15-17] The primary outcome event evaluated was the combined risk of death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complication, whichever happened first. Rates of individual events (including death from all causes, death from all vascular causes, first ischemic stroke, first cardiac event, and major bleeding complications) and other event combinations were also analyzed secondarily. Whereas treatment was open-label, the auditing of outcome events was blinded.[15,16]

A total of 2739 patients were enrolled in the aspirin-alone (n = 1376) and combination aspirin plus dipyridamole (n = 1363) arms between July 1997 and December 2005.[15] The mean (± SD) duration of follow-up was 3.5 ± 2 years. The median dose of aspirin in both groups was 75 mg (range: 30–325 mg). The majority (83%) of the patients in the combination group used ER-DP. In the intent to treat analysis, patients in the combination aspirin plus dipyridamole group experienced fewer primary outcome events (13% *v* 16%) compared with those taking aspirin. The absolute risk reduction associated with combination therapy was 1% per year, and the hazard ratio (HR) for the primary outcome event was 0.80 (95% confidence interval [CI], 0.66–0.98).[15] In the on-treatment analysis, the HR for the primary outcome event was 0.82 (95% CI, 0.66-1.02). Analysis of individual outcomes demonstrated that combination therapy had no adverse effect on coronary heart disease; first cardiac events occurred in 43 of 1363 patients in the combination therapy group and 60 of 1376 patients in the aspirin monotherapy group (HR 0.87; 95% CI, 0.56–1.37).[15] Major bleeding complications were uncommon, occurring in 35 of 1363 patients in the combination therapy group and 53 of 1376 patients in the aspirin monotherapy group (HR 0.58; 95% CI, 0.35–0.97).

As anticipated, dipyridamole therapy was associated with headaches in some patients; of the 470 patients (34%) who discontinued combination therapy, 123 (26%)