Stroke Council, American Heart Association. Circulation 1998; 97:501-9.
4. Findlay JM, Tucker WS, Ferguson GG, Holness RO, Wallace MC, Wong JH. Guidelines for the use of carotid endarterectomy: current recommendations from the Canadian Neurosurgical Society. Can Med Assoc J 1997; 157:653-9.

## Aspirin and Dipyridamole for the Secondary Prevention of Stroke

Wahlgren NG. Critical analysis of the combination of dipyridamole plus acetylsalicylic acid versus acetylsalicylic acid alone in the secondary prevention of stroke. Int J Clin Pract 1998; 97(suppl):3-6.

***Clinical question*** **Are low-dose acetylsalicylic acid (ASA) or modified-release dipyridamole efficacious in secondary prevention of ischemic stroke?**

***Background*** Persons with a history of ischemic stroke are at increased risk for recurrence, making secondary prevention desirable. Previous studies, summarized by the 1994 Antiplatelet Trialist's Collaboration meta-analysis, found no difference in the rates of ischemic stroke in patients treated with a combination of ASA and dipyridamole combined with those treated with ASA alone (relative risk [RR] = 0.95; 95% confidence interval [CI], .75 - 1.19).[1] The Second European Stroke Prevention Study (ESPS-2) was a randomized double-blind clinical trial of low-dose ASA versus modified-release dipyridamole versus combination of the 2 versus placebo, in the secondary prevention of ischemic stroke.[2] The article under review is a critical reappraisal of the meta-analysis noted above in light of the results from the ESPS-2.

***Population studied*** The ESPS-2 studied 6602 patients with previous transient ischemic attack (23.7%) or ischemic stroke (76.3%) recruited from 59 centers in 13 European countries. The Antiplatelet Trialists' meta-analysis included a total of 1574 subjects with prior ischemic stroke from 3 trials.

***Study design and validity*** In ESPS-2, patients recruited were randomly assigned to 1 of 4 treatment groups: ASA 25 mg twice daily; modified-release dipyridamole 200 mg twice daily; the 2 treatments in combination; or placebo. This population was treated for 2 years. This critical reappraisal alters the Antiplatelet Trialists' meta-analysis to include the ESPS-2 data. A detailed description of the methodology is not given.

***Outcomes measured*** The primary end points in ESPS-2 were stroke, death, and stroke and death together. The meta-analysis end point is a vascular event (defined as the composite end point of stroke, myocardial infarction, and vascular death).

***Results*** In the ESPS-2 a total of 824 patients suffered a stroke: 250 patients in the placebo group, 157 in the combined therapy group, 206 in the ASA-alone group, and 211 in the dipyridamole-alone group. Pairwise analysis revealed an 18% risk reduction for stroke in the group receiving ASA alone ($P$ =.013), 16% risk reduction with dipyridamole alone ($P$ =.039), and 37% risk reduction in the combination therapy group ($P$ <.001), compared with placebo. Thus, the combination of aspirin and dipyridamole prevents further strokes or deaths with a number needed to treat (NNT) of 18. The further addition of dipyridamole to a patient already on low-dose ASA prevents strokes or deaths with an NNT of 38. Risk of stroke or death was also reduced: 13% by ASA alone ($P$ =.016); 15% by dipyridamole alone ($P$ =.015); and 24% by combination therapy ($P$ <.001). There was no statistically significant risk reduction for death alone in any of the treatment groups. Risk reduction for occurrence of transient ischemic attack was similarly reduced in all the treatment groups, with the greatest percentage reduction (36%) in the combination group ($P$ <.001). Headache was the most frequent adverse event reported, occurring more frequently in patients receiving dipyridamole. All site bleeding and gastrointestinal bleeding were significantly more common in patients receiving ASA than in those receiving placebo.

Addition of the ESPS-2 data to the Antiplatelet Trialists' meta-analysis data results in a decrease in the calculated relative risk for vascular events, defined as stroke, myocardial infarction, or vascular death, from .95 (95% CI, .75 - 1.19) to .83 (95% CI, .72 - .95) when comparing ASA alone treatment with ASA/dipyridamole combination treatment.

***Recommendations for clinical practice*** **Both low-dose aspirin and modified release dipyridamole are efficacious in the secondary prevention of stroke in patients with a history of ischemic stroke or transient ischemic attack. Moreover, combination treatment with both of these agents is significantly more efficacious than treatment with either agent alone. The combination approach should be used in patients who can tolerate it.**

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REFERENCES

1. Antiplatelet Trialist's Collaboration. Collaborative overview of randomized trials of antiplatelet therapy — 1. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994; 308:81-106.
2. The ESPS-2 Group. European Stroke Prevention Study 2. Efficacy and safety data. J Neurol Sci 1997; 151:S1-S77.