of routine care for mild hypertension and hyperlipidemia. This study does not answer this question, but the National Cancer Institute is making available the risk assessment software used in this trial at http://cancertrials.nci.nih.gov.

Francis W. Sweeney, MD
Warren P. Newton, MD, MPH
Department of Family Medicine
University of North Carolina – Chapel Hill
E-mail: uncwpn@med.unc.edu

Carotid Endarterectomy for Symptomatic Moderate Stenosis

Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. N Engl J Med 1998; 339:1415-25.

Clinical question Is carotid endarterectomy indicated for patients with symptomatic and moderate (< 70%) stenosis?

Background The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST), both reported in 1991, showed the striking clinical benefit of surgery over drug therapy for patients with symptomatic carotid stenoses > 70%.[1,2] These studies also clearly demonstrated the lack of benefit of carotid endarterectomy (CEA) for patients with mild lesions (0% to 29%). It is not clear, however, whether patients with moderate stenosis (30% to 70%) benefit from surgery. Recent evidence-based guidelines from both the Stroke Council of the American Heart Association and the Canadian Neurosurgical Society consider such patients "uncertain candidates for CEA."[3,4]

Population studied These investigators enrolled 2226 patients with < 70% carotid stenosis by angiography who had either transient ischemic attack (TIA) or nondisabling stroke in the previous 180 days. Patients were excluded for cardiac lesions likely to cause cardioembolism, prior ipsilateral CEA, severe internal carotid artery stenosis, or any medical illness that would preclude a 5-year life expectancy. The average age was 66 years, with 15% of subjects older than 75 years. Patients were enrolled from 1987 to 1996.

Study design and validity This was an international randomized clinical trial in 106 centers. Patients were randomized after angiography to the medical arm (n = 428) or surgical/CEA arm (n = 430) of the study. Patients were stratified by degree of stenosis, and there were no significant differences between the groups in baseline variables. The average duration of follow-up was 5 years; complete outcome measures were available for 99.7% of enrolled patients. All patients were given antiplatelet treatment throughout the study; hypertension and hyperlipidemia were treated, when present, in both groups. Analysis was by intention-to-treat. Patients in the medical arm were offered CEA if their lesions progressed to >70% stenosis, and these crossover patients were appropriately analyzed in the medical group.

Outcomes measured The primary outcomes were fatal and nonfatal stroke ipsilateral to the stenosis for which the patient was randomized. Outcome assessments (territory, type, severity, and duration of all strokes, and cause of death) were effectively blinded. Secondary outcomes included rates of perioperative disabling stroke and death at 30 and 90 days.

Results For symptomatic patients with 50% to 69% stenosis, the failure rate (any ipsilateral stroke) was 15.7% in the surgical group and 22.2% in the medical group (P = .045). The number needed to treat (NNT) to prevent one ipsilateral stroke over 5 years was 15 (95% CI, 11-29). Subgroup analysis showed that the benefit of CEA over medical treatment is greater in men than women, greater in patients with stroke than those with TIA, and greater in patients with hemispheric opposed to retinal symptoms. The highly expert surgeons in this series achieved perioperative combined death or disabling stroke rates of 2.8% at 30 days and 2.0% at 90 days. There was no benefit for CEA in patients with stenoses <50%.

Recommendations for clinical practice **Endarterectomy is of marginal benefit for symptomatic patients with carotid stenosis between 50% and 69%. If the combined surgical risk of death and disabling stroke exceeds 2%, this benefit is lost completely. We should refer these patients only to surgeons whose patients have low rates of complications as determined by independent audits.**

Sean Gaskie, MD
Santa Rosa, California
E-mail: GaskieS@sutterhealth.org

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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.**

Rafal Zielinski, MD
Linda French, MD
Oakwood Healthcare System
Dearborn, Michigan
E-mail: Lmfrench@aol.com

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