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Letters to the Editor

Stroke welcomes Letters to the Editor and will publish them, if suitable, as space permits. They should not exceed 1000 words (excluding references) and may be subject to editing or abridgment. Please submit letters in duplicate, typed double-spaced. Include a fax number for the corresponding author and a completed copyright transfer agreement form (published in the January and July issues).

Supplement to the AHA Guidelines for the Management of Transient Ischemic Attacks

To the Editor:

I read with interest the recent supplement to the guidelines on management of patients with transient ischemic attacks.[1] However, with regard to carotid endarterectomy (CE), I was disappointed that Albers et al made no attempt to interpret the clinical trial results in the context of real-world surgical performance.

For example, in the updated section on CE for 50% to 69% symptomatic stenosis, the authors state that symptomatic patients with 50% to 69% benefit from surgery and that these patients should be considered for CE. However, should clinicians conclude that because patients in the surgical arm of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) had a marginal statistically significant benefit (P=0.045) that this result is clinically meaningful and that this can be routinely achieved in clinical practice?

One must keep in mind that the benefit of surgery in the 50% to 69% group was very modest. For the important clinical outcome of disabling, ipsilateral stroke, the absolute difference between the medical and surgical groups was only 4.4% at 5 years, or less than 1% per year.[2] This modest result was achieved in the ideal setting of low-risk patients being operated on by surgeons screened for their excellence. In NASCET as a whole, the perioperative mortality was 1.1% and the stroke and death rate was 6.5%.

In terms of the real world, Wennberg et al[3] analyzed CE results in over 100 000 Medicare beneficiaries in 1992–1993 and found the perioperative mortality at an average volume hospital to be 1.9%. This was in a mixed symptomatic/asymptomatic cohort. Had the analysis been restricted to symptomatic patients only, the perioperative mortality would likely have been even higher.

With regard to other recent studies, Hartmann et al[4] studied symptomatic patients over a two year period at their hospital and the stroke/death rate was 11.1%. In the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), the rate of *disabling* stroke and death in the CE group was 5.9%, almost 3 times as high as the NASCET figure (M. Brown, personal communication, 1999).

With these considerations, I think that the extremely modest benefit seen in the high-moderate NASCET group is not generalizable and that these patients will not benefit from CE in the real world. The comments of Wennberg et al[3] on the utilization of CE should be heeded when these authors stated that "the caution called for by those advocating restraint is warranted."

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To the Editor:

I must respectfully disagree with the recent AHA Scientific Statement on the management of transient ischemic attacks.[1]

First, the inclusion of the combination antiplatelet agent extended release dipyridamole and aspirin (ERDP/ASA) as a "recommended therapy" is premature. The current data are insufficient to definitively establish that ERDP/ASA offers anything in addition to aspirin alone. Although the results of the ESPS-2 trial[2] of ERDP/ASA are encouraging and generate great optimism for this and other combination strategies, serious questions remain. The ESPS-2 results are highly inconsistent with previous data on 5317 patients treated with the combination.[3] Although a heterogeneous set of trials, these data were sufficient to all but abandon use of dipyridamole in the 1980s. Further, the high rate of subject dropout,[2] the lack of any benefit in vascular death despite the stunning benefit in stroke,[2] the 50-mg dose of ASA,[2,4] and the scientific misconduct[5] discovered in the trial collectively make ESPS-2 inadequate to certify ERDP/ASA as an established therapy by the AHA or any other body.[6] Any new scientific finding that is a large departure from previous data or theory requires independent conformation. Such is true of ERDP/ASA.

Second, a variety of commonly used antithrombotic strategies deserve mention with ERDP/ASA as potentially useful, if unproven, alternatives. This includes the use of clopidogrel or ticlopidine with aspirin,[7–9] a well-accepted standard for post-stenting prophylaxis. For some warfarin patients, the addition of any antiplatelet agent can help also.[10,11] Further, for those who are impressed with the dramatic ESPS-2 results of ERDP/ASA, comparable efficacy was observed in the ESPS-1 trial using the inexpensive (and currently available) combination of aspirin (325 mg) and regular dipyridamole (75 mg) 3 times a day.[12] Time and more data will tell if any of these combinations, ERDP/ASA included, can be recommended for general use.

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Response to Dr Chaturvedi:

We thank Dr Chaturvedi for his comments regarding the carotid endarterectomy recommendations in the recently published American Heart Association Guidelines for the Management of Transient Ischemic Attacks. We agree that the efficacy of therapies in the community setting, medical or surgical, may differ from the results obtained in carefully controlled clinically trials. Application of clinical trial results to clinical practice is always problematic and requires clinical judgement. We also agree that surgical morbidity and mortality rates may be higher in the "real world" than those achieved in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). However, the stroke and death rate is also likely to be higher in medically managed patients in a routine practice setting due to variations in the management of comorbid risk factors, decreased emphasis on medical compliance, and less frequent systematic follow-up. In addition, patients selected for participation in clinical trials frequently have relatively favorable outcomes in both active treatment and control groups. Therefore, we do not think it is valid to compare the surgical morbidity and mortality rates in populations such as Medicare beneficiaries with the rates observed in a clinical trial. It is also noteworthy that the NASCET trial enrolled patients with moderate carotid stenosis at 106 diverse clinical sites; therefore, the complication rates reported do exist in the "real world."

Our evidence-based guidelines rely heavily on scientific data from randomized clinical trials. The NASCET and European Carotid Surgery Trial (ECST) provide the highest quality data regarding the risks and benefits of carotid endarterectomy for patients with moderate symptomatic stenosis. The guidelines state that carotid endarterectomy should be "considered" for patients with a recent transient ischemic attack or minor stroke with ipsilateral carotid stenosis of 50% to 69%, but that "the absolute benefit of surgery is relatively small for these patients." The degree of benefit "is highly dependent on surgical risk" and "consideration should be given to clinical features that influence stroke risk and surgical morbidity." These features should include the overall health and gender of the patient, the nature of the neurological symptoms, the degree of stenosis, and the availability of a surgical team with a demonstrated low perioperative morbidity and mortality rate.

Response to Dr Hughes:

We appreciate the opportunity to respond to Dr Hughes. After carefully considering his concerns, we do not believe any modifications of the American Heart Association recommendations[1] are justified. A balanced review of all available data regarding the efficacy of the combination of aspirin/dipyridamole was recently published.[2] When all studies performed in cerebrovascular patients are considered, a substantial and statistically significant benefit of aspirin/dipyridamole over aspirin therapy alone for stroke prevention was detected. The most compelling data supporting the benefits of this combination come from the second European Stroke Prevention Study (ESPS-2) trial that evaluated an extended-release form of dipyridamole (400 mg/d) in combination with aspirin (50 mg/d).[3] As discussed in detail in our report,[1] there is no evidence that the 50-mg dose of aspirin is any less effective for stroke prevention than higher doses, and the aspirin dose recommended by the Food and Drug Administration for stroke prevention is 50 to 325 mg/d. The "scientific misconduct" referred to by Dr Hughes in the ESPS-2 trial reflects a single fraudulent investigator who was identified prior to study completion. The data supplied by this investigator were removed prior to unblinding and analyzing the ESPS-2 data and did not influence the results of study. The dropout rate in the ESPS-2 study did not differ from many similar stroke prevention trials. In addition, a high dropout rate typically dilutes, rather than accentuates, the benefits of an effective agent. The failure of ESPS-2 to demonstrate a reduction in vascular death is also not unique to the aspirin/extended-release dipyridamole combination; neither ticlopidine, clopidogrel, nor any single trial of aspirin therapy has demonstrated a significant reduction in vascular death in patients with cerebrovascular disease.

The American Heart Association is not the first group to recognize the aspirin/extended-release dipyridamole combination as a safe and effective therapy for stroke prevention—this combination was recently approved by the Food and Drug Administration. Other combinations of antiplatelet agents or anticoagulants have not been adequately tested in stroke or transient ischemic attack patients. Therefore, their safety and efficacy are not established.

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1. Albers GW, Hart RG, Lutsep HL, Newell DW, Sacco RL. Supplement to the guidelines for the management of transient ischemic attacks: a statement from the Ad Hoc Committee on Guidelines for the Management of Transient Ischemic Attacks, Stroke Council, American Heart Association. *Stroke.* 1999;30:2502–2511.
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Which Targets Are Relevant for Therapy of Acute Ischemic Stroke?

To the Editor:

The report by Heiss et al[1] describing ranges of cerebral blood flow (CBF) decline in 10 patients studied within 3 hours of