

Letter Regarding Article by Markus et al, "Dual Antiplatelet Therapy With Clopidogrel and Aspirin in Symptomatic Cardiac Stenosis Evaluated Using Doppler Embolic Signal Detection: The Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial"

To the Editor:

We read with interest the report by Markus et al of the CARESS trial,¹ in which dual antiplatelet therapy resulted in more effective control of microembolic signals (MESs) than single antiplatelet therapy. There was an associated reduction in the prevalence of transient ischemic attacks (TIAs) and strokes.

Immediately after a TIA or stroke, there is a rise in transcranial Doppler (TCD)-detected MESs. Those patients who continue to experience embolization are at greater risk of another neurological event.² Markus et al "emphasize the importance of operating urgently in patients wherever possible." However, a recent systematic review of the risks of carotid endarterectomy in relation to both the clinical indication for and timing of surgery has shown that urgent carotid surgery carries a much higher risk (19.2%, 95% CI 10.7% to 27.8%) than elective surgery (OR 3.9, 95% CI 2.7% to 5.7%; $P < 0.001$; 13 studies).³

Recurrent or crescendo TIA patients represent a particularly high-risk group. It is possible to stop both emboli and further symptoms in these patients with TCD-directed intravenous antiplatelet agents, the dose being increased incrementally until the MESs cease. Consequently, it is possible to influence the timing of surgical intervention, allowing patients to undergo carotid endarterectomy safely on the next elective list,⁴ avoiding the risks associated with urgent or emergency surgery³ or the risks associated with delay in patients whose MESs persist despite oral antiplatelet therapy.^{1,2}

MESs are surrogate markers for the risk of future embolic events. The pharmacological efficacy of therapeutic interventions can now be assessed rapidly, noninvasively, and inexpensively. TCD emboli detection appears to offer an important advance that enables optimal integration of medical therapy and timing of surgery.

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1. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection. *Circulation*. 2005;111:2233–2240.
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3. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–301.
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To the Editor:

The study by Markus and colleagues using transcranial Doppler (TCD) to evaluate evidence of ongoing embolic events and the effect of dual antiplatelet therapy versus monotherapy in

patients with symptomatic carotid stenosis raises several important questions.¹ In this study, the ischemic stroke rate in the first 7 days after entering the trial was 7.1% for patients given aspirin monotherapy. Patients in the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) treated with aspirin monotherapy had a much lower 30-day ischemic stroke rate.^{2,3} It might be tempting to attribute the higher rate of stroke to the presence of microembolic signals required for patients in the present trial. However, even if we assume that there were no strokes in any of the 120 patients screened but excluded from this trial because of the absence of microembolic signals, the 7-day stroke rate would only drop to approximately 3.5%. This is still far higher than the rates for aspirin monotherapy in NASCET or ECST. The authors should address their apparent excessive 7-day stroke rate compared with comparable patients in larger trials.

In the discussion, the authors state that their results suggest that dual antiplatelet therapy with "clopidogrel and aspirin is likely to be more effective in patients with large vessel atherosclerotic stroke in the acute phase." Their Table 2 indicates that fewer than 40% of their patients entered the trial within 7 days of the qualifying event. In fact, entry criteria allowed patients to enter up to 3 months after their qualifying event. Because more than 60% of patients entered the study more than 1 week after the initial event, it would appear that the data presented do not justify a comment about the efficacy of any treatment in the acute phase.

The authors suggest that placing patients on dual therapy while waiting for a planned carotid endarterectomy is "an attractive option." Anecdotal experience by surgeons at our hospital suggests that pretreatment with a combination of aspirin and clopidogrel may place a patient at excessive risk of bleeding complications during and after an endarterectomy. Do the authors have any data to support the safety of their recommendation?

This report provides important information on the utility of TCD in identifying potentially high-risk patients with carotid stenosis and on its role as a surrogate marker for clinical outcomes. However, much more work needs to be done before any clinical conclusions can be drawn about the value of dual antiplatelet therapy in this clinical setting.

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1. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial. *Circulation*. 2005;111:2233–2240.
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Response

We agree with Imray and colleagues that Doppler embolic signal detection is a promising method of detecting individuals with symptomatic carotid stenosis at high risk of recurrent stroke. This is supported not only by the CARESS trial¹ but also by a recent series of 200 symptomatic carotid stenosis subjects in whom embolic signals (ESs) predicted not only the combined risk of transient ischemic attack (TIA) and stroke but also the risk

of stroke alone.² The CARESS study demonstrates that more aggressive antiplatelet therapy does reduce ESs, and there is a suggestion that it reduces recurrent clinical events, although the study was not powered to examine this end point. Certainly, there is a case for treating patients with large-artery atherosclerotic stroke with more aggressive antiplatelet therapy, although ideally, this should be tested in large clinical trials with clinical end points first.

We also agree that the technique may be useful in stratifying risk and monitoring response to therapy in unstable patients with symptomatic carotid stenosis before endarterectomy. However, it is important to remember that in most patients with TIA or minor stroke, the optimal treatment, if resources allow, is urgent endarterectomy, as clearly shown by endarterectomy trial data.³ The meta-analysis quoted by Imray and colleagues shows that in patients with a single recent stroke/TIA, risk of endarterectomy in the acute setting is low.⁴ The higher risk they cite is for the small group of unstable patients with progressing symptoms or crescendo TIAs. Certainly, in this group, more aggressive antiplatelet therapy until the situation has stabilized appears an attractive option.

Cohen raises a number of concerns about the results of the CARESS study and provides an opposing view to that of Imray et al. He suggests that patients in our study were not high risk. In fact, as stated in the report, the vast majority (77.1%) had experienced symptoms in the last month. Furthermore, the use of a technique to detect asymptomatic embolization means we studied patients who were likely to have unstable plaques and to be at particularly high risk.

Cohen is concerned about what he perceives as a high recurrent stroke risk in the CARESS study population. The study was not powered to look at clinical end points, and any conclusions on clinical event rate should be drawn cautiously. Nevertheless, the rate is less than cited in his letter. There were 4 recurrent strokes, which equates to a risk of 3.7%. We know from previous data that the risk is much higher in this group than in patients who have no ES detected.² Furthermore, more recent analyses of risk of stroke after TIA have demonstrated rates as high as 8% to 12%.⁵

Cohen suggests pretreatment with aspirin and clopidogrel may place a patient at excessive risk of bleeding complications during and after endarterectomy. In fact, there has been a randomized trial, published in *Circulation*, comparing pretreatment with aspirin versus aspirin and clopidogrel.⁶ Combination therapy resulted in a significant reduction in postoperative embolization. There was an increase in time to skin closure but no major bleeding complications. Many surgeons operate on patients who are taking clopidogrel and indeed believe that adequate antiplatelet cover during the postoperative phase is important to prevent early recurrent stroke.

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1. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial. *Circulation*. 2005;111:2233–2240.
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