Premature Trial Suspension Will Inevitably Alter Equipoise

To the Editor:

The research report by the EVA-3S Investigators has implications which could far exceed their understandable desire to optimize safety within the trial. Following an early interim analysis, the investigators observed that the death/stroke rate after unprotected carotid angioplasty was 10.3% (6/58), as compared with 26.7% (4/15) following unprotected angioplasty. This led to a recommendation that all future angioplasties in the trial should be performed with protection. This is despite the fact that the trial was neither powered to make this judgment, nor was the difference statistically significant.

I can readily sympathize with the dilemma faced by the Investigators but, in publishing this alert, they have probably rendered continuation of EVA-3S all but impossible. They have now revealed the outcome data for the entire angioplasty limb of the trial (12.5% death/stroke) and it is likely that this is considerably higher than anticipated when the trial was conceived. Consequently, this alert will inevitably alter the equipoise of physicians (and especially surgeons) considering continued randomization within the study.

With the increasing trend toward “individual ethics” (ie, the needs of the individual outweigh the needs of the many), what risk will the EVA-3S Investigators now be advised to quote, bearing in mind that the actual data are public knowledge and also accessible to their prospective patients?

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Response:

Professor Naylor suggests that we should stop the EVA-3S trial because we have revealed the outcome data for the angioplasty arm of the trial and the presumed “higher than anticipated” stroke and death rate within 30 days of carotid angioplasty “will alter the equipoise of physicians considering continued randomisation within the study.” On behalf of the EVA-3S Investigators, we disagree with Professor Naylor for several reasons.

First, the overall stroke and death rate within 30 days of angioplasty reported in the present paper is a rough estimate of the rate of outcome events. As shown by the 95% CI confidence interval, the “true rate” of events in patients treated with protected angioplasty may be as low as 4.3% and as high as 21.8%. In addition, most of these strokes were nondisabling strokes. Clearly, a larger number of patients are needed to obtain a reasonably precise estimate of the true stroke and death rate in this population.

Second, in the single completed prospective multicenter trial (CAVATAS) to which we can compare our results, the stroke and death rate within 30 days of angioplasty was similar to that of surgery and to that found in the angioplasty arm of our study.

Third, the Safety Committee of the EVA-3S trial, which issued the recommendation to stop unprotected angioplasty, also recommended continuing randomization between surgery and angioplasty with cerebral protection, which means that in patients included so far in this trial, equipoise is maintained between surgery and protected angioplasty. Patients and study investigators can be assured that the Safety Committee of the EVA-3S trial will remain particularly vigilant to detect any difference in the rate of serious outcome events between surgery and protected angioplasty arms. Of note, patient recruitment in EVA-3S has remained unchanged since this clinical alert.

Finally, although our results were not based on a randomized comparison of unprotected versus protected carotid angioplasty and stenting and were not statistically significant, they are in keeping with available evidence suggesting that protected carotid angioplasty may be safer than unprotected angioplasty. We thought that this result could be of interest to the medical community.

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