Neurosurgical forum
Letters to the editor

Crossover and clinical outcomes in the Barrow Ruptured Aneurysm Trial

To The Editor: The article by Dr. Spetzler and colleagues on the Barrow Ruptured Aneurysm Trial (BRAT) (Spetzler RF, McDougall CG, Albuquerque FC, et al; The Barrow Ruptured Aneurysm Trial: 3-year results. Clinical article. J Neurosurg 119:146–157, July 2013) provided us with interesting reflections regarding the choice of treatment for ruptured aneurysms.

In the International Subarachnoid Aneurysm Trial (ISAT), randomization of patients with subarachnoid hemorrhage (SAH) was appropriate for those harboring aneurysms judged to be suitable for either coiling or clipping based on the angiographic anatomy when clinical equipoise existed in these patients. The patient population in ISAT represented only a subgroup of patients, specifically those whose SAH was deemed a good grade and whose anterior circulation aneurysm was less than 10 mm in diameter. One reason the ISAT authors posited to explain their relatively low enrollment rate was a lack of equipoise on the part of neurointerventionists and neurosurgeons responsible for recruiting patients.

To cope with these limitations of the ISAT, the BRAT study was designed to enroll all patients with acute nontraumatic SAH without the criterion of equipoise selection. Compared to ISAT, this design led to a greater proportion of patients being randomized in BRAT (nearly 65%) and to a sample population that was more diverse with respect to SAH grade and aneurysm location and size. However, as a consequence of the all-inclusive protocol in BRAT, a large proportion of patients in the coil-assigned group whose lesions were considered unsuitable for coiling did cross over to clip treatment (38%). This reflected the fact that fewer patients were deemed eligible for either treatment than patients judged suitable for clipping overall.

The intention-to-treat analysis in BRAT counted crossover patients with their originally assigned group regardless of what treatment was actually received. Results at the 1-year follow-up demonstrated that the mean patient outcome in the coil-assigned group (modified Rankin Scale Score > 2) was not as poor as that in the clip-assigned group (OR 1.68, 95% CI 1.08–2.61; p = 0.02). A subgroup analysis that excluded crossover patients showed even better outcomes in the coil-coil group than in the clip-clip group (OR 2.28, 95% CI 1.30–4.13; p = 0.005). This disparity could be attributed to the poorer mean outcome in patients who crossed over from clipping to clipping therapy than in patients who received their assigned clipping treatment (33.9% vs 18.4% of poor outcome, respectively). If the coil-clip crossover group had had an even worse mean patient outcome, it would be fair to think that the benefit of coiling shown in the intent-to-treat analysis at 1 year would have been lost.

In the 3-year follow-up BRAT paper, the difference in the primary outcome between the coil-assigned and clip-assigned groups was no longer significant. However, the authors did not comment on whether the subgroup analysis that excluded crossover patients at 3 years of follow-up still favored a better outcome for the coil-clip group. In fact, although the results are displayed in Table 2, the p value in the footnote is missing a number: “Coil-coil compared to coil-clip at 3 years: p = 0.007. Coil-clip compared to clip-clip at 3 years: p = 0.26. Coil-coil compared to clip-clip at 3 years: p = 0.0.”

Interestingly, the mean patient outcome in the coil-clip crossover group worsened at 3 years compared with the mean outcome at 1 year (42.2% vs 33.9% poor outcome, respectively). It would be interesting if the authors would discuss the worsening of outcome in the coil-clip crossover group to explain the loss of statistical difference in the primary outcome at 3 years. Was there a bias created toward the null hypothesis when the mean outcome in the coil-clip crossover group became worse? Large crossover in randomized studies decreases statistical power, an effect that is amplified by long-term analysis when more patients are lost to follow-up, their outcomes change, or they die.

Secondarily, an erratum should be issued for a typographical error. In the Methods section of the abstract, the word “coiling” should replace the word “clipping” at the end of the following sentence: “Of the 170 patients who had been originally assigned to coiling, 64 (38%) crossed over to clipping, whereas 4 (2%) of 179 patients assigned to surgery crossed over to clipping.”

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Disclosure
The author reports no conflict of interest.

References
Response: We thank Dr. Denis for his careful review of our article and his most thoughtful questions. His points are clearly made and his questions appropriate and well taken.

We will address Dr. Denis’s points in order, beginning with his observation that “if the coil-clip crossover group had had an even worse mean patient outcome, it would be fair to think that the benefit of coiling shown in the intent-to-treat analysis at 1 year would have been lost.” We agree that the impact of crossing patients from the clipping to coiling procedure was to diminish the size of the treatment effect measured, in effect diluting the benefit. The significance of this must be interpreted with caution, however, as patient selection for crossover was not made randomly. While it is true that patients who crossed over to clipping treatment fared worse than patients who did not cross over, it is not assured that their outcomes would have been better had they, in fact, been treated with the coiling procedure to which they were initially randomized.

Next, with respect to the subgroup analysis at 3 years for “coil-coil compared to clip-clip” treatment, the mean outcomes in these two groups did remain statistically significantly different, with the difference continuing to favor coiling at 3 years. Twenty-four (22.6%) of 106 patients randomized to coil therapy and treated by coiling and 60 (34.3%) of 175 patients randomized to clip therapy and treated by clipping had poor outcomes. We regret that the p value of 0.04 for this comparison was inadvertently omitted from Table 2. We are correcting this omission and the typographical error that Dr. Denis observed, and we are noting these changes in an erratum notice. Again, caution is needed in interpreting this subgroup analysis, as the two groups in question were not randomly chosen. The “clip-clip” group certainly contained some patients who would have been excluded from coil therapy had they been randomized to that treatment arm.

Regarding the deterioration in outcomes observed between Years 1 and 3 among patients who originally were assigned to coiling but crossed over to clipping, the small sizes of the groups mean that a large percentage change is accounted for by a relatively small number of patients. Worse outcomes occurred in 22 (33.9) of the 65 patients in the coil-clip group at 1 year, but by 3 years the number of poor outcomes in this group had increased to 27 (42.2%) of the 64 patients. This 8.3% change resulted from deterioration in the condition of 5 patients in this group between Years 1 and 3. The deteriorations in condition were due to lung cancer in 1 patient and progression of dementia in 1 elderly patient. The conditions of the remaining 3 patients deteriorated from modified Rankin Scale Score 2 to Score 3, with all patients citing symptoms relating to difficulties with concentration, memory, and depression. One of these three, a patient with a history of psychiatric illness and substance abuse, reported new strokes but would not cooperate with our attempts to obtain more detailed follow-up.

This observation is interesting, but given what is known about the causes of the deterioration in these patients, it does not seem influential in recommending one treatment modality over another. In essence, it again highlights the limitations of an underpowered trial, and, in particular, brings to light the hazards of examining subgroups that were not specified beforehand. It is reasonable to use such data to generate hypotheses, but post hoc choices for subgroup analysis and limited statistical power should preclude overinterpretation of these results.

In the final analysis, the primary outcome of BRAT credibly demonstrated that a policy of coiling as a first choice led to fewer poor outcomes 1 year after treatment. Subsequent subgroup analysis does not change this result, but legitimately raises questions as to why this occurred. Similarly, at 3 years, failure to detect the continued statistically significant benefit of the primary outcome raises questions as to whether, in fact, the benefit was lost or rather that the study simply lacks the statistical power needed to detect a narrowed margin of benefit.

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Complications with cranial perforators

To The Editor: We read with great interest the paper on intraoperative complications of cranial perforators by Vogel et al.1 (Vogel TW, Dlouhy BJ, Howard MA III: Don’t take the plunge: avoiding adverse events with cranial perforators. Clinical article. J Neurosurg 115:570–575, September 2011). The authors describe the complications in using cranial perforators during a 2-year period in 1652 cranial procedures. Plunging, defined as “an uncontrolled rapid increase in depth of the cranial perforator or drill,” occurred in 9 procedures (0.54%). This overall complication rate is relatively low, and plunging in these 9 cases did not result in any serious or irreversible damage to the patient.

Trephtining the skull is one of the basic skills that must be acquired during neurosurgical training. There are various methods of performing a craniotomy, all starting with 1 or multiple holes.1 These holes can be created using mechanical, electrical, or pneumatic devices, and the size and method of the bur hole vary among the

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This article contains some figures that are displayed in color online but in black-and-white in the print edition.