EDITORIAL

Clip or coil? Six years of follow-up in BRAT

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ALFRED Blalock, a visionary in surgery, is reported to have said, “It usually requires a considerable time to determine with certainty the virtues of a new method of treatment and usually still longer to ascertain the harmful effects.” In neurosurgery, we are confronted with this cautionary view in the consideration of endovascular coiling for ruptured intracranial aneurysms, which is pitted against traditional neurosurgical clipping, at least in cases where there is said to be clinical equipoise. The matter is again raised in this issue of the Journal of Neurosurgery, where the results of the 6-year follow-up in the Barrow Ruptured Aneurysm Trial (BRAT) are published. Has enough time passed to conclude that coiling is efficacious in some patients? Is another randomized trial needed?

The conclusions of this paper contain a number of post hoc speculations that are certain to incite a flurry of letters and editorials, including this one. The authors should be heartened that this reflects the importance of this data set. Basically, at the 6-year follow-up when the entire data are considered, no difference is observed in poor outcome (that is, a score of > 2 on the modified Rankin Scale [mRS]) between patients undergoing clipping and patients undergoing coiling. The authors conclude that the study was underpowered to detect a difference between the 2 treatments. They also note that both modalities give the same outcomes for aneurysms of the anterior circulation but that coiling results in better outcomes for those of the posterior circulation. They further observed that coiled aneurysms are less likely to be obliterated and more likely to require retreatment. Obliteration rates and retreatment did not matter much because no rebleeding events occurred, and presumably any complications of retreatment would be reflected in the mRS outcomes. The authors also advocate for another randomized trial.

Let us examine some of these conclusions. BRAT used what has been called a prerandomization strategy, which randomized patients with a subarachnoid hemorrhage (SAH) to clipping or coiling as soon as the SAH was diagnosed. This randomization approach has advantages and disadvantages, the main disadvantage being inclusion of patients who did not have aneurysms and who thus never had an aneurysm repair. In addition, this strategy resulted in a high crossover rate between the 2 treatment modalities, which is one of the fundamental unfixable issues with BRAT. Randomization was sequential and would therefore be considered pseudorandomization. Various analyses have been published excluding various subsets of these patients. The current analysis is based mainly on “intention to treat according to the assigned treatment group.” My understanding of this analysis design is that this means the crossover cases are left in the group to which they were originally assigned, the implications of which I will discuss below. Patients who died before any treatment could be initiated were excluded, but because only 3 patients in each group died, including them in the analysis is not going to materially change the results. Fifty-seven (12%) of 471 patients did not have aneurysms and were therefore excluded from this analysis. Since these patients’ outcomes were the same regardless of which group they were randomized to, including them would only reduce any potential differences between clipping and coiling.

The authors report that 38% (75 of 199) of patients assigned to coiling crossed over to clipping. This is a high crossover rate and is very problematic because these patients are now not randomized. They crossed over mainly because they had intracerebral hemorrhages, and they did much worse than the other patients. There is no good way to analyze these cases, and arguments that the crossovers favor or penalize coiling could be made. In the analysis, including the crossover patients in the coiled group to which they were randomized will bias against coiling, and

ACCOMPANYING ARTICLE See pp 609–617. DOI: 10.3171/2014.9.JNS141749.

INCLUDE WHEN CITING Published online June 26, 2015; DOI: 10.3171/2014.11.JNS142261.

DISCLOSURE Dr. Macdonald receives grant support from the Physicians Services Incorporated Foundation, Brain Aneurysm Foundation, Canadian Institutes for Health Research, and the Heart and Stroke Foundation of Canada; he is a chief scientific officer of Edge Therapeutics, Inc.
including them in the clipping group would do the reverse. But this is based only on the outcomes after the crossover patients underwent clipping, and it is not known whether their outcomes would have been different had they undergone coiling. The outcomes with the crossovers excluded may also be biased if, for example, the surgeons performing the clipping had declined to treat these patients in order to make sure the results of the procedures they performed were not affected by patients with a poor prognosis. I do not know of any post hoc randomization analysis that can adjust for this bias caused by the crossovers.

Regarding the lack of statistically significant differences in outcomes between the 2 modalities at the 6-year follow-up, some caveats may be mentioned. While it is commendable that the authors could follow up 336 (82%) of 408 of patients for 6 years, the loss of 18% of the patients during the follow-up is a limitation. The International Subarachnoid Aneurysm Trial (ISAT), another trial comparing clipping and coiling, had a five-year or longer follow-up rate of 74% (1582 of 2143 patients). In the 6-year BRAT analysis, the last known mRS score was carried forward, but this still resulted in no difference in outcome between clipping and coiling. However, another possible assumption would be to take the worst-case scenario, in which all of the patients lost to follow-up died. I estimate that this would not affect the results, because both groups lost similar numbers of patients during follow-up.

The fundamental issue, however, is the small difference in mRS scores at 1 year in BRAT and also in ISAT. This is taken as evidence that the treatments do not differ much in efficacy. There is another potential explanation, less savory for those performing clipping, which is as follows. The mRS was developed by John Rankin in 1957, who was studying the natural history of 252 patients with cerebral vascular accidents that included a mixture of ischemic strokes, intracerebral hemorrhages, and SAHs. It is unclear what the actual diagnoses were, and most of the patients affected had focal deficits and probably not an SAH. Good stroke outcomes, as most commonly defined, are those with an mRS score of 0–2, indicating that patients with a score in this range can look after themselves without assistance. Different questionnaires may be used to assess the mRS score, and they do not necessarily give the same results. The main issue that has been raised is that patients with SAHs and mRS scores of 0–2 often nevertheless have cognitive deficits that prevent them from working and participating in other activities. It has been reported that clipping is associated with better cognitive outcomes than clipping among patients whose level of dependence is rated as 0–2 on the mRS. Thus, it is possible that there might be a big difference in these outcomes between clipping and coiling but that the mRS is insensitive to it.

The next question is: how long should patients be followed up in studies of clipping versus coiling? Whether the ruptured aneurysm is clipped or coiled, a patient is going to die eventually. This outcome is going to be the same for each group, so carrying on with follow-up forever is not useful. In this regard, Table 1 is the key table in the 6-year BRAT study. My interpretation of the data in this table is that at 6 months and at 1 year, outcomes with clipping are better than with clipping and that the results are very similar to those of ISAT. The trend persists after that, but fewer patients are followed up, so the confidence intervals widen, and death from other causes, such as lung cancer and other diseases, creeps in. At the 6-year follow-up in BRAT, poor outcomes were observed in 41% of patients (72 of 174) who underwent clipping versus 35% of patients (57 of 162) undergoing coiling, with an absolute risk reduction (ARR) for clipping of 6% and a relative risk reduction (RRR) of 17%. At the 5-year follow-up in ISAT, 273 (32%) patients of 857 who underwent clipping did poorly, versus 241 (28%) patients of 867 who underwent coiling (with an ARR of 4% and RRR of 14% for coiling).9 Thus, regardless of statistical significance, the clinical differences are similar between the 2 trials. At the end of the day, coiling extended patients’ time with better mRS scores.

The second conclusion was that clipping and coiling resulted in equivalent outcomes among the patients with anterior circulation aneurysms and that those with posterior circulation aneurysms did better with clipping. Aneurysm location, however, was not a prespecified subgroup. The Consolidated Standards of Reporting Trials (CONSORT) guideline suggests that subgroups be prespecified. The point of this guideline is to disclose a post hoc data analysis that was not driven by a hypothesis generated before the trial began. However, prespecifying a subgroup does not mean the results of that analysis are necessarily true. Regardless of this lack of prespecification, and as the authors state, BRAT was underpowered to begin with, so subgroup analysis is not going to be adequately powered, either (whatever it is being powered to detect).

The study also contains a detailed analysis of the posterior circulation aneurysm outcomes; this analysis indicated major imbalances in the actual aneurysm repair method that was used after the treatment assignment. It was not clear how many of these imbalances were caused by the crossovers. Are we to conclude that clipping achieves better outcomes for the posterior circulation aneurysms, especially those at the posterior inferior cerebellar artery, for which clipping was worse, even though this is traditionally the “easy” posterior circulation location? And can we assume equivalent outcomes for the basilar bifurcation aneurysms? It is not scientifically possible to reach any conclusions on the basis of this analysis. The numbers of patients are too low, and the crossovers from clipping to coiling are unknown.

The study also presents a detailed analysis of aneurysm obliteration rates and retreatments. These are surrogate outcomes for rebleeding, which is but one factor leading to poor outcomes. Surrogate outcomes have many limitations, and very rigorous criteria have to be met for their acceptance, at least as primary outcomes in clinical trials. In this study, no rebleeding events were identified, so unfortunately, incomplete aneurysm obliteration does not matter much.

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