EDITORIAL

Clip versus coil: the debate continues?

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THIS month's *Journal* includes the publication of the 10-year results from the Barrow Ruptured Aneurysm Trial (BRAT).⁷ It's hard to believe that it has already been 10 years since this trial concluded and even harder to believe that we are still debating the merits of clips versus coils more than 15 years after the publication of the International Subarachnoid Aneurysm Trial (ISAT).⁵ For many neurovascular practitioners the debate has moved on from a head-to-head comparison to a more nuanced view of individualized care based on numerous factors, but for others the desire to have another randomized comparison remains.

In the current publication, the authors present a post hoc analysis of a subgroup of the original BRAT patients. Their primary finding is that there was no statistically significant difference in the rates of poor outcome (modified Rankin Scale [mRS] score > 2) between the clip-assigned and the coil-assigned patients with saccular aneurysms at 10 years. The central question for the reader is what does this mean for today's management of patients with ruptured intracranial aneurysms? For the reasons described below, the simple answer to this question is "not much."

As has been pointed out previously in comments regarding the publication of other delayed results from BRAT,⁴ the main difficulty in drawing any substantial conclusions from these results is the fact that they are based on an unplanned analysis of a subgroup of the original study population. In this publication only saccular aneurysms are compared with regard to the primary outcome, and other comparisons such as retreatment rates and rebleed rates use still different subsets. A nice example of the implications of this can be seen in a comparison of the 1-year outcomes published in the original paper and those published here. In the original paper, a comparison of the 205 clip-assigned patients to the 198 coil-assigned patients showed a 10.5% difference in the occurrence of a poor outcome.³

The result favored the coil-assigned patients and was statistically significant. In the present paper (Table 1),⁷ looking only at saccular aneurysms (159 vs 158), there is a 5.5% difference at 1 year, still favoring coiling, but the result, although perhaps still clinically significant, is no longer statistically significant. Whereas post hoc analyses are useful for hypothesis generation, they are not useful for drawing definitive conclusions.

The finding that the outcomes eventually converge does not negate the initial benefit. After the 1st year, we do not see that the patients who undergo clipping improve (as has been proposed by some); rather we see that both groups get worse. As has been pointed out previously,² and is evident in Table 1, a greater percentage of coil-assigned than clip-assigned patients spent more time with a good outcome. Unfortunately, everyone dies eventually, so when death is part of your primary outcome measure, if you wait long enough your outcomes will converge. In the case of BRAT, we know of only 2 deaths related to aneurysms (and one of these was not even from the target aneurysm). Although both were in the coil-assigned and -treated group, these deaths are overwhelmed by deaths from other causes that constitute the major reason for the increasing poor outcomes over time.

A few secondary issues, specifically the impact of aneurysm recurrence and rebleeding, as well as concerns regarding the skill of the original ISAT surgeons, warrant some discussion. Although both ISAT and BRAT showed increased rates of recurrence, retreatment, and rebleeding in aneurysms treated with coil embolization, these secondary outcomes were all represented within the primary outcome. In other words, the small differences in these secondary outcomes did not affect the overall incidence of morbidity and mortality. It might be argued that the mRS is insensitive to subtle problems related to retreatment, but when neurocognitive outcomes were specifically looked

at in the ISAT cohort, the results strongly favored those allocated to endovascular treatment.⁶

Much has also been made of the purportedly poor outcomes of the surgical patients in ISAT. At 1 year 33.7% of patients in the BRAT surgical arm had a poor outcome as compared to 30.6% of ISAT surgical patients. Because approximately 95% of ISAT patients had a good clinical grade (World Federation of Neurosurgical Societies I–III) on presentation and only about 80% of BRAT patients were Hunt and Hess I–III, this is believed to be evidence that the neurosurgical care in the United Kingdom was not of the same quality as that in the North America. However, ISAT results are very much in line with results from the North American Tirilizad Study,¹ in which 11.6% of good-grade patients died at 3 months compared to 8.3% in ISAT's neurosurgical group at 1 year. In addition, there does not appear to be any significant lack of experience among the ISAT surgeons, with all participating centers having treated more than 60 subarachnoid hemorrhage cases per year and surgeons having clipped 3 aneurysms outside of the trial for every 1 randomized.⁵

Of course, no discussion of 10-year follow-up data would be complete without some mention of the impact of technology. Although some may discount this as an overused axiom of the endovascular community, there is little doubt that endovascular aneurysm embolization technology has advanced considerably since 2003 when BRAT first began enrolling patients. As noted in the original BRAT paper, the majority of embolized patients were treated with the Matrix coil (Stryker), a coil that was later withdrawn from the market due to unacceptably high recurrence rates. To think that advances in endovascular technology over the last 10-plus years have not made aneurysm embolization safer and more effective is to ignore a wealth of data to the contrary.

In many ways, these results should serve to remind us of just how impressive the original BRAT results were. This relatively small study, with no published protocol and no power analysis, actually demonstrated an impressive benefit for coil embolization. The original intent-to-treat analysis yielded a poor outcome (mRS score > 2) in 33.7% of the patients assigned to clipping and in 23.2% of those assigned to coil embolization ($p = 0.02$). It is equally important to remember that such an analysis placed those who crossed over from coiling to clipping (approximately 36%) squarely in the coiling group. That the cross-over patients did worse than the actual coil-treated patients, but no worse on average than the clip-assigned and -treated patients, suggests that the overall result underestimated the benefit of coiling. This should take nothing away from the surgical abilities of the treating physicians. The fact that there were no cross-overs from clipping to coiling, despite numerous posterior circulation aneurysms, a finding unlikely to be repeated at many centers then or since, indicates a highly skilled open surgical team. In the end, it is much harder to show benefit for an aneurysm occlusion procedure in subarachnoid hemorrhage when so much of the final outcome is determined by the patient's initial condition and the subsequent critical care management of their various complications.

Some, including the authors, believe that results such as these indicate the necessity of another prospective randomized controlled trial (PRCT). In the years since ISAT and BRAT were initiated much has also changed in the way investigators and the NIH view PRCTs, particularly when it comes to devices and procedures. Ideally for a good-quality PRCT, patients and investigators are blinded to the intervention and confounders are equally distributed due to randomization. However, for devices and procedures, double-blinding is almost impossible, and with the lack of equipoise in the field today, finding a group of patients appropriate for randomization will be difficult. As BRAT shows us, without equipoise cross-overs will be rampant, and cross-overs are problematic, potentially even more so for surgical trials. Intent-to-treat analyses are important for drug trials where side effects and patient compliance can significantly impact a drug's actual delivery. However, for devices and procedures there is no question as to whether the care will actually be delivered once the decision is made in the appropriate patient, thus making it all the more important to find a study population that can be successfully managed with either technique. In situations like this the best course of action may be a prospective, adjudicated, and consecutive registry in which pockets of differing treatment strategies around the country may eventually lead to the collection of worthwhile comparative data.

I leave the reader with one final thought. If you take these 10-year results at face value (and I am certainly not suggesting that you do), then this would suggest that if you have your ruptured aneurysm treated with open craniotomy and clipping by arguably one of the best cerebrovascular surgeons in the country, if not the world, at a facility known for its surgical prowess, your best hope at 10 years is that you will have the same chance of a poor outcome as someone who had their aneurysm coiled with what is now 15-year-old technology. If that is the case, then why in this day and age would anyone choose to have their aneurysm clipped?

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References

1. Haley EC Jr, Kassell NF, Apperson-Hansen C, Maile MH, Alves WM: A randomized, double-blind, vehicle-controlled trial of tirilizad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. *J Neurosurg* **86**:467–474, 1997
2. MacDonald RL: Editorial. Clip or coil? Six years of follow-up in BRAT. *J Neurosurg* **123**:605–608, 2015
3. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, et al: The Barrow Ruptured Aneurysm Trial. *J Neurosurg* **116**:135–144, 2012
4. Molyneux A, Kerr R, Birks J: Editorial. Barrow Ruptured Aneurysm Trial. *J Neurosurg* **119**:139–145, 2013
5. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet* **360**:1267–1274, 2002
6. Scott RB, Eccles F, Molyneux AJ, Kerr RS, Rothwell PM, Carpenter K: Improved cognitive outcomes with endovas-

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cular coiling of ruptured intracranial aneurysms: neuropsychological outcomes from the International Subarachnoid Aneurysm Trial (ISAT). **Stroke** **41**:1743–1747, 2010

7. Spetzler RF, McDougall CG, Zabramski JM, Albuquerque FC, Hills NK, Nakaji P, et al: Ten-year analysis of saccular aneurysms in the Barrow Ruptured Aneurysm Trial. **J Neurosurg** [epub ahead of print March 8, 2019. DOI: 10.3171/2018.8.JNS181846]

Disclosures

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