A Randomized Trial of Unruptured Brain Arteriovenous Malformations Trial
An Editorial Review

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A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) is the first randomized trial that attempts to answer the clinical question: what is the best management for an unruptured brain arteriovenous malformation (AVM). More concisely, is the natural history or is treatment the riskier management choice? Unquestionably, the investigators engaged in a difficult task. AVMs are different in each individual and so are their treatments. Therefore, any randomized trial of AVM management will pose many methodological problems and provoke criticisms from the outset and may not be able to provide definitive answers to many pivotal questions.

ARUBA separated unruptured AVMs into a medical treatment alone group (109 patients) and an interventional group subjected to open surgery, radiosurgery, endovascular intervention, or combinations (114 patients). The study followed all of these patients until primary end points, such as death or symptomatic stroke, were reached. The study was terminated prematurely at 33.3 months because the incidence of primary end points was dramatically higher in the treatment group compared with the medical management group (30.7% versus 10.1%).

The first great concern with this study is the generalization that one treatment method is equal in complexity to the other, that is, a simple either/or choice between 2 management methods. Medical management (observation) is a homogenous management delivery system with almost zero clinical variability between practitioners. Interventional therapy, however, represents several individual technologies and methods that are heterogeneous and complex. Surgery, endovascular intervention, and radiosurgery are not the same in any shape or form, and when combinations of therapy are included in the analysis, the outcomes become even more difficult to assess.

The second major concern is that brain AVMs as a group are not homogeneous. Each AVM is individually different, and any asymptomatic group, as represented in this trial, represents a spectrum of a disorder with extremely complex and varied clinical and anatomic individual characteristics including size, shape, nidus density, location, source of arterial input, and venous drainage. This variability is demonstrated in the patient selection treated in both groups. Overall, 32% were larger, exhibiting a nidus size >3 cm in maximum diameter. Approximately 47% arose in eloquent locations. As classified by the Spetzler–Martin surgical risk grading system, 29% were grade I, 39% were grade II, 28% were grade III, and 8% were grade IV.

Unfortunately, although the authors do provide subgroup analysis according to Spetzler grades, they do not provide the outcomes of each treatment groups, probably because of a too small sample size to perform these subgroup analyses. Treatment risks clearly increase with higher grades and more eloquent locations, and lumping the treatment risks of the grade I patient (which should be treated) with those of grade IV patients (which should be left untreated) given the almost identical hemorrhage rate of 2% to 3% per year identified in the study is a flawed concept.

Past clinical trials comparing medical therapy with intervention (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis [SAMMPRIS], North American Symptomatic Carotid Endarterectomy Trial [NASCET], Extracranial-Intracranial Bypass Trial [EC-IC]) all looked at a treatment modality with considerably less variation than the spectrum of treatments offered in ARUBA. Likewise, they all focused on a disease entity that was clinically and anatomically a much more precise target for meaningful analysis compared with something as heterogeneous as the brain AVMs included in this study. The lack of clear guidelines on how to treat in the treatment group creates heterogeneity in management approaches.

A third point of concern in ARUBA is the treatment selection and the variations of the end points. The goal of surgical AVM therapy is complete obliteration. We know that endovascular therapy alone does not achieve this goal in most cases and that radiosurgery requires 2 to 3 years to obliterate ≈80% of AVMs (>50% of patients had <3 years of follow-up time in ARUBA). However, in the majority of treated patients, treatment was not aiming at immediate and complete AVM obliteration, 5 patients had neurosurgical intervention only, 30 had
embolization only, and 31 had radiosurgery only. Another 20 patients were enrolled in the intervention treatment limb of the study but never received intervention. This lack of AVM obliteration for the majority of the treated group is reflected in the Kaplan–Meier estimated event rates in the treatment curve. We would expect a price to pay for a treatment directed at eliminating the AVM, that is, event rates rising immediately after treatment, but then remaining rather stable thereafter, as, for example, shown after carotid endarterectomy. Surprisingly, the opposite is found in this study, with steadily rising event rates even after treatment.1

A fourth concern is the unknown influence of feeding artery aneurysms and venous outlet obstructions. Nearly 20% of the medically treated group of patients had feeding artery aneurysms. Another unknown number supposedly had evidence of venous outlet obstruction (ie, venous aneurysms or stenosis) that most likely places the patient at greater risk of hemorrhage. The contributions of these factors were not analyzed within the management groups, probably because of the small sample size. By extension of the authors’ logic, however, is this study telling us that a patient harboring a 1- to 2-cm temporal polar AVM and a 7- to 8-mm middle cerebral feeding artery aneurysm should be treated medically? If the AVM is not treated, will not the same forces that generated the feeding artery aneurysm still be present to allow further aneurysm enlargement or generate more aneurysms over time? In a 30-year-old patient, those aneurysm risks could extend over a 50+-year interval (assuming an 80-year life expectancy) and pose a substantial risk in addition to the threat of the AVM’s natural history itself.

A fifth problem is the short follow-up period. Certain brain AVMs will predictably be more likely to develop a treatment-related deficit.6 Those lesions in eloquent areas (47% of patients) are obviously more likely to experience at least a transient neurological deficit after intervention in that area. It may take months or even several years for any intervention-related deficits to resolve. It will likely take years for the natural history of the untreated lesion to catch up to the intervention risks. Certainly, 33 months is not a sufficient interval for observation to pick up an almost certain crossover of risks, assuming that the AVM was completely cured with the intervention. Although a longer follow-up period was planned, the study was unfortunately stopped. Hopefully, long-term follow-up will probably be performed by most centers, although National Institutes of Health/National Institute of Neurological Disorders and Stroke will not fund this follow-up.

Despite our criticisms, the ARUBA investigators are to be commended for their efforts. Their study contributes important results of the natural history of brain AVMs. The prospectively collected data of the natural course of medical management of AVMs confirm previous natural history studies and tell the reader that an AVM carries a substantial risk of rupture.6 A 10.1% risk within <3 years is on the high end of previous estimates and obviously can add up to a large number over time because of their congenital nature and lifelong presence.

What is generally known is that at least some risks of an AVM will persist as long as the AVM remains in place. Therefore, ARUBA can be considered as a wake-up call that the untreated risks of a cranial AVM is high, and they remain so (or even increase) if the lesion is not treated to cure. This study is also an indication of the need to find out the optimal treatment approach to achieving cure. This process begins with the diagnostic workup that might include functional imaging of eloquent areas and selection of the optimal treatment (or combinations) that will lead to cure. ARUBA is not the end of research in brain AVMs; it is just the end of the beginning of new research into their management.

Disclosures
None.

References

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