The Case:  
A 25-year-old woman presents with right-sided headaches. Brain MRI reveals a superficial 4-cm right parietal arteriovenous malformation without evidence of previous hemorrhage (Spetzler–Martin grade 3).

The Questions:  
(1) Should she be referred for neurosurgery or endovascular treatment?  
(2) Is endovascular treatment superior to medical treatment in this patient?  

The Controversy:  
ARE THE RESULTS OF A RANDOMIZED TRIAL OF UNRUPTURED BRAIN ARTERIOVENOUS MALFORMATIONS (ARUBA) TRIAL APPLICABLE TO ALL ARTERIOVENOUS MALFORMATION PATIENTS?

ARUBA Results Are Not Applicable to All Patients With Arteriovenous Malformation

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For brain arteriovenous malformations (AVMs), rupture represents the primary concern. Both prospective and retrospective observational studies have helped to define the natural history of AVMs and highlight potential risk factors. Estimates for bleeding from unruptured AVMs range from 1.3% to 4% per year with mortality of 10% to 30% from incident hemorrhage and neurological disability of 20% to 30%. Angioarchitectural features (eg, intranidal aneurysms, exclusive deep drainage, and restricted venous outflow), lesional features (eg, small size and deep location), and patient-specific features (eg, age, seizure history, and pregnancy) have all been described as affecting the rupture risk.

The efficacy and risk of treatment vary based on the modality used (surgical, endovascular, or radiosurgical) and AVM specific location and features. For surgical treatment, the most robust risk stratification is based on the Spetzler–Martin classification that considers size, eloquence, and venous drainage in a 5-point scale, which predicts 95% to 100% excellent outcome for grade 1 to 2 AVMs and 50% to 73% for grade 4 to 5 AVMs. Consequently, the former are typically considered favorable for surgical intervention and the latter, high risk. This places grade 3 AVMs in the gray zone, whereby additional stratification focused on each of the elements of the grading system reveals variability in risk, which can range from 3% to 15% dependent on specific features. Parallel, but modality-specific, classification systems predicting treatment risk after radiosurgery and endovascular embolization have also been developed. In addition, the treatment options vary in regards to expected timeframe to eradication, ranging from immediate durable cure with surgery to delayed obliteration >2 to 3 years with radiosurgery. Any treatment offered must be individualized to the specific AVM, and similarly, the choice of modality may substantially alter the outcome.

Given the unique features of any given AVM, which may dictate prognosis and treatment outcome, the patient in question should certainly be referred to a specialist for evaluation of treatment options. With a life expectancy of ≈60 years, her lesion conservatively carries a lifetime rupture risk of 70%. If she becomes pregnant, recent data additionally indicates an 8-fold risk of puerperal hemorrhage. Based on the grade 3 designation, this 4-cm AVM may either have deep drainage or reside in eloquent territory; dependent on those specific features, choice of treatment modality can be tailored to achieve an expected >90% favorable outcome. Weighing these options, treatment becomes the clearly superior strategy, and although any risk is borne up front, her aggregate morbidity and mortality strongly favor intervention.

Does A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) help us in decision making for this, or all, patients with AVM? Unfortunately, no. ARUBA compared interventions (using any treatment modality alone or in combination) with medical management in a heterogenous group of unruptured AVMs. The trial was halted after enrollment of 223 patients over 7 years. Of the recruited cohort, >10% were grade 4 and >25% were grade 3 AVMs, namely those known to carry higher risks with treatment. The trial’s
stoppage was related to higher rates of the primary outcome (death and stroke) in the intervention arm (29% versus 10%), over 33-month mean follow-up. This short-term result is hardly surprising in the face of the known immediacy of risk with intervention as opposed to the risk with expectant management borne out for many years. Furthermore, the study’s high rates of embolization as solo treatment (32%), with its known low success rate in AVM eradication, versus immediately curative surgery alone (5%), despite two-thirds of patients harboring surgically favorable grade 1 and 2 AVMs, does not reflect standard practice in the United States. The heterogeneous mix of lesions, including higher risk AVMs, and the different treatment modalities used create variability in outcomes, which would be inappropriate to generalize to a given patient with a given lesion and a given treatment. As noted above, the specific features of an individual AVM and the specific treatment type will result in their own particular risk profile, difficult to extrapolate from aggregate data. Although attempts to analyze the AVMs in subgroups will surely be attempted, pitfalls of such post hoc analyses are well known.

Furthermore, that a study is randomized does not inherently immunize it to the effects of bias, particularly pre-enrollment selection bias. Clinical equipoise is a necessary element in ensuring unbiased enrollment of patients into trials. Although ARUBA investigators thought that all treatable unruptured AVMs meet this criteria, they failed to capture the attitudes of the clinical community accurately, and the heterogeneity of the disease, as evidenced by the poor relative participation of US centers, a primary objection being concerns for lack of equipoise and resultant selective enrollment. In acknowledgment of this concern, the investigators planned a parallel registry, but the inability to realize this component sheds much doubt over the generalizability of the trial results.

Ultimately, ARUBA cannot address if patients with unruptured AVMs should be treated because the study has failed to establish a reasonable prospect of external validity; in addition, ARUBA provides little insight into which patient should be treated or which treatment is superior given the heterogeneity of AVMs and treatment modalities in the small study cohort with limited follow-up. Thus, misinterpretation of ARUBA as a justification for universal denial of referral or treatment to all patients with unruptured AVMs would be, at best, irresponsible.

Disclosures

None.

References


Key Words: arteriovenous malformation ■ radiotherapy ■ surgery ■ therapeutic embolization
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The version of the article, “ARUBA Results Are Not Applicable to All Patients With Arteriovenous Malformation” by Amin-Hanjani that published ahead-of-print on March 11, 2014, and appears in the May issue (Stroke. 2014;45:1539–1540) had several errors.

In the second paragraph, it should read, “Consequently, the former are typically considered favorable for surgical intervention, and the latter, high risk.” In the third paragraph, it should state, “Based on the grade 3 designation, this 4-cm AVM may either have deep drainage or reside in eloquent territory; dependent on these specific features, choice of treatment modality can be tailored to achieve an expected $>90\%$ favorable outcome.” Finally, the last sentence of the article should read, “Thus, misinterpretation of ARUBA as a justification for universal denial of referral or treatment to all patients with unruptured AVMs would be, at best, irresponsible.” The publisher regrets the error.

This has been corrected in the online and print version of the article.