Unruptured Brain Arteriovenous Malformations
Keep Calm or Dance in a Minefield
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Although there is general consensus favoring interventional treatment of ruptured brain arteriovenous malformation (bAVMs) to reduce the risk of rebleeding, the management of unruptured bAVMs is less clear. Recent natural history studies indicate that the annual risk of intracerebral hemorrhage for patients with unruptured bAVMs is low (1%–2%), but the cumulative risk increases during the patient’s lifetime. However, the rate of short-term complications of intervention seems greater than initially thought. Therefore, preventive eradication of unruptured bAVMs has been a matter of extensive and sometimes visceral debates in the past decade. The essence of the debate is whether one should keep calm and await the bAVM explosion before intervention or dance in a minefield using different bomb deactivation strategies.

A Randomised Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) trial was designed to test whether preventive lesion eradication, using any interventional treatment modality alone or in combination, offers a clinical benefit compared with medical management for patients with unruptured bAVMs. The acronym ARUBA, a reminder of the calm and peaceful Caribbean island, could not be more premonitory of the final results. The trial was prematurely stopped because of the clear superiority of medical management compared with interventional therapy. The risk of death or stroke was increased 3-fold in the interventional group. Although death or stroke was increased 3-fold in the interventional group compared with the medical management group after a mean follow-up of 33 months. Despite announcing a clear winner, the ARUBA trial results ignited more controversy and left several open questions unanswered.

Dr Amin-Hanjani argues that our patient would clearly benefit from intervention. Given the patient’s long life expectancy, her bAVM carries an extremely high lifetime rupture risk and could be aggravated further in case of an eventual pregnancy. She considers that any treatment offered must be individualized to the specific bAVM features, and that the choice of interventional modality may markedly alter the outcome, it is just a matter of picking the right carrot with the right tool. She predicts an excellent outcome after intervention, based not only on the Spetzler–Martin grading score but also on additional patient and bAVM characteristics, and ignores ARUBA warnings. Dr Amin-Hanjani is willing to pick nice carrots even in a minefield. In contrast, Dr Mohr thinks that medical management would be the best treatment for our patient based on ARUBA’s results. He prefers to avoid any potentially devastating explosions in the minefield and to pick his carrots at the Save Mart supermarket. Although these differences in opinion between Dr Mohr (a Neurologist) and Dr Amin-Hanjani (a Neurosurgeon) may be partly related to their specialties and what they perceive as minefields, each provides a partly valid argument to support his/her opinion.

Are the results of ARUBA trial applicable to all bAVM patients? In ARUBA, like in other interventional stroke prevention trials, there was a big gap between screened (n=1740) and enrolled (n=226) patients suggesting selection bias. In fact, ≤20% of all eligible patients were not randomized and received interventional therapy outside the trial in ARUBA centers, and no follow-up data are available for any of these patients. The lack of treatment equipoise for some patients and the absence of a parallel prospective registry may have potentially led to a reverse cherry-picking avoiding randomization of those bAVM patients with perceived low risk of intervention. This may explain, along with potential referral and reimbursement bias, the relative low recruitment and participation of potentially high-volume US centers. However, the majority (62%) of those randomized to ARUBA had smaller size and more superficial bAVM thought most favorable for attempted eradication, which favors in any case the interventional group. In contrast, clinical presentation with focal neurological deficit was twice more frequent in the interventional group. Although death or strokes were similarly distributed across the entire range of scores in the Spetzler–Martin grading score, the complexity of the disease process and variations in treatment options make it difficult to stratify the risk of postintervention complications based solely on the Spetzler–Martin grading score. Spetzler–Martin grading score was developed to stratify the surgical risk of bAVM, but this scale has not been validated fully to...
assess the risk of other interventional modalities, including endovascular embolization or radiosurgery. Unfortunately, the early termination of ARUBA precludes any secondary analysis of predictors of bleeding and treatment risk; and the sample size does not provide adequate power to assess the outcome by interventional treatment modality.

Despite its limitations, ARUBA sounds a loud alarm. Its results are in line with previous natural history and population-based studies that suggested a low spontaneous bAVM rupture rate and an increased risk of stroke for unruptured bAVM patients undergoing an intervention. Randomization in ARUBA was prematurely halted because of the superiority of the medical group not only on the primary event rate but also on functional outcome at 30 months. This relative short-term follow-up raises the question of whether the expected higher proportion of stroke and death in the interventional arm could be balanced by long-term increase in the rates of spontaneous bleedings in the medical management arm. This is the cornerstone to the decision making in our 25-year-old patient. Currently, ARUBA is continuing its observational phase to see whether these disparities in event rates and functional status will persist during the next 5 years. Until then, if you find an unruptured bAVM… you may want to keep calm and don’t touch it!

Disclosures
None.

References


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