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## Will A Randomized Trial of Unruptured Brain Arteriovenous Malformations Change Our Clinical Practice?

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when an aneurysm is completely occluded, it is not necessary to try to force another (“last”) coil in, with subsequent risk of the need for retrieval.

With these technical precautions, unraveling of a coil during withdrawal will be rare. We believe that the drawback of possible coil stretching and unraveling in standard coils without stretch resistance is only a minor clinical issue that is outweighed by the shortcomings of the SR filament in terms of handling, safety, and obtained packing attenuation.

Standard coils are hardly available on the market any more. We plead for a renewed appreciation of the better physical properties of standard coils without SR filaments, so that operators can choose between standard or SR coils in every coil type.

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## EDITORIAL

# Will A Randomized Trial of Unruptured Brain Arteriovenous Malformations Change Our Clinical Practice?

L. Pierot, J. Fiehler, C. Cognard, M. Söderman, and L. Spelle

**A** Randomized Trial of Unruptured Brain Arteriovenous malformations (ARUBA) was stopped on April 15, 2013, because of the superiority of the medical management group.<sup>1</sup> We congratulate the ARUBA investigators for designing this trial and being able to include 223 patients.

The ARUBA study was designed to determine whether medical management is superior or noninferior to interventional therapy for the prevention of the composite outcome of death from any cause or symptomatic stroke in the management of unruptured brain arteriovenous malformations (bAVMs), and whether it decreases the risk of death or clinical impairment (modified Rankin Scale score of  $\geq 2$ ) at 5-year postrandomization. The evaluation of the interventional treatment efficacy for bAVM was not an aim of the study.

The primary end point (death or symptomatic stroke) was reached in 10% of patients in the medical management group and in 31% in the interventional therapy group (hazard ratio, 0.27). Unfortunately, the causes of death (AVM-related or not) were not given. “Stroke” was defined as “a clinically symptomatic event (any new focal neurologic deficit, seizure, or new-onset headache)

that was associated with imaging findings of hemorrhage or ischemia.”<sup>1</sup> Unfortunately, the respective percentage of patients with new focal neurologic deficit, seizure, or new-onset-headache was not given. Imaging findings were also not precisely described, and the respective number of patients with subarachnoid hemorrhage, intraventricular hemorrhage, and parenchymal hematoma was not given. Ischemic lesions were also not described. Due to the absence of these data, a precise analysis of the primary end point is nearly impossible. Additionally, it is also not possible to correlate the primary end point with the 36-month risk of death and neurologic disability because no specific information was provided. In the limited number of patients (87) with 36 months’ follow-up, the risk of death and neurologic disability (modified Rankin Scale score of  $\geq 2$ ) was significantly lower for the medical management (14%) compared with the interventional therapy (39%) group.

Brain AVMs represent a very heterogeneous group with regard to clinical presentation (hemorrhage, seizures, headache, focal neurologic deficit), anatomic characteristics (feeding arteries, nidus, draining veins), and modalities of treatment (surgery, radiation therapy, embolization, or combination of modalities).<sup>2–4</sup> For unruptured bAVMs, the strategy of treatment is a matter of debate because the balance between therapeutic risks and the risk of natural history is difficult to determine and is dependent on several factors, including the ones mentioned above.<sup>2,5</sup>

In certain bAVM subgroups with specific anatomic characteristics (ie, deep location or deep venous drainage), the risk of bleeding is higher, thus requiring specific treatment strategies or modalities. However, the clinical outcomes even within a subgroup of patients will vary depending on the treatment strategies used because strategy differs as to the mode of action and complication type and rate.

Indeed, one shortcoming of the study design was inclusion of a heterogeneous population of AVM types and their treatment options. The AVM population included 62% of AVMs smaller than 30 mm; diverse Spetzler-Martin-grade AVMs, including 29% grade 1, 32% grade 2, 28% grade 3, and 10% grade 4; associated aneurysms in 16%; and any deep venous drainage in 33% of cases. Furthermore, the treatment modalities were quite heterogeneous: neurosurgery alone (5%); embolization alone (32%); radiation therapy alone (33%); embolization and neurosurgery (12%); embolization and radiation therapy (16%); and, finally, embolization, neurosurgery, and radiation therapy combined (1%). No details were given regarding the precise modalities of treatment (glue or Onyx [Covidien, Irvine, California] for embolization; gamma knife or linear accelerator for radiation therapy). By study design and due to the relatively small population included in the trial before stopping, subgroup analyses will not be conducted.

Therefore, the ARUBA trial data suggest that in a very heterogeneous population of patients with AVM with a mix of different therapeutic approaches, there is a higher short-term risk of death or stroke. However, the generalizability of ARUBA results is quite debatable.

Thirty-nine active centers recruited 226 patients during 6 years, with an average rate of inclusion of 1 patient/center/year. Among the 39 active sites, 7 (18%) included  $>10$  patients; 7

(18%) included 5–10 patients; and 25 (64%) included <5 patients during the study period. Site selection was based on center experience, with management of at least 10 bAVMs per year. Given that some bAVMs treated in the centers would be ruptured, it is clear that not all unruptured AVMs were included in ARUBA. This assumption is confirmed by the fact that for 177 patients (78% of the total randomized), clinicians selected the treatment outside the randomization process. Finally, the proportion of randomized cases (226) versus screened patients (1740) was quite low (13%), and the specific reasons (and numbers) for noneligibility were not given. The data presented above certainly question the representativeness of the population included in the study.

Data from this study will also impact the physician-patient conversation and patient management. The treating physician will have to report that if untreated, the spontaneous AVM rupture rate is 2.2% per year (in ARUBA) and that the risk progressively increases with time (it is certainly useful to evaluate the risk of bleeding at 10, 20, 30 years, and later). This rate is similar to that previously reported in the literature.<sup>2,5</sup> They will also have to share the result that when patients with brain AVMs are evaluated as a whole group and with varying treatment modalities, the short-term risk of death and stroke is higher with interventional management than with medical management. Additionally, the physician will have to explain the definition of “stroke” in the ARUBA trial “as any new focal neurologic deficit, seizure, or new-onset headache associated with imaging findings of hemorrhage or infarction.”<sup>1</sup> He or she will also have to explain that the respective percentages of different clinical conditions (headache, seizure, new focal neurologic deficit) are unknown. While some patients might consider a few episodes of seizures or headache an acceptable price for having the AVM cured and suppressing the risk of bleeding, others may be reluctant. Patients should know the rate of death or persistent deficit following either treatment strategy, but this information cannot be gathered from the data presented from the ARUBA study.

Additionally, when a patient seeks information about potential outcomes on the basis of their age, clinical condition, and AVM anatomy, physicians will not be able to give any guidance because a detailed analysis of these variables is not available and will not be conducted. Physicians will also have to explain that the mean follow-up in ARUBA was only 33.3 months, though the goal of any interventional treatment is to prevent the risk of AVM rupture and bleeding for a lifetime.

How should physicians use ARUBA results to make management decision in patients with unruptured brain AVMs? Should they immediately stop any interventional treatment for all patients with unruptured bAVMs? This is certainly not reasonable because the study data are from a heterogeneous pool of patients treated with differing treatment modalities, insufficient precision and analysis of the data, and very limited follow-up. In fact, 5-year follow-up may also be insufficient to evaluate the benefit and role of the interventional therapy option in a life-long threatening condition. The heterogeneity of patients included in the study will unfortunately limit the use of these data in the management (in-

terventional treatment or not) of patients with AVMs because the natural history risk/ therapeutic risk was not evaluated in patients or AVM subgroups (or AVM subgroups). Although it may be easy to decide the medical treatment strategy in a 70-year-old man with a lobar 5-cm AVM with superficial venous drainage and no associated aneurysm, these data do not help identify the best strategy for a 25-year-old women traveling all over the world and having a deep-located AVM measuring 2-cm with deep venous drainage and an intranidal aneurysm. Additionally, due to the heterogeneity of treatment methods used, ARUBA will also not be helpful in selecting the best strategy if interventional treatment is indicated. Therefore, physicians will have to continue to reinforce their careful decision-making process on the basis of multidisciplinary discussions and a precise analysis of the clinical situation and AVM characteristics.

Finally, ARUBA demonstrates that interventional treatment of brain AVMs is associated with clinical risks that will occur immediately or closely after the treatment and that these risks are higher than those related to the natural history, at least in the following 33 months. We are looking forward to information about the clinical status of the patients 20 or 30 years after medical or interventional treatment. Unfortunately, follow-up of the ARUBA patients is foreseen for only 5 years. Because subgroup analysis related to AVM anatomy or therapeutic modalities will not be conducted in ARUBA, further studies will certainly be useful to determine whether ARUBA results are applicable to all patients with unruptured AVMs, regardless of their age and clinical status, the anatomic characteristics of the lesion, and the modalities of treatment used.

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