lished outcome predictors, and technical expertise developed at a high-volume AVM center.

These critiques beg for another trial to re-establish the role of surgery in AVM management, this time conducted and embraced by the neurosurgical community: *Beyond ARUBA: Randomized Low-Grade Brain AVM study*, Observation versus Surgery (BARBADOS). Effort is ongoing to organize, fund, and initiate it. There is now urgency among neurosurgeons to respond to ARUBA, which we expect to increase acceptance of such a trial. In the meantime, the management of ruptured AVMs should remain unaffected by ARUBA and surgery should be regarded as the first-line or criterion standard therapy for most low-grade AVMs, with conservative embolization as a preoperative adjunct. High surgical cure rates and excellent functional outcomes in patients with both ruptured and unruptured AVMs support a dominant surgical posture, with radiosurgery reserved for risky AVMs in deep, inaccessible, and highly eloquent locations.

REFERENCES

1. Spetzler RF, Martin NA. **A proposed grading system for arteriovenous malformations.** *J Neurosurg* 1986;65:476–83
2. Lawton MT, Kim H, McCulloch CE, et al. **A supplementary grading scale for selecting patients with brain arteriovenous malformations for surgery.** *Neurosurgery* 2010;66:702–13; discussion 713
3. Lawton MT. *Seven AVMs: Tenets and Techniques for Resection.* New York: Thieme Medical Publishers; 2014
4. Mohr JP, Parides MK, Stapf C, et al. **Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial.** *Lancet* 2014;383:614–21
5. Potts MB, Lau D, Abula AA, et al; UCSF Brain AVM Study Project. **Current surgical results with low-grade brain arteriovenous malformations.** *J Neurosurg* 2015 Feb 6. [Epub ahead of print]
6. Rutledge WC, Abula AA, Nelson J, et al. **Treatment and outcomes of ARUBA-eligible patients with unruptured brain arteriovenous malformations at a single institution.** *Neurosurg Focus* 2014;37:E8

EDITORIAL

A Randomized Trial of Unruptured Brain Arteriovenous Malformations Study: What Impact on Clinical Care and Therapeutic Decision?

C. Cognard

One hundred nine patients presenting with an unruptured AVM have been recruited in A Randomized Trial of Unruptured Brain Arteriovenous Malformations (ARUBA) in the no-treatment arm and have been followed up for 33.7 months (306.1 patient years).¹ Eight hemorrhages (2.6% annual bleed rate) and 4 ischemic strokes (1.3%) occurred, bringing the annual stroke risk to 3.9%. ARUBA confirmed what we already knew—that is, leaving an AVM untreated brings a high lifetime stroke risk.

According to the New York Islands AVM Study,^{2,3} there are 3 identified factors associated with an increased risk of rupture of an AVM (previous rupture, deep venous drainage, deep location), leading to a reported annual risk from 0.9% to 32%. Some other factors such as arterial/nidal aneurysms and venous stenosis or dilations are considered to increase the annual risk of bleeding, even if there are no good estimates of their respective impacts.

Interventional treatments have been developed in the past decades to select patients presenting with an unruptured AVM; but in the absence of exhaustive data on the comparative risks of treatment/no treatment, the decision to offer treatment or observation lies entirely on the individual center and physician running the risk of intervention or rather the risk of rupture without treatment. Even more contingency-dependent, a patient with an unruptured AVM is offered the option of surgery, endovascular embolization, radiosurgery, or a combination of these 3 options, depending on the level of skill, experience, or mere availability of a trained operator.

Despite a plethora of single-center or multicenter reports in the literature, the methodology is rather weak and nothing could support the drafting of guidelines for this very difficult therapeutic decision.

The only piece of evidence useful to this purpose is a randomized controlled trial comparing the different options, ideally featuring a large number of patients, a long follow-up, a precise clinical end point, and an analysis of the influence of the risk factors of natural history and different treatments.

The objective of such a trial would be to define the option with the longest deficit-free survival stratified for AVM characteristics.

Randomized controlled trials (RCTs) are particularly adapted to homogeneous diseases. As an example, coronary stenosis is ideal for randomization: The disease appears homogeneous for the sake of screening, the study sample is very large, and the time of observation is short, with an expected outcome at short term. The interventional procedure is well-established and standardized across centers.

Brain AVMs are not ideal subjects for RCTs. The disease is rare and extremely heterogeneous (age, AVM size, location, eloquence, depth, architecture, and flow dynamics, just to mention a few variables), and therapeutic options can vary among centers and among physicians in the same centers on the basis of their experience and their level of technology expertise.

Designing an RCT that could compare multiple treatment options in such a heterogeneous disease is definitely a challenge, one that ARUBA could not handle but that we still need to take.

To give a patient the highest chance of deficit-free survival, the operator should be able to do the following:

- 1) Identify factors of increased bleeding risk
- 2) Identify factors of the increased interventional treatment risk
- 3) Compare the risk of death and handicap in the long term of an untreated AVM with the risk of performing an intervention (also evaluating the option of complete or incomplete occlusion of the AVM).

To answer these questions, we have 2 options: either running an RCT that looks at a limited study population (eg, no treatment versus surgery in superficial small AVMs in a noneloquent area or no treatment versus radiosurgery in deeply located deep venous

drainage AVMs), or alternatively, we need to design an RCT with a large volume of patients with long-term follow-up that would allow a strong subgroup analysis to try to determine which patients should or should not be treated and how.

Why ARUBA Is Not the RCT We Need

ARUBA starts from the hypothesis that no treatment is better than any interventional treatment for unruptured brain AVMs. The success of ARUBA was meant to show that interventions should not be performed.⁴

The original design approved by the National Institutes of Health/National Institute of Neurological Disorders and Stroke planned randomization of 800 patients during a 30-month period, with a statistical power analysis based on an expected 5-year event rate of 12% in the no-treatment group and 22% in the interventional therapy group. There was an intention-to-treat analysis, and 2 interim analyses were planned.

Due to slow randomization, the recruitment period was extended to 60 months and the targeted study population was reduced to 400 participants. Enrollment was halted after the second preplanned interim analysis, when data for 223 patients were available and the predetermined threshold for safety/efficacy was met, as reviewed by the independent Data and Safety Monitoring Board of the trial.

Primary End Point

The primary end point of the trial was time to a composite event of death or stroke, defined as “any new focal neurologic deficit, seizure, or new-onset headache associated with imaging findings.”¹

It is difficult to understand why time to this composite end point was selected. It is very unusual to consider a new-onset headache associated with minimal bleed on MR imaging that does not carry any permanent morbidity as a stroke. That complications of interventions occur early in the observed period while complications of the natural evolution of the untreated disease occur in the long term is also fairly normal. With this design, not surprisingly, the primary end point was reached by 11 (10.1%) patients in the no-treatment arm versus 35 (30.7%) in the interventional arm.

The primary end point should have been the mRS score at last follow-up, a criterion that is used in all stroke trials and that actually reflects, in a simple way, the clinical status of the patient.

The secondary end point was risk of death and neurologic disability, with an mRS score of ≥ 2 . At 36 months, this secondary end point was 6/43 patients (14%) in the no-treatment versus 17/44 (38.6%) in the treatment arm. Most interesting, the difference in the number of deaths between the 2 groups was not statistically significant, with 3 in the interventional arm and 2 in the medical management arm. A 38.6% severe (death and neurologic disability with mRS score of ≥ 2) complication rate is very high compared with that published in the literature for surgery of small unruptured AVMs in a noneloquent territory or for radiosurgery in small AVMs. No analysis is available on the factors associated with these complications (a technique in particular or a specific AVM profile?).

Duration of Follow-Up

In fact, for a patient presenting with a lifetime risk of stroke, the main question is which strategy will give him or her the better life in the long term?

In ARUBA, the design of the study was to obtain the last follow-up clinical data at 5 years. The mean follow-up was 33.3 months at the intermediate preplanned analysis when the study was stopped. Such a protocol is aimed at comparing a preventive interventional treatment that is supposed to cure the AVM and eliminate the risk of bleed but induces a treatment risk with a nontreatment strategy not producing any therapeutic risk but leaving a lifetime risk of bleed. In the treatment group, death and neurologic disability happens immediately at the time of treatment. In the nontreatment group, it happens progressively due to AVM bleed in the follow-up. The real question is when will the 2 curves of death and neurologic disability cross? It was obvious before ARUBA that a long follow-up was needed to show the potential benefits of the treatment. The shorter the follow-up, the higher is the risk of the procedure and the lower is the risk of the disease and the benefit of the intervention. A 10-year follow-up was mandatory in ARUBA as it was used in the Trial on Endovascular Aneurysm Management study⁵ and a shorter one would bias the results toward the benefit of no treatment. It is even more amazing to analyze the results of radiosurgery after 36 months, the time required for radiosurgery to cure the AVM. Then only complications of radiosurgery are evaluated, not the benefit of it.

Methodology

From April 4, 2007, to April 15, 2013, 1740 patients were screened for eligibility, and finally, 223 were randomized. Indeed, 1514 patients were not randomized because 1014 of them were ineligible for enrollment due to evidence of previous hemorrhage or a history of previous treatment. In the other 500 patients deemed eligible, 323 refused to participate in the trial, and 177 patients were treated outside the randomization process. Finally, 226 patients were randomized, but 3 were excluded because randomization occurred after database lock, 109 were randomized to no treatment, 114 were randomized to intervention, and only 91 finally received an interventional therapy (neurosurgery alone, 5; embolization alone, 30; radiosurgery alone, 31; embolization and surgery, 12; embolization and radiosurgery, 15; embolization, surgery, and radiosurgery, 1). The number of patients in all the different types of interventions is then extremely small, and indeed ARUBA could not explain the potential benefit of one type of intervention in 1 selected patient. For sure, the risk is that the results of ARUBA will lead to the conclusion that abstinence is better than any interventions. This conclusion cannot be derived from ARUBA due to the very limited number of patients in every treatment type. How could it be possible to conclude that surgery should not be performed in unruptured AVMs after the inclusion of 5 patients or that radiosurgery should not be performed after inclusion of 31?

Centers and Operators

Of the proposed 104 centers, only one-third participated (39 centers). Of these 39 centers, 10 centers included only 1 patient each,

questioning their qualification as high-volume centers, one of the initial criteria to participate to the study ("center experience with management of at least 10 brain AVMs per year").¹ Nevertheless, during a time when each center managed at least 60 patients, 10 centers (25% of total) included only 1 patient each or 1.7% of all their patients with AVMs. Furthermore, 22 centers (56% of total) included only $\leq 5\%$ of all their patients with AVMs seen during the study period. Recruitment looks biased; we do know the reason for excluding many patients from randomization, with 323 refusing to participate and 177 patients being treated outside the study, leaving only 114 subjects in the intervention arm and 91 finally treated.

The idea of equipoise on which the decision to randomize relies is a difficult one: We do not randomize patients whose disease seems (to us) to have a low risk of intervention and a high natural risk. We randomize patients in whom treatment is difficult (risky) as well as those having a long-term natural risk, but then we only observe the short-term results. Those are biases that undermine the validity of the conclusions.

When one conducts an RCT on AVMs, every patient presenting with a brain AVM should be randomized consecutively and none treated outside. As in the most recent MR CLEAN trial (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands), comparing intravenous with intravenous and intra-arterial mechanical thrombectomy for acute stroke, institutions performing thrombectomies were not reimbursed for patients treated outside the trial.⁶ Some raw data show that in 44 months, 502 patients underwent randomization in 16 Dutch centers and almost all treated patients were randomized.

Impact of ARUBA on Patient Clinical Care and Therapeutic Decisions

If we follow the conclusions of ARUBA (no treatment is better than any interventional treatment for unruptured brain AVMs), at long-term follow-up, we will be faced with consequences of no treatment, consequences that are unknown and about which ARUBA does not provide an answer.

We are eliminating the option of surgery, relying on 5 patients included in the study, or of radiosurgery, which is clearly a long-term suitable treatment strategy for a life-long risky condition, moreover whose results cannot be measured in a short 36-month follow-up period.

The authors replied that the National Institutes of Health/National Institute of Neurological Disorders and Stroke does not fund trials with longer than 5 years of follow-up.

Well, we have an answer, valid for 3 years, to a problem that lasts an entire life. Like the built-in obsolescence in industrial design, we can offer our patients a solution with an expiration date, a solution that will not serve their long-term safety.

In my own center serving nearly 3 million inhabitants, people are relatively settled and we follow patients for decades. My main concern with a patient presenting an unruptured AVM is his or her condition in the next 10, 15, or 20 years, not in the next 36 months.

The results of the New York Islands AVM Study (which were at the origin of the design of ARUBA) were very useful by giving a

better knowledge of the annual risk of bleeds, depending on the presence of risk factors. On the contrary, the results of ARUBA will not give any new information that could be used in the decision process.

Why ARUBA Is Helpful

ARUBA showed the risk of unruptured AVM interventions. There are multiple reasons that encourage an operator to intervene. Many do not concern the patient and his or her disease, but the operator or his or her institution, for example, the operator and hospital financial turnover, the need for increasing center caseload for the operator and hospital reputation, partnership with industry, and even operator self-persuasion that the technique is safe and efficient. There are then definitely many patients who are treated for murky reasons and who probably have complications of a treatment that should not have been performed. The results of ARUBA should then convince the operators that they should only treat a limited number of selected patients because of these arguments.

What Is Next?

There are not many options. We still need a well-designed randomized trial, which is the best reliable level of evidence.

Minimal Requirements

A very large number of patients are needed to overcome the extreme heterogeneity of the disease (patient and AVM characteristics) and the huge variety of proposed interventions.

A very long follow-up (at least 10 years) is needed to depict the long-term morbidity/mortality of the disease and not only the treatment complication rate.

A consecutive enrollment is needed to avoid patient-selection biases.

A method to try to somehow counterbalance cultural resistances to necessary trials is to use the modified Zelen trial method, with preconsent randomized allocation to treatment groups, a method that had previously saved difficult breast cancer trials.^{7,8}

A suboptimal alternative to randomization would be a cluster study, comparing centers oriented toward no treatment or toward 1 treatment type. Such a study has the advantage of being easier to organize and might enroll a huge number of patients much more rapidly. The minimal requirement would be the independent evaluation of the primary end point (mRS score) at long term (see Safe Implementation of Treatments in Stroke-OPEN as an example, <https://sitsinternational.org/studies/open>).

REFERENCES

1. Mohr JP, Parides MK, Stapf C, et al; international ARUBA investigators. **Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre, non-blinded, randomised trial.** *Lancet* 2014;383:614–21
2. Stapf C, Mast H, Sciacca RR, et al; New York Islands AVM Study Collaborators. **The New York Islands AVM Study: design, study progress, and initial results.** *Stroke* 2003;34:e29–33
3. Stapf C, Mast H, Sciacca RR, et al. **Predictors of hemorrhage in patients with untreated brain arteriovenous malformation.** *Neurology* 2006;66:1350–55

4. Stapf C, Mohr JP, Choi JH, et al. **Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy.** *Curr Opin Neurol* 2006;19:63–68
5. Raymond J, Darsaut TE, Molyneux AJ; TEAM Collaborative Group. **A trial on unruptured intracranial aneurysms (the TEAM trial): results, lessons from a failure and the necessity for clinical care trials.** *Trials* 2011;12:64
6. Berkhemer OA, Fransen PS, Beumer D, et al; MR CLEAN Investigators. **A randomized trial of intraarterial treatment for acute ischemic stroke.** *N Engl J Med* 2015;372:11–20
7. Zelen M. **Randomised consent trials.** *Lancet* 1992;340:375
8. Taylor KM, Margoless RG, Soskolne CL. **Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer.** *N Engl J Med* 1984;310:1363–70