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Management of unruptured brain arteriovenous malformations in the post- ARUBA era

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The ideal management of arteriovenous malformations (AVMs) of the brain (BAVM) has been the subject of debate and discussion for the past several decades. The management can range from conservative therapy to interventions such as micro-surgical resection, embolization and radiosurgery. Accordingly, practitioners of different disciplines such as cerebrovascular surgery, endovascular neurosurgery and radiosurgery, have claimed the lead role in the management of BAVMs, for their specialty. The variable natural history of BAVMs (with the risk of rupture ranging from 2-4% per annum) is a contributory factor for the lack of clarity in the ideal management strategy. Biases in the management strategies adopted by different centres, result from the facilities available at an individual centre and the training and expertise of the personnel working at the centre.

There is general agreement on the management for a ruptured BAVM with all clinicians agreeing that some form of intervention is needed as the rebleed rate in these BAVMs is high. However, when it comes to the management of unruptured BAVMs (uBAVMs), the value of intervention is not so well accepted. The publication of ARUBA (A Randomized Trial of Unruptured Brain Arteriovenous Malformations) and The Scottish Intracranial Vascular Malformation Study (SIVMS) has re-ignited the debate about the relative value of conservative therapy and any form of intervention for uBAVMs. Although conservative management has always been a management option for selected group of uBAVMs, such as Spetzler-Martin (SM) grade IV and V AVMs, the above mentioned studies suggest that the value of masterly inactivity (with the philosophy of “primum non nocere”)^[1,2] may also be appropriate for patients with better grade uBAVMs (namely, SM grades I, II and III). Meling *et al*^[3] have questioned the three foundations on which the argument for intervention for an uBAVM is based: 1. An untreated uBAVM poses a considerable annual risk of bleed; 2. The morbidity and mortality associated with such bleeds is high; and, 3. The risk of treatment is minimal compared to the risks of not intervening.

ARUBA and SIVMS have forced neurosurgeons to rethink strategies which were considered to have been fairly well accepted for the management of an uBAVM. Moreover, the burden of proof now lies with neurosurgeons and interventional neuroradiologists to convince clinicians that the risks of intervention do not outweigh the risks of conservative therapy for uBAVMs.^[3]

Overview of AVM management

Historically, the rationale of surgical management of BAVMs has been based on the Spetzler- Martin classification^[4] (**Table 1**). While there have been several modifications of the SM classification, it still remains the basis for most surgical management algorithms. The advent of Gamma Knife radiosurgery (GKRS) heralded a sea-change in management strategies of BAVMs and made some types of BAVMs safer and easier to treat. Endovascular management is an important adjunct and can be used to reduce the nidus size. It plays a key role in the definitive treatment of small BAVMs with one or two feeding arteries where the entire nidus can be addressed ‘completely’. In current practice, embolization has been mainly limited to obliteration of ruptured intra/perinidal aneurysms and as an adjunct to reduce the size of the AVM prior to GKRS or make it more amenable to microsurgery,

The consensus guidelines on BAVM management guidelines prior to ARUBA study are listed in **Table 2**. While for Grades I, II, IV and V, there is a broad consensus in management strategies, the management of grade III BAVMs has been a bone of contention. It needs to be pointed out that SM grade III is a heterogeneous group. De Oliveria *et al*^[6] suggested that

Table 1. Spetzler- Martin classification^[4]

FEATURE		POINTS ASSIGNED
SIZE OF AVM	Small (<3cm)	1
	Medium (3-6cm)	2
	Large (>6cm)	3
ELOQUENCE OF ADJACENT BRAIN	Non-eloquent	0
	Eloquent	1
PATTERN OF VENOUS DRAINAGE	Superficial only	0
	Deep	1

Table 2. The consensus guidelines on AVM management prior to ARUBA (American Heart Association Science Advisory and Coordinating Committee, February 2001)^[5]

TREATMENT MODALITY	RECOMMENDATION
MICROSURGERY	<ol style="list-style-type: none"> 1. Surgical extirpation should be strongly considered as the primary mode of therapy for Spetzler-Martin grade I and II lesions. 2. For patients with small lesions, where surgery offers some increased risk based on location or the feeding vessel anatomy, radiosurgery should be strongly considered. 3. For grade III lesions, a combined modality approach with embolization followed by surgery is often feasible (see below). 4. Surgical treatment only is often not recommended for grade IV and V lesions because it confers a high risk.
ENDOVASCULAR MANAGEMENT	<ol style="list-style-type: none"> 1. Recommendations for endovascular management of AVMs can be divided into pre-surgical, pre-radiosurgical, or palliative management for focal neurological symptoms or uncontrolled seizures. 2. The decision to perform embolization of an AVM should take into consideration the Spetzler-Martin grade as well as the combined surgical and endovascular risk for a particular patient. 3. The risks of embolization must be weighed against other risks in terms of combined morbidity and mortality for surgery and/or radiosurgery. 4. Currently, all data available constitute either level III or IV evidence, because no prospective randomized trials exist concerning embolization therapy. 5. In general, Spetzler-Martin grade II or III lesions may be embolized before surgery or radiosurgery. Grade IV or V lesions should not be embolized unless this is to be done in conjunction with other treatment modalities (surgery or radiosurgery) for the goal of complete care. 6. The only exception to this may be in a patient with a grade IV or V lesion with venous outflow obstruction, in whom embolization is used to reduce arterial inflow to control edema, or in a patient with true "steal," in whom embolization is used to relieve the amount of shunt through the AVM.
RADIOSURGERY	<ol style="list-style-type: none"> 1. Radiosurgery can be considered in lesions thought to be at high risk from a surgical or endovascular standpoint. The overall efficacy of radiosurgery is higher for small lesions, and therefore, this modality may be considered as a primary treatment for smaller, as opposed to larger lesions. 2. However, size is not the only factor in the final determination of treatment. 3. The exact location, patient age, symptoms, and angiographic anatomy must be considered in this decision process. For small, surgically accessible lesions (Spetzler- Martin grade I or II), surgery has fewer risks than radiosurgery. Radiosurgery may be considered in larger lesions (Spetzler-Martin grade II through V) only if the overall goal is complete obliteration of the lesion. 4. Partial treatment of a larger lesion with radiosurgery or embolization subjects the patient to the risks of the procedure without eliminating the risk of hemorrhage.
MULTIMODALITY MANAGEMENT	<ol style="list-style-type: none"> 1. Multimodality therapy should be performed only if it is part of a total treatment plan to eradicate an AVM. 2. The goals of the different modalities should be clear at the outset. 3. Due to the variability of resources available in any one area of the country or world, some patients are offered partial treatment with a single technique. Such treatments are unjustified. 4. Although it is difficult to make generalizations about specific uses of the multimodality treatment, such treatments do appear to play a helpful role in larger lesions (Spetzler-Martin grade III or V) for which complete obliteration is the goal. 5. The hope is that with combined techniques, the overall risk of therapy will be reduced, although this is yet to be proven statistically.
PREGNANCY	<ol style="list-style-type: none"> 1. If a woman anticipates pregnancy and has a known AVM, treatment should be considered before the pregnancy. 2. If the lesion is discovered during pregnancy, a decision should be made regarding the treatment risks versus the risk of hemorrhage during the remainder of the pregnancy if the lesion is left untreated. 3. This also must include the potential risk to the fetus during intervention, whether it be by embolotherapy, surgical extirpation, or radiation, and the associated diagnostic tests. 4. In most cases, such risk-benefit analysis will not support elective treatment of AVMs during pregnancy.
PEDIATRIC	<ol style="list-style-type: none"> 1. The younger the patient, the more conclusively treatment is warranted. 2. More aggressive treatment strategies can be justified in dealing with pediatric patients, whereas only low-risk strategies should be offered to elderly patients.

SM grade III AVMS may be subdivided into A (large) and B (small and eloquent). Lawton,^[7] however, suggested 4 subgroups and this classification was later supported by Pandey *et al.*^[8]

Grade III can be subdivided as follows:^[7]

- Grade III a - a small AVM (size <3 cm, presence of deep venous drainage, eloquent location);
- Grade III b - a medium/deep AVM (size 3–6 cm, presence of deep venous drainage, non-eloquent location);
- Grade III c - a medium/eloquent AVM (size 3–6 cm, absence of deep venous drainage, eloquent location); and
- Grade III d - a large AVM (size > 6 cm, absence of deep venous drainage, non-eloquent location).

Needless to say, the complication rates for each of these sub-grades are likely to be different. Pandey *et al.*^[8] reported a surgical morbidity of 4.8% in SM Grade IIIa, 14.4% in SM Grade IIIb, 15.7% in SM Grade IIIc, and 28.6% in SM Grade IIId BAVMs. Hence, the management options for each sub-grade will vary and need to be decided on a case-by-case basis. Thus, it is inappropriate to suggest a single management strategy for all Grade III patients.

Grade IV and V BAVMs usually present in an unruptured state and there is consensus that they should be managed conservatively. Multimodality methods have failed to achieve complete obliteration^[11] and partial AVM obliteration does not improve the natural history of these lesions and may actually make it worse.^[11]

ARUBA trial

Controversies in the management of unruptured cerebral aneurysms prompted Mohr *et al* to conduct the first trial of uBAVMs, namely ARUBA. ARUBA was a prospective, multicenter, parallel design, non-blinded, randomized controlled trial, initially involving 104 clinical sites in 9 countries (<https://clinicaltrials.gov/ct2/show/NCT00389181>).^[11] The aim of the ARUBA trial was to compare two arms: medical management alone or medical management and interventional therapy (including surgery, embolization, and radiotherapy, alone or combined). The primary outcome was time to the composite event of death from any cause or symptomatic stroke, defined as any symptom associated with any imaging finding. An interim analysis performed after 6 years in 223 patients showed that the primary outcome was reached in 35 (30.7%) of the 114 patients assigned to interventional therapy and in 11 (10.1%) of the 109 patients assigned to medical management. The trial was prematurely stopped since the trial had shown an overwhelming superiority for the medical management arm. Since the publication of the results, there has been a wave of editorials and comments on the shortcomings of the trial and its results. In a nutshell, ARUBA showed that the outcome of any intervention in uBAVMs was inferior to that of conservative management when looking at outcomes at 5 years.

SIVMS study - Another nail in the coffin?

SIVMS analyzed observational data collected from Scottish residents aged 16 or older with BAVMs. SIVMS had the primary outcome as death or sustained morbidity from any cause. The authors of SIVMS concluded that at a median follow-up of 6.9 years, the rate of progression to the primary outcome was lower with conservative management during the first 4 years of follow-up (36 vs.39 events).^[12]

Critical appraisal of ARUBA

A systematic review of all the articles, which have critiqued ARUBA, revealed multiple fallacies in the methodology of the trial.^[12] A total of 10 such articles were identified and the shortcomings pointed out by them are shown in **Table 3**. Magro *et al.*^[12] made several suggestions as to how the trial could have been improved (**Table 4**). Despite all the shortcomings of ARUBA, it was still a wake-up call for neurosurgeons and interventional radiologists who seek to intervene in every case. The investigators had the daunting task of asking a difficult question, designing a complex protocol,

recruiting patients from multiple centers and obtaining long-term financial support. Add to this, the slow patient accrual and the need to deliver interpretable results made the tasks facing the ARUBA investigators extremely formidable. They have undeniably

Table 3. Critique of ARUBA^[12,13]

DESIGN	Inappropriate primary and secondary end points Heterogeneity of patients and selection criteria Lack of standardization of the treatment arm Design and primary hypothesis in favor of the medical arm	<ol style="list-style-type: none"> 1. Explanatory trials have tightened the selection criteria with controlled protocols whereas pragmatic trials mimic the real world with a broad cohort of patients and diverse treatments. 2. ARUBA being a pragmatic trial was never designed to test the outcome of a particular treatment, rather it was aimed to answer the question “does therapy work in usual circumstances?” 3. End points were too “soft”, as headache and seizures with mild blood on CT is common on post embolization or post surgery scans, and thus was reached in 30.7% cases. 4. The fundamental tenets of the study favoured the medical arm.
CONDUCT	Low enrolment Recruitment bias Premature interruption of enrolment	<ol style="list-style-type: none"> 1. There was a low rate of surgical management for Spetzler-Martin Grade I–II AVMs and a high rate of embolization or radiosurgery alone. 2. A large gap existed between the screened and selected patients. 3. A few cases were treated with surgery alone. 4. It was a difficult, costly and a slow-recruiting trial. 5. The short follow up of 5 years detected all complications but not all benefits.
ANALYSIS AND INTERPRETATION	Lack of subgroup analysis Short follow up Lack of details regarding treatment arms Inappropriate conclusions	<ol style="list-style-type: none"> 1. Since stroke with any imaging findings was considered as the outcome, any notion of “long-term” outcome was not possible. 2. Secondary outcome of impairment at 5 years was achieved only in 39% cases and that too at 36 months. 3. Since any preventive intervention can increase the risk of stroke during the interventional procedure, all analysis of outcome should have been done after a significant follow-up had been achieved, when the benefits of intervention have been realized. 4. The results of the study were published even before the treatment was completed in 73 of the 114 patients (“at the time of analysis, 53 patients randomized to the interventional therapy had ongoing treatment plans, whereas 20 had not yet initiated therapy”).

Table 4: How ARUBA could have been better designed and executed^[12,13]

STEP	ALTERATIONS
DESIGN	<ol style="list-style-type: none"> 1. The trial should have addressed a specific modality of treatment with respect to another. 2. With multiple treatment arms aggregated as one, result of each treatment arm should have been given separately. 3. Results of any treatment arm could not have been compared to each other, as they were not randomized.
CONDUCT	<ol style="list-style-type: none"> 1. To reduce bias and a low selection rate, other than constantly reminding clinicians that they should participate in ongoing trials, there are no easy solutions. 2. Integration of trials into clinical practice is the only solution to increase participation.
ANALYSIS AND INTERPRETATION	<ol style="list-style-type: none"> 1. Comparing intervention to conservative therapy was incorrect, as proving the benefit of intervention requires a long time after the intervention. 2. mRS score at 5 or 10 years would have been a better outcome measure. 3. The study should have been interrupted when one treatment was found to be superior to the other rather than when conservative management was found to be superior to intervention.

confirmed that experimenting with treatments, with unproven efficacy and outcomes, in uBAVMs is indefensible.

Critical appraisal of the SIVMS study

The shortcomings of SIVMS study are quite evident. First, it was an observational study and secondly, despite the availability of 12-year follow up data, the authors chose to analyze outcomes at 4 years. When the data was critically analyzed, it was clear that patients managed with intervention had better functional outcomes at 12 years. It seems that to achieve statistical significance, the authors chose to analyze outcomes at 4 years. In fact, after an approximately 5-year follow-up, the percentage of patients who were fully functional in the treatment arm remained steady at 40-50%, while this percentage declined steeply in the conservative arm from 40% to nearly 10%. This information was omitted from the results.

Annual risk of rupture of 4%: A false sense of security?

The first question that arises is whether or not the term 'risk of rupture' (ROR) being used is reflective of the truth. It has often been said that the annual hemorrhage rate of ruptured BAVMs is 2-4%, with the re-bleed rate during the first year increasing to 6% and then remaining more or less equal to that of uBAVMs. This is not reflected in the literature.^[13] This annual hemorrhage rate of 2-4% is a blanket number covering all grades of BAVM, both ruptured and unruptured. It may range from as low as 0.9% for patients with low grade unruptured superficially located BAVMs with superficial drainage, to as high as 34% for deep seated large volume BAVMs with deep venous drainage and intranidal aneurysms.^[1,14]

Outcomes of intervention – can one number fit all?

While the outcomes of conservative (non-intervention) therapy are hardly expected to vary across different centres, can one use a single average number to reflect the outcomes of intervention (surgery, embolization or radiosurgery), as has been done in ARUBA? It is evident that the outcomes of intervention vary from center to center depending on the expertise of the personnel performing either the surgical or endovascular intervention. The outcomes of microsurgery for uBAVMs from different centres are shown in **Table 5**.

Outcomes of SRS – prematurely reported in ARUBA

Stereotactic radiosurgery (SRS) has been shown to have a reasonably high rate of nidus obliteration along with minimal radiation side effects and risk of hemorrhage. The effects of SRS can only be seen after an extended follow-up of upto 3 years. In the interim period, these patients continue to face the same risk of hemorrhage as they did prior to treatment and may even have some complications from the radiation therapy. This probably skewed the outcome of SRS in ARUBA, as patients treated with SRS alone or SRS with embolization had a follow up period of only 33 months, causing selective reporting. While obliteration rates of SRS have always been lower than microsurgery, in expert hands, it can be considered as an alternative especially in older and unfit patients. Yen *et al*^[28] in a series of 31 cases of uBAVMs with a follow-up of 20 years have shown an overall AVM obliteration rate of 84% (n = 26 patients) on the basis of angiography (n = 19) or MRI (n = 7). The actuarial obliteration rate was 55% and 78% at 3 and 5 years, respectively. They included 4 patients in SM Grade I, 13 patients in Grade II, 12 patients in Grade III and 2 patients in Grade IV. The only factor predictive of AVM obliteration in their series was a small nidus volume. Hemorrhage occurred in 2 cases during the latency period with residual hemiparesis in 1 case. A summary of studies reporting outcomes in patients with uBAVMs after GKRS is shown in **Table 6**.

Outcomes of surgery and SRS in “ARUBA eligible” patients

After the publication of ARUBA, there have been many prospective and retrospective studies involving “ARUBA eligible patients” managed either by microsurgery or SRS.^[39] There have been 4 such studies (**Table 7**). The results of surgical series published by

Rutledge *et al*^[41] and Bervini *et al*^[40] suggest that outcomes in patients with uBAVMs are better in the surgically managed group than those obtained in the conservatively treated group from ARUBA. Similarly, well-designed studies by Yen *et al*^[36] and Pollock *et al*^[42] also report better outcomes in ARUBA eligible patients when treated with SRS than those obtained in the conservatively treated group from ARUBA.

In 2012, Guo *et al*^[43] published their interesting observations on the prevalence of silent intralesional micro-hemorrhages in BAVM and its association with both index and remote intracranial hemorrhages (ICH). This finding has highlighted the need for identifying evidence of old hemorrhages, and risk stratification especially for uBAVM. The presence of microhemorrhages within an uBAVM might confer on it the risks of a ruptured BAVM and also render conservative therapy inappropriate in that case.

Table 5. The outcomes of microsurgery in patients with uBAVMs

Authors	Number of patients	Morbidity (%)	Mortality (%)	Cure rate (%)
Spletzler and Martin, 1986 ^[4]	100	10 minor 4 major	0	NA
Heros <i>et al</i> , 1990 ^[15]	153	7.8	1.3	NA
Sundt <i>et al</i> , 1991 ^[16]	279	2.5	0	NA
Sisti <i>et al</i> , 1993 ^[17]	67	1.5	0	94
Hamilton and Spletzler, 1994 ^[18]	120	Grades I-III-0% Grade IV-21.9% Grade V-16.7%	1	100
Schaller and Schramm 1997 ^[19]	62	9.7%	0	98.4
Schaller <i>et al</i> , 1998 ^[20]	150	15.3%	0.67	NA
Pikus <i>et al</i> , 1998 ^[21]	72	8.3%	0	98.6
Hartmann <i>et al</i> , 2000 ^[22]	124	38%	NA	NA
Morgan <i>et al</i> , 2004 ^[23]	220	0.9%	0.5%	100
Davidson and Morgan <i>et al</i> , 2010 ^[24]	529	9%	2%	98.1
Lawton <i>et al</i> , 2003 ^[7]	74	3.9	3.9	97.4
Theofanis <i>et al</i> , 2010 ^[25]	264	7.2	2.6	100
Wong <i>et al</i> , 2017 (ARUBA) ^[26]	155	4.5	NA	94.2
Schramm <i>et al</i> , 2016 ^[27]	288	5.6	1.7	99

NA: Not available; uBAVMs: Unruptured brain arteriovenous malformations

Table 6. Outcomes following GKRS in patients with uBAVMs

Authors	1p7.533	Obliteration rate (%)	Hemorrhage rate (%)	Morbidity (%)	Follow up (years)
Steiner <i>et al</i> 1992 ^[29]	247	81	3.7	9	NA
Flickinger <i>et al</i> 2002 ^[30]	351	75	NA	NA	3-11
Shin <i>et al</i> 2004 ^[31]	400	87	1.9	9	5
Liscak <i>et al</i> 2007 ^[32]	330	92	2.1	11	3
Lundsford <i>et al</i> 2008 ^[33]	906	78	4	4	3
Columbo <i>et al</i> 2009 ^[34]	102	71.5	8	8	3
Starke <i>et al</i> 2013 ^[35]	1012	69	1.1	12	8
Yen <i>et al</i> 2013 ^[36]	1053	69	2.5	NA	6
Wang <i>et al</i> 2014 ^[37]	116	82	3.3	1	8
Starke <i>et al</i> 2017 ^[38]	2236	65	1.1	12	7

GKRS: Gamma knife radiosurgery; NA: Not available; uBAVMs: Unruptured brain arteriovenous malformations

Table 7. Outcomes in ARUBA eligible patients with intervention: Methodology, Results and Conclusions

Study	Methodology	Number in each group	Results	Conclusion
Bervini <i>et al</i> ^[40]	Stratified Spetzler-Ponce Class A, Class B, Class C. Each class was offered surgery (alone or with prior embolization). Sensitivity analyses were performed to predict the risk from surgery for the total ubAVM cohort by incorporating outcomes of surgical cases as well as cases excluded from surgery because of perceived risk, and assuming an adverse outcome for these excluded cases.	427 Cases: 1. Class A (n=190), all underwent microsurgery. 2. Class B (n=107), 2 cases were treated non-operatively 3. Class C (n=44), 25 cases were treated non-operatively	Rate of permanent neurological deficit with increased mRS>1 1. Class A 1.6% (all surgical) 2. Class B 14% (surgical) vs 15.6% (non-operative) 3. Class C 38.6% (surgical) vs 60.9% (non-operative)	Surgery had a better outcome when compared to non-operative management
Rutledge <i>et al</i> ^[41]	Compared treatment and outcomes of ARUBA-eligible patients during the ARUBA enrolment period of April 2007-April 2013 at University of California, San Francisco.	74 patients eligible (out of 473) 1. 61 intervention (with or without embolization): a. 70.5 % surgery b. 29.5% SRS 2. 13 observation only	After follow up in the intervention (21mos) and observation group (30 mos): 1. Stroke or death risk was 14.8% in the intervention group, compared with 7.7% in the observed group(p=0.68). 2. Number of patients with mRS>2 was 7.7% in the observation group vs 13.8% in the intervention group (p>0.99). 3. Surgery was associated with an 11.6% risk of stroke or death. 4. Complete obliteration of AVM occurred in 93 %	The ARUBA eligible cohort included a similar population to that of the ARUBA trial, but had better treatment outcomes than ARUBA. There was no significant difference in the functional outcome between the observed and treated patients.
Pollock <i>et al</i> ^[42]	ARUBA eligible patients treated with SRS	174 patients: Median lesion diameter- 27mm Volume-5.6 cm ³ SM Grade I and II - 48.9% SM Grade III - 31.6% SM Grade IV and V -19.5%)	. Follow up 64 months. . AVM obliteration rate 78.9% . Mean time to obliteration- 40m . Hemorrhage -8.6% . Focal neurological deficits- 3.5% . Mortality- 2.3%	Radiosurgery is a relatively safe modality for uBAVMs
Yen <i>et al</i> ^[36]	uBAVMs treated with Gamma Knife surgery	31 patients Median margin dose- 20 Gy. Median nidus volume- 3.2 cm ³ 4 cases- repeat GKRS	Mean follow up 78 months. 61.3% AVM obliteration. Annual hemorrhage rate of 1.7%.	GKRS achieves a reasonable outcome with low procedure-related morbidity.

uBAVM: Unruptured brain AVM; SM: Spetzler Martin; SRS: Stereotactic radiosurgery; GKRS: Gamma Knife radiosurgery; mRS: modified Rankin scale

Consensus Guidelines for ARUBA eligible patients

In 2017, European consensus conference on uBAVM treatment published the most balanced recommendations in the light of current evidence.^[44]

The salient conclusions of the conference were:

1. BAVM is a complex disease associated with a potentially severe natural history;
2. The results of a randomized trial (ARUBA) cannot be applied equally for all uBAVMs and for all treatment modalities;
3. Considering the multiple treatment modalities available, patients with uBAVMs should be evaluated by an interdisciplinary neurovascular team consisting of neurosurgeons, neurointerventionists and radiosurgeons experienced in the diagnosis and treatment of BAVM;
4. Balancing the risk of hemorrhage and the associated restrictions of everyday activities related to untreated uBAVMs against the risk of treatment, there are sufficient indications to treat uBAVMs of SM grades I and II;
5. There may be indications for treating patients with higher grades, based on a case-to-case consensus decision of the experienced team;
6. If treatment is indicated, the primary strategy should be defined by the multidisciplinary team prior to the beginning of the treatment and should aim at complete eradication of the uBAVM; and,
7. In place of a randomized control trial, a registry is a better option considering the ethical issues involved and the unsettled natural history of the disease.

Our perspective on AVM management and the future

ARUBA questioned the basis of management of uBAVMs. While the management of ruptured BAVMs has not changed significantly in the post ARUBA era, a relook at the management of uBAVMs is necessary.^[45-48] In simple terms, ARUBA has not changed the management practice in the world but has made us all aware of the need for better assessment of treatment options.^[12] Based on the volume of evidence, we believe that in the current era, uBAVMs need to be managed on a case-by-case basis. A 'one size fits all' policy is clearly undesirable. We believe that management options need to be tailored, after a thorough discussion with the patient, based on the expertise available at a particular center, as this will go a long way in providing optimal care (**Figure 1**).

The proposal to conduct another trial - BARBADOS (Beyond ARUBA – Randomized low-grade Brain AVM study: Observation versus Surgery), comparing medical surveillance

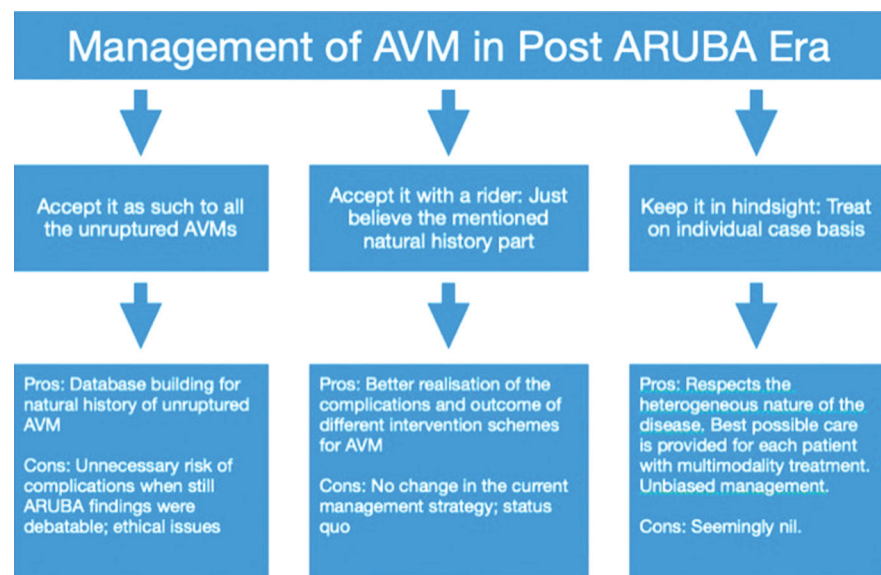


Figure 1: Options for management of uBAVMs in the post ARUBA era with possible pros and cons.

and microsurgical resection for patients with unruptured grade I or II AVMs, should also be seriously considered.^{149]} Along with an estimated sample size of 200 cases, the minimal eligibility criteria to qualify as a recruiting centre have also been proposed. It is hoped that this will ensure uniformity in the expertise with which interventions are performed for patients with uBAVMs, and hence, reduce the variability in outcomes across centres. This will go a long way in making the comparison of the interventional and the medically treated arms more evenly balanced, and possibly answer the question once and for all, regarding the relative utility of intervention in patients with uBAVMs.

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