Stroke

SPECIAL REPORT

Most Promising Approaches to Improve Brain AVM Management: ARISE I Consensus Recommendations

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ABSTRACT: Brain arteriovenous malformations (bAVMs) are complex, and rare arteriovenous shunts that present with a wide range of signs and symptoms, with intracerebral hemorrhage being the most severe. Despite prior societal position statements, there is no consensus on the management of these lesions. ARISE (Aneurysm/bAVM/cSDH Roundtable Discussion With Industry and Stroke Experts) was convened to discuss evidence-based approaches and enhance our understanding of these complex lesions. ARISE identified the need to develop scales to predict the risk of rupture of bAVMs, and the use of common data elements to perform prospective registries and clinical studies. Additionally, the group underscored the need for comprehensive patient management with specialized centers with expertise in cranial and spinal microsurgery, neurological endovascular surgery, and stereotactic radiosurgery. The collection of prospective multicenter data and gross specimens was deemed essential for improving bAVM characterization, genetic evaluation, and phenotyping. Finally, bAVMs should be managed within a multidisciplinary framework, with clinical studies and research conducted collaboratively across multiple centers, harnessing the collective expertise and centralization of resources.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: aneurysm ■ arteriovenous malformation ■ embolization ■ imaging ■ liquid embolic

Brain arteriovenous malformations (bAVMs) are vascular lesions that involve abnormal connections between dysplastic cerebral arteries and veins and are considered a rare disease by the National Institutes of Health of the United States. The incidence of bAVMs is not entirely clear due to the rarity of the condition and the existence of asymptomatic patients. The estimated prevalence of bAVMs has been calculated at 1.3 per 100 000 person-years.[1] The rate of detection for symptomatic bAVMs is estimated at 0.94 per 100 000 person-years.[2,3] However, the incidence and prevalence of bAVM are complex and might be influenced by geography and ethnicity.[4]

Collaborative research has been sparse for this uncommon condition, traditionally confined to isolated efforts. There is an evident gap in comprehensive, interinstitutional endeavors to set research agendas. The Brain Vascular Malformation Consortium, backed by the National Institute of Neurological Disorders and Stroke, was initiated to catalyze cooperation among experts. Its focus was to create cross-sectional and longitudinal patient registries for conditions like angiomas, Sturge-Weber, and hereditary hemorrhagic telangiectasia. Brain bAVMs, however, were not a primary focus in the original research roadmap of the Brain Vascular Malformation Consortium.[5] The Aneurysm, Arteriovenous Malformation,

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Nonstandard Abbreviations and Acronyms

ARISE	Aneurysm, Arteriovenous Malformation, and Chronic Subdural Hematoma Roundtable Discussion With Industry and Stroke Experts
ARUBA	The Medical Management With or Without Interventional Therapy for Unruptured Brain Arteriovenous Malformations
bAVM	brain arteriovenous malformation
CTA	computed tomography angiography
DSA	digital subtraction angiography
fMRI	functional magnetic resonance imaging
ICH	intracerebral hemorrhage
KRAS	Kirsten rat sarcoma virus
MARS	Multicenter Arteriovenous Malformation Research Study
MRI	magnetic resonance imaging
OR	odds ratio
SIVMS	Scottish Intracranial Vascular Malformation Study
SM	Spetzler-Martin
SRS	stereotactic radiosurgery
TOBAS	Treatment of Brain Arteriovenous Malformations Study
VEGF	vascular endothelial growth factor

and Chronic Subdural Hematoma Roundtable Discussion With Industry and Stroke Experts (ARISE I, 2023) met in Arlington, VA, and represents a consensus of experts in the field. The primary aim of this roundtable was to identify and address the most critical research issues pertaining to brain bAVMs. This article serves as a comprehensive compilation of the consensus recommendations that emerged from the discussion.

DETERMINATION OF SYMPTOMS

The natural history of bAVMs remains unclear. The first studies were derived from observational data. Subsequently multiple surgical series reported the percentage of patients with bAVM who presented with hemorrhage. Meta-analysis has reported an overall annual rate of hemorrhage between 1.3% and 3% for unruptured bAVMs,[6,7] and at least 6% in the first year after initial hemorrhage.[6] Although intracerebral hemorrhage (ICH) is recognized as the most severe complication associated with bAVMs,[7] the more frequent manifestations include headaches and seizures.[8] Additionally, there have been instances where patients experience progressive neurological deficits.[9]

In patients with incidental bAVMs, there is an ≈8% risk of first-time seizure within 5 years of diagnosis. A symptom that often is poorly characterized and undiagnosed is cognitive impairment resulting from flow rearrangement triggered by the shunting of arterialized blood into the venous outflow. This phenomenon can lead to the stealing of arterialized flow from eloquent cerebral regions and compartmentalization.[10] The redistribution of a high flow shunt from the arterial to the venous systems can lead to venous hypertension in downstream areas, contributing to cognitive deficits.[11] Patients with bAVMs may exhibit varying degrees of impairment in verbal and visuospatial functions.[12] Some studies suggest that the variability in neuropsychological impairment among patients with bAVM could be attributed to atypical organization of brain functions.

Imaging techniques such as positron emission tomography are instrumental in measuring local cerebral function and blood flow, providing insights into metabolic demands and oxygen consumption. This information may be used to assess the status of the brain parenchyma surrounding the bAVM, which may experience a range of effects from mass displacement, ischemia due to blood flow diversion, and venous congestion leading to swelling.[13] Anglani et al[14] have documented a case where cortical hemispheric hypometabolism improved following the treatment of the ipsilateral bAVM.

ARISE Consensus

The disturbances in blood flow caused by arteriovenous shunting away from vital brain tissue can lead to cognitive decline. To understand the adverse effects of these steal phenomena better, it is essential to perform thorough neurocognitive assessments and brain imaging to evaluate the cognitive abilities of patients with bAVMs. Currently, there is a scarcity of data on how bAVMs affect the metabolic condition of adjacent brain tissue and its relation to clinical symptoms. Specialized diagnostic methods that analyze the hemodynamic activity of bAVMs and nearby brain tissue before and after intervention could enhance the detection and characterization of steal phenomena.

IMAGING DIAGNOSIS OF bAVMS

Imaging for bAVMs fulfills several crucial goals, ranging from initial diagnosis to detecting bAVM-related bleeding, planning treatment, and follow-up. It determines angiographic characteristics predictive of hemorrhage and evaluates the suitability, progress, and potential risks associated with treatment. Several distinct imaging modalities can be employed, each offering its unique set of advantages and disadvantages.[15–29] Typically, the initial step in the assessment of bAVMs involves noninvasive cross-sectional neuroimaging using computed tomography and magnetic resonance imaging (MRI). While plain computed tomography can reveal the presence of a bAVM, it is primarily reserved for evaluating

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bAVM-related brain hemorrhage and associated complications, such as intraventricular hemorrhage, mass effect, and hydrocephalus. Computed tomography angiography (CTA) has excellent resolution, is minimally invasive, fast, and readily available.[30] Furthermore, standard CTA can provide valuable information about the angioarchitecture of the bAVM for endovascular intervention because of the possibility of multiplanar reconstruction.[27] However, it lacks temporal resolution, which is an important factor when considering the treatment of bAVMs.[27] To overcome the lack of temporal resolution, time-resolved CTA (4D-CTA) has been developed.[21] When compared with digital subtraction angiography (DSA), 4D-CTA demonstrated higher specificity and sensitivity for the detection of bAVM and dural arteriovenous fistula-related shunts; however, similar to advanced magnetic resonance angiography (MRA) techniques, the spatial and temporal resolutions of 4D-CTA are still inferior to DSA.[21]

Standard MRI sequences could precisely determine the bAVM's location and its relationship with adjacent eloquent and noneloquent parenchyma.[27] MRI also sheds light on neighboring edema or gliosis (via fluid-attenuated inversion recovery and T2-weighted sequences), thrombosis of intracranial varices (through T1 sequences), tissue atrophy, and prior hemorrhages identified by susceptibility artifacts (using susceptibility-sensitive sequences). In the study conducted by Guo et al,[31] which involved 975 patients, 6.5% of patients who presented with ICH had evidence of previous hemorrhages as detected by susceptibility-weighted imaging. Standard 3D time-of-flight MRA provides limited information in the evaluation of bAVMs, other than possibly identifying feeding pedicle aneurysms.

Advanced noninvasive imaging has been proposed for the evaluation of bAVMs. Each advanced technique may have a specific purpose and offer different benefits.[15–17,19,24–26,29] Several MR-based protocols have been described to aid in the assessment of bAVMS. These include time-resolved imaging of contrast kinetics MRA,[17] 4D radial acquisition contrast-enhanced MRA (4D rCE-MRA),[19] 4D flow MRI using constrained reconstruction (HYPRflow),[16,17] MR-tractography,[29] functional MRI (fMRI), and quantitative MRA.[15,24–26] Time-resolved imaging of contrast kinetics MRA, 4D rCE-MRA, and HYPRflow are particularly useful to characterize the anatomic features of bAVMs. As opposed to DSA, these imaging modalities are noninvasive and in the future may have the potential to provide similar information to DSA.[16,17,19] Studies have demonstrated that the use of these techniques can provide detailed information about the bAVM nidus, arterial feeders, flow-related aneurysms, characteristics of draining veins, and venous outflow restriction. Importantly, there is a strong correlation between the information provided by these techniques and that obtained from DSA.[16,17,19] On the other hand, fMRI, MR-tractography, and quantitative MRA provide information that cannot be directly obtained from DSA albeit with significant differences in spatial and temporal resolution.[15,24–26,29] MR-tractography and fMRI can potentially play a crucial role in treatment planning by providing clinically relevant information. MR-tractography and fMRI serve as valuable tools for the identification of eloquent areas situated in close proximity to bAVMs and for tracing their axonal pathways.[29] However, it is important to note that fMRI may be susceptible to distortions due to bAVM-induced hemodynamic changes, potentially leading to misinterpretations, especially in cases of high flow artifacts.[32] In contrast, navigated transcranial magnetic stimulation produces a potent magnetic field to either stimulate or inhibit underlying brain tissue, offering a reliable method for generating evoked potentials and mapping sensory and motor cortex regions.[33] Importantly, navigated transcranial magnetic stimulation is not affected by bAVM-induced hemodynamic variations, making it a more dependable choice than fMRI when assessing the presence of eloquent areas in proximity to bAVMs. Numerous studies have successfully employed navigated transcranial magnetic stimulation mapping for surgical planning, resulting in modifications to the Spetzler-Martin (SM) grading system.[34–36] Quantitative MRA provides quantitative information about blood frow through feeding arteries and draining veins. Therefore, quantitative MRA can be used to monitor both spontaneous flow-related changes and treatment response, especially following staged embolization or stereotactic radiosurgery (SRS).[15,24–26]

DSA remains currently the gold standard for the assessment of bAVMs. Its temporal and spatial resolution are unparalleled, providing detailed angioarchitectural information, including arterial feeders, draining veins, presence of flow-related and intranidal aneurysms, venous ectasia and stenosis, presence of macroshunts and fistulas.[27] The incorporation of rotational angiography with 3D reconstruction may further enhance the characterization of angiographic features that could be obscured by 2D images. More recently, 4D-DSA (time-resolved 3D-DSA) reportedly improved the visualization of nidal structures, offering the flexibility to view the nidus from any projection, angle, and contrast bolus timing.[20,22,23] Image fusion of 3D-DSA, 4D-DSA, and MRI/computed tomography has emerged as another promising imaging technique to enhance the understanding of the anatomic angioarchitectural features of the bAVM, its relationship to adjacent brain parenchyma, and other structures; thereby advancing our diagnostic capabilities (Figure 1).[18,28] Additionally, cone beam CTA is extremely valuable in delineating the target bAVM for stereotactic radiosurgery (Figure 2).[37] Although DSA is a gold standard diagnostic tool, it carries the risk of thromboembolic stroke,[38] exposes patients to radiation,[39] and is generally more time-consuming and costly compared with noninvasive imaging modalities.

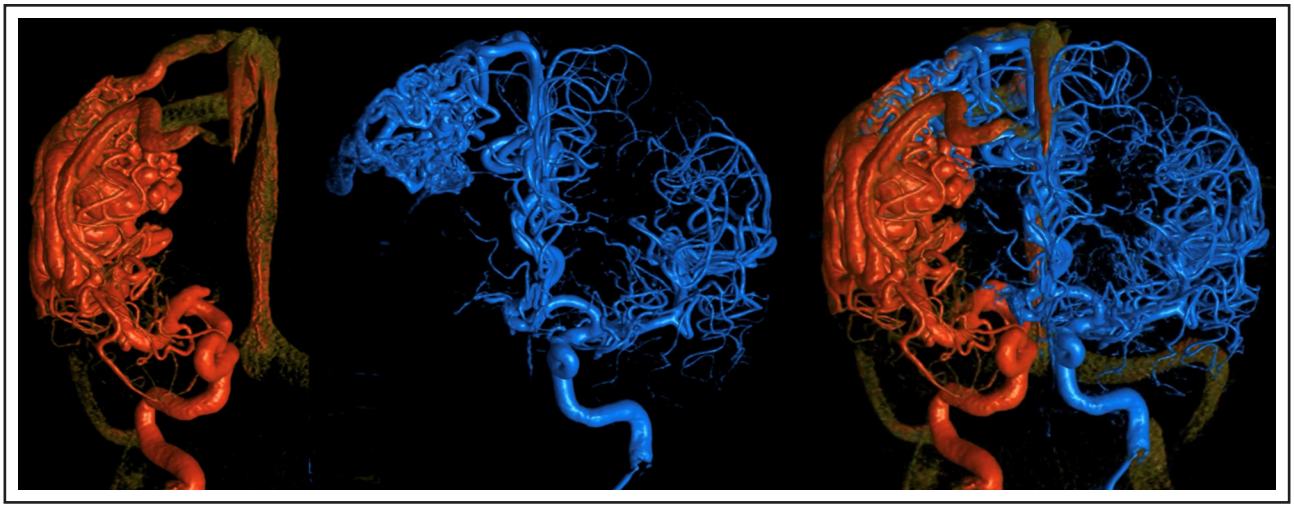

Figure 1. Six-dimensional reconstruction of a large right hemispheric arteriovenous malformation.
A bihemispheric 3-dimensional rotational angiogram is fused to produce a 6-dimensional view of the entire cerebral vasculature. The superimposition of images allows a detailed characterization of the brain arteriovenous malformation angioarchitecture and flow dynamics of different vascular territories. Images courtesy of Eytan Raz, MD, and Maksim Shapiro, MD, NYU Langone Medical Center.

ARISE Consensus

DSA remains the gold standard for evaluating bAVMs, yielding vital data on angioarchitecture, including the number and characteristics of arterial feeders, size and location of the nidus, drainage patterns, presence of flow-related and intranidal aneurysms, venous stenosis and ectasia, as well as the presence of macroshunts and fistulas. Due to the associated risks of an invasive study, DSA may be best performed at the time of surgical planning and not as a primary diagnostic tool. Furthermore, where resistance or contraindications to DSA exist, alternative noninvasive imaging techniques like MRI, MRA, and CTA can be utilized. MRI provides information about the anatomic location, surrounding brain parenchyma and hemorrhage. MR-tractography, fMRI, and navigated transcranial magnetic stimulation can be valuable tools for treatment planning and determining surgical approaches and risks. The use of advanced neuroimaging should be confined to specialized centers with routine application and expertise.

IMAGING FOLLOW-UP OF bAVMS

The optimal approach for long-term surveillance of bAVMs has not been determined. Noninvasive modalities like MRI and contrast-enhanced MRA, which avoid ionizing radiation, could serve for the extended follow-up of patients with bAVM. Given the dynamic and flow-dependent nature of bAVMs, they can evolve over time. MRI is accurate at detecting new gliosis or hemorrhagic

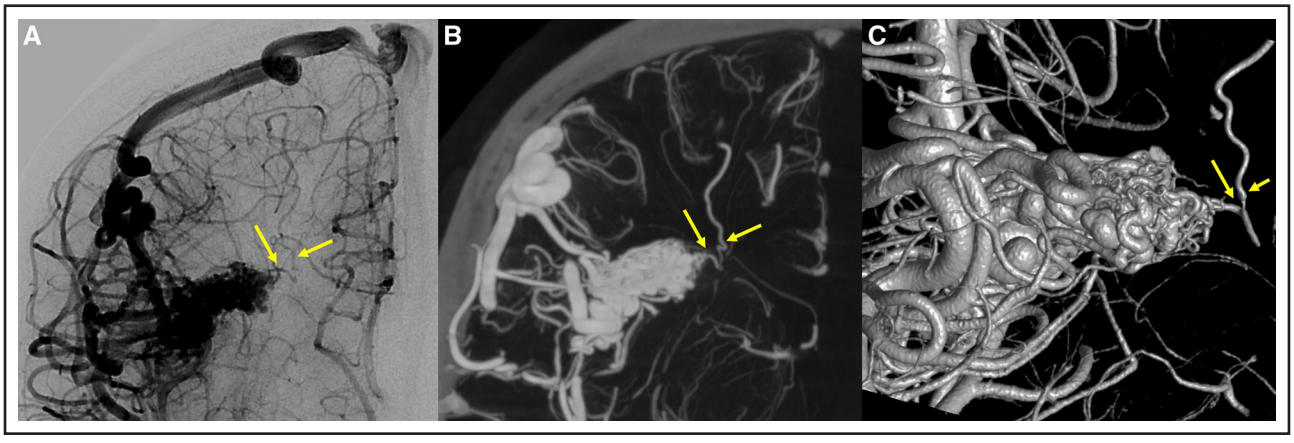

Figure 2. Digital subtraction angiography and cone beam computed angiography of a right hemispheric brain arteriovenous malformation.
A, Diagnostic cerebral angiogram shows the nidus and no evidence of deep venous drainage. **B**, Cone beam computed angiography demonstrates the presence of a small deep vein, which can be seen more clearly in the 3-dimensional reconstruction (**C**, arrows). Images courtesy of Eytan Raz, MD, and Maksim Shapiro, MD, NYU Langone Medical Center.

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areas, while MRA can reveal the development of intranidal and flow-related aneurysms.

Posttreatment imaging also presents challenges, as DSA remains the definitive method to conclusively exclude the presence of residual nidus, early draining veins, or shunting. MRI and 4D-MRA may contribute to long-term postoperative surveillance; however, DSA is favored for initial posttreatment assessments due to its precision. O'Connor and Friedman[40] studied the accuracy of MRI in 120 patients post-radiosurgery and showed an 82% concordance rate with DSA for identifying residual nidus, although the efficiency dropped for smaller bAVM volumes. In pediatric patients, delayed follow-up with DSA is particularly valuable, as there is a higher tendency for recurrence in this group.[41]

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There is currently no clear scientific evidence on how treated and untreated bAVMs should be monitored. Recurrence after angiographically proven complete resection in children and adolescents is a well-recognized phenomenon and in this age group long-term follow-up imaging is warranted. It is also advisable to follow patients with untreated bAVMs with noninvasive imaging at 2- to 5-year intervals to rule out angioarchitecture changes such as interval development and growth of venous varices, venous outflow obstruction, or de novo aneurysm formation. The need for continuing follow-up imaging after successful bAVM resection in adults should be considered on an individual basis. For patients treated with radiosurgery, the frequency of DSA follow-ups until cure and beyond has not been stablished and requires further investigation.

CLASSIFICATION SCALES OF BAVMS

Grading systems of bAVM surgical risk such as the SM scale have been used extensively to classify bAVMs.[42] The SM scale has been widely adopted because of its simplicity and acceptable interobserver agreement.[43] The Lawton-Young grading system supplements the SM system by incorporating additional factors important to surgical selection and outcome, including patient age, hemorrhagic presentation, and compactness of the nidus.[44] However, these classifications are not aimed at determining the risk of hemorrhage, their main objective is to estimate the risk of surgical resection. Therefore, there has been an effort to develop prognostic models for the prediction of ICH. Kondziolka et al[45] published their estimate lifetime risk of bleeding based on patient age at 2% to 4% per annum. Mansmann et al[46] conducted a study examining the angioarchitecture features in 662 patients and their association with ICH presentation. The Mansmann scoring system assessed various bAVM characteristics, including the size of the nidus (<3, 3 to 6, or >6 cm), the presence of single or multiple nidus compartments, presence of arterial stenosis, arterial angioectasia, deep venous drainage, location, and the presence of intranidal aneurysms. Additional factors considered in the study encompassed the presence of angiogenesis, thrombosis of the venous outlet, the presence of arteriovenous fistulas, and pial venous reflux. Venous outflow stenosis increased the rate of ICH. A high risk of rebleeding has been reported with the presence of intranidal aneurysms.[46] Aneurysms proximal to the bAVM are usually flow-related aneurysms and may decrease in size on follow-up imaging after the bAVM is treated. These studies highlight the heterogenous angioarchitecture of bAVM.

The R2eD bAVM score was developed through a comprehensive analysis of a database consisting of 789 patients with bAVM.[47] This analysis led to the creation of a practical scoring system and a risk prediction formula. Each risk factor considered in the model was assigned a score of 1 point, except for race, which was assigned 2 points. The total score ranges from 0 to 6, and the model incorporated various risk factors, including non-White race (odds ratio [OR]=1.8; P=0.02), small nidus (OR=1.4; P=0.14), deep location (OR=2.3; P<0.01), single arterial feeder (OR=2.2; P≤0.01), and exclusive deep venous drainage (OR=2.07; P=0.02). The predicted probability of hemorrhage increased from 16% for patients with no risk factors (score of 0) to 78% for patients with all the risk factors (score of 6). A study analyzed the R2eD scoring system in 122 patients with bAVMs.[48] An area under the curve of 0.711 was reported using R2eD. Race had the highest odds ratio in univariable analysis. However, only 10 subjects were non-White, and most of these patients (60%) had hypertension. Hypertension has been shown to be associated with an increased risk of bAVM rupture; therefore, it can be an important confounder in establishing race as a risk factor.

Chen et al published a registry of 3962 patients with bAVMs in China. The investigators developed the VALE scoring system, which included the involvement of the cerebral ventricles, venous aneurysm, deep location of the nidus, and exclusively deep venous drainage.[49] The 10-year hemorrhage-free rate was 95.5% (95% CI, 87.1%–100%) in the low-risk group, 92.8% (95% CI, 88.8%–97.0%) in the moderate-risk group, and 75.8% (95% CI, 65.1%–88.3%) in the high-risk group.

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The previous predictive scores for determining risk of ICH in unruptured bAVMs were developed retrospectively, mainly relying on the analysis of the ICH presentation. Caution is warranted when considering the true predictive value of these scores for determining the risk of rupture a priori.

CLINICAL TRIALS AND REGISTRIES

To obtain a more reliable assessment of the risk of bAVM rupture, randomized clinical trials (RCTs) and prospective registries are required. The ARUBA trial (Medical Management With or Without Interventional Therapy for Unruptured Brain Arteriovenous Malformations), is the first RCT that studied the management of unruptured bAVMs. ARUBA reported that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured bAVMs followed up for 33 months.[50] The risk of death or stroke was significantly lower in the medical management group than in the interventional therapy group (hazards ratio, 27 [95% CI, 0.14–0.54]).

Criticism of the ARUBA trial includes the low rate of microsurgery performed in the interventional arm (19%), the relatively short follow-up period, the lack of reporting on the cure rate, and the low enrollment at centers with concern for selection bias.[51] Importantly, the publication of ARUBA appears to have influenced the treatment approach to unruptured bAVMs in the United States, leading to a more cautious stance. Following the publication of ARUBA in 2014, there has been a notable decrease in the likelihood of intervention for unruptured bAVMs, coinciding with an increase in the incidence of ruptured bAVMs. These findings suggest that a decrease in the number of treatments for unruptured bAVMs may contribute to a higher occurrence of bAVM rupture. Luther et al[52] reported a significant average annual percent change of 0.49% (P=0.0001) for rupture incidence and a decrease of 1.17% (P=0.0001) for the intervention rate. By contrast, Reynolds et al[53] also used National in-patient sample data used by Luther et al and found no reduction in the rate of bAVM surgery following publication of ARUBA.

The TOBAS (Treatment of Brain Arteriovenous Malformations Study) is a comprehensive, pragmatic, prospective, multicenter, RCT and registry designed to assess the best management strategies for patients with brain bAVMs, including those that are unruptured or ruptured. It examines whether preventive interventions such as surgery, embolization, and radiation therapy, alone or in combination, can improve patient outcomes compared with conservative management. The study includes 2 RCTs and will enroll up to 2000 patients from ≈30 centers, to be followed for 10 years.[54] This care trial, aims at replacing singular treatment choices with a systematic 1:1 randomized assignment when established knowledge is insufficient, thereby converting unconfirmed traditional medical practices into evidence-based health care.[55]

Other efforts such as multicenter registries with prospectively acquired data and long-term follow-up are underway. The MARS (Multicenter Arteriovenous Malformation Research Study) is a collaborative multicenter study with a target enrollment of 4500 unruptured bAVMs.[56] Initial findings from MARS indicate that a hemorrhagic presentation is a significant predictor of subsequent hemorrhage and that the likelihood increases with the patient's age.[7] Another significant registry is the SIVMS (Scottish Intracranial Vascular Malformation Study), a prospective population-based registry including patients diagnosed with any type of vascular malformation in Scotland.[57] Additionally, the Multimodality Treatment for Brain Arteriovenous Malformation in Mainland China registry is another large-scale prospective registry aimed at characterizing the natural history of bAVMs in the Asian population (NCT 36253875).[58]

ARISE Consensus

Despite multiple shortcomings, RCTs such as ARUBA have a critical role in determining optimal management strategies of bAVMs. Studies such as TOBAS, which offer both randomized allocation and a registry for patients managed exclusively based on clinical judgment, are invaluable for gathering comprehensive data on individuals with complex neurovascular conditions. MARS, SIVMS, Multimodality Treatment for Brain Arteriovenous Malformation in Mainland China and similar registries are encouraged to collect as extensive data as possible, covering patient demographics, comorbidities, and detailed angioarchitectural characteristics of bAVMs. Leveraging these studies promotes a deeper and more robust understanding of the risks associated with bAVM rupture. It is also crucial to standardize the use of common data elements when identifying and defining subject characteristics and bAVM angioarchitecture. This would facilitate the exchange of information and the analysis of multiple datasets.

MANAGEMENT OF UNRUPTURED bAVMs

The approach to managing unruptured brain bAVMs remains contentious, particularly in the wake of the ARUBA trial's conclusions. While ARUBA, despite its constraints, stands as the only RCT focusing on unruptured bAVMs, it advocates for a cautious treatment philosophy due to the absence of compelling evidence favoring the intervention of unruptured bAVMs. SIVMS followed 204 patients over a median span of 12 years and reported that conservative management was associated with a lower rate of progression to sustained disability or death of any cause over 4 years and a lower risk of bAVM-related symptomatic stroke or death over 12 years.[59] One of the limitations of bAVM studies is the length of follow-up, as there is no evidence to suggest that hemorrhage risk declines over time. Is also noteworthy that these studies excluded pediatric patients,

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curtailing the potential extrapolation of the results of these studies on this population.

ARISE Consensus

The management of unruptured bAVMs demands a cautious and comprehensive approach, overseen by a multidisciplinary team. Current data suggest that the overall risk of ICH is relatively low. Decisions regarding treatment should be influenced by various factors, such as the patient's age, symptoms, the angioarchitecture of the bAVM, the available resources, and the expertise of the healthcare providers at the treating facility. To ensure the best possible outcomes, the workgroup strongly advocates for these complex lesions to be treated at high-volume centers equipped with comprehensive capabilities in open microsurgery, endovascular therapy, and SRS. Such specialized centers possess the necessary expertise and resources to deliver optimal care and achieve successful treatment outcomes. Based on the results from ARUBA, a conservative approached is justified in asymptomatic patients with unruptured bAVMs.

MANAGEMENT OF RUPTURED bAVMs

The optimal timing for definite treatment of ruptured bAVMs is not standardized. Typically, definitive treatment requires complete eradication of the bAVM. Treatment modalities have historically been used in combination to improve patient outcomes. For example, preoperative embolization was an adjunctive use of endovascular surgery before microsurgical resection. The risk of rerupture ranges from 6% to 15.8% within the first year and from 2% to 7.9% in subsequent years.[60–62] The modest recurrence rate of hemorrhage permits consideration of a delayed intervention, allowing comprehensive assessment of the lesion and careful treatment by a multidisciplinary medical team. The presence of intracranial aneurysms associated with the bAVM significantly increases the risk of rehemorrhage and may prompt treatment at the time of the initial presentation with ICH. Intracranial aneurysms are detected in 7% to 20% of patients with bAVM.[63] In patients with bAVMs but no intracranial aneurysms, the rate of rehemorrhage has been reported as 9.7% per year.[64] To facilitate decision-making, a comprehensive evaluation of the bAVM's angioarchitecture using DSA can identify potential bAVM-associated aneurysms. This evaluation could assist in triage of patients for early treatment based on the presence of aneurysms.

ARISE Consensus

While there is no one-size-fits-all approach, a careful assessment of the risk factors, including the presence of associated intracranial aneurysms, can guide decisions about the optimal timing for treatment of ruptured bAVMs. Individualized decision-making, in collaboration with a multidisciplinary team, remains essential to ensure the best possible outcomes for patients. When it is deemed that patients are stable, they should be transferred to specialized high-volume centers with expertise in open microsurgery, endovascular surgery, and SRS.

SURGICAL TREATMENT MODALITIES

Microsurgery remains the established standard for managing bAVMs, particularly for low-grade lesions. Surgical resection of these lesions is highly effective with favorable cure rates, an acceptable safety profile, and immediate results.[65] While microsurgery alone can achieve optimal resection rates and good clinical outcomes without embolization, embolization plays a valuable role in the multimodality treatment of high-grade bAVMs. However, determining the optimal treatment modality or combined approach is challenging due to the inherent heterogeneity of bAVMs. In the ARUBA trial, embolization was utilized in 31.9% of patients as monotherapy, 29.8% as adjuvant treatment before microsurgery or SRS, and only 5.3% of patients underwent microsurgical resection alone.[50] Therefore, ARUBA was not powered to perform meaningful comparisons among treatment modalities. Data from TOBAS suggest that endovascular embolization in a presurgical setting presents added risk to the overall management. The study suggests that endovascular embolization should be reserved for selected cases where a benefit to surgery is highly anticipated.[66]

In selected cases involving small- or medium-sized nidus located in noneloquent areas, with accessible feeding arteries and compact niduses and without en passage feeders, transarterial curative bAVM embolization may be possible.[67] Embolization can serve various purposes, including achieving a cure and refining surgical resection. Embolization before or after radiosurgery remains a topic of discussion due to the small series that have been published during the continued improvement of SRS and endovascular techniques. Embolization could also be targeted at closing high-risk components of the bAVM, such as aneurysms, or at achieving palliative symptom relieve in patients with large bAVMs and limited treatment options.[68] Although SRS may follow embolization, some studies have suggested that SRS is less effective after embolization due to the presence of the liquid embolic cast in the target area causing shielding of the bAVM from the specified radiation dose.

SRS presents an alternative to microsurgical resection and endovascular embolization, particularly for deep bAVMs with challenging microsurgical and endovascular access. By delivering an adequate radiation dose to the bAVM, this approach induces closure of the bAVM vessels' lumen and eventual obliteration of the bAVM

over a latency period of 2 to 3 years.[69] In a series of 232 ARUBA-eligible patients with SM grade I-II bAVMs, obliteration rates were 72% and 87% at 5 and 10 years, respectively.[70] The annual post-SRS hemorrhage rate was low at 1.0%. Additionally, symptomatic radiation-induced changes occurred in 8% of cases, while permanent changes were observed in only 1%. Overall, a favorable outcome was achieved in 76% of patients.

Combined approaches involving presurgical embolization of both ruptured and unruptured bAVMs have become standard practice. A meta-analysis demonstrated that presurgical embolization of microsurgically treated bAVMs significantly reduces the lesion volume with active arteriovenous shunting, contributing to improved outcomes.[71]

ARISE Consensus

The key to achieving good outcomes is appropriate patient selection in high-volume, and multidisciplinary centers. The treatment decision to perform microsurgery, endovascular surgery, SRS, or a combination of these treatments, should be based on considerations, which include local expertise as well as patient-specific clinical, functional, and angioarchitectural features.

MICROSURGERY

The stepwise goals of this intervention are wide exposure of the relevant anatomy, occlusion of the feeding arteries while preserving parenchymal vessels, circumferential dissection of the lesion, disconnection of the draining veins, and finally en bloc extirpation of the nidus. The advantages of microsurgery, compared with alternate bAVM interventions, are a high rate of complete obliteration, immediate elimination of hemorrhage risk, and long-term durability. The disadvantages of bAVM resection are craniotomy, longer hospital stay, longer recovery, and the risk of perioperative neurological and systemic morbidity.[72] Prognostic scales to determine the surgical risk have been described earlier. Microsurgical resection is best suited for low-grade bAVMs (ie, SM grades I and II), whereas high-grade bAVMs (ie, SM grades IV and V) should often be managed conservatively.[73] Surgical outcomes for the heterogenous group of intermediate-grade bAVMs (ie, SM grade III) depend on specific angioarchitecture features such as the size of the nidus, location of the nidus, and venous drainage.[74] Small-sized intermediate-grade bAVMs with eloquent location and deep venous drainage may have surgical risks similar to low-grade bAVMs. However, medium-sized intermediate-grade bAVMs with noneloquent location and deep venous drainage or eloquent location and exclusively superficial venous drainage seem to carry surgical risks comparable to those of high-grade bAVMs.[75]

ARISE Consensus

Microsurgery comprises the mainstay treatment of bAVMs. Multicenter prospective RCTS and registries focused on microsurgical resection of specific bAVMS (ie, SM grade III) have the potential to provide insight into the safety and efficacy of this approach and improve patient selection. Preoperative embolization may be considered on a case-by-case basis.

ENDOVASCULAR TREATMENT MODALITIES

In general, excellent obliteration rates with standalone bAVM embolization are only achieved for carefully selected patients. The caliber and proximity of feeding arteries, number of arterial feeders, venous drainage, flow phenomena with presence of shunting, and presence of en passage feeders, should be studied in detail with DSA when considering endovascular treatment. A transarterial approach aims at closing most of the feeding arteries that can be safely catheterized for embolization. Different embolization techniques include the use of coils, liquid embolics,[76,77] and low-profile balloons for flow arrest.[78] Transarterial approaches are most effective when there are only a few feeding arteries and when performed with minimal number of sessions.[68] Several series have reported bAVM cure by standalone endovascular treatment in bAVMs with 1 to 3 arterial feeders.[79,80] Achieving angiographic cure with embolization is more feasible if the bAVM is supplied by superficial feeders.[81] bAVMs with en passage feeders supplying normal brain parenchyma have reduced angiographic occlusion rates with embolization and pose a greater risk of complications.[81] In the registries from the TOBAS study, the rate of achieving an endovascular cure for brain bAVMs through embolization was reported to be <40%. Moreover, significant neurological complications leading to disability (as measured by a modified Rankin Scale score >2) were documented in 11% of the cases, largely attributed to hemorrhagic events.[82]

Newer transvenous approaches have recently been reported. Transvenous embolization has been considered when specific features are present, such as deep location, small nidus size, a single draining vein, inaccessibility via the arterial route, and limited feasibility of alternative treatment options.[68] Nevertheless, it is important to note that the evidence for this approach primarily relies on relatively small single-center series, which inherently carry selection bias. Although still in development, attempts at definitive treatment of bAVMs using only endovascular techniques are underway. Newer embolic agents have been used to achieve greater antegrade (transarterial) and retrograde (transvenous) nidal penetration and occlusion. Large case series utilizing newer embolic agents have reported cure rates of up to 51%

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with endovascular surgery.[83] Efforts to refine these techniques may reduce the associated complication rates. A systematic review and meta-analysis, which included 66 cases, reported a technical complication rate of 8%, with an overall good functional outcome of 89% (95% CI, 82%–96%).[84] A prospective randomized phase 2 clinical trial aimed at evaluating whether transvenous embolization is superior to transarterial embolization is underway (NCT03691870).[85]

ARISE Consensus

Curative endovascular embolization of bAVMs as a standalone treatment could be performed in selected cases with favorable angioarchitecture. To establish the most suitable endovascular treatment modalities for specific bAVMs, it is crucial to conduct RCTs and other multicenter prospective studies.

STEREOTACTIC RADIOSURGERY

SRS is best suited for small- or medium-sized bAVMs (volume <12 cm^3 or diameter ≤3 cm) located in deep or eloquent brain regions.[30,86] Unlike bAVM resection or embolization, both the beneficial and adverse effects of SRS may not be fully apparent for years afterward. Radiation stimulates the vascular endothelium and induces smooth muscle cell proliferation and extracellular collagen accumulation, leading to progressive intimal thickening, thrombosis of irradiated vessels, and eventual occlusion of the vascular lumen.[87] Selected lesions with small volumes, and in younger patients, can be completely obliterated with SRS in 60% to 80% of cases after 3 to 5 years of follow-up.[88] The advantage of SRS is that it is not invasive; however, during the latency period, there is a risk of hemorrhage ≈1% to 3% per year.[89]

A case series of 189 patients with pediatric bAVM treated with SRS reported an annual hemorrhage rate of 2.8%.[90] The cumulative hemorrhage rates after SRS were 3.3%, 8.5%, and 11.9% at 3, 5, and 10 years, respectively. Higher SM grade was significantly associated with intracranial hemorrhages during the latency period (P<0.001). The actuarial nidus obliteration rates with repeated SRS were 64% and 81% at 5 and 10 years, respectively. Radiation-induced imaging changes are frequently observed following SRS for bAVMs, manifesting radiologically in ≈36% of patients. However, these radiographic findings might not directly correlate with clinical symptoms.

Large-volume (>10 cm^3) bAVMS may be treated with volume-staged or dose-staged SRS. Volume-staged SRS is a treatment strategy that involves dividing large bAVMs into distinct volumes, each independently targeted by SRS with intervals of 2 to 9 months until the entire bAVM is treated.[91] On the other hand, dose-staged-SRS entails repeated delivery of fractionated radiation dose to the entire bAVM until a cumulative total dose is achieved over a period of a few sessions.[92,93] Both techniques can be utilized as standalone approaches to achieve obliteration. Alternatively, they can be employed in conjunction with embolization or before resection after the nidus has regressed. Ilyas et al performed a systematic review to compare volume versus dose-staged outcomes for large bAVMs.[94] Volume-staged SRS had a higher obliteration rate than dose-staged-SRS, although with a less favorable complication profile. However, the overall cure rates for large bAVMs with SRS are low. The study results are constrained by the heterogeneity of baseline and outcomes data.

ARISE Consensus

SRS is considered highly suitable for treating small bAVMs located in deep and eloquent regions. However, the safety and effectiveness of SRS in large volume and ruptured bAVMs, postembolization cases, and bAVMs with higher SM grade are yet to be firmly established. To obtain higher-quality data and conclusive evidence, it is essential to conduct RCTs and large multicenter studies with well-defined inclusion criteria, treatment parameters, and surveillance imaging. Such studies will contribute significantly to enhancing our understanding of SRS outcomes in the treatment of bAVMs.

NONSURGICAL TREATMENT MODALITIES

bAVMs consist of a mass of abnormal arteries and veins with no intervening normal tissue. The size and thickness of vessels within the bAVM are heterogeneous. Transmission electron microscopy has shown an incompetent blood-brain barrier in both nidal and perinidal vessels.[95] These intranidal vessels are subjected to abnormally high blood flow and shear forces, activating molecular pathways in smooth muscle cells and brain endothelial cells. This activation induces proliferation and vascular remodeling.[96] Microscopic animal models have demonstrated that cerebral bAVMs exhibit various pathological changes within the nidal vessels. These changes encompass heterogeneously thickened vessel walls, splitting of the elastic lamina, thickened endothelial layers, impaired tight and adherent junctions, disrupted endothelial continuity, and filopodia extending into the lumen.[95] These diverse changes provide multiple potential molecular targets for pharmacotherapy (Table). It has been postulated that these changes lead to a hyperangiogenic environment and ultimately to endothelial impairment.[97]

Studies conducted on both mouse models and human bAVM specimens have consistently highlighted the significant role of VEGF (vascular endothelial growth factor) in the formation and progression of bAVMs.[98] A noteworthy study demonstrated the proof of concept by inducing bAVMs in Alk1-deficient mice through viral delivery of VEGF. Interestingly, the dysplastic vascular phenotype

Table. Promising Targeted Medical Therapies for bAVMs

	Mechanism	Potential treatment
VEGF[70]	Angiogenesis	Bevacizumab
Tyrosine kinase	Downstream mediator of VEGF	Sorafenib, pazopanib, nintedanib, and sunitinib
Angiopoieting-2[124]	Downstream target of SMAD4	Angiopoieting-2 inhibitor: MEDI3617[125] Nesvacumab[126]
KRAS/BRAF mutation.[104] mTOR	Dysregulation of the MAPK-ERK pathway, alters cell growth, metabolism, survival and proliferation.	MEK inhibitors: sirolimus (rapamycin), selumetinib, and trametinib[127,128]

bAVM indicates brain arteriovenous malformation; SMAD4, mothers against decapentaplegic homolog 4; and VEGF, vascular endothelial growth factor.

improved when VEGF antagonism was applied using bevacizumab.[99] Bevacizumab, a humanized monoclonal antibody specific to VEGF, has subsequently been incorporated into several clinical studies, including a randomized phase III clinical trial involving patients with hereditary hemorrhagic telangiectasia (NCT03227263).[100] More than 1200 dysregulated genes have been identified in human bAVM tissue.[101,102] The functions of these genes are directly linked to inflammation, angiogenesis, vasculogenesis, cell migration, and the cytoskeletal system.[103]

The Kirsten rat sarcoma virus (KRAS) and v-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations have been identified with a high prevalence in brain and spinal cord bAVMs.[104] While both KRAS and BRAF mutations are commonly associated with cancers and tumor growth, in the context of bAVMs, they might be connected to endothelial proliferation, angiogenic signaling, or vascular remodeling processes. In a recent meta-analysis of 6 studies involving 1726 patients with bAVM, the estimated frequency of KRAS somatic mutations were 55%, while BRAF somatic mutations were 7.5%.[105] Endothelial KRAS activating mutations induce conformational changes in KRAS, leading to its constant activation by inhibiting GTP hydrolysis.[106] Subsequently, BRAF, a downstream effector of KRAS induces activation of the mitogen-activated protein kinases (MAPKs), and extracellular signal-regulated kinases (ERKs) signaling pathway in brain endothelial cells.[107] Given the absence of available direct pharmacological inhibitors for KRAS, small-molecule MEK inhibitors, which are already used in clinical practice for treating cancers, are promising candidates for testing in clinical trials to treat bAVMs.[108]

ARISE Consensus

The medical treatment of bAVMs holds tremendous potential. The numerous molecular mechanisms that could potentially lead to angiogenesis processes could serve as pharmacotherapy targets in bAVMs.

ANIMAL MODELS OF bAVMs

bAVMs are considered embryonic in origin; however, there is evidence of adult onset as well, suggesting a highly dynamic postnatal development. Therefore, it is important to understand the molecular mechanisms of bAVM progression and formation.[109] Animal models in the past have been developed to test pharmacological and surgical approaches[110–112] and to simulate arteriovenous shunts with nidus-like structures.[113,114] These models often exhibit vascular changes that closely resemble those observed in human bAVMs. The presence of a diffuse network of small capillaries at the skull base of sheep and pig, known as "rete mirabile," has been used as a default vascular model for the study of bAVMs. The size of swine's rete mirabile's vessels (70–275 µm) is close to that of the nidus of human bAVMs (≈150 µm),[110] making this vascular structure suitable for reproducing nidal components of bAVMs. An important limitation of the rete mirabile model is that this is an entirely arterialized system, whereas the bAVM nidus exhibits a higher-pressure gradient between feeding and draining vessels. Initial approaches to create an arteriovenous shunt between the swine rete mirabile and the cavernous sinus included the transorbital puncture with a needle of the internal carotid artery and the cavernous sinus.[115] Massoud et al[116] created a model of induced high flow across the retia by surgical formation of a side-to-side arteriovenous fistula between the common carotid artery and the external jugular vein, with ligation of the common carotid artery proximal to the fistula on the right side. Based on Massoud's model, modified swine bAVM models were introduced, increasing the pressure gradient closer to values found in humans, and thereby reducing the rate of spontaneous thrombosis in the rete.[117–119] Recent swine angiogenesis models have created an occlusion of the common carotid artery, with a significant increase in the volume of the rete mirabile and histological changes of angiogenesis similar to those seen in bAVMs.[120] These models have also been tested with pharmacological treatments, such as intra-arterial injection of bevacizumab, which resulted in decreased endothelial proliferation, but no change in vascular diameter.[121] A limitation of this model is that it does not replicate in any way the actual pathology underlying the formation of bAVMs. Moreover, the lack of relevant somatic mutations makes the vessels respond to any stimulus in a different manner than true bAVM vessels. The presence of genetic mutations, as seen in hereditary hemorrhagic telangiectasia, has been particularly helpful in the development of bAVM animal models, particularly in mice. Through genetic transformations, these mice models

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successfully induce the bAVM phenotype, replicating key characteristics of the condition.[114,122,123] These genetic mutations alter inflammatory factors, angiogenesis, vasculogenesis, and structural proteins.[97]

ARISE Consensus

There is a pressing need to further advance the development of animal models for bAVMs to comprehensively understand the phenotypic changes responsible for the characteristic angioarchitecture of bAVMs. This endeavor would significantly enhance the progress in both pharmacological and surgical treatment approaches. In line with this objective, establishing a collaborative tissue bank comprising resected bAVM specimens could yield a substantial collection of samples for thorough analysis. To ensure consistency and comparability, it is strongly recommended to implement standardized processes for sample collection and analysis. Such efforts will greatly contribute to the advancement of our understanding of bAVM pathophysiology and aid in the development of effective treatments.

CONCLUSIONS

bAVMs are rare and heterogeneous lesions that require multidisciplinary and cross-institutional efforts to enhance research. To better understand bAVMs' natural history, both cross-sectional and longitudinal registries are necessary. RCTs can yield high-quality data to guide treatment approaches that encompass surgical interventions and medical therapy. Research priorities include creating predictive scales to calculate the hemorrhage risk and developing animal models to mimic bAVM biology. For optimal outcomes, it is recommended that treatment for these complex lesions be centralized at specialized centers with substantial expertise.

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