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Brain arteriovenous malformations: A review of natural history, pathobiology, and interventions

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Abstract:

Brain arteriovenous malformations (AVMs) are anomalous direct shunts between cerebral arteries and veins that convalesce into a vascular nidus. The treatment strategies for AVMs are challenging and variable. Intracranial hemorrhage and seizures comprise the most common presentations of AVMs. However, incidental AVMs are being diagnosed with increasing frequency due to widespread use of noninvasive neuroimaging. The balance between the estimated cumulative lifetime hemorrhage risk versus the risk of intervention is often the major determinant for treatment. Current management options include surgical resection, embolization, stereotactic radiosurgery (SRS), and observation. Complete nidal obliteration is the goal of AVM intervention. The risks and benefits of interventions vary and can be employed in a combinatorial fashion. Resection of the AVM nidus affords high rates of immediate obliteration, but it is invasive and carries a moderate risk of neurological morbidity. AVM embolization is minimally invasive, but cure can only be achieved in a minority of lesions. SRS is also minimally invasive and has little immediate morbidity, but AVM obliteration occurs in a delayed fashion, so the

patient remains at risk for hemorrhage during the latency period. Whether obliteration can be achieved in unruptured AVMs with a lower risk of stroke or death compared to the natural history of AVMs remains controversial. Over the past 5 years, multicenter prospective and retrospective studies describing AVM natural history and treatment outcomes have been published. This review provides a contemporary and comprehensive discussion of the natural history, pathobiology, and interventions for brain AVMs.

Introduction

Arteriovenous malformations (AVMs) of the brain are rare anomalous arteriovenous shunts comprising tangles of dysplastic cerebral arteries and veins that converge at a vascular nidus without normal intervening parenchyma. Traditionally, parenchymal AVMs have been considered congenital lesions. However, several reports of *de novo* AVM formation and the observation that parenchymal brain AVMs (unlike vein of Galen AVMs) are never seen on prenatal ultrasound, have challenged this dogma.[1] Concordant with the increasingly pervasive use of noninvasive neuroimaging, incidental AVMs are being detected with greater frequencies. Hemorrhage is often considered the primary source of morbidity and mortality from AVMs, and thus, natural history studies have sought to identify factors predictive of rupture. Consequently, the balance between the estimated cumulative lifetime hemorrhage risk versus the risk of intervention often guides AVM management.

Current management options for AVM patients include observation, surgical resection, embolization, stereotactic radiosurgery (SRS), or multimodality treatment strategies. The goal of AVM intervention is complete endoluminal closure or obliteration of the nidus. The cerebrovascular community continues to debate whether interventional obliteration of an

unruptured AVM can be achieved with a lower risk of stroke or death than its natural history. Recent multicenter studies have helped to refine AVM management and clarify natural history and treatment outcomes. In this review, we provide a contemporary and comprehensive discussion of the natural history, pathobiology, and interventions for brain AVMs.

Natural History

The true prevalence and incidence of brain AVMs remain incompletely defined. The estimated prevalence of AVMs among autopsy studies varies widely between 5 and 613 cases per 100,000.[2] Across population-based studies, the overall incidence of AVMs range from 1.10 to 1.42 cases per 100,000 (**Table 1**).[3-9]

Intracranial hemorrhage is the most common symptomatic manifestation of AVMs.[10, 11] Although the prognosis of AVM hemorrhage is better than primary spontaneous intracerebral hemorrhage, the one month case fatality and poor outcome rates have been reported to be 11% and 40%, respectively.[12] The overall hemorrhage risk of an untreated, unruptured AVM is estimated to be 1%–3% per year (**Table 2**).[11, 13-20] This risk is higher among ruptured versus unruptured AVMs, especially within the first year after initial hemorrhage.[11, 13, 15-17] Prior hemorrhage is the most consistent predictor of subsequent hemorrhage (**Table 3**).[11, 14-17] AVM angioarchitectural features, including venous drainage pattern, fewer draining veins, nidus location, nidus size, presence of associated arterial aneurysms or venous varices, are other potential risk factors.[10, 11, 13, 15, 16, 21-23] It is unclear if patient demographics, such as age and sex, influence an AVM's hemorrhage risk.[11, 14, 15]

Seizures are the second most common clinical AVM presentation (approximately one-third of cases).[24] However, due to the morbidity and mortality associated with AVM hemorrhage, seizures have not been at the forefront of treatment outcome or natural history studies. In patients with incidentally detected AVMs, there is an approximate 8% risk of first-time seizure within 5 years of diagnosis.[25] However, this risk is estimated to be 23% for those presenting with hemorrhage or focal neurological deficit. The risk of developing epilepsy is estimated to be 58% for patients without hemorrhage or neurological deficit who had a first-time seizure at presentation or during follow-up. Cortical AVMs, particularly those involving the temporal lobe, confer the highest risk for seizures.[25-27] Other potential risk factors for AVM-associated seizures are larger nidus size, superficial venous drainage, and arterial border zone location.[24]

Pathobiology

Genetic disorders, such as hereditary hemorrhagic telangiectasia and Sturge-Weber syndrome, have provided some insight regarding the crucial signaling pathways that govern AVM pathogenesis.[28] AVM phenotypes have been shown to manifest from impaired transforming growth factor-β (TGF-β) signaling and activation of the MAPK pathway.[29] Polymorphisms in activin receptor-like kinase 1 (*ALK1*), endoglin (*ENG*), integrin β8 (*ITGB8*), interleukin-1β (*IL1B*), angiopoietin-like 4 (*ANGPTL4*), G protein-couples receptor 124 (*GPR124*), vascular endothelial growth factor (*VEGF*), and metallopeptidase 3 (*MMP3*) have also been detected in sporadic AVMs.[28] It is uncertain whether these genetic risk factors increase an individual's susceptibility to AVM development. VEGF represents a crucial family of signaling molecules that regulates angiogenesis, and its overexpression in response to hypoxia-induced factors within the AVM nidus and adjacent astroglia is believed to contribute to AVM formation.[30, 31]

Differential expression of angiopoietins (ANG) has been associated with AVM vessel stability, and interactions between ANGs and VEGFs may have a role in AVM development.[30] Although genetic risk factors have been identified, AVMs are not generally hereditary, and genetic counseling for relatives of AVM patients is not typically necessary.

Inflammation and extracellular matrix remodeling have been implicated in AVM growth and rupture. Polymorphisms in interleukin-6 (*IL6*), *IL1-・*, ephrin type-B receptor 4 (*EPHB4*), apolipoprotein E (*APOE*) ε2 allele, and tumor necrosis factor-α (*TNF-・*)-238G>A allele are genetic modifiers associated with AVM hemorrhage.[28] Neutrophilia and increased macrophage migration inhibitory factor could promote instability of nidalvasculature.[30, 31] Metalloproteinases also appear to have important roles in AVM growth and stability, wherein degradation of pericellular substances by proteolytic enzymes induces vascular destabilization and altered angiogenesis.[30]

In addition to the consequences of AVM rupture, the nidus itself can cause neurological morbidity from locoregional effects on the adjacent brain regions. High-flow arteriovenous shunts within the nidus can divert blood flow away from the surrounding capillary network of normal parenchyma. The ensuing hypoperfusion state can lead to dilatation of the perinidal capillary network and recruitment of leptomeningeal collaterals.[28] Venous congestion and hypertension resulting from high-flow shunts or restricted outflow due to stenosis of draining veins can actuate neurological symptoms and epilepsy. Neuronal cell loss, gliosis and abnormal glial physiology, altered neurotransmitter levels, free radical generation, and aberrant cell signaling induced by chronic ischemia have all been hypothesized to contribute to the

pathogenesis of AVM-associated seizures.[26] The molecular and physiological interactions between the AVM and perinidal parenchyma is not static, but rather, evolves over time.[28]

Interventions

Microsurgery

Microsurgical resection is a mainstay in the treatment of AVMs, and the stepwise goals of this intervention are wide exposure of the relevant anatomy, occlusion of the feeding arteries while preserving en-passage vessels, circumferential dissection of the lesion, disconnection of the draining veins, and finally en-bloc extirpation of the nidus. Adjuncts to resection include advanced preoperative neuroimaging, preoperative endovascular embolization, frameless stereotactic neuronavigation, and intraoperative vascular imaging (*e.g.*, digital subtraction angiography, indocyanine green videoangiography, and fluorescein videoangiography), intraoperative electrophysiological monitoring and mapping, and each technological advance has improved the safety and efficacy of AVM surgery. The risk to benefit profile of microsurgery for AVMs has been described in numerous retrospective cohort studies (**Table 4**).[32-36] The advantages of microsurgery, compared to alternate AVM interventions, are a high rate of complete obliteration, immediate elimination of hemorrhage risk, and long-term durability.[37] The disadvantages of AVM resection are that it requires an open craniotomy, longer hospital stay, longer recovery, and the risk of perioperative neurological and systemic morbidity.[38]

Grading scales have been developed to predict outcomes after AVM surgery in order to stratify patients by operative risk (**Table 5**). The Spetzler-Martin (SM) grading scale is the most commonly used classification system.[39] The SM grade comprises 5 tiers, with points allocated

for size, venous drainage pattern, and location. Although the selection of variables and points allocation were based largely on clinical experience and intuition without elaborate statistical methods, the grading scale has proven to be a reliable tool for estimating AVM surgical risk.

The SM grading scale was simplified into the 3-tier Spetzler-Ponce classification system.[40] SM grades I and II were categorized as Spetzler-Ponce class A, SM grade III as Spetzler-Ponce class B, and SM grades IV and V as Spetzler-Ponce class C. The reported risks of adverse surgical outcomes for Spetzler-Ponce class A, B, and C AVMs were 8% (95% CI:6–10%), 18% (95% CI:15–22%), and 32% (95% CI:27–38%), respectively.[40] The definition of adverse outcome and heterogeneity of cutoff thresholds could have contributed to an overestimation of Spetzler-Ponce class A AVMs.[41] In contrast, selection bias may have resulted in an underestimation of adverse outcome rates for Spetzler-Ponce class C AVMs.[42] These results suggest that resection is best suited for low-grade AVMs (*i.e.*, SM grades I and II or Spetzler-Ponce class A), whereas high-grade AVMs (*i.e.*, SM grades IV and V or Spetzler-Ponce class C) should often be managed conservatively. Surgical outcomes for the heterogenous group of intermediate-grade AVMs (*i.e.*, SM grade III or Spetzler-Ponce class B) depend on the specific combinations of size, location, and venous drainage.[43] Small-sized intermediate-grade AVMs with eloquent location and deep venous drainage may have surgical risks similar to that of low-grade AVMs. However, medium-sized intermediate-grade AVMs with non-eloquent location and deep venous drainage or eloquent location and exclusively superficial venous drainage appear to carry surgical risks comparable to that of high-grade AVMs.

The supplementary grading scale was devised to enhance the predictive capability of the SM classification scheme.[34, 44] The supplementary grade adds patient age, prior hemorrhage, and nidus morphology to the SM grade, yielding a total maximum of 10 points for the combined supplemented SM grading system. A multicenter analysis of 1,009 surgically treated AVMs found that a supplemented SM grade of 6 is a reasonable cutoff for operative consideration.[34] Patients with a supplemented SM grade ≤6 versus >6 had a 0–24% versus 39–63% risk of an adverse postoperative outcome. These grading scales should only be regarded as a starting point in the evaluation of AVM operability, rather than the entire basis of a decision regarding the appropriateness of resection. Other factors that affect surgical decision-making in AVM patients include natural history, medical comorbidities, life expectancy, alternative treatment modalities, and patient expectations and surgical expertise.

Endovascular Treatment

Embolization is frequently employed in multimodality management of AVMs (**Table 4**).[45-50] Preoperative embolization is the most common application of endovascular AVM intervention, and the goals are to reduce intraoperative bleeding and facilitate safer dissection of the nidus, thereby decreasing surgical complications. Preoperative embolization can expand the range of operable AVMs. Embolization can be performed in a single stage or in multiple stages, depending on the angioarchitectural complexity of the nidus, to gradually reduce blood flow to the AVM before resection. Feeding artery pedicles supplying deep portions of the nidus that are not readily accessible during early stages of the dissection are preferentially targeted. A range of embolysates have been used in the endovascular treatment of AVMs, including polyvinyl alcohol

(PVA) foam particles, platinum coils, and liquid N-butyl cyanoacrylate (NBCA). More recently, ethylene vinyl alcohol (EVOH, Onyx) has become the embolysate of choice for AVMs.[51]

Embolization with a curative intent have been employed as a standalone treatment approach for AVMs. Although higher rates can be achieved among angioarchitecturally simple AVMs, complete obliteration rates with AVM embolization alone have been reported in up to 51%.[46, 48, 49] Although the vast majority of AVM embolizations are performed from a transarterial approach, transvenous embolization has recently emerged as a potentially curative technique for appropriately selected lesions.[52] A prospective, randomized, phase II trial comparing the effectiveness of transvenous versus transarterial AVM embolization for achieving complete obliteration is currently under way.[53]

Embolization has also been used to reduce the volume of a large AVM before SRS. Although theoretically appealing, the effectiveness of this strategy has recently been questioned and pre-SRS embolization may lower post-SRS obliteration rates.[54] Proposed mechanisms for the reduced obliteration rates after SRS for embolized AVMs include absorption or scattering of radiation beams by the embolysate, obscuration of the residual nidus by embolic cast preventing accurate adequate radiosurgical targeting, recanalization of embolized portions of the nidus, and embolization-induced angiogenesis.[54] The effect of embolization on AVM SRS outcomes could also be confounded by the angioarchitectural complexity of the nidus. Currently, pre-SRS embolization is primarily employed to selectively target high-risk angiographic features (*e.g.*, intranidal or prenidal arterial aneurysms, intranidal arteriovenous fistulas) that predispose the

AVM to rupture during the latency period between SRS and obliteration.[37] Finally, embolization is used in inoperable AVMs for palliative reduction of venous hypertension.

The most common complications of AVM embolization are intraoperative or postoperative hemorrhage and ischemic stroke, with permanent neurological morbidity and death occurring in approximately 7% of cases.[38] Hemorrhage can occur as a result of iatrogenic vessel wall injury (intraoperative) or premature draining vein occlusion leading to AVM rupture (postoperative), whereas ischemic stroke can result from thromboembolic complications of catheterization or off-target embolization.[37, 49] A handful of grading scales have been developed to estimate adverse outcomes after AVM embolization, but none are routinely used in contemporary neuroendovascular practice.[45] Plausible explanations for the lack of widespread adoption of an AVM embolization grading system include variations in embolysates, endovascular techniques, microcatheter technology, and intent of embolization.

Stereotactic Radiosurgery

SRS is a definitive therapy for AVMs initially reserved for surgically high-risk lesions. However, with increased experience and availability, it has become an integral part in the management of patients with AVMs (**Table 4**).[55-57] SRS is best suited for small- or medium-sized AVMs (volume<12cm^3 or diameter≤3cm) located in deep or eloquent brain regions.[37] Unlike AVM resection or embolization, both the beneficial and adverse effects of SRS may not be fully apparent for months to years afterwards.[37] Radiation stimulation of the vascular endothelium 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.[58] For ideally selected lesions (small volumes, younger age), obliteration rates as high as 60–80% can be observed after 3–5 years of follow-up.[55, 57] The risk of hemorrhage during the latency period persists, and a putative role of SRS in conferring partial protection from AVM rupture prior to obliteration is controversial.[10, 59] There is a sigmoid dose-response relationship between radiosurgical margin dose and obliteration rates, and the balance between obliteration and adverse radiation effects to the surrounding parenchyma has been extensively studied.[60]

Scoring systems for predicting outcomes after AVM SRS have been formulated (**Table 5**). The modified Radiosurgery-Based AVM Score (RBAS) incorporated nidus volume, patient age, and nidus location in the following calculation: 0.1×nidus volume+0.02×patient age+0.5× nidus location.[61] RBAS inversely correlates with rates of excellent outcome, defined as AVM obliteration without a new neurological deficit. However, the value of age for predicting AVM SRS outcomes was refuted by recent multicenter studies.[62, 63] The Virginia Radiosurgery AVM Scale (VRAS) includes prior hemorrhage, instead of age, as a predictor.[64] The VRAS comprises nidus volume, location, and prior hemorrhage. Favorable outcome, defined as obliteration without post-SRS hemorrhage or permanent symptomatic radiation-induced complication, was observed in 80%, 70%, and 45% of patients with VRAS scores of 0–1, 2, and 3–4, respectively.

Radiation-induced changes (RIC) are the most frequently observed complication after SRS for AVMs, and they are radiologically evident in up to 36% of patients.[65] RIC typically manifest between 6–18 months after SRS as perinidal T2-weighted hyperintensities on magnetic resonance imaging. The majority of RIC are asymptomatic and transient. However,

approximately 10% of all SRS-treated AVM patients will develop neurological symptoms secondary to RIC, including headache, seizure, and focal neurological deficit. A smaller subset of patients, approximately 3% overall, will suffer permanent neurological deterioration related to RIC. Lack of prior AVM hemorrhage, repeat SRS, and deep AVM location are potential risk factors for RIC.

Delayed effects of SRS are uncommon but may manifest years after the original treatment. Cyst formation occurs in approximately 1–3% of AVM patients treated with SRS at a mean interval of 6.5 years after intervention.[66] Approximately 70% of post-SRS cysts are asymptomatic and can be observed. Surgical intervention, including stereotactic drainage, resection, or shunting, should be considered for symptomatic or enlarging cysts. Post-SRS cysts are believed to develop from the formation of frail telangiectatic perinidal vessels that are prone to rupture, thereby promoting serum and protein exudation, edema accumulation, and eventual cyst formation. Risk factors for cyst formation include high radiosurgical dose, large nidus volume, and lobar nidus location. The risk of a secondary intracranial malignancy in SRS-treated patients is very low, and it appears similar to the risk of a primary brain tumor in the general population.[67]

Seizure and Headache Outcomes with AVM Interventions

The importance of ameliorating or abolishing AVM-associated seizures with intervention is often underappreciated, as the primary goal of AVM treatment remains hemorrhagic risk reduction. Seizure freedom after microsurgical resection can be achieved in 70–80% of patients with AVM-associated epilepsy.[68] Compared to other interventions, resection affords the highest rate of seizure freedom, as well as the shortest interval to achieving this endpoint, in AVM

patients with pre-treatment seizures.[69-71] Although uncommon, de novo seizures can be incited by AVM intervention in those without pre-existing seizures. Among patients without pre-treatment seizures, AVM embolization is associated with the highest rate of new onset seizures, followed by resection and SRS in descending order.[69, 72] Despite the unclear pathogenesis of AVM-associated epilepsy, nidal obliteration after resection and SRS has been found to increase seizure control rates.[69, 73, 74] However, a notable degree of seizure improvement following SRS appears to be independent of residual arteriovenous shunting.[73] Inhibition of protein synthesis and neuromodulatory effects of ionizing radiation have been hypothesized to account for the anticonvulsant effects of SRS.[75]

Contrary to intervention case series, controlled studies have not reported improved seizure outcomes from AVM treatment. In the A Randomized trial of Unruptured Brain Arteriovenous Malformations (ARUBA) trial, intervention and conservative management conferred similar seizure outcomes, and at long-term follow-up, intervention may have been associated with a higher likelihood of seizure occurrence.[19, 76] In the Scottish Audit of Intracranial Vascular Malformations (SAIVM) prospective, population-based study, intervention did not affect the 5-year risk of a first or recurrent unprovoked seizure in AVM patients, and the probabilities of achieving 2-year seizure freedom in those with seizure presentation were similar following intervention or observation over 5 years of follow-up.[77] Furthermore, the comparative seizure outcomes did not vary by AVM intervention modality or achievement of obliteration. Although limited by the number of controlled studies that reported seizure outcome data, a subsequent meta-analysis found insufficient evidence to determine whether intervention is superior to conservative management for the treatment AVM-associated epilepsy.[71] Inclusion of

standardized seizure-specific screening protocols and outcome measures seems warranted in future AVM trials.

The paucity of headache outcome data in the AVM literature may signify the lack of necessary attention that this patient complaint has received to date. Interventions in ARUBA did not reduce headache frequency compared to conservative management.[19, 76] Pharmacotherapies for headache and their long-term results in AVM patients require further study and optimization. Consistent reporting of headache outcomes in future AVM interventional case series and controlled studies could provide important information for patient counseling.

Conservative Management versus Intervention

Management decisions for AVM patients are based on a balance between the risks of intervention versus observation. Despite limited evidence from randomized controlled trials, treatment of ruptured AVMs is deemed acceptable if the patient is determined high risk of recurrent hemorrhage. The impetus to intervene on unruptured AVMs was challenged by the results of the SAIVM prospective AVM cohort study and ARUBA.[19, 78] The former analysis of the SAIVM was a prospective, population-based cohort study comparing conservative management (n=101) versus intervention (n=103) for unruptured AVMs.[78] In this study, conservative management was associated with better clinical outcomes for up to 12 years of follow-up. ARUBA randomly assigned patients with unruptured AVMs to medical management (n=109) or intervention (n=114), and the trial was prematurely terminated six years after the initiation of randomization due to superiority of the medical management arm (death or symptomatic stroke in 10% vs. 31%; hazard ratio 0.27, 95% CI:0.14–0.54).[19] Notably,

hemorrhage rates of unruptured AVMs reported by the Multicenter AVM Research Study (MARS) were comparable to those of the conservative management arms of ARUBA and the SAIVM AVM study.

Subsequent post-hoc analysis of ARUBA found concordant superiority of conservative management with regarding to functional disability.[79] The results of ARUBA were maintained with extended follow-up.[76] However, the methodology and findings of the ARUBA trial has been contentious, due to its follow-up duration, heterogeneity of treatment modalities, and higher-than-expected primary endpoints and hemorrhage rates in the intervention arm compared to prior observational studies.[80-82] It is important to note that, despite funding support from the National Institutes of Health (NIH), participation and enrollment by centers in the United States were relatively low.

Embolization was the sole treatment performed in 26% and 21% of patients in the intervention arms of ARUBA and the SAIVM AVM study, respectively.[19, 78] The relatively generous utilization of standalone embolization contrasts with modern AVM management, in which embolization is relegated to a largely adjunctive role. Low-grade AVMs, which are favorable targets for resection or SRS, comprised the majority of the ARUBA (67%) and SAIVM AVM study (55%) intervention arms.

In the SAIVM AVM study, the obliteration rates for embolization versus resection were 45% versus 83%, respectively.[78] In ARUBA, the obliteration rates for embolization versus resection were 50% versus 100%, respectively.[83] Therefore, resection achieved obliteration in a

considerably higher proportion of AVMs than standalone embolization in both prospective studies. SRS alone yielded a low obliteration rate of 18% in ARUBA. Taken together, the frequent use of embolization, particularly for operable low-grade AVMs, and short-term follow-up after SRS likely contributed to the modest overall obliteration rate of 44% in intervention arm of ARUBA.[83]

The primary endpoint (*i.e.*, death or symptomatic stroke) occurred in 50% of ARUBA patients treated with embolization alone or combined with another modality. The majority of patients in ARUBA who reached the primary endpoint had a hemorrhagic stroke (67%). One could hypothetically attribute the early difference in hemorrhagic stroke rates between the medical and intervention arms to procedure-related hemorrhages. However, the survival curves for the two arms did not converge or intersect over time, which is likely due to delayed hemorrhages from the large proportion of incompletely obliterated AVMs. As such, patients assigned to intervention in ARUBA underwent treatments that may not have sufficiently improved the natural history of their AVMs (*i.e.*, through flow reduction or obliteration of the nidus).

Following ARUBA, many retrospective studies have been conducted to investigate the treatment outcomes for unruptured AVMs with modern procedural management. Overall, intervention rates for unruptured AVMs in the United States do not appear to have changed significantly since the publication of ARUBA.[84] A multicenter study of 509 ARUBA-eligible patients treated with SRS reported obliteration in 75% and adverse neurological outcomes (defined as any new or worsening neurological symptoms or death) in 13% after a mean follow-up of 86 months, with an annual post-SRS hemorrhage rate of 0.9%.[85] The estimated follow-up duration to realize a

benefit from SRS for unruptured AVMs was over a decade, but the young age of most AVM patients appeared to translate into an overall benefit of intervention with SRS over a patient's lifetime, particularly in the pediatric population.[86-88] Surgical series of unruptured AVMs reported superior outcomes compared to ARUBA for low-grade AVMs, with obliteration rates of nearly 100% and permanent neurological deficits rates of less than 4%.[36, 89] A study of 61 ARUBA-eligible patients treated with Onyx embolization, including embolization alone in 41%, embolization and SRS in 57%, and embolization and resection in 2%, reported obliteration, stroke or death, and treatment-related mortality rates of 77%, 20%, and 7% after a median follow-up of 60 months.[90]

A recent comparison of Kaplan-Meier plots between 142 ARUBA-eligible patients treated with multimodal therapy and those enrolled in ARUBA found a significantly lower rate of symptomatic stroke or death in the ARUBA-eligible cohort than the intervention arm of ARUBA.[82] Although the outcomes were comparable between the ARUBA-eligible cohort and the medical management arm of ARUBA, the annualized stroke rate of the ARUBA-eligible cohort compared favorably to ARUBA's medical management arm and other natural history studies.[11, 91] Therefore, with appropriate patient and treatment selection, the risks of natural history may exceed that of intervention after 5 to 10 years of follow-up for a subset of unruptured AVMs. However, one must acknowledge these retrospective, observational data are subject to bias and confounding and therefore additional prospective studies are warranted to further guide proper management of unruptured AVMs.

Based on the available literature, intervention for ruptured low- to intermediate-grade AVMs is frequently pursued, while multimodality treatment is occasionally employed for ruptured high-grade AVMs. Most patients with unruptured low-grade AVMs may benefit from resection, but the decision should be made by a multidisciplinary team comprising neurosurgeons, neurointerventionalists, vascular neurologists, and radiation oncologists. SRS is a reasonable intervention for small- or medium-sized unruptured intermediate-grade AVMs in patients with at least a decade of life expectancy and for unruptured low-grade AVMs in patients who are medically unfit for surgery or refuse a craniotomy.[92, 93] There is insufficient evidence to endorse embolization as a primary intervention for unruptured AVMs, but it continues to have an important adjunctive role in multimodality treatment approaches. Conservative management is often the preferred option for the majority of unruptured high-grade AVMs and large-volume intermediate-grade AVMs, due to the poor outcomes afforded by intervention for these lesions.[89, 94]

Data from ongoing trials and observational studies may shed further light on AVM intervention and its associated risks. The Treatment of Brain AVMs study (TOBAS), which has been recruiting since 2015, is a randomized controlled trial comparing the 10-year risks of disabling stroke or death between conservative management and intervention for ruptured or unruptured AVMs, with a registry for AVMs managed outside the randomized trial.[95] TOBAS also includes a nested trial assessing the role of embolization in patients allocated to surgery or radiation therapy. The NIH-funded MARS consortium is investigating the long-term outcomes and treatment risks of unruptured AVMs.[96] The results of these studies will provide crucial evidence that guides future AVM clinical trials.

Conclusions

This review provides an up-to-date, comprehensive discussion of the natural history, pathobiology, and management strategies for brain AVMs. Currently available data support intervention for most ruptured AVMs and appropriately selected unruptured AVMs. The risk to benefit profile of the available treatment modalities, alone or in combination, should be carefully weighed against an AVM's expected natural history in the context of each patient's life expectancy and preferences. Grading scales developed for AVM resection and SRS have helped guide treatment decisions. Critique of prior prospective studies comparing intervention to conservative management for unruptured AVMs has limited their impact to guide evidence-based practice. Additional prospective, comparative trials incorporating modern procedural approaches to unruptured AVMs versus conservative management are needed.

Name	Location	Contribution
Ching-Jen Chen, MD	University of Virginia, Charlottesville, VA	Design and conceptualization of study, data analysis and interpretation, drafting of manuscript, critical revision of the manuscript for important intellectual content
Dale Ding, MD	University of Louisville, Louisville, KY	Drafting of manuscript, critical revision of the manuscript for important intellectual content
Colin P. Derdeyn, MD	University of Iowa, Iowa City, IA	Critical revision of the manuscript for important intellectual content
Giuseppe Lanzino, MD	Mayo Clinic, Rochester, MN	Critical revision of the manuscript for important intellectual content
Robert M. Friedlander, MD, MA	University of Pittsburgh, Pittsburgh, PA	Critical revision of the manuscript for important intellectual content
Andrew M. Southerland, MD MSc	University of Virginia, Charlottesville, VA	Critical revision of the manuscript for important intellectual content
Michael T. Lawton, MD	Barrow Neurological Institute, Phoenix, AZ	Critical revision of the manuscript for important intellectual content
Jason P. Sheehan, MD PhD	University of Virginia, Charlottesville, VA	Design and conceptualization of study, critical revision of the manuscript for important intellectual content, study supervision.

Appendix 1: Authors

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Additional References can be found here: https://doi.org/10.5061/dryad.1ns1rn8rj

Table 1. Incidence of brain AVMs.

				Detection Rate, number per 100,000 patient-years (95% CI)		
Study	**Location**	**Time Period**	**Population**	**Ruptured**	**Unruptured**	**Total**
Jessurun et al., 1993[3]	The Netherlands Antilles	1980–1990	155,000	1.03 (0.59–1.68)	0.06 (0.002–0.36)	1.10 (0.64–1.75)
Brown et al., 1996[4]	Olmsted County, Minnesota, United States	1965–1992	—	—	—	1.11 (0.68–1.54)
Hillman, 2001[5]	Linköping, Sweden	1989–1999	986,000	0.87 (0.70–1.06)	0.38 (0.27–0.51)	1.24 (1.04–1.47)
Stapf et al., 2002 (NOMASS)[6]	Northern Manhattan, New York City, United States	1993–1997	136,623	0.55 (0.11–1.61)	—	—
Al-Shahi et al., 2003 (SIVMS)[7]	Scotland, United Kingdom	1999–2000	4,114,052	0.51 (0.37–0.69)	0.61 (0.45–0.80)	1.12 (0.90–1.37)
Stapf et al., 2003 (NYIAVMS)[8]	New York islands, United States	2000–2002	9,429,541	0.51 (0.41–61)	0.83 (0.71–0.96)	1.34 (1.18–1.49)
Gabriel et al., 2010 (KPMCP)[9]	Northern California, United States	1995–2004	~3,000,000	0.70 (0.60–0.80)	0.72 (0.63–0.83)	1.42 (1.29–1.57)

CI=confidence interval; NYIAVMS=New York Islands AVM Study; KPMCP=Kaiser Permanente Medical Care Program; SIVMS=Scottish Intracranial Vascular Malformation Study; NOMASS=Northern Manhattan Stroke Study.

Table 2. Hemorrhage risk of untreated brain AVMs.

			Hemorrhage Risk, crude annual percentages (95% CI)			Functional Outcome
Study	**Sample Size, n**	**Follow-up, years (mean/median)**	**Ruptured**	**Unruptured**	**Total**	
Graf et al., 1983[13]	191	3.0	2%†	2%–3%	—	—
Crawford et al., 1986[14]	217	10.4	—	—	2%	Cumulative neurological disability rates of 17% and 27% at 10 and 20 years, respectively.
Brown, et al., 1988[20]	168	8.2	—	2.25%	—	Mortality rate of 5.4% at last follow-up.
Mast et al., 1997[15]	281	0.8	17.8%	2.2%	8.8%	Moderate to severe disability (mRS score>2) rate of 9.5% for patients with hemorrhage in follow-up.
Hernesniemi et al., 2008[16]	238	13.5	2.8%	1.6%	2.4%	Severe hemorrhage (Hunt-Hess grade >2) in 64% of patients with hemorrhage in follow-up.
Da Costa, et al., 2009[17]	678	2.9	7.48%	3.35%	4.61%	Poor outcome (GOS score<4) in 37% of patients with hemorrhage in follow-up.
Kim et al., 2014 (MARS)[11]	2,525	2.4	4.8% (3.9%–5.9%)	1.3% (1.0%–1.7%)	2.3% (2.0%–2.7%)	—
Yang et al., 2018[18]	160	8.0	5.78%	1.09%	2.74%	Moderate to severe disability (mRS score>2) rate of 15.2% at last follow-up. Worse mRS score in 20.6% of patients at last follow-up compared to baseline.
Mohr et al., 2020 (ARUBA)[76]	110	4.4	—	2.94%*	—	Neurological disability (mRS score>1) rate of 18% at 5 years.

CI=confidence interval; n=number; ARUBA=A Randomised trial of Unruptured Brain Arteriovenous malformations; MARS=Multicenter AVM Research Study; mRS=modified Rankin Scale; GOS=Glasgow Outcome Scale
*2.2% in the initial ARUBA study (n=125).[19]
†6% in 1st year

Table 3. Predictors of AVM hemorrhage.

Study	Sample size, n	Initial presentation vs. follow-up	Predictors of hemorrhage
Graf et al., 1983[13]	191	Follow-up	• Smaller size (diameter ≤3 cm) in unruptured AVMs • Neurological condition in previously ruptured AVMs
Crawford et al., 1986[14]	217	Follow-up	• Prior hemorrhage • Older age at diagnosis
Mast et al., 1997[15]	281	Follow-up	• Prior hemorrhage • Male sex • Exclusively deep venous drainage
Stefani et al., 2002[21]	390	Follow-up	• Deep location • Larger diameter (>3 cm)
Stefani et al., 2002[22]	390	Initial presentation	• Presence of venous ectasias • Deep location • Fewer number of draining veins
Khaw et al., 2004[23]	623	Initial presentation	• Infratentorial location • Exclusively deep venous drainage • Presence of associated arterial aneurysm • Smaller diameter
Hernesniemi et al., 2008[16]	238	Follow-up	• Prior hemorrhage • Infratentorial location • Deep location • Larger diameter (>5 cm)
Da Costa, et al., 2009[17]	678	Follow-up	• Prior hemorrhage
Kim et al., 2014[11]	2,525	Follow-up	• Prior hemorrhage • Older age at diagnosis • Presence of associated arterial aneurysm
Ding et al., 2019[10]	2,338	Initial presentation	• Superficial location

			• Exclusively superficial venous drainage • Larger volume

Table 4. Outcomes after AVM interventions.

Study	Location	Study period	Follow-up, months	Patients, n	Ruptured, n (%)	Adverse outcome, n (%)	Obliteration rate, n (%)
Microsurgery							
Hartmann et al., 2000[32]	United States	1990–1998	12	124	40.3%	New neurological deficit, 37.9%	—
Davidson and Morgan, 2010[33]	Australia	1989–2009	12	529	—	mRS score >1, 9.1%	97.0%
Kim et al., 2015[34]	United States; Australia	—	—	1,009	48.3%	Worse mRS score, 22.0%	—
Schramm et al., 2017[35]	Germany	1983–2012	64	288	50.0%	Permanent neurological deficit, 12.2%	99.0%
Wong et al., 2017[36]	Canada	1994–2014	36	155	0%	Permanent neurological deficit, 16.1%	98.1%
Endovascular Embolization							
Starke et al., 2009[45]	United States	1997–2006	43	202 (377 procedures)	39.1%	New clinical deficit, 2.5%	—
Saatci et al., 2011[46]	Turkey	1999–2008	47	350 (607 procedures)	46.6%	Permanent neurological deficit, 7.1%	51.1%
Sahlein et al., 2012[47]	United States	1997–2006	—	130 (168 procedures)	43.8%	Worse clinical outcome, 6.1%	32.8%
Pierot et al., 2013[48]	Germany; Italy; Belgium; The Netherlands;	2005–2008	—	117 (237 procedures)	34.2%	mRS score >2, 5.1%	23.5%

	Latvia; France						
Baharvahdat et al., 2014[49]	France	2000–2012	—	408 (846 procedures)	48.0%	Permanent disability, 12.0%	48.5%
Crowley et al., 2015[50]	United States	1995–2012	—	327 (446 procedures)	47.6%	Permanent neurological morbidity, 9.6%	—
Stereotactic Radiosurgery							
Paul et al., 2014[55]	Spain	1993–2005	132	662	45.6%	Hemorrhage, 6.1%; Neurological damage, 3.8%	71.2%
Pollock et al., 2016[56]	United States	1990–2009	93	381	31.0%	Hemorrhage, 8.9%; Permanent RIC, 6.0%	66.7%
Starke et al., 2017[57]	United States; Canada	1988–2013	84	2,236	39.3%	Hemorrhage, 7.4%; RIC, 29.2%; Symptomatic RIC, 9.4%; Permanent RIC, 2.7%	64.7%

mRS=modified Rankin Scale; RIC=radiation-induced changes; n=number

Table 5. Comparisons of AVM grading systems.

Grading Scales	Components	Predicted Outcomes
Surgery		
Spetzler-Martin grading scale[39]	Size (diameter) <3cm = 1 point 3–6cm = 2 points >6cm = 3 points Venous drainage pattern Superficial only = 0 points Deep component = 1 point Location Non-eloquent = 0 points Eloquent = 1 point*	Neurological deficit 1 point (grade I) = 0% 2 points (grade II) = 5% 3 points (grade III) = 16% 4 points (grade IV) = 27% 5 points (grade V) = 31%
Spetzler-Ponce classification[40]	Class A = Spetzler-Martin grades I + II Class B = Spetzler-Martin grade III Class C = Spetzler-Martin grades IV + V	Adverse outcomes Class A = 8% (95% CI:6–10%) Class B = 18% (95% CI:15–22%) Class C = 32% (95% CI:27–38%)
Supplementary grading scale[44]	Age <20 years = 1 point 20–40 years = 2 points >40 years = 3 points Unruptured presentation No = 0 points Yes = 1 point Diffuse nidus No = 0 points Yes = 1 point	Worse neurological outcome[34]† 2 points (grade II) = 0% 3 points (grade III) = 2% 4 points (grade IV) = 10% 5 points (grade V) = 19% 6 points (grade VI) = 24% 7 points (grade VII) = 39% 8 points (grade VIII) = 63% 9 points (grade IX) = 55%** 10 points (grade X) = 0%**
Radiosurgery		
Modified radiosurgery-based AVM score[61]	0.1×nidus volume (in cm^3) + 0.02×patient age (in years) + 0.5× nidus location (deep [basal ganglia, brainstem,	AVM obliteration without new deficits ≤1.00 = 62% 1.01–2.00 = 53%

	or thalamus]=1; other=0)	<2.00 = 32%
Virginia radiosurgery AVM scale[e-64]	AVM volume <2 cm^3 = 0 points 2–4 cm^3 = 1 point >4 cm^3 = 2 points Location Non-eloquent = 0 points Eloquent = 1 point* History of hemorrhage No = 0 points Yes = 1 point	Favorable outcome‡ 0 points = 83% 1 point = 79% 2 points = 70% 3 points = 48% 4 points = 39%

AVM=arteriovenous malformation

*Sensorimotor, language and visual cortex, hypothalamus, thalamus, internal capsule, brainstem, cerebellar peduncles, and deep cerebellar nuclei
†Worse final modified Rankin Scale score compared to before surgery. This grading scale is combined with the Spetzler-Martin grading score for a total of 10 points.
**Limited sample size
‡ AVM obliteration with no post-treatment hemorrhage and no permanently symptomatic radiation-induced changes.