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Management of Brain Arteriovenous Malformations

A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

The American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Cerebrovascular Section affirms the educational benefit of this document.

Endorsed by the Society of NeuroInterventional Surgery

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Purpose—The aim of this statement is to review the current data and to make suggestions for the diagnosis and management of both ruptured and unruptured brain arteriovenous malformations.

Methods—The writing group met in person and by teleconference to establish search terms and to discuss narrative text and suggestions. Authors performed their own literature searches of PubMed, Medline, or Embase, specific to their allocated section, through the end of January 2015. Prerelease review of the draft statement was performed by expert peer reviewers and by the members of the Stroke Council Scientific Oversight Committee and Stroke Council Leadership Committee.

Results—The focus of the scientific statement was subdivided into epidemiology; diagnosis; natural history; treatment, including the roles of surgery, stereotactic radiosurgery, and embolization; and management of ruptured and unruptured brain arteriovenous malformations. Areas requiring more evidence were identified.

Conclusions—Brain arteriovenous malformations are a relatively uncommon but important cause of hemorrhagic stroke, especially in young adults. This statement describes the current knowledge of the natural history and treatment of patients with ruptured and unruptured brain arteriovenous malformations, suggestions for management, and implications for future research. **(*Stroke*. 2017;48:e200-e224. DOI: 10.1161/STR.0000000000000134.)**

Key Words: AHA Scientific Statements ■ arteriovenous malformations ■ cerebral hemorrhage ■ diagnosis ■ embolization, therapeutic ■ intracranial hemorrhages ■ neurosurgery ■ radiosurgery

Brain arteriovenous malformations (bAVMs) are uncommon vascular lesions that present with spontaneous intracranial hemorrhage (ICH), seizures, or headache and typically in young adults.[1–3] A large proportion of patients are diagnosed with incidental asymptomatic bAVMs after brain imaging is obtained for other reasons.[4] Current treatment options include conservative management, surgical resection, stereotactic radiosurgery (SRS), endovascular embolization, or combinations of these treatments (multimodal therapy). The primary goal of these interventions is to prevent hemorrhagic stroke. The risks of

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these treatments must be weighed against the natural history risks. There have been considerable advances in our knowledge of the natural history and outcomes of treatment of bAVMs since the American Heart Association (AHA) statement in 2001.[5] These include the accumulation of new data related to epidemiology, biology, imaging, outcomes with treatment, and introduction of new embolic agents. Most notable of these data are the results of the first randomized trial of intervention for unruptured bAVMs, the ARUBA trial (A Randomized Trial of Unruptured Brain Arteriovenous Malformations).[6] The purpose of this statement is to review the current data, to make recommendations for the management of patients with bAVMs, and to provide an update to the prior AHA statement.

Methods

The members of the writing group were selected by the AHA to represent the breadth of healthcare professionals who manage these patients. Experts in each field were screened for important conflicts of interest and then met by telephone to determine subcategories to evaluate. These subcategories included incidence; natural history and outcome; diagnosis; prevention of rebleeding; surgical, endovascular, and stereotactic radiosurgical treatment; and management of ruptured and unruptured bAVMs. Together, these categories were thought to encompass all of the major areas of management. Each subcategory was led by 1 author, with 1 or 2 additional coauthors who made contributions. Full online searches were conducted independently by each author and coauthor of all English-language articles on bAVMs in humans, following the practices of the AHA Task Force on Practice Guidelines for literature searches.[7] Searches were limited to literature after the original 2001 guideline was published. Drafts of summaries and suggestions were circulated to the entire writing group for feedback. Sections were revised and merged by the writing group chair. The resulting draft was sent to the entire writing group for comment. Comments were incorporated into the draft by the writing group chair and vice chair, and the entire writing group was asked to approve the final draft. The chair and vice chair revised the document in response to peer review, and the document was again sent to the entire writing group for additional suggestions and approval.

This statement complies with the recent changes for AHA guidelines and scientific statements. Formal recommendations with grades and levels of evidence are now generally left to the comprehensive guidelines. For the present subject of patients with unruptured or ruptured bAVMs, these include the primary and secondary prevention guidelines and the ICH guideline. Scientific statements such as this one are more narrowly focused and serve to increase the knowledge and awareness of healthcare professionals. Some suggestions for management will be made when appropriate.

Epidemiology and Biology

bAVMs have an asymptomatic prevalence on brain magnetic resonance (MR) studies of 0.05% (95% confidence interval [CI], 0.01–0.10)[4] and a prevalence of detected asymptomatic or symptomatic bAVMs in the population of 10 to 18 per 100 000 adults (95% CI, 0.010–0.018).[8,9] The new detection rate (incidence) is ≈1.3 per 100 000 person-years.[10–12] In population-based studies, symptomatic bAVMs manifest with hemorrhagic stroke (58%), epileptic seizure(s) (34%), or other symptoms such as progressive neurological deficit (8%).[5,9,11,13–19]

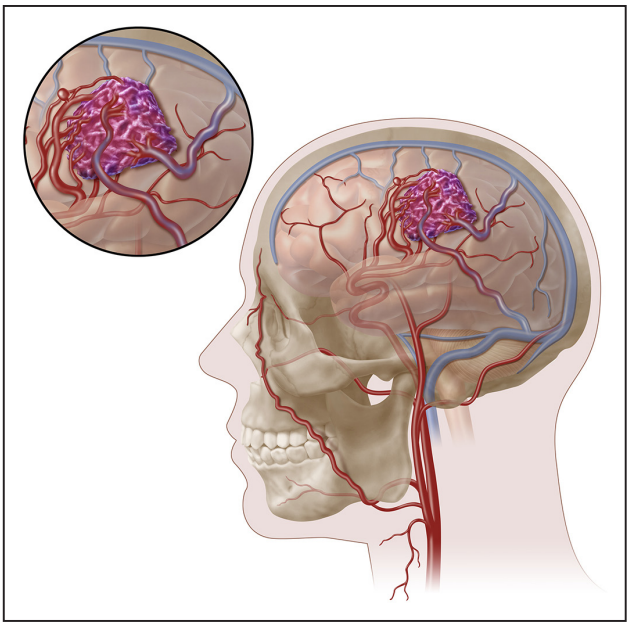


Figure 1. Artist's rendition of a superficial brain arteriovenous malformation on the cortical surface. The primary feeding arteries are branches of the middle cerebral artery. There is a small feeding artery aneurysm seen best on the magnified inset in the **top left** corner. The nidus is depicted as a mix of red and blue vessels. The draining veins are superficial (on the cortical surface and draining to the sagittal and transverse sinuses).

bAVMs are characterized by their unique anatomy and hemodynamic physiology: direct connections from artery to vein with no intervening capillary bed (Figure 1).[20] These connections consist of a tangle of abnormal dilated channels that are neither arterial nor venous. This tangle is called the nidus. Blood is shunted from artery to vein through the nidus, resulting in higher-than-normal flow in both feeding arteries and draining veins and higher-than-normal pressure on the venous side. Other factors that contribute to complex vascular physiology include high flow rates and shear stress, venous outflow obstruction that can result from longstanding arterial flow rates, arterial steal, and compartmentalization. Anatomic features associated with hemorrhagic presentation include the presence of intranidal aneurysms (Figure 2) or deep venous drainage (drainage into the galenic system), venous outflow obstruction, and deep or infratentorial location.[21–23] Identification of these features is critically important and guides treatment in many patients. Genetic factors and microscopic hemorrhage have also been associated with hemorrhage as a clinical presentation.[24]

The past decade has seen dramatic advances in our knowledge of the genetic, molecular, and cellular factors involved in bAVM formation, growth, and rupture. Although this information has no impact on current recommendations for management, it has great potential for defining future therapeutic options or rupture risk. Hereditary hemorrhagic telangiectasia is an autosomal-dominant vascular disease and the most common genetic cause of bAVMs.[25,26] The mutation for hereditary

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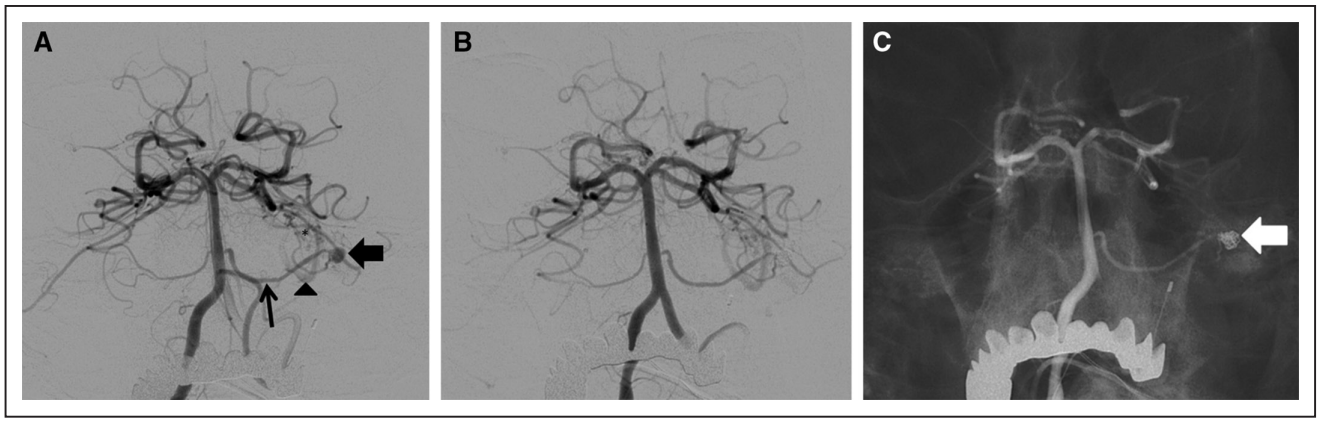


Figure 2. A, Feeding artery aneurysm. This is an anteroposterior projection from a digital subtraction angiography after injection of the right vertebral artery. The long black **arrow** points to an enlarged anterior inferior cerebellar artery. The large **arrow** points to a feeding artery aneurysm at the point where the nidus (asterisk) begins. The black **arrowhead** points to the early venous drainage, the angiographic hallmark of a brain arteriovenous malformation (bAVM). **B**, The bAVM after coil embolization of the aneurysm. **C**, The unsubtracted view showing the coils (white **arrow**).

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hemorrhagic telangiectasia involves haploinsufficiency of signaling genes for transforming growth factor-β. Ten percent to 25% of people with hereditary hemorrhagic telangiectasia will have at least 1 bAVM.[26,27] Mutations in RASA1 are associated with the capillary malformation–arteriovenous malformations (AVM) syndrome.[28] The variable expression in this syndrome supports the hypothesis that somatic second hits are necessary for the development of vascular malformations.[28] These data, as well as the observation of de novo development of bAVMs, support the idea that many of these lesions are acquired and not congenital.[29–31]

Natural History

The natural history of bAVMs is a widely studied topic, with much of the emphasis centered on ICH event rate because it represents the most common and morbid clinical manifestation of the disease. bAVM ICH tends to have a more benign natural history than primary ICH.[32–34] Knowledge about the untreated clinical course of bAVMs is based on observational research studies of everyday clinical practice and the conservative management group in the ARUBA trial (although some of these participants received bAVM treatment).[6] In these studies, outcomes are usually described for participants who are never selected to undergo treatment of their bAVMs, participants until the time they are selected to undergo treatment, or participants with partially obliterated bAVMs. None of these studies have described an unselected group of people who do not undergo bAVM treatment, so true natural history remains unknown, and our knowledge is based on studies of untreated clinical course.[33]

In addition, ICH is not the only long-term consequence of bAVMs. Many patients with bAVMs develop seizure disorders.[35] Some patients may also develop progressive and disabling neurological deficits, although this is rare.[36] The latter phenomenon has been attributed to local tissue ischemia from either arterial steal or venous outflow obstruction leading to venous hypertension.[36,37] This physiology may also contribute to the risk of seizures.[38] Finally, headaches are a common complaint in patients with bAVMs.

Hemorrhage Risk

An individual patient data meta-analysis of 2525 patients with 141 ICHs during 6074 person-years of follow-up in a variety of population- and hospital-based studies provides the most reliable data on untreated bAVM clinical course.[21] In this meta-analysis, the overall annual risk of ICH was 2.3% (95% CI, 2.0–2.7) per year over 10 years; however, the annual risk differed according to whether a bAVM was unruptured (1.3%; 95% CI, 1.0–1.7) or ruptured (4.8%; 95% CI, 3.9–5.9) when first diagnosed (Table 1).

Table 1. Annual Rupture Risks for Ruptured and Unruptured bAVMs

Study	Patients, n	Year	Study Type	Annual ICH Risk (Unruptured) (95% CI)	Annual ICH Risk (Ruptured) (95% CI)
Kim et al[21]*	2525	2014	Pool patient-level data	1.3 (1.0–1.7)	4.8 (3.9–5.9)
Gross and Du[22]†	3923	2013	Meta-analysis	2.2 (1.17–2.7)	4.5 (3.7–5.5)
Abecassis et al[23]	…	2014	Review article	2.1–4.1	…
Mohr et al[6]	233	2016	Prospective clinical trial	2.0 (0.9–4.5)	…

bAVMs indicates brain arteriovenous malformations; CI, confidence interval; and ICH, intracranial hemorrhage.

*The study by Kim et al[21] includes 4 published series: Kaiser Permanente of Northern California Arteriovenous Malformation Study (n=856), Halim et al[39]; University of California San Francisco Brain Arteriovenous Malformation Study Project (n=787), Kim et al[40]; the Columbia Arteriovenous Malformation Database Project (n=672), Stapf et al[15]; and the Scottish Intracranial Vascular Malformation Study (n=210), Al-Shahi et al.[12]

†The study by Gross and Du[22] includes 4 published series: Da Costa et al,[16] Kim et al,[40] Stapf et al,[15] and Yamada et al.[41]

Table 2. Hazard Ratios for Rupture Risk for Clinical and Anatomic Features From Longitudinal Studies of Unruptured bAVMs

Study	n	Year	Study Type	Exclusively Deep Venous Drainage (95% CI)	Any Deep Venous Drainage (95% CI)	Increasing Age at Diagnosis (95% CI)	Deep Nidus Location (95% CI)	Associated Aneurysms (95% CI)	Female Sex (95% CI)	Size <3 cm (95% CI)
Kim et al[21]	2525	2014	Pooled patient-level data	1.60 (0.95–2.68)	…	**1.34 (1.17–1.53)**	…	…	1.49 (0.96–2.30)	1.02 (0.90–1.16)
Gross and Du[22]	3923	2013	Meta-analysis	**2.4 (1.1–3.8)**	1.3 (0.9–1.75)	1.0 (0.4 -1.6)	**2.4 (1.4–3.4)**	**1.8 (1.6–2.0)**	1.4 (0.6–2.1)	1.0 (0.8–1.2)

bAVMs indicates brain arteriovenous malformations; and CI, confidence interval.
Boldface type indicates statistical significance.

Prognostic Factors

The most consistently reported prognostic factor for ICH after diagnosis is initial presentation with ICH. In the individual patient data meta-analysis described above, the annual risk of first-ever ICH for people with unruptured bAVMs was 1.3% (95% CI, 1.0–1.7), whereas the risk of recurrent ICH was 4 times higher at 4.8% (95% CI, 3.9–5.9) for people with ruptured bAVMs.[21] Findings were similar in other systematic reviews and meta-analyses.[22,23] Increasing age was the only other prognostic factor significantly associated with future ICH in the individual patient data meta-analysis with a 1.34-fold increase per decade, although this has not been consistently found in smaller individual studies (Table 2). Exclusively deep venous drainage seems to be another prognostic factor for ICH, conferring a 1.6- to 2.4-fold increase in annual risk. Deep AVM nidus location and associated arterial aneurysms may be prognostic factors, but better-powered studies are needed to be more confident about this. Validated risk prediction models have not been produced.

Unruptured bAVMs

Many observational cohorts have examined the natural history of bAVMs. Ondra et al[42] and Hernesniemi et al[43] followed up 160 and 238 patients for a mean of 23.7 and 13.4 years, yielding the often-cited 2% to 4% annual risk of hemorrhage. In a meta-analysis of 3923 patients, Gross and Du[22] reported overall (3.0%) ICH rates and those in the setting of no (2.2%) and prior (4.5%) rupture. The authors noted prior hemorrhage (hazard ratio [HR], 3.2; 95% CI, 2.1–4.3), deep AVM location (HR, 2.4; 95% CI, 1.4–3.4), exclusively deep venous drainage (HR, 2.4; 95% CI, 1.1–3.8), and associated aneurysms (HR, 1.8; 95% CI, 1.6–2.0) were statistically significant risk factors for hemorrhage (Tables 1 and 2).

The annual ICH rate in the observation arm of the ARUBA trial was ≈2.0% per year. The sample size was small (223 subjects), however, and some patients randomized to observation went on to intervention.[6]

Additional angioarchitectural risk factors are noted in other series (Table 3). Lv et al,[46] in a review of 302 patients with bAVMs, noted a 1.9% annual ICH rate and multiple risk factors for hemorrhage, including deep and infratentorial location (odds ratio [OR], 2.718; P=0.007), single draining vein (OR, 0.404; P=0.008), venous varices (OR, 0.488; P=0.018), and all-type (OR, 8.541; P=0.002) or flow-related (OR, 2.923; P=0.002) hemorrhages. The size of the bAVM has also been implicated as a risk factor, although in the larger cohorts cited above, this association has not been replicated.

The hereditary hemorrhagic telangiectasia bAVM population is an interesting subgroup as it relates to predicting ICH risk in part because of the characteristic angioarchitectural manifestations (small bAVM size, cortical location, and multiplicity[47]) but also the genotypes (ENG, ALK1, or SMAD4) involved. The capillary malformation–AVM syndrome (RASA1) is interesting for the same reasons.[28] Although there is no evidence that any of the genotypes confer higher ICH risk or a particular bAVM appearance,[26,48] the concept of combining imaging and genetic information to assess risk will grow as biomarker investigation expands.

Ruptured bAVMs

As described above, relative to unruptured bAVMs, ruptured bAVMs have higher rates of rebleeding, particularly within the first year from ictus. Kim et al[21] harmonized data from 4 large studies including 2525 patients with ruptured and unruptured bAVMs followed up for 6074 patient-years. The annual risk for recurrent hemorrhage in patients with ruptured bAVMs was 4.8% (95% CI, 3.9–5.9). This finding is the primary reason cited for treatment of ruptured bAVMs.

The clinical outcomes from bAVM ICH are less well defined. Ko et al[49] compared variables that associated with

Table 3. Angioarchitectural Features Associated With Ruptured bAVMs (Retrospective Studies Comparing Ruptured and Unruptured bAVMs; Potential Prognostic Significance)

Study	n	Year	Larger Size	Aneurysm	Venous Stenosis	Venous Ectasia	Exclusively Deep Draining	Single Draining Vein
Stapf et al[15]	464	2006	Yes	Yes	…	…	Yes	Yes
Sahlein et al[44]	122	2014	…	Yes	Yes	…	…	Yes
Alexander et al[45]	519	2015	…	…	…	Yes	Yes	Yes
Lv et al[46]	302	2011	…	Yes	…	Yes	Yes	Yes

bAVMs indicates brain arteriovenous malformations.

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primary and bAVM-related ICH, whereas Van Beijnum et al[34] described the differences in outcomes between primary and bAVM hemorrhagic groups. The authors noted that independent predictors of death at 1 year were primary ICH (OR, 21; 95% CI, 4–104) and increasing ICH volume (OR, 1.03; 95% CI, 1.01–1.05) and independent predictors of death or dependence at 1 year were primary ICH (OR, 11; 95% CI, 2–62) and Glasgow Coma Scale score on admission (OR, 0.79; 95% CI, 0.67–0.93). More recently, Appelboom et al[50] examined the utility of a historical ICH scale and a new bAVM-based scale, shifted in age and hemorrhagic volume, in their ability to predict poor (modified Rankin Scale score ≥3) clinical outcomes. The authors reported good agreement between the scales and increased specificity of the novel scale to predict outcome (87.9% versus 68.2%; $P<0.001$).

There is also less reported in relation to bAVM-specific imaging characteristics and ICH-related clinical outcomes. There are reports concerning ICH volume, a potential surrogate for clinical outcome, and its relationship with anatomic characteristics. Alén et al,[51] in a review of 28 patients with bAVMs with a nidus <1 cm, noted a mean ICH volume of 25 cm^3. As it relates to bAVM location, ICH within the posterior fossa tends to have poorer clinical outcomes relative the supratentorial compartment. Abla et al,[52] in a review of 154 patients, noted smaller ICH volumes (10.1 versus 25.6 cm^3; $P=0.003$) in the infratentorial than in the supratentorial location despite poorer clinical outcomes (OR, 4.96; $P=0.003$). This is not surprising given the potential involvement of the brainstem, through either direct hemorrhagic extension or local mass effect. Furthermore, location within the posterior fossa has been noted to manifest associated aneurysms[52–56] more frequently then supratentorial bAVMs.

Pediatric bAVMs

There are differences in the natural history of bAVMs particularly as it relates to ICH event rate. Fullerton et al,[57] in review of 1219 patients with bAVMs (251, 21% children) comparing adult with pediatric index ICH and subsequent ICH rates, noted higher rates of ICH presentation in children (56% versus 43%; $P<0.001$) and in univariable analysis similar (2.0% versus 2.2%) annual hemorrhagic rates. In multivariate analysis, however, the authors noted a 90% reduction in subsequent ICH rates compared with adults (HR, 0.10; $P=0.036$). In review of 106 pediatric patients with bAVMs presenting with ICH, Blauwblomme et al[58] noted a subsequent annual ICH rate of 2.71%. They noted the presence of an associated aneurysm (HR, 2.43; $P=0.0001$) and deep venous drainage (HR, 1.89; P 0.01) as risk factors for subsequent hemorrhage. Furthermore, evidence suggests that for those patients with bAVMs not presenting with hemorrhage, the incident ICH rate may be lower during the first decade of life.[59] This effect may be related to hormonal changes at puberty, as is the case for many extracranial AVMs.[60] Another situation influenced by fluctuating hormone levels is pregnancy, and special attention has been given to the bAVM ICH during and after pregnancy. Liu et al,[61] in review of 774 female patients 18 to 40 years of age (393 with ICH, 381 without ICH) encompassing 452 pregnancies, found no increased risk (OR, 0.71; 95% CI, 0.61–0.82) of pregnancy or puerperium.

Risk of a First Seizure, Risk of Epilepsy After a First Seizure

bAVMs may cause focal or secondary generalized seizures or both.[35] The mechanism is unclear. Increased venous backpressure, perhaps related to venous outflow obstruction, may be involved.[38,62] A population-based study found that the 5-year risk of first seizure was 8% (95% CI, 0–20) for patients with bAVMs. ICH or focal neurological deficit increased the risk of seizure to 23% for patients with bAVMs. Younger age, temporal location, cortical involvement, and nidus diameter >3 cm increased seizure risk. The 5-year risk of developing epilepsy after a first seizure was 58%.[63,64] One prospective observational study collected records of 101 consecutive patients with unruptured and ruptured bAVMs during a 10-year period and compared patients with and without seizures. Multivariate logistic regression showed that clinical presentation with seizures correlated with a location in the temporal and frontal lobes and with a superficial topography. The strongest association (OR, 3.48; 95% CI, 1.77–6.85) was observed between seizures and bAVM location in the temporal lobe.[65] A study of 302 consecutive patients with unruptured bAVMs added superficial venous drainage and presence of varices in the venous drainage as features associated with seizures ($P=0.005$ and $P=0.022$, respectively). Posterior fossa and deep locations and coexisting aneurysms were statistically associated with the absence of seizures.[66] A study of 155 consecutive patients with bAVMs from a prospective, single-center database identified an independent effect of arterial border-zone location on seizure occurrence. All patients with seizures showed the presence of a superficial venous drainage component.[67]

Imaging Diagnosis and Evaluation

The definitive diagnosis of a bAVM is currently supplied by digital subtraction angiography (DSA), although many bAVMs can be reliably identified by computed tomography (CT) and MR imaging (MRI), including angiographic imaging (CTA and MRA). The imaging evaluation of bAVMs can be separated into 3 clinical settings: diagnosis, treatment planning, and follow-up. The various imaging modalities may be used in isolation at any stage in this process but are often used in combination given the additive information they provide.

bAVMs are found on imaging as incidental findings or as part of the evaluation for patients with new-onset seizures, neurological deficits, or brain hemorrhage. Depending on the location of the bAVM and the site of rupture, isolated or concurrent intraparenchymal, intraventricular, or subarachnoid hemorrhage may occur.

Computed Tomography

Noncontrast CT has >90% sensitivity for acute subarachnoid hemorrhage[68,69] and hemorrhagic stroke.[70] Although limited in detecting bAVMs, noncontrast CT can demonstrate features, including enlarged or calcified vessels along the margin of the hemorrhage or regions of increased density corresponding to the vascular nidus, suggestive of an underlying vascular anomaly.[71] The clinical scenario and location of intraparenchymal hemorrhage can also be helpful in differentiating a primary from secondary pathogenesis of the hemorrhage in

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which the deep cerebral and brainstem regions are more related to primary hypertensive causes.[72,73] Delgado Almandoz et al[71] studied 623 patients presenting with intraparenchymal hemorrhage and used features on noncontrast CT to separate studies into low (29.4%), indeterminate (67.6%), and high probability (3%) for an underlying vascular anomaly. They found the positive predictive (84.2%) and negative predictive (97.8%) values for the low- and high-probability populations in identifying the presence or absence of a vascular anomaly. It should be noted, however, that the majority of vascular anomalies found came from patients with indeterminate noncontrast CT findings.

The presence of any vascular anomaly, as defined by catheter DSA or operative inspection, in the setting of intraparenchymal hemorrhages evident on CT varies.[71,74] In a systematic review of convenience samples of people with ICH investigated with catheter angiography, bAVMs were found in association with 20% of ICHs overall, and they were more common in people <50 versus ≥50 years of age (27% versus 18%), in normotensive versus hypertensive (28% versus 6%) individuals, and in those with lobar (31%) and posterior fossa (37%) hemorrhages.[73] As described above, the overwhelming majority of patients will have noncontrast CT features indeterminate for a vascular anomaly, bAVM or otherwise, and should undergo cross-sectional angiography. CTA has excellent spatial resolution and is minimally invasive, fast, and readily available.[75–77] In a meta-analysis of 526 patients undergoing CTA in the setting of ICH, Josephson et al[74] reported pooled estimates of sensitivity and specificity of 0.95 (95% CI, 0.90–0.97) and 0.99 (95% CI, 0.95–1.00) for the diagnosis of an underlying vascular cause. CTA is, however, limited in that it involves ionizing radiation and is degraded by metallic streak artifacts, often encountered in patients after treatment. More advanced multidetector CTA techniques now permit temporal encoding, an advantage historically limited to DSA. Such 4-dimensional techniques permit better delineation of arterial, nidal, and venous components, although the technology is not uniformly available and its accuracy relative to DSA is not known.[78] CT perfusion imaging of nidal and perinidal flow patterns may provide prognostic information on bAVM-related neurological deficits; however, the use of this information is not established, and perfusion imaging requires added radiation exposure.[79] CTA compares well with catheter-based DSA with high degrees of sensitivity (83.6%–100%) and specificity (77.2%–100%) for the detection of an underlying vascular anomaly in the setting of intraparenchymal hemorrhage.[71,74,80,81]

Magnetic Resonance

Advances in MR and MRA technology have improved the spatial and temporal resolution so that they approach CT and CTA in their accuracy to detect bAVMs in the setting of ICH.[74] In the aforementioned meta-analysis by Josephson et al,[74] data on 401 patients undergoing MRA in the setting of ICH yielded a sensitivity and specificity of 0.98 (95% CI, 0.80–1.00) and 0.99 (95% CI, 0.97–1.00). MRA, both time-of-flight and contrast-bolus type, is more limited in the detection of smaller vessels (<1-mm diameter), aneurysms,[82,83] smaller bAVM nidi (<10 mm),[84] and venous outflow anatomy.[85,86] These features, although not essential in making the diagnosis of bAVM, are important in treatment planning.

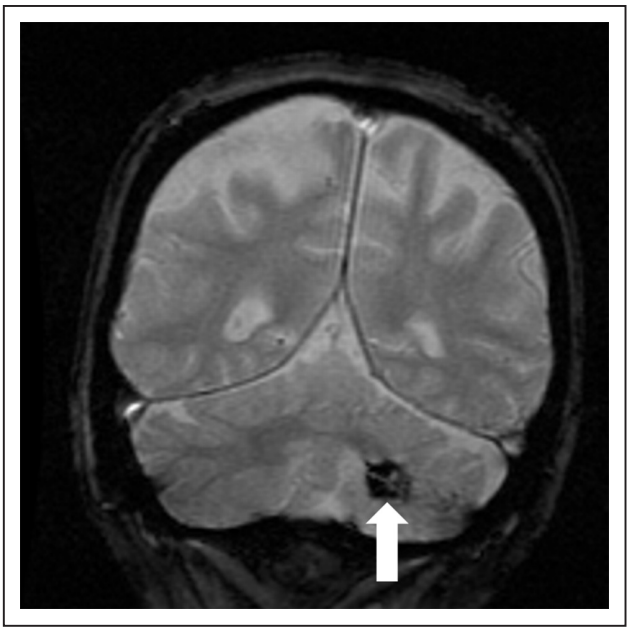


Figure 3. Microhemorrhage. Susceptibility-weighted coronal magnetic resonance image through the cerebellum showing signal loss consistent with prior hemorrhage (white **arrow**) adjacent to a brain arteriovenous malformation (not shown). This area did not correspond to calcification on computed tomography or a vascular structure on other imaging sequences. Microhemorrhage may be an indicator of higher risk for future hemorrhage in clinically unruptured patients.

For a subset of patients with acute hemorrhagic bAVMs and those without ICH presentation, MR may identify prior subclinical microhemorrhage using susceptibility-weighted imaging (Figure 3). In a review of 975 cases, Guo et al[24] noted evidence of old hemorrhage by susceptibility-weighted imaging in 6.5% of patients that was associated with ICH presentation (OR, 3.97; $P<0.001$) and new-onset ICH (OR, 3.53; P 0.010). These results were confirmed by histopathological assessment for hemosiderin within resected bAVM samples (n=129) whereby 36.2% were positive and again with strong correlation with ICH presentation (OR, 3.64; $P<0.034$). MR also permits advanced imaging methods such as arterial spin labeling that may differentiate individual arterial afferents and perfusion qualities in and around the bAVM nidus.[38,87] These, along with other advanced encoding techniques, in combination with physiological data permit derivation of computational fluid dynamic measures describing flow and pressure conditions for arterial, venous, and global cerebral anatomy.[88,89] Functional MRI may be useful in assessing language and somatosensory centers in relation to bAVMs.[90] In a retrospective analysis of 68 patients with bAVMs, Gallagher et al[90] noted that blood oxygen level–dependent functional MRI lesion-to-activation distance was not predictive of postoperative motor or language deficits. This result may be related in part to compromised blood oxygen level–dependent activation from either hemosiderin deposition, causing susceptibility artifact, or high flow from the nidus itself.

Both CT and MR are cross section–based modalities and provide information about the bAVM and the adjacent brain.

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This non-bAVM information is essential because it relates to assessing treatment planning.[91] The more widespread availability of CT and MR also affords more opportunity to translate techniques used for non-bAVM pathology. For example, advanced segmentation algorithms[92–94] and fractal analysis[95,96] of bAVMs have shed new light on ways to advance our understanding of the disease and to clinically manage patients. MR also has a more versatile array of contrast agents that may serve as markers of inflammation.[97–99] Modern angiographic systems permit flat-panel CT acquisition and 3-dimensional rotational angiography. These modalities improve spatial understanding of bAVM angioarchitecture and the ability to fuse DSA data with CT and MR data. Such fusion has proved helpful in treatment planning.[100] Lastly, temporally encoded 3-dimensional rotational angiography has recently been described and has been demonstrated to be effective in detailing bAVM anatomy for microsurgical[101] and radiosurgical[102] planning.

Digital Subtraction Angiography

DSA is the reference standard for the diagnosis of bAVMs. In addition, DSA provides the most detailed and accurate information on bAVM angioarchitecture and hemodynamics. Once a bAVM is identified or suspected by CT or MR, DSA is generally pursued to further characterize the lesion if treatment is being considered. Lesions with a small nidus may not be visible on CTA or MRA or may not be distinguishable from normal vessels. In addition, the dynamic aspect of angiographic imaging facilitates the identification of an early draining vein relative to the normal parenchyma. For these reasons, DSA is often performed after negative CT and MR studies in patients presenting with an ICH. In some cases, an AVM nidus may be missed on all imaging modalities, including the initial DSA, likely because of compression by adjacent hematoma. Follow-up vascular imaging after resolution of the thrombus is important for some patients, depending on the clinical situation.

DSA has the highest degree of both spatial and temporal (ie, identification of shunting between arteries and veins) resolution of all diagnostic imaging modalities.[5,76,103–105] In addition, it will allow a more informed decision in terms of both the feasibility of and the need for endovascular treatment. The immediate risks of DSA relate primarily to neurological complications such as thromboembolic stroke. These risks are low, likely related to the relatively young age and good health of patients with bAVMs compared with patients presenting with ischemic stroke.[106] In addition to stroke risk, DSA entails radiation exposure with potential long-term consequences.[107] bAVM DSA studies often require high frame rates, magnified views, and multiple injections, which, together with CT studies and potential additional exposure from endovascular procedures, may lead to high doses to the head and lens of the eye.[107] For these reasons and the highly specific angioarchitectural information (discussed below) obtained in these studies, DSA may be best performed by the members of the cerebrovascular team contemplating treatment.

Angiographic features that have been associated with hemorrhage in retrospective studies comparing ruptured and unruptured bAVMs include the specific drainage patterns such as the number of veins, presence of subependymal venous involvement, and number of veins reaching a sinus.[5] Additional features associated with prior hemorrhage include venous ectasia, venous reflux or occlusion, flow-related or nidal arterial aneurysms, angiopathy, angiogenesis, or pial-pial collaterals.[5,15,16]

Alexander et al,[45] in a review of 519 patients with bAVMs, noted an association of only deep venous drainage (OR, 3.42; $P<0.01$) and a single draining vein (OR, 1.98; $P=0.02$) with ICH presentation. The authors also noted an inverse relationship between ICH presentation and presence of venous ectasia (OR, 0.52; $P=0.02$). Sahlein et al[44] reviewed DSA-based angioarchitectural features in 122 patients with bAVMs under the premise that ICH risk is related primarily to flow impedance. They noted significant interactions between single venous outflow and deep or infratentorial location, exclusively deep venous drainage, and small nidus size, all variables that have been linked to ICH in other large retrospective studies. Their multivariate model found the presence of a single draining vein (OR, 6.6; $P=0.001$), presence of venous stenosis (OR, 2.6; $P=0.023$), and aneurysm (OR, 2.4; $P=0.49$) to be linked to higher ICH risk.

Associated aneurysms occur in 2.7% to 58% of patients, with larger, modern series noting 15% to 30%,[108,109] and may be remote, arising from arterial afferents, or intranidal in location, with the last 2 types being associated with a higher annual rate of ICH,[9,110,111] in addition being entities with their own inherent rupture risk. There is evidence that the significance of an associated aneurysm is more than its mere presence. In a review of 314 patients with aneurysms and bAVMs, Kim et al[109] noted that the presence of any nonnidal aneurysm (OR, 3.0; $P<0.001$), particularly those along the distal aspect of arterial afferent (OR, 5.3; $P=0.011$), was associated with ICH. When ICH was classified into bleeding abutting the nidus or aneurysm (feeding artery or intranidal), only the association with the aneurysms remained (OR, 3.0; $P=0.002$) in the former clinical scenario. Stein et al,[108] in a series of 409 bAVMs within the supratentorial brain, noted a 14% prevalence of aneurysm, and although they noted no significant differences in aneurysmal hemorrhage as it relates to location relative the nidus, they did note that those that ruptured were significantly larger than those that did not (6.6 versus 4.4 mm; $P=0.0046$). This finding is supported by the work of Platz et al,[53] who also reported a significant difference in the sizes of ruptured and nonruptured bAVM–associated aneurysms (6.25 versus 4.17 mm; $P<0.001$). For a subset of the flow-related aneurysms, after bAVM treatment, the lesions may involute without directed therapy.[109,111]

Other angioarchitectural features have also been noted. Stapf et al,[112] in a review of 464 patients with bAVMs, noted that lesions supplied by branches of ≥2 major (anterior, middle, or posterior) cerebral divisions had lower risk of ICH (OR, 0.40; $P<0.001$). The authors noted positive associations with ICH for bAVM size (OR, 0.96; $P<0.001$), solely deep venous drainage (OR, 3.19; $P<0.001$), and associated aneurysm (OR, 2.72; $P<0.001$). Using DSA-based evaluation, Shankar et al[113] reviewed 78 patients with nonhemorrhagic bAVMs presenting with (n=33) and without (n=45) seizures for distinguishing angioarchitectural features. They noted location (frontal,

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parietal, temporal lobe; OR, 4.52; 95% CI, 0.95–21.47), venous outflow stenosis (OR, 6.71; 95% CI, 1.99–22.56), and long (>3-cm superficial course) pial draining vein (OR, 5.71; 95% CI, 1.32–24.56). The authors enumerated these values as a 3-point score with a receiver-operating characteristic curve of 0.841 (95% CI, 0.749–0.933). Alternatively, Sahlein et al[44] modeled an ICH prediction scale, as discussed previously, denoting a single draining vein, venous stenosis, and the presence of any aneurysm as significant risk factors for hemorrhage.

The angiographic architectural findings pertinent in the adult setting are similar to those in the pediatric setting. Ellis et al[114] reviewed imaging on 135 pediatric patients with bAVMs reporting bAVM size (OR, 0.57; $P<0.01$), exclusively deep venous drainage (OR, 4.94; $P=0.02$), and an infratentorial location (OR, 9.94; $P=0.01$) as associated with hemorrhagic presentation. Hetts et al[115] compared angioarchitectural features in adult (n=630) and pediatric (n=203) patients. The authors noted that ICH presentation was more common in children (59% versus 41%; $P<0.001$), as was exclusively deep venous drainage (28% versus 14%; $P<0.001$). They also observed fewer flow-related aneurysms (13% versus 29%; $P<0.001$) and venous ectasia (35% versus 52%; $P<0.001$).

There are few data describing the relative utility of imaging in the diagnosis of bAVMs within the pediatric population. Brunelle et al[116] described the use of CT and catheter angiography to define bAVMs with moderate specificity (77%). More recently, Koelfen et al[117] examined 67 children undergoing MR with neurological disorders, 5 of whom had vascular malformations. The nidus and major arterial feeders were demonstrated, although definition was more difficult for larger, more complex, and hemorrhagic lesions. Despite limited data on the topic, the literature describing contemporary adult imaging may be largely applicable to the pediatric population. Use, however, should be different between adult and pediatric groups to minimize ionizing radiation, although long-term posttreatment follow-up angiography may be useful in children because there are reports of bAVM recurrence.[118] In addition, DSA in children often requires general anesthesia, which brings additional safety concerns when considering the imaging workup of pediatric patients.

Long-Term Surveillance

There are few data for the utility of imaging surveillance for untreated bAVMs. Long-term surveillance is important after treatment, particularly after SRS. DSA is the reference standard for the assessment of bAVM treatment outcome because the presence of an early draining vein without a visible nidus indicates some residual risk for hemorrhage and will not be identified by MR or CT. As with treatment planning, the excellent spatial and temporal resolution it provides allows the greatest ability to assess for remaining nidus or an early draining vein. Thus, there is a premium on making this finding. MR and MRA are improving in their sensitivity and specificity to assess for residual bAVMs, particularly in the postradiosurgical treatment setting.[83,119] Buis et al,[120] in a review of T2 and time-of-flight MRA in 120 patients with bAVMs after radiosurgery, reported a specificity of 89% of 95% and sensitivity of 52% relative to DSA for the identification of residual nidus. In a review of contrast-enhanced, 4-dimensional MRA in 36 patients with bAVMs after radiosurgery, Lim et al[121] reported a sensitivity of 64% to 80% relative to DSA for the identification of residual nidus. In the more general posttreatment (microsurgical, radiosurgical, or endovascular) setting, Soize et al,[122] in a review of contrast-enhanced, 4-dimensional MRA in 36 patients with bAVMs, reported a specificity of 100% and sensitivity of 74% relative to DSA for the identification of residual nidus. MR, however, is insensitive for smaller (<10 mm) lesions and for those having undergone embolization. O'Connor and Friedman[123] reviewed MRIs in 120 patients with bAVMs after radiosurgery and reported an 82% accuracy relative to DSA for the identification of residual nidus, although they noted that the performance declines with smaller bAVM volumes (<2.8 cm^3, 70%; >2.8 cm^3, 90%). The need for long-term surveillance and the imaging methods used will depend on an assessment of the clinical situation, the relative risks of imaging, and the ultimate use of the information.

For those patients presenting as children, delayed follow-up DSA has proved helpful in identifying recurrent bAVMs. Recurrence of bAVMs has been reported in a small number of case series with a disproportionate number of cases in children and in the setting of ICH presentation.[118,124] Because of the ionizing radiation of DSA and the frequent need for general anesthesia, there are efforts to advance MR techniques, particularly in children.[58]

Treatment Modalities

The definitive treatment of bAVMs should be complete elimination of the nidus and the arteriovenous shunt. Partial nidal obliteration does not appear to reduce hemorrhage risk.[125] There are anecdotal reports of patients with neurological symptoms related to hemodynamic factors in whom partial treatment may improve these symptoms, at least temporarily.[62,126,127]

Three, often complementary, therapeutic tools have been developed to achieve these goals. The first is microsurgical resection. This may be performed primarily or after endovascular embolization to reduce bleeding risks during surgery and to facilitate complete and uncomplicated removal. The second is SRS. This also may be done primarily or after embolization to reduce nidal volumes and potentially to improve nidal obliteration rates. The final method is endovascular embolization itself. Although this is most often used as a precursor to microsurgery or radiosurgery, there are cases in which it may be definitive therapy. This section briefly reviews recent data on techniques, risks, perioperative management, and the relative advantages and disadvantages of each modality.

Microsurgery

Microsurgical resection via craniotomy is a common approach for treating patients with bAVMs. The primary goal is definitive cure: to safely and completely resect the bAVM to eliminate the morbidity and mortality associated with its potential rupture. The sequential steps associated with this treatment approach include the following: (1) perform a craniotomy to obtain adequate exposure to the bAVM, including its arterial feeders and venous outflow; (2) isolate and divide its arterial feeders; (3) circumferentially dissect the nidus from the adjacent brain parenchyma and surrounding neurovascular structures; (4)

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Table 4. Surgical Outcomes Case Series

Study	n	Year	Design	Ruptured, %	SM Grade	Surgical Risk (95% CI), %	Obliteration Rate, %
Davidson and Morgan[147]	296	2010	Prospective database	49	I–II	0.7 (0–3)	96.9 Overall
	65	…	…	…	III–IV (Noneloquent)	17 (10–28)	…
	168	…	…	…	III–V (Eloquent)	21 (15–28)	…
Spetzler and Ponce[148]*	250	2011	Pooled case series	NR	I	4 (2–7)	NR
	485	…	…	…	II	10 (7–13)	…
	455	…	…	…	III	18 (15–22)	…
	218	…	…	…	IV	31 (25–37)	…
	68	…	…	…	V	37 (26–49)	…

CI indicates confidence interval; NR, not reported; and SM, Spetzler-Martin.

*Spetzler and Ponce[148] reported pooled surgical outcomes from 7 studies of ruptured and unruptured brain arteriovenous malformations, including the original data set for the outcome scale. Two studies were published after 2000, by Davidson and Morgan[147] and Lawton et al.[149]

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disconnect the venous outflow; and (5) close the wound. The main advantages of microsurgical resection over other treatment options include its high rate of complete nidus obliteration, its ability to immediately eliminate hemorrhage risk, and its long-term durability. Its main disadvantages are its invasiveness, length of recovery, and associated neurological risks.

Surgical Adjuncts

A variety of adjuncts have been introduced over the years to improve the safety and efficacy of bAVM surgery. Functional MRI and diffusion tensor imaging–based tractography have been applied to more accurately determine the proximity of bAVMs to eloquent cortex and critical white matter tracts, information that can be used to improve patient selection and to guide surgical approach to minimize the chance of postoperative neurological deficits.[128,129] Stereotactic neuronavigation has been used to permit smaller, more accurate, and more effective approaches to bAVM surgery. This technique involves quantitative spatial fusion of the patient's preoperatively obtained CT or MRI with a fiducial coordinate system that permits guidance of surgical exposure and real-time localization of the bAVM and surrounding neurovascular structures.[130–132] As described in detail below, endovascular embolization has frequently been applied to improve surgical safety and to potentially expand the pool of bAVMs amenable to safe surgical extirpation. Specific goals of this catheter-based adjunct include elimination of arterial feeders (especially those that would be difficult to access in early stages of surgery), reduction in flow or nidus volume that would permit safer surgical removal, and treatment of high-risk angiographic features, including feeding artery and intranidal aneurysms. Intraoperative vascular imaging, including DSA, indocyanine green videoangiography, and fluorescein videoangiography, has been applied to bAVM surgery.[133–146] The primary goal of DSA is to verify complete nidus obliteration at the time of surgery, whereas the main utility of videoangiography with either fluorescein or indocyanine is to intraoperatively map the angioarchitecture of the bAVM, including differentiating arterial feeders from arterialized draining veins. Taken together, these surgical adjuncts have likely improved patient selection, reduced operative morbidity, and enhanced patient recovery, although the benefits associated with these iterative enhancements will be difficult to determine conclusively in clinical studies.

Outcome After Microsurgery

A large number of case series have been published over the years that demonstrate the safety profile and overall efficacy of microsurgery for the treatment of patients with bAVMs (Table 4).[147,150] Most microsurgical series are single-center, retrospective cohort studies. From such studies, microsurgery appears most indicated for a specific subset of patients with bAVMs who are at lowest risk for perioperative neurological complications. As mentioned below, grading scales have been developed to predict patient outcome after bAVM microsurgery to inform the patient and to guide the treating physician in terms of the optimal bAVM management. As is the case with all studies examining treatment outcomes, local expertise and rigorously documented patient outcomes must be included in the treatment algorithm.

Surgical Treatment Outcome Scales

The Spetzler-Martin (SM) grading scale, by far the most commonly used classification system, uses 3 anatomic factors (nidus size, nidus location relative to eloquent brain, and pattern of venous drainage) to enumerate 5 bAVM grades.[151] The SM grading scale is a well-validated tool for estimating the risks of surgical resection using baseline imaging data. The scale often requires both DSA and cross-sectional imaging to make these determinations. The SM grading scale uses the following point system to assign bAVM grade: nidus size (<3 cm=1point; 3–6 cm=2 points; and >6 cm=3 points), nidus location (noneloquent=0 points; eloquent=1 point), and pattern of venous drainage (superficial only=0 points; deep=1 point). The largest dimension by CT/MR and DSA in centimeters should be used for SM grading, although assessment in 3 orthogonal dimensions and volume estimated with the ABC/2 formula is also recommended.[5] Eloquence can be determined

with physiological imaging or neuropsychological testing, although using anatomic criteria, the Joint Writing Group on bAVM report standards list the sensorimotor, visual, and language cortices, basal ganglia, thalamus, hypothalamus, brain stem, cerebellar peduncle, internal capsule, and deep cerebellar nuclei as being eloquent regions.[5,151] Spetzler and Martin[151] dichotomize venous drainage into superficial or deep patterns. Superficial drainage refers to venous outflow into veins on the cortical surface. Deep drainage indicates outflow into deeper structures such as the ventricular system or basal veins that drain to the galenic system. Venous drainage is considered deep if any or all of the drainage is through deep veins such as internal cerebral veins, basal veins, and precentral cerebellar vein.

This system has proved to be an accurate predictor of surgical risk and shows that patients harboring low-grade bAVMs (SM grades I and II) have significantly less chance of postoperative permanent neurological deficit than those with high-grade bAVMs (SM grades IV and V).[9,151,152] The relative prevalence of each SM grade is unknown, although a multisite tertiary care center review of 1289 patients found that 55% of patients had a 30- to 60-mm lesion, 55% had deep venous drainage, and 71% involved eloquent anatomy.[18] These figures would suggest that the majority of bAVMs are grade III or higher, although the referral bias to these academic medical centers likely misrepresents the volume of grade I and II lesions treated in the community at large.

Multiple large, mostly retrospective single-institution case series have been published documenting rates of radiographic cure and patient outcomes using the SM grading system,[147,149–151,153–156] and a pooled analysis including many of these studies has been published.[148] Angiographic cure rates were shown to be very high across all SM grades (95%–99%[148]). Rates of poor outcome, on the other hand, were highly correlated to SM grade.[148] Specifically, rates of poor outcome were calculated as follows: SM grade I=4% (95% CI, 2–7), SM grade II=10% (95% CI, 7–13), SM grade III=18% (95% CI, 15–22), SM grade IV=31% (95% CI, 25–37), and SM grade V=37% (95% CI, 26–49).[148] These results demonstrate that microsurgical removal is best suited for low-grade bAVMs (SM grades I and II), whereas surgical removal of high-grade bAVMs (SM grades IV and V) carries high risk of poor patient outcome.

Efforts to identify a subset of intermediate-grade bAVMs (SM grade III) that may benefit from surgical removal have been proposed by Lawton[157] and Davies et al.[158] In this system, SM grade III bAVMs are subcategorized on the basis of specific combinations of size, location, and venous drainage. It showed that SM grade III bAVMs (combination of small size, eloquent location, and deep venous drainage) have surgical outcomes similar to that of low-grade bAVMs, whereas SM grade III bAVMs (combination of medium size, noneloquent location, and deep venous drainage) and SM grade III+ bAVMs (combination of medium size, eloquent location, and superficial venous drainage) have worse surgical outcomes similar to that reported for high-grade bAVMs.[157]

Finally, a supplementary scoring system to the traditional SM grading scale has been proposed to enhance its predictive power for expected outcomes after microsurgical resection of bAVMs.[149] Based on past studies examining additional factors predictive of patient outcome after bAVM surgery,[159] this supplementary scoring system added the following factors to augment the traditional SM grading scheme: patient age (<20 years=1 point; 20–40 years=2 points; >40 years=3 points), bleeding or hemorrhagic presentation (yes=0 points; no=1 point), and nidus configuration (compact=0 points; diffuse=1 point). Using receiver-operating characteristic curve analyses, these investigators showed in a single-institution case series[149] and later in a multicenter case series[156] that the supplemented SM system was more accurate at predicting patient outcome than the SM system alone. This scale, referred to as the Lawton-Young supplementary grading scale, has been validated in a separate cohort of 1009 patients.[156,160]

It should be emphasized, however, that the use of this or any other surgical grading system should be viewed as a starting point for the evaluation of bAVM operability. Many other issues should be considered, including the natural history of the bAVM, patient comorbidities and life expectancy, whether preoperative endovascular embolization will be required, including assessment of its neurological risks, whether the bAVM is amenable to other treatment modalities, and individual patient expectations concerning the risks and recovery time associated with bAVM hemorrhage versus the risks and recovery time associated with bAVM intervention.

Stereotactic Radiosurgery

SRS is typically performed to achieve obliteration of bAVMs that are deemed too risky for resection because of anatomic factors such as location or general medical problems. SRS leads to endothelial cell proliferation, progressive, concentric vessel wall thickening, and eventually luminal closure.[161,162] Most series with long-term follow-up demonstrate obliteration in 70% to 80% of bAVMs after SRS (Table 5).[166–177] Unlike microsurgery or embolization, both the beneficial and adverse effects of SRS may not be fully apparent for several years after treatment. Radiation-induced necrosis, edema, and cyst formation can develop long after treatment.[170,178] In addition, there is a risk of hemorrhage during the latency period before obliteration.[166–176] During this latency period, the risk of hemorrhage is ≈1% to 3% per year and does not appear to be appreciably altered from the natural history of bAVMs.[179,180]

Indications for SRS

A large number of published series demonstrate the clinical efficacy and general safety of SRS for the treatment of patients with bAVMs.[166–177] Most bAVM SRS series are single-center, retrospective cohort studies.[166–177] Such studies indicate that SRS appears to be best suited for small- to moderate-volume bAVMs that are generally <12 cm^3 in volume or <3 cm in maximum diameter. SRS is also well suited for bAVMs located in deep or eloquent regions of the brain.[181] Other factors, including nidus volume, prior embolization, history of hemorrhage, and patient age, have also been demonstrated to affect the outcome of SRS for bAVMs, and thus, these factors frequently affect the decision-making process concerning bAVM management with SRS.[174,182]

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Table 5. Radiosurgical Outcomes for Unruptured bAVMs

Study	n	Year	Design	Follow-Up	Obliteration Rate, %	Annual Hemorrhage Rate Before Obliteration, %	Permanent Radiation Injury, %
Ding et al[163]	444	2013	Retrospective	86 mo (mean)	62	1.6	2.0
Starke et al[164]	2236	2016	Multicenter registry	7 y (median)	64.7	1.1	2.7
Pollock[165]	174	2013	Retrospective	64 mo (mean)	78.9	NR	4

bAVMs indicates brain arteriovenous malformations; and NR, not reported.

Outcomes After SRS

Obliteration of the bAVM is the primary goal for SRS. With obliteration, prevention of hemorrhage from the bAVM nidus is achieved. Most studies show bAVM obliteration in 70% to 80% of bAVMs, and obliteration is typically achieved within 2 to 3 years after treatment.[166–177,183] After confirmation of obliteration on angiography, hemorrhage becomes a rare event.

Secondary goals of SRS are the preservation or improvement of neurological function, including lessening of bAVM-associated epilepsy or other nidus-associated neurological signs or symptoms.[184] In those patients with pre-SRS epilepsy, seizure-free status or well-controlled epilepsy on anticonvulsants was typical in the long term after SRS. Improvements in seizures have generally been observed in patients with a reduction in or complete obliteration of the bAVM nidus after SRS.[184–186] Neurological function after SRS appears preserved or improved in the vast majority of patients with bAVMs.[174]

Although prior embolization can reduce the size of a large nidus to a suitable target volume for SRS and obliterate high-risk features associated with a bAVM (eg, a perinidal or intranidal aneurysms), it may reduce the overall obliteration rate after SRS.[177,187] This association is not certain and, if real, may be related to difficulties in accurately targeting residual nidus after embolization rather than any impact of embolization material on SRS dose.[188]

Delayed effects after radiosurgery include adverse radiation effects. During the latency period after SRS, symptomatic changes attributable to adverse radiation effects occur in ≈10% of patients, but this risk varies by bAVM location, target volume, and margin dose (dose to surrounding normal tissue). Corticosteroids and, less frequently, bevacizumab have been used to ameliorate symptomatic adverse radiation effects.[189,190] Permanent neurological changes from adverse radiation effects are seen in 2% to 3% of patients.[174,177] Radiation-induced changes seen on MRI as T2-weighted MRI hyperintensities around the nidus have also been associated with eventual nidus obliteration. Such MRI features may represent changes in vascular flow, indicating progressive and impending bAVM occlusion. Other changes such as delayed cyst formation and radiation-induced neoplasia are rare but may occur ≥10 years after SRS.[191,192]

Radiosurgical Outcome Scales

Additional pretreatment scales have been put forward for radiosurgical and embolization outcomes.[158] The radiosurgical metrics emphasize patient age, lesion size, location relative eloquent brain, and surrogates of arteriovenous shunt volume (eg, feeding artery diameter, number of draining veins). These variables have been validated retrospectively and prospectively.[193,194] In a study of obliteration outcomes in 139 patients undergoing radiosurgery, Taeshineetanakul et al[195] reported bAVM size (OR, 0.88; 95% CI, 0.81–0.96), noneloquent location (OR, 3.2; 95% CI, 1.29–7.93), low-flow pattern (OR, 3.47; 95% CI, 1.6–7.53), and an absence of perinidal angiogenesis (OR, 2.61; 95% CI, 1.21–5.64) as predictive of bAVM obliteration. The association of noneloquent location and bAVM obliteration may be related to higher isodose.

Repeat Radiosurgery

In instances of partial regression of the nidus, protection from hemorrhage does not seem substantial.[196] Thus, additional treatment may be advised. If SRS is the best option, repeat treatment can be considered. Provided that it is performed ≥3 years after the initial treatment, repeat SRS generally confers a rate of obliteration and adverse radiation effects comparable to the initial treatment.[197,198]

Endovascular Treatment

Embolization is commonplace in the multidisciplinary treatment of bAVMs.[199–201] Therefore, it is used in a number of different clinical scenarios. Preoperative embolization constitutes the most common application for endovascular treatment. The advent of the liquid embolisate ethyl vinyl alcohol copolymer (EVOH) has expanded the use of this approach.[202] Occasionally, embolization may be a curative, stand-alone treatment modality for the complete occlusion of bAVMs. The development of detachable-tip microcatheters, which may mitigate the risks of catheter adhesion and withdrawal, may facilitate this curative strategy. Another indication for endovascular treatment is as an adjunct to surgery or radiosurgery. In this scenario, embolization can be used either to diminish the size of a bAVM or to occlude high-risk features such as ruptured nidal and perinidal aneurysms before definitive treatment of the remaining portion of a bAVM.[203] Finally, embolization has been used as a palliative treatment in which flow is reduced in an effort to reduce symptoms potentially caused by vascular steal.

Preoperative Embolization

The goals of preoperative embolization depend on the location and anatomy of the bAVM and the planned surgical approach. The primary goal is to aid in the resection of the AVM by reducing intraoperative bleeding or postoperative complications such as normal perfusion pressure breakthrough. Normal perfusion pressure breakthrough is thought to be related to

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chronic low perfusion pressure in the normal brain surrounding an AVM.[204,205] When the AVM is partially or completely removed, these areas are subject to normal perfusion pressure, and their ability to autoregulate may be impaired initially. This results in delayed brain hemorrhage, swelling, and seizures, similar to that seen after carotid revascularization procedures. Staged embolization of large bAVMs is often pursued to gradually reduce flow to the AVM before removal. Finally, elimination of feeding artery pedicles that may be deep in the surgical exposure is often a goal.

The timing of embolization in relation to surgery is controversial, with no good evidence supporting either an immediate presurgical or delayed surgical approach.[206,207] Similarly, the extent and staging of embolization are also not defined in the current literature. Standard embolization techniques and materials are used and include EVOH, n-butyl cyanoacrylate, polyvinyl alcohol particles, and coils. Often, a combination of these materials is used as dictated by specific anatomic features of the bAVM.[207] In the immediate postembolization period, strict management of blood pressure and attention to changes in the neurological examination are paramount for ensuring improved patient outcomes.[207,208]

Curative Strategies

Angiographic cures with embolization as a stand-alone treatment have been reported in several small case series. A complete occlusion rate of 20% has been reported with the use of cyanoacrylate-based liquid embolic agents.[209] The use of EVOH has increased total obliteration rates to as high as 51% among all bAVMs and up to 96% for select bAVMs with simple angiographic features.[201,202,210,211] The advent of detachable-tip microcatheters, which facilitate prolonged Onyx infusion, may improve the rate of curative embolization. Intuitively, smaller bAVMs with fewer arterial feeders are most amenable to complete obliteration with embolization. These characteristics are also common to SM grade I and II bAVMs, which can be treated safely with surgery.[212] Thus, the comparative risk of curative embolization must be weighed carefully against this proven therapeutic modality. Other concerns with curative embolization are the durability of the embolic materials used and the length of follow-up required to ascertain a definitive cure. There are several case reports of bAVM recurrence after initially complete angiographic obliteration.[213]

Complications of Embolization

The 2 most common complications of embolization are intracerebral hemorrhage and ischemic stroke, and the list of potential causes is long.[214] The causes of ischemic stroke include thromboembolic complications of catheterization and nontarget embolization. Brain hemorrhage may occur from vessel wall injury or AVM rupture.[215] Microcatheter or wire perforation of arterial feeders may occur as a result of access through small tortuous pial arteries, often without normal vessel wall. Feeder artery aneurysms rarely rupture as a consequence of mechanical or hemodynamic forces related to embolization. Finally, and most commonly, the AVM nidus may rupture during embolization or in the hours or days after the procedure. There are several potential causes of this rupture. Some are certainly related to inadvertent closure of the draining vein before elimination of the nidus.[215] Others may relate to changes in pressures of flow dynamics in the AVM itself. These 2 mechanisms constitute the rationale for blood pressure reduction after embolization.[208]

Endovascular Outcome Scales

Endovascular planning measures are less well established, in part because of the varied role of embolization in bAVMs.[216–218] More akin to the SM grading scale, embolization scales emphasize procedural outcomes rather than completeness of bAVM obliteration as with the radiosurgical measures. Feliciano et al[217] put forward a 5-point scale detailing the number of arterial afferents (<3, 3–6, and >6), location-relative eloquent brain, and presence of direct arteriovenous shunting. This scale was established with risk factors identified from a retrospective case series and has not been validated. Starke et al[218] reviewed the clinical data and outcomes after 377 procedures on 202 patients. Twenty-nine had new clinical deficits after embolization (8% of procedures and 14% of patients). In multivariable analysis, the following variables remained associated with new deficits: >1 embolization session, bAVM diameter >3 cm, bAVM diameter >6 cm, deep venous drainage, and eloquent location. A scale was developed weighting these variables and creating a 0- to 4-point scale. Higher scores correlated strongly with increased risk of a neurological deficit. These also have not been validated in a prospective data set. It is interesting that these parameters are similar to the SM scale.

Before Radiosurgery

Embolization, as a means of reducing the size of a bAVM nidus, is commonly used before radiosurgery for bAVMs with >3-cm diameter. Despite the obvious benefits of size reduction, there is some concern that embolization may result in lower rates of obliteration during the latency period.[177,187,219] This may be the result of inaccurate targeting of the lesion because of the artifact of the radiopaque embolic material. Another is the possibility that recanalization of embolized portions may produce delayed recurrences.[203]

Targeted Embolization

Targeted embolization can be used to treat high-risk angiographic features that predispose to bAVM rupture. In general, this strategy is used in cases when definitive treatment is not possible or is deemed too risky. High-risk features include nidal and perinidal aneurysms and arteriovenous fistulas.[16,62,220] As described above, this targeted approach can be undertaken not only as a solitary treatment of the bAVM but also as a means of reducing the likelihood of rupture in the period after radiosurgery.[62] This later application is a new approach, with few clinical data to support it. In addition, the risks of embolization must be taken into account.

Palliative Embolization

Occasionally, bAVMs are thought to produce focal neurological deficits caused by vascular steal or local venous hypertension. In this scenario, embolization of select, high-flow feeders may decrease steal or venous hypertension and thereby palliate symptoms.[221] Although data in support of this paradigm are limited to small series and case reports, the practicality of flow reduction would seem to offer the potential for an improvement in quality of life.[62,126,127]

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Table 6. Multimodal Series for Embolization Followed by SRS

Study	n	Year	Modalities	Obliteration Rate, %	Hemorrhage Before Obliteration	Permanent Complication Rates, Embo/SRS, %
Mathis et al[222]	24	1995	Embo/SRS	50	0	0/4
Gobin et al[223]	30	1996	Embo/SRS	60	3.6%/y	12.6/0
Mizoi et al[224]	29	1998	Embo/SRS	38	1 Patient	11/0
Blackburn et al[203]	19	2011	Embo/SRS	84	0	14/5

Embo indicates embolization; and SRS, stereotactic radiosurgery.

Multimodality/Staged Therapy

For large bAVMs, selection of multimodality or staged therapy should be given careful consideration. As discussed above, one form of multimodal therapy is endovascular embolization followed by surgical resection. Here, the SM grading system and its subsequent modifications provide excellent guidance for this treatment approach for large bAVMs. Another form of multimodal therapy is endovascular embolization followed by SRS (Table 6). Several groups have reported their single-institution results with this approach, with radiographic obliteration rates of 38% to 83% and permanent neurological morbidity rates of 4% to 14%.[203,222–225] Keys to success with this approach include embolizing with a strategy of bAVM volume reduction rather than simply decreasing bAVM flow, targeting a postembolization nidus volume of ≤10 cm^3 to optimize the effectiveness of subsequent SRS, and using sufficient prescription marginal doses during SRS (typically 18–22 Gy).[203] Other multimodal approaches include SRS followed by surgery and a combination of embolization, SRS, and surgery. Results from single-institution case series using such approaches show bAVM obliteration rates of 35% to 58% and treatment-related permanent neurological morbidity rates of 2% to 15%.[199,226]

Finally, a strategy of staged SRS can be considered for the treatment of large bAVMs. Multiple groups have reported their single-institution experience with this approach, which entails dividing the large bAVM into ≥2 subvolumes and treating each of these sections in separate sessions that are separated into 2- to 9-month intervals.[227–233] Results from these case series show bAVM obliteration rates of 33% to 74% and treatment-related permanent neurological morbidity rates of 3% to 13%. Factors associated with improved outcomes include dose per stage, compact nidus, and total bAVM volume.[232] Because staged SRS for large bAVMs produces volume reduction but not complete radiographic cure in a significant portion of patients, repeat SRS or additional salvage approaches, including surgery, may be required.[52,229,234,235]

Follow-Up After Treatment

Following up after treatment depends on the approach taken. A clinical evaluation of the patient should generally coincide with neuroimaging follow-up. For patients who undergo a resection, intraoperative or postoperative angiography should be performed shortly thereafter to confirm complete resection of the bAVM nidus. If there is residual nidus, repeat resection or other treatment options can be used.

For embolization or radiosurgery, follow-up requires repeat neuroimaging. The optimal frequency and method are not well defined, and clinical practice is variable. After radiosurgery, repeat MRI/MRA is most frequently performed at 6-month intervals during the latency period. If MRI is contraindicated (eg, in the setting of a cardiac pacemaker), CT/CTA can be substituted. Similarly, those undergoing embolization generally have follow-up MRI/MRA or angiograms to assess for recanalization or neovascularization.[210,236]

If there is an indication of SRS-induced obliteration of the nidus on MRI/MRA or CT/CTA, a catheter angiogram should be performed to confirm obliteration of the bAVM nidus. Although cerebral angiography is the reference standard for the assessment of bAVM obliteration, some patients refuse angiography to assess for obliteration. MRI has been demonstrated to have 100% specificity, 80% sensitivity, and 91% negative predictive value for the identification of obliteration compared with angiography.[237] In a modern series, O'Connor and Friedman[123] demonstrated an accuracy of 82% for MRI compared with angiography, which increased to 90% for bAVMs <2.8 cm^3 in volume and conversely decreased to 70% for bAVMs >2.8 cm^3 in volume. Because delayed effects such as radiation-induced cyst formation or neoplasia may occur after radiosurgery, long-term follow-up with MRI or CT may be useful.[191,192]

Management of Unruptured bAVMs

The optimal approach to management of unruptured bAVMs remains a subject of debate because of insufficient high-quality, consistent evidence about the lifetime risks of ICH and its predictors and the complications associated with treatment.

Only 1 randomized controlled trial exists to inform the management of unruptured bAVMs: ARUBA. This study recruited 226 adult patients (≥18 years old) with unruptured bAVMs between 2007 and 2013 and randomly allocated them to medical management alone or medical management with interventional therapy (eg, resection, embolization, or SRS alone or in combination).[6] On May 10, 2013, the National Institute of Neurological Disorders and Stroke announced that ARUBA stopped enrollment.[238] A preplanned interim analysis was reviewed by the trial's independent Data and Safety Monitoring Board on April 15, 2013. The data showed that after a mean follow-up of 33 months, the risk of stroke or death in the intervention group (30.7%) was >3 times higher than in the medical management group (10.1%). The Data and Safety Monitoring Board's decision was based on the primary outcome in the study, time to stroke or death. This analysis

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included data from 224 participants enrolled at 39 sites worldwide. On the recommendation of the ARUBA Data and Safety Monitoring Board, the National Institute of Neurological Disorders and Stroke stopped enrollment of patient volunteers in the trial. The National Institute of Neurological Disorders and Stroke stated that "under the experimental conditions in this trial, the interim analysis of data collected to date shows that medical management is superior to intervention in patients with unruptured brain arteriovenous malformations. The DSMB [Data and Safety Monitoring Board] further recommended extended follow-up to determine whether the disparity in event rates will persist over time." ARUBA continues in an observational phase to establish additional 5 years of follow-up.[6]

Otherwise, evidence supporting the management of unruptured bAVMs is restricted to observational studies. In a prospective population-based inception cohort of 204 patients >16 years of age with an unruptured bAVM, 103 underwent intervention (ie, embolization, resection, radiosurgery, or some combination of the same), and the remaining 101 patients had conservative management.[239] The study cohorts were not randomized, so they were not balanced: Those who underwent intervention were younger, more likely to have presented with a seizure, and less likely to have a large bAVM. With a primary outcome of death or sustained morbidity, those with conservative management were less likely to progress to this end point (adjusted HR, 0.59; 95% CI, 0.35–0.99). In evaluating the secondary outcome of nonfatal, symptomatic stroke or death associated with the bAVM, conservatively managed patients were also less likely to achieve this poor outcome during a 12-year follow-up period (adjusted HR, 0.37; 95% CI, 0.19–0.72).

Although these 2 studies support a more conservative approach to unruptured bAVMs, they suffer from 2 major limitations that weaken the conclusions. The first is the very long duration of hemorrhage risk for patients with untreated bAVMs and the relatively short follow-up of the 2 studies above. There is no evidence that hemorrhage risk declines over time. The studies excluded pediatric patients, so the generalizability of the findings to this patient population is not entirely clear. The second criticism is that the complication rates in the treatment arms were much higher than expected. The primary end points of ARUBA in the intervention group for SM grade I (14.3%), II (43.3%), and III (57.1%) AVMs are higher than would have been expected in contemporary series, particularly for surgery or radiosurgery performed alone. These higher complication rates may be related to the large proportion treated with embolization alone or as an adjunct to surgery or SRS. Of the 114 ARUBA patients allocated to intervention, 5 had surgery alone, 30 had embolization alone, and 31 had SRS alone. Twenty-eight had embolization followed by surgery (n=12), SRS (n=15), or both (n=1). Either surgery or SRS for low-SM-grade bAVMs may have yielded better outcomes.

Given its low upfront risks, radiosurgery has specifically been evaluated as a treatment option for patients with unruptured bAVMs. In a retrospective study of 444 patients with bAVMs without evidence of rupture before radiosurgery and a mean duration of clinical follow-up of 86 months, the cumulative obliteration rate was 62%, and the post-radiosurgical annual hemorrhage rate before obliteration was 1.6%.[163] Temporary and permanent radiation-induced changes were symptomatic in 13.7% and 2.0% of patients, respectively. Clinical deterioration occurred in 30 patients and was most frequently observed in patients who had a hemorrhage during the latency period.[163] A recent report from a registry of 2236 patients by Starke et al[164] reported similar outcomes. Favorable outcome, defined as AVM obliteration without recurrent hemorrhage or permanent radiation-induced complications, was observed in 60.3%. In a smaller retrospective study of 174 patients with unruptured bAVMs treated with radiosurgery and with a median follow-up of 64 months, overall obliteration was achieved in 78.9% of patients; 4% (7 patients) had neurological impairment related to radiation-induced complications. The risk of hemorrhage or stroke was noted to be 10.3% at 5 years and 11.5% at 10 years.[165]

In a series of 61 patients with unruptured bAVMs, 9 of the 61 patients (14.8%) treated with microsurgery alone or in combination with SRS and/or embolization had a stroke or died.[240] In that same series, complete obliteration of the bAVM after resection was documented by angiography in 93% of cases. Although treatment of unruptured bAVMs is not without risk, SRS and resection appear to confer a substantial rate of obliteration in these patients.[164]

bAVM Treatment Effect on Seizures and Headaches

The importance of achieving freedom from seizures in the treatment of bAVMs remains poorly defined. Few of the published case series report seizure risk after treatment. Complete obliteration of the bAVM nidus probably reduces the subsequent occurrence of epilepsy.[35] The few studies with concurrent control groups must be addressed with more randomized trials.[63]

Among 440 prospective patients undergoing microsurgical resection of supratentorial bAVMs, 130 (30%) experienced preoperative seizures, and 23 (18% of the 130) with seizures progressed to medically refractory epilepsy. After resection, 96% of patients had freedom from seizures (80%) or only 1 postoperative seizure (16%; mean follow-up, 20.7±2.3 months). Freedom from seizures did not depend on whether there were any preoperative seizures. Deep artery perforator supply to the bAVM was associated with postoperative seizures.[241] A systematic literature review was performed in patients with both bAVMs and presenting seizures treated with SRS. Nineteen case series with data for 997 patients with available seizure outcome data were evaluated. Of these, 437 patients (43.8%) achieved seizure-free status after SRS, and 530 of 771 patients (68.7%) with available data achieved seizure control (seizure freedom or seizure improvement) after SRS. Seizure-free status was achieved in 82% and 41.0% of patients with complete and incomplete bAVM obliteration, respectively. Complete bAVM obliteration offered superior seizure-free rates (OR, 6.13; 95% CI, 2.16–17.44; P=0.0007).[184] In a retrospective study of 164 patients with bAVMs treated with radiosurgery or surgery, bAVM obliteration was predictive of seizure freedom at last

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follow-up (P=0.002). In patients presenting without seizures, 18.4% experienced de novo seizures after treatment, for which surgical resection was an independent risk factor (HR, 8.65; 95% CI, 3.05–24.5; P<0.001).[186]

To determine the effectiveness of different treatments and time to seizure-free state according to the treatment modalities, 399 patients with bAVMs were treated with surgical resection, radiosurgery, or embolization, either alone or in combination. The median follow-up period was 6.0 years (range, 3.0–16.2 years). Seizure-free outcomes after microsurgery, radiosurgery, or embolization were 78%, 66%, and 50%, respectively. In the surgery group, the median time to seizure-free status was 1.1 months (95% CI, 0.7–1.2), whereas the radiosurgery group and embolization-alone group had a median time to seizure-free status of 20.5 months (95% CI, 18.3–23.8) and 8.1 months (95% CI, 6.0–13.5), respectively.[242]

The first meta-analysis designed to study the relative rates of seizure outcomes after the currently used bAVM treatment modalities evaluated all published data describing seizure status as an outcome goal over the prior 20 years. Seizure outcomes after microsurgery, endovascular embolization, or SRS were compared; 24 studies with a total of 1157 patients were analyzed. The microsurgical group had the best seizure control (P<0.01), with the relative predicted rates of seizure outcome after microsurgery of 78.3% (95% CI, 70.1–85.8), after SRS of 62.8% (95% CI, 55.0–70.0), and after endovascular embolization of 49.3% (95% CI, 32.1–66.6). Patients in the SRS group who had complete obliteration of their bAVMs achieved the highest seizure control (85.2%; 95% CI, 79.1–91.2; P<0.01). New-onset seizures occurred more frequently in patients undergoing endovascular embolization (39.4%; 95% CI, 8.1–67.8) compared with those undergoing microsurgery (9.1%; 95% CI, 5.0–13.1) and SRS (5.4%; 95% CI, 3.0–7.8; P<0.3 and P<0.01, respectively).[185]

In the ARUBA trial, intervention appeared to confer no benefit on the occurrence of seizures.[6] In a prospective, population-based observational study of adults newly diagnosed with bAVMs, annual general practitioner follow-up, patient questionnaires, and medical records surveillance were used to quantify the 5-year risk of seizures and the chances of achieving 2-year seizure freedom for adults undergoing bAVM treatment compared with those managed conservatively. For 229 subjects during 1862 person-years of follow-up, there was no significant difference in the rate of first or recurrent seizure over 5 years after bAVM treatment compared with the first 5 years after presentation in conservatively managed patients when stratified by presentation (intracerebral hemorrhage, 35% versus 26%, P=0.5; seizure, 67% versus 72%, P=0.6; incidental, 21% versus 10%, P=0.4). For patients with epilepsy, the chances of achieving 2-year seizure freedom during 5 years of follow-up were similar after bAVM treatment (n=39; 52%; 95% CI, 36–68) or conservative management (n=21; 57%; 95% CI, 35–79; P=0.7).[243]

These data suggest that the risk of seizures after treatment is lowest after surgery and highest after embolization. How this compares with natural history is unclear.

Headache

With regard to headache outcome after bAVM intervention, almost no information is available in the literature, suggesting that these patient complaints have to date not received the necessary attention. The long-term treatment results for chronic headache need further study and optimization.[244] Rates of response to pharmacological headache treatment in patients with bAVMs also have not been studied to date. No specific therapy has been uniquely successful in headache management. Use of vasoconstrictive therapy is often advised against, under the assumption that it might lead to rupture, but there are few data to support or deny a relationship.[245] In a randomized trial of unruptured bAVMs, there was no difference in headache as an outcome between interventional and medical management.[6]

Management of Ruptured AVMs

Patients with ruptured bAVMs have an increased risk of recurrent hemorrhage relative to those with unruptured lesions.[21] Treatment options are identical for those with unruptured bAVMs: surgical resection, embolization, SRS, or a combination of these methods.

Initial management of the patient with a ruptured bAVMs is detailed in the "Guidelines for the Management of Spontaneous Intracerebral Hemorrhage" produced by the AHA and the American Stroke Association in 2010 and 2015.[246,247] These recommendations detail management paradigms for the prehospital, emergency department, and intensive care unit phases of patient care. Prehospital care focuses mainly on stabilizing the patient's cardiorespiratory status.[246,248] Emergency department management provides a continuation of cardiorespiratory support and an assessment of the patient's overall health and comorbidities. Crucial to this phase of treatment is ready access to trained consulting services, specifically neurosurgery, neurology, and neuroradiology. Emergency treatment, including evacuation of the ICH and placement of an external ventricular drain or other invasive monitoring devices, may be required at this stage.

In the event that the patient does not require emergency neurosurgical treatment, transfer to a dedicated neurological intensive care unit is preferred. Here, efforts are geared toward maintaining patient stability and monitoring for signs of neurological deterioration. Specific management concerns for patients with bAVMs include treatment of systemic hypertension, reversal of coagulopathic conditions, and prophylaxis against deep venous thrombosis.[246,248] Anticonvulsant administration is initiated in the event of clinical seizures.[246,248–250] Other common clinical scenarios in which treatment is warranted include fever, hyperglycemia, and intracranial hypertension.[246,248–250] The evidence for these interventions has been covered by the ICH guideline mentioned above and is not reviewed here.

Surgical evacuation of an ICH is warranted in the event of life-threatening mass effect, regardless of whether it is associated with a bAVM.[250] Typically, surgery is tailored toward the removal of the hematoma and control of acute bleeding. Small, superficial bAVMs can be removed during emergency surgery. The resection of larger, deep bAVMs, however, may be deferred for a period of 2 to 6 weeks.[248,250] This interval

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allows a reduction in brain swelling and better delineation of the residual bAVM both angiographically and surgically. Immediate removal of a ruptured bAVM may, in and of itself, be associated with a greater likelihood of neurological morbidity and mortality.[250] There is no evidence beyond case series guiding treatment decisions in this setting. High-risk features for recurrent hemorrhage such as perinidal or intranidal aneurysms can be addressed surgically or endovascularly in lieu of complete resection.[251]

Surgical resection of high-SM-grade bAVMs is associated with significant morbidity and mortality.[148] Nonetheless, in patients who demonstrate a fixed neurological deficit that is unlikely to worsen as a result of surgery, resection can be considered. Although preoperative embolization in such cases would seem to facilitate and lower the risks of surgical resection, no randomized controlled trials have compared the efficacy and safety of embolization followed by surgery with surgery alone.

Embolization can be used in a variety of scenarios for ruptured bAVMs. As mentioned above, targeted embolization of nidal or perinidal aneurysms may reduce the risk of rerupture.[251] This can be undertaken as the sole treatment of high-grade lesions or as a means of reducing the risk of rerupture in the interval before definitive surgical resection or SRS. Preoperative embolization may facilitate and lower the risks of surgical resection.[250] Typically, the goal of embolization in this scenario is to target inaccessible portions of the bAVM or deep arterial feeders that are difficult to control surgically. Finally, embolization as a means of reducing bAVM volume in preparation for SRS can also be considered.[203]

N-butyl cyanoacrylate and EVOH are commonly used liquid embolisates for the treatment of bAVMs. A prospective randomized trial established the equivalence of these agents in terms of safety and efficacy (comparing N-butyl cyanoacrylate with polyvinyl alcohol and EVOH with N-butyl cyanoacrylate).[252,253] The development of detachable-tip microcatheters, which allow prolonged EVOH infusion, has made curative embolization of AVMs feasible in select cases.[210,254–256] Detachable coils may also be used to close large arterial feeders or high-flow arteriovenous shunts.[255] Liquid embolisates and coils are frequently used in combination to treat AVMs.[257,258]

The role of SRS in the treatment of ruptured AVMS is complicated because of the delayed obliterative effects and persistent risk for hemorrhage until obliteration. Some authors advocate the use of SRS for the treatment of ruptured bAVMs, after the source of hemorrhage has been addressed through either embolization or microsurgery.[259] Radiosurgery is most effective in small bAVMs and is often preferred over microsurgery in lesions within eloquent brain.[260,261] Targeted radiosurgery of the deep portions of large AVMs followed by delayed surgical resection of the superficial portion has also been reported.[260,261]

Implications for Future Research

The suggestions for management made in the summary section reflect the considerable uncertainties that face physicians managing patients with ruptured and unruptured bAVMs. Annual risks of hemorrhagic stroke and epileptic seizure are often assumed to be constant throughout life, but they may not be; therefore, long-term, prospective, inclusive, population-based studies with complete follow-up are required to better define these long-term risks. Specific predictors of hemorrhagic stroke for patients with unruptured bAVMs are unknown, and they need to be defined in studies that will require large-scale participation and collaboration to attain sufficiently large sample sizes. Long-term follow-up of participants in the ARUBA trial will be valuable for determining whether the superiority of conservative management over intervention observed in that study persists in the long term. Further randomized controlled trials are justified to investigate the reproducibility of the findings of ARUBA and to investigate whether the balance of risk between conservative management and intervention is different in specific groups (eg, patients with SM grade I bAVM). A better understanding of the relative risks and benefits of the different treatment modalities (eg, endovascular embolization, SRS, and microsurgical excision) or combinations of treatment modalities in different patient populations is also needed. The establishment of an adjudicated registry would be useful in this regard.

The recent advances in our knowledge of the vascular biology and genomic factors involved in bAVM development also offer great promise. Further investigation of the factors that lead to bAVM formation and rupture may result in the development of effective medical therapies for the treatment of patients with bAVMs.

Summary

The past 15 years have seen a tremendous growth in our knowledge of the biology and genetics of bAVMs. We have a much better understanding of the natural history of unruptured bAVMs. In addition, new endovascular agents have been introduced, and there have been advances in our experience with SRS and microsurgery. The first randomized trial of treatment versus conservative management for unruptured bAVMs was also completed. Nevertheless, we still lack compelling evidence for many of the treatment decisions that are routinely made for patients with ruptured and unruptured bAVMs. The results of ARUBA point to the need for a better understanding of the risks of different treatment options, longer-term follow-up of untreated patients, and further randomized controlled trials to investigate the remaining therapeutic uncertainties.

Suggestions for the management of patients with unruptured bAVMs include the following:

- Patients can be informed about natural history risks, which are reliably quantified over ≈10 years for ICH and ≈5 years for epileptic seizure.
- The annual risk of a first-ever ICH from an unruptured bAVM is ≈1%. Prognostic factors that modify this risk are uncertain.
- The 5-year risk of developing a first seizure for people with an unruptured bAVM is ≈8%, and the 5-year risk of developing epilepsy after a first seizure is ≈58%.
- The discussion of treatment options with patients should include consideration of these risks weighed carefully against the relative risks of different intervention strategies and life expectancy.

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- The SM scale is useful for predicting the risk of surgical resection.

The following are suggestions for the management of patients with ruptured bAVMs:

- CTA, MRA, and DSA can be useful to evaluate for underlying bAVMs in patients presenting with nontraumatic ICH when there is clinical or radiological suspicion (paraphrased from the 2015 ICH guidelines; Class IIa, Level of Evidence B).
- Recommendations for management of the initial hemorrhage should follow the 2015 ICH guidelines.
- The annual risk of recurrent ICH from a ruptured bAVM is ≈5%. Increasing age, deep venous drainage, arterial aneurysms, and female sex may raise this risk.
- Treatment decisions should weigh the relative risks and benefits of different interventional strategies and their combinations.

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*Modest.

†Significant.

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