The Natural History and Predictive Features of Hemorrhage From Brain Arteriovenous Malformations

Leodante da Costa, MD; M. Christopher Wallace, MD, MSc; Karel G. ter Brugge, MD; Cian O’Kelly, MD; Robert A. Willinsky, MD; Michael Tymianski, MD, PhD

Background and Purpose—Patients harboring brain arteriovenous malformations (bAVMs) are at a lifelong risk for hemorrhagic strokes, but the natural history is poorly understood. We examined the impact of demographic and angiographic features on the likelihood of future hemorrhage.

Methods—A prospectively accrued database of bAVM patients maintained at the Toronto Western Hospital was analyzed; 678 consecutive, prospectively enrolled bAVM patients were followed for 1931.7 patient-years. The rate of hemorrhage over long-term follow-up was recorded. The impact of baseline clinical and radiographic features and partial treatment on time to hemorrhage were analyzed using survival analysis. Neurological outcome after hemorrhage was assessed using the Glasgow Outcome Score.

Results—Hemorrhage rates were 4.61% per year for the entire cohort (n=678), 7.48% per year for bAVMs with initial hemorrhagic presentation (n=258), 4.16% per year for initial seizure presentation (n=260), 3.99% per year for patients not harboring aneurysms (n=556), and 6.93% per year for patients with associated aneurysms (n=122). Hemorrhagic presentation was a significant independent predictor of future hemorrhage (HR, 2.15; P<0.01), whereas associated aneurysms (HR, 1.59; P=0.07) and deep venous drainage (HR, 1.59; P=0.07) showed a trend toward significance. Hemorrhage risk was unchanged in patients who underwent partial arteriovenous malformation embolization (n=211; HR, 0.875; P=0.32).

Conclusion—Brain arteriovenous malformations presenting with hemorrhage, with deep venous drainage, or associated aneurysms have a 2-fold greater likelihood of a future hemorrhage. Partial treatment by embolization does not alter these risks. This natural history should be taken into account in the treatment strategy. (Stroke. 2009;40:100-105.)

Key Words: arteriovenous malformations | intracerebral hemorrhage

The most feared complication of brain arteriovenous malformations (bAVMs) is intracranial hemorrhage, and individuals harboring bAVMs are subjected to a lifelong risk of hemorrhagic stroke.1-7 Management of these lesions is complicated by the fact that bAVMs form a very heterogeneous group of lesions. The variable arteriovenous malformation (AVM) locations, morphologies, and angioarchitectural characteristics may impart a different risk of hemorrhage for each patient,8-15 requiring individualized treatment decisions. Key among the goals of treating bAVMs is to reduce the risk of future hemorrhagic stroke. However, the risks associated with treating a given bAVM patient also vary16-21 and, consequently, must be weighed individually against the natural history of hemorrhage anticipated in that particular patient. Currently, the natural history of hemorrhage from bAVMs is controversial, as is the impact of certain therapies. Reported yearly hemorrhage rates may be as low as 2% or as high as 32.6%.2-5,7,22,23 The appropriate management of patients with AVMs can therefore vary from simple observation to aggressive multimodality treatment aimed at total AVM obliteration.8 Because risks of treatment must be weighed against those of conservative management of bAVMs, we sought to obtain a better understanding of the natural history and factors predictive of hemorrhage in bAVM patients.

Subjects and Methods
We conducted a prospective cohort study assessing the natural history of AVMs, specifically determining the rate of hemorrhage and the impact of various clinical and morphological characteristics; 678 consecutive, prospectively enrolled bAVM patients were derived from a prospectively maintained database (University of Toronto Brain AVM Study Group) capturing demographic, clinical, morphological, and treatment characteristics for all patients referred for multidisciplinary management. The study comprised patients with previously untreated AVMs presenting to our institution (Toronto Western Hospital) between 1986 and 2004. The database was checked for completeness and accuracy using a combination of chart
abstraction and, when information was lacking, telephone interviews with patients or their families. Patients with dural arteriovenous fistulas, cavernous malformations, and other types of brain vascular malformations were excluded. We also excluded patients with insufficient baseline or follow-up information (81 patients from a total of 759, leaving 678 for analysis). The diagnosis of a brain AVM was made using CT, MRI, and digital subtraction angiography, or a combination of these methods.

Baseline clinical characteristics, including age, sex, and modes of presentation (hemorrhage, seizure, other symptoms), were derived from the database. AVM size and location were determined from axial CT or MRI images. Size was measured using the Spetzler-Martin grading scale method, which divides AVMs into 3 groups according to nidus size (<3 cm, 3–6 cm, >6 cm). Deep location was defined as the larger portion of the nidus localized in deep white matter tracts, basal ganglia and thalamus, peri-ventricular regions, or posterior fossa. Angioarchitectural features were determined from the digital subtraction angiography. Associated aneurysms were defined as saccular arterial dilatations with a diameter at least equal to the parent artery and included prenidal, intranidal, and remote aneurysms. Simple arterial ectasias, infundibular dilatations, venous pouches, and variceal dilatations were excluded. Prenidal aneurysms were those arising along the course of arteries that eventually supplied directly the AVM; intranidal aneurysms were those in the nidus, filling in the arterial phase of the angiography, before substantial venous filling had occurred; and remote aneurysms were those arising in arteries not related directly with the AVM blood supply. Deep venous drainage was defined as the presence of any nidus drainage toward the deep venous system of the brain. The primary outcome was time from diagnosis to AVM hemorrhage defined as intracranial hemorrhage related to the AVM, demonstrated on either CT or MRI. As a secondary analysis, clinical outcome after hemorrhage was recorded using the Glasgow Outcome Scale.

### Statistical Analysis

All analyses were conducted using SAS statistical software (Version 9.0; SAS Institute). Hemorrhage rates were calculated according to patient-years of follow-up (number of hemorrhage events divided by years of patient follow-up). The impact of baseline clinical and angiographic features on time to hemorrhage was analyzed using survival methods. Censoring events included death unrelated to AVM and AVM obliteration. Survival curves were estimated using the Kaplan-Meier method. Univariate survival analysis was conducted using the log rank test, whereas a Cox proportional hazards method was used to conduct a multivariate analysis. A multivariate logistic regression was used to analyze potential predictors of poor Glasgow Outcome Scale (Glasgow Outcome Scale ≤3).

### Results

Between 1986 and 2004, a total of 759 consecutive prospectively enrolled brain AVM patients were identified, of which 81 were lost to follow-up; 678 patients were followed-up for a total of 1931.7 patient-years (mean, 2.9 years; maximum, 17.4 years). Baseline presentation and AVM characteristics for the patient cohort are presented in Table 1. There was no significant male or female predilection. A wide range of ages at presentation was observed; however, the majority of patients presented during their fourth and fifth decades. Hemorrhage and seizure were the most frequent presentations, seen at equal frequencies. Approximately half of the patients had bAVMs with deep venous drainage, and most bAVMs measured <3 cm. The majority of lesions were superficially located, whereas associated aneurysms were found in 17.9% of bAVM patients.

### Table 1. Patient Demographics and Baseline Arteriovenous Malformation Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Total N of Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Male: female</td>
<td>366:312</td>
</tr>
<tr>
<td></td>
<td>Mean age (range)</td>
<td>39 (1–78)</td>
</tr>
<tr>
<td>Presentation</td>
<td>Hemorrhage</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>260</td>
</tr>
<tr>
<td></td>
<td>Other*</td>
<td>160</td>
</tr>
<tr>
<td>Angioarchitecture</td>
<td>Deep drainage</td>
<td>365</td>
</tr>
<tr>
<td></td>
<td>Deep location</td>
<td>85</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;3 cm</td>
<td>418</td>
</tr>
<tr>
<td></td>
<td>3–6 cm</td>
<td>239</td>
</tr>
<tr>
<td></td>
<td>&gt;6 cm</td>
<td>21</td>
</tr>
<tr>
<td>Associated aneurysms</td>
<td>141†</td>
<td>18.0%</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Prenidal</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Intranidal</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Remote</td>
<td>23</td>
</tr>
</tbody>
</table>

*Incidental, nonhemorrhagic neurological deficit, headache.
†141 aneurysms in 122 patients.

EIGHTY-NINE HEMORRHAGES OCCURRED DURING THE FOLLOW-UP, CORRESPONDING TO A YEARLY RISK OF HEMORRHAGE OF 4.61%. SIX PERCENT (5/89) OF PATIENTS DIED AS A RESULT OF THE HEMORRHAGE, WHEREAS 35% HAD SIGNIFICANT FUNCTIONAL IMPAIRMENT (GLASGOW OUTCOME SCALE 2 OR 3). UNIVARIATE AND MULTIVARIATE ANALYSES OF PREDICTORS OF POOR OUTCOME (GLASGOW OUTCOME SCALE 3 OR LESS) FAILED TO REVEAL ANY SIGNIFICANT DEMOGRAPHIC OR ANGIOARCHITECTURAL PREDICTORS, SUGGESTING THAT ONCE HEMORRHAGE OCCURS, CLINICAL OUTCOME IS DETERMINED MOSTLY BY BLEED SEVERITY. THE RISK OF HEMORRHAGE WAS SLIGHTLY HIGHER IN THE FIRST YEAR AFTER DIAGNOSIS, DECREASING AFTER THE SECOND YEAR. CHANGES IN THE RISK OF HEMORRHAGE OVER THE YEARS ARE SHOWN IN TABLE 2. THE CLINICAL OUTCOME AFTER HEMORRHAGE IN FOLLOW-UP, AS MEASURED BY THE GLASGOW OUTCOME SCALE, IS SHOWN IN FIGURE 1. FORTY-FOUR OF THE 89 HEMORRHAGES OCCURRED IN PATIENTS WHO PRESENTED WITH HEMORRHAGE. THIS GROUP OF PATIENTS HAD A HIGH RISK OF HEMORRHAGE IN FOLLOW-UP, WITH THE HIGHEST RISK DURING THE INITIAL YEAR OF FOLLOW-UP. A SIMILAR TEMPORAL PATTERN WAS OBSERVED FOR THE PATIENTS WITH AVMS HARBOURING ASSOCIATED ANEURYSMS AND DEEP VENOUS DRAINAGE. THE RATE OF HEMORRHAGE AMONG PATIENTS PRESENTING WITH SEIZURES WAS SIMILAR TO THE OVERALL COHORT (TABLE 2).

In univariate survival analysis, hemorrhagic presentation (HR, 2.21; P<0.001), associated aneurysms (HR, 1.83; P=0.01), and deep venous drainage (HR, 1.81; P=0.01) were each associated with a significantly increased risk of hemorrhage (Table 3). The hazard ratios indicate an approximate doubling of the risk of hemorrhage in patients with these baseline characteristics. In multivariate analysis, hemorrhagic presentation (HR, 2.15; P<0.01) was a significant predictor of increased risk of future hemorrhage. There was a trend toward increased risk with the presence of associated aneu-
rysms (HR, 1.59; P=0.07) and deep venous drainage (HR, 1.59; P=0.07). Age, gender, seizure presentation, size, and deep location were not associated with any increased risk of hemorrhage in either univariate or multivariate analysis. The Kaplan-Meier survival curves stratified by selected predictors are shown in Figure 2. There were insufficient events to study the impact of specific subtypes of associated aneurysms on the subsequent risk of hemorrhage in the multivariate analysis. However, in univariate analysis, prenidal (HR, 1.7; P=0.030) and intranidal (HR, 2.1; P=0.030) aneurysms were associated with increased risk, whereas remote aneurysm did not significantly increase the risk of hemorrhage (HR, 1.6; P=0.35).

Embolization is used frequently to occlude deep feeders before surgical resection, to decrease nidus size to allow for radiosurgery, or to eliminate perceived weak points such as associated aneurysms; 211 of 678 patients underwent embolization without complete AVM obliteration (partial embolization). The risk of hemorrhage for brain AVMs submitted to partial embolization for any reason (preoperative, palliative, preradiosurgical, targeted, or in a failed cure attempt) was 3.95% per year, as compared with 4.79% per year for AVMs not submitted to embolization (HR, 0.875; P=0.32). A subgroup analysis showed that partial embolization may actually increase the risk of hemorrhage when used to treat target points of the AVM, mostly associated intranidal aneurysms (4.79% vs 8.91%; P=0.049) or to palliate symptoms (4.79% vs 6.24%; P=0.003). The results of the subgroup analysis should be interpreted with care because the groups were small, and we still evaluate the treatment options for patients with bAVMs and associated aneurysms, including target embolization, in a case-by-case basis. Associated aneurysms may herald a more severe vasculopathy with increased risk of hemorrhage, and therefore comparison would not be appropriate, and perhaps more aggressive interventions are justified. Nevertheless, considering the whole cohort, we found no evidence that partial embolization reduced future hemorrhage risk from a brain AVM. These results should not alter the fundamental role of endovascular therapy in the management of bAVMs, especially as surgical and radiosurgical adjuvants.

**Discussion**

Despite major advances in diagnostic and therapeutic resources, management decisions in the treatment of brain AVMs may still be a challenge. Improved diagnostic modalities, such as MRI, contribute to an increasing number of incidentally diagnosed AVMs, and better and new therapeutic strategies allow for treatment of previously untreatable lesions, but unfortunately with potential morbidity. The main goal of the treatment of brain AVMs is to preserve neurological function mainly by preventing intracranial hemorrhage and its consequences. Therefore, understanding the natural history of brain AVMs, especially related to risk of future hemorrhage, is crucial. Ondra et al published the results of almost 24 years of follow-up in a cohort of bAVM patients in Finland, and established an annual risk of bAVM hemorrhage of 4% per year, regardless of bAVM characteristics and clinical presentation. Graf, Crawford, and Fults showed that bAVMs may have different behavior during follow-up, with an increased risk of bleeding in the first year after diagnosis. In a more recent series, Mast et al demonstrated that the risk of hemorrhage in follow-up can be widely variable, from 2.2% to 17.8% per year, depending on presentation, AVM venous drainage, and sex.

It is becoming increasingly evident that bAVMs represent a heterogeneous group of lesions, with different clinical presentations and most likely different outcomes. With more

---

**Figure 1.** Glasgow outcome score after AVM hemorrhage in 89 patients.

**Table 2.** Yearly Hemorrhage Risks for the Entire Cohort and Selected Subgroups

<table>
<thead>
<tr>
<th>Hemorrhage Risks</th>
<th>Entire Cohort</th>
<th>Hemorrhagic Presentation</th>
<th>Seizure Presentation</th>
<th>Associated Aneurysms</th>
<th>Deep Venous Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall annual risk</td>
<td>4.61%</td>
<td>7.48%</td>
<td>4.16%</td>
<td>6.93%</td>
<td>5.42%</td>
</tr>
<tr>
<td>Risk in first year</td>
<td>4.80%</td>
<td>9.65%</td>
<td>3.60%</td>
<td>9.35%</td>
<td>6.87%</td>
</tr>
<tr>
<td>Annual risk 2–5 yr</td>
<td>3.95%</td>
<td>6.30%</td>
<td>3.58%</td>
<td>5.41%</td>
<td>4.60%</td>
</tr>
<tr>
<td>Annual risk beyond 5 yr</td>
<td>3.90%</td>
<td>3.67%</td>
<td>4.37%</td>
<td>6.01%</td>
<td>4.22%</td>
</tr>
</tbody>
</table>

**Table 3.** Risk of Hemorrhage in Follow-Up (Univariate and Multivariate Survival Analysis)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Univariate HR</th>
<th>Univariate P Value</th>
<th>Multivariate HR</th>
<th>Multivariate P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation with seizure</td>
<td>0.92</td>
<td>0.70</td>
<td>1.17</td>
<td>0.53</td>
</tr>
<tr>
<td>Presentation with hemorrhage</td>
<td>2.21</td>
<td>&lt;0.001</td>
<td>2.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Deep venous drainage</td>
<td>1.81</td>
<td>0.01</td>
<td>1.59</td>
<td>0.07</td>
</tr>
<tr>
<td>Spetzler-Martin size</td>
<td>0.98</td>
<td>0.89</td>
<td>0.92</td>
<td>0.64</td>
</tr>
<tr>
<td>Sex</td>
<td>1.11</td>
<td>0.64</td>
<td>1.00</td>
<td>0.82</td>
</tr>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.65</td>
<td>1.23</td>
<td>0.37</td>
</tr>
<tr>
<td>Associated aneurysm</td>
<td>1.83</td>
<td>0.01</td>
<td>1.59</td>
<td>0.07</td>
</tr>
<tr>
<td>Deep location</td>
<td>1.01</td>
<td>0.98</td>
<td>0.721</td>
<td>0.39</td>
</tr>
</tbody>
</table>
therapeutic options available, determination of the future risk of bleeding is crucial to provide adequate management, either guiding toward an aggressive treatment plan aiming at complete occlusion for bAVMs with risk factors for hemorrhage or supporting a more conservative approach for those at lesser risk. Multiple factors are mentioned as being related to increased risk of hemorrhage: presentation with hemorrhage, presence of deep venous drainage, associated aneurysms, AVM location, size, male gender, venous outlet restriction, mean pressure and type of feeding arteries, and age. Some agreement is present concerning the role of presentation with hemorrhage and the presence of deep venous drainage as risk factors for intracranial hemorrhage, but the literature provides divergent information regarding other factors. A common confounder in most series is the inclusion of the presenting hemorrhage in the number of bleeding events, making it difficult to determine accurately the risk of follow-up hemorrhage. Mast et al reported that the most important risk factor for future hemorrhage from a brain AVM after diagnosis is presentation with hemorrhage. In a later report with data from the same group, Stapf et al showed that the risk of hemorrhage can vary widely depending on the presence and number of risk factors that included age, hemorrhagic presentation, deep location, and deep venous drainage. The risk was evaluated from the time of diagnosis to the beginning of treatment, with a relatively short follow-up time, and excluding partially treated bAVMs. Instead of reflecting pure natural history, we chose not to remove from analysis lesions partially treated by embolization because this had no effect on hemorrhage risk in this subgroup, because the risk of hemorrhage is present until complete AVM obliteration, and because the management of brain AVMs often requires multiple interventions and different modalities of treatment, sometimes taking years before the lesion is completely obliterated. We believe that the inclusion of partially treated bAVMs provides useful information because they are a relatively common occurrence in any center treating cerebrovascular disease, and also allowed us to analyze the impact of partial embolization.

Our data indicate that presentation with hemorrhage, deep venous drainage, and the presence of associated aneurysms raise the risk for future AVM hemorrhage. The practical implication is that intervention, if warranted, should commence sooner rather than later after diagnosis of bAVMs that have these risk factors. The reported rate of aneurysms associated with bAVMs vary widely (2.7%–58%) in the literature, depending on the definition of what would represent an associated aneurysm, the type of angiography utilized (selective vs superselective) and referral patterns. Regarding the cause of the hemorrhage, in an earlier review of our series, Redekop reported that the cause of hemorrhage was almost equally

Figure 2. Time to hemorrhage stratified by hemorrhagic presentation (A). Presentation with seizure (B). Presence of associated aneurysms (C) and deep venous drainage (D).
distributed between aneurysms and AVMs. In our cohort, brain AVMs with associated aneurysms represented 17.9% of the patients and had an increased risk of bleeding in follow-up. Furthermore, this risk remained elevated even after 5 years of follow-up (6% per year), and partial treatment, most of the time targeting endovascular occlusion of the aneurysm, did not alter the risk significantly. This may suggest that the risk of hemorrhage in these complex lesions is not just the simple summation of the risk of each separated lesion, but that each angioarchitectural characteristic is actually a marker of a more severe intracranial vasculopathy and therefore of a condition more prone to hemorrhage.

Conclusion
Our results show that presentation with hemorrhage, the presence of associated aneurysms, and the presence of deep venous drainage are independent risk factors for future hemorrhage from bAVMs. Lesions that present with hemorrhage or have associated aneurysms have a risk of rebleeding that is twice that of bAVMs without these characteristics, and the risk is highest in the first years after diagnosis. The bAVMs with associated aneurysms have a higher risk of hemorrhage even after 5 years of diagnosis. This information should be taken into consideration when deciding among therapeutic options for bAVMs, and more effective means in the short-term (surgery or total embolization) might be advantageous for patients harboring high-risk lesions. However, therapeutic approaches that entail longer obliteration times might be targeted to patients having a lower-risk natural history for hemorrhage.

Disclosures
None.

References


The Natural History and Predictive Features of Hemorrhage From Brain Arteriovenous Malformations
Leodante da Costa, M. Christopher Wallace, Karel G. ter Brugge, Cian O’Kelly, Robert A. Willinsky and Michael Tymianski

*Stroke*. 2009;40:100-105; originally published online November 13, 2008;
doi: 10.1161/STROKEAHA.108.524678

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/40/1/100

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/