Hemorrhage Rate in Patients With Spetzler-Martin Grades IV and V Arteriovenous Malformations
Is Treatment Justified?

Mahesh V. Jayaraman, MD; Mary L. Marcellus, RN; Huy M. Do, MD; Steven D. Chang, MD; Jarrett K. Rosenberg, PhD; Gary K. Steinberg, MD, PhD; Michael P. Marks, MD

Background and Purpose—We sought to examine the prospective annual risk of hemorrhage in patients harboring Spetzler-Martin grades IV and V arteriovenous malformations (AVMs) before and after initiation of treatment.

Methods—Medical records of 61 consecutive patients presenting with Spetzler-Martin grades IV and V AVMs were retrospectively reviewed for demographics, angiographic features, presenting symptom(s), and time of all hemorrhage events, before or after treatment initiation. Pretreatment hemorrhage rates (excluding hemorrhages at presentation) and posttreatment rates were subsequently calculated. Modified Rankin Scale (mRS) scores before and after treatment were recorded.

Results—The annual pretreatment hemorrhage rate for all patients was 10.4% per year (95% CI, 2.2 to 15.4%), 13.9% (95% CI, 3.5 to 22.1%) in patients with hemorrhagic presentation and 7.3% (2.6 to 14.3%) in patients with nonhemorrhagic presentation. Posttreatment hemorrhage rates were 6.1% per year (95% CI, 2.5 to 13.2%) for all patients, 5.6% (95% CI, 2.1 to 11.8%) for patients presenting with hemorrhage and 6.4% (95% CI, 1.6 to 10.1%) in patients with nonhemorrhagic presentation. A noninferiority test showed that the posttreatment hemorrhage rate was less than or equal to the pretreatment hemorrhage rate ($P < 0.0001$), with some indication that the reduction was greatest in patients with hemorrhagic presentation. Of the 62 patients, 51 (82%) had an mRS score of 0 to 2 before treatment, and 47 (76%) had an mRS score of 0 to 2 at the last follow-up after treatment.

Conclusions—The annual rate of hemorrhage in grades IV and V AVMs is higher in this series than reported for all AVMs, which may reflect some referral bias in this single-center study. Nevertheless, initiation of treatment does not appear to increase the rate of subsequent hemorrhage. Treatment for these lesions may be warranted, given their poor natural history. (Stroke. 2007;38:325-329.)

Key Words: arteriovenous malformation ▪ brain arteriovenous malformation ▪ hemorrhage, intracranial

The natural history of pial arteriovenous malformations (AVMs) in the brain is incompletely understood. In the literature, the annual hemorrhage rate for these lesions varies from 2% to 5% per year.1–6 Recent studies have suggested that the rate of recurrent hemorrhage might be significantly higher, especially within the first year after diagnosis.5,6 Several angiographic determinants have been previously described as being associated with a higher risk for intracranial hemorrhage.7,8 In addition, AVMs in the basal ganglia and thalamus have been shown to have a higher annual hemorrhage rate.9

Whereas small AVM nidus size may be associated with an increased risk of hemorrhagic presentation,5 the prospective risk of hemorrhage has been shown to be higher with larger AVMs.10 However, a recent intention-to-treat analysis from a single center reported an annual hemorrhage rate for Spetzler-Martin grades IV and V AVMs of 1.5% and suggested that initiation of treatment for these large AVMs might increase the hemorrhage risk.11 The purpose of our study was to determine the prospective risk of hemorrhage in patients at our center harboring Spetzler-Martin grades IV and V AVMs and to determine whether initiation of treatment increased the hemorrhage rate.

Patients and Methods
The medical records of consecutive patients with Spetzler-Martin grades IV and V AVMs presenting to our center during a 6-year period (1998 to 2004) were retrospectively reviewed. Patients who were partially treated in the past at other centers were also included in this analysis. Patient demographics, including age, sex, presenting symptoms, and date of diagnosis were collected. In all patients, the diagnosis of brain AVM was made on the basis of imaging studies, including computed tomography, magnetic resonance imaging, or...
TABLE 1. Demographic and Angiographic Features in 61 Patients

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mean age at diagnosis, y</td>
<td>29.7 ± 16.8</td>
<td></td>
</tr>
<tr>
<td>Male/female</td>
<td>32 (52%)/29 (48%)</td>
<td></td>
</tr>
<tr>
<td>Mean pretreatment interval, y</td>
<td>3.45 (0–29)</td>
<td></td>
</tr>
<tr>
<td>Mean time from presentation to first new hemorrhage</td>
<td>5.6 y (4 d–28 y)</td>
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Presenting signs/symptoms

- Seizure: 22 (36.1)
- Hemorrhage: 20 (32.8%)
- Focal neurological deficit: 11 (18%)
- Headache: 7 (11.5%)
- Incidental: 1 (1.6%)

AVM characteristics

- Spetzler-Martin grade IV: 40 (65.6%)
- Spetzler-Martin grade V: 21 (34.4%)
- Deep location: 11 (18%)
- Venous drainage: 41 (67.2%)
- Exclusively deep: 17 (27.9%)
- Exclusively superficial: 3 (4.9%)

A timeline was generated for each patient, consisting of pretreatment and posttreatment phases. The pretreatment phase spanned the time from presentation to the time that any treatment targeted at the AVM (partial or total surgical resection, endovascular embolization, or radiosurgery) was initiated. The posttreatment phase was the period from initiation of treatment onward. In patients considered cured, the posttreatment interval was considered to be concluded at the time of angiographic documentation of no residual AVM. In patients with a residual angiographic AVM, the posttreatment period spanned the period from initiation of treatment onward. All treatments targeted at the AVM (surgical resection, endovascular embolization, or radiosurgery) were also noted.

The specific dates of all hemorrhages were recorded on either the pretreatment or posttreatment timeline. A hemorrhage was defined as a clinical event with acute onset of 1 or more symptoms, such as headache, loss of consciousness, or focal neurological deficit, with contemporaneous imaging (computed tomography or magnetic resonance imaging) demonstrating acute intracranial hemorrhage. All pretreatment hemorrhages (excluding the hemorrhages at presentation) were included in the calculation of prospective hemorrhage rate. The posttreatment hemorrhages occurred during the follow-up period (starting with the initiation of treatment), all symptomatic hemorrhages, including those considered to be procedural complications of endovascular or surgical treatment, were included in the hemorrhagic event count. Imaging findings at the follow-up magnetic resonance imaging or angiography were recorded and classified into residual or no residual AVM. For all patients, a modified Rankin Scale (mRS) score was recorded before the initiation of treatment and at the last clinical follow-up.

The data were entered into a Microsoft Access database. The prospective hemorrhage rates were calculated by dividing the total number of hemorrhages by the number of patient-years of follow-up in each group. This database was also used to generate the subgroups used for this analysis, including patients with hemorrhagic and nonhemorrhagic presentations, cortical and deep AVMs, and short- and long-term hemorrhage rates. Analysis of the data was performed with an 1-sided test of noninferiority on the incidence rates, with an equivalence interval of 0.25%. Statistical analysis was performed with Stata 9.1 software (Stata Corp).

### Results

A total of 61 patients were identified, 32 men and 29 women, with a mean age at diagnosis of 29.7 ± 16.8 years. Presenting symptoms and angiographic features are summarized in Table 1.

The mean pretreatment interval was 3.49 years (range, 0 to 29). There were 42 hemorrhages that occurred in the pretreatment period. Twenty of these occurred at the time of presentation, and 22 occurred after presentation. Fourteen of the postpresentation hemorrhages occurred in patients with hemorrhagic presentation, and 8 occurred in patients without a hemorrhagic presentation. Seven of the 20 patients (35%) with hemorrhagic presentation had 1 or more additional hemorrhages before treatment, and 7 of 41 patients (17.1%) with nonhemorrhagic presentation had 1 or more hemorrhages before treatment. The mean time from presentation to the first postpresentation hemorrhage was 5.6 years (range, 4 days to 28 years). Of the 27 patients with pretreatment hemorrhages, 19 (70%) had 1 hemorrhage and 8 (30%) had 1 hemorrhage. All of the patients with multiple hemorrhages except for 1 presented with hemorrhage.

Table 2 shows the pretreatment and posttreatment hemorrhage rates. There was a prospective hemorrhage rate of 10.4% per year for all patients in the pretreatment period. The rate was 13.9% per year for patients with hemorrhagic

### Table 2. Rate of Hemorrhage Before and After Treatment in Patients With Grades IV and V AVMs

<table>
<thead>
<tr>
<th>Group</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>Difference Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemorrhages</td>
<td>Time (Patient-Years)</td>
<td>Rate (per Year)</td>
</tr>
<tr>
<td>All (N=61)</td>
<td>22</td>
<td>210.56</td>
<td>10.4% (2.2%–15.4%)</td>
</tr>
<tr>
<td>Presented with hemorrhage</td>
<td>14</td>
<td>100.52</td>
<td>13.9% (3.5%–22.1%)</td>
</tr>
<tr>
<td>(n=20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhemorrhagic presentation</td>
<td>8</td>
<td>110.04</td>
<td>7.3% (2.6%–14.3%)</td>
</tr>
</tbody>
</table>

95% CIs are in parentheses.
presentation and 7.3% per year for those with a nonhemorrhagic presentation.

During the treatment period, 56 of 61 (91.8%) patients underwent a total of 201 sessions of endovascular embolization. Surgical resection was performed in 28 of 61 (45.9%) patients, with a total of 41 resections performed. Radiosurgery was performed in 40 of 61 (65.6%) patients, with a total of 62 separate treatments performed. During the posttreatment time period, a total of 14 hemorrhages occurred, including 5 hemorrhages in patients with hemorrhagic presentation and 9 hemorrhages in patients with nonhemorrhagic presentation. Two of the 14 hemorrhages were complications of embolization. This resulted in a posttreatment hemorrhage rate of 6.1% per year for all patients, 5.6% per year for patients with hemorrhagic presentation and 6.4% per year for patients with nonhemorrhagic presentation. Eighteen patients had angiographic obliteration of the AVM, and in these patients, there were no hemorrhages during 19.04 patient-years of cumulative follow-up after angiographic obliteration.

Thirty-four patients had no hemorrhages before treatment initiation (ie, they did not present with hemorrhage and did not bleed during the pretreatment interval). After treatment was initiated, 5 hemorrhages occurred in this group, with 124.40 patient-years of follow-up, yielding a posttreatment hemorrhage rate of 4.0% per year.

As shown in Table 2, the pretreatment hemorrhage rate for all patients was 10.4%, and the posttreatment hemorrhage rate was 6.1%. A noninferiority test of the difference in incidence rates indicated that the posttreatment hemorrhage rate was less than or equivalent to the pretreatment rate for patients with and without hemorrhagic presentation (with hemorrhage, \( P<0.0003 \); without hemorrhage, \( P<0.045 \); all patients, \( P<0.0001 \); see the Figure). Equivalence in this context was defined as a posttreatment hemorrhage rate no higher than 0.05 (5%) more than the pretreatment rate. The rates of hemorrhage for deep versus cortical AVMs are summarized in Table 3. The pretreatment risk of hemorrhage in the first 36 months after diagnosis (short term) versus the time period beyond the first 36 months after diagnosis (long term) is summarized in Table 4.

Angiographic cure of the AVM was documented in 18 of 61 patients (30%). A residual AVM was noted in 41 patients (67%), with 25 of these patients having had stereotactic radiosurgery within the past 3 years. The mRS scores of the patients are summarized in Table 5. Thirteen patients had a worsening of their mRS scores after initiation of treatment and 3 had improvement, a difference that was not significant on the basis of a Bowker test of symmetry (\( \chi^2 \ [8]=8.67, P<0.37 \)). In 6 of the 13 with a worsening mRS score, this deterioration was considered to have been due directly to treatment-related complications. One patient experienced a postembolization hemorrhage and died, 1 patient had a stroke with neurological deficit after embolization, 1 patient developed neurological deficits after surgical resection, and 3 patients had symptomatic radiation necrosis. The other 7 patients with a worsening mRS score developed AVM-related hemorrhages (4 patients) or progressive neurological symptoms (3 patients) after their initial treatment. The mean

### TABLE 3. Hemorrhage Rates Before and After treatment in Deep and Cortical Grades IV and V AVMs

<table>
<thead>
<tr>
<th>Group</th>
<th>Before Treatment</th>
<th>After Treatment</th>
<th>Difference Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical (n=50)</td>
<td>7 (Patient-Years) 78.38 8.9% (3.6%–18.5%)</td>
<td>10 (Patient-Years) 155.42 6.4% (3.1%–11.8%)</td>
<td>2.5% (–10.2%–5.2%)</td>
</tr>
<tr>
<td>Deep (n=11)</td>
<td>15 (Patient-Years) 142.62 10.5% (5.9%–17.3%)</td>
<td>4 (Patient-Years) 76.54 5.2% (1.4%–13.4%)</td>
<td>5.3% (–12.7%–2.1%)</td>
</tr>
</tbody>
</table>

95% CIs are in parentheses.
time from the last hemorrhage to the last clinical follow-up in patients who hemorrhaged after initiation of treatment was 2.05 years (range, 0 days to 7.62 years; SD, 2.32 years).

Before initiating treatment, 10 patients (16.4%) had an mRS score \( \geq 3 \). At last follow-up, there were 14 patients (22.9%) with an mRS score \( \geq 3 \). One patient died after a postembolization hemorrhage and represented the only patient who was disabled directly as a complication of treatment.

**Discussion**

The intention-to-treat analysis by Han et al.\(^{11}\) reported an annual hemorrhage rate for grades IV and V AVMs of 1.5% per year. They calculated the overall hemorrhage rate of the AVMs from birth. They suggested that this rate was lower than that usually reported for AVMs. However, most annual hemorrhage rates are reported from the time of presentation,\(^{3,5,6,8,10,13,14}\) not from the time of birth. Indeed, if a lifetime hemorrhage risk (pretreatment) is calculated for the grades IV and V AVMs in this series, it is 2.08% per year, which is very similar.

Han et al.\(^{11}\) also postulated that initiation of treatment directed toward an AVM can increase the risk of hemorrhage. They reported a 10.4% annual hemorrhage rate after initiation of treatment in a small minority of patients seen at their institution (19%) who actually underwent treatment. This annual rate was not reported over the lifetime of the patients but only for the period after the start of treatment, making comparison with their reported lifetime hemorrhage rate difficult. In addition, it is not clear what bias, if any, might be introduced by selection of this minority for treatment (such as a history of prior hemorrhage).

In our series of grades IV and V AVMs, the overall hemorrhage rate of 10.4% per year for all patients is substantially higher than that previously reported for AVMs as a whole. Prior hemorrhage is a well-established significant risk factor for future hemorrhage.\(^{5,6,15}\) Mast et al.\(^{6}\) examined the

risk of recurrent hemorrhage in patients with AVMs and found that in patients with hemorrhage at presentation, the risk of recurrent hemorrhage was 17.8% per year, compared with a hemorrhage rate of 2.2% per year in patients without prior hemorrhage. Our population of patients with a hemorrhagic presentation had an annual pretreatment bleed rate of 13.9%, which is similar.

Halim et al.\(^{6}\) found that the risk of recurrent hemorrhage was higher initially (6% in the first year after diagnosis), that this risk decreased over time, and that it converged with the risk in patients with nonhemorrhagic presentation, approaching 3% per year at 10 years of follow-up, compared with 2% per year for patients with nonhemorrhagic presentation. When we examined the short- and long-term risks of hemorrhage in our population, the risk of hemorrhage in the first 36 months after diagnosis was 12.0% per year and 9.7% per year from 36 months onward (Table 4), suggesting that although the rate of hemorrhage may be slightly higher initially after diagnosis, the rate of subsequent hemorrhage in these larger AVMs remains higher than that in the general AVM population.

Our patients with a nonhemorrhagic presentation had a prospective pretreatment hemorrhage rate of 7.3%, which is higher than is usually reported for AVMs that have not presented with bleeding. The exact reason for this higher hemorrhage rate in our population is uncertain. Stefani et al.\(^{10}\) examined the prospective risk of future hemorrhage in 390 patients with AVM and found that, in their final multivariate analysis, an AVM nidus $\geq 2.5$ cm was associated with an odds ratio of 2.5. The presence of deep venous drainage is a risk factor for hemorrhage,\(^{4,7,8}\) and as expected, the majority of our patients (95%) had either mixed or exclusively deep drainage. In separate univariate analysis, Stefani et al.\(^{8}\) documented an odds ratio of hemorrhagic presentation for deep venous drainage of 2.04 and an odds ratio of 2.17 for future hemorrhage.\(^{10}\)

**TABLE 5.** mRS Scores Before and After Treatment

<table>
<thead>
<tr>
<th>mRS Score at Last Follow-Up</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS score at presentation</td>
<td>Total</td>
</tr>
<tr>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>1</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
</tr>
<tr>
<td>Total 0–2</td>
<td>47</td>
</tr>
</tbody>
</table>

**TABLE 4.** Short- vs Long-Term Risk of Hemorrhage During the Pretreatment Interval

<table>
<thead>
<tr>
<th>Follow-Up Interval, Patient-Years</th>
<th>Hemorrhage Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–36 months</td>
<td>12.0% (5.2%–23.6%)</td>
</tr>
<tr>
<td>&gt;36 months</td>
<td>9.7% (5.3%–16.2%)</td>
</tr>
<tr>
<td>Difference</td>
<td>−2.3% (−12.0%–7.5%)</td>
</tr>
</tbody>
</table>
Fleetwood et al. showed that the annual hemorrhage risk in patients with deep (basal ganglia or thalamic) AVMs was 9.8% per patient-year in their series of 96 patients. Sixty-one of their 96 patients (64%) had Spetzler-Martin grade IV or V AVMs. Deep location was also one of the factors that reached statistical significance in the that series as a risk factor for both hemorrhagic presentation and future hemorrhage, with odds ratios of 3.26 and 5.26, respectively.8,10 However, in our series, only 18% of the AVMs were in a deep location, and our pretreatment hemorrhage rates for deep and cortical AVMs were similar, at 10.5% and 8.9% per year, respectively (Table 3). As such, deep location alone also appears unable to explain the increased hemorrhagic risk.

There are some drawbacks to any single-center analysis. Our patients represent a select population and therefore, may have been subject to selection bias. However, because we used the same patients to evaluate pretreatment bleeding risk versus posttreatment bleeding risk, we can say that in this patient group, treatment did not confer a statistically significant increased risk of hemorrhage. Nevertheless, a randomized, controlled trial would ideally answer the question of the appropriateness of therapy in this or any other AVM group. Our current recommendations are to offer multimodality treatment for most patients with grades IV and V AVMs. Obviously, the hemorrhage rates presented herein would be one of several factors used to decide whether treatment would be offered on a patient-by-patient basis. Thirty percent of the patients in this series were angiographically cured. Although 67% have residual AVMs, 25 of these patients (41% overall) are within 3 years of their last radiosurgery treatment.

Conclusions
In our series, the annual rate of hemorrhage seen with grades IV and V AVMs was higher than that generally reported for AVMs as a whole, although this annual rate of hemorrhage may reflect referral bias in this single-center case series. Nevertheless, initiation of treatment does not appear to cause any statistically significant increase in the hemorrhage rate. In addition, initiation of treatment in patients with hemorrhagic presentation lowers the hemorrhage rate to the level of those with a nonhemorrhagic presentation. As demonstrated in other AVM natural history series, patients with grades IV and V AVMs and prior hemorrhage are at higher risk for recurrent hemorrhage.

Disclosures
None.

References
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