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RESEARCH ARTICLE

Grades of brain arteriovenous malformations and risk of hemorrhage and death

Marco A. Stefani[1,2,3], Diego Sgarabotto Ribeiro[1,4] & Jay P. Mohr[5]

[1]Postgraduate Program in Surgical Sciences, Faculty of Medicine, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
[2]Department of Morphological Sciences, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil
[3]Neurosurgeon at Moinhos de Vento Hospital, Porto Alegre, Brazil
[4]Radiologist and Neuroradiologist, Porto Alegre, Brazil
[5]Neurologist at the Institute of Neurology, Columbia University Medical Center, New York, New York

Correspondence
Marco Antonio Stefani, Department of Morphological Sciences, Institute of Basic Health Sciences, Federal University of Rio Grande do Sul. 500, Sarmento Leite Street, Porto Alegre, RS 90020-090, Brazil. Tel: +55 (51) 3308 3146/3308 3915; Fax: +55 (51) 3308 3146; E-mails: marco.stefani@ufrgs.br/ marco@stefani.med.br

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Abstract

Objective: To assess the relationship of the grade of unruptured and untreated Brain Arteriovenous Malformations (AVMs), with the risk of subsequent stroke and death during follow-up. **Methods**: This prospective study was drawn from a cohort of adult patients with unruptured AVMs, who participated in the conservative treatment arm (medical management only for headache or seizures) of the randomized clinical trial of unruptured brain AVMs (ARUBA study). The grade of AVMs (Spetzler–Martin scale) was dichotomized into categories: AVMs of grades I and II were considered low grade; AVMs of grades III and IV were considered high grade. There were no grade V AVM patients in ARUBA. The primary outcome was symptomatic stroke (hemorrhagic or ischemic – documented by imaging) or death. **Results**: The conservative treatment group had 123 patients ("as treated" analysis). 71 (57.7%) had lesions characterized for this analysis as low-grade lesions and 52 (42.2%) as high grade. From the total of 10 (8.13%) primary outcomes, three occurred (4.22%) in low-grade AVMs and seven (13.46%) in high-grade AVMs ($P = 0.0942$). **Interpretation**: Statistical analysis of the cohort of patients with unruptured and untreated AVMs from ARUBA study showed that the graduation categories (Spetzler–Martin grades) were not associated with the outcome of subsequent stroke or death.

Introduction

Brain Arteriovenous Malformations (AVMs) are complex lesions with potential to cause hemorrhagic and nonhemorrhagic events followed by devastating neurological deficits, long-term disability, and death.[1–8] Annual ICH rates in untreated AVMs range from about 2 to 4%.[2,9,10] These rates may vary according to several AVM characteristics, such as location, venous drainage, lesion size, presence of associated aneurysms, or history of previous bleeding.[11,12] It has long been hypothesized that unruptured and untreated high-grade AVMs may have a higher risk of subsequent bleeding than those of low-grade lesions.

The ARUBA study[13] was registered in the database "www.clinicaltrials.gov," under the number NCT00389181. Participation in the trial was approved by institutional committees or ethics committees in the 39 international institutions involved, and all participants gave informed consent prior to randomization[13]. The study received support, monitoring and funding from NIH and NINDS (National Institutes of Health, National Institute of Neurological Disorders and Stroke, respectively).[13] All outcome events were adjudicated by a 4-member panel of internationally recognized clinicians experienced with AVM diagnosis and management. The ARUBA data quality was reviewed by an NINDS-appointed Data and Safety Monitoring Board (DSMB). Randomization was halted by the DSMB after 226 patients had been entered, with 223 of them participating in the trial long enough for outcome assessments to be made.[13]

The results of a randomized clinical trial involving brain AVMs discovered without having bled (unruptured) –

ARUBA, offers an excellent opportunity for further studies on the risks of bleeding and intervention in unruptured AVMs. The purpose of this study was to use the published trial data (from ARUBA) to assess the relationship between the grades (according to the Spetzler and Martin[14] scale) of unruptured and untreated brain AVMs and the risk of subsequent hemorrhagic stroke and death in the natural history of these lesions.

Methods

The ARUBA trial[13] database consisted of two prospective randomized arms of AVM patients, one to receive conservative treatment alone (observation only, without intervention, medical therapy for headache or seizures) and the other to receive the same medical therapy but with intervention intended to eradicate the AVM. All patients had the AVMs characterized in relation to its angioarchitecture and stratified according to the Spetzler–Martin[14] classification, including lesion size, location in eloquent brain area and type of venous drainage as some of the evaluated parameters. The combined primary outcome was the occurrence of an event of symptomatic stroke (hemorrhagic or ischemic) or death from any cause in the evaluated patients. Intracranial hemorrhage (ICH) was characterized as an episode of focal neurological deficit, seizure or new onset headache, associated with hemorrhage imaging findings. A stroke of death outcome ended formal participation of the individual patient in the trial.[13] During ARUBA study, Kaplan–Meier curves of time from randomization to outcome event documented the course for those "as randomized" and a separate analysis was made for those "as treated."[13]

The analysis of this article used data from the conservative treatment arm of ARUBA.[13] The influence of the grades of brain AVMs, established by the classification of Spetzler and Martin,[14] on the risk of hemorrhagic stroke or death during the natural history of these lesions, was examined.

The ARUBA study[13] provided data from its "as treated" analysis for the group receiving conservative treatment (unruptured and untreated AVMs). This group of patients had 125 individuals.[13] The data show the patients and their respective AVMs stratified according to the Spetzler–Martin classification grades and identify the number of primary outcomes that occurred in each of these grades.

Randomization to ARUBA was permitted based on Magnetic Resonance Imaging (MRI) alone. Nevertheless, all but two patients also underwent catheter angiography. These two patients imaged by MRI alone (catheter angiography not available) had been randomized to the conservative arm, and the Spetzler–Martin grade was not available for them. Thus, the final sample of this study ("as treated" analysis) was composed of 123 patients with unruptured and untreated AVMs originated from ARUBA conservative treatment arm (Table 1).

For this study, statistical analysis was made of data available from ARUBA study.[13] Using the AVM stratification according to the Spetzler–Martin scale, the lesion grade variable was dichotomized into categories: AVMs of grades I and II of the Spetzler–Martin classification were considered low-grade AVMs; Spetzler–Martin grades III, IV and V AVMs were considered high-grade AVMs. In the available data there were no records of Spetzler–Martin grade V AVMs. Outcome variables of symptomatic stroke (hemorrhagic or ischemic) or death were also dichotomized according to their occurrence (yes, positive; no, negative). In a first step, data regarding to AVMs stratification in the Spetzler–Martin classification and the respective number of patients in each grade of this scale were obtained. Next, the number of patients in each AVM high- and low-grade category was calculated as follows: the number of patients whose lesions were classified in Spetzler–Martin grades I and II was summed to constitute the category of low-grade AVMs; the number of patients whose lesions were classified in Spetzler–Martin grades III and IV was summed to constitute the category of high-grade AVMs. In a second step, data regarding to the outcome over the follow-up period were extracted.

Statistical analysis was performed considering the categorical variables of high and low grade and correlating them with the occurrence of the outcome (stroke or death), in each of these graduation categories. According to the study hypothesis, the group of low-grade AVMs (Spetzler–Martin I and II) would represent patients not exposed to a higher risk of hemorrhagic stroke or death; the group of high-grade AVMs (Spetzler–Martin III, IV and V) would represent patients exposed to a higher risk of hemorrhagic stroke or death. Data analysis was performed using Fisher's exact test, conducted through

Table 1. The Spetzler–Martin classification and number of patients distributed in each grade with the respective number of outcomes occurred.

Spetzler–Martin classification	Number of patients[1]	Outcome events[2]
Grade I AVMs	37	2
Grade II AVMs	34	1
Grade III AVMs	34	3
Grade IV AVMs	18	4
Grade V AVMs	0	0

Source: prepared by the authors.
AVMs, Brain Arteriovenous Malformations.
[1]Total of 123 patients in ARUBA database who had angiographic data available to be classified according to the Spetzler–Martin system.
[2]Total of 10 outcomes occurred during the follow-up period.

GraphPad Instat statistical software (version 3 for Windows, GraphPad Software, San Diego, CA; http://www.graphpad.com). The $P < 0.05$ was used to consider the statistically significant results and 95% confidence intervals (CI) were used to display the results found.

Results

During the ARUBA study period, 226 patients were recruited.[13] However, the final sample of the population included in ARUBA was 223 patients, which were randomized with adequate follow-up data.[13] From this total, according to the study's original randomization, 114 were allocated to the prospective arm that received interventional treatment, and 109 were allocated to the conservative treatment arm. During ARUBA, some patients chose to change their treatment assignment from conservative to intervention or the opposite. The outcomes for these patients were reported "as treated" analysis, that is, as the treatment groups were actually composed. Therefore, drawing on the "as treated" cohort, the data analyzed in this study was formed by these 125 individuals with unruptured and untreated AVMs. However, of 125 patients in the conservative treatment arm of ARUBA database, the Spetzler–Martin scale grade was not available for two patients (catheter angiography not available at the time of inclusion in the study).[13]

Of the total of 123 patients with unruptured and untreated lesions stratified into grades of the Spetzler–Martin scale, 71 (57.7%) AVMs were considered of low grade (I and II) and 52 (42.2%) AVMs were considered of high grade (III and IV). Primary outcome (symptomatic stroke or death from any cause) occurred in 10 (8.13%) of 123 patients randomized to receive conservative treatment. From this total of primary outcomes, among AVMs considered of low grade, there were three (4.22%) events of symptomatic stroke or death; among AVMs considered to be of high grade there were seven (13.46%) events of symptomatic stroke or death (Table 2).

The correlation of primary outcome occurrences between the two AVM Spetzler–Martin grades categories showed a p value of 0.0942 (RR = 0.319; 95% CI: 0.085–1.157), a result considered not statistically significant (Fig. 1). This finding indicated that, in this cohort of patients with unruptured and untreated AVMs, the grading categories formed by the Spetzler–Martin classification were not associated with subsequent hemorrhagic stroke or death.

Table 2. The total number of patients in AVMs grades categories and the number of primary outcomes identified during follow-up.

AVMs graduation categories	Patients	Outcome events
Low grade (Spetzler–Martin grades I and II)	71	3
High grade (Spetzler–Martin grades III and IV)	52	7
Total	123	10

Source: prepared by the authors.
AVMs, brain arteriovenous malformations.

Discussion

The complexity of brain AVMs makes them a heterogeneous group of lesions, with several factors assumed possible to affect the risk of rupture with subsequent hemorrhagic stroke.[9,15] Since brain AVMs can be associated with a potentially severe natural history,[16] determining the rupture risk is crucial to establish the appropriate treatment.[5,17]

Cohort studies and meta-analyses have improved the ability to predict the hemorrhagic event in AVMs.[18] Several descriptions of angioarchitectural features of AVMs that would be associated with an increased hemorrhagic risk have been reported,[18] both as initial hemorrhagic presentation[19–22] and during the natural course of AVMs (subsequent, future hemorrhages).[15,23,24]

The ARUBA study[13] provided the first results of a randomized trial involving unruptured brain AVMs. These results triggered a detailed examination of the relationship between Spetzler–Martin grades and the hemorrhagic outcome and clinical severity of these events. The AVM classification proposed by Spetzler and Martin[14] allows to assess the complexity of these lesions and to estimate the risk related to surgical treatment. This classification system is currently the most widely used, due to its ease of application and its correlation with the prognosis.[23] The Spetzler–Martin system relates morphology (size and venous drainage of the AVM) and localization (neurological eloquence of the brain adjacent to the AVM) in order to grade the lesion and predict its surgical risk. The results from the present analysis indicates that the evaluated unruptured and untreated AVMs failed to show an association between the original grades of Spetzler–Martin scale and the occurrence of subsequent hemorrhagic stroke. Although not from a randomized sample, similar failure was reported by Padilla-Vazquez et al.[25] and Tasic et al.[26]

The risks and outcomes related to the natural history of high-grade AVMs (Spetzler–Martin grades IV and V) are of special interest, particularly considering the high risk of treatment of these lesions.[27] A prospective study investigating the natural history of 63 untreated high-grade AVMs found that 23 patients (37%) suffered subsequent bleeding, resulting in an annual mean hemorrhage rate of 3.3% for untreated high-grade lesions.[27] Malformations classified in grades IV and V (Spetzler–Martin) and with large sizes may have a higher prospective

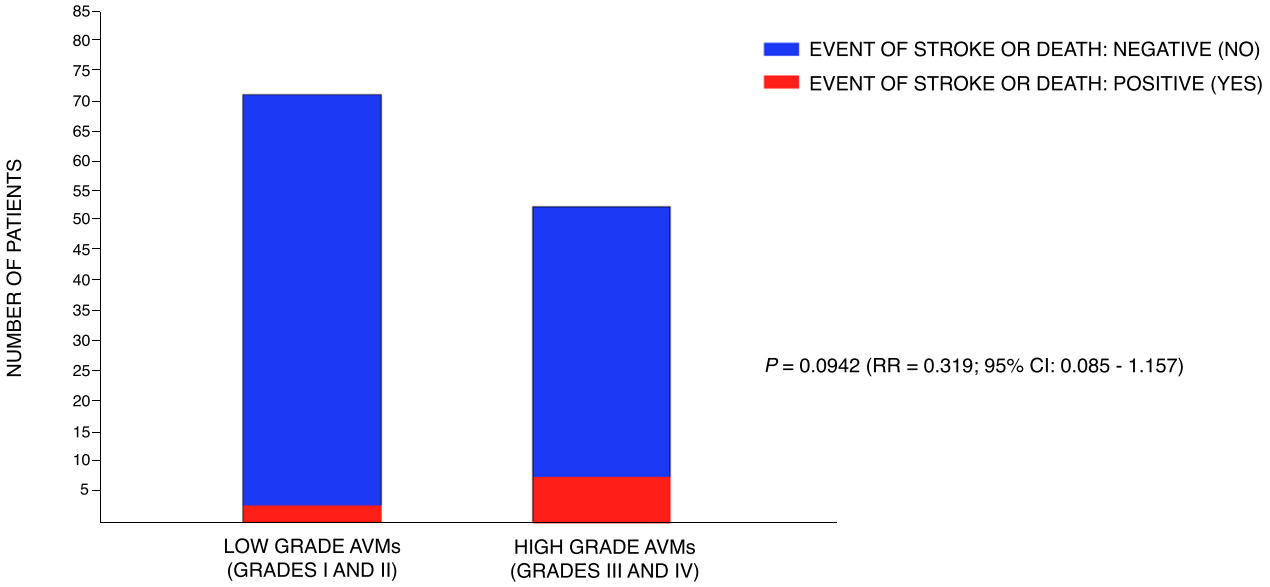

Figure 1. Brain Arteriovenous Malformations (AVMs) Grades (Derived from the Spetzler–Martin Classification System) versus Primary Outcome. The graph relates AVMs grades categories (composed by the Spetzler–Martin scale) with the occurrence of primary outcome. Source: adapted by the authors from GraphPad Instat (version 3, GraphPad Software, San Diego, CA).

hemorrhagic rate,[24,28] but not in other studies,[27,29] demonstrating that there is no consensus on this subject.

Some authors have suggested that AVMs located in deep regions, such as the basal ganglia, the periventricular or intraventricular space, are at increased risk of bleeding.[22,30] Several locations of AVMs were associated with a higher occurrence of hemorrhage at the initial presentation, such as the cerebellum, brainstem, temporal lobe, insula, corpus callosum, the basal ganglia, and ventricles.[22,31] Yang et al.[32] conducted a study seeking factors associated with hemorrhage in AVMs, observing that variables such as nonfrontal lobar location, basal ganglia location or brainstem location were associated with hemorrhagic presentation in brain AVMs. Stefani et al.[33] reported that deep location was a factor significantly associated with initial hemorrhage in AVMs, whereas Tong et al.[31] verified that infratentorial and deep location may be associated with initial hemorrhage in AVMs. Ellis et al.[34] observed that infratentorial location was independently associated with hemorrhagic presentation in pediatric AVMs. A retrospective study reported that hemorrhagic presentation was significantly more common in deep pediatric AVMs, located in the basal ganglia, thalamus, and brainstem.[35]

Consistently implicated in subsequent hemorrhage related to AVMs would be infratentorial and deep cerebral location.[9,15] Nevertheless, according to Santos et al.,[36] the incidence of hemorrhage related to the location of AVM nidus is controversial. Mohr and Yaghi[37] stated that encephalic location appears to have no influence on the size, vascular complexity and tendency for hemorrhage of brain AVMs. Analyzing the natural history of AVMs, several studies did not show a relationship between location and bleeding risk.[27,38,39] Ma et al.[40,41] analyzed pediatric patients with AVMs seeking risk factors for hemorrhagic presentation and subsequent hemorrhage (follow-up), obtaining conflicting results.

The venous characteristics of AVMs have been widely evaluated and implicated in the hemorrhage of these lesions.[42,43] The association between deep venous drainage and a higher incidence of hemorrhagic presentation was reported by several studies.[19,20,22,39,44,45] Studies involving pediatric AVM patients found that deep venous drainage was associated with hemorrhagic presentation.[34,35]

The studies of Alexander et al.,[5] Kubalek et al.,[11] Padilla-Vazquez et al.[25] and Hernesniemi et al.[15] supported previous reports that exclusively deep venous drainage in brain AVMs is more commonly associated with bleeding than exclusively superficial venous drainage or mixed venous drainage. However, the studies by Ma et al.[40,41] analyzed characteristics of pediatric AVMs and showed that deep (and exclusively deep) venous drainage was not a predictor of hemorrhagic presentation in these lesions. The same authors[41] also found that deep venous drainage did not affect the risk of subsequent rupture. More information is needed to delineate the role of complex venous features and its influence in the natural history of AVMs.[5,9,23]

The issue of AVMs size and its relation to hemorrhagic risk in the natural history of these lesions has already been analyzed by several authors, with different results.[19,38,46,47] The association between size and hemorrhagic presentation,

especially in the group of small AVMs (<3 cm), has already been suggested.[32,48,49] In the study by Yang et al.,[32] small size was associated with hemorrhagic presentation, with a reduction of 0.35 in the odds ratio (OR) for hemorrhagic risk every 1 cm increase in AVM size (OR = 0.65; $P < 0.01$). Fok et al.,[1] Tong et al.[45] and Sahlein et al.[50] showed that small size was a risk factor for hemorrhagic presentation. Ma et al.[40] analyzed characteristics of AVMs to assess hemorrhagic risk in children, concluding that a smaller nidal size was a risk factor for initial hemorrhage. In the study by Alexander et al.,[5] AVM size was inversely related to hemorrhagic presentation. Other authors stated that small AVMs are associated with an increased hemorrhagic risk.[11,17,36,51–54]

Conversely, several authors did not verify a predictive value of hemorrhage risk for AVM size, including natural history hemorrhages.[30,55] Analyzing untreated AVMs in children, Ma et al.[41] found no association between size and risk of subsequent hemorrhage. Neither the meta-analysis performed by Gross and Du[56] nor the cohorts of the MARS study[57] ("Multicenter AVM Research Study") found association of size with increasing risk of AVM-related hemorrhage. According to Morgan et al.,[23] size would be unlikely to play a significant role in relation to the risk of subsequent hemorrhage in AVMs.

Demonstrating the disagreement regarding the role of size in hemorrhagic risk, some authors have pointed out that large AVMs (>3 cm) are associated with a higher risk of subsequent bleeding.[9,15,16,24,58] Brain AVMs with large sizes may present in nonhemorrhagic forms, which could lead to an overestimation of hemorrhage rate in small AVMs.[39] The finding that small size predicts hemorrhagic presentation but significantly decreases the risk of future bleeding, suggests that a significant proportion of small unruptured AVMs remain undetected throughout life or are not discovered until a hemorrhage occurs, possibly not being accounted for in natural history studies.[9] Beyond that, patients with small AVMs may proportionally experience more episodes of hemorrhage, not because the smaller size would indeed be a risk factor, but through its association with previous hemorrhage.[15]

In contrast to this study, most similar publications are retrospective, not population-based and certainly nor randomized-based. Additionally, publications that report only their referral cohort may be unintentionally biased by their sample. Many previous studies have examined hemorrhagic risk in AVMs, but most have not included the Spetzler–Martin grade as a factor that may be associated with bleeding.

This study had some limitations. In the statistical analysis of data obtained from ARUBA[13], follow-up times of patients in each category of grades from the Spetzler–Martin scale were not included in the calculation. The combination of the number of patients available in each of the Spetzler–Martin[14] grades, to compose the categories, may have interfered with the result. The fact that the study had a combined outcome (death or stroke), may have influenced analysis. Hence, the current result should be interpreted with caution.

In conclusion, this article analyzed the relationship between the grades of cerebral AVMs and the risk of symptomatic stroke or death. Analysis of the cohort of patients with unruptured and untreated AVMs from ARUBA showed that the graduation categories (formed by the Spetzler–Martin grades) were not associated with the outcome of subsequent stroke or death. Our result raises the question whether it is possible to predict which patients will bleed based on Spetzler–Martin grade, not demonstrated in the only randomized trial to date. This article will contribute to the process of understanding the influence of AVMs grades on the risk of subsequent hemorrhage throughout the natural history of these lesions. We recommend that the results of this article serve as a starting point for further investigations into hemorrhagic risk factors in unruptured and untreated AVMs.

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Author Contribution

Marco Antonio Stefani participated in the conception and design of the study; performed data collection; analyzed and interpreted the data; revised and edited the manuscript. Diego Sgarabotto Ribeiro participated in the conception of the study; conducted scientific literature search; prepared and organized the data; undertook statistical analysis; contributed to data interpretation; drafted the manuscript and prepared the figures and tables. Jay P. Mohr participated in the conception and design of the study; performed data collection; contributed to final data analysis and interpretation; conducted final revision and edition of the manuscript.

Conflict of Interest

Dr. Stefani has nothing to disclose. Dr. Sgarabotto Ribeiro has nothing to disclose. Dr. Mohr has nothing to disclose.

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