

Patterns of Brain Arteriovenous Malformation Treatment Prospective, Population-Based Study

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Background and Purpose—The extent of variation in the interventional treatment of brain arteriovenous malformations (AVMs) is unknown, so we explored patterns of treatment at 4 neuroscience centers in one European country.

Methods—We included every participant with an AVM in a prospective, population-based cohort study of adults aged ≥ 16 years residing in Scotland at the time of AVM diagnosis in 1999 to 2003.

Results—Only 11 (5%) of the 229 adults were not managed at a neuroscience center. Adults who received interventional treatment were younger (median, 43 versus 54 years), more likely to have presented with hemorrhage (OR, 2.8; 95% CI, 1.6 to 4.9), and had smaller AVMs (median nidus diameter, 2 cm versus 3 cm; $P=0.003$) than those who did not. Adults seen at the 4 centers only differed in AVM Spetzler-Martin grade ($P=0.04$). The 4 centers did not differ in the proportion of adults with AVMs who received interventional treatment ($P=0.16$), but they differed in the Spetzler-Martin grade of the AVMs they treated (Grades III to IV, $P=0.01$) and the interventional treatments used ($P=0.004$). The 2 largest centers differed from each other in the likelihood of surgical resection (OR, 0.2; 95% CI, 0.1 to 0.6) and stereotactic radiosurgery (OR, 2.8; 95% CI, 1.3 to 6.1), and the choice of modality varied within some Spetzler-Martin grades.

Conclusions—Patient characteristics and patterns of AVM interventional treatment differ between neuroscience centers in the same population necessitating careful consideration of these factors when comparing one hospital's outcome with another. (*Stroke*. 2008;39:3216-3221.)

Key Words: aneurysm ■ arteriovenous malformations ■ AVM ■ cerebral aneurysm ■ hematoma ■ other stroke treatment—surgical ■ subarachnoid hemorrhage

Brain arteriovenous malformations (AVMs) are an important cause of intracranial hemorrhage,^{1,2} which accounts for half of the presentations that lead to AVM diagnosis.^{3,4} The main purpose of interventional treatment of AVMs is to prevent first or recurrent intracranial hemorrhage and related death and disability.

Treatment is usually targeted at AVMs with a future risk of hemorrhage that is thought to outweigh the risks of intervention on the basis of comparisons of estimates of untreated clinical course from hospital-based studies with local measures of treatment outcome.^{5,6} Microsurgical resection, endovascular embolization, or stereotactic radiosurgery are used either alone or in various combinations in an attempt to obliterate the AVM nidus and thereby eliminate the risk of

hemorrhage.² However, these interventions are not without risk; new neurological deficits may occur after these procedures in 10% to 42% of patients.^{7–10} The Spetzler-Martin grading scale (based on AVM nidus size, pattern of venous drainage, and “eloquence” of adjacent brain) was derived to predict the risk of death and disability after neurosurgical excision.¹¹

Randomized, controlled trials have not informed AVM management so far.¹² Although A Randomized trial of Unruptured Brain Arteriovenous malformations (ARUBA) is comparing interventional and conservative management, there is no trial randomizing participants between different interventions. Despite the lack of strong evidence on which to base management, patients deserve consistent approaches to treatment.

Received April 30, 2008; accepted May 6, 2008.

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*See Al-Shahi R, et al. *Stroke*. 2003; 34:1156–1162, and Wedderburn C, et al. *Lancet Neurol*. 2008; 7:223–230 for lists of SIVMS collaborators (updates at www.sivms.org).

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DOI: 10.1161/STROKEAHA.108.523662

The American Heart Association management guidelines recommend, for example, surgical excision as the first treatment option for Spetzler-Martin Grade I and II AVMs unless surgery confers increased risk based on location or feeding vessel anatomy, in which case radiosurgery is recommended; at the other extreme, the American Heart Association guidelines recommend Grade IV or V lesions should only be embolized if subsequent surgery or radiosurgery follows with the aim of complete obliteration.² Nevertheless, institutional, regional, national, and international variations in practice may exist, due to referral practices, selection for particular treatment modalities, availability of technical equipment, personal preference, and policies of health insurance systems, to name just a few reasons.¹³

We sought to explore whether there were any detectable influences on regional patterns of AVM interventional treatment in one of the 2 ongoing, prospective, population-based cohort studies of AVM outcome.^{3,4}

Materials and Methods

Clinical Practice for Patients With Arteriovenous Malformations in Scotland

Specialist neuroscience services are delivered to the Scottish population of 5.1 million inhabitants at 4 neuroscience centers incorporating neurologists, neurosurgeons, neuroradiologists, stroke physicians, and neuropathologists in Glasgow, Edinburgh, Aberdeen, and Dundee. Patients attending their local hospitals access these specialist neuroscience services at the discretion of the physician directing their care. Care for patients with AVMs is coordinated in multidisciplinary AVM clinics in Edinburgh and Glasgow, whereas it is distributed between individual specialists in Aberdeen and Dundee. Neurosurgery is available in all 4 centers. Endovascular embolization is available in Glasgow and Edinburgh (suitable patients from Aberdeen and Dundee can be referred to Edinburgh). Linear accelerator radiosurgery is available in Edinburgh, and patients may be referred to the National Center for Stereotactic Radiosurgery in Sheffield, UK, for gamma knife radiosurgery (www.shef.ac.uk/~ns).

Scottish Intracranial Vascular Malformation Study

The Scottish Intracranial Vascular Malformation Study (SIVMS) is a prospective, population-based register of Scottish residents aged ≥ 16 years at the time they were first diagnosed with any type of intracranial vascular malformation in the years 1999 to 2003 (www.sivms.org).⁴ Methods of case ascertainment and data collection have been described elsewhere.¹⁴ The register's twin objectives of clinical audit and observational epidemiological research are overseen by a multidisciplinary steering committee representative of the 4 Scottish neuroscience centers. SIVMS plays no role in decisions about whether or how to treat patients' intracranial vascular malformations. This analysis was restricted to participants with brain AVMs recruited to the SIVMS cohort in 1999 to 2003. The variables we examined at the patients' first presentation with an AVM were²: age at diagnosis, gender, socioeconomic status measured by the deprivation category of their residential postcode sector according to the 2001 census obtained from the MRC Social and Public Health Sciences Unit in Glasgow (www.msoc-mrc.gla.ac.uk), type of presentation (hemorrhage, seizure[s], incidental, or other), Oxford Handicap Scale at presentation, first referral center for treatment if the patient was referred (Scottish neuroscience centers were anonymized using the codes A, B, C, and D), Spetzler-Martin grade (determined by AVM maximum nidus diameter, eloquence of brain area, and pattern of venous drainage),¹¹ presence of associated aneurysms (on the AVM nidus or a feeding artery), and type of interventional procedures (microsurgery \pm embolization, radiosurgery \pm embolization, or embolization alone for AVMs; coiling or clipping for associated aneurysms).

Ethical Approval

The Multicenter Research Ethics Committee for Scotland approved SIVMS (MREC/98/0/48).

Statistical Analysis

We compared demographic, clinical, and radiological characteristics between patients who were seen at the 4 centers versus those who were diagnosed elsewhere and not referred and between patients who received interventional treatment and those who did not. Subsequently, we compared the patterns of presentation and treatment among the 4 centers (A/B/C/D) and then searched for any differences between the 2 largest centers (C and D) in the patients who they did and did not treat. If a patient attended more than one neuroscience center, they were allocated to the first neuroscience center that they attended. We used SPSS Version 13.0 and StatsDirect Version 2.4.6 to calculate parametric statistics when data obeyed a normal distribution and nonparametric statistics when they did not.

Results

Two hundred twenty-nine adults were first diagnosed with an AVM while residing in Scotland in 1999 to 2003. Data completeness was 100% for baseline variables apart from socioeconomic status (226 patients [99%]), eloquence of AVM brain area (226 [99%]), and AVM nidus size (208 [91%]); angiographic pattern of venous drainage (181 [79%]) and Spetzler-Martin grade (175 [76%]) reflected the uptake of catheter angiography (185 [81%]).

Two hundred eighteen (95%) adults with AVMs were managed at one of the 4 neuroscience centers, and 11 (5%) were not; 4 of these 11 were diagnosed at postmortem (only one death was due to the AVM), and 2 patients died soon after presenting with a hemorrhage, but it was unclear why the remaining 5 were not referred. Those not referred tended to be older, their AVM was more likely to have been detected incidentally, they never had catheter angiography, and they did not have interventional treatment.

Comparison of the baseline characteristics of the patients who were seen at one of the neuroscience centers revealed differences in socioeconomic status between centers ($P=0.02$) and dichotomized Spetzler-Martin grade (I to II versus III to V, $P=0.04$; Supplemental Table I, available online at <http://stroke.ahajournals.org>). If only the 2 largest centers (C and D) were compared, the difference in socioeconomic status was no longer significant (Fisher exact test, $P=0.1$), but the difference in dichotomized Spetzler-Martin grade remained (χ^2 test, $P=0.03$). Patients from Center C were more likely to have a Spetzler-Martin Grade II than patients from Center D (OR, 2.2; 95% CI, 1.1 to 4.4) and presented more frequently with seizure(s) (OR, 2.3; 95% CI, 1.2 to 4.6).

Compared with patients who did not receive interventional treatment, those who did were more likely to have presented with hemorrhage (OR, 2.8; 95% CI, 1.5 to 5.1) and less likely to have presented incidentally (OR, 0.30; 95% CI, 0.1 to 0.6) so they had a different pattern of dependence on the Oxford Handicap Scale at presentation and they were also younger, more likely to have had a catheter angiogram, and they had smaller AVM nidus diameters (Table 1). In the 2 largest centers (C and D), we found the same overall differences between treated and untreated patients in age, mode of presentation, and receipt of a catheter angiogram, but the

Table 1. Comparison of the Demographic, Clinical, and Radiological Characteristics of Patients Who Received Interventional Treatment and Those Who Did Not*

	Untreated (n=77)	Treated (n=152)	Statistics
Mean age±SD (range)	54±17 (16–85)	43±13 (16–68)	<i>t</i> test: <i>P</i> =0.0000005
Male gender	41 (53, 42–64)	86 (57, 49–64)	χ^2 test: <i>P</i> =0.6
Socioeconomic status			
DepCat 1–2	8 (10.5, 5–19)	32 (21, 16–29)	χ^2 test: <i>P</i> =0.1
DepCat 3–5	50 (66, 55–76)	89 (59, 51–67)	
DepCat 6–7	18 (24, 15–34)	29 (19, 14–26)	
Initial presentation			
Hemorrhage	26 (34, 24–45)	89 (59, 51–66)	Fisher exact: all, <i>P</i> =0.0003;
Seizure(s)	20 (26, 18–17)	38 (25, 19–32)	χ^2 test: hemorrhagic, <i>P</i> =0.0005; incidental, <i>P</i> =0.003
Other	6 (8, 4–16)	6 (4, 2–8)	
Incidental	25 (32.5, 23–44)	19 (12.5, 8–19)	
OHS at presentation			
0	8 (10, 5–19)	6 (4, 2–8)	Fisher exact, for all groups: <i>P</i> =0.02
1	26 (34, 18–37)	51 (34, 27–41)	
2	14 (18, 11–28)	34 (22, 17–30)	χ^2 test (OHS 0–2 versus 3–6): <i>P</i> =0.8
3	6 (8, 4–16)	19 (12.5, 8–19)	
4	5 (6.5, 3–14)	17 (11, 7–17)	
5	13 (17, 10–27)	25 (16, 11–23)	
6	5 (6.5, 3–14)	0 (0, 0–3)	
Catheter angiogram	40 (52, 41–63)	145 (95, 91–98)	χ^2 test: <i>P</i> = 3×10^{-15}
AVM nidus size, mm			
Median (IQR)	30 (19–40)	20 (14.5–30)	Mann–Whitney <i>U</i> test: <i>P</i> =0.003
<30	27 (41, 30–53)	92 (65, 57–72)	Fisher exact: <i>P</i> =0.0002
30–60	35 (53, 41–65)	50 (35, 28–43)	
>60	4 (6, 2–15)	0 (0, 0–3)	
Eloquent AVM area	38† (51, 40–62)	83 (55, 47–62)	χ^2 test: <i>P</i> =0.6
Venous drainage			
Superficial only	27 (69, 54–81)	103 (72.5, 65–79)	χ^2 test: <i>P</i> =0.7
Any deep	12 (31, 19–64)	39 (27.5, 21–35)	
Spetzler–Martin grade			
I	9 (22.5, 12–38)	38 (28, 21–36)	Fisher exact: <i>P</i> =0.2
II	12 (30, 18–45)	53 (39, 31–48)	χ^2 test: SMG I–II versus III–V: <i>P</i> =0.08
III	13 (32.5, 20–48)	35 (26, 19–34)	
IV	5 (12.5, 6–26)	9 (7, 4–12)	
V	1 (2.5, 0.4–13)	0 (0, 0–3)	
Associated aneurysms	13 (17, 10–27)	43 (28, 22–36)	χ^2 test: <i>P</i> =0.058

*Numbers of patients in each category (%; 95% CI) are provided unless stated otherwise.

†Eloquence was not available in 3 patients.

DepCat indicates deprivation score (ranging from 1 [less deprived] to 7 [more deprived]); OHS, Oxford Handicap Scale (ranging from 0 [no symptoms] to 6 [death]); IQR, interquartile range; SMG, Spetzler–Martin grade.

overall difference in size between untreated and treated patients was found in Center D (*P*=0.009) but not in C (*P*=0.3).

There was no detectable difference among the 4 centers in the proportions of patients receiving interventional treatment overall nor when they were subdivided by Spetzler–Martin grade and mode of presentation, although there were some interesting trends (Table 2).

When comparing the characteristics of the patients who did receive interventional treatment at the 4 centers (Supplemental Table II), the 2 statistically significant differences were in the Spetzler–Martin grades of the AVMs that were treated and the types of interventional treatment given (Figure 1). Numbers of untreated and treated patients at each of the 4 centers differed in Spetzler–Martin Grades I to II (zero untreated versus 13 treated patients in Center A, zero versus 9 in B, 12

Table 2. The Proportions of Patients Who Received Interventional Treatment Subdivided by Neuroscience Center, Spetzler-Martin Grade, and Mode of Presentation*

Spetzler-Martin Grade	I-II		III-V	
	Unruptured	Ruptured	Unruptured	Ruptured
Center A				
26 (73, 54–86)	4 (100, 40–100)	9 (100, 66–100)	2 (50, 6.8–93)	1 (50, 1.3–99)
Center B				
11 (91, 62–98)	3 (100, 29–100)	6 (100, 54–100)
Center C				
69 (63, 51–73)	10 (53, 29–76)	20 (87, 66–97)	3 (38, 8.5–76)	5 (63, 25–92)
Center D				
112 (72, 63–80)	17 (77, 55–92)	22 (85, 65–96)	14 (78, 52–94)	19 (86, 65–97)
Statistics (Fisher exact test)				
<i>P</i> =0.16	<i>P</i> =0.12	<i>P</i> =0.73	<i>P</i> =0.078	<i>P</i> =0.24

*Numbers of patients in each category (% , 95% CI) are provided.

versus 30 in C, 9 versus 39 in D; Fisher exact test, *P*=0.05) and Grades III to V (3 versus 3 in A, one versus zero in B, 8 versus 8 in C, 7 versus 33 in D; *P*=0.01).

Comparison of patients treated in Centers C and D revealed the same differences noted overall for both Spetzler-Martin grade and type of interventional treatment. There were more Spetzler-Martin Grade II (25%; 95% CI, 6% to 42%) and fewer Spetzler-Martin Grade III (–22%; 95% CI, –4% to –36%) AVMs treated in Center C compared with Center D, which could have reflected the patterns of presentation at these 2 centers (Supplemental Table I). However, as a proportion of the patients in each Spetzler-Martin grade, Center D treated more Spetzler-Martin Grade III AVMs (87%) than Center C (50%; 37% difference; 95% CI, 6% to 68%). We found no significant differences for the other Spetzler-Martin grades. Patients at Center C were less likely to receive surgical treatment (OR, 0.2; 95% CI, 0.1 to 0.6), and more likely to receive radiosurgical treatment (OR, 2.8; 95% CI, 1.3 to 6.1). In Center C, 18 patients (75%) were treated with linear accelerator radiosurgery and 6 patients

(25%) with gamma knife radiosurgery, but in the remaining centers, every patient receiving radiosurgery was treated with the gamma knife (Fisher exact test, *P*<0.0001). Furthermore, the modalities used to treat AVMs by Spetzler-Martin grade varied between Centers C and D (Figure 2).

Discussion

In this prospective, population-based study of the contemporary management of adults with AVMs in one European country, we found expected overall differences between adults who were treated and those who were not, but there were no detectable differences in the proportion of patients treated at each neuroscience center. However, the spectrum of Spetzler-Martin grades, and the types of interventions used when AVMs were treated did differ between the centers.

Patients who were treated were more likely to have presented with hemorrhage, and this reflects the general recommendation that a ruptured AVM should be treated because hemorrhagic presentation may be associated with a 5-fold increased risk of a subsequent bleed.⁵ That smaller

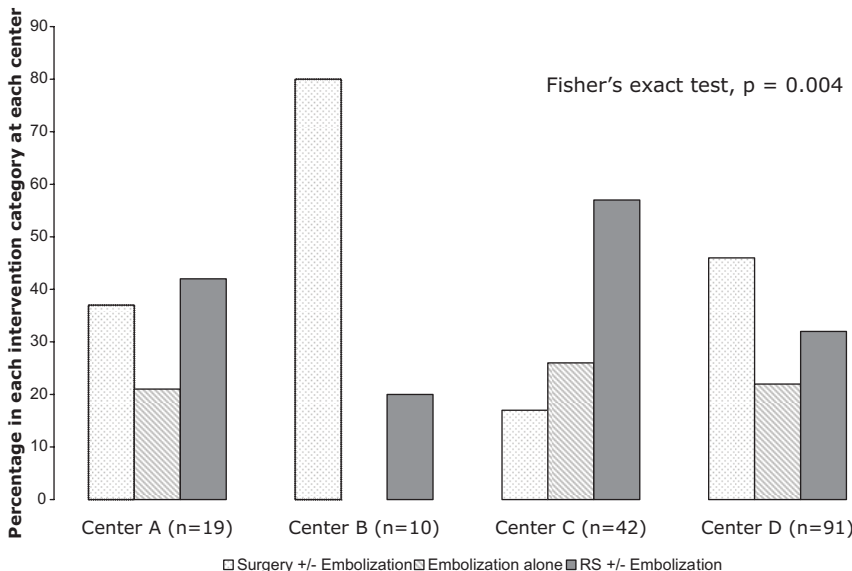


Figure 1. Patients receiving interventional treatment at each neuroscience center subdivided by type of intervention.

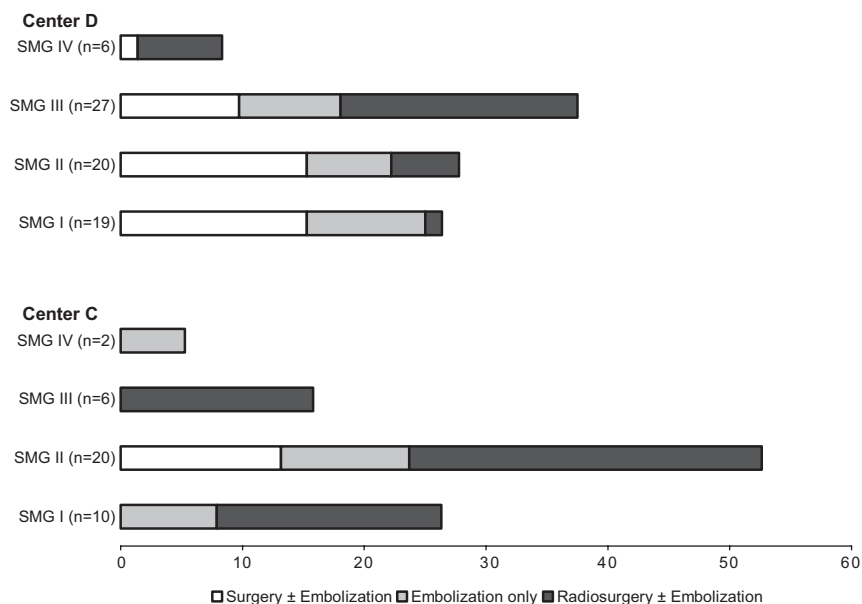


Figure 2. Patients receiving interventional treatment in Centers C and D subdivided by Spetzler-Martin grade (SMG) and types of intervention used in each grade.

AVM sizes tend to have been treated may be because smaller AVMs are more amenable to treatment,^{2,8} and they are more likely to have bled at presentation.^{15–17} The high proportion of surgically treated AVMs in Center B may be explained by all treated patients having Spetzler-Martin Grade I or II AVMs with only superficial drainage, which were therefore suitable for microsurgery.¹⁸ There was evidence of some heterogeneity in the therapeutic approach at centers C and D (Figure 2) with use of microsurgical excision for almost all Spetzler-Martin grades in Center D, whereas Center C only operated on those with Grade II AVMs.² These findings may have been influenced by local referral patterns, local treatment preferences, and differential access to treatment modalities between centers (also found in a global comparison of specialist centers¹⁹).

The main strengths of this study were its thorough case ascertainment in a population of 5.1 million inhabitants, and its representative description of contemporary AVM treatment practice in 1999 to 2003 in one European country with known provision of neuroscience services for adults with AVMs, all freely accessible on the National Health Service.¹⁴

Of the potential weaknesses of the study, chance effects are the greatest threat in view of the sample size. Further details about the angioarchitecture of AVMs that were diagnosed at referring hospitals only, or were not treated, were incomplete due to the lower uptake of diagnostic catheter angiography in these groups. It is arguable whether the decision to refer or to treat always requires catheter angiography,²⁰ because age, comorbidities, and severity of intracranial hemorrhage may militate against intervention. However, the interventional practices observed in this study are representative of those who are seen at neuroscience centers.²¹

No studies describing patterns of treatment within countries, between countries, or between continents have been published before and this is, to our knowledge, the first study describing different patterns of interventional treatment within a defined population. Two other studies have described AVM treatment within a population,^{22,23} but neither

intended to describe regional patterns of intervention. A study of AVM management and outcome in 1989 to 1999 in a population of one million residents in a part of Sweden served by a university hospital and 10 local hospitals attempted to quantify the need for different treatment modalities for this population.²³ However, international, national, and perhaps even regional differences can be inferred from the patterns of intervention in case series published in the literature.^{24–30} In North America, suitable AVMs (such as Spetzler-Martin Grades I and II) seem to be excised more often than they are embolized,² but endovascular treatment (with or without radiosurgery) appears to have been used more frequently in Europe.¹³

This study found minimal detectable heterogeneity between patients with AVMs evaluated at 4 neuroscience centers serving an entire population, but it detected differences in patterns of interventional AVM treatment and in particular differences between the 2 largest centers in the treatments used within the same Spetzler-Martin grade. Different patterns of interventional treatment may have arisen because of variation in the local availabilities of interventions, because of the lack of robust experimental evidence to inform our choice of whose AVM to treat and how¹² or for reasons that could not be assessed by this study.

These data help inform the development of core standards for national audit, provide a benchmark for comparison with the American Heart Association guidelines² and patterns of AVM treatment in other populations, and reinforce the need for large studies with an experimental design (ideally, randomized, controlled trials) to improve the evidence base on which to make treatment decisions. In the meantime, decisions to treat a patient with an AVM should be individualized based on the AVM's characteristics and the estimated risk of intervention (based on a representative assessment of the center's outcome after intervention).³¹

Acknowledgments

We are grateful to Rosemary Anderson, Aidan Hutchison, and all the participants in the Scottish Intracranial Vascular Malformation

Study. The Scottish Intracranial Vascular Malformation Study (SIVMS) was funded by the Medical Research Council (Clinical Training Fellowship G84/5176 and Clinician Scientist Fellowship G108/613), The Chief Scientist Office of the Scottish Executive Health Department (Project Grants K/MRS/50/C2704, CZB/4/35, and CZG/2/265), and a Project Grant from the Stroke Association (TSA04/01). J.v.B. was funded by The Netherlands Organization for Scientific Research (NWO) and The Netherlands Heart Foundation (Grant 2002B138).

Disclosures

None.

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