

Outcome after interventional or conservative management of unruptured brain arteriovenous malformations: a prospective, population-based cohort study



Catherine J Wedderburn,* Janneke van Beijnum,* Jo J Bhattacharya, Carl E Counsell, Vakis Papanastassiou, Vaughn Ritchie, Richard C Roberts, Robin J Sellar, Charles P Warlow, Rustam Al-Shahi Salman, on behalf of the SIVMS Collaborators†

Summary

Background The decision about whether to treat an unruptured brain arteriovenous malformation (AVM) depends on a comparison of the estimated lifetime risk of intracranial haemorrhage with the risks of interventional treatment. We aimed to test whether outcome differs between adults who had interventional AVM treatment and those who did not.

Methods All adults in Scotland who were first diagnosed with an unruptured AVM during 1999–2003 (n=114) entered our prospective, population-based study. We compared the baseline characteristics and 3-year outcome of adults who received interventional treatment for their AVM (n=63) with those who did not (n=51).

Findings At presentation, adults who were treated were younger (mean 40 vs 55 years of age, 95% CI for difference 9–20; $p < 0.0001$), more likely to present with a seizure (odds ratio 2.4, 95% CI 1.1–5.0), and had fewer comorbidities (median 3 vs 4, $p = 0.03$) than those who were not treated. Despite these baseline imbalances, treated and untreated groups did not differ in progression to Oxford Handicap Scale (OHS) scores of 2–6 (log-rank $p = 0.12$) or 3–6 (log-rank $p = 0.98$) in survival analyses. In a multivariable Cox proportional hazards analysis, the risk of poor outcome (OHS 2–6) was greater in patients who had interventional treatment than in those who did not (hazard ratio 2.5, 95% CI 1.1–6.0) and was greater in patients with a larger AVM nidus (hazard ratio 1.3, 95% CI 1.1–1.7). The treated and untreated groups did not differ in time to an OHS score of 2 or more that was sustained until the end of the third year of follow-up, or in the spectrum of dependence as measured by the OHS at 1, 2, and 3 years of follow-up.

Interpretation Greater AVM size and interventional treatment were associated with worse short-term functional outcome for unruptured AVMs, but the longer-term effects of intervention are unclear.

Introduction

Brain arteriovenous malformations (AVMs) are the leading cause of intracerebral haemorrhage (ICH) in young adults,¹ but ICH is the presenting symptom in only half of incident AVM diagnoses.^{2,3} The widespread availability and use of non-invasive brain imaging has led to the detection of AVMs as a cause of epileptic seizures and focal neurological deficits not associated with ICH,⁴ and has also increased the detection of incidental, asymptomatic AVMs in their unruptured state.^{2,3,5,6}

The diagnosis of an unruptured AVM presents an opportunity to prevent future ICH by obliteration of the AVM, any associated aneurysms, or both, by endovascular embolisation, microsurgical excision, or unfractionated stereotactic radiotherapy (radiosurgery), used alone or in various combinations. Although such interventional treatment might prevent future ICH, it can also be complicated by disability or death.^{7–10} Because randomised controlled trials have not yet compared interventional treatment of AVMs with conservative management,¹¹ clinicians are left to make difficult decisions about how to treat individual patients on the basis of indirect evidence, by comparison of published or local estimates of treatment effect with the reported clinical course of AVMs that have been left untreated.

Research on the outcome of AVM treatment consists of case series, few of which have measured functional outcome, and most of which do not describe outcome according to whether the initial presentation was with ICH.¹² Of concern is a preliminary analysis¹³ of the Columbia AVM Databank (a large case series from a tertiary referral centre), in which the outcome after interventional treatment of unruptured AVMs was far worse than the untreated clinical course, whether outcome was assessed by subsequent ICH rates or functional measures. This abstract has caused controversy about how best to manage unruptured AVMs^{13–16} and has led to a randomised trial of unruptured brain AVMs (ARUBA). While the ARUBA study is ongoing, we sought to confirm or refute the findings from the Columbia AVM Databank by comparison of the functional outcome of adults who had interventional treatment for an unruptured AVM with those who did not, in an observational, prospective, contemporary, population-based cohort study.^{2,17}

Methods

Participants

The Scottish Intracranial Vascular Malformation Study (SIVMS) is a prospective, population-based disease register of patients resident in Scotland who were at

Lancet Neurol 2008; 7: 223–30

Published Online

February 1, 2008

DOI:10.1016/S1474-

4422(08)70026-7

See [Reflection and Reaction](#) page 195

*Catherine J Wedderburn and Janneke van Beijnum contributed equally to this report

†Collaborators listed at end of report

Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh, UK

(C J Wedderburn BA, J van Beijnum MD, R J Sellar FRCP, C P Warlow FRCP,

R Al-Shahi Salman FRCP Edin); Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht, Netherlands

(J van Beijnum MD); Institute of Neurological Sciences, Southern General Hospital, Glasgow, UK

(J J Bhattacharya FRCP, V Papanastassiou FRCS[SN]);

Department of Neurology, Aberdeen Royal Infirmary, Aberdeen, UK

(C E Counsell MRCP); Fauldhouse Health Centre, Fauldhouse, Edinburgh, UK (V Ritchie MB);

Department of Neurology, Ninewells Hospital and Medical School, Dundee, UK (R C Roberts FRCP)

Correspondence to:

Rustam Al-Shahi Salman, Bramwell Dott Building, Division of Clinical Neurosciences, Western General Hospital, Edinburgh EH4 2XU, UK rustam.al-shahi@ed.ac.uk

For the ARUBA website see <http://www.arubastudy.org>

For the SIVMS website see <http://www.sivms.org>

	Untreated (n=51)	Treated (n=63)	Statistical tests*
Male	30 (59%)	36 (57%)	OR 1.1 (0.5–2.3)
Mean age (SD, range)	55 (17, 16–85)	40 (13, 16–65)	t test, p<0.0001
Type of presentation			
Incidental	25 (49%)	19 (30%)	OR 0.5 (0.2–0.97)
Seizure	20 (39%)	38 (60%)	OR 2.4 (1.1–5.0)
Other	6 (12%)	6 (10%)	OR 0.8 (0.2–2.6)
OHS at presentation			OHS 0–1 vs 2–6: OR 2.1 (0.9–5.0), p=0.08 OHS 0–2 vs 3–6: OR 11.5 (1.4–95.6), p=0.01
0	8 (16%)	6 (10%)	
1	26 (51%)	45 (71%)	
2	9 (18%)	11 (17%)	
3	1 (2%)	0 (0%)	
4	2 (4%)	1 (2%)	
5	1 (2%)	0 (0%)	
6	4 (8%)	0 (0%)	
Median number of comorbidities (range)	4 (2–8)	3 (1–6)	Mann-Whitney U test, p=0.03
Specific comorbidities			
Ischaemic heart disease	13 (25%)	6 (10%)	OR 0.3 (0.1–0.9)
Prestroke hypertension	7 (14%)	4 (6%)	OR 0.4 (0.1–0.5)
Smoking	23 (45%)	18 (29%)	OR 0.5 (0.2–1.1)
Catheter angiogram done	26 (51%)	60 (95%)	OR 19.2 (5.3–69.4)
Spetzler-Martin grade			Fisher's exact test, p=0.6
I	6 (23%)	15 (28%)	
II	8 (31%)	19 (36%)	
III	6 (23%)	13 (25%)	
IV	5 (19%)	6 (11%)	
V	1 (4%)	0 (0%)	
AVM size			Fisher's exact test, p=0.04
Small (<3 cm)	16 (35%)	31 (52%)	
Medium (3–6 cm)	27 (59%)	29 (48%)	
Large (>6 cm)	3 (7%)	0 (0%)	
Eloquence of brain area			χ^2 test, p=0.7
Eloquent	25 (49%)	33 (52%)	
Not eloquent	26 (51%)	30 (48%)	
Venous drainage			Fisher's exact test, p=0.8
Superficial	20 (80%)	46 (78%)	
Deep	1 (4%)	5 (8%)	
Both	4 (16%)	8 (14%)	
Coexisting aneurysms			χ^2 test, p=0.3
Associated†	8 (16%)	15 (24%)	
Remote	4 (8%)	7 (11%)	

*For odds ratios (OR), untreated adults are the referent category, and numbers in parentheses are 95% CI. †Combined intranidal or feeding artery aneurysms.

Table 1: Demographic, clinical, and morphological characteristics in adults who presented with an unruptured brain AVM

least 16 years of age when first diagnosed with any type of intracranial vascular malformation in the years 1999–2003.² The twin objectives of the register—clinical audit and observational epidemiology—are overseen by a multidisciplinary steering committee that represents the four Scottish neuroscience centres

	n	Obliterated	Partially obliterated	No follow-up imaging
Surgery*	20	19	0	1
Radiosurgery†	26	13	12‡	1
Embolisation alone§	17	10	7¶	0

*Six patients had surgery alone and 14 had surgery plus embolisation.
†14 patients had radiosurgery alone and 12 had radiosurgery plus embolisation.
‡Of the patients who had radiosurgery and embolisation, one also had endovascular aneurysm coiling. †Six patients were investigated with magnetic resonance angiography, and the other six underwent a catheter angiogram. §One patient also underwent endovascular aneurysm coiling. ¶Three patients had a follow-up angiogram, but in the others the extent of obliteration was assessed only at the end of the embolisation procedure.

Table 2: Intervention used and extent of angiographic obliteration after treatment

(Aberdeen Royal Infirmary, Aberdeen; Institute of Neurological Sciences, Glasgow; Ninewells Hospital, Dundee; and Western General Hospital, Edinburgh). SIVMS uses multiple, overlapping sources of case ascertainment to identify incident cases.¹⁷ In this analysis, we included everyone who entered SIVMS in 1999–2003 who had a definite diagnosis of a brain AVM that was unruptured at presentation.¹⁷ We used follow-up data accrued until the analysis date of October 1, 2007.

Procedures

Baseline demographic data extracted from routine medical records included sex, age at the presentation that led to AVM diagnosis, and socioeconomic status, measured as the deprivation category of residential postcode sector according to the 2001 UK census, obtained from the MRC Social and Public Health Sciences Unit in Glasgow. We also extracted the following data from routine clinical records: type of AVM presentation (incidental, seizure, or other); Oxford Handicap Scale (OHS) at presentation; comorbidities listed in the records of family doctors at or before presentation; and smoking status. The OHS is a derivative of the modified Rankin Scale that has been used extensively to assess outcomes after stroke^{18–20} and AVM.^{7–9,21} The scale ranges from 0 (no symptoms) to 6 (death), and differs from the modified Rankin scale in that it uses impairment and lifestyle wording to detect the effect of factors such as disability, handicap, or seizures.

The two study neuroradiologists (JJB and RJS) collected data from participants' first diagnostic imaging,²² including the following: AVM size (maximum nidus diameter on MRI or catheter angiography); pial arteriovenous fistulae without a nidus were scored as 0 cm; venous drainage pattern (on catheter angiography);²³ whether the adjacent brain area was eloquent;²³ Spetzler-Martin grade (a composite score based on the three aforementioned variables);²³ deep brain location (any location that involves the basal ganglia, internal

capsule, thalamus, hypothalamus, limbic system, or corpus callosum); and AVM-associated aneurysms (on feeding arteries or within the nidus).²² Interventional treatment was defined as any type of intervention done on the AVM or associated aneurysms, and AVM nidus obliteration was confirmed radiologically (preferably by catheter angiography, but otherwise by magnetic resonance angiography).

During follow-up, we collected annual OHS ratings of dependence provided by the patients' family doctors. We also surveyed medical records annually for the occurrence of ICH, cerebral infarction, or focal neurological deficit (FND). We defined ICH as a symptomatic clinical event (headache, seizures, global neurological deficit, FND, or any combination of these events) with signs of intracranial blood on brain imaging, in the CSF, or on post-mortem examination. We defined cerebral infarction by clinical signs of focal or global neurological disturbance that developed rapidly and lasted for 24 h or longer, on the condition that this diagnosis was supported by brain imaging or pathological examination. We defined an FND as a clinical impairment that was referable to the location of the AVM nidus and was not post-ictal, migrainous, or attributable to ICH or infarction after radiological or pathological investigation. FNDs that lasted more than 24 h were classed as persistent, and those that lasted more than 24 h with further deterioration thereafter were classed as progressive. Transient FNDs (those that lasted <24 h) were excluded from this analysis. One investigator (CPW) assessed death, ICH, cerebral infarction, and FNDs on the basis of details in participants' medical records, brain imaging, and pathology reports; he was unaware of the prognostic features of interest, to keep bias to a minimum. CPW confirmed the type of outcome event, and whether it was due to the AVM, intervention, or another mechanism.

Statistical analysis

We compared demographic, clinical, and radiological characteristics between treated and untreated patients, by use of parametric statistics when data obeyed a normal distribution and non-parametric statistics when they did not. We used odds ratios and corresponding 95% CIs to compare categorical variables.

In the survival analyses, OHS scores were dichotomised at 0–1 versus 2–6 as the primary outcome measure, and at 0–2 versus 3–6 in a sensitivity analysis; OHS grade 2 signifies “some restrictions to lifestyle, but the patient can look after themselves”, and grade 3 corresponds to “significant restriction to lifestyle; unable to lead a totally independent existence”.²⁰ Although OHS 3–6 (which signifies death or dependence) is a common measure of functional outcome in stroke research,¹⁹ we preferred OHS 2–6 because of the low-to-moderate morbidity incurred by unruptured AVMs.¹⁵ The primary analysis was of the time to the first occurrence of OHS 2–6 or 3–6

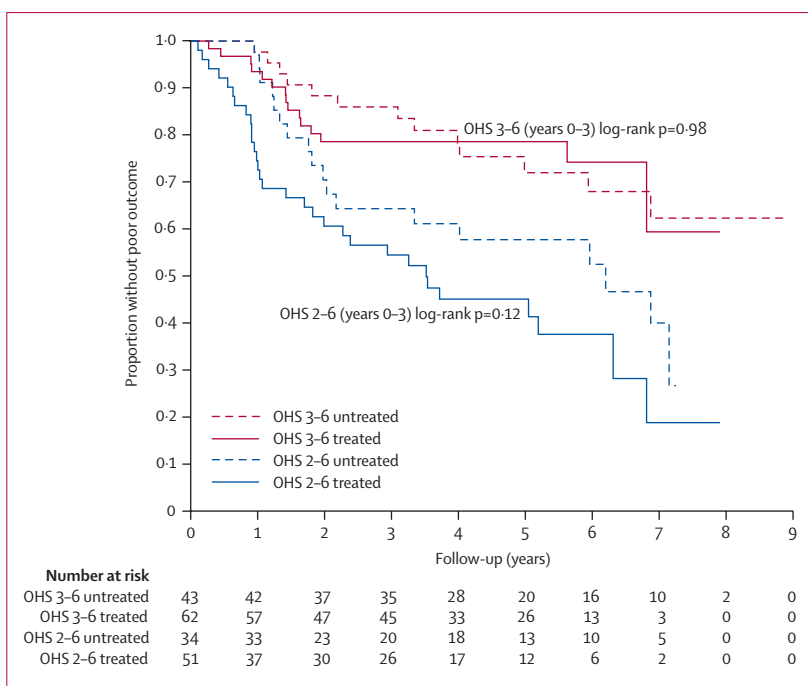


Figure 1: Kaplan-Meier estimates of progression to poor functional outcome
 Poor outcome was defined as the first OHS score of 3–6 (upper two lines) or 2–6 (lower two lines) during all available follow-up after presentation (untreated group, broken lines) or after first interventional treatment (treated group, unbroken lines).

	Univariate analyses HR (95% CI)	Multivariable analysis* HR (95% CI)
Sex	0.63 (0.31–1.29)	..
Age	0.99 (0.98–1.02)	1.01 (0.98–1.03)
Type of presentation		
Incidental vs other	0.44 (0.20–0.97)†	..
Seizure vs other	1.99 (1.00–3.95)‡	..
Socioeconomic status	1.08 (0.88–1.33)	..
Comorbidities	0.99 (0.91–1.09)	..
Ischaemic heart disease	0.71 (0.25–2.01)	..
Prestroke hypertension	0.30 (0.04–2.16)	..
Smoking	1.20 (0.61–2.36)	..
Spetzler-Martin grade	1.11 (0.77–1.59)	..
AVM size	1.20 (1.01–1.44)§	1.34 (1.08–1.65)¶
Eloquence of brain area	0.95 (0.49–1.84)	..
Venous drainage (any deep)	0.78 (0.30–2.00)	..
Deep brain location	0.53 (0.07–3.90)	..
Associated aneurysms	3.20 (1.61–6.39)	..
Interventional treatment	1.52 (0.75–3.05)	2.53 (1.06–6.04)**

*Three prespecified variables were entered into the multivariable analysis.
 †p=0.04. ‡p=0.05. §p=0.04. ¶p=0.007. ||p=0.001. **p=0.04.

Table 3: Univariate and multivariable analyses of first progression to OHS 2–6 during the first 3 years of follow-up

during follow-up, but we also assessed the time to an OHS score of 2 or more that did not fall to below 2 before the end of the third year of follow-up. In the survival

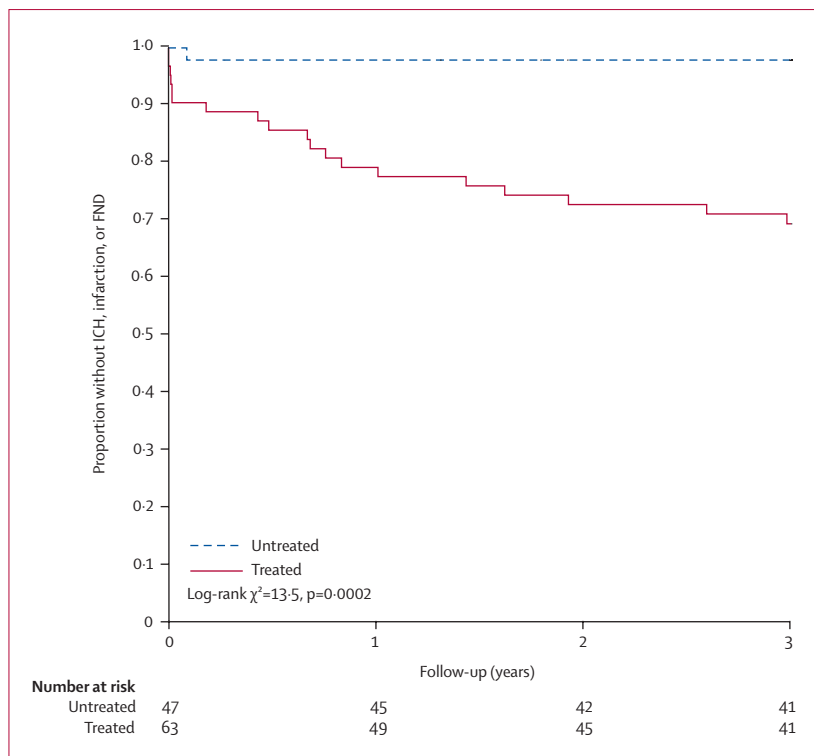


Figure 2: Kaplan-Meier estimates of progression to first ICH, infarction, persistent FND, or progressive FND
Follow-up was for 3 years from presentation (untreated group, broken line) or first interventional treatment (treated group, unbroken line).

analyses, we calculated time to the relevant outcome from presentation onwards for the untreated group and from first interventional treatment for the treated group. We did not include the period from presentation to first intervention in the survival analyses, but we recorded events during this time and included the period in sensitivity analyses for the untreated group, to investigate whether the inclusion of pre-intervention events made the early untreated outcome seem worse. We censored patients at the time of the most recent follow-up if they did not reach an outcome of interest (OHS 2–6 or 3–6) during the study period, or at presentation if they already had the outcome of interest at baseline. The occurrence of ICH, infarct, persistent FND, or progressive FND was an explanatory secondary outcome measure.

We constructed Kaplan-Meier curves for the entire period of follow-up available but, because at least three complete years of follow-up should have been available for every patient in the 1999–2003 cohort at the time of this analysis, all group comparisons in univariate analyses (with the log-rank test or hazard ratios [HRs]) and multivariable analyses (with Cox proportional hazards) were applied to only the first 3 years of follow-up. We used Cox regression only when proportional hazards assumptions were satisfied.²⁴ We did not prespecify the sample size, but the analysis was a

core aim of the SIVMS register at a point in longitudinal follow-up when there was sufficient power to enter three predictor variables in a multivariable analysis for the primary outcome. We prespecified age, AVM size, and receipt of any interventional AVM treatment for the multivariable analyses on the following bases: their clinical relevance; the accuracy, reliability, and completeness of their ascertainment by SIVMS; their known or hypothesised influence on outcome; and the baseline imbalances found in this analysis.²⁵ Aneurysms associated with AVMs were not included in the multivariable analysis because of the incomplete uptake of catheter angiography.

All statistical tests were two-tailed ($\alpha=0.05$), and SPSS version 14.0 and StatsDirect version 2.4.6 were used for statistical analysis.

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

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Results

Of 229 adults with AVMs identified by SIVMS in 1999–2003, 114 did not present with ICH (ie, presented with an unruptured AVM); 63 (55%) of these patients received interventional treatment, and the remaining 51 (45%) did not. We recorded demographic, clinical, and radiological characteristics from all 114 patients for all baseline variables apart from socioeconomic status (treated $n=62$, untreated $n=50$; 98% overall), AVM size (treated $n=60$, untreated $n=46$; 93% overall), venous drainage pattern (treated $n=59$, untreated $n=25$; 74% overall), and Spetzler-Martin grade (treated $n=53$, untreated $n=26$; 69% overall). At presentation, adults who did not subsequently receive interventional treatment were significantly older, were more likely to have an OHS score of 3–6, had more comorbidities, and were more likely to have had their AVM detected as an incidental finding (table 1). Participants who were treated were more likely to have been investigated with a catheter angiogram than those who were not treated, and their AVMs were smaller (table 1). Seven participants who were treated had an ICH, infarct, persistent FND, or progressive FND between presentation and intervention, which was significantly more than in the untreated group (log-rank $\chi^2=7.5$, $p=0.006$). Socioeconomic status did not differ between the treated and untreated groups (Fischer's exact test, $p=0.3$).

Interventional treatments were decided by local clinicians (table 2).²⁶ Treatment began a median of 1 year (IQR 0.5–1.5) after presentation and ended before the

analysis date. The AVM nidus was completely obliterated in 42 (67%) patients who received treatment and partially obliterated in 19 (30%) patients; follow-up imaging data were not available for two (3%) patients.

635 patient-years of follow-up were available (median of 6.0 years per adult, IQR 4.4–7.1, 93% completeness).²⁷ At baseline, 29 (25%) of all participants were OHS 2–6 (table 1). All OHS scores of 2–6 at baseline could be explained by comorbidities or AVM-associated epilepsy. Functional outcome did not differ between the treated and untreated groups during all available follow-up (figure 1), whether poor outcome was defined as OHS 2–6 or OHS 3–6. Progression to OHS 2–6 did not differ between the treated and untreated groups when the pre-intervention period for the treated participants was included in the untreated curve (webfigure 1) or when the treatment group was restricted to the AVMs that were obliterated on angiography (webfigure 2). Further statistical analyses were restricted to the first 3 years of follow-up, when OHS scores as rated by family doctors were most complete (90/108 [83%] living patients in year 1, 100/108 [93%] in year 2, and 93/107 [87%] in year 3). We established that our data fulfilled the Cox proportional hazards assumptions of non-overlapping hazard functions, and had a satisfactory log-linear relationship between the independent variables and the underlying hazard function in a log(–log[cumulative hazards]) plot (webfigure 3). A subsequent multivariable analysis based on data from the 33 participants who had a first occurrence of OHS 2–6 during the first 3 years revealed that the occurrence of this outcome was associated most strongly with the receipt of interventional AVM treatment and AVM size (table 3). This difference between treatment groups is largely explained by the preponderance of ICH, FND, and cerebral infarction after interventional treatment (figure 2). Of the first 25 events after intervention, 13 (52%) were after AVM embolisation, seven (28%) were after gamma-knife radiosurgery, four (16%) were after surgical AVM excision, and one (4%) was after aneurysm coiling. Time to first seizure after presentation did not differ between participants who received interventional treatment and those who did not, even after adjustment for initial presentation with seizures (Cox proportional hazards, HR 0.7, 95% CI 0.4–1.3; $p=0.2$).

Despite the association of interventional treatment with the time to first occurrence of OHS 2–6, an analysis of time to progression to OHS 2–6 that was sustained until the end of the third year of follow-up did not differ between the treated and untreated patients (figure 3). The spectrum of dependence as measured by the OHS for all participants who were alive at presentation, regardless of their baseline dependence, did not differ significantly between the treated and untreated groups after 1, 2, or 3 years of follow-up (figure 4). There were two deaths due to AVM ICH during the first 3 years after intervention: one occurred 18 months after an

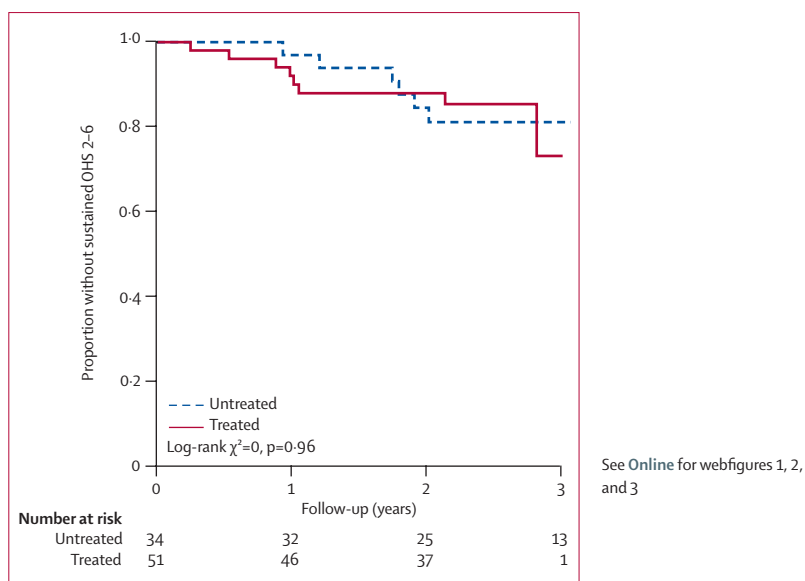


Figure 3: Kaplan-Meier estimates of progression to sustained poor outcome
Poor outcome was defined as OHS 2–6 that was sustained until the end of the third year after presentation (untreated group, broken line) or after first interventional treatment (treated group, unbroken line).

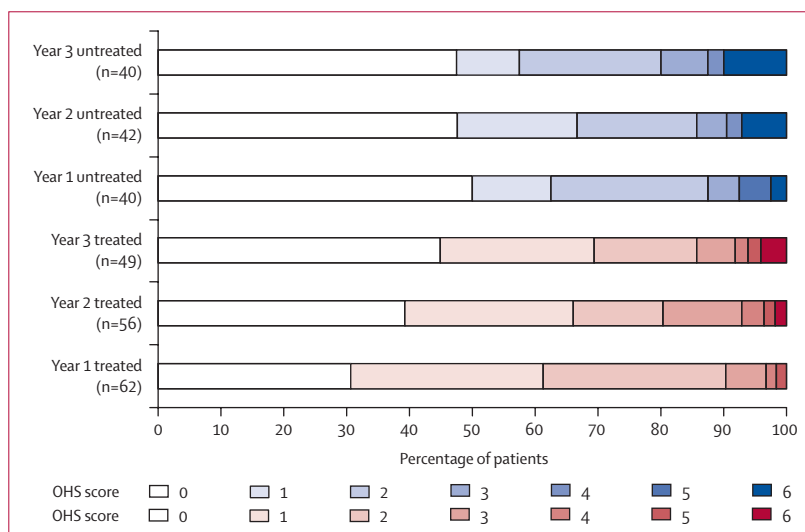


Figure 4: Functional outcome on the OHS

Changes are shown for the 3 years after presentation (untreated group, blue) or after first interventional treatment (treated group, red). Deaths (OHS score=6) are cumulative; all other grades represent the ratings available for the patients alive at the end of each year of follow-up.

embolisation that had partially obliterated an AVM, and the other occurred 2 years after radiosurgery that seemed to have obliterated an AVM on catheter angiography a few weeks before the ICH. Four deaths occurred in the untreated group: one was due to subarachnoid haemorrhage from an aneurysm on an AVM feeding artery, and the other three had unrelated causes (pneumonia, bowel perforation, and morphine intoxication).

Discussion

In this prospective, population-based study of the contemporary management of adults with AVMs in Scotland, interventional treatment and AVM size were independent predictors of progression to poor outcome (OHS 2–6) in the first 3 years after presentation or interventional treatment (table 3). The difference in outcome between treated and untreated patients seemed to be explained by differences in the rate of ICH, cerebral infarction, persistent FND, and progressive FND (figure 2), but not epileptic seizures. However, the treated and untreated participants did not differ in progression to OHS 2–6 that was sustained until the end of the third year of follow-up (figure 3), or in the overall spectrum of dependence over the same time (figure 4).

The strengths of this study were its thorough case ascertainment in a population of 5·1 million inhabitants,¹⁷ its prospective annual follow-up procedures, with blinded scrutiny of outcomes and high percentage of complete ratings on a validated measure of dependence, and its representation of present clinical and interventional practice. The use of a concurrent, albeit non-randomised, untreated control group within the same population avoided the problems of indirect comparisons between different treated and untreated case series (eg, from different time periods and geographical locations). Although the traditional measure of outcome in AVM research has been the occurrence of haemorrhage during follow-up, we also used a measure of functional outcome, and we chose an OHS score of 2 or more as a meaningful level of dependence because it implies restriction to lifestyle, which would not be expected for most patients with an unruptured AVM (table 1). The analysis of progression to first OHS 2–6 fulfilled the main assumptions of proportional hazards analyses (figure 1),²⁵ and there were adequate outcome events to allow us to use a multivariable model that included three prespecified variables.²⁸

The main weakness of this study was the potential confounding of its results by imbalances between treated and untreated groups at baseline (table 1). This imbalance can be explained by the feasibility of interventional treatment, and the selection of patients for interventional treatment according to perception of likely future benefit (eg, on the bases of age and comorbidities). However, there were no apparent imbalances in two variables that seem to raise the risk of future haemorrhage from an unruptured AVM: deep venous drainage and associated aneurysms (table 1).^{1,29} One of the five main imbalances at baseline (AVM size) had an independent effect on outcome in both univariate and multivariable analyses (table 3). Although patients had an unruptured AVM at presentation, the subsequent course of some of these patients probably affected whether treatment was given (at least for the seven [11%] participants who had an ICH or FND between presentation and treatment). Our assessment of the effect of AVM vascular anatomy on

outcome was complicated by the incomplete uptake of catheter angiography, both at diagnosis and for assessment of AVM obliteration after treatment, although this uptake is similar to everyday clinical practice, in which invasive investigation is reserved for patients thought to be most in need. Where results from catheter angiography were unavailable, we improved the completeness of data on AVM size by MRI, but we did not use MRI to collect data about venous drainage. The incompleteness of these angiographic data reduced the power of the study to show an effect of detailed vascular anatomy, and potentially biased and confounded its assessment, but this would apply to any study of AVM vascular anatomy that does not give every patient a catheter angiogram. For this reason, we did not prespecify coexistent aneurysms as a variable for the multivariable analyses, despite the apparent association with poor outcome in a univariate analysis (table 3). Although this study benefited from a 3-year assessment of functional outcome, because AVM treatment has a recognised early complication rate and is ultimately intended to prevent future ICH (especially when angiographic obliteration has been achieved),³⁰ longer-term follow-up of this cohort is essential.

The prospective, population-based design of SIVMS is comparable to the design of only one other study, based on part of the New York area; that study has not yet done an analysis comparable to that reported here.³ Hospital-based studies of contemporary interventions have quantified the short-term risk of new neurological deficits after the treatment of unruptured AVMs,^{7,9} and a study of the Columbia AVM Databank found a substantial increase in risk over the medium term after intervention at a tertiary referral centre.¹³ Although similar to our study in the finding that interventional treatment was associated with poor short-term outcome,¹³ the larger difference in outcome between the treated and untreated groups in the Columbia AVM Databank can be explained by the methods of assessment and analysis. Independent assessment by a neurologist soon after treatment will detect any early deterioration after intervention,¹³ whereas our annual follow-up by family doctors is orientated towards detection of enduring deficits in the medium term and long term. Furthermore, time to first deterioration (figure 1) is likely to be affected by complications of interventional treatment (figure 2), but sustained deterioration is likely to cause most trouble for patients (figure 3). These outcomes should be analysed for both the Columbia AVM Databank and the SIVMS register over patients' lifetimes. Interventional treatment of unruptured AVMs is likely to remain controversial until these long-term follow-up data are available.^{15,31,32}

In present clinical practice, the best management of unruptured AVMs remains unclear, with decisions to treat made on a case-by-case basis according to regional guidelines where they exist.³⁰ Randomised trials could resolve the dilemma of whether to treat unruptured

AVMs, particularly by removal of baseline imbalances between treated and untreated groups (which can never be fully adjusted for in observational studies) and use of meticulous, independent neurological assessment.¹⁴ For the ARUBA randomised trial of unruptured AVMs—which currently has 56 sites enrolled in the USA, Canada, South America, Australia, and Europe—long-term follow-up will also be essential.

Contributors

The study was conceived, designed, and conducted by RASS and CPW under the supervision of a steering committee (JJB, CEC, VP, VR, RCR, RJS, CPW and RASS). JJB and RJS collected radiological data. CJW and JvB contributed equally, along with RASS, to analysis, reviewing and updating of clinical and radiological data, and writing of the manuscript, which was reviewed and revised by the steering committee. All authors saw and approved submission of the final version of the manuscript.

SIVMS collaborators

Aberdeen Royal Infirmary, Aberdeen, UK—J MacKenzie, A Murray, S Olson, O Robb, R Coleman, C Counsell, L Gerrie, G Hall, M-A Macleod, C Derry, R Hewett, E Visser, D Currie, I Fouyas, E Labram, M Shanmuganathan, M Macleod, J McLay, J Webster, S Wilkinson, D Williams. *Ayr Hospital, Ayr, UK*—M Ablett. *Borders General Hospital, Melrose, UK*—P Syme, L Ferrando, D Hardwick, H McRitchie, A Pearson, J Reid. *Caithness General Hospital, Wick, UK*—T Shallcross, I Malik. *Crosshouse Hospital, Kilmarnock, UK*—M McMillan, E Lindsay, D Rawlings. *Cumberland Infirmary, Carlisle, UK*—J Edge, R England, F Fallahi, J Jackson, P Jennings. *Dr Gray's Hospital, Elgin, UK*—J Addison, S Forbat, K Brown. *Dumfries and Galloway Royal Infirmary, Dumfries, UK*—U Spelmeyer, M Aird, D Hill, P Kelly. *Edinburgh Royal Infirmary, Edinburgh, UK*—D Patel, T Fitzgerald, G McKillop, A Coull, S Hart, G Mead. *Edinburgh University Medical School, Edinburgh, UK*—JC Arango, A Busuttill, G Kernbach-Wighton. *Falkirk and District Royal Infirmary, Falkirk, UK*—L Buchanan, C Neumann, E Beveridge, R Burgul, R Johnstone, L Stewart. *Gartnavel General Hospital, Glasgow, UK*—R Vallance. *Glasgow Royal Infirmary, Glasgow, UK*—J Burns, P Langhorne, D Stott, J Taylor, F Wright, A Reid, G Roditi, G Lowe. *Hairmyres Hospital, East Kilbride, UK*—B MacInnes, B Martin, B Yip, J Ballantyne, G Harold, D Edwards, A Forrester, F Gardner, F Lau, C Murch. *Institute of Neurological Sciences, Glasgow, UK*—A Burke, S Robinson, A Mallik, C Mann, A Russell, C Santosh, A Ramsay, J Bhattacharya, D Hadley, S Jenkins, D Kean, A Siddiqui, S Sloss, E Teasdale, L Walker, T Baird, R Duncan, W Durward, M E Farrugia, G Gorrie, J Greene, D Grosset, O Jack, P Kennedy, J Leach, R Metcalfe, K Muir, C O'Leary, J Overell, R Petty, R Thomas, A Tyagi, H Willison, K Brennan, P Connick, S Cooper, K Dani, S Finlayson, P Foley, V Marshall, S Miller, I Morrison, E Newman, S Razvi, J Reid, U Schultz, K Taylor, L Alankandy, P Barlow, J Brown, L Dunn, R Johnston, K Lindsay, P Littlechild, J St George, M Behebani, E Campbell, C Gavin, K Goyal, A Kumar, I Liaquat, C Mathieson, R Sangra, N Simms, D Walsh, M White. *Inverclyde Royal Hospital, Greenock, UK*—F Kelly, P Walsh. *Lorn and Islands District General Hospital, Oban, UK*—H Fattah, F Johnson. *Monkland District General, Airdrie, UK*—K Wallers. *Newcastle General Hospital, Newcastle-upon-Tyne, UK*—D Birchall, K Tay, A Gholkar, V Jayakrishnan, D Mitra. *Ninewells Hospital, Dundee, UK*—A Kanodia, G Houston, G Main, J Tainsh, I Zealley, J O'Riordan, R Roberts, R Swingle, V Szepielow, K White, Z Dean, C Heath, A Kivajozovas, P Shah, E Ballantyne, S Eljamel, D Mowle, R Elashall, A Doney, R MacWalter. *Perth Royal Infirmary, Perth, UK*—R Murray, J Harper, S Johnston, I Lightbody. *Queen Margaret Hospital, Dunfermline, UK*—M Connor, G Stewart, H Ireland, N Chapman, J McKenzie, S Pound. *Raigmore Hospital, Inverness, UK*—P Findlay, J Miller, G Aitken, D Goff, P Henry, A Macleod, D Nichols, H Shannon, A Todd. *Royal Alexandra Hospital, Paisley, UK*—A Wallace, L Erwin. *St John's Hospital, Livingston, UK*—D Farquhar, K Jackson, S Ramsay, J Wilson, J Stone, S Chambers. *Stirling Royal Infirmary, Stirling, UK*—R Prempeh, M Macleod, S McCallan, P McDermott. *Stobhill NHS Trust, Glasgow, UK*—P Fraser, C McAlpine, T Bryant, F Bryden, H Griffiths, A McCafferty, I Mcleod, J Shand, R Stevens. *Stracathro Hospital, Brechin, UK*—I Gillanders, J Tainsh.

Victoria Hospital, Kirkcaldy, UK—M Zeidler, S Bahnsen, B Reid, C Clark, V Cvorovic. *Victoria Infirmary, Glasgow, UK*—M Roberts, J Lauder, J Calder, A Downie, M Gronski, I McLaughlin. *Western General Hospital, Edinburgh, UK*—G Chohan, S Erridge, A Gregor, M Porteous, J Ironside, C Smith, G Moran, A Farrall, P Keston, G Potter, D Summers, D Collie, R Gibson, B Innes, S Kealey, R Sellar, J Wardlaw, P White, E Wood, R Al-Shahi Salman, R Davenport, R Grant, R Knight, C Mumford, P Sandercock, G Stewart, C Sudlow, C Warlow, B Weller, R Will, C Butler, P Fox, A Kelso, K Murray, D Simpson, W Whiteley, A Williams, F Doubal, M Fitzpatrick, L Myles, T Russell, P Statham, J Steers, I Whittle, H Cook, F Hughes, W Young, S Al-Haddad, C Balasubramaniam, P Bodkin, P Brennan, R Dubey, M Dennis, S Keir. *Western Infirmary, Glasgow, UK*—M Brodie, M Walters, K Kelly, E Kalkman, N McMillan, K Lees, G McInnes, J Reid, P Semple. *Wishaw General Hospital, Wishaw, UK*—D Alcorn, M Callaghan, M El-Sayed, M Fleet, B Macpherson, S Reid, J Roberts. *Woodend General Hospital, Aberdeen, UK*—S Hamilton, F Smith.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgments

We thank CJM Klijn (University Medical Center, Utrecht) and Steff Lewis (University of Edinburgh) for their comments on this manuscript. We also thank Rosemary Anderson, Aidan Hutchison, and all the participants in the SIVMS. 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). JvB was funded by the Netherlands Organization for Scientific Research (NWO) and the Netherlands Heart Foundation (grant number 2002B138).

References

- Al-Shahi R, Warlow C. A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults. *Brain* 2001; **124**: 1900–26.
- Al-Shahi R, Bhattacharya JJ, Currie DG, et al. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke* 2003; **34**: 1163–69.
- Stapf C, Mast H, Sciacca RR, et al. The New York Islands AVM Study: design, study progress, and initial results. *Stroke* 2003; **34**: e29–33.
- Choi JH, Mohr JP. Brain arteriovenous malformations in adults. *Lancet Neurol* 2005; **4**: 299–308.
- Al-Shahi Salman R, Whiteley WN, Warlow C. Screening using whole-body magnetic resonance imaging scanning: who wants an incidentaloma? *J Med Screen* 2007; **14**: 2–4.
- Brown RD Jr, Wiebers DO, Torner JC, O'Fallon WM. Incidence and prevalence of intracranial vascular malformations in Olmsted County, Minnesota, 1965 to 1992. *Neurology* 1996; **46**: 949–52.
- Hartmann A, Mast H, Mohr JP, et al. Determinants of staged endovascular and surgical treatment outcome of brain arteriovenous malformations. *Stroke* 2005; **36**: 2431–35.
- Kim LJ, Albuquerque FC, Spetzler RF, McDougall CG. Postembolization neurological deficits in cerebral arteriovenous malformations: stratification by arteriovenous malformation grade. *Neurosurgery* 2006; **59**: 53–59.
- Lawton MT, Du R, Tran MN, et al. Effect of presenting hemorrhage on outcome after microsurgical resection of brain arteriovenous malformations. *Neurosurgery* 2005; **56**: 485–93.
- Pollock BE, Flickinger JC. A proposed radiosurgery-based grading system for arteriovenous malformations. *J Neurosurg* 2002; **96**: 79–85.
- Al-Shahi R, Warlow CP. Interventions for treating brain arteriovenous malformations in adults. *Cochrane Database Syst Rev* 2006; **1**: CD003436.
- Al-Shahi R, Stapf C. The prognosis and treatment of arteriovenous malformations of the brain. *Pract Neurol* 2005; **5**: 194–205.
- Mohr JP, Stapf C, Sciacca RR, et al. Natural history versus treatment outcome in patients with unruptured brain arteriovenous malformation (AVM). *Stroke* 2004; **35**: 328 (abstr).

- 14 Al-Shahi R, Warlow C. Arteriovenous malformations of the brain: ready to randomise? *J Neurol Neurosurg Psychiatry* 2005; **76**: 1327–29.
- 15 Stapf C, Mohr JP, Choi JH, Hartmann A, Mast H. Invasive treatment of unruptured brain arteriovenous malformations is experimental therapy. *Curr Opin Neurol* 2006; **19**: 63–68.
- 16 Davis SM, Donnan GA. Unruptured brain arteriovenous malformations: another asymptomatic conundrum. *Stroke* 2007; **38**: 3312.
- 17 Al-Shahi R, Bhattacharya JJ, Currie DG, et al. Scottish Intracranial Vascular Malformation Study (SIVMS): evaluation of methods, ICD-10 coding, and potential sources of bias in a prospective, population-based cohort. *Stroke* 2003; **34**: 1156–62.
- 18 New PW, Buchbinder R. Critical appraisal and review of the Rankin scale and its derivatives. *Neuroepidemiology* 2006; **26**: 4–15.
- 19 Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. *Stroke* 2007; **38**: 1091–96.
- 20 Bamford JM, Sandercock PA, Warlow CP, Slattery J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; **20**: 828.
- 21 Pollock BE, Brown RD Jr. Use of the Modified Rankin Scale to assess outcome after arteriovenous malformation radiosurgery. *Neurology* 2006; **67**: 1630–34.
- 22 Joint Writing Group of the Technology Assessment Committee, American Society of Interventional and Therapeutic Neuroradiology; Joint Section on Cerebrovascular Neurosurgery, a Section of the American Association of Neurological Surgeons and Congress of Neurological Surgeons; and Section of Stroke and the Section of Interventional Neurology of the American Academy of Neurology. Reporting terminology for brain arteriovenous malformation clinical and radiographic features for use in clinical trials. *Stroke* 2001; **32**: 1430–42.
- 23 Spetzler RF, Martin NA. A proposed grading system for arteriovenous malformations. *J Neurosurg* 1986; **65**: 476–83.
- 24 Bradburn MJ, Clark TG, Love SB, Altman DG. Survival analysis part III: multivariate data analysis—choosing a model and assessing its adequacy and fit. *Br J Cancer* 2003; **89**: 605–11.
- 25 Lewis S. Regression analysis. *Pract Neurol* 2007; **7**: 259–64.
- 26 Fleetwood IG, Steinberg GK. Arteriovenous malformations. *Lancet* 2002; **359**: 863–73.
- 27 Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet* 2002; **359**: 1309–10.
- 28 Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 1995; **48**: 1503–10.
- 29 Stapf C, Mast H, Sciacca RR, et al. Predictors of hemorrhage in patients with untreated brain arteriovenous malformation. *Neurology* 2006; **66**: 1350–55.
- 30 Ogilvy CS, Stieg PE, Awad I, et al. AHA scientific statement: recommendations for the management of intracranial arteriovenous malformations: a statement for healthcare professionals from a special writing group of the Stroke Council, American Stroke Association. *Stroke* 2001; **32**: 1458–71.
- 31 Heros RC, Tu YK. Is surgical therapy needed for unruptured arteriovenous malformations? *Neurology* 1987; **37**: 279–86.
- 32 Aminoff MJ. Treatment of unruptured cerebral arteriovenous malformations. *Neurology* 1987; **37**: 815–19.