

## Original Investigation

# Outcome After Conservative Management or Intervention for Unruptured Brain Arteriovenous Malformations

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**IMPORTANCE** Whether conservative management is superior to interventional treatment for unruptured brain arteriovenous malformations (bAVMs) is uncertain because of the shortage of long-term comparative data.

**OBJECTIVE** To compare the long-term outcomes of conservative management vs intervention for unruptured bAVM.

**DESIGN, SETTING, AND POPULATION** Population-based inception cohort study of 204 residents of Scotland aged 16 years or older who were first diagnosed as having an unruptured bAVM during 1999-2003 or 2006-2010 and followed up prospectively for 12 years.

**EXPOSURES** Conservative management (no intervention) vs intervention (any endovascular embolization, neurosurgical excision, or stereotactic radiosurgery alone or in combination).

**MAIN OUTCOMES AND MEASURES** Cox regression analyses, with multivariable adjustment for prognostic factors and baseline imbalances if hazards were proportional, to compare rates of the primary outcome (death or sustained morbidity of any cause by Oxford Handicap Scale [OHS] score  $\geq 2$  for  $\geq 2$  successive years [0 = no symptoms and 6 = death]) and the secondary outcome (nonfatal symptomatic stroke or death due to bAVM, associated arterial aneurysm, or intervention).

**RESULTS** Of 204 patients, 103 underwent intervention. Those who underwent intervention were younger, more likely to have presented with seizure, and less likely to have large bAVMs than patients managed conservatively. During a median follow-up of 6.9 years (94% completeness), the rate of progression to the primary outcome was lower with conservative management during the first 4 years of follow-up (36 vs 39 events; 9.5 vs 9.8 per 100 person-years; adjusted hazard ratio, 0.59; 95% CI, 0.35-0.99), but rates were similar thereafter. The rate of the secondary outcome was lower with conservative management during 12 years of follow-up (14 vs 38 events; 1.6 vs 3.3 per 100 person-years; adjusted hazard ratio, 0.37; 95% CI, 0.19-0.72).

**CONCLUSIONS AND RELEVANCE** Among patients aged 16 years or older diagnosed as having unruptured bAVM, use of conservative management compared with intervention was associated with better clinical outcomes for up to 12 years. Longer follow-up is required to understand whether this association persists.

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Unruptured brain arteriovenous malformations and their associated feeding/nidal arterial aneurysms (collectively called bAVMs) have approximately 1% annual risk of intracranial hemorrhage,<sup>1,2</sup> which has a 1-year case fatality of 12%,<sup>3</sup> in studies lasting up to 10 years.<sup>4</sup> Interventional treatment by neurosurgical excision, endovascular embolization, or stereotactic radiosurgery can be used alone or in combination to attempt to obliterate bAVMs, depending on their vascular anatomy.<sup>5</sup> Because interventions may have complications<sup>6</sup> and the untreated clinical course of unruptured bAVMs can be benign,<sup>1-4</sup> some patients choose conservative management (without intervention). Unruptured bAVM intervention has been compared with conservative management in a concurrent control group in just 1 randomized trial (ARUBA)<sup>7-9</sup> and only a few observational studies, all of which have shown harm from intervention in the short term.<sup>10,11</sup> Guidelines have endorsed both intervention and conservative management for unruptured bAVMs.<sup>12,13</sup> Therefore, we commenced a study in 1999 to assess the long-term outcome for adults affected by bAVM, with or without intervention, in everyday clinical practice.<sup>14,15</sup>

## Methods

The Scottish Intracranial Vascular Malformation Study (SIVMS) is a prospective, population-based cohort study that uses anonymized data extracted from the National Health Service Scottish Audit of Intracranial Vascular Malformations, which includes Scottish residents aged 16 years or older when first diagnosed as having a bAVM in 1999-2003 or 2006-2010 (<http://www.saivms.scot.nhs.uk>). The audit protocol ([http://www.saivms.scot.nhs.uk/pdf/2008\\_06\\_SAIvMs%20protocol\\_v2.pdf](http://www.saivms.scot.nhs.uk/pdf/2008_06_SAIvMs%20protocol_v2.pdf)) and research protocol (<http://docdat.ic.nhs.uk>) have been published. The Scottish Audit of Intracranial Vascular Malformations identified patients through multiple overlapping sources of case ascertainment that included a Scotland-wide collaborative network of neurologists, neurosurgeons, stroke physicians, radiologists, and pathologists and central registers of hospital discharges and death certificates.<sup>15</sup>

The Multicenter Research Ethics Committee for Scotland and the Fife and Forth Valley Research Ethics Committee approved the conduct of observational studies (to which an opt-out consent policy applied) and postal questionnaire studies (which required opt-in consent).

### Eligibility Criteria

In this analysis, we included patients in SIVMS who had a radiographically or pathologically confirmed first-in-a-lifetime definite diagnosis of a bAVM in 1999-2003 or in 2006-2010 that was unruptured when diagnosed. The term bAVM included associated nidus/feeding arterial aneurysms but not intracranial aneurysms remote from the bAVM or its arterial supply. We classified patients as receiving an intervention if they underwent any of the following treatments for their unruptured bAVM, either alone or in any combination, before the end of follow-up: microsurgical excision, stereotactic radiosurgery, or endovascular (glue or coil) embolization. We classified pa-

tients as undergoing conservative management if they did not receive any of these interventions. Decisions about intervention were left to patients and their physicians.

### Diagnostic Verification

Four experienced neuroradiologists verified certainty of bAVM diagnosis on diagnostic brain imaging that had been performed in clinical practice (supported by the Systematic Image Review System tool [<http://www.neuroimage.co.uk/sirsinfo/>]). The neuroradiologists determined surgical eloquence of nidus location<sup>16</sup> and used catheter angiography to describe vascular anatomy<sup>10</sup> or magnetic resonance imaging to measure nidus size.<sup>17,18</sup>

### Baseline Characteristics

We reviewed family (general) practitioner and hospital medical records to establish demographics, medical histories, and the consequences of bAVM presentation on the Oxford Handicap Scale (OHS), which is a derivative of the modified Rankin Scale ranging from 0 (no symptoms) to 6 (death).<sup>19</sup> We reviewed these medical records, brain imaging, and reports of pathological examinations to classify the mode of bAVM presentation and clinical outcome events during follow-up. When assessing clinical events at presentation and during follow-up, we also classified whether they were definitely, possibly, or definitely not attributable to the bAVM or to an intervention complication. We classified events as possibly attributable to the bAVM when clinical features were anatomically consistent with bAVM location but another cause (eg, ischemic stroke) was possible and neuroradiological investigation had identified neither bAVM hemorrhage nor an alternative cause. We regarded presentations as incidental if the patient had been asymptomatic or if we could not definitely relate the patient's symptoms to the underlying bAVM (eg, headache); we attributed presentations to epileptic seizure(s) if a seizure was neither symptomatic of a concomitant intracranial hemorrhage nor more likely to be due to another cause.

### Follow-up

The inception point for conservative management was patient presentation, which was the date of symptom onset or medical consultation (if asymptomatic) that led to an investigation diagnosing the bAVM. The inception point for intervention was the date of the first intervention for an unruptured bAVM that proceeded after presentation. Follow-up occurred prospectively on an uninterrupted annual basis using a postal questionnaire sent to every participant's family practitioner and annual surveillance of family practitioner and hospital medical records to identify outcome events that had occurred during the preceding year. Consenting participants completed postal questionnaires on each anniversary of bAVM diagnosis to identify outcome events and assess handicap on the OHS. Two investigators (R.A.-S.S. or C.P.W.) independently assessed symptomatic clinical outcome events,<sup>10</sup> using all the contemporaneous clinical, radiographic, and pathological records available. In attributing the mode and cause of death, we reviewed death certificates, autopsy reports if per-

formed, and clinical records and brain imaging if death occurred in a hospital. Extent of bAVM obliteration was assessed from reports of angiographic brain imaging after intervention. We gave precedence to obliteration confirmed by catheter angiography; otherwise, we relied on magnetic resonance angiography.

### Statistical Analysis

For analyses of clinical covariates, age was a continuous variable, OHS at presentation was dichotomized into 0 to 1 vs 2 to 5, and mode of presentation was dichotomized into seizure(s) vs other (although if following presentation a clinical event occurred that led to intervention, this subsequent event became the mode of presentation in the intervention group). We dichotomized bAVM nidus location into deep (involving the basal ganglia, internal capsule, thalamus, hypothalamus, limbic system, or corpus callosum) vs other. We dichotomized venous drainage into exclusively deep vs other and bAVM nidus maximum diameter into smaller than 3 cm vs 3 cm or larger. We separately derived the bAVM Spetzler-Martin grade, which predicts the likelihood of morbidity from bAVM excision based on bAVM size, venous drainage pattern, and eloquence of surrounding brain (grade 1 = lowest risk and grade 5 = highest risk).<sup>16</sup>

The primary outcome was the first occurrence of handicap (OHS score of 2-5, signifying “some restrictions to lifestyle, but the patient can look after themselves” or worse), sustained for at least 2 successive years after inception (ie, the baseline OHS rating was not included in the outcome measure) or death (OHS score of 6) due to any cause. The secondary outcome was nonfatal symptomatic stroke (intracranial hemorrhage, cerebral infarction, or focal neurological deficit persisting or progressing for >24 hours) or death due to the bAVM or intervention.

The number of patients diagnosed as having unruptured bAVM in our population over 10 years determined our sample size, but the timing of our analyses during follow-up was determined by the accumulation of sufficient primary and secondary outcomes to power the multivariable model to include 5 important covariates without overfitting.<sup>20</sup>

We conducted analyses according to a statistical analysis plan approved by the steering committee before data extraction ([http://www.saivms.scot.nhs.uk/pdf/resPaper/2013\\_07\\_05\\_SAP.pdf](http://www.saivms.scot.nhs.uk/pdf/resPaper/2013_07_05_SAP.pdf)). Completeness of follow-up data was quantified as a proportion of all the potential follow-up time that could have been accrued prior to death or the last available follow-up.<sup>21</sup> Survival analyses of time to first event started at inception and stopped at the date of the first outcome or the date of censoring, whichever occurred sooner. For the primary outcome censoring occurred at last available follow-up, before which we disregarded missing OHS scores. For the secondary outcome, censoring occurred at last available follow-up or death (possibly or definitely not attributable to bAVM). Adults managed conservatively who had a secondary outcome event that led to intervention remained in the conservative management group for outcome analyses.

Bivariate analyses were performed using life tables and Kaplan-Meier estimates to analyze follow-up data accrued by

12 years (when approximately 10% of the cohort remained under follow-up<sup>22</sup>), with differences between intervention and conservative management determined by the log-rank test and hazard ratio (HR) from Cox regression, with intervention as the reference category. We prespecified multivariable analyses to adjust HRs when proportional hazards assumptions were satisfied.<sup>23</sup> Covariates were selected from the following list, in the following order, which was determined by the clinical relevance and likely completeness of the covariates, until the number of outcomes per covariate would be less than 10 with the addition of another covariate<sup>20</sup>: clinical influences on functional outcome ([1] age at inception, [2] mode of clinical presentation,<sup>24</sup> and [3] baseline OHS score [for the primary outcome only]) and vascular anatomy that influences either the risk of bAVM hemorrhage ([4] bAVM nidus location and [5] bAVM venous drainage pattern<sup>1,2</sup>) or the risk of intervention ([6] maximum bAVM nidus diameter<sup>10,16</sup>). Covariates were entered simultaneously into the regression model. In a supplementary analysis, we derived a model to predict the occurrence of intervention (using age at presentation, receipt of a catheter angiogram, and sex) and adjusted the multivariable models of the primary and secondary outcomes for these propensity scores.

We used SPSS Statistics (version 19.0), Stata (version 11.2), StatsDirect (version 2.7.8), and Confidence Interval Analysis software to calculate parametric statistics for between-group comparisons when continuous data obeyed a normal distribution and nonparametric statistics when they did not; exact tests in the analysis of categorical data; and HRs with Cox regression analyses. All reported *P* values are 2-sided ( $\alpha = .05$ ).

## Results

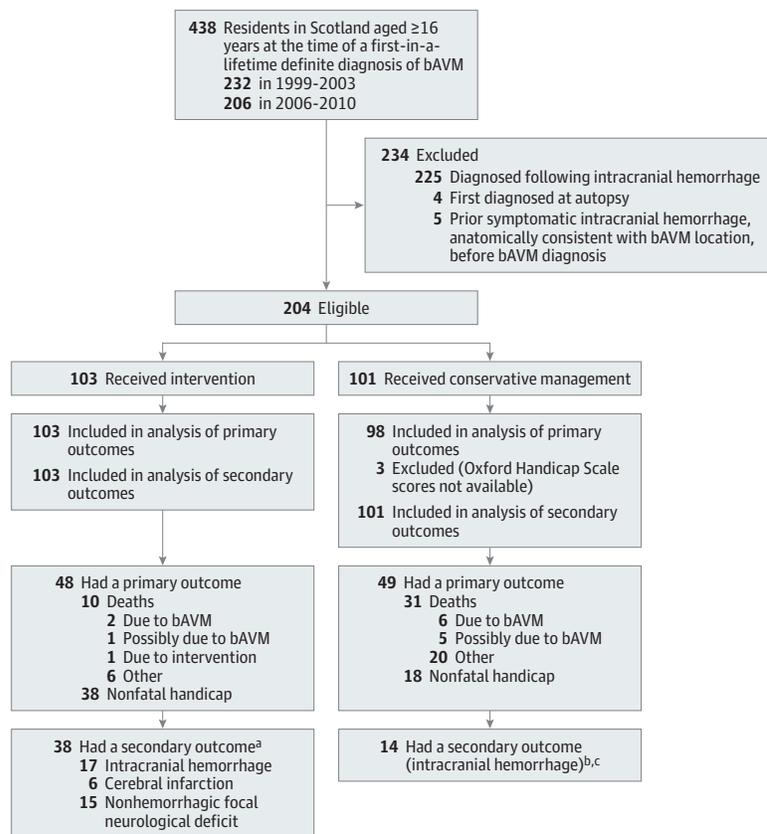
### Baseline Characteristics

During 1999-2003 and 2006-2010, 213 patients were newly diagnosed as having at least 1 definite unruptured bAVM, of whom 204 were eligible for analysis (**Figure 1**). One hundred three underwent intervention and 101 underwent conservative management (5 of whom had intracranial hemorrhage during follow-up and subsequently underwent intervention). Patients who received intervention were younger, more likely to present with seizure(s), more likely to have a catheter angiogram, and less likely to have a maximum bAVM diameter of 6 cm or larger (**Table 1**).

### Conservative Management

Conservative management (n=101) involved usual care (eg, pharmacological treatment of seizures) but no intervention. In this group, embolization was attempted but not completed in 2 participants (because of spontaneous bAVM obliteration 12 days after presentation in 1 participant and demonstration of unsuitable vascular anatomy on superselective angiography in the other) and 3 participants underwent intervention for a remote intracranial aneurysm but the bAVM was not treated. A second patient was found to have spontaneous bAVM obliteration 2.4 years after presentation.

Figure 1. Participant Flow



bAVM indicates brain arteriovenous malformation

<sup>a</sup>Ten secondary outcomes were due to bAVM and 28 were due to intervention complications.

<sup>b</sup>Five patients experiencing bAVM hemorrhage during conservative management subsequently had intervention but remained in the conservative management group for analysis of the primary outcome.

<sup>c</sup>All 14 secondary outcomes were due to bAVM.

## Intervention

First intervention ( $n=103$ ) occurred after a median of 13 months (interquartile range [IQR], 7-19 months; range, 0-97 months) following presentation (eFigure 1 in the Supplement). Embolization was attempted but did not proceed because of unsuitable vascular anatomy in 4 patients (subsequently embolization was possible in 1, and 3 underwent stereotactic radiosurgery). Two-thirds received single-mode intervention and one-third received multimodal intervention during a median of 12 months (eFigure 2 and eTable 1 in the Supplement). Eighty-three patients had catheter angiography and 14 had magnetic resonance angiography following their last intervention, demonstrating bAVM obliteration in 63% after single-mode intervention and 71% following multimodal intervention (eTable 1 in the Supplement). Patients undergoing stereotactic radiosurgery had their most recent imaging study after a mean of 32 (SD, 15) months following their most recent intervention.

## Outcome After Intervention or Conservative Management

Among the 204 eligible patients with bAVM who were alive at presentation, follow-up continued for a median of 6.9 years (IQR, 4.0-11.0 years) and for a total of 1479 person-years (of 1567 potential person-years; overall completeness, 94%<sup>21</sup>). The median duration of follow-up was longer after intervention (9.4 years [IQR, 5.0-11.9 years]) than during conservative manage-

ment (5.2 years [IQR, 3.0-9.7 years];  $P = .002$ ) because three-quarters of the 41 deaths occurred during conservative management (Figure 1 and eFigure 3 and eFigure 4 in the Supplement).

For the primary outcome, the proportional hazards assumption was met during the first 4 years of follow-up. During this time, the rate of progression to the primary outcome was lower during conservative management than after intervention (36 vs 39 events; 9.5 vs 9.8 per 100 person-years; adjusted HR, 0.59; 95% CI, 0.35-0.99) (Table 2 and Figure 2), but rates were not different when subsequent periods were analyzed separately (for 4-8 years, 8 vs 8 events; adjusted HR, 1.07; 95% CI, 0.37-3.16; for 8-12 years, 5 vs 1 event; adjusted HR, 4.70; 95% CI, 0.29-77.42). Over 12 years, the death rate was higher during conservative management than after intervention (31 vs 10 events; 3.7 vs 1.1 per 100 person-years; HR, 3.64; 95% CI, 1.78-7.43) (eFigure 3 in the Supplement). This was unrelated to bAVM or intervention (log-rank  $P = .29$ ) but attributable to deaths from other causes (log-rank  $P < .001$ ); these differences disappeared after age adjustment (eTable 2 in the Supplement).

For the secondary outcome, the proportional hazards assumption was met throughout 12 years of follow-up, during which time the rate of progression to the secondary outcome was lower with conservative management than after intervention (14 vs 38 events; 1.6 vs 3.3 per 100 person-years; adjusted HR, 0.37; 95% CI, 0.19-0.72) (Table 2 and Figure 3), largely because of symptomatic strokes due to intervention (Figure 1),

7 of which occurred within 30 days of first intervention. After these first events, there were 12 more secondary outcomes in the intervention group and 1 during conservative management.

### Sensitivity and Supplementary Analyses

In prespecified sensitivity analyses, the association of conservative management with the primary outcome remained the same over 4 years after removing patients who experienced outcomes before bAVM intervention (34 vs 39 events; 9.0 vs 9.8 per 100 person-years; adjusted HR, 0.58; 95% CI, 0.34-0.99) or when the 2 patients who had intervention attempted but not given were reallocated to the intervention group (34 vs 41 events; 9.3 vs 10.0 per 100 person-years; adjusted HR, 0.53; 95% CI, 0.32-0.90). The association with the secondary outcome was similar whether including preintervention clinical course in the conservative management group (18 vs 39 events; 2.1 vs 3.4 per 100 person-years; unadjusted HR, 0.27; 95% CI, 0.16-0.47), including preintervention clinical course in the intervention group (14 vs 33 events; 1.5 vs 2.8 per 100 person-years; adjusted HR, 0.50; 95% CI, 0.25-0.98),<sup>25</sup> including secondary outcomes that were possibly due to the bAVM (18 vs 39 events; 2.1 vs 3.3 per 100 person-years; adjusted HR, 0.43; 95% CI, 0.23-0.78), or reallocating the 2 patients who had intervention attempted but not given to the intervention group (14 vs 38 events; 1.6 vs 3.2 per 100 person-years; adjusted HR, 0.42; 95% CI, 0.22-0.79).

We prespecified a supplementary analysis of ARUBA's primary outcome (the composite event of death or symptomatic stroke due to any cause). However, the proportional hazards assumption was violated (eFigure 5 in the Supplement), precluding multivariable analysis, because of the excess of deaths due to any cause in the conservative management group in our study (Figure 1 and eFigure 3 in the Supplement).

A post hoc analysis restricted to patients who had OHS scores of 0 to 1 at baseline did not change the association between conservative management and the primary outcome (12 vs 24 events; 5.5 vs 9.0 per 100 person-years; adjusted HR, 0.42; 95% CI, 0.20-0.89 over 4 years) or the secondary outcome (7 vs 20 events; 1.3 vs 2.5 per 100 person-years; adjusted HR, 0.35; 95% CI, 0.14-0.87 over 12 years).

In post hoc analyses, we found differences between the 2 cohort epochs in some covariates. Therefore, we added a cohort epoch term to our multivariable models, which had sufficient outcomes to allow the addition of another covariate. The strength and statistical significance of the associations in our multivariable analyses of the primary and secondary outcomes (Table 2) did not change, but the 2006-2010 cohort was associated with faster progression to the secondary outcome (27 vs 25 events; 4.6 vs 1.8 per 100 person-years; adjusted HR, 2.37; 95% CI, 1.28-4.36). Post hoc multivariable analyses also adjusted for scores modeled on propensity to intervention did not change the association between conservative management and the primary outcome (36 vs 39 events; 9.5 vs 9.8 per 100 person-years; adjusted HR, 0.50; 95% CI, 0.27-0.94) (eTable 3 in the Supplement) or secondary outcome (14 vs 38 events; 1.6 vs 3.3 per 100 person-years; adjusted HR, 0.39; 95% CI, 0.20-0.74) (eTable 4 in the Supplement).

**Table 1. Baseline Characteristics of Adults With a Definite Diagnosis of Unruptured bAVM<sup>a</sup>**

Characteristics	Conservative Management (n = 101)	Intervention (n = 103)
Age at inception, mean (SD), y	53 (16)	41 (13)
Female	39 (39)	44 (43)
Mode of presentation		
Incidental	61 (60)	40 (39)
Seizure(s)	33 (33)	52 (50)
First seizure	15	26
Epilepsy	18	26
Focal neurological deficit	7 (7)	11 (11)
Presentation Oxford Handicap Scale score 0-1	61 (60)	69 (67)
bAVM nidus location		
Brain stem	3 (3)	1 (1)
Cerebellum	1 (1)	2 (2)
Deep	3 (3)	7 (7)
Lobar	94 (93)	93 (90)
Eloquent bAVM nidus location	50 (50)	54 (52)
Maximum bAVM nidus diameter, cm (n = 182)		
<3	45 (51)	50 (54)
3-6	36 (40)	43 (46)
≥6	8 (9)	0 (0)
Catheter angiogram performed	46 (46)	96 (93)
Venous drainage pattern (n = 142)		
Superficial	30 (65)	69 (72)
Both deep and superficial	13 (28)	20 (21)
Exclusively deep	3 (7)	7 (7)
Spetzler-Martin grade <sup>16</sup> (n = 142)		
I	9 (20)	21 (22)
II	15 (33)	36 (38)
III	12 (26)	29 (30)
IV	8 (17)	10 (10)
V	2 (4)	0 (0)
Coexisting intracranial aneurysms		
Associated only	20 (20)	19 (18)
Remote and associated	1 (1)	6 (6)
Remote only	4 (4)	2 (2)

Abbreviation: bAVM, brain arteriovenous malformation.

<sup>a</sup> Data are expressed as No. (%) unless otherwise indicated.

## Discussion

In a prospective, population-based inception cohort study of patients with unruptured bAVM, we found that conservative management was associated with a lower rate of progression to sustained handicap or death of any cause over 4 years and a lower risk of bAVM-related symptomatic stroke or death over 12 years, having adjusted for baseline imbalances and performed several sensitivity analyses.

One randomized clinical trial comparing conservative management with intervention for unruptured bAVMs (ARUBA) was

published recently.<sup>8</sup> Nonrandomized observational studies and randomized trials sometimes concur,<sup>26,27</sup> and in this case the similarities support the generalizability of the results: treated participants were similar in age, sex, incidental mode of presentation, lobar bAVM nidus location, superficial venous drainage pattern, and Spetzler-Martin grades (Table 1), and they re-

ceived multimodal intervention with the same frequency (eTable 1 in the Supplement).<sup>9</sup> Furthermore, the association between conservative management and stroke or death related to bAVM or its intervention over 12 years in this observational study (adjusted HR, 0.37; 95% CI, 0.19-0.72) was similar to the effect of conservative management on stroke or death

Table 2. Bivariate and Multivariable Cox Proportional Hazards Analysis of the First Occurrence of a Primary or Secondary Outcome

	Primary Outcome <sup>a</sup>				Secondary Outcome <sup>b</sup>			
	Cases, No.	Outcomes, No.	Hazard Ratio (95% CI)		Cases, No.	Outcomes, No.	Hazard Ratio (95% CI)	
			Unadjusted Bivariate	Multivariable Adjusted <sup>c</sup>			Unadjusted Bivariate	Multivariable Adjusted <sup>d</sup>
<b>Treatment</b>								
Conservative management	98	36	0.82 (0.52-1.29)	0.59 (0.35-0.99)	101	14	0.31 (0.17-0.58)	0.37 (0.19-0.72)
Intervention	103	39	Reference	Reference	103	38	Reference	Reference
Age at inception (per year increase)	201	75	1.01 (0.99-1.03)	1.01 (0.99-1.03)	204	52	0.98 (0.96-0.99)	0.99 (0.97-1.01)
<b>Presentation</b>								
Seizure(s)	85	33	1.04 (0.66-1.65)	0.74 (0.43-1.29)	85	26	1.42 (0.82-2.44)	1.21 (0.68-2.16)
Other	116	42	Reference	Reference	119	26	Reference	Reference
<b>Presentation OHS score</b>								
2-5	74	39	2.23 (1.41-3.50)	2.48 (1.49-4.12)				
0-1	127	36	Reference	Reference				
<b>bAVM location</b>								
Deep	10	3	0.75 (0.24-2.39)	0.73 (0.23-2.39)	10	5	1.99 (0.79-5.01)	1.71 (0.66-4.46)
Other	191	72	Reference	Reference	194	47	Reference	Reference

<sup>a</sup> First occurrence during 4 years of follow-up after inception of death or handicap (Oxford Handicap Scale [OHS] score 2-5) sustained for 2 or more successive years.

<sup>c</sup> Adjusted for treatment, age at inception, mode of presentation, bAVM location, and OHS at presentation.

<sup>b</sup> First occurrence during 12 years of follow-up after inception of a nonfatal intracranial hemorrhage, cerebral infarction, or persistent/progressive nonhemorrhagic focal neurological deficit or death due to a brain arteriovenous malformation (bAVM) or intervention complication.

<sup>d</sup> Adjusted for treatment, age at inception, mode of presentation, and bAVM location.

Figure 2. Progression to the Primary Outcome During 12 Years of Prospective Follow-up

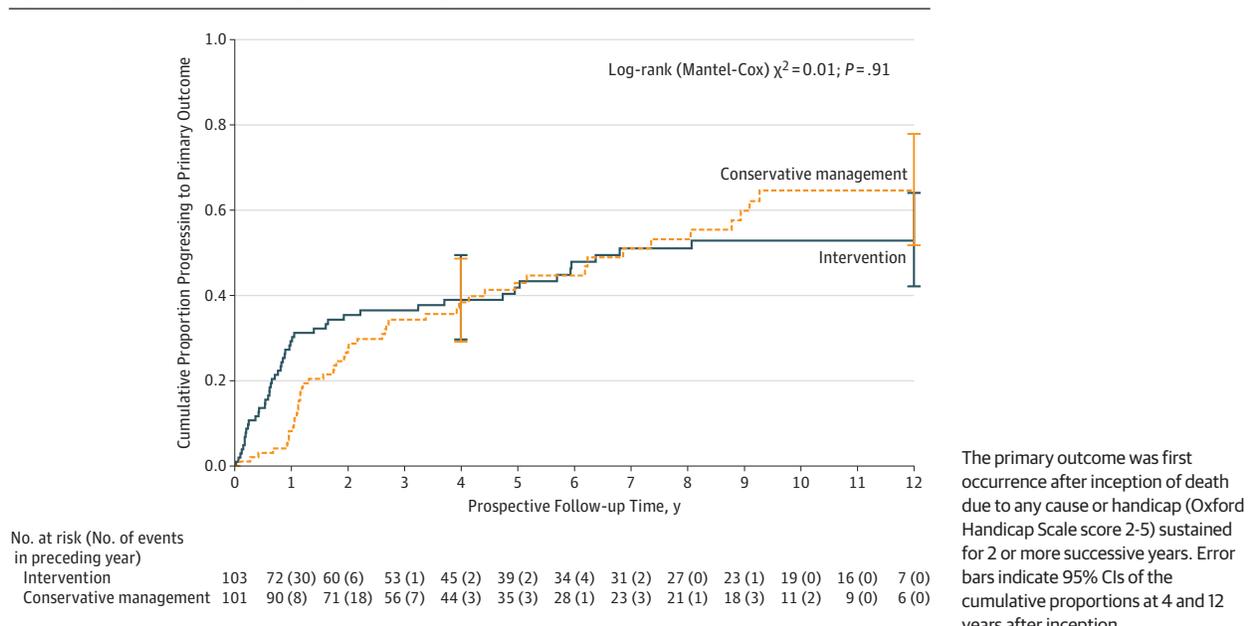
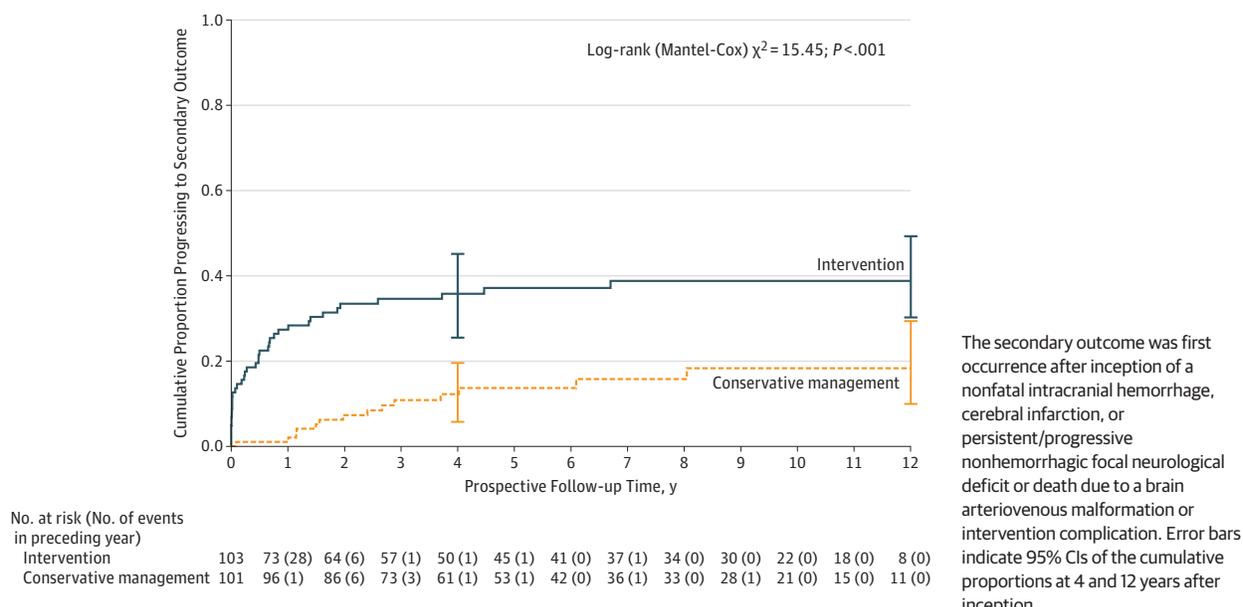


Figure 3. Progression to the Secondary Outcome During 12 Years of Prospective Follow-up



due to any cause over 6 years in the ARUBA as-randomized analysis (HR, 0.27; 95% CI, 0.14-0.54).<sup>9</sup> The similarity of the results of this observational study and ARUBA and the persistent difference between the outcome of conservative management and intervention during 12-year follow-up in our study support the superiority of conservative management to intervention for unruptured bAVMs, which may deter some patients and physicians from intervention.

The strengths of this study include thorough case ascertainment<sup>15</sup>; a population-based sampling frame to maximize external validity; a concurrent control group; sufficient time to allow the effects of multimodal intervention and stereotactic radiosurgery to be complete by the end of follow-up; internal validity from using independent imaging review and outcome assessment with reference to published criteria; minimization of bias by using outcomes that were rated and adjudicated independently of the physicians caring for these patients in clinical practice; and 94% completeness of the entire duration of follow-up for all patients. The clinical outcome and proportions of bAVM obliterated by intervention in Scotland appear generalizable by being at least as good as reports in systematic reviews<sup>6</sup> and the US Nationwide Inpatient Sample database.<sup>28</sup> Furthermore, the rate of hemorrhage from unruptured bAVMs (18%; 95% CI, 11%-30% after 12 years) (Figure 3) was consistent with reported rates.<sup>1,2</sup>

This study also has several limitations. Our comparison of intervention and conservative management was not randomized, so selection bias led to patients undergoing interven-

tion being younger, presenting more often with seizure(s), and having smaller AVM nidus diameters (Table 1). Confounding by indication may affect our results, but the bAVM intervention group appeared to have favorable prognostic factors, and adjustment for propensity to intervention did not change our findings. Both the robustness of our findings in sensitivity analyses and the consistency between our findings and ARUBA<sup>9</sup> are reassuring. The primary outcome did not include the baseline measurement of handicap (and therefore allowed recovery from initial presentation) and, crucially, it allowed for recovery from the known early complications after intervention by requiring handicap to be sustained for at least 2 successive years. The primary outcome was difficult to interpret beyond 4 years because of the high frequency of bAVM-unrelated deaths in the conservative management group, which was attributable to the imbalance in age between the groups at baseline. Long-term follow-up in both this study and the ARUBA trial is needed to establish whether the superiority of conservative management will persist or change.

## Conclusions

Among patients aged 16 years or older who were diagnosed as having unruptured bAVM, the use of conservative management compared with intervention was associated with better clinical outcomes for up to 12 years. However, longer follow-up is required to understand whether this association is persistent.

### ARTICLE INFORMATION

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#### Scottish Audit of Intracranial Vascular

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