Outcome after conservative management or intervention for unruptured brain arteriovenous malformations

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ABSTRACT

Importance – Whether conservative management is superior to interventional treatment ('intervention') for unruptured brain arteriovenous malformations (bAVMs) is uncertain, because of the shortage of long-term comparative data.

Objective – Long-term comparison of outcomes of conservative management versus intervention for unruptured bAVM.

Design – Population-based inception cohort study of adults resident in Scotland, first diagnosed with an unruptured bAVM during 1999-2003 or 2006-2010, and followed prospectively using multiple sources to assess handicap and to identify and validate outcome events over 12 years of prospective follow-up.

Exposures – We compared associations with conservative management (without intervention) versus intervention (endovascular embolization ± neurosurgical excision ± stereotactic radiosurgery).

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, Oxford Handicap Scale score [OHS] ≥2 for at least two successive years [0=no symptoms and 6=death]) and the secondary outcome (non-fatal symptomatic stroke or death due to bAVM, associated arterial aneurysm or intervention).

Results – Of 204 adults, 101 underwent intervention; they were younger, more likely to have presented with seizure(s), and less likely to have large bAVMs than adults 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 four years of follow-up [16 deaths (4.0 per 100 person-years) and 20 OHS 2-5 (5.5 per 100 person-years) versus 4 deaths (1.0

per 100 person-years) and 35 OHS 2-5 (8.8 per 100 person-years), adjusted hazard ratio (HR) 0·59, 95% confidence interval (CI) 0·35 to 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 events (1.6 per 100 person-years) versus 38 events (3.3 per 100 person-years), adjusted HR 0·37, 95% CI 0·19 to 0·72].

Conclusions and relevance – Among adults diagnosed with unruptured bAVM, the use of conservative management compared with intervention was associated with better clinical outcomes over 4 years. Longer follow-up is required to understand whether this association persists.

INTRODUCTION

Unruptured brain arteriovenous malformations and their associated feeding/nidal arterial aneurysms (collectively termed 'bAVM') have ~1% annual risk of intracranial hemorrhage,[1,2] which has a one year case fatality of 12%,[3] in studies lasting up to ten years.[4] Interventional treatment ('intervention') by neurosurgical excision, endovascular embolization, or stereotactic radiosurgery can be used alone, or in combination, to attempt to obliterate bAVMs, dependent on their vascular anatomy.[5] Because interventions may have complications[6] and the untreated clinical course of unruptured bAVMs can be benign,[1-4] some patients choose conservative management (without intervention). Unruptured bAVM intervention has been compared with conservative management in a concurrent control group in just one randomized trial (ARUBA [ISRCTN44013133])[7-9] and only a few observational studies, all of which have shown harm from intervention in the short-term.[10,11] Guidelines have endorsed both intervention and conservative management for unruptured bAVMs.[12,13] Therefore, we began a study in 1999 to assess the long-term outcome for adults affected by bAVM, with or without intervention, in everyday clinical practice.[14,15]

METHODS

The Scottish Intracranial Vascular Malformation (IVM) Study (SIVMS) is a prospective, population-based cohort study that uses anonymized data extracts from the National Health Service Scottish Audit of IVMs (SAIVMs). SAIVMs included adults who were aged ≥16 years and resident in Scotland when first diagnosed with bAVM in 1999-2003 or 2006-2010 (www.saivms.scot.nhs.uk). The audit protocol (www.saivms.scot.nhs.uk/pdf/2008_06_SAIVMs%20protocol_v2.pdf) and research protocol (http://docdat.ic.nhs.uk) are published. SAIVMs 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.[15]

Ethical approval

The Multicentre Research Ethics Committee for Scotland (MREC/98/0/48) and the Fife and Forth Valley Research Ethics Committee (08/S0501/76) 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 adults in SIVMS with a radiographically- or pathologically-confirmed first-in-a-lifetime definite diagnosis of a bAVM in 1999-2003 or in 2006-2010 inclusive, which was unruptured when diagnosed. The term 'bAVM' included associated nidal/feeding arterial aneurysms, but not intracranial aneurysms remote from the bAVM its arterial supply. We classified adults as receiving 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 adults 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/). They determined surgical eloquence of nidus location[16] and used catheter angiography to describe vascular anatomy[10] or MRI to measure nidus size.[17,18]

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).[19] 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 an intervention complication. We classified events as possibly attributable to the bAVM when clinical features were anatomically consistent with bAVM location, but another cause (e.g. ischaemic stroke) was possible and neuroradiological investigation had identified neither bAVM hemorrhage nor an alternative cause. We regarded presentations as 'incidental' if the adult had been asymptomatic or if we could not definitely relate their symptoms to the underlying bAVM (e.g. 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.

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149 **Follow-up**

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151 The inception point for conservative management was an adult's presentation, which was the date
152 of symptom onset or medical consultation (if asymptomatic) that led to an investigation
153 diagnosing the bAVM. The inception point for intervention was the date of the first intervention
154 for an unruptured bAVM that proceeded after presentation. Follow-up occurred prospectively on
155 an uninterrupted annual basis, using a postal questionnaire to every adult's family practitioner and
156 annual surveillance of family practitioner and hospital medical records, to identify outcome events
157 that had occurred over the preceding year. Consenting participants completed postal
158 questionnaires on each anniversary of bAVM diagnosis, to identify outcome events and assess
159 handicap on the OHS. Two investigators (CPW or RA-SS) independently assessed symptomatic
160 clinical outcome events,[10] using all the contemporaneous clinical, radiographic and pathological
161 records available. In attributing the mode and cause of death we reviewed death certificates,
162 autopsy reports if performed, and clinical records and brain imaging if death occurred in hospital.
163 Extent of bAVM obliteration was assessed from reports of angiographic brain imaging after
164 intervention. We gave precedence to obliteration confirmed by catheter angiography, otherwise
165 we relied on magnetic resonance angiography.

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167 **Statistical methods**

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169 *Baseline characteristics*

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171 For analyses of clinical covariates, age was a continuous variable, OHS at presentation was
172 dichotomized into 0-1 versus 2-5, and mode of presentation was dichotomized into seizure(s)

versus other (although, if following presentation a clinical event occurred which 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) versus other. We dichotomized venous drainage into exclusively deep versus other, and bAVM nidus maximum diameter into <3cm versus ≥3cm. 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 to grade 5 highest risk).[16]

Follow-up

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

Sample size

The number of adults diagnosed with unruptured bAVM in our population over ten 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 five important covariates without over-fitting.[20]

198 *Analytical methods*

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200 RA-SS conducted analyses according to a statistical analysis plan approved by the Steering
201 Committee before data extraction (www.saivms.scot.nhs.uk/pdf/resPaper/2013_07_05_SAP.pdf).
202 Completeness of follow-up data was quantified as a proportion of all the potential follow-up time
203 that could have been accrued prior to death or the last available follow-up.[21] Survival analyses of
204 time to first event started at inception and stopped at the date of the first outcome or the date of
205 censoring, whichever occurred sooner. For the primary outcome censoring occurred at last
206 available follow-up, before which we disregarded missing OHS scores. For the secondary outcome,
207 censoring occurred at last available follow-up or death (possibly or definitely not attributable to
208 bAVM). Adults managed conservatively who had a secondary outcome event that led to
209 intervention remained in the conservative management group for outcome analyses.

210

211 Bivariate analyses were performed using life tables and Kaplan-Meier estimates to analyze follow-
212 up data accrued by 12 years (when ~10% of the cohort remained under follow-up[22]) with
213 differences between intervention and conservative management determined by the log-rank test
214 and hazard ratio (HR) from Cox regression, with intervention as the referent category. We pre-
215 specified multivariable analyses to adjust HRs when proportional hazards assumptions were
216 satisfied.[23] Covariates were selected from the following list, in the following order which was
217 determined by the clinical relevance and likely completeness of the covariates, until the number of
218 outcomes per covariate would be below ten with the addition of another covariate[20]: clinical
219 influences on functional outcome ([1] age at inception, [2] mode of clinical presentation,[24] and [3]
220 baseline OHS score [for the primary outcome only]) and vascular anatomy that influences either
221 the risk of bAVM hemorrhage ([4] bAVM nidus location and [5] bAVM venous drainage pattern[1,2])
222 or the risk of intervention ([6] maximum bAVM nidus diameter[10,16]). 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.

RA-SS used IBM 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 non-parametric statistics when they did not; exact tests in the analysis of categorical data; and HRs with Cox regression analyses. All reported P values are two-sided (α=0·05).

RESULTS

Baseline characteristics

During 1999-2003 and 2006-2010, 213 adults were newly diagnosed with at least one definite unruptured bAVM, of whom 204 were eligible for analysis (Figure 1). 103 underwent intervention. 101 underwent conservative management (five of whom had a bleed during follow-up and subsequently underwent intervention). Adults receiving 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 >6cm (Table 1).

Conservative management

101 adults were managed conservatively, which involved usual care (e.g. pharmacological treatment of seizures) but no intervention. In this group, embolization was attempted but did not proceed in two adults (because of spontaneous bAVM obliteration 12 days after presentation in one adult and the demonstration of unsuitable vascular anatomy on superselective angiography in another) and three adults underwent intervention for a remote intracranial aneurysm, but the bAVM was not treated. A second bAVM spontaneously obliterated 2·4 years after presentation.

Intervention

103 adults received their first intervention after median 13 months (inter-quartile range [IQR] 7-19, range 0-97) following presentation (eFigure 1). Embolization was attempted but did not proceed because of unsuitable vascular anatomy in four adults (subsequently embolization was possible in one and three underwent stereotactic radiosurgery). Two-thirds received single-modality intervention and one-third received multi-modality intervention over median 12 months (eFigure 2 and eTable 1). 83 adults had catheter angiography and 14 had magnetic resonance angiography following their last intervention, demonstrating bAVM obliteration in 63% after single-modality and 71% following multi-modality intervention (eTable 1). Adults undergoing stereotactic radiosurgery had their most recent imaging study after mean 32±15 months following their most recent intervention.

Outcome after intervention or conservative management

We followed 204 adults with bAVM who were alive at presentation for a median of 6·9 years (IQR 4.0-11.0) and a total of 1,479 person-years (of 1,567 potential person-years; overall completeness 94%[21]). The median duration of follow-up was longer after intervention (9·4 years, IQR 5·0-11·9) than during conservative management (5·2 years, IQR 3·0-9·7; p=0·002) because three-quarters of the 41 deaths occurred during conservative management (Figure 1 and eFigure 3 and eFigure 4).

For the primary outcome, the proportional hazards assumption was met over the first four 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% confidence interval [CI] 0·35-0·99; Table 2 and Figure 2), but rates were not different when subsequent time periods were analysed separately (4-8 years, 8 vs. 8 events, adjusted HR 1·07, 95% CI 0·37-3·16; 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). This was unrelated to bAVM or intervention (log-rank p=0·29) but attributable to deaths from other causes (log-rank p<0·001); these differences disappeared after age-adjustment (eTable 2).

For the secondary outcome, the proportional hazards assumption was met over 12 years of follow-up, during which time the rate of progression to the secondary outcome was lower during 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 one during conservative management.

Sensitivity and supplementary analyses

In pre-specified sensitivity analyses, the association of conservative management with the primary outcome remained the same over four years after removing adults 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 two adults who had intervention attempted but not given were re-allocated 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 pre-intervention 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 pre-intervention 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),[25] 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 two adults 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 pre-specified a supplementary analysis of ARUBA's primary outcome (the composite event of death from any cause or symptomatic stroke). However, the proportional hazards assumption was violated (eFigure 5) precluding multivariable analysis, because of the excess of deaths of any cause in the conservative management group in our study (Figure 1 and eFigure 3).

A post hoc analysis restricted to adults who were OHS 0-1 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 four years) or 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).

In post hoc analyses, we found differences between the two 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 modelled 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) 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).

DISCUSSION

In a prospective, population-based inception cohort study of adults 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 four 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 controlled trial comparing conservative management with intervention for unruptured bAVMs (ARUBA) was published recently.[8,9] Non-randomized observational studies and randomized trials sometimes concur,[26,27] 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 received multi-modality intervention with the same frequency (eTable 1).[9] 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 of any cause over six years in the ARUBA as-randomized analysis (HR 0·27, 95% CI 0·14-0·54).[9] 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 these patients and physicians from intervention.

The strengths of this study include: thorough case ascertainment[15]; a population-based sampling frame to maximize external validity; a concurrent control group; sufficient time to allow the effects of multi-modality 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; minimisation of bias by using outcomes that were rated and adjudicated independently of the doctors caring for these adults in clinical practice; and 94% completeness of the entire duration of follow-up for all adults. 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[6] and the USA Nationwide Inpatient Sample

database.[28] Furthermore, the rate of hemorrhage from unruptured bAVMs (18%, 95% CI 11-30 after 12 years; Figure 3) was consistent with reported rates.[1,2]

This study also has several limitations. Our comparison of intervention and conservative management was not randomized, so selection bias led to adults undergoing intervention 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 favourable prognostic factors, and adjustment for propensity to intervention did not change our findings. Both the robustness of our findings in sensitivity analyses, as well as consistency between our findings and ARUBA[9] 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 two successive years. The primary outcome was difficult to interpret beyond four 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 as well as the ARUBA trial is needed to establish whether the superiority of conservative management will persist or change.

Conclusions

Among adults diagnosed with unruptured bAVM, the use of conservative management compared with intervention was associated with better clinical outcomes over 4 years. However, longer follow-up is required to understand whether this association is persistent.

CONTRIBUTORS

RA-SS and CPW designed the study, supported by the SAIVMs Steering Committee. RA-SS, JvB, CBJ, TW, CJW, and ZS collected data. RJS, JdP, and PMW assessed brain imaging. RA-SS checked, analysed and interpreted the data according to a statistical analysis plan developed and approved by the SAIVMs Steering Committee. RA-SS drafted the paper, and all co-authors reviewed the final version.

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McLaughlin, Jan Potter, Margaret Roberts. *Western General Hospital, Edinburgh, UK*— Rustam Al-Shahi Salman, Rebecca Aylward, Chandra Balasubramaniyam, Jeanne Bell, Peter Bodkin, Paul Brennan, Chris Butler, Gurjit Chohan, Helen Cook, Don Collie, Roger Cull, Richard Davenport, Martin Dennis, Chris Derry, Fergus Doubal, Rahul Dubey, Sara Erridge, Andrew Farrall, Mike Fitzpatrick, Ioannis Fouyas, Rod Gibson, Robin Grant, Anna Gregor, Gordon Gubitz, Julie Hall, Peter Hand, Colm Henry, Fiona Hughes, Brian Innes, James Ironside, Susan Kealey, Sarah Keir, Andrew Kelso, Peter Keston, Richard Knight, Joseph Kwan, Marco Lee, Richard Lindley, Christian Lueck, Greg Moran, Colin Mumford, Katy Murray, Lynn Myles, Mary Porteous, Gillian Potter, Jerard Ross, Thomas Russell, Peter Sandercock, Robin Sellar, Colin Smith, Patrick Statham, James Steers, Jon Stone, Cathie Sudlow, David Summers, Joanna Wardlaw, Charles Warlow, Nick Weir, Belinda Weller, Phil White, Will Whiteley, Ian Whittle, Bob Will, Anna Williams, Edith Wood, Wendy Young, Adam Zeman. *Western Infirmary, Glasgow, UK*—Martin Brodie, Michael Cowan, Ed Kalkman, Kevin Kelly, Gordon McInnes, Nigel McMillan, John Reid, Peter Semple, Matthew Walters. *Western Isles Hospital, Stornoway, UK*—Ian Riach. *Wishaw General Hospital, Wishaw, UK*—Desmond Alcorn, Marie Callaghan, Mohammed El-Sayed, Mustafa Fleet, Barbara Macpherson, Susan Reid, John Roberts. *Woodend General Hospital, Aberdeen, UK*—Steven Hamilton, Francis Smith.

CONFLICTS OF INTEREST

Professor White reports grants and personal fees from Covidien during the conduct of the study. All other authors have nothing to disclose.

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FIGURE LEGENDS

FIGURE 1 – Flowchart of included participants.
bAVM = arteriovenous malformation
* Oxford Handicap Scale scores were not available for three patients. ¶ Five patients experiencing bAVM hemorrhage during conservative management subsequently had intervention, but remained in the conservative management group for analysis of the primary outcome

FIGURE 2 – Progression to the primary outcome (first occurrence after inception of death of any cause or handicap [Oxford Handicap Scale Score 2-5] sustained for two or more successive years) during 12 years of prospective follow-up.
Error bars represent the 95% confidence intervals of the cumulative proportions at four and 12 years after inception.

FIGURE 3 – Progression to the secondary outcome (first occurrence after inception of a non-fatal intracranial hemorrhage, cerebral infarct, or persistent/progressive non-hemorrhagic focal neurological deficit, or death, due to a brain arteriovenous malformation [bAVM] or intervention complication) during 12 years of prospective follow-up.
Error bars represent the 95% confidence intervals of the cumulative proportions at four and 12 years after inception.

TABLE 1 – Baseline characteristics of adults with a definite diagnosis of an unruptured brain arteriovenous malformation (bAVM).

	Conservative management (n=101)		Intervention (n=103)		Significance (p value)
Age at inception (mean ± SD), years	53	± 16	41	± 13	<0.001
Female	39	(39%)	44	(43%)	0.551
Mode of presentation					0.009
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 0-1	61	(60%)	69	(67%)	0.097
bAVM nidus location					0.404
Brainstem	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%)	0.676
Maximum bAVM nidus diameter (n=182)					0.012
<3cm	45	(51%)	50	(54%)	
3-6cm	36	(40%)	43	(46%)	
>6cm	8	(9%)	0	(0%)	
Catheter angiogram done	46	(46%)	96	(93%)	<0.001
Venous drainage pattern (n=142)					0.618
Superficial	30	(65%)	69	(72%)	
Both deep and superficial	13	(28%)	20	(21%)	
Exclusively deep	3	(7%)	7	(7%)	
Spetzler-Martin Grade[16] (n=142)					0.212
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%)	
Co-existing intracranial aneurysms					0.236
Associated only	20	(20%)	19	(18%)	
Remote and associated	1	(1%)	6	(6%)	
Remote only	4	(4%)	2	(2%)	

TABLE 2 – Bivariate and multivariable Cox proportional hazards analyses of the first occurrence of a primary or secondary outcome.

	Primary outcome[¶]				Secondary outcome[ʃ]			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)		Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)	
			Unadjusted bivariate	Multivariable adjusted*			Unadjusted bivariate	Multivariable adjusted[§]
Treatment								
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 (referent)	103	39			103	38		
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)
Presentation								
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 (referent)	116	42			119	26		
Presentation OHS								
2-5	74	39	2·23 (1.41-3.50)	2·48 (1·49-4·12)	-	-	-	-
0-1 (referent)	127	36			-	-		
bAVM location								
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 (referent)	191	72			194	47		

[¶] first occurrence during four years of follow-up after inception of death or handicap [Oxford Handicap Scale Score (OHS) 2-5] sustained for two or more successive years; [ʃ] first occurrence during 12 years of follow-up after inception of a non-fatal intracranial hemorrhage, cerebral infarct, or persistent / progressive non-hemorrhagic focal neurological deficit, or death, due to a brain arteriovenous malformation [bAVM] or intervention complication; * adjusted for intervention, age at inception, mode of presentation, bAVM location, and OHS at presentation; [§] adjusted for intervention, age at inception, mode of presentation, and bAVM location

FIGURE 1 – Flowchart of included participants.
bAVM = arteriovenous malformation
* Oxford Handicap Scale scores were not available for three patients. ¶ Five patients experiencing bAVM hemorrhage during conservative management subsequently had intervention, but remained in the conservative management group for analysis of the primary outcome

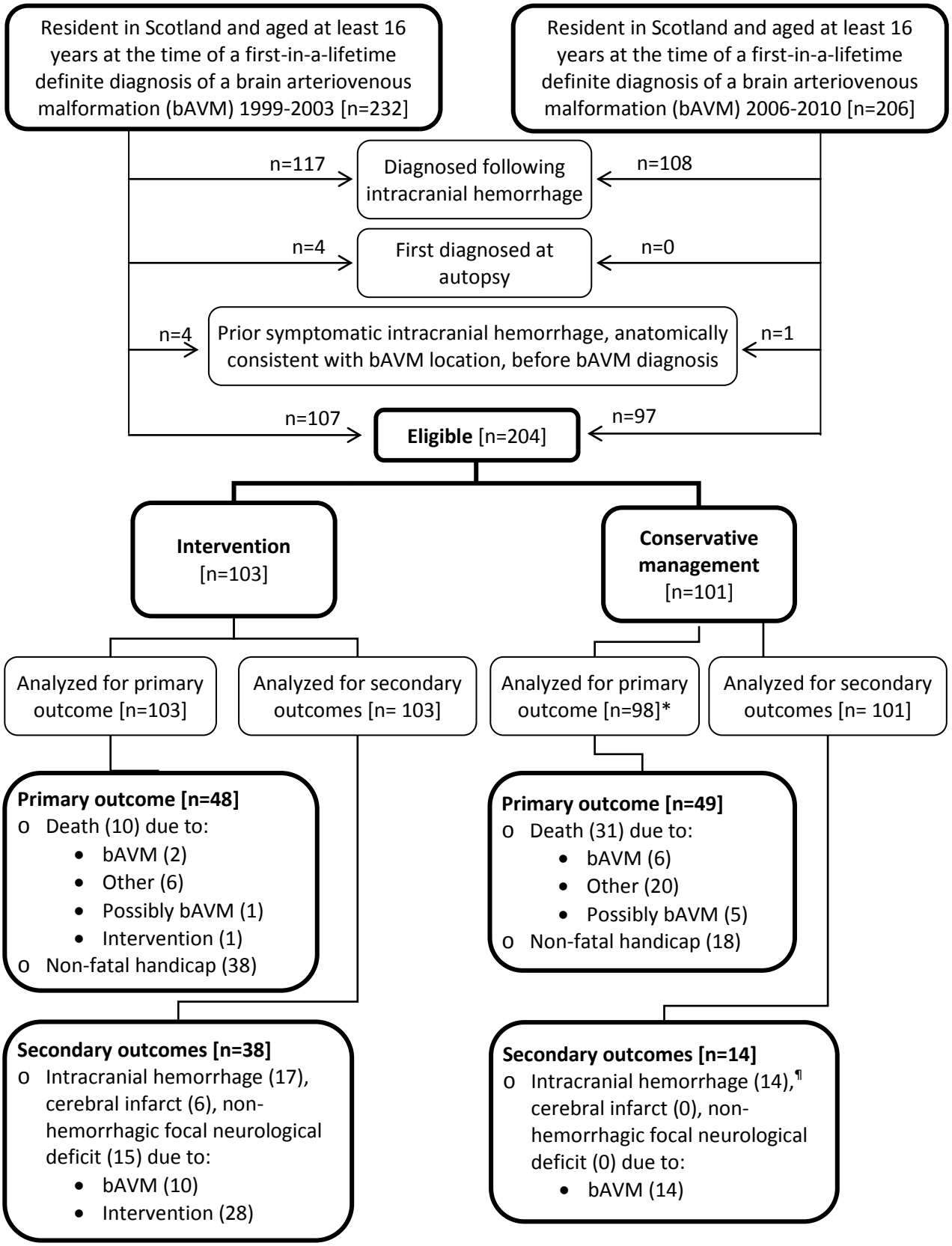
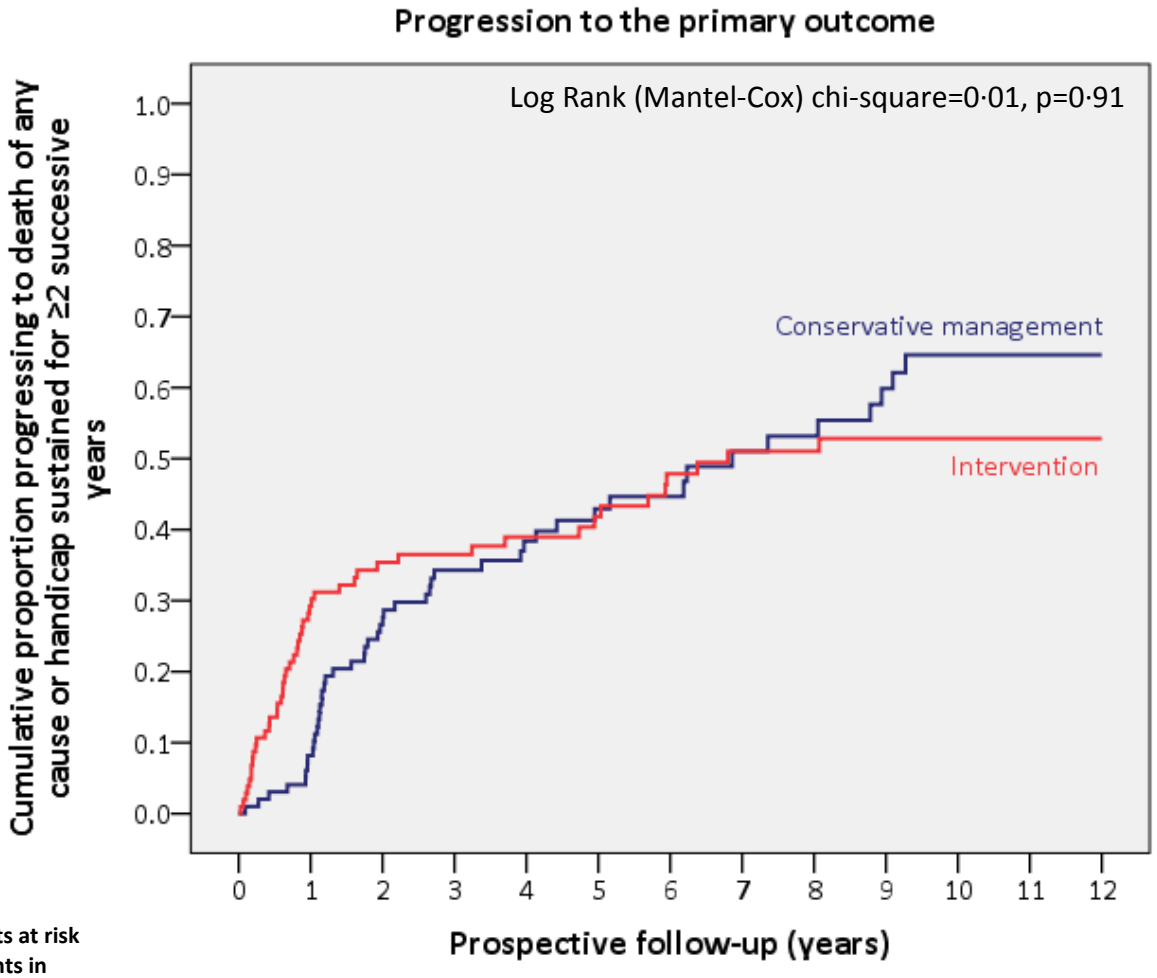
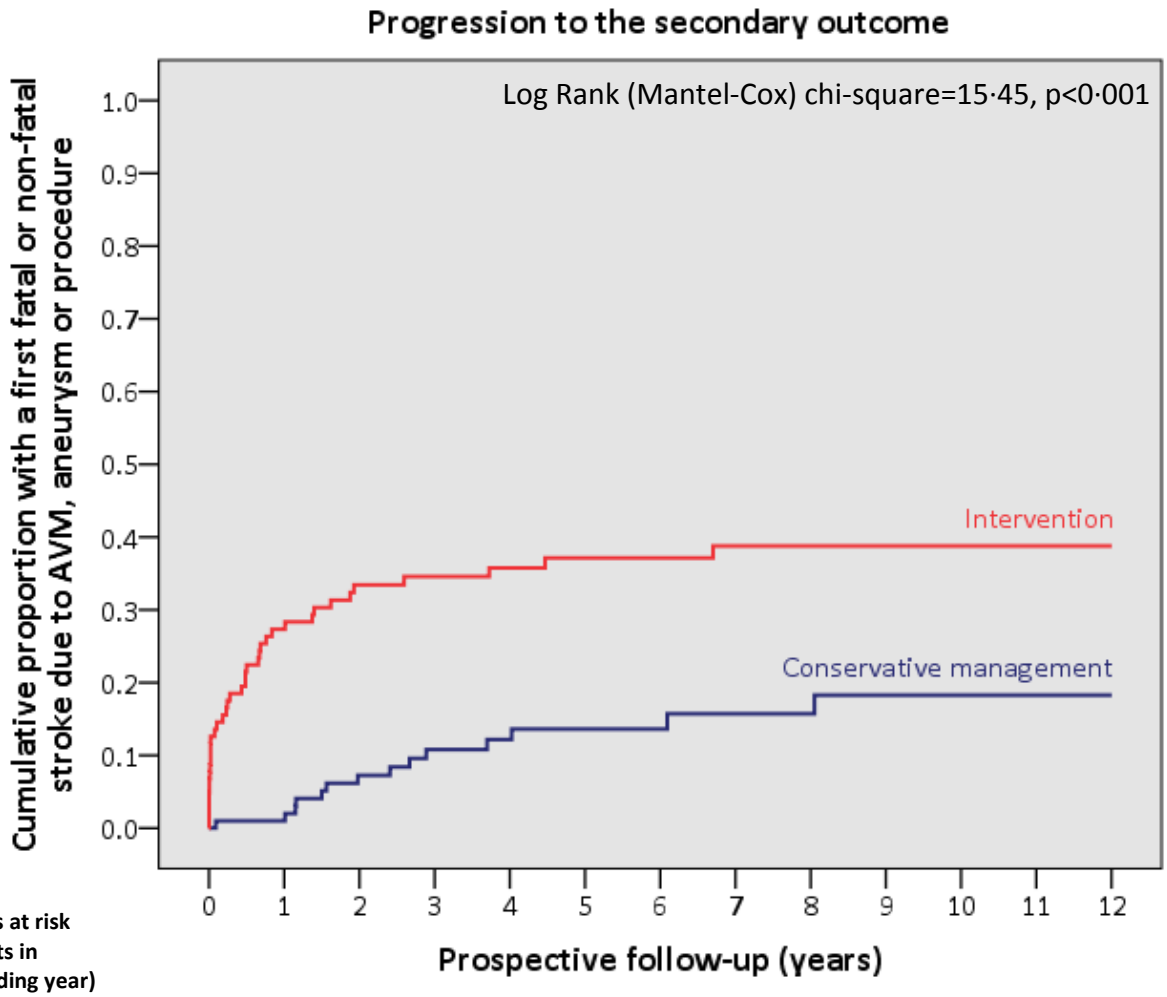


FIGURE 2 – Progression to the primary outcome (first occurrence after inception of death of any cause or handicap [Oxford Handicap Scale Score 2-5] sustained for two or more successive years) during 12 years of prospective follow-up.



Adults at risk (events in preceding year)												
Intervention	103	72 (30)	60 (6)	53 (1)	45 (2)	39 (2)	34 (4)	31 (2)	27 (0)	23 (1)	19 (0)	16 (0)	7 (0)
Conservative	101	90 (8)	71 (18)	56 (7)	44 (3)	35 (3)	28 (1)	23 (3)	21 (1)	18 (3)	11 (2)	9 (0)	6 (0)

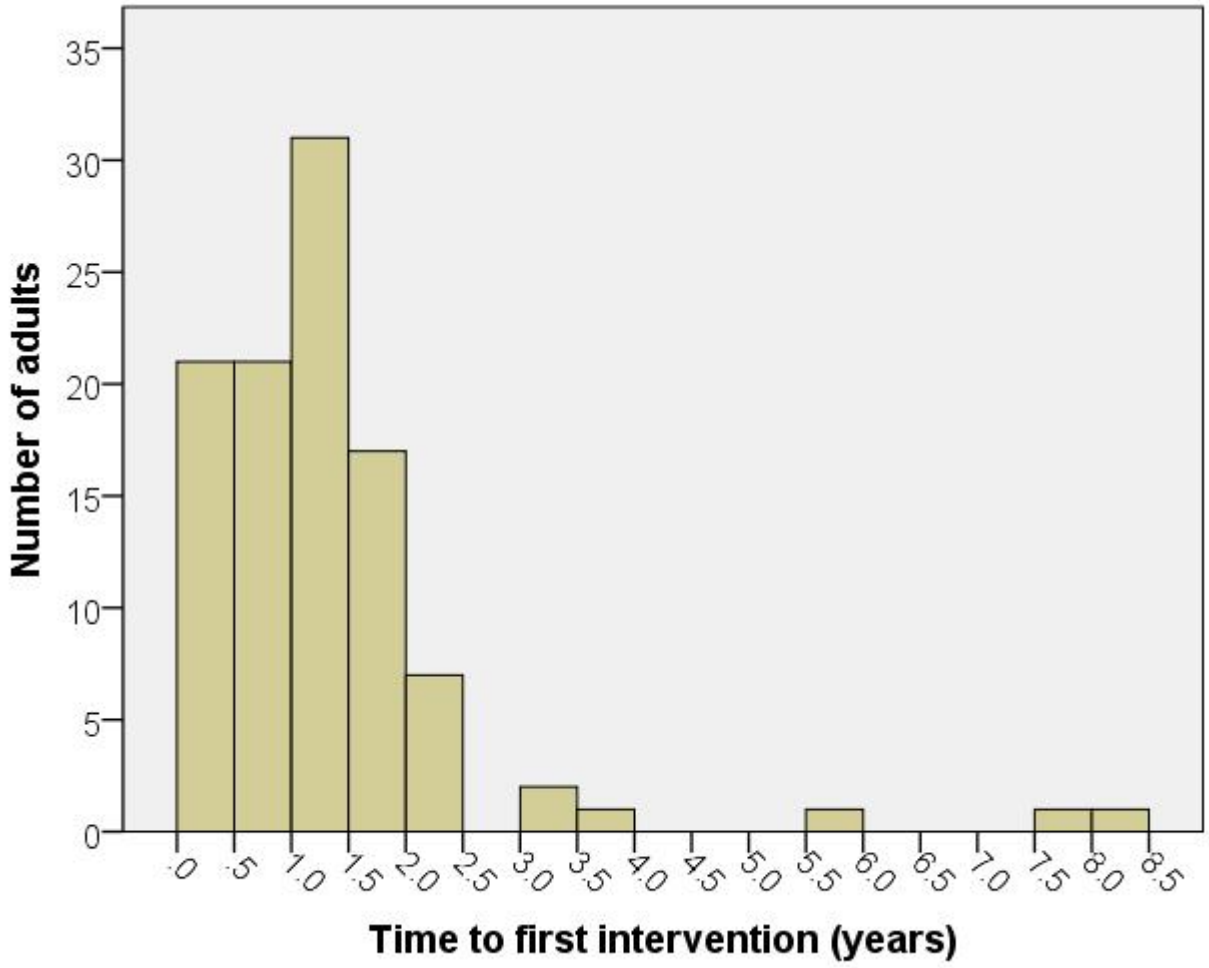
FIGURE 3 – Progression to the secondary outcome (first occurrence after inception of a non-fatal intracranial hemorrhage, cerebral infarct, or persistent/progressive non-hemorrhagic focal neurological deficit, or death, due to a brain arteriovenous malformation [bAVM] or intervention complication) during 12 years of prospective follow-up.



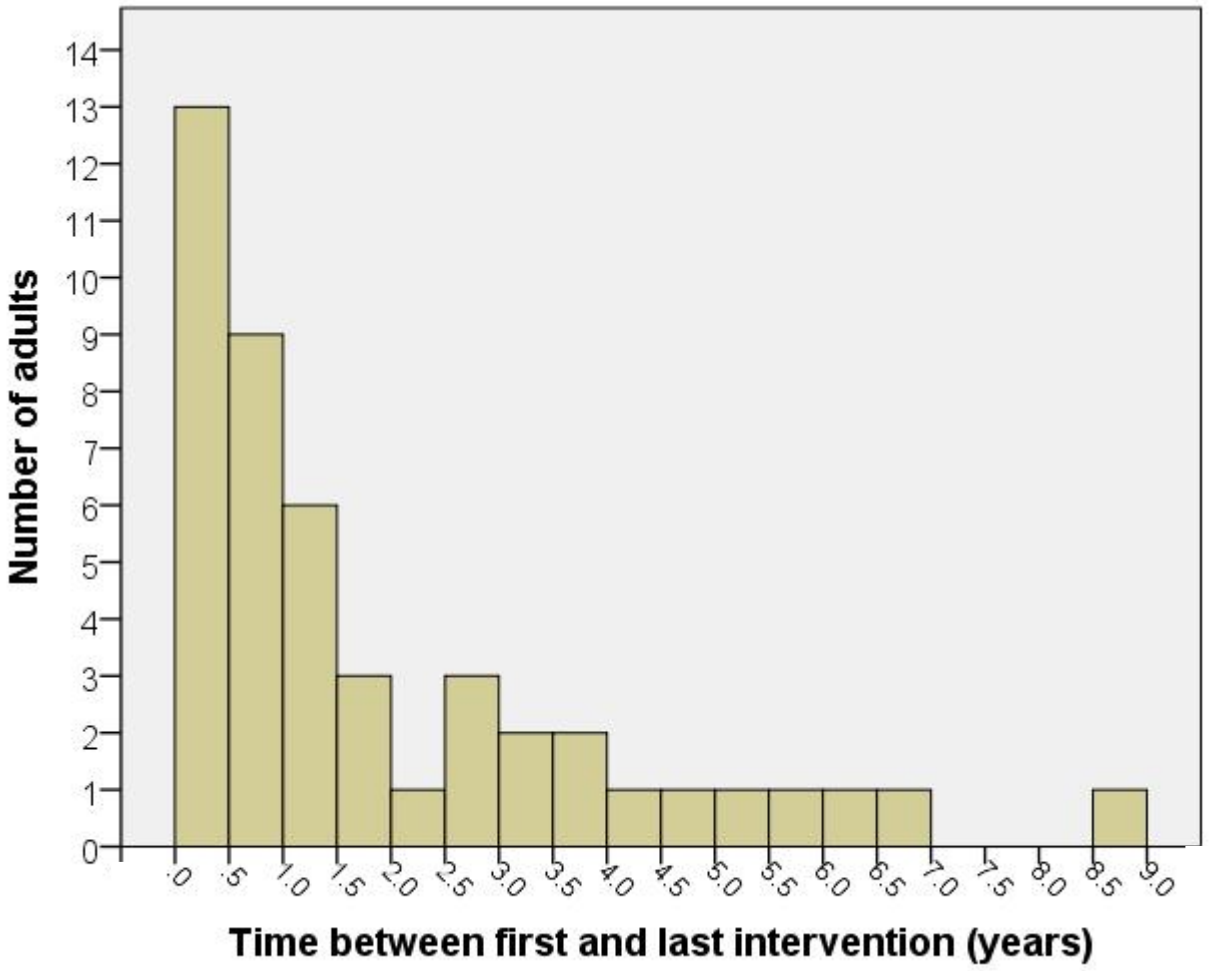
Adults at risk (events in preceding year)												
Intervention	103	73 (28)	64 (6)	57 (1)	50 (1)	45 (1)	41 (0)	37 (1)	34 (0)	30 (0)	22 (0)	18 (0)	8 (0)
Conservative	101	96 (1)	86 (6)	73 (3)	61 (1)	53 (1)	42 (0)	36 (1)	33 (0)	28 (1)	21 (0)	15 (0)	11 (0)

ONLINE-ONLY SUPPLEMENT

eFIGURE 1 – Time to first intervention for an unruptured brain arteriovenous malformation or associated arterial aneurysm after initial presentation among the 103 adults in the intervention group.
Each bin includes values greater than or equal to the lower limit and less than the upper limit.



eFIGURE 2 – Time between first and last intervention for an unruptured brain arteriovenous malformation or associated arterial aneurysm among the 103 adults in the intervention group.
Each bin includes values greater than or equal to the lower limit and less than the upper limit.

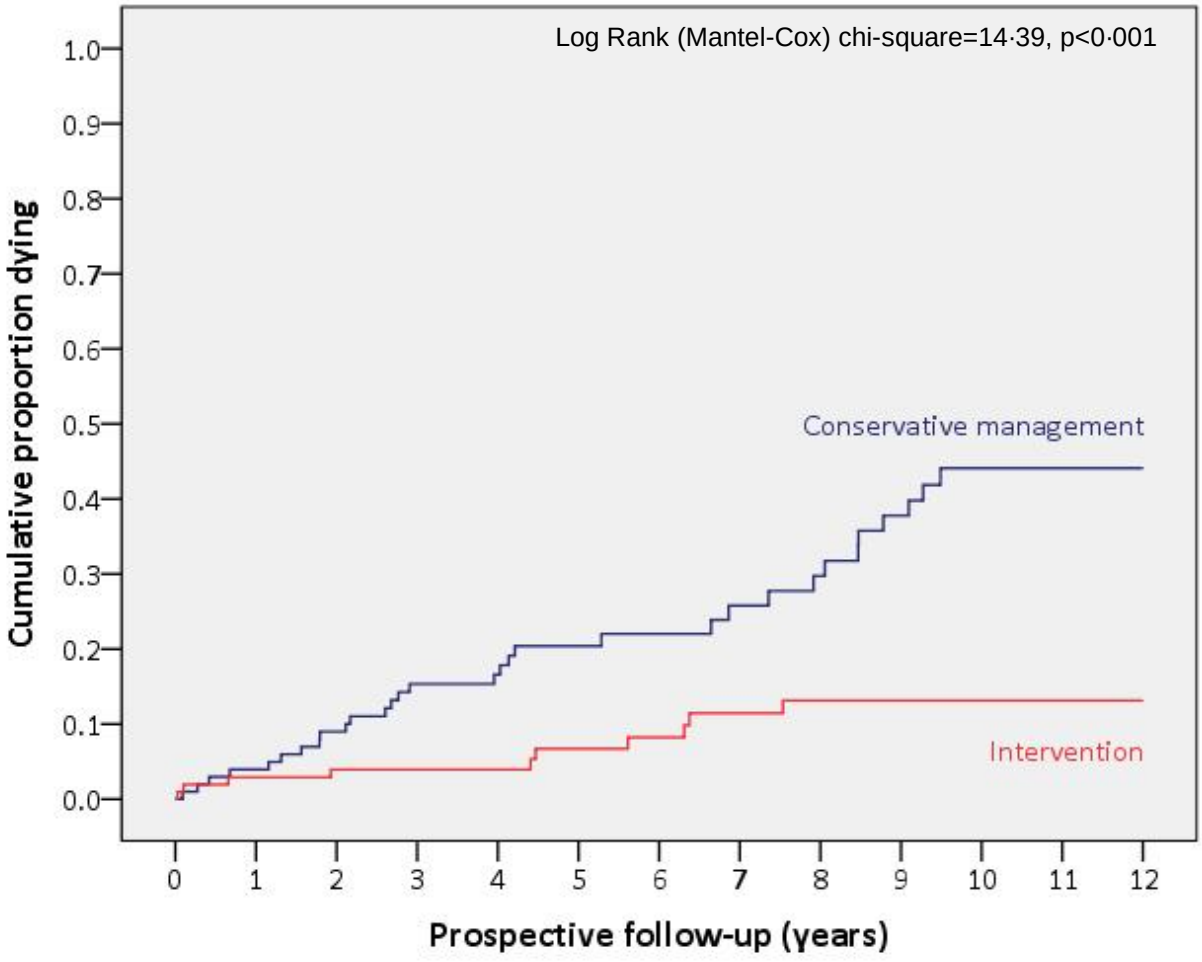


eTABLE 1 – Type of intervention and extent of angiographic obliteration among the 103 adults in the intervention group.

Intervention	n	Completely obliterated		Partially obliterated		No follow-up imaging	
Single modality							
Stereotactic radiosurgery	28	18	(64%)	8	(29%)	2	(7%)
Endovascular embolisation	22	10	(45%)	10	(45%)	2	(10%)
Microsurgical excision	18	15	(83%)	1	(6%)	2	(11%)
Sub-total	*68*	*43*	*(63%)*	*19*	*(28%)*	*6*	*(9%)*
Multimodality **							
Endovascular embolisation and stereotactic radiosurgery	20	11	(55%)	9	(45%)	0	(0%)
Endovascular embolisation and microsurgical excision	12	12	(100%)	0	(0%)	0	(0%)
Stereotactic radiosurgery and microsurgical excision	2	2	(100%)	0	(0%)	0	(0%)
Endovascular embolisation, microsurgical excision, and stereotactic radiosurgery	1	0	(0%)	1	(100%)	0	(0%)
Sub-total	*35*	*25*	*(71%)*	*10*	*(29%)*	*0*	*(0%)*

** $p<0.01$ comparing the proportion completely obliterated in four multimodality approaches

eFIGURE 3 – Progression to death of any cause among the 204 adults with unruptured bAVM during 12 years of prospective follow-up.



Adults at risk (events in preceding year)													
Conservative	101	96 (4)	90 (5)	78 (6)	66 (1)	57 (3)	45 (1)	39 (2)	35 (2)	31 (4)	24 (3)	15 (0)	11 (0)
Intervention	103	99 (3)	94 (1)	82 (0)	72 (0)	63 (2)	59 (1)	53 (2)	50 (1)	43 (0)	32 (0)	26 (0)	12 (0)

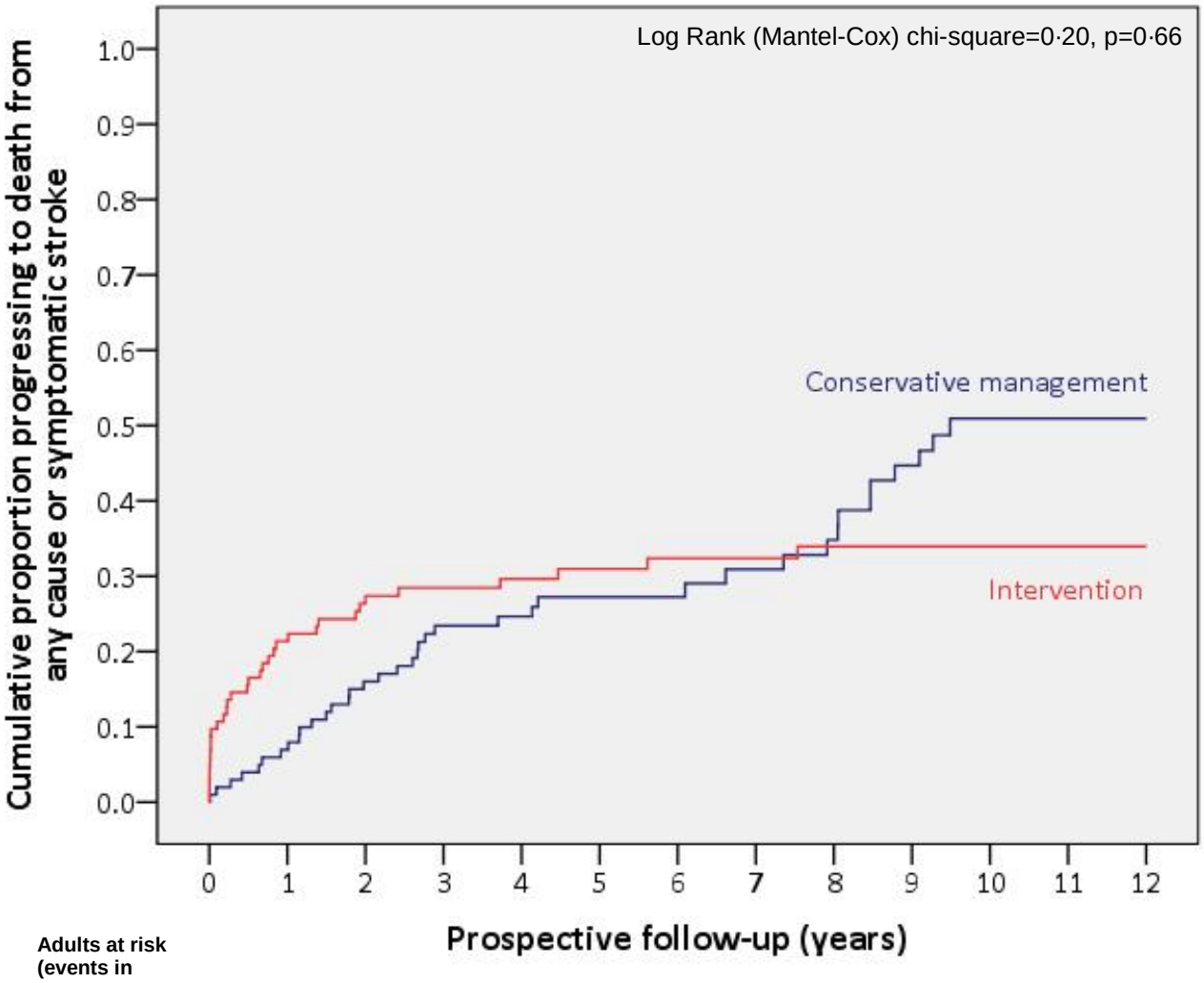
eTABLE 2 – Bivariate and multivariable Cox proportional hazards analyses of the first occurrence of death of any cause among the 204 adults with unruptured bAVM during 12 years of prospective follow-up.

	Death of any cause			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)	
			Unadjusted bivariate	Multivariable adjusted*
Treatment				
Conservative management	101	31	3·64 (1·78-7·43)	1·62 (0·72-3·65)
Intervention (referent)	103	10		
Age at inception (per year increase)	204	41	1·07 (1·04-1·09)	1·04 (1·02-1·07)
Presentation				
Seizure(s)	85	11	0·41 (0·21-0·82)	0·45 (0·20-0·98)
Other (referent)	119	30		
Presentation OHS				
2-5	74	23	3·30 (1·76-6·16)	3·50 (1·77-6·89)
0-1 (referent)	130	18		

* adjusted for intervention, age at inception, mode of presentation, and OHS at presentation

eFIGURE 4 – Stacked bar chart of the proportions of the 204 adults with unruptured bAVM who were followed-up in each year on the Oxford Handicap Scale, stratified by treatment group for comparison.
Deaths are illustrated cumulatively so the annual case fatality rate is over-estimated.

eFIGURE 5 – Progression to death from any cause or symptomatic stroke among the 204 adults with unruptured bAVM during 12 years of prospective follow-up.



Adults at risk (events in preceding year)													
Conservative	101	93 (7)	83 (9)	71 (7)	59 (1)	52 (2)	41 (0)	36 (2)	33 (2)	28 (5)	21 (3)	15 (0)	11 (0)
Intervention	103	80 (22)	72 (5)	63 (2)	56 (1)	50 (1)	46 (1)	44 (0)	41 (1)	36 (0)	28 (0)	24 (0)	10 (0)

eTABLE 3 – Multivariable Cox proportional hazards analysis of the first occurrence of the primary outcome during four years of follow-up among the 204 adults with unruptured bAVM, adjusted for propensity score.

Primary outcome (over four years), adjusted for propensity score			
	Cases (n)	**Outcomes (n)**	**Hazard ratio (95% confidence interval)**
			Multivariable adjusted
Treatment			
Conservative management	98	36	0·50 (0·27-0·94)
Intervention (referent)	103	39	
Age (per year increase)	201	75	1·01 (0·99-1·03)
Presentation			
Seizure(s)	85	33	0·69 (0·39-1·23)
Other (referent)	116	42	
bAVM location			
Deep	10	3	0·73 (0·22-2·41)
Other (referent)	191	72	
Presentation OHS			
2-5	74	39	2·48 (1·47-4·19)
0-1 (referent)	127	36	

eTABLE 4 – Multivariable Cox proportional hazards analysis of the first occurrence of the secondary outcome during 12 years of follow-up among the 204 adults with unruptured bAVM, adjusted for propensity score.

Secondary outcome (over 12 years), adjusted for propensity score			
	Cases (n)	Outcomes (n)	Hazard ratio (95% confidence interval)
			Multivariable adjusted
Treatment			
Conservative management	101	14	0·39 (0·20-0·74)
Intervention (referent)	103	38	
Age (per year increase)	204	52	0·99 (0·97-1·01)
Presentation			
Seizure(s)	85	26	1·15 (0·65-2·04)
Other (referent)	119	26	
bAVM location			
Deep	10	5	1·69 (0·65-2·04)
Other (referent)	194	47	