

Outcome after spontaneous and arteriovenous malformation-related intracerebral haemorrhage: population-based studies

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Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) has a high case-fatality and leaves many survivors disabled. Clinical characteristics and outcome seem to vary according to the cause of ICH, but population-based comparisons are scarce. We studied two prospective, population-based cohorts to determine differences in outcome [case-fatality and modified Rankin Scale (mRS)] after incident ICH due to brain arteriovenous malformations (AVM) [Scottish Intracranial Vascular Malformation Study (SIVMS), $n=90$] and spontaneous ICH [Oxford Vascular Study (OXVASC), $n=60$]. Patients with AVM-ICH were younger, had lower pre-stroke and admission blood pressure (BP), higher admission Glasgow Coma Scale (GCS) and were more likely to have an ICH in a lobar location than patients with spontaneous ICH (sICH). Case fatality throughout 2-year follow-up was greater following sICH than AVM-ICH [34/56 (61%) versus 11/90 (12%) at 1 year, odds ratio (OR) 11 (95% Confidence Interval (CI) 5–25)], as was death or dependence (mRS ≥ 3) [40/48 (83%) versus 26/65 (40%) at 1 year, OR 8 (3–19)]. Differences in outcome persisted following stratification by age and sensitivity analyses. In multivariable analyses of 1 year outcome, independent predictors of death were sICH (OR 21, 4–104) and increasing ICH volume (OR 1.03, 1.01–1.05), and independent predictors of death or dependence were sICH (OR 11, 2–62) and GCS on admission (OR 0.79, 0.67–0.93). Outcome after AVM-ICH is better than after sICH, independent of patient age and other known predictors of ICH outcome.

Keywords: intracranial arteriovenous malformations; intracerebral haemorrhage; outcome

Abbreviations: AVM = arteriovenous malformation; BP = blood pressure; CI = confidence interval; CT = computed tomogram; GCS = Glasgow coma scale; GP = general practitioner; ICH = intracerebral haemorrhage; IQR = interquartile range; IVM = intracranial vascular malformation; MRI = magnetic resonance imaging; mRS = modified Rankin scale; sICH = spontaneous intracerebral haemorrhage.

Introduction

Spontaneous (non-traumatic) intracerebral haemorrhage (ICH) accounts for 10% of all strokes and has a 1-month case fatality of ~50% (Dennis, 2003; Fogelholm *et al.*, 2005; Lovelock *et al.*, 2007). Radiological investigations are used to identify structural causes of ICH such as intracranial vascular malformations (IVMs) and tumours, because identifying these abnormalities can influence prognosis and treatment. However, in most patients such identifiable underlying causes are absent and ICH appears to occur 'spontaneously' (sICH); in these cases, cause is inferred on the basis of patients' possession of risk factors such as arterial hypertension, or characteristic clinical features or pathological examination implicating diseases such as cerebral amyloid angiopathy (Knudsen *et al.*, 2001; Jackson *et al.*, 2006).

ICH due to a brain arteriovenous malformation (AVM-ICH) appears to have a lower 1-month case fatality than sICH (Rosenow *et al.*, 1997; Hartmann *et al.*, 1998; Al Shahi *et al.*, 2001; Choi *et al.*, 2006), based on indirect comparisons of sICH prognosis (Dennis 2003; Fogelholm *et al.*, 2005; Lovelock *et al.*, 2007) with the findings of one small, retrospective population-based study of AVM-ICH (Brown Jr *et al.*, 1996), and hospital-based studies with potential ascertainment bias (Hartmann *et al.*, 1998; Choi *et al.*, 2006). These observations could be explained by differences in study design and epoch, the tendency for AVM-ICH to occur in young adults who may recover better from ICH (Al Shahi *et al.*, 2001) or perhaps the underlying disease processes.

Because direct comparisons of population-based studies of sICH and AVM-ICH outcome have not been undertaken, and few previous studies have explored the reasons for any differences in outcome, we sought to compare AVM-ICH and sICH outcome in two contemporaneous population-based studies (Al Shahi *et al.*, 2003; Lovelock *et al.*, 2007).

Methods

Data collection

Adults with AVM-ICH

The Scottish Intracranial Vascular Malformation Study (SIVMS) is an epidemiological analysis of an anonymized data extract of an ongoing, prospective, population-based national clinical audit of adults (aged ≥ 16 years) who are resident in Scotland at the time of their first diagnosis with any type of IVM during 1999–2003 (www.saivms.scot.nhs.uk). Incident diagnoses were identified by multiple, overlapping sources of case ascertainment. The main source was a collaborative nationwide network of physicians, surgeons, radiologists and pathologists affiliated with the clinical neurosciences and brain imaging facilities in Scotland. Furthermore, we searched for people meeting our inclusion criteria in centralized, routine coding of hospital discharge and death certificates. Finally, every general (family) practitioner (GP) in Scotland was approached to find any eligible people as yet unknown to SIVMS (Al Shahi *et al.*, 2003).

We selected every adult in the SIVMS cohort whose presentation with ICH (with or without intraventricular, subarachnoid, or subdural haemorrhage) had led to a definite brain AVM diagnosis (established by radiological or pathological examination). Haemorrhagic

presentation was defined as a symptomatic clinical event (any or all of headache \pm seizure(s) \pm global neurological deficit \pm focal neurological deficit), with signs of intracranial blood on brain imaging or on post mortem examination, both of which were anatomically referable to the AVM nidus. The two SIVMS neuroradiologists classified the type and location of intracranial haemorrhage using hard copies of the first axial brain imaging performed after a haemorrhagic presentation. Another author (CC, or RA-SS in cases of doubt) cross-checked the images, rated them for predominant ICH location, and measured and calculated haematoma volumes blinded to clinical data (Cordonnier *et al.*, 2008). We collected demographic and clinical data from patients' medical records. All surviving adults were followed-up from haemorrhagic presentation by medical records surveillance, and an annual rating of their level of dependence on the Oxford Handicap Scale [a derivative of the modified Rankin Scale (mRS)] by their GP. We used follow-up data accrued until September 2007.

Adults with sICH

We identified all cases of sICH between April 2002 and March 2007 in the Oxford Vascular Study (OXVASC), a population-based prospective study of all vascular events including stroke in a population of approximately 91 000 individuals. Multiple overlapping methods of hot and cold pursuit were used to ensure nearly complete ascertainment of all cases of stroke. Particular effort was also made to identify all out-of-hospital deaths due to stroke and all cases of minor stroke who were not admitted to hospital. Out-of-hospital deaths were identified via the Coroner's office, by review of all death certificates in the study primary care practices, by searching mortality data on the population for ICD10 vascular codes provided by the local Department of Public Health, and by regular contact with hospital bereavement officers to identify cases who arrived death at hospital or who died prior to medical assessment (Rothwell *et al.*, 2004; Lovelock *et al.*, 2007). People with minor stroke were identified through the study's daily emergency TIA and stroke clinic, and by regular contact with local nursing homes.

We included every adult with sICH (with or without intraventricular, subarachnoid, or subdural haemorrhage), diagnosed using brain imaging and/or post mortem (98%), in whom subarachnoid haemorrhage, and haemorrhage secondary to transformation of infarction, intracranial tumour, trauma, haematological malignancy, and thrombolysis, or an underlying structural abnormality (such as an AVM) had been excluded by five neuroradiologists using magnetic resonance imaging (MRI) or catheter angiography, especially when ICH occurred below age 50 years and in the absence of other risk factors (Lovelock *et al.*, 2007). Pre-morbid clinical data were collected by interviewing patients shortly after presentation, or by interviewing family members and reviewing the primary care and hospital medical records. All surviving adults were followed up from incident sICH by a study neurologist/nurse at 1, 12, 24 and 60 months after sICH onset, and their mRS was assessed. We used follow-up data accrued until September 2007.

Statistical analysis

We calculated haematoma volume (cm³) on the first brain image obtained after stroke onset using the ABC/2 formula (Newman, 2007), by identifying the axial imaging slice with the largest area of ICH, and halving the product of the maximum haematoma width (A, cm), the width perpendicular to A (B, cm) and the depth (C, cm). We determined depth by multiplying the number of slices on which ICH was visible by the slice thickness of the relevant part(s) of the brain CT or MRI.

We calculated the ICH score (Hemphill *et al.*, 2001), which is a composite score of known predictors of ICH outcome, by summing the following scores: Glasgow Coma Scale (GCS) [3–4 (=2 points), 5–12 (=1), 13–15 (=0)], age [≥ 80 years (=1), < 80 years (=0)], infratentorial origin [yes (=1), no (=0)], ICH volume [≥ 30 cm³ (=1), < 30 cm³ (=0)] and presence of intraventricular haemorrhage [yes (=1), no (=0)].

We compared demographic and radiological characteristics and outcome measures in the two cohorts using parametric statistics when data obeyed a Normal distribution, and non-parametric statistics when they did not. We compared outcomes using odds ratios (ORs) and differences of proportions [with accompanying 95% confidence intervals (CIs)] at 1, 6, 12 and 24 months for case fatality, and at 12 and 24 months for death or dependence (mRS ≥ 3). We determined the cut-off for age-stratified analyses by the extent of overlap between the cohorts.

We used a multivariable logistic regression model to test the effect of cause of ICH (AVM-ICH versus sICH), patient age, ICH volume, ICH location, admission GCS, presence of associated IVH, admission blood pressure (BP) and pre-stroke hypertension on case-fatality and poor functional outcome (defined as mRS ≥ 3) at 1 year. We pre-specified the aforementioned variables for the multivariable analyses based on: their clinical relevance; the accuracy, reliability and completeness of their ascertainment by SIVMS and OXVASC; their known (Ariesen *et al.*, 2003) or hypothesized influence on outcome; and the baseline imbalances found in this analysis (Lewis, 2007). In a separate multivariable analysis, we examined whether ICH cause was independent of the ICH score in predicting outcome. We tested the robustness of these analyses by repeating them using stepwise variable selection following univariate analyses.

Ethical approval

The Multicentre Research Ethics Committee for Scotland approved SIVMS (MREC/98/0/48). OXVASC had local research ethics committee approval.

Results

Baseline characteristics

Of 229 adults incident with a brain AVM in SIVMS during 1999–2003, 90 (39%) presented with AVM-ICH. Of 512 incident strokes in OXVASC during 2002–2007, 60 (12%) presented with incident sICH. The median delays from AVM-ICH symptom onset to imaging were 0 [InterQuartile Range (IQR) 0–25] days for CT and 22 (IQR 0–52) days for MRI. The median delay from sICH onset to imaging was 2 (IQR 1–6) days.

The completeness of demographic, clinical and characteristics was 100% for baseline characteristics, apart from admission BP (47% in AVM-ICH and 88% in sICH) and admission GCS (77% and 98%, respectively), pre-stroke hypertension (86% in AVM-ICH), haematoma volume (94% and 93%, respectively), haematoma location (98% in sICH), intraventricular haemorrhage (75% in sICH), such that the ICH score could be calculated in 76% of AVM-ICH and 73% of sICH.

At baseline, patients with sICH were significantly older (median 79 years versus 47 years; Fig. 1), more likely to have had pre-stroke hypertension, had a higher BP and lower GCS on admission, and had a higher admission ICH score, but there were no differences in sex, ICH volume and associated IVH (Table 1).

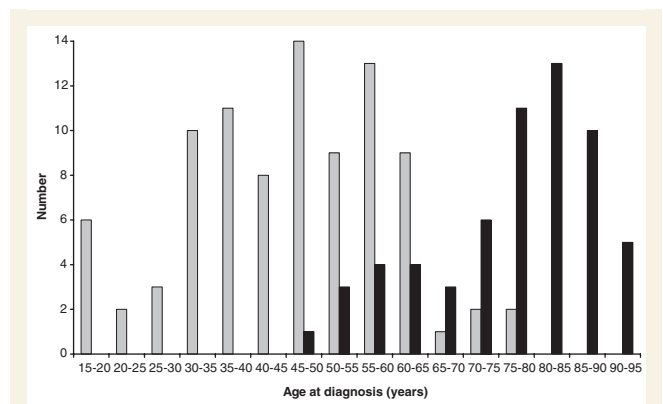


Fig. 1 Age at the time of ICH for AVM-ICH (grey bar) and sICH (black bar). Each bar represents the number of patients with ICH in a 5-year age range.

Case fatality

Case-fatality throughout 2-year follow-up was greater following sICH than AVM-ICH (Table 2). Case fatality at 1 month was 50% for patients with sICH and 11% for those with AVM-ICH (OR 8.0, 95% CI 3.5–18). At 2 years the risk of death remained higher after sICH than after AVM-ICH (OR 14, 95% CI 6.1–34). After age stratification, case-fatality remained higher in patients with sICH as compared to AVM-ICH at almost every time point (Table 2 and Fig. 2). These findings were extremely robust in sensitivity analyses if all missing data were assumed to be deaths or survivors (Webtables 1 and 2), and if missing data were assumed to be deaths in AVM-ICH and survivors in sICH, or vice versa (Webtables 3 and 4).

Functional outcome

The median 1 year mRS score was 2 (IQR 1–3) after AVM-ICH and 6 (IQR 4–6) after sICH (Fig. 3). The proportion of patients who were dead or dependent (mRS ≥ 3) at 1 and 2 years follow-up was higher after sICH than after AVM-ICH (Table 2). The risk of death or dependence for patients with sICH was more than seven times higher than AVM-ICH at 1 year (OR 7.5, 95% CI 3.0–19), and 15 times higher at 2 years (OR 15, 95% CI 5.0–47). After age stratification, the risk of death and dependence remained significantly higher after sICH than after AVM-ICH in patients of 60 years and older, but we could not confirm this finding in patients younger than 60 years because of the paucity of data. These findings were reasonably robust in sensitivity analyses, if all missing data were assumed to be deaths or survivors (Webtables 1 and 2), or if all missing data were assumed to be deaths or dependent survivors in AVM-ICH and independent survivors in sICH, or vice versa (Webtables 3 and 4).

Predictors of poor outcome

Cause of ICH and haematoma volume were independent predictors of death in a multivariable logistic regression analysis of 124 patients, 39 of whom died after 1 year (Table 3). A subsequent multivariable analysis, based on data from 90 patients, 56 of whom were dead or dependent at 12 months, revealed that the occurrence of this outcome was associated with cause of ICH and GCS (Table 4). Finally, multivariable logistic regression models

Table 1 Baseline clinical and radiological characteristics of adults with AVM-ICH and sICH

	SIVMS AVM-ICH N = 90	OXVASC sICH N = 60	P-value
Male sex	48 (53%)	29 (48%)	0.55 ^a
Median age (IQR)	47 (35–56)	79 (70–85)	<0.0001 ^b
Pre-stroke hypertension	14 (18%)	37 (62%)	<0.0001 ^a
BP on admission			
Median systolic BP (IQR)	140 (125–165)	190 (158–220)	<0.0001 ^b
Median diastolic BP (IQR)	81 (66–90)	100 (80–109)	0.0017 ^b
Median GCS on admission (IQR)	15 (12–15)	14 (9–15)	0.033 ^b
ICH volume (cm ³)			
Median (IQR)	16 (4.8–40)	13 (5.0–48)	0.58 ^b
Volume ≥ 30 cm ³	28 (33%)	21 (38%)	0.58 ^a
ICH location			
Lobar	66 (73%)	24 (41%)	<0.0001 ^a
Deep	10 (11%)	26 (44%)	
Infratentorial	14 (16%)	9 (15%)	
Intraventricular haemorrhage	31 (34%)	23 (51%)	0.062 ^a
Median ICH score (IQR)	1 (0–2)	2 (1–3)	0.0064 ^b

Statistics were calculated using either ^a χ^2 test or ^bMann–Whitney U test.

The ICH score was calculated using GCS on admission, ICH volume (cm³), presence/absence of intraventricular haemorrhage, supra- or infratentorial location, and age (Hemphill *et al.*, 2001).

Table 2 Cross-sectional comparison of case fatality and functional dependence between AVM-ICH and sICH

	Overall					
	AVM-ICH N = 90	sICH N = 60	Odds ratio ^a			
Case fatality						
At 1 month	10/90 (11%)	30/60 (50%)	8.0 (3.5–18)			
At 6 months	11/90 (12%)	32/57 (56%)	9.2 (4.1–21)			
At 12 months	11/90 (12%)	34/56 (61%)	11 (4.9–25)			
At 24 months	13/90 (13%)	34/48 (71%)	14 (6.1–34)			
Death or dependence (mRS ≥ 3)						
At 12 months	26/65 (40%)	40/48 (83%)	7.5 (3.0–19)			
At 24 months	31/81 (38%)	38/42 (90%)	15 (5.0–47)			
	< 60 years			≥ 60 years		
	AVM-ICH N = 76	sICH N = 10	Odds ratio ^a	AVM-ICH N = 14	sICH N = 50	Odds ratio ^a
Case fatality						
At 1 month	7/76 (9.2%)	5/10 (50%)	9.9 (2.3–43)	3/14 (21%)	25/50 (50%)	3.7 (0.91–15)
At 6 months	8/76 (11%)	5/8 (63%)	14 (2.8–71)	3/14 (21%)	27/49 (55%)	4.5 (1.1–18)
At 12 months	8/76 (11%)	5/8 (63%)	14 (2.8–71)	3/14 (21%)	29/48 (60%)	5.6 (1.4–23)
At 24 months	10/76 (13%)	5/6 (83%)	33 (3.5–310)	3/14 (21%)	29/42 (69%)	8.2 (2.0–34)
Death or dependence (mRS ≥ 3)						
At 12 months	21/55 (38%)	5/7 (71%)	4.1 (0.72–23)	5/10 (50%)	35/41 (85%)	5.8 (1.3–27)
At 24 months	27/68 (40%)	5/6 (83%)	7.6 (0.84–69)	4/13 (31%)	33/36 (92%)	25 (4.7–130)

^aFor odds ratios (OR), adults with AVM-ICH are the referent category.

including cause of ICH and ICH score (based on 110 patients for case fatality and 82 patients for death or dependence) found both variables to be significant and independent outcome predictors: sICH conferred a 23-fold (95% CI 6.8–79) greater risk of death and a 14-fold (95% CI 3.5–60) greater risk of death or dependence; an increase of one point on the ICH score roughly doubled the risk of death (OR 2.3 95% CI 1.4–3.8) and almost tripled the risk of death or dependence (OR 2.9 95% CI 1.5–5.6). These

findings remained unchanged in sensitivity analyses (Webtables 4 to 6), and when variables entered into the model were determined by stepwise selection.

Discussion

This comparison of two prospective, population-based studies showed that outcome was better in patients with AVM-ICH

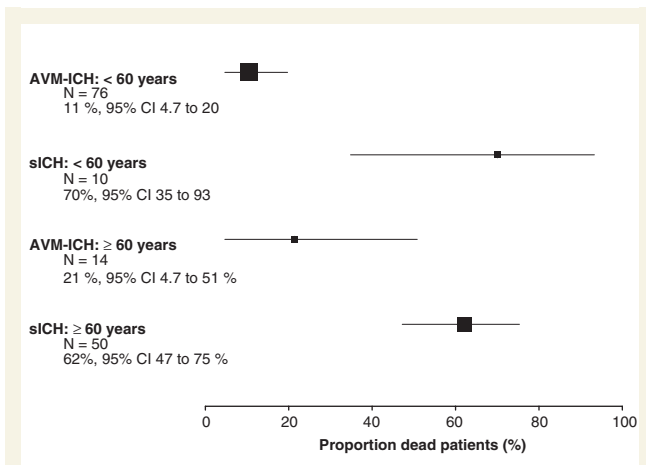


Fig. 2 One year case fatality following AVM-ICH or sICH, stratified by age (<60 years versus ≥60 years). The area of the point estimates is proportional to sample size, and the error bars represent 95% CIs.

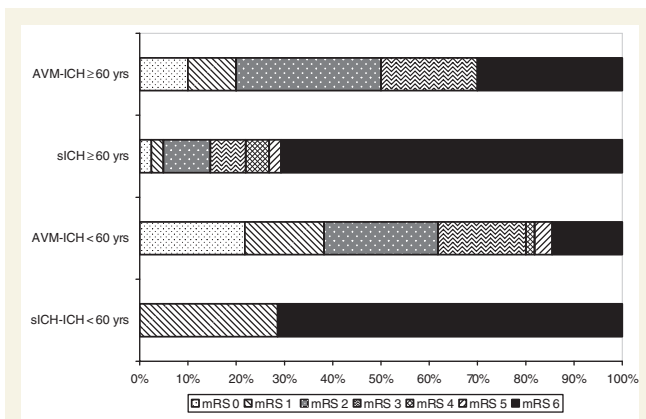


Fig. 3 Comparison of mRS of patients with spontaneous intracerebral haemorrhage (sICH) and AVM-related ICH (AVM-ICH) at 12 months stratified by age.

than patients with sICH, independent of factors known to predict ICH outcome, or which were imbalanced at baseline in this study. Other independent predictors of outcome were ICH volume, GCS on admission and the ICH score (Hemphill *et al.*, 2001).

The strengths of this study lie in the thorough methods of case ascertainment and follow-up in the two population-based studies, their conduct at overlapping times, and analysis at a time when the number of outcomes was sufficient to power multivariable analyses.

The better outcome observed in patients with AVM-ICH may have been due in part to under-diagnosis of an AVM in everyday clinical practice following an incident ICH that was disabling or fatal. A patient's age, comorbidities, or ICH severity might militate against further investigation in clinical practice, as might doctors' beliefs about causes of ICH according to their location, but these are unlikely to fully account for the observed differences in outcome. We did not account for re-bleeding during follow-up, but both groups are susceptible to this: 8.6% of patients surviving sICH have recurrent ICH with a mean interval between the first

Table 3 Influences on death at 1 year

	Univariate analyses	Multivariable analyses
	Odds ratio ^a (95% CI)	Odds ratio ^a (95% CI)
Cause (sICH versus AVM-ICH)	11 (4.9–25)	21 (4.2–104)
Age	1.1 (1.0–1.1)	1.0 (0.96–1.0)
Male sex	0.87 (0.43–1.8)	–
History of hypertension	2.6 (1.2–5.5)	–
BP on admission		
Systolic BP	1.0 (1.0–1.0)	–
Diastolic BP	1.0 (0.99–1.0)	–
GCS score on admission	0.83 (0.75–0.91)	–
ICH volume (cm ³)	1.0 (1.0–1.0)	1.0 (1.0–1.1)
ICH volume ≥ 30 cm ³	4.3 (2.0–9.4)	–
ICH location		
Lobar	0.37 (0.18–0.77)	–
Infratentorial	1.0 (0.38–2.7)	–
Intraventricular extension	2.8 (1.1–5.1)	–
ICH score	2.5 (1.7–3.8)	–

^aFor odds ratios (OR), adults with AVM-ICH are the referent category. The ICH score was calculated using GCS on admission, ICH volume (cm³), presence/absence of intraventricular haemorrhage, supra- or infratentorial location, and age (Hemphill *et al.*, 2001).

Table 4 Influences on death or dependence at 1 year

	Univariate analyses	Multivariable analyses
	Odds ratio ^a (95% CI)	Odds ratio ^a (95% CI)
Cause (sICH vs AVM-ICH)	7.1 (3.1–17)	11 (1.8–62)
Age	1.0 (1.0–1.1)	0.99 (0.96–1.0)
Male sex	0.71 (0.36–1.4)	–
History of hypertension	2.6 (1.2–5.6)	–
BP on admission		
Systolic BP	1.0 (1.0–1.0)	–
Diastolic BP	1.0 (0.99–1.0)	–
GCS score on admission	0.72 (0.62–0.84)	0.79 (0.67–0.93)
ICH volume (cm ³)	1.0 (1.0–1.0)	1.0 (0.98–1.0)
ICH volume ≥ 30 cm ³	3.4 (1.6–7.2)	–
ICH location		
Lobar	0.33 (0.16–0.69)	0.62 (0.19–2.1)
Infratentorial	1.2 (0.48–3.1)	–
Intraventricular extension	3.4 (1.6–7.3)	–
ICH score	3.4 (2.1–5.6)	–

^aFor odds ratios (OR), adults with AVM-ICH are the referent category. The ICH score was calculated using GCS on admission, ICH volume (cm³), presence/absence of intraventricular haemorrhage, supra- or infratentorial location, and age (Hemphill *et al.*, 2001).

and second haemorrhages of 39 months (range, 1 month to 12 years) (Gonzalez-Duarte *et al.*, 1998) and AVM-ICH annual re-bleeding rates vary from 4.5% to 34.3% (Al Shahi *et al.*, 2001; Stapf *et al.*, 2006). Although interventional treatment of AVMs during follow-up may have an impact on case-fatality and functional outcome by attenuating the risk of re-bleeding,

AVM treatment can also be harmful and result in poor functional outcome and even death (Ogilvy *et al.*, 2001; Choi *et al.*, 2005).

Others have reported outcome to be better after AVM–ICH than after sICH (Rosenow *et al.*, 1997; Hartmann *et al.*, 1998; Ko *et al.*, 2003; Choi *et al.*, 2006). However, patients in these studies were from tertiary referral centres, whereas the control group were survivors from non-AVM-related ICH recruited from a community stroke study (Hartmann *et al.*, 1998; Choi *et al.*, 2006), so referral bias may have affected their results. Furthermore, results may have been confounded by AVM haemorrhage also including subarachnoid and/or intraventricular haemorrhages without ICH which have a different prognosis from ICH (Choi *et al.*, 2006). After first AVM haemorrhage in a hospital-based cohort, the investigators found no disability (Rankin 0 or 1) in 49%, moderate disability (Rankin 2 or 3) in 37%, and severe disability (Rankin ≥ 4) in 14%, but no patient died (Hartmann *et al.*, 1998; Choi *et al.*, 2006). In contrast, in a population-based design, SIVMS found 30-day case-fatality to be 11%, and 38% of the patients with AVM-ICH were dead or dependent after 1 year. In the hospital-based cohort comparing AVM haemorrhage and sICH, there was a difference in mean age of roughly 30 years, but this age difference was not taken into account in multivariable analyses (Hartmann *et al.*, 1998; Choi *et al.*, 2006).

One month case-fatality after so-called 'hypertensive ICH' has been reported to be lower in patients aged ≤ 40 years (Ruiz-Sandoval *et al.*, 2006). These younger patients with 'hypertensive ICH' had different clinical characteristics and a better prognosis compared to older patients presenting with 'hypertensive ICH' (Ruiz-Sandoval *et al.*, 2006). Our data on sICH do not indicate a better prognosis in younger patients although firm conclusions cannot be made based on these small numbers; we could not perform analyses with a cut-off at 40 years because of the lack of overlap between the cohorts in this age range (Fig. 1).

Because outcome after AVM-ICH is better than after sICH, independent of patient age and other known predictors of ICH outcome, thorough radiological investigation of the underlying cause of ICH is important.

Funding

Rustam Al-Shahi Salman was funded by the UK Medical Research Council (Clinical Training Fellowship G84/5176 and Clinician Scientist Fellowship G108/613). The Scottish Intracranial Vascular Malformation Study was funded by the Chief Scientist Office of the Scottish Government (Project Grants K/MRS/50/C2704 and CZB/4/35), and the UK Stroke Association (TSA04/01). The Oxford Vascular Study was funded by the Medical Research Council, UK Stroke Association, Dunhill Medical Trust, National Institute of Health Research, Thames Valley Primary Care Partnership and the Oxford Biomedical Research Centre. Janneke van Beijnum was funded by the Netherlands Organization for Scientific Research (NWO); and the Netherlands Heart Foundation (grant number 2002B138). Catharina Klijn was funded by the Netherlands Heart Association (2003B263); and by the Netherlands Organization for Health Research and Development (907-00-103).

Supplementary material

Supplementary material is available at *Brain* online.

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Appendix

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