

The Prognosis for Adults with Arteriovenous Malformations of the Brain. A Systematic Review of the Literature

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The widening availability and increasing use of brain imaging have led to arteriovenous malformations (AVMs) being detected more frequently, and posing a regular management problem. The biggest dilemma is whether to treat a particular individual with a particular type of AVM. Because there are no randomized controlled trials comparing interventional strategies with conservative management, the decision to treat rests on a comparison of the case series reporting treatment effectiveness with existing knowledge about the clinical course of AVMs. This systematic review of the literature on the prognosis of AVMs has found only a very small number of studies from which reliable information is available. This is partly because AVMs are so heterogeneous and difficult to study, but also because the methodological quality of studies on prognosis is notoriously poor. In this review, the best information available is summarized, and recommendations are made for furthering knowledge about the prognosis for people with AVMs: future studies should be large, prospective, population-based, and should use clear and reproducible clinical and angioarchitectural definitions.

The main dilemma for the neurointerventionist managing a person diagnosed with an arteriovenous malformation (AVM) of the brain is how the risks and benefits of treatment compare with the individual's predicted, untreated clinical course. In general, this question is best answered by large, randomized, controlled trials comparing intervention(s) with each other, or with conservative management, when there is clinical equipoise or individual uncertainty. The rarity and heterogeneity of AVMs themselves may explain, at least in part, why there are no randomized, controlled trials of their treatment [1]. In the absence of high-level evidence, it is only possible to indirectly compare the risks and benefits of treatment with the best available data on the prognosis of AVMs.

"The natural course of the disease is elusive because of an obstacle, which in present-day medicine amounts to a contradiction: the representative sample population must come

under close medical scrutiny and at the same time not have its natural course modified by treatment!" HB Locksley (1966) [2].

However, it has been inevitable that the pace of development and interest in endovascular, surgical, and radiation therapies would overtake the impetus to study the prognosis of AVMs. For the neurointerventionist wishing to indirectly compare prognosis with treatment, this leaves only two options, which are described in this article: to systematically review the available literature on prognosis [3], and to study prognosis anew.

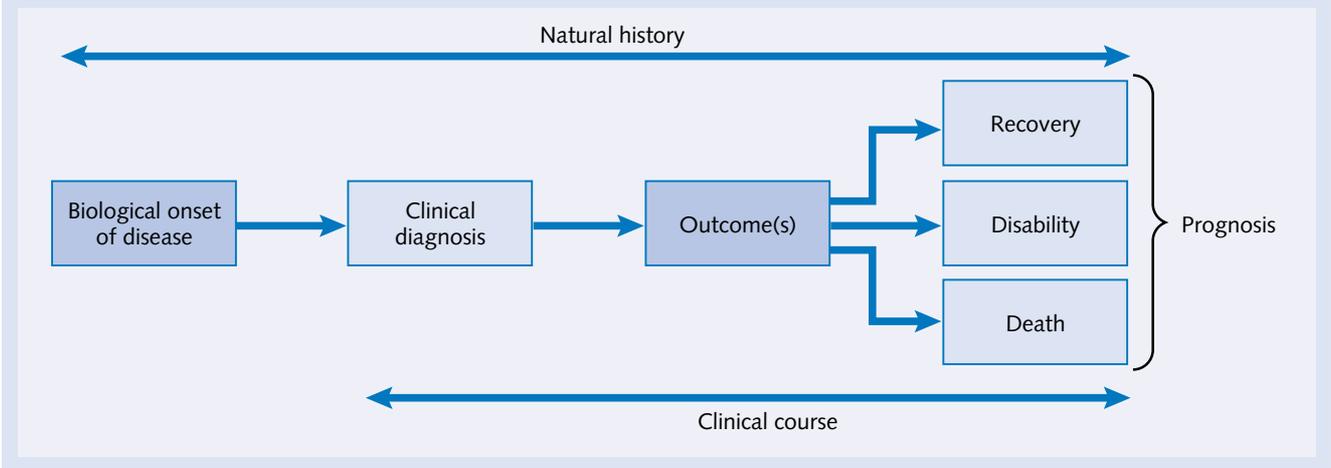
The difference between prognosis and natural history

From the outset, it is important to be clear about terminology, because 'prognosis' and 'natural history' are often confused. Whilst the former is quantifiable, complete information about the latter is practically inaccessible for people with AVMs. Distinguishing these concepts may seem pedantic, but it is essential for a clear understanding of the design, inherent assumptions, and results of many studies in the AVM literature (Fig. 1).

Natural history describes the time course of an AVM from its biological onset to a chosen outcome. Many

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Figure 1. Concepts of the time course of a disease.



retrospective studies have attempted to assess natural history assuming that AVMs are congenital (biological onset at birth), and that the at-risk period for any outcome has been the lifetime of each individual. These assumptions are insecure given the uncertainty about a congenital etiology of AVMs and the well-recognized evolution of angioarchitecture over time (such as spontaneous appearance and regression) [4].

More tangible, quantifiable, accurate, and useful concepts are the clinical course and prognosis of AVMs. Clinicians observe the clinical course of their patients, each of whom has a prognosis for particular outcomes governed by their own unique set of risk factors. The clinical course refers to a subset of the natural history from the time of diagnosis, while prognosis refers to the relative probabilities of the different outcomes of the clinical course at any given time [5].

A systematic search of the literature

To find studies of AVM prognosis, an exhaustive search of the medical literature was performed. Using a 14-line electronic search strategy with 94% sensitivity, a search was made for any publication on AVMs in:

- Medline from 1966 to February 2001 inclusive
- Embase from 1980 to February 2001 inclusive
- Cochrane Library 2001, Issue 1.

Publications predating 1966, and others missed by the search, were found by scanning the reference lists of retrieved articles, whilst other articles published between February 2001 and the time of writing (August 2001) were detected by surveillance of paper and electronic journals.

Of more than 8000 references detected by this search strategy, 2500 were found to be relevant to any aspect of AVMs. More important than the volume of the literature, is the quality of new and existing studies of AVM prognosis, because a high proportion of

prognostic studies in all areas of medicine are found to be methodologically poor [6]. Therefore, those studies amongst the 2500 citations that appeared to focus on prognosis were critically appraised.

What are the important features of a good study of AVM prognosis?

Existing guides for the assessment [5,7] and reporting [8] of articles on prognosis provide common-sense appraisal criteria (Table 1), and a widely-accepted evidence grading system (Table 2). By being moderately puritanical, yet pragmatic, these criteria ensured selection of studies only minimally affected by bias and confounding.

Formulate clear diagnostic criteria and definitions

Adequate radiological or pathological investigation should have been used to reliably diagnose an AVM of the brain according to a clear, explicit definition, so that the study sample has not been contaminated by dural AVMs or other types of intracranial vascular malformation.

Collect data prospectively

Ideally, studies of prognosis should be performed prospectively in longitudinal cohort studies: data are collected around the time at which they occur, starting at an early and uniform point in each patient's clinical course (inception) before any form of treatment. The most meaningful and practical inception point to choose is the time of the clinical presentation that led to the first-ever AVM diagnosis, which is when an estimate of prognosis would be most useful to patient and clinician alike. Choosing the first-ever symptom as the inception point usually involves retrospective (and so, inaccurate) data collection, whilst choosing the first presentation to a particular hospital is not uniform because it could occur at any time after the onset of symptoms. Retrospective evaluation of an accumulated case series,

Table 1. The ideal study of arteriovenous malformation prognosis.

- Diagnostic certainty at baseline (i.e. adequate investigation and a clear definition)
- Inception cohort
- Prospective data collection
- Population-based sample
- Sample size ≥ 100
- Objective, predefined outcome events, and validated measures of functional status
- Assessment of outcome blinded to baseline factors of interest
- Stratification of outcome by differences in treatment
- Follow-up $\geq 80\%$ complete
- ≥ 5 -year follow-up
- A 5-year survival rate and an actuarial analysis of the chosen outcomes

Table 2. Grades of recommendation and levels of evidence for studies of prognosis.

Grade of recommendation	Level of evidence	Type of study
A	1a	Systematic review with homogeneity of inception cohort studies; validated in different populations
	1b	Individual inception cohort study with $\geq 80\%$ follow-up; validated in a single population
	1c	All or none case series
B	2a	Systematic review (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs
	2b	Retrospective cohort study or follow-up of untreated control patients in an RCT
	2c	Outcomes research
	3a	Not applicable to studies of prognosis
	3b	Not applicable to studies of prognosis
C	4	Cases series, and poor quality prognostic cohort studies
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

RCT: randomized controlled trial.

(Adapted from the Oxford Centre for Evidence-based Medicine, May 2001, <http://cebim.jr2.ox.ac.uk/>)

as a survival cohort, usually omits people who died early, underestimates morbidity (especially outcomes occurring outside hospital), and risks gathering incomplete data on risk factors and follow-up.

Sample a population

Despite their provision of excellent clinical care, hospital-based studies are likely to be unrepresentative of the general population, particularly at specialized centers that are geographically or financially inaccessible to certain people, which may attract 'problem' cases for particular treatments, and may miss people diagnosed at smaller hospitals. Retrospective, hospital-based data acquisition will not account for early community mortality, making prognosis appear better than it actually is; conversely, people with a bad, non-fatal outcome, such as hemorrhage, constitute a larger proportion of hospital-based series, which may make prognosis appear worse than it actually is. Moreover, studies at specialist AVM centers are

dissimilar from each other, and this sort of sampling bias affects prognostic subgroups unequally [9].

Bigger is better

In general, the sample size criterion for this systematic review has been set arbitrarily at a minimum of 100 people, to maximize the precision of study results, and to increase the power to detect large (let alone small) effects. Moreover, because outcome events for AVMs are relatively infrequent, a large sample size is even more important. Because the number of outcome events is the main determinant of the power of a study of prognosis, it is really a combination of the sample size and the duration of follow-up that governs the utility of any individual study.

Long, complete follow-up

Follow-up should be prospective and as complete ($\geq 80\%$) as possible, starting at the inception point in all cases. Incomplete follow-up jeopardizes study results,

as the reasons for it are often linked to poor prognostic outcomes, thereby making prognosis appear more benign. Follow-up needs to be lengthy, especially because the average interval between hemorrhages from AVMs may be anything up to 8 years [10,11].

Important outcomes

The most important adverse outcomes of AVMs are death and morbidity (hemorrhage, epilepsy, and neurological deficit). These should be measured in an explicit, objective fashion (e.g. radiological confirmation of hemorrhage) and at defined time-points (such as 5-year survival) to enable their comparison, and meta-analyses of studies. A researcher's assessment of outcome should be blind to a patient's risk-factor profile, to avoid any over-interpretation of investigations according to the researcher's preconceptions.

Statistical essentials

Although an analysis of prognostic outcome as an annual percentage, averaged over the period of the study, has the virtues of simplicity and ease of comparison across studies, it obscures variation between patient subgroups and variation over time. Performing an actuarial analysis (e.g. time to death) and plotting a survival curve, provides more enlightening information about the pattern over time, accounts for variable lengths of follow-up, and still provides a percentage risk at any time point.

Studies of the average clinical course for people with AVMs can be used to identify factors that may help predict the prognosis of a particular event for a specific individual. The evaluation of prognostic factors (including differences in treatment) should include not only their statistical significance, but also their clinical significance in terms of an odds ratio or relative risk, with 95% confidence intervals (CIs), and, if possible, a multivariate analysis.

Disentangling true determinants of prognosis from those merely associated with particular outcomes in a univariate analysis is difficult. Insights into clinically useful predictors of outcome, which may be either associated with particular outcomes or actual determinants of them, can be gleaned from a Cox proportional hazards regression model by adjusting for extraneous factors. These models are not accurate unless there are adequate numbers of people and outcome events per variable studied [5,12], nor are they generalizable unless their robustness has been externally validated in other AVM populations.

What is known about the prognosis for people with AVMs?

Sadly, these ideals have been met by very few of the existing observational cohort studies, leading to

varying degrees of bias. There have been several common failings:

- Clear definitions and diagnostic criteria are usually lacking, especially in the earlier literature.
- There has often been unavoidable selection bias at tertiary referral centers.
- Retrospective survival cohorts far outweigh studies with a prospective design, mainly because large amounts of data are available immediately for analysis, but the data are, by their nature, incomplete and inaccurate.
- The inception point has been unclear in many studies.
- Scarcely any studies have achieved more than 10 years of follow-up.
- The assessment of outcome has never been blinded to features of the people under study that are hypothesized to determine prognosis, and has often lacked standardization, with authors frequently adopting their own arbitrary outcome scales.
- Outcome has usually been assessed at varying time intervals, often without actuarial analysis, and without stratification by differences in treatment after inception, making comparison of different cohorts virtually impossible.

Studies of factors associated with the mode of presentation

One of the most fundamental errors made in an effort to gain an understanding of why prognosis differs between AVMs has been to retrospectively correlate the angioarchitecture described on the diagnostic angiogram after presentation with how a patient first presented. Angioarchitecture retrospectively associated with a hemorrhagic presentation does not necessarily predict future hemorrhage. These factors are merely associated with a prior mode of presentation and not necessarily causative of a future occurrence of the same event. Factors associated with the first occurrence of hemorrhage or epilepsy could be very different from those conferring a higher risk of recurrence, which is what is important to patients, and to any discussion of treatment.

There is not only speculation about how repeated modification of angioarchitecture through life eventually determines clinical presentation, but also some evidence that the angioarchitecture of an AVM changes in both the short- and long-term after vessel rupture [13–15]. The mere occurrence of hemorrhage may distort angioarchitecture so that any factors found in association with a prior hemorrhage could be a consequence of the initial hemorrhage, rather than a cause of future hemorrhage. Moreover, a particular feature of AVMs may be so prevalent in those with

Table 3. Angioarchitectural features retrospectively associated with a prior hemorrhagic presentation (these are merely putative risk factors, which should be tested in proper studies of prognosis).

Factor	Statistically significant ($p < 0.05$) association found	No association found
Deep venous drainage	Duong et al. 1998 [39] Langer et al. 1998 [41] Nataf et al. 1998 [37] Turjman et al. 1995 [42] Kader et al. 1994 [43] Miyasaka et al. 1992 [44]	
Single draining vein	Shi et al. 1993 [45] Miyasaka et al. 1992 [44] Albert et al. 1990 [46]	
Venous stenosis	Nataf et al. 1998 [37] Mansmann et al. 2000 [40] Miyasaka et al. 1992 [44]	
High feeding mean arterial pressure	Duong et al. 1998 [39]	
Intranidal aneurysm	Redekop et al. 1998 [47] Nataf et al. 1998 [37] Turjman et al. 1995 [42]	Meisel et al. 2000 [34] Duong et al. 1998 [39] Langer et al. 1998 [41] Mansmann et al. 2000 [40]
Small nidus size	Langer et al. 1998 [41] Kader et al. 1994 [43] Shi et al. 1993 [45] Albert et al. 1990 [46] Crawford et al. 1986 [20] Mansmann et al. 2000 [40]	Duong et al. 1998 [39]
Deep location	Mansmann et al. 2000 [40] Turjman et al. 1995 [42]	Duong et al. 1998 [39] Langer et al. 1998 [41]
Venous reflux	Nataf et al. 1998 [37]	

one type of presentation that it is useless for predicting future events, if hospital-based series of mainly ruptured AVMs are studied. For example, a study of the first occurrence of seizures found presentation with hemorrhage to be a predictive factor, yet 86% of the cohort had presented in this fashion [16].

Table 3 summarizes the findings of retrospective association studies involving at least 100 people, and examining associations with a hemorrhagic presentation. Studies relying on retrospective inference are only useful for identifying putative factors that might predict the occurrence, or recurrence, of a particular symptom, and which should be tested in true studies of prognosis.

True studies of clinical course/prognosis

Table 4 reflects how the quality of the true studies of AVM prognosis has varied, when compared with the systematic review criteria used here (Table 1), and when rated against the Oxford Centre for Evidence-Based Medicine's levels of evidence (Table 2). A vast number of studies detected by the literature search of level 4 and grade C evidence have been omitted as they fulfilled very few of the systematic review criteria.

The extent to which some studies met particular criteria has been either unclear or unavailable from the methods sections; for example, whether diagnostic

certainty was established at baseline, and whether outcome was stratified by differences in treatment. Furthermore, in the absence of more detailed data on, for example, how inception was chosen, whether follow-up was truly prospective, and whether the study was truly population-based, the interpretation of whether certain criteria were met may be more lenient if reviewed by others than it was here.

What is the prognosis for death?

There are no long-term population-based data on the risk of death due to an AVM with epidemiological methods of analysis, so the AVM 'mortality rate' (number of deaths per 1000 per unit time) is unknown. Studies only yield information about the proportion of people with an AVM who die at a particular time (the 'case fatality').

In the only truly population-based study to date, based in Olmsted County, MN, USA [17], the 30-day case fatality following a first intracranial hemorrhage from an AVM was 18% (95% CI 4–43%). However, in hospital-based survival cohorts, case fatality following hemorrhage has ranged from 0% over approximately 1 year in recent studies [10,18], to 17% over at least 1 year following an initial or recurrent hemorrhage in another [19], presumably because of selection bias.

Table 4. The extent to which the best studies of prognosis have met the selection criteria for this review.

	Systematic review selection criteria (Table 1)											OCEBM ratings (Table 2)	
	Diagnostic certainty	Inception cohort	Purely prospective	Population-based	Sample size ≥100	Objective outcomes	Blinded assessment of outcome	Stratified by differences in treatment	Follow-up ≥80%	≥5-year follow-up	Actuarial analysis	Level of evidence	Grade of recommendation
Mast et al. 1997 [18]	?	●	●	○	●	●	○	NA	●	○	●	1b	A
Osipov et al. 1997 [25]	?	●	●	○	○	●	○	○	●	○	○	1b	A
Brown Jr. et al. 1996 [17]	●	●	○	●	○	●	○	○	●	○	○	1b	A
Porter et al. 1998 [19]	?	●	●	○	●	●	○	?	●	○	○	1b	A
Brown Jr. et al. 1988 [14]	●	●	○	○	●	●	○	●	●	●	●	2b	B
Brown Jr. et al. 1990 [21]	●	●	○	○	○	●	○	●	●	●	●	2b	B
Crawford et al. 1986 [16,20]	?	●	○	○	●	●	○	●	○	●	●	2b	B
Ondra et al. 1990 [11]	●	?	○	○	●	●	○	●	●	●	○	2b	B
Hartmann et al. 1998 [10]	?	●	●	○	●	●	○	NA	●	○	NA	2c	B
Graf et al. 1983 [22]	●	●	○	○	●	●	○	?	?	●	●	2b	B
Forster et al. 1993 [48]	?	○	○	○	●	●	○	●	?	NA	○	4	C
Horton et al. 1990 [49]	●	NA	○	○	●	●	○	●	●	NA	○	4	C

●: criterion was met; ○: criterion was not met; ?: unknown; NA: not applicable; OCEBM: Oxford Centre for Evidence-based Medicine.

Interestingly, there does not seem to be a long-term difference in survival between people presenting with or without hemorrhage. Long-term, crude, annual case fatality rates are 1–1.5% per annum, with no factors apparently conferring a greater risk of death, although 50–70% of all deaths are due to hemorrhage [11,20].

What is the prognosis for intracranial hemorrhage?

One important distinction that has not always been clear is between the risk of first-ever hemorrhage occurrence, and the risk of hemorrhage recurrence. The risk factors for first-ever hemorrhage occurrence might be different from the risk factors for recurrence, thereby altering the approach to people who have an unruptured AVM at presentation, and those who are first diagnosed after a hemorrhage.

Although the crude annual rate of intracranial hemorrhage from AVMs is widely quoted to be approximately 2% in the existing hospital-based studies of prognosis, this must mask important variations in the behavior of different subgroups.

First hemorrhage occurrence. From the few studies of the clinical course of unruptured AVMs, the crude annual risk of a first-ever hemorrhage appears to be approximately 2% [14,18]. Whilst one study found no factors that predicted the first occurrence of hemorrhage [14], a substudy of the same patient group with complete angiographic examinations at baseline

found the co-existence of aneurysms (96% were on an arterial feeder) conferred a higher annual rate of hemorrhage for people with unruptured AVMs [21].

Hemorrhage recurrence. People who have already experienced hemorrhage are thought to carry a risk of recurrence greater than the 2% annual risk of first-ever occurrence, possibly up to 18% in the first year [18]. Some studies have found the risk of rupture after a hemorrhagic presentation to be greater than after any other type of presentation [18,20], whilst other methodologically less-sound studies have not [11,22]. Studies have found other features to predict recurrence of hemorrhage, including exclusively deep venous drainage and male gender [18], increasing age [20], and ‘small’ (<3 cm nidus diameter) size [22], although the studies are not all in agreement. None of these factors predictive of recurrence were identified by a celebrated long-term prospective study that found a 4% crude annual risk of hemorrhage [11]. This Finnish study was, however, flawed in some respects:

- It enrolled people before the modern era of neuro-imaging, making the diagnosis of intracranial hemorrhage potentially inaccurate.
- By being based at a specialist center, although serving most of its country, it was not entirely population-based.

- It calculated bleeding rates in 5-year intervals, without an actuarial analysis, potentially masking a short-term higher risk of recurrence.

Hemorrhage prediction models. In an effort to simplify the issue of risk prediction, a general 2–4% annual risk of hemorrhage has been used to determine the likelihood of survival free of hemorrhage using the multiplicative law of probability (A) and a recent, even more simplistic model (B):

- A. Risk of hemorrhage = $1 - (\text{risk of no hemorrhage})^x$
where x = expected years of remaining life [23]
- B. Lifetime risk of hemorrhage = $105 - \text{patient's age in years}$ [24].

However, these calculations make two unlikely assumptions that:

- the risks are equally applicable to different people
- there is a uniform risk of hemorrhage (either occurrence or recurrence) over time.

In the current absence of consistent risk factors for the occurrence and recurrence of hemorrhage from multivariate analyses in methodologically sound studies, the ability to generate meaningful prognostic models is poor.

What is the prognosis for epilepsy?

The risk of developing epilepsy from AVMs, and the likelihood of it remitting, have been given little attention, especially by studies stating that seizure disorders, although common, were too difficult to quantify [11]. From the data that are available, it appears that people with AVMs carry an annual risk of developing *de novo* seizures of 1%, and they may be at a greater risk following presentation with hemorrhage, or if they are older [16]. However, when they do occur, at least three quarters of seizures come under good control on first-line anticonvulsants [25].

Despite the large number of studies of the clinical course of AVMs, very few have met rudimentary standards for an ideal design, and fewer still provide consistent results. The studies that are consistent tend to be of lower quality, and the variation in AVM prognosis that is familiar to clinicians is only detected by more recent, higher quality studies.

Challenges for ongoing and future studies of prognosis

The quality of the existing studies, and the limited data available — especially for long-term outcomes — justify a renewed interest in AVM prognosis. Existing knowledge needs further exploration, especially in the long-term, and external validation (confirmation) in

other populations. It is, of course, difficult to assess the clinical course of AVMs because of their heterogeneity and because they tend to be treated when discovered, but these challenges can be accounted for with good study design.

Large, prospective, population-based studies are needed

Prospective population-based studies of the clinical course of large, unbiased samples of people with AVMs will be the only way to resolve the existing uncertainties. These studies will elucidate the mortality rate, case fatality, and prognosis for first, or recurrent, hemorrhage or seizures from AVMs. Multicenter studies, possibly with international collaboration, will be required to collect sufficient people with untreated AVMs to establish their clinical course. Since 1999, such studies have been underway in Scotland [26] (The Scottish Intracranial Vascular Malformation Study, <http://www.dcn.ed.ac.uk/ivm/>, accessed on 13 August 2001) and New York, USA (The New York Islands Arteriovenous Malformation Study, <http://cpmcnet.columbia.edu/dept/avm>, accessed on 13 August 2001).

Whilst people with AVMs may be subject to treatment selection bias, current variation in practice — reflecting uncertainty about whether and how to treat AVMs — will mean that a representative sample is eventually collected. In view of this tendency to treat AVMs once they are discovered, the assessment of outcome should be stratified according to any therapeutic intervention during follow-up. Factoring treatment into a contemporary analysis of prognosis is the only way to evaluate current therapies, pending randomized controlled trials.

Consistent definitions of clinical and angioarchitectural risk factors

For current and future studies to be comparable, and potentially combinable in a meta-analysis, clear definitions of the variables used to assess prognosis must be used. There are undoubtedly differences between research groups and individual specialists in their interpretation of clinical events and angioarchitecture, both of which are used to guide estimation of prognosis. A study of the observer variation amongst interventional neuroradiology experts in interpreting AVM angioarchitecture is underway in the UK. This will help identify areas where clearer definitions are needed. A multidisciplinary American writing group has made a helpful initial contribution [27]. Sadly, this paper lacked definitions of the important clinical events affecting people with AVMs, guidance on how to allow for uncertainty about whether an event is attributable to an AVM or not, and

Figure 2, Intra-arterial digital subtraction angiogram demonstrating a posteriorly diffuse nidus (arrow). How would the size of this nidus be measured?

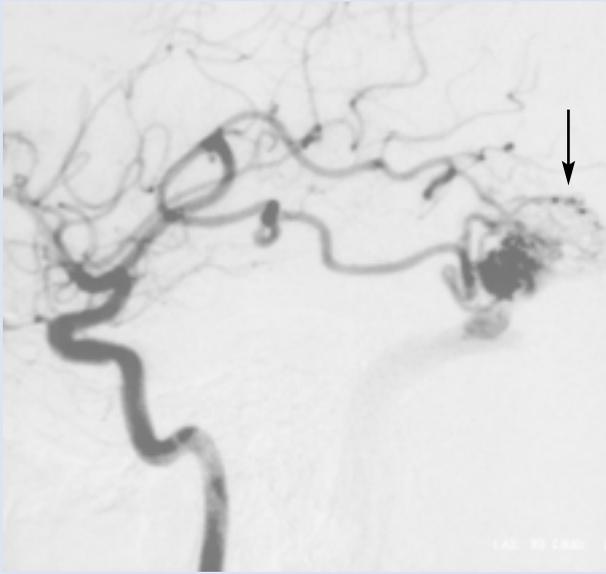


Figure 3. Intra-arterial digital subtraction angiogram of a left frontal corticoventricular arteriovenous malformation showing an intranidal aneurysm (arrow).

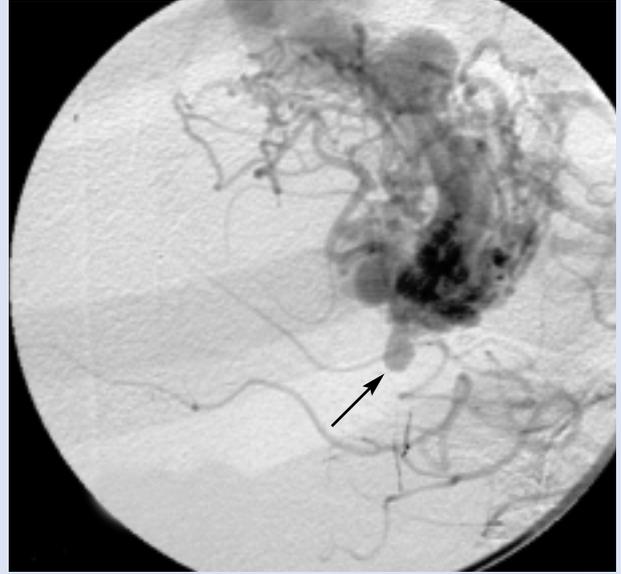
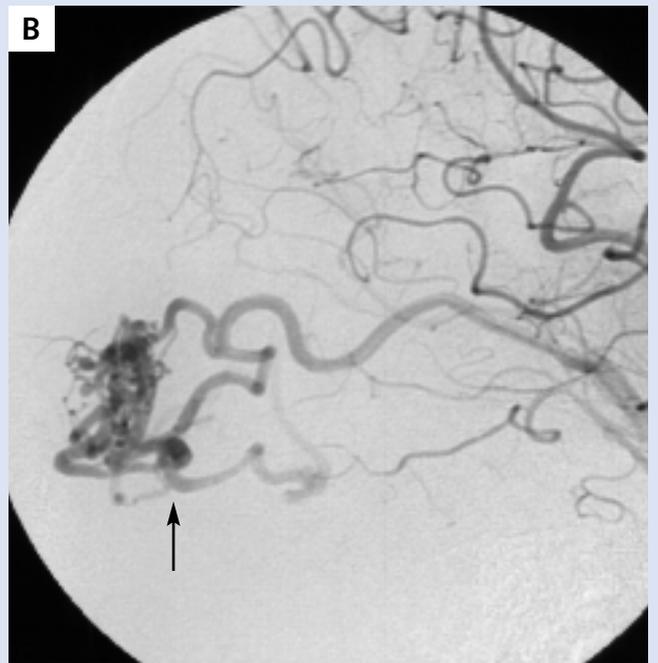
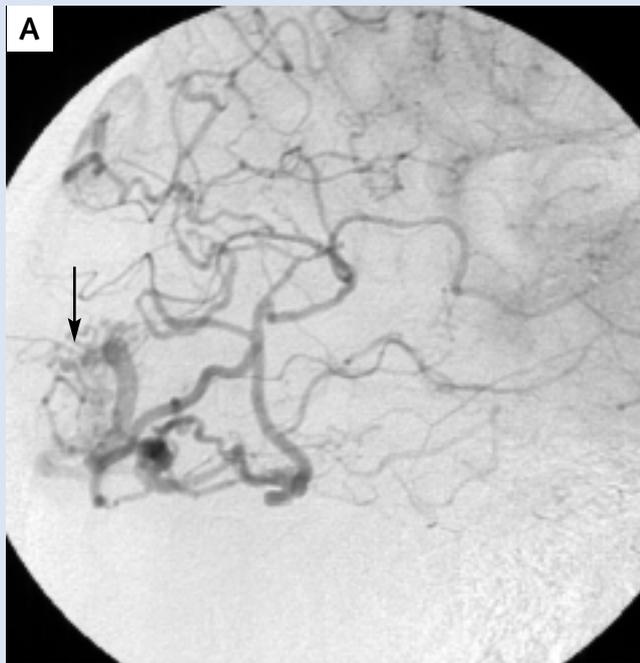


Figure 4. Intra-arterial digital subtraction angiograms showing (A) angiogenesis and (B) *en passage* arterial supply (arrows). Do you agree?



how to regard the timing of these events during a patient's clinical course.

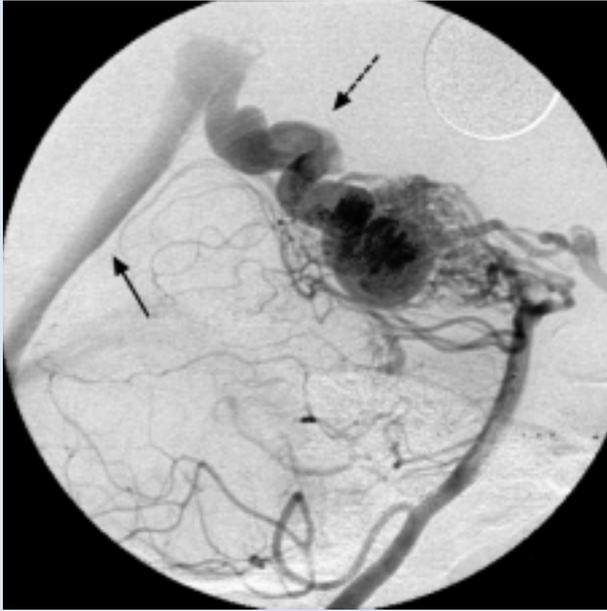
This review ends with some important aspects of angioarchitecture that should be studied as potential prognostic factors (Table 3), but where consensus amongst neurointerventionists is needed. An extra challenge, posed by the analysis of such data, is that some people will not undergo catheter angiography, and this may well be linked to perceptions about their prognosis, thereby biasing subgroups depending on

angiographic data in an analysis of prognosis. A reductionist approach may be needed, or at least a method of gleaned information about some of the features from computed tomography and magnetic resonance imaging (MRI), as well as catheter angiography.

Nidus size measurement

There are a variety of factors that must be considered in measuring a nidus:

Figure 5. A lateral intra-arterial digital subtraction angiogram of the vertebrobasilar system which shows an arteriovenous malformation in the midbrain and right thalamus, with deep venous drainage to the straight sinus (solid arrow) and venous ectasia (dashed arrow).



- If the nidus of an AVM is regarded as the area towards which multiple feeding arteries converge, and from which enlarged veins drain [28], then what are its limits (Fig. 2)?
- Should maximum linear dimensions be chosen to measure the nidus and, if so, which method should be used to correct for angiographic magnification [29], or should MRI be the reference standard [30]?
- Because AVMs are often supplied by more than one vascular territory, should catheter angiograms be used to measure size at all?
- Should assumptions about shape be made in calculating its volume, or should more sophisticated methods be used [31,32]?

Aneurysms

Different classification systems have been proposed for aneurysms (Fig. 3) associated with AVMs, and they evolve as new concepts, such as pseudoaneurysms associated with hemorrhage, emerge. Some research groups stipulate the number of orthogonal views an aneurysm should be present on, others require the aneurysm to be at least twice the width of the parent vessel, and others have sometimes classified large infundibula (>3 mm) as aneurysms [33,34].

Arterial anatomy

Variations in arterial tortuosity/ectasia are often subjectively graded and may involve comparison with

the same contralateral vessel or the surrounding ipsilateral vessels. Arterial angiopathy (dilatation and/or stenosis) is again subjectively graded, but may instead be called moya-moya-type change, defined as collateral recruitment with distal feeding artery angiopathy [27]. The terms angiogenesis, angiomatous change, and collateral supply, have generated some confusion (Fig. 4). It may be helpful to distinguish sprouting (i.e. new vessel formation) from non-sprouting (i.e. collateral supply) angiogenesis. Collaterals represent arterial supply to the AVM and/or brain distal to the AVM from dural or pial/leptomeningeal vessels supplying adjacent vascular territories or between pedicles within the same vascular territory, yet this is partly encompassed by some definitions of angiogenesis [35].

Venous anatomy

Lastly, what is the most meaningful way to think of the venous drainage from an AVM? Should the number of separate draining veins be counted reaching a sinus [27], or leaving the nidus? Are all groups in agreement about what 'deep venous' drainage is (Fig. 5), usually classified according to the Spetzler–Martin grading system [36]? In terms of the characteristics of these draining veins, should venous ectasia (dilatation) be a qualitative feature in relation to surrounding vessels (Fig. 5), or quantified as a >two-fold calibre change [27], and is it a segmental or continuous dilatation [37]? A related feature, the venous varix, best regarded as an aneurysmal dilatation/pouch, is not recorded by some groups [27], and others merely regard varices as markedly ectatic veins [38]. Similar ambiguity has surrounded the estimation of venous stenosis. Whilst this is clearly the narrowing of a draining vein, must it occur in two angiographic views [27]? In measuring stenosis, is an absolute percentage value needed (and if so, in relation to what?), such as <50% of the expected vein diameter [35,37,39], or should stenosis be a qualitative, rather than quantitative, feature [40]?

Summary and conclusion

Studies of prognosis in most areas of medicine are notorious for being methodologically flawed. This systematic review reveals that the literature concerning the prognosis for adults with AVMs of the brain is no exception. It is difficult to assess the prognosis of AVMs because of their rarity, heterogeneity, and because they are often treated when discovered. However, some generalizations can be made:

- Long-term, crude, annual case fatality is 1–1.5%.
- Crude annual risk of first occurrence of hemorrhage from an unruptured AVM is approximately 2%.

- Risk of recurrent hemorrhage may be as high as 18% in the first year, with uncertainty about the risk thereafter.
- Annual risk of *de novo* seizures is 1%.

Consistent risk factors for hemorrhage have not been observed, but presentation with hemorrhage, the existence of nidus/feeding artery aneurysms, and deep venous drainage, probably confer a higher risk.

There is a pressing need for multicenter, prospective, population-based studies of AVM prognosis, and standardized definitions of both clinical and angioarchitectural features.

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