A systematic review of the frequency and prognosis of arteriovenous malformations of the brain in adults

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Summary
By systematically reviewing the literature, we have found that there is very little information about the frequency and clinical course of arteriovenous malformations (AVMs) of the brain in adults because the methods of most studies have been flawed, and AVMs tend to be treated once they are discovered. The incidence of AVMs is ~1 per 100 000 per year in unselected populations, and the point prevalence in adults is ~18 per 100 000. AVMs account for between 1 and 2% of all strokes, 3% of strokes in young adults, 9% of subarachnoid haemorrhages and, of all primary intracerebral haemorrhages, they are responsible for 4% overall, but for as much as one-third in young adults. AVMs are far less common causes of first presentations with unprovoked seizures (1%), and of people presenting with headaches in the absence of neurological signs (0.3%). At the time of detection, at least 15% of people affected by AVMs are asymptomatic, about one-fifth present with seizures and for approximately two-thirds of them the dominant mode of presentation is with intracranial haemorrhage. The limited high quality data available on prognosis suggest that long-term crude annual case fatality is 1–1.5%, the crude annual risk of first occurrence of haemorrhage from an unruptured AVM is ~2%, but the risk of recurrent haemorrhage may be as high as 18% in the first year, with uncertainty about the risk thereafter. For untreated AVMs, the annual risk of developing de novo seizures is 1%. There is a pressing need for large, prospective studies of the frequency and clinical course of AVMs in well-defined, stable populations, taking account of their prognostic heterogeneity.

Keywords: intracranial arteriovenous malformations; intracranial aneurysm; diagnostic imaging; epidemiologic measurements; prognosis

Abbreviations: 95% CI = 95% confidence interval; AOVM = angiographically occult vascular malformation; AVF = arteriovenous fistula; AVM = arteriovenous malformation; FMAP = feeding mean arterial pressure; HHT = hereditary haemorrhagic telangiectasia; IADSA = intra-arterial digital subtraction angiography; IVM = intracranial vascular malformation; PICH = primary intracerebral haemorrhage; SAH = subarachnoid haemorrhage

Introduction
Since their first clear description over a century ago (Steinheil, 1895), arteriovenous malformations (AVMs) of the brain have been increasingly recognized as an important cause of death and long-term morbidity, mostly due to intracranial haemorrhage and epilepsy. Technological advances in imaging the vasculature of the brain and the widening availability of CT, MRI and intra-arterial digital subtraction angiography (IADSA) have augmented the rate of detection of AVMs (Brown et al., 1996a), to the extent that they now pose a regular management problem. There is a growing interest in the frequency and clinical course of AVMs, although the pace of development of endovascular, surgical and radiation therapies seems to have overtaken the impetus to study their clinical course (Sellar, 2000). The prognosis

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for any individual remains uncertain, as do the risks and benefits of the available treatments, leading to variation in practice and disagreement about the need for randomized trials.

There are no systematic reviews of existing knowledge about the frequency and clinical course of AVMs, although there are many narrative reviews of the medical literature concerning AVMs (Arteriovenous Malformation Study Group, 1999), AVMs affecting the dura (Malek et al., 1998), arteriovenous fistulae (AVFs) of the vein of Galen and AVMs affecting children (Lasjaunias et al., 1995), some of which offer new insights (Stapf and Mohr, 2000). For this reason, we have gathered all the available research on AVMs of the brain in adults using thorough search methods, critically evaluated the literature against objective methodological criteria and summarized the best studies according to modern standards in observational epidemiology (Stroup et al., 2000).

We have tried to straddle the objective statistical technique of meta-analysis and the subjective art of a traditional narrative review (Slavin, 1995; Centre for Reviews and Dissemination, 1996). Where possible, scientific evidence has been given precedence over anecdotal clinical experience.

**Critical appraisal of the literature**

Using strict methodological criteria, we have selected the highest quality studies from an exhaustive systematic electronic and hand search of the medical literature. We looked for any publication about AVMs in Medline and Embase from 1966 and 1980, respectively, to the end of February 2001, and in the Cochrane Library 2001, Issue 1, using a 14-line search strategy. This strategy had a 94% sensitivity when evaluated against a hand search of two journals in which the largest number of studies of AVMs have been published (Journal of Neurosurgery and American Journal of Neuroradiology). Publications antedating 1966, and others missed by the search, were sought by scanning the bibliographies of retrieved articles, and by surveillance of paper and electronic journals. More than 9000 publications were found by this combination of search methods, of which ~2500 were germane to the scope of this review. The titles and available abstracts of the pertinent papers were scrutinized, and those of direct relevance were read in full. We chose to cite only those studies whose results were least likely to be affected by systematic bias, confounding and chance in their design and conduct.

The criteria for including studies in our analysis are specified in each section of the review. Generally, we have sought unbiased studies of high internal and external validity involving large, unselected, prospective, population-based cohorts. Following our objective assessment of the quality of the published literature on AVMs, where appropriate we have summarized comparable data from the independent studies of best quality. We have been cautious not to draw firm conclusions from a small number of inconsistent, observational studies of average quality and poor external validity, whose heterogeneous biases could be amplified if we chose to combine their results in a pooled estimate (Egger et al., 1998).

**Background**

Clear diagnostic criteria for AVMs and definitions of the complex variations in their vascular anatomy (angioarchitecture) are essential to define entry criteria to research studies, and correctly apply information gleaned from research to future patients in clinical practice. The role that brain imaging plays in the diagnosis of AVMs, and the scrutiny that angioarchitecture is subject to in studies of prognosis, necessitate a brief discussion of their classification and radiological features.

**How should AVMs be classified?**

The contemporary integrated classification shown in Table 1 best reflects the main morphological groupings of intracranial vascular malformations (IVMs), and fundamentally distinguishes ‘malformations’ (which have normal endothelial cell turnover and, if they grow at all, do so by hypertrophy) from ‘haemangiomas’, which grow by endothelial hyperplasia (Mulliken and Glowacki, 1982). An array of synonyms has been used to describe the arteriovenous shunting malformations reflecting developments in understanding their nature over time, including angioma arteriale racemosum (Virchow, 1863), varix aneurysmaticus (Steinheil, 1895), arteriovenous angiomas and anomalies. Some unity of terminology is required, so the subject of this review has been termed an ‘arteriovenous malformation of the brain’. The abnormality is a ‘malformation’ (it is not neoplastic, and therefore not an ‘angioma’), the constituent vessels may be anywhere on the morphological spectrum between arteries and veins (the safest generalization being ‘arteriovenous’), and their location almost anywhere within the brain parenchyma makes ‘pial’

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**Table 1 An integrated classification scheme for vascular malformations of the brain**

<table>
<thead>
<tr>
<th>Category</th>
<th>Specifics</th>
</tr>
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<tbody>
<tr>
<td>Benign proliferating vascular anomalies</td>
<td>Haemangioma</td>
</tr>
<tr>
<td>Non-proliferating vascular anomalies</td>
<td>Capillary malformation (telangiectasis)</td>
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<tr>
<td></td>
<td>Venous malformation (developmental venous anomaly)</td>
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<td></td>
<td>Cavernous malformation (cavernoma)</td>
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<tr>
<td>Arteriovenous shunting malformations</td>
<td>Brain arteriovenous malformation</td>
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<tr>
<td></td>
<td>Brain arteriovenous fistula</td>
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<tr>
<td></td>
<td>Dural arteriovenous malformation</td>
</tr>
<tr>
<td></td>
<td>Vein of Galen arteriovenous fistula</td>
</tr>
<tr>
<td>Mixed malformations</td>
<td></td>
</tr>
</tbody>
</table>

From Chaloupka and Huddle (Chaloupka and Huddle, 1998) (with some rewording and truncation of their original terms).
Multiple feeding arteries converge, and from which enlarged calibre in which arteriovenous shunting occurs in a central inappropriate terms. AVMs are tangle anastomoses of blood vessels of varying calibre in which arteriovenous shunting occurs in a central nidus (Latin nidus, nest), which is the area towards which multiple feeding arteries converge, and from which enlarged veins drain (Doppman, 1971). AVFs are distinguished from AVMs by the presence of a direct, high flow fistula between a single artery and vein. AVMs and AVFs may be located within the brain parenchyma or dura mater; the great cerebral vein of Galen may be involved in mural or choroidal AVFs, which almost exclusively affect neonates, or secondarily involved by a high flow AVM of the brain draining into the vessel (Lasjaunias et al., 1996). Such a classification based on morphology, and location of the nidus or fistula, is less arbitrary than one based on the sources of afferent and efferent vessels, which are endlessly diverse (Morcos and Spetzler, 1995). Angiographic and pathological studies of the angioarchitecture and haemodynamics of arteriovenous shunting malformations have reinforced these simple morphological descriptions, but also illustrated the complexity of their anatomy (Houdart et al., 1993).

Overall, a clinically relevant classification (Table 1) that integrates knowledge about IVM morphology with our current understanding of aetiology, broad differences in prognosis and differences in response to treatment serves best to distinguish AVMs from the other IVMs. This distinction usually depends on careful and appropriate investigation using non-invasive and/or catheter imaging techniques. A brief appraisal of the sensitivities and specificities of these imaging techniques is pertinent to studies of the frequency of AVMs, whilst an understanding of the complexities of AVM angioarchitecture is required for the interpretation of studies of AVM prognosis.

**How useful are different imaging techniques for the detection of AVMs?**

AVMs have been recognized increasingly since the development of catheter angiography in the early 20th century (Moniz, 1927), and the wider availability, growing use and improved image resolution of CT since the 1970s and MRI since the 1980s have increased their detection further (Brown et al., 1996a). Despite this rise, how good are CT, MRI and IADSA at differentiating AVMs from normal brain, other pathologies and intracranial haemorrhage?

**Differentiating an AVM from normal brain and other pathologies**

The widespread availability and immediacy of CT pragmatically make it the first test an individual with an AVM might have had at their initial presentation. Unenhanced scans may only show an asymmetry in tissue density to suggest an AVM (Fig. 1), and smaller AVMs can be missed altogether. Enhanced CT is probably a more sensitive investigation, because it may reveal the dilated vasculature of an AVM (Fig. 1) with a serpiginous pattern of contrast enhancement (Kumar et al., 1984). On the other hand, the specificity of CT, either with or without enhancement, is affected by the occasional difficulty in distinguishing an AVM from a low-grade glioma, especially when the AVM is thrombosed (Wharen et al., 1982). The particular strengths of MRI lie in its evaluation of AVM nidus size (Noorbehesht et al., 1987) and its anatomical relationships (Figs 2 and 3). The specificity of both MRI and IADSA is affected by the occasional similarity of neoplasms to AVMs. Occasionally CT or MRI appearances suggest an IVM that is not demonstrated on complete IADSA at all. These ‘cryptic’ or ‘angiographically occult’ vascular malformations (AOVMs), when subjected to pathological examination, are morphologically heterogeneous, but cavernous malformations and AVMs are the main contributors (Lobato et al., 1988; Robinson et al., 1993; Tomlinson et al., 1994; Hallam and Russell, 1998).

There is, therefore, no single definitive investigation for AVMs, which means that existing evaluations of the diagnostic accuracy of these imaging modalities do not have a reference standard, but rely on pathological confirmation or direct comparisons of different techniques (Pott et al., 1992). Despite the recognition of these sources of error, there are no adequate studies (because they have been small, retrospective and radiologists were usually not blinded to clinical features) evaluating the sensitivity and specificity of MRI or IADSA against any reference standard for the detection of AVMs.

Important areas for future AVM research are surely the diagnostic sensitivities and specificities of the available imaging studies in various clinical situations, and any (as yet unquantified) inter- or intra-observer variability in their interpretation. The possible utility of other techniques such as transcranial Doppler ultrasonography (Mast et al., 1995a; Baumgartner et al., 1996), technological advances such as three-dimensional reconstruction (Aoki et al., 1998), and functional imaging (Leblanc et al., 1995; Turski et al., 1998), all need further investigation.

**Detecting an AVM underlying intracranial haemorrhage**

The investigation of primary intracerebral haemorrhage (PICH) with unenhanced CT has a sensitivity for identifying an underlying AVM of between 50 and 77% and a specificity of between 84 and 99%, when compared against a reference standard of IADSA, with or without pathological confirmation (Hayward and O’Reilly, 1976; Laissy et al., 1991; Halpin et al., 1994). However, some of these studies have been limited by being retrospective and unblinded, with selected patient groups, varying CT matrix sizes and inconsistent use
Arteriovenous malformations of the brain

Fig. 1 CT of the brain in the axial plane without (above) and with (below) intravenous contrast demonstrates an AVM in the right temporal lobe (arrows).

Fig. 2 Coronal, unenhanced, T1-weighted MRI demonstrates an AVM in the left parietal lobe (arrow).

of intravenous contrast. Although there are, as yet, no adequate studies of MRI as a diagnostic test in identifying an underlying cause for a PICH, it is a helpful investigation in the follow-up of PICH (Meyer and Gorey, 1998), especially in the context of recurrent PICH (Heier et al., 1986). The usefulness of IADSA in the investigation of PICH has been studied in terms of its diagnostic yield. Some of these studies have been retrospective and used the same series of patients (Toffol et al., 1986; Loes et al., 1987) but, even when prospective, others have been conducted on highly selected groups of patients (Zhu et al., 1997); therefore, unsurprisingly, the authors of these studies have drawn varying conclusions. On the basis of the available evidence, for the further investigation of a suspected AVM (or other underlying condition) as a cause of PICH demonstrated on CT, a minimum standard is IADSA in everyone apart from those over 45 years of age with pre-existing hypertension and haemorrhage in deep locations (Zhu et al., 1997). Whilst early IADSA reveals most AVMs, a normal study close to the onset of a PICH should be supplemented by delayed IADSA or MRI, although which should be used is debatable (Lemme-Plaghos et al., 1986; Sigal et al., 1990; Willinsky et al., 1993; Halpin et al., 1994). Of course, these algorithms may be superseded by the need for surgical intervention and their appropriateness may depend on the clinical condition and age of the patient. The investigation of subarachnoid haemorrhage (SAH) with CT and adequate IADSA is widely
accepted, but the value of repeat IADSA is questionable, and MRI might be helpful if an underlying AVM is strongly suspected, although this strategy has not been evaluated formally. A second IADSA tends to be recommended only if the patient suffers a recurrent haemorrhage, or if the initial examination was technically inadequate, affected by vasospasm or did not cover both carotid and vertebral arteries (Forster et al., 1978; von Holst et al., 1988; Gilbert et al., 1990; du Mesnil de Rochemont et al., 1997).

What are the important aspects of AVM angioarchitecture?
There is a growing literature on angioarchitecture (Houdart et al., 1993; Valavanis, 1996), haemodynamics (Kader and Young, 1996), and an interest in creating artificial models of AVMs to understand better their haemodynamic complexity (Gao et al., 1998), including unusual outcomes such as spontaneous regression without treatment (Nehls and Pittman, 1982). Whilst IADSA may only be necessary to establish diagnostic certainty in some cases, the interest in how angioarchitecture and haemodynamics might determine prognosis has made it a requisite, and often an entry criterion, for some studies of the clinical course of AVMs.

However, clear objective and consistent definitions of the variations in angioarchitecture are few, and experts disagree about their existence and prognostic value. Furthermore, the accuracy of detailed angioarchitectural information may depend not only on inter- and intra-observer variation, but also on the use of super-selective IADSA, which involves the coaxial catheterization of individual arterial branches with flow-guided or wire-guided microcatheters. By avoiding the superimposition of other arterial vessels, this technique may better determine the type of feeding artery and the detailed angioarchitecture of the nidus. In some radiologists’ hands, super-selective IADSA is used for measurement of arterial pressures if coupled to a pressure transducer, and also for functional localization by the injection of barbiturate (Viñuela et al., 1984).

The AVMs that are detected by CT, MRI and IADSA are perhaps unsurprisingly mostly supratentorial, appearing to be distributed in proportion to brain volume, with a tendency to a frontoparietal distribution along the middle cerebral artery, and without any particular lateralization. Their configuration is often compared with a cone or wedge (Fig. 2), with a superficial base, covered by thickened meninges, extending to an apex in the deep white matter.

Feeding arteries and aneurysms
There are usually several tortuous, branching, high flow arterial vessels of varying calibre and wall thickness that supply the central nidus where arteriovenous shunting occurs through one or more fistulae. These afferent vessels are typically recruited from more than one intracranial branch of the internal carotid and/or vertebrobasilar systems, and occasionally from branches of the external carotid or vertebral arteries through transdural anastomoses (Miyachi et al., 1993). The high flow, low resistance shunt of an AVM may
recruit collateral supply from surrounding vascular territories in addition to the main feeding vessels, sometimes called ‘angiomatous change’. Chronic high flow blood in the feeding arteries is thought, by some, to cause stenotic and/or dilated arterial ‘angiopathy’ due to endothelial thickening and intimal hyperplasia (Pile-Spellman et al., 1986), which may resemble the angiographic appearance of moyamoya disease (Montanera et al., 1990). The arterial feeders may terminate in the nidus, continue to supply brain beyond the nidus (giving ‘en passage’ supply) or arise indirectly from an artery in close proximity to the nidus.

The aetiology, classification, frequency, prognosis and treatment of aneurysms found in association with AVMs have been the subject of considerable interest and speculation (Redekop et al., 1998). They may occur as infundibula at arterial bifurcations (Miyasaka et al., 1982), and as saccular or fusiform aneurysms on vessels remote from the AVM, on feeding arteries and within the AVM nidus (Lasjaunias et al., 1988). Aneurysms are associated with AVMs in ~10% of patients in many series (Crawford et al., 1986a; Brown et al., 1990; Al-Shahi et al., 2000; Westphal and Grzyska, 2000), although they are identified in up to 50% of patients in series with greater use of super-selective angiography and an endovascular treatment interest (Meisel et al., 2000). Multiple aneurysms are not unusual.

### Nidus

The nidus itself is usually compact, but occasionally occupies a large proportion of a cerebral hemisphere, taking a more diffuse configuration (Chin et al., 1992). Super-selective IADSA has revealed the diversity of arteriovenous shunts within the nidus, from a simple fistula to a complex plexus (Houdart et al., 1993). Nidus size has been the subject of great interest in many studies of AVM prognosis and treatment, although its accurate and consistent measurement is plagued by several difficulties. The definition of a nidus as the area towards which multiple feeding arteries converge and from which enlarged veins drain is somewhat arbitrary. The nidus often is not imaged in its entirety by injecting a single vascular territory during IADSA. Neither consistent magnification factors nor calibrated markers are in frequent use (Pott et al., 1992). Moreover, there are different methods of calculating size, including the maximum linear diameter in any dimension (when authors’ interpretations of ‘small’ may be anything less than between 2 and 3.5 cm), and various volume calculations dependent on assumptions about the shape of the nidus (Pasqualin et al., 1991; Soderman et al., 2000).

### Draining veins

One or more dilated veins originate deep within the AVM nidus, and reach its surface acquiring tributaries along the way to drain, directly or via collateral pathways, into the superficial and/or deep venous systems (Fig. 3). Through the loss of the normal resistance to flow in the capillary bed, the arteriovenous shunt transmits arterial pressure to the compliant venous system, causing venous hypertension. The draining veins are often anomalous (Fig. 3), due to haemodynamic stresses causing stenosis, ectasia and varix formation (Viñuela et al., 1985).

### How common are AVMs?

The proportions of any population newly diagnosed with an AVM over a period of time (incidence), or living with the diagnosis at a single point in time (prevalence), provide fundamental information on disease burden, comparison with other populations and decision making about prognosis and treatment. Accurate estimates of these measures of disease frequency should, of course, be based on complete, prospective ascertainment from a well-defined, stable population, or a representative sample of one. In view of the rarity of AVMs, the size of the population (the ‘denominator’ in the frequency calculation) should be large enough to ascertain an adequate number of cases (the ‘numerator’), thereby ensuring sufficient precision with a small confidence interval around the estimate of frequency. Moreover, the validity of these studies is enhanced by a standard definition of what actually constitutes an AVM and adequate non-invasive brain imaging and IADSA to detect it.

We sought studies of AVM frequency with as many of these criteria as possible in unselected populations (Fig. 5), and in samples of people with stroke, PICH, SAH, epilepsy, headache and hereditary haemorrhagic telangiectasia (HHT) (Fig. 6). Where there were no population-based data meeting these criteria, we resorted to the best available hospital-based studies of AVM frequency, although these are likely to be unrepresentative of the population in ways that are impossible to assess (such as selection bias and under-ascertainment of
particularly severe or particularly mild cases). If no prospective studies were available, we resorted to the existing retrospective data. Whilst the uptake of imaging was complete in the studies we have chosen, a clear AVM definition was lacking in so many of them that if we had excluded any studies on this criterion alone, there would have been hardly any left.

**Incidence in unselected populations**

In the published literature, there are only two population-based studies of AVM incidence, although they were both retrospective (Jessurun et al., 1993; Brown et al., 1996a). The first was based in the only hospital serving a population of 155 000 living on the islands of Curacao and Bonaire in the Dutch Antilles, between 1980 and 1990 (Jessurun et al., 1993). The crude incidence of people affected by an AVM over the 10-year period was 1.1 [95% confidence interval (CI) 0.6–1.8] per 100 000 person-years. However, this study is only approximate because there was just one source of case ascertainment, sudden deaths in the community due to as yet undiagnosed AVMs were unaccounted for, information about the means of AVM identification was scanty, all cases were symptomatic and there was an unusually high frequency of multiple AVMs (probably attributable to the large proportion of people with HHT). The second study used the comprehensive Mayo Clinic Medical Records Linkage system to identify 26 AVMs over a period of 27 years in Olmsted County, Minnesota (Brown et al., 1996a). The age- and sex-adjusted incident AVM detection rate was 1.1 (95% CI 0.7–1.5) per 100 000 person-years between 1965 and 1992. However, the AVM detection rate increased over time due to the escalating use of progressively more advanced brain imaging during the study period.


**Prevalence in unselected populations**

There has been one population-based study of the prevalence of AVMs (Al-Shahi et al., 2000). This study in the Lothian region of Scotland was retrospective, and found a minimum point prevalence of 15 AVMs (untreated or previously treated) per 100 000 unselected living adults over 16 years of age. Overall AVM prevalence is likely to be higher than this, because case ascertainment must have been incomplete. Applying capture–recapture methods to these data, the prevalence in the Lothian region could have been as high as 18 (95% CI 16–23) per 100 000. Naturally, any clinical study will under-ascertain asymptomatic AVMs. Large post-mortem studies could give a more accurate picture of the prevalence of both symptomatic and clinically silent AVMs, although the method of cohort selection and the thoroughness of lesion ascertainment during pathological examination are potential and often insuperable difficulties. Hospital-based post-mortem series have reported AVM prevalences up to 600 per 100 000 (Courville, 1950; Sarwar and McCormick, 1978; Jellinger, 1986).

Frequency data are available from elsewhere in the world, including Switzerland, Singapore, Malaysia, Taiwan, China, Nigeria, Senegal and Lebanon, although they fall short of our required standards for studies of AVM frequency.
### Arteriovenous malformations of the brain

#### Fig. 6
Frequency of AVMs in different patient and age groups, with point estimates and 95% confidence intervals.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study numbers</th>
<th>AVM/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke (any age)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bogousslavsky <em>et al.</em>, 1988</td>
<td>Prospective hospital</td>
<td>14/1000 (1.4%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke (age 15-44 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radhakrishnan <em>et al.</em>, 1986</td>
<td>Prospective population</td>
<td>2/63 (3.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary intracerebral haemorrhage (any age)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furlan <em>et al.</em>, 1979</td>
<td>Retrospective population</td>
<td>7/180 (3.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary intracerebral haemorrhage (age &lt;40 years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ruiz-Sandoval <em>et al.</em>, 1999</td>
<td>Retrospective hospital</td>
<td>67/200 (33.5%)</td>
<td></td>
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<tr>
<td><strong>Spontaneous subarachnoid haemorrhage</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Kloster, 1997</td>
<td>Prospective population</td>
<td>7/76 (9.2%)</td>
<td></td>
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<tr>
<td><strong>Newly diagnosed unprovoked seizures</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forsgren, 1990</td>
<td>Prospective population</td>
<td>1/107 (0.9%)</td>
<td></td>
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<tr>
<td><strong>Headache with a normal neurological examination</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Frishberg, 1994</td>
<td>Pooled synthesis</td>
<td>6/1825 (0.3%)</td>
<td></td>
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<tr>
<td><strong>Migraine</strong></td>
<td></td>
<td>1/1432 (0.07%)</td>
<td></td>
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</tbody>
</table>

![Percentage attributable to AVMs](chart.png)

Fig. 6 Frequency of AVMs in different patient and age groups, with point estimates and 95% confidence intervals.

**Stroke**
There have been several population-based studies of the frequency of stroke, but their primary aim was not to describe the frequency of AVMs as a cause of stroke. It was therefore unsurprising that, of eight comparable stroke incidence studies performed in the modern era of brain imaging meeting strict methodological criteria and providing data about pathological subtypes, none commented on AVMs as a cause of stroke (Sudlow and Warlow, 1997). For example, the Oxfordshire Community Stroke Project found that 10% of first-ever-in-a-lifetime strokes were due to primary intracerebral haemorrhage, but no underlying AVMs were found because...
the use of MRI was infrequent, and only two patients with PICH ever had IADSA (Bamford et al., 1988, 1990; Boonyakarnkul et al., 1993).

We therefore sought prospective, hospital-based studies with adequate rates of CT (>90%) and the appropriate use of IADSA, at least, to give a rough estimate of the frequency of AVMs as a cause of first-ever-in-a-lifetime stroke. Even then, only two stroke registries provide any information about AVMs. The Lausanne Stroke Registry is a prospective study of patients with first-ever-in-a-lifetime stroke, excluding SAH (Bogousslavsky et al., 1988). By imaging every patient with CT, and almost a third of all strokes with IADSA, AVMs were detected in 1.4% (95% CI 0.8–2.3%) of patients. We excluded the Harvard Co-operative Stroke Registry from our analysis because CT was not widely used, and AVMs were lumped with aneurysms as a cause of stroke.

We applied similar selection criteria to eight studies giving information about AVMs as a cause of first-ever-in-a-lifetime stroke in young people, whose ages generally ranged from a minimum of 15 years to a maximum of 44 years. The only truly prospective population-based study found that AVMs account for ~3% (95% CI 1–11%) of first-ever-in-a-lifetime strokes in young adults (Radhakrishnan et al., 1986). Several retrospective hospital-based series were excluded because they were not explicit about studying first-ever-in-a-lifetime strokes, did not specify the extent of brain imaging or combined AVMs and aneurysms in one aetiological category.

**Primary intracerebral haemorrhage**

Overall, ~10% of first-ever-in-a-lifetime strokes in Whites are caused by PICH (Bamford et al., 1990; Thrift et al., 1995). The importance of PICH, and of AVMs as their cause, has been recognized since the increasingly widespread use of CT in the early investigation of stroke (Broderick et al., 1989). Many studies have varied in the extent of their further investigation of an underlying cause, and their inclusion criteria by aetiology or location of haemorrhage.

There is a paucity of satisfactory population-based data on the frequency of AVMs as a cause of first-ever-in-a-lifetime PICH. The only truly population-based study was retrospective, and was performed before the CT era, although it did use the comprehensive Mayo Clinic Medical Records Linkage system to study cases of first-ever PICH in Rochester, Minn. USA, of which 4% (95% CI 2–8%) were attributable to AVMs (Furlan et al., 1979). Four other studies were hospital-based, of which two did not study explicitly first-ever-in-a-lifetime PICH, and the two others combined AVMs with the other IVMs in one aetiological group. Two retrospective autopsy studies of fatal spontaneous PICH found an underlying AVM in 15–16% of cases, probably an overestimate due to case selection bias (McCormick and Rosenfield, 1973; Jellinger, 1977).

There are no population-based studies, either prospective or retrospective, of the frequency of AVMs as a cause of first-ever-in-a-lifetime PICH in young people. The best available estimate comes from a retrospective, hospital-based study of people under 40 years of age with PICH, that confirmed AVMs with MRI or IADSA in all cases (Ruiz-Sandoval et al., 1999). In this study, AVMs were the leading cause of PICH in the young, affecting 33% (95% CI 27–40%) of people. Four other similar, retrospective hospital-based studies did not study specifically first-ever-in-a-lifetime PICH, and their IADSA rates ranged from 40 to 85%.

**Subarachnoid haemorrhage**

In Western populations, the most frequent cause of spontaneous SAH is rupture of a saccular aneurysm on or near the Circle of Willis. AVMs are a much less common cause. One recent prospective, population-based study in Norway, that studied every patient with CT and 76% of those with IADSA, found AVMs as a cause of SAH in 9% (95% CI 5–18%) of people (Kloster, 1997). All the other studies of SAH that mention AVMs as a cause have been hospital-based, and mostly retrospective. There seems to be variation between geographical regions and ethnic groups (Becker, 1998); it is debated whether AVMs are more common than aneurysms as a cause of SAH in Asian populations, on the basis of studies which do not meet our inclusion criteria (Chee and Loh, 1988).

**Epilepsy**

Despite the frequency of epileptic seizures, there have been few prospective, community-based studies of people with newly diagnosed epilepsy in the general population (Sander et al., 1990). The estimation of the true frequency of epilepsy is complicated by the difficulty of achieving comprehensive case ascertainment and the heterogeneity of different diseases causing epilepsy. The contribution made by AVMs is often hidden by the investigators’ classification of aetiologies into broad categories. Furthermore, the extent and rate of investigation with neuroimaging have been variable between studies, so structural causes, such as AVMs, have not always been identified reliably. The use of neuroimaging, ideally MRI, is indicated for patients whose epilepsy cannot be controlled with first-line anticonvulsants, and those with localization-related epilepsies or fixed/progressive neurological deficits (Duncan, 1997), particularly for the identification of AVMs. The best information about AVMs as a cause of epilepsy in the general adult population comes from a Swedish prospective, population-based incidence study of first presentations with seizures. Using either CT or MRI in all patients, the study found 0.9% (95% CI 0.2–5.1%) of apparently unprovoked seizures to be attributable to an AVM (Forsgren, 1990).

**Headache**

In the general population, AVMs are an extremely infrequent cause of headache. Largely because of neurologists’ very
reasonable aversion to unnecessary investigation, studies have not attempted to ascertain the frequency of structural causes of headache syndromes, defined according to the International Headache Society criteria, in unselected populations of people with headache and normal neurological examination. Rather, the majority of existing studies have described small, retrospective, selected series of patients at tertiary referral centres, mostly using first-generation CT scanners without intravenous contrast, thereby decreasing the chance of detecting an underlying AVM. A pooled synthesis of these imaging studies of the frequency of detection of structural brain abnormalities in samples of >18 people with unspecified headache and no abnormal neurological signs up to 1991 found 0.3% of them (95% CI 0.1–0.7%) to harbour an AVM of the brain (Frishberg, 1994). Only 0.07% (95% CI 0.006–0.4%) of migraineurs were found to have an AVM in similar studies, several of which used MRI (Frishberg, 1997).

**Hereditary haemorrhagic telangiectasia (HHT) and other neurocutaneous disorders**

HHT is a generalized vascular dysplasia that manifests itself in the mucocutaneous membranes, lungs and gastrointestinal tract as well as in the brain, where capillary, venous and arteriovenous malformations are found. The prevalence of AVMs in the brain with HHT has been estimated to lie between 4 and 13% (Román et al., 1978; Porteous et al., 1992). However, AVMs tend to be small in the context of HHT, often involving a direct fistula between a single afferent and efferent vessel, and their detection is particularly dependent on the use of IADSA (Putman et al., 1996; Fulbright et al., 1998; Willems et al., 2000). Due to the limited uptake of IADSA in many of the existing studies of HHT, the prevalence of AVMs is likely to have been underestimated. Interestingly, at least one-third of people with HHT may have multiple AVMs (Willems et al., 2000), far in excess of the infrequent multiplicity observed in people with sporadic AVMs (Willinsky et al., 1990). Despite the higher prevalence of AVMs of the brain amongst people with HHT, they seem to be asymptomatic more often than sporadic AVMs, perhaps because they are deliberately screened for. In fact, two-thirds of any neurological complications are attributable to pulmonary AVMs and not brain AVMs (Guttmacher et al., 1995). There is a relatively higher prevalence of migrainous aura amongst people with HHT, which suggests over-ascertainment by repeated questioning, embolic phenomena from pulmonary AVMs or perhaps a real association with AVMs of the brain (Steele et al., 1993).

Occasionally, single or multiple AVMs occur in the context of two other rare neurocutaneous disorders, usually diagnosed in childhood. In Wyburn–Mason syndrome, AVMs affect not only the brain, but also the orbit and face, and in the blue rubber bleb naevus syndrome AVMs also occur in the kidneys and lungs (Kim et al., 1998; Fernandes et al., 1999).

**Summary**

Despite a considerable volume of literature about AVMs, many of the existing studies have not met our selection criteria, or the studies are no longer appropriate because of the radical improvements in imaging of the brain’s vasculature over the last two decades. On the basis of current knowledge (Figs 5 and 6), AVMs have an incidence of ~1 per 100 000 per year in unselected populations, and a point prevalence in adults of ~18 per 100 000 (1 in approximately every 5500 adults). AVMs account for between 1 and 2% of all strokes, but maybe ~4% of strokes in young adults. AVMs are identified in ~9% of people presenting with SAH, and are the cause of ~4% of all PICHs, but as many as one-third of PICHs in young adults. AVMs are far less common causes of first presentations with unprovoked seizures (1%), and of people presenting with headaches in the absence of any neurological signs (0.3%). Clearly, there is still a need for some large, prospective studies of the incidence and prevalence of AVMs in well-defined, stable populations across the world, with widespread availability and uptake of CT, MRI and IADSA.

**What are the clinical manifestations of AVMs?**

Whilst AVMs occasionally are a purely incidental finding, they are usually discovered when searching for a potential structural cause of intracranial haemorrhage, epilepsy, headache or focal neurological deficit. Sometimes an AVM is suggested by a distinctive combination of these features. An understanding of the different modes of presentation, and their relative frequencies, is important to raise the clinical suspicion of an AVM, so that radiological investigation is undertaken appropriately. Furthermore, an appreciation of the frequency of presentation with haemorrhage has implications for clinical practice, it is useful for assessing the burden of AVMs and it may have implications for prognosis compared with a non-haemorrhagic presentation.

**How common are the different modes of presentation?**

A representative assessment of the way AVMs manifest themselves should, of course, be undertaken in population-based samples. However, because of the paucity of population-based data on AVMs, we have had to include hospital-based studies without an explicit treatment selection bias. We have selected those with >100, preferably consecutive, patients and, for each and every individual, an explicit allocation to a single mode of presentation at diagnosis. In view of the re-publication of some eligible studies following the accrual of additional patients, and occasional duplicate publication, we have restricted our analysis to the largest single series from each hospital meeting these criteria.
Most studies describing the clinical presentation of AVMs share many of the methodological failings of the studies of AVM frequency; their small, retrospective nature often leaves uncertainty about the presentation of every patient, because of either the lack of radiological investigation or incomplete data collection. In addition, ‘presentation’ has been interpreted variously as the clinical event that led to the diagnosis of an AVM, or the first symptom in someone’s lifetime that was attributable to an AVM. Probably in an attempt to estimate the prevalence of particular symptoms amongst people with AVMs, more than one mode of presentation has tended to be allocated to each individual; for example, the occurrence of seizures and headache with acute intracranial haemorrhage. Furthermore, the role that AVMs play in the aetiology of headache, dizziness and cognitive dysfunction is subject to varying interpretation, resulting in some clinicians attributing the symptoms to the AVM, and others declaring the AVM asymptomatic.

Despite these limitations, some general comments can be made about three studies. Although the sample size was small and the data were collected retrospectively, we have included the population-based study from Olmsted County (Brown et al., 1996b), but not the study from the Dutch Antilles because of the limitations of its sources of case ascertainment. The only large, multidisciplinary hospital-based studies that allocated a single mode of presentation to each individual and did not have a treatment selection bias (which was either declared in the text, or was implicit in the focus of the paper and the interests of the authors), originate from the UK (Crawford et al., 1986a) and the USA (Mast et al., 1997).

The study in Olmsted County provides the most reliable population-based data on the clinical events that led to the diagnosis of an AVM, although the small sample size resulted in large confidence intervals around every estimate, and headache, focal neurological deficit and rarer modes of presentation were not mentioned (Brown et al., 1996b). Whilst 15% of people harbouring AVMs were asymptomatic, and seizures affected 20%, intracranial haemorrhage was the predominant mode of presentation in 65% of the sample.

The two hospital-based series portray different patterns from the population-based study, especially in the proportion of people who are declared asymptomatic (Fig. 7). Many of the differences are likely to have arisen from some of the biases inherent in hospital-based studies. For example, some patients may never reach tertiary referral centres, either because they have died or because their symptoms are not thought to merit referral, and others may be referred only because of the availability of a particular treatment. Not only are there differences between population-based and hospital-based series, but large differences have also been demonstrated between three hospital-based series in the relative frequencies of different modes of presentation, age at presentation and AVM angioarchitecture (Hofmeister et al., 2000). In general, however, the ratio of males to females appears equal, and the mean age at presentation is ~35 years, with a standard deviation of ~15 years.

**How do AVMs present clinically, and which AVM characteristics are associated with the different modes of presentation?**

There has been more interest in any distinguishing features of each mode of presentation than in an accurate appreciation of their relative frequencies. Certainly, characteristic manners of presentation might help to raise the clinical suspicion of an underlying AVM, leading to appropriate investigations. In an effort to gain a quick understanding of why AVMs express themselves differently, some of the hospital-based studies have not only described clinical features at presentation, but also sought factors that are associated with a particular mode of presentation, sometimes making the further inference that these factors are causative. Almost all studies of this nature have involved a retrospective correlation of angioarchitecture described after diagnosis, with prior presentation with haemorrhage or epilepsy. Although many of these studies have used univariate and multivariate analysis, no amount of statistical sophistication can overcome tenuous cause and effect assumptions.

There are many potential flaws in this attempt to elucidate why some AVMs present with haemorrhage, some present with epilepsy and others never cause any symptoms at all. There is not only speculation about how repeated modification of angioarchitecture through life eventually determines clinical presentation, but also good evidence that the angioarchitecture of an AVM changes in both the short and long term after vessel rupture (Stein and Wolpert, 1980; London and Enzmann, 1981; Brown et al., 1988). The mere occurrence of haemorrhage may distort angioarchitecture so that any factors found in association with haemorrhage could be a consequence rather than a cause of it. For example, the interpretation of whether an AVM or an associated aneurysm is the cause of haemorrhage can be difficult, with pure SAH around the aneurysm being the principal argument in favour of the aneurysm being responsible (Borraclough, 1982; Hartmann et al., 1998; Redekop et al., 1998). The occurrence of pseudoaneurysms (attributable to haemorrhage) on distal feeding arteries and within the nidus in the presence of SAH may lead to their overinterpretation as the cause, but the only way to know for sure is pathological examination or comparison with prior IADSA (Garcia-Monaco et al., 1993; Redekop et al., 1998). Factors associated with the first occurrence of haemorrhage or epilepsy not only might be spurious for these reasons, but also they could be very different from those conferring a higher risk of recurrence, which is what is really of interest to patients, and in any discussion of treatment. A particular feature of AVMs may be so prevalent in those with one type of presentation, such as haemorrhage, that it is useless for predicting future events if hospital-based series of mainly ruptured AVMs are studied;
Fig. 7 Comparison of the relative frequencies of clinical events at diagnosis in one population-based study and two hospital-based studies, with point estimates and 95% confidence intervals. Headache, focal neurological deficit and other modes of presentation were not mentioned in Brown et al. 1996b.
for example, a study of the first occurrence of seizures found presentation with haemorrhage to be a predictive factor, yet 86% of the cohort had presented in this fashion (Crawford et al., 1986b). This perception may also lead to bias due to the expectation of finding the feature in those with a first occurrence, or recurrence, of haemorrhage. For example, AVMs that present with haemorrhage on the whole are smaller and have fewer draining veins than those with other clinical features; these features may be difficult to disentangle as predictors of recurrent haemorrhage, all the more so when cohorts subject to treatment selection bias (usually favouring small AVMs) are used to study prognosis.

Where appropriate, we have summarized the findings of studies involving at least 100 patients using this retrospective approach. Such studies relying on retrospective inference are probably only useful for identifying putative factors that might predict the occurrence, or recurrence, of a particular symptom, and even then the factors must not be subject to the biases mentioned above.

**Haemorrhage**

Before the advent of non-invasive imaging of the brain, haemorrhage from AVMs was underestimated because the only possible means for its detection in life was examination of the CSF (and lumbar puncture would understandably have been avoided in many such cases). Therefore, when haemorrhage was detected, it was attributed excessively to SAH, so the site of rupture was thought to be predominantly into the subarachnoid space. With or without subarachnoid or intraventricular extension, PICH is now known to be the principal type of haemorrhagic presentation. In the Olmsted County study, PICH accounted for 41%, SAH for 24%, intraventricular haemorrhage for 12% and a combination of these types for 23% of all haemorrhages (Brown et al., 1996b).

Hospital-based studies retrospectively comparing the angioarchitecture of AVMs that presented with haemorrhage with those with other initial manifestations have identified several factors that seem to be associated consistently with haemorrhage (Table 2): deep venous drainage, a single draining vein, venous stenosis and high feeding mean arterial pressure (FMAP). Studies have been more inconsistent about intranidal aneurysms, small nidus size, deep location of the nidus and venous reflux being associated with haemorrhagic presentation. Some studies have identified systemic hypertension and vertebrobasilar or perforating artery supply in association with haemorrhagic presentation (Turjman et al., 1995a; Langer et al., 1998), but these remain unconfirmed by others. Increasing age at presentation (Langer et al., 1998) and smoking (Taha et al., 1982; Langer et al., 1998) have not been confirmed as associated factors. Potential protective factors that have been investigated are arterial stenosis and ectasia (Mansmann et al., 2000), dural arterial supply (Langer et al., 1998), venous recruitment (Nataf et al., 1998) and angiogenesis (Mansmann et al., 2000).

Of course, many of these factors may confound each other; for example, small AVMs tend to have only one draining vein and higher FMAP (Albert et al., 1990; Shi et al., 1993). Furthermore, small AVMs may present with haemorrhage because they rarely present with epilepsy or other neurological symptoms before diagnosis (Crawford et al., 1986a; Brown et al., 1988), and deeply located AVMs tend to be supplied by perforating arteries or the vertebrobasilar system (Turjman et al., 1995a).

The consistent findings of a single draining vein, deep venous drainage, venous stenosis and high FMAP associated with a haemorrhagic presentation may reflect the haemodynamics of these AVMs, and suggest that high intranidal pressure may be the major determinant of AVM rupture (Hademenos and Massoud, 1996). However, just because these factors are associated with a haemorrhagic presentation does not necessarily mean they are also predictors of either the occurrence or recurrence of haemorrhage. This has to be tested in large, prospective studies.

**Epilepsy**

Although their relative frequencies are not described in potentially unbiased samples, epileptogenic AVMs clearly can express themselves as apparently generalized seizures, as well as by simple or complex partial seizures with or without secondary generalization (Miserocchi et al., 1984; Osipov et al., 1997). A few studies have examined factors that are associated retrospectively with a presentation with epilepsy. They have unsurprisingly found the AVMs to have statistically significant associations with a larger (>6 cm) nidus diameter (Crawford et al., 1986b), and that several other factors (which may well confound each other) seem to be associated, including supratentorial cortical location, feeders from the middle cerebral artery, cortical feeders, venous varix, the absence of intranidal aneurysms (Turjman et al., 1995b) and location in an arterial border zone (Stapf et al., 2000). These factors too should be tested for their prognostic value for the occurrence or recurrence of seizures in long-term, prospective studies.

**Headache**

There has been more curiosity and controversy about the semeiology of headache, especially migraine and cluster headache, amongst patients known to have AVMs than there has been about how often AVMs are a cause of headache in the general population. Again, the absence of prospective, population-based studies with a validation of headache diagnosis has generated conflicting opinions about whether the relationship between headache and AVMs is no more than coincidental (Ozer et al., 1964; Mohr, 1984), in which case the AVMs may be dubbed asymptomatic, or whether there is a greater than chance association (Bruyn, 1984; Monteiro et al., 1993).

Publication bias is most likely to explain the reporting of
Table 2 Angioarchitectural features in association with a prior haemorrhagic presentation in retrospective studies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Statistically significant (P &lt; 0.05) association found</th>
<th>No association found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep venous drainage</td>
<td>Duong et al. (1998)</td>
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<td></td>
<td>Langer et al. (1998)</td>
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<td></td>
<td>Nataf et al. (1998)</td>
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<td></td>
<td>Turjman et al. (1995a)</td>
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<td></td>
<td>Kader et al. (1994)</td>
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<tr>
<td></td>
<td>Miyasaka et al. (1992)</td>
<td></td>
</tr>
<tr>
<td>Single draining vein</td>
<td>Shi et al. (1993)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Miyasaka et al. (1992)</td>
<td></td>
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<tr>
<td>Venous stenosis</td>
<td>Nataf et al. (1998)</td>
<td></td>
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<tr>
<td></td>
<td>Miyasaka et al. (1992)</td>
<td></td>
</tr>
<tr>
<td>High feeding mean arterial pressure</td>
<td>Duong et al. (1998)</td>
<td></td>
</tr>
<tr>
<td>Intranidal aneurysm</td>
<td>Redekop et al. (1998)</td>
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<td></td>
<td>Nataf et al. (1998)</td>
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<tr>
<td></td>
<td>Turjman et al. (1995a)</td>
<td></td>
</tr>
<tr>
<td>Small nidus size</td>
<td>Langer et al. (1998)</td>
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<tr>
<td></td>
<td>Kader et al. (1994)</td>
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<td></td>
<td>Shi et al. (1993)</td>
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<tr>
<td></td>
<td>Albert et al. (1990)</td>
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<td></td>
<td>Crawford et al. (1986a)</td>
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<tr>
<td></td>
<td>Mansmann et al. (2000)</td>
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<tr>
<td>Deep location</td>
<td>Mansmann et al. (2000)</td>
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</tr>
<tr>
<td></td>
<td>Turjman et al. (1995a)</td>
<td></td>
</tr>
<tr>
<td>Venous reflux</td>
<td>Nataf et al. (1998)</td>
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</table>

atypical migraine and cluster headache in AVM patients, as unusual cases are more likely to be reported in the literature. The migraines reported to accompany AVMs are usually characterized by atypical features, although these are not specific for identifying an underlying AVM in a person with migraine (Troost and Newton, 1975). The reported headaches tend always to be on the same side, ipsilateral to the AVM, with disruption of the classical migraine tempo and sequence (Lees, 1962; Troost et al., 1979; Bruyn, 1984; Monteiro et al., 1993; Frishberg, 1994).

A large, prospective cohort study using semi-structured interviews and/or validated questionnaires based on the International Headache Society criteria would be required to determine the true prevalence of different types of headache amongst people with AVMs. Studying the converse, the prevalence of AVMs amongst patients with various headache syndromes would be a huge undertaking.

**Focal neurological deficit**

Rarely, AVMs may cause focal symptoms and signs in the absence of prior or concomitant intracranial haemorrhage. These deficits often have an insidious onset, and their subsequent course may be transient, persistent or, infrequently, progressive. Occasionally they give rise to fluctuations and slow progression suggesting the diagnosis of multiple sclerosis (Stahl et al., 1980). Their exact frequency in the population is unknown, but they account for up to 10% of presentations in hospital-based series (Crawford et al., 1986a; Mast et al., 1995b, 1997). Whilst these deficits traditionally have been attributed to reduced perfusion pressure (steal) due to high flow in the feeding arteries of the AVM, the actual measurement of feeding artery pressures and flow velocities in selected patients has not supported this (Mast et al., 1995b).

**Cognitive dysfunction**

Despite early suggestions that cognitive disorders affect up to 50% of people with AVMs (Olivecrona and Riives, 1948), there are few data on their prevalence amongst people harbouring AVMs; rather, case reports of unusual syndromes and studies of the neuropsychological outcome following treatment populate the literature. Existing research does, however, shed some light on the time of onset of cognitive dysfunction, and the areas of the brain implicated.

Although adults diagnosed with AVMs seem to have met their developmental milestones during childhood, a single, retrospective case–control study found that 44 patients affected by AVMs were more likely to have had a disorder of learning or behaviour during their school years (Lazar et al., 1999). Subsequent psychological impairments that
develop in relation to unruptured AVMs do not appear to be equivalent to those from other focal lesions of similar size, nor do they appear to be related just to the area or side of the brain in which the AVM resides (Waltimo and Putkonen, 1974; Brown et al., 1989; Lazar et al., 1997). Controversial explanations for cognitive deficits related to areas of the brain distant from an AVM are steep, although this is as yet unproven, and venous hypertension (Mahalick et al., 1991; Mast et al., 1995).}

Other complications

Although pulsatile tinnitus is a celebrated feature of AVMs, in particular those affecting the dura mater, it is in fact unusual (Sabra, 1959). On the limited evidence available, it is a symptom with poor specificity, but which certainly merits auscultation over the orbit and cranium, and probably non-invasive investigation (Dietz et al., 1994; Waldvogel et al., 1998). Raised intracranial pressure is another infrequent manifestation of AVMs, resulting from CSF outflow obstruction by an enlarged draining vein, or the haemodynamic effect of venous hypertension leading to poor CSF resorption (U and Kerber, 1983; Chimowitz et al., 1990). Of course, other deficits depend on the location and size of an AVM, so those in the occipital lobes may cause atypical visual disturbance (Maleki and Kirkham, 1983), those in the posterior fossa can cause cranial nerve palsies (Hatori et al., 1991), trigeminal neuralgia (Johnson and Salmon, 1968) and hemifacial spasm (Kim et al., 1991), whilst movement disorders can be caused by AVMs of the basal ganglia (Lobo-Antunes et al., 1974).

Health-related quality of life

Whilst only one published study of untreated AVMs has used validated self-reported measures of disability (Hartmann et al., 1998), there has also been only one study of people affected by AVMs to explore their perceptions of health and risks for the future. A small study, using the standard gamble technique to compare patients’ different health states by the utility values they assigned to them, demonstrated considerable variation in individuals’ perceptions of their quality of life (Shin et al., 1997). This clearly suggests that patients should be involved in decision making about their own management, as their future quality of life is affected not only by their prognosis, but also by their interpretation of it. Larger studies are needed to evaluate the factors associated with patients’ different perceptions of their health, especially in the context of their treatment and the design of clinical trials.

Summary

There is a shortage of data on the presentation of AVMs in community-based populations. The frequencies of the various modes of presentation are different from those in the majority of hospital-based studies, which themselves are different from each other. Although every AVM affecting an adult is asymptomatic at an early stage, nowadays at least 15% of people are asymptomatic when the AVM is detected. About one-fifth of individuals with AVMs present with seizures, and in approximately two-thirds the dominant mode of presentation is haemorrhage, half of which are PICH.

The factors that govern whether someone with an AVM presents with haemorrhage, epilepsy, headache, focal neurological deficit or another event are uncertain, although presentation probably depends at least in part on the location of the AVM, and its size. Several studies have attempted to correlate factors identified after diagnosis with the mode of presentation, but there are numerous biases involved in any such analysis, and the assumption that they determine the prognosis for the future occurrence or recurrence of certain outcomes is dubious. However, certain radiological features that may confer a higher risk of haemorrhage, such as deep venous drainage, a single draining vein, venous stenosis and high FMAP, might benefit from further evaluation alongside clinical and demographic factors, in robust, prospective studies of clinical course.

What determines prognosis for people with AVMs?

Just as the initial presentation of AVMs is diverse, so too is their subsequent behaviour. To explore this heterogeneity and establish the behaviour of the ‘average patient’, the clinical course of large, representative samples of people with AVMs needs to be investigated. Insights into the factors that predict and explain future risk can be gleaned from such studies to help estimate the prognosis for any individual person. With this knowledge, stratification of individuals according to their subsequent risk of death (due to haemorrhage, for example), or their risk of the future occurrence of haemorrhage, epilepsy, focal neurological deficit and cognitive impairment, might help decide whether they should be considered for treatment or not. However, the findings of studies of prognosis are extremely susceptible to imperfections in study design, which makes a careful appraisal of study methods essential.

Ideal design

The criteria that have guided our selection of the best available studies of the clinical course and prognosis of AVMs are based on published guides (Sackett et al., 1991; Laupacis et al., 1994), and subsume many of the aforementioned requirements of studies of AVM frequency and presentation (Table 3). Adequate radiological or pathological investigation should have been used to diagnose an AVM of the brain reliably according to a clear, explicit definition, so that the study sample is not contaminated by dural AVMs or other types of IVM. The sample should be followed prospectively from an
Table 3  **Ideal characteristics for studies of the clinical course of AVMs**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<td>Diagnostic certainty at baseline (i.e. adequate investigation and a clear definition)</td>
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<tr>
<td>Inception cohort</td>
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<tr>
<td>Prospective data collection</td>
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<tr>
<td>Population-based sample</td>
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<tr>
<td>Sample size &gt;100</td>
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<tr>
<td>Objective, pre-defined outcome events and validated measures of functional status</td>
</tr>
<tr>
<td>Assessment of outcome blinded to baseline factors of interest</td>
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<tr>
<td>Stratification of outcome by differences in treatment</td>
</tr>
<tr>
<td>Follow-up ≥90% complete</td>
</tr>
<tr>
<td>&gt;5-year follow-up</td>
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<tr>
<td>5-year survival rate and an actuarial analysis of the chosen outcomes</td>
</tr>
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</table>

Early and uniform (‘inception’) point in the clinical course. The most meaningful and practical point to standardize as ‘zero time’ is the onset of the clinical presentation that led to the first-ever AVM diagnosis, bearing in mind that diagnosis may well be occurring earlier nowadays, perhaps making prognosis seem better than before because of lead-time bias. Choosing the first-ever symptom as the inception point usually involves retrospective 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 a person’s symptoms, and for various difficult reasons.

The individuals being studied should be a representative sample, preferably from a well-defined population including people diagnosed at smaller hospitals and those who died in the community. Studies at specialist AVM centres are likely to represent patients with more aggressive disease, and this sort of sampling bias affects prognostic subgroups unequally (Hofmeister et al., 2000).

Again, our choice of sample size has been set arbitrarily at a minimum of 100 patients, to maximize the precision of the studies’ results, and to increase the power to detect large, let alone small, effects. Moreover, because outcome events for AVMs are relatively infrequent, and by being treated many patients may be censored from an actuarial analysis before the occurrence of an outcome, a large sample size is all the 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 any study’s utility.

The outcomes studied should be clinically important (such as death and morbidity from haemorrhage and epilepsy), and their objectivity should be enhanced by clear definitions or the use of generic outcome measures. The assessment of morbidity preferably should be blinded to the prognostic factors under investigation (to minimize the effect of measurement bias due to clinicians’ prior expectations), and it should be as accurate and consistent as possible with, for example, radiological evidence of intracranial haemorrhage. Moreover, in view of the current tendency to treat many AVMs once they are discovered, the assessment of outcome should be stratified according to any therapeutic intervention during follow-up. When outcome measures are used to evaluate impairment, disability, handicap or health-related quality of life, their validity, reliability and responsiveness for people with AVMs should have been demonstrated.

Follow-up should be prospective and as complete (≥90%) 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 important prognostic outcomes. Follow-up needs to be lengthy, especially because the interval between haemorrhages from AVMs may be anything up to 8 years (Ondra et al., 1990; Hartmann et al., 1998). Although an analysis of prognostic outcome as an annual rate, 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 over time. For example, the prognosis for a dichotomous variable such as dead versus alive can be evaluated at a specific time (e.g. at 1 year after diagnosis) or as a proportion of people affected (e.g. case fatality). On the other hand, using an actuarial analysis (e.g. time to death) and plotting a survival curve provides far more enlightening information about the pattern over time, which would otherwise be lost in an annualized survival rate.

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 should include not only their statistical significance, but also their clinical significance in terms of an odds ratio or relative risk, with 95% 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 patients and outcome events per variable studied (Sackett et al., 1991; Peduzzi et al., 1996), nor are they
generalize unless their robustness has been externally validated in other AVM populations.

Methodological problems with studies of AVM prognosis

Sadly, these ideals have been met by very few of the existing observational cohort studies, leading to varying degrees of bias. We have therefore chosen the studies that best meet our requirements, explicitly mentioning their failings in particular areas (Tables 3 and 4).

Definitions of the diagnostic criteria for an AVM or its angiarchitectural features, and information about the extent of investigation to achieve adequate diagnostic certainty, are provided so infrequently that we have not rejected any studies on this criterion alone. Some studies have used restrictive entry criteria (including only those patients with ‘adequate’ imaging and complete data collection) to produce a more homogeneous cohort, although this inevitably results in a more selective cohort. Furthermore, many of the older studies enrolled patients before the modern era of brain imaging (Graf et al., 1983; Crawford et al., 1986a). Because there is only one truly population-based study, we have not rejected any study solely on the grounds of being hospital-based, but the fact that they are all likely to suffer selection bias should not be ignored. Retrospective survival cohorts far outweigh studies with a prospective design, mainly because large amounts of data are available immediately, but the data are, by their nature, incomplete and inaccurate.

The inception point has been unclear in many studies. The uncertainty about exactly when an AVM develops, and its evolution during the latent period of ‘maturation’ before clinical presentation, surely make a ‘lifetime’ period of risk with inception at birth an invalid assumption, inevitably involving a retrospective assessment of the clinical course (Martin et al., 1995). The inclusion of this latent period in the denominator of the calculation of time at risk attenuates the apparent annual risk of an outcome. Moreover, the prognosis from the point of diagnosis onwards is what concerns patients and clinicians alike, especially from the point of view of treatment.

Follow-up has been variable in both duration and completeness. Scarcely any studies have achieved >10 years of follow-up. In retrospective studies, completeness has been quoted as near 100%, but we have already discussed the vagaries of this method of data collection. In prospective studies, the completeness of follow-up has been more variable, having potentially dramatic effects on less frequent outcomes in particular. 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.

Again, we have been careful to include only the largest series from each research group, because existing series have been republished, either when they have enlarged, or after further follow-up (Troupp, 1965; Troupp et al., 1970; Ondra et al., 1990). An overall synthesis of the included studies has not been possible because comparable outcomes cannot be derived from them, they have poor generalizability due to variations in confounding effect modifiers and there are different selection biases operating at specialist treatment centres (Egger et al., 1998). Instead, we have tabulated the best available evidence (Tables 5, 6 and 7).

What is the risk of death?

Detailed information about the early and long-term risk of death for people with an AVM is sparse (Table 5). Because there are no long-term population-based data on the risk of death due to an AVM with epidemiological methods of analysis, the AVM ‘mortality rate’ (number of deaths per 1000 per unit time) is unknown, and studies only yield information about the proportion of people with an AVM who die (the ‘case fatality’).

People with a haemorrhagic presentation of an AVM do appear to have a lower case fatality compared with other causes of PICH (Rosenow et al., 1997) and aneurysm rupture (Perret and Nishioka, 1966). In the Olmsted County study (Brown et al., 1996b), the 30 day case fatality following a first intracranial haemorrhage from an AVM was 18% (95% CI 4–43%). Presumably because of selection bias, in hospital-based survival cohorts case fatality following haemorrhage has ranged from 0% over 1 year in recent studies (Mast et al., 1997; Hartmann et al., 1998) to 17% over at least 1 year following an initial or recurrent haemorrhage in another (Porter et al., 1998). Interestingly this does not seem to translate into a long-term difference in survival between patients presenting with and without haemorrhage. Long-term crude annual case fatality rates appear to lie between 1 and 1.5% per annum, with no factors apparently conferring a greater risk of death, although 50–70% of all deaths are due to haemorrhage (Crawford et al., 1986a; Ondra et al., 1990).

What is the risk of developing intracranial haemorrhage?

Because intracranial haemorrhage is the most feared outcome of an AVM, there has been an overwhelming curiosity about the frequency and risk of its occurrence and recurrence, and a tendency to treat AVMs early to avoid it. The crude annual rate of intracranial haemorrhage from AVMs is widely quoted to be ~2% in the existing hospital-based studies of prognosis (Table 6), although this must mask important variations in the behaviour of different subgroups.
First-ever haemorrhage
From the few studies of the clinical course of unruptured AVMs, the crude annual risk of a first-ever haemorrhage appears to be ~2% (Brown et al., 1988; Mast et al., 1997). Whilst one study found no factors that predicted the occurrence of haemorrhage (Brown et al., 1988), a substudy of the same patient group with complete IADSA examinations found that the co-existence of aneurysms at baseline conferred a higher annual rate of haemorrhage for people with unruptured AVMs (Brown et al., 1990).

Recurrent haemorrhage
Because the majority of AVMs present with haemorrhage, their risk of recurrent haemorrhage has been studied more often than the risk of its first-ever occurrence. Early treatment following haemorrhage may, of course, preclude the study of the risk of recurrence. People who have already experienced haemorrhage 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 (Mast et al., 1997). Some studies have found the risk of rupture after a haemorrhagic presentation to be greater than after any other type of presentation (Crawford et al., 1986a; Mast et al., 1997), whilst other methodologically less sound studies have not (Graf et al., 1983; Ondra et al., 1990). These studies have found other features to predict recurrence of haemorrhage, including exclusively deep venous drainage and male sex (Mast et al., 1997), increasing age (Crawford et al., 1986a) and small nidus size (Graf et al., 1983), although the studies are not all in agreement (Table

Table 4 The extent to which the best studies of prognosis have met our selection criteria

<table>
<thead>
<tr>
<th>Study details</th>
<th>Diagnostic certainty</th>
<th>Inception cohort</th>
<th>Purely prospective</th>
<th>Population based</th>
<th>Sample size &gt;100</th>
<th>Objective outcomes</th>
<th>Blinded outcome assessment</th>
<th>Stratified by treatment differences</th>
<th>Follow-up ≥90%</th>
<th>&gt;5 year follow-up</th>
<th>Actuarial analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>German et al. (1988)</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Brown et al. (1990)</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Brown et al. (1996b)</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Crawford et al. (1986a, b)</td>
<td>?</td>
<td>?</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Forster et al. (1993)</td>
<td>?</td>
<td>?</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Graf et al. (1983)</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
</tr>
<tr>
<td>Hartmann et al. (1998)</td>
<td>?</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>?</td>
<td>?</td>
<td>•</td>
<td>•</td>
</tr>
<tr>
<td>Horton et al. (1990)</td>
<td>•</td>
<td>?</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>•</td>
<td>•</td>
<td>o</td>
</tr>
<tr>
<td>Mast et al. (1997)</td>
<td>?</td>
<td>?</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>•</td>
<td>o</td>
</tr>
<tr>
<td>Ondra et al. (1990)</td>
<td>•</td>
<td>?</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>•</td>
<td>o</td>
</tr>
<tr>
<td>Osipov et al. (1997)</td>
<td>?</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>•</td>
<td>o</td>
</tr>
<tr>
<td>Porter et al. (1998)</td>
<td>?</td>
<td>•</td>
<td>•</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>o</td>
<td>?</td>
<td>o</td>
<td>•</td>
<td>o</td>
</tr>
</tbody>
</table>

• = criterion was met; o = criterion was not met; = not applicable; ? = unknown.

Table 5 Studies of AVM clinical course after first presentation with information about case fatality

<table>
<thead>
<tr>
<th>Study details</th>
<th>Patient group</th>
<th>n</th>
<th>Outcome</th>
<th>Assessed at</th>
<th>% Dead</th>
<th>Factors predicting death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies</td>
<td>Mast et al. (1997)</td>
<td>Presentation with haemorrhage (n = 142) or other symptoms (n = 139)</td>
<td>281</td>
<td>Case fatality</td>
<td>8–12 months (mean)</td>
<td>0%</td>
</tr>
<tr>
<td>Porter et al. (1998)</td>
<td>First haemorrhage at presentation (n = 75) or during follow-up (n = 56)</td>
<td>131</td>
<td>Case fatality due to haemorrhage</td>
<td>≥12 months</td>
<td>17%</td>
<td>Haemorrhage during follow-up</td>
</tr>
<tr>
<td>Hartmann et al. (1998)</td>
<td>First haemorrhage at presentation (n = 115) or during follow-up (n = 4)</td>
<td>119</td>
<td>Case fatality</td>
<td>≥1 month. 16 months (mean)</td>
<td>0%</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Mixed prospective and retrospective studies</td>
<td>Ondra et al. (1990)</td>
<td>Presentation with haemorrhage (n = 114) or other symptoms (n = 46)</td>
<td>160</td>
<td>Crude annual case fatality (all cause)</td>
<td>24 years (mean)</td>
<td>1% per annum</td>
</tr>
<tr>
<td>Retrospective studies</td>
<td>Brown et al. (1996b)</td>
<td>Presentation with haemorrhage</td>
<td>17</td>
<td>Case fatality</td>
<td>30 days after bleed</td>
<td>18%</td>
</tr>
<tr>
<td>Crawford et al. (1986a)</td>
<td>Presentation with haemorrhage (n = 139) or other symptoms (n = 78)</td>
<td>217</td>
<td>Crude annual case fatality (all cause)</td>
<td>7–10 years (mean)</td>
<td>~1.5% per annum</td>
<td>Location anywhere except the parietal lobe</td>
</tr>
</tbody>
</table>

Where no overall average period of follow-up is given in the original studies, the range of average follow-up for the subgroups is given.
Table 6 Studies of AVM clinical course after first presentation with information about the prognosis for intracranial haemorrhage

<table>
<thead>
<tr>
<th>Study details</th>
<th>Patient group</th>
<th>n</th>
<th>Outcome</th>
<th>Assessed at</th>
<th>% with outcome</th>
<th>Factors predicting outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mast et al. (1997)</td>
<td>Presentation with haemorrhage (n = 142) or other symptoms (n = 139)</td>
<td>28</td>
<td>Haemorrhagic presentation: annual re-bleed rate (risk at 5 years) 8–12 months (mean)</td>
<td>18% (58%)</td>
<td>Haemorrhagic presentation, male sex and exclusively deep venous drainage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other presentations: annual first and recurrent bleed rate (risk at 5 years)</td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porter et al. (1998)</td>
<td>First haemorrhage at presentation (n = 75) or during follow-up (n = 56)</td>
<td>131</td>
<td>Recovery. Permanent deficit. ≥12 months</td>
<td>45%</td>
<td>PICH and any haemorrhage during follow-up predicted permanent deficit</td>
<td></td>
</tr>
<tr>
<td>Hartmann et al. (1998)</td>
<td>First haemorrhage at presentation (n = 115) or during follow-up (n = 4)</td>
<td>119</td>
<td>Recovery or Rankin 1, 16 months (mean) Rankin 2–3, Rankin ≥4.</td>
<td>84%</td>
<td>PICH as opposed to other types of intracranial haemorrhage</td>
<td></td>
</tr>
<tr>
<td>Mixed prospective and retrospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondra et al. (1990)</td>
<td>Presentation with haemorrhage (n = 114) or other symptoms (n = 46)</td>
<td>160</td>
<td>Annual bleed rate (mean)</td>
<td>4% per annum</td>
<td>None discovered</td>
<td></td>
</tr>
<tr>
<td>Retrospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brown et al. (1990)</td>
<td>Unruptured AVMs</td>
<td>91</td>
<td>With aneurysm: annual bleed rate at 5 years ≥4 years</td>
<td>7% per annum</td>
<td>Co-existent aneurysm</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Without aneurysm: annual bleed rate at 5 years</td>
<td>1.7% per annum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford et al. (1986a)</td>
<td>Presentation with haemorrhage (n = 139) or other symptoms (n = 78)</td>
<td>217</td>
<td>Annual bleed rate (mean)</td>
<td>2% per annum</td>
<td>Haemorrhagic presentation and increasing age</td>
<td></td>
</tr>
<tr>
<td>Graf et al. (1983)</td>
<td>Presentation with haemorrhage (n = 134) or other symptoms (n = 57)</td>
<td>191</td>
<td>Annual bleed rate (mean)</td>
<td>2% per annum</td>
<td>Small nidus size</td>
<td></td>
</tr>
</tbody>
</table>

Where no overall average period of follow-up is given in the original studies, the range of average follow-up for the subgroups is given. PICH = primary intracerebral haemorrhage.

Table 7 Studies of AVM clinical course after first presentation with information about the prognosis for seizures

<table>
<thead>
<tr>
<th>Study details</th>
<th>Patient group</th>
<th>n</th>
<th>Outcome</th>
<th>Assessed at</th>
<th>% with outcome</th>
<th>Factors predicting outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed prospective and retrospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osipov et al. (1997)</td>
<td>Presentation with seizures alone (all treated with anticonvulsants)</td>
<td>92</td>
<td>Seizure cessation. ≤1 seizure per year. Weekly–monthly seizures.</td>
<td>2 years (median)</td>
<td>75%</td>
<td>None discovered</td>
</tr>
<tr>
<td>Retrospective studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford et al. (1986b)</td>
<td>No prior seizures Presentation with haemorrhage (n = 210) or other symptoms (n = 35)</td>
<td>245</td>
<td>Annual risk of developing de novo seizures 7 years (median)</td>
<td>1% per annum</td>
<td>Haemorrhagic presentation and increasing age at diagnosis</td>
<td></td>
</tr>
</tbody>
</table>
Morbidly caused by haemorrhage
The recognition of a lower case fatality in comparison with other causes of intracranial haemorrhage has generated further interest in the morbidity attributable to haemorrhage caused by AVMs (Table 6). Theoretically, the morbidity of AVM rupture may be ameliorated by patients being younger than their counterparts with PICH, by haemorrhage occurring from vessels at a lower pressure than aneurysmal SAH or spontaneous PICH, by there being less vasospasm than after aneurysmal SAH (Sasaki et al., 1981), and by the limitation of haemorrhage to the nidus of the AVM. Furthermore, the morbidity of intracranial haemorrhage may be less than previously thought, perhaps because the improved resolution and availability of non-invasive imaging have augmented the detection of small PICHs. In a recent study, up to 84% of patients with a first occurrence of haemorrhage made a full recovery or scored only one on the Rankin scale (Hartmann et al., 1998), whilst in another only 45% made a recovery without a permanent deficit (Porter et al., 1998). These findings were, however, based on hospital-based survival cohorts, and are probably subject to their inherent biases, in particular that more severe cases may not have been ascertained at presentation. Whether recurrent bleeds carry a similar morbidity is even less certain (Hartmann et al., 1998; Porter et al., 1998).

Prediction models
Prognostic models are useful for making informed decisions in routine clinical practice, in particular for deciding who may be at greatest risk with conservative management. However, in the absence of a relatively uniform consensus on the important prognostic factors for patients with AVMs, the generalizability of the conflicting results of the existing multivariate analyses is poor. In an effort to simplify the issue of risk prediction, a general 2–4% annual risk of haemorrhage has been used to determine the likelihood of survival free of haemorrhage using the multiplicative law of probability (Kondziolka et al., 1995; Brown, 2000). However, these calculations assume population homogeneity and a uniform risk of haemorrhage over time, both of which are very unlikely to be the case.

What is the risk of developing seizures?
Little attention has been given to the risk of epilepsy from AVMs (Table 7), especially by authors who thought that seizure disorders, although common, were too difficult to quantify (Ondra et al., 1990). From the data that are available, it appears that patients with AVMs carry an annual risk of developing de novo seizures of 1%, and they may be at a greater risk following presentation with haemorrhage, or if they are older (Crawford et al., 1986b). However, when they do occur, at least three-quarters of patients’ seizures come under good control on first-line anticonvulsants (Osipov et al., 1997).

Pregnancy
Controversy has dogged the influence that pregnancy, labour, different modes of delivery and the puerperium may have on bleeding rates from AVMs. Some women with AVMs are advised against pregnancy, others are sterilized, and those who do become pregnant may or may not be encouraged to have a Caesarean section or a termination (Horton et al., 1990; Velut et al., 2000). One retrospective study of women of child-bearing age in an untreated survival cohort being considered for stereotactic radiosurgery, without information on the completeness of follow-up or a statistical analysis, compared their crude rates of first or recurrent haemorrhage outwith and during pregnancy (Forster et al., 1993). Compared with the bleeding rate of 4.5% per annum when they were not pregnant, there was a higher rate of haemorrhage during the second trimester (17% per annum), but not in the other stages of gestation. A second similar study found no influence of pregnancy on haemorrhage rates, although its conclusions are invalidated in a sensitivity analysis by changing the arbitrary duration of pregnancy that they chose (Horton et al., 1990).

Of course, there are several biases inherent in these studies; in particular, the occurrence of haemorrhage may have a fatal outcome so preventing future pregnancy, or may discourage some women from becoming pregnant if the haemorrhage is not fatal. Although it is logistically difficult to resolve this dilemma, only a population-based, prospective cohort study could examine pregnancy as a risk factor for the development of haemorrhage.

Hereditary haemorrhagic telangiectasia
Despite the prevalence of AVMs in people with HHT, there is a paucity of information about their prognosis, and whether it is any different from sporadic AVMs. AVMs of the brain were an infrequent cause of death in a population-based study of people with HHT (Kjeldsen et al., 1999). A small study in which a large proportion of patients were asymptomatic, with a short prospective follow-up period in which no haemorrhages were observed, suggested that the risk of haemorrhage from an AVM in the context of HHT
may be lower than for people with sporadic AVMs, based on an annual bleeding rate of 0.41% (95% CI 0.08–1.19%) derived from a lifetime risk assumption. Clearly, here too, large prospective, population-based studies are needed.

Summary

Despite the large number of studies of the clinical course of AVMs, very few meet rudimentary standards for an ideal design, and fewer still provide consistent results that can be extrapolated to the generality of people with AVMs. It is, of course, difficult to assess the clinical course of AVMs because of their heterogeneity and because they are often treated when discovered. Although the heterogeneous characteristics of the hospital-based studies of clinical course may explain the discrepancies in their results, some general comments can be made. Long-term crude annual case fatality lies somewhere between 1 and 1.5%. Whilst the population-based Olmsted County study found case fatality to be ~20% at 30 days following haemorrhage, hospital-based studies found a similar case fatality at 1 year, probably due to the omission of people dying in the community. The crude annual risk for the first occurrence of a haemorrhage from an unruptured AVM is ~2%, and this may be increased by co-existent aneurysm(s). However, the risk of haemorrhage recurrence may be as high as 18% in the first year, although consistent risk factors for haemorrhage recurrence have not yet been observed. The morbidity attributable to haemorrhage from an AVM remains to be quantified in representative samples, but it does seem less than PICH and SAH due to other causes. AVMs seem to carry an annual risk of developing de novo seizures of 1%, with a good prospect of control on anticonvulsants. The risk of rupture during pregnancy and for patients with HHT has not been established accurately.

Therefore, further studies of the clinical course of large, unbiased samples of people with AVMs, both ruptured and unruptured, are needed. Prospective population-based studies meeting some basic requirements (Table 3) may help to elucidate the mortality rate, case fatality and prognosis for first or recurrent haemorrhage or seizures from AVMs. Even with thorough, targeted investigation of their presenting symptoms, the number of AVMs will still be comparatively small. Therefore, multicentre studies, possibly with international collaboration, will be required to collect sufficient people with untreated AVMs to establish their natural history. Whilst these people may be subject to treatment selection bias, current variation in practice, reflecting uncertainty about whether and how to treat AVMs, will eventually mean that a representative sample is collected. In the interim, these studies will generate useful observational data about both beneficial and adverse effects of treatment, which may lead to appropriate randomized trials. However, it is likely that the true natural history of AVMs established by methodologically sound studies of prognosis, be it identical to or different from existing knowledge, will be the last uncertainty to be resolved.

Concluding remarks

Despite the recognition of AVMs for over a century, and a sizeable literature about them, there is a shortage of high quality studies of their imaging, frequency, presentation and clinical course. Residual areas of uncertainty include the aetiology of AVMs, the sensitivities and specificities of the available imaging techniques (and any observer variability in their interpretation), the incidence and prevalence of AVMs in different populations, the untreated clinical course for large groups of people, and the factors that determine prognosis for particular individuals.

The widespread availability and uptake of brain imaging now provide a timely opportunity to address many of the unanswered questions about AVMs. However, to add anything to existing knowledge, future studies will need to be population-based and large, with an inception cohort and complete follow-up over a long period of time if examining prognosis.

The great variation in, and so uncertainty surrounding, the clinical course of AVMs in different populations, particularly the risk of haemorrhage, makes non-randomized comparison of the outcome of groups of patients treated in different ways all but impossible. However, absolutely no randomized trials of stereotactic radiotherapy, endovascular embolization or surgical excision have ever been reported. Although these trials will be difficult to do, and will clearly require multicentre collaboration, they are particularly necessary in the context of a condition where the prognosis is uncertain for groups of people, let alone for any particular individual.

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