A Population-Based Study of Brain Arteriovenous Malformation
Long-Term Treatment Outcomes

H.T. ApSimon, FRACR; H. Reef, FRCP; R.V. Phadke, MD; E.A. Popovic, FRACS

Background and Purpose—By undertaking long-term follow-up of a functionally isolated population study group, we sought to achieve a true picture of intrinsic brain arteriovenous malformation (BAVM). We sought to assess the validity of earlier population-based series and to determine the effects of newer treatment methods on the overall morbidity and mortality of BAVM.

Methods—We excluded other intracranial vascular pathologies by defining criteria. By retrospective and prospective study, 240 patients with BAVM were followed for a mean of 10.11 years from first diagnosis.

Results—Death rates were as follows: all causes, 12.9%; all BAVM related, 8.75%; BAVM related during conservative management, 24.6%; and BAVM related during active management, 3.9% \( (P=0.031) \). Mean diagnosis-to-death interval was 10.6 years. Oxford neurological disability scale grades of 209 survivors (July 2001) were as follows: grades 0 to 2, 74.1%; grade 3, 17.2%; and grades 4 to 5, 9.5%. Death rates were higher for patients who had bled or suffered nonhemorrhagic neurological deficit at original presentation. Incidence of first-ever hemorrhage in untreated patients was as follows: 0 to 9 years, 4.6% \( (P=0.0035) \); 30 to 39 years, 21% \( (P=0.02) \); and 60 to 69 years, 40.0% \( (P=0.045) \). The first bleed was fatal in 4.6%.

Conclusions—We find no evidence of a substantial undiagnosed reservoir of nonsymptomatic BAVM. All BAVM are potentially hazardous. The great majority of BAVM patients become symptomatic during the patient’s lifetime, and the majority will bleed. The risk of first hemorrhage is lifelong and rises with age. Compared with earlier population-based series, our low overall patient mortality is predominantly due to higher proportions of active treatment in the 1980s and 1990s. (Stroke. 2002;33:2794-2800.)

Key Words: cerebral arteriovenous malformations ■ epidemiology ■ hemorrhage ■ mortality ■ treatment outcome

Western Australia is a relatively isolated and stable community well suited to population-based study. The population in 1970 approximated 1.1 million. According to the last 5-year census in 2001, the population was 1.85 million (male/female ratio 1/1.001). Throughout the 20th century, neuroscience services have been provided only in the capital city of Perth, and all brain arteriovenous malformation (BAVM) patients continue to be managed there (as of July 2002).

By undertaking long-term follow-up of a functionally isolated population study group, we sought to achieve a true picture of intrinsic BAVM. We sought to assess the validity of earlier population-based series and to determine the effects of newer treatment methods on the overall morbidity and mortality of BAVM. In assembling the database for our study, we adopted the following definitions and exclusions: BAVM includes all pial arteriovenous malformation (AVM) and single-vessel fistula confirmed by imaging and surgical or pathological findings. BAVM excludes infantile vein of Galen aneurysmal malformation, dural arteriovenous fistula with or without cortical venous drainage, cavernous hemangioma, venous malformation, and anomalous venous drainage.

Subjects and Methods
The study was conducted with the consent and support of the neurosurgical departments and other clinical neuroscience departments of the teaching hospitals based in Perth, Western Australia. The project has the approval of the Human Rights and Ethics Committee of Royal Perth Hospital and conforms to the committee’s requirements for human patient research.

The basic study cohort comprises all patients with a new diagnosis of BAVM from 1972 through June 30, 1996, and all patients previously diagnosed with BAVM who were still alive and under management from 1972 onward. Thus, 350 patients under the care of neuroscience disciplines were primarily included in the database. After exclusion of interstate and overseas patients, 22 misdiagnoses,
and other aforementioned exclusions, 240 patients constituted the study group (n = 240).

Clinical study of prospective patients was undertaken during 1987–1996 (H.R.). Assessment of clinical and imaging records (H.T.A. and R.V.P.) was supplemented by clinical examination (H.R.), home visit (H.R.), telephone interview, or family physician interview from 1992 through July 2001 (H.R., H.T.A.).

Results

Epidemiology and Presentation

The distribution by decade and annual incidence of definitive diagnosis are summarized in Table 1. On the basis of 86 symptomatic and 2 asymptomatic BAVM first diagnosed from 1990 to June 1996, the age- and sex-adjusted incidence of detected BAVM for that period is 0.89/100 000 person-years (95% CI, 0.69 to 1.09/100 000 person-years). The calculated age- and sex-adjusted prevalence is 5.47/100 000 population (95% CI, 4.31 to 6.63/100 000 population).

The distribution of age at first diagnosis and associated epidemiology are summarized in Figure 1. The percent lobar distribution of superficial hemisphere BAVM (n = 192/240) is summarized in Figure 2. The percent distribution of deep supratentorial and infratentorial BAVM (n = 45/240) is summarized in Figure 3. With the exclusion of midline but inclusion of other deep supratentorial lesions, the right/left ratio of hemisphere BAVM is 1.16/1 (n = 114/98).

The manifestations of BAVM at the time of first diagnosis are summarized in Table 2. Included in the 58.75% of patients with intracranial hemorrhage at or before first diagnosis was a small number with subarachnoid or subdural hemorrhage; some were attributed to aneurysmal as opposed to BAVM origin. The 2.5% incidental diagnoses represent asymptomatic BAVM detected during investigation of unrelated conditions, mainly head injuries. The data are subdivided into acute presentation (definition: first diagnosis at acute admission to hospital previously undiagnosed; n = 143; Figure 4) and nonacute presentation (definition: all other forms of diagnosis; n = 97; Figure 5). We found no patients with previously unsuspected BAVM who were first diagnosed postmortem. Among the nonacute presentations, headache as the presenting symptom did not exceed the incidence of headache in the general community.1,2 Disabling headache was part of the presentation of some patients with progressive neurological deficit, mainly associated with disorders of cerebral perfusion.

Management Categories

The major categories of management are summarized in Figure 6. In the surgery only group, the nonexcisional modalities in 13 patients were the only definitive procedures performed. Patients who subsequently went on to 1 of the other 3 categories of definitive treatment are shown under those categories and not in the surgery only group. Five patients initially managed conservatively (interval range, 4 to 21 years; mean, 14.5 years) and later treated actively are...
included in the appropriate categories, not in the conservative management group.

Patients who underwent short-term or permanent ventricular drainage, but no other procedure as part of the management of acute presentation, are included in the conservative management group. Small numbers of our patients were treated by conventional radiotherapy in earlier years. In the absence of documented or imaging evidence of any patient benefit, we present no data on conventional radiotherapy.

Results of Follow-Up and Patient Outcomes

Contact was maintained in 97.9% of the 240 patients. At most recent contact there are 204 known survivors (85%) and 31 known deaths (12.9%). The death rates (all causes) are as follows: acute presentation, 23/143 (16.1%); nonacute presentation, 8/97 (8.2%) \((P=0.08)\). BAVM-related death rates are as follows: acute presentation, 15/143 (10.5%); nonacute presentation, 6/97 (6.2%) \((P=0.14)\).

The mode of death in the 31 patients is summarized in Table 3. Of the 14 delayed deaths during conservative management, 11 were AVM related; 1 of the deaths from unknown causes was probably AVM related, but cause of death was not recorded. Two patients suffered their first and fatal intracranial hemorrhage within 3 days of the institution of anticoagulant therapy for nonrelated vascular diseases.

Hemorrhage was the proximate cause of death in 21 patients, including 3 BAVM-related delayed deaths after incomplete surgical resection and all 11 BAVM-related deaths during conservative management. No patient with documented complete surgical resection suffered recurrent hemorrhage, and all 5 deaths in this group were due to non-BAVM-related causes.

Five patients (8.8%) of the conservatively managed group achieved documented spontaneous occlusion of their BAVM during observation. None exceeded 2 cm in diameter. Four had bled. Four had only a single draining vein. There were no other distinguishing anatomic or clinical features.

We used the Oxford Scale of neurological handicap (modified Rankin Scale) to assess the status of patients. An abbreviated description of the grades is given in Table 4. At last contact in all survivors, the grade distribution was as follows: 0, 25.8%; 1, 22.5%; 2, 25.8%; 3, 17.2%; 4, 8.1%; 5, 1.4%. When subdivided, there was a moderate increase in grades 2 and 3 in the acute presentation relative to the nonacute presentation subgroups, but otherwise there was little difference between the subgroups.

With the exclusion of 4 procedural and 3 first acute admission deaths, there were 24 delayed deaths, with a mean survival of 12.2 years and a range of 0.4 to 49.4 years. There were 3 BAVM-related and 1 non-BAVM-related deaths in the first year. Eleven of 12 deaths of known cause during conservative management were BAVM related.

To assess the possible effects of incomplete information (Table 3), we constructed a “worst case” scenario, considering the 2 deaths of unknown cause and 3 at-risk patients as BAVM-related deaths (Table 5). Whichever figures are used, the BAVM-related death rate of patients managed conserva-
Outcomes in Survivors (n=209)
The mean duration of survival for all presentations was 10.1 years (10.7 years for 120 acute presentations and 9.3 years for 89 nonacute presentations). (These data include known survival of 5 patients not responding to contact in July 2001.)

Outcomes for Patients With Epilepsy
The incidence of epilepsy not associated with hemorrhage was 27%. At final follow-up, 46% of survivors previously had, or still have, epilepsy. We found that 14.9% of survivors developed epilepsy after first diagnosis; the majority of these followed intracranial hemorrhage or craniotomy. One hundred six survivors suffered epilepsy at some stage. The final status relative to onset was worse in 13.2%, unchanged in 21.7%, improved in 62.3%, and not known in 2.8%.

Outcomes for Patients With Neurological Deficit Not Associated With Hemorrhage (n=19)
Outcomes were as follows: improvement of deficit in 16%, unchanged in 42%, worse in 26%, and death in 16%.

Hemorrhage During Follow-Up
With the exclusion of 3 acute admission deaths and 4 procedural deaths, 9% of patients suffered hemorrhage (n=21/233): 13 recurrent hemorrhages (mean interval, 11.7 years) and 8 first-ever hemorrhages (mean interval, 11.6 years) after diagnosis. Fifteen of the 21 patients died, sometimes after multiple recurrent bleeds, with a mean survival from first diagnosis of 17.2 years.

First-Ever Hemorrhage in Untreated BAVM
Figure 7 shows the percent incidence in each decade from birth. The percent incidence values of 2 other events, definitive treatment before any hemorrhage and last patient contact before the end of the decade, are shown to scale in each column. These 2 events combine with first hemorrhages to reduce the cohort numbers available for analysis in each subsequent decade. The incidence of first hemorrhage rises from 4.6% (P=0.0035) in the first decade to 40.0% (P=0.045) in the seventh decade.

Discussion
When screening cases for potential admission into the study, we accepted imaging or surgical demonstration of fistulous communication from intrinsic brain arteries to superficial or deep venous systems without intervention of normal capillaries. We are aware that other population-based series included some of the entities that we excluded.3,4 Our definitions and exclusions were reached independently but correspond closely to the recent American Heart Association Scientific Statement of Recommendations for Terminology.

Our state population contains a majority of white people of European origin with minorities of indigenous, Asian, and North American origin. The continued residence in Australia of most patients has facilitated continuing follow-up.

The proportion of patients that become symptomatic in their lifetime is central to management decisions. Patients who have bled or have neurological deficit should be recommended for active treatment when the balance of risks is appropriate. Although recently disputed,6 the high incidence

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<th>TABLE 3. Mode of Death in BAVM Patients 1972–2000 (n=31/240*)</th>
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*Lost during follow-up: at risk, 3; clinical cure, 2.
†All due to intracerebral hemorrhage: recurrent, 6; denovo, 5.
‡Two fatal intracerebral hemorrhage, anticoagulant related.

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<th>TABLE 4. Oxford Scale of Neurological Handicap: Abbreviated Description of Grades</th>
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<th>TABLE 5. Known and “Worst Case” Death Rates in BAVM</th>
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<td>Overall death in study, n=31/240</td>
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<td>AVM-related deaths, n=21/240</td>
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<td>AVM-related deaths during conservative management, n=14/57</td>
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<td>AVM-related deaths in active management group, n=7/180</td>
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*Including 3 acute admission deaths managed supportively.
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of postmortem demonstration of BAVM in earlier series implied a substantial proportion or majority of undiagnosed non–life-threatening BAVM. The dilemma thus involves managing the patient who is incidentally discovered or presents with only minor symptoms.

The rising incidence of new diagnoses (Table 1), which peaked at 1.46/100,000 population in 1989, exceeded the population increase. The incidence then decreased despite state CT and MRI unit numbers rising from 9.9 (1985) to 34.3 per million population in 2000. The percentage of patients with only minor symptoms or incidental diagnoses remained unchanged throughout our survey period. The findings indicate that the great majority have detected BAVM.

Prevalence

In a critical review, Berman et al demonstrated that most accepted rates of BAVM prevalence are too high. From the overall 1.1/100,000 detection rate of a single study, they derived an estimated detection rate for symptomatic lesions of 0.94/100,000 person-years (95% CI, 0.57 to 1.30/100,000 person-years). They concluded that “the prevalence of detected active (at risk) AVM disease . . . can be inferred . . . to be lower than 10.3 per 100,000 population.” Our calculated prevalence of BAVM is 5.47/100,000 population (95% CI, 4.31 to 6.63).

Characteristics in Comparison With Other Series

Current views on the natural history and management of symptomatic BAVM are based on multiple reported series. Of varying selection biases, the applicability of the findings is questionable. Earlier population-based series with high proportions of conservative management provide much of the knowledge about conservatively managed patients. In more recently reported series, including our own, the proportion of patients managed conservatively is much lower.

The age range for first diagnosis, mean age of presentation, and male/female preponderance (Figure 1) in our study are similar to other population-based studies. The distribution of hemisphere BAVM (Figure 2), posterior fossa, deep location, and right hemisphere preponderance (Figure 3) are also similar.

When the modes of presentation at time of first diagnosis are compared, there are major similarities. Hemorrhage is the most frequent in all series; our 56% rate is intermediate between the lowest rate of 42% and the highest rates of 69.6%, 71%, and 72%. Our 28% epilepsy rate is the highest. Our rate of 8% neurological deficit not associated with hemorrhage and 2.5% incidental diagnosis are close to those of other series. Our findings support series predominantly devoted to the long-term study of conservatively managed patients.

Before our mortality and morbidity findings are compared, it is necessary to discuss the composition of patient management groups. Overall, 23.8% of our patients were treated conservatively compared with 63% in the study of Crawford et al, 64% in the study of Ondra et al, and 5.2% in the study of Hillman. The main reasons for selection to conservative management differ. In the study of Ondra et al, random assignment by the treating physician appears to have been the primary determinant. In the study of Crawford et al, a rising proportion for surgical treatment for hemorrhagic presentation and a falling proportion for nonhemorrhagic epilepsy presentation were noted during 1940–1984. The study of Hillman is the most recent, with the lowest percentage for conservative management.

We used clinical and anatomic/morphological criteria to compare our conservative and active management groups. The criteria indicate that our conservative management group contains more older patients (P = 0.002), fewer patients who have bled (P = 0.004), and higher proportions of patients who are poor risks for surgery (P = 0.0001), embolization (P = 0.17), or radiosurgery (P = 0.02). Four of 6 patients with incidental diagnosis were in the conservative group. There is no evidence that selection bias toward a worse natural history underlies the high mortality outcome of conservative management. During the 1970s, patients with large or deep-seated AVM, those involving eloquent brain, and those with nonhemorrhagic presentation with epilepsy were increasingly treated conservatively. During the 1980s and 1990s, smaller malformations were increasingly treated by surgery alone or radiosurgery alone. Larger and previously
inal operable malformations were increasingly managed by combined therapy.

Ondra et al and Crawford et al separately reported increased mortality rates and shortened life expectancy for both conservatively treated and actively managed patients. Therefore, in our assessments and comparisons we discuss both AVM-related and whole group mortality figures. Our death rates of 12.9% (all causes) and 8.75% (AVM related) and mean survival period of 10.6 years are lower than those of Crawford et al (calculated risk of death [all causes] at 10 years of 18% and at 20 years of 29%) and those of Ondra et al (death rates overall of 43%, death rates due to AVM hemorrhage of 23%, mean follow-up 23.7 years, calculated mortality from AVM hemorrhage 1%/y). The 9% overall mortality figure for Hillman is more difficult to compare because the study was predominantly an analysis of initial presentation and treatment mortality at 1- and 2-year assessments, and the overall mean duration of follow-up was not stated.

Our series mortality is higher in the acute presentation group than in the nonacute presentation group. Both Ondra et al and Crawford et al found no difference in mortality expectation for the hemorrhagic and nonhemorrhagic presentation groups, despite a higher risk of recurrent hemorrhage demonstrated by Crawford. Mast et al found a higher risk of subsequent bleeding in patients initially presenting with hemorrhage than with other symptoms. In our series, acute presentation with hemorrhage was the main predictor of fatal outcome in both the active management and the conservative management groups. Among survivors who had acute presentation with hemorrhage and were managed conservatively, recurrent hemorrhage, with a small peak in the first year, was the predominant cause of death.

Risk of First Hemorrhage in Untreated Patients

Other studies used statistical regression analysis (including Kaplan-Meier and life survival tables) to derive cumulative and per annum hemorrhage risk. It is sometimes concluded that the risk rises with age, declines, or is static after an early peak. Variable inclusion of recurrent and previous hemorrhage may explain the variations.

We have adopted a simple (nonstatistical) regression technique to analyze by decades the risk of first-ever hemorrhage in untreated patients (Figure 7). With \( P=0.05 \) used as the criterion, the results are significant in 6 of the first 8 decades. Prior treatment reduces the risk in the middle decades (particularly the fifth), but the effect is not quantifiable. The risk may be underestimated but not overestimated by our technique. In untreated patients the risk of first hemorrhage is lifelong and rises with age. We report our technique in detail in the hope that it will be applied to material from other studies to determine if our finding is reproducible.

In our series, active management appears to have played the major role in lowering the death rate. When the 4 procedural deaths are included, our actively managed patient group mortality (overall, 7.8%; AVM related, 3.9%) is clearly less than that of the conservatively managed group (overall, 29.8%; AVM related, 24.6%). Improved technology in radiosurgery planning, increased experience with embolization, and the appropriate selection of modalities should further reduce the mortality.

To assess long-term morbidity, we elected not to use the Glasgow Outcome Scale, which is designed for assessment after severe head injury. In practice, the Oxford Scale worked well for assessing neurological handicap, particularly grades \( \geq 2 \), but the differentiation between grades 0 and 1 was more difficult to use. Many of the changes between grades 0, 1, and 2 related to improvement or remission on treatment for epilepsy and do not reflect neurological deficit. Because of these limitations, we present only the final percent distribution of Oxford grades.

In summary, at final contact 48.3% of survivors had only minor or no symptoms with a normal lifestyle, 25.8% had minor handicap and lifestyle restriction but were fully independent, 17.2% had moderate handicap with some lifestyle restriction but were independent with help, and 9.5% had severe or moderately severe handicap and were dependent. Survivor outcome grades were somewhat worse among patients initially presenting with hemorrhage, but the differences were small. Among patients presenting with initial nonhemorrhagic neurological deficit, 42% had an increased deficit or were dead.

In patients surviving their first acute presentation and/or definitive treatment, our 9% overall hemorrhage rate with a mean hemorrhage-free period of 11.6 years is low compared with the 30% 10-year risk after first diagnosis for Crawford et al. 4%/y risk for Ondra et al and 2.2%/y risk for Brown et al. Even after exclusion of the 3 acute admission deaths, hemorrhage was the proximate cause of death in 20.4% (n=11/54) of patients undergoing elective conservative management. Thus, by achieving a higher proportion of definitive treatment, we reduced the long-term risk of hemorrhage and lowered the overall mortality. The higher proportion of hemorrhage at first presentation in the series of Ondra et al and Crawford et al may imply a selection bias toward more hemorrhagic and potentially fatal malformations. However, the series of Hillman has a high rate of hemorrhage, the lowest proportion of conservatively managed patients, and the lowest overall mortality figures.

Hemorrhage After Diagnosis

After a small peak in the first year, the mean hemorrhage-free interval in our series is long, with a wide scatter. New or recurrent hemorrhage occurred in a small minority of patients treated by embolization and/or radiosurgery. Incomplete nidus occlusion by either or both in combination does not fully protect the patient from the risk of rebleeding. Even imaging evidence of complete occlusion is not totally reliable. These patients, together with incompletely treated and conservatively managed patients, remain at risk of new or recurrent hemorrhage. Without prolonged follow-up with good-quality imaging, a false presumption of clinical cure may occur.

Patient Management Implications

Overall, 149 patients (62.1%) suffered hemorrhage either at or before original presentation or during conservative management. Only 7 patients died of their first hemorrhage (4.6% of those who bled, 2.9% overall). The mortality rate may be
lowered if patients are warned of the risk of anticoagulant therapy. When patients present with known hemorrhage and/or a high probability of future hemorrhage, active management should be employed whenever the balance of risks is in the patient’s favor. When the patient has never bled and the hazards of definitive treatment are considerable, the probability of several hemorrhage-free years and initial survival from a future first hemorrhage should influence appropriate clinical management.7

In summary, the epidemiology and natural history of symptomatic BAVM, described by the work of Ondra et al8 and Crawford et al9 and supported by our study, represents a true picture of the whole spectrum of BAVM. The “iceberg” concept of an underlying body of nonthreatening and symptomless BAVM is flawed and does not have an evidential concept of an underlying body of nonthreatening and symptomless lesion.12 Therefore, we should regard all detected spectra of probabilities but not a discrete identifiable profile of a supported by grants from medical audit funds and the diagnostic Research Foundation of Western Australia. This study is also symptomatic BAVM, described by the work of Ondra et al8 from a future first hemorrhage should influence appropriate ability of several hemorrhage-free years and initial survival.

In the patient management should be employed whenever the balance of risks is in the patient’s favor. Our efforts should be concentrated on identifying and quantifying the risks of different modalities of treatment and choosing the best options for the individual patient.7,10a,20,23,29

Acknowledgments

Grants in aid have been made via the peer-reviewed Medical Research Foundation of Western Australia. This study is also supported by grants from medical audit funds and the diagnostic radiology trust fund of Royal Perth Hospital. We acknowledge the assistance of Gordon Murray, Max Le, Mark Khangure, Bryant Stokes, Constantine Photouros, David Rosen, Barbara Taylor, Jacque Burns, Lisa Kelly, Jenny Linto, Teresa O’Shannassy, Jenny Trench, and members of clinical neuroscience departments and medical record departments of Western Australian Teaching Hospitals, Perth, National Death Index, and Australian Institute of Health and Welfare Canberra Australia. More detailed treatment of some aspects and an extended reference list are available at our Web site.

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Stroke. 2002;33:2794-2800; originally published online November 21, 2002;
doi: 10.1161/01.STR.0000043674.99741.9B
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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