Prospective, Population-Based Detection of Intracranial Vascular Malformations in Adults
The Scottish Intracranial Vascular Malformation Study (SIVMS)

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Background and Purpose—Intracranial vascular malformations (IVMs) are an important cause of intracranial hemorrhage, epilepsy, and long-term disability in adults. There are no published prospective, population-based studies dedicated to the detection of any type of IVM (cavernous malformations, venous malformations, and arteriovenous malformations [AVMs] of the brain or dura). Therefore, we established the Scottish Intracranial Vascular Malformation Study (SIVMS) to monitor detection and long-term prognosis of people with IVMs.

Methods—We used multiple overlapping sources of case ascertainment to identify adults (aged ≥16 years) with a first-ever-in-a-lifetime diagnosis of any type of IVM made between January 1, 1999, and December 31, 2000, while resident in Scotland (mid-1999 adult population estimate 4 110 956).

Results—Of 418 notifications to SIVMS, 190 adults (45%) were included, 181 (95%) of whom were deemed to harbor a definite IVM after review of diagnostic brain imaging and/or reports of autopsy/surgical excision pathology. The crude detection rate (per 100 000 adults per year) was 2.27 (95% CI, 1.96 to 2.62) for all IVMs, 1.12 (95% CI, 0.90 to 1.37) for brain AVMs, 0.56 (95% CI, 0.41 to 0.75) for cavernous malformations, 0.43 (95% CI, 0.31 to 0.61) for venous malformations, and 0.16 (95% CI, 0.08 to 0.27) for dural AVMs.

Conclusions—In addition to providing data on the public health importance and comparative epidemiology of IVMs, continuing recruitment and follow-up of this prospective, population-based cohort will provide estimates of IVM prognosis. (Stroke. 2003;34:1163-1169.)

Key Words: central nervous system ■ cerebral arteriovenous malformations ■ incidence ■ prognosis ■ registries ■ vascular malformations
models, and potentially provide a cohort for case-control studies and recruitment into randomized controlled trials.\textsuperscript{10}

Hospital-based studies will not suffice. Until recently,\textsuperscript{13} prevalence estimates have been derived from hospital-based autopsy series, but these are subject to each institution’s frequency of postmortem examination and various referral/selection biases, as well as the special interests and meticulousness of the pathologists.\textsuperscript{14} Hospital-based studies, especially those from tertiary referral centers, are also unrepresentative of the population because they tend to miss both sudden deaths in the community and people who are not thought to warrant hospital admission (be they asymptomatic or unsuitable for treatment).\textsuperscript{1} Moreover, there is a growing appreciation of the long-suspected differences between these hospital-based series, which are likely to reflect regional investigation and referral patterns and specialists’ access to and interest in particular interventional treatments, and varying classifications used by research groups.\textsuperscript{15–17}

Until now, there has been 1 population-based study of the detection rates of all IVMs. This study was retrospective and was based on the population (approximately 124 000) of Olmsted County, Minnesota, over 27 years, using the comprehensive Mayo Clinic Medical Records Linkage System.\textsuperscript{18} Other studies of detection rates have included only brain AVMs and may not have been truly population based. A retrospective study based on the population of the islands of Bonaire and Curaçao in the Netherlands Antilles (population approximately 155 000) over 10 years was actually based at a single referral center, used catheter angiography as the diagnostic standard, and only identified symptomatic people among whom there was an uncharacteristically high prevalence of multiple brain AVMs and hereditary hemorrhagic telangiectasia.\textsuperscript{19} A prospective study based at a single neurosurgical referral center in Linköping, Sweden, over 11 years has been extrapolated to its catchment area (population 986 000) by retrospectively searching databases at its 10 local referring hospitals, although not autopsy records.\textsuperscript{20}

Because of the absence of contemporary, truly population-based prospective studies and evidence that the detection of IVMs has been increasing over recent decades, probably because of the increasing availability, use, and quality of diagnostic imaging,\textsuperscript{18,21,22} we established the Scottish Intracranial Vascular Malformation Study (SIVMS) in 1998 (http://www.dcn.ed.ac.uk/ivm).\textsuperscript{1,23} We herein report the detection rates of all IVMs in the adult population of Scotland in 1999 and 2000.

Subjects and Methods

Inclusion Criteria

SIVMS included people with a first-in-a-lifetime diagnosis of an IVM made on or after January 1, 1999, when they were aged ≥16 years and were permanently resident in Scotland. The year of detection was determined by the date of the pathological or radiological examination that established a definite IVM diagnosis.\textsuperscript{1} Detection data in this analysis relate only to definite diagnoses made in 1999 and 2000 of the following IVMs: AVMs of the brain and dura, cavernous malformations, and venous malformations.

Exclusion Criteria

Adults with indefinite diagnoses of IVMs, pure vein of Galen malformations, spinal vascular malformations, capillary malformations (telangiectasia), and aneurysms without an accompanying IVM were excluded from the study.

Study Design

Incident diagnoses were identified by multiple, overlapping sources of case ascertainment. The main source was a collaborative nationwide network of physicians, surgeons, radiologists, and pathologists affiliated with the clinical neurosciences and brain imaging facilities in Scotland. Second, we searched for people meeting our inclusion criteria in centralized, routine coding of hospital discharge and death certificates, but because of the limitations of the International Statistical Classification of Diseases, 10th Revision (ICD-10), we were only able to search for brain AVMs (Q28.2 and I60.8). Third, we approached every general (family) practitioner (GP) in Scotland to find any eligible people as yet unknown to SIVMS. These sources are described and evaluated in an accompanying article.\textsuperscript{1}

Statistical Analysis

The crude detection rate was calculated cumulatively for 1999 and 2000 as the proportion of the adult (aged ≥16 years) mid-year population estimate for Scotland that was detected as having an IVM during that year.

Ideally, the detection rate calculation should remove prevalent people from the denominator. We could not do this because the prevalence of all IVMs has not yet been estimated accurately,\textsuperscript{9,14} although we have recently estimated the point prevalence of brain AVMs.\textsuperscript{13} However, the number of prevalent people is likely to be so small as to make a negligible impact on our detection rates.

We calculated 95% CIs around detection rate estimates according to the Poisson distribution.\textsuperscript{24} Age-standardized detection rate estimates were directly age-adjusted to the last census in Great Britain in 1991 (http://www.census.ac.uk) and the last census in the United States in 2000 (http://factfinder.census.gov).

Results

Detection Rate of IVMs

Figure 1 illustrates the recruitment to SIVMS from January 1, 1999, to December 31, 2000, inclusive. The collaborative nationwide network notified the largest number of people to SIVMS, followed by routine coding of hospital discharge data and death certificates. Scotland’s GPs contributed so few eligible people in 1999 who were as yet unknown to the study that we abandoned this source in the second year of the study. Of 418 notifications, 190 (45%) were eligible and were included in SIVMS.

Crude Detection Rate

After review of diagnostic brain imaging and reports of pathological examinations, 181 (95%) of those included were deemed to harbor a definite IVM (Figure 1 and Table 1). There was an increase in the number of definite cases detected from 85 to 96 between 1999 and 2000, which was not statistically significant, with a concomitant rise in the mid-year adult population estimate for Scotland from 4 110 956 to 4 114 052. Although some 95% CIs around the crude estimates of the detection rate of each IVM type overlapped, brain AVMs were the most common type of IVM detected (Table 2). Brain AVMs had the highest age-specific detection rate across all 10-year mid-decade age bands, and there was a tendency toward a peak detection rate in the group aged 46 to 55 years (Figure 2). Age-standardized detection rates directly age-adjusted to the last decennial censuses in Great Britain and the United States were essentially the same as the crude estimate of detection for every IVM type (Table 2).
Presenting Features

The sex ratio was approximately equal for each IVM type, and there was no difference in the sex ratio between the IVM types ($\chi^2=0.9 \ [df=3], \ P=0.83$) (Table 1). There was a significant difference between the median ages at presentation of each IVM type ($\chi^2=8.7 \ [df=3], \ Kruskal-Wallis \ test, \ P=0.03$) due to people with dural AVMs being older despite the median ages at presentation for the other IVM types being similar. Aneurysms were found in association with one fifth of brain AVMs but were significantly less frequent among the other IVMs.

Symptomatic Detection

We segregated IVMs that were clinically silent from those that were symptomatic and subdivided them by mode of presentation (Table 3). There were well-recognized, significant differences between IVM types in the proportions of adults who were detected with clinically silent lesions and those who were incident with symptomatic lesions. Incidental discovery at autopsy accounted for only 12% of asymptomatic IVMs being discovered in the investigation of unrelated symptoms (such as headache and tinnitus). Brain AVMs accounted for the vast majority of intracranial hemorrhages. Coexisting aneurysms were found to account for 4 of the 42 first-ever brain AVM hemorrhages, although only 74% of the cohort of brain AVMs were investigated with catheter angiography. The detection rate of first-ever hemorrhage from a brain AVM (or associated aneurysm) was 0.51 (95% CI, 0.37 to 0.69) per 100,000 adults per year.

Adjustment for Incomplete Case Ascertainment of Brain AVMs

We used capture-recapture analysis to assess the completeness of case ascertainment. This technique relies on the observed overlap between 2 sources of case ascertainment to estimate the number of people missed. Brain AVMs were the only IVM type to have another source apart from the collaborative network because ICD-10 codes do not exist for any of the other IVMs. We used a 2-source model to estimate the upper detection rate of brain AVMs based on the degree of overlap in ascertainment between the collaborative network and routine coding of hospital discharge data and death certificates. Of the 92 people with brain AVMs in 1999 and

<table>
<thead>
<tr>
<th>TABLE 1. Adults With Definite IVMs Detected by SIVMS</th>
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</thead>
<tbody>
<tr>
<td>1999 Cases</td>
</tr>
<tr>
<td>Brain arteriovenous malformation</td>
</tr>
<tr>
<td>Cavernous malformation</td>
</tr>
<tr>
<td>Venous malformation</td>
</tr>
<tr>
<td>Dural arteriovenous malformation</td>
</tr>
<tr>
<td>Overall</td>
</tr>
</tbody>
</table>

*Total includes 36 people with a solitary cavernous malformation, 4 people with multiple cavernous malformations, and 6 people with a coexisting venous malformation.

§This total does not include the 6 people with a coexisting cavernous malformation.

IQR indicates interquartile range.
2000, 34 were identified by collaborators alone, 4 by routine coding alone, and 54 by both sources. Capture-recapture analysis estimated that the 2 sources missed 3 (95% CI, 1 to 9) people. The number of incident adults with brain AVMs could have been between 93 and 101. This resulted in a negligible change of the estimated detection rate from 1.12 per 100,000 adults per year to between 1.13 and 1.23 (95% CI, 1.00 to 1.49) per 100,000 adults per year.

Discussion

We used multiple, overlapping sources of case ascertainment to prospectively recruit a population-based cohort, which we have shown to be distributed in proportion to the Scottish population and which would have been biased had we relied on fewer and simplified sources of ascertainment. Over 2 whole years of the study, we found the crude detection rate of adults harboring a first-ever-in-a-lifetime definite radiologi-

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### Table 2. Detection Rates of Definite IVMs

<table>
<thead>
<tr>
<th>Detection Rate of</th>
<th>Detection Rate of</th>
<th>Crude Detection Rate in Scottish Adults 1999 &amp; 2000 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic Lesions 1999 &amp; 2000 (95% CI)*</td>
<td>Asymptomatic Lesions 1999 &amp; 2000 (95% CI)*</td>
<td>1.12 (0.90–1.37)</td>
</tr>
<tr>
<td>Brain arteriovenous malformation</td>
<td>0.69 (0.70–1.12)</td>
<td>0.23 (0.14–0.36)</td>
</tr>
<tr>
<td>Cavernous malformation</td>
<td>0.24 (0.15–0.38)</td>
<td>0.32 (0.21–0.46)</td>
</tr>
<tr>
<td>Venous malformation</td>
<td>0.02 (0.01–0.09)</td>
<td>0.41 (0.29–0.58)</td>
</tr>
<tr>
<td>Dural arteriovenous malformation</td>
<td>0.14 (0.07–0.24)</td>
<td>0.02 (0.01–0.09)</td>
</tr>
<tr>
<td>All IVMs</td>
<td>1.29 (1.06–1.56)</td>
<td>0.98 (0.78–1.22)</td>
</tr>
<tr>
<td><strong>Age-Standardized Crude Detection Rate</strong></td>
<td><strong>Great Britain†</strong></td>
<td><strong>United States‡</strong></td>
</tr>
<tr>
<td><strong>Brain arteriovenous malformation</strong></td>
<td>1.10</td>
<td>1.12</td>
</tr>
<tr>
<td><strong>Cavernous malformation</strong></td>
<td>0.55</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Venous malformation</strong></td>
<td>0.42</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Dural arteriovenous malformation</strong></td>
<td>0.16</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>All IVMs</strong></td>
<td>2.25</td>
<td>2.30</td>
</tr>
</tbody>
</table>

*See Table 3 for further description of asymptomatic/incidental and symptomatic adults.
†Directly age-adjusted to the 1991 census population of Great Britain (Great Britain includes England, Wales, and Scotland, but not Northern Ireland).
‡Directly age-adjusted to the 2000 census population of the United States.
§This detection rate calculation includes the 6 adults with a coexistent cavernous and venous malformation.
cal and/or pathological diagnosis of any type of IVM to be 2.27 (95% CI, 1.96 to 2.62) per 100 000 adults per year. Brain AVMs were the most common type of IVM, with a crude detection rate of 1.12 (95% CI, 0.90 to 1.37) per 100 000 adults per year. The upper 95% CI around this estimate of brain AVM detection could be as high as 1.49 per 100 000 adults per year after adjustment for incomplete ascertainment by capture-recapture analysis.

**Incidence Versus Detection**

Strictly, incidence refers to the development of disease in a population initially free of it.9,14,26 SIVMS will undoubtedly have missed as-yet-undiagnosed asymptomatic IVMs, which could be considered “prevalent” and which may declare themselves—thereby becoming “incident”—at a later date or remain asymptomatic until death (Table 3). Therefore, our quantification of incidence is really a reflection of the rate of detection of IVMs. However, this is also true of many other diseases for which the term incidence is used, and we prefer the widely understood term incidence to the more semantically correct term detection rate.

Studies of asymptomatic volunteers undergoing MRI have found 2 (0.2%) of 1000 people of all ages and 5 (0.14%) of 3672 adults aged ≥65 years to harbor asymptomatic cavernous malformations.27,28 Although these studies have not detected asymptomatic brain AVMs, a “brain check-up” system in Japan has found, using MR angiography, 3 (0.1%) of 3085 apparently healthy people to harbor a brain AVM (Yukito Shinohara, MD, Tokai University School of Medicine, written communication, 2001). Hospital-based postmortem series have reported the prevalence of all brain AVMs to be approximately 600 per 100 000 (0.6%)29–31; in this study there were 3 incidental brain AVMs identified among 14 630 postmortem brains in Scotland (0.02%).1 although these will have been underascertained. In any case, the number of asymptomatic IVMs at any one time remains imponderable because of their likely dynamic development and the de novo appearance of some types.32–35

Because the extent of detection of asymptomatic IVMs is undoubtedly affected by regional autopsy rates, the availability and resolution of brain imaging, and the propensity of clinicians to use it, some prefer to adapt epidemiological terminology and describe detection rates, given that the number of truly incident IVMs is immeasurable.14,36 The most meaningful comparison between studies is the detection rate of symptomatic IVMs because they are the most clinically relevant (Tables 2 and 3). However, because of the tendency of some interventionists to treat IVMs regardless of their mode of presentation, a quantification of asymptomatic detection rate is also important.

**Comparison With Other Studies**

We found the proportion of symptomatic IVMs in our study to be very similar to that of the Mayo Clinic study18 and the detection rate of first-ever hemorrhage from a brain AVM to be very similar to the rate in the North Manhattan Stroke Study.37 The New York Islands Arteriovenous Malformations Study (NYIAMS) (http://cpmcnet.columbia.edu/dept/avm) is an ongoing study (similar to SIVMS) that began in 2000, focuses on brain AVMs only, and is based on a population more mobile than that of Scotland with a 4% annual flux at the state and/or county level (http://factfinder.census.gov).38 Despite the design limitations of other studies, it is interesting that their estimates are comparable to the estimates of SIVMS of the crude detection rate (Figure 3).18–20

Our contemporary estimate of the detection rate of cavernous malformations is significantly greater than the detection rate observed during 1965–1992 in the Mayo Clinic study.18 The apparent increased detection rate of cavernous malformations is most likely due to the growing availability, uptake, and resolution of MRI, on which their diagnosis is dependent,18 leading to their greater detection rather than to any real increase in the incidence of disease. This is borne out by the similarity of the detection rate of cavernous malformations in SIVMS to their detection rate in the latter years of the Mayo Clinic study (when MRI was available).18

**Potential Biases and Limitations**

Design, regional biases, and challenges posed by IVMs themselves will inevitably affect estimates of detection rates. Truly population-based studies may detect people missed by studies based at tertiary referral centers because their IVMs were not thought to warrant specialist attention or because their IVMs caused sudden death in the community from devastating intracranial hemorrhage. Regional variations in autopsy rates, the availability of neurologists, neurosurgeons, and stroke physicians, and the availability of brain imaging will govern how headache, epilepsy, and intracranial hemorrhage are cared for in the community.

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**TABLE 3. Mode of Clinical Presentation of Adults With Definite IVMs Detected by SIVMS**

<table>
<thead>
<tr>
<th>Mode of Presentation</th>
<th>Brain Arteriovenous Malformation</th>
<th>Cavernous Malformation</th>
<th>Venous Malformation</th>
<th>Dural Arteriovenous Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Imaging</td>
<td>16</td>
<td>21</td>
<td>27</td>
<td>2</td>
</tr>
<tr>
<td>Total (%)</td>
<td>19 (21)</td>
<td>26 (57)</td>
<td>28 (93)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>42</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>25</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Total (%)</td>
<td>73 (79)</td>
<td>20 (43)</td>
<td>2 (7)</td>
<td>11 (85)</td>
</tr>
</tbody>
</table>
hemorrhage are investigated. These regional factors are discussed elsewhere. SIVMS did not seek every intracranial hemorrhage in Scotland, precluding an estimate of how many underlying IVMs might have been missed because of lack of investigation.

IVMs themselves can be difficult to diagnose accurately given their occasional morphological overlap, the existence of angiographically occult brain AVMs, and the perceived inappropriateness of definitive investigation of certain people, particularly the elderly. Moreover, the presence of an IVM underlying an intracranial hemorrhage can sometimes only be inferred because of the obliteration of a brain AVM nidus or cavernous malformation by the hemorrhage itself, leaving only clues to its cause, such as an early draining vein on a catheter angiogram. Furthermore, there will be an inevitable bias toward the detection of IVMs with a more aggressive prognosis because people with recurrent hemorrhage or epilepsy after prior events (perhaps in the distant past) are more likely to have further or repeated investigation.

Conclusions
SIVMS provides contemporary estimates of the detection rate of all IVMs in adults, which help to assess their public health importance. The study is also the foundation for future studies of the comparative epidemiology of IVMs and their clinical course and prognosis. It remains to be seen whether recruitment and patterns of identification and presentation in SIVMS will remain the same; as larger numbers are recruited, the precision of our estimates will increase, and significant dissimilarities could emerge. We plan to assess the cumulative detection rate of IVMs with continued recruitment to the cohort (which will span a total of at least 6 years), paying particular attention to any trends in the detection of asymptomatic IVMs. Given the poor quality of existing studies of IVM prognosis, other population-based studies are essential.
for future evaluations of the clinical course of IVMs and the
effects of their treatment, as are randomized controlled
trials.10

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for the SIVMS Collaborators

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