Prevalence and Risk of Rupture of Intracranial Aneurysms
A Systematic Review

Gabriel J.E. Rinkel, MD; Mamuka Djibuti, MD; Ale Algra, MD; J. van Gijn, MD, FRCPE

Background and Purpose—The estimates on the prevalence and the risk of rupture of intracranial saccular aneurysms vary widely between studies. We conducted a systematic review on prevalence and risk of rupture of intracranial aneurysms and classified the data according to study design, study population, and aneurysm characteristics.

Methods—We searched for studies published between 1955 and 1996 by means of a MEDLINE search and a cumulative review of the reference lists of all relevant publications. Two authors independently assessed eligibility of all studies and extracted data on study design and on numbers and characteristics of patients and aneurysms.

Results—For data on prevalence we found 23 studies, totalling 56,304 patients; 6,685 (12%) of these patients were from 15 angiography studies. Prevalence was 0.4% (95% confidence interval, 0.4% to 0.5%) in retrospective autopsy studies, 3.6% (3.1 to 4.1) for prospective autopsy studies, 3.7% (3.0 to 4.4) in retrospective angiography studies, and 6.0% (5.3 to 6.8) in prospective angiography studies. For adults without specific risk factors, the prevalence was 2.3% (1.7 to 3.1); it tended to increase with age. The prevalence was higher in patients with autosomal dominant polycystic kidney disease (relative risk [RR], 4.4 [2.7 to 7.2]), a familial predisposition (RR, 4.0 [2.7 to 6.0]), or atherosclerosis (RR, 2.3 [1.7 to 3.1]). Only 8% (5 to 11) of the aneurysms were 10 mm.

For the risk of rupture, we found nine studies, totalling 3,907 patient-years. The overall risk per year was 1.9% (1.5 to 2.4); for aneurysms =10 mm, the annual risk was 0.7% (0.5 to 1.0). The risk was higher in women (RR, 2.1 [1.1 to 3.9]) and for aneurysms that were symptomatic (RR, 8.3 [4.0 to 17]), >10 mm (RR, 5.5 [3.3 to 9.4]), or in the posterior circulation (RR, 4.1 [1.5 to 11]).

Conclusions—Data on prevalence and risk of rupture vary considerably according to study design, study population, and aneurysm characteristics. If all available evidence with inherent overestimation and underestimation is taken together, for adults without risk factors for subarachnoid hemorrhage, aneurysms are found in approximately 2%. The vast majority of these aneurysms are small (=10 mm) and have an annual risk of rupture of approximately 0.7%. (Stroke. 1998;29:251-256.)

Key Words: subarachnoid hemorrhage ■ aneurysms ■ epidemiology ■ systematic review

Uncertainty surrounds the prevalence of unruptured saccular aneurysms on intracranial arteries. In angiographic and autopsy studies, estimates for prevalence vary between 2 and 90 per 1000.1,2 This wide range probably reflects methodological differences between studies: prospective or retrospective design, diagnostic tools (angiography or autopsy), and study populations. Many studies have included patients with ruptured aneurysms, which results in too high a prevalence. On the other hand, studies reviewing routine autopsy records or angiograms of only a single carotid artery probably underestimate the prevalence. Accurate data on the prevalence of intracranial aneurysms are essential in evaluating the results of screening programs for aneurysms in patients with increased risk for SAH such as patients with ADPKD3 or first-degree relatives of patients with SAH. Also, the management strategy for unruptured aneurysms is influenced by the prevalence; because the incidence of SAH has been properly assessed and is stable, a higher than previously assumed prevalence of aneurysms would mean that unruptured aneurysms are less dangerous.

We conducted a systematic review of all reports on prevalence of intracranial aneurysms and classified the data according to study design, diagnostic methods, and study population. To assess the accuracy of the data on prevalence, we also systematically reviewed data on the risk of SAH in patients with unruptured intracranial aneurysms because prevalence combined with annual risk of rupture should equal the incidence of SAH. This calculated incidence can then be compared with the incidence observed in the population.5

Methods
Identification of Studies
To identify studies published between 1955 and June 1996 on prevalence and natural history of intracranial saccular aneurysms, we first performed a MEDLINE search from 1966 onward. Second, we searched the reference lists of all relevant publications for additional studies. The references of the publications thus found were checked.
Intracranial Aneurysms: Prevalence and Risk of Rupture

Selected Abbreviations and Acronyms

- ACA = anterior communicating artery
- ADPKD = autosomal dominant polycystic kidney disease
- ICA = internal carotid artery
- MCA = middle cerebral artery
- SAH = subarachnoid hemorrhage

again for additional studies published between 1955 and June of 1996. This method of cross-checking was continued until no further publications were found. In case of multiple publications on the same study population, we used the most recent publication. Language other than English was not an exclusion criterion.

Eligibility Studies

To assess eligibility, two authors independently reviewed all studies with a set of predefined inclusion criteria. A first inclusion criterion for all studies was that the presentation of data included crude numbers or allowed recalulation into crude numbers. In autopsy studies, additional inclusion criteria were that ruptured saccular aneurysms and also fusiform and mycotic aneurysms had to be excluded or separately reported. In angiography studies on prevalence, additional criteria were (1) angiography had to be intra-arterial, (2) the indication for angiography had to be given, and (3) the number of patients had to be more than 10. In studies that used CT angiography or MR angiography, the presence of aneurysms had to be confirmed by conventional angiography. The inclusion criteria for follow-up studies about the risk of bleeding in patients with unruptured aneurysms were (1) the type of aneurysm had to be identifiable as one of three categories: incidental (found by chance), additional (multiple aneurysms in patients with SAH), or symptomatic but unruptured; (2) in patients with additional aneurysms, the ruptured (“index”) aneurysm had to have been clipped (wrapping was considered inadequate to prevent further ruptures); and (3) in patients with previously clipped aneurysms, the source of subsequent bleeding had to be identified by CT, surgery, or autopsy, to exclude rerupture of the previously clipped aneurysm as a cause for the hemorrhage. In some studies, only subsets of patients met all inclusion criteria; only those patients were included in the review.

Data Extraction

After the initial assessment for eligibility, two authors independently extracted the following data for studies on prevalence: total number of patients; number of patients with aneurysms; age and sex of all patients and of patients with aneurysms; and site and size of the aneurysms found. The indications for angiography were categorized into the following groups: family history of SAH, ADPKD, atherosclerosis (carotid artery disease or ischemic heart disease), suspected pituitary adenoma, brain tumor, and other. The ages of the patients were grouped into decades; the sites of the aneurysms were grouped into one of four locations: (1) ICA, (2) ACA or anterior cerebral and pericallosal artery, (3) MCA, and (4) vertebrobasilar arteries. The sizes of the aneurysms were categorized into categories of 5-mm increases, and the size was also dichotomized into 10 mm or larger. For follow-up studies in patients with unruptured aneurysms, we recorded the total number of patients, the period of follow-up, and the number of patients with SAH. When possible, we stratified data according to age and sex of the patients and to site and size of the aneurysms.

Data Analysis

For calculating the risk of SAH in patients with unruptured aneurysms, we multiplied the number of patients by the average period of follow-up to obtain the total number of patient-years of follow-up. The number of patients with subsequent SAH was then divided by this number of patient-years, yielding the risk of SAH per patient-year. We used this method for calculating the risk of SAH in all patients as well as in the prespecified subgroups (according to age group and sex or to type, site, and size of aneurysms).

Results

For the overview of prevalence of aneurysms, we found 8 autopsy and 15 angiography studies that fulfilled all the inclusion criteria (Fig 1). One of these 23 publications was in French, another in Japanese, and the remaining 21 were in English. The number of patients studied in these 23 series totalled 56,304; 49,619 of these patients (88%) were from autopsy studies, and 6685 patients (12%) were from angiography studies. In 738 patients, one or more aneurysms were found; 405 of these patients (55%) were from autopsy studies. Data on whether more than one aneurysm was found in single patients could be extracted from two autopsy studies1,2 and from all angiography studies; the number of extra aneurysms was 23 in the autopsy studies and 69 in the angiography studies. The total number of aneurysms found was 830.

The prevalence in the retrospective autopsy studies was much lower than in prospective autopsy studies or in angiography studies (retrospective or prospective) (Fig 1). The prevalence in these last three types of studies combined was 4.3 (95% confidence interval, 4.0 to 4.7) per 100. The prevalence of aneurysms was very low in the first two decades of life and steadily increased after the third decade; this increase was statistically significant in a weighted linear regression (Fig 2).

Autopsy studies did not allow relating the frequency of aneurysms to sex, comorbidity, or cause of death. In angiography studies, more men (n = 1754) than women (n = 1254) were studied; the prevalence was lower in men (Table 1). If subdivided according to the indication for angiography, patients with ADPKD and patients with a positive family history had the highest risk for aneurysms, but patients with a suspected pituitary adenoma (in whom the angiogram was often specifically done to exclude an aneurysm as cause of compression on the optic nerve) and patients with atherosclerosis also had a higher risk than patients with a brain tumor or other indications for angiography (Table 1).

The site of the aneurysm was recorded for 563 aneurysms, from all angiography studies and two autopsy studies. ICA aneurysms were most commonly found, and posterior circulation aneurysms least commonly (Table 2). The size of the aneurysm could be studied for categories of 5 mm in 356 aneurysms, from 10 angiography and 2 autopsy studies (Table 2). The proportions within these categories were similar in the autopsy and angiography studies. One study used categories of 10 mm18; when the 83 aneurysms ≤10 mm and the 10 aneurysms >10 mm from this study were added, the proportion of aneurysms 10 mm remained essentially the same (8%; 95% confidence interval, 5% to 11%).

For the analysis of the risk of SAH in patients with unruptured aneurysms, nine studies, totalling 3907 patient-years, fulfilled the inclusion criteria (Table 3).28–36

The risk of rupture of aneurysms depended more on the characteristics of the aneurysm than on those of the patient. Women and patients at higher age tended to have an increased risk of rupture, but the 95% confidence intervals were wide. Symptomatic aneurysms, posterior circulation aneurysms, and large (>10 mm) aneurysms had a higher risk of rupture. Additional aneurysms also had a higher risk of rupture than accidentally found asymptomatic aneurysms, but this difference was not statistically significant. Data provided in the publica-
tions were insufficient for a multivariate analysis to assess whether these factors are independent prognosticators.

Discussion

The frequency of incidental aneurysms varied considerably according to the indication for the imaging studies. The prevalence of 2.3 per 100 in patients with brain tumors or miscellaneous indications may most closely represent the prevalence in the general population, although this number probably overestimates the actual rate because the prevalence in patients younger than 20 years is very low and this age group is obviously underrepresented in this study sample. The frequency of aneurysms is higher in patients investigated for ADPKD or with a familial predisposition for SAH, suspected pituitary adenomas, and atherosclerosis; moreover, it tends to increase with age in adults.

The methods used to detect the aneurysms markedly influenced the proportion of aneurysms. In retrospective autopsy studies, the prevalence was much lower (0.4%) than in prospective autopsy studies or in angiography studies of either design. A probable explanation for this low prevalence in retrospective autopsy studies is that these review old files, rather than original materials, in contrast to retrospective angiography studies that can review the actual studies. The data derived from the retrospective autopsy studies are therefore probably an underestimation of the prevalence. The much higher prevalence found in prospective angiography studies compared with prospective autopsy studies is probably explained by selection bias because patients with ADPKD, a familial predisposition for SAH, or atherosclerosis are overrepresented in the prospective angiography series. The prospective angiography series therefore seem to overestimate the prevalence.

For the risk of rupture, the type of aneurysm is an important factor. Incidentally found aneurysms tend to have a lower risk of rupture than aneurysms found additional to a ruptured aneurysm. Symptomatic aneurysms, aneurysms larger than 10 mm, and basilar artery aneurysms were all found to have a
markedly increased risk of rupture. Because symptomatic aneurysms are often large, size and being symptomatic may not be independent risk factors, but unfortunately the data provided in the publications did not allow us to assess the interdependence of these factors.

Despite all these sources of bias, the data seem reasonably accurate. A hypothetical calculation of the incidence from the data on prevalence and risk of rupture should approximate the incidence of SAH observed in the population (6 per 100 000 patient-years). If one assumes a cohort of 100 000, only the proportion (75%) of individuals older than 20 years is at risk for aneurysms. Most of these 75 000 individuals will not have risk factors for the presence of aneurysms and will therefore have a prevalence comparable to the subset of patients with “brain tumor and other indications for angiography” (2.3%). In these 75 000 individuals, 1725 will have an aneurysm. Because 93% of aneurysms are $\leq 10$ mm, 1605 subjects in the cohort will have an aneurysm $\leq 10$ mm, and 120 subjects an aneurysm $>10$ mm. If the annual risk of rupture in this cohort (0.7% for aneurysms $<10$ mm and 4% for those of $\geq 10$ mm) is corrected on the assumption that in the general population almost all ruptured aneurysms are previously asymptomatic and not additional to a ruptured aneurysm (0.8/1.9 = 0.4) in a single year, 0.4*0.7% of the 1605 small aneurysms (n=4.6) and 0.4*4% of the 120 large aneurysms (n=1.9) will rupture; the total number of SAHs within the cohort of 100 000 subjects will therefore be 6.5. This calculated incidence is similar to the incidence of 6 per 100 000 patient-years observed in the population.

Other factors also corroborate the accuracy of the data in this review. First, women more often had aneurysms than men and their aneurysms had a greater risk of rupture, which explains the higher incidence of SAH in women. Second, patients with ADPKD and patients with a familial predisposition for SAH had an increased risk of aneurysms. This finding is in keeping with the increased risk of SAH for first-degree relatives of patients with SAH and suggests that at least part of the increased risk for SAH is explained by a higher frequency

### TABLE 1. Risk Factors for Presence of Intracranial Aneurysms in Angiography Studies

<table>
<thead>
<tr>
<th>Sex</th>
<th>No. Investigated</th>
<th>No. of Aneurysms</th>
<th>Prevalence per 100 (95% CI)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>1754</td>
<td>61</td>
<td>3.5 (2.7-4.5)</td>
<td>0.8 (0.5-1.1)</td>
</tr>
<tr>
<td>Women</td>
<td>1254</td>
<td>58</td>
<td>4.6 (3.5-5.9)</td>
<td>Ref</td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>476</td>
<td>45</td>
<td>9.5 (7.0-12)</td>
<td>4.0 (2.7-6.0)</td>
</tr>
<tr>
<td>ADPKD</td>
<td>202</td>
<td>21</td>
<td>10 (6.2-15)</td>
<td>4.4 (2.7-7.3)</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>3676</td>
<td>196</td>
<td>5.3 (4.6-6.1)</td>
<td>2.3 (1.7-3.1)</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>183</td>
<td>11</td>
<td>6.0 (3.0-11)</td>
<td>2.6 (1.4-4.9)</td>
</tr>
<tr>
<td>Brain tumor + other</td>
<td>2052</td>
<td>48</td>
<td>2.3 (1.7-3.1)</td>
<td>Ref</td>
</tr>
</tbody>
</table>

Ref indicates reference category; CI, confidence interval. Data on sex are derived from nine studies, on family history from three studies, on ADPKD from three studies, on atherosclerosis from five studies, on pituitary adenoma from two studies, and on other (including brain tumor) conditions from five studies.

### TABLE 2. Sites and Sizes of Aneurysms

<table>
<thead>
<tr>
<th>Size of aneurysm, total number with data on size</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\leq 6$</td>
<td>257</td>
<td>72 (68-77)</td>
</tr>
<tr>
<td>$&gt;6$</td>
<td>74</td>
<td>21 (17-25)</td>
</tr>
<tr>
<td>$11-20$</td>
<td>23</td>
<td>6.5 (4.1-9.5)</td>
</tr>
<tr>
<td>$&gt;20$</td>
<td>2</td>
<td>0.8 (0.09-2.8)</td>
</tr>
</tbody>
</table>

PC indicates posterior circulation.

*Sites of aneurysms found in 2 autopsy studies and 15 angiography studies and sizes of aneurysms in 2 autopsy studies and 10 angiography studies.
of aneurysms and not only, or not at all, by a higher risk of rupture. Third, patients with atherosclerosis also had an increased frequency of aneurysms, which corresponds with the finding that cardiovascular diseases and SAH share the risk factors smoking, hypertension, and alcohol abuse. Fourth, the relative risk of ADPKD and familial predisposition was higher than that of atherosclerosis, which confirms previous findings that hypertension contributes less to the familial predisposition for SAH than other, probably genetic, factors.

In conclusion, data on prevalence vary considerably according to methods used to detect aneurysms. Retrospective autopsy studies probably give an underestimation and prospective angiography studies an overestimation of the actual prevalence. If all available evidence is taken together, for adults without risk factors for SAH, aneurysms can be found in approximately 2%; it is possible that the prevalence increases with age, but we could not convincingly demonstrate this. The large majority of these aneurysms are small (<10 mm), and the annual risk of rupture of these small aneurysms is low (0.7% per year). These data should be kept in mind when one is confronted with the task of advising patients with an accidentally found asymptomatic aneurysm. In patients with atherosclerosis and especially in patients with familial predisposition or ADPKD, aneurysms are found more often. Prospective studies should evaluate whether screening and treating these patients with an increased risk is beneficial.

Acknowledgments

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References


<table>
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<th>TABLE 3. Risk of Rupture of Aneurysms28-36</th>
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<tr>
<td>Risk of Rupture per 100 Patient-Years (95% CI)</td>
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<td>-------------------------------------------</td>
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<tr>
<td>Patient-Years</td>
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<td>Sex</td>
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<td>Age, y</td>
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<td>Type of aneurysm</td>
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<td>Site</td>
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<td></td>
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<tr>
<td>Size, mm</td>
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</tbody>
</table>

Ref indicates category; CI, confidence interval; PC, posterior circulation; and NA, not available.
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