Progress Review

# Risk of Rupture of Unruptured Intracranial Aneurysms in Relation to Patient and Aneurysm Characteristics

## An Updated Meta-Analysis

Marieke J.H. Wermer, MD; Irene C. van der Schaaf, MD;
Ale Algra, MD, FAHA; Gabriël J.E. Rinkel, MD, FAHA

***Background and Purpose***—We updated our previous review from 1996 on the risk of rupture of unruptured intracranial aneurysms, aiming to include the newly published articles.

***Methods***—We reviewed all studies from our former meta-analysis and performed a Medline search for new studies published after 1996. We calculated overall risks of rupture for studies with a mean follow-up time of <5, 5 to 10, and >10 years. Relative risks (RR) were calculated by comparing the risk of rupture in patients with and without potential risk factors. We aimed to perform multivariable analyses of the different risk factors with meta-regression analysis.

***Results***—We included 19 studies (10 new) with 4705 patients and 6556 unruptured aneurysms (follow-up 26 122 patient-years). The overall rupture risks were 1.2% (follow-up <5 years), 0.6% (follow-up 5 to 10 years), and 1.3% (follow-up >10 years). In the univariable analysis, statistically significant risk factors for rupture were age >60 years (RR 2.0; 95% confidence interval [CI], 1.1 to 3.7), female gender (RR 1.6; 95% CI, 1.1 to 2.4), Japanese or Finnish descent (RR 3.4; 95% CI, 2.6 to 4.4), size >5 mm (RR 2.3; 95% CI, 1.0 to 5.2), posterior circulation aneurysm (RR 2.5; 95% CI, 1.6 to 4.1), and symptomatic aneurysm (RR 4.4; 95% CI, 2.8 to 6.8). Meta-regression analysis yielded implausible results.

***Conclusions***—Age, gender, population, size, site, and type of aneurysm should be considered in the decision whether to treat an unruptured aneurysm. Pooled multivariable analyses of individual data are needed to identify independent risk factors and to provide more reliable risk estimates for individual patients. **(*Stroke*. 2007;38:1404-1410.)**

**Key Words:** cerebral aneurysm ■ meta-analysis ■ subarachnoid hemorrhage



Intracranial aneurysms are relatively common. Approximately 2% of adults harbor an unruptured aneurysm.[1] With the ongoing improvement of imaging techniques, the chance that an asymptomatic aneurysm is detected has increased. In patients with unruptured aneurysms, the decision whether to treat is often not straightforward. The risk of treatment has to be carefully balanced against the risk of rupture. Although the morbidity and mortality rates associated with clipping and coiling are relatively well-known, the natural course of unruptured aneurysms remains controversial.[2,3]

In 1996 our group performed a meta-analysis on the risk of rupture of unruptured intracranial aneurysms.[1] In this meta-analysis, however, no multivariate analysis was performed. Moreover, since 1996 several new studies on the risk of rupture of aneurysms have been published.

We updated our former meta-analysis with all relevant articles on the follow-up of unruptured aneurysms. Our aims were to: (1) incorporate the new information in the existing pooled data; (2) to increase the amount of data in subgroups of patients according to location of the aneurysm, size of the aneurysm, and to clinical risk factors such as age, gender, smoking, a history of subarachnoid hemorrhage (SAH) or familial intracranial aneurysms; (3) to perform multivariable analyses with meta-regression analysis; and (4) to incorporate new insights on growth of aneurysms in the review.

## Materials and Methods

We reviewed all publications on the risk of rupture of unruptured aneurysms used in the former meta-analysis.[1] This meta-analysis included studies published from 1955 until 1996. We performed a new MEDLINE search to retrieve all articles on risk of rupture of unruptured aneurysms published between July 1996 and March 2006. The following key words were used in different combinations: unruptured, untreated, incidental, additional, symptomatic, risk of rupture, subarachnoid hemorrhage, intracranial aneurysm(s), intracerebral aneurysm(s), growth, and follow-up. We searched the reference lists of all relevant publications for additional studies. In addition, we checked the Web of Science for articles that cited our former meta-analysis.

Studies were included if: (1) if the presentation of data included crude numbers or allowed recalculation into crude numbers; (2)

Received August 9, 2006; final revision received November 11, 2006; accepted November 17, 2006.

From Department of Neurology (M.J.H.W., A.A., G.J.E.R.), Rudolf Magnus Institute of Neuroscience, Department of Radiology (I.C.v.d.S.), and Julius Center for Health Sciences and Primary Care (A.A.), University Medical Center Utrecht, The Netherlands.

Correspondence to M.J.H. Wermer, MD, Department of Neurology: G03.228, University Medical Center Utrecht, Heidelberglaan 100, 3484 CX Utrecht, The Netherlands. E-mail m.wermer@neuro.azu.nl



*Stroke* **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000260955.51401.cd**

the type of aneurysm was identifiable (aneurysms were classified as incidental if they were found with screening in asymptomatic individuals or with examination for symptoms unrelated to the aneurysms, as additional if they were found in patients with a history of SAH, and as symptomatic if they caused symptoms other than SAH); (3) in patients with a history of SAH and additional unruptured aneurysms the ruptured ("index") aneurysm had been treated by clipping or coiling; and (4) in patients with previously treated aneurysms the source of subsequent bleeding was identified by computed tomography, surgery, or autopsy (to exclude rerupture of the previously treated aneurysm as cause for the hemorrhage).

In some studies only subsets of patients met the inclusion criteria; therefore, only these patients were included in the review. Studies that primarily evaluated growth of untreated aneurysms were only included if all patients were studied in whom follow-up was intended and the report was not restricted to those patients who had ≥2 follow-up scans. Case reports and articles published in a language other than English were excluded. If multiple publications reported on the same study population, the most recent publication was used.

## Data Extraction

Two reviewers (M.W. and I.S. or M.W. and G.R.) independently extracted data from the studies that met the inclusion criteria. Information was extracted on patient and aneurysm characteristics. In case of disagreement between the 2 reviewers, consensus was reached by joint review.

The location of the aneurysms was classified as follows: (1) posterior communicating artery; (2) internal carotid artery other than posterior communicating artery; (3) anterior circulation (anterior cerebral artery, anterior communication artery and the pericallosal artery); (4) middle cerebral artery; (5) posterior circulation (vertebral artery, basilar artery, posterior cerebral artery); and (6) cavernous sinus. In most studies the posterior communicating artery was considered to be part of the internal carotid artery. Therefore, we calculated the risk of rupture of posterior communicating artery aneurysms in combination with the other internal carotid artery aneurysms and the risk of rupture of posterior communicating artery aneurysms alone and other internal carotid artery aneurysms alone. Because in the studies different cut points were used for aneurysm size we made the following categories: <5 mm, < 7 mm, 5 to 10 mm, >10 mm, >12 mm, and >15 mm. No strict definition for familial intracranial aneurysms was used; aneurysms were classified familial if the authors of the article undergoing review reported them as familial. We assessed methodological quality of all included studies. The quality of a study was rated good when it fulfilled all following 3 criteria: (1) prospective study design; (2) loss to follow-up was <3%; and (3) if a distinction was made between certain SAH (confirmed by computed tomography, magnetic resonance imaging, autopsy, or xanthochromia in the cerebrospinal fluid) and possible SAH (from history or medical records) during follow-up. Finally, because the incidence of SAH is higher in Japan and Finland than in other Western countries,[4] we classified the studies according to origin of study population.

## Data Analysis

For data analysis we prespecified the following subgroups according to age (decades), gender, family history of intracranial aneurysms, smoking (current versus former/never), hypertension, excessive alcohol use (>5 glasses per day), location of the aneurysm, size of the aneurysm, type of aneurysm (incidental, additional, or symptomatic), prospective or retrospective study design, good quality studies versus studies of less quality, and origin of study population (Japanese/Finnish versus other populations).

The risk of rupture was reported for studies with a mean follow-up time of <5 years, with a mean follow-up time between 5 and 10 years, and with a mean follow-up time of >10 years. First, we used the "SAH per patient-years at risk" method to calculate the risk of rupture in the prespecified subgroups. With this method we divided the number of SAH (in each subgroup) by the number of person-years or aneurysm-years of follow-up (in that subgroup), yielding the risk of SAH per patient-year. When the specific follow-up time in a certain subgroup could not be extracted from the article, we multiplied the number of patients by the average period of follow-up of all patients to obtain the total number of person-years. Data were reported for those studies that reported the specific follow-up time for the prespecified subgroups and for all studies combined (studies with specific follow-up times for subgroups and studies in which the average follow-up time for calculations was used).

Second, we used Poisson meta-regression analysis to evaluate the influence of patient, aneurysm, and study characteristics on the risk of rupture. In this analysis we used the same prespecified subgroups as in the "SAH per patient-year at risk" method. Age of the patients was analyzed as continuous variable (mean age). The characteristics gender, family history of intracranial aneurysms, smoking, hypertension, excessive alcohol use, location of the aneurysm, size of aneurysm, and type of aneurysm were incorporated in the analysis as proportion of patients with this particular characteristic. The size of the aneurysm was analyzed both as continuous variable (mean size) and by proportion of patients with an aneurysm of a certain size. Design of the study, study quality, and population of the study were analyzed as dichotomous variable. Finally, we assessed the influence of the mean follow-up time of the studies on the risk of rupture.

# Results

## Included Studies

We found 23 studies (9 from the previous meta-analyses from 1996 and before and 14 new studies between 1996 and 2006) that fulfilled the inclusion criteria. Three studies reported on patients who were also included in later publications and were therefore combined with these later studies[5–7]; one study was excluded because patients were selected on basis of availability of follow-up scans.[8] The 19 included studies are listed in Table 1. The median year of publication was 1998 (range, 1966 to 2005). If rupture of an aneurysm had occurred, the diagnosis SAH was established only by taking history of patients or their relatives in 2 studies,[9,10] by review of medical records in 2,[11,12] by computed tomography, magnetic resonance, surgery, or autopsy in 8,[7,13–19] or not specified in 7 studies.[12,20–25] The follow-up of the patients was performed by telephone in combination with reviewing medical records in 4 studies,[11,15,25,26] by annual questionnaires in 1,[14] by questionnaires in combination with review of medical records in 2,[16,27] by outpatient clinic visits, telephone calls, and letters in 7,[7,9,10,13,17,18,20] or was not specified in another 5 studies.[12,21–24] Eleven studies reported the proportion of patients lost to follow-up; this proportion was 0% in 7 studies, and 0.2%, 5%, 6%, and 35% in the other 4 studies (Table 1).

## Patients

The 19 studies included a total of 4705 patients with 6556 aneurysms with a mean follow-up of 5.6 years (26 122 patient-years). Seventeen studies provided data on the age of the patients; the weighted mean age was 55.6 years. Fourteen studies with 4148 patients provided data on the gender of the patients; 2891 (70%) were women.

## Risk of Rupture by the "SAH Per Patient-Year at Risk" Method

The overall risk of rupture of untreated aneurysms in the studies with a mean follow-up <5 years was 1.2% (95% confidence interval [CI], 1.0 to 1.5), in the studies with a mean follow-up between 5 and 10 years 0.6% (0.5% to

**TABLE 1. Overview of the 19 Included Studies**

| First Author | Year of Publication | Mean FU Time (range) | Study Design | Country | Loss to FU, % | No. of Patients | No. of PY | No. of SAH | SAH/PY, % |
|---|---|---|---|---|---|---|---|---|---|
| Locksley[23] | 1966 | 3.4 (0–12.0) | R? | US | 6 | 32 | 108 | 9 | 2.5 |
| Zacks[22] | 1980 | 2.8 (0.1–7.5) | R | Canada | ? | 10 | 28 | 0 | 0 |
| Przelomski[18] | 1986 | 6.4 (1.0–12.0) | R | US | 0 | 9 | 58 | 0 | 0 |
| Eskesen[10] | 1987 | 2.1 (2.0–2.2) | P | Denmark | 5 | 22 | 46 | 4 | 8.7 |
| Wiebers[27] | 1987 | 8.3 (5.0–?) | R | US | 0 | 130 | 1079 | 15 | 1.4 |
| Inagawa[9] | 1992 | 5.2 (0.5–10.9) | R? | Japan | ? | 47 | 244 | 1 | 0.4 |
| Asari[25] | 1993 | 3.6 (0–9.7) | R? | Japan | ? | 54 | 197 | 11 | 5.6 |
| Mizoi[15] | 1995 | 4.3 (0.4–10.0) | R | Japan | ? | 49 | 211 | 8 | 3.8 |
| Yasui[11] | 1997 | 6.3 (0.3–22.5) | R | Japan | 35 | 234 | 1465 | 34 | 2.3 |
| ISUIA I[16] | 1998 | 8.3 (?) | R | US/Can/Eur | 0 | 1449 | 12 023 | 32 | 0.3 |
| Kamitani[21] | 1999 | 8.6 (1.3–20.0) | R | Japan | ? | 11 | 95 | 3 | 3.2 |
| Tsutumi[13] | 2000 | 4.3 (0.5–17.0) | R | Japan | 0 | 62 | 266 | 7 | 2.6 |
| Juvela (combined)[6,7,31] | 2000 | 18.1 (0.8–39.9) | P and R | Finland | 0 | 142 | 2575 | 33 | 1.3 |
| Tsukahara/Inoue[5,20] | 2002 | 2.0 (1.0–4.9) | P | Japan | ? | 110 | 218 | 7 | 3.2 |
| Matsumoto[26] | 2003 | 2.6 (?) | R? | Japan | ? | 91 | 237 | 5 | 2.1 |
| ISUIA II[14] | 2003 | 4.1 (0–6.0) | P | US/Can/Eur | 0.2 | 1692 | 6544 | 51 | 0.8 |
| Yonekura[24] | 2004 | 1.2 (0.5–3.0) | P | Japan | ? | 321 | 378 | 4 | 1.1 |
| Matsubara[12] | 2004 | 1.5 (0.3–7.0) | P | Japan | 0 | 140 | 207 | 0 | 0 |
| Wermer[17] | 2005 | 1.6 (0.7–3.8) | P | Netherlands | 0 | 92 | 143 | 0 | 0 |

Eur indicates Europe; FU, follow-up; P, prospective; PY, patient-year; R, retrospective; SAH, subarachnoid hemorrhage; US, United States.

0.7%), and in the studies with a mean follow-up time >10 years 1.3% (0.9 to 1.8). The patient characteristics that had a statistically significant association with an increased risk of rupture of intracranial aneurysms were age older than 60, female gender, and Japanese or Finnish descent (Table 2). In addition, smoking increased the risk of rupture, but this factor was not statistically significant. There were not enough data to evaluate the effects of excessive alcohol use or a family

**TABLE 2. Relative Risk of Rupture According to Patient Characteristics**

| | Studies With Specified Follow-Up Time per Subgroup | | | | | All Studies With Data | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | No. of Studies | Mean FU Time (range) | No. of PY | No. of SAH | Relative Risk (95% CI) | No. of Studies | Range of FU | No. of PY | No. of SAH | Relative Risk (95% CI) |
| Age | | | | | | | | | | |
| <20 y | 0 | … | … | … | … | 0 | … | … | … | … |
| 20–29 y | 4 | 8.2 (0–39.9) | 815 | 12 | 1.1 (0.5–2.2) | 6 | 6.5 (0–39.9) | 848 | 12 | 1.1 (0.5–2.2) |
| 40–59 y | 5 | 7.9 (0–39.9) | 1523 | 21 | Ref | 8 | 5.8 (0–39.9) | 1830 | 24 | Ref |
| 60–79 y | 5 | 5.3 (0–20.0) | 209 | 3 | 1.0 (0.3–3.5) | 9 | 4.1 (0–20.0) | 709 | 19 | 2.0 (1.1–3.7) |
| >80 y | 0 | … | … | … | … | 1 | 1.2 (0.5–3.0) | 12 | 0 | … |
| Gender | | | | | | | | | | |
| Male | 4 | 5.3 (0–20.0) | 72 | 1 | Ref | 10 | 5.7 (0–39.9) | 2255 | 32 | Ref |
| Female | 4 | 5.3 (0–20.0) | 218 | 11 | 3.6 (0.5–28.1) | 10 | 5.7 (0–39.9) | 2885 | 65 | 1.6 (1.1–2.4) |
| Hypertension | | | | | | | | | | |
| No | 0 | … | … | … | … | 4 | 6.5 (0–39.9) | 2357 | 35 | Ref |
| Yes | 0 | … | … | … | … | 4 | 6.5 (0–39.9) | 572– | 9 | 1.1 (0.5–2.2) |
| Smoking | | | | | | | | | | |
| No | 1 | 18.1 (0.8–39.9) | 1352 | 13 | Ref | 1 | 9.8 (0.7–39.9) | 1404 | 13 | Ref |
| Yes | 1 | 18.1 (0.8–39.9) | 1223 | 20 | 1.7 (0.9–3.4) | 1 | 9.8 (0.7–39.9) | 1304 | 20 | 1.7 (0.8–3.3) |
| Population | | | | | | | | | | |
| Not Japanese/Finnish | 11 | 4.6 (0.3–39.9) | 20 422 | 111 | Ref | 11 | 4.6 (0.3–39.9) | 20 422 | 111 | Ref |
| Japanese or Finnish | 8 | 5.3 (0–12) | 6093 | 113 | 3.4 (2.6–4.4) | 8 | 5.3 (0–12) | 6093 | 113 | 3.4 (2.6–4.4) |

CI indicates confidence interval; Ref, reference.

**TABLE 3. Relative Risk of Rupture According to Aneurysm Characteristics**

| | Studies With Specified FU Time per Subgroup | | | | | All Studies With Data | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Variable | No. of Studies | Mean FU Time (range) | No. of PY | No. of SAH | Relative Risk (95% CI) | No. of Studies | Mean FU time (range) | No. of PY | No. of SAH | Relative Risk (95% CI) |
| Site of aneurysm | | | | | | | | | | |
| ACA | 4 | 4.3 (0.1–22.5) | 343 | 11 | 0.7 (0.4–1.5) | 14 | 5.1 (0–39.9) | 1083 | 19 | 1.4 (0.8–2.3) |
| ICA including Pcom | 4 | 4.3 (0.1–22.5) | 455 | 20 | Ref | 14 | 5.1 (0–39.9) | 3558 | 46 | Ref |
| ICA without Pcom | 3 | 4.9 (0.1–20.0) | 82 | 3 | 0.8 (0.3–2.8) | 6 | 5.5 (0–20.0) | 813 | 8 | 0.7 (0.4–1.6) |
| Pcom | 3 | 4.9 (0.1–20.0) | 76 | 6 | 1.8 (0.7–4.5) | 5 | 5.3 (0–20.0) | 317 | 7 | 1.7 (0.8–3.8) |
| MCA | 4 | 4.3 (0.1–22.5) | 471 | 9 | 0.4 (0.2–1.0) | 14 | 5.1 (0–39.9) | 2734 | 33 | 0.9 (0.6–1.5) |
| Posterior circulation† | 4 | 3.0 (0.1–22.5) | 213 | 6 | 0.8 (0.3–2.8) | 11 | 4.9 (0–39.9) | 791 | 26 | 2.5 (1.6–4.1) |
| Cavernous sinus | 1 | 2.8 (0.1–7.5) | 3 | 0 | ... | 5 | 6.1 (0–20.0) | 2159 | 2 | 0.1 (0–0.3) |
| Size of aneurysm | | | | | | | | | | |
| <5 mm | 4 | 3.7 (0.1–20.0) | 565 | 5 | Ref | 10 | 3.9 (0.1–20.0) | 1939 | 10 | Ref |
| <7 mm | 3 | 7.7 (0.1–39.9) | 2249 | 23 | * | 5 | 7.1 (0.1–39.9) | 7206 | 32 | * |
| 5–10 mm | 4 | 7.9 (0.1–39.9) | 329 | 8 | 2.8 (0.9–8.4) | 9 | 6.1 (0.1–39.9) | 1187 | 14 | 2.3 (1.0–5.2) |
| >10 mm | 3 | 8.1 (0–39.9) | 216 | 10 | 5.2 (1.8–15.3) | 9 | 6.2 (0–39.9) | 3670 | 55 | 2.9 (1.5–5.7) |
| >12 mm | 1 | 8.6 (1.3–20.0) | 5 | 0 | ... | 3 | 5.7 (0–20.0) | 1089 | 42 | 7.5 (3.8–14.9) |
| Giant (>15 mm) | 2 | 6 (0–20.0) | 22 | 3 | 15.4 (3.7–64.5) | 8 | 5.0 (0–39.9) | 293 | 18 | 11.9 (5.5–25.8) |
| Type of aneurysm | | | | | | | | | | |
| (%) Incidental | 4 | 5.5 (0.1–22.5) | 1439 | 31 | Ref | 12 | 5.5 (0–39.9) | 3315 | 50 | Ref |
| (%) Additional | 2 | 7.5 (0.3–22.5) | 526 | 13 | 1.2 (0.6–2.2) | 8 | 5.5 (0–39.9) | 3158 | 46 | 1.0 (0.7–1.4) |
| (%) Symptomatic | 2 | 5.9 (0–22.5) | 110 | 9 | 3.8 (1.8–8.0) | 8 | 5.9 (0–39.9) | 472 | 31 | 4.4 (2.8–6.8) |

*Because size <5 is part of the category size <7, no relative risk for the subgroup <7 is given.
†Posterior circulation=vertebral artery, basilar artery, and posterior cerebral artery.
ACA indicates anterior cerebral artery; ICA, interior carotid artery; MCA, middle cerebral artery; Pcom, posterior communicating artery; Ref, reference.



history of SAH on the risk of rupture of intracranial aneurysms. The aneurysm characteristics that were related to an increased risk of rupture were site at the posterior circulation, size >5 mm, and symptoms caused by the aneurysm other than SAH (Table 3). The risk of rupture was lower in high-quality studies than in studies with limited quality (Table 4). The relative risks found in studies that reported the specific follow-up time of the subgroups were mostly comparable with those in all studies combined but their CI was wider because of less data (left columns of Tables 2 and 3).

### Risk of Rupture by the Meta-Regression Analysis

In the univariable Poisson regression analysis, the relative risk (RR) of the dichotomous variables study design (RR 1.0; 95% CI, 0.7 to 1.3) and study quality (RR 0.8; 95% CI, 0.6 to 1.1 for a good-quality study) and Japanese or Finnish study population (RR 3.4; 95% CI, 2.6 to 4.4) were identical to the relative risks found by the "SAH per patient-year at risk method" (results not shown in the tables). The continuous variable size had an RR of 1.05 (per 1-mm increase in size, 95% CI, 0.93 to 1.18) and age of 1.06 (per 1-year increase in age, 95% CI, 1.03 to 1.08). The RR for the mean follow-up time of a study was 0.97 (95% CI, 0.94 to 1.01), meaning that the risk of rupture decreased with 3% for each additional year of follow-up in a study. The variables with proportions of patients with a certain characteristic showed an RR that was in the opposite direction compared with the "SAH per patient-year at risk method". For example, the RR for percentage women was 0.94 (95% CI, 0.93 to 0.97) and the RR of aneurysms <5 mm was 1.03 (95% CI, 1.02 to 1.04), meaning that women had a lower risk of rupture than men and aneurysms <5 mm had a higher risk of rupture than aneurysms of a larger size. Because the latter results of the univariable analysis were not considered plausible and most studies did not report enough data for all our prespecified subgroups to allow multivariable analysis, no further regression analysis was performed.

**TABLE 4. Relative Risk of Rupture According to Study Design**

| Variable | No. of Studies | Mean FU Time (range) | No. of PY | No. of SAH | Relative Risk (95% CI) |
|---|---|---|---|---|---|
| Study Design | | | | | |
| Retrospective | 13 | 6.3 (0–39.9) | 18586 | 158 | Ref |
| Prospective | 6 | 2.1 (0–7.0) | 7929 | 66 | 1.0 (0.7–1.3) |
| Quality of Studies | | | | | |
| Limited quality | 17 | 5.6 (0–39.9) | 19435 | 173 | Ref |
| High quality | 2 | 2.6 (0–6.0) | 7080 | 51 | 0.8 (0.6–1.1) |

Ref indicates reference.

## Discussion

### Main Findings

We found that patient characteristics increasing the risk of rupture are higher age, female gender, Japanese or Finnish descent, and smoking, although this last factor was not statistically significant. Aneurysms characteristics that increase the risk

of rupture are location at the posterior circulation, increasing size, and symptoms other than SAH caused by the aneurysm. In prospective studies the risk of rupture was similar to that in retrospective studies. In high-quality studies the risk tended to be lower than that in studies of limited quality. We were not able to perform multivariable analysis because meta-regression analysis yielded implausible results.

The addition of new articles to the previous review resulted in an increase in patient-years from 3906 to 26 122, with narrowing of the CI surrounding the estimates. Furthermore, in the present meta-analysis additional risk factors such as smoking, hypertension, and Japanese or Finish origin were assessed. In Japan and Finland, the incidence of SAH is much higher than that in other Western countries.[4] In Finland the prevalence of intracranial aneurysms is similar to that in other countries.[28] To our knowledge, comparable Japanese data on the prevalence of aneurysms are lacking. Our results suggest that the increased risk of rupture of intracranial aneurysms is an important reason for the high SAH risk in the Finnish and Japanese populations.

### Meta-Regression Analysis

Because individual risk factors for rupture might be influenced by other risk factors, we aimed to perform a multivariable analysis by means of meta-regression analysis. Unfortunately, this method appeared to be not suitable for analysis of most risk factors in our study. We found in the meta-regression analysis a statistically significant higher risk of rupture in aneurysms <5 mm (RR >1) compared with large aneurysms when size was incorporated as proportion of aneurysms within a certain size category. The most likely explanation for these contradictive results is that the meta-regression analysis is not based on crude data. Size can be incorporated as the proportion of aneurysms <5 mm in a study as a risk factor for aneurysmal rupture. The outcome of such an analysis is that when the proportion of aneurysms <5 mm increases by 1%, the risk of rupture changes with a certain factor X. When the meta-analysis includes a study with a relatively low overall rupture risk and a percentage of aneurysms <5 mm of 20%, and a study with a higher overall rupture risk and a percentage of aneurysms <5 mm of 40%, the conclusion of the analysis will be that when the proportion of aneurysms <5 mm increases, the risk of rupture also increases (RR for aneurysms <5 mm >1). However, the meta-regression method ignores the fact that all SAHs in the study with 40% might have appeared in the large aneurysms. Furthermore, even if the univariable meta-regression analysis had shown plausible results, multivariable analyses could have only been performed for very few variables because many studies did not report data for all of the subgroups and therefore would have been excluded from the multivariable analysis. Therefore, multivariable analysis is only possible by pooling the crude patient data of multiple studies.

## Methodological Considerations

Because we could not perform multivariable analysis with the data presently available in the literature, we could not assess the independent contribution of patient and aneurysm characteristics to the risk of aneurysm rupture. We found that both large aneurysms and symptomatic aneurysms had a high rate ratio for rupture. It is, however, unlikely that these risk factors are independent because aneurysms that cause cranial nerve palsies are often large.[29] We could not confirm a higher risk of rupture in additional aneurysms than in incidental aneurysms as suggested in both ISUIA studies. However, the lack of a difference in rupture risk between incidental and additional aneurysms in our study should not be considered as proof of absence of such a difference. A potential explanation is that the additional aneurysms were smaller than the incidental aneurysms; a higher risk for additional aneurysms therefore may have been masked by smaller size with inherently lower rupture risk.

Unfortunately, most studies did not provide specific data on all subgroups of patients. The number of patients, the number of SAHs, or both the number of patients and SAHs were frequently not reported for the subgroups of our interest. In 6 studies, no complete data on age and gender of the patients were reported. Although the ISUIA studies together included 3141 patients and therefore have a great impact on the overall risk of rupture in our study, most of their data could not be used for the subgroup analysis because of lack of detailed information. Furthermore, in most studies limited information was provided on study design, methods, completeness of follow-up, and data analysis, and only 2 studies fulfilled our criteria for good quality.[14,17]

Except for size, other aneurysm characteristics may be involved in the risk of rupture. Aneurysms of irregular shape or with nipples might have higher risks of rupture and thrombosed or calcified aneurysms lower risks, but these factors have not been taken into account in the parent studies. Moreover, bias may have been introduced through selection of patients for treatment. For example, unruptured aneurysms in old and sick patients with cerebrovascular diseases might be left untreated. It is unclear how these factors involved in the treatment decision have influenced the results of the studies. In addition, in some studies patients in the initially conservative group were treated during follow-up of the study. In the ISUIA II study, this proportion of patients was almost one-third.[14] Although the reasons for treatment were not specified, it is likely that the most frequent reason is growth of the aneurysm at serial follow-up. Because enlarging aneurysms have a higher risk of rupture, treating patients with growing aneurysms probably resulted in an underestimation of the risk of rupture.[30]

Not all risk factors found in the analyses that included all studies were also found when only those studies with specific follow-up times for certain subgroups were considered. In our view, the analysis of the subgroup with specified follow-up time per subgroup is not a statistically more sound analysis than the overall analysis. The subgroup analyses on studies with specific follow-up times seem more accurate from a methodological point of view, but they include less patient data, and therefore the confidence intervals are wide. The lack of statistical significance in the subgroup analysis can be attributed to small numbers and does not necessarily means a weaker association.

Finally, we performed 44 univariable tests, with data presented in Tables 2 to 4. Based on an $\alpha$ level of 0.05, the 44

univariable tests may have led to at least 2 by chance findings throughout the analysis. This number may have led to an overestimation of the precision of the relative risks.

### Growth of Aneurysms

The "SAH per patient-year at risk method" assumes constant rupture rates of aneurysms over the years. In a mathematical model, we recently found that growth of intracranial aneurysms is probably not constant and time-independent, but rather an irregular and discontinuous process with periods with and without growth (Koffijberg et al, unpublished data, 2006). In our opinion, it is not correct to assume that the average rupture risks per year calculated by the "SAH per patient-year at risk" method holds true for the rest of a patients life. In our regression analysis we found that the risk of rupture tends to decrease for every (mean) year increase in follow-up. It would be better to calculate rupture risks in relation to the follow-up time of the patients (for example, the rupture risk in all patients followed-up during the first year after aneurysm detection, during the second year, etc). However, for this calculation, again the crude patient data are needed. Because these data are not available we pooled the rupture risks of the studies based on mean follow-up time and range of follow-up. Thus, we think that more reliable risks of rupture are reported for defined periods of time.

### Conclusion

We conclude that the main patient and aneurysm risk factors for rupture of intracranial aneurysms are older age, female gender, Japanese or Finnish descent, larger size, location of the aneurysm at the posterior circulation, and symptoms caused by the aneurysm. A statistically significant relation between rupture risk and older age and descent was not found in the previous meta-analysis. The risk of rupture depended on the follow-up time and was 1.2% for follow-up in the first 5 years, 0.6% for follow-up between 5 and 10 years, and 1.3% for >10 years of follow-up time. The addition of new studies to the previous review resulted in an increase in patient-years with narrowing of the CI. More accurate estimates are of great importance because they are used as input in decision models and for treatment decisions of individual patients.

Meta-regression analysis was not feasible for our data; therefore, it is not known to what extent these risk factors are independent of each other. Although over the past 40 years 6556 aneurysms have been followed-up for >26 515 years, it is still not possible to perform multivariable analysis with the data that are currently available. Therefore, uncertainty still abounds for individual risk calculation. New follow-up studies on intracranial aneurysms should have a prospective study design, provide detailed information on follow-up of patients and data analysis, and report the number of SAHs and the number of follow-up years for all subgroups of patients. Because meta-regression analysis is not a suitable method for multivariable analysis of risk factors for rupture, collaborative efforts with pooled analysis of individual data are needed to identify independent risk factors for aneurysm rupture. In this pooled analysis, the follow-up time should be taken into account because the growth of aneurysms is probably not constant over time. Only in this way will more reliable risk estimates be available to enable physicians and patients to make a sound decision on whether to treat an unruptured aneurysm.



## Sources of Funding

This study was in supported by a grant from the Netherlands Organization for Scientific Research/ZonMw (grant 945-02-007).

## Disclosures

None.

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