Chapter Thirteen

Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics:

an updated meta-analysis

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Abstract

Background and purpose

We updated our previous review from 1996 on the risk of rupture of intracranial aneurysms, aiming to include newly published papers.

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, 5-10 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 aneurysms (follow-up 26122 patient-years). The overall rupture risks were 1.2% (FU <5 years), 0.6% (FU 5-10 years) and 1.3% (FU >10 years). In the univariable analysis, statistically significant risk factors for rupture were age > 60 years (RR 2.0, 95% CI 1.1-3.7), female gender (RR 1.6, 95% CI 1.1-2.4), Japanese or Finnish descent (RR 3.4, 95% CI 2.6-4.4), size more than five mm (RR 2.3, 95% CI 1.0-5.2), a posterior circulation aneurysm (RR 2.5, 95% CI 1.6-4.1) and a symptomatic aneurysm (RR 4.4, 95% CI 2.8-6.8). Meta-regression analysis yielded implausible results.

Conclusions

Age, gender, population, size, site and type of aneurysm should be considered in the decision whether or not 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.

Introduction

Intracranial aneurysms are relatively common; approximately 2% of the 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 or not 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 firstly to incorporate the new information in the existing pooled data, secondly 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 SAH or familial intracranial aneurysms, thirdly to perform multivariable analyses with meta-regression analysis, and finally to incorporate new insights on growth of aneurysms in the review.

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 1) if the presentation of data included crude numbers or allowed recalculation into crude numbers; 2) if 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) if in patients with a history of SAH and additional unruptured aneurysms the ruptured ("index") aneurysm had been treated by clipping or coiling and 4) if in patients

with previously treated aneurysms the source of subsequent bleeding was identified by CT, surgery or autopsy (to exclude re-rupture of the previously treated aneurysm as cause for the hemorrhage).
In some studies only subsets of patients met the inclusion criteria and 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 two or more follow-up scans. Case reports and papers published in another language than English were excluded. In case multiple publications reported on the same study population the most recent publication was used.

Data-extraction

Two reviewers (M.W./I.S. or M.W./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 two reviewers, consensus was reached by joint review.
The location of the aneurysms was classified as follows: 1. posterior communicating artery (Pcom), 2. internal carotid artery (ICA) other than Pcom, 3. anterior circulation (anterior cerebral artery, anterior communicating artery and the pericallosal artery), 4. middle cerebral artery (MCA), 5. posterior circulation (vertebral artery, basilar artery, posterior cerebral artery) and 6. cavernous sinus. In most studies the Pcom was considered to be part of the ICA. Therefore, we calculated the risk of rupture of Pcom aneurysms in combination with the other ICA aneurysms and the risk of rupture of Pcom aneurysms alone and other ICA aneurysms alone. Because in the studies different cut points were used for aneurysm size we made the following categories: < 5 millimeters (mm), < 7 mm, 5-10 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 under review reported them as familial. We assessed methodological quality of all included studies. The quality of a study was rated high when it fulfilled all following three criteria: 1. prospective study-design, 2. loss to follow-up less than 3% and 3. if a distinction was made between certain SAH (confirmed by CT, MRI, 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, high 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 5-10 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 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 variables. 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 (nine 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] and 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 1966-2005). If rupture of an aneurysm had occurred, the diagnosis SAH was established only by taking history of patients or their relatives in two studies,[9,10] by review of medical records in two,[11,12] by CT, MR, surgery or autopsy in eight[7,13-19] or not specified

in seven studies.[12,20-25] The follow-up of the patients was done by telephone in combination with reviewing medical records in four studies,[11,15,25,26] by annual questionnaires in one,[14] by questionnaires in combination with review of medical records in two,[16,27] by outpatient clinic visits, telephone calls and letters in seven[7,9,10,13,17,18,20] or was not specified in another five studies.[12,21-24] Eleven studies reported the proportion of patients lost to follow up; this proportion was 0% in seven studies, and 0.2%, 5%, 6% and 35% in the other four 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 (26122 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% CI 1.0-1.5), in the studies with a mean follow-up between the 5 and 10 years 0.6% (0.5-0.7%) and in the studies with a mean follow-up time > 10 years 1.3% (0.9-1.8). The patient characteristics that had a statistically significant association with an increased risk of rupture of intracranial aneurysms were age > 60 years, 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 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 larger than five millimeters 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 **Tables 2** and **3**).

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	12023	32	0.3%
Kamitani[31]	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, 32]	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%

?= unknown/uncertain, FU= folluw-up, R= retrospective, P= prospective, No.= number, PY= patient-year

Table 2 *Relative risk of rupture according to patient characteristics*

Variable	Studies with specified FU time per subgroup					All studies with data				
	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 years	0	-	-	-	-	0	-	-	-	-
20-29 years	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 years	5	7.9 (0-39.9)	1523	21	Ref	8	5.8 (0-39.9)	1830	24	Ref
60-79 years	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 years	0	-	-	-	-	1	1.2 (0.5-3.0)	12	0	-
Gender										
Men	4	5.3 (0-20.0)	72	1	Ref	10	5.7 (0-39.9)	2255	32	Ref
Women	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										
Non Japanese /Finnish	11	4.6 (0.3-39.9)	20422	111	Ref	11	4.6 (0.3-39.9)	20422	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)

FU= folluw-up, No.= number, PY= patient-year, 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)
VB	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 < 7 no relative risk for the subgroup < 7 is given.*
FU= folluw-up, No.= number, PY= patient-year, Ref= reference

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 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)

FU= folluw-up, No.= number, PY= patient-year, Ref= reference

Risk of rupture by the meta-regression analysis

In the univariable Poisson regression analysis the relative risk of the dichotomous variables study design (RR 1.0, 95% CI 0.7-1.3) and study quality (RR 0.8, 95% CI 0.6-1.1 for a high quality study) and Japanese or Finnish study population (RR 3.4, 95% CI 2.6-4.4) 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 0.93-1.18) and age of 1.06 (per 1 year increase in age, 95% CI 1.03-1.08). The RR for the mean follow-up time of a study was 0.97 (95% CI 0.94-1.01), 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 a 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 0.93-0.97) and the RR of aneurysms smaller than five mm was 1.03 (95% CI 1.02-1.04), meaning that women had a lower risk of rupture than men and aneurysms smaller than five 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.

Discussion

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 caused by the aneurysm other than SAH. 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 the risk in studies of limited quality. We were not able to perform multivariable analysis because meta-regression analysis yielded

implausible results.
The addition of new papers to the previous review resulted in an increase in patient-years from 3906 to 26122 with narrowing of the confidence intervals 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 population.
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 several risk factors in our study. We found in the meta-regression analysis a statistically significant higher risk of rupture in aneurysms smaller than five millimeters (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 smaller than five millimeters in a study as a risk factor for aneurysmal rupture. The outcome of such an analysis is that when the proportion of aneurysms smaller than five millimeters increases with one percent, 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 smaller than five millimeters of 20% and a study with a higher overall rupture risk and a percentage of aneurysms smaller than five millimeters of 40%, the conclusion of the analysis will be that when the proportion of aneurysms smaller than five millimeters increases the risk of rupture also increases (RR for aneurysms smaller than five 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 only have been performed for very few variables because many studies did not report data for all of the subgroups and would have been excluded from the multivariable analysis. Multivariable analysis is therefore only possible by pooling the crude patient data of multiple studies.
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 risk of 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 compared with 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 may therefore 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 six studies not even complete data on age and gender of the patients were reported. Although the ISUIA studies together included 3141 patients and have therefore 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 two studies fulfilled our criteria for high 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 trombosed 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 probable resulted in an underestimation of the risk of rupture.[30]

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 (H. Koffijberg et al. 2006; unpublished data). 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 hold 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 patients (for example the rupture risk in all patients followed during the first year after aneurysm detection, during the second year etcetera). 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.

We conclude that the main patient and aneurysm risk factors for rupture of intracranial aneurysms are higher age, female gender, Japanese of Finnish descent, larger size, location

of the aneurysm at the posterior circulation and symptoms caused by the aneurysm. It is not known to what extent these risk factors are independent of each other. Although over the last 40 years 6556 aneurysms have been followed for over 26515 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 SAH 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 also the follow-up time should be taken into account because the growth of aneurysms is probably not constant over time. Only in this way more reliable risk estimates will be available to enable physicians and patients to make a sound decision on whether or not to treat an unruptured aneurysm.

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