Aneurysm diameter as a risk factor for pretreatment rebleeding: a meta-analysis

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OBJECT Aneurysmal rerupture prior to treatment is a major cause of death and morbidity in aneurysmal subarachnoid hemorrhage. Recognizing risk factors for aneurysmal rebleeding is particularly relevant and might help to identify the aneurysms that benefit from acute treatment. It is uncertain if the size of the aneurysm is related to rebleeding. This meta-analysis was performed to evaluate whether an association could be determined between aneurysm diameter and the rebleeding rate before treatment. Potentially confounding factors such as age, aneurysm location, and the presence of hypertension were also evaluated.

METHODS The authors systematically searched the PubMed, Embase, and Cochrane databases up to April 3, 2013, for studies of patients with aneurysmal subarachnoid hemorrhage that reported the association between aneurysm diameter and pretreatment aneurysmal rebleeding. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria were used to evaluate study quality.

RESULTS Seven studies, representing 2121 patients, were included in the quantitative analysis. The quality of the studies was low in 2 and very low in 5. Almost all of the studies used 10 mm as the cutoff point for size among other classes, and only one used 7 mm. An analysis was performed with this best unifiable cutoff point. Overall rebleeding occurred in 360 (17.0%) of 2121 patients (incidence range, from study to study, 8.7%–28.4%). The rate of rebleeding in small and large aneurysms was 14.0% and 23.6%, respectively. The meta-analysis of the 7 studies revealed that larger size aneurysms were at a higher risk for rebleeding (OR 2.56 [95% CI 1.62–4.06]; $p = 0.00$; $I^2 = 60\%$). The sensitivity analysis did not alter the results. Five of the 7 studies reported data regarding age; 4 studies provided age-adjusted results and identified a persistent relationship between lesion size and the risk of rebleeding. The presence of hypertension was reported in two studies and was more prevalent in patients with rebleeding in one of these. Location (anterior vs posterior circulation) was reported in 5 studies, while in 4 there was no difference in the rebleeding rate. One study identified a lower risk of rebleeding associated with posterior location aneurysms.

CONCLUSIONS This meta-analysis showed that aneurysm size is an important risk factor for aneurysmal rebleeding and should be used in the clinical risk assessment of individual patients. The authors' results confirmed the current guidelines and underscored the importance of acute treatment for large ruptured aneurysms.

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KEY WORDS subarachnoid hemorrhage; intracranial aneurysm; recurrence; risk; meta-analysis; vascular disorders

THE incidence of aneurysmal subarachnoid hemorrhage (SAH) is about 5–10 cases per 100,000.^{21,26} Closure of the aneurysm after initial SAH is the primary goal to prevent aneurysmal rebleeding, which has an associated mortality rate of up to 50%.³² The incidence of rebleeding after an SAH has been estimated to be 14%–17% during the first 24 hours, and studies have shown that 87%–92% of all rebleeding occurs within the first 6 hours

after the initial bleed.^{9,32} Endovascular coiling or clipping to secure the aneurysm is advised as early after rupture as is feasible to reduce the rate of rebleeding.⁸ Currently, ultra-early treatment, considered to be within 24 hours, is advised for patients in good clinical condition.³⁴ Although nonmodifiable causes, such as transfer from other hospitals and late diagnosis, might delay treatment, ultra-early treatment can also be difficult due to internal logistics is-

ABBREVIATIONS GRADE = Grading of Recommendations Assessment, Development and Evaluation; SAH = subarachnoid hemorrhage.

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sues like limited 24/7 surgical coverage and access to operating theaters and anesthetic and nursing staff.³⁴

Recognizing risk factors for aneurysmal rebleeding is particularly relevant and might help to identify the aneurysms that benefit from acute treatment. In recent years, several risk factors, such as hypertension and the location and size of the aneurysm, have been shown to be associated with rebleeding.^{9,10,19,28,37} Biomechanical studies have indicated that cerebral aneurysmal rupture occurs when there is a decrease in the ratio of the artery wall thickness to the radius of the aneurysm.⁷ This concept might explain the possible relationship between aneurysm diameter and the risk of rebleeding. However, the association between the risk of rebleeding and aneurysm size might be confounded by age.²⁸ In particular, older patients may have larger aneurysms, and their general condition makes it more likely that treatment is postponed, leaving these individuals more prone to rebleeding. This meta-analysis was performed to evaluate whether an association could be established between aneurysm diameter and rebleeding rate before treatment. Potentially confounding factors like age, aneurysm location, and the presence of hypertension were also evaluated.

Methods

Search Strategy and Selection Criteria

The meta-analysis was constructed using the MOOSE guidelines.³⁸ In particular, an independent, experienced librarian systematically searched the PubMed, Embase, and Cochrane databases up to April 3, 2013, for studies of patients with aneurysmal SAH that reported the association between aneurysm diameter and pretreatment aneurysmal rebleeding. The search strategy is set out in Table 1.

Data Extraction

Two authors (J.V.L. and H.B.) independently read all titles and abstracts and selected those that appeared to be relevant for a full text review without language restrictions. Conference abstracts, reviews, meta-analyses, editorials, and animal studies were excluded. From the

remaining studies, full-text articles were obtained and independently evaluated by two of the authors (J.V.L. and H.B.). Studies were deemed to be eligible if they included: 1) patients with SAH in either a prospective or retrospective population-based design; 2) the association between aneurysm diameter and the rebleeding rate; and 3) results that included or enabled the calculation of an odds ratio. A third author (R.B.) was consulted to resolve any disagreements. Reference screening was conducted to identify additional studies from the full-text articles that were evaluated. Included studies were selected for a quality review. The methods recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for rating the quality of evidence were applied.^{2,11–17} The ORs and 95% CIs between small and large intracranial aneurysms were extracted or calculated. Size categories were then registered. The cutoff between small and large size had to be established according to the published data. In cases of overlapping cohorts, we excluded the one with the lesser-quality data or, if equal in quality, the one with the fewest patients to prevent an artificial increase in effect size.

Statistical Analysis

Comprehensive Meta-Analysis software (Version 2.2.046, 2007, Biostat, Inc.) was used to perform statistical analysis. The odds ratio for the risk of the rebleeding of small compared with large intracranial aneurysms was used as the effect size. Size cutoff was determined based on the presence of a (close to) common value across the studies. Both fixed- and random-effect models were used to calculate the summary ORs and 95% CIs. The significance of the overall OR was determined using a Z-test. For the sensitivity analysis, each study was removed from the total and the remaining studies were reanalyzed. The Type I error was set at 0.05 and the tests were 2-tailed. We assessed the heterogeneity between the study estimates using the I^2 statistic, with thresholds for a low degree of heterogeneity set at 40%.¹³ The funnel plots were inspected, and the Egger test was used to look for evidence of publication bias.

TABLE 1. Search strategy and results in PubMed, Embase, and Cochrane databases

Step	Search Terms	No. of Studies		
		PubMed	Embase	Cochrane
1	subarachnoid haemorrhage.ti,ab. OR Subarachnoid Hemorrhage[Mesh:noexp] OR (subarachnoid.ti,ab. AND hemorrhage.ti,ab.) OR subarachnoid hemorrhage.ti,ab. OR subarachnoid haemorrhages.ti,ab. OR subarachnoid hemorrhages.ti,ab. OR SAH.ti,ab. OR SAHs.ti,ab. OR subarachnoid hematoma.ti,ab. OR subarachnoid bleeding.ti,ab. OR ((Brain Aneurysm.ti,ab. OR brain aneurysms.ti,ab. OR Cerebral Aneurysm.ti,ab. OR cerebral Aneurysms.ti,ab. OR "Intracranial Aneurysm"[Mesh]) AND (rupture*.ti,ab.))))) †‡	25,423	35,627	998
2	("Recurrence"[Mesh] OR Recurrence.ti,ab. OR Recurrences.ti,ab. OR Rebleed*.ti,ab.)	306,816	339,678	21,206
3	Step 1 & Step 2	1844	2151	75
4	("Risk"[Mesh] OR Risk.ti,ab. OR sized.ti,ab. OR sizes.ti,ab. OR 10 mm.ti,ab. OR 7 mm.ti,ab. OR 5 mm.ti,ab. OR 6 mm.ti,ab. OR 8 mm.ti,ab. OR 9 mm.ti,ab. OR diameter.ti,ab.)	1,849,179	2,355,608	111,279
5	Step 3 & Step 4	610	773	25
6	Limits: none	610	773	25

MeSH = Medical Subject Headings; mm = millimeter; noexp = no explosion of MeSH heading; ti,ab = title/abstract.

† The asterisk in this field indicates that rupture was a major topic of these articles.

‡ Quotation marks indicate that the entire phrase was searched.

Results

Included Studies

The literature search revealed a total of 1408 records: 610 in PubMed, 773 in Embase, and 25 in the Cochrane database (Fig. 1, Table 1). An additional study was found by screening the references. After the removal of duplicates, we were able to identify 867 studies. Review of the abstracts left us with 26 studies for the full-text evaluation.^{3–6,9,10,18–20,22–25,27–31,33,35–37,39,41} Ten studies were excluded because they did not evaluate aneurysm diameter as a risk factor for rehemorrhage rate.^{4,6,9,18,22,24,29,36,39,41} Two other articles were excluded because one was a review and the other was an editorial.^{25,36} One study was written in Japanese and was thus also excluded.³¹ Four studies used an overlapping cohort, and the one with most appropriate data was selected.^{5,19,20,27,28,30,35} In total we identified 9 studies that met our inclusion criteria.^{3,10,19,23,27,28,33,37,41} Clinical and/or radiological definitions of rebleeding were given in 8 studies and these are listed in Table 2. Only 1 study reported the median time to rebleeding and the median time to aneurysm repair.³ Aneurysm size categories were given in 7 studies, while 2 others reported the mean size for the lesions in the non-rebleeding group compared with the rebleeding group (Table 2). Four studies reported on time to treatment or time to rebleeding (Table 2).

Quality Assessment

The methodological quality of the 9 included studies

was assessed. Of a total of 45 scores, there was no disagreement (Table 3). As a consequence of their observational design, all of the studies started with a maximal quality score of low. None of the studies were rated down based on serious inconsistency, indirectness, imprecision, or publication bias. In 5 studies, however, the quality was rated down because of serious limitations: Adjustment of the rebleeding rate for the time after the initial hemorrhage was not performed, or consecutive series were not reported.^{10,19,23,33,37}

Data Analysis

Seven of 9 studies provided core data, making calculation of the OR possible.^{10,19,23,28,33,37,41} Almost all of the studies used 10 mm as the cutoff point for aneurysm size among others classes, with only 1 study using 7 mm (Table 4). An analysis was performed with this best unifiable cutoff point. Overall rebleeding occurred in 360 (17.0%) of 2121 patients (incidence range, from study to study, 8.7%–28.4%). The rate of rebleeding in small and large aneurysms was 14.0% and 23.6%, respectively (absolute risk difference 9.6%). The meta-analysis of the 7 studies revealed that larger size aneurysms had an overall OR for rebleeding of 2.32 (95% CI 1.77–3.04; $p = 0.00$) and an OR of 2.56 (95% CI 1.62–4.06; $p = 0.00$) for a fixed- and a random-effect model, respectively (Fig. 2 upper). The results were subject to heterogeneity, which was determined by the I^2 statistic to be 60%, indicating that the random-effect

FIG. 1. Chart showing the results of the literature search.

TABLE 2. Definitions of aneurysmal rebleeding, time to treatment, and aneurysm size categories

Authors & Year	No. of Centers	Definition of Rebleeding			Aneurysm Size Categories
		Clinical	Radiological	Max Follow-Up (time to last rebleed)	
Kassell & Torner, 1983	12	NR	NR	NR	0–4.9, 5–9.9, 10–14.9, 15–19.9, 20–30 mm
Paré et al., 1992	1	Rebleeding confirmed by bloody ventricular drainage, cataclysmic clinical deterioration, or intraoperatively	Rebleeding confirmed on CT	NR	<1.0 cm, ≥1.0 cm
Beck et al., 2006	1	Any deterioration; new neurological deficit; a decrease in the level of consciousness; or severe headache. In comatose patients, any suspicious event like bradycardia & sudden rise in blood pressure or appearance of new blood on ventricular drainage	NR	Mean time at risk for non-rebleeding & rebleeding group: 80 ± 157 vs 97 ± 139 hrs (p = 0.91)	NR: reported mean size in non-rebleeding & rebleeding group: 6.9 ± 4.7 vs 11.2 ± 9.2 mm (p = 0.002)
Machiel Plezier et al., 2006	1	Sudden decrease in consciousness or a sudden increase in headache	Any increase of hemorrhage on CT	Max 30 days	≤10 mm, >10 mm
Inagawa, 2010	1	Definite clinical deterioration	Fresh blood on CT	Max 14 days	<5, ≥5–10, ≥10 mm
Guo et al., 2011	1	Sudden deterioration in consciousness or sudden increase in headache	Any increase of hemorrhage on CT	Max 72 hrs	≤5, >5 to ≤10, >10 to ≤15, >15 to ≤20, >20 mm
Shiue et al., 2011	4	NR	Fresh hemorrhage found on repeat neuroimaging	NR	<5, 5–9, ≥10 mm
Lord et al., 2012	1	Acute deterioration in neurological status in conjunction w/ CT changes	New hemorrhage or increase in hemorrhage burden on repeat CT	NR	NR: reported mean size in non-rebleeding & rebleeding group: 7 mm (5–10) vs 8 mm (6–15) (p = 0.001)
Wu et al., 2012	1	NR	Active bleeding w/ contrast extravasation during CTA or hematoma vol difference (max diameter difference, >3 mm) or new hematoma location between 2 consecutive CT scans	NR	<7 mm, ≥7 mm

CTA = CT angiography, NR = not reported.

TABLE 3. GRADE quality assessment

Authors & Year	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication	
						Bias	Quality
Kassell & Torner, 1983	Observational	Serious	None	None	None	None	Very low
Paré et al., 1992	Observational	Serious	None	None	None	None	Very low
Beck et al., 2006	Observational	None	None	None	None	None	Low
Machiel Plezier et al., 2006	Observational	None	None	None	None	None	Low
Inagawa, 2010	Observational	Serious	None	None	None	None	Very low
Guo et al., 2011	Observational	Serious	None	None	None	None	Very low
Shiue et al., 2011	Observational	Serious	None	None	None	None	Very low
Lord et al., 2012	Nested case-control study	None	None	None	None	None	Low
Wu et al., 2012	Observational	None	None	None	None	None	Low

model is appropriate. The sensitivity analysis did not alter the results (Fig. 2 lower). The funnel plot gave no indication of publication bias, but the findings are of limited value because of the small number of studies considered (Fig. 3). The Egger regression test revealed an intercept of 2.3 with a 2-tailed *p* value of 0.22, and it was accordingly not statistically significant. Five of the 7 studies reported data on age; 4 studies provided age-adjusted results and identified a persistent relationship between size and the risk of rebleeding.^{10,19,28,37} The presence of hypertension was reported in 2 studies and was more prevalent in patients with rebleeding in 1 of these studies.^{10,19} Location (anterior vs posterior circulation) was reported in 5 studies, while in 4 there was no difference in the rebleeding rate.^{10,19,33,37,41} One study identified a lower risk of rebleeding associated with posterior circulation aneurysms.³⁷ These findings provide insufficient evidence to relate hypertension and/or location of the aneurysm with the rebleeding rate.

Only a single study evaluated the risk of rebleeding over time dichotomized for size; the authors found a difference of rebleeding rate within 24 hours that persisted for 3 days after the initial hemorrhage.²⁸ They reported a

hazard ratio for large aneurysm of 2.4 (95% CI 1.2–4.5). In another study, median time to aneurysm obliteration did not differ between rebleeding and non-rebleeding groups but was not stratified according to lesion size.³

The use of antifibrinolytic agents was reported only by 1 study; the investigators included patients from 1996 to 2011, and from 2003 on, they used, on a routine basis, aminocaproic acid for all patients before aneurysm clipping or coiling.²⁷

Conflicting results have been reported regarding the effect of clinical grade on the risk of rebleeding. Six studies evaluated Hunt and Hess grade as a factor in relation to rebleeding. One study matched for Hunt and Hess grade found a significant difference in aneurysm size in those with rebleeding versus those without rebleeding.²⁷ Two studies reported no significant association between Hunt and Hess grade and rebleeding risk.^{32,40} The authors of one study concluded that the larger the aneurysm, the worse was the World Federation of Neurosurgical Societies grade, but did not report it as an independent risk factor.¹⁴ Two studies found Hunt and Hess grade to be a statistically significant independent risk factor for rebleeding (ORs

TABLE 4. Rebleeding rates

Authors & Year	Aneurysm Size Used for Analysis		Rebleeding Rate (%)*		
	Small	Large	Small	Large	Total Rebleeding
Kassell & Torner, 1983	<10 mm	≥10 mm	49/469 (10.4)	21/195 (10.7)	70/664 (10.5)
Paré et al., 1992	<10 mm	≥10 mm	2/61 (3.3)	13/67 (19.4)	15/128 (11.7)
Beck et al., 2006	NA: reported mean size in non-rebleeding & rebleeding group; 6.9 ± 4.7 vs 11.2 ± 9.2 mm (<i>p</i> = 0.002)		NR	NR	NA
Machiel Plezier et al., 2006	≤10 mm	>10 mm	68/281 (24.2)	22/73 (30.1)	90/354 (25.4)
Inagawa, 2010	<10 mm	≥10 mm	48/205 (23.4)	33/80 (41.3)	81/285 (28.4)
Guo et al., 2011	≤10 mm	>10 mm	18/169 (10.7)	52/157 (33.1)	70/326 (21.5)
Shiue et al., 2011	<10 mm	≥10 mm	13/195 (6.7)	9/59 (15.3)	22/254 (8.7)
Lord et al., 2012	NA: reported mean size in non-rebleeding & rebleeding group; 7 mm (5–10) vs 8 mm (6–15) (<i>p</i> = 0.001)		NR	NR	NA (case-control study)
Wu et al., 2012	<7 mm	≥7 mm	5/75 (6.7)	7/35 (20.0)	12/110 (10.9)
Total	NA	NA	203/1455 (14.0)	157/666 (23.6)	360/2121 (17.0)

NA = not applicable.

* The rebleeding rate is the percentage derived by dividing the number of patients with a rebleed by the total number of patients.

Meta-Analysis: rebleed risk in large vs small aneurysms

Sensitivity-Analysis: rebleed risk in large vs small aneurysms

FIG. 2. Forest plots showing results of the meta-analysis of studies reporting rebleeding risk of large versus small aneurysms (upper) and sensitivity analysis (lower). The squares indicate the mean, the whiskers indicate the 95% CI, and the diamonds indicate the pooled estimate (the width of the diamond represents the 95% CI).

2.5 and 4.9).^{5,7} Clinical grade at admission is a possible independent risk factor for rebleeding.

Discussion

The findings of this meta-analysis show that aneurysm size is an important determinant of aneurysmal rebleeding. Age and location are unlikely to be confounding factors. The presence of hypertension was insufficiently registered to determine the role of possible confounding effects. To reduce rebleeding rates, patients with large aneurysms should, when feasible, undergo acute treatment rather than ultra-early treatment, despite possible logistical issues. Additionally, if patients are referred from other centers, or if the diagnosis is delayed, those with large aneurysms still require urgent treatment because it has been shown that the effect size of this association might persist for up to 72 hours after the initial bleed.²⁸ An increased risk is seen even within 24 or 48 hours, the time window in which most aneurysm are currently treated.²⁵

The results of this analysis for ruptured aneurysms correspond with those of the ISUIA study, in which the pri-

FIG. 3. Funnel plot. The points correspond to the treatment effects from individual studies, the diagonal lines show the expected 95% confidence intervals around the summary estimate. Odds ratios are plotted on a logarithmic scale.

mary bleeding risk was greater for individuals with larger unruptured aneurysms.⁴⁰

The present research has several limitations. First, there is a potential for publication bias; studies showing no association between aneurysm diameter and rebleeding rate are less likely to be published. The estimated effect size in this meta-analysis could therefore be overestimated. Second, the studies considered did not include data from patients who had died before hospital admission, and this rate would be estimated to be as high as 15%.²⁶ Rebleeding rates during transfer to the hospital were also included and may be as high as 24%.¹⁰ Moreover, the average time to hospital admission varied considerably after the initial SAH. Only one study reported median time to aneurysm repair and aneurysm rebleeding.¹⁰ The research by Machiel Pleizier et al. revealed that there is no significant difference between small and large aneurysms when it comes to the risk of rebleeding 72 hours after the initial SAH.²⁸ Third, only one study reported the use of aminocaproic acid.²⁷ Although antifibrinolytic therapy does not improve survival or the chance of being independent in activities of daily living, it does reduce the risk of rebleeding by approximately 35%, as indicated in a recent Cochrane review.¹ Therefore, it is an important factor in rebleeding rate; unfortunately, the published studies did not provide data with which to evaluate the effects of both size and antifibrinolytic therapy together. Fourth, the cutoff for aneurysm size at 10 mm is artificial and chosen based on the categories set out in the published literature. Fifth, even if rebleeding is prevented in patients with large aneurysms, there is still a substantial rate of rebleeding events (14.0%) in cases involving small aneurysms. Only the acute treatment of all patients is optimal for prevention of rebleeding.²⁸

Hypothetically, acute treatment could be associated with additional treatment risks like increased intraoperative rupture due to the newly formed instable thrombus. However, for treatment within 24 hours, it has been shown that this timeframe was associated with improved clinical outcomes, although the benefit was more pronounced for coiling than clipping.³⁴ Moreover, it is unlikely that the risks of acute treatment will accrue in such a way that they outweigh the very high morbidity and mortality rates associated with rebleeding.

Conclusions

This meta-analysis showed that aneurysm size is an important risk factor for aneurysmal rebleeding and should be used in the clinical risk assessment of individual patients. Our results confirmed the current guidelines and stressed the importance of acute treatment for large ruptured aneurysms.

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