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Mortality and Morbidity of Surgery for Unruptured Intracranial Aneurysms

A Meta-Analysis

Theodora W.M. Raaymakers, MD; Gabriel J.E. Rinkel, MD; Martien Limburg, MD; Ale Algra, MD

Background and Purpose—Greater availability and improvement of neuroradiological techniques have resulted in more frequent detection of unruptured aneurysms. Because prognosis of subarachnoid hemorrhage is still poor, preventive surgery is increasingly considered as a therapeutic option. Elective surgery requires reliable data on its risks. Therefore, we performed a meta-analysis on the mortality and morbidity of surgery for unruptured intracranial aneurysms.

Methods—Through Medline and additional searches by hand, we retrieved studies on clipping of unruptured (additional, symptomatic, or incidental) aneurysms published from 1966 through June 1996. Two authors independently extracted data. We used weighted linear regression for data analysis.

Results—We included 61 studies that involved 2460 patients (57% female; mean age, 50 years) and at least 2568 unruptured aneurysms (27% >25 mm, 30% located in the posterior circulation). Mortality was 2.6% (95% confidence interval [CI], 2.0% to 3.3%). Permanent morbidity occurred in 10.9% (95% CI, 9.6% to 12.2%) of patients. Postoperative mortality was significantly lower in more recent years for nongiant aneurysms and aneurysms with an anterior location; the last 2 characteristics were also associated with a significantly lower morbidity.

Conclusions—In studies published between 1966 and 1996 on clipping of unruptured aneurysms, mortality was 2.6% and morbidity was 10.9%. In calculating the pros and cons of preventive surgery, these proportions should be taken into account. **(*Stroke*. 1998;29:1531-1538.)**

Key Words: aneurysm, unruptured ■ cerebral aneurysm ■ meta-analysis ■ surgery

Prognosis of subarachnoid hemorrhage (SAH) has improved slightly over the last 3 decades, but outcome is still poor, with a case-fatality rate of ≈50% and a dependency rate of 10% to 20%.[1] The overall annual risk of rupture of intact intracranial aneurysms is 1.9%.[2] Supported by some decision analyses,[3–7] many neurologists and neurosurgeons advise preventive surgery for unruptured aneurysms, at least under some circumstances. This advice applies not only to additional aneurysms found in patients with SAH from a ruptured aneurysm or to symptomatic unruptured aneurysms but also to incidental aneurysms. Improvement and greater availability of neuroradiological techniques such as CT or MR angiography have led to increases in fortuitous and intentional detection of these incidental aneurysms. Intentional detection can result from screening programs in patients with polycystic kidney disease or with a family history of intracranial aneurysms.[8,9]

Advising an individual patient about whether or not to undergo surgery for an unruptured aneurysm represents a clinical dilemma. Adequately balancing benefits and risks requires reliable data on surgical outcome. Results of treatment used in previous decision analyses on this subject[3–7] are based on relatively few studies. We therefore performed an extensive meta-analysis on the mortality and morbidity of surgery for unruptured intracranial aneurysms.

Subjects and Methods

Eligible Studies

All studies on mortality and morbidity of surgery for unruptured aneurysms published in journals, books, or book chapters from 1966 through June 1996 were eligible for our meta-analysis. We accepted studies in all languages. Each study had to provide data on postoperative mortality or morbidity of at least 5 adult patients. We included all types of unruptured aneurysms: incidental, symptomatic, or additional to a ruptured aneurysm (also referred to as multiple). In cases of multiple aneurysm, the unruptured aneurysm must have been surgically treated in a separate procedure. The method of operation had to be clipping. Patients who received other treatments for their unruptured aneurysms (such as wrapping, trapping, coating, or embolization) were excluded. Studies describing surgical results not for each patient individually but for the complete patient group were included only if at least 90% of patients were treated by direct clip placement. We excluded mycotic, bacterial, posttraumatic, and dissecting aneurysms and aneurysms in the cavernous sinus. A list of excluded studies and the corresponding reasons for exclusion is available on request.

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Search Strategy

To identify studies published between 1966 and June 1996, we performed an extensive Medline search from 1966 onward (with the use of 13 key words in all relevant combinations) and a search by hand of 18 relevant general medical, neurological, and neurosurgical journals from 1990 onward; we also scrutinized the reference lists of all retrieved publications for additional studies. The references of the publications thus found were checked again for additional studies. This method of cross-checking was continued until no further publications were found. In the case of overlapping study populations, we excluded patients described twice or used the most recent publication.

Data Extraction

Two readers (T.R. and G.R. or M.L.) independently assessed eligibility of studies and extracted data from the included studies on the following items: year of publication; midyear of study (defined as average calendar year of surgery); language; study design (prospective or retrospective); use of operation microscope; experience of the surgeon; number of patients; sex and age of patients; presence of polycystic kidney disease or familial aneurysms; preoperative condition of the patient (by Rankin score whenever possible)[10]; number, site, and size of aneurysms; presenting symptom (SAH from another aneurysm, symptomatic or incidental as defined by the original authors); criteria for postoperative mortality and morbidity; results of postoperative angiography; duration of follow-up; judgment of outcome (by neurosurgeon or independent physician); number of patients with transient morbidity; and finally number of patients with postoperative mortality and morbidity. Mortality was defined as all-cause postoperative mortality. Morbidity was defined as all permanent morbidity (eg, any neurological or other deficit) not present before operation and was specified by Rankin score when possible. If outcome was described in different categories (eg, good, fair, poor), any outcome except the most favorable was considered as morbidity.

In case of disagreement between the 2 readers, consensus was reached by joint review of the study. For the translated studies, we relied on data extraction by the translator only.

Data Analysis

We calculated the percentage of mortality and morbidity for each study separately and all studies combined. Corresponding exact 95% confidence intervals (CIs) for single proportions were determined. We used univariate and multivariate weighted linear regression to evaluate the influence on postoperative mortality and morbidity of the following variables: study design; language of publication; year of publication; midyear of study; sex and age of subjects; preoperative Rankin score; site, size, and presentation of aneurysms (additional, symptomatic, or incidental); and duration of follow-up. The number of patients per study was used as a weighting factor, so that larger studies had more impact than small studies. Because the number of studies with data on the use of operation microscope or on experience of the neurosurgeon was limited, we could not perform univariate linear regression analyses for these 2 items. Finally, we calculated postoperative mortality and morbidity in the subgroup of studies that fulfilled the following 3 criteria for "studies of good quality": clear definitions of outcome measures, no selection of specific groups of patients or aneurysms, and predefined moment of follow-up.

Results

A total of 394 studies in 15 different languages were read and considered for this meta-analysis. Sixty-one studies with 2460 patients (varying from 6 to 331 patients per study) met all inclusion criteria (Figure).[11–71] The number of aneurysms was at least 2568. We tried to exclude patients who were included in more than 1 study, but for approximately 30 patients we could not rule out double counting because of an insufficient description in the parent publications.

After we consulted the original authors, a large study with >700 patients was excluded because <90% of aneurysms had been clipped.[72]

Study Characteristics

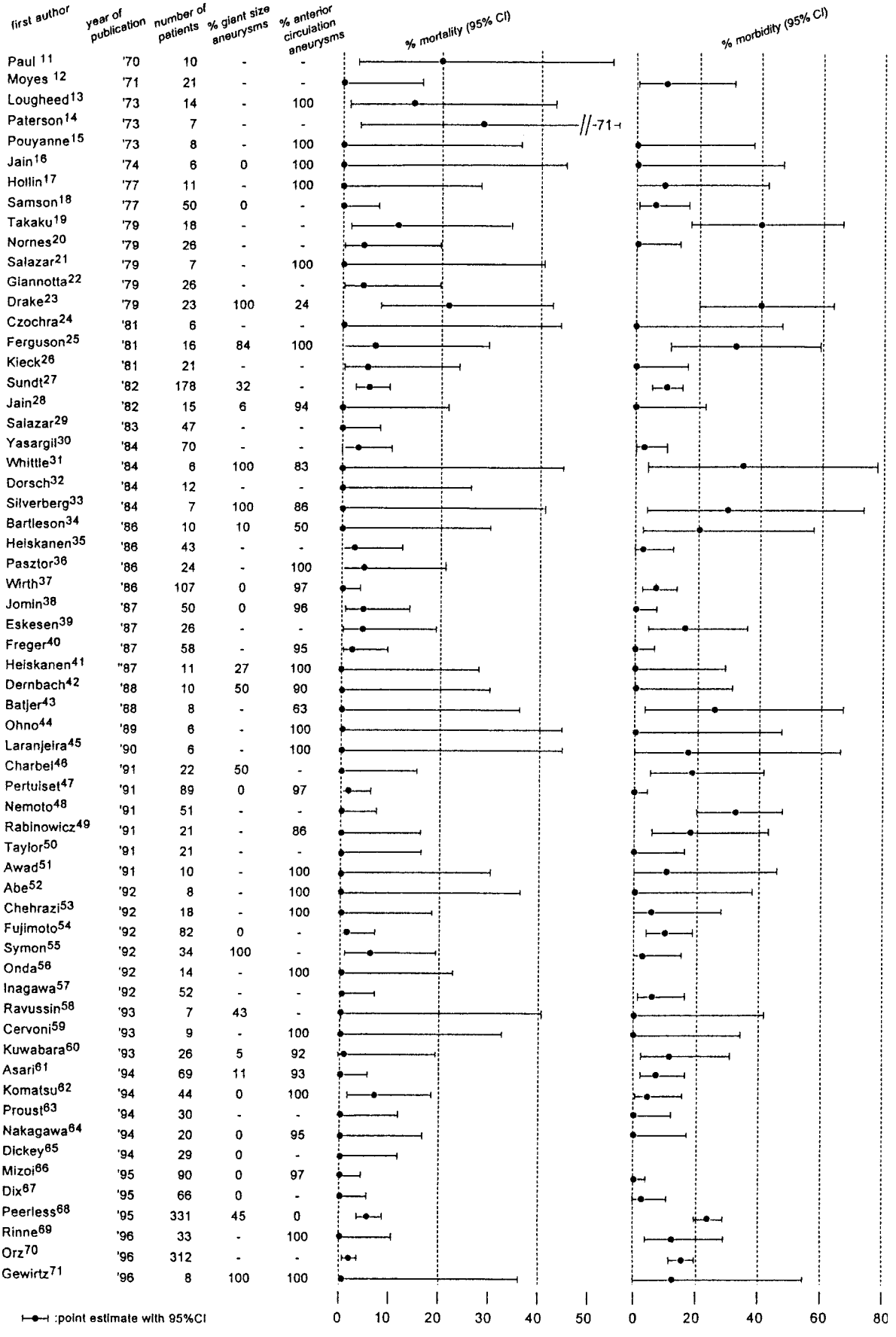
The median year of publication was 1987 (range, 1970 to 1996). Midyear of surgery ranged from 1959 to 1992 (median, 1981). Languages of publication were English (n=50), French (n=5), Japanese (n=5), and Polish (n=1). Only 8 studies were prospective; the other 53 were retrospective or unspecified. Forty studies described patients selected for aneurysm site (n=9), aneurysm size (n=7), aneurysm presentation (multiple, symptomatic, or incidental) (n=13), or other characteristics (n=6); in 21 studies, there was no selection regarding characteristics of aneurysms. In 18 studies, an operation microscope was used; in 1 this was not the case (42 studies not specified). Information on the neurosurgeons' experience was never explicit. In almost all studies (55 of 61), the neurosurgeon performing the operations was also the author of the study and observer of postoperative outcome. In half of the studies (30 of 61), outcome was classified by means of clearly defined outcome measures. Twenty-nine studies specified the moment of follow-up: in 8 studies outcome was evaluated at discharge, in 21 studies duration of follow-up was reported (median, 24 weeks; range, 2 to 234 weeks).

Patient Characteristics

Data on sex were provided for 705 of 2460 patients: 405 women (57.4%) and 300 men (42.6%). Data on age were available for 757 patients: mean age was 50.2 years (range, 15 to 79 years). The preoperative condition of the patients was described in 33 studies (882 patients). Eighty-one patients (9.2%) had no symptoms or signs, 795 patients (90.1%) were independent in daily life but had symptoms or signs (from a symptomatic unruptured aneurysm, a previous SAH, or unrelated diseases), and 6 patients (0.7%) were dependent in daily life. None of the studies contained information on the presence of polycystic kidney disease. Ten patients were known to have familial aneurysms.

Aneurysm Characteristics

In 2460 procedures, at least 2568 aneurysms were clipped; thus, 108 patients received treatment for more than 1 unruptured aneurysm in 1 procedure. Data on aneurysm site were available in 40 studies for 1324 aneurysms. The majority (934 aneurysms; 70.3%) were located in the anterior circulation (carotid artery or its branches, anterior and middle cerebral arteries, anterior communicating artery); fewer (395 aneurysms; 29.7%) were in the posterior circulation (basilar, vertebral, and posterior cerebral arteries). Twenty-nine studies provided data on aneurysm size: 691 (54.4%) were <10 mm, 235 (18.5%) were between 10 and 25 mm, and 345 (27.1%) were giant aneurysms (≥25 mm). For 1252 patients, information was available on the presentation of the unruptured aneurysms: 430 patients (34.3%) had SAH and 1 or more additional unruptured aneurysms, 358 patients (28.6%)



Overview of included studies and their characteristics.

TABLE 1. Univariate Weighted Linear Regression Analyses of Several Characteristics on Mortality and Morbidity

Variable	Mortality, β (95% CI)	Studies With Data, n	Morbidity, β (95% CI)	Studies With Data, n
Study design (prospective vs not prospective)	0.68 (−1.97 to 3.33)	61	−2.53 (−10.15 to 5.15)	51
Language, English vs non-English	−0.78 (−3.13 to 1.57)	61	−5.46 (−12.10 to 1.18)	51
Year of publication	−0.17 (−0.31 to −0.03)*	61	0.30 (−0.15 to 0.75)	51
Midyear of study	−0.21 (−0.32 to −0.09)*	56	0.08 (−0.39 to 0.55)	46
Sex, % women	−0.05 (−0.24 to 0.15)	26	0.30 (−0.03 to 0.63)	20
Mean age, y	−0.06 (−0.29 to 0.18)	25	0.19 (−0.32 to 0.70)	24
Preoperative Rankin score, % ≤2	0.19 (−0.34 to 0.72)	33	0.05 (−1.32 to 2.52)	27
Site, % anterior aneurysms	−0.05 (−0.07 to −0.02)*	40	−0.20 (−0.26 to −0.15)*	31
Size, % giant aneurysms	0.08 (0.04 to 0.12)*	29	0.25 (0.15 to 0.35)*	26
Presentation, %				
Additional	−0.02 (−0.05 to 0.02)	40	0.02 (−0.08 to 0.12)	33
Symptomatic	0.03 (−0.01 to 0.06)		0.05 (−0.04 to 0.14)	
Incidental	−0.02 (−0.06 to 0.03)		−0.11 (−0.23 to 0.01)	
Duration of follow-up, wk	−0.01 (−0.03 to 0.01)	21	0.00 (−0.05 to 0.05)	18

β indicates regression coefficient (β being −0.17 for the variable "year of publication" means that for each additional recent year, mortality decreases 0.17%; β being 0.08 for the variable "% giant aneurysms" means that for each additional 1% giant aneurysms, mortality increases 0.08%).

*Significant ($P<0.05$).

had asymptomatic aneurysms discovered by screening or during workup for another neurological disease, and in 464 patients (37.1%) aneurysms were symptomatic (as defined by the original authors). One third of patients categorized as symptomatic in the original studies had only nonspecific symptoms such as headache or dizziness; two thirds had objective signs such as visual loss, cranial nerve palsy, or other neurological deficits.

Effectiveness of Operation

In 10 studies, a postoperative angiogram was performed to verify adequate clip placement. The results of these angiograms were given in only 5 studies with 158 patients: 11 aneurysms were clipped incompletely.

Postoperative Mortality

In total, 64 of the 2460 patients died after the operation (2.6%; 95% CI, 2.% to 3.3%). Between studies, this proportion ranged from 0% (38 of 61 studies) to 29%.

In the univariate weighted linear regression analysis (Table 1, middle column), mortality appeared to be significantly related to the year of publication, midyear of study, and site and size of aneurysms. Mortality decreased (negative regression coefficients) with a more recent year of publication, a more recent midyear of surgery, and a higher proportion of anterior circulation aneurysms. Mortality increased (positive regression coefficient) with a higher proportion of giant aneurysms. All other items mentioned in Table 1, including mean age and sex, were not significantly related to postoperative mortality.

In the multivariate weighted linear regression analysis (Table 2, right column), year of publication and site (model 1) independently contributed to the prediction of mortality in the 35 studies in which both characteristics were available. Year of publication (model 2) failed to reach statistical significance when combined with the item size, suggesting that these 2 items are not completely independent. The coefficient of size in these studies (model 2) was equal (0.08) for both univariate and multivariate analysis, which suggests that the increased risk associated with giant aneurysms did not change in more recent years. In model 3, site and size did not independently contribute to postoperative mortality, which suggests a relation between the 2 variables (giant aneurysms being more often located at the posterior circulation). Multivariate analyses with midyear of study yielded essentially the same results as those with year of publication.

Postoperative Morbidity

Fifty-one (of 61) studies with 2270 patients provided data on postoperative morbidity. Permanent morbidity was found in 248 patients (10.9%; 95% CI, 9.6% to 12.2%). In 47 studies, the severity of postoperative morbidity was specified for 238 patients: 112 had symptoms or signs but were independent in daily life and 126 were dependent. These numbers indicate that about half of patients with postoperative morbidity were dependent.

In univariate weighted linear regression analysis (Table 1, right column), morbidity was statistically related to site and size of aneurysms. Morbidity decreased (negative regression coefficient) with a higher proportion of anterior circulation aneurysms and increased (positive regression coefficient) with a higher proportion of giant aneurysms. All other items mentioned in Table 1, including mean age and sex, were not of significant prognostic value for postoperative morbidity.

In multivariate weighted linear regression analysis (Table 2, model 4), the variables site and size had independent prognostic value with regard to morbidity. However, the coefficients of both variables decreased (from −0.21 to

TABLE 2. Multivariate Analyses for Studies With Data on More Than 1 Prognostic Characteristic Simultaneously

Variable	Univariate Analysis, β (95% CI)	Multivariate Analysis, β (95% CI)
Mortality		
Model 1: 35 studies		
Year of publication	−0.10 (−0.34 to 0.15)	−0.31 (−0.53 to 0.09)*
Site, % anterior circulation aneurysms	−0.05 (−0.07 to −0.02)*	−0.06 (−0.09 to −0.03)*
Model 2: 27 studies		
Year of publication	−0.08 (−0.31 to 0.16)	−0.07 (−0.25 to 0.12)
Size, % giant aneurysms	0.08 (0.04 to 0.12)*	0.08 (0.04 to 0.12)*
Model 3: 19 studies		
Site, % anterior circulation aneurysms	−0.05 (−0.08 to −0.02)*	−0.02 (−0.06 to 0.02)
Size, % giant aneurysms	0.09 (0.04 to 0.14)*	0.07 (−0.002 to 0.13)
Morbidity		
Model 4: 19 studies		
Site, % anterior circulation aneurysms	−0.21 (−0.27 to −0.15)*	−0.11 (−0.16 to −0.06)*
Size, % giant aneurysms	0.36 (0.27 to 0.45)*	0.25 (0.16 to 0.34)*

β indicates regression coefficient. *Significant ($P<0.05$).

−0.11 and from 0.36 to 0.25). This indicates, similar to the data on mortality, that site and size of aneurysms are not completely independent characteristics.

Subgroup Analysis of Studies of Good Quality

Seven studies fulfilled all 3 criteria of good quality (clearly defined outcome measures, no selection of patients or aneurysms, and a predefined moment of follow-up).[11,19,27,29,57,61,70] In these studies, 17 of 686 patients died after operation (2.5%; 95% CI, 1.5% to 3.9%). Data on morbidity were available in 5 of 7 studies: 80 of 629 patients had postoperative sequelae (12.7%; 95% CI, 10.1% to 15.3%). In these 7 studies, outcome was assessed after a mean follow-up period of 2 weeks (1 study), 24 weeks (2 studies), or at discharge (4 studies).

Discussion

In this meta-analysis of 61 studies, we found that clipping of unruptured aneurysms was associated with a mortality of 2.6% (95% CI, 2.0% to 3.3%) and a morbidity of 10.9% (95% CI, 9.6% to 12.2%). Half the patients with surgical morbidity became dependent in daily life. A location on the posterior circulation and giant size were the most important prognostic factors for poor outcome.

The data extraction from the parent publications had several limitations. We had to rely on mortality and morbidity data as provided by the authors, who were often the neurosurgeons who had performed the operations. This may have led to underestimation of surgical complications.[73] Adequate descriptions of outcome measures were often lacking, and assessment of neuropsychological function or quality of life was not performed in any of the studies. Duration of follow-up was not specified in most studies. Only very few publications provided data on effectiveness of clipping; hence, no reliable figures could be presented for this item.

We included a large number of studies that had variable patient inclusion criteria, definitions of outcome, length of follow-up, and collection of other variables of interest. This variability affects the interpretation of the results of our meta-analysis. Pending more prospective, well-designed studies, our study analyzed the best available evidence that can be used to make treatment decisions. The subgroup analysis for studies that fulfilled criteria of good quality showed mortality figures, which were essentially the same for the complete group of 61 studies; the morbidity percentages tended to be somewhat higher (although not significant) in the studies of high quality (12.7%) compared with the overall percentage (10.9%). This finding supports the consistency of our results.

We found mortality and morbidity rates to be much higher than those used in previous decision analyses on surgery for unruptured intracranial aneurysms.[3–7] These decision analyses estimated baseline cumulative surgical mortality plus morbidity at 4% to 6.5%. The higher rates for mortality and morbidity in our study indicate that advice on whether or not to proceed with surgery will change toward a more conservative attitude in many cases.

We included studies published from 1966 onward in this meta-analysis, although postoperative mortality and morbidity might be less now than 3 decades ago. Indeed, in univariate analysis, mortality decreased in more recent years. For postoperative morbidity, however, no time trend was found. In 5 of the 6 studies published before 1977, probably no operation microscope was used; if we exclude these studies from the analysis, postoperative mortality and morbidity were similar to those of the complete group of studies. We conclude that aneurysm characteristics, particularly an-

eurysm size, are much more important prognostic factors for outcome than year of publication.

The coefficients we found in multivariate analyses allow a rough estimate of mortality and morbidity for specific groups of patients (see Appendix). Patients with nongiant aneurysms of the anterior circulation have an estimated mortality of 0.8% and morbidity of 1.9%. Extremely high risks apply for patients with giant posterior circulation aneurysms: 9.6% mortality and 37.9% morbidity. Patients with giant anterior circulation aneurysms have a 7.4% chance of death and 26.9% of morbidity. For patients with nongiant posterior aneurysms, this would be 3.0% and 12.9%, respectively.

We used rather broad categories to describe aneurysm size: $<$10 mm, between 10 and 25 mm, and $\geq$25 mm. It would have been preferable to make a further distinction between aneurysms of 10 to 15 mm and of 15 to 25 mm. The information on aneurysm size in the source publications was not sufficient to allow for more detailed analysis.

The proportion of giant aneurysms and aneurysms in the posterior circulation in our meta-analysis is relatively high. This may cause an overestimation of mortality and morbidity. The percentage of symptomatic unruptured aneurysms was also high, which might be attributed to the rather broad definitions of the original authors, since aneurysms in patients investigated for headache or dizziness were often considered "symptomatic."

A Medline search for randomized clinical trials retrieves only about 50% of relevant studies[74]; the yield for observational studies has not been studied yet but might be even lower. We therefore extended our search by checking and cross-checking the reference lists of all identified studies and by means of extensive searches by hand. In addition, we did not restrict our search to English publications and included publications in all languages.[75] Nevertheless, it is likely that we missed some publications; however, we do not think that omission of a few, probably small, studies has influenced our results to an important extent. Other sources of bias might be more important. Studies that found rates for mortality and morbidity to be much higher than in the literature may have been left unpublished, because public awareness of these results might be disadvantageous for the neurosurgeon or the hospital. This type of bias leads to an underestimation of mortality and morbidity. Another type of bias is that a study on outcome after operation for unruptured aneurysms is more likely to be undertaken by a neurosurgeon with some interest in aneurysm surgery than by a neurosurgeon without special interest. A neurosurgeon with interest in aneurysm surgery probably performs more operations, with inherently better results. Again, this type of bias leads to too-favorable results. To prevent bias from highly selected case reports, we excluded studies with data on $<$5 patients.

We included studies with direct clipping as method of treatment. Methods other than clipping (such as wrapping and coating) do not definitively exclude the aneurysm from the circulation and are rarely applied today. Again, this restriction may have led to an underestimation of postoperative mortality and morbidity because large aneurysms, with inherent greater risks of complications, used to be treated by coating or wrapping.

We could not perform univariate regression analysis for the use of an operation microscope and experience of the surgeon because of the limited number of studies providing data on these items. Limited power may also explain why we did not observe a statistically significant influence of some factors that are likely to influence outcome, such as age and preoperative condition. Multivariate regression analysis was possible for a limited number of variables only (Table 2) because few studies provided data on more than 1 prognostic characteristic simultaneously.

We found 1 previous meta-analysis by King et al[76] on surgery for asymptomatic unruptured aneurysms. This included 28 studies (733 patients) published from 1966 onward and reported a mortality rate of 1.0% (95% CI, 0.4% to 2.0%) and a morbidity rate of 4.1% (95% CI, 2.8% to 5.8%). These complication rates are lower than those in our meta-analysis. The difference may be the result of several factors: (1) the exclusion of symptomatic aneurysms, (2) a higher proportion of small ($<$10 mm) aneurysms and aneurysms located at the anterior circulation (72% and 94%, respectively, against 54% and 70% in our study), and (3) the less-complete study retrieval (the total number of patients is less than one third of the number in our meta-analysis).

We conclude that surgery for unruptured intracranial aneurysms has an overall mortality of 2.6% and a morbidity of 10.9%. Half the patients with postoperative morbidity became dependent in daily life. The most important risk factors for poor outcome were giant aneurysm size and location at the posterior circulation of the aneurysm. For patients with nongiant anterior circulation aneurysms, mortality is estimated at 0.8% and morbidity is 1.9%; for patients with giant posterior circulation aneurysms, estimations are 9.6% for mortality and 37.9% for morbidity. These results should be taken into account when making a balanced decision on whether to proceed with surgery in an individual patient with an unruptured aneurysm.

Appendix

General formula: dependent$=\alpha+(\beta 1)\times$(variable 1)$+(\beta 2)\times$(variable 2).

% Mortality$=3.0-0.02\times$(% anterior aneurysms)$+0.07\times$(% giant aneurysms).

% Morbidity$=12.9-0.11\times$(% anterior aneurysms)$+0.25\times$(% giant aneurysms).

In patients with anterior aneurysms: % anterior aneurysms$=100$.

In patients with posterior aneurysms: % anterior aneurysms$=0$.

In patients with giant aneurysms: % giant aneurysms$=100$.

In patients with nongiant aneurysms: % giant aneurysms$=0$.

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