Treatmen of Unruptured Cerebral Aneurysms in California

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Background and Purpose—The impact of endovascular therapy on treatment outcomes of unruptured cerebral aneurysms has not been studied in a defined geographic area.

Methods—All primary diagnoses of unruptured aneurysms were retrieved from a statewide database of hospital discharges in California from January 1990 through December 1998. Admissions for initial treatment and all follow-up care were combined to reflect the entire course of therapy. An adverse outcome was defined as an in-hospital death or discharge to nursing home or rehabilitation hospital at any point during the treatment course. Multivariable analyses were performed with generalized estimating equations with adjustment for age, sex, ethnicity, source of admission, year of treatment, hospital volume, and clustering of observations at institutions.

Results—A total of 2069 patients were treated for unruptured aneurysms. Adverse outcomes were more frequent in the 1699 patients treated with surgery (25%) than in those treated with endovascular therapy (10%; P<0.001). The difference persisted after multivariable adjustment (surgery versus endovascular therapy: odds ratio for adverse outcomes, 3.1; 95% CI, 2.5 to 4.0; P<0.001). Adverse outcomes declined from 1991 to 1998 in patients treated with endovascular therapy (P<0.005) but not for surgery. In-hospital deaths occurred in 3.5% of surgical cases and 0.5% of endovascular cases (P=0.003), and the difference remained significant after adjustment (odds ratio, 6.3; 95% CI, 3.5 to 11.4; P<0.001). Total length of stay and hospital charges were greater in surgical cases (both P<0.001). Results were similar in a confirmatory analysis focusing on treatment differences between institutions. Institutional treatment volume was also associated with outcome but did not account for the differences between surgery and endovascular therapy.

Conclusions—in California, endovascular therapy of unruptured aneurysms is associated with less risk of adverse outcomes and in-hospital death, lower hospital charges, and shorter hospital stays compared with surgery. Differences between therapies became more distinct through the years. Uncontrolled differences in prognosis of patients receiving endovascular therapy and surgery cannot be ruled out in this study of discharge abstracts. (Stroke. 2001;32:597-605.)

Key Words: cerebral aneurysm | endovascular therapy | surgical treatment

Endovascular coil embolization was first used in California in 1990 as an alternative to surgical clipping for treatment of cerebral aneurysms.1,2 It is a minimally invasive technique and has been used to treat an increasing number of aneurysms.3 A number of case series describing outcomes of surgery and endovascular therapy have been published,3,4 but there have been few efforts to directly compare the short-term risks of therapy. In a cohort of ruptured and unruptured basilar artery apex aneurysms, patients treated with endovascular therapy had better outcomes among those who were judged to be candidates for either procedure.5 In a study at our center, rates of new disability were significantly lower with coil embolization than with surgery in a cohort of patients with unruptured aneurysms in which the risks of treatment were balanced in a blinded fashion.6 Results from a consortium of academic medical centers also suggested that endo-

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vascular therapy was safer, with fewer adverse outcomes for unruptured aneurysms7 and lower rates of adverse outcomes and in-hospital mortality for ruptured and unruptured aneurysms at facilities that used endovascular therapy more frequently.3

To evaluate the impact of endovascular therapy on unruptured cerebral aneurysm treatment in a defined population, we studied all patients treated for unruptured aneurysms in California during 1990–1998 using a statewide database of discharge abstracts. We chose to study patients with unruptured aneurysms because they were unlikely to have a disability before treatment,3,8,9 and deaths and discharges to nursing homes or rehabilitation hospitals could be considered adverse outcomes attributable to the procedure rather than to the aneurysm itself. We used traditional analytical techniques as well as a new method that reduces the potential for biased
comparison of therapies introduced when low-risk patients at a hospital are disproportionately selected for a specific therapy. Furthermore, since 2 previous studies found that institutions treating more aneurysms had lower rates of in-hospital death, it was important to evaluate the independent contribution of institutional treatment volume in patient outcomes. An estimate of rupture rates after treatment was also obtained by identifying subsequent admission for subarachnoid hemorrhage among California residents.

Subjects and Methods

Study Cohort

The Office of Statewide Health Planning and Development (OSHPD) of California maintains a database of discharge abstracts for all admissions to nonfederal hospitals. Hospitals began contributing cases in January 1990, with complete participation after June 1990. To develop a cohort of patients treated for unruptured cerebral aneurysms, we searched the OSHPD hospital discharge database from January 1990 through December 1998 for patients with a primary diagnosis of unruptured cerebral aneurysm (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 437.3) and 1 of 2 procedure codes for aneurysm treatment (clipping of aneurysm, ICD-9-CM 39.51; other repair of aneurysm, ICD-9-CM 39.52). We did not include patients initially treated by parent vessel occlusion (ICD-9-CM 38.81). Patients with a prior diagnosis of subarachnoid hemorrhage, identified from any coding of ICD-9-CM 430, were excluded to ensure that recovery from a prior subarachnoid hemorrhage would not complicate assessment of new deficits from treatment and to allow estimation of rupture rates in patients without a previously ruptured aneurysm. Since prior studies had shown that patients treated with endovascular therapy are more likely to return for follow-up angiography and further treatment of the initial aneurysm, it was important to compare entire courses of treatment. Therefore, we used a unique patient identifier to combine all admissions for aneurysm treatment in a given patient. In this way, we produced a single course of therapy for which hospital length of stay and charges were summed, and outcome was taken as the most adverse for all admissions. A prior validation study found 91% specificity for identifying treatment courses of unruptured cerebral aneurysms using this approach with a similar discharge database.

The ICD-9-CM code for endovascular treatment of an aneurysm is also used for surgical wrapping, which was performed in 4% of cases in a prior study. To distinguish endovascular coil embolization from surgical wrapping, we obtained an annual list of hospitals receiving platinum coils from the only manufacturer (Boston Scientific–Target). Patients with ICD-9-CM 39.52 were considered surgically wrapped if they were treated at hospitals that had never received coils or where treatment occurred before coils were received. Others with this procedure code were considered endovascular cases.

Predictor Variables and Outcomes

Since pretreatment disability is unusual, any discharge to a facility other than home could be considered an adverse outcome. Furthermore, discharge to a nursing home or rehabilitation hospital has been shown to correlate with Rankin Scale score at discharge and therefore can serve as a surrogate for functional outcome measure. Therefore, the primary outcome measure, any adverse outcome, was defined as in-hospital death or discharge to a nursing home or rehabilitation facility in patients who arrived from home. In-hospital death was determined regardless of source of admission. Hospital charges and length of stay were compared only for patients surviving to discharge; in this way, the expected shorter lengths of stay and lower charges in those dying would not bias results.

To estimate rates of aneurysm rupture after treatment for an unruptured aneurysm, we identified all admissions for subarachnoid hemorrhage (ICD-9-CM 430) in patients after initial treatment. For this analysis, patients with a primary or secondary diagnosis of arteriovenous malformation (ICD-9-CM 747.81) were excluded from this analysis (n=16), as well as those who were not California residents (n=189). Person-years of follow-up were estimated by totaling the number of months from initial treatment until the end of the study period.

Individual-Level Analysis

Surgery and endovascular therapy were compared in univariate analyses by Pearson’s χ² test for dichotomous outcomes and variables. Because the categorical variables age, hospital charges, and lengths of stay were not expected to be normally distributed because of skew from outliers, the nonparametric Wilcoxon rank sum test was used in analyzing these variables. Cuzick’s nonparametric trend test was used to evaluate changes in treatment and outcomes through the years; these analyses were restricted to admissions beginning after 1990 since complete case ascertainment was not achieved until 1991.

Patient age, sex, ethnicity, year of treatment, and admission source (transfer, emergency department, other) were included in all multivariable analyses. Since variables were expected to cluster by hospital (correlation between patients at a given institution), logistic regression, which ignores correlation, would tend to overestimate the precision of the results. Therefore, we used generalized estimating equations to account for clustering of observations within institutions and provide more accurate CIs; equal correlation between all interhospital observations (compound symmetry) was chosen as the initial covariance structure. Length of stay and hospital charges were transformed by using their natural logs. In this way a normal distribution could be approximated by reducing the positive skew in these data. We confirmed that variable distributions were approximately normal by comparing the actual distributions of transformed variables with idealized normal distributions using quantile plots. Results of log-linear models were expressed as the adjusted ratio of geometric means.

Institutional-Level Analysis

Greater hospital experience with aneurysm repair has been shown to be associated with improved outcomes. Since experience with treating ruptured aneurysms is likely to improve outcomes of patients treated for unruptured aneurysms, we chose to evaluate the overall treatment volume (ruptured and unruptured aneurysms) as a predictor of outcome. Subarachnoid hemorrhage cases were identified as patients with a primary diagnosis of ICD-9-CM code 430. To eliminate the bias from post hoc definition of cut points, we decided a priori to divide hospital treatment volume into quartiles of approximately equal numbers of patients.

If patients are selected for a particular treatment on the basis of factors that influence prognosis, a bias could be introduced. For example, if only small, asymptomatic aneurysms were chosen for endovascular therapy, outcomes of those treated by this modality could be better because these aneurysms are more easily treated rather than because endovascular therapy is a lower-risk procedure. Standard multivariable analysis adjusts for demographic characteristics and admission source, but other potentially important factors, such as aneurysm size and location, are unmeasured. Analyzing treatment effects by comparing outcomes between institutions rather than between individuals avoids selection bias at the individual level. Therefore, we evaluated treatment effects using an institutional treatment variable—the percentage of cases treated by endovascular therapy at the treating hospital—as a predictor of an individual’s outcome. In univariate analyses, institutions treating >10% of unruptured aneurysms with endovascular therapy were compared with others; we assumed that those institutions treating >10% by endovascular techniques were using the technique as an acceptable treatment alternative. For multivariable analyses, the portion of cases treated by endovascular techniques was defined as a continuous variable, and results were adjusted for age, sex, ethnicity, year of treatment, source of admission, and quartile of hospital treatment volume. When analyzing institutional effects on length of stay and hospital charges, we used natural-log-transformed variables.
over the time period (from 13% to 22%; participation of hospitals was not complete for the full year. The proportion of cases treated by endovascular therapy increased steadily through the years (from 27 to 55). In addition, the proportion of cases treated surgically and 370 patients (18%) were treated with endovascular therapy. A total of 117 of the surgical cases (6.9%) were aneurysm wrappings. The annual number of unruptured cerebral aneurysms treated surgically and 370 patients (18%) were treated with endovascular therapy, from 179 to 199; endovascular therapy, (1991 versus 1998: 26% versus 4%; P=0.13). Total hospital charges increased for both procedures (surgery, from $50 000 to $73 000; endovascular, from $41 000 to $43 000). Charges were $9000 less for endovascular therapy in 1991 (P=0.02) and $30 000 less in 1998 (P<0.001).

Analyses were repeated after adjustment for age, sex, ethnicity, source of admission, and year of treatment using multivariable models (Table 3). As in the unadjusted analysis, patients treated with surgery were more likely to die (P<0.001) and to experience an adverse outcome (P<0.001). In addition, surgery remained associated with longer hospital stays (P<0.001) and greater charges (P=0.001).

In univariate analysis, adverse outcomes occurred in 427 surgical cases (25.4%) and 36 endovascular cases (9.7%) (P<0.001) (Table 2). In-hospital deaths were nearly 7-fold more frequent in surgical cases (P=0.003). Length of stay was 4.7 days longer and charges were $27 000 greater in surgical cases (both P<0.001). Analyses were repeated after elimination of the 170 patients arriving through the emergency department since these patients may have represented more acute and symptomatic cases, and they may have been at greater risk for procedural complications. All differences persisted after exclusion of emergency department cases (Table 2) or when the cohort was limited to California residents (n=1880; 91%, results not shown).

Adverse outcomes declined steadily for endovascular therapy (1991 versus 1998: 26% versus 4%; P<0.005 for trend) but not for surgery (26% versus 21%; P=0.10) (Figure 2). There were no significant changes in mortality rates (P>0.20). From 1991 to 1998, lengths of stay decreased for both treatment modalities (surgery, from 14.1 to 8.5 days; endovascular, 13.1 to 4.8 days). Lengths of stay were shorter for endovascular therapy than surgery in 1998 (mean, 3.7 days shorter; P<0.001) but not in 1991 (1.0 day shorter; P=0.13). Total hospital charges increased for both procedures (surgery, from $50 000 to $73 000; endovascular, from $41 000 to $43 000). Charges were $9000 less for endovascular therapy in 1991 (P=0.02) and $30 000 less in 1998 (P<0.001).

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Institutional-Level Analysis
Since the combined experience in treating unruptured and ruptured aneurysms was more likely than volume of unruptured aneurysms alone to correlate with an institution’s proficiency at treating either type of aneurysm, we analyzed treatment volume on the basis of the total number of unique patients with treated aneurysms. Annual aneurysm treatment volumes varied broadly, ranging from <1 case per year at 3 hospitals to 107 cases per year at the highest-volume hospital. Hospital treatment volume was divided into quartiles to distribute patients into 4 groups of approximately equal size (quartile 1, 0 to 15.7 cases per year; quartile 2, 15.8 to 28; quartile 3, 29 to 67; quartile 4, 68 to 107). Adverse outcomes for unruptured aneurysms decreased with increasing hospital volume (from 33% in quartile 1 to 14% in quartile 4; P<0.005 for trend; Figure 3A). In addition, in-hospital deaths decreased with increasing hospital volume (quartile 1 versus 4, 5.2% versus 1.8%; P<0.005 for trend; Figure 3B). Lower-
volume hospitals also had longer lengths of stay (quartile 1 versus 4, 13.6 versus 8.4 days; \( P < 0.001 \)) and greater hospital charges ($60,000 versus $34,000; \( P < 0.001 \)).

More than half of the patients (\( n = 1106 \)) were treated at hospitals that did not offer endovascular therapy. The remaining patients (\( n = 963 \)) were treated at 11 hospitals where the portion of unruptured aneurysm patients treated with endovascular therapy ranged from 1% to 67%, and 7 hospitals treated >10% of cases with endovascular therapy. Hospitals treating >10% of unruptured aneurysms with endovascular therapy had lower rates of adverse outcomes (14% versus 28%; \( P < 0.001 \)) and fewer in-hospital deaths (1.2% versus 4.0%; \( P < 0.001 \)) than those using endovascular therapy less frequently (Figure 3). Hospitals using endovascular therapy more frequently also had shorter lengths of stay (8.6 versus 12.4 days; \( P < 0.001 \)) and smaller hospital charges ($49,000 versus $65,000; \( P < 0.001 \)). Results were similar when those hospitals that had ever used endovascular therapy were compared with others (for adverse outcomes, 16% versus 28% \( P < 0.001 \); for deaths, 1.9% versus 3.9% \( P = 0.007 \)).

Hospitals that used endovascular therapy more frequently also tended to have larger volumes (\( R = 0.59; P < 0.001 \)). To evaluate the independent effects of treatment volume and use of endovascular therapy and to adjust for differences in demographic characteristics, we analyzed predictors of adverse outcomes and in-hospital mortality in multivariable models. These models included percentage of patients treated with endovascular therapy, volume quartile, age, sex, ethnicity, year of treatment, and source of admission and accounted for institutional clustering of observations. After adjustment, adverse outcomes were more likely at hospitals using endovascular therapy less frequently, with a modeled odds ratio (OR) of 3.7 (95% CI, 2.6 to 5.4; \( P < 0.001 \)) for adverse outcomes with surgery compared with endovascular therapy. In-hospital deaths were also more likely at hospitals treating a smaller portion of patients with endovascular therapy, producing a modeled OR of 5.2 (95% CI, 2.1 to 12.8; \( P < 0.001 \)) for death with surgery versus endovascular therapy. At hospitals with lower rates of endovascular therapy, there were significantly longer lengths of stay (2.3-fold

### TABLE 2. Univariate Comparison of Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Surgical Treatment (( n = 1699 ))</th>
<th>Endovascular Treatment (( n = 370 ))</th>
<th>( P^* )</th>
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<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adverse outcomes†</td>
<td>25.4% (23.3%–27.4%)</td>
<td>9.7% (6.7%–12.8%)</td>
<td>&lt;0.001</td>
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<td>In-hospital deaths</td>
<td>3.5% (2.6%–4.3%)</td>
<td>0.5% (0.0%–1.3%)</td>
<td>0.003</td>
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<td>Length of stay, d</td>
<td>11.8 (11.4–12.4)</td>
<td>7.1 (6.2–8.0)</td>
<td>&lt;0.001</td>
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<td>Hospital charges</td>
<td>$64,000, ($60,000–$68,000)</td>
<td>$37,000 ($33,000–$41,000)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Excluding admissions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse outcomes†</td>
<td>24.8% (22.6%–26.9%)</td>
<td>9.6% (6.6%–12.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital deaths</td>
<td>3.1% (2.2%–3.9%)</td>
<td>0.6% (0.0%–1.3%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>11.0 (10.4–11.6)</td>
<td>7.0 (6.2–7.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital charges</td>
<td>$63,000 ($59,000–$67,000)</td>
<td>$37,000 ($33,000–$40,000)</td>
<td>&lt;0.001</td>
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*Pearson’s \( \chi^2 \) test for dichotomous outcomes; Wilcoxon rank sum test for categorical outcomes.
†Adverse outcomes were defined as deaths or discharges to a nursing home or rehabilitation hospital among patients not admitted from a nursing home.
‡Based on 1534 patients treated by surgery and 365 patients treated with endovascular therapy.
Values are mean (95% CI).

### Figure 2

Annual event rates of adverse outcomes (solid symbols and lines) and mortality (open symbols and dashed lines) for surgery (squares) and endovascular therapy (circles). Adverse outcomes tended to decline for endovascular therapy (\( P < 0.005 \) for trend) but not for surgery (\( P = 0.10 \)). Mortality rates did not change significantly through the years (\( P > 0.20 \)).

### TABLE 3. Multivariable Comparison of Treatment Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Ratio (95% CI)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse outcomes† (OR)</td>
<td>3.1 (2.5–4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital deaths (OR)</td>
<td>6.3 (3.5–11.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Length of stay (ratio of days)</td>
<td>1.4 (1.3–1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospital charges (ratio of $)</td>
<td>1.6 (1.2–2.1)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

†Adverse outcomes were defined as deaths or discharges to a nursing home or rehabilitation hospital among patients not admitted from a nursing home.
*Results are derived from generalized estimating equations and adjusted for age, sex, ethnicity, source of admission hospital volume, and year of treatment; for length of stay and hospital charges, they are expressed as ratios of geometric means.
Discussion

On the basis of our analysis of patients with unruptured cerebral aneurysms treated in California during 1990–1998, endovascular therapy appears to be significantly safer than surgery, with ≮3-fold lower rates of adverse outcomes and ≮6-fold lower rates of mortality with endovascular therapy (Table 3). Differences in outcomes persist after adjustment for demographic characteristics, treatment source, year of treatment, and hospital volume. Although we considered the possibility that these results reflected a tendency to triage low-risk patients to endovascular therapy, endovascular therapy also appeared safer when institutional characteristics were used as predictors, a method that reduces the potential for significant selection bias.

These results confirm 2 recent direct comparisons of outcomes after treatment of unruptured aneurysms. In the University Health Systems Consortium, an organization that includes 80 academic medical centers across the United States, adverse outcomes were twice as likely and mortality was 6-fold more likely with surgery than with endovascular therapy in patients treated between January 1994 and June 1996. These results were later confirmed using institutional predictor variables, which supports that the difference was not due to selection of low-risk patients for endovascular therapy. A study from the University of California at San Francisco found 3-fold higher rates of new disability in unruptured aneurysm patients treated with surgery in a cohort of patients who were blindly assessed to balance risks of therapy. Some of the patients in these prior studies were likely included in the present study, and therefore it should not be interpreted as a completely independent confirmation of prior results. However, this study included all institutions in a specified region and spanned a longer time period, and therefore the impact of endovascular therapy could be evaluated over time in a defined region.

Several important limitations of these data must be acknowledged. The reliability of coding in databases of discharge abstracts, such as the one used in this study, is imperfect. We have tried to reduce known sources of misclassification, including misidentification of surgical wrapping cases as patients treated with endovascular therapy. Furthermore, demographic variables and outcomes are likely to be correctly specified on the basis of a prior validation study using a similar administrative database.

It is possible that selection of lower-risk aneurysms for endovascular therapy led to a selection bias. We cannot rule this out because important prognostic variables, such as aneurysm size and location, are not available in the OSHPD database and were not included in our model. However, neurointerventional radiologists and vascular neurosurgeons tend to rate the risks of treatment differently, with more superficial aneurysms favored by neurosurgeons and those with smaller necks preferred by neurointerventional radiolo-
gists (Reference 6 and S.C. Johnston, MD, MPH, unpublished data, 2000). This reduces the likelihood that a systematic difference in overall prognosis is produced by selection for a particular therapy. In addition, the institutional-level analysis argues against selection bias as the source of better outcomes for endovascular therapy. Patient outcome for surgery or endovascular therapy at a particular hospital improved as a function of the percentage of patients treated with endovascular therapy at that hospital. This is not explained by the hypothesis that lower-risk patients are selected for endovascular therapy at these centers because, in that case, no overall benefit would be expected at hospitals using endovascular therapy more frequently. The institutional-level analysis supports the conclusion that, regardless of who is receiving endovascular therapy, by reducing the risk in a subgroup that otherwise would have been treated surgically, a hospital’s overall outcome improves.

Another limitation of our study is that outcomes were assessed at the time of hospital discharges. Recovery from surgery may be delayed but dramatic, and this is not assessed in our data. However, lengths of stay were longer for surgery, increasing the time for recovery compared with endovascular therapy, and prior studies have shown that short-term disability is associated with long-term dysfunction after treatment of unruptured aneurysms.6,9

Finally, we cannot confirm long-term efficacy of therapy in terms of reduced rupture rates. The only subarachnoid hemorrhages identified after treatment occurred in patients who were surgically clipped. However, posttreatment rupture is rare, and our sample size was not sufficient to confirm a trend toward more ruptures after surgery. Furthermore, this analysis of discharge abstracts has many potential sources of error in the determination of rupture rates, including imperfect case definitions and incomplete follow-up.

This study has several advantages over case series. First, outcomes were clearly specified a priori. The assessment of outcomes was objective, not susceptible to researcher bias, and identical for the 2 procedures. Second, the study was done statewide rather than at a few targeted institutions where greater expertise with one of the procedures could result in conclusions that would not be supported elsewhere. We included all nonfederal hospitals in California. However, it should be recognized that 2 of the most experienced centers for endovascular therapy, the University of California at San Francisco and the University of California at Los Angeles, are in the state. Results in other states may not be as favorable for endovascular therapy. Third, comparison of results at multiple centers allows evaluation of the influence of institutional characteristics on outcomes. This provides further confirmation of treatment effects.

A randomized trial would provide the highest level of evidence comparing surgery and endovascular therapy. It would ensure balance in important prognostic variables, including the location and size of the aneurysm. An ongoing study in ruptured aneurysms, the International Study of Aneurysm Treatment,16 will provide results that could be extended to unruptured aneurysms. However, a study of unruptured aneurysm treatment would provide direct evidence and would assist in making decisions about which aneurysms should be treated.17,18 Furthermore, a randomized trial for patients with unruptured aneurysms is likely to be more efficient because differences in outcome are more reasonably attributed to the therapy (since most patients are unimpaired before treatment) than for patients presenting with ruptured aneurysms, who often have neurological deficits before treatment. Such a study should include a substantial follow-up period to compare successful reduction of aneurysm rupture rates since there have been a number of documented ruptures after treatment with both modalities, particularly concerning endovascular therapy.2,19–22

Experience with aneurysm treatment also appears to be important to outcomes. We found strong associations between the number of cerebral aneurysm treated annually at an institution and rates of mortality and adverse outcomes, with half the rates of each at hospitals in the highest volume quartile compared with the lowest (Figure 3). A similar effect was seen in prior reports from New York and with Medicare data.11,12 We also noted a dramatic decline from 1991 to 1998 in adverse outcomes of patients treated with endovascular therapy (Figure 2). An interruption in the decline occurred in 1995, when the Food and Drug Administration approved platinum coils for aneurysm treatment and several new hospitals began using them. These data support a strong association between experience and outcome, which may have been even more dramatic if physician rather than institutional experience were measured. Advances in technology, such as a move to platinum coils from balloons for endovascular occlusion of aneurysms, may also account for some of the reduction in adverse events through the years.

Acknowledgments
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References
Unruptured Intracranial Aneurysms: In Search of the Best Management Strategy

Anueral subarachnoid hemorrhage (SAH) is a devastating disease with a high case-fatality rate. Most patients succumb to or are left disabled from the effects of the initial bleed, a factor minimally affected by any medical or surgical intervention. Because of the devastating effects of SAH, intracranial aneurysms should ideally be excluded from the circulation before rupture ensues. Widespread use of noninvasive neuroimaging testing has resulted in an increasing number of patients diagnosed with unruptured intracranial aneurysms. Consequently, many patients harboring unruptured intracranial aneurysms have been treated prophylactically. Preliminary findings of the International Study of Unruptured Intracranial Aneurysms (ISUIA) investigators, published in the New England Journal of Medicine in December 1998,


In the preceding article, Johnston and coworkers add more controversy to the ongoing debate on the best management strategy for unruptured intracranial aneurysms. They set out to study the effect on outcome of endovascular therapy of unruptured intracranial aneurysms. They report on 2164 patients with unruptured intracranial aneurysms treated in California between 1991 and 1998 and compare complication rates, costs, and lengths of hospital stay between surgical and endovascular treatment. The information for the study was abstracted from a statewide database of hospital discharges. Adverse events (defined as an in-hospital death or discharge to nursing home or to rehabilitation) occurred in 25.4% of surgical and 9.7% of endovascular cases. Length of stay was longer and charges were higher in surgical patients. Similar trends had been reported by the same group after analyzing outcomes of unruptured aneurysms treatment at their own institution22 and at 60 university hospitals (part of University Health System Consortium).18 Based on these observations, the authors would like us to believe that endovascular therapy is associated with a lower risk of adverse outcomes and in-hospital death and lower charges and shorter hospital stay. While endovascular therapy may indeed be superior to surgery for unruptured intracranial aneurysms in the State of California and inevitably will be
the therapy of choice of most intracranial aneurysms in the future as the technology evolves, there are insufficient scientific data in their study to validate this conclusion.

The foundation of the scientific approach to clinical decision making is to compare the outcome in groups of patients that are similar in all respects with the exception of the treatment modality employed. To make a valid comparison between patients who are treated with endovascular therapy and those treated with surgery, the key prognostic factors must be known or, if unequal, they must be adjusted for. In this study, key prognostic factors such as size and location of the aneurysm as well as skill of the operator are unknown. Large and giant aneurysms have wide necks and are often not suitable for endovascular treatment; consequently, one can assume that, in the study under scrutiny, these aneurysms were more commonly treated with surgery. Giant and large aneurysms pose a significant surgical challenge and account for a substantial number of the complications encountered in surgical series of unruptured aneurysms.19,20 Furthermore, as shown in Table 1, significant differences between the 2 groups in terms of age, ethnicity, and mode of admission were present. In particular, patients who underwent surgical treatment were more likely (16% of surgical patients versus 1% of the patients treated endovascularly) to be admitted to the treating hospitals through the emergency room (although outcomes were not significantly different after adjustment for this variable). Uneasiness with the data provided is heightened by the observation that 16 patients with surgically treated aneurysms were later admitted for an SAH (presumably from the previously unruptured aneurysm). Rebleeding from ruptured aneurysms postoperatively is an extremely rare occurrence, and bleeding from previously unruptured aneurysms after surgery was virtually unheard of prior to publication of this article. This observation tends to bring into question the reliability of the data on which the conclusions were made.

There is no doubt that treatment strategies for unruptured aneurysms need to be optimized. Surgery continues to be associated with a significant morbidity and mortality.1,17,18,21 In the ISUIA report, surgical complications were prospectively assessed at the 53 participating centers. Unlike many previous surgical series, cognitive impairment was assessed and included in the outcome analysis. In patients with unruptured aneurysms and no history of SAH 1 year after surgery, surgery-related mortality was 3.8% and morbidity (including impaired mental status) 12%.1 In a large cohort of patients with unruptured intracranial aneurysms treated at 60 university hospitals in North America between 1994 and 1997, in-hospital mortality was 2.3% and adverse events were observed in an additional 18.5% of patients.18 Similarly, Yamashita and coworkers21 reported on a large cohort of patients with unruptured intracranial aneurysms treated aggressively with prophylactic surgery at different neurosurgical centers in the Yamaguchi prefecture in Japan. Surgical intervention in these patients was accompanied by a combined morbidity and mortality rate as high as 20%.21

Endovascular treatment represents an appealing strategy likely to undergo further refinements, and increasing numbers of intracranial aneurysms will be treated by endovascular means in the future. In patients with aneurysmal SAH, coil embolization definitively reduces the rebleeding rates in the acute phase compared with the natural history of ruptured aneurysms.22 However, the efficacy of coil embolization in preventing growth and reperfusion of unruptured aneurysms has not yet been demonstrated, and many limitations currently exist. Incomplete obliteration of coiled unruptured aneurysms is not uncommon, and patients may display aneurysm recanalization on follow-up angiograms. These patients often necessitate retreatment. Rupture of previously unruptured aneurysms treated with coil embolization at follow-up have been reported.23–25 One wonders about the effect of incomplete obliteration in modifying intra-aneurysmal hemodynamic forces, thus promoting, in some cases, the growth and even rupture of aneurysms.

What to do with patients who are found to have unruptured aneurysms is a burning question—in fact, probably the most vexing scientific question confronting neurosurgeons, neurologists, and interventional neuroradiologists. The major question is: which aneurysms are a threat to the patients and require treatment? The closely related question is, what therapy is best, endovascular or microsurgery? The ideal way to obtain a robust conclusion would be a randomized multicenter trial of no therapy versus endovascular therapy versus microsurgery, in which an adequate number of patients were available to balance out differences in key prognostic factors, such as age, sex, smoking, hypertension, size, location, and number of aneurysms. While such a study would be enormously appealing from a theoretical perspective, from a pragmatic perspective it is impossible. Intracranial aneurysms, while a weighty issue to neurosurgeons, occur with sufficient scarcity that adequate numbers of patients to permit meaningful conclusions could not be accrued. To evaluate the efficacy of either therapeutic strategy in preventing future ruptures of the treated aneurysm, many years of follow-up are necessary. The other problem is that endovascular therapy is in its infancy, and the technology is evolving. In fact, there are reasons to believe that a breakthrough in technology will occur in the next several years. Accordingly, it is impossible to conduct a randomized trial when the therapy being tested is not stable. In light of the above, what is needed is a registry, or an epidemiological survey, in which data are collected prospectively in a standardized format from a large number of patients. While this does not provide nearly robust information as a randomized trial, it is a good second bet. Hopefully, more information to guide proper management of unruptured aneurysms will be available with the publication of the final results of the ISUIA investigators. Until better data are available, treatment of patients with unruptured aneurysms will continue to be based primarily on the clinical judgment of the treating physician.
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References
Treatment of Unruptured Cerebral Aneurysms in California
S. Claiborne Johnston, Shoujun Zhao, R. Adams Dudley, Mitchell F. Berman and Daryl R. Gress

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