Which unruptured cerebral aneurysms should be treated?: A cost–utility analysis
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Which unruptured cerebral aneurysms should be treated?

A cost–utility analysis

S. Claiborne Johnston, MD, MPH; Daryl R. Gress, MD; and James G. Kahn, MD, MPH

Article abstract—Objective: To determine which unruptured cerebral aneurysms should be treated considering the risks, benefits, and costs. Background: Asymptomatic unruptured cerebral aneurysms are commonly treated by surgical clipping or endovascular coil embolization to prevent subarachnoid hemorrhage (SAH). Methods: We performed a cost–utility analysis comparing surgical clipping and endovascular coil embolization with no treatment for unruptured aneurysms. Eight clinical scenarios were defined based on aneurysm size, symptoms, and history of SAH from a different aneurysm. Health outcomes of a hypothetical cohort of 50-year-old women were modeled over the projected lifetime of the cohort. Costs were assessed from the societal perspective. We compared net quality-adjusted life years (QALYs) and cost per QALY of each therapy to no treatment. Results: For an asymptomatic unruptured aneurysm less than 10 mm in diameter in patients with no history of SAH from a different aneurysm, both procedures resulted in a net loss in QALYs, and confidence intervals (CI) were not compatible with a benefit from treatment (clipping, loss of 1.6 QALY [95% CI 1.1 to 2.1]; coiling, loss of 0.6 QALY [95% CI 0.2 to 0.8]). For larger aneurysms (≥10 mm), those producing symptoms by compressing neighboring nerves and brain structures, or in patients with a history of SAH from a different aneurysm, treatment was cost-effective. Coiling appeared more effective and cost-effective than clipping but these differences depended on relatively uncertain model parameters. Conclusions: Treatment of small, asymptomatic, unruptured cerebral aneurysms in patients without a history of SAH worsens clinical outcomes, and thus is neither effective nor cost-effective. For aneurysms that are ≥10 mm or symptomatic, or in patients with a history of SAH, treatment appears to be cost-effective.

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An estimated 0.4 to 6% of adults harbor asymptomatic, unruptured cerebral aneurysms.1 Unruptured aneurysms may be discovered incidentally, found when another aneurysm ruptures, or produce symptoms, such as headache or cranial nerve palsy, due to compression of neighboring structures. When aneurysms rupture, they produce subarachnoid hemorrhage (SAH) with substantial rates of mortality (30 to 60%) and permanent disability (15 to 30%).2 Measured rates of rupture have been variable but generally have been between 0.2% and 3% annually.13 The risk of SAH has been believed to justify difficult open-cranium surgeries to place a clip on the neck of the aneurysm.45 More recently, neuro-interventional radiologists have developed endovascular coil embolization, a technique for treating aneurysms with a catheter inserted through the femoral artery.67 Whether all unruptured cerebral aneurysms should be treated has been debated for years.8 Because clinical outcomes depend on a variety of factors and require balancing early and delayed risks, this issue has been examined by several decision and cost–utility analyses (see Appendix).9–15 These analyses have found that aneurysm treatment is cost-effective. However, they were based on earlier estimates of rupture and complication rates that have been supplanted by newer, more precise estimates, and aneurysm characteristics were not considered. In addition, coil embolization and surgical clipping have not been compared.

Thus, we conducted a comprehensive cost–utility analysis to evaluate these preventive strategies for unruptured cerebral aneurysms, incorporating new data, notably results of the recently published International Study of Unruptured Intracranial Aneurysms (ISUIA).16

Methods. The model. Treatment of unruptured aneurysms creates a short-term risk of procedural complications followed by a reduction in the risk of SAH over the remaining lifetime of the patient. To model the protracted effect of elevated risk on the average life of a patient given competing mortality risks, we used Markov models.17,18 We
designed these models to track a hypothetical cohort of patients until all are dead, placing them into one of four health states: healthy, mild disability (independent), moderate–severe disability (dependent), or dead. Yearly rates of SAH and all-cause mortality were applied to the cohort, and the number of patients in each health state recorded for each year. Similar models were used for each treatment option, and the total cost and quality-adjusted life years (QALYs) per hypothetical patient were totaled for each model. Although standard practice in cost–utility analysis is to compare each treatment to the next best option, we chose to compare both treatments to no intervention as coiling is only practiced in large centers and data comparing clipping to coiling are sparse.

We assumed that aneurysms were discovered prior to entry into the model, so we did not consider screening as part of the clinical scenarios. The three treatment options compared were no treatment, surgical clipping, and endovascular coil embolization (coiling). Models for each of these options were constructed from decision trees (figure 1). The no-treatment option does not involve initial procedure-related risk, but there is an ongoing risk of SAH. Surgical clipping is associated with an initial risk of death or disability due to surgical complications, but if the patient survives, we assume there is no subsequent risk of SAH because the aneurysm is fully treated. For endovascular coiling, we have included both an early, procedure-related risk and a delayed risk of SAH; lack of long-term follow-up raises the possibility that coil embolization reduces but does not eliminate risk of SAH. Surgical and endovascular complications produce focal and diffuse brain injury resulting in neurologic deficits similar to those seen after SAH, so we assumed that the disability states were interchangeable.

We modeled all direct medical costs associated with the clipping and coiling procedures and with SAH (hospital, physician fees, outpatient, rehabilitation, and nursing home/home care). We have taken a societal perspective; i.e., costs are included regardless of who pays. A discount rate of 3% was applied to all costs and benefits.

Model inputs were derived from the literature and a study of costs at our institution (table 1). Rupture rates were taken from the ISUIA. For other inputs, the following hierarchy was followed according to availability of each type of data: the most recent meta-analysis; prospective

![Figure 1. Decision trees for no treatment, clipping, and coiling. Each decision tree was converted to a Markov model. SAH = subarachnoid hemorrhage.](image-url)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Best estimate</th>
<th>Source</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>50</td>
<td>Definition</td>
<td>30–70*</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Definition</td>
<td>Male, female</td>
<td>CDC, 1998</td>
</tr>
</tbody>
</table>

**Risks**

<table>
<thead>
<tr>
<th>Background mortality</th>
<th>US age/sex specific</th>
<th>Actual rates</th>
<th>CDC, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm rupture rates (per y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With no history SAH, &lt;10 mm</td>
<td>0.05%</td>
<td>ISUIA</td>
<td>0–0.15%†</td>
</tr>
<tr>
<td>With no history SAH, ≥10 mm</td>
<td>1.00%</td>
<td>ISUIA</td>
<td>0.46–1.54%†</td>
</tr>
<tr>
<td>With history SAH, &lt;10 mm</td>
<td>0.50%</td>
<td>ISUIA</td>
<td>0.26–0.74%†</td>
</tr>
<tr>
<td>With history SAH, ≥10 mm</td>
<td>1.00%</td>
<td>ISUIA</td>
<td>0–2.3%†</td>
</tr>
<tr>
<td>SAH case fatality</td>
<td>0.45</td>
<td>Meta-analysis</td>
<td>0.32–0.67‡</td>
</tr>
<tr>
<td>SAH case permanent mild disability</td>
<td>0.14</td>
<td>Cohort study</td>
<td>0.10–0.20</td>
</tr>
<tr>
<td>SAH case permanent moderate/severe disability</td>
<td>0.15</td>
<td>Meta-analysis</td>
<td>0.10–0.20;</td>
</tr>
<tr>
<td>RR mortality with mild disability</td>
<td>1.96</td>
<td>Cohort study</td>
<td>1.53–2.50</td>
</tr>
<tr>
<td>RR mortality with moderate/severe disability</td>
<td>3.73</td>
<td>Cohort study</td>
<td>2.74–5.07</td>
</tr>
</tbody>
</table>

**Clipping**

| Case fatality | 2.6% | Meta-analysis | 2.0–3.3% | Raaymakers, 1998 |
| Case permanent mild disability | 5.1% | Meta-analysis | 4.5–5.7% | Raaymakers, 1998 |
| Case permanent moderate/severe disability | 5.8% | Meta-analysis | 5.1–6.5% | Raaymakers, 1998 |
| Post-treatment yearly rupture rate | 0 | Estimate | Estimate |

**Coiling**

| Case fatality | 0.4% | Cohort study | 0–1.2% | Johnston, 1999 |
| Case permanent mild disability | 2.5% | Extrapolation | 1.4–4.1% | Johnston, 1999 |
| Case permanent moderate/severe disability | 2.8% | Extrapolation | 1.6–4.7% | Johnston, 1999 |
| Post-treatment RR rupture | 0.1 | Estimate | 0–0.4†‡ | Estimate |
| Post-procedure yearly rupture rate | Rupture rate × RR rupture | Estimate | Estimate |

**Costs**

| Clipping | $25,150 | Cohort study | $18,000–$35,000†‡ | Calculated |
| Coiling | $20,660 | Cohort study | $14,000–$31,000†‡ | Calculated |
| SAH admit | $46,980 | Cohort study | $33,000–$67,000†‡ | Calculated |
| Moderate/severe disability (annual) | $20,000 | Estimate | $13,000–$30,000†‡ | Gage, 1995 |
| Mild disability (annual) | $2,200 | Estimate | $1,000–$5,000†‡ | Gage, 1995 |
| Discount rate | 3.00% | Standard | 0–5%* | Gold, 1996 |

**Utilities**

| No health effect from aneurysm/treatment | 1 | Definition |
| Death | 0 | Definition |
| Permanent mild disability | 0.76 | Extrapolation | 0.5–1.0‡ | Gage, 1996 |
| Permanent moderate/severe disability | 0.25 | Extrapolation | 0–0.5‡ | Gage, 1996 |

**Untreated aneurysm**

| No symptoms | 1–5 × (rate of rupture) | Estimate | Estimate |
| Mild symptoms | 0.84 | Estimate | 0.80–1.00%‡ | Torrance, 1996 |

Input ranges are derived from the literature and normal, unless noted.

* Not included in Monte Carlo analysis.
† Lognormal distribution.
‡ Estimated range.

CDC = Centers for Disease Control and Prevention; RR = relative risk; ISUIA = International Study of Unruptured Cerebral Aneurysms; SAH = subarachnoid hemorrhage.
and cohort studies; case-control and case-series data; esti-
mations based on consultation with experts in the field. For
sensitivity analysis, the 95% confidence intervals (CI) for
ISUIA results, meta-analyses, and cohort studies were
used to establish the input range tested. For other inputs,
conservatively large CIs were estimated.

For multivariable Monte Carlo sensitivity analysis it
was also important to define the distribution of the range.
We assumed a distribution was normal if an input was
derived from a study that reported normal statistics. For
other variables, we assumed that each input was a best
estimate of a true population value, and values more dis-
tant from this best estimate would be less likely to repre-
sent the true population mean, but no value would be
impossible unless it was precluded by physical reality (e.g.,
rate of rupture less than zero). To reflect this, we modeled
input variability using the normal distribution if the lower
and upper estimates of the ranges were symmetrical
around the best estimate and the log-normal distribution if
skewed.20,21

Scenarios. Aneurysm rupture rates vary depending on
the size of the aneurysm and whether there is a history of
SAH from a different aneurysm.16 To account for variable
aneurysm characteristics and include the possibility that
an untreated aneurysm may produce disutility from symp-
toms, we modeled 8 different clinical scenarios (table 2).
We chose scenario A, a 50-year-old woman with an asymp-
tomatic unruptured aneurysm smaller than 10 mm and no
history of SAH, for the primary analysis (the base case)
because it was most common in the ISUIA16 and asymptom-
tic aneurysms had been the focus of prior cost–utility
analyses.13,14

Risks. Cohort age was taken as 50 years because this
approximated the average age of treated patients in the
ISUIA (see table 1). All-cause mortality rates were taken
from US mortality figures from 1990 through 1995, specific
for age and sex.22 Age-specific mortality was determined
within 10-year categories and after age 85 years by geo-
metric interpolation and extrapolation, respectively. For
disabled patients, the relative risks of mortality were
taken from rates in disabled head trauma patients;23 similar
to victims of procedural complication and SAH, their
excess mortality should be defined by neurologic deficits
rather than underlying risk factors (such as hypertension
and atherosclerosis in ischemic stroke patients). These rel-
ative risks were similar to those reported for minor and
severe disability after stroke compared to no disability.24,25

The yearly risk of SAH for untreated aneurysms was
taken from the ISUIA for each clinical scenario.16 Case
fatality and permanent dependent disability rates for SAH
were taken from a recent meta-analysis.26 Rates of mild
disability were calculated from 1-year follow-up data on
SAH survivors.27

Mortality and permanent complication rates for surgical
clipping were obtained from a recent meta-analysis (clip-
ing, 2.6% mortality and 10.9% permanent morbidity).2 In
this meta-analysis, 53% of patients with a morbidity compi-
cation were dependent on others for care. These results
were very similar to those of the ISUIA, in which surgery-
related death was 3.2% and morbidity was 12% at 1 year.16

Published reports of results of endovascular coiling are
limited. Therefore, we relied on a single, large study of
coeiling outcomes in the University Health Systems Consor-
tium in which in-hospital mortality was 0.4% (see table
1).28 This study did not measure long-term outcomes, but
compared rates of discharge to nursing homes/rehabilita-
tion hospitals for surgically and endovascularly treated
patients. Because this short-term outcome is likely to cor-
relate well with permanent disability,28 the multivariable
odds ratio (OR) of nursing home/rehabilitation hospital
discharge (clipping to coiling: OR 2.1, 95% CI 1.4 to 3.3)
was used to estimate the rate of mild and moderate/severe
complications after coiling using surgical outcomes as a
reference.2 We assumed that coiled aneurysms provided
90% protection against SAH based on results from treat-
ment of ruptured aneurysms.29-33 We relied on data for
previously ruptured aneurysms for this model input because
rupture rates of untreated, unruptured aneurysms are too
small to expect useful information from available data.16

Costs. We determined costs for clipping and coiling of
unruptured aneurysms at the hospital of the University of
California, San Francisco (UCSF) from 1994 to 1997. Be-
cause of the need to maintain confidentiality in bargaining
for health contracts, UCSF asked that we publish only
aggregate costs. Thus, all reported cost figures combine
costs of hospital and physician professional fees, converted
to 1997 dollars using the Medical Care category of the Con-
sumer Price Index.34

Our inclusion criteria were: age greater than 18 years,
no other aneurysm treatment within 2 months, no SAH
from another aneurysm within 6 months, and no coexis-
tent arteriovenous malformation. Thirty-three clipped pa-
tients and 70 coiled patients met these criteria. Hospital
costs were determined for each unit of activity and con-
sumption using a state-of-the-art cost accounting system
implemented throughout UCSF (Transition Systems Incor-
porated, Boston, MA). Costs of treatment were determined
for the entire inpatient course of therapy, including
follow-up admissions for further treatment, through De-
cember 1997. Inclusion of subsequent admissions was im-
portant because it accounted for 20% of coiling hospital
costs and 8% of clipping costs.

We estimated physician professional fees for clipping
and coiling and associated diagnostic procedures using the
Medicare fee schedule, which is also used by Medicaid and
many health maintenance organizations to set reimburse-
ment rates for procedures. We used the 1997 fee schedule
for San Francisco. We assumed that aneurysms were al-
ready identified in all cases and that angiograms were not
performed in untreated patients as further aneurysm char-
acterization would not be required. We assumed that two
complete 3-vessel angiograms were performed for coiled
aneurysms (one before and one follow-up). For clipped
cases, we assumed that a 3-vessel angiogram was per-
formed before treatment and a single vessel angiogram
after. Professional fees for inpatient care were determined
from mean lengths of stay in the University Health Sys-
tems Consortium comparative study (9.1 days for clipping
and 4.3 days for coiling) using high-acuity initial and
follow-up visit reimbursement rates.

To determine the cost of subarachnoid hemorrhage, we
used an estimate of 12% out-of-hospital mortality from a
population-based retrospective cohort study and assumed
these patients accrued no cost.35 For patients arriving at
the hospital, we estimated hospital costs by determining
the average cost of all 70 SAH patients treated at UCSF
during fiscal year 1997. Professional fees were determined as described above except we assumed that all patients had two complete angiograms. For costs after the acute hospitalization, we used published figures for 1991 Medicare costs during the first 6 months after a stroke,36 escalated to 1997 dollars. The annual direct costs for caring for disabled patients were taken from data on long-term care in stroke patients.37

Utility. Benefits were measured in QALYs. Death was assigned a utility of 0, and no disability from the procedures or SAH a utility of 1. Individuals without aneurysm-related problems, of course, may have other medical problems and associated disutilities, upon which our dis-

utilities would be additive. We could find no empirical studies of the disutility of disability due to SAH or the procedures, but we did find studies of disability due to brain injury. Gage and colleagues used time tradeoff and standard gamble methods to obtain relative utility valuations for permanent disability states after stroke for 83 patients with atrial fibrillation.38 Median utilities for mild strokes and an average of moderate and major strokes were used to define the utilities for mild and moderate–severe disability health states, respectively.

The psychological disutility associated with concern that an aneurysm could rupture at any time is important but unmeasured. Prior cost-effectiveness analyses of un-

<table>
<thead>
<tr>
<th>Scenario</th>
<th>QALYs Total</th>
<th>Added (95% CI)</th>
<th>Cost Total</th>
<th>Added</th>
<th>$/QALY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (base case): no symptoms, &lt;10 mm, no past SAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>19.1</td>
<td></td>
<td>$800</td>
<td></td>
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<tr>
<td>Coiling</td>
<td>18.5</td>
<td>-0.6 (-0.8, -0.2)</td>
<td>$29,400</td>
<td>$29,000</td>
<td>Ineffective*</td>
</tr>
<tr>
<td>Clipping</td>
<td>17.5</td>
<td>-1.6 (-2.1, -1.1)</td>
<td>$42,700</td>
<td>$42,000</td>
<td>Ineffective*</td>
</tr>
<tr>
<td>B: no symptoms, &lt;10 mm, past SAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>18.0</td>
<td></td>
<td>$7,400</td>
<td></td>
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<td>18.5</td>
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<td>$30,100</td>
<td>$23,000</td>
<td>$42,000 (10,000, ineffective)</td>
</tr>
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<td>-0.5 (-1.1, 0.5)</td>
<td>$42,700</td>
<td>$35,000</td>
<td>Ineffective</td>
</tr>
<tr>
<td>C: no symptoms, ≥10 mm, no past SAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No treatment</td>
<td>16.7</td>
<td></td>
<td>$14,300</td>
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</tr>
<tr>
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<td>18.4</td>
<td>1.7 (0.6, 3.2)</td>
<td>$30,800</td>
<td>$16,000</td>
<td>$10,000* (2,000, 45,000)</td>
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<td>$42,700</td>
<td>$28,000</td>
<td>$38,000 (10,000, ineffective)</td>
</tr>
<tr>
<td>D: no symptoms, ≥10 mm, past SAH</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>16.7</td>
<td></td>
<td>$14,300</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>18.4</td>
<td>1.7 (0.1, 4.5)</td>
<td>$30,800</td>
<td>$16,000</td>
<td>$10,000 (0, 230,000)</td>
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<td>$42,700</td>
<td>$28,000</td>
<td>$38,000 (0, ineffective)</td>
</tr>
<tr>
<td>E: symptoms, &lt;10 mm, no past SAH</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>No treatment</td>
<td>16.1</td>
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<td>$800</td>
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</tr>
<tr>
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<td>18.6</td>
<td>2.5 (2.2, 2.7)</td>
<td>$29,400</td>
<td>$29,000</td>
<td>$12,000* (8,000, 17,000)</td>
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<td>1.4 (1.1, 1.8)</td>
<td>$42,700</td>
<td>$42,000</td>
<td>$30,000* (5,000, 51,000)</td>
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</tr>
<tr>
<td>No treatment</td>
<td>15.5</td>
<td></td>
<td>$7,400</td>
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<td></td>
</tr>
<tr>
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<td>18.5</td>
<td>3.0 (2.6, 3.5)</td>
<td>$30,100</td>
<td>$23,000</td>
<td>$8,000* (4,000, 13,000)</td>
</tr>
<tr>
<td>Clipping</td>
<td>17.5</td>
<td>2.0 (1.5, 2.7)</td>
<td>$42,700</td>
<td>$35,000</td>
<td>$17,000* (10,000, 29,000)</td>
</tr>
<tr>
<td>G: symptoms, ≥10 mm, no past SAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No treatment</td>
<td>14.8</td>
<td></td>
<td>$14,300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coiling</td>
<td>18.4</td>
<td>3.6 (2.8, 4.5)</td>
<td>$30,800</td>
<td>$16,000</td>
<td>$5,000* (1,000, 10,000)</td>
</tr>
<tr>
<td>Clipping</td>
<td>17.5</td>
<td>2.7 (2.3, 3.8)</td>
<td>$42,700</td>
<td>$28,000</td>
<td>$11,000* (4,000, 20,000)</td>
</tr>
<tr>
<td>H: symptoms, ≥10 mm, past SAH</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No treatment</td>
<td>14.8</td>
<td></td>
<td>$14,300</td>
<td></td>
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<tr>
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<td>$30,800</td>
<td>$16,000</td>
<td>$5,000* (~1,000, 11,000)</td>
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<td>$28,000</td>
<td>$11,000* (1,000, 24,000)</td>
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</tbody>
</table>

* 95% Confidence interval of Monte Carlo sensitivity analysis excludes $100,000/QALY.

QALY = quality-adjusted life-year; SAH = subarachnoid hemorrhage.
ruptured aneurysm treatment have assumed that untreated patients have a utility of 0.95 due to worry.13,14 Because this burden should depend on rupture rates as long as physicians are appropriately reassuring, we assumed that the utility for untreated patients would vary with the rupture rates as follows: RU = 1 − 5 × [rupture rate]. The factor 5 is an estimate of the emotional dimension of living with a low-risk, high-consequence condition.39 For an aneurysm with 1% yearly rupture rate, this reproduces the prior estimate of 0.95 and is very similar to the mildly impaired emotional state (“occasionally fretful, angry, irritable, anxious, depressed, or suffering” = 0.93) in the Health Utilities Index Mark 2.40 For pain or compressive symptoms produced by an unruptured aneurysm, we estimated a utility of 0.84 from valuation of the state with frequent pain relieved by medications described in Health Utilities Index Mark 2.40 We assumed that treatment completely relieved symptoms, as has been shown for the majority of surgical and endovascular cases.61-44

Sensitivity analysis. Univariate sensitivity analysis was performed by varying each input variable throughout its full range while holding other variables constant. Multivariable sensitivity analysis was performed using a Monte Carlo simulation with all input variables (except age and discount rate) and 10,000 trials (Crystal Ball, version 4.0, Decisioneering, Denver, CO). Ninety-five percent CIs were obtained nonparametrically from the output distribution. We considered an upper limit of the 95% CI less than $100,000/QALY to be strong evidence of cost-effectiveness. The $100,000/QALY criterion was chosen as a reasonable cut-point to define moderate evidence for adoption and appropriate utilization of a medical technology.45

Results. The eight scenarios with different combinations of aneurysm size, history of SAH, and symptoms are reported in table 2 and figure 2. For scenario A, the base case of a 50-year-old woman with no symptoms or history of SAH from another aneurysm with an unruptured aneurysm less than 10 mm in diameter, the no-treatment

Figure 2. Cost–utility ratios for unruptured aneurysm case scenarios. Scenario descriptions are given in table 2. Lines represent the 95% confidence intervals, which were determined from Monte Carlo analysis. QALY = quality-adjusted life year.
option was preferred. Both surgical clipping and endovascular coil embolization resulted in a net loss in QALY and were more costly than no treatment. Univariate sensitivity analysis showed that two variables, untreated aneurysm rupture rate and utility for an untreated aneurysm, were most important in the model (figures 3 and 4). However, aneurysm treatment did not produce a gain in QALY unless rupture rates were as high as 0.3%/year for coiling and 0.7%/year for clipping, and higher rupture rates were required to attain reasonable cost–utility ratios (see figure 3). The rupture rate would need to be sevenfold higher than that found in the ISUIA for coiling (0.37%/year) and 15-fold higher for clipping (0.81%/year) to meet a cost-effectiveness criterion of $100,000/QALY.16 These values are well above the upper limit of the 95% CI in that study. For utility of an unruptured, untreated aneurysm, values of 0.95 for coiling and 0.89 for clipping were required to reach marginal cost-effectiveness at $100,000/QALY (see figure 4). These utilities are well below the base-case estimate of 0.9975. Even if there were no complications from treatment, neither therapy would be cost-effective. Treatment was not compatible with cost-effectiveness in multivariable sensitivity analysis (p < 0.001 for both clipping and coiling).

Seven other scenarios were tested in the model (see table 2, figure 2). Multivariable sensitivity analyses were performed for each. For clipping, all scenarios with aneurysms greater than 10 mm in diameter or with symptoms associated with the aneurysm were cost-effective, with cost–utility ratios ranging from $11,000/QALY to $38,000/QALY; clipping in scenario B was not effective. For coiling, all scenarios other than the base case were cost-effective, with cost–utility ratios of $5,000/QALY to $42,000/QALY, and CIs were less than $100,000/QALY for all symptomatic aneurysms and those larger than 10 mm in patients with no prior history of SAH.

Comparing clipping to coiling, there were marginally

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**Figure 3.** Univariate sensitivity analysis for the base case, scenario A, evaluating net quality-adjusted life year (QALY) (A) and net $/QALY (B) comparing clipping (solid line) and coiling (dotted line) to no treatment for a range of untreated aneurysm rupture rates. Net QALY of 0 corresponds to equivalent effectiveness of treatment with no treatment. Treatments with cost–utility ratios less than $100,000/QALY are often considered cost-effective. Arrows correspond to the input value in the base case (0.05%/year).

**Figure 4.** Univariate sensitivity analysis for the base case, scenario A, evaluating net quality-adjusted life year (QALY) (A) and net $/QALY (B) comparing clipping (solid line) and coiling (dotted line) to no treatment for a range of utilities of untreated aneurysms. Net QALY of 0 corresponds to equivalent effectiveness of treatment with no treatment. Interventions with cost–utility ratios less than $100,000/QALY are often considered cost-effective. Arrows correspond to the input value in the base case (utility = 0.9975).
lower cost–utility ratios for coiling, and net QALYs were 0.9 to 1.0 greater for coiling in all scenarios. In univariate analysis, for clipping to be equivalent to coiling in any scenario, coiling effectiveness (in terms of reduction in rupture rates) would need to be 25% or less. The procedures were also equivalent when coiling mortality reached 6%. However, 95% CIs determined from Monte Carlo sensitivity analysis always overlapped.

In univariate analysis, cost-effectiveness depended most sensitively on patient age and SAH rates of untreated aneurysms. Whenever varying any input over its range resulted in a cost–utility ratio of $100,000/QALY or more, the same was true for the multivariable Monte Carlo analysis of that scenario (data not shown).

**Discussion.** The implications of the low aneurysm rupture rates found in the ISUIA were immediately obvious to many clinicians: it would be very difficult to justify treatment for asymptomatic patients with no history of SAH from another aneurysm and an unruptured aneurysm less than 10 mm in diameter.** Therefore, it is not surprising that this cost-effectiveness analysis using the ISUIA results confirms those suspicions. We found that treatment was not only cost-inefficient, it was also ineffective, with overall net loss in QALYs for treatment of these patients. Approximately 40% of treated patients had aneurysms less than 10 mm in diameter and no history of SAH in the prospective cohort of ISUIA, suggesting that this low-rupture-rate group comprises a significant proportion of treated aneurysms. Therefore, based on these new findings, it appears that a large number of unruptured aneurysms are treated with high procedural risk and no overall benefit to the patient.

Of course, our findings are dependent on the validity of the ISUIA results. Rupture rates in the ISUIA study have been reported only from retrospective data, and may be subject to selection bias if physicians failed to enroll patients who have already died from aneurysm rupture, for example. However, our sensitivity analysis shows that the rupture rate for the base case would need to be at least sevenfold higher for coiling and 15-fold higher for clipping before these treatments would reach a borderline cost–utility ratio of $100,000/QALY. Bias of this magnitude in the ISUIA seems highly improbable. Therefore, until prospective data are available on rupture rates, it seems advisable to recommend avoiding surgery or coil embolization in patients with small, asymptomatic aneurysms and no history of SAH from another aneurysm.

However, for symptomatic unruptured aneurysms, treatment appears to be cost-effective, with net cost–utility ratios varying from $5,000 to $12,000 per QALY for coiling and $11,000 to $30,000 for clipping. The discomfort of symptoms in untreated patients is extended throughout their lifetime, leading to a large relative decrease in QALYs for this management strategy. These cost–utility ratios are small compared to some stroke and cardiovascular disease prevention strategies. For example, hypertension control in a 50-year-old woman with a diastolic blood pressure of 100 mm Hg is associated with a cost–utility ratio of approximately $30,000/QALY in 1997 dollars.

The severity of symptoms is important in determining cost-effectiveness. We assumed a utility of 0.84 for symptomatic patients, corresponding to a state of frequent pain relieved by oral medications. Anxiety alone may be considered a symptom that justifies treatment, as the state of being "often fretful, angry, irritable, anxious, or depressed" corresponds to similar level of utility. However, this should not be seen as justification for treating all unruptured aneurysms, because anxiety should be alleviated much more safely by reassurance in patients with low rupture rates. For small, asymptomatic aneurysms, the risk of rupture is similar to the risk of dying in an automobile accident, also 1/5,000 per year, and few are truly disturbed by this fear in daily life.

For large asymptomatic aneurysms, treatment was cost-effective. In these cases, elevated rupture rates of untreated aneurysms tipped the balance toward treatment despite high up-front risks of either therapy. The benefit was marginal in some cases with 95% CIs including $100,000/QALY. Patient preference, comorbidities, and life expectancy may be particularly important in making treatment decisions in these situations.

There was a marginal increase in cost-effectiveness for coil embolization compared to surgical clipping in all scenarios. Lower complication rates in endovascular coiling were responsible for the difference. However, these complication rates were derived from a single, nonrandomized cohort study and should be accepted with caution. Also, CIs for clipping and coiling always overlapped. Further studies comparing these therapies are required to better delineate their relative indications.

Other cost-effectiveness analyses of unruptured aneurysm treatment have been performed. King et al. completed a cost–utility analysis of surgical treatment in a 50-year-old patient with an asymptomatic unruptured aneurysm of unspecified size. They estimated a yearly rupture rate of 1% (20 times greater than our base case), surgical mortality of 1% (less than one half our rate), and utility of 0.95 for living with an untreated aneurysm. They found surgery to be cost-effective at $24,200/QALY. This result is very different from our base case but similar to our finding of $25,000/QALY for clipping in patients with asymptomatic aneurysms larger than 10 mm and no history of SAH, a scenario with a similar 1% yearly risk of rupture. By identifying the specific scenarios and integrating new data, our model allows greater specification of the indications for treatment.

Kallmes et al. performed a cost–utility analysis for endovascular coil embolization of unruptured aneurysms that were not treatable surgically using preliminary input values. Estimating a yearly ruptu-
ture rate of 1.4%, 65% treatment efficacy, and no effect on utility for an untreated aneurysm, they found a cost–utility ratio of $23,000/QALY for coil embolization compared with no treatment. Again, this is very different from our base case. However, for coiling in asymptomatic large aneurysms with a yearly risk of rupture of 1%, we found a cost–utility ratio of $9,000. For this scenario, our estimate was somewhat lower than theirs because we estimated a higher rate of treatment effectiveness and lower utility for untreated aneurysms, but the conclusions of the models are the same: that coiling is cost-effective when rupture rates are about 1%/year. Our model clarifies that this is only a subset of patients with relatively high rupture rates.

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Appendix

Base case: Clinical scenario and input assumptions used in the primary analysis.

Cost–utility analysis: A type of cost-effectiveness analysis in which the relative value of health states are considered, acknowledging that a year of life with a disabling condition may have less value than a year of healthy life. The units of analysis are cost per quality-adjusted life year.

Discount rate: The annual decrease in value of costs and benefits accrued in the future, acknowledging that people tend to value a dollar or a health state more if present today than in 10 years.

Markov model: An analytic construct in which a hypothetical cohort of patients is followed through specified disease states until all die or a fixed time period has elapsed; costs and QALYs (see below) are tallied for the cohort.

Monte Carlo sensitivity analysis: A method to assess how model results vary with multiple input parameters. The model is run repeatedly, each time assigning each input variable a value randomly chosen from a specified statistical distribution. The distribution obtained indicates how model results vary in response to uncertainty in many or all inputs.

Quality-adjusted life year (QALY): Year of life adjusted for the utility (see below) of the health state in that year. A value of 1 is equivalent to a year of perfect health.

Sensitivity analysis: Technique of varying model inputs to determine how results are affected.

Utility: The value assigned to a health state, often on a scale from 0 (death) to 1 (perfect health). These values are determined by standard methodology. For example, in determining the utility of a health state with a stroke, subjects might be asked, “How many years of healthy life are equivalent to 10 years of hemiparesis and aphasia?” (time tradeoff method), or “What risk of death would you be willing to accept to avoid 1 year with a hemiparesis and aphasia?” (standard gamble method).

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