Comparative Effectiveness of Unruptured Cerebral Aneurysm Therapies
Propensity Score Analysis of Clipping Versus Coiling

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Background and Purpose—Endovascular therapy has increasingly become the most common treatment for unruptured cerebral aneurysms in the United States. We evaluated a national, multi-hospital database to examine recent utilization trends and compare periprocedural outcomes between clipping and coiling treatments of unruptured aneurysms.

Methods—The Premier Perspective database was used to identify patients hospitalized between 2006 to 2011 for unruptured cerebral aneurysm who underwent clipping or coiling therapy. A logistic propensity score was generated for each patient using relevant patient, procedure, and hospital variables, representing the probability of receiving clipping. Covariate balance was assessed using conditional logistic regression. Following propensity score adjustment using 1:1 matching methods, the risk of in-hospital mortality and morbidity was compared between clipping and coiling cohorts.

Results—A total of 4899 unruptured aneurysm patients (1388 clipping, 3551 coiling) treated at 120 hospitals were identified. Following propensity score adjustment, clipping patients had a similar likelihood of in-hospital mortality (odds ratio [OR], 1.43; 95% confidence interval [CI], 0.49–4.44; P=0.47) but a significantly higher likelihood of unfavorable outcomes, including discharge to long-term care (OR, 4.78; 95% CI, 3.51–6.58; P<0.0001), ischemic complications (OR, 3.42; 95% CI, 2.39–4.99; P<0.0001), hemorrhagic complications (OR, 2.16; 95% CI, 1.33–3.57; P<0.0001), postoperative neurological complications (OR, 3.39; 95% CI, 2.25–5.22; P<0.0001), and ventriculostomy (OR, 2.10; 95% CI, 1.01–4.61; P=0.0320) compared with coiling patients.

Conclusions—Among patients treated for unruptured intracranial aneurysms in a large sample of hospitals in the United States, clipping was associated with similar mortality risk but significantly higher periprocedural morbidity risk compared with coiling. (Stroke. 2013;44:00-00.)

Key Words: aneurysm ■ comparative effectiveness research ■ outcome assessment (health care)
ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) codes were used to identify all cases of unruptured aneurysm hospitalizations (ICD-9 diagnostic code 437.3) recorded from 2006 to 2011. Patients were included if they underwent aneurysmal clipping (ICD-9 procedural code 39.51 [clipping of aneurysm]) or coiling (ICD-9 procedural code 39.52 [other repair of aneurysm], 39.72 [endovascular repair of occlusion of head and neck vessels], 39.75 [endovascular embolization or occlusion of vessel(s) of head or neck using bare coils], 39.76 [endovascular embolization or occlusion of vessel(s) of head or neck using bioactive coils], or 39.79 [other endovascular repair (of aneurysm) of other vessels]) during hospitalization. Because these diagnostic codes may not be specific for clipping or coiling, patients were included in the clipping or coiling groups if their billing record included an aneurysm clip or endovascular coil(s), respectively. Patients were excluded if they had a concurrent ruptured aneurysm diagnosis (ICD-9 diagnostic code 430 or 431).

Outcome Variables
The primary outcome variables of this study were death during hospitalization, discharge to long-term care (hospice, skilled nursing facility, long-term care hospital, or rehab facility), ischemic complications (aphasia [ICD-9 diagnostic code 784.3], hemiplegia or paraplegia [342.0–342.9], or cerebral artery occlusion [434.0–434.9], and hemorrhagic complications (subarachnoid hemorrhage [430] or intracerebral hemorrhage [431]). Secondary outcomes were defined as hydrocephalus (331.3–331.4), postoperative neurological complications ([997.0–997.09], other postoperative surgical complications ([997.2–997.95, 998.59, 998.0], ventriculostomy (ICD-9 procedural code 02.2), ventriculoperitoneal shunt surgery (02.34), or tracheostomy (31.3–31.29) that occurred after clipping or coiling.

Statistics
Data were extracted from the Perspective database using SAS (version 9.3; SAS Institute, Inc., Cary, NC) and analyzed using JMP (version 9, SAS Institute) and R (version 2.15, R Foundation for Statistical Computing, Vienna, Austria). Continuous results are presented as median and interquartile range (IQR) to account for nonparametric data distributions. Categorical results are presented as relative frequencies (%). Patient, procedure, and hospital covariates and outcome incidences were compared between clipping and coiling groups using Wilcoxon rank–sum test for continuous variables and Fisher’s exact test for categorical variables. Propensity score adjustment using 1:1 matching methods were performed using the MatchIt package in R.9

Propensity Score Analysis
Propensity score analysis was performed as previously described.10 Propensity scores, representing the probability of receiving clipping treatment, were calculated for each patient in the clipping and coiling groups using a logistic regression model. Twenty-seven covariates were used to generate this propensity score, including patient variables (age, sex, race, admission status, admission source, priority of unruptured aneurysm diagnosis, Charlson comorbidity score [calculated from ICD-9 diagnostic codes as previously described],11 and payor source), clipping/coiling procedure variables (priority of procedure and day of procedure), and hospital variables (region, number of beds, urban or rural location, and teaching or nonteaching status). After propensity score generation, clipping and coiling patients underwent 1:1 nearest neighbor (Greedy-type) matching of the logit of the propensity score with a caliper width of 0.25. Matching was performed without replacement and unpaired treated and control patients not meeting matching criteria were excluded. Each propensity score-derived matched pair was assigned a unique pair ID using an R script. Improvement in covariate balance after matching was determined using conditional logistic regression, conditioned on the pair ID. Odds ratios of primary and secondary outcomes were calculated after matching using Fisher’s exact test.

Sensitivity Analysis
Sensitivity analysis was performed as described by Lin et al12 to assess whether observed differences in outcomes between clipping and coiling groups could be completely attributed to an unmeasured confounder. The lower 95% confidence interval (CI) of the odds ratio (OR) of the primary outcome that was the closest to equivalency (1.00) when comparing clipping and coiling groups was used for this analysis. Hemorrhagic complications were chosen for sensitivity analysis because the lower 95% CI (1.33) was closest to equivalency of all primary outcomes significantly different between clipping and coiling groups.

Results
Patient Demographics
Between 2006 and 2011, 4899 patients from 120 unique medical facilities were hospitalized with ruptured aneurysms within the Perspective database. Within this patient population, 1388 patients (28%) underwent clipping and 3551 patients (72%) underwent coiling (Table 1). Significant differences between

| Table 1. Patient and Hospital Demographics of Unruptured Aneurysm Patients |
|-----------------------------|-----------------------------|-----------------------------|
| No. of patients, n          | Clipping        | Coiling        | P Value*         |
| Age, median (IQR)           | 55 (47–63)      | 58 (50–67)     | <0.0001         |
| Female, n (%)               | 1019 (73%)      | 2776 (78%)     | 0.0005          |
| Race                        | White          | 1020 (73%)     | 2530 (71%)      | 0.12 |
|                            | Black          | 207 (15%)      | 431 (12%)       | 0.0095 |
|                            | Hispanic       | 52 (4%)        | 186 (5%)        | 0.0267 |
|                            | Other          | 109 (8%)       | 404 (11%)       | 0.0002 |
| Admission status            | Elective       | 1170 (84%)     | 2629 (74%)      | <0.0001 |
|                            | Urgent         | 66 (5%)        | 358 (10%)       | <0.0001 |
|                            | Emergency      | 352 (11%)      | 564 (16%)       | <0.0001 |
| Admission source            | Non-medical source | 976 (70%)      | 2623 (74%)      | 0.0127 |
|                            | Transfer from hospital/care facility | 45 (3%) | 262 (7%) | <0.0001 |
|                            | Emergency department | 100 (7%) | 237 (7%) | 0.53 |
|                            | Clinic         | 267 (19%)      | 429 (12%)       | <0.0001 |
|                            | Charlson score | 1 (1–2)        | 1 (1–2)         | <0.0001 |
| Endovascular procedure      | Day of procedure | 1 (1–2)        | 1 (1–1)         | 0.0119 |
| Hospital                    | Region         | Midwest        | South           | Northeast       | West           |
|                            |                | 202 (15%)      | 671 (48%)       | 394 (28%)       | 121 (9%)       |
|                            |                | 479 (13%)      | 1463 (41%)      | 1268 (36%)      | 341 (10%)      |
|                            | No. of beds    | 623 (338–709)  | 623 (438–661)   | 1377 (99%)      | 0.27 |
|                            | Urban location (vs rural) | 3449 (97%) | <0.0001 |
|                            | Teaching (vs nonteaching) | 1079 (78%) | 2596 (73%) | 0.0007 |

*P values calculated from Wilcoxon rank–sum test or Fisher’s exact test.
clipping and coiling patients were observed. Specifically, patients who underwent clipping were younger (median age of 55 versus 58, \( P < 0.0001 \)), less likely to be female (73% versus 78%, \( P = 0.0005 \)), and more likely to be electively admitted (84% versus 74%, \( P < 0.0001 \)) compared with patients who underwent coiling. The majority of hospitals that performed clipping or coiling were urban (99% clipping and 97% coiling) and classified as teaching hospitals (78% clipping and 73% coiling).

**Temporal Trends in Clipping Versus Coiling**

Trends in the utilization of clipping and coiling were examined from 2008 to 2011. Because of the low utilization of these procedures in this database in 2006 and 2007, these data were excluded from analysis. The proportion of patients who underwent clipping gradually decreased from 30% in 2008 to 24% in 2011 (Figure 1).

**Propensity Score Adjusted Characteristics**

The distribution of unmatched propensity scores for the clipping and coiling groups is shown in Figure 2. Propensity score distributions were very similar between clipping and coiling groups. Following 1:1 matching, 1386 clipping and 1386 coiling patients were matched based on similarities in their demographic and clinical characteristics (Table 2). Following matching, all covariates were statistically indistinguishable between the clipping and coiling groups.

**Propensity Score Adjusted Outcomes**

Propensity score adjusted outcome incidence rates and odds ratios are shown in Table 3. Following 1:1 matching, clipping patients had a similar rate of in-hospital mortality as coiling patients (clipping: 0.7% [10/1386]; coiling: 0.5% [7/1386]), respectively (OR, 1.43; 95% CI, 0.49–4.44; \( P = 0.47 \)). The
incidence rate of discharge to long-term care was significantly higher in clipping patients compared with coiling patients (clipping: 17% [232/1386]; coiling: 3.7% [51/1386], P<0.0001). There was also an increased likelihood of ischemic complications (OR=3.42; 95% CI, 2.39–4.99; P<0.0001), hemorrhagic complications (OR, 2.16; 95% CI, 1.33–3.57; P=0.0012), and postoperative neurological complications (OR, 3.39; 95% CI, 2.25–5.22; P<0.0001) in clipping patients compared with coiling patients. Likelihood of ventriculostomy (OR, 2.10; 95% CI, 1.01–4.61; P=0.0320) was also higher in the clipping group compared with the coiling group. Likelihood of hydrocephalus, other postoperative surgical complications, ventriculoperitoneal shunt surgery, or tracheostomy was similar between clipping and coiling groups.

Sensitivity Analysis

Because the Perspective database lacks information on the size and location of cerebral aneurysms, we examined how such an unmeasured potential confounder could affect our findings using a sensitivity analysis. The sensitivity analysis, shown in Figure 3, examines the relationship between confounder prevalence in the clipping and coiling groups and the odds ratio of the confounder with respect to hemorrhagic complications.

Discussion

In this study of patients undergoing endovascular therapy for unruptured cerebral aneurysms from a large sample of US hospitals, patients treated with surgical clipping are at similar risk of in-hospital mortality but significantly greater risk of adverse outcomes than patients treated with endovascular coiling. Clipping recipients were more likely to be discharged to long-term care and were more likely to have periprocedural complications compared with coiling recipients. The relative merits of endovascular therapy versus open surgery or observation cannot be ascertained for individual cases in the Perspective database. Therefore, these findings do not indicate that all clipping recipients should have been offered coiling, because coiling would likely have been an inappropriate option for many of these patients. However, our study offers persuasive evidence that surgical clipping continues to be performed at a higher periprocedural risk of morbidity than coiling for a large number of patients in the United States.

Our findings corroborate other retrospective studies of large patient databases that also demonstrated a higher risk of mortality or morbidity after clipping as compared with coiling.3–7 However, our study offers substantial advances compared with these previous studies. First, we performed propensity score adjustment using numerous patient and hospital covariates to better match clipping and coiling patients and minimize selection bias, and we performed a sensitivity analysis to measure the effect of a possible unmeasured confounder. These findings suggest that selection bias, if present, does not account for the observed differences in outcomes between clipping and coiling therapies. Second, the Perspective database enabled identification of clipping and coiling patients through billing information instead of ICD-9
Table 3.  Patient Outcomes After 1:1 Matching by Propensity Score

<table>
<thead>
<tr>
<th>Incidence in Clipping</th>
<th>Incidence in Coiling</th>
<th>Odds Ratio* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality</td>
<td>10/1380 (0.7%)</td>
<td>7/1380 (0.5%)</td>
<td>1.43 (0.49–4.44)</td>
</tr>
<tr>
<td>Discharge to long-term care</td>
<td>232/1380 (17%)</td>
<td>56/1380 (4.1%)</td>
<td>4.78 (3.51–6.58)</td>
</tr>
<tr>
<td>Ischemic complications†</td>
<td>137/1380 (10%)</td>
<td>49/1380 (3.6%)</td>
<td>3.42 (2.39–4.99)</td>
</tr>
<tr>
<td>Hemorrhagic complications‡</td>
<td>57/1380 (4.1%)</td>
<td>27/1380 (2.0%)</td>
<td>2.16 (1.33–3.57)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>15/1380 (1.1%)</td>
<td>11/1380 (0.8%)</td>
<td>1.37 (0.58–3.30)</td>
</tr>
<tr>
<td>Postop neuro complications</td>
<td>106/1380 (7.7%)</td>
<td>33/1380 (2.4%)</td>
<td>3.39 (2.25–5.22)</td>
</tr>
<tr>
<td>Other postop surgical complications</td>
<td>21/1380 (1.5%)</td>
<td>13/1380 (0.9%)</td>
<td>1.62 (0.77–3.54)</td>
</tr>
<tr>
<td>Ventriculostomy</td>
<td>25/1380 (1.8%)</td>
<td>12/1380 (0.9%)</td>
<td>2.10 (1.01–4.61)</td>
</tr>
<tr>
<td>Ventriculoperitoneal shunt surgery</td>
<td>5/1380 (0.4%)</td>
<td>2/1380 (0.1%)</td>
<td>2.50 (0.41–26.35)</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>13/1380 (0.9%)</td>
<td>5/1380 (0.4%)</td>
<td>2.61 (0.87–9.39)</td>
</tr>
</tbody>
</table>

Cl indicates confidence interval.
*Odds ratio of clipping vs coiling.
†Defined as aphasia, hemiplegia or paraplegia, or cerebral artery occlusion not present at admission.
‡Defined as subarachnoid hemorrhage or intracerebral hemorrhage not present at admission.

Published studies of the NIS spanning 2001 to 2008 showed that centers that preferentially offered coiling with clipping had better outcomes than those that preferentially offered clipping.19 Results from the International Study of Unruptured Intracranial Aneurysms (ISUIA) study, which included neurophysiological outcomes, also showed lower complication rates among patients treated with endovascular clipping compared with those treated with surgical clipping.13

Size and location of an intracranial aneurysm are key determinants in assessing the risk of future rupture according to the ISUIA trial13 and a large study in Japan.20 Based on these studies, the risk of rupture of small (<7 mm) anterior circulation aneurysms is quite low, and for most patients would not justify the risks of treatment with clipping or coiling observed in our study. The American Heart Association’s recommendations21 state that treatment of small, unruptured cerebral aneurysms cannot generally be advocated. Information about location and size of aneurysms treated is not available in the Perspective database, so we cannot predict the relative risk of rupture according to the natural history data from literature. But the majority of unruptured aneurysms are <7 mm and located in the anterior circulation,22 so it is reasonable to assume that a substantial portion of patients treated in the Perspective database population had small, anterior circulation aneurysms. Distribution of aneurysm location is certainly expected to differ in the clipping and coiling cohorts (for example, more basilar aneurysms in the clipping cohort and more middle cerebral artery aneurysms in the clipping cohort), and we cannot ascertain aneurysm size or location from this database. However, our sensitivity analysis suggests that a very powerful unmeasured confounder with relatively dissimilar prevalence rates between treatment groups would be necessary to account for the outcome differences observed in this study. Because such a powerful confounder is unlikely to exist in this dataset, the observed outcome differences are likely not affected by confounding bias.

Although long-term outcomes cannot be evaluated with the Perspective database, discharge status can serve as a reasonable surrogate. In the ISUIA13 trial, morbidity and mortality at 30 days was 13.7% with surgery and 9.3% with procedural codes. Billing information has the advantage of greater specificity for cerebral coiling procedures, particularly before the creation of specific coiling ICD-9 codes in 2009, because earlier coiling procedures were routinely grouped into nonspecific ICD-9 procedural codes. Finally, the Perspective database contains hospitalizations through 2011, enabling an examination of more current clinical practice trends and outcomes compared to these previous studies.

Published guidelines for the treatment of unruptured cerebral aneurysms recommend that “microsurgical clipping rather than endovascular clipping should be the first treatment choice in low-risk cases.”14 Presumably, all patients treated with clipping in the Perspective database were offered clipping because the treating surgeon thought that it was a reasonably low-risk procedure relative to coiling. The outcomes in the Perspective database, however, suggest that the perioperative risk is significantly higher than for coiling. A recent literature review found that retrospective in-hospital morbidity and mortality reported by single centers was reported to be an average of 7.9% for clipping and 8.1% for coiling.15 Following propensity score matching of patients with similar demographic and clinical characteristics, our current study shows a much higher morbidity and mortality for clipping patients compared to these single center studies. This difference could be attributable in part to publication bias, where centers with better results are more likely to publish their findings. It is also possible that single center series are less accurate than an administrative database in reporting their own outcomes, a phenomenon demonstrated in the carotid endarterectomy literature where adverse event rates are significantly lower when assessed by the treating surgeon than when assessed by a neurologist.16,17

Overall use of clipping as compared with coiling of unruptured aneurysms has shown a steady decline from 2008 to 2011. The fraction of unruptured aneurysms treated by coiling in the Nationwide Inpatient Sample (NIS) increased from 11% in 199818 to 55.8% in 2007.2 As coiling has become more refined as a therapy, it is reasonable to expect that treating centers are becoming more practiced at recognizing patients who can be expected to have a good outcome with coiling. Previously
endovascular therapy, and at 1 year it was 12.6% and 9.8%, respectively. It might be argued that the higher recurrence rate associated with coiling compared with clipping could result in hemorrhages or complications of retreatment that negate the better periprocedural outcome with coiling. However, the International Subarachnoid Aneurysm Trial (ISAT),23 Cerebral Aneurysm Rerupture After Treatment (CARAT),24,25 and the Barrow Ruptured Aneurysm Trial (BRAT) 26 studies demonstrated only minimally elevated risks of rehemorrhage of ruptured aneurysms with coiling relative to clipping, and it is reasonable to expect that coiling offers a similar relative efficacy for preventing hemorrhage from unruptured aneurysms. Small differences in hemorrhage rates in the clipping and coiling cohorts over years are not likely to become so large as to overcome the relatively large differences in periprocedural morbidity.

Our study has several limitations. First, we recognize that coding errors undoubtedly occur and can affect the retrospective evaluation of an administrative database, but this limitation is no different than in other studies of cerebral aneurysms using such databases, and such errors are likely to be equally prevalent in the clipping and coiling groups. Second, because patients were not randomized to clipping or coiling in our retrospective study, selection bias may exist. Although propensity score adjustment of patient age, sex, comorbidities, admission status and source, and hospital variables minimized differences between the clipping and coiling patient groups, other unmeasured variables may have still contributed to selection bias. Our evaluation of the Perspective data are by no means a randomized study but rather a retrospective look at outcomes based on prevailing practices. Observational data from large clinical databases can complement the findings of prospective clinical trials, because the database may better reflect real-world practice. A randomized trial would be useful to definitively assess the efficacy of treatment of unruptured cerebral aneurysms.27

Conclusions
In patients treated at a large group of hospitals in the United States from 2006 to 2011, surgical clipping of unruptured intracranial aneurysms was associated with significantly greater morbidity risk than endovascular coiling.

Disclosures
None.

References


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