Current Trends and Results of Endovascular Treatment of Unruptured Intracranial Aneurysms at a Single Institution in the Flow-Diverter Era

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ABSTRACT

BACKGROUND AND PURPOSE: During the past several years, the number of unruptured aneurysms treated with endovascular techniques has increased. Traditionally, coil embolization was the treatment of choice for these lesions; however, recently flow diversion has become a viable, and in some cases superior, treatment option. The current single-center study presents results and trends of endovascular treatment with flow diversion and coil embolization in an unselected group of patients with unruptured intracranial aneurysms in a “real world” setting during the flow-diverter era.

MATERIALS AND METHODS: Three hundred ten patients with 318 treated unruptured aneurysms from June 2009 to May 2015 were included. Patient demographics, clinical characteristics, aneurysm/treatment characteristics, and outcomes were collected prospectively. We studied the following: intensive care unit admission/reasons, perioperative and mid-/long-term complications, target aneurysm rupture, retreatment/recurrence rates, and long-term neurologic outcome using the mRS.

RESULTS: The flow-diverter group had a larger mean aneurysm size (12.3 ± 8.6 mm versus 8.7 ± 6.3 mm, P < .0001). There were no significant differences in the immediate (P = .43) and mid-/long-term complication rates (P = .54) between groups. Periprocedural neurologic morbidity and mortality rates were 2.1% and 0.5% in the coiling group and 2.5% and 1.6% in the flow-diverter group. Patients with coiling were more likely to be retreated than those with flow diversion (14.8% versus 5.7%, P < .009). Worsening of the mRS due to the target aneurysm was noted in only 3.2% of patients.

CONCLUSIONS: The endovascular treatment of unruptured aneurysms can be performed with very low rates of neurologic complications. Both flow-diverter and coil therapy were safe and effective.

ABBREVIATIONS: FD = flow diverter; ICU = intensive care unit; PED = Pipeline Embolization Device

During the past several years, the number of unruptured aneurysms treated with endovascular techniques has increased. Traditionally coil embolization was the treatment of choice for these lesions; however, the introduction of endoluminal flow diversion has heralded the beginning of a new endovascular era. Flow diversion achieves high rates of aneurysm occlusion with acceptable safety profiles.1-6 However, with increasing experience and widespread use of flow diversion, several problems and complications have been recognized.7-8 These include intraparenchymal hemorrhage, postprocedural subarachnoid hemorrhage, and ischemic stroke.9,10

Newer endovascular treatment options allow better patient selection for flow-diversion and coiling techniques. At this stage, the potential influence of flow diversion on the use of coils in treatment of intracranial aneurysms remains unknown.11 These devices are being used in greater numbers of patients with various aneurysm locations and morphologies.6,12-14 While observing the changing endovascular treatment trends is interesting, it is crucial to assess the risk-benefit ratio for treatment by flow diverters (FDs) compared with coiling. The current single-center study presents results and trends of endovascular treatment with flow diversion and coil embolization in a group of unselected patients with unruptured intracranial aneurysms in a “real world” setting.

MATERIALS AND METHODS

Patient Population and Data Collection

Following institutional review board approval, all patients included in a prospective database of unruptured aneurysms from June 2009 to May 2015 were included in this study. Information collected in this database included patient demographics and
baseline clinical characteristics, aneurysm characteristics, treatment characteristics, and treatment outcomes. Patient demographic data collected included age, sex, baseline symptoms, baseline neurologic status, history of subarachnoid hemorrhage, and family history of intracranial aneurysms. Aneurysm characteristics included location and size. Treatment characteristics included type of device used, number of flow diverters used, and use of stent or balloon assistance.

The periprocedural pharmacologic protocol for patients undergoing flow-diverter therapy was uniform throughout the study period. Starting clopidogrel (Plavix), 75 mg, and aspirin, 325 mg, daily for 5 days before the procedure was recommended. Postoperatively, patients were maintained on the same clopidogrel and aspirin dosage for 3 months. After 3 months, clopidogrel was discontinued for patients undergoing on-label treatment (ie, aneurysms of the internal carotid artery proximal to the takeoff of the posterior communicating artery). For cases that were not off-label, and especially in high-risk locations, we have continued antiplatelet therapy for a longer time due to a potentially higher risk of thromboembolic events. Patients with aneurysms distal to the origin of the posterior communicating artery or involving the posterior circulation were usually maintained on clopidogrel for a longer time, and the antiplatelet therapy was recommended according to the results of their follow-up conventional angiography. After discontinuation of clopidogrel, low-dose aspirin (81 mg/day) indefinitely was recommended. Loading doses of clopidogrel and aspirin were given on the day before or the day of the procedure for patients who were not electively admitted. Platelet reactivity was not tested in any patient.

**Outcomes**

Treatment outcomes included intraprocedural and periprocedural technical events, clinical events (including aneurysm perforation, thrombosis, neurologic symptoms, medical symptoms, ophthalmologic symptoms, and groin complications), and late technical and clinical events at follow-up. Periprocedural complications were defined as those occurring within 30 days following the procedure, and late events were defined as events occurring after 30 days. Clinical follow-up was collected by telephone within the first 30 days, at the time of radiographic follow-up at 6 and 12 months and 3 years, and by telephone at 24 months. Clinical follow-up was obtained by a specialized nurse not directly involved with the original procedure. At the time of follow-up, patients were asked to rate themselves on the basis of the modified Rankin Scale. Patients were also asked to specify the reason for any score higher than zero. A baseline assessment, following the same methodology, was also obtained at the first encounter before aneurysm treatment.

For patients with flow diverters, radiologic follow-up with conventional angiography was recommended at 6, 12, and 36 months, and for patients with coiling, conventional angiography or MRA was recommended 6 or 12 months after the original procedure, depending on aneurysm characteristics. Afterward, imaging follow-up for patients with coiling was individualized according to various patient and aneurysm factors. Aneurysm occlusion on follow-up angiography, MRA, and/or CTA was categorized as “complete” (no filling of the aneurysm sac), “near-complete” (>90% occlusion), and “incomplete” (<90% occlusion). We also reported FD angiographic outcomes by the number of FDs used in treatment.

We studied the following outcomes: 1) the presence of perioperative complications, 2) mid- and long-term complications, 3) target aneurysm rupture, 4) retreatment rates, 5) major recurrence rates, and 6) long-term neurologic outcome. Long-term neurologic outcome was assessed by using the modified Rankin Scale and with the methodology detailed above. We also determined whether neurologic disability was secondary to the aneurysm or other symptoms (ie, back pain, intercurrent nonrelated illness, and so forth). “Neurologic morbidity” was defined as any neurologic deficit that appeared either due to target aneurysms or their endovascular treatment. “Neurologic mortality” was defined as any death of the patient related to target aneurysms and/or their treatment complications.

**Statistical Analysis**

Baseline characteristics and outcomes were compared between the flow-diverter and coiling groups. Descriptive statistics are presented as means and proportions. Means are presented with SDs. Categoric variables were compared by using a χ² test, and continuous variables were compared by using a Student t test. Statistical significance was a P value < .05. All statistical analysis was performed by using JMP 10.0 (SAS Institute, Cary, North Carolina).

**RESULTS**

**Patient Population**

During the study period (September 2009 to April 2015), 332 patients were recommended for endovascular treatment of 341 unruptured intracranial aneurysms. Twenty-two patients with 23 target aneurysms were excluded due to missing Minnesota Research Authorization. Three hundred ten patients with 318 target aneurysms treated with endovascular coil or flow diverters were included in the study. One hundred ninety-six aneurysms were initially treated with coiling, and 87 aneurysms were initially treated with flow diversion. Thirty-five aneurysms were treated with flow diversion following recanalization after coiling (these aneurysms were either coiled at other institutions or coiled at our institution prior to the study period). Of the 318 target aneurysms treated during the study period, 34 required retreatment. Thus, there were 352 aneurysm treatments during the study period. Demographic and aneurysm characteristics are listed in Table 1. Two hundred forty-nine patients (80.3%) were women, and 61 patients (19.7%) were men. The mean age at presentation was 57.4 years (range, 20–83 years). Most of the treated aneurysms were asymptomatic (249 aneurysms, 78.3%), while 69 aneurysms (21.7%) were symptomatic. Headache (11.0%) and visual problems (5.7%) were the most common presenting symptoms. Two hundred ten aneurysms (66.0%) were incidentally discovered.

Radiologic follow-up was available for 290 aneurysms (91.2%), while 28 aneurysms (8.8%) have not yet undergone radiologic follow-up because they were recently treated. The mean length of radiologic follow-up was 20 months (range, 0–67 months), and the mean clinical follow-up was 23.4 months (range, 1–67 months). From 2009 to 2014, the proportion of aneurysms treated with flow diversion increased from 15.8% to...
Aneurysms between the 2 groups (P < .0001). There was a significant difference in the location of treated aneurysms, major recurrences were present and retreated in 29 aneurysms (14.8%) in the coiling group. In the FD group, there were more large and giant aneurysms in the FD group compared with the coiling group (26.2% versus 9.7%, P < .0001). There was a significant difference in the location of treated aneurysms between the 2 groups (P < .0001): Twenty-six cavernous sinus aneurysms (21.3%) were treated with FDs compared with 1 (0.5%) in the coil embolization group; 70 (57.4%) supraclinoid/paracclinoid aneurysms were treated in the FD group versus 34 (17.3%) aneurysms in the coiling group. All anterior cerebral artery/anterior communicating artery aneurysms (56/17.6%) were treated with coiling only. Characteristics of treated aneurysms are summarized in Table 1.

### Angiographic Results

Angiographic results and basic characteristics of techniques and devices are listed in Table 2. Radiologic follow-up was available for 290 (91.2%) aneurysms, after a mean time of 20 months (range, 0–67 months), while 28 aneurysms (8.8%) have not yet undergone radiologic follow-up.

Complete occlusion at the last radiologic follow-up was achieved in 165 (51.9%) aneurysms, and near-complete occlusion, in 112 (35.2%) aneurysms. Among patients with at least 6 months of imaging follow-up, the complete occlusion rate was 55.1% (147/267) and the near-complete occlusion rate was 34.5% (92/267). For patients with flow diverters with 6 months of imaging follow-up, the complete occlusion rate was 64.4% (67/104) and the near-complete occlusion rate was 22.1% (23/104). For patients with coiling with at least 6 months of imaging follow-up, the complete occlusion rate was 49.1% (80/163) and the near-complete occlusion rate was 42.3% (69/163).

Of 352 endovascular treatments and 318 treated unruptured aneurysms, major recurrences were present and retreated in 29 aneurysms (14.8%) in the coiling group. In the FD group, there were no instances of recanalization; however, 7 aneurysms (5.7%) were retreated due to persistent filling of the aneurysm sac. The rate of retreatment was significantly higher in the coiling group (P = .009). Of 29 aneurysm retreatments in the coiling group, 18 (9.2%) were retreated with recoiling; 2 (1.0%), with surgical clipping; and 8 (4.1%), with FDs. All 7 retreatments (5.7%) from the FD group were retreated with the Pipeline Embolization Device (PED; Covidien, Irvine, California).

In the FD group, the overall rate of complete occlusion at last follow-up was 56.6% (69/122) and the near-complete occlusion rate was 21.3% (26/122). Complete occlusion rates were 49.5% (45/91) for patients treated with 1 FD, 66.7% (12/18) for patients treated with 2 FDs, and 92.3% (12/13) for patients treated with ≥3 FDs. These data are summarized in Table 3.

### Technical Outcomes and Immediate Complications

Immediate complications following the endovascular procedure occurred in 32 patients (10.3%). These complications included 20 patients (10.6%) from the coiling group and 12 patients (9.8%)

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**Table 1: Demographic characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n = 310)</th>
<th>Patients with Coiling (n = 188)</th>
<th>Patients with Flow Diverters (n = 122)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD) [yr]</td>
<td>57.4 (20–83)</td>
<td>57.9 (24–80)</td>
<td>55.7 (23–80)</td>
<td>.10</td>
</tr>
<tr>
<td>Female sex (No.) (%)</td>
<td>249 (80.3%)</td>
<td>145 (77.1%)</td>
<td>104 (85.2%)</td>
<td>.01</td>
</tr>
<tr>
<td>Mean (range) follow-up (mo)</td>
<td>23.4 (1–67)</td>
<td>24.5 (1–67)</td>
<td>22.4 (1–61)</td>
<td></td>
</tr>
<tr>
<td>No. of aneurysms</td>
<td>318</td>
<td>196</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Aneurysm location</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Cavernous ICA</td>
<td>27 (8.5%)</td>
<td>1 (0.5%)</td>
<td>26 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>Paraclinoid/supraclinoid ICA</td>
<td>104 (32.7%)</td>
<td>34 (17.3%)</td>
<td>70 (57.4%)</td>
<td></td>
</tr>
<tr>
<td>ICA terminus</td>
<td>13 (4.1%)</td>
<td>10 (5.1%)</td>
<td>3 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>ICA PcomA</td>
<td>36 (11.3%)</td>
<td>24 (12.2%)</td>
<td>12 (9.8%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>19 (6.0%)</td>
<td>16 (8.2%)</td>
<td>3 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>ACA/AcomA</td>
<td>56 (17.6%)</td>
<td>56 (28.6%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>2 (0.6%)</td>
<td>1 (0.5%)</td>
<td>1 (0.8%)</td>
<td></td>
</tr>
<tr>
<td>Basilar artery</td>
<td>37 (11.6%)</td>
<td>35 (17.9%)</td>
<td>2 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td>10 (3.2%)</td>
<td>7 (3.6%)</td>
<td>3 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (4.4%)</td>
<td>12 (6.1%)</td>
<td>2 (1.6%)</td>
<td></td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>263 (82.7%)</td>
<td>148 (75.5%)</td>
<td>115 (94.3%)</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>55 (17.3%)</td>
<td>48 (24.5%)</td>
<td>7 (5.7%)</td>
<td></td>
</tr>
<tr>
<td>Mean size (SD)</td>
<td>8.7 (±6.3 mm)</td>
<td>12.3 (±6.6 mm)</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Small (&lt;5 mm)</td>
<td>60 (18.9%)</td>
<td>46 (23.5%)</td>
<td>14 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Medium (5–15 mm)</td>
<td>207 (65.1%)</td>
<td>131 (66.8%)</td>
<td>76 (62.3%)</td>
<td></td>
</tr>
<tr>
<td>Large (16–25 mm)</td>
<td>26 (8.3%)</td>
<td>21 (5.6%)</td>
<td>15 (12.3%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Giant (&gt;25 mm)</td>
<td>25 (7.9%)</td>
<td>8 (4.1%)</td>
<td>17 (13.9%)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>249 (78.3%)</td>
<td>159 (81.1%)</td>
<td>90 (73.8%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>69 (21.7%)</td>
<td>37 (18.9%)</td>
<td>32 (26.2%)</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>35 (11.0%)</td>
<td>21 (10.7%)</td>
<td>14 (11.5%)</td>
<td></td>
</tr>
<tr>
<td>Visual problems</td>
<td>18 (5.7%)</td>
<td>9 (4.6%)</td>
<td>9 (7.4%)</td>
<td></td>
</tr>
<tr>
<td>Aneurysm discovered incidentally</td>
<td>210 (66.0%)</td>
<td>144 (73.5%)</td>
<td>66 (54.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: —PcomA indicates posterior communicating artery; AcomA, anterior communicating artery; ACA, anterior cerebral artery; PICA, posterior inferior cerebellar artery.
Midterm and Long-Term Clinical Outcomes

Midterm and long-term complications following endovascular procedures occurred in 12 patients (3.9%) and are listed in Table 4. Midterm/long-term complications occurred in 6 patients (3.2%) from the coiling group and 6 patients (4.9%) from the FD group (P = .54). Six patients (1.9%) had thromboembolic complications, and 4 patients (1.3%) experienced peribortal pain. Only 1 of all mid-/long-term complications (0.3%) resulted in a permanent neurologic deficit. This 73-year-old woman with a left-sided giant symptomatic carotid cavernous aneurysm treated with flow diversion developed a permanent mild right-sided hemiparesis.

Clinical follow-up with mRS assessment before and after treatment was available for all patients, with a mean follow-up time of 23.4 months (range, 1–67 months). The mean length of clinical follow-up was not significantly different between groups (24.5 months; range, 1–67 months in the coiling group; and 22.4 months; range, 1–61 months in the FD group).

Ten patients (3.2%) reported mRS worsening due to the target aneurysm or endovascular therapy (7 in the coiling group and 3 in the FD group). Three patients experienced postoperative rupture (1.0%). Twenty-two patients (7.1%) died during the study period; however, only 3 (1.0%) of the deaths were related to their target aneurysms or stroke. One patient died following delayed rupture of a previously coiled unruptured aneurysm, 1 patient died from a distal intraparenchymal hemorrhage 8 days after treatment with a PED, and 1 patient had a posttreatment rupture from a giant left ICA aneurysm 11 months after PED deployment. Long-term neurologic outcomes are listed in Table 5. A summary of patients who experienced postoperative rupture is provided in Table 6.

**DISCUSSION**

Our consecutive prospective series of 318 aneurysms in 310 unselected patients demonstrated that endovascular treatment of unruptured aneurysms can be performed with low rates of neurologic complications and high rates of satisfactory angiographic occlusion. Both flow-diverter and coil therapy were safe and effective. However, coil treatment was associated with higher rates of recurrence and retreatment. Only 3.2% of patients noticed a deterioration of symptoms due to aneurysm or endovascular treatment. Our study also demonstrated that since the introduction of flow diversion at our institution, there has been a significant upward trend in the use of FDs as approximately 50% of unruptured aneurysms are now treated by using these methods.
Aneurysms, Shigematsu et al.\textsuperscript{16} demonstrated a cumulative complete occlusion rate of 93% and 96% at 6 and 12 months, respectively. In larger studies,\textsuperscript{17-23} similar to our finding of 8% in the coiling group.

The rate of complete occlusion in the FD group at least 6 months of follow-up of 64.4% is lower than that in other flow-diverter studies; however, the low rate of retreatment (6%) is in line with those previously reported.\textsuperscript{24-26} In the Pipeline for Uncoilable or Failed Aneurysms Study,\textsuperscript{24} the rate of complete occlusion was 82% at 6 months and 86% at 12 months. Likewise, in a large single-center consecutive series of 54 patients, Lylyk et al.\textsuperscript{25} found high rates of complete aneurysm occlusion of 93% and 96% at 6 and 12 months, respectively.

In our series, we encountered 3 cases of posttreatment rupture. In comparison, the Cerebral Aneurysm Rerupture After Treatment (CARAT) investigators reported annual rates of rupture after 1 year of 0.11% (95% CI, 0%-0.63%) for coiling. However, rerupture rates of incompletely obliterated aneurysms were as high as 17.6% during a mean follow-up of 4 years, when <70% of the aneurysm was occluded. In large series of flow-diversion treatments,\textsuperscript{2,27-30} the incidence of an-
eurysm rupture was found to be between 0.4% and 2.6%. Brinjikji et al reported similar results (3%) in their meta-analysis of published case series.

Clinical Outcomes
In our series, we observed neurologic morbidity and mortality rates of 2.3% and 1.0% for patients, respectively. Only a minority of patients (3.2%) reported mRS worsening related to the target aneurysm or endovascular therapy (3.7% in the coiling group and 2.5% in the FD group). Neurologic morbidity and mortality rates in the FD group were 2.5% and 1.6%, respectively. This is lower than that reported in the International Retrospective Study of the Pipeline Embolization Device (IntrePED), which reported a combined neurologic morbidity and mortality rate of 8.4%. This rate may be due to patient selection because the proportion of patients with treated non-ICA aneurysms in our study was lower than that in IntrePED. Other previously published studies have reported morbidity and mortality rates following FD treatment ranging from 0% to 12% and 0% to 7%, respectively.

During our study period, we have changed our daily practice of admitting patients with unruptured intracranial aneurysms after treatment directly to the ICU. Arias et al showed that most significant postprocedural events (74%) after uncomplicated aneurysm intervention occur within 4 hours. These events become less frequent with increasing time. Likewise, Eisen et al found that in the absence of intraoperative events with the potential for ongoing cerebral ischemia, most patients undergoing elective endovascular treatment of unruptured cerebral aneurysms can be managed without direct ICU admission. Our experience and findings have been similar. Improved ICU admission rates are likely due to a combination of increasing operator experience and patient selection.

Limitations
The limitations of this study are related to the absence of randomization and the variable duration of follow-up. However, the data for all patients were collected prospectively. This was a single-center case series of aneurysms treated by a group of experienced neurointerventionalists and endovascular neurosurgeons. Thus, our data may not be generalizable to other practices. With increasing experience with the PED, the off-label use of the PED has been widening in our practice, which could contribute to higher complication rates. Another limitation of the study is that there was no independent assessment of angiographic or clinical outcomes. The determination of final radiologic results was by the treating physician. In addition, there were significant differences in the baseline characteristics of patients undergoing coiling and flow-diverter therapy, which could confound our statistical analyses. These limitations notwithstanding, our study summarizes the results in an unselected group of patients with unruptured aneurysms in a real world setting and provides a contemporary view indicating that both endovascular techniques are safe and clinically effective in treating unruptured intracranial aneurysms. No patient was lost to follow-up. Moreover, clinical outcome, in accordance with International Subarachnoid Aneurysm Trial methodology, was by a patient self-assessment.

CONCLUSIONS
Our study of >300 patients with 318 unruptured aneurysms treated with flow-diverter therapy or coil embolization found that endovascular treatment of unruptured aneurysms is both safe and effective. Coil embolization was associated with higher recurrence and retreatment rates, but the rates of poor neurologic outcome were similar between groups. Flow diversion has been a disruptive technology at our institution because >50% of unruptured aneu-
ryms are now treated with this technique. Last, we found that in most cases, routine ICU admission is not necessary, and we have changed our practice accordingly. Our findings highlight the safety and efficacy profile of the endovascular treatment of unruptured aneurysms in a real world setting.


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