Endovascular Treatment of Very Small (3 mm or Smaller) Intracranial Aneurysms
Report of a Consecutive Series and a Meta-Analysis

Waleed Brinjikji, BS; Giuseppe Lanzino, MD; Harry J. Cloft, MD, PhD; Alejandro Rabinstein, MD; David F. Kallmes, MD

Background and Purpose—We performed a meta-analysis of published studies on the endovascular treatment of very small intracranial aneurysms, including 71 patients treated at our institution.

Methods—We conducted a computerized MEDLINE search of the literature for reports on the treatment of intracranial aneurysms with a maximum dimension of ≤3 mm by using the search terms “small,” “tiny,” “intracranial aneurysm,” “endovascular,” and “coil.” A total of 7 studies, including our institution’s consecutive case series of 71 intracranial aneurysms, were included in this study. We extracted information regarding intraoperative complications, procedural mortality and morbidity, immediate- and long-term angiographic outcomes, and retreatment rate. The meta-analysis was performed with the statistical package Comprehensive Meta-Analysis.

Results—Approximately 61% of the aneurysms in this meta-analysis presented as ruptured, whereas 39% of the aneurysms were unruptured. Procedural rupture rates for very small aneurysms was 8.3% (95% CI, 6.0% to 11.4%). The mortality rate due to procedural rupture was 2.4% (95% CI, 1.2% to 4.7%). The morbidity rate due to thromboembolic complications was 1.9% (95% CI, 0.9% to 3.9%). Subarachnoid hemorrhage within 1 month of treatment occurred in 1.6% (95% CI, 0.6% to 3.7%) of cases. There was no statistically significant difference between unruptured and ruptured aneurysms for any of these outcomes.

Conclusion—Our meta-analysis suggests that treatment of very small aneurysms is feasible and effective in >90% of treated aneurysms. However, the risk of periprocedural rupture is higher than that reported for larger aneurysms. Similarly, the combined rate of periprocedural mortality and morbidity is not negligible (7.3%) and should be considered when considering the best therapeutic option for these aneurysms. (Stroke. 2010;41:116-121.)

Key Words: subarachnoid hemorrhage • neuroradiology • neurosurgery • coils • aneurysm

With advances in endovascular techniques, coiling of intracranial aneurysms is considered a valid alternative to surgical treatment. However, very small intracranial aneurysms, generally considered to be those of 3-mm diameter or smaller, pose particular technical challenges for the endovascular surgeon. These challenges are related to the inability to obtain a stable microcatheter position, given the small amount of catheter purchase typically achievable, as well as to the perceived increased risk of perforation related to placing coils into small, confined spaces.1 For these reasons, very small aneurysms were excluded from the landmark study by Viiuela et al,2 a study that led to approval of the Guglielmi detachable coils in the United States, and from the International Subarachnoid Aneurysm Trial (ISAT).3 However, with improved devices, increasing operator experience, and the introduction and widespread adoption of adjunctive techniques such as balloon- and stent-assisted coiling, several single-center series have suggested acceptable rates of mortality and morbidity in the treatment of very small intracranial aneurysms.4–9

To improve understanding of safety and efficacy profiles associated with coiling of very small intracranial aneurysms, we report both our own experience as well as the results of a meta-analysis of the literature regarding coil embolization of very small intracranial aneurysms.10

Methods

Patients
After institutional review board approval, we performed a retrospective analysis of all consecutive adult patients who underwent attempted coil embolization of intracranial aneurysms at our institution between January 2002 and November 2008 to identify embolization procedures performed in very small (maximum dimension, ≤3 mm) intracranial aneurysms. All patients provided approval for the use of their medical records for retrospective analysis. Patients were identified through a search of angiographic records and then further identified on the basis of the size of their intracranial aneurysms.
aneurysms. For each patient, demographic data, clinical presentation, clinical outcome, aneurysm size (maximum dimension as measured by 2D digital subtraction angiography [DSA]), aneurysm rupture status, and aneurysm location were collected. For patients who presented with subarachnoid hemorrhage, Hunt and Hess scores were provided by the neurology team who was responsible for the management of the patient. The modified Rankin Scale (mRS) was retrospectively used to describe patient disability at last follow-up.

Indications for Endovascular Treatment
All patients were evaluated by a multidisciplinary group that included vascular neurologists, neurosurgeons, and interventional neuroradiologists. In general, small unruptured aneurysms were treated for any of the following reasons: (1) association with a ruptured aneurysm in another location, (2) symptomatic aneurysm, (3) presence of a family history of aneurysmal subarachnoid hemorrhage, (4) irregularities of the aneurysm profile thought to be indicative of a theoretical higher risk of rupture, and (5) patient preference. Once the decision to treat the aneurysm was made, endovascular treatment was preferred to open surgical treatment based on (1) “equipoise” between the 2 treatment strategies, as assessed by the operators involved in the endovascular and surgical treatment of the aneurysm; (2) patient preference; (3) posterior circulation location; and (4) clinical conditions making a less invasive treatment preferable.

Angiographic Technique
Typically, 5F or 6F guiding catheters or guiding sheaths were placed into the internal carotid or vertebral arteries. All of the DSA examinations were performed by using a biplane, digital angiography suite (Integris Philips Medical Systems, Best, Netherlands). A volume of 16 mL of nonionic contrast medium was injected through a 5F to 6 F catheter by use of an injector with a velocity of 4 mL/s. Biplane DSA images of the entire circulation were usually performed, followed by “working-projection” DSA.

Coiling Technique
Patients typically were treated while under general anesthesia. A coaxial technique was used for microcatheter, balloon, and stent catheter access. In general, balloons were used when there was even a moderate suspicion that balloon assist would be needed. Even in cases where balloons had been placed across the aneurysm neck, at least 1 attempt at coil placement was made before balloon inflation. Balloon inflation was typically performed only when the initial or subsequent coils were not retained in the aneurysm cavity without balloon inflation. Stents were typically used in cases of failed balloon-assist coiling. Three operators (D.F.K. with 15 years of experience, G.L. with 6 years of experience, and H.J.C. with 15 years of experience) were involved in the coiling of these aneurysms. Coiling techniques varied among the 3 operators, and the types of coils used varied by operator and changed over the period of the study. In 35 cases, 1 coil was used; in 25 cases, 2 coils were used; in 5 cases, 3 coils were used; and in 5 cases, >3 coils were used. The types of coils used varied; bare platinum coils from Microvention, Cordis, and Micrus were used in the treatment of 64 aneurysms. In the remaining 7 cases, “modified” coils were used, consisting of Cereryte coils (used either alone or in conjunction with bare platinum coils) in 6 cases and Hydrocoils in 1 aneurysm.

Outcomes and Complications
Outcomes for endovascular coiling were stratified into 3 outcomes based on the degree of angiographic aneurysm filling evaluated immediately after completion of the coiling procedure: (1) complete or nearly complete occlusion (defined as a lack of angiographic filling of the sac and the neck, or no filling of the sac but small residual neck filling, respectively); (2) incomplete occlusion (defined as persistent angiographic filling of a portion(s) of the sac); and (3) failed occlusion. Failed occlusion was defined as an aneurysm that could not be embolized; thus, no coil was introduced or remained in the aneurysm. The outcome of each procedure was determined by the operator, who analyzed the postoperative 2D-DSA images of the treated aneurysm. Immediate postoperative outcomes as well as a 6-month angiographic follow-up were gathered for this study. Immediate complications resulting from each procedure were also recorded. Complications were stratified into 3 groups: (1) thromboembolic complications, (2) parent artery occlusion, and (3) aneurysm perforation. Complications were determined by the operator who performed the endovascular coiling. For obtaining information on thromboembolic complications, patient files were examined for clinical evidence of thromboembolism originating at the site of the coiling. Data on morbidity and mortality resulting from these complications were also recorded. Data were also collected on retreatment rates and early recurrent hemorrhage.

Meta-Analysis Data
Study Selection
We performed a computerized MEDLINE search of the literature from January 1990 to May 2009 for reports of endovascular embolization of small (maximum dimension, ≤3 mm) intracranial aneurysms by using the key words “cerebral aneurysm,” “coil,” “small,” “tiny,” and “endovascular” in both “AND” and “OR” combinations. The search was restricted to human studies in English. Studies dealing with dissecting aneurysms and “blister” aneurysms were excluded because these aneurysms have different pathologic and therapeutic implications than berry aneurysms. For larger studies that explicitly mentioned the inclusion of small aneurysms in their study but did not stratify their data on the basis of our size criterion, authors were E-mailed monthly for 3 months and asked whether they could provide data on those aneurysms ≤3 mm that were part of their study. The authors from the ATENA study7 provided us with data on their treatment of small aneurysms; however, the authors of 3 other studies whom we E-mailed did not respond or were unable to provide us with the requested data.

Identified studies from the MEDLINE search were then further evaluated for inclusion in the meta-analysis. Inclusion criteria for the meta-analysis were the following: (1) studies that treated a consecutive series of small intracranial aneurysms, (2) studies that were not restricted to treatment of aneurysms in certain anatomic locations, and (3) studies that reported whether treated intracranial aneurysms were ruptured or unruptured. Each study was analyzed to collect information on the following variables: (1) use of adjunctive devices in the treatment of the aneurysms, (2) intraoperative complications, (3) morbidity and mortality resulting from inoperative complications, (4) immediate angiographic outcomes, (5) rate of aneurysm retreatment, (6) early recurrent hemorrhage rate and mortality, and (6) long-term angiographic results.

Statistical Methods of Meta-Analysis
Frequency (percentage) and its 95% CI are provided in all 3 tables. The overall summary from the meta-analysis was deduced by combining all studies, and the meta-analysis was performed with a fixed-effect model.11 The average rate and 95% CI were calculated for the outcomes previously outlined. The meta-analysis was performed with use of the statistical software package Comprehensive Meta-Analysis, version 2.0.040 (www.meta-analysis.com).

Results
Current Consecutive Series
Patient Characteristics
A total of 71 consecutive patients were included in the single-center series (61 female, 10 male). The mean±SD age was 57±12 years (range, 37 to 86). Of the 47 patients who presented with unruptured aneurysms, indications for treatment were a history of subarachnoid hemorrhage from another aneurysm in 20 patients, a family history of subarachnoid hemorrhage in 17 patients, and patient preference in 8 patients, and other risk factors (irregular shape) were cited in...
Table 1. Aneurysm Location in Consecutive Case Series

<table>
<thead>
<tr>
<th>Location</th>
<th>Total, No. (%)</th>
<th>Ruptured, No. (%)</th>
<th>Unruptured, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior circulation</td>
<td>60 (84.5)</td>
<td>22 (91.7)</td>
<td>38 (80.9)</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>32 (45.1)</td>
<td>12 (50.0)</td>
<td>20 (42.6)</td>
</tr>
<tr>
<td>Anterior cerebral artery,</td>
<td>17 (23.9)</td>
<td>7 (29.2)</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>posterior communicating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>11 (15.5)</td>
<td>3 (12.5)</td>
<td>8 (17.0)</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>11 (15.5)</td>
<td>2 (8.3)</td>
<td>9 (19.1)</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>7 (9.9)</td>
<td>0 (0.0)</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>Vertebral artery</td>
<td>2 (2.8)</td>
<td>2 (8.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>2 (2.8)</td>
<td>0 (0.0)</td>
<td>2 (4.3)</td>
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</table>

Aneurysm Treatment and Angiographic Outcomes

Of the 71 aneurysms, 36 (50.7%) were treated without the assistance of adjunctive techniques, 32 (45.1%) were treated with balloon assistance, and 3 (5.6%) were treated with stent assistance. Results from immediate postcoiling angiography demonstrated that 62 (87.3%) aneurysms had complete or nearly complete occlusion, 5 (7.0%) aneurysms had incomplete occlusion, and 4 (5.6%) aneurysms had failed occlusion. Of those aneurysms with incomplete occlusion, 4 of the 5 were unruptured aneurysms, and of those aneurysms with failed occlusion, all 4 were unruptured. Fifty-eight (81.6%) patients had a follow-up angiogram at least 6 months after the original treatment; the average time between original treatment and last imaging follow-up was 10.6 months. The follow-up modality was DSA in 39 cases, magnetic resonance angiography in 17 cases, and computed tomography angiography in 2 cases. Among those cases, 53 (91.4%) aneurysms were completely or nearly completely occluded, and 5 (8.6%) were incompletely occluded on angiographic follow-up. Nine aneurysms incompletely occluded showed progression to complete occlusion on the follow-up angiogram, and there was recanalization in 1 aneurysm.

Intraprocedural Complications and Early Recurrent Hemorrhage

Among unruptured aneurysms, there were 4 cases of intraprocedural rupture/perforation (8.5%), 1 case of parent artery occlusion (2.1%), and 2 cases of thromboembolism (4.2%). Among ruptured aneurysms, there were 4 cases of intraprocedural rupture/perforation (16.7%) and no cases of parent artery occlusion or thromboembolism. Of the 8 intraprocedural ruptures, 3 occurred in cases where adjunctive devices were not used and 5 occurred in cases where adjunctive devices were used. Of the 2 thromboemboli, 1 occurred in a case where adjunctive devices were not used and 1 occurred in a case where adjunctive devices were used specifically. The case of parent artery occlusion happened in a case where no adjunctive device was used. None of the procedural complications resulted in any mortality or persistent morbidity in either ruptured or unruptured cases. There was 1 case of early postoperative hemorrhage in an aneurysm that originally presented as ruptured. This aneurysm was coiled with no complications, but occlusion was incomplete and the patient subsequently had a fatal rebleeding event 10 days after the original procedure.

Retreatment

Of the 71 aneurysms included in this study, 6 (8.5%) were retreated. All retreated aneurysms initially presented as unruptured. Two aneurysms were retreated within 10 days of the original procedure by surgical clipping, and 4 aneurysms were retreated at the time of long-term follow-up through endovascular coiling.

Meta-Analysis

Search Results

The search criteria led to a total of 236 unique articles. Review articles and editorials were excluded (29 total), as well as were articles whose titles indicated that the studies were irrelevant to our subject of interest. Ultimately, 11 articles were read, 2 articles dealt with aneurysms located in specific locations and thus did not meet our criteria, and 3 articles met our criteria but had not stratified the data in a way that we could extract effectively for the meta-analysis. The authors of these 3 studies were E-mailed monthly for 3 months as mentioned previously and were unable to provide us with data. One of the study groups whom we E-mailed did respond with data, and thus, we were able to include 6 studies in addition to our single-center series for this analysis.

Studies

Including the single-center data presented in this article, a total of 7 studies were included in this meta-analysis.4–9 Of these 7 studies, 3 provided data on unruptured aneurysms,7,9 and 6 provided data on ruptured aneurysms.4–6,8,9 A total of 422 aneurysms were included in this meta-analysis, with 171 aneurysms unruptured and 271 aneurysms ruptured. All studies provided data on the use of adjunctive techniques, intraprocedural complications, and morbidity and mortality resulting from these complications. Six of the 7 studies provided additional data on short- and long-term angiographic outcomes, retreatment rate, and early recurrent hemorrhage rate and mortality. One study (Nguyen et al) only
provided information on the use of adjunctive techniques, intraprocedural complications, and morbidity and mortality resulting from these complications. Information regarding these studies is summarized in Table 2.

### Endovascular Technique and Short-Term Angiographic Outcomes

Results from the meta-analysis showed that 31.8% (95% CI, 26.3% to 38.0%) of small aneurysms were treated with adjunctive devices. Overall, 95.3% (95% CI, 91.4% to 97.5%) of small aneurysms were completely or nearly completely occluded at immediate postoperative angiographic follow-up, whereas 3.8% (95% CI, 1.3% to 10.4%) of aneurysms had failed occlusion. Occlusion rates for ruptured and unruptured aneurysms were similar, as CIs for the event rates overlapped (Table 3).

### Morbidity and Mortality From Endovascular Treatment

Intraprocedural rupture rate in unruptured aneurysms was 5.0% (95% CI, 2.3% to 10.4%) compared with 10.7% (95% CI, 7.4% to 15.1%) in ruptured aneurysms. Morbidity due to intraprocedural rupture was 1.2% (95% CI, 0.3% to 4.6%) in unruptured aneurysms compared with 1.8% (95% CI, 0.6% to 5.4%) in ruptured aneurysms. Mortality due to intraprocedural rupture was 1.2% (95% CI, 0.3% to 4.6%) for unruptured aneurysms compared with 3.1% (95% CI, 1.5% to 6.3%) for ruptured aneurysms. Morbidity due to thromboembolic complications was 1.3% (95% CI, 0.3% to 5.1%) for unruptured aneurysms compared with 2.2% (95% CI, 1.0% to 5.0%) for ruptured aneurysms. The risk of early postprocedural hemorrhage was 0.9% (95% CI, 0.2% to 4.3%) for unruptured aneurysms compared with 2.4% (95% CI, 1.0% to 6.0%) for ruptured aneurysms. Early postprocedural hemorrhage was uniformly fatal in both previously ruptured and unruptured aneurysms. These data are summarized in Table 4.

### Discussion

In this article, we have presented a single-center series as well as a meta-analysis focused on the safety, procedural techniques, and short- and long-term occlusion rates for coil embolization of very small aneurysms, arbitrarily defined as aneurysms with a maximum dimension of 3 mm or less. Our results have demonstrated high rates of complete or nearly complete occlusion and at follow-up. However, the incidence of intraprocedural rupture, irrespective of rupture status of the aneurysm, was not insignificant across series in this meta-analysis. This relatively high rate of rupture seems predictable, given the technical challenges associated with very small aneurysms, in which coils are being placed into confined spaces. This increases the risk of intraprocedural rupture/perforation. Microcatheterization of the aneurysm is difficult, and perforation can be caused by manipulation of the microguidewire or the microcatheter. Usually, microguidewire perforations are dealt with successfully by reversal of anticoagulation and subsequent coiling of the aneurysm. Microcatheter perforations can be more troublesome. Another step of the procedure when intraprocedural perforation/rupture can occur is the coiling itself. Because of the very small size, there is increased friction against the

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<th>Table 2. Meta-Analysis of Studies Reporting on Endovascular Treatment of Consecutive, Very Small Intracranial Aneurysms</th>
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<tr>
<td><strong>Study</strong></td>
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<tr>
<td>Nguyen et al*</td>
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<tr>
<td>Chen et al⁴</td>
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<tr>
<td>Suzuki et al⁵</td>
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<tr>
<td>Gupta et al⁶</td>
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<tr>
<td>Van Rooij et al⁷</td>
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<tr>
<td>Our series</td>
</tr>
<tr>
<td>Pierot et al (ATENA)⁸</td>
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<tr>
<td><strong>Total</strong></td>
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*Data from the 1 unruptured aneurysm in this study was not included in the meta-analysis because both meta-analysis methods and the software advised against including single data points.

<table>
<thead>
<tr>
<th>Table 3. Meta-Analysis: Short-Term Angiographic Outcomes</th>
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<tr>
<td><strong>Short-Term Angiographic Outcomes</strong></td>
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<tr>
<td>---------------------------------</td>
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<tr>
<td>Postoperative complete occlusion</td>
</tr>
<tr>
<td>Postoperative incomplete occlusion</td>
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<tr>
<td>Postoperative failed occlusion</td>
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aneurysm wall and less room for error, especially in the coiling of freshly ruptured intracranial aneurysms. Several studies have examined risk factors for intraprocedural rupture of intracranial aneurysms, and it has been consistently shown that rupture rates are higher in smaller and ruptured aneurysms when compared with larger and unruptured aneurysms.\(^6\)\(^,\)\(^12\) In this meta-analysis, we found that the incidence of any perforation or frank intraoperative rupture during the different phases of coiling was 8.3% among published studies, resulting in permanent morbidity in 1.4% of cases and mortality in 2.4%.

The advent of adjunctive techniques, such as balloon- or stent-assisted coiling, has made possible the endovascular occlusion of an increasing number of very small aneurysms. Modern compliant balloons are easier to navigate through the tortuositousness of the intracranial circulation. A balloon can be placed across the neck of the aneurysm and inflated to maintain the stability of the microcatheter while coiling is performed, thus increasing the likelihood that the coils will stay within the aneurysm without migrating into the parent vessel. In some instances, a balloon can be “parked” across the aneurysm neck and inflated only in case of rupture of the aneurysm to arrest the bleeding while the ruptured site and the remaining portion of the aneurysm are coiled. Limitations of the balloon are the need for additional endovascular manipulation and intermittent flow occlusion of the parent vessel during balloon inflation, which may increase the risk of thromboembolic complications.\(^13\)\(^,\)\(^15\) The balloon-remodeling technique in the case of very small aneurysms can be associated with an increased risk of perforations, as the inflated balloon may increase friction of the advancing coil against the fragile aneurysm wall. However, should a perforation occur under these circumstances, the result is often not catastrophic, as the balloon prevents blood extravasation. In some cases, a stent can be placed across the neck of the aneurysm and acts as a scaffold to stabilize the coil mass within the aneurysm. The main disadvantage of this approach is the need for long-term dual-antiplatelet therapy with its risks of bleeding complications. In this meta-analysis, we found that “adjuncts” were used in one third of the procedures.

Another potential limitation of endovascular treatment for very small intracranial aneurysms is the incomplete protection from further bleeding. In the ISAT study and the CARAT study, the rates of incomplete aneurysm occlusion with coiling were substantial, and the risks of rebleeding after endovascular therapy were significantly higher compared with the surgically treated group.\(^14\)\(^,\)\(^15\) Not surprisingly, this risk was greater within the first month after treatment and negligible after the first 6 months. Our own experience and this meta-analysis corroborate these observations. In our series early rebleeding occurred in 1 patient, and in the meta-analysis we found that the rate of rebleeding was 2.4% among ruptured very small aneurysms. It must be highlighted that all of these cases of early rebleeding were fatal.

The indication for treatment of very small, unruptured intracranial aneurysms is controversial. Data from the ISUIA study have shown that the risk of subarachnoid hemorrhage from a small, unruptured intracranial aneurysm is exceedingly low unless the patient has had a prior subarachnoid hemorrhage from another aneurysm.\(^16\) Therefore, when treating very small intracranial aneurysms, the risk of treatment has to be balanced against the very benign natural history. This meta-analysis has shown that the risk of treating very small, unruptured intracranial aneurysms is not negligible, as it resulted in a combined morbidity and mortality of 4.6%. Studies are under way to ascertain whether treatment of small unruptured aneurysms is better than their benign natural history.

This study has various limitations. Most of the series included, except for the ATENA study, were single-center retrospective analyses. Moreover, there is a possible publication bias, as series with more positive results may have been more likely to be reported and published. Nevertheless, this analysis has shown that endovascular treatment of very small intracranial aneurysms can be done with an acceptable risk. However, this risk is not negligible. The combined morbidity and mortality related to intraprocedural rupture, thromboembolic complications, and late rebleeding is 7.3%, and this morbidity/mortality is higher in patients with ruptured aneurysms. Although there is a trend toward favoring less invasive treatments (which we support), it is also important to remember that surgical treatment of very small aneurysms can be done with a very low complication rate and usually ensures permanent obliteration. Therefore, we think that for very small aneurysms, surgery continues to play a significant role, and endovascular treatment should be considered in selected cases. Moreover, as we have stressed in other publications, it is also important that the risk assessment is carried forward well into the procedure.\(^17\) If, during coiling of a very small aneurysm, the procedure is judged to be technically more
challenging than expected, we have a very low threshold to take the patient to surgery. Based on the morbidity and mortality rates observed in this meta-analysis among patients with very small unruptured aneurysms, endovascular treatment of these cases should be pursued very selectively.

Disclosures
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References
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