

The Barrow Ruptured Aneurysm Trial

Clinical article

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Object. The purpose of this ongoing study is to compare the safety and efficacy of microsurgical clipping and endovascular coil embolization for the treatment of acutely ruptured cerebral aneurysms and to determine if one treatment is superior to the other by examining clinical and angiographic outcomes. The authors examined the null hypothesis that no difference exists between the 2 treatment modalities in the setting of subarachnoid hemorrhage (SAH). The current report is limited to the clinical results at 1 year after treatment.

Methods. The authors screened 725 patients with SAH, resulting in 500 eligible patients who were enrolled prospectively in the study after giving their informed consent. Patients were assigned in an alternating fashion to surgical aneurysm clipping or endovascular coil therapy. Intake evaluations and outcome measurements were collected by nurse practitioners independent of the treating surgeons. Ultimately, 238 patients were assigned to aneurysm clipping and 233 to coil embolization. The 2 treatment groups were well matched. There were no anatomical exclusions. Crossing over was allowed, but primary outcome analysis was based on the initial treatment modality assignment. Posttreatment care was standardized for both groups. Patient outcomes at 1 year were independently assessed using the modified Rankin Scale (mRS). A poor outcome was defined as an mRS score > 2 at 1 year. The primary outcome was based on the assigned group; that is, by intent to treat.

Results. One year after treatment, 403 patients were available for evaluation. Of these, 358 patients had actually undergone treatment. The remainder either died before treatment or had no identifiable source of SAH. A poor outcome (mRS score > 2) was observed in 33.7% of the patients assigned to aneurysm clipping and in 23.2% of the patients assigned to coil embolization (OR 1.68, 95% CI 1.08–2.61; $p = 0.02$). Of treated patients assigned to the coil group, 124 (62.3%) of the 199 who were eligible for any treatment actually received endovascular coil embolization. Patients who crossed over from coil to clip treatment fared worse than patients assigned to coil embolization, but no worse than patients assigned to clip occlusion. No patient treated by coil embolization suffered a recurrent hemorrhage.

Conclusions. One year after treatment, a policy of intent to treat favoring coil embolization resulted in fewer poor outcomes than clip occlusion. Although most aneurysms assigned to the coil treatment group were treated by coil embolization, a substantial number crossed over to surgical clipping. Although a policy of intent to treat favoring coil embolization resulted in fewer poor outcomes at 1 year, it remains important that high-quality surgical clipping be available as an alternative treatment modality. (DOI: 10.3171/2011.8.JNS101767)

KEY WORDS • intracranial aneurysm • subarachnoid hemorrhage • randomized trial • coil embolization • clip occlusion • vascular disorders

ENDO VASCULAR coil embolization of ruptured intracranial aneurysms has become a widely accepted treatment alternative to surgical clipping. This acceptance increased in 2002 with the results of the ISAT.¹⁹ That trial demonstrated that, for the study population, endovascular treatment resulted in patients suffering fewer poor clinical outcomes at 1 year compared with patients who underwent surgical clipping. There has been continued discussion regarding how broadly applicable these results are to current practices. As a result of this con-

troversy, there is wide variability among cerebrovascular centers in the proportional use of these 2 methods for the treatment of ruptured intracranial aneurysms.

No single study can be expected to resolve all aspects of such debate, and no study is perfect in its design or execution. Since the publication of the ISAT results, there has been intense debate regarding the significance and limitations of the trial.^{1–7,10,12,13,18,24,26,29} Over the ensuing years since it was first published, there have been several updates regarding the ISAT results, and the authors have articulately addressed many of the criticisms of the trial.^{8,14,17,20–23, 27,28}

A major criticism of ISAT has been that a large number of patients treated at trial centers during the study were not included in the trial. The primary objective of ISAT

Abbreviations used in this paper: BRAT = Barrow Ruptured Aneurysm Trial; GCS = Glasgow Coma Scale; ISAT = International Subarachnoid Aneurysm Trial; mRS = modified Rankin Scale; SAH = subarachnoid hemorrhage.

was “to determine whether a policy of endovascular treatment compared with a policy of neurosurgical treatment reduced the proportion of patients dependent or dead, as defined by modified Rankin Scale (mRS) 3–6, at one year by 25%.”¹⁹ Central to the tenet of equipoise in this trial was the requirement that enrolled patients were “suitable for either treatment.” Implicit in determining eligibility for ISAT with respect to this requirement was a preview of the intracranial aneurysm’s angiographic anatomy by both neurosurgeon and interventional neuroradiologist; consensus that either technique would be a suitable treatment option; and consensus that it was uncertain whether the ruptured aneurysm should be treated by neurosurgical or endovascular means. As a result of this policy, more than 9559 aneurysms were screened, but only 2143 patients were enrolled. Questions have understandably persisted regarding the applicability of the study results to the almost 80% of aneurysms that were screened but excluded from ISAT.

A second criticism questioned the relative proficiencies of the treating physicians, and in particular, whether the surgical clipping arm represented the best that neurosurgery had to offer.^{3,6,7,12,18,29} Intuitively, it is evident that for the trial to be a meaningful reflection of the merits of the modalities, the practitioners of each modality must be matched in terms of their level of experience. It is understandably difficult for an individual practicing in an environment significantly different from that studied in the trial to gauge how differences in practice pattern may influence the applicability of the trial results.

An additional issue that had some impact on the ISAT outcome is the fact that more patients in the surgical clipping group suffered rehemorrhage before treatment than did patients in the coil embolization group—23 versus 14 patients. Arguably, a practice pattern that incorporates earlier surgical intervention may decrease the treatment gap identified by ISAT.²

The BRAT is a prospective, randomized, controlled trial designed to compare the results of surgical clipping to those of endovascular coil therapy for the treatment of ruptured intracranial aneurysms. The BRAT was designed to reflect real-world practicalities of ruptured aneurysm treatment in North America. This was reflected in the design of the trial in the sense that patients were assigned to a surgeon with a preselected treatment intent (coil or clip), but before embarking on that intended treatment, the assigned surgeon would naturally, as in daily practice, make a treatment decision based on what that practitioner believed would provide the best outcome for that particular patient. This decision may be to proceed with the “intended” or assigned treatment, or it may be that surgeon’s judgment that a particular patient would be better served by the other treatment modality, in which case the patient would “cross over” to the alternative treatment. In either event the primary outcome was based on the assigned treatment, so that one treatment modality could not comparatively benefit by the crossing over of poor-grade patients. In practice, this method of assignment functioned as a form of “right of first refusal”—the practitioner of endovascular or open surgery to whom the patient was first assigned had the option of treating the patient with the assigned modality or crossing the patient over to the

alternative modality, but in either event, the outcome was assigned to the originally intended treatment modality.

It was hoped that an intent-to-treat analysis that included all patients with aneurysmal SAH would improve understanding of the applicability of the ISAT data. This single-center study was not expected to be powered sufficiently to demonstrate differences in outcomes. Rather, it was designed as a pilot study to demonstrate the feasibility of conducting a multicenter trial that would be practical in its application and that would help define the relative roles of open versus endovascular techniques. The BRAT is an ongoing trial, with follow-up planned to continue for at least 6 years after completion of enrollment. Understanding which patients are treated with each technique when the a priori policy is biased toward one technique or the other may help the broader applicability of the ISAT results to be evaluated.

This report is confined to describing the methods and to reporting the initial clinical outcomes 1 year after treatment. Although multiple outcome assessment modalities were included in the trial, this report is limited to outcomes as defined by the mRS. Multiple outcome measurements were collected, with the idea that as a pilot study, the additional information gathered might help guide the design of a larger multicenter study. The dichotomized mRS outcome was chosen so that results could be compared and contrasted with those from ISAT.

The purpose of this ongoing study is to compare the safety and efficacy of microsurgical clipping and endovascular coil embolization for the treatment of acutely ruptured cerebral aneurysms and to determine if one treatment is superior to the other by examining clinical and angiographic outcomes. We examined the null hypothesis that no difference exists between the treatment modalities in the setting of SAH. Although this trial has a planned follow-up period of up to 6 years, the current report is limited to the clinical results at 1 year after treatment.

Methods

Patient Population

Between March 2003 and January 2007, 725 patients were screened for this study (Fig. 1). Enrollment was completed as planned, with entry of 500 patients in whom informed consent was obtained. The 225 patients who were excluded by the screening were treated in the usual fashion, at the discretion of the attending surgeon and appropriate to the presenting pathological entity. Consent was obtained erroneously in 28 patients, leaving 472 individuals eligible for analysis. Reasons for consent errors included events such as hemorrhage more than 14 days before presentation, age exclusions, and ultimate determination of nonaneurysmal SAH (that is, trauma or other vascular lesion) or a determination that SAH had not occurred.

Of the remaining 472 patients initially included in the study, 239 were assigned to surgical clipping and 233 to coil embolization. One patient assigned to clipping withdrew consent before being treated, leaving 471 patients (238 in the surgical clipping and 233 in the coil embolization group). In all, 408 patients underwent treat-

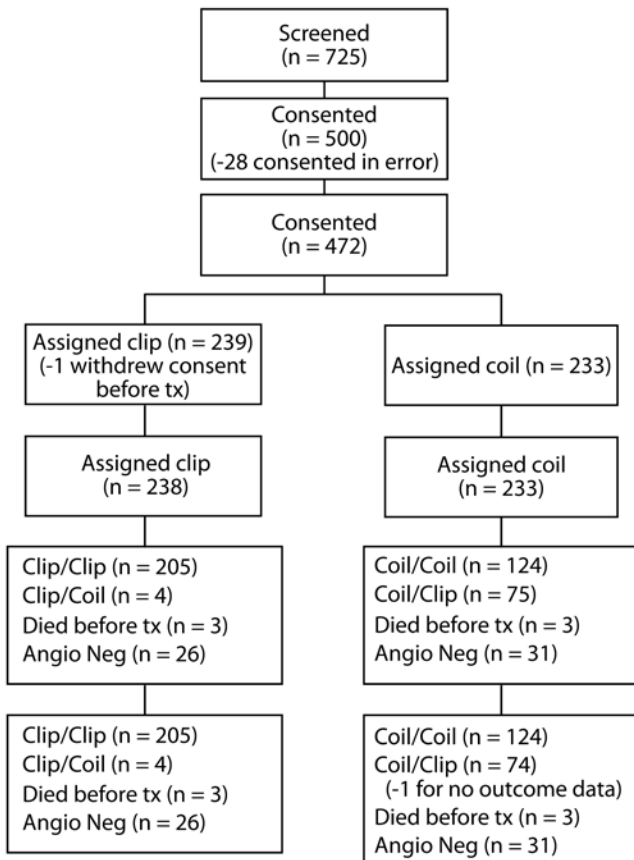


FIG. 1. Flowchart of patient assignments and treatments. Angio Neg = patients admitted with SAH for which no source was ever identified; Clip/Clip = assigned to and treated by surgical clipping; Clip/Coil = assigned to surgical clipping, crossed over to coil embolization; Coil/Clip = assigned to coil embolization, crossed over to surgical clipping; Coil/Coil = assigned to and treated with coil embolization; consented = informed consent was given; Died before tx = moribund patients assigned to treatment group, but not treated due to moribund state.

ment. Patients not treated (but followed, evaluated, and accounted for in the study) included those who died before treatment (3 in each group), as well as 57 patients in whom no aneurysm or other source of SAH could be identified. As a result of a communication failure, no outcome data were collected for 1 patient. Therefore, a minimum of hospital discharge outcome data was available for 470 patients (238 in the surgical clipping and 232 in the coil embolization group). Outcomes were evaluated at discharge and at 6 and 12 months thereafter.

The treatment groups were well matched (Table 1). There were no statistical differences between the 2 groups with respect to the following characteristics: age; sex; comorbidities (that is, smoking history, hypertension, diabetes, cocaine use); aneurysm location; aneurysm size; or presentation grades (GCS score, Hunt and Hess grade [Table 2], Fisher grade).

No outcome data were collected prospectively from 2 patients. One of these patients had been assigned to coil therapy, but crossed over to surgical clipping for actual treatment, and the other had been assigned to clipping, but withdrew consent for the study before treatment.

TABLE 1: Patient and aneurysm characteristics in the BRAT*

Characteristic	No. Assigned to Clip Group (%)	No. Assigned to Coil Group (%)	p Value†
total no. of patients	238	233	
mean age in yrs	53.1 ± 12.8	54.3 ± 12.0	0.33
female	166 (69.7)	166 (71.2)	0.72
race/ethnicity			0.33‡
Caucasian	152 (63.9)	158 (67.8)	
Hispanic	63 (26.5)	50 (21.5)	
African American	13 (5.5)	9 (3.9)	
Asian	3 (1.3)	8 (3.4)	
other	7 (2.9)	8 (3.4)	
comorbidities			
diabetes	20 (8.4)	17 (7.3)	0.66
hypertension	103 (43.3)	104 (44.6)	0.77
smoking	147 (61.8)	145 (62.2)	0.91
cocaine	21 (8.8)	21 (9.0)	0.92
methamphetamines	17 (7.1)	20 (8.6)	0.53
status at presentation			
mean GCS score	12.3 ± 3.6	12.5 ± 3.6	0.75
mean Hunt & Hess grade	2.6 ± 1.1	2.6 ± 1.1	0.94
mean Fisher grade	2.7 ± 0.7	2.7 ± 0.6	0.77
aneurysm feature			
size in mm§			0.61
mean	6.8 ± 4.1	6.6 ± 4.0	
median; IQR	6.0; 4–8	6.0; 4–8	
location			0.62‡
posterior circulation	38 (16.0)	32 (13.7)	
anterior circulation	174 (73.1)	169 (72.5)	
angiography negative	26 (10.9)	31 (13.3)	
other	not applicable	1 (0.4)	

* IQR = interquartile range.

† Continuous variables were analyzed using the Wilcoxon test, and nominal variables using chi-square tests, unless otherwise noted. The means are expressed ± SD throughout.

‡ Analyzed using the Fisher exact test.

§ Calculated based on 212 cases for the surgical clipping group and 201 for the coil embolization group.

This latter patient's data were not included in the study. Therefore, potentially useful outcome data were available for analysis in 238 patients in the surgical clipping group and 232 in the coil embolization group.

The study was designed to evaluate a policy of alternating clinical services between neurosurgeons performing open and endovascular procedures. The study protocol and all facets of the study were approved and overseen by the institutional review board, with the initial approval being given on November 12, 2002. All patients between the ages of 18 and 80 years who were admitted to the ICU with acute nontraumatic SAH (confirmed by CT scan or lumbar puncture) were eligible for participation and were included if they or their health care decision surrogate consented. Excluded were patients with traumatic SAH

TABLE 2: Hunt and Hess grades at presentation in 471 patients in the BRAT*

Hunt & Hess Grade	No. Assigned to Clip Group (%)	No. Assigned to Coil Group (%)
I	32 (13.4)	31 (13.3)
II	92 (38.7)	93 (39.9)
III	71 (29.8)	61 (26.2)
IV	29 (12.2)	34 (14.6)
V	14 (5.9)	14 (6.0)

* The number originally assigned to surgical clipping was 238; the number originally assigned to coil therapy was 233.

and those presenting to the hospital more than 14 days after hemorrhage. No anatomical inclusion or exclusion criteria were incorporated into the study design. To maximize the comprehensive nature of this study, patients with SAH of initially undetermined cause were enrolled and continued to be tracked, even if no source of hemorrhage was ever identified.

Patients were admitted to the care of the study's "open" or "endovascular" neurosurgeons in an alternating fashion. Two surgeons for each modality participated in the study. Patients were informed of both open and endovascular options for treatment of their aneurysm, of the attending surgeon's intent to treat according to his usual modality, and of the option for crossing over to the alternative modality. In this manner, patients entering the trial were randomized to open or endovascular therapy with a 1:1 ratio. Attending surgeons did not have the opportunity to review or decline patients before the intent-to-treat assignment. When possible, the aneurysm was treated within 24 hours of admission, regardless of a patient's assigned treatment modality.

The primary outcome was analyzed on an intent-to-treat basis. Inability to perform or complete the assigned therapy resulted in a crossing over to the other treatment modality when the alternative treatment provided a viable option. For the final 100 patients enrolled, the admission policy was changed to demonstrate that randomization by lottery would not lead to a significant decrease in study recruitment. This change was made in anticipation of a future multicenter trial and in consideration of the fact that a policy of alternating treatment services may not be embraced universally by prospective study centers. For these last 100 patients admitted to the ICU with SAH, consent for the study was obtained, after which the patient was randomized by envelope draw to 1 of the 2 treatment arms. The patient was then assigned to a study surgeon appropriate to the randomization. To minimize a potential delay from enrollment to treatment, recruitment for the trial was active only if a surgeon from each treatment modality was available.

After a patient was assigned to treatment, the open or endovascular neurosurgeon reviewed the imaging studies. The study investigators included 4 neurosurgeons who performed all open surgical and endovascular procedures at a single institution. The treating physicians included 2 surgeons (J.M.Z., R.F.S.) responsible for open surgical

clipping and 2 surgeons (C.G.M., F.C.A.) responsible for endovascular treatments. At the beginning of the trial, all participating surgeons had a minimum of 3 years of independent clinical practice and independent experience with more than 50 aneurysms. When the assigned physician judged an aneurysm to be more appropriate for treatment via the other modality, crossing over was permitted as deemed clinically indicated. Crossing over was also permitted if attempted treatment with the assigned modality failed.

A dedicated research nurse practitioner acted as coordinator, oversaw patient accrual and randomization, and also was responsible for collecting follow-up data and for assessing mRS scores. The remainder of the study team consisted of residents and fellows involved in patient accrual and care, statisticians, and data managers. Imaging data, which were analyzed by an independent neuroradiologist with experience in coil therapy for aneurysms, are the subject of a future report. All clinical intake data and outcome evaluations were independently obtained by the study coordinators, who were not involved with the treatments, but were not blinded as to the treatment modality.

After enrollment all patients received the same protocol of pre- and postoperative care currently used at our institution for patients with SAH. All patients underwent a complete admission history, physical examination, and standard screening laboratory work. Admitting data collection included calculation of GCS score, Hunt and Hess grade, and Fisher grade. All patients underwent diagnostic cerebral angiography or CT angiography before surgical or endovascular intervention, unless they had been transferred from another hospital and already had adequate studies. All patients requiring external ventricular drainage were so treated, and all patients received appropriate vasospasm prophylaxis and treatment.

The primary outcome was the proportion of patients with a mRS score of 3–6 at 1 year, with the understanding that this score indicated an outcome of dependency or death. Secondary analyses included results based on actual treatment as opposed to the primary intent-to-treat analysis and separate evaluation of patients' crossing over from their assigned group to the alternative treatment group. Sentinel events during a patient's postoperative course were identified and tracked, and included aneurysm-related rebleeding, retreatment, and death.

The initial degree of aneurysm occlusion was evaluated independently of the treating physicians, as will be follow-up imaging. Clinical and imaging follow-up is planned for the 3- and 6-year follow-up visits and will be reported as it becomes available.

Statistical Analysis

Treatment groups were compared by assignment to surgical clipping or coil embolization by using the Wilcoxon rank-sum test for continuous variables and the Mantel-Haenszel chi-square test for categorical variables. Likewise, patients who were assigned to the coil embolization group and received that treatment were compared with patients assigned to coil treatment who crossed over to surgical clipping. Our primary analysis, which examined the risk of a poor outcome (defined as an mRS

score > 2 [signifying death or dependency] at 1 year), consisted of an intent-to-treat analysis in those patients in whom mRS data were reported at 1 year postprocedure (403 individuals); this analysis was performed using logistic regression methods, with assigned treatment as a predictor of outcome. We tested the null hypothesis that no difference in outcome would be detected between the endovascular and surgical treatment arms based on the dichotomized mRS score. A statistically significant difference would be interpreted as evidence in favor of the alternative hypothesis, that one treatment is superior to the other. We then examined multivariable models by first adjusting our primary predictor (assigned treatment) by age > 50 years and baseline Hunt and Hess score > II. We assessed for interactions between treatment modality and both age > 50 years and Hunt and Hess score > II by adding these terms to the model. Because neither of these interactions was statistically significant, they were omitted from our final model.

Secondary analyses of outcome based on actual treatment were conducted using logistic regression models in a process identical to that described above for assigned treatment. Rates of rebleeding and retreatment between the 2 groups were compared using odds ratios and confidence intervals calculated from 2×2 tables using Stata software, version 10. All other analyses were conducted with SAS software, version 9.2.

Results

Primary Outcome

At 1 year, 403 patients were available for independent evaluation by the study coordinator. The primary outcome of death or dependency, as defined by a modified mRS score of 3–6, was found in 69 (33.7%) of the 205 patients assigned to the surgical clipping group (intent to treat) and in 46 (23.2%) of the 198 patients assigned to the coil embolization group (intent to treat). Therefore, the odds ratio for a poor outcome after clipping compared with after coil therapy was 1.68 (95% CI 1.08–2.61, $p = 0.02$) (Table 3). When patients were assigned to the coil embolization rather than the surgical clipping group, the absolute difference was 10.5% fewer poor outcomes. This effect remained significant in multivariable logistic regression analysis adjusted for both age > 50 years and baseline Hunt and Hess score > II. Even after adjusting for these potential confounders, patients who were assigned to the surgical clipping group were 72% more likely to have a poor outcome at 1 year (OR 1.72, 95% CI 1.09–2.76; $p = 0.02$) than patients assigned to the coil embolization group. Age > 50 years and baseline Hunt and Hess score > II were each significantly associated with a poor outcome at 1 year, independent of treatment modality (Table 4). We tested for potential interactions between treatment modality and both age and baseline Hunt and Hess score. Because neither interaction was significant, we excluded these terms from our final model.

Secondary Analyses

Of patients who actually underwent treatment, 358 were available for evaluation at 1 year. Patients whose an-

eurysms were clipped included those who were assigned to and who underwent surgical clipping (“clip-clip”), as well as patients who underwent clipping after crossing over from being assigned to coil therapy (“coil-clip”). Conversely, patients who underwent coil embolization included those assigned to and actually treated by coil therapy (“coil-coil”), as well as those assigned to clipping but crossing over to endovascular treatment (“clip-coil”). Of the 245 patients who actually underwent open surgical clipping, 83 (33.9%) had a poor outcome, compared with 23 (20.4%) of the 113 patients who actually underwent endovascular coil embolization. Therefore, the absolute difference was 13.5%, and the OR was 2.01 (95% CI 1.20–3.46, $p = 0.01$) (Table 3). These secondarily analyzed groups did not include patients who received no treatment, for whom the source of SAH could not be identified in most cases. Multivariable logistic regression analysis examining the effect of actual treatment modality adjusted for age > 50 years and baseline Hunt and Hess score > II yielded similar results to the intent-to-treat analysis, with surgical clipping, age > 50 years, and baseline Hunt and Hess score > II each independently predictive of a poor outcome at 1 year, and no significant interactions (results not shown).

When patients who crossed over were excluded from the subgroup analysis, there were again fewer poor outcomes at 1 year in the coil-coil subgroup (20 [18.4%] of 109) compared with those in the clip-clip subgroup (61 [33.9%] of 180). In this case, the OR for a poor outcome with surgical clipping was 2.28 (95% CI 1.30–4.13, $p = 0.005$). Given the wider disparity between outcomes in those who actually underwent treatment compared with those assigned to treatment, it would be tempting to attribute the disparity to the patients who crossed over. Seventy-five patients crossed over from coil embolization to surgical clipping, but only 4 patients assigned to clip occlusion crossed over to coil embolization.

Of the 65 patients with 1 year of follow-up who crossed over to surgical clipping from coil embolization, 22 (33.9%) had a poor outcome at 1 year. This is the same rate of unfavorable outcome as occurred in the surgical clipping group when patients who crossed over were excluded (that is, patients who were assigned to and who actually underwent clip occlusion fared no better than the patients who crossed over from coil therapy to clipping; see Table 3). The characteristics of the patients who crossed over from coil to clip treatment are compared with the patients who were assigned to coil embolization and did not cross over in Table 5. No significant differences were noted in the presentation grades or comorbidities of the patients who crossed over to surgical clipping, but the mean size of the aneurysms in the patients who crossed over was slightly smaller, and the aneurysms were more likely to be located in the anterior circulation. Of the 4 patients who crossed over to coil therapy from surgical clipping, 3 (75%) had a poor outcome.

The reasons for crossing over from one modality to the other varied. Fourteen patients crossed over from coil embolization to surgical clipping because they had a hematoma that required evacuation. Most patients, however, crossed over to clipping because they had anatomical features judged to render endovascular coil embolization

TABLE 3: Proportion of patients with poor outcome (mRS score > 2) at 1 year in the BRAT

Clip Group			Coil Group			OR (95% CI)	p Value
Subgroup	No.*	No. w/ mRS Score >2 (%)	Subgroup	No.*	No. w/ mRS Score >2 (%)		
assigned clip	205	69 (33.7)	assigned coil	198	46 (23.2)	1.68 (1.08–2.61)	0.02
assigned clip & received clip	180	61 (33.9)	assigned coil & received coil	109	20 (18.4)	2.28 (1.30–4.13)	0.005
crossover: assigned coil & received clip	65	22 (33.9)	crossover: assigned clip & received coil	4	3 (75.0)	0.17 (0.01–1.42)†	0.14
total actually treated w/ clip	245	83 (33.9)	total actually treated w/ coil	113	23 (20.4)	2.01 (1.20–3.46)	0.01

* Total number of patients in each category in whom the mRS score at 1 year was available.

† Reference group; those assigned to coil embolization who crossed over to surgical clipping.

impossible or disproportionately difficult compared with the clipping procedure. Although many aneurysms could be partially occluded with coils, the value of doing so is poorly defined, and our philosophy was that long-term durability was desired. This concern about long-term durability was considered particularly important for young patients. Another consideration was the presence of multiple aneurysms when the ruptured aneurysm could not be identified with certainty. Patients did not cross over from coil embolization to surgical clipping based on grade or clinical condition. There were no significant differences in the clinical grade or comorbidities of the patients crossing over to clipping, but their aneurysms were more likely to be small and in the anterior circulation.

The primary outcome and secondary analyses are summarized in Tables 3 and 4.

Rebleeding During Initial Hospitalization and Subsequent Year

Rebleeding before treatment was documented in 2 patients, both of whom had been assigned to the surgical clipping group. One patient suffered aneurysmal rehemorrhage during diagnostic angiography on the same day as her presenting hemorrhage. The second patient, who was scheduled for surgical clipping on the morning after admission, rebled in the early morning hours prior to the scheduled surgery and underwent surgical clipping later that same day.

Rebleeding after treatment was documented during the initial hospitalization of 2 patients. One patient was assigned to the surgical clipping group, treated with aneurysm clipping and wrapping, and subsequently experienced rebleeding. The second patient was assigned

to the coil embolization group, but had crossed over to and underwent surgical clipping. During surgery a dissecting type of aneurysm involving the posterior inferior cerebellar artery was discovered, which was then clipped and wrapped, leaving a small residual. Despite the open surgical procedure, the patient suffered a second hemorrhage from the treated aneurysm. The resulting death was attributed to coil embolization as a result of the intent-to-treat analysis.

No patient treated by coil embolization rebled after treatment within the 1st year of follow-up. At the time of this writing, all patients are at least 3 years posttreatment. No rebleeding has been reported in any patient treated by coil embolization or by clip occlusion, except as noted above with respect to the initial hospitalization.

Retreatment During Initial Hospitalization and Subsequent Year

Retreatments are summarized in Table 6.

Twelve retreatment events took place during the initial hospitalization (12 [2.55%] of 470 patients). More appropriately, however, this rate may be reported as 12 (2.94%) of 408 actual treatments. Seven (3.02% of 232 patients) of these 12 patients were initially assigned to coil embolization. However, coil embolization was the initial treatment in only 3 of the 12 patients who required retreatment during their initial hospitalization, whereas surgical clipping was the actual treatment for 9 patients. During the rest of the year, an additional 2 retreatments were performed in patients originally assigned to the surgical clipping group. An additional 9 retreatments were needed in patients originally assigned to and treated by coil embolization.

Three patients assigned to and treated by surgical clipping underwent a second open surgical procedure during their initial hospital stay. An additional 2 patients assigned to and treated by surgical clipping underwent endovascular retreatment during their initial hospitalization.

Four patients assigned to coil embolization but treated by surgical clipping required a second procedure during their initial hospital stay. Three of these second procedures were open surgical procedures. The fourth patient had a carotid blister-type aneurysm and was initially assigned to coil embolization, but crossed over to surgical

TABLE 4: Multivariable analysis of patients with poor outcome (mRS score > 2) at 1 year in the BRAT

Characteristic	OR (95% CI)	p Value
clipping*	1.72 (1.09–2.76)	0.020
age >50 yrs	2.03 (1.23–3.42)	0.007
Hunt & Hess grade >III†	3.51 (2.21–5.68)	<0.0001

* Includes all patients assigned to surgical clipping (intent to treat).

† The Hunt and Hess grade is entered into the regression as a binary variable.

TABLE 5: Patients crossing over from coil therapy to open surgery in the BRAT

Characteristic	No. Assigned to Coil Group; Actually Treated w/ Coils (%)	No. Assigned to Coil Group; Crossed Over to Clip Group (%)	p Value*
total no. of patients	124	75	
female	90 (72.6)	54 (72.0)	0.93
mean age in yrs	54.6 ± 11.0	54.2 ± 13.3	0.89
race/ethnicity			0.67†
Caucasian	83 (66.9)	53 (70.7)	
Hispanic	31 (25.0)	14 (18.7)	
African American	4 (3.2)	3 (4.0)	
Asian	3 (2.4)	4 (5.3)	
other	3 (2.4)	1 (1.3)	
mean Hunt & Hess grade	2.6 ± 1.0	2.8 ± 1.1	0.44
mean Fisher grade	2.7 ± 0.6	2.7 ± 0.6	0.73
mean GCS score	12.3 ± 3.5	12.2 ± 3.7	0.94
history of diabetes	7 (5.6)	6 (8.0)	0.51
history of hypertension	60 (48.4)	35 (46.7)	0.81
history of smoking	83 (66.9)	48 (64.0)	0.71
aneurysm size in mm			0.01
mean	6.8 ± 3.7	6.1 ± 4.5	
median; IQR	6; 5–8	5; 3–8	
aneurysm location			0.007
anterior	98 (79.0)	70 (93.3)	
posterior	26 (21.0)	5 (6.7)	

* Continuous variables were analyzed using the Wilcoxon test, and nominal variables using the chi-square test, unless otherwise noted. The means are expressed ± SD throughout.

† Analyzed using the Fisher exact test.

clipping (clipping and wrapping), and then crossed back to endovascular treatment with stent placement after clip occlusion failed.

Retreatment calculations given below and in Table 6 are presented on both an intent-to-treat basis and on an actual treatment basis. The 2 presentations represent best- and worst-case retreatment rates for coil embolization. The denominator for the intent-to-treat analysis is all patients assigned to the respective treatment group, whereas the denominator for the actual treatment includes only patients available for follow-up at 1 year. This smaller denominator is a more accurate reflection of retreatment rates for the 2 treatment modalities, but is based on the

assumption that no patient lost to follow-up underwent retreatment elsewhere. By the end of Year 1 on an intent-to-treat basis, there were 7 retreatment events (2.94%) in the 238 patients assigned to receive surgical clipping for whom follow-up was available. On an intent-to-treat basis, there were 16 retreatment events (6.9%) in the 232 patients assigned to receive coil embolization for whom follow-up was available.

Retreatments During the 1st Year Based on Actual Treatment

Of 280 patients actually treated by surgical clipping, 9 (3.21%) were retreated during their initial hospitaliza-

TABLE 6: Retreatment of aneurysms within 1 year in the BRAT

Category*	Total No.	No. w/ Retreatment (%)		OR (95% CI)		p Value	
		By Discharge	By 1 Yr†	By Discharge	By 1 Yr†	By Discharge	By 1 Yr†
assigned to coil group	232	7 (3.02)	16 (6.90)	1.45 (0.39–5.88)	2.44 (0.93–7.2)	0.53	0.05
assigned to clip group	238	5 (2.10)	7 (2.94)				
actual coil Tx	113	3 (2.66)	12 (10.62)	0.72 (0.12–2.97)	2.57 (0.98–6.55)	0.62	0.03
actual clip Tx	245	9 (3.67)	11 (4.49)				

* Intent-to-treat and actual treatment categories. For actual treatment, the total number of patients includes only those who were actually treated and in whom follow-up information was available.

† Numbers at 1 year include patients who underwent retreatment during initial hospitalization.

tion. During the remainder of the 1st year, 2 more retreatments in this group increased the total to 11 retreatments (4.49%) among the cohort of 245 patients actually treated by surgical clipping and having 1 year of follow-up.

Of the 128 patients actually treated by coil embolization (124 assigned to the coil therapy group, in addition to 4 initially assigned to the surgical clipping group who crossed over to coil treatment), 3 (2.34%) were retreated during their initial hospitalization. During the entire 1st year, 9 more retreatments were performed. Therefore, among the cohort of 113 patients actually treated by coil embolization and having 1 year of follow-up, there were 12 retreatments (10.62%). This secondary analysis demonstrates the significantly increased probability of retreatment in patients actually treated by coil embolization compared with those actually treated by clip occlusion (OR 2.57, 95% CI 0.98–6.55; $p = 0.03$).

Discussion

In this study we aimed to determine if either surgical clipping or coil embolization was superior by analyzing clinical and angiographic outcomes. The 1-year clinical outcomes are reported. We tested the null hypothesis that no difference exists between the 2 treatment modalities in the setting of SAH. In this trial a policy of intent-to-treat by endovascular coil embolization resulted in significantly fewer poor outcomes (10.5%) at 1 year of follow-up (OR 1.68, 95% CI 1.08–2.61; $p = 0.02$).

Because of the design of this trial, some patients were assigned to the coil embolization group, but in fact were not considered to be good candidates for endovascular therapy. Nevertheless, the results favoring endovascular coil embolization include such patients, with their outcomes being allotted to the assigned coil treatment. When only patients who received their assigned treatments are considered, the absolute difference favoring endovascular therapy increases to a highly significant 15.5% (OR 2.28, 95% CI 1.30–4.13; $p = 0.005$). No patient treated by coil embolization suffered from recurrent SAH. Delayed retreatment was more commonly performed in patients assigned to coil embolization.

Several issues need to be considered in the interpretation of our results. The trial was conceived as a pilot study. Consequently, we considered it important to account for all aneurysmal SAH encountered in our tertiary cerebrovascular center. Although casting a wide net to capture and account for all such patients is useful in planning future studies, doing so results in a broader data set than that required to answer specific questions. This trade-off resulted in including patients who ultimately added no useful information to the study: for example, patients with no demonstrable aneurysm, patients who required surgical evacuation of hematomas, and patients with dissecting rather than saccular aneurysms.

Although this study is in many ways a response to the ISAT, there are key differences. First and foremost, the intent-to-treat study design approximates a clinical practice pattern that could be described as a policy of “right of first refusal” for the 2 treatment arms. In this trial, the treating surgeons did not need to review the imaging studies to determine whether patients could be treated

by both methods before they were enrolled. Instead, this trial presupposed that either surgical clipping or coil embolization was the modality of first choice. Under these circumstances, 62.3% of the aneurysms that presented to the endovascular service were treated by coil embolization. In comparison, in the ISAT, 6745 (70.6%) of 9559 screened patients were excluded.¹⁹ In the BRAT, the desire was to be more inclusive, to elucidate whether the results of ISAT were more broadly applicable or applicable at all in our institution. By including all patients with SAH, a clearer picture of the potential role for endovascular coil embolization is apparent. In the BRAT, when the intent to treat was by endovascular coil therapy, 62.3% of the treated aneurysms underwent coil embolization, and fewer poor outcomes were associated with that treatment policy compared with the alternative policy in which surgical clipping was the first-choice treatment.

It is important to understand the role of crossing over between groups, particularly in patients crossing from coil embolization to surgical clipping, because this group was the most numerous (75 vs 4). Some of the reasons that patients with aneurysms crossed over to surgical clipping were relatively uncontroversial. For example, 14 patients assigned to coil embolization had hematomas thought to require evacuation. As was the case for all patients, the outcomes of those who crossed over due to hematoma accrued to the assigned (coil therapy) treatment arm. Any poor outcomes attributable to the presenting hematoma thus counted as a poor outcome for coil therapy.

Most other patients who crossed over from coil embolization to surgical clipping did so because of anatomical concerns related to the aneurysm itself or because multiple aneurysms were present and the source of the SAH could not be ascertained. The most common anatomical limitation to coil therapy was that the target aneurysm was judged to be too small to be treated safely with coils. In other cases the configuration of the aneurysm was unfavorable for coil therapy: for example, because the neck was too wide or because the presence of a branch vessel rendered the probability of complete coil occlusion unlikely. These decisions based on technical limitations of coil embolization are somewhat subjective, and the balance may vary across institutions depending on specific judgments about the strengths of the respective treatment modalities. Although the crossing over of patients with hematomas may not be controversial, the appropriate treatment for the remainder of the patients who crossed over remains undefined. A more aggressive approach to coil embolization may result in a higher complication rate that would offset the benefits of endovascular therapy demonstrated in this trial. Similarly, incomplete coil occlusion of complex aneurysms could increase the frequency of aneurysmal recurrences or even rehemorrhage.

The intent-to-treat design of the BRAT eliminates any realistic way to “game” the system or to “cherry pick” good-grade patients, and no patients crossed over from coil therapy to surgical clipping because of poor clinical grade. Furthermore, poor outcomes observed in the patients who crossed over continued to be attributed to the original assigned treatment for the primary analysis.

The results of this study are striking in that they are remarkably consistent with the results of the ISAT. It is

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also noteworthy that the first prospective randomized trial comparing endovascular and surgical treatment of ruptured aneurysms reported a similar magnitude of benefit from endovascular therapy, but the sample was small and no statistical differences were found at 1 year.¹⁶ In this pioneering study from 2000, Koivisto et al.¹⁶ reported good outcomes (based on the Glasgow Outcome Scale) in 40 (76.9%) of 52 endovascularly treated patients but in only 38 (66.7%) of 57 patients treated with open surgery, an absolute difference of 10.2% favoring endovascular therapy.

The results of the secondary analysis (that is, BRAT patients who actually received their assigned treatment) more closely correspond to those of patients studied in ISAT. Effectively, the BRAT patients who were assigned to and who actually underwent coil embolization were those judged by the endovascular surgeon to be eligible for either treatment. Given that only 4 patients crossed over from surgical clipping to coil embolization, almost all aneurysms treated were considered appropriate for clipping. By ISAT criteria, however, the BRAT patients who crossed over from the coil embolization group would have been ineligible for either treatment and therefore would have been excluded in the ISAT trial.

It seems unlikely that the patients in the BRAT who crossed from coil embolization to surgical clipping could have skewed the outcomes associated with clipping, because the only difference in the parameters in this group compared with the patients who did not cross over was that the aneurysms in the patients who crossed over were, on average, smaller, anterior circulation aneurysms. This conjecture is supported by the fact that the outcome of these patients who crossed over after surgical clipping did not differ from the outcome of the patients originally assigned to and undergoing clipping.

Initially, the outcomes associated with both coil embolization and surgical clipping appear slightly better in the ISAT than in the BRAT. In the ISAT, however, most patients presented with a good grade (88% were World Federation of Neurosurgical Societies Grade I or II). In contrast, in the BRAT, 19.3% of patients were Hunt and Hess Grades IV or V at presentation. If BRAT outcomes for only those patients who entered the study with a Hunt and Hess grade of I or II are considered (107 of those assigned to the coil embolization group and 106 of those assigned to the surgical clipping group), the poor outcomes associated with the procedures were 9.4% and 19.8% for coil therapy and surgical clipping, respectively, comparing favorably with 23.5% and 30.9%, respectively, in the ISAT.²¹ Although the results are not directly comparable, the BRAT findings probably benefit from improvements in endovascular technology that have occurred since the ISAT was completed. Despite the relatively small sample in the BRAT, the absence of recurrent hemorrhages in the patients treated with coils is notable. During the 1st year of the ISAT, rehemorrhage occurred in 20 (4.2%) of the patients assigned to the coil embolization group.

In terms of technological improvements, first-generation Matrix coils were used in the majority of the BRAT coil embolization procedures. These coils have since been withdrawn from the market because numerous studies have suggested that aneurysms treated with these

coils had unacceptably high recurrence rates.^{11,15,16,25,30} It is likely that current endovascular results are, in fact, superior to those reported in this study.

The rate of retreatment during initial hospitalization was similar in both study arms, but delayed retreatment was most often associated with coil-treated aneurysms. Additional retreatment will probably be required over the years, and patients will need to be followed for this possibility even beyond the 6-year follow-up mandated by BRAT. However, the experience of ISAT and the Cerebral Aneurysm Rerupture After Treatment study suggest that there is little likelihood of the initial treatment benefit of endovascular coil embolization being overwhelmed by delayed hemorrhages or complications related to retreatment.^{9,27}

Conclusions

This trial has demonstrated that a policy of intent to treat by endovascular coil embolization results in fewer poor clinical outcomes after 1 year of follow-up. This policy, however, should be applied judiciously: the BRAT results do not imply that all aneurysms should be treated by coil embolization. Therefore, ruptured intracranial aneurysms should be treated in centers that offer high-quality treatment with both modalities. Within a single institution, relative strengths among specialties can influence outcomes. Ideally, the broader applicability of these results would be tested by an expanded multicenter trial.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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