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The Barrow Ruptured Aneurysm Trial: 6-year results

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OBJECT The authors report the 6-year results of the Barrow Ruptured Aneurysm Trial (BRAT). This ongoing randomized trial, with the final goal of a 10-year follow-up, compares the safety and efficacy of surgical clip occlusion and endovascular coil embolization in patients presenting with subarachnoid hemorrhage (SAH) from a ruptured aneurysm. The 1- and 3-year results of this trial have been previously reported.

METHODS In total, 500 patients with an SAH met the entry criteria and were enrolled in the study. Of these patients, 471 were randomly assigned to the treatments: 238 to surgical clipping and 233 to endovascular coiling. Six patients who died before treatment and 57 patients with nonaneurysmal SAHs were excluded, leaving a total of 408 patients who underwent clipping (209 assigned) or coiling (199 assigned). Whether to treat patients within the assigned group or to cross over patients to the other group was at the discretion of the treating physician; 38% (75/199) of the patients assigned to coiling were crossed over to clipping and 1.9% (4/209) assigned to clipping were crossed over to coiling. The outcome data were collected by a dedicated nurse practitioner. The primary outcome analysis was based on the assigned treatment group; poor outcome was defined as a modified Rankin Scale (mRS) score > 2 and was independently adjudicated. Six years after randomization, 336 (82%) of 408 patients who had been treated were available for examination.

RESULTS On the basis of an mRS score of > 2, and similar to the results at the 3-year follow-up, no significant difference in outcomes ($p = 0.24$) was detected between the 2 treatment groups. Complete aneurysm obliteration at 6 years was achieved in 96% (111/116) of the clipping group and in 48% (23/48) of the coiling group ($p < 0.0001$). In the period between the 3- and 6-year follow-ups, 3 additional patients assigned to coiling and none assigned to clipping received retreatment, for overall retreatment rates of 4.6% (13/280) for clipping and 16.4% (21/128) for coiling ($p < 0.0001$).

When aneurysm location was considered, the 6-year results continued to match the previously reported results, with no difference in outcome for anterior circulation aneurysms at most time points. Of the anterior circulation aneurysms assigned to coiling treatment, 42% (70/168) were crossed over to clipping treatment. The outcomes for posterior circulation aneurysms continued to favor coiling. The randomization process was unexpectedly skewed, with 18 of 21 treated aneurysms of the posterior inferior cerebellar artery (PICA) being assigned to clipping, but even when PICA aneurysms were removed from the analysis, outcomes for the posterior circulation aneurysms still favored coiling.

CONCLUSIONS Although BRAT was statistically underpowered to detect small differences, these results suggest little difference in outcome between the 2 treatments for anterior circulation aneurysms. This was not the case for the posterior circulation aneurysms, where coil embolization appeared to provide a sustained advantage over clipping. Aneurysm obliteration rates in BRAT were significantly lower and retreatment rates significantly higher in the patients undergoing coiling than in those undergoing clipping. However, despite the fact that retreatment rates were higher after coiling, no recurrent hemorrhages were known to have occurred in patients undergoing coiling in BRAT who were followed up for 6 years. Sufficient questions remain about the relative benefits of the 2 treatment modalities to warrant further well-designed randomized trials.

Clinical trial registration no.: NCT01593267 (clinicaltrials.gov)

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KEY WORDS BRAT; clip occlusion; coil embolization; intracranial aneurysm; ISAT; randomized trial; subarachnoid hemorrhage; vascular disorders

ABBREVIATIONS BRAT = Barrow Ruptured Aneurysm Trial; ISAT = International Subarachnoid Aneurysm Trial; mRS = modified Rankin Scale; PICA = posterior inferior cerebellar artery; SAH = subarachnoid hemorrhage.

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Endovascular coil embolization and surgical clip occlusion are the currently accepted treatment options for patients with ruptured intracranial aneurysms. Since the publication of results from the International Subarachnoid Aneurysm Trial (ISAT) in 2002, endovascular treatment has become the mainstay in many centers, especially in Europe.[6] The 1-year results of ISAT showed that for the treatment of ruptured aneurysms, coil embolization was superior to clip occlusion, but most of the trial patients had small aneurysms in the anterior circulation and were in good clinical condition. Therefore, evidence that the 1-year ISAT results apply to all patients with aneurysms or that the ISAT results could be replicated has been lacking. To address the issue of the broader applicability of the ISAT results, the Barrow Ruptured Aneurysm Trial (BRAT) used a prospective intent-to-treat design that randomized all patients admitted with a diagnosis of subarachnoid hemorrhage (SAH). The 1- and 3-year results have been published previously,[5,10] and we present here the 6-year results of BRAT. The BRAT remains an ongoing trial with a final follow-up to occur 10 years after enrollment.

Methods

The study protocol was approved by the Institutional Review Board of St. Joseph's Hospital and Medical Center, Phoenix, Arizona, on November 12, 2002. The trial is registered at ClinicalTrials.gov (NCT01593267). A brief summary of the study protocol is provided below; the protocol was described in detail in the report of the 1-year follow-up.[5]

Patient Cohort

All patients admitted for nontraumatic SAHs between March 2003 and January 2007 at our institution were eligible for the study and were enrolled after giving informed consent. Of 500 eligible patients, 28 patients were consented in error, and 1 patient rescinded consent, leaving 471 patients who were randomly assigned to treatment: 238 to the intent-to-clip cohort and 233 to the intent-to-coil cohort.

Because patients were not excluded on the basis of anatomical criteria, patients with nonaneurysmal SAHs were also enrolled in this study. As a result, 63 patients received no treatment: 3 patients in each cohort who died before treatment could be initiated and 57 patients who had a nonaneurysmal SAH (26 in clip group; 31 in coil group). Although our 1-year outcome analysis included data from these untreated patients, these data were excluded from the analysis in the 3-year and 6-year studies because the outcomes in these patients were not associated with any treatment decision; the outcomes in this nontreated cohort were identical between the 2 assigned groups. Of 408 patients who did receive treatment, 209 had been randomized to the clip group and 199 to the coil group (Fig. 1).

Once a patient was assigned to a treatment, the treating surgeon determined whether the patient was better served by receiving the assigned treatment or by crossing over to the alternative treatment. Of the 209 patients assigned to clipping, 4 (1.9%) were crossed over to coiling. Of the 199 patients assigned to coiling, 75 (38%) were crossed over to clipping. Hematomas were the reason for 14 (19%) of the 75 patients being crossed over from coiling to clipping. The remaining patients were crossed over because of a dissecting aneurysm, an aneurysm size that was considered too large or too small for coiling, or because of other anatomical features that the endovascular surgeon believed would be better treated by clipping.

Outcome Analysis

A research nurse practitioner collected the follow-up data and performed the modified Rankin Scale (mRS) assessments. Outcome data were collected at 6 months and at 1, 3, and 6 years after treatment, with a final follow-up scheduled for 10 years after treatment.

The primary outcome was based on patients' mRS scores and was analyzed on the basis of intent-to-treat according to the assigned treatment group. The dichotomized mRS score was chosen as an outcome measure to enable comparison with the ISAT results. Subgroup analyses were not prespecified in the protocol. As previously reported,[5] the 2 groups were well matched, with the exception of aneurysm location in the posterior circulation.

Additional data that were analyzed included outcome based on actual treatment, outcome of crossover patients, rebleeding, death, aneurysm size, aneurysm location, and frequency of aneurysm obliteration as assessed on images studied by a neuroradiologist not involved in treatment (R.C.W.).

Statistical Analysis

Our previously reported primary analysis, which examined the risk for a poor outcome (defined as mRS score > 2, signifying death or dependency), showed fewer poor outcomes in patients assigned to coiling than in those assigned to clipping at 1 year,[5] and this difference persisted but was not statistically significant at 3 years.[10] An intent-to-treat analysis with assigned treatment as the primary predictor of outcome was conducted with logistic regression methods to compare mRS scores at 6 years postprocedure in available patients. Although the analysis of outcomes at 1 year included patients who were randomized but not treated (because of a nonaneurysmal SAH [n = 57] or death before treatment [n = 6]), these patients were excluded from both the 3-year analysis and the current 6-year analysis for 2 reasons. First, there was no difference in the outcomes between them at any time point. Second, because they were not treated, they were not subject to the decision to either treat as assigned or to cross over to the alternative treatment.

We tested the null hypothesis that no difference in dichotomized mRS scores would be detected between the endovascular and the surgical treatment arms of this study. Because our test was 2-sided, a statistically significant difference would support the alternative hypothesis that the 2 treatments were not equivalent.

In multivariable models, we adjusted our primary predictor (assigned treatment) by age > 50 years, baseline Hunt and Hess grade > II (indicating a poorer neurological status), and aneurysm location (anterior vs posterior circulation). Potential interactions between treatment modali-

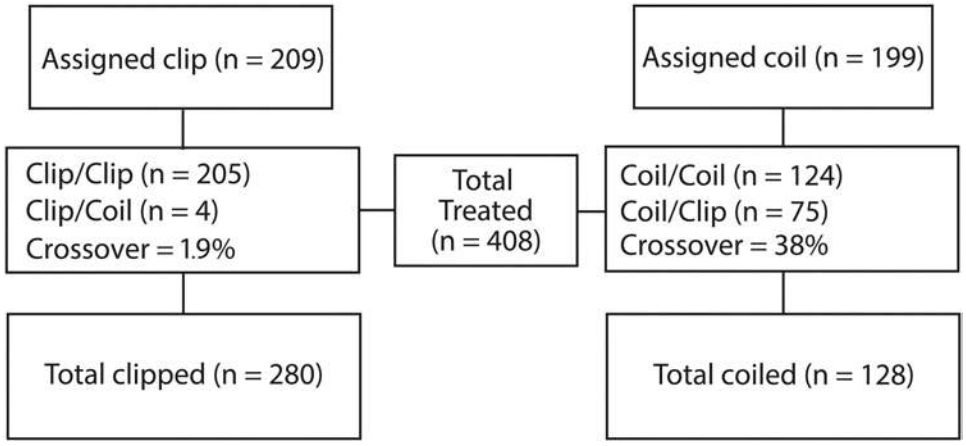

FIG. 1. Flow chart showing assignments and actual treatments of the patients in this study. Clip/Clip = assigned to and treated by surgical clipping; Clip/Coil = assigned to clipping and crossed over to coil embolization; Coil/Coil = assigned to and treated by coil embolization; Coil/Clip = assigned to coil embolization and treated by clipping.

ties and both age > 50 years and Hunt and Hess grade > II were investigated by including these terms in the model. Because these interaction terms were not significant, they were excluded from the final model.

We then conducted secondary analyses of outcome based on actual treatment using logistic regression models as described above for the assigned treatment. Rates of rebleeding and retreatment were compared using odds ratios calculated from 2 × 2 tables using Stata v12.

Results

At the 6-year follow-up, 336 (82%) of the 408 treated patients were available for analysis. One hundred seventy-four had been assigned to clipping; 162 to coiling.

Primary Outcome

For the primary outcome, 57 (35%) of 162 coil-assigned patients and 72 (41%) of 174 clip-assigned patients had a poor outcome (that is, an mRS score of > 2) at 6 years. This difference failed to reach statistical significance (p = 0.24; Table 1).

For a sensitivity analysis, we assigned to patients who had been seen at the 1- or 3-year follow-up, but who were not available at the 6-year follow-up, their most recent mRS scores and included them in the analysis. This increased our cohort to 365 (89%) of 408 patients; 60 (34%) of 177 patients in the coil-assigned group and 73 (39%) of 188 patients in the clip-assigned group had an mRS score of > 2, resulting in an even larger p value (p = 0.33).

Crossover Analysis

Of the 75 patients who were crossed over to clipping after assignment to coiling, 61 were available for analysis at the 6-year follow-up. Among these coil-to-clip patients, 46% (28/61) had a poor outcome, compared with 29% (29/101) of those in the uncrossed coil group (p = 0.03).

TABLE 1. Proportion of patients with mRS scores > 2 across the BRAT follow-ups to date by assigned treatment*

Time Point	No. of Patients Available for Analysis	Treatment Assignment				OR (95% CI)	p Value
		Coil†		Clip†			
		No. of Patients	(%)	No. of Patients	(%)		
At discharge	406	127/198	64.1	147/208	70.7	1.35 (0.89–2.05)	0.16
6 mos	341	40/171	23.4	62/170	36.5	1.88 (1.18–3.03)	0.009
1 yr	358	42/174	24.1	64/184	34.8	1.68 (1.06–2.67)	0.03
3 yrs	349	51/170	30.0	64/179	35.8	1.30 (0.83–2.04)	0.25
3 yrs–CF†	366	51/178	28.7	64/188	34.0	1.29 (0.83–2.00)	0.27
6 yrs	336	57/162	35.2	72/174	41.4	1.30 (0.84–2.02)	0.24
6 yrs–CF‡	365	60/177	33.9	73/188	38.8	1.24 (0.81–1.90)	0.33

CF = carry forward; OR = odds ratio.

* ORs, CIs, and p values were determined with unadjusted logistic regression. In total, 408 patients were available for analysis at randomization (199 patients assigned to coiling and 209 to clipping). Data for discharge and randomization and the 6-month, 1-year, and 3-year follow-ups have been previously reported.[5,10]

† Includes patients seen at the 1-year follow-up, but not at the 3-year follow-up.

‡ Includes patients seen at the 1- and 3-year follow-ups, but not at the 6-year follow-up; it does not include patients no longer in the study and patients who could not be contacted at the 1-, 3-, and 6-year follow-ups.

TABLE 2. Assigned and actual treatments of and crossover rates for 339 anterior circulation aneurysms and 69 posterior circulation aneurysms (N = 408)*

Aneurysm Location	Assigned		Actual		Crossover Rate (%)	
	Clip	Coil	Clip	Coil	Clip to Coil	Coil to Clip
Ant circulation	171	168	240	99	0.6	42.0
Post circulation	38	32†	40	29	8.0	16.0

ant = anterior; post = posterior.

* Values represent number of aneurysms, unless indicated otherwise. The data have been previously reported.[10]

† Total includes 1 patient assigned to coiling who died before treatment.

Moreover, at the 6-year follow-up, 77% (10/13) of the 14 coil-to-clip crossovers with a hematoma had a poor outcome. In accordance with the intent-to-treat analysis design of this study, these poor outcomes were attributed to coiling. Three of the 4 patients who were crossed over from the clip to the coil cohort had a poor outcome at 6 years, and these poor outcomes were attributed to the clipping treatment arm.

Aneurysm Size

The number of aneurysms assigned to treatment group by location and size was reported previously in the 1-year follow-up study.[5] Briefly, the median size of all aneurysms was 6 mm, equally distributed between the 2 treatment groups.

Aneurysm Location

Because ISAT predominantly included patients with anterior circulation aneurysms (97.3% of all patients), we compared our results separately for the anterior and posterior circulation aneurysms. As previously reported,[5] we noted a marked difference in the crossover rate (Table 2) and in outcomes when the data were analyzed by aneurysm location. For the anterior circulation, except at the 6-month follow-up when clipping showed a significantly worse outcome in the actual treatment group, no statistically significant difference in outcome was detected at the other time points, including the 6-year follow-up (Table 3). However, for the posterior circulation cohort, mRS scores were significantly better in the coil-assigned arm at every measured time point, including the latest 6-year follow-up (Table 4).

Of all 408 treated patients, most (339 [83%]) had anterior circulation aneurysms; about one-fifth (69 [17%]) had posterior circulation aneurysms. Most crossovers occurred in the anterior circulation group, in which 70 of the 168 patients (42%) assigned to coiling were crossed over to clipping, whereas only 1 of 171 patients (0.6%) was crossed over from clipping to coiling. In the posterior circulation group, 16% (5/31) of patients were crossed over from coiling to clipping, and 8% (3/38) of patients were crossed over from clipping to coiling (Table 2).

For the anterior circulation aneurysms, the 2 treatment cohorts were almost equally represented among the various anatomical locations of the aneurysm in this region

TABLE 3. Proportion of patients with anterior circulation aneurysms and mRS scores > 2 at the BRAT follow-ups to date by assigned treatment

Time Point	No. of Patients Available for Analysis	Treatment				p Value†
		Coil*		Clip*		
		No. of Patients	(%)	No. of Patients	(%)	
Assigned Treatment						
Discharge	337	107/167	64.1	114/170	67.1	0.56
6 mos	285	36/145	24.8	42/140	30.0	0.33
1 yr	297	37/146	25.3	43/151	28.5	0.57
3 yrs	287	44/142	31.0	43/145	29.7	0.81
3 yrs–CF*	304	44/150	29.3	43/154	27.9	0.79
6 yrs	272	48/133	36.1	50/139	36.0	0.98
6 yrs–CF‡	301	51/148	34.5	51/153	33.3	0.84
Actual Treatment						
Discharge	337	58/99	58.6	163/238	68.5	0.08
6 mos	285	16/88	18.2	62/197	31.5	0.02
1 yr	297	18/87	20.7	62/210	29.5	0.12
3 yrs	287	21/84	25.0	66/203	32.5	0.21
3 yrs–CF*	304	21/89	23.6	66/215	30.7	0.21
6 yrs	272	24/78	30.8	74/194	38.1	0.25
6 yrs–CF‡	301	25/87	28.7	77/214	36.0	0.23

* Includes patients seen at the 1-year follow-up, but not at the 3-year follow-up.

† p values were calculated with χ^2 tests. In total, 339 patients were available for analysis (168 patients assigned to coiling and 171 to clipping; 99 underwent coiling and 240 clipping). Data for discharge and the 6-month, 1-year, and 3-year follow-ups for the assigned treatment and the 3-year carry-forward follow-up in the actual treatment have been previously reported.[5,10]

‡ Includes patients seen at the 1- and 3-year follow-ups, but not at the 6-year follow-up; it does not include patients no longer in the study and patients who could not be contacted at the 1-, 3-, and 6-year follow-ups.

TABLE 4. Patients with posterior circulation aneurysms and an mRS score > 2

Time Point	No. of Patients Available for Analysis (n)	Treatment				p Value†
		Coil*		Clip*		
		No. of Patients	(%)	No. of Patients	(%)	
Assigned Treatment						
Discharge	69	20/31	64.5	33/38	86.8	0.03
6 mos	56	4/26	15.4	20/30	66.7	<0.0001
1 yr	61	5/28	17.9	21/33	63.6	<0.0001
3 yrs	62	7/28	25.0	21/34	61.8	0.004
3 yrs–CF*	62	7/28	25.0	21/34	61.8	0.004
6 yrs	64	9/29	31.0	22/35	62.9	0.01
6 yrs–CF‡	64	9/29	31.0	22/35	62.9	0.01
Actual Treatment						
3 yrs–CF*	62	7/26	26.9	21/36	58.3	0.01
6 yrs–CF‡	64	8/27	29.6	23/37	62.1	0.01

* Includes patients seen at the 1-year follow-up, but not at the 3-year follow-up.

† p values were calculated with χ^2 tests. In total, 69 patients were available for analysis (31 patients assigned to coiling and 38 to clipping). Data for discharge and the 6-month, 1-year, and 3-year follow-ups for the assigned treatment and the 3-year carry-forward follow-up in the actual treatment have been previously reported.[5,10]

‡ Includes patients seen at the 1- and 3-year follow-ups, but not at the 6-year follow-up; it does not include patients no longer in the study and patients who could not be contacted at the 1-, 3-, and 6-year follow-ups.

(Fig. 2). However, the randomization failed to achieve a commensurate treatment distribution in the posterior circulation (Fig. 3): 5 (83%) of the 6 superior cerebellar artery aneurysms and 18 (86%) of 21 treated posterior inferior cerebellar artery (PICA) aneurysms were randomized to clipping; 1 PICA patient (coil-assigned) died before treatment. In contrast, most aneurysms of the posterior cerebral artery, vertebral artery, or basilar artery were assigned to coiling. This disparity would be of no consequence if the aneurysm location were independent of outcome; however, at all recorded time points, patients with PICA aneurysms were much more likely to have a poor outcome than patients with aneurysms at other anatomical locations (Table 5). These poor outcomes occurred despite patients with PICA aneurysms not presenting with Hunt and Hess grades worse than those of other patients with posterior fossa aneurysms.

Among patients who underwent coiling, poor outcomes were similar for those with posterior circulation aneurysms compared to those with anterior circulation aneurysms. By contrast, for patients who were treated by clipping, outcomes were worse for those with posterior circulation aneurysms than for those with anterior circulation aneurysms. Of the 19 patients with PICA aneurysms who underwent clipping, most (70.6% [12/17]) had a poor outcome at 6-year follow-up. This rate was not significantly different from the rate for the 21 clip-treated patients with non-PICA posterior circulation aneurysms, 55% (11/20) of whom had a poor outcome. Poor outcomes were observed in 32% (n = 8) of the 25 non-PICA posterior circulation patients who underwent coiling and had 6-year follow-up. When the 21 disproportionately randomized patients with treated PICA aneurysms were eliminated from the analysis, leaving mostly aneurysms of the upper basilar artery, a statistically significant difference was no longer detected between the clip- and coil-assigned cohorts at 1 year, the time point at which significance was previously present (Table 6).

Aneurysm location appeared to confound the relationship between treatment and outcome; an interaction term included in the model was highly significant (p = 0.009).

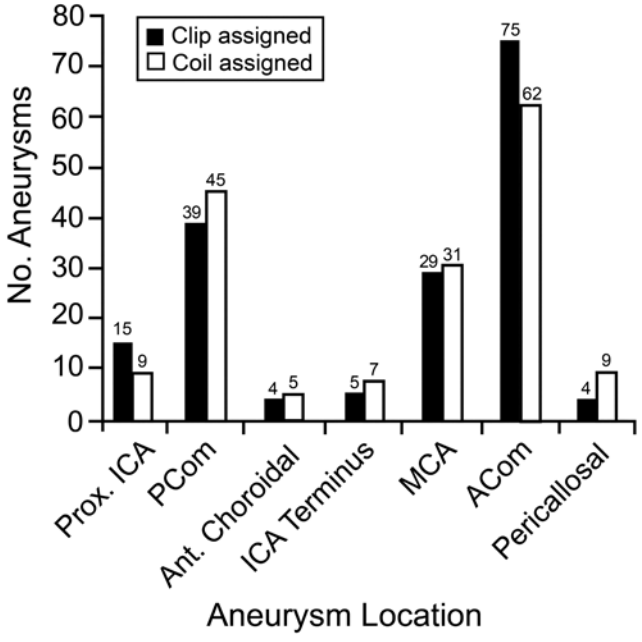

FIG. 2. Location of anterior circulation aneurysms. Figure modified with permission from Spetzler et al: *J Neurosurg 119:*146–157, 2013. ACom = anterior communicating artery; Ant. Choroidal = anterior choroidal artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCom = posterior communicating artery; Prox. = proximal.

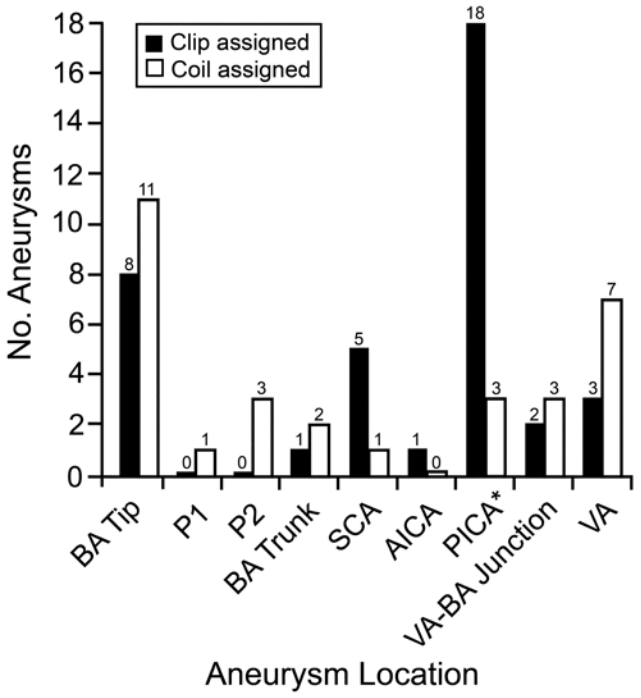

FIG. 3. Randomization of patients by aneurysm location for posterior circulation aneurysms. *In the PICA group (n = 22), 1 of 4 coil-assigned patients died before treatment. Figure modified with permission from Spetzler et al: *J Neurosurg 119:* 146–157, 2013. AICA = anterior inferior cerebellar artery; BA = basilar artery; P1 = first segment of the posterior cerebral artery; P2 = second segment of the posterior cerebral artery; SCA = superior cerebellar artery; VA = vertebral artery.

Rebleeding After Year 1

As previously reported, 2 hemorrhages occurred during the initial hospitalization in patients treated by surgical clipping: 1 from an incompletely clipped aneurysm, which was reclipped the following day, and the other from a dissecting aneurysm, which was wrapped. There were no recognized SAHs from the time of hospital discharge through Year 6 in either cohort.

Retreatment of Aneurysms

At the end of the 6-year posttreatment period, 4.6% (13/280) of the patients with clipped aneurysms required retreatment; all retreatments were performed within the first 6 months. In the coiling group, 16.4% (21/128) required retreatment at least once (3 patients required 2 retreatments). This difference was statistically significant ($p < 0.0001$; Table 7).

Aneurysm Obliteration

The results of aneurysm obliteration are summarized in Table 8. Aneurysm neck remnants were counted as a failure of obliteration. Most of the patients in both groups were followed up noninvasively. At the 6-year follow-up, 96% (111/116) of the clipped aneurysms were found to be obliterated, versus 48% (23/48) of the coiled aneurysms ($p < 0.0001$).

TABLE 5. Comparison of the number of poor-outcome patients (mRS score > 2) by aneurysm location (PICA vs non-PICA) at each time point*

Time Point	No./Total of Patients (%)		p Value
	PICA	Non-PICA	
Discharge	19/21 (90.5)	255/387 (65.9)	0.02
1 yr	11/18 (61.1)	95/340 (27.9)	0.003
3 yrs	11/18 (61.1)	104/331 (31.4)	0.009
6 yrs	12/19 (63.2)†	117/317 (36.9)	0.02

* Of 471 patients, 57 were angiographically negative; 22 presented with PICA aneurysms (1 was not treated due to death); and 392 presented with non-PICA aneurysms (5 were not treated due to death).
† One patient lost to 1-year and 3-year follow-up initiated contact for 6-year follow-up.

Discussion

Randomizing all nontraumatic SAH patients to either coiling or clipping allowed us not only to compare the 2 treatments, but also to determine how often experienced surgeons felt the need to cross over patients to the alternative treatment. A drawback in this intent-to-treat trial is that by including all SAH patients, those with nonaneurysmal SAHs were also included. However, this all-inclusiveness had the advantage of providing results that are based on the entire cohort of aneurysmal SAH patients, particularly because among the patients with nonaneurysmal SAHs, outcomes were identical for the 2 assigned groups. The continued need for clipping expertise is emphasized by the 38% crossover rate from coiling to clipping for the entire group and by the 42% crossover rate for the anterior circulation group. The fact that patients with an acute SAH could be randomized and treated within 24 hours of admission is encouraging for considering another all-inclusive multicenter trial.

The BRAT has several limitations. In this pilot study, which was meant to explore hypotheses and to demonstrate feasibility for more tightly designed future trials, the subgroup analyses were not prespecified, and the study was markedly underpowered to detect differences between the 2 treatment modalities of the sizes observed in ISAT. It is also extremely difficult to accurately measure whether a true difference exists between interventions when many patients cross over from one intervention to the other, because any difference will be blunted in direct proportion to the number of patients crossing over. Thus, if a benefit of coiling were to exist, the observable size of this benefit would be reduced when patients are crossed over to clipping. As noted, most crossovers in BRAT were patients with aneurysms in the anterior circulation who crossed over from coiling to clipping.

Of 4 published randomized trials comparing coiling and clipping—a Li et al. study, the Finnish study, ISAT, and BRAT—only ISAT was sufficiently powered to detect relatively small differences between the treatment modalities.[2,3,5,9] While these trials, with the exception of ISAT, reported reductions in poor outcomes of 5.3%–10.5%, these benefits failed either to reach statistical significance or to remain statistically significant over time.

TABLE 6. Patients with aneurysms in all locations except PICA and mRS scores > 2 across the BRAT follow-ups to date*

Time of Assessment	No. of Patients Available for Analysis	Treatment Assignment				OR (95% CI)	p Value
		Coil		Clip			
		No. of Patients	(%)	No. of Patients	(%)		
Discharge	385	125/195	64.1	130/190	68.4	1.21 (0.79–1.85)	0.37
6 mos	326	40/169	23.7	52/157	33.1	1.60 (0.98–2.60)	0.06
1 yr	340	42/171	24.6	53/169	31.4	1.40 (0.87–2.26)	0.16
3 yrs	331	50/167	29.9	54/164	32.9	1.15 (0.72–1.83)	0.56
3 yrs–CF†	344	50/172	29.1	54/172	31.4	1.12 (0.70–1.77)	0.64
6 yrs	317	56/159	35.2	61/158	38.6	1.16 (0.73–1.83)	0.53
6 yrs–CF‡	346	59/174	33.9	62/172	36.0	1.10 (0.71–1.71)	0.68

* ORs, CIs, and p values were determined with unadjusted logistic regression. In total, 387 patients were available for analysis at randomization (196 patients assigned to coiling and 191 to clipping).

† Includes patients seen at the 1-year follow-up but not at the 3-year follow-up.

‡ Includes patients seen at the 1- and 3-year follow-ups but not at the 6-year follow-up; it does not include patients no longer in the study and patients who could not be contacted at the 1-, 3-, and 6-year follow-ups.

Because > 97% of the patients enrolled in ISAT had aneurysms located in the anterior circulation, an analysis of BRAT limited to the anterior circulation is warranted. Both the intent-to-treat and the as-treated analyses of BRAT did not indicate any benefit of coiling over clipping for anterior circulation aneurysms at any time point, except at the 6-month follow-up when coiling resulted in significantly better outcomes in the as-treated group (Table 3), although the study was not designed, and is clearly too underpowered, to draw conclusions from such subgroup analyses. At 6 years posttreatment in BRAT, there continued to be a significant difference in outcome favoring coiling for treating posterior circulation aneurysms (Table 4). These data are confounded by a skewed randomization: of the 21 PICA aneurysms that were treated, 18 were randomized to clipping and 3 to coiling. Eleven (61.1%) of the 18 patients with PICA aneurysms who were randomized to surgical clipping had a poor outcome. Of the 4 patients with PICA aneurysms who were randomized to coiling, 2 were treated by coiling and had good outcomes; 1 was moribund, not treated, and died; and 1 was crossed over to and treated by clipping but also died.

Although the patients with PICA aneurysms presented with Hunt and Hess grades similar to those of patients with other posterior fossa aneurysms, it is possible that the poor outcomes after clipping in this trial were a spurious result confounding the overall data. If, for a sensitivity analysis, the PICA aneurysms were excluded from the 6-year time point, 11 (61%) of 18 patients with posterior fossa aneurysms assigned to clipping exhibited poor outcomes. With the PICA aneurysms removed from the coiling-assigned cohort, the corresponding number of poor outcomes in the remaining patients with posterior fossa aneurysms was 7 (28%) of 25. While outcomes for patients who underwent clipping were worse for aneurysms in the posterior fossa than in the anterior circulation (with or without the PICA aneurysms), the outcomes for patients who underwent coiling were similar regardless of aneurysm location. We emphasize that conclusions drawn from small numbers in subgroup analyses must be viewed cautiously.

Because the main goal of aneurysm treatment is the prevention of recurrent bleeding, an assessment of treatment effectiveness is essential. In ISAT, the higher risk for rebleeding of the coil group in the as-treated analysis was statistically significant. Further comparison of the 2 treatment groups in ISAT's last report shows that the risk for rebleeding after coiling is 2.5 times higher than after clipping and that the risk for death from an SAH is twice as high after coiling as after clipping (Table 9).[8,9] Overall, however, the rate of recurrent SAHs from the target aneurysm after > 1 year was very low in both groups: 10 SAHs in 8447 person-years of follow-up in the coiling group versus 3 SAHs in 8177 patient-years of follow-up in the clipping group, and only 3 deaths occurred in each group.

The benefit of coiling compared with clipping observed in BRAT, as in ISAT, is largely due to the reduced surgical morbidity and mortality rates associated with coiling and not to the effectiveness of the treatment.

In comparing the BRAT and ISAT results at 1 year, the

TABLE 7. Retreatment in the 2 groups at the 6-year follow-up

Retreatment	No. of Patients (%)		p Value
	Coil	Clip	
No	107 (83.6)	267 (95.4)	<0.0001
Yes	21 (16.4)	13 (4.6)	

TABLE 8. Obliteration of aneurysms determined on diagnostic images after actual treatment*

Time of Assessment	Coil		Clip		p Value
	No. of Aneurysms	(%)	No. of Aneurysms	(%)	
Postop	73/126	57.9	229/269	85.1	<0.0001
3 yrs	36/69	52.2	122/140	87.1	<0.0001
6 yrs	23/48	47.9	111/116	95.7	<0.0001

* Data for the postoperative and 3-year follow-ups have been previously reported.[5,10]

TABLE 9. Rebleeding and death due to SAH in the ISAT studies (2005 and 2009)[8,9]*

Time of Assessment	Treatment	
	Coil	Clip
Before Tx	17 (7)	28 (19)
Total after Tx up to 1 yr	28 (15)	11 (5)
After 1 yr	17 (7)	7 (6)
Total after Tx (after approx 9 yrs)	45 (22)	18 (11)

approx = approximately; Tx = treatment.
* Values represent the number of events; number of deaths is given in parentheses.

sole time period available for comparison, we note that the only BRAT patients who would have been considered appropriate for inclusion in ISAT were those with anterior circulation aneurysms who were randomized to and actually underwent coiling. A BRAT patient who was crossed over to clipping would have been ineligible for ISAT, as such a patient would not have reached clinical equipoise in the treating physicians' experience.

Despite BRAT having a larger percentage of patients with low Hunt and Hess grades (16% vs < 5% in ISAT) and a smaller percentage of patients with good grades (60% vs 88% in ISAT) than ISAT, we observed fewer poor outcomes in the coiling cohort in BRAT than in ISAT (20% vs 24%; Table 10). Because no difference in outcome was observed in BRAT between the clipping and coiling cohorts for the anterior circulation, it is apparent that the surgical results have to be the same. If the surgical results in ISAT had been similar to those in BRAT, it would warrant an entirely different conclusion favoring clipping.

As previously discussed, BRAT considered all SAH patients for randomization and thus its findings are much more generalizable than those of ISAT. We note that in treatments of anterior circulation aneurysms, no significant difference in outcomes was observed between coiling and clipping at almost all time points in BRAT; we also observed a persistent benefit of coiling for treating the posterior fossa aneurysms. These are critical data to consider when planning treatment for ruptured intracranial aneurysms. Complete occlusion rates are clearly lower for coiling, and the results of the Cerebral Aneurysm Rerupture After Treatment (CARAT) study, while indicating no difference in rehemorrhage rates between clipping and coiling, showed a strong association between the degree of residual aneurysm size and risk for rehemorrhage. For patients having an aneurysmal rupture after treatment, the mortality rate in the CARAT study was 58%.[1]

Besides the aforementioned literature, several recent randomized trials have compared different types of endovascular coils, and all of these trials report obliteration rates. The Cerecyte trial reported a combined success rate, defined as stable angiographically visible occlusion, stable neck remnant, or improved occlusion of the aneurysm, of 57% (245/433) for ruptured and unruptured aneurysms at the 6-month follow-up.[7] The hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS) trial reported a major angiographically confirmed recurrence in 24%–33% of patients at the 18-month follow-up in a per-protocol analysis.[11]

The Matrix and Platinum Science (MAPS) trial reported a core-lab–adjudicated complete obliteration rate of 204 (42%) of 485 aneurysms at 1 year, with residual aneurysm filling in 164 (34%) of 485 aneurysms and aneurysm neck remnants in 117 (24%) of 485 aneurysms.[4] Between the time of the initial treatment and the 1-year follow-up, of 484 aneurysms, 176 (36%) exhibited worsening occlusion, 167 (34%) showed no change, and 141 (29%) improved. Despite the significant rates of residual aneurysm filling reported in all 3 trials, the rehemorrhage rates in patients with ruptured aneurysms are very low. Posttreatment hemorrhages in patients with ruptured aneurysms were not observed in the HELPS trial but were observed in 3 (1.3%) of 228 patients in MAPS at the 1-year follow-up. In the Cerecyte trial, only 1 posttreatment hemorrhage (0.2%) was noted to occur among 499 randomized patients, but the timing and pretreatment rupture status of the patient affected were not specified. Importantly, in MAPS, residual aneurysm filling (Raymond class 3) was a strong predictor of the composite primary end point of the Target Aneurysm Recurrence (TAR) trial.[4] Overall, the best endovascular results, including those for treatment of ruptured and unruptured aneurysms, show complete obliteration < 60% of the time.

Conclusions

Recognizing the limitations of this study, and in con-

TABLE 10. Comparison between ISAT and BRAT of outcomes, status at presentation, and aneurysm location*

Study	mRS >2 at 1 yr		HH/WFNS Grade at Presentation		Aneurysm Location in Circulation		Eligible Randomized
	Coil Group	Clip Group	I or II	IV or V	Ant	Post	
ISAT	24	31	88	<5	97	3	22
BRAT (coil-coil)†	20	~20‡	60	16	100	0	48

HH = Hunt and Hess; WFNS = World Federation of Neurosurgical Societies.
* Values represent percentages of patients in the given cohort. Data have been previously reported.[5,9]
† The anterior circulation coil-to-coil subcohort in BRAT was the only group of patients who reached the level of clinical equipoise for inclusion in ISAT.
‡ The number is approximate because no difference in results for the anterior circulation aneurysms was detected between the assigned coiling and clipping groups.

trast to ISAT, we note that there appeared to be only a marginal difference in outcome between clipping and coiling for treating anterior circulation aneurysms as observed over a 6-year period. This was not the case for aneurysms in the posterior circulation, where there appeared to be a sustained benefit of coil embolization over surgical clipping. Consistent with the current literature, aneurysm obliteration rates in BRAT were lower for coiling than for clipping, but despite the fact that rehemorrhage rates were higher after coiling, no recurrent hemorrhages were known to have occurred in either treatment group 6 years after discharge. Sufficient questions remain regarding the relative benefits of the 2 treatment modalities to warrant further well-designed randomized trials.

References

1. Johnston SC, Dowd CF, Higashida RT, Lawton MT, Duckwiler GR, Gress DR: Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. **Stroke 39:**120–125, 2008
2. Koivisto T, Vanninen R, Hurskainen H, Saari T, Hernesniemi J, Vapalahti M: Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms. A prospective randomized study. **Stroke 31:**2369–2377, 2000
3. Li ZQ, Wang QH, Chen G, Quan Z: Outcomes of endovascular coiling versus surgical clipping in the treatment of ruptured intracranial aneurysms. **J Int Med Res 40:**2145–2151, 2012
4. McDougall CG, Johnston SC, Gholkar A, Barnwell SL, Vazquez Suarez JC, Massó Romero J, et al: Bioactive versus bare platinum coils in the treatment of intracranial aneurysms: the MAPS (Matrix and Platinum Science) trial. **AJNR Am J Neuroradiol 35:**935–942, 2014
5. McDougall CG, Spetzler RF, Zabramski JM, Partovi S, Hills NK, Nakaji P, et al: The Barrow Ruptured Aneurysm Trial. **J Neurosurg 116:**135–144, 2012
6. Molyneux A, Kerr R, Stratton I, Sandercock P, Clarke M, Shrimpton J, et al: International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. **Lancet 360:**1267–1274, 2002
7. Molyneux AJ, Clarke A, Sneade M, Mehta Z, Coley S, Roy D, et al: Cerecyte coil trial: angiographic outcomes of a prospective randomized trial comparing endovascular coiling of cerebral aneurysms with either cerecyte or bare platinum coils. **Stroke 43:**2544–2550, 2012
8. Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, et al: Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. **Lancet Neurol 8:**427–433, 2009
9. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al: International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. **Lancet 366:**809–817, 2005
10. Spetzler RF, McDougall CG, Albuquerque FC, Zabramski JM, Hills NK, Partovi S, et al: The Barrow Ruptured Aneurysm Trial: 3-year results. **J Neurosurg 119:**146–157, 2013
11. White PM, Lewis SC, Gholkar A, Sellar RJ, Nahser H, Cognard C, et al: Hydrogel-coated coils versus bare platinum coils for the endovascular treatment of intracranial aneurysms (HELPS): a randomised controlled trial. **Lancet 377:**1655–1662, 2011

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