Retreatment of Ruptured Cerebral Aneurysms in Patients Randomized by Coiling or Clipping in the International Subarachnoid Aneurysm Trial (ISAT)

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***Background and Purpose*—**Because the long-term security of endovascular treatments remains uncertain, a follow-up study of the patients treated in the International Subarachnoid Aneurysm Trial was performed to compare the frequency, timing, and consequences of aneurysm recurrence.

***Methods*—**Patient data were reclassified by actual treatment performed. Aneurysm and patient characteristics, including occlusion grades, time and type of retreatment, and clinical outcomes, were compared. The relationship between these variables and late retreatment as a surrogate for recurrence was analyzed by means of the Cox proportional hazards model.

***Results*—**Retreatment was performed in 191 of 1096 (17.4%) patients after primary endovascular coiling (EVT) and in 39 of 1012 patients (3.8%) after neurosurgical clipping. After EVT, 97 (8.8%) patients were retreated early and 94 (9.0%) late, 7 (0.6%) after rebleeding and 87 (8.3%) without. The mean time to late retreatment was 20.7 months. After neurosurgical clipping, 30 (2.9%) patients were retreated early and 9 (0.85%) late, 3 (0.3%) after rebleeding and 6 (0.6%) without. The mean time to late retreatment was 5.7 months. The hazard ratio (HR) for retreatment after EVT was 6.9 (95% CI=3.4 to 14.1) after adjustment for age (P=0.001, HR=0.97, 95% CI=0.95 to 0.98), lumen size (P=0.006, HR=1.1, 95% CI=1.03 to 1.18), and incomplete occlusion (P<0.001, HR=7.6, 95% CI=3.3 to 17.5).

Conclusions*—**Late retreatment was 6.9 times more likely after EVT. Younger age, larger lumen size, and incomplete occlusion were risk factors for late retreatment after EVT. After neurosurgical clipping, retreatments were earlier; whereas EVT retreatments continued to be performed throughout the follow-up period. Short-term follow-up imaging is therefore insufficient to detect recurrences after EVT. (Stroke*. 2007;38:1538-1544.**)

Key Words: aneurysm ■ rebleeding ■ recurrence ■ retreatments ■ subarachnoid hemorrhage

Patients allocated to endovascular coiling (EVT) in the International Subarachnoid Aneurysm Trial (ISAT) had better outcomes at 12 months[1] and during follow up extended to 7 years.[2] However, concern about the long-term benefit remains because several reports have shown that aneurysm recurrence attributable to inadequate initial occlusion or late reopening is more frequent after EVT.[3–6]

Although aneurysm remnants have been observed in 4% to 18% of neurosurgical clipping (NST) patients,[7–9] regrowth and rebleeding are rare. After EVT, angiographic studies have reported incomplete occlusion in 2% to 17%[4,11–18] and remnants in up to 40%[19,20] of aneurysms. This higher frequency of incomplete occlusion is not associated with proportionally elevated rebleeding rates (approximately 0% to 2% patients) in ISAT[2] or other reports.[2,15,16,21,22]

The follow up of ISAT patients provides an opportunity to study potential differences in the security of aneurysm occlusions provided by clip or coil and the consequences of recurrences in a large cohort of patients. This study was performed to measure the incidences of aneurysm reopening or recurrence requiring retreatment because such data are a crucial part of the continued evaluation of the benefit demonstrated by ISAT and the long-term role of EVT.

Materials and Methods

Patients and Primary Aneurysm Treatments

For the present study, the ISAT case record forms[1] of patients undergoing more than one procedure to the target aneurysm were reanalyzed on the basis of actual rather than allocated treatments. Between 1994 and 2002, 2143 recruited patients were randomly allocated to EVT (1073) or NST (1070), but 48 treatment crossovers occurred. Nine patients crossed from EVT to NST and 39 patients in the opposite direction. Thirty-three patients were not treated because either they died (26 patients) or were too unwell to undergo treatment

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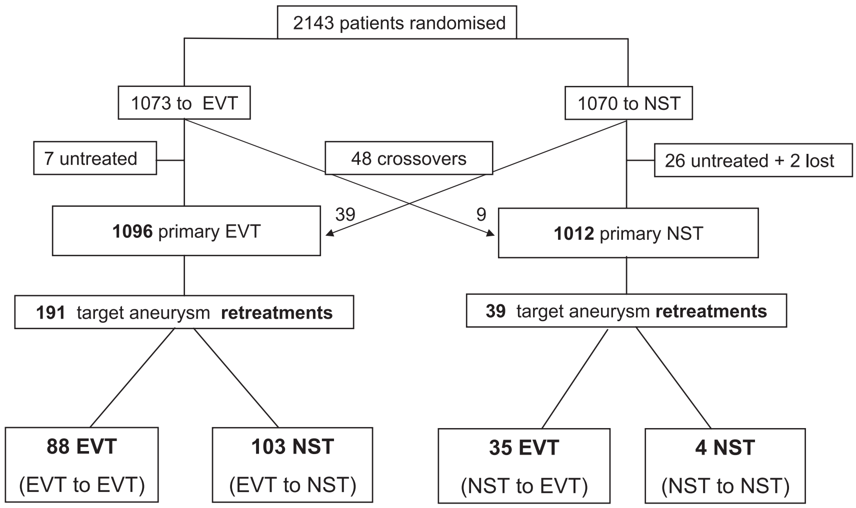

Figure 1. Outcome of ISAT patients after randomization. Categorization of retreated patients based on initial and subsequent EVT or NST treatments performed.

(7 patients). Information was incomplete on 2 patients randomized to NST. Thus, a total of 2108 primary treatments were actually performed: 1096 EVT and 1012 NST (Figure 1).

Aneurysm Retreatments

Retreatment resulting from aneurysm reopening, regrowth, or rebleeding after completed primary treatment was distinguished from retreatment performed after incomplete or failed initial treatment by classifying patients on the basis of the time interval between first and subsequent intervention. Retreatment was defined as "late" if performed later than 3 months after the first EVT or 1 month after the first NST. For the purpose of this study, such late retreatment was considered a surrogate for aneurysm recurrence. Retreatments performed before these time points were considered "early" and attributed to incomplete or failed primary treatment. A longer time delay was chosen for EVT patients because some centers practiced a policy of "staged" embolization, ie, partially treating the aneurysm acutely and performing planned retreatments up to 3 months later. Patients who were subjects of successful early retreatments were then followed up in the cohort appropriate to the completed treatment method.

Clinical Data

The following data were extracted from case record forms: patient age and gender; target aneurysm characteristics (maximum aneurysm lumen size, neck width, and location); and treatment outcomes. Details of retreatment procedures and any sequelae were recorded along with contemporaneous clinical outcome assessments. Late retreatments were performed after rebleeding or on the basis of identified aneurysm reopening or regrowth by local investigators. The "time to retreatment" was calculated as the interval between the date of the primary treatment and date of retreatment. Clinical assessments were recorded using the modified Rankin Scale (mRS)[1,23] immediately after retreatment and annually thereafter for 4.5 to 12 years. Data were analyzed separately for patients who rebled. Their case record forms, CT scans, and any relevant angiograms were reviewed centrally by 2 neuroradiologists and included only if adjudicated to be attributable to rerupture of the treated aneurysm.

Angiographic Data

Local investigators assessed the anatomic result of treatment visually during NST or from final angiograms after EVT. Angiographic follow up was generally performed 6 months after treatment and repeated at variable intervals. Most follow-up imaging was by intraarterial angiography, but some centers also performed magnetic resonance angiography. Eight hundred and eighty-one patients (88.2%) had follow-up angiograms in the EVT group and 450 (45.8%) in the NST group (Table 1). Treatment success was graded by the extent of occlusion of the treated aneurysm using an "occlusion grade" score.

Occlusion grades after EVT (OGe) were defined as: OGe1=total occlusion, no contrast filling of the aneurysm sac; OGe2=subtotal occlusion, minor residual sac filling or neck remnant; and OGe3=incomplete occlusion, substantial residual sac filling.

Occlusion grades after NST (OGs) were defined as: OGs1=total occlusion, no blood flow or contrast filling of the aneurysm sac; and OGs2=incomplete occlusion (clipping or wrapping), any blood flow or contrast filling of the aneurysm sac.

TABLE 1. Primary Occlusion Grades in Patients Retreated Late for Aneurysm Recurrence

Endovascular Patients (n=1045‡)				Neurosurgical Patients (n=1063§)			
OGe*	Retreated Patients	With Follow-Up Angiogram (n=881)	Retreatments as Percent of Patients With Angiogram	OGs*	Retreated Patients	With Follow-Up Angiogram† (n=450)	Retreatments as Percent of Patients With Angiogram
1	34	584	5.8%	1	9	370	2.4%
2	47	228	20.6%	2	0	80‖	
3	13	69	18.8%				
Total	94 (9.0%)‡				9 (0.85%)§		

*Occlusion grade after the first procedure.
†Occlusion grade at follow-up angiogram.
‡One thousand forty-five total EVT patients followed=999 patients successfully treated by primary treatment plus 46 early retreated patients.
§One thousand sixty-three total NST patients followed=982 patients successfully treated by primary treatment plus 81 early retreated patients.
‖Retreatments in all patients with incompletely clipped or wrapped aneurysms were performed early.

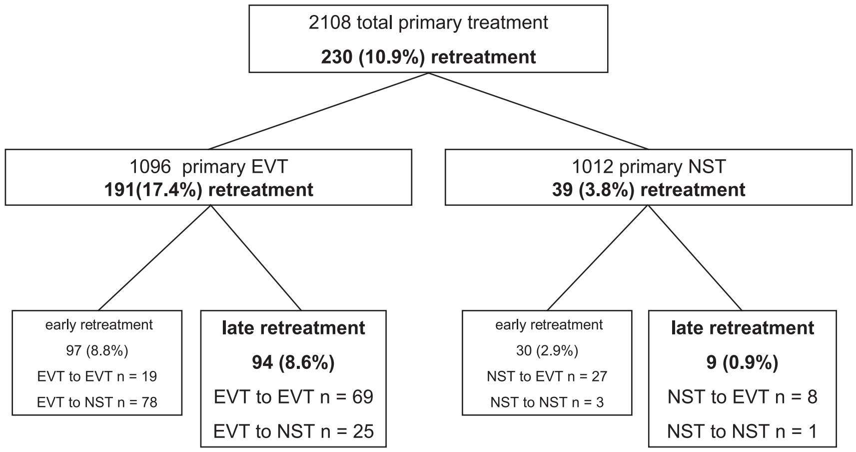

Figure 2. Number and percentage of treated patients showing retreatment timing.

Aneurysm size was defined by maximum sac dimension and neck width, and categorized as: small (≤5 mm), medium (6 to 10 mm), and large (≥11 mm) by the former and wide-necked (>4 mm) by the latter.

Aneurysm locations were categorized as: anterior cerebral artery including anterior communicating artery, anterior cerebral/anterior communicating artery junction, and pericallosal artery locations; internal carotid artery including the carotid siphon, ophthalmic artery origin, and carotid bifurcation; posterior communicating artery; middle cerebral artery; and posterior circulation including basilar trunk, basilar bifurcation, posterior cerebral artery, anterior inferior cerebellar artery, posterior inferior cerebellar artery, and superior cerebellar artery locations.

Data Analysis

Differences between patient groups were tested by univariate analysis using χ^2 test, Fisher exact test, 2-sample *t* test, Mann–Whitney *U* test, or log rank as appropriate. Logistic regression was used to derive odds ratios (OR) for multilevel categorical variables. A Cox proportional hazards model with a forward stepwise regression procedure was used to determine predictors of retreatment based on baseline characteristics. Multivariate models were adjusted for age, gender, aneurysm lumen size, neck width greater than 4 mm, and occlusion grade. All analyses were performed using SPSS (version 14.0; SPSS Inc). A 2-tailed probability value of <0.05 was considered to be statistically significant.

Results

Retreatments After Primary Endovascular Treatment

Retreatments were performed in 191 (17.4%) of 1096 patients after EVT with 88 receiving EVT (EVT-EVT) and 103 NST (EVT-NST) (Figure 1).

Early Retreatments

Early retreatments were performed in 97 (8.8%) patients (Figure 2) because of failure to deploy coils (75 patients) or incomplete occlusion (22 patients) at initial EVT. Retreatments were performed within 30 days in 92 patients and between 1 and 3 months in 5. These retreatments were attributable to unsuccessful primary treatment and not recurrence so were not considered further, although patients continued to be followed.

Late Retreatments

Late retreatments were performed in 94 patients after aneurysm recurrence or rebleeding. This represents 9.0% of the 1045 patients followed after completed EVT (ie, 999 primary EVT and 46 early EVT retreatments) and 10.6% of the 881 EVT patients who underwent follow-up angiography (Table 1). The mean interval to retreatment was 20.7 months with a median of 13.7 months (range, 3 to 80 months).

Patient and Aneurysm Characteristics

On univariate analysis, the mean age of retreated patients was significantly lower than of those not retreated (Student *t* test, $P<0.001$), but gender was not related to retreatment (χ^2 test, $P=0.3$).

Aneurysm occlusion grades were associated with frequency of retreatment: 20.6% of OGe2 and 18.8% of OGe3 aneurysms requiring retreatment compared with 5.8% of OGe1. Logistic regression analysis on occlusion grade showed an OR of 4.5 for OGe2 (95% CI=2.8 to 7.3) and 15.5 for OGe3 (95% CI=6.7 to 35.9) aneurysms when compared with OGe1 (Table 2).

The mean interval to late retreatment was 24 months (range, 3 to 80 months) for OGe1, 17 months (range, 4 to 71 months) for OGe2, and 12 months (range, 3 to 28 months) for OGe3. Between 2 and 3 years, the retreatment rate was not significantly different for each OGe group, but after 3 years, it was highest in OGe1 patients (Figure 3).

Relative to the entire EVT cohort, retreated aneurysms tended to be larger ($P=0.043$); being large in 13 of 83 (16%), small in 41 of 552 (7%), and medium-sized in 40 of 438 (9%). Aneurysms with wide necks (>4 mm) were not retreated more often ($P=0.412$). Only posterior communicating artery aneurysms (47%) underwent significantly more retreatments than other locations ($P=0.03$) (Table 2).

The crude hazard ratio (HR) for retreatment after EVT was 10.4 (95% CI=5.2 to 20.7). Stepwise introduction of significant variables into the multivariate model resulted in statistical significance for age ($P=0.001$, HR=0.97, 95% CI=0.95 to 0.98), lumen size ($P=0.006$, HR=1.1, 95% CI=1.03 to 1.18), and incomplete occlusion. With OGe1 being the reference category, the HR was 4.1 for OGe2 (95% CI=2.6 to 6.4) and 7.6 for OGe3 (95% CI=3.3 to 17.5). We found no significant influence of gender, aneurysm location, or neck size on multivariate analysis. After adjustment, the HR for retreatment after EVT was 6.9 (95% CI=3.4 to 14.1) compared with NST.

TABLE 2. Patient and Aneurysm Characteristics

	EVT (n=1045)				NST (n=1063)	
	OGe 1	OGe 2	OGe 3	EVT Cohort	OGs 1	NST Cohort
Number retreated	34	47	13	94 (9)	9	9 (0.8)
Mean age* (range)	46 (26–75)	45 (19–68)	41 (24–66)	52 (18–87)	58 (33–66)	52 (18–84)
Female sex	23 (68)	31 (66)	9 (69)	673 (64)	5 (55)	673 (63)
Lumen size*						
Small	16 (47)	22 (47)	3 (23)	552 (51)	4 (44)	572 (53)
Medium	16 (47)	15 (32)	9 (69)	438 (41)	4 (44)	426 (40)
Large	2 (6)	10 (21)	1 (8)	83 (8)	1 (12)	72 (7)
Neck size greater than 4 mm	5 (15)	9 (19)	3 (23)	236 (22)	4 (44)	347 (32)
Aneurysm location						
Anterior cerebral artery	19 (56)	16 (34)	7 (54)	541 (50.5)	9 (100)	543 (51)
Posterior communicating artery*	8 (23)	22 (47)	3 (23)	262 (24)	0	0
Internal carotid artery	3 (8.8)	4 (8.5)	3 (23)	85 (8)	0	0
Middle cerebral artery	3 (9)	5 (11)	0	162 (15)	0	0
Posterior circulation	1 (3)	0	0	23 (2)	0	0

Numbers in parentheses represent percentages unless otherwise indicated.
*Significantly associated with occurrence of retreatment on univariate analysis (P=0.05).

Clinical Outcomes After Late Retreatment

Late retreatments were performed in 87 (8.3%) patients without rebleeding and after angiographic demonstration of reopening or regrowth. For 65 EVT-EVT patients, the mRS scores at last follow up were not significantly different from those before the second treatment (see Table 3). Procedural complications occurred in 6% and resulted in transient neurological symptoms only. For 22 EVT-NST patients, no procedural complications were reported. Their mRS scores remained the same in 17 and worsened in 2 patients.

Late retreatments were performed in 7 (0.6%) patients (4 EVT-EVT, 3 EVT-NST) after rebleeding. In 2 patients, "de novo" aneurysm was reported in continuity with the treated aneurysm. The mean interval between primary treatment and rebleeding was 41.4 months (range, 12 to 68 months). At last follow up (mean, 6.1 years; range, 1 to 10 years), 4 patients (2 EVT-EVT and 2 EVT-NST) were independent (mRS 0 to 2), whereas 2 (one EVT-EVT and one EVT-NST) were disabled (mRS 3 to 5). One patient died 12 months after EVT retreatment after further rebleeding. No procedural complications were recorded. On logistic regression analysis, rebleeding was not significantly associated with poor outcome after retreatment (P=0.3).

Retreatments After Primary Neurosurgical Treatment

Retreatments were performed in 39 (3.8%) of 1012 patients after primary NST with 35 receiving EVT (NST-EVT) and 4 NST (NST-NST) (Figure 1).

Early Retreatments

Early retreatments were performed in 30 patients because no clip was applied (24 patients, 21 retreated by EVT and 3 by NST) and 6 aneurysm were wrapped (all retreated by EVT). All patients were retreated within 2 weeks and then continued to be followed up (Figure 2).

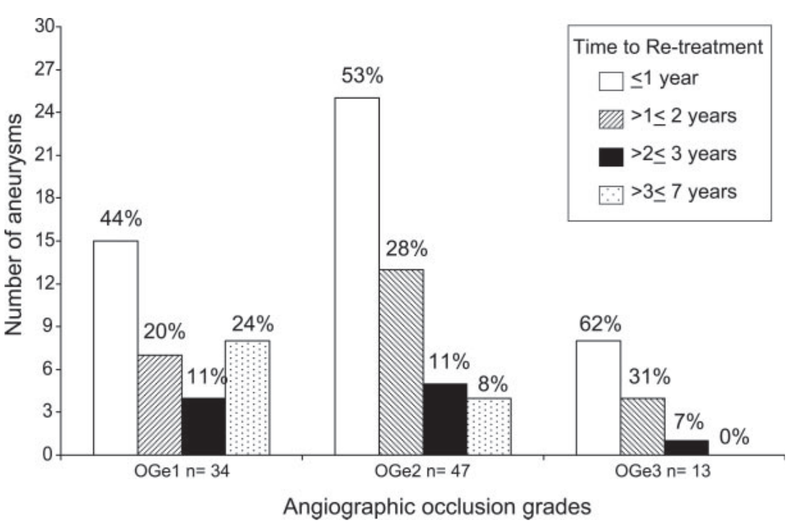

Figure 3. Time to late retreatments after primary endovascular treatment. Bar graphs show the aneurysm numbers grouped by primary occlusion grades. The percentages express the proportions of retreatments in each occlusion grade group.

TABLE 3. Outcome at Last Follow Up in Patients Retreated Without Rebleeding

		Before Retreatment		After Retreatment	
	Total	mRS 0–2	mRS 3–6	mRS 0–2	mRS 3–6
EVT to EVT	65	53 (81)	12 (19)	52 (81)	13 (19)
EVT to NST	22	19 (86)	3 (14)	17 (77)	5 (23)
NST to EVT	6*	6 (100)	0	4 (80)	1 (20)
†NST to NST	0	…	…	…	…

*One patient lost to the last follow up.
†No NST patient was retreated (NST to NST) without rebleeding.

Late Retreatments

Late retreatments were performed in 9 patients after recurrence or rebleeding, representing 0.9% of the 1063 followed after completed NST (ie, 982 primary and 81 early retreatments) and 2% of 450 neurosurgical patients who underwent follow-up angiography (Table 1). The mean interval to retreatment was 5.7 months (range, 1 to 18 months; median, 4.2 months) and therefore considerably shorter than after EVT (log rank, $P<0.001$).

Patient and Aneurysm Characteristics

On univariate analysis, age and gender were not significantly different compared with the nonretreated group. Aneurysm location, size, neck width, and location were also not associated with retreatment frequency despite all retreated aneurysms being located on the anterior cerebral artery territory (compared with a frequency of 51% in the randomized cohort) (Table 2).

Clinical Outcomes After Late Retreatment

Late retreatments were performed in 6 patients without rebleeding. All were NST-EVT and their mRS scores at last follow up were not significantly different from those before retreatment (see Table 3). Procedural complications occurred in one patient (16%) with transient neurological symptoms and no change in mRS score.

Retreatments were performed after rebleeding in 3 patients (2 NST-EVT and one NST-NST). The mean interval between primary treatment and rebleeding was only 2.3 months (range, 2 to 3 months). At last follow up (range, 5 to 8 years), the 2 NST-EVT patients were mRS 0 to 2 and the one NST-NST patient was mRS grade 3. No procedural complications were recorded. The numbers were too small for statistical analysis.

Rebleeding rates overall were not statistically different (3 of 1012 versus 7 of 1096) between the two treatment cohorts ($P=0.3$). Pooling the rebleeding cases together across groups (EVT and NST) and performing Fisher exact test did not show any significant relationship between rebleeding and clinical outcome ($P=0.23$).

Discussion

In this study, we used late retreatment as a surrogate for aneurysm recurrence because it is an objective end point, and ISAT investigators continue to return details of participant patients whenever they require readmission to the hospital. This reliance on a surrogate has limitations because the diagnosis of aneurysm reopening depends on patients developing symptoms or on imaging demonstrating recurrence. Follow-up imaging was more frequently performed in EVT patients.

Retreatments were collectively (early and late) 4 times less frequent (3.8% versus 17.4%) and late retreatments approximately 7 times less frequent for NST patients. These huge differences in frequency may in part be explained by the lower frequency of follow-up angiograms, and it is possible that more recurrences would have been detected if a systematic long-term imaging follow-up strategy had been in place. It may also be a factor in explaining why post-NST rebleedings were diagnosed more frequently relative to asymptomatic recurrences (3 of 9) than for EVT (7 of 94).

Rates of aneurysm recurrence after coiling have been provided in single[4,10,11,13,15–17,20,22] and multicenter studies[24–26] and calculated in meta-analyses of such reports.[19] Aneurysm reopening has been defined as unstable residual contrast filling[15] and its reported incidence is 20% (range, 15% to 33%) in larger case series.[4,20,22,24] This wide range of incidences has been attributed to different evaluation methodologies and case mix. Aneurysm remnants are more frequent after EVT, having been identified on 34% of follow-up angiograms in a previous report on the ISAT data,[2] but the retreatment rate identified in the present study was substantially less at 9.0%. This high incidence of remnants and comparatively low retreatment rate is consistent with single-center studies reporting that fewer than 50% of recurrences are of sufficient concern to warrant retreatment[20,24] and supports the conclusion that a proportion of aneurysm remnants are stable and unlikely to enlarge and rebleed,[15] at least in the medium term. The low frequency of retreatments among ISAT participants, and by inference aneurysm recurrence, may be attributable to the relatively high number of small aneurysms compared with case series reports.[6]

A further factor may be our use of a surrogate that involves a decision to treat rather than merely an observation of aneurysm remnant or angiographic regrowth.

After NST, late retreatments were performed after a shorter interval (mean, 5.4 months) than after EVT in which retreatments were spread over the entire posttreatment period and the latency was longer for initially completely occluded aneurysms. This could be explained by an undefined characteristic of the aneurysm disease process or delayed coil failure causing aneurysms to reopen despite initial anatomic cure. It could also reflect a lower frequency of follow-up angiograms obtained in asymptomatic patients who are considered cured. Whatever the cause, it appears to affect a minority of patients and because recurrence after EVT is more frequent when imaging surveillance is prolonged, no safe time limit to follow up can currently be recommended.[16,20] The challenge remains to identify which patients are most at risk so that follow-up imaging can be effectively targeted.

Factors previously identified as significant predictors of aneurysm recurrence include suboptimal initial angiographic result, packing density ratio, treatment after rupture, and aneurysm size.[16,20,27,28] In the present study, predictors of retreatment in the EVT cohort were younger age, large

aneurysm size, and incomplete initial occlusion. The effect of patient age is difficult to understand unless there was a bias toward more frequent surveillance imaging in younger patients. The relationship of initial occlusion rate and aneurysm size to retreatment rates has been previously reported.[6,16,20] Reports that packing density ratios[27,28,29,30,31] can predict recurrences cannot be substantiated by our data, except in as far as packing density is reflected by the initial occlusion grade. We also found a higher frequency of recurrences in posterior communicating artery aneurysms after EVT and anterior communicating artery aneurysms after NST and suspect that this may reflect technical difficulties in treating aneurysms located at these anatomical sites.[32,33]

Overall, rebleeding rates were low and not statistically different (3 of 1012 versus 7 of 1096) between the two cohorts. At only 0.3%, the risk of rebleeding for NST patients supports the practice of not performing prolonged imaging surveillance after NST once aneurysm occlusion has been assured.

Viewed against the EVT rebleed latency of 12 to 68 months, the finding that the NST rebleed latency was only 3 months may imply that rebleeding was the result of undetected incomplete clipping or, if recurrence necessarily precedes rebleeding, that it occurs at a faster rate after NST than after EVT. The latter conclusion is partially supported by our finding that most retreatments after NST were performed in the first 12 months of follow up. Certainly, the timing is strikingly different between NST and EVT in which one or 2 patients rebled during each follow-up year.

In the EVT cohort, the latency of rebleeding was longer and in 2 patients “de novo” aneurysms, in continuity with the initial target aneurysm, were diagnosed at retreatment. A proportion of very late rebleeding has previously been attributed to “de novo” aneurysms,[9,34] and a recent study reported that 20% of coincidental aneurysms, detected more than 5 years after successful clipping of ruptured aneurysms, were “de novo.”[9] The scale of this complication has yet to be defined, but its recognition is a warning that some degree of imaging surveillance of some patients with aneurysm, however treated, may need to be prolonged.

Aneurysm retreatment did not cause significant additional morbidity. Our findings are consistent with a previous report of a low complication rate after EVT retreatments[35] and are reassuring of the overall benefit previously demonstrated for EVT patients.[2]

In summary, our study provides data from a large series of patients randomized in a controlled trial and found that late retreatments were performed approximately 7 times more frequently among EVT patients. Younger age, larger lumen size, and incomplete occlusion were risk factors for late retreatment after EVT. The rates for aneurysm retreatment were lower than previous EVT reports but similar to previous NST reports. The latency to rebleeding and retreatment was shorter after NST and evenly distributed throughout the follow-up period after EVT. Therefore, follow-up imaging needs to be more frequent and prolonged for EVT patients and, as practiced, was insufficient to detect all recurrences or prevent rebleeding.

Disclosures

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