Predictors of Rehemorrhage After Treatment of Ruptured Intracranial Aneurysms

The Cerebral Aneurysm Rerupture After Treatment (CARAT) Study

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Background and Purpose—The primary purpose of intracranial aneurysm treatment is to prevent rupture. Risk factors for rupture after aneurysm treatment have not been clearly established, and the need to completely occlude aneurysms is debated.

Methods—The Cerebral Aneurysm Rerupture After Treatment (CARAT) study is an ambidirectional cohort study of all patients with ruptured intracranial aneurysms treated with coil embolization or surgical clipping at 9 high-volume centers in the United States from 1996 to 1998. All subjects were followed through 2005, and all potential reruptures were adjudicated by a panel of 3 specialists without knowledge of the initial treatment or aneurysm characteristics. Degree of aneurysm occlusion post-treatment was evaluated as a predictor of nonprocedural rerupture in univariate Kaplan–Meier analysis (log-rank test) and in a Cox proportional-hazards model after adjustment for potential confounders and censoring at time of retreatment.

Results—Among 1001 patients during a mean of 4.0 years follow-up, there were 19 postprocedural reruptures; median time to rerupture was 3 days and 58% led to death. The degree of aneurysm occlusion after treatment was strongly associated with risk of rerupture (overall risk: 1.1% for complete occlusion, 2.9% for 91% to 99% occlusion, 5.9% for 70% to 90%, 17.6% for <70%; $P<0.0001$ in univariate and multivariable analysis). Overall risk of rerupture tended to be greater after coil embolization compared with surgical clipping (3.4% versus 1.3%; $P=0.092$), but the difference did not persist after adjustment ($P=0.83$).

Conclusions—Degree of aneurysm occlusion after the initial treatment is a strong predictor of the risk of subsequent rupture in patients presenting with subarachnoid hemorrhage, which justifies attempts to completely occlude aneurysms. **(*Stroke*. 2008;39:120-125.)**

Key Words: coil embolization ■ intracranial aneurysm ■ subarachnoid hemorrhage ■ surgical clipping

Delayed rerupture is rare after a ruptured intracranial aneurysm is treated with either coil embolization or surgical clipping.[1–3] However, early rerupture of treated aneurysms occurs more frequently and has major consequences. In the Cerebral Aneurysm Rerupture After Treatment (CARAT) study, we previously noted a 1.8% overall risk of rerupture in the first year after treatment. Similarly, the International Subarachnoid Aneurysm Treatment (ISAT) found a 1.7% risk of rerupture in the first year.[2]

Predictors of rerupture after aneurysm treatment have not been carefully studied. Several case series have suggested that subtotal occlusion of an aneurysm either with a surgical clip or with coils is associated with a higher risk of subsequent hemorrhage compared with complete occlusion,[4–8] but these studies have generally not been controlled and follow-up has been variable.[9,10] Nonetheless, most practitioners strive to completely occlude aneurysms even if this entails additional risk of retreatment. Identifying the risk of rehemorrhage after subtotal occlusion could clarify in whom the risk of retreatment is justified. Similarly, other predictors of rehemorrhage risk could also be useful in defining indications for retreatment.

We sought to identify risk factors for rerupture after treatment of intracranial aneurysms, paying particular attention to degree of aneurysm occlusion, using data from CARAT, an ambidirectional cohort study of 1010 patients treated with coil embolization or surgical clipping treated at 9 hospitals in 8 high-volume centers in the United States.[1] We evaluated patient, aneurysm, and treatment characteristics as potential predictors of rerupture risk at any time after initial treatment.

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*Listing provided in the Appendix.

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Table 1. Characteristics of Patients at Baseline by Complete or Partial Aneurysm Occlusion

Variable Name	Complete (n=760), mean±SD or n (%)	Partial (n=241), mean±SD or n (%)	P†
Age, years	53.9±13.9	57.7±14.9	0.001
Women	521 (68.6)	169 (70.1)	0.69
Race/ethnicity			0.84
White, non-Hispanic	460 (60.5)	148 (61.4)	
Black	72 (9.5)	22 (9.1)	
Hispanic	88 (11.6)	22 (9.1)	
Asian	45 (5.9)	16 (6.6)	
Others and unknown	95 (12.5)	33 (13.7)	
Hypertension	332 (43.9)	111 (47.2)	0.37
Diabetes	40 (5.3)	14 (6.0)	0.74
Chronic obstructive pulmonary disease	41 (5.4)	26 (11.1)	0.007
Coronary artery disease	65 (8.6)	30 (12.8)	0.08
Current smoking	347 (45.9)	115 (48.7)	0.46
Hyperlipidemia	48 (6.4)	21 (9.0)	0.19
History of ischemic stroke	22 (2.9)	11 (4.7)	0.21
History of peripheral vascular disease	13 (1.7)	8 (3.4)	0.12
Family history of intracranial aneurysm	38 (5.6)	17 (7.7)	0.26
Hunt Hess Grade			0.11
1	49 (6.5)	23 (9.7)	
2	347 (45.8)	84 (35.4)	
3	220 (29.0)	72 (30.4)	
4	105 (13.9)	42 (17.7)	
5	37 (4.9)	16 (6.8)	
Rankin score, prehemorrhage	0.4±0.8	0.5±1.0	0.13
Rankin score, on presentation	2.9±1.2	3.0±1.4	0.15
Aneurysm size*			0.12
0–5 mm	197 (36.8)	67 (31.2)	
>5–10 mm	238 (44.5)	101 (47.0)	
>10 mm	100 (18.7)	47 (21.9)	
Aneurysm location			0.002
Anterior cerebral artery	266 (35.0)	65 (27.0)	
Internal carotid artery	235 (30.9)	74 (30.7)	
Middle cerebral artery	109 (14.3)	27 (11.2)	
Posterior circulation	150 (19.7)	75 (31.1)	
Aneurysm coiled	114 (15.0)	181 (75.1)	<0.001

*n=535 clipped and 215 coiled.

†*P* values derived from Fisher exact test for dichotomous and categorical variables and the Wilcoxon rank-sum test for others.

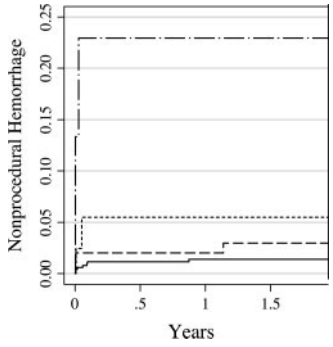

Figure. Kaplan–Meier survival curves of nonprocedural rerupture after various degrees of aneurysm occlusion: complete (solid line), small residual neck (long dash), residual neck (dash), and incomplete occlusion (dot-dash). The analysis was censored at time of first retreatment or nonprocedural rerupture. There were no reruptures after year 2. Rerupture was more frequent in those with incomplete occlusion, with a steady increase in rates in those with less completely occluded aneurysms ($P<0.0001$ for trend by log-rank test).

Methods

The CARAT study was designed to directly compare rerupture rates after subarachnoid hemorrhage in unselected patients treated initially with coil embolization and surgical clipping. The methods of the study have been previously detailed.[1] Briefly, in an ambidirectional cohort design, all patients treated at 9 US hospitals from 1996 to 1998 were followed for up to 9 years. All study procedures were approved by human subjects review boards at each participating institution.

Investigators at 9 US hospitals that treated >30 patients per year with subarachnoid hemorrhage were asked to participate and all agreed. All patients discharged 1996 to 1998 with a primary diagnosis of subarachnoid hemorrhage were identified by a medical record search of hospital administrative databases, and detailed medical records were reviewed. Patients were included if subarachnoid hemorrhage was due to rupture of a saccular intracranial aneurysm and a coil or clip was deployed in an attempt to treat the index aneurysm. Patients were excluded if they were younger than 18 years at follow-up; an intracranial arteriovenous malformation or fistula was present; vessel occlusion was used to treat the aneurysm; an endovascular balloon was used for embolization; or, the patient did not have a US Social Security number. For this analysis, we also excluded those without information on degree of aneurysm occlusion after treatment (n=9).

Information about the patient, the index ruptured aneurysms, any unruptured aneurysms, and details of the procedure were abstracted from medical records. Any aneurysm considered a possible source of the initial subarachnoid hemorrhage and treated during the first procedure was defined as an index aneurysm, so some patients had >1 index aneurysm. Quality was monitored by comparing data with centralized abstraction of the first 5 medical records and of a random sample of 5% of subsequent records.

Degree of aneurysm occlusion after treatment was abstracted from procedural reports. For coiled patients, postprocedural angiography was the source of this information. For clipped patients, angiography was used when available; otherwise, the operative report was used. Percentage occlusion was recorded directly when reported by the treating practitioner. After review of the subgroup of cases in which both percentage occlusion and less precise categorization was reported, the following scheme was used to convert descriptive terms to categories of occlusion: complete occlusion, 100%; small residual neck, 91% to 99%; residual neck, 70% to 90%; partial occlusion (residual aneurysm), 1% to 69%; and not occluded, 0%. Data from any subsequent treatments of the index aneurysm were abstracted similarly.

Table 2. Nonprocedural Rerupture From the Index Aneurysm by Degree of Occlusion*

	Overall					Coiling					Clipping				
	n	Person-Years	Hemorrhages, n (%)	Rate/100 Person-Years	*P*	n	Person-Years	Hemorrhages, n (%)	Rate/100 Person-Years	*P*	n	Person-Years	Hemorrhages, n (%)	Rate/100 Person-Years	*P*
Overall	1001	3453	19 (1.9)	0.6		295	788	10 (3.4)	1.3		706	2645	9 (1.3)	0.3	
Degree of occlusion					<0.0001					<0.0001					0.01
Complete (100%)	760	2831	8 (1.1)	0.3		114	358	2 (1.8)	0.6		646	2472	6 (0.9)	0.2	
Small residual neck (91%–99%)	173	503	5 (2.9)	1.0		128	363	3 (2.3)	0.8		45	140	2 (4.4)	1.4	
Residual neck (70%–90%)	51	67	3 (5.9)	4.5		41	46	2 (4.9)	4.3		10	21	1 (10.0)	4.8	
Partial (<70%)	17	32	3 (17.6)	9.4		12	20	3 (25.0)	15.0		5	12	0 (0.0)	0.0	

*Based on Kaplan–Meier analysis and the log-rank test with censoring at time of rupture, retreatment, or loss to follow-up.

A variety of public resources were used to locate patients, including the US Social Security Death Index, hospital records, and national search services. Postal questionnaires and telephone interviews of all living patients were designed to identify any symptoms or hospital visits suggesting recurrent subarachnoid hemorrhage. Medical records were gathered when there was any suggestion of subarachnoid hemorrhage, either from patient information or from initial review of the medical records. Masked records were subsequently reviewed independently by members of an adjudication panel composed of 1 neurologist, 1 neurosurgeon, and 1 neurointerventionalist, who were asked to determine whether, more likely than not, the treated index aneurysm reruptured. Agreement of at least 2 of 3 reviewers was required to classify an event as a rerupture.

Statistical Analysis

Characteristics of patients with and without complete index aneurysm occlusion were compared first using the Wilcoxon rank-sum test for continuous and ordinal data and Fisher exact test for dichotomous variables. Kaplan–Meier survival analysis with log-rank tests was used to compare rates of rerupture with censoring at the time of first retreatment. We evaluated age, gender, race, treatment type (coiling versus clipping), medical history, aneurysm size, aneurysm location (anterior cerebral, internal carotid, middle cerebral, posterior circulation), and percentage occlusion of the aneurysm post-treatment as potential predictors of nonprocedural rerupture after aneurysm treatment. These characteristics were evaluated individually in univariate Cox proportional-hazards models, and all variables associated with rehemorrhage ($P<0.20$) were included in a multivariable model. The assumption of proportional hazards was confirmed by testing Schoenfeld residuals. Follow-up was censored at first nonprocedural rerupture, death, or first retreatment. Hemorrhages during initial or follow-up treatment were not considered reruptures. Statistical analyses were performed with SAS (version 8e, SAS Institute) and Stata (version 8).

Results

Overall, index aneurysms were completely occluded after the first intervention in 760 of 1001 included patients (75.9%), 173 (17.3%) were 91% to 99% occluded, 51 (5.1%) were 70% to 90% occluded, and 17 (1.7%) were <70% occluded. Rates of total occlusion were greater in patients treated with clipping (646 of 706, 92%) than with coiling (114 of 295, 39%; $P<0.0001$). Patients with complete aneurysm occlusion were younger, less likely to have chronic obstructive pulmonary disease, and less likely to have posterior circulation aneurysms compared with those with partial aneurysm occlusion (Table 1).

During a mean of 3.6 years follow-up (median 4.4 years, range 0 to 9.6 years), there were 19 nonprocedural reruptures (overall risk ignoring loss to follow-up, 1.9%). The median time to rerupture was 3 days (range 1 day to 1.1 year). In Kaplan–Meier analysis, the risk of rupture was 2.2% in the first year, 0.2% in the second year, and 0% thereafter. Rerupture resulted in death within 1 month in 58% of reruptures.

The degree of aneurysm occlusion after treatment was strongly associated with risk of rerupture (cumulative risk: 1.1% for complete occlusion, 2.9% for 91% to 99% occlusion, 5.9% for 70% to 90%, 17.6% for <70%; $P<0.0001$ by log-rank test; Figure and Table 2). The association persisted with censoring at time of retreatment and in a multivariable model including all potential predictors identified in univariate analysis ($P<0.001$; Table 3). Overall, 17 of 19 reruptures occurred in the first month after treatment, so early reruptures accounted for differences by degree of occlusion. Among those with rerupture, degree of aneurysm occlusion was not associated with risk of death ($P=0.22$).

Risk of rerupture tended to be greater after coil embolization compared with surgical clipping in univariate analysis (cumulative hazard 3.4% versus 1.3%; $P=0.09$), and this difference was significant after censoring at retreatment (hazard ratio, 2.91; 95% CI, 1.18 to 7.16; $P=0.02$). However, the difference did not persist after adjustment for degree of aneurysm occlusion and other potential confounders (hazard ratio, 1.09; 95% CI, 0.32 to 3.69; $P=0.89$). A history of peripheral vascular disease was the only other patient or aneurysm characteristic that independently predicted rerupture (Table 3).

There were no reruptures after retreatment. The association between degree of aneurysm occlusion remained a strong predictor of risk of rerupture in an analysis without censoring at time of retreatment ($P<0.001$). There was no evidence that attempting more complete aneurysm occlusion was associated with a greater risk of complications in the index procedure. Specifically, among those treated with clipping, there was no association with degree of occlusion and either perioperative disability/mortality (defined as a worsening in Rankin score of 2 or more points; $P=0.31$) or intraprocedural rupture ($P=0.77$). For those treated with coiling results of degree of occlusion and risk of intraprocedural rupture were similar ($P=0.38$); however, there was an insignificant trend toward greater risk of new disability with greater degrees of occlusion achieved during the index treatment ($P=0.07$).

Discussion

In a sample of centers that treat a large number of intracranial aneurysms, we found that early rerupture was

Table 3. Predictors of Nonprocedural Rerupture

	Unadjusted			Adjusted		
	HR	(95% CI)	*P**	HR	(95% CI)	*P**
Age, per decade	1.00	(0.73–1.38)	0.98			
Women	0.98	(0.37–2.57)	0.96			
Race/ethnicity						
Non-Hispanic	ref					
Black	2.36	(0.64–8.74)	0.20	3.02	(0.78–11.7)	0.11
Hispanic	0.89	(0.11–7.05)	0.93	1.10	(0.14–8.96)	0.93
Asian	3.46	(0.94–12.8)	0.063	2.67	(0.62–11.5)	0.19
Others and unknown	1.70	(0.46–6.29)	0.42	1.94	(0.48–7.87)	0.35
Hypertension	0.88	(0.36–2.20)	0.79			
Diabetes†	undefined		0.62			
Chronic obstructive pulmonary disease	1.55	(0.36–6.71)	0.56			
Coronary artery disease	1.77	(0.52–6.08)	0.36			
Current smoking	1.28	(0.52–3.16)	0.59			
Hyperlipidemia	0.72	(0.10–5.36)	0.75			
History of ischemic stroke	3.71	(0.86–16.1)	0.080	1.70	(0.33–8.77)	0.53
History of peripheral vascular disease	5.51	(1.27–23.9)	0.022	5.54	(1.14–26.9)	0.034
Family history of intracranial aneurysm	0.92	(0.12–6.97)	0.94			
Hunt Hess grade‡	1.61	(1.05–2.45)	0.028	1.81	(0.79–4.15)	0.16
Rankin score, prehemorrhage‡	1.12	(0.70–1.80)	0.64			
Rankin score, on presentation‡	1.35	(0.95–1.91)	0.094	0.81	(0.40–1.62)	0.55
Aneurysm size						
0–5 mm	ref					
>5–10 mm	0.79	(0.30–2.12)	0.65			
>10 mm	0.45	(0.10–2.12)	0.32			
Aneurysm location						
Anterior cerebral artery	ref			ref		
Internal carotid artery	0.14	(0.02–1.18)	0.071	0.14	(0.02–1.19)	0.072
Middle cerebral artery	1.31	(0.38–4.47)	0.67	1.33	(0.36–4.88)	0.67
Posterior circulation	1.38	(0.48–3.94)	0.55	1.25	(0.40–3.93)	0.71
Aneurysm coiled	2.91	(1.18–7.16)	0.020	1.09	(0.32–3.69)	0.89
Degree of aneurysm occlusion			<0.001§			<0.001§
Complete (100%)	ref			ref		
Small residual neck (91%–99%)	2.94	(0.96–9.02)	0.17	2.82	(0.73–10.9)	0.13
Residual neck (70%–90%)	6.89	(1.82–26.1)	0.004	5.04	(1.04–24.4)	0.045
Partial (<70%)	21.7	(5.74–82.2)	<0.001	12.8	(2.55–64.3)	0.002

**P* values derived from Fisher exact test for dichotomous and categorical variables and the Wilcoxon rank-sum test for others.
†No patient with diabetes experienced rerupture.
‡Per point.
§For trend.

an infrequent but important early complication of treatment, particularly among those treated with coil embolization. Incomplete occlusion of the aneurysm was a strong predictor of risk of rerupture and appeared to account for the difference in risk between clipped and coiled patients. Half of reruptures occurred during the first 3 days after treatment.

There has been debate about the necessity of achieving complete aneurysm occlusion.[9,11] Most hemorrhages after aneurysm treatment reported in the literature have occurred in incompletely occluded aneurysms, but methods have been variable and the studies have been too small to evaluate the association between degree of occlusion and risk of rerupture.[9] Also, there have been several reports of reruptures in aneurysms that have been completely occluded by surgery or endovascular therapy.[7,12,13] Our study demonstrates that the risk of rerupture is significantly lower after complete aneurysm occlusion and supports attempts to achieve this result. We found that the risk of rupture in aneurysms that were <70% occluded was 24.5% in the first year, similar to rerupture rates in prior studies of untreated ruptured aneurysms,[14] with intermediate rates

of rerupture among those more completely occluded. Thus, a partially treated aneurysm is still at substantial risk of early rerupture, and attempts to lower this risk with early retreatment are probably justified. We did not find evidence to suggest that attempting complete occlusion was associated with increased procedural risk, though there was a trend in patients treated with coiling; further studies on this issue are required.

Complete aneurysm occlusion after initial treatment did not guarantee that rerupture would not occur, though the risk of rerupture was only 1.1% in this group with all events occurring during the first year. However, many patients underwent retreatment so rerupture may have been more common if these aneurysms were not followed. Given the non-negligible risk of rerupture, follow-up imaging in all patients with treated aneurysms may be justified, particularly during the first year after initial treatment. Reported risks of retreatment have been very low, so re-intervention to achieve complete occlusion is probably justified.[15] The risk of rerupture and the inconvenience and risk of retreatment should be considered when consenting patients for treatment.

Eighteen of the 19 reruptures in our study occurred during the first year after treatment, with half occurring during the first 3 days. After 1 year, the annual risk of rerupture was 0.11% in patients treated with coil embolization, and there were no reruptures among clipped patients.[1] Results from ISAT were similar, with a 1.7% risk of rerupture in the first year and 0.14% per year thereafter (0.21% per year for those treated with coiling and 0.03% per year for those treated with clipping).[2,3] The consequences of early rerupture were incorporated into the primary 1-year outcome of the ISAT trial, so only long-term risks are relevant to the durability of the reported outcome advantage of coil embolization. Nonetheless, given the risks of rerupture in the first year in both studies, attempts to reduce the risk of rupture with new devices, such as stents and coated coils, appear to be justified.[16–20]

The most obvious limitation of our study is the lack of standardization in assessment of degree of aneurysm occlusion. Although angiography was routine immediately after coil embolization, it was performed only in a subset of patients after clipping, and degree of occlusion was derived from operative reports in these instances. The accuracy of such reports, particularly given the various methods used to gauge degree of occlusion, is unknown. Nonetheless, we found that these estimates of degree of occlusion were highly predictive of risk of rerupture, and the true underlying association would only be expected to be stronger because noise in the determination of degree of occlusion would reduce the strength of the apparent association. Thus, the primary finding of an association between incomplete aneurysm occlusion and risk of rerupture remains valid. Further studies that included source-imaging could also identify other factors that predict rerupture, such as flow direction. In addition, the determination that a rerupture occurred was based on review of medical records, and these were incomplete in some instances. However, records were reviewed and adjudicated by 3 physicians blinded to degree of occlusion after the original treatment, so this should not have introduced systematic bias.

Though this was a large study, the actual number of patients with rerupture was small, thus limiting our power. This may have impacted our ability to identify other factors associated with rerupture, including larger aneurysm size, which has been associated with risk of rerupture before treatment[21] and also with the likelihood of achieving complete aneurysm occlusion with coil embolization.[22–25] On the other hand, we evaluated multiple factors as potential confounders, so the association of aneurysm rerupture with peripheral vascular disease could have been due to chance and requires independent confirmation.

Appendix

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Disclosures

None.

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