

From the Southern Association for Vascular Surgery

Endovascular aneurysm repair at 5 years: does aneurysm diameter predict outcome?

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Objective: The appropriate size threshold for endovascular repair of small abdominal aortic aneurysms (AAA) is unclear. We studied the outcome of endovascular aneurysm repair (EVAR) as a function of preoperative aneurysm diameter to determine the relationship between aneurysm size and long-term outcome of endovascular repair.

Methods: We reviewed the results of 923 patients treated in a prospective, multicenter clinical trial of EVAR. Small aneurysms were defined according to two size thresholds of 5.5 cm and 5.0 cm. Two-way analysis was used to compare patients with small aneurysms (<5.5 cm, n = 441) to patients with large aneurysms (≥5.5 cm, n = 482). An ordered three-way analysis was used to compare patients with small AAA (<5.0 cm, n = 145), medium AAA (5.0 to 5.9 cm, n = 461), and large AAA (≥6.0 cm, n = 317). The primary outcome measures of rupture, AAA-related death, surgical conversion, secondary intervention, and survival were compared using Kaplan-Meier estimates at 5 years.

Results: Median aneurysm size was 5.5 cm. The two-way comparison showed that 5 years after EVAR, patients with small aneurysms (<5.5 cm) had a lower AAA-related death rate (1% vs 6%, $P = .006$), a higher survival rate (69% vs 57%, $P = .0002$), and a lower secondary intervention rate (25% vs 32%, $P = .03$) than patients with large aneurysms (≥5.5 cm). Three-way analysis revealed that patients with small AAAs (<5.0 cm) were younger ($P < .0001$) and were more likely to have a family history of aneurysm ($P < .05$), prior coronary intervention ($P = .003$), and peripheral occlusive disease ($P = .008$) than patients with larger AAAs. Patients with smaller AAAs also had more favorable aortic neck anatomy ($P < .004$). Patients with large AAAs were older ($P < .0001$), had higher operative risk ($P = .01$), and were more likely to have chronic obstructive pulmonary disease ($P = .005$), obesity ($P = .03$), and congestive heart failure ($P = .004$). At 5 years, patients with small AAAs had better outcomes, with 100% freedom from rupture vs 97% for medium AAAs and 93% for large AAAs ($P = .02$), 99% freedom from AAA-related death vs 97% for medium AAAs and 92% for large AAAs ($P = .02$) and 98% freedom from conversion vs 92% for medium AAAs and 89% for large AAAs ($P = .01$). Survival was significantly improved in small (69%) and medium AAAs (68%) compared to large AAAs (51%, $P < .0001$). Multivariate Cox proportional hazards modeling revealed that aneurysm size was a significant independent predictor of rupture ($P = .04$; hazard ratio [HR], 2.195), AAA-related death ($P = .03$; HR, 2.007), surgical conversion ($P = .007$; HR, 1.827), and survival ($P = .001$; HR, 1.351). There were no significant differences in secondary intervention, endoleak, or migration rates between small, medium, and large AAAs.

Conclusions: Preoperative aneurysm size is an important determinant of long-term outcome following endovascular repair. Patients with small AAAs (<5.0 cm) are more favorable candidates for EVAR and have the best long-term outcomes, with 99% freedom from AAA death at 5 years. Patients with large AAAs (≥6.0 cm) have shorter life expectancy and have a higher risk of rupture, surgical conversion, and aneurysm-related death following EVAR compared to patients with smaller aneurysms. Nonetheless, 92% of patients with large AAAs are protected from AAA-related death at 5 years. Patients with AAAs of intermediate size (5 to 6 cm) represent most of the patients treated with EVAR and have a 97% freedom from AAA-related death at 5 years. (*J Vasc Surg* 2006;44:920-30.)

Aneurysm size is the primary determinant of the risk of aneurysm rupture and is an important predictor of long-term survival in patients with abdominal aortic aneurysms (AAAs).¹ The differentiation between small and large aortic

aneurysms is usually a threshold diameter of 5.5 cm. Aneurysms <5.5 cm in diameter are considered to be small, whereas those >5.5 cm are considered to be large. A number of prospective randomized clinical trials of both open and endovascular aneurysm treatment have used this threshold definition, and different treatment strategies have been proposed for small and large aneurysms.²⁻⁸ Yet, all clinical trials of endovascular aneurysm repair (EVAR) include patients with both small and large aneurysms, with most aneurysms sized 5 to 6 cm. The mean diameter of aneurysms treated in prospective clinical trials leading to US Food and Drug Administration (FDA) endograft device approval was 5.6 cm.⁹

Although it is recognized that patients with small aneurysms have a better early and late outcome after EVAR than patients with large aneurysms,¹⁰⁻¹³ the precise relationship between aneurysm size and outcome after EVAR is

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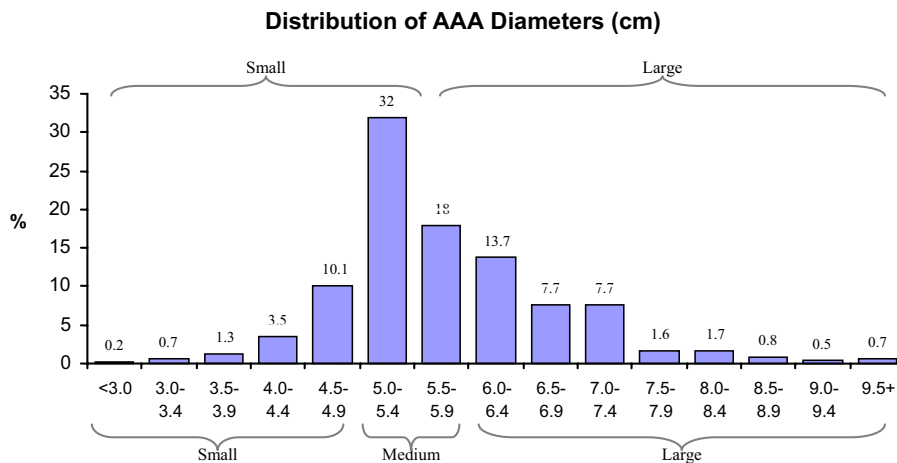


Fig 1. Distribution of abdominal aortic aneurysms (AAA) according to maximum preoperative diameter.

unclear. The purpose of this investigation was to better define the relationship between preoperative aortic aneurysm diameter and long-term outcome after EVAR. We differentiated between small and large aneurysms by using both the usual 5.5-cm threshold diameter and also by segmenting the population of patients treated into small (<5.0 cm), medium (5.0 to 5.9 cm), and large (≥6.0 cm) aortic aneurysms.

METHODS

We reviewed the early and long-term results of 923 patients treated in the prospective, multicenter investigational device exemption (IDE) clinical trial of EVAR using the AneuRx stent graft (Medtronic, Minneapolis, Minn). Results of the entire 1193-patient cohort have been previously reported.^{14,15} These reports include all patients treated during the course of the clinical trial, including off-protocol/emergent-use patients and those treated with early device designs (stiff modular bifurcation, pre-RPM fabric) that are not in clinical use. In this study, we included only patients treated with the commercially available device (flexible bifurcation module, RPM fabric).

Patients were treated from 1998 to 1999 and followed up with periodic clinical examination and computed tomographic (CT) scan or other imaging for a minimum of 5 years as required by the FDA as a condition of device approval. The 19 clinical sites that participated in the clinical trial were externally monitored, and data were entered into the New England Research Institute (NERI) data base.¹⁶

Baseline aneurysm diameter was defined as the maximum transverse aneurysm diameter as measured on the preprocedure CT scan. Median preoperative aneurysm size was 5.5 cm, and a histogram of aneurysm sizes is shown in Fig 1. Because there was no clear separation between small and large aneurysms, we considered the relationship between aneurysm size and outcome in two ways:

1. We used the customary threshold diameter of 5.5 cm to compare patients with small aneurysms (≤5.4 cm) with

patients with large aneurysms (≥5.5 cm) by using a two-way comparison.

2. We compared patients with small AAA (<5.0 cm), medium AAA (5.0 to 5.9 cm), and large AAA (≥6.0 cm) by using a three-way comparison.

Baseline characteristics were evaluated for each of the three groups (small, medium, large) and included age, gender, aneurysm neck diameter, neck length, and other risk factors such as American Society of Anesthesiologists (ASA) grade, family history of aneurysm disease, myocardial infarction, angina, obesity, hypertension, chronic renal failure, previous abdominal surgery, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), prior coronary intervention, prior stroke, peripheral occlusive disease, diabetes, smoking, and cancer.

Five long-term primary outcome measures were evaluated using Kaplan-Meier analysis and included aneurysm rupture (perioperative and late), aneurysm-related death (perioperative and late), surgical conversion (elective and emergent), secondary intervention (excluding surgical conversion), and survival (all-cause mortality). Secondary outcome measures (endoleak, stent-graft migration, and AAA enlargement) were also evaluated and compared across the three groups.

Statistical analysis. Statistical analyses were performed using SAS 9.1 (SAS Inc, Cary, NC). Baseline descriptive statistics for each group are expressed as means and standard deviations for continuous outcomes and percentages for binary or ordered factors. Differences among the three groups for baseline factors were determined using the Jonckheere-Terpstra test. The null hypothesis that all three groups were equal was tested against the one-sided ordered alternative hypothesis (small ≥ medium ≥ large; or small ≤ medium ≤ large, with at least one strict inequality).

The five outcomes of freedom from rupture, AAA-related death, conversion, secondary intervention, and survival were expressed as Kaplan-Meier estimates with standard errors. Difference among the three groups with

Table I. Patient characteristics*

	<i>Small AAA</i> <i><5.0 cm (%)</i>	<i>Medium AAA</i> <i>5.0-5.9 cm (%)</i>	<i>Large AAA</i> <i>≥6.0 cm (%)</i>	P
Age	71.3 ± 7.1	73.4 ± 7.6	74.6 ± 8.6	<.0001
Gender (M:F)	90:10:00	88:12:00	88:12:00	NS
ASA Grade				0.01
I	0	0.4	0.3	
II	10	7	4	
III	61	65	60	
IV	28	28	34	
V	1	0.2	1	
Family AAA history	11	9	7	.05
Myocardial infarction	34	38	38	NS
Angina	20	17	18	NS
Obesity	12	17	20	.03
Hypertension	65	66	65	NS
Chronic renal failure	2	3	3	NS
Previous procedure				
Abdominal surgery	33	23	23	.03
Coronary intervention	48	47	37	.003
COPD	25	29	36	.005
CHF	8	9	14	.004
Prior stroke	13	11	10	NS
POD	34	26	22	.008
Diabetes	12	12	13	NS
Smoking	82	83	85	NS
Cancer	28	22	23	NS
Neck diameter (mm)	21.1 ± 2.3	22.4 ± 2.4	22.5 ± 2.3	<.0001
Neck length (mm)	29.6 ± 13.2	28.0 ± 12.2	26.8 ± 12.9	.004

AAA, Abdominal aortic aneurysm; COPD, chronic obstructive pulmonary disease; CHF, congestive heart failure; POD, peripheral occlusive disease.

*Ordered data are expressed as percentages; continuous data are expressed as means ± SD.

respect to these five outcomes was determined using the ordered log-rank test. The null hypothesis that the results for all three groups are equal was tested against the ordered alternative hypothesis.

To consider the effect of influential baseline covariates that were out of balance between the three groups, multivariate Cox proportional hazard models were created for outcomes found to be statistically significantly different across the three groups. Differences between the two groups (small AAAs vs large AAAs) were assessed for significance using χ^2 for binary factors, Wilcoxon two-sample rank test for ASA grade, or the *t* test for continuous factors. The five long-term outcomes were stratified into small AAAs vs large AAAs and were expressed as Kaplan-Meier estimates with standard errors and compared using the log-rank test. Statistical significance was defined as $P < .05$.

RESULTS

Aneurysm size distribution. The distribution of preoperative aneurysm diameters among the 923 patients included in this study is shown in Fig 1. Median aneurysm size was 5.5 cm (mean, 5.7 ± 1.5 cm). Among the 923 patients, 441 (48%) had small aneurysms and 482 (52%) had large aneurysms in the two-group analysis. For the three-way analysis, 145 patients (16%) had small aneurysms, 461 (50%) had medium aneurysms, and 317 (34%) had large aneurysms.

Patient characteristics. Baseline patient characteristics for the three-group comparison of aneurysm sizes are

summarized in Table I. Compared with patients with larger AAAs, patients with small AAAs were younger ($P < .0001$), had more peripheral occlusive disease ($P = .008$), and were more likely to have a family history of aneurysm ($P = .05$). They were also a better operative risk (lower ASA grade) ($P = .01$) and were more likely to have had coronary intervention before aneurysm repair. Patients with larger AAAs were more likely to have COPD ($P = .005$), CHF ($P = .004$), and obesity ($P = .03$).

Baseline aortic neck morphology. Patients with small aneurysms had more favorable preoperative aortic neck anatomy for endovascular repair. They had smaller aortic neck diameters ($P < .0001$) and greater aortic neck lengths compared with patients with larger aneurysms (Table I).

Small vs large aneurysms (two-way comparison). Primary end-point analyses of small (<5.5 cm) compared with large (≥ 5.5 cm) aneurysms are summarized in Table II. Five years after EVAR, patients with small aneurysms were less likely to have died of an aneurysm-related event ($P = .006$) or to have required a secondary intervention ($P = .03$), and they had a higher survival rate ($P = .0002$) than patients with large aneurysms. There was no significant difference in risk of rupture or surgical conversion between small and large aneurysms.

Small AAA vs medium AAA vs large AAA (three-way comparison). Three-way primary end-point comparisons using Kaplan-Meier analyses are shown in Figs 2 through 6.

Table II. Two-way comparison of small vs large aneurysms treated with EVAR by Kaplan-Meier analysis at 5 years

Freedom from	Small* (<5.5 cm)	Large* (≥ 5.5 cm)	P
Rupture	98 \pm 1	95 \pm 2	.08
AAA death	99 \pm 1	94 \pm 2	.006
Conversion	94 \pm 1	90 \pm 2	.06
Secondary intervention	75 \pm 3	68 \pm 3	.03
Survival	69 \pm 3	57 \pm 3	.0002

AAA, abdominal aortic aneurysm.

*Data presented are Kaplan-Meier estimate \pm standard error.

Rupture: Freedom from rupture at 5 years was 100% for small AAA, 97% for medium, and 93% for large. These differences were significant by ordered log-rank test ($P = .02$; Fig 2).

Aneurysm-related death: Freedom from AAA-related death at 5 years was 99% for small AAA, 97% for medium, and 92% for large. These differences were significant by ordered log-rank test ($P = .02$; Fig 3).

Surgical conversion: Freedom from surgical conversion at 5 years was 98% for small AAA, 92% for medium, and 89% for large. These differences were significant by ordered log-rank test ($P = .01$; Fig 4.)

Secondary interventions: Freedom from secondary intervention at 5 years was 76% for small AAA, 73% for medium, and 67% for large. These differences were not statistically significant (ordered log-rank test, $P = .09$; Fig 5).

Survival: Survival at 5 years was 89% for small AAA, 68% for medium, and 51% for large. These differences were significant by ordered log-rank test ($P < .0001$; Fig 6).

Multivariate analysis. Cox proportional hazards models revealed that even after adjusting for baseline covariates that were out of balance between the three groups, AAA size remained a significant predictor of rupture ($P = .04$; hazard ratio [HR], 2.195), AAA-related death ($P = .03$; HR, 2.007), surgical conversion ($P = .007$; HR, 1.827), and survival ($P = .001$; HR, 1.351). The results of applying the Cox proportional hazard model for survival are summarized in Table III. This multivariate regression model revealed that in addition to aneurysm size, significant predictors of survival included age ($P < .0001$), surgical risk by ASA grade ($P = .0003$), COPD ($P < .0001$), and peripheral vascular disease ($P = .002$).

Secondary outcome measures. Secondary outcome measures as recorded by the clinical centers are listed in Table IV as rates at each annual follow-up time point. No significant differences were found in endoleak rate or migration rate between small, medium, and large aneurysms over a 4-year period, nor was a significant difference found in aneurysm enlargement rate between small, medium, and large aneurysms through 3 years. At 4 years, however, 19% of large aneurysms were enlarged >5 mm over baseline, a considerably increased rate compared with the 14% in

medium-sized AAA group and 7% in the small-sized AAA group ($P = .05$).

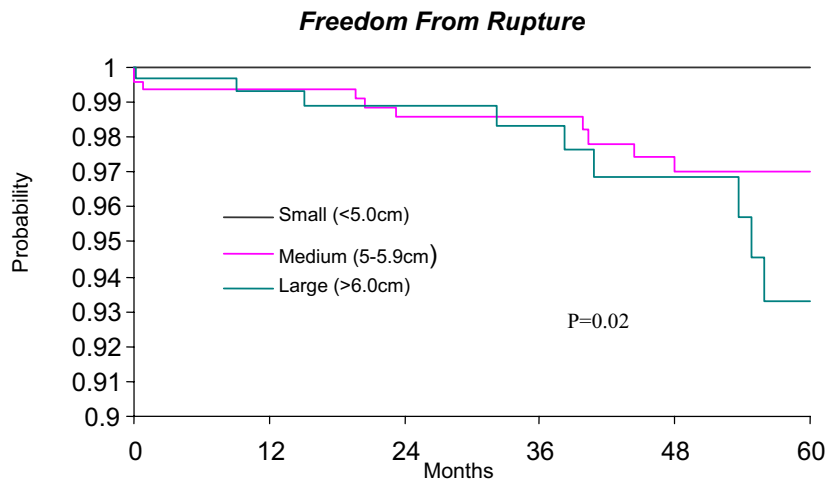
DISCUSSION

A diameter of 5.5 cm is commonly considered to represent the dividing line between small and large aneurysms; however, aneurysm size distribution is approximated by a unimodal normal bell-shaped curve, as shown in Fig 1, rather than by a bimodal distribution curve of small and large aneurysms. Thus, if a diameter of 5.5 cm is used to compare small with large aneurysms, a large number of patients in both groups will have “average-sized” aneurysms, close to the mean. Indeed, the mean aneurysm size treated in this study was 5.7 cm (median, 5.5 cm), and 50% of patients had aneurysms in the diameter range of 5.0 to 5.9 cm. The mean aneurysm diameter reported in the Lifeline Registry of 2664 patients treated in 4 IDE clinical trials leading to FDA device approval was 5.6 ± 1.0 cm.⁹ The largest number of patients treated in our series were in the size range of 5.0 to 5.4 cm. A similar size frequency distribution was noted in The Cleveland Clinic experience,¹⁶ with the largest number of patients having a diameter of 5.0 to 5.5 cm. In the prospective small aneurysm trials,^{3,17} the cohort with this aneurysm size (5.0 to 5.4 cm) had the highest risk of aneurysm rupture and death among patients with small aneurysms randomized to surveillance.^{3,18}

This raises the question of whether aneurysms of 5.0 to 5.4 cm are truly representative of “small aneurysms,” particularly in women, or whether they more closely resemble “medium size” aneurysms. We addressed this issue by defining small aneurysms to be those <5.0 cm in diameter and performing an ordered three-way comparison of small, medium, and large aneurysms. We also performed a two-way analysis using the traditional 5.5-cm threshold to differentiate small from large aneurysms. Using the traditional 5.5-cm threshold of aneurysm size, we found that 48% of our patients had small aneurysms (<5.5 cm). This is similar to the EUROSTAR Registry, where 45% of patients had small aneurysms,¹⁰ and lower than The Cleveland Clinic, where 59% of patients had small aneurysms.¹²

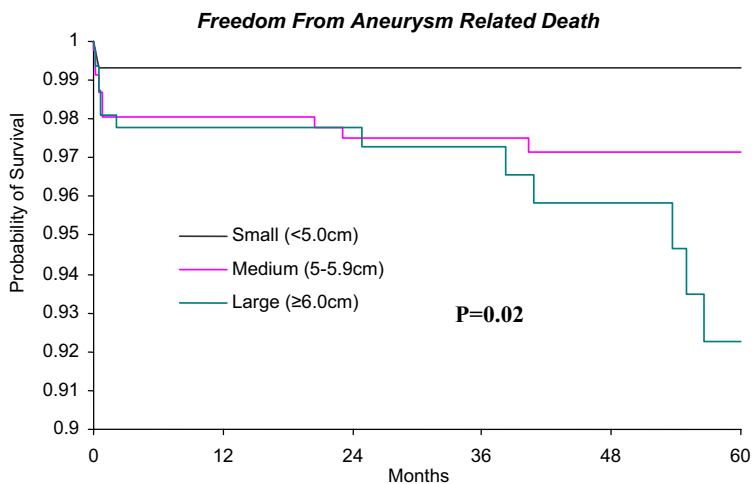
Our two-way analysis of small vs large aneurysms showed that patients with large aneurysms were older (75 years vs 72 years, $P < .0001$), had a higher AAA-related death rate at 5 years (6.4% vs 1.4%, $P = .006$), and had reduced survival at 5 years (57% vs 69%, $P = .0002$) compared with patients with small aneurysms. Patients with large aneurysms were more likely to need a secondary procedure during the 5-year follow-up period (32% vs 25%, $P = .03$). Although there was a trend for increased rupture (5.3% vs 1.8%, $P = .08$) and increased surgical conversion (10.2% vs 5.7%, $P = .06$) in patients with large aneurysms at 5 years, these differences were not statistically significant. Similar findings were reported from the EUROSTAR and The Cleveland Clinic experiences.^{10,12,13}

In our three-way analysis, we used a 5.0-cm threshold for small aneurysms and defined *small AAA* as <5.0 cm, *medium AAA* as 5.0 to 5.9 cm and *large AAA* as ≥ 6.0 cm.



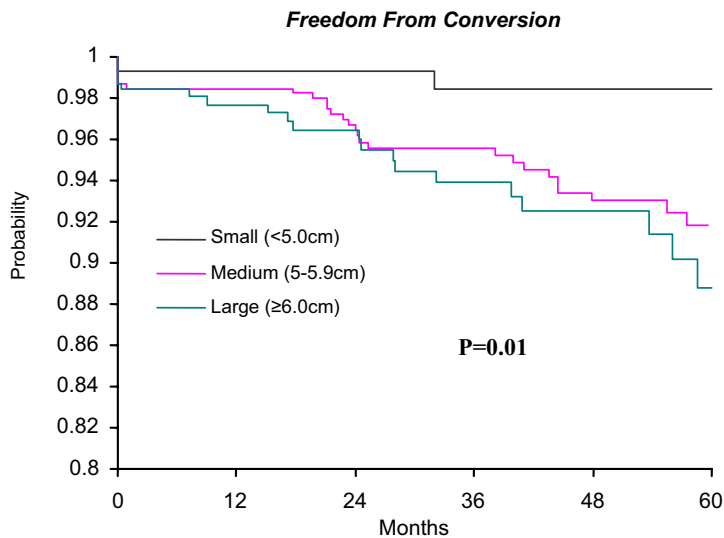
Small (<5.0)	# at Risk	133	115	109	87	54
	%	100	100	100	100	100
Medium (5.0 – 5.9)	# at Risk	410	362	300	229	116
	%	99	99	99	97	97
	+/- std error	0.4	1	1	1	1
Large (≥6.0)	# at Risk	262	205	159	109	45
	%	99	99	98	97	93
	+/- std error	1	1	1	1	2

Fig 2. Aneurysm size and freedom from rupture during 5 years by Kaplan-Meier analysis.



Small (<5.0)	# at Risk	133	115	109	86	54
	%	99	99	99	99	99
	std error	1	1	1	1	1
Medium (5.0 – 5.9)	# at Risk	410	362	300	229	114
	%	98	98	98	97	97
	std error	1	1	1	1	1
Large (≥6.0)	# at Risk	260	205	159	108	45
	%	98	98	97	96	92
	std error	1	1	1	1	2

Fig 3. Aneurysm size and freedom from aneurysm-related death during 5 years by Kaplan-Meier analysis.



Small (<5.0)	# at Risk	133	115	109	86	54
	%	99	99	98	98	98
	std error	1	1	1	1	1
Medium (5.0– 5.9)	# at Risk	409	360	301	229	116
	%	99	97	96	93	92
	std error	1	1	1	1	2
Large (≥6.0)	# at Risk	260	205	159	109	45
	%	98	97	94	93	89
	std error	1	1	2	2	3

Fig 4. Aneurysm size and freedom from conversion during 5 years by Kaplan-Meier analysis.

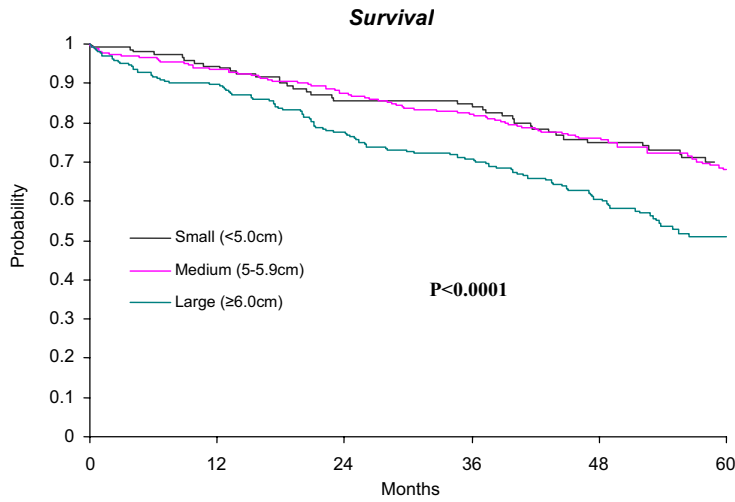
The small AAA group comprised 16%, the medium AAA group comprised 50%, and the large AAA group comprised 34% of the patients treated.

Although our two-way analysis had found that age and COPD were the only significant differences between patients with small and large aneurysms, the three-way analysis suggested that patients with small AAA might represent a different patient population from patients with large AAA, with medium AAA patients having intermediate baseline characteristics. Patients with smaller aneurysms were younger, had more peripheral occlusive disease, and were more likely to have a family history of aneurysm. They also were more likely to have undergone coronary revascularization and were in a lower ASA risk category, which may have contributed to improved survival. Patients with larger aneurysms, on the other hand, were older, had higher preoperative risk classification, and were more likely to have COPD, obesity, and CHF.

Comparison of the Kaplan-Meier curves shows that patients with large AAAs have a significantly shorter life expectancy than those with smaller AAAs. This is consistent with the EUROSTAR finding that EVAR patients with the largest aneurysms had the shortest survival¹⁰ and the findings by Ouriel et al¹² that patients with large aneurysms have diminished survival at 24 months.

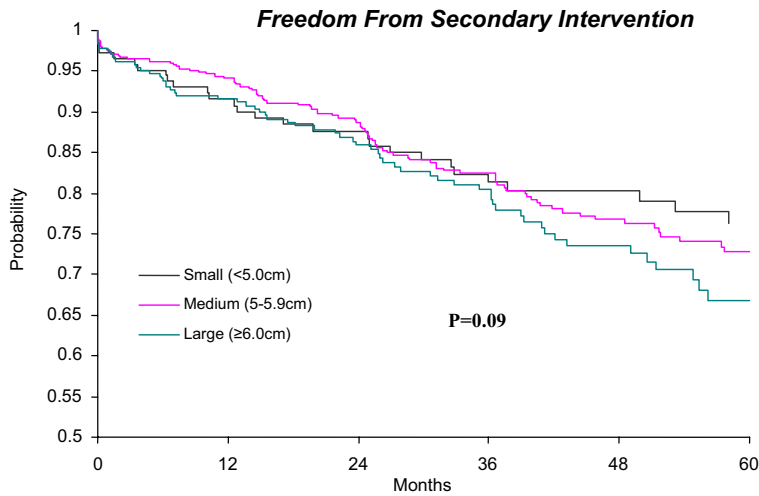
Interestingly, our medium AAA group was very similar to the small AAA group with respect to survival (68% and 69%) but paralleled the large AAA group on the Kaplan-Meier analyses of aneurysm-specific outcome measures such as rupture, aneurysm-related death and surgical conversion (see Figs). Multivariate analysis showed that aneurysm size was a significant independent predictor of survival, but that other factors were also important in predicting survival, including age, surgical risk, COPD, and peripheral occlusive disease. The EUROSTAR analysis similarly showed that increased aneurysm size was a significant predictor of decreased survival along with age, renal dysfunction, and pulmonary disease.¹³

Aneurysm-specific endpoints showed that patients with small AAA had the best outcomes compared with patients with medium and large AAA. There were no aneurysm ruptures among the small AAA patients, and larger aneurysm size was the only significant independent predictor of the risk of rupture. Although the risk of aneurysm rupture in patients with small aneurysms is known to be low, it is not negligible. In a population-based study, Reed et al¹⁹ estimated the annual risk of rupture of 1% for aneurysms sized 4.0 cm to 4.9 cm, with 95% confidence intervals of 0% to 5% per year. Scott et al²⁰ reported an annual rupture rate of 0.7% for aneurysms sized 3.0 to 4.4 cm and an annual



Small (<5.0)	# at Risk	133	115	109	86	54
	%	94	86	85	75	69
	std error	2	3	3	4	4
Medium (5.0 – 5.9)	# at Risk	410	362	300	229	114
	%	93	87	82	76	68
	std error	1	2	2	2	3
Large (≥6.0)	# at Risk	260	205	159	108	45
	%	90	78	71	61	51
	std error	2	3	3	3	4

Fig 5. Aneurysm survival during 5 years by Kaplan-Meier analysis.



Small (<5.0)	# at Risk	121	100	88	67	38
	%	92	88	81	80	76
	std error	2	3	4	4	4
Medium (5.0 – 5.9)	# at Risk	385	318	246	175	85
	%	94	89	83	77	73
	std error	1	2	2	2	3
Large (≥6.0)	# at Risk	239	178	133	85	33
	%	92	86	80	74	67
	std error	2	2	3	3	4

Fig 6. Aneurysm size and freedom from secondary intervention during 5 years by Kaplan-Meier analysis.

Table III. Cox proportional hazards models

Covariate	Survival		Rupture		AAA Death		Conversion	
	P	HR	P	HR	P	HR	P	HR
AAA size*	.001	1.351	.04	2.195	.03	2.007	.007	1.827
Age	<.0001	1.047	.18	1.043	.06	1.052	.18	0.976
ASA grade	.0003	1.475	.86	1.078	.61	1.196	.58	1.153
Family AAA history	.11	0.664	.22	2.181	.54	1.458	.02	2.322
Obesity	.17	0.787	.96	1.036	.84	1.111	.71	0.876
Previous procedures								
Abdominal surgery	.33	0.870	.39	0.579	.90	1.059	.71	1.131
Coronary intervention	.17	1.184	.93	1.042	.54	1.278	.78	0.921
COPD	<.0001	1.839	.98	0.987	.18	1.746	.83	1.073
PVD	.002	1.492	.81	0.871	.05	2.178	.89	1.046

HR, Hazard ratio; AAA, abdominal aortic aneurysm; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease.

*Small (<5.0 cm), medium (5.0-5.9 cm), and large (≥5.5 cm).

Table IV. Secondary end points of endoleak, migration, and enlargement

	Visit	Small*, %	Medium*, %	Large*, %	P
Endoleak	1 year	13 (17/126)	14 (52/379)	16 (36/226)	NS
	2 years	12 (13/109)	16 (54/328)	19 (35/182)	NS
	3 years	10 (10/100)	17 (46/270)	12 (17/139)	NS
	4 years	8 (6/79)	14 (29/213)	11 (10/94)	NS
Migration	1 year	2 (3/125)	2 (8/372)	2 (4/224)	NS
	2 years	4 (4/105)	4 (12/320)	6 (11/178)	NS
	3 years	5 (5/99)	4 (11/270)	6 (9/142)	NS
	4 years	5 (4/79)	6 (12/211)	10 (9/90)	NS
Enlargement	1 year	5 (5/91)	7 (19/273)	10 (17/163)	NS
	2 years	9 (8/86)	8 (18/234)	8 (10/130)	NS
	3 years	5 (4/77)	12 (23/199)	12 (12/101)	NS
	4 years	7 (4/58)	14 (22/152)	19 (12/62)	.05

*Small (<5.0 cm), medium (5.0-5.9 cm), and large (≥5.5 cm).

rupture rate of 1.7% for aneurysms of 4.5 to 4.9 cm. Similar estimates were reported from the UK Small Aneurysm Trial, where the annual risk of rupture was 0.3% for aneurysms <4 cm and 1.5% for aneurysms of 4.0 to 4.9 cm.²¹ Thus, the 5-year risk of rupture in untreated aneurysms <5 cm may exceed 5%.

Our finding of complete protection from aneurysm rupture through a 5-year period after endovascular repair of aneurysms <5.0 cm demonstrates the effectiveness of this form of therapy in patients with small aneurysms. More favorable preoperative aortic neck anatomy in patients with small-sized aneurysm may have been an important factor in this long-term success. Ruptures were confined to patients with large-sized (rupture in 7% of patients at 5 years) and medium-sized aneurysms (rupture in 3% of patients at 5 years) and were consistent with the known increased risk of rupture with increasing aneurysm size.

Factors that may be important in predisposing to rupture, such as endoleak and migration, were no different in patients with small, medium, or large aneurysms. However, aneurysm enlargement after EVAR was significantly more likely in patients with large aneurysms (19% at 4 years) than in patients with smaller aneurysms.

Only one aneurysm-related death occurred among our small AAA patients, and this was a perioperative death in a patient who died of respiratory failure 2 weeks after device implantation. There were no late AAA-related deaths in small AAA patients. Aneurysm-related death rate by Kaplan-Meier analysis at 4 and 5 years in our small AAA (<5.0 cm) group was 0.7% compared with a 3% AAA death rate at 4 years reported for small aneurysms from the EUROSTAR registry, where small aneurysms were defined as 4.0 to 5.4 cm.¹⁰ The AAA death rate at 4 years was 3% for medium sized aneurysms (5.0 to 5.9 cm) and 8% for large aneurysms (≥6.0 cm) in our study ($P = .02$). The 4-year AAA-related death rates for those in the middle size range (5.5 to 6.4 cm) in the EUROSTAR registry was 5% with the highest AAA-related death rate of 12% at 4 years occurring in their largest aneurysm group (≥6.5 cm).¹⁰ Thus, the risk of aneurysm-related death was exceedingly low for patients with aneurysms <5.0 cm.

Patients with aneurysms <5.0 cm were also much less likely to require surgical conversion during a 5-year follow-up period than were patients with larger aneurysms. Only two patients in our small AAA group underwent surgical conversion. One was at the time of the initial procedure owing

to failure to access the aorta through small iliac arteries. The other was an elective surgical conversion at 32 months because of a persisting type II endoleak and aneurysm enlargement.

Kaplan-Meier analysis showed that the risk of surgical conversion at 5 years was 1.6% in the small AAA group compared with 8% for medium and 11% for large aneurysms ($P = .01$). These favorable results may in part be due to more favorable aortic neck morphology in small AAA patients. The rate of surgical conversion for small (4.0 to 5.4 cm) and large (5.5 to 6.4 cm) aneurysms was 7% at 4 years in the EUROSTAR registry, comparable to our 7% conversion rate for both medium AAA and large AAA aneurysms at 4 years. A higher risk of surgical conversion at 4 years was noted in the EUROSTAR registry for patients with the largest aneurysms (14% for aneurysms ≥ 6.5 cm).¹⁰

There were significantly fewer secondary interventional procedures in patients with small aneurysms (< 5.5 cm) than large aneurysms (25% vs 31%, $P = .03$) in our two-way analysis. In the three-way analysis, however, the differences in secondary intervention rate at 5 years among small (24%), medium (27%), and large AAAs (33%, $P = .09$, ordered log-rank test) did not reach statistical significance. Patients with large aneurysms were more likely to have late (4 year) aneurysm enlargement, consistent with the increased risk of late aneurysm rupture.

Thus, defining small aneurysms as < 5.0 cm identified a patient population that had the best long-term outcomes of endovascular repair with no aneurysm ruptures and almost no aneurysm-related deaths. Furthermore, it differentiated a population of aneurysm patients with more favorable preoperative characteristics and lower risk than patients with larger aneurysms. Patients with aneurysms of 5.0 to 5.4 cm represented the largest single aneurysm size cohort, and inclusion of these patients in the small aneurysm group could potentially mask real differences in long-term outcome analysis of patients with small aneurysms, particularly with respect to aneurysm-related outcomes.

Prospective randomized clinical trials of small AAAs have used all-cause mortality (survival) as the primary end point and a diameter threshold of 5.5 cm for defining small aneurysms. Both the UK Small Aneurysm Trial³ and the Aneurysm Detection and Management (ADAM) trial⁴ found no survival advantage for early surgery compared with ultrasound surveillance. In the UK Small Aneurysm Trial, 5-year survival was 71% in the early surgery group and 62% in the surveillance group. This was not statistically different until late follow-up at 9 years, when survival was 53% in the early surgery group and 45% in the surveillance group 45%.²² The use of a 5.0-cm threshold to define small aneurysms and aneurysm-specific end points should be considered in future small aneurysm trials.

Prospective randomized clinical trials comparing endovascular with open surgical repair have been conducted using different aneurysm size inclusion criteria. The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial included patients with aneurysms at least 5.0 cm in diameter,⁷ and the Endovascular Aneurysm Repair (EVAR-1) trial used a 5.5 cm threshold to define large aneurysms.²³

Both studies found a significant reduction in 30-day operative mortality with endovascular repair.^{7,23} However, the early advantage of EVAR in operative mortality was not reflected in improved survival at 2 years²⁴ or at 4 years,⁵ despite a persisting significant reduction in the aneurysm-related mortality rate at 4 years.⁵

The lack of a late survival advantage for endovascular repair has caused some to question its use for patients who are fit for open surgery^{6,23} and others to question the usefulness of all-cause mortality as the primary end point with which to compare aneurysm treatment strategies.²⁵⁻²⁷ Our finding and that of others^{10,28} that patients with the largest aneurysms have the least favorable long-term outcomes suggests the size distribution of aneurysms in a study cohort may be a major determinant of the ultimate outcome. Indeed, preoperative aneurysm size was a significant independent predictor of rupture, aneurysm related death, surgical conversion, and survival in Cox proportional hazard models. Whereas there were other predictors of survival, such as age, surgical risk, and peripheral occlusive disease, preoperative aneurysm size was the only factor that was predictive of the aneurysm-specific end point of rupture, AAA-related death, and conversion. This suggests that the aneurysm size group of 5 to 6 cm may be the most appropriate group to consider for long-term clinical trials evaluating different aneurysm treatment strategies or different endovascular devices. Such a selection criterion would provide access to the largest group of patients undergoing treatment and would exclude the smallest and largest aneurysms, which may distort the results for most patients.

Despite the fact that patients with large aneurysms in this trial had less favorable outcomes than patients with small aneurysms, it should be noted that the outcomes of endovascular repair in patients with aneurysms ≥ 6.0 cm was, nonetheless, very good. Five years after endovascular repair, freedom from aneurysm rupture was 93%, and freedom from AAA related death was 92%, which is considerably better than the expected natural history for large aneurysms.¹ These results are not dissimilar to the results of the EVAR-1 trial of good-risk patients with slightly smaller aneurysms (≥ 5.5 cm) which reported freedom from AAA-related death in 96% of patients 4 years after endovascular repair.⁵ Thus, endovascular repair is a good treatment option for suitable patients with both large and small aneurysms.

CONCLUSIONS

Preoperative aneurysm size is an important determinant of long-term outcome after EVAR. Patients with aneurysms < 5.0 cm tend to be younger, better-risk patients with more favorable anatomy for EVAR. Patients with large aneurysms (≥ 6.0 cm) are older, at higher risk, and have less favorable aortic neck anatomy. Patients with small aneurysms had the most favorable long-term outcomes after EVAR, with no aneurysm ruptures, only one AAA-related death, and two surgical conversions. Large aneurysm patients have the shortest life expectancy and have a higher risk for aneurysm-specific adverse events such as rupture,

surgical conversion, and aneurysm-related death. Nonetheless, EVAR is effective in preventing aneurysm rupture and aneurysm-related death in appropriately selected patients with small, medium, and large aneurysms.

AUTHOR CONTRIBUTIONS

Conception and design: CKZ
Analysis and interpretation: CKZ, TC, DAB, FRA
Data collection: CKZ, FRA, RAW
Writing the article: CKZ
Critical revision of the article: CKZ, DAB, FRA, KO
Final approval of the article: CKZ, TC, DAB, FRA, KO, RAW
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DISCUSSION

Dr Charles Sternbergh, III (New Orleans, LA). We have a great deal of good data on the natural history of small AAA. In the ADAM VA cooperative trial, the rupture rate of AAA between 4.0 and 5.4 cm in the observational group was 0.6% per year. With an operative mortality of 2.1% in the open group, there were *no* differences in long-term patient outcome between observation and

open surgery after 4.9 years. Importantly, the majority of observational patients with AAA of less than 5 cm did *not* go on to require repair in this time interval. Can endografting improve on this rather benign natural history of small AAA? Based on the VA cooperative data, I'm skeptical. But there is no level I evidence directly addressing this controversy. To help definitively answer

this question, Medtronic has recently begun the PIVOTAL trial, which is designed to enroll 1700 patients with AAA of less than 5 cm, randomized to AneuRx treatment or observation.

Dr Zarins and colleagues have demonstrated that when compared with small AAA, patients with large AAA have much poorer long-term outcomes after EVAR. While this is not new information, it bears repeating. It is well known that patients with larger AAA have, on average, more unfavorable aortic neck anatomy. However, when groups are controlled for variable anatomy and other cohort differences, AAA size remains as independent risk factor for poorer outcome. This was first demonstrated from the EUROSTAR database and has been confirmed today.

How can this be explained? My hypothesis is a simple one. If there is late endograft failure in a large AAA, the risk of subsequent rupture is significant. However, if there is endograft failure in a small AAA that already has a negligible risk of rupture, the incidence of aneurysm-related problems is low.

Thus, knowing *why* endografts fail is crucial, especially if they are being used to treat patients with a high risk of rupture. In The Cleveland Clinic report of disparate outcome of small vs large AAAs, there was a fourfold increase in type I endoleaks and a threefold increase in migration in AAA greater than 5.5 cm (Ouriel et al, *J Vasc Surg* 2003;37:1206). The EUROSTAR report demonstrated similar findings (Peppelenbosch et al, *J Vasc Surg* 2004; 39:288-97). It is perplexing, therefore, that in the current study, there were no differences in these outcome measures. This leads me to my first question:

1. How do you explain the significant increase in AAA expansion in the large AAA group compared to the smaller AAA group, if there were no differences in endoleak or migration rates? Is it simply a coincidence that a greater percentage of these patients ultimately had rupture of their AAA?
2. At this meeting 3 years ago, you reported an 18.8% risk of endograft migration at 3 years in this same cohort of AneuRx patients, but in the current report, 3-year migration is reported at about 5%. Please explain this discrepancy.
3. Migration is a time-dependent variable and must be reported with Kaplan-Meier life-table analysis. To do otherwise is statistically invalid and misleading. What are the 5-year Kaplan-Meier estimates of freedom from migration in these patient cohorts?
4. In patients with AAA 6 cm or greater, the curve of relative risk of AAA rupture or aneurysm-related death remained fairly flat in the first 4 years of follow-up but increased steeply between the fourth and fifth year, going from approximately 4% to 8%. Based on this disturbing geometric increase in late endograft failure, should these patients have intensified surveillance?

Dr Christopher Zarins. In response to the question of whether endografting can improve on the natural history of small AAA, I would like to remind you that the UK and ADAM small aneurysm trials reported a low risk of rupture in selected, good risk patients who were closely monitored with ultrasound surveillance

every 3–6 months and promptly referred for surgery if the aneurysm enlarged or became symptomatic. Despite this, 1% of the small aneurysms ruptured each year—that is 5% in 5 years. Thus ultrasound surveillance does not appear to have been a successful strategy, particularly when rupture mortality was 90% and when 75% of the surveillance patients ultimately required surgery. In contrast to surveillance of small aneurysms, endovascular repair was very successful in our experience of small aneurysms <5 cm. There were no ruptures over 5 years, only one aneurysm-related death and only two surgical conversions. Clearly the size difference in definition of small aneurysms is a critical factor in this difference and this is one of the major points of this study. Aneurysms 5.5 cm in diameter are average in size, not small.

I agree with Dr. Sternberg's comments regarding large aneurysms. Results are not as good as for small aneurysms and the risk of late failure and rupture is higher. Since large aneurysms are more likely to rupture if they are untreated, late device failures are a greater concern in patients with large aneurysms. We did not note a relationship between endoleak and enlargement in this study, but this does not rule out this possibility. However, greater risk does not mean that patients with large aneurysms should not be treated with EVAR. Despite higher operative risk and less favorable anatomy, early results for large aneurysms are similar to smaller AAAs with differences appearing only after 4 years. The cumulative aneurysm related death rate for large aneurysms at 5 years is still only 8%, which is considerably below the expected mortality from rupture of non-treated large aneurysms.

With regard to migration, there is debate as to whether Kaplan-Meier analysis is the preferred way to report migration since migration is not a fixed endpoint, such as rupture or death, and can start and stop. Kaplan-Meier analysis will give higher estimates of migration and we have reported both Kaplan-Meier estimates as well as migration prevalence rates at specific time points in our previous migration analysis. In this study we focused on primary outcome measures and reported migration, endoleak and enlargement as prevalence rates at each annual follow up time, since all are variable end-points.

Finally, Dr. Sternbergh asked about the increase in relative risk of rupture and aneurysm related death after 4 years in large AAA patients. Further follow up is needed to determine whether this risk will continue to rise, but this finding highlights the importance of life-long image based surveillance of patients with aneurysms >6 cm following endovascular repair. At the same time, the absence of late rupture in patients with small aneurysms raises the question of whether patients with aneurysms <5 cm need less intensive follow up and imaging following successful endovascular repair. Perhaps this is where simple ultrasound surveillance will find a place. These questions deserve further study. Our findings suggest that answers to these questions may be easier to find by differentiation aneurysm size groups into small (<5 cm), medium (5-6 cm) and large (>6 cm).

INVITED COMMENTARY

Mark F. Fillinger, MD, Lebanon, NH

This study demonstrates important differences in outcomes after endovascular aneurysm repair (EVAR) that are associated with aneurysm size. When reading this article, it is important to keep in mind a critical fact: these patients were *selected* for repair at a given aneurysm size. Decisions about aneurysm repair must be made within the context of the natural history of the abdominal aortic aneurysm (AAA), the risk of repair, and the patient's life expectancy. The results indicate that the surgeons in this clinical trial took these factors into account when they selected patients for repair.

Patients with smaller aneurysms in this study were significantly younger, had better operative risk, and had more favorable anat-

omy for EVAR. Their AAAs were likely repaired at a smaller size because their life expectancy suggested potential benefit from "early" repair¹ or they had a higher than typical risk of rupture (eg, female or family history of aneurysm)² or both. It is logical to assume that they had EVAR rather than open repair owing to favorable anatomy for EVAR.

Older patients with more comorbidities might not have been considered candidates for repair at a smaller aneurysm size because they were not ideal candidates for either open repair or EVAR. They underwent repair when the natural history of rupture became worse than the expected results from repair. Less ideal anatomy for