Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: Does size matter? A report from EUROSTAR

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Objectives: **This study was undertaken to determine the effect of the preoperative diameter of abdominal aortic aneurysms on the midterm outcome after endovascular abdominal aneurysm repair (EVAR).**
Method: **The data for 4392 patients who had undergone EVAR were analyzed. Patients were enrolled over 6 years to June 2002 in the EUROSTAR database. Outcomes were compared between three groups defined by the preoperative diameter of the aneurysm: group A (n = 1962), 4.0 to 5.4 cm; group B (n = 1528), 5.5 to 6.4 cm; and group C (n = 902), 6.5 cm or larger. Patient characteristics, details of aortoiliac anatomy, operative procedures, old or current device generation, and postoperative complications in the three patient groups were compared. Outcome events included aneurysm-related death, unrelated death, conversion, and post-EVAR rupture of the aneurysm. Life table analysis and log-rank tests were used to compare outcome in the three study groups. Multivariate Cox models were used to determine whether baseline and follow-up variables were independently associated with adverse outcome events.**
Results: **Patients in group C were significantly older than patients in groups A and B (73 years vs 70 and 72 years, respectively; $P = .003$ – $P < .0001$ for different group comparisons), and more frequently were at higher operative risk (American Society of Anesthesiologists classification ≥3; 63% vs 48% and 54%; $P = .0002$–$P < .0001$). Device-related (type I) endoleaks were more frequently observed at early postoperative arteriography in group C compared with groups A and B (9.9% vs 3.7% and 6.8%; $P = .01$–$P < .0001$). Postoperatively systemic complications were more frequently present in group C (17.4% vs 12.0% in group A and 12.6% in group B; $P < .0001$ and .001). The first-month mortality was approximately twice as high in group C compared with the other groups combined (4.1% vs 2.1%; $P < .0001$). Late rupture was most frequent in group C. Follow-up results at midterm were less favorable in groups C and B compared with group A (freedom from rupture, 90%, 98%, and 98% at 4 years in groups C, B, and A, respectively; $P < .0001$ for group C vs groups A and B). Aneurysm-related death was highest in group C (88% freedom at 4 years, compared with 95% in group B and 97% in A; $P = .001$ and $P < .0001$, respectively; group B vs A, $P = .004$). The annual rate of aneurysm-related death in group C was 1% in the first 3 years, but accelerated to 8.0% in the fourth year. Incidence of unrelated death also was higher in groups C and B than in group A (76% and 82% freedom at 4 years vs 87%; $P < .0001$ for both comparisons). Ratio of aneurysm-related to unrelated death was 23%, 21%, and 50% in groups A, B, and C, respectively. Cox models demonstrated that the correlation between large aneurysms (group C) and all assessed outcome events was independent and highly significant. Older generation devices had an independent association with aneurysm-related and unrelated deaths ($P = .02$ and $P = .04$, respectively). However, this correlation was less strong than large aneurysm diameter ($P = .0001$ and $P = .0009$, respectively).**
Conclusions: **The midterm outcome of large aneurysms after EVAR was associated with increased rates of aneurysm-related death, unrelated death, and rupture. Reports of EVAR should stratify their outcomes according to the diameter of the aneurysm. Large aneurysms need a more rigorous post-EVAR surveillance schedule than do smaller aneurysms. In small aneurysms EVAR was associated with excellent outcome. This finding may justify reappraisal of currently accepted management strategies. (J Vasc Surg 2004;39:288-97.)**

Endovascular aneurysm repair (EVAR) has gained an increasingly important role in clinical management of abdominal aortic aneurysms since its introduction in the early 1990s. The availability of EVAR may change hitherto accepted surgical decision-making for abdominal aortic aneurysm (AAA) repair. In conventional surgical AAA repair the risks of the procedure are considerable, and must be considered against the benefits of preventing death from rupture. Similarly, differences in early and late outcome after EVAR must be balanced against the natural history of untreated AAA. Since the publication by Szilagyi et al,[1] size of the aneurysm has been recognized as the predominant risk factor for death from rupture, with low risk associated

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with small aneurysms, intermediate risk with medium-sized aneurysms, and dramatically increased risk with large aneurysms.[1-6] The definition of a small aneurysm has changed somewhat after recently published results of two trials that compared the outcome of an initially conservative approach with primary open repair.[7,8] The threshold diameter for a small aneurysm in both trials was 5.5 cm, as measured on the largest section of the aneurysm. Randomized comparative studies for aneurysms with diameter larger than 5.5 cm are generally considered unethical, on the basis of indirect but compelling evidence of high risk for rupture from natural history studies in patients unfit for open repair or refusing treatment.[5,6,9,10]

A large number of cohort studies of open AAA repair, published over two decades, have identified several patient-related variables that determine either excellent or less optimal operative or long-term outcomes of treatment, with age, female gender, comorbid conditions, and required level of aortic clamping the most frequently cited risk factors.[11-13] However, almost all series on open AAA repair have neglected to assess the achieved modification of the risk for rupture according to patient cohorts stratified according to aneurysm size. In contrast, in a previous publication on the EUROSTAR collaborative series on patients unfit for open repair undergoing EVAR, a positive correlation was observed between comorbidity-related and aneurysm-related death, and larger aneurysm size.[14] Meanwhile, a few other studies on outcome of EVAR have demonstrated this correlation of aneurysm size with midterm outcome after treatment as well.[15-17] The objective of the present study was to assess the influence of aneurysm size on the early and late outcome of EVAR in the entire prospectively enrolled series of patients in the EUROSTAR database.

METHOD

Data for 4392 patients operated on over 6 years, ending in June 2002, who were enrolled prospectively in the EUROSTAR database constituted the basis of this analysis. An account of the organization of the EUROSTAR Registry and reports on various aspects after EVAR have been published.[18-20] For all patients, minimal follow-up was 1 month. Patients with an aneurysm smaller than 4.0 cm in diameter, including those with large iliac aneurysms, had been excluded from the study cohort. This cohort represents patients from 110 European institutions (Appendix 1, online only). All patients received commercially available, CE-approved devices, including AneuRx, EVT/Ancure, Excluder, Stentor, Talent, Vanguard, Zenith, and "other." Four thousand fifty (92.2%) patients received an endograft of bifurcated configuration, 193 (4.4%) patients received an aortouniiliac endograft, and 149 (3.4%) patients received a straight tube endograft. To assess the influence of size on the early and midterm outcome after EVAR the study cohort was subdivided according to preoperative aneurysm diameter: group A, 4.0 to 5.4 cm; group B, 5.5 to 6.4 cm; and group C greater than 6.5 cm.

Inclusion criteria, as defined in the Registry protocol, comprised elective treatment for AAA and vascular anatomy suitable for implantation of a stent graft. Baseline data including comorbidity, estimate of unfitness for open repair,[14] anatomic aspects, and operative details were recorded by the participating institutions on case record forms and were submitted for inclusion to the Data Registry Center. Findings at follow-up visits, which involved clinical examination, computed tomography (CT), or (in 5% of visits) angiography, magnetic resonance imaging, or ultrasound studies, were recorded on data forms and were returned at regular intervals to the Data Registry Center for processing and analysis. There was no outside monitoring of the centers or involvement of a core laboratory for the evaluation of CT or other imaging studies. Follow-up visits, according to the protocol, were scheduled at 1, 6, 12, 18, and 24 months, and annually thereafter. Reminders for overdue follow-up data were regularly sent to the institutions participating in the project. Outcome reporting adhered to the guidelines outlined by the Ad Hoc Committee for Standardized Reporting Practices in Vascular Surgery of The Society for Vascular Surgery/American Association for Vascular Surgery.[21] Deaths that occurred within 30 days of the initial procedure were categorized as operative deaths, and late deaths as those that occurred after 30 days. Deaths were also classified as aneurysm-related or unrelated. Aneurysm-related deaths included operative deaths and deaths that occurred as a result of aneurysm rupture, endograft infection, or within 1 month after a secondary surgical procedure to treat late complications of the aneurysm.

Other outcome events observed during follow-up included endoleaks, device migration, severe device kinking, occlusion, and aneurysm growth. Only endoleaks that were identified at 1 month and thereafter were included in the analysis; endoleaks at completion angiography were not considered. Endoleaks were classified as follows: type I, or endoleaks originating from the attachment site at the proximal infrarenal aortic neck or from the distal extremity of the endograft at the level of the iliac arteries; type II, or reperfusion endoleaks from the inferior mesenteric, lumbar, accessory renal, sacral, and hypogastric arteries; and type III, or endoleaks from the endograft itself, either from fabric damage or from connection sites between different device components. In cases in which different types of endoleaks were observed at different follow-up periods, types I and III were considered above type II for the analysis. The interval between the date of surgery and the date on which an endoleak was identified for the first time was used for life-table analysis.

Aneurysm growth was determined on the recording of an increase in aneurysm diameter measured at its largest section, from outer wall to outer wall across the minor diameter on the axial CT section. Aneurysm enlargement was defined as a diameter increase of at least 8 mm relative to the preoperative measurements on CT scans. The maximum recorded aneurysm diameter during follow-up was used for this analysis, and any subsequent smaller diameter

Table I. Demographic characteristics, comorbidity, and details of aortoiliac anatomy in 4392 patients

	Group A 4.0-5.4 cm (1962 *patients*)		*Group B 5.5-6.4 cm (1528 patients)*		*Group C ≥ 6.5 cm (902 patients)*		P		
Aneurysm diameter	*n*	*%*	*n*	*%*	*n*	*%*	*Group A vs group B*	*Group B vs group C*	*Group A vs group C*
Patient age (y)									
Mean	69.7		72.1		73.3		<.0001	.0093	<.0001
Range	43-94		49-109		50-93				
Male gender	1822	93	1416	93	857	95	NS	.02	.03
ASA class ≥3	944	48	831	54	565	63	.0002	<.0001	<.0001
History of cardiac symptoms or interventions	1040	56	899	62	588	68	.002	.002	<.0001
Renal insufficiency	304	17	265	18	193	23	NS	.01	.0001
Pulmonary symptoms	673	37	619	43	400	47	.0003	.06	<.0001
Diameter of infrarenal aortic neck (mm)									
Mean	22.7		23.3		23.9		<.0001	<.0001	<.0001*
Range	12-40		13-38		10-40				
Significant angulation									
Infrarenal neck	268	14	392	26	334	37	<.0001	<.0001	<.0001
Aneurysm	164	8	183	12	137	15	.0004	.02	<.0001
Iliac arteries	741	38	704	46	452	50	<.0001	.05	<.0001
Aneurysmatic common iliac arteries	276	15	271	19	184	23	<.003	.0006	<.0001

Missing data on comorbidity figures ranged from 220 to 318 per item; in aneurysmatic common iliac arteries, 374 missing data.

Table II. Devices used in 4392 patients

		Group A 4.0-5.4 cm (1962 patients)		*Group B 5.5-6.4 cm (1528 patients)*		*Group C ≥6.5 cm (902 patients)*	
	No. of devices	*n*	*%*	*n*	*%*	*n*	*%*
AneuRx	877	438	50*	296	34	143	16
EVT/Ancure	150	62	41	56	37	32	21
Excluder	341	158	46	129	38	54	16
Stentor	282	142	50	93	33	47	17
Talent	821	307	37	322	39	192	23†
Vanguard	905	438	48‡	295	33	172	19
Zenith	891	344	37	300	34	247	28§
Other	108	62	57‖	31	29	15	14
Unknown	17	11		6			

Only more frequent use of brand in device groups A and C is indicated.
*$P = .0002$ more frequent use in group A.
†$P < .0001$ more frequent use in group C.
‡$P = .04$ more frequent use in group A.
§$P < .0001$ more frequent use in group C.
‖$P = .004$ more frequent use in group A.

that may have occurred because of secondary treatment was omitted.

Results were reported as mean, range, and percentage of patients with discrete variables, unless otherwise specified. Preoperative patient characteristics, comorbid conditions, aneurysm anatomy at the initial procedure, and details regarding the procedure and devices were correlated with the defined study groups with univariate analysis. Differences in findings between study groups were assessed with χ^2 tests for discrete variables and with Mann-Whitney tests for continuous variables. All variables, including size classification, with a significant correlation with an adverse outcome event were entered in a multivariate Cox analysis to assess independent associations. A dichotomous categorization of used device brands was defined, with Stentor and Vanguard in one category and any other endograft in the other. This variable "device category" was entered in the model irrespective whether a significant correlation with the outcome event was found at univariate analysis. $P < .05$ was considered to represent a significant difference. Cumulative rates of freedom from aneurysm-related deaths, unrelated deaths, aneurysm rupture, conversion to

open repair, and various types of endoleaks were assessed with life-table analysis. Only rates with less than 10% SE are indicated in the Results and in the figures. Significant differences between study groups were assessed with log-rank testing. All statistical analyses were performed with SAS Statistical Software (version 1.12; SAS Institute, Cary, NC).

RESULTS

The 4392 patients, 4095 men and 297 women, ranged in age from 42 to 100 years. Average diameter of the aneurysm sac was 57.2 cm (range, 4.0-14.5 cm) in minor dimension. Group A included 1962 patients with aneurysm diameter 4.0 to 5.4 cm, group B included 1528 patients with aneurysm diameter 5.5 to 6.4 cm, and group C included 902 patients with aneurysm diameter greater than 6.4 cm. Patients in group C were on average 1.2 to 3.6 years older than those in groups A and B, more frequently had American Society of Anesthesiologists (ASA) class 3 or 4 disease, and more frequently had cardiac, renal, and pulmonary comorbidity, compared with the other groups (Table I). Regarding existing anatomy, patients in group C had a higher incidence of significant angulation in the neck, the aneurysm, and the iliac arteries, and on average a 0.6 to 1.2 mm wider infrarenal neck. In addition, aneurysm dilatation of the common iliac arteries was more frequently observed in group C than in the other groups (Table I). Operative time was 157 minutes in group C, compared with 140 minutes in group A and 132 minutes in group B ($P < .0001$). Talent and Zenith endografts were significantly more frequently used in group C (Table II). Other operative aspects more frequently observed in group C included use of additional procedures (37% vs 31% in group B and 30% in group A; $P = .0007$) and a higher incidence of type I endoleak at completion angiography (9.9% vs 6.8% in group B and 3.7% in group A; group A vs group B, $P = .001$; group A vs group C, $P < .0001$; group B vs group C, $P = .01$). Primary or first-month conversion to open repair was performed in 1.1% of patients (n = 21) in group A, 1.4% of patients (n = 22) in group B, and 2.3% of patients (n = 21) in group C (group A vs group C, $P = .009$; other group comparisons, not significant [NS]).

The overall first-month mortality was 2.5% (108 patients). Mortality was 4.1% in group C, compared to 2.1% in groups A and B combined ($P < .0001$; 2.6% in group B and 1.6% in group A). The first-month mortality in the Stentor and Vanguard category was 3.0%, and in other endografts was 2.2% (NS).

Cardiac complications occurred in 5.6% of patients in group C, 3.3%, in group B, and 2.8% in group (group A vs group C, $P = .003$; group B vs group C, $P = .008$; group A vs group B, NS). Pulmonary complications occurred in 3.0% of patients in group C, 2.0% in group B, and 1.6% in group A (group A vs group C, $P = .01$; other comparisons, NS). First-month systemic complications combined were observed in 17.4% of patients in group C, 12.6% of patients in group B, and 12.0% of patients in group A (group A vs group C, $P < .0001$; group B vs group C, $P = .001$; group A vs group B, NS). There was no difference in early procedure-related or device-related complications (3.3%, 2.8%, and 2.9% in groups C, B, and A, respectively). Hospital stay was longer in groups C and B (7.0, 6.1, and 5.5 days in groups C, B, and A, respectively (group A vs group B, $P = .004$; group A vs group C, $P = <.0001$; group B vs group C, $P = .001$).

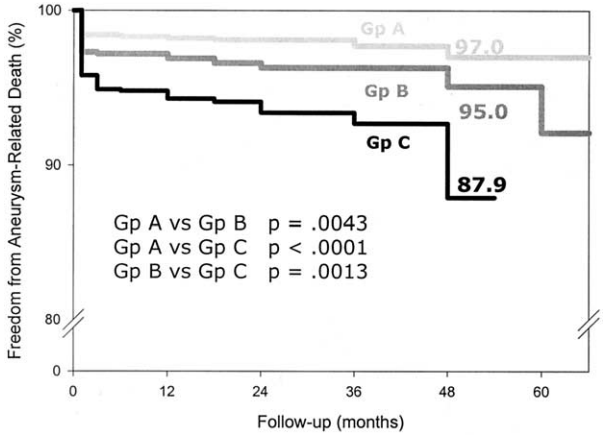

Fig 1. Cumulative freedom from aneurysm-related death. Note low attrition of survival in first 3 years of follow-up and rapid attrition in fourth year. *Gp,* Group.

Mean duration of follow-up was 18.4 months (range, 1-72 months), with 20.9 months (range, 1-96) in group A, 17.4 months (1-84 months) in group B, and 14.5 months (1-84 months) in group C. The difference in follow-up duration was significant ($P < .0001$ for any group comparison). The percentage of patients lost to follow-up after 2 years was 52% in group A, 55% in group B, and 62 in group C (NS). Patient survival was 76.0% at 5 years. Group C had significantly lower survival compared with groups B and A (62.0%, 69.6%, and 84.2%, respectively, at 5 years; group A vs group B, $P < .0001$; group B vs group C, $P < .0001$; group A vs group C, $P < .0001$).

Aneurysm-related deaths. The freedom from aneurysm-related death in the entire study cohort was 93.9% at 5 years. Aneurysm-related deaths occurred in 53 patients in group C, 52 patients in group B, and 39 patients in group A, for a freedom from aneurysm-related death at 5 years of 87.9%, 95.0%, and 97.0% in the three groups, respectively (group A vs group B, $P = .004$; group A vs group C, $P < .0001$; group B vs group C, $P = .001$; Fig 1; numbers of patients in Appendix 2, online only). Most aneurysm-related deaths in groups B and C during follow-up occurred in the fourth year. In group C the aneurysm-related death rate was 1% annually in the first 3 years (operative deaths not included) and 8% in the fourth year. In group B the aneurysm-related annual death rate was 0.3% in the first 3 years and 2.1% in the fourth and fifth years. This pattern can be described as a gradual increase in the first 3 years, followed by an accelerated increase in aneurysm-related deaths in the fourth year in groups B and C (Fig 1). This trend was not apparent in group A.

Table III. Risk factors for aneurysm-related death, outcome of multivariate analysis

Variable	*Hazard ratio*	*95% Confidence interval*
Baseline variables (early and late aneurysm-related death)		
Aneurysm size, group C	2.5	1.6-4.0
Age	1.1	1.04-1.09
Renal insufficiency	1.8	1.2-2.7
Pulmonary condition	1.7	1.1-2.4
Unfit for open aneurysm repair	1.7	1.1-2.4
Stentor or Vanguard device	1.5	1.1-2.3
Follow-up variables (only late aneurysm-related death)		
Aneurysm size, group C	6.0	2.6-14.1
Type I proximal endoleak	3.5	1.4-9.0
Kinking of device	3.5	1.5-8.3
Aneurysm growth	10.5	4.8-23.0

Table IV. Risk factors for rupture of aneurysm, outcome of multivariate analysis

Follow-up variables	*Hazard ratio*	*95% Confidence interval*
Aneurysm size, group C	7.7	3.1-18.7
Type III endoleak	3.8	1.7-8.3
Aneurysm growth	4.1	1.4-12.1

Table V. Risk factors for conversion to open repair, outcome of multivariate analysis

Follow-up variables	*Hazard ratio*	*95% Confidence interval*
Aneurysm size, group C	1.6	1.1-2.3
Type I proximal endoleak	4.0	2.7-5.8
Type II endoleak	2.0	1.4-2.9
Type III endoleak	1.7	1.2-2.5
Migration	1.7	1.1-2.5
Occlusion of limb	6.4	4.6-9.0
Aneurysm growth	3.9	2.4-6.4

Table VI. Risk factors for death not related to aneurysm, outcome of multivariate analysis

Baseline variables	*Hazard ratio*	*95% Confidence interval*
Aneurysm size, group C	1.5	1.1-2.1
Aneurysm size, group B	1.5	1.1-1.9
Age of patient	1.0	1.0-1.1
Renal insufficiency	1.4	1.1-1.9
Pulmonary condition	1.6	1.3-2.1
Unfit for open aneurysm repair	1.8	1.4-2.4
Stentor or Vanguard device	1.3	1.0-1.7

Freedom from aneurysm-related deaths at 3 years stratified by device category was 95.2% in patients with Stentor and Vanguard devices and 96.9% in patients with other endografts ($P = .01$). Multivariate analysis indicated that large aneurysm (group C), patient age, renal insufficiency, pulmonary comorbidity, unfitness for open repair, and use of Stentor and Vanguard devices as factors with an independent correlation with increased risk for aneurysm-related death (Table III). The level of significance was less for the device category ($P = 0.02$) than for size group C ($P = .0001$). A multivariate model of variables observed at follow-up, with aneurysm-related deaths omitting the first-month deaths (ie, "late" aneurysm-related death) as outcome event indicated an independent significant correlation with large aneurysms (group C), proximal endoleak (type I), kinking of the device, and aneurysm expansion during follow-up (Table III). In this Cox model there was no correlation with use of Stentor and Vanguard device.

Aneurysm-related complications. Rupture post-EVAR occurred in 32 patients in the entire study cohort, with 16 ruptures in group C, 9 ruptures in group B, and 7 ruptures in group A. Freedom from rupture after 4 years was observed in 97.2% of the entire group, 90.5% in group C, 98.3% in group B, and 98.3% in group A (group A vs group B, $P = .13$; group A vs group C, $P < .0001$; group B vs group C, $P < .0001$; Fig 2; numbers of patients in Appendix 2, online only). The rate of rupture during the study period per patient-year was 0.005 in the entire cohort, 0.015 in group C, 0.004 in group B, and 0.002 in group A. Ruptures occurred in patients who had received an AneuRx (3 of 877), Excluder (1 of 341), Stentor (6 of 282), Talent (5 of 821), Vanguard (15 of 905), Zenith (1 of 891) and "other" (1 of 108) devices. No single device brand was significantly associated with a higher risk for post-EVAR rupture. The dichotomized variable of used endograft at univariate analysis was not associated with a significantly increased risk for rupture. The 3-year rate of freedom from rupture was 98.5% with Stentor and Vanguard and 99.2% with other device brands. Variables observed at follow-up that were independently associated with a higher risk for rupture included large aneurysms (group C), midgraft endoleak type III, and aneurysm expansion during follow-up (Table IV). In this Cox model the use of the Stentor or Vanguard device did not significantly correlate with rupture.

Type I proximal endoleak had a higher incidence in group C (89.5% freedom from endoleak at 4 years) compared with group A (94.7%; $P = .002$) and group B (95.1%; $P = .002$). Type I distal endoleak also had a higher incidence in group C (84.9% freedom from endoleak at 4 years) compared with group A (88.7%; $P = .0004$). There was no significant difference between groups C and B, and groups A and B. The incidence of type III endoleaks was not significantly different in the three size groups (freedom from endoleak at 4 years, 90.3%, 87.7%, and 85.6% for groups C, B, and A, respectively). Similarly, the incidence of type II endoleaks, migration, kinking, and limb stenosis or thrombosis was comparable in the three groups.

Late conversion to open repair (after the first postoperative month) had a higher incidence in group C (86.2%

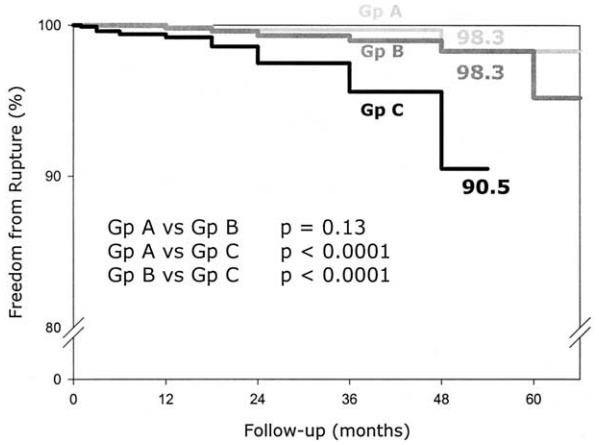

Fig 2. Cumulative freedom from rupture after endovascular aneurysm repair. *Gp,* Group.

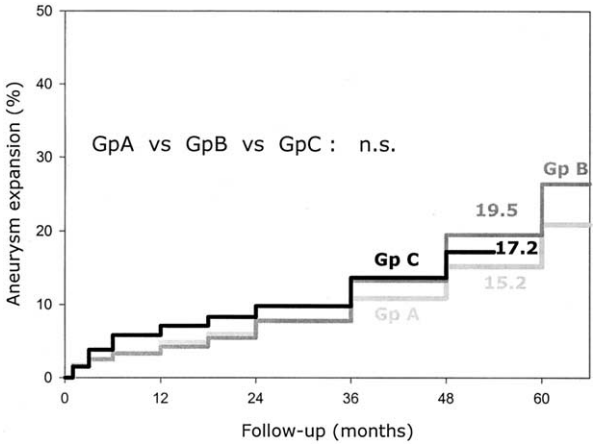

Fig 3. Cumulative proportion of patients with aneurysm growth after endovascular aneurysm repair. *Gp,* Group; *NS,* not significant.

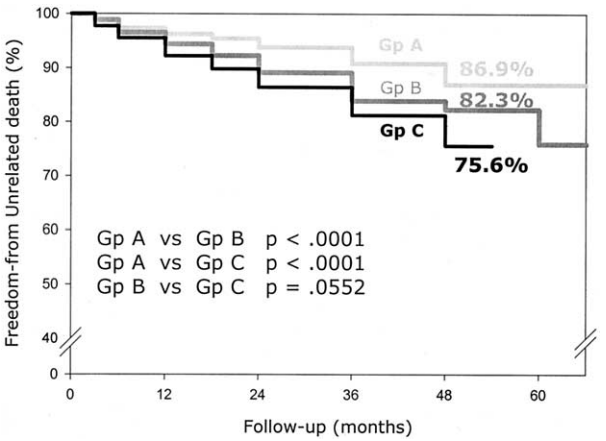

Fig 4. Cumulative freedom from unrelated death. *Dashed arrow,* Progressive attrition of survival throughout follow-up period. *Gp,* Group.

freedom from conversion at 4 years) compared with group A (93.4%; $P = .003$) and group B (93.2%; $P = .01$). Variables observed during follow-up with an independent correlation with the decision to open conversion included large aneurysm (group C), proximal endoleak (type I), mid-graft endoleak (type III), type II endoleak, device migration, limb occlusion, and aneurysm expansion (Table V). Correlation of the device category Stentor or Vanguard and conversion did not achieve significance ($P = .05$). The incidence of aneurysm growth was not significantly different in groups C, B, and A (Fig 3; numbers of patients in Appendix 2, online only).

Unrelated deaths. Freedom from aneurysm- unrelated death in the entire study cohort was 81.0% at 5 years of follow-up. Cumulative death rates due to comorbidity were significantly lower in groups B and C compared with group A (freedom from unrelated death at 4 years, 75.6% in group C, 82.3% in group B, 86.9% in group A; Fig 4; numbers of patients in Appendix 2, online only). There was no statistical difference between unrelated deaths between groups C and B. In contrast with aneurysm-related deaths, there was a progressive attrition of freedom from unrelated deaths over the first 5 years of follow-up (5.8% and 4.8% annually in groups C and B; Fig 4). Of factors recorded at baseline, aneurysm size groups B and C, patient age, presence of renal dysfunction, adverse pulmonary condition, and subjective assessment of unfitness for open repair by the managing physicians had a significant independent correlation with the risk for death unrelated to aneurysm or treatment (Table VI). The use of the Stentor or Vanguard device had a borderline significant correlation with unrelated death ($P = .04$), as opposed to a highly significant correlation of groups C ($P = .009$) and B ($P = .007$).

DISCUSSION

Size of an AAA has several implications for management with EVAR. First, it was recognized that large-diameter aneurysms were less often suitable for endograft repair than smaller aneurysms.[22-24] Most frequently aortic necks were either too wide, too short, severely angulated, or these factors combined, rendering reliable infrarenal endograft fixation and sealing uncertain. However, with the newer generation of devices sealing and fixation is achievable in aneurysms that, on the basis of anatomy, previously would have been rejected for stent-graft treatment.[25-30] This is in keeping with the findings in the present study of patients undergoing EVAR. The size of the neck and angulation at several levels of the aortoiliac segment and aneurysm dilatation in iliac arteries demonstrated a significant correlation with size groups C and B.

The correlation of larger aneurysm with a higher incidence of preoperative comorbidity is appreciable in this study. Cardiac, renal, and pulmonary conditions and generic estimates of increased operative risk, such as ASA class 3 and 4 disease and subjective assessment of patients as

unfit, had a higher prevalence in patients in group C. A correlation of increased operative risk and larger aneurysm size had been observed previously.[14,16,31] Comparison of operative details in the present assessment demonstrated unfavorable outcome in large (group C) or medium-sized (group B) aneurysms in operating time, length of hospital stay, and increased rate of type I endoleaks at completion arteriography. These events are typically associated with more complex anatomy or reflected greater postoperative morbidity.[22,32,33] Moreover, additional procedures were more frequently required in group C than in the other groups.

A low perioperative mortality in comparison with conventional surgery as the benchmark has been one of the assumed assets of EVAR from the beginning of its development. A perioperative mortality of 4.1% with large aneurysms is higher than in institutional series and in the EUROSTAR series as a whole,[20,34] but still compares favorably with the mean procedural mortality of 5.5% reported in a recent review of several studies of open aneurysm surgery.[35] However, comparison of perioperative mortality rates in different series is always a dubious exercise, owing to differences in patient selection and study design.

When reporting midterm and long-term results after EVAR, it has been advised that outcome events related to the aneurysm or treatment be differentiated from events associated with preexisting comorbid factors, that is, unrelated events.[36] With regard to death rates during follow-up, a number of interesting findings came out of the present analysis. First, we noted a relatively smaller contribution of aneurysm-related death to the rate of death from all causes in the entire study cohort (freedom from death at 5 years, 94% vs 76%, respectively). Second, there was a progressive increase in both aneurysm-related and unrelated death rates with increasing aneurysm diameter. Third, the ratio of aneurysm-related to unrelated death rates demonstrated notable differences between groups, with the contribution of related deaths being largest in group C (approximately 50%, compared with 28% and 23% at 4 years in groups B and A, respectively; compare Figs 1 and 4). Thus the aneurysm-related death rate is largest in group C in an absolute sense and in a relative sense. In theory, one might conclude that the potential advantage of the minimally invasive technique becomes smaller in patients with large aneurysms, which is in agreement with previous obervations that EVAR is most durable in patients with small and medium-sized aneurysms.[37] On the other hand, one must consider that prevention of death from rupture in the vast majority in the patient category with the most unfavorable natural history and highest risk for open repair may be the best indication for EVAR.[14]

The relatively high rate of aneurysm-related midterm mortality is linked to high-risk events, such as late conversion and aneurysm rupture. The underlying cause for these events must be sought in the same unfavorable anatomic conditions that cause postoperative morbidity. In addition, a higher frequency of thrombus lining in aneurysm necks and common iliac arteries, and calcifications in the sealing zones are causes of less favorable outcome.[26,30] Although these latter characteristics were not recorded as such, because they are difficult to quantify in a multicenter registry, their importance must not be underestimated. Adverse anatomy–related findings including a significantly higher incidence of type I endoleaks of both the proximal and distal variety were more frequently observed in large aneurysms. Thus detected and undetected anatomic characteristics may account for the higher rate of rupture, conversion, and aneurysm-related deaths in patients with large aneurysms compared with medium-sized and small aneurysms.

Distribution of the various outcome events during follow-up demonstrated characteristic patterns. Unrelated deaths occurred with a relatively constant annual failure rate of 5.8% in group C throughout 5 years of follow-up. In contrast, aneurysm-related death after the first month clearly was delayed by 3 years before events occurred with higher frequency, a phenomenon that was most apparent in group C. Within the first 3 years the annual failure rate in group C was 1%, compared with an interval failure of 8% in the fourth year. If we assume that aneurysm-related death and rupture are preventable, it may be argued that after 3 years of follow-up intensified imaging surveillance may be effective for early detection of indicators of procedural failure, such as aneurysm enlargement, migration, type I or III endoleaks, device kinking, or device deterioration. These factors demonstrated an independent correlation in the multivariate analysis (Table III). Regarding intensified surveillance, one may consider more frequent follow-up visits, with precise screening of plain abdominal x-ray films, volume measurements of the aneurysm sac, and three-dimensional reconstruction of CT scans.[38-40]

Although aneurysm diameter was the main variable in this outcome study, other variables recorded either at baseline or during follow-up were assessed as potential confounders. Several variables were found to have an independent association with adverse outcome measures. Recently an increased incidence of late complications has been attributed to devices of older generations, presently withdrawn from the market.[41] In our analysis we included this variable, defined as the use of Stentor or Vanguard endografts, in the multivariate Cox models. We observed that there was an independent correlation of old-technology endografts with aneurysm-related and unrelated deaths. However, this correlation was not so strong as the initial presence of a large aneurysm (group C) for aneurysm-related death, and medium-sized and large AAA (groups B and C) for unrelated death.

Of surprise, enlargement of the aneurysm, although correlating with rupture, conversion, and aneurysm-related death, was not associated with any of the size categories. One may only speculate why growth was not different in the size groups. Measurement of diameter in a multicenter registry is not so standardized as in a single-center study with a few CT scan readers and uniform imaging technique. While aneurysm diameter at the minor dimension of the

largest diameter is part of the EUROSTAR protocol, the absence of a core laboratory to independently assess diameter measurements may enhance the lack of uniformity. To enable larger interobserver variation, a relatively large threshold of 8 mm was used to define the presence of absence of growth. Nevertheless, data accumulated in a registry no doubt will lack the accuracy of smaller studies. Third, and equally important, in many cases smaller degrees of aneurysm growth, endoleak, or migration may lead to secondary interventions before the preset threshold of 8 mm diameter increase was reached. In this regard, hard end points such as rupture and aneurysm-related death may constitute a better parameter than the more subjective measurement of diameter.

Proponents of EVAR have been criticized because they failed to clearly demonstrate any advantage of the technique with respect to protecting patients from AAA rupture.[42] In this respect, it should be noted that the risk for rupture of small aneurysms (diameter <5.5 cm) after EVAR in the present study was 0.002 ruptures per patient-year, which compares favorably with 0.008 in the similar size category in the trial arm with the initially conservative management from the UK Small Aneurysm Trial. Rupture rates per size group were calculated as Number of ruptures/(Number of patients in group × mean duration of follow-up). Reduction of the risk for rupture with EVAR in medium-sized and large aneurysms as observed in the present study demonstrated, as expected, even larger differences. The rupture rate in patients in group B was 0.004, and should be compared with rates of 0.03 to 0.14, as derived from the literature in untreated aneurysms of 5 to 5.9 cm.[4-6,43] In group C we found a rupture rate of 0.015, which may be compared with 0.25 per patient-year.[4,44] Although these comparisons may not be statistically robust, it must be considered that with regard to larger aneurysms a scientifically sound assessment may not likely be performed and comparison of the outcome of different management strategies must be judged on alternative sources of information.

Post-EVAR rupture, the ultimate failure of stent-graft treatment, was observed after use of most of the device brands reported on in this registry. Analysis of many cases with post-EVAR rupture reported in the literature have revealed potentially avoidable causes, such as poor patient selection, deployment errors, or unrecognized or untreated endoleaks.[45,46] In a previous EUROSTAR publication a cumulative rupture rate of 1% per year was documented.[18] The present 0.7% annual rupture rate at 4 years in the entire series signifies some improvement, but still differs from annual cumulative rates of approximately 0.2% found in a number of institutional series.[34,47-49]

It was surprising that at our screening of articles on open AAA repair no studies were found in which the initial aneurysm diameter was included as a covariate for outcome analysis. The single exception was a study of the data for patients with primary surgery enrolled in the UK Small Aneurysm Trial.[12] It is understandable that the aneurysm diameter in this particular study demonstrated little variation (<5.5 cm), precluding a useful conclusion about a possible correlation. A comparison of the relation between aneurysm size and procedural outcome after open AAA surgery and EVAR at this time is essentially muddled by two aspects: First, the distribution of small, medium, and large aneurysms is unknown for almost any published study on open repair; and second, the respective contribution from aneurysm-related and unrelated death to the overall mortality was differentiated in few studies.[36,50] For this reason a size-stratified analysis within the randomized trials that are under way will be important.

The limitations of this study include the large number of patients who were lost to follow-up. Data for more than half of the patients after the 2-year interval were not available, despite regular reminders to participants in the study. This aspect, which probably is inherent to a voluntary registry such as EUROSTAR, may improve with the recent introduction of electronic data submission via a website. The proportion of patients with missing follow-up data was comparable in the three groups. A standard error well below 10% after 4 years is adequate for a valid assessment. However, missing data may detract from the accuracy of the cumulative event rates during follow-up.

Overall, size differences are strongly associated with adverse outcomes during follow-up. Underlying causes, such as various types of endoleak, migration, limb kinking, thrombosis, and aneurysm enlargement, correlated sometimes disparately with aneurysm size groups. However, all of these variables correlated with either end point, conversion, rupture, or aneurysm-related death, underscoring the interrelation between one another. The high incidence of medical risk factors still makes EVAR the preferred management option in most patients with large aneurysms. Old-technology stent grafts appeared important to some extent for adverse outcome, but less so than larger size of the aneurysm. Careful analysis of the causes of treatment failure remains indicated to achieve optimal long-term outcome. Until these interrelationships are better understood, intensified surveillance of patients receiving endograft treatment of a large aneurysm after 3 years of follow-up, when adverse events occur most frequently, appears a reasonable approach. With regard to patients with small aneurysms, the outcome of EVAR appears excellent. This finding may justify reappraisal of currently accepted management strategies.

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DISCUSSION

Dr Kenneth Ouriel (Cleveland, Ohio). I want to congratulate you on a nice analysis of a very large group of patients. I was intrigued by the very low rate of all-cause death and aneurysm-related death in the smaller aneurysm group, rates that compete successfully with the surveillance arm of the UK Small Aneurysm Trial. In fact, the risks for all-cause mortality was 11% after endografting in your study, versus 18% in the ultrasound surveillance group in the UK Small Aneurysm Trial. I have one question. Is it time for a randomized trial of endovascular repair versus surveillance in patients with small aneurysms?

Dr A. G. Peppelenbosch. Admittedly, long-term results of early death rates and aneurysm-related death rates, and rupture rates are excellent in small aneurysms. However, we still believe that, owing to the complication rates in the long term, and that's not sure, it should be still that small aneurysms should not be treated. Regarding your question of whether this should be a randomized trial, I think it should be. Yes, it is time for such a trial.

Dr Piergiorgio Cao (Perugia, Italy). Ken Ouriel found out my question. Anyway, I'd like to say another thing. In your very low aneurysm rate and mortality rate in small aneurysms, you have 48% of patients treated with Vanguard; is that correct? The oldest patients were treated with Vanguard. Thus many of the aneurysm-related deaths were related to failure of a graft that is no longer on the market. Do you have any comment on that? Can you expect that the results concerning the small aneurysm treated with EVAR are better than reported in your study, if you extrapolated it out from Vanguard?

Dr Peppelenbosch. Well, we have done a univariate analysis of device brands, and we found no correlation with any of the device brands. However, we also have done this with all brands combined, and that's the subject of our next study. And we find that there is a significant difference between the old brands combined and the newer brands.

Dr Christopher K. Zarins (Stanford, Calif). It seems intuitively obvious that patients with large aneurysms may not do quite so well as patients with small aneurysms. But I should note that your group sizes—small, medium, and large aneurysms—were not comparable, particularly in the type of device used in each group.

In our own analysis of more than 1200 patients over 6 years using a single device, with multivariate and univariate analysis, there was no relationship between aneurysm size and outcome measures. So I wonder if you have done Cox proportional hazards models, including the device and the aneurysm size, not the aneurysm group size, to determine whether, indeed, aneurysm size is a significant variable for your outcome results?

Dr Peppelenbosch. We have done that, and aneurysm size is one of the predictors of this outcome.