EDITORIALS

Endovascular Aneurysm Repair — Is It Durable?

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Abdominal aortic aneurysm is a lethal condition associated with an 85% risk of death after rupture. Optimal treatment relies on early detection followed by prophylactic surgical intervention. Although aneurysms are traditionally treated with open surgery, the use of endovascular repair has increased dramatically and is the most frequent form of therapy in the United States.[1] As is often the case with new surgical techniques, there may be trade-offs, including reduced invasiveness, durability, and cost. To weigh these trade-offs, two randomized trials comparing endovascular repair with open surgery have been conducted, the United Kingdom Endovascular Aneurysm Repair 1 (EVAR-1) trial[2] and the Dutch Randomized Endovascular Aneurysm Repair (DREAM) trial,[3] with their long-term results reported in this issue of the *Journal.*

The findings of both studies are remarkably similar. Thirty-day mortality is markedly improved in patients treated with endovascular versus open repair. However, over time this benefit disappears, with patients having equivalent long-term survival with both interventions. Among patients undergoing endovascular repair, the early advantage in mortality is short-lived, with the curves merging within 2 years. In a third recently published trial, the Open Versus Endovascular Repair (OVER) trial, the early advantage of endovascular repair also disappeared by year 2.[4] The merging of the mortality curves is related to late deaths in the endovascular-repair cohort, and at least in the EVAR-1 trial these late deaths appeared to be aneurysm-related.

After the initial reports of these trials, there was concern that continued aneurysm-related deaths beyond 2 years in the endovascular-repair groups might result in increased long-term mortality for endovascular repair, as compared with open surgery. Thus, the important finding of these new analyses is that long-term rates of death for both interventions remain equivalent. A simplistic conclusion might be that endovascular repair provides early advantage and late equivalence and thus is the better option.

However, there is more to consider. Patients undergoing endovascular repair require long-term monitoring, and for some patients there is a need to reintervene. In the DREAM and EVAR-1 trials, at 6 and 8 years, the cumulative rate of reintervention for patients undergoing endovascular repair was approximately 30%. Alternatively, there is also a frequent need for reintervention after open aneurysm repair, including reoperation for incisional hernia, wound infection, pseudoaneurysm, and bowel obstruction. In the DREAM trial, in which some of these late complications were measured, the cumulative 6-year rate of reintervention for open surgery was approximately 20% (laparotomy-related complications were not measured in the EVAR-1 trial). Moreover, in a recently published analysis of the U.S. Medicare database, rates of reintervention after endovascular repair and open surgery were equivalent.[5]

Another major issue that remains unresolved is cost. In the EVAR-1 trial, the long-term expense of endovascular repair versus open surgery was estimated as an additional £3,019 ($4,568) per patient. However, many important expenses were not included in this analysis. Open surgery is associated with an increased incidence of perioperative morbidity, such as renal failure and stroke, which can lead to long-term expense.[6] Also not evaluated were expenses associated with monitoring patients after endovascular repair

and with reinterventions after open surgery. Although ultimately endovascular repair may be more expensive than open repair, the extent of this difference and how the two will fare in a true cost-effective analysis are not clear. In an era of comparative effectiveness, further evaluation will be essential.

Trials that are designed to evaluate new interventions are frequently confounded by continued evolution of the technology. The DREAM and EVAR-1 trials were initiated 10 and 11 years ago, respectively, and over time, endovascular-graft design has evolved substantially. Moreover, patient selection, surgeon experience, and treatments for graft complications have also improved over time. It is not unreasonable to assume that current outcomes for endovascular repair are substantially better than those reported in these trials. It is also important to note that many patients with treatable aneurysms fall outside the inclusion criteria for these studies. In the EVAR-1 trial, nearly 5000 patients were screened to identify the 1252 who underwent randomization. Thus, clinicians should be cautious not to generalize these findings to all patients needing aneurysm repair.

Also included in this issue of the *Journal* are the results of the United Kingdom Endovascular Aneurysm Repair 2 (EVAR-2) trial,[7] a randomized study comparing endovascular repair with no treatment for patients with abdominal aortic aneurysm who were considered to be at high risk for death and complications with open surgery. The authors conclude that patients who are at high risk if they undergo open aneurysm repair will not benefit from endovascular repair. The results of this trial provide an important message. Prophylactic repair of abdominal aortic aneurysm is designed to prolong life, and patients with a poor life expectancy because of coexisting illnesses or those who cannot safely tolerate a minimally invasive procedure should not be treated. What is not clear from the EVAR-2 trial is how to determine which patients are at high risk. In an analysis of the U.S. Medicare database, only 3.4% of 67,000 patients who underwent endovascular repair had an operative risk of more than 5%.[8] Thus, the high-risk cohort is small, and the majority of patients with large aneurysms are indeed candidates for intervention.[8]

The finding of an early mortality advantage followed by long-term equivalence will probably lead most patients to select endovascular repair. Currently in the United States, more than 60% of infrarenal aneurysms are repaired by endovascular techniques (unpublished data), and it is unlikely that this number will diminish as a consequence of these new findings. However, decisions need to be individualized. The need for reintervention after endovascular repair persists even at 8 years. Thus, patients with a favorable life expectancy should consider open repair, and careful follow-up of patients undergoing endovascular repair is essential, since some late deaths are potentially preventable with close monitoring and appropriate reintervention. All patients should be informed of the advantages and disadvantages of endovascular repair; some will be willing to assume the up-front risk of open surgery to avoid the late consequences of endovascular repair, and others will not.

The authors of the DREAM and EVAR-1 and 2 trials are to be commended for recognizing the need for long-term and comparative evaluation of new surgical techniques. Although many questions remain unanswered, the results of these studies provide additional insight into how we should treat patients with aneurysmal disease.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Endovascular versus Open Repair of Abdominal Aortic Aneurysm

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ABSTRACT

BACKGROUND

Few data are available on the long-term outcome of endovascular repair of abdominal aortic aneurysm as compared with open repair.

METHODS

From 1999 through 2004 at 37 hospitals in the United Kingdom, we randomly assigned 1252 patients with large abdominal aortic aneurysms (≥5.5 cm in diameter) to undergo either endovascular or open repair; 626 patients were assigned to each group. Patients were followed for rates of death, graft-related complications, reinterventions, and resource use until the end of 2009. Logistic regression and Cox regression were used to compare outcomes in the two groups.

RESULTS

The 30-day operative mortality was 1.8% in the endovascular-repair group and 4.3% in the open-repair group (adjusted odds ratio for endovascular repair as compared with open repair, 0.39; 95% confidence interval [CI], 0.18 to 0.87; P=0.02). The endovascular-repair group had an early benefit with respect to aneurysm-related mortality, but the benefit was lost by the end of the study, at least partially because of fatal endograft ruptures (adjusted hazard ratio, 0.92; 95% CI, 0.57 to 1.49; P=0.73). By the end of follow-up, there was no significant difference between the two groups in the rate of death from any cause (adjusted hazard ratio, 1.03; 95% CI, 0.86 to 1.23; P=0.72). The rates of graft-related complications and reinterventions were higher with endovascular repair, and new complications occurred up to 8 years after randomization, contributing to higher overall costs.

CONCLUSIONS

In this large, randomized trial, endovascular repair of abdominal aortic aneurysm was associated with a significantly lower operative mortality than open surgical repair. However, no differences were seen in total mortality or aneurysm-related mortality in the long term. Endovascular repair was associated with increased rates of graft-related complications and reinterventions and was more costly. (Current Controlled Trials number, ISRCTN55703451.)

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Abdominal aortic aneurysm is a common condition of increasing prevalence, particularly among older men. As the size of the aneurysm increases, so does the risk of rupture. Therefore, prophylactic repair with insertion of a prosthetic graft is offered. Since 1951, open surgical repair has been practiced.[1] Minimally invasive endovascular aneurysm repair was first reported in 1986.[2] The three principal randomized trials comparing endovascular and open repair of abdominal aortic aneurysm have all shown a marked benefit of endovascular repair with respect to 30-day operative mortality,[3-5] and these results have been supported by data from large registries.[6] Therefore, endovascular repair has become a common treatment option.

There is strong evidence that open repair is durable,[7,8] but there has been little careful long-term follow-up of endovascular repair. The European Collaborators on Stent/Graft Techniques for Aortic Aneurysm Repair (EUROSTAR) Registry, which is the largest registry of patients undergoing endovascular repair, provides data for a mean follow-up of only 3 years on patients who received first-generation endografts, which had relatively poor performance as compared with endografts that are currently in use.[9] In the three major randomized trials, the follow-up period was also fairly short (mean, 2 to 3 years).[5,10,11] Good-quality data regarding the longer-term durability, costs, and effects of endovascular repair are limited. In the current trial, called the United Kingdom Endovascular Aneurysm Repair 1 (EVAR 1) trial, we compared the long-term results of endovascular versus open repair of large aneurysms.

Methods

Trial Design

The methods that we use in this trial have been described previously[3,11,12] and are discussed in detail in the Supplementary Appendix (available with the full text of this article at NEJM.org). In summary, EVAR 1 was a randomized trial designed by the principal investigator in consultation with the grant applicants, the members of the trial-management and steering committees, and the trial manager. The trial was sponsored by the Health Technology Assessment Programme of the National Institute for Health Research in the United Kingdom. No support was provided by pharmaceutical or medical-device companies. Full approval of the trial was granted by the United Kingdom's North West Multicentre Research Ethics Committee.

The trial was conducted at 37 hospitals that met the criteria for participation in the trial (for details, see the Supplementary Appendix). Trained local coordinators were responsible for recruitment of patients, data collection, and follow-up.

Trial Procedures

Patients of both sexes who were at least 60 years of age with an abdominal aortic aneurysm measuring at least 5.5 cm in diameter on computed tomography (CT) were evaluated for trial participation. Patients who were considered to be anatomically and clinically suitable candidates for either open surgical repair or endovascular repair were offered enrollment in the EVAR 1 trial (see the Supplementary Appendix for details regarding candidate evaluation). Patients who were not considered to be candidates for open surgical repair but who were considered to be candidates for endovascular repair were offered enrollment in the Endovascular Aneurysm Repair 2 (EVAR 2) trial, reported elsewhere in this issue of the *Journal*.[13] All patients provided written informed consent.

The patients in EVAR 1 were randomly assigned to undergo either open repair or endovascular repair. Patients were encouraged to undergo repair within 1 month after randomization, although such scheduling was not always possible for logistic or other reasons. CT was performed at 1 and 3 months in patients undergoing endovascular repair and annually in all patients in the two study groups. The primary outcome was death from any cause, but aneurysm-related death was also assessed, as were graft-related complications and graft-related reinterventions. (Full definitions of the trial end points are available in the Supplementary Appendix.) For patients who died, we obtained death certificates from the Office for National Statistics and classified the deaths using codes from the *International Classification of Diseases, 10th Revision*. An independent end-points committee whose members were unaware of study-group assignments reviewed all deaths. The methods that we used to assess the completeness of data for all outcomes and to account for loss to follow-up are described in the Supplementary Appendix.

Statistical Analysis

All analyses were performed according to a predefined statistical-analysis plan and were based

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Endovascular Repair (N=626)	Open Repair (N=626)
Age — yr	74.1±6.1	74.0±6.1
Male sex — no. (%)	565 (90.3)	570 (91.1)
Diameter of abdominal aortic aneurysm (626 and 625 patients) — cm	6.4±0.9	6.5±1.0
Body-mass index (625 and 620 patients)†	26.5±4.6	26.5±4.3
Diabetes (624 and 620 patients) — no. (%)	61 (9.8)	68 (11.0)
Smoking status (625 and 625 patients) — no. (%)		
Current smoker	134 (21.4)	136 (21.8)
Former smoker	419 (67.0)	444 (71.0)
Never smoked	72 (11.5)	45 (7.2)
History of cardiac disease — no. (%)‡	269 (43.0)	261 (41.8)
Blood pressure — mm Hg		
Systolic (621 and 624 patients)	148±22	147±21
Diastolic (619 and 623 patients)	82±12	82±13
Ankle–brachial pressure index (613 and 599 patients)§	1.01±0.18	1.03±0.18
Forced expiratory volume in 1 second (618 and 622 patients) — liters	2.1±0.7	2.2±0.7
Serum creatinine (625 and 622 patients) — μmol/liter		
Median	102	102
Interquartile range	91–118	90–120
Serum cholesterol (608 and 601 patients) — μmol/liter	5.1±1.2	5.1±1.1
Statin use (619 and 623 patients) — no. (%)	216 (34.9)	224 (36.0)
Aspirin use — no. (%)	338 (54.0)	325 (51.9)

* Data were available for all patients except for characteristics where numbers in the endovascular-repair group and the open-repair group, respectively, are shown. Plus–minus values are means ±SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Cardiac disease was defined as any of the following: myocardial infarction, angina, cardiac revascularization, cardiac-valve disease, clinically significant arrhythmia, and uncontrolled congestive heart failure.

§ The ankle–brachial pressure index is the ratio of the blood pressure in the lower legs to the blood pressure in the arms; the mean for both legs is shown.

on the intention-to-treat principle, with outcomes assessed from the time of randomization. Logistic regression was used to compare operative and in-hospital mortality among patients who had undergone aneurysm repair, and Cox regression was used to compare total mortality, aneurysm-related mortality, and rates of graft-related complications and reinterventions. Kaplan–Meier estimates were used to present results for 8 years, when just over 200 patients remained in follow-up. Crude regression estimates are presented, as well as estimates adjusted for baseline covariates (see the Supplementary Appendix).

Hazard ratios were calculated for total follow-up and for three predefined periods: randomization to 6 months, more than 6 months to 4 years, and after 4 years. A per-protocol analysis was performed on data from patients who had undergone their randomly assigned treatment. This analysis excluded patients who did not undergo aneurysm repair, those who underwent emergency repair, those in whom the repair was abandoned during surgery (i.e., the aorta was left unrepaired), and those who did not undergo the randomly assigned procedure. All reported P values are two-sided. All analyses were performed with the use of Stata statistical software, version 10. (Additional information on the statistical methods that were used, including detailed methods for assessment of costs, is provided in the Supplementary Appendix.)

Table 2. Deaths from Any Cause and from Aneurysm-Related Causes, According to Time since Randomization.

Outcome	Endovascular Repair (N=626)	Open Repair (N=626)	Hazard Ratio (95% CI)		P Value†
			Unadjusted	Adjusted*	
	no./total no. (rate/100 person-yr)				
Any death					
All patients	260/626 (7.5)	264/626 (7.7)	0.98 (0.82–1.16)	1.03 (0.86–1.23)	0.72
Time since randomization					
0–6 mo	26/626 (8.5)	45/626 (15.0)	0.57 (0.35–0.92)	0.61 (0.37–1.02)	0.06
>6 mo–4 yr	125/599 (6.7)	116/581 (6.3)	1.06 (0.82–1.37)	1.12 (0.86–1.45)	0.39
>4 yr	109/472 (8.4)	103/461 (7.9)	1.04 (0.80–1.37)	1.09 (0.82–1.44)	0.57
Aneurysm-related death					
All patients	36/626 (1.0)	40/626 (1.2)	0.89 (0.57–1.39)	0.92 (0.57–1.49)	0.73
Time since randomization					
0–6 mo	14/626 (4.6)	30/626 (10.0)	0.46 (0.24–0.87)	0.47 (0.23–0.93)	0.03
>6 mo–4 yr	12/599 (0.6)	8/581 (0.4)	1.48 (0.60–3.61)	1.46 (0.56–3.82)	0.44
>4 yr	10/472 (0.8)	2/461 (0.2)	4.96 (1.09–22.65)	4.85 (1.04–22.72)	0.05

* Hazard ratios have been adjusted for baseline age, sex, diameter of abdominal aortic aneurysm, forced expiratory volume in 1 second, serum creatinine level (log transformed), use or nonuse of statins, body-mass index, smoking status, systolic blood pressure, and serum cholesterol level. A total of 77 patients were excluded from the follow-up analysis because of missing data.

† P values have been adjusted for baseline covariates.

RESULTS

PATIENTS

From September 1, 1999, through August 31, 2004, we recruited 1252 patients to participate in EVAR 1, with patients equally and randomly divided into the two surgical groups. This overall group consisted of the 1082 patients included in a planned midterm analysis that was reported in 2005[11] and an additional 170 patients who were enrolled between January 2004 and August 2004, who were not included in the midterm analysis (Fig. 1 in the Supplementary Appendix). There were no significant differences between the two treatment groups with respect to baseline characteristics (Table 1). The mean (±SD) age was 74.1±6.1 years, and 1135 of the patients (90.7%) were men. The mean aneurysm diameter was 6.4±0.9 cm.

Patients were followed until September 1, 2009 (minimum, 5 years; maximum, 10 years). The median follow-up until death or the end of the study was 6.0 years (interquartile range, 3.9 to 7.3), and only 1% of patients were lost to follow-up in terms of mortality. During the study period, 1216 aneurysm-repair procedures were actually performed, including 8 emergency procedures (Fig. 1 in the Supplementary Appendix). For patients undergoing aneurysm repair, the median time from randomization to surgery was 44 days (interquartile range, 29 to 70) in the endovascular-repair group and 35 days (interquartile range, 20 to 57) in the open-repair group.

Of the 12 patients in the endovascular-repair group who did not undergo aneurysm repair, 7 died within 6 months after randomization (3 as a result of rupture), 3 became physically ineligible, 1 declined surgery, and 1 became anatomically unsuitable because of a change in the shape of the aorta. Of the 24 patients in the open-repair group who did not undergo aneurysm repair, 7 died within 6 months after randomization (3 as a result of rupture), 7 became physically ineligible, 8 declined surgery (of whom 3 died), and 2 had an unknown reason (of whom 2 died).

OPERATIVE MORTALITY

At 30 days after surgery, the numbers of patients who had died were 11 of 614 patients (1.8%) in the endovascular-repair group (including 1 patient who underwent emergency repair) and 26 of 602 patients (4.3%) in the open-repair group (including 1 patient who underwent emergency re-

pair) (adjusted odds ratio in the endovascular-repair group, 0.39; 95% confidence interval [CI], 0.18 to 0.87; P=0.02). The total numbers of patients who died during hospitalization for aneurysm repair were 14 of 614 patients (2.3%) in the endovascular-repair group (including 2 patients who underwent emergency repair) and 36 of 602 patients (6.0%) in the open-repair group (including 3 patients who underwent emergency repair) (adjusted odds ratio, 0.39; 95% CI, 0.20 to 0.76; P=0.006).

TOTAL AND ANEURYSM-RELATED MORTALITY

During 6904 person-years of follow-up, 524 deaths occurred, 76 of which were aneurysm-related. Table 2 presents total mortality and aneurysm-related mortality on the basis of Cox regression analysis. The overall total mortality was 7.5 deaths per 100 person-years in the endovascular-repair group and 7.7 deaths per 100 person-years in the open-repair group (adjusted hazard ratio in the endovascular-repair group, 1.03; 95% CI, 0.86 to 1.23; P=0.72). The overall aneurysm-related mortality was 1.0 deaths per 100 person-years in the endovascular-repair group and 1.2 deaths per 100 person-years in the open-repair group (adjusted hazard ratio, 0.92; 95% CI, 0.57 to 1.49; P=0.73).

There was evidence of deviation from the proportional-hazards assumption for aneurysm-related mortality (P=0.004), with an early benefit of endovascular repair during the first 6 months (adjusted hazard ratio, 0.47; 95% CI, 0.23 to 0.93; P=0.03) being counteracted by an increase in aneurysm-related mortality after 4 years (adjusted hazard ratio, 4.85; 95% CI, 1.04 to 22.72; P=0.05). There was no significant evidence of deviation from the proportional-hazards assumption for total mortality (P=0.11). Kaplan–Meier curves for total mortality and aneurysm-related mortality are shown in Figure 1, with rates of death from any cause in the two groups converging at 2 years and rates of aneurysm-related death converging at 6 years.

Causes of death are listed in Table 2 in the Supplementary Appendix, stratified according to the time of death in relation to the time of aneurysm repair. Sensitivity analyses that included patients with missing baseline adjustment covariates produced results that were almost identical to the results of analyses that included only patients with complete data. There was no evidence of significant interactions between the randomly assigned treatment and age, sex, or aneurysm diameter for either total mortality or aneurysm-related mortality (P>0.10 for all comparisons). Per-protocol analysis was performed for the 1165 patients who had undergone their randomly assigned treatment (Fig. 1 in the Supplementary Appendix). A total of 469 deaths occurred (56 of which were aneurysm-related) in the per-protocol group. The overall total mortality was 7.2 deaths per 100 person-years in the endovascular-repair group and 7.1 deaths per 100 person-years in the open-repair group (adjusted hazard ratio in the endovascular-repair group, 1.05; 95% CI, 0.87 to 1.27; P=0.61). The overall aneurysm-related mortality was 0.9 deaths per 100 person-years in the endovascular-repair group and 0.8 deaths per 100 person-years in the open-repair group (adjusted hazard ratio, 1.06; 95% CI, 0.60 to 1.88; P=0.85).

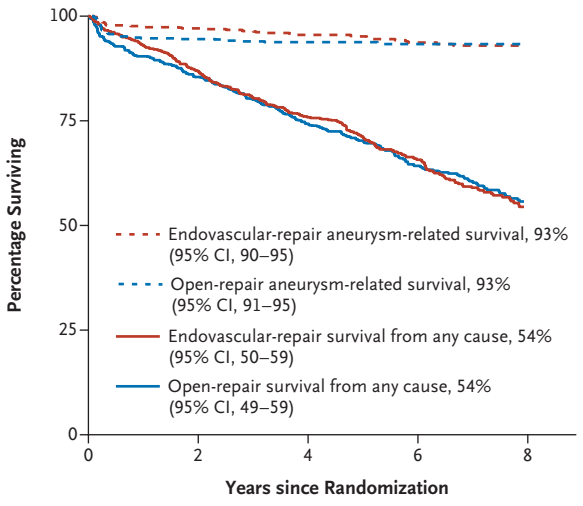

Figure 1. Kaplan–Meier Estimates for Total Survival and Aneurysm-Related Survival during 8 Years of Follow-up.

Among patients randomly assigned to either endovascular repair or open repair of an abdominal aortic aneurysm, an early benefit with respect to aneurysm-related mortality in the endovascular-repair group was lost by the end of the study, at least partially because of fatal endograft ruptures (adjusted hazard ratio with endovascular repair, 0.92; 95% CI, 0.57 to 1.49; P=0.73). By the end of 8 years of follow-up, there was no significant difference between the two groups in the risk of death from any cause (adjusted hazard ratio, 1.03; 95% CI, 0.86 to 1.23; P=0.72).

GRAFT-RELATED COMPLICATIONS AND REINTERVENTIONS

During 5309 person-years of follow-up, 567 graft complications were reported in 360 patients, with

Table 3. First Graft-Related Complication or Reintervention, According to Time since Randomization.

Outcome	Endovascular Repair (N=626)	Open Repair (N=626)	Hazard Ratio (95% CI)		P Value†
			Unadjusted	Adjusted*	
	no./total no. (rate/100 person-yr)				
Complication					
All patients	282/626 (12.6)	78/626 (2.5)	4.38 (3.41–5.63)	4.39 (3.38–5.70)	<0.001
Time since randomization					
0–6 mo	132/626 (48.7)	45/626 (15.6)	3.08 (2.20–4.33)	3.18 (2.23–4.52)	<0.001
>6 mo–4 yr	114/473 (9.0)	18/550 (1.1)	8.37 (5.09–13.76)	7.92 (4.80–13.09)	<0.001
>4 yr	36/280 (5.1)	15/413 (1.4)	3.65 (2.00–6.67)	3.33 (1.76–6.29)	<0.001
Reintervention					
All patients	145/626 (5.1)	55/626 (1.7)	2.78 (2.04–3.80)	2.86 (2.08–3.94)	<0.001
Time since randomization					
0–6 mo	66/626 (22.9)	40/626 (13.8)	1.65 (1.12–2.44)	1.75 (1.16–2.63)	0.007
>6 mo–4 yr	55/537 (3.4)	6/555 (0.3)	9.97 (4.29–23.15)	9.12 (3.90–21.3)	<0.001
>4 yr	24/377 (2.4)	9/428 (0.8)	3.12 (1.47–6.80)	3.24 (1.48–7.11)	0.003

* Hazard ratios have been adjusted for baseline age, sex, diameter of abdominal aortic aneurysm, forced expiratory volume in 1 second, serum creatinine level (log transformed), use or nonuse of statins, body-mass index, smoking status, systolic blood pressure, serum cholesterol level, top neck diameter (aortic diameter at the lowest renal artery), neck length (distance from the lowest renal artery to the start of the aneurysm expansion), and common iliac diameter (log maximum for both legs). A total of 91 patients were excluded from the follow-up analysis because of missing data.

† P values have been adjusted for baseline covariates.

1 complication in 238 patients, 2 complications in 67 patients, 3 complications in 33 patients, 4 complications in 17 patients, 5 complications in 2 patients, and 6 complications in 3 patients (Table 3 in the Supplementary Appendix). Graft rupture occurred in 25 patients after the placement of the endograft, with conversion to open repair attempted in 7 patients, 5 of whom survived. Conversion to open repair occurred for other reasons in an additional 18 patients, 15 of whom survived. Mortality was high after graft rupture, with 17 of 25 patients (68.0%) dying within 30 days and 1 patient dying after 30 days (Table 2 in the Supplementary Appendix). A total of 257 graft-related reinterventions were performed in 200 patients, with 1 reintervention in 161 patients, 2 reinterventions in 26 patients, and 3 to 5 reinterventions in 13 patients.

The overall rates of graft-related complications and reinterventions were higher by a factor of three to four in the endovascular-repair group than in the open-repair group (Table 3 and Fig. 2). There was evidence of deviation from the proportional-hazards assumption for both complications (P=0.01) and reinterventions (P=0.001), with most of the deviation attributable to a high relative increase in graft-related events in the endovascular-repair group from 6 months to 4 years after surgery.

COSTS

Detailed costs are provided in Table 4 in the Supplementary Appendix. The mean cost of the primary aneurysm repair was £13,019 (U.S. $19,698) in the endovascular-repair group and £11,842 ($17,917) in the open-repair group (mean difference, £1,177 [$1,781]; 95% CI, −374 to 2,728 [−566 to 4,127]). The mean cost of aneurysm-related readmissions was £2,283 ($3,454) in the endovascular-repair group and £442 ($669) in the open-repair group (mean difference, £1,841 [$2,785]; 95% CI, 913 to 2,770 [1,381 to 4,191]). During 8 years of follow-up, the total average cost of aneurysm-related procedures in the endovascular-repair group was £3,019 ($4,568) more than in the open-repair group (mean costs, £15,303 [$23,153] and £12,284 [$18,586], respectively). The primary admission and the later admissions for graft-related reinterventions contributed almost equally to the cost difference.

DISCUSSION

The results over a median follow-up period of 6 years confirm our previously published midterm findings that operative mortality associated with endovascular repair of abdominal aortic aneurysm was only a third of that associated with the open-repair procedure and that aneurysm-related mortality was reduced during the early years after endovascular repair.[11] However, the early benefit was completely lost in the longer term, with substantially higher aneurysm-related mortality after 4 years in the endovascular-repair group than in the open-repair group. We found no significant difference in total mortality between the two study groups. The rate of graft-related complications after endovascular repair remained substantial after 4 years, as did the need for reinterventions. Secondary rupture after aneurysm repair was reported only after endovascular repair and appeared to explain the long-term increase in aneurysm-related mortality. In contrast, open repair was very durable but was associated with higher operative mortality. These findings have implications for the selection of patients for endovascular repair, the choices for patients, surveillance after repair, and cost-effectiveness. The results also confirm that careful long-term follow-up of surgical innovations is essential, as highlighted in recent research recommendations.[14]

After the postoperative period, just under half of all deaths were attributed to cardiovascular disease (including aneurysm), a slightly lower proportion than that reported for the 4-year results,[11] which may reflect improvements in medical therapy.[15] Just over one quarter of deaths were attributed to cancer. A total of 20 patients in the endovascular-repair group and 6 patients in the open-repair group died from aneurysm-related causes after the postoperative period; 2 of the late deaths in the open-repair group were from graft ruptures in patients who had been assigned to open repair but had undergone endovascular repair. In total, 25 secondary aneurysm ruptures were reported, and of those 18 (72.0%) were fatal. Therefore, the loss of the aneurysm-related survival benefit in the endovascular-repair group would appear to be attributable principally to endograft rupture. Many of the patients in whom such an event occurred had graft-related complications that were detected before rupture.

Very few of the patients in our study either did not undergo the assigned treatment or were lost to follow-up, and there were few missing data. Per-protocol analysis yielded results that were very similar to those of the intention-to-treat analysis. However, this study had some limitations that could affect the interpretation of our findings. First, although the trial used principally second- and third-generation endografts, subsequent iterations of the grafts would now be the more common choices of device. The long-term durability of these later iterations of endografts has not

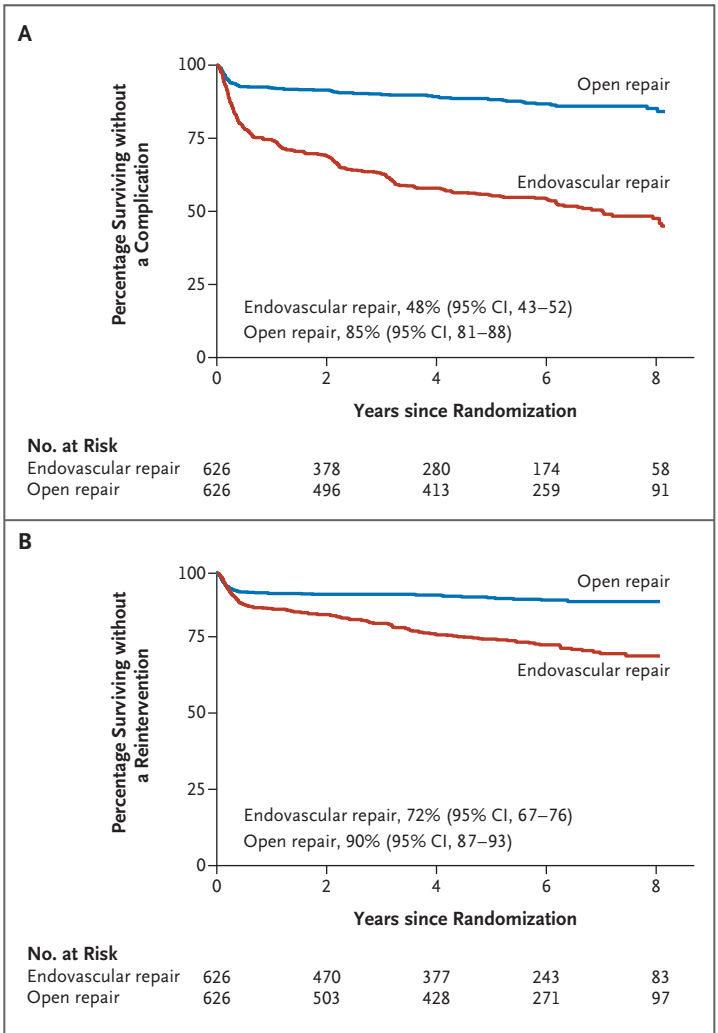

Figure 2. Kaplan–Meier Estimates for the Time to the First Graft-Related Complication or Reintervention during 8 Years of Follow-up.

The rates of graft-related complications (Panel A) and reinterventions (Panel B) were higher among patients in the endovascular-repair group than among those in the open-repair group. New complications occurred throughout the 8-year follow-up period, contributing to the higher overall costs of the endovascular procedure.

been evaluated, but it is hoped that they would be associated with lower complication rates. Second, the trial started 3 years before the standardized reporting of graft-related complications.[16] Thus, the reporting of complications reflected the assessments made by radiologists in the participating centers, and these reports were not evaluated in a core laboratory. Third, we did not record outpatient procedures, which would have included minor procedures, such as diagnostic angiography, that are often performed after endovascular repair to obtain more detailed information on any potential complications. A corresponding underestimation of reintervention rates and costs may also have occurred for the open-repair group, since readmission data were not collected for abdominal hernias or other complications related to open repair.

New graft-related complications and reinterventions continued to be reported for as long as 8 years after endovascular procedures were performed. Future work should determine whether specific complications, or combinations of complications, of endovascular repair may signal an increased risk of endograft rupture or death. The continuing occurrence of graft-related complications and reinterventions underscores the need for continued surveillance, and these clinical episodes contribute to the increase in the lifetime cost of aneurysm-related events after endovascular repair as compared with open repair. A streamlined post-repair surveillance algorithm designed to minimize the exposure of patients to radiation without limiting the future detection and management of potentially dangerous complications of graft failure is likely to enhance cost-effectiveness. More detailed modeling is under way to assess whether endovascular repair is cost-effective for all patients or only for selected subgroups. Currently, patients strongly prefer endovascular repair to open repair.[17,18] However, these preferences were declared on the basis of early and midterm evidence alone. Although there is still an early mortality reduction with endovascular repair, which is less invasive than open repair, it is difficult to predict what effect these late results will have on patients' preferences or on the implications for cost-effectiveness, factors that will influence future clinical-management decisions and policy recommendations.

In conclusion, among patients who were considered to be suitable candidates for either endovascular repair or open repair of abdominal aortic aneurysm, the endovascular procedure was associated with a significantly lower operative mortality. However, no significant differences were seen in total mortality or aneurysm-related mortality in the long term. Endovascular repair was associated with increased rates of complications and reinterventions and was more costly.

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The views expressed in this article are those of the authors and do not necessarily represent those of the United Kingdom National Health Service.

APPENDIX

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ORIGINAL ARTICLE

Endovascular Repair of Aortic Aneurysm in Patients Physically Ineligible for Open Repair

The United Kingdom EVAR Trial Investigators*

ABSTRACT

BACKGROUND

Endovascular repair of abdominal aortic aneurysm was originally developed for patients who were considered to be physically ineligible for open surgical repair. Data are lacking on the question of whether endovascular repair reduces the rate of death among these patients.

METHODS

From 1999 through 2004 at 33 hospitals in the United Kingdom, we randomly assigned 404 patients with large abdominal aortic aneurysms (≥5.5 cm in diameter) who were considered to be physically ineligible for open repair to undergo either endovascular repair or no repair; 197 patients were assigned to undergo endovascular repair, and 207 were assigned to have no intervention. Patients were followed for rates of death, graft-related complications and reinterventions, and costs until the end of 2009. Cox regression was used to compare outcomes in the two groups.

RESULTS

The 30-day operative mortality was 7.3% in the endovascular-repair group. The overall rate of aneurysm rupture in the no-intervention group was 12.4 (95% confidence interval [CI], 9.6 to 16.2) per 100 person-years. Aneurysm-related mortality was lower in the endovascular-repair group (adjusted hazard ratio, 0.53; 95% CI, 0.32 to 0.89; P=0.02). This advantage did not result in any benefit in terms of total mortality (adjusted hazard ratio, 0.99; 95% CI, 0.78 to 1.27; P=0.97). A total of 48% of patients who survived endovascular repair had graft-related complications, and 27% required reintervention within the first 6 years. During 8 years of follow-up, endovascular repair was considerably more expensive than no repair (cost difference, £9,826 [U.S. $14,867]; 95% CI, 7,638 to 12,013 [11,556 to 18,176]).

CONCLUSIONS

In this randomized trial involving patients who were physically ineligible for open repair, endovascular repair of abdominal aortic aneurysm was associated with a significantly lower rate of aneurysm-related mortality than no repair. However, endovascular repair was not associated with a reduction in the rate of death from any cause. The rates of graft-related complications and reinterventions were higher with endovascular repair, and it was more costly. (Current Controlled Trials number, ISRCTN55703451.)

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*The investigators in the United Kingdom Endovascular Aneurysm Repair (EVAR) trial are listed in the Appendix.

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Endovascular repair of abdominal aortic aneurysm was originally developed for patients who were considered to be physically ineligible for open surgical repair,[1] since it was thought that life expectancy would be prolonged by eliminating the risk of fatal rupture of an aneurysm. We designed the United Kingdom Endovascular Aneurysm Repair 2 (EVAR 2) trial to test this hypothesis.[2] The midterm results of the trial, reported in 2005, showed no benefit of endovascular repair on total or aneurysm-related mortality in up to 4 years of follow-up.[3] One factor underlying this unexpected result was an operative mortality rate that was higher than anticipated (9%). Other studies have also shown a high operative mortality rate for endovascular repair among patients considered to be physically ineligible for open repair.[4,5] In addition, our midterm analysis showed high total mortality (68% at 4 years).

Another contributing factor in the unexpected outcome of EVAR 2 was a rate of rupture of large, untreated aneurysms that was lower than anticipated (9 ruptures per 100 person-years). Subsequent analysis has suggested that the rate of aneurysm rupture appears to be lower among patients with an aortic anatomy that is suitable for endovascular repair (in particular, a long aneurysm neck) and that the use of statins may have further attenuated the rate of aneurysm rupture.[6] Nevertheless, since progressive enlargement is the natural history of large aneurysms, the benefits of endovascular repair may take longer than 4 years to become apparent. We now report the long-term follow-up of patients enrolled in the EVAR 2 trial.

METHODS

TRIAL DESIGN

The methods that we used in this trial have been published previously[2,3] and are described in detail in the Supplementary Appendix (available with the full text of this article at NEJM.org). In summary, EVAR 2 was a randomized trial designed by the principal investigator in consultation with the grant applicants, the members of the trial-management and steering committees, and the trial manager. The trial was sponsored by the Health Technology Assessment Programme of the National Institute for Health Research in the United Kingdom. No support was provided by pharmaceutical or medical-device companies. Full approval of the trial was granted by the United Kingdom's North West Multicentre Research Ethics Committee.

The trial was conducted at 33 hospitals that met the criteria for participation in the trial (for details, see the Supplementary Appendix). Trained local coordinators were responsible for recruitment of patients, data collection, and follow-up.

TRIAL PROCEDURES

Patients of both sexes who were at least 60 years of age with an abdominal aortic aneurysm measuring at least 5.5 cm in diameter on computed tomography (CT) were evaluated for trial participation. Patients who were considered to be physically ineligible for open repair but who were candidates for endovascular repair were offered enrollment in the EVAR 2 trial (see the Supplementary Appendix for details regarding the evaluation of candidates). Patients who were considered to be suitable candidates for either procedure were offered enrollment in the Endovascular Aneurysm Repair 1 (EVAR 1) trial, reported elsewhere in this issue of the *Journal*.[7] All patients provided written informed consent.

The patients in EVAR 2 were randomly assigned to undergo endovascular aneurysm repair or to have no intervention. Patients in the endovascular-repair group were encouraged to undergo repair within 1 month after randomization, though this scheduling was not always possible for logistic or other reasons. CT was performed at 1 and 3 months in patients undergoing endovascular repair and annually in all patients in the two study groups. The primary outcome was death from any cause, but aneurysm-related death was also assessed, as were graft-related complications and graft-related reinterventions. (Full definitions of the trial end points are available in the Supplementary Appendix.) An independent end-points committee whose members were unaware of study-group assignments reviewed all mortality outcome events. The methods that we used to assess the completeness of data for all outcomes and to account for loss to follow-up are described in the Supplementary Appendix.

STATISTICAL ANALYSIS

All analyses were performed according to a predefined statistical-analysis plan with the use of Stata statistical software, version 10. All analyses were based on the intention-to-treat principle, with outcomes assessed from the time of ran-

domization. Cox-regression analysis was used to compare total mortality and aneurysm-related mortality (with data censored for deaths due to causes other than aneurysm) between the study groups in the EVAR 2 trial and to compare the rates of graft-related complications and reinterventions (in both cases with data censored for deaths) between the endovascular-repair groups in EVAR 2 and EVAR 1.[7] Unadjusted hazard ratios were calculated as well as hazard ratios adjusted for baseline covariates (see the Supplementary Appendix). Hazard ratios were calculated for total follow-up and for three predefined time periods: randomization to 6 months, more than 6 months to 4 years, and after 4 years.

Kaplan–Meier estimates were used to present results for 8 years of follow-up, but 6-year estimates are reported because of the high attrition after this time. An overall rate of aneurysm rupture was estimated in the no-intervention group after the censoring of data for patients who died from a cause other than aneurysm rupture or who underwent elective aneurysm repair. A per-protocol analysis excluded patients at the time of protocol deviation. (Additional information on the statistical methods that we used, including details of the per-protocol classification, assessment of the proportional-hazards assumption, interaction testing, and assessment of costs, is provided in the Supplementary Appendix.)

RESULTS

PATIENTS

Between September 1, 1999, and August 31, 2004, we recruited 404 patients to participate in EVAR 2. This overall group consisted of the 338 patients included in the planned midterm analysis that was reported in 2005[3] and an additional 66 patients who were enrolled between January 2004 and August 2004, who were not included in the midterm analysis (Fig. 1 in the Supplementary Appendix). A total of 197 patients were randomly assigned to the endovascular-repair group, and 207 were assigned to the no-intervention group. There were no significant differences between the two study groups with respect to baseline characteristics (Table 1). The mean (±SD) age was 76.8±6.5 years, and 347 of the patients (86%) were men. The mean aneurysm diameter was 6.7±1.0 cm.

Patients were followed until September 1, 2009 (minimum, 5 years; maximum, 10 years). The median follow-up until death or the end of the study was 3.1 years (interquartile range, 1.3 to 5.4), and less than 1% of patients were lost to follow-up in terms of mortality. During the study period, 249 aneurysm-repair procedures were actually performed, including 10 emergency procedures (Fig. 1 in the Supplementary Appendix). For the 179 patients in the endovascular-repair group who underwent aneurysm repair, the median time from randomization to surgery was 55 days (interquartile range, 38 to 77), and for the 70 patients in the no-intervention group who underwent repair, the median time from randomization to surgery was 244 days (interquartile range, 83 to 643).

Of the 18 patients in the endovascular-repair group who did not undergo aneurysm repair, 7 died within 6 months after randomization (2 as a result of rupture), 8 became physically ineligible or anatomically unsuitable for endovascular repair, 1 declined aneurysm repair, and 2 had an unknown reason. Of the 70 patients in the no-intervention group who underwent repair, 64 underwent elective procedures for the following reasons: 14 had aneurysms that became tender on examination, 8 had aneurysms that grew quickly, 1 had symptoms, 1 was incorrectly enrolled in trial 2 rather than trial 1, 24 declined surveillance, and 16 had an unknown reason. By September 2009, a total of 99 patients remained alive; 14 of these patients had not undergone aneurysm repair.

OPERATIVE MORTALITY

Among the 179 patients in the endovascular-repair group who underwent aneurysm repair, 13 patients (7.3%) died within 30 days after the procedure, and 15 patients died in the hospital (8.4%); among the 175 patients who underwent elective repair, 10 (5.7%) died within 30 days after the procedure, and 11 (6.3%) died in the hospital. In the no-intervention group, among the 70 patients who underwent aneurysm repair, 2 patients (3%) died within 30 days after the procedure, and 3 patients died in the hospital (4.3%); among the 64 patients who underwent elective repair, 1 patient (2%) died within 30 days after the procedure, and 2 patients (3%) died in the hospital.

TOTAL AND ANEURYSM-RELATED MORTALITY

During 1413 person-years of follow-up, 305 deaths occurred, 78 of which were aneurysm-related (Table 2). The overall total mortality was 21.0 deaths

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Endovascular Repair (N=197)	No Repair (N=207)
Age — yr	77.2±6.3	76.4±6.7
Male sex — no. (%)	168 (85.3)	179 (86.5)
Diameter of abdominal aortic aneurysm — cm	6.8±1.0	6.7±1.0
Body-mass index (196 and 206 patients)†	26.4±5.0	26.5±4.4
Diabetes (195 and 205 patients) — no. (%)	30 (15.4)	29 (14.1)
Smoking status — no. (%)		
Current smoker	33 (16.8)	37 (17.9)
Former smoker	152 (77.2)	156 (75.4)
Never smoked	12 (6.1)	14 (6.8)
History of cardiac disease — no. (%)‡	132 (67.0)	153 (73.9)
Blood pressure — mm Hg		
Systolic	140±20	139±23
Diastolic (197 and 204 patients)	79±12	79±12
Ankle–brachial pressure index (187 and 199 patients)§	0.99±0.20	0.98±0.19
Forced expiratory volume in 1 second (190 and 203 patients) — liters	1.6±0.6	1.7±0.7
Serum creatinine (197 and 205 patients) — μmol/liter		
Median	107	112
Interquartile range	90–134	94–140
Serum cholesterol (184 and 200 patients) — mmol/liter	4.8±1.2	4.8±1.1
Statin use (196 and 207 patients) — no. (%)	82 (41.8)	86 (41.5)
Aspirin use (196 and 207 patients) — no. (%)	114 (58.2)	114 (55.1)

* Data were available for all patients except for characteristics where numbers in the endovascular-repair group and the no-repair group, respectively, are shown. Plus–minus values are means ±SD. To convert the values for creatinine to milligrams per deciliter, divide by 88.4. To convert the values for cholesterol to milligrams per deciliter, divide by 0.02586.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Cardiac disease was defined as any of the following: myocardial infarction, angina, cardiac revascularization, cardiac-valve disease, clinically significant arrhythmia, and uncontrolled congestive heart failure.

§ The ankle–brachial pressure index is the ratio of the blood pressure in the lower legs to the blood pressure in the arms; the mean for both legs is shown.

per 100 person-years in the endovascular-repair group and 22.1 deaths per 100 person-years in the no-intervention group (adjusted hazard ratio with endovascular repair, 0.99; 95% confidence interval [CI], 0.78 to 1.27; P=0.97). The overall aneurysm-related mortality was 3.6 deaths per 100 person-years in the endovascular-repair group and 7.3 deaths per 100 person-years in the no-intervention group (adjusted hazard ratio, 0.53; 95% CI, 0.32 to 0.89; P=0.02).

There was evidence of deviation from the proportional-hazards assumption for aneurysm-related mortality (P<0.001), with a nonsignificant increase in aneurysm-related deaths in the endovascular-repair group during the first 6 months (adjusted hazard ratio, 1.78), reflecting operative deaths. This increase was counterbalanced by a decrease in aneurysm-related deaths in the same group after 6 months (adjusted hazard ratio for the period from randomization to 4 years, 0.26) (Table 2). There was no significant evidence of deviation from the proportional-hazards assumption for total mortality (P=0.07). Kaplan–Meier curves for total and aneurysm-related mortality are shown in Figure 1.

Causes of death, stratified according to the time of death relative to the time of randomization, are listed in Table 2 in the Supplementary

Table 2. Deaths from Any Cause and from Aneurysm-Related Causes, According to Time since Randomization.

Outcome	Endovascular Repair (N=197)	No Repair (N=207)	Hazard Ratio (95% CI)		P Value†
			Unadjusted	Adjusted*	
	no./total no. (rate/100 person-yr)				
Death from any cause					
All patients	145/197 (21.0)	160/207 (22.1)	0.95 (0.76–1.19)	0.99 (0.78–1.27)	0.97
Time since randomization					
0–6 mo	24/197 (26.0)	19/207 (19.0)	1.38 (0.76–2.52)	1.32 (0.68–2.54)	0.41
>6 mo–4 yr	92/173 (21.4)	108/188 (23.6)	0.90 (0.69–1.20)	1.02 (0.75–1.37)	0.92
>4 yr	29/81 (17.3)	33/80 (20.0)	0.86 (0.52–1.42)	0.72 (0.42–1.24)	0.24
Aneurysm-related death					
All patients	25/197 (3.6)	53/207 (7.3)	0.50 (0.31–0.81)	0.53 (0.32–0.89)	0.02
Time since randomization					
0–6 mo	15/197 (16.3)	9/207 (9.0)	1.82 (0.80–4.16)	1.78 (0.75–4.21)	0.19
>6 mo–4 yr	10/173 (2.3)	35/188 (7.6)	0.31 (0.15–0.62)	0.34 (0.16–0.72)	0.005
>4 yr	0/81	9/80 (5.5)	0	NC	NC

* Hazard ratios have been adjusted for baseline age, sex, diameter of abdominal aortic aneurysm, forced expiratory volume in 1 second, serum creatinine level (log transformed), use or nonuse of statins, body-mass index, smoking status, systolic blood pressure, and serum cholesterol level. A total of 34 patients were excluded from the follow-up analysis because of missing baseline data. NC denotes data that could not be calculated.
† P values have been adjusted for baseline covariates.

Appendix. A total of 68 ruptures, 63 of which were fatal, occurred in both study groups. A total of 55 ruptures occurred in the no-intervention group, for an unadjusted rupture rate of 12.4 ruptures (95% CI, 9.6 to 16.2) per 100 person-years.

Sensitivity analyses that included patients with missing baseline adjustment covariates produced results that were almost identical to the results of analyses that included only patients with complete data. There was no evidence of significant interactions between the study group and age, sex, or aneurysm diameter for either aneurysm-related mortality or total mortality (P>0.10 for all comparisons). In the per-protocol analyses (Fig. 2), overall rates of death from any cause were 21.1 deaths per 100 person-years in the endovascular-repair group and 27.6 deaths per 100 person-years in the no-intervention group (adjusted hazard ratio, 0.82; 95% CI, 0.63 to 1.07; P=0.14). The overall aneurysm-related mortality was 3.7 deaths per 100 person-years in the endovascular-repair group and 10.9 deaths per 100 person-years in the no-intervention group (adjusted hazard ratio, 0.41; 95% CI, 0.24 to 0.69; P=0.001).

GRAFT-RELATED COMPLICATIONS AND REINTERVENTIONS

During 1084 person-years of follow-up, 158 graft complications were reported in 97 patients, with 1 complication in 52 patients, 2 complications in 33 patients, 3 complications in 8 patients, and 4 complications in 4 patients (Table 3 in the Supplementary Appendix). Graft rupture occurred in two patients after the placement of an endograft (one patient underwent insertion of a stent on an emergency basis and survived, and the other underwent attempted conversion to open repair but died). Conversions to open repair occurred for other reasons in an additional two patients, and both survived. A total of 66 graft-related reinterventions were performed in 55 patients, with 1 reintervention in 48 patients, 2 reinterventions in 3 patients, and 3 reinterventions in 4 patients.

The rates of graft-related events did not differ significantly between the endovascular-repair groups in EVAR 1 and EVAR 2, despite the considerable disparity in fitness between the two trial cohorts (Fig. 3A). The unadjusted hazard ratio for complications (with endovascular repair in trial 2 as compared with endovascular repair in trial 1) was 1.02 (95% CI, 0.79 to 1.32; P=0.87). The unad-

justed hazard ratio for reinterventions was 1.20 (95% CI, 0.85 to 1.70; P=0.31).

COSTS

Detailed costs for aneurysm-related procedures are provided in Table 4 in the Supplementary Appendix. The mean cost of the primary aneurysm repair was £13,301 (U.S. $20,124) in the endovascular-repair group. In the no-intervention group, fewer patients actually underwent repair; the mean cost in this group was thus lower, at £4,467 ($6,759) (mean difference, £8,834 [$13,366]; 95% CI, 7,068 to 10,599 [10,802 to 16,127]). The mean cost of aneurysm-related readmissions was £1,694 ($2,563) in the endovascular-repair group and £702 ($1,062) in the no-intervention group. During 8 years of follow-up, the total average cost of aneurysm-related procedures was £14,995 ($22,687) in the endovascular-repair group and £5,169 ($7,821) in the no-intervention group (cost difference, £9,826 [$14,867]; 95% CI, 7,638 to 12,013 [11,556 to 18,176]). Most of the cost difference was attributed to the primary aneurysm-repair procedure itself.

DISCUSSION

In 2005, when the midterm results of the EVAR 2 trial were reported, they offered little support for endovascular repair of abdominal aortic aneurysms in patients considered to be physically ineligible for open surgical repair. With longer follow-up, we found a benefit of endovascular repair in terms of aneurysm-related mortality. However, these patients had a limited life expectancy, regardless of whether the aneurysm was repaired or no intervention was performed, with few surviving after 8 years.

The operative mortality after endovascular repair in EVAR 2 (7.3%) was considerably higher than that reported among the patients in EVAR 1 (1.8%).[7] The midterm results of EVAR 2[3] showed a slightly higher operative mortality, at 8.7%, which appears to have been attenuated with the recruitment of an additional 66 patients. The rate of statin use increased during the course of the EVAR 2 trial (from 39.5% before December 2003 to 53.0% afterward); this may have reduced the operative rate of death.[8,9] Other improvements in clinical practice and efforts to optimize fitness may have been implemented.[10] Another analysis of EVAR 2 data suggested that the rate

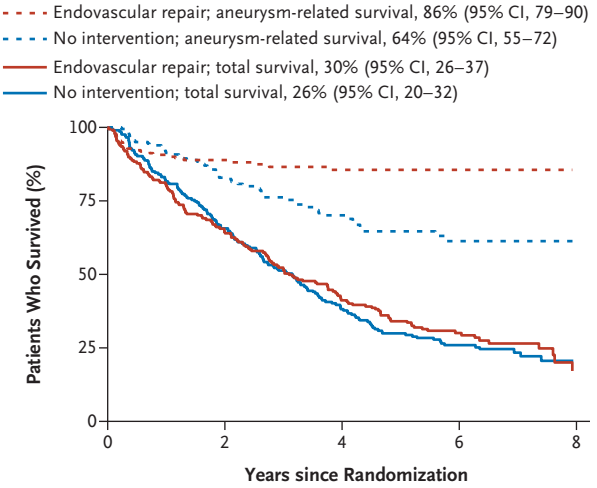


Figure 1. Kaplan–Meier Estimates for Total and Aneurysm-Related Survival at 8 Years, According to Study Group.

Survival curves are shown for patients with abdominal aortic aneurysm who were randomly assigned to the endovascular-repair group and for those assigned to the no-intervention group. Kaplan–Meier estimates were used to present results for 8 years of follow-up, but estimates for 6 years are shown because of the high attrition after this time.

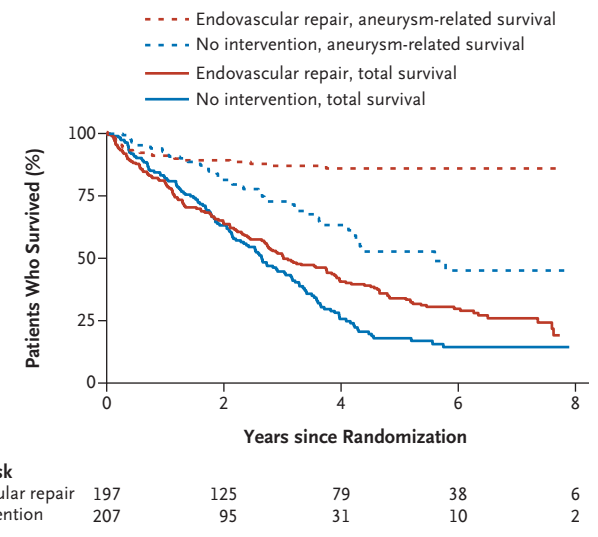
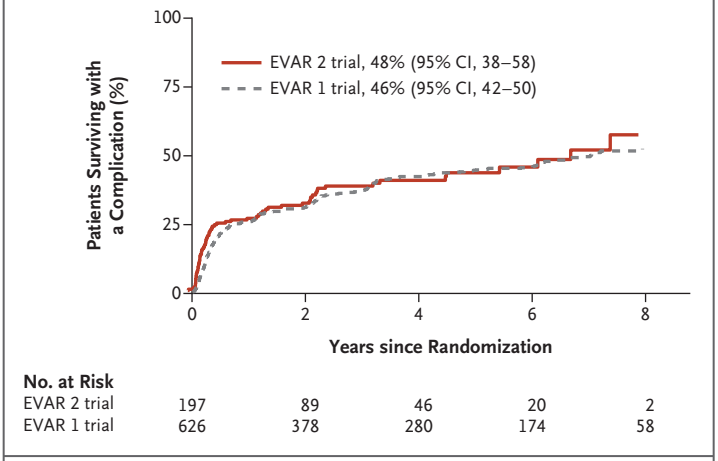


Figure 2. Kaplan–Meier Estimates for Per-Protocol Analysis of Total and Aneurysm-Related Survival, According to Study Group.

Survival curves are shown for patients with abdominal aortic aneurysm who were treated according to trial protocol in the endovascular-repair group and the no-intervention group.



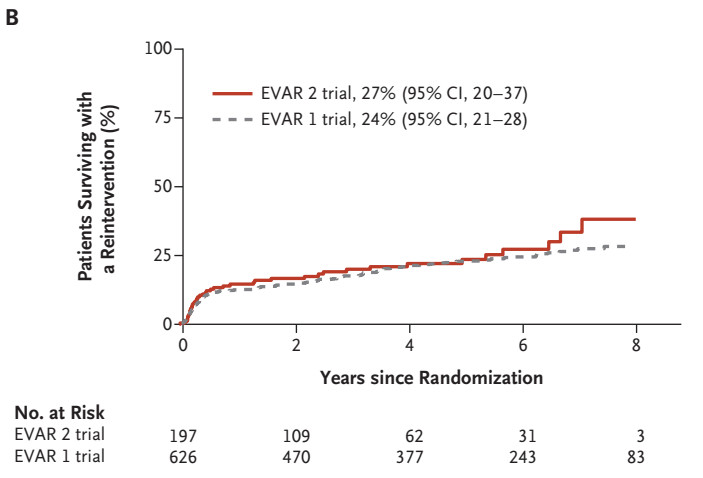


Figure 3. Kaplan–Meier Estimates for the Time to the First Graft-Related Complication or Reintervention.

The time to the first graft-related complication (Panel A) and the time to the first reintervention (Panel B) are shown for the 626 patients assigned to undergo endovascular repair in the EVAR 1 trial and the 197 patients assigned to undergo endovascular repair in the EVAR 2 trial. Kaplan–Meier estimates were used to present results for 8 years of follow-up, but estimates for 6 years of follow-up are shown because of the high attrition after this time.

of cardiovascular events (myocardial infarctions and strokes) was higher in the endovascular-repair group than in the no-intervention group, although this difference was not statistically significant.[11] Thus, the previous recommendation[3] that optimization of fitness for intervention should be given priority over placement of an endovascular graft remains valid.

In this longer-term study, placement of an endovascular graft led to a significant reduction in aneurysm-related mortality, primarily through prevention of late aneurysm rupture. The rupture rate of 12.4 per 100 person-years in the no-intervention group is somewhat lower than the rates in other cohorts of patients with large aneurysms who were considered to be physically ineligible for open surgical repair,[12,13] but it remains high, and the danger of large aneurysms should not be downplayed. Previous studies have suggested that anatomical suitability may impart some protection against rupture.[4] Also, the aneurysm repairs that were performed against protocol may have led to a reduced number of ruptures; thus, the rupture rate in our study may not reflect the true natural history of large aneurysms if they are left untreated in the long term.

Although endovascular repair reduced the rate of aneurysm rupture, it did not lead to an improvement in overall survival. The factors leading to the judgment that these patients were physically ineligible for open repair (primarily because of cardiovascular disease, as noted in Table 1 in the Supplementary Appendix) seem likely to have contributed to a high subsequent rate of death from any cause; this rate was not influenced by assignment to endovascular repair. Thus, on the basis of these data, a decision to perform endovascular repair when open surgical repair is deemed inadvisable should presumably balance the risk of the intervention itself against the risk of aneurysm rupture, with the expectation that survival would probably be unaffected.

During the course of the trial, a substantial minority of patients in the no-intervention group and their physicians opted in favor of repair, resulting in a loss of equipoise. A post hoc analysis comparing baseline fitness in the patients who crossed over to endovascular repair with patients assigned to endovascular repair who underwent repair showed that the patients who crossed over were significantly more fit (details are available in the Supplementary Appendix). Per-protocol analyses showed a greater benefit of endovascular repair in terms of aneurysm-related mortality. A nonsignificant benefit with respect to total mortality was also shown. However, the interpretation of these data is problematic, since the analyses were not performed according to study group and therefore were potentially biased. Regardless of these considerations, the rate of crossover in the trial suggests that it may prove difficult to withhold endovascular repair in the future.

Graft-related complications and reinterventions were common after endovascular repair, but they were not associated with increased mortality. Very few procedure-related deaths occurred 6 or more months after the primary procedure. Despite gross differences in the fitness of patients and overall mortality between the EVAR 1 and EVAR 2 cohorts, the rates of complications and reinterventions were remarkably similar; suitability for open repair, as determined by an anesthesiologist, appears to be of little relevance in the development of subsequent graft-related events. Other studies investigating baseline factors that might be associated with serious graft-related complications and reinterventions after endovascular aneurysm repair have shown that older age and a larger aneurysm diameter appear to be strongly influential.[14] However, differences in these factors between EVAR 1 and EVAR 2 did not lead to different rates of graft-related events. This finding may be explained in part by the attrition due to high mortality in EVAR 2, leaving less time for graft-related complications to develop. This attrition may also explain why only two endovascular-graft ruptures occurred in EVAR 2, as compared with 25 ruptures in EVAR 1.

In conclusion, the EVAR 2 trial showed that in patients with abdominal aortic aneurysm who were considered to be physically ineligible for open surgical repair, endovascular repair, as compared with no intervention, was associated with a significantly lower rate of aneurysm-related mortality in the long term, but with no reduction in total mortality. Endovascular repair was considerably more expensive than no intervention.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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