ORIGINAL ARTICLE

Open versus Endovascular Repair of Abdominal Aortic Aneurysm

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ABSTRACT

BACKGROUND

Elective endovascular repair of an abdominal aortic aneurysm results in lower perioperative mortality than traditional open repair, but after 4 years this survival advantage is not seen; in addition, results of two European trials have shown worse long-term outcomes with endovascular repair than with open repair. Long-term results of a study we conducted more than a decade ago to compare endovascular repair with open repair are unknown.

METHODS

We randomly assigned patients with asymptomatic abdominal aortic aneurysms to either endovascular repair or open repair of the aneurysm. All the patients were candidates for either procedure. Patients were followed for up to 14 years.

RESULTS

A total of 881 patients underwent randomization: 444 were assigned to endovascular repair and 437 to open repair. The primary outcome was all-cause mortality. A total of 302 patients (68.0%) in the endovascular-repair group and 306 (70.0%) in the open-repair group died (hazard ratio, 0.96; 95% confidence interval [CI], 0.82 to 1.13). During the first 4 years of follow-up, overall survival appeared to be higher with endovascular repair than with open repair; from year 4 through year 8, overall survival was higher in the open-repair group; and after 8 years, overall survival was once again higher in the endovascular-repair group (hazard ratio for death, 0.94; 95% CI, 0.74 to 1.18). None of these trends were significant. There were 12 aneurysm-related deaths (2.7%) in the endovascular-repair group and 16 (3.7%) in the open-repair group (between-group difference, −1.0 percentage point; 95% CI, −3.3 to 1.4); most deaths occurred during the perioperative period. Aneurysm rupture occurred in 7 patients (1.6%) in the endovascular-repair group, and rupture of a thoracic aneurysm occurred in 1 patient (0.2%) in the open-repair group (between-group difference, 1.3 percentage points; 95% CI, 0.1 to 2.6). Death from chronic obstructive lung disease was just over 50% more common with open repair (5.4% of patients in the endovascular-repair group and 8.2% in the open-repair group died from chronic obstructive lung disease; between-group difference, −2.8 percentage points; 95% CI, −6.2 to 0.5). More patients in the endovascular-repair group underwent secondary procedures.

CONCLUSIONS

Long-term overall survival was similar among patients who underwent endovascular repair and those who underwent open repair. A difference between groups was noted in the number of patients who underwent secondary therapeutic procedures. Our results were not consistent with the findings of worse performance of endovascular repair with respect to long-term survival that was seen in the two European trials. (Funded by the Department of Veteran Affairs Office of Research and Development; OVER ClinicalTrials.gov number, NCT00094575.)

Elective repair of an abdominal aortic aneurysm can prevent aneurysm rupture and death, as shown in randomized trials of aneurysm screening,[1] but it is responsible for more perioperative deaths than any other general or vascular surgical procedure.[2] Randomized trials have shown that endovascular repair results in lower perioperative mortality than open repair, but after a few years this advantage is no longer seen because of excess late mortality among patients who had undergone endovascular repair[3] — a pattern that has also been seen in large observational studies.[4] If this pattern were to continue over time, endovascular repair could become the inferior strategy; this possibility underscores the need for long-term follow-up information. Two European trials (the United Kingdom Endovascular Aneurysm Repair Trial 1 [EVAR-1] and the Dutch Randomised Endovascular Aneurysm Management [DREAM] trial)[5,6] have recently shown higher long-term mortality with endovascular repair than with open repair. We report here data on extended follow-up of patients in the Veterans Affairs (VA) Open versus Endovascular Repair (OVER) trial.

Methods

Trial Design and Oversight

The trial methods have been described previously.[7,8] The authors designed and conducted the trial, performed the analyses, wrote the manuscript, and vouch for the completeness and accuracy of the data and analyses and for adherence of the trial to the protocol. The trial was approved by a central human rights committee and the institutional review board at each participating center. An independent data and safety monitoring committee reviewed the data at regular intervals. The protocol is available with the full text of this article at NEJM.org. Enrollment began on October 15, 2002, and ended on April 15, 2008. Active follow-up ended on October 15, 2011, which was the cutoff date for our previous report.[8] In October 2010, the VA Cooperative Studies Program approved an additional analysis that extended follow-up to December 31, 2016; the results of this analysis are reported here. No commercial sponsor was involved in the trial.

Patients and Procedures

Eligible patients had abdominal aortic aneurysms for which elective repair was planned and were candidates for either endovascular or open repair.[7,8] Patients were randomly assigned to one of the two repair procedures in a 1:1 ratio.[7] The specific type of endovascular-repair device intended for a particular patient, in the event that the patient was assigned to endovascular repair, was reported to the coordinating center before randomization to permit subgroup comparisons. The protocol required that the vascular surgeons and interventional radiologists had performed a minimum of 10 previous endovascular-repair and open-repair procedures and had subspecialty training, device-specific education as approved by the Food and Drug Administration, and centralized endovascular expert training that included didactic, flow model simulation, and live-case education. Aneurysm repair was performed within 6 weeks after randomization. Trial patients were followed regularly through October 15, 2011.[7,8]

For this report of extended follow-up, we obtained no additional information from patients or participating centers since the previous report.[8] All new data on deaths, causes of death, and clinical encounters were obtained from VA and other national data sets. To identify secondary therapeutic procedures, we examined *International Classification of Diseases, 9th Revision* (ICD-9), codes and Current Procedural Terminology (CPT) codes related to aortic aneurysm procedures (ICD-9 codes 38.34, 38.36, 38.44, 38.46, 39.41, 39.49, 39.52, 39.71, and 39.79; CPT codes 33880 through 33891, 34800 through 35142, 35472, 35537 through 35540, 35637, 35638, 35721, and 35840) and ventral and incisional hernia repair (ICD-9 codes 53.5 through 53.69; CPT codes 49560 through 49568 and 49652 through 49657). These aortic procedure codes were sufficient to determine that secondary therapeutic procedures had been performed. For other codes (ICD-9 codes 39.25 and 39.26; CPT codes 75894 and 75952 through 75959), we required accompanying diagnostic codes for aortic aneurysm (ICD-9 codes 441.0 through 442.9). The cause of death was determined from the information on the death certificate, which was captured in the National Death Index. We obtained information on deaths through 2016 and on causes of death and clinical encounters through 2015.

Outcomes

The primary outcome was all-cause mortality. Secondary outcomes were all-cause mortality as assessed in prespecified subgroups[8] and secondary therapeutic procedures that resulted directly

or indirectly from the initial procedure (with each trip to the procedure suite counting as one secondary procedure), including any unplanned surgical procedures performed within 30 days after the initial procedure and any additional aortoiliac or other related procedures (such as incisional hernia repair) that were performed at any time.

The cause of death and the secondary therapeutic procedures were adjudicated by an outcomes committee (whose members were unaware of the group assignments) during active follow-up and by the authors in the case of more recent deaths. All deaths that occurred within 30 days after the repair or during the hospitalization for the repair were considered to be related to the aneurysm, as were all deaths that occurred after 30 days and were adjudicated as having resulted directly or indirectly from the aneurysm or its treatment. In the current article, we report all-cause mortality and the secondary outcomes, including those that occurred over the extended follow-up period since the previous report.

STATISTICAL ANALYSIS

The trial was designed to provide 80% power to detect 25% lower relative mortality in the endovascular-repair group than in the open-repair group, at a two-sided alpha level of 0.05, at the end of active follow-up in 2011.[7] The analysis was performed according to the intention-to-treat principle. The Kaplan–Meier method was used to calculate estimated cumulative event rates. Hazard ratios and confidence intervals were estimated with the use of Cox proportional-hazards models.[9] We evaluated possible departures from the proportional-hazards assumption by using the P value for the interaction of mortality with ($\log_{10}$) time and by plotting Schoenfeld residuals (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The effect of treatment in prespecified subgroups was assessed by including treatment-by-subgroup interactions in the Cox models. Variables were compared with the use of chi-square tests and Student's t-tests. Two-sided P values of less than 0.05 were considered to indicate statistical significance. No correction for multiple comparisons was performed. Statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). Restricted mean survival time (analogous to the area under the curve for a survival plot) was assessed with the use of the pseudo-mean values approach.[10] To facilitate comparison with EVAR-1 and the DREAM trial,[5,6] we report hazard ratios according to time periods. To avoid data-driven selection of time periods, we adopted the time periods used by EVAR-1, the larger of the European trials.[5]

RESULTS

PATIENTS

From October 2002 through April 2008, we randomly assigned 881 patients at 42 VA medical centers to undergo endovascular repair (444 patients) or open repair (437 patients). Details of exclusions before randomization and characteristics at randomization were described previously (Fig. 1, and Table S2 in the Supplementary Appendix).[7] The two groups were similar, with no significant differences except that a higher percentage of patients in the open-repair group than in the endovascular-repair group were taking aspirin (63.4% vs. 55.0%). More than 95% of patients underwent the assigned repair; in 2% of patients, the assigned repair was attempted but was not completed (Fig. 1).

Vital status was known for all patients at the end of active follow-up on October 15, 2011. Assessment of participants was extended to December 31, 2016 (minimum follow-up, 0.02 years; maximum follow-up, 14.2 years; mean, 8.4 years; median, 9.4 years [interquartile range, 5.7 to 11.2]). We identified 316 additional deaths since the end of active follow-up, for a total of 608 deaths (69.0% of all patients who underwent randomization).

PRIMARY OUTCOME AND CAUSES OF DEATH

Our principal finding is that no significant difference in the primary outcome of all-cause mortality was noted between the endovascular-repair group and the open-repair group. A total of 302 deaths occurred in the endovascular-repair group, and 306 deaths occurred in the open-repair group (hazard ratio with endovascular repair vs. open repair, 0.96; 95% confidence interval [CI], 0.82 to 1.13; P=0.61) (Fig. 2A and Table 1).

The postoperative survival advantage with endovascular repair was significant for the first

3 years; after 3 years, the advantage disappeared, as previously reported.[8] Table 2 shows hazard ratios for death according to time since randomization. A survival advantage with endovascular repair was seen early; from years 4 through 8, a survival advantage was seen with open repair; however, after 8 years, no difference was observed (hazard ratio, 0.94; 95% CI, 0.74 to 1.18; P=0.59).

The interaction of time with treatment was not significant, which suggests the absence of a significant departure from the proportional-hazards assumption. The restricted mean survival time was also not significantly different between the groups. After 5 years, the restricted mean survival time was 4.53 years in the endovascular-repair group and 4.40 years in the open-repair group (difference, 0.13 years; 95% CI, −0.04 to 0.29), and after 14.2 years it was 9.03 years and 8.81 years, respectively (difference, 0.22 years; 95% CI, −0.34 to 0.79).

We previously reported 10 aneurysm-related deaths in the endovascular-repair group (2 occurred during the perioperative period [during the hospitalization for the repair or within 30 days after the repair], and 8 occurred late [more than 30 days after the repair]) and 16 aneurysm-related deaths in the open-repair group (13 occurred in the perioperative period and 3 occurred late).[8] In our previous report, 6 aneurysm ruptures had occurred in the endovascular-repair group (of which 3 were fatal), and none had occurred in the open-repair group. We now add 3 aneurysm-related deaths (2 in the endovascular-repair group and 1 in the open-repair group), 2 of which were caused by rupture (Table 1). One death in the endovascular-repair group had a code of "aortic aneurysm without rupture," which usually refers to a complication of a procedure performed on an unruptured aneurysm. In this case, no procedure had been performed in the patient for several years before death, the patient was known to have had severe heart disease, medical records included a code for abdominal pain 4 days before death, and the patient had a cardiac arrest in the ambulance on the day of death. We considered this to be a probable aneurysm rupture, although we were unable to rule out a cardiac cause. Another death in the endovascular-repair group was coded as "thoracic aortic aneurysm, without rupture." This patient underwent an endovascular repair of the descending thoracic aorta 7 weeks before death and an endovascular implantation of an abdominal aortic graft 2 weeks before death, which falls within the 30-day time frame for our definition of an aneurysm-related death. The third patient (who had been assigned to the open-repair group) was transported to the hospital by air ambulance, where computed tomography of the chest was performed; clinical and death codes were recorded for "thoracic aortic aneurysm, ruptured," a diagnosis we accepted (therefore, the death of this patient was not counted with

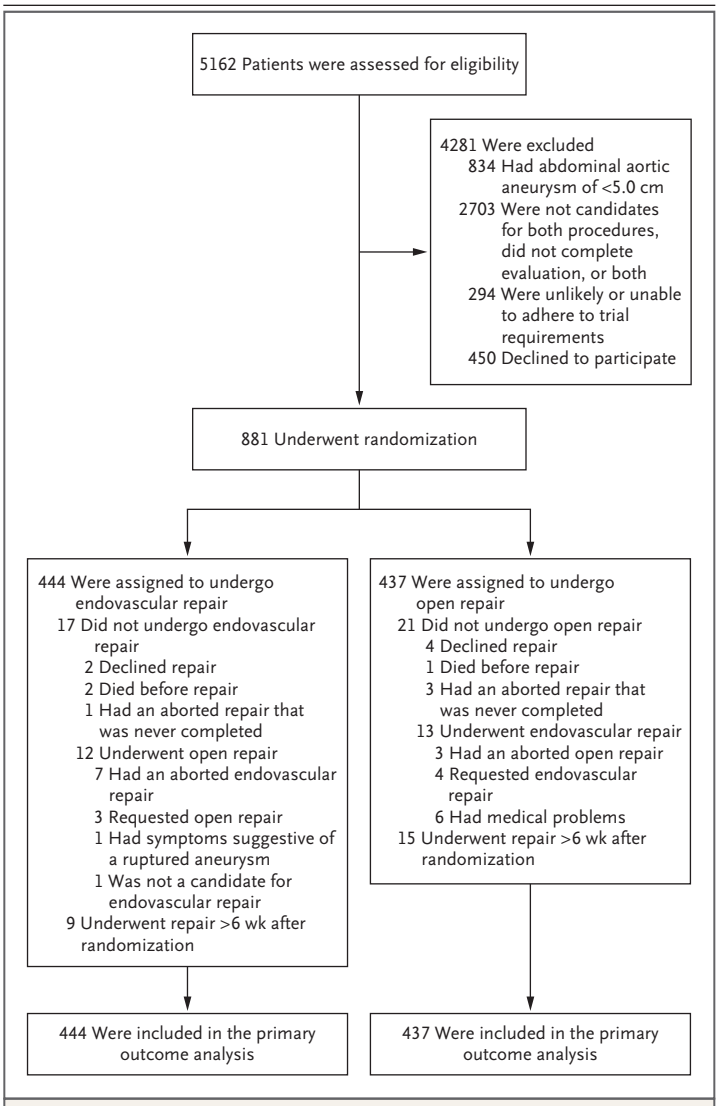

Figure 1. Randomization and Treatment.

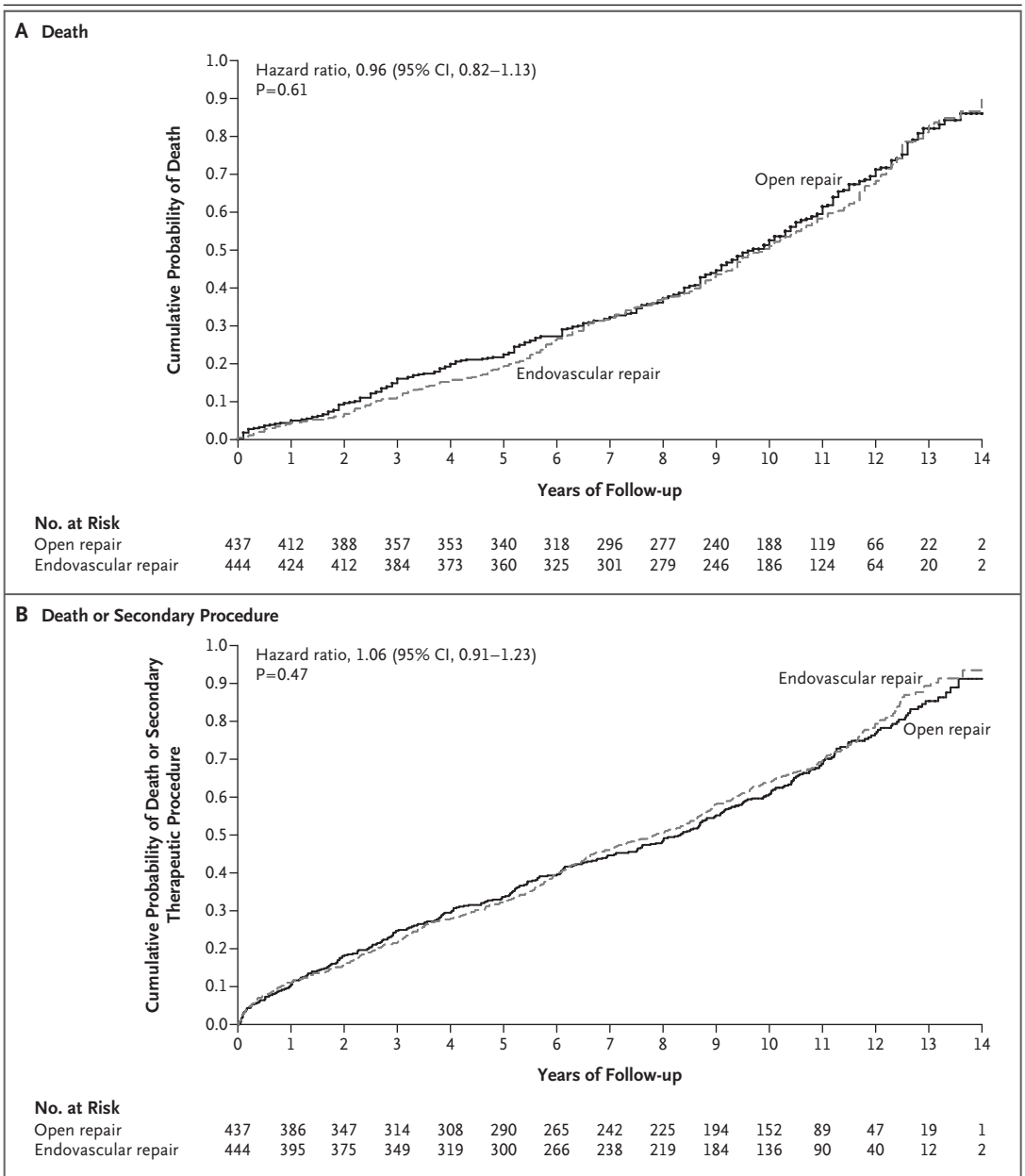

Figure 2. Kaplan–Meier Plots of the Cumulative Probability of Death and of Death or a Secondary Therapeutic Procedure.

Panel A shows the cumulative probability of death from any cause from the time of randomization among patients with an abdominal aortic aneurysm who underwent endovascular repair or open repair. Panel B shows the cumulative probability of death or a secondary therapeutic procedure. At the end of follow-up, 608 of 881 patients had died, and 675 of 881 patients had either undergone a secondary therapeutic procedure or had died.

the other aneurysm-related deaths). As a result, the totals are now 12 aneurysm-related deaths (2.7%) in the endovascular-repair group and 16 (3.7%) in the open-repair group (between-group difference, –1.0 percentage point; 95% CI, –3.3 to 1.4), and 7 ruptures (1.6%) in the endovascular-repair group and 1 (0.2%) in the open-repair group (between-group difference, 1.3 percentage

Table 1. Clinical Outcomes.*

Variable	Endovascular Repair (N=444)	Open Repair (N=437)	Between-Group Difference (95% CI)
			percentage points
All deaths — no. (%)	302 (68.0)	306 (70.0)	−2.0 (−8.1 to 4.1)
Deaths according to cause — no. (%)			
Abdominal aneurysm–related cause	12 (2.7)	16 (3.7)	−1.0 (−3.3 to 1.4)
During hospitalization or within 30 days after repair	2 (0.5)	11 (2.5)	−2.1 (−3.7 to −0.5)
Cardiovascular cause	88 (19.8)	69 (15.8)	4.0 (−1.0 to 9.1)
Cerebrovascular cause	14 (3.2)	9 (2.1)	1.1 (−1.0 to 3.2)
Cancer	80 (18.0)	85 (19.5)	−1.4 (−6.6 to 3.7)
Pneumonia or influenza	14 (3.2)	16 (3.7)	−0.5 (−2.9 to 1.9)
Other infection	9 (2.0)	6 (1.4)	0.7 (−1.1 to 2.4)
Chronic obstructive lung disease	24 (5.4)	36 (8.2)	−2.8 (−6.2 to 0.5)
Accident	12 (2.7)	6 (1.4)	1.3 (−0.5 to 3.2)
Suicide	2 (0.5)	0	0.5 (−0.2 to 1.1)
Homicide	0	2 (0.5)	−0.5 (−1.1 to 0.2)
Most likely but not confirmed to be caused by rupture of abdominal aortic aneurysm	0	1 (0.2)	−0.2 (−0.7 to 0.2)
Possibly but most likely not caused by rupture of abdominal aortic aneurysm	9 (2.0)	5 (1.1)	0.9 (−0.8 to 2.5)
Unknown or insufficient data†	38 (8.6)	55 (12.6)	
Aneurysm rupture — no. (%)	7 (1.6)	1 (0.2)‡	1.3 (0.1 to 2.6)
Secondary therapeutic procedures			
No. of secondary procedures	193	116	
Patients who underwent secondary procedures — no./total no. (%)	117/439 (26.7)	85/429 (19.8)	6.9 (2.0 to 17.5)
Patients who died or underwent secondary procedures — no. (%)	345 (77.7)	330 (75.5)	2.4 (−3.2 to 7.9)

* Some values may differ from the expected value because of rounding.
† This category includes patients with uninformative codes for cause of death (e.g., ICD-9 codes I46.9, R99) or patients whose deaths could not be attributed to a cause on the basis of available information.
‡ The aortic aneurysm in this patient was a thoracic aneurysm.

Table 2. Deaths from Any Cause According to Time since Randomization.*

Time since Randomization	Endovascular Repair	Open Repair	Hazard Ratio (95% CI)	P Value	P Value for Interaction†
	no. of deaths/total no. (%)				
Any time	302/444 (68.0)	306/437 (70.0)	0.96 (0.82–1.13)	0.61	0.25
0 to 6 mo	11/444 (2.5)	14/437 (3.2)	0.77 (0.35–1.69)	0.51	0.43
>6 mo to 4 yr	59/433 (13.6)	70/423 (16.5)	0.81 (0.57–1.14)	0.22	0.88
>4 to 8 yr	93/374 (24.9)	76/353 (21.5)	1.18 (0.87–1.60)	0.29	0.50
>8 yr	139/281 (49.5)	146/277 (52.7)	0.94 (0.74–1.18)	0.59	0.25

* Time-period categories were selected to coincide with those used in the United Kingdom Endovascular Aneurysm Repair Trial 1 (EVAR-1).[5]
† The P value is for the interaction of treatment with time.

points; 95% CI, 0.1 to 2.6 [values for percentage points may differ from the expected value because of rounding]).

Deaths from other causes were similar in the two groups, except for death from chronic obstructive lung disease, which was just over 50% more common in the open-repair group than in the endovascular-repair group (5.4% in the endovascular-repair group vs. 8.2% in the open-repair group; between-group difference, −2.8 percentage points; 95% CI, −6.2 to 0.5) (Table 1). Of note, deaths from cancer were not more common in the endovascular-repair group than in the open-repair group, despite the presumed higher exposure to ionizing radiation among patients in the endovascular-repair group.

SECONDARY PROCEDURES AND OTHER OUTCOMES

We previously reported 148 secondary therapeutic procedures in 98 patients in the endovascular-repair group and 105 secondary therapeutic procedures in 78 patients in the open-repair group.[8] To these we now add 45 procedures in 19 patients in the endovascular-repair group and 11 procedures in 7 patients in the open-repair group. The totals are now 193 secondary therapeutic procedures in 117 patients in the endovascular-repair group and 116 procedures in 85 patients in the open-repair group. The between-group difference in the numbers of procedures is significant (P=0.04), as is the between-group difference in the percentage of patients who underwent a secondary procedure (26.7% in the endovascular-repair group vs. 19.8% in the open-repair group; difference, 6.9 percentage points; 95% CI, 2.0 to 17.5) (Table 1). The total number of patients who either died or underwent a secondary therapeutic procedure was similar in the two groups (345 patients in the endovascular-repair group and 330 in the open-repair group; between-group difference, 2.2 percentage points; 95% CI, −3.4 to 7.8), which suggests that many of the excess procedures in the endovascular-repair group occurred in patients who later died. The incidence of a secondary therapeutic procedure or death, evaluated on the basis of Kaplan–Meier survival estimates, was also similar in the two groups throughout the trial (hazard ratio for death or secondary procedure, 1.06; 95% CI, 0.91 to 1.23; P=0.47) (Fig. 2B).

Figure 3 shows the risk of death in prespecified subgroups defined according to characteristics at entry. Among patients younger than 70 years of age, overall survival appeared to be higher in the endovascular-repair group than in the open-repair group, but the difference was not significant (hazard ratio for death, 0.81; 95% CI, 0.62 to 1.05; P=0.10). Among patients 70 years of age or older, there was a trend in the opposite direction (hazard ratio for death with endovascular repair vs. open repair, 1.20; 95% CI, 0.98 to 1.47; P=0.08), and the interaction of age (<70 years vs. ≥70 years of age) with treatment group was significant (P=0.02). However, no correction was made for multiple comparisons, so the data must be interpreted with caution. There was no evidence of a significant differential effect of endovascular repair or open repair on long-term mortality in other prespecified subgroups.

DISCUSSION

In this multicenter, randomized trial with an extended follow-up period, no difference was observed between endovascular and open repair in the primary outcome of all-cause mortality. Among younger patients, endovascular repair resulted in somewhat higher long-term overall survival than open repair, but among older patients, endovascular repair resulted in somewhat lower long-term overall survival than open repair. More deaths from chronic obstructive lung disease occurred in the open-repair group than in the endovascular-repair group. We found between-group differences in the number of secondary therapeutic procedures that were performed and in the number of patients who underwent secondary procedures.

Much of the early enthusiasm for endovascular repair focused on an expected advantage in old or frail patients who were not good candidates for open repair. Our finding that endovascular repair resulted in more benefit than open repair in younger patients and less benefit in older patients was therefore surprising. This conclusion is not statistically robust. The clinical implications of this age effect must be reconciled with our finding that all ruptures of infrarenal aneurysms occurred in the endovascular-repair group, which makes this procedure seemingly less desirable for use in younger patients. However, the percentage of ruptures in

Subgroup	Endovascular Repair	Open Repair	Hazard Ratio for Death (95% CI)	P Value for Interaction
	no. of patients who died/total no. of patients (%)			
Randomization period				0.81
Up to April 15, 2005	156/212 (73.6)	155/201 (77.1)	0.98 (0.79–1.23)	
After April 15, 2005	146/232 (62.9)	151/236 (64.0)	0.95 (0.76–1.20)	
Age				0.02
<70 yr	120/218 (55.0)	111/188 (59.0)	0.81 (0.62–1.05)	
≥70 yr	182/226 (80.5)	195/249 (78.3)	1.20 (0.98–1.47)	
AAA diameter				0.99
<5.5 cm	132/192 (68.8)	127/190 (66.8)	0.96 (0.75–1.23)	
≥5.5 cm	170/252 (67.5)	179/247 (72.5)	0.96 (0.78–1.19)	
Surgical risk				0.19
Low	145/240 (60.4)	152/228 (66.7)	0.87 (0.69–1.10)	
Intermediate or high	154/200 (77.0)	149/204 (73.0)	1.09 (0.87–1.37)	
Coronary artery disease				0.54
No	184/270 (68.1)	175/252 (69.4)	1.00 (0.81–1.23)	
Yes	118/174 (67.8)	131/185 (70.8)	0.91 (0.71–1.17)	
Intended endovascular-repair device				
Cook Zenith	108/166 (65.1)	117/175 (66.9)	0.97 (0.74–1.26)	
Gore Excluder	117/177 (66.1)	105/150 (70.0)	0.91 (0.70–1.19)	0.65
Medtronic AneuRx	67/88 (76.1)	72/98 (73.5)	1.06 (0.76–1.48)	0.56
All patients	302/444 (68.0)	306/437 (70.0)	0.96 (0.82–1.13)	

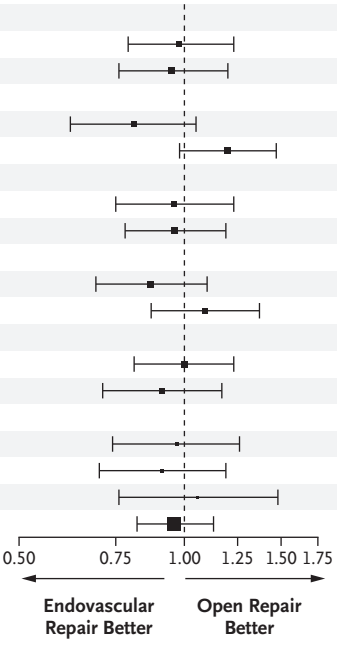

Figure 3. Hazard Ratios for Death According to Baseline Characteristics.

The size of the box is proportional to the total number of deaths in each subgroup. The P value for the interaction of age with treatment group has not been corrected for multiple comparisons and therefore should not be considered robust. Surgical risk was determined on the basis of RAND criteria (Table S1 in the Supplementary Appendix).[11] RAND scores were not reported for 8 patients who died (3 patients in the endovascular-repair group and 5 patients in the open-repair group). P values for the Gore Excluder and the Medtronic AneuRx devices are for the comparisons with the other two intended endovascular-repair devices. A total of 22 patients who died (10 patients in the endovascular-repair group and 12 patients in the open-repair group) had an intended endovascular-repair device that was different from the three listed devices. AAA denotes abdominal aortic aneurysm.

our trial was low (0.9%). Five of the eight ruptures, including three of the five fatal ruptures, occurred in patients older than 70 years of age at entry; at least three of the eight ruptures occurred in patients who did not receive the recommended intervention, and two were ruptures of thoracic aneurysms. Extended survival after repair of an infrarenal aneurysm may permit detection of aortic aneurysms at other sites.

Chronic obstructive lung disease caused just over 50% more deaths in the open-repair group than in the endovascular-repair group. This difference was significant, and it is supported by strong trends in the two European trials. In EVAR-1, a total of 55 patients (8.8%) in the endovascular-repair group and 73 (11.7%) in the open-repair group died from respiratory disease (P=0.09).[5] In the DREAM trial, 8 patients (4.6%) in the endovascular-repair group and 14 (7.9%) in the open-repair group died from pulmonary causes (P=0.26).[6] These differences cannot be explained by baseline rates of smoking or respiratory disease. Data on changes in tobacco use after randomization were not reported for the current trial or for the European trials.

In all three long-term randomized trials and in a large Medicare study, endovascular repair conferred a perioperative survival advantage that continued for several years and then disappeared because of increased deaths in the endovascular-repair groups.[4-6,8] The important questions are, what caused these later deaths in the endovascular-repair groups, and would the trend continue, with the result that endovascular repair would become the inferior strategy? The first question remains unanswered, but the most widely ac-

cepted explanation is that the perioperative deaths after open repair most likely occurred in the frailest patients, so the curves converged as later deaths occurred in the frailest patients in the endovascular-repair groups.[8]

The second question can be addressed empirically, now that long-term results have been reported for all three trials. In EVAR-1,[5] aneurysm-related mortality and adjusted total mortality were higher in the endovascular-repair group than in the open-repair group after 8 years; in the DREAM trial,[6] more late secondary procedures were performed in the endovascular-repair group than in the open-repair group. In contrast, we found numerically fewer deaths after 8 years in the endovascular-repair group than in the open-repair group (hazard ratio, 0.94; 95% CI, 0.74 to 1.18; P=0.59), very few late aneurysm-related deaths in either group, and little evidence for a late increase in secondary therapeutic procedures in the endovascular-repair group (Fig. 2B). Even though the result of the primary analysis (the hazard ratio) suggests that there is no significant difference in the outcome between the two groups, an assessment of the hazard ratio at various time periods suggests that this estimated overall hazard ratio might not be a good summary statistic for long-term follow-up.

Why might our results differ from those of the two European trials? First, the European trials began several years before our trial, during a time when endovascular-repair devices, techniques, and strategies were changing rapidly. The OVER trial required investigators performing the procedures to have specific skills as well as device training and trial-associated training to avoid potential increased mortality resulting from inexperience.[12] In addition, evaluation strategies in the early years of endovascular repair involved high doses of radiation, which may have been responsible for the significantly higher number of deaths from cancer in the endovascular-repair group than in the open-repair group in EVAR-1[5]; there was a similar trend in the DREAM trial.[6] In contrast, in our trial, the total number of deaths from cancer was lower in the endovascular-repair group than in the open-repair group. There were 37 deaths from cancer in the open-repair group and 41 in the endovascular-repair group since our last report,[8] for a total of 165 deaths (80 in the endovascular-repair group and 85 in the open-repair group).

Second, postoperative mortality was lower in our trial than in the European trials. The percentages of patients who died within 30 days after undergoing endovascular repair or during hospitalization were 1.2% in the DREAM trial, 2.1% in EVAR-1, and 0.5% in our trial; among patients who underwent open repair, the percentages were 4.6%, 6.2%, and 2.5%, respectively.[13,14] We discussed possible reasons for these differences extensively in a previous article.[7] Besides the difference in timing noted above, operative mortality has been shown to be lower in the United States than in Europe, and this was reflected in the data from the three trials discussed here. The quality of the surgical procedure may affect the long-term durability of the device as well as perioperative clinical outcomes. It is less clear that higher surgical quality would result in better long-term outcomes after endovascular repair, but it is possible that the steep learning curve for endovascular repair resulted in differences in surgical quality that were reflected in later results.

Finally, although the procedures for which we report long-term results were performed more than a decade ago, the operative mortality in our trial was lower than that currently reported nationally in the United States.[15] This suggests that our results can have ongoing relevance.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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Outcomes Following Endovascular vs Open Repair of Abdominal Aortic Aneurysm
A Randomized Trial

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Context Limited data are available to assess whether endovascular repair of abdominal aortic aneurysm (AAA) improves short-term outcomes compared with traditional open repair.

Objective To compare postoperative outcomes up to 2 years after endovascular or open repair of AAA in a planned interim report of a 9-year trial.

Design, Setting, and Patients A randomized, multicenter clinical trial of 881 veterans (aged ≥49 years) from 42 Veterans Affairs Medical Centers with eligible AAA who were candidates for both elective endovascular repair and open repair of AAA. The trial is ongoing and this report describes the period between October 15, 2002, and October 15, 2008.

Intervention Elective endovascular (n=444) or open (n=437) repair of AAA.

Main Outcome Measures Procedure failure, secondary therapeutic procedures, length of stay, quality of life, erectile dysfunction, major morbidity, and mortality.

Results Mean follow-up was 1.8 years. Perioperative mortality (30 days or inpatient) was lower for endovascular repair (0.5% vs 3.0%; *P*=.004), but there was no significant difference in mortality at 2 years (7.0% vs 9.8%, *P*=.13). Patients in the endovascular repair group had reduced median procedure time (2.9 vs 3.7 hours), blood loss (200 vs 1000 mL), transfusion requirement (0 vs 1.0 units), duration of mechanical ventilation (3.6 vs 5.0 hours), hospital stay (3 vs 7 days), and intensive care unit stay (1 vs 4 days), but required substantial exposure to fluoroscopy and contrast. There were no differences between the 2 groups in major morbidity, procedure failure, secondary therapeutic procedures, aneurysm-related hospitalizations, health-related quality of life, or erectile function.

Conclusions In this report of short-term outcomes after elective AAA repair, perioperative mortality was low for both procedures and lower for endovascular than open repair. The early advantage of endovascular repair was not offset by increased morbidity or mortality in the first 2 years after repair. Longer-term outcome data are needed to fully assess the relative merits of the 2 procedures.

Trial Registration clinicaltrials.gov Identifier: NCT00094575

JAMA. 2009;302(14):1535-1542 www.jama.com

EACH YEAR IN THE UNITED STATES, 45 000 patients with unruptured abdominal aortic aneurysm (AAA) undergo elective repair, resulting in more than 1400 perioperative deaths.[1] Endovascular repair was developed to provide a less invasive method than the standard open procedure and has been reported to reduce perioperative mortality, hospital stay, and intensive care unit (ICU) stay. However, more frequent reinterventions have also been reported and the early survival advantage was lost within 2 years in previous randomized trials conducted in Europe,[2-4] leaving the preferred approach for AAA repair in doubt. Furthermore, the relative effects of the 2 procedures on quality of life and erectile function remain unclear.

Devices and techniques continue to improve and operative mortalities and morbidities were relatively high in the European trials, raising the question of how relevant their results are to current US practice. We report short-term perioperative outcomes after elective endovascular and open repair of AAA from a US multicenter randomized trial.

METHODS

Study Oversight

The study was approved by a central human rights committee and the institutional review boards at each participating center. An independent data monitoring committee reviewed the data at regular intervals.

Patients

Eligible patients had AAA for which repair was planned and had (1) a maxi-

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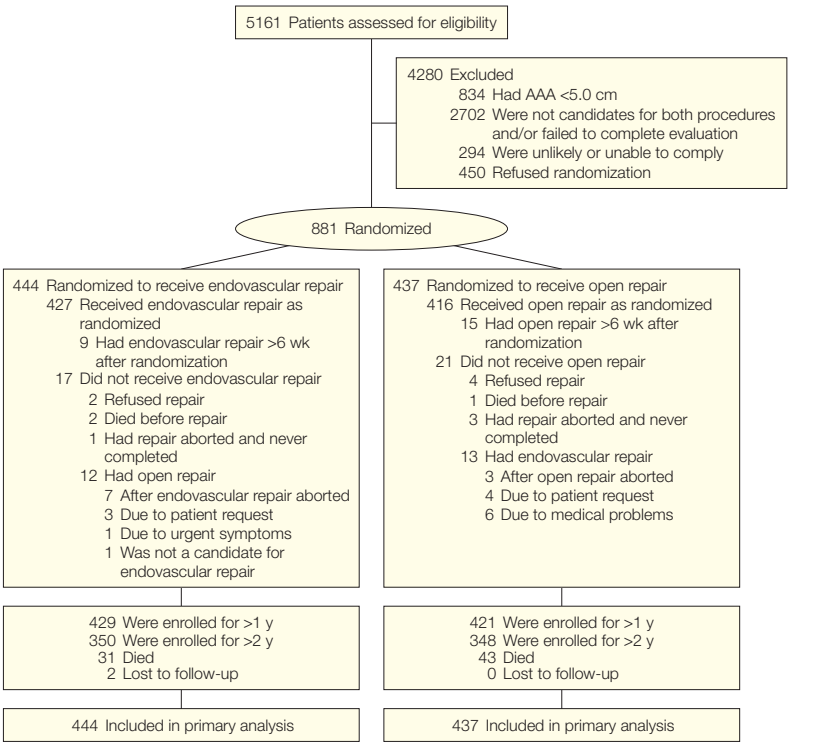
Figure 1. Flow Diagram of Study Patients



AAA indicates abdominal aortic aneurysm.

mum external diameter of at least 5.0 cm, (2) an associated iliac aneurysm with a maximum diameter of at least 3.0 cm, or (3) a maximum diameter of at least 4.5 cm plus either rapid enlargement (at least 0.7 cm in 6 months or 1.0 cm in 12 months) or saccular morphology. To be randomized, a patient had to have completed all preoperative evaluation, be considered a candidate for both procedures by the participating vascular surgeon, and meet the manufacturer's indications for the endovascular system that would be used if so assigned. Patients were excluded if they had previous abdominal aortic surgery, needed urgent repair, or were unable or unwilling to give informed consent or follow the protocol.

Procedures

Entry evaluation included demographics (race was recorded by study nurses using predefined categories of white, not of Hispanic origin; black, not of Hispanic origin; Hispanic; Asian/Oriental or Pacific Islander; American Indian or Alaskan Native; or other); comorbidities; medications; surgical risk using criteria developed by the RAND Corporation (eAppendix; available online at http://www.jama.com)[5]; measurement of height, weight, brachial, and ankle blood pressure; measurement of serum creatinine; and various parameters from preoperative aortic imaging.

Patients provided informed consent for preoperative evaluation and randomization. Randomization assigned equal probability to open or endovascular repair and was stratified by medical center using a permuted block design. Allocation was made by telephone to the coordinating center after baseline information was received and eligibility verified. Although patient assignment was of necessity unblinded, outcome data by treatment group were available during enrollment only to the biostatistician and data monitoring committee.

Open repair involves sutured anastomoses of an anatomically placed vascular graft through an abdominal or retroperitoneal incision and was performed as usual at each participating medical center. Endovascular repair involves the transluminal introduction of an expandable graft system through the femoral or iliac arteries into the aneurysmal region of the aorta and iliac arteries to exclude the aneurysm from arterial pressure. Only endovascular systems approved by the US Food and Drug Administration could be used in the study. To permit subgroup comparisons with randomized controls, the endovascular system intended for a particular patient if so assigned was reported to the coordinating center before randomization.

The protocol specified that repair should occur within 6 weeks of randomization and a study-approved vascular surgeon or interventional radiologist should perform all aneurysm repairs. Criteria for study approval were vascular surgery fellowship, certification or equivalent, or equivalent training for interventional radiologists. Individuals performing study endovascular procedures were required to have completed at least 12 procedures with adequate supervision.

Follow-up visits were scheduled 1 month after aneurysm repair, 6 and 12 months after enrollment, and then yearly. All follow-up visits after endovascular repair included computed tomography and plain radiography of the abdomen, whereas after open repair, only computed tomography at 1 year was specified, a difference intended to reflect usual clinical practice. Patients were called monthly during the first 14 months after repair and then annually midway between study visits to identify outcomes and were asked to log all health care visits. Additional follow-up information was obtained by the coordinating center using national data sets.

Outcome Measures

The primary outcome is long-term (5-9 years) all-cause mortality (October 15, 2002-October 15, 2011). Secondary outcomes included (1) procedure failure, defined as failure to complete the initial repair or any secondary thera-

peutic procedures resulting directly or indirectly from the initial procedure and requiring a separate trip to the procedure suite (each trip to the procedure suite counted as 1 secondary procedure, and these included any unplanned surgical procedures within 30 days of the initial procedure and any additional aorto-iliac procedures at any time); (2) short-term major morbidity, defined as myocardial infarction, stroke, amputation, or renal failure requiring dialysis within 1 year after the initial repair; (3) days in hospital and ICUs associated with the initial repair; (4) other procedure-related morbidities, such as incisional hernia, or new or worsened claudication; (5) health-related quality of life; and (6) erectile dysfunction. These secondary outcomes pertain primarily to the short-term perioperative period and are the main focus of this report.

Outcomes were adjudicated by an outcomes committee blinded (to the extent possible) to the randomized group. Aneurysm-related mortality was not a prespecified outcome because of the potential for ascertainment bias[4] but is presented for comparison with other trials. All deaths within 30 days after repair or during the hospitalization for repair were considered aneurysm-related, as were all late deaths adjudicated as resulting directly or indirectly from the AAA or treatment of the AAA.

Health-related quality of life was assessed by using 2 brief questionnaires, the 36-item Short Form Health Survey (SF-36) and EQ-5D (EuroQol, Rotterdam, the Netherlands), completed at baseline and follow-up visits. The SF-36 evaluates 8 health dimensions that have been aggregated into 2 summary measures, a mental component summary and a physical component summary.[6] We also computed the physical component transformed with deaths included.[7] The EQ-5D[8] consists of 5 questions used to generate an index score with US population-based preference weights, and a 20-cm visual analog scale. Erectile function was assessed by using the previously validated 5-item International Index of Erectile Func-

Table 1. Patient Characteristics at the Time of Randomization[a]

Characteristics	Endovascular Repair (n = 444)	Open Repair (n = 437)
Age, mean (SD), y	69.6 (7.8)	70.5 (7.8)
Male sex, No. (%)	441 (99.3)	435 (99.5)
White race, No. (%)	387 (87.2)	379 (86.7)
Weight, mean (SD), kg	89.9 (16.8)	89.7 (17.8)
BMI, mean (SD)	28.6 (5.2)	28.7 (5.6)
BMI ≥35, No. (%)	47 (10.6)	44 (10.1)
Smoking history, No. (%)		
Ever	428 (96.4)	413 (94.5)
Current	170 (38.3)	193 (44.2)
Blood pressure, mean (SD), mm Hg		
Systolic	133.5 (18.6)	133.0 (18.8)
Diastolic	75.8 (10.9)	74.3 (10.6)
Current history, No. (%)		
Coronary artery disease	174 (39.2)	185 (42.3)
Myocardial infarction	105 (23.6)	110 (25.2)
Coronary revascularization	159 (35.8)	153 (35.0)
Cerebrovascular disease	67 (15.1)	70 (16.0)
Hypertension	347 (78.2)	330 (75.5)
Claudication	66 (14.9)	81 (18.5)
Cancer (other than skin)	83 (18.7)	70 (16.0)
Diabetes	100 (22.5)	100 (22.9)
Chronic obstructive pulmonary disease	126 (28.4)	133 (30.4)
Medications, No. (%)		
β-Blocker	282 (63.5)	282 (64.5)
Aspirin[b]	244 (55.0)	277 (63.4)
ACE inhibitor	192 (43.2)	180 (41.2)
Anticoagulants	44 (9.9)	34 (7.8)
Ankle-brachial index on at least 1 side, No. (%)		
≤0.9	159 (35.8)	155 (35.5)
≤0.4	48 (10.8)	45 (10.3)
Maximum activity level, No. (%)		
Sedentary or mild	182 (41.0)	185 (42.4)
Moderate or vigorous	262 (59.0)	252 (57.6)
Serum creatinine, mean (SD), mg/dL	1.2 (0.5)	1.1 (0.4)
GFR <60 mL/min per 1.73 m^2, No. (%)	140 (31.5)	136 (31.1)
Surgical risk (RAND score), No. (%)		
Low	240 (54.1)	227 (51.9)
Intermediate	169 (38.1)	176 (40.3)
High	31 (7.0)	29 (6.6)
Family history of AAA, No. (%)	70 (15.8)	51 (11.7)
AAA diameter, No. (%), cm		
Mean (SD)	5.7 (0.8)	5.7 (1.0)
<5.0	23 (5.2)	18 (4.1)
<5.5	192 (43.2)	190 (43.5)
5.5-5.9	133 (30.0)	123 (28.1)
6.0-6.9	86 (19.4)	83 (19.0)
≥7.0	33 (7.4)	41 (9.4)
Intended device, No. (%)		
Cook Zenith	166 (37.4)	175 (40.0)
Gore Excluder	177 (39.6)	150 (34.3)
Medtronic AneuRx	88 (19.8)	98 (22.4)
Other	13 (2.9)	14 (3.2)

Abbreviations: AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); GFR, glomerular filtration rate.
SI conversion factor: To convert serum creatinine to μmol/L, multiply by 88.4.
[a] Ever smoking history is smoking more than 100 cigarettes over lifetime. The GFR was estimated using the 4-variable Modification of Diet in Renal Disease Study equation.[14] For surgical risk (RAND score), see online eAppendix at http://www.jama.com.[5] Intended device indicates if assigned to endovascular repair.
[b] $P = .01$.

tion.[9] Questionnaires were completed by the patient and reviewed for completeness by study personnel.

Statistical Analysis

We originally assumed a mortality rate of 5.6% per year following open repair[10-12] and 5% loss to follow-up, and planned a 4.5-year enrollment period and a minimum follow-up of 3.5 years. Three years after enrollment began in October 2002, the study was reconfigured by the investigators with the approval of the data and safety monitoring board without knowledge of results by randomized group to reflect lower than planned enrollment rate, higher mortality rate (6.6% per year), and lower losses to follow-up (1%). By increasing enrollment to 5 years and follow-up to 4 years, 872 patients would provide 80% power to detect a 25% relative reduction in mortality with 2-sided $\alpha = .05$. To reach this number of patients, enrollment was continued an additional 6 months at 3 centers.

The analysis was by intention-to-treat. Estimates of cumulative event rates were calculated by the Kaplan-Meier method, and hazard ratios (HRs) with confidence intervals (CIs) were estimated by Cox proportional hazards regression models.[13] The effect of treatment in prespecified subgroups was assessed by treatment-subgroup interactions in the Cox proportional hazards regression model. Variables were compared by using χ^2 and t tests. P values were 2-sided and $P < .05$ was considered statistically significant. Statistical analyses were performed by using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

The protocol originally specified publication of 1-year results when available on all patients to ensure that short-term postoperative outcomes would be disseminated while still maximally relevant. Because of the important changes in the effect size for survival noted during the second year of follow-up in previously published trials,[2-4] this plan was amended by the investigators with the approval of the data and safety monitoring board without knowledge of the results in February 2007 to include all follow-up data to 2 years after randomization as of the same date of October 15, 2008.

Table 2. Details of Aneurysm Repair by Randomly Assigned Group[a]

	Median (Interquartile Range)	
	Endovascular Repair (n = 439)	Open Repair (n = 429)
Patients with aorta as distal attachment site (vs iliac/femoral), No. (%)	23 (5.2)	190 (44.3)
Time from randomization to repair, d	18.0 (10.0-28.0)	17.0 (9.0-26.0)
Duration of procedure, h	2.9 (2.3-3.7)	3.7 (2.9-4.7)
Duration of mechanical ventilation, h	3.6 (3.0-4.5)	5.0 (4.0-9.1)
Duration of fluoroscopy, min	23.0 (17.0-31.0)	0
Volume of contrast used, mL	132.5 (96.5-176.0)	0
Estimated blood loss, mL	200 (150-400)	1000 (650-2000)
Banked red cell transfusion within 24 h, unit	0	1.0 (0-3.0)
Duration of hospital stay for initial repair, d	3.0 (2.0-5.0)	7.0 (6.0-10.0)
Time in intensive care unit, d	1.0 (1.0-2.0)	4.0 (3.0-6.0)

[a] Patients who had no repair (refused, aborted and never completed, or died before repair as shown in Figure 1) are not included. $P < .001$ for all comparisons of means, except time from randomization to repair ($P = .36$).

Table 3. All Outcome Measures

	No. (%) of Patients		
Outcomes	Endovascular Repair (n = 444)	Open Repair (n = 437)	*P* Value
All-cause mortality	31 (7.0)	43 (9.8)	.13
Before AAA repair	2 (0.5)	1 (0.2)	>.99
Within 30 d after repair	1 (0.2)	10 (2.3)	.006
Within 30 d after repair or during hospitalization	2 (0.5)	13 (3.0)	.004
AAA diameter <5.5 cm	1 (0.5)	5 (2.6)	.10
AAA diameter ≥5.5 cm	1 (0.4)	8 (3.2)	.02
After 30 d or hospitalization	27 (6.1)	29 (6.6)	.74
Cause of death	(n = 31)	(n = 43)	
AAA-related[a]	6 (1.4)	13 (3.0)	.10
Cardiovascular	9 (2.0)	4 (0.9)	.26
Cancer	10 (2.3)	15 (3.4)	>.99
Other[b]	5 (1.1)	7 (1.6)	.54
Unknown	1 (0.2)	4 (0.9)	.21
Patients with procedure failure	58 (13.1)	51 (11.7)	.53
Patients with no repair attempted	4 (0.9)	5 (1.1)	.75
Patients with aborted initial procedure	8 (1.8)	6 (1.4)	.61
Patients having secondary therapeutic procedures	46 (10.4)	40 (9.2)	.73
All secondary therapeutic procedures, No. of events	61	55	
Patients with any 1-year major morbidity	18 (4.1)	20 (4.6)	.70
Myocardial infarction	6 (1.4)	12 (2.7)	.14
Stroke	7 (1.6)	4 (0.9)	.38
Amputation	1 (0.2)	3 (0.7)	.37
Renal failure requiring dialysis	5 (1.1)	3 (0.7)	.73
Patients with new or worsened claudication	37 (8.3)	20 (4.6)	.02
All postrepair aneurysm-related hospitalizations, No. of events	108	86	

Abbreviation: AAA, abdominal aortic aneurysm.
[a] Includes all deaths within 30 days after repair or during hospitalization.
[b] Includes cerebrovascular disease, injury, pneumonia, other infections, and unexplained sudden deaths not considered AAA-related.

RESULTS

We randomized 881 patients (aged ≥49 years) at 42 medical centers (FIGURE 1).

The 2 groups were similar at baseline (TABLE 1), with no significant differences except for a greater proportion using aspirin in the open repair group. Of the 41 patients randomized with AAA of less than 5.0 cm, reasons for eligibility were iliac aneurysm in 34 patients, rapid enlargement in 4 patients, and saccular morphology in 3 patients. Fifteen patients (8 endovascular repair and 7 open repair) had abdominal or back pain noted before repair, but no aneurysm ruptures were identified at any time during the study period. More than 95% of randomized patients had the assigned repair (n=843) and in another 2% (n=14), the assigned repair was attempted but aborted (Figure 1).

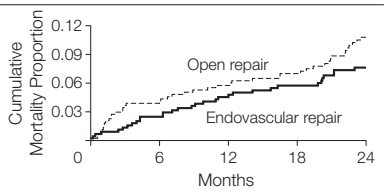
All 109 lead proceduralists for aneurysm repair were vascular surgeons. An endovascular system other than the one prespecified as intended was used in 43 patients in the endovascular group. Endovascular repair resulted in significantly reduced procedure time, duration of mechanical ventilation, hospital and ICU stays, blood loss, and transfusion requirement, but required substantial exposure to fluoroscopy and contrast (TABLE 2).

Mean follow-up was 1.8 years, and 80% of patients (n=710) had either completed 2 years of follow-up or died before 2 years (follow-up was truncated at 2 years for both study groups). Perioperative mortality was significantly higher for open repair at 30 days (0.2% vs 2.3%; $P=.006$), and at 30 days or during hospitalization (0.5% vs 3.0%; $P=.004$) (TABLE 3), a difference that did not appear to vary with AAA diameter (P for interaction=.25). Vital status after 2 years or by October 15, 2008, was confirmed for all but 2 patients, and national data sets contained no death reports on these 2 patients. There was no significant difference in all-cause mortality at 2 years (7.0% vs 9.8%; HR, 0.7; 95% CI, 0.4-1.1; $P=.13$) (FIGURE 2). Mortality after the perioperative period was similar in the 2 groups (6.1% vs 6.6%) (Table 3), but 4 of the late deaths in the endovascular group were aneurysm-related compared with none in the open repair group. No significant differences in mortality were observed for any of the prespecified subgroups shown in FIGURE 3, including patients with coronary artery disease ($P=.06$). No significant interactions were found between treatment effect and any subgroup characteristic.

No differences were observed between the 2 groups in procedure failures, secondary therapeutic procedures, aneurysm-related hospitalizations, or 1-year major morbidity (Table 3). The 61 secondary therapeutic procedures in the endovascular repair group included 42 endovascular procedures, 3 explantations of the graft with conversion to open repair, 9 other arterial procedures with an open component, 5 groin wound procedures, and 2 amputations (both legs of 1 patient). The 55 secondary therapeutic procedures in the open-repair group included 24 incisional hernia repairs, 7 aortic graft procedures, 4 procedures for wound complications, 4 amputations (1 toe, 1 leg, and below and above knee on same leg), 4 laparotomies for bowel obstruction, 2 laparotomies for hematoma, 2 procedures to relieve claudication, and 8 miscellaneous minor procedures.

Incisional hernia was reported in 30 patients who had open repair, resulting in secondary therapeutic procedures in 21 patients (4.9%), all of whom had undergone an anterior surgical approach in the original open repair. In the endovascular repair group, there were 134 endoleaks (blood flow between the graft and the aneurysm wall) in 110 patients (25%), resulting in 21 secondary therapeutic procedures in 18 patients (4.1%).

Figure 2. Kaplan-Meier Curve of Cumulative Probabilities of Death From Time of Randomization

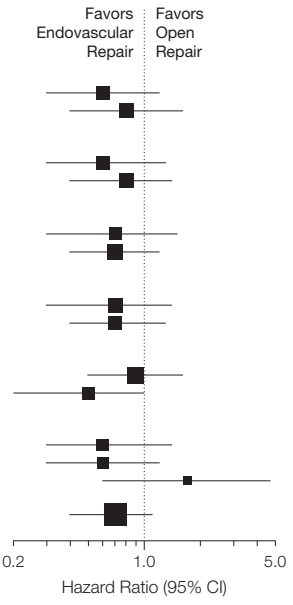


No. at risk					
Open repair	437	420	396	363	310
Endovascular repair	444	433	411	371	326

There was no significant difference in cumulative mortality for open vs endovascular repair (hazard ratio, 0.7; 95% confidence interval, 0.4-1.1; log-rank $P=.13$).

Figure 3. Hazard Ratios for Death According to Baseline Characteristics

Subgroup	No. Patients	No. Deaths	Hazard Ratio (95% CI)
Randomization period			
Before April 15, 2005	413	40	0.6 (0.3-1.2)
After April 15, 2005	468	34	0.8 (0.4-1.6)
Age, y			
<70	406	26	0.6 (0.3-1.3)
≥70	475	48	0.8 (0.4-1.4)
AAA diameter, cm			
<5.5	382	27	0.7 (0.3-1.5)
≥5.5	499	47	0.7 (0.4-1.2)
Surgical risk (RAND score)			
Low	467	29	0.7 (0.3-1.4)
Intermediate or high	405	42	0.7 (0.4-1.3)
Coronary artery disease			
No	522	43	0.9 (0.5-1.6)
Yes	359	31	0.5 (0.2-1.0)
Intended endovascular system			
Cook Zenith	341	26	0.6 (0.3-1.4)
Gore Excluder	327	28	0.6 (0.3-1.2)
Medtronic AneuRx	186	15	1.7 (0.6-4.7)
Overall	881	74	0.7 (0.4-1.1)



AAA indicates abdominal aortic aneurysm; CI, confidence interval. Size of the data markers is relative to the number of deaths in that subgroup. All $P>.10$ for interaction with treatment effect. For surgical risk (RAND score), see online eAppendix at http://www.jama.com.[5]

Table 4. Quality of Life and Erectile Dysfunction[a]

	Mean (SD)					
	Baseline		1 Year Minus Baseline		2 Years Minus Baseline	
Measures	Endovascular Repair	Open Repair	Endovascular Repair	Open Repair	Endovascular Repair	Open Repair
SF-36						
MCS	50.6 (10.9)	51.7 (10.4)	–0.77 (10.2)	–0 (10.0)	–0.01 (10.0)	–0.93 (9.8)
PCS	40.5 (10.4)	40.1 (10.5)	–1.2 (9.8)	–1.2 (10.1)	–2.2 (10.2)	–2.0 (10.8)
PCTD	62.5 (22.8)	61.6 (22.8)	–3.0 (22.0)	–2.8 (22.3)	–5.0 (23.3)	–4.29 (23.4)
EQ-5D						
Index score	0.79 (0.16)	0.79 (0.16)	–0.02 (0.16)	–0 (0.17)	–0.01 (0.19)	–0.02 (0.16)
Visual analog scale	71.5 (19.1)	70.3 (18.6)	–1.3 (18.9)	0.88 (17.8)	–2.2 (22.3)	–1.4 (20.3)
IIEF-5	11.4 (8.7)	10.3 (8.8)	–2.5 (8.3)	–2.3 (7.8)	–3.0 (8.5)	–2.9 (8.5)

Abbreviations: EQ-5D, EuroQol; IIEF-5, 5-item International Index of Erectile Function; MCS, mental component summary; PCS, physical component summary; PCTD, physical component transformed with deaths included; SF-36, 36-item Short Form Health Survey.

[a] For endovascular vs open repair, all $P > .05$. The MCS, PCS, and PCTD scores are 0 to 100, with 100 representing better health. The EQ-5D (EuroQol, Rotterdam, the Netherlands) index scores range from 0 (death) to 1.0 (perfect health) and visual analog scale scores from 0 ("worst imaginable health state") to 100 ("best imaginable health state"). The IIEF-5 scores range from 5 to 25, with 25 representing better function.

As shown in TABLE 4, there were no significant differences between the 2 groups in health-related quality of life or erectile function over the 2 years of follow-up.

COMMENT

In this interim report of 2-year outcomes after elective AAA repair, endovascular repair resulted in lower perioperative mortality than open repair without evidence of excess late mortality. Hospital and ICU stays were shorter with endovascular repair and need for transfusion was decreased. No significant differences were observed in major morbidities, secondary procedures, or aneurysm-related hospitalizations.

Two European trials, the United Kingdom Endovascular Aneurysm Repair Trial 1 (EVAR-1)[15] and the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial,[16] previously reported lower operative mortality with endovascular vs open repairs. Perioperative mortality in our study was lower than in the European trials for both treatments. Mortality within 30 days or during hospitalization for endovascular repair was 2.1% in the EVAR-1 trial, 1.2% in the DREAM trial, and 0.5% in our study, and for open repair, mortality was 6.2% in the EVAR-1 trial, 4.6% in the DREAM trial, and 3.0% in our study.[15,16] We did not observe the increased mid-term mortality after endovascular repair that resulted in the loss of its early survival advantage in those trials,[2,3] but all 4 late aneurysm-related deaths in our study occurred in the endovascular group.

The lower perioperative mortality in our study compared with the previous trials could result from several possible factors. First, our procedures were performed more recently, from 2002-2007 compared with 1999-2003 in the EVAR-1 and DREAM trials. Of the 15 deaths within 30 days after repair or during hospitalization in our study, 10 occurred in the first 412 patients, enrolled before April 15, 2005, including the 2 deaths in the endovascular group.

Second, our results could have been improved by enrollment of patients with small AAA. Forty-three percent of our patients (n=382) had aneurysms smaller than 5.5 cm in diameter and therefore would not have been eligible for enrollment in the EVAR-1 trial. However, perioperative mortality rates (Table 3) and treatment effects (Figure 3) were similar between patients with AAA of less than 5.5 cm and those with larger AAA, suggesting that AAA diameter was not an important factor.

Third, there could be differences in surgical technique and postoperative care between our trial and the European trials. Procedures in our trial were performed by experienced university-affiliated vascular surgeons. Although the participation of more than 100 surgeons in our trial supports generalizability within this group, and procedures in the European trials were also performed by experienced vascular surgeons, differences between trials in surgical technique and postoperative care cannot be completely excluded. Inpatient mortality following nonruptured open AAA repair in the United States during our enrollment period was 4.5%,[1] roughly half that in the United Kingdom during the EVAR-1 enrollment period,[17,18] a difference that reflects the differences in operative mortalities between trials. Furthermore, previous studies have reported low perioperative mortality for AAA repair in the Veterans Affairs health system compared with other US health care organizations.[19,20]

Fourth, there were differences in the endovascular systems used. The EVAR-1 trial used the Medtronic Talent (which was not approved for use in the United States until after our enrollment ended) in a third of the patients and used the Gore Excluder and Medtronic AneuRx much less frequently than in our study. We did not find significant interactions between device selection and treatment effect in our study, although there was a nonsignificantly less favorable outcome after endovascular repair with AneuRx compared with other endovascular systems (Figure 3), and the 2 perioperative deaths and 2 of the 4 late aneurysm-related deaths in our endo-

vascular group were in the AneuRx subgroup, suggesting that greater use of this device probably did not improve survival in our study relative to the European trials. In 2008, the US Food and Drug Administration issued a public health notification regarding higher than expected late aneurysm–related mortality with AneuRx.[21] Longer follow-up is needed to monitor performance of the various graft systems.

Our findings of no difference in major morbidities or secondary therapeutic procedures contrast with the EVAR-1 findings of highly significant differences favoring open repair in complications and reinterventions.[2] At least some of these differences between the 2 trials may result from how the categories were defined. For example, the EVAR-1 trial appears to have counted as reinterventions only procedures directly related to graft placement, whereas our study included any secondary therapeutic procedures resulting from the original procedure, such as incisional hernia repairs. Incisional hernia repairs were the most common secondary therapeutic procedures in the open-repair group in our study, occurring in 4.9% of patients at 2 years. This is comparable with the 5.8% rate reported in a Medicare population within 4 years after open repair.[22] A recent meta-analysis found that open AAA repair carries a 5-fold greater risk of incisional hernia than does surgery for aortoiliac occlusive disease, possibly reflecting an underlying collagen defect in patients with AAA.[23]

Health-related quality of life decreased in the early postoperative period in the European trials, particularly following open repair, but these changes resolved before 6 months.[4] In the DREAM trial,[24] quality of life at 6 months and 1 year was lower in the endovascular group. Our study focused on later postoperative quality of life and found no differences between the 2 groups at 1 and 2 years.

Open AAA repair results in erectile dysfunction in some patients, although most of the dysfunction observed after repair in 1 large trial was not new.[25] Erectile dysfunction has been reported to be reduced after endovascular repair compared with open repair, but these data are from nonrandomized retrospective surveys and are subject to recall and response bias.[26,27] Our finding of no difference between open and endovascular repair in erectile dysfunction at 1 and 2 years is in agreement with randomized prospective data from the DREAM trial, which reported no difference between open and endovascular repair in erectile dysfunction at 3, 6, and 12 months.[28]

CONCLUSION

In this randomized trial, endovascular repair resulted in fewer perioperative deaths than open repair, even though open repair was performed with low mortality. This early advantage was not offset by increased morbidity or mortality in the endovascular group in the first 2 years after repair. Longer-term data are needed to fully assess the relative merits of the 2 procedures.

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Additional Information: Online eAppendix is available at http://www.jama.com.

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Open versus Endovascular Repair of Abdominal Aortic Aneurysm

TO THE EDITOR: Lederle and colleagues (May 30 issue)[1] report similar long-term overall survival after endovascular or open surgical repair of infrarenal aortic aneurysms in the Open versus Endovascular Repair (OVER) trial. These results contrast with those from two trials conducted in Europe.[2,3]

An important issue is the generalizability of the results. It is noteworthy that a majority (52%) of patients who underwent screening in the OVER trial were excluded because they were ineligible to undergo both procedures. However, no anatomical criteria are provided in the protocol (available with the full text of their article at NEJM.org) except that patients had to be suitable candidates for both techniques. It is well established that a long aortic proximal neck is associated with lower incidences of device migration, proximal endoleaks, and aneurysm-related death.[4] Furthermore, wide infrarenal aneurysm necks are associated with an increased risk of proximal complications.[5] Therefore, there is a concern that the excellent results regarding endovascular repair in the OVER trial may be due to the inclusion of a highly selected patient population and may not be reflective of routine treatment of patients. In addition, outcomes that are more specific, such as aneurysm-related mortality (2.2% vs. 0.6%) and morbidity during follow-up, still favor open repair.

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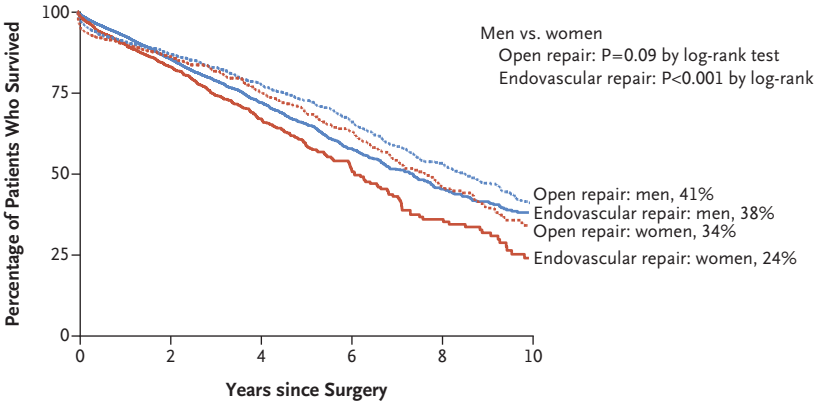
TO THE EDITOR: Lederle et al. examined long-term survival after open or endovascular repair of abdominal aortic aneurysm in the OVER trial. They report no difference in survival according to repair type, although European trials[1,2] have shown worse survival after endovascular repair than after open repair. In addressing this discordance, the authors did not discuss the potential effects of the near absence of women from the OVER trial (0.6% of the trial population) — a percentage that is substantially lower than the 6% in EVAR-1 (United Kingdom Endovascular Aneurysm Repair Trial–1),[1] and the 9% in the DREAM (Dutch Randomised Endovascular Aneurysm Management) trial.[2]

We studied 14,439 patients, 22% of whom were women, who underwent elective repair of abdominal aortic aneurysm within the Vascular Quality Initiative.[3,4] The 10-year survival after endovascular repair was 14 percentage points lower among women than among men (P<0.001) (Fig. 1), and there was no difference between men and women in mortality after open repair (P=0.09). These differences contributed to an overall survival advantage for open repair (10-year survival, 39% in the open-repair group vs. 34% in the endovascular-repair group; P<0.001), a finding similar to those in the European trials.



No. at Risk			
Open repair			
Men	1847	364	108
Women	813	142	40
Endovascular repair			
Men	9454	441	84
Women	2325	111	20

Figure 1. Survival among Men and Women Undergoing Elective Endovascular or Open Surgical Repair of Abdominal Aortic Aneurysm.

The study involved 14,439 patients who underwent elective repair (endovascular or open) of abdominal aortic aneurysm within the Vascular Quality Initiative.[3,4]

Although the OVER trial shows similar long-term survival among men who underwent open or endovascular repair of abdominal aortic aneurysm, these results may not be generalizable to women.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Pellenc et al. ask about the length and diameter of the infrarenal aortic neck — a critical factor in stable device placement. The protocol of the OVER trial required that a participant "be considered a candidate for both procedures by the participating vascular surgeon, and meet the manufacturer's indications" for a Food and Drug Administration–approved system.[1] In our trial, the mean aortic-neck length (26 mm) was shorter than that reported in regulatory trials of the two most common devices that were used in our trial (29 mm and 33 mm) and was slightly longer than the length of subsequently approved devices for treatment of shorter necks (23 mm and 24 mm). In our trial, the mean proximal-neck diameter (23 mm) was within the range that was used in trials for defining on-label use (22 to 26 mm).[2,3] Aortic-neck anatomy in the OVER trial was representative of that found in routine elective management of abdominal aortic aneurysm. The excellent results of endovascular repair may be attributable to the exclusive use of

approved devices, device improvements after 2004, and the requirements regarding the experience, training, and subspecialty certification of the surgeon.

Neither aneurysm-related mortality (2.7% in the endovascular-repair group vs. 3.7% in the open-repair group) nor all-cause mortality differed substantially during late follow-up in the OVER trial.

Ramkumar et al. note the small number of women who were enrolled in this trial that was conducted at 42 Veterans Affairs medical centers — a situation that limits generalizability on the basis of sex. Imbalanced enrollment on the basis of sex is also related to the lower prevalence of aneurysm disease among women, whose smaller iliac arteries may preclude the use of early systems involving large sheath diameters. Research in the VA system has the advantage of robust cost analysis and high-fidelity ascertainment of vital status in long trials.[4]

Ramkumar and colleagues also note the paucity of women in the two European trials (only 6% and 9% of the trial populations) and present data regarding 14,439 elective repairs of abdominal aortic aneurysm in a population in which 22% of the patients were women. However, the Vascular Quality Initiative comparison is not a randomized trial, and the comparison involved groups with differing percentages of women (20% in the endovascular-repair group vs. 31% in the open-repair group). There may be bias in the selection of repair type, and caution is warranted in interpreting the results of nonrandomized studies in which treatment methods are compared on the basis of data from large quality and administrative registries.

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Since publication of their article, the authors report no further potential conflict of interest.

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