wish to stop anticoagulation, a switch to aspirin at a dose of 100 mg daily will reduce by one third the risk of recurrent venous thromboembolism, as well as of arterial cardiovascular events, and may also attenuate the early burst of thrombosis recurrence after cessation of oral anticoagulation. Aspirin is inexpensive, does not require monitoring (in contrast to warfarin), and does not accumulate in patients with renal insufficiency (in contrast to dabigatran and rivaroxaban); in addition, if major bleeding occurs or the patient requires urgent surgery, the antiplatelet effects of aspirin can be reversed with transfusion of platelets. Among patients with unprovoked venous thromboembolism who have completed initial anticoagulation, aspirin would seem to be a reasonable option for long-term dual prevention of recurrent venous thromboembolism and arterial cardiovascular events.

A current faculty member of McMaster University was a member of the steering committee of the ASPIRE study, but no patients from that institution participated in the study, and the author had no role in the design or conduct of the study or the analysis of the data.

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

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1. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86. [Erratum, BMJ 2002;324:141.]
2. Harris WH, Salzman EW, Athanasoulis CA, Waltman AC, DeSanctis RW. Aspirin prophylaxis of venous thromboembolism after total hip replacement. N Engl J Med 1977;297:1246-9.
3. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012; 141:Suppl:e278S-e325S.
4. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med 2012;366:1959-67.
5. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-87.
6. Boutitie F, Pinede L, Schulman S, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials. BMJ 2011;342:d3036.
7. Kearon C. A conceptual framework for two phases of anticoagulant treatment of venous thromboembolism. J Thromb Haemost 2012;10:507-11.
8. Prandoni P, Bilora F, Marchiori A, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003; 348:1435-41.
9. Green D. Risk of future arterial cardiovascular events in patients with idiopathic venous thromboembolism. Hematology Am Soc Hematol Educ Program 2009;1:259-66.

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Is the Dream of EVAR Over?

Joshua A. Beckman, M.D.

Abdominal aortic aneurysm (AAA) is a vascular disorder fraught with contradictions. It is mostly benign, causing no limitation in daily activity. Yet the first occasion of symptoms, aneurysm rupture, is often lethal. Moreover, surgical repair of the asymptomatic AAA causes substantial morbidity and is considered the exemplar of high-risk elective surgery.[1] Research over the past two decades has made it clear that screening reduces AAA-related deaths[2] and that the appropriate timing of surgical repair improves outcomes.[3] This large body of work resulted in the acceptance of AAA screening as a benefit by the Centers for Medicare and Medicaid Services and in the creation of multispecialty guidelines concerning proper methods for identifying patients, carrying out follow-up, and determining the timing of surgery.[4]

Just when the issue of how to care for patients with AAA was becoming settled, however, a disruptive innovation was introduced that threatened to upend the established treatment paradigm. Endovascular repair of AAA was pioneered in Argentina in the early 1990s[5] and had the potential to dramatically alter the medical landscape because it guaranteed safety similar to that seen with open surgical repair but resulted in less injury to the patient. Through the 1990s, this new technology spread and improved rapidly, creating a base of expertise. By the end of the decade, registry data suggested that the rate of AAA rupture after endovascular repair was similar to that seen in the large trials evaluating the timing of open surgical repair, and morbidity was lower.[6] The time was ripe for clinical trials to compare these two types of repair. Indeed,

investigators hoped that the use of endovascular repair would significantly lower total mortality and extend AAA repair to patients for whom the risks associated with open repair were considered to be too high.

Three large clinical trials were performed: the United Kingdom Endovascular Repair 1 trial (EVAR 1),[7] the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial,[8] and the Open versus Endovascular Repair (OVER) Veterans Affairs Cooperative Study.[9] The results of the three trials were remarkably consistent, each showing significant reductions in perioperative morbidity and mortality. Soon after these findings were published, the use of endovascular repair surged and became the dominant method of AAA repair.[10]

In 2010, the long-term results of the EVAR 1 and DREAM trials were reported in the *Journal*, and both showed that 24-month mortality was the same in the endovascular-repair and open-repair groups.[7,8] The initial reductions in morbidity and mortality were offset by a "mortality catch-up" among the patients in the endovascular-repair group. Although this result was surprising initially, a broader view provided some explanation. First, among patients with previously diagnosed AAA, aneurysm rupture represents a small portion of all-cause mortality. Second, the strong relationship between cigarette smoking and aneurysm formation makes this patient group susceptible to the numerous, more common diseases associated with smoking, including coronary artery and cerebrovascular atherosclerotic disease, cancer, and chronic obstructive pulmonary disease. In the DREAM trial, 118 of the 351 patients (34%) died during a median follow-up of 6 years, yet only 2 (<1%) died of aneurysm rupture. In EVAR 1, a total of 524 of the 1252 patients (42%) died during a median follow-up of 6 years, but only 76 (5%) died of aneurysm-related causes.

As reported by Lederle et al. in this issue of the *Journal*,[11] outcomes in the OVER study were similar. In this study, the largest of the three trials comparing endovascular repair and open repair, 881 patients were followed for a mean of 5.2 years, during which time one third of the patients died, but only 3% died from aneurysm-related causes. The OVER investigators noted the same pattern of outcomes as in the earlier trials: an upfront reduction in mortality with catch-up later. In the OVER study, the benefit was sustained for 3 years (instead of 2, as in the other two trials) and was similarly lost thereafter.

Thus, the results of these three clinical trials were incredibly consistent. Moreover, they raise several important points. First, proper care of the patient with AAA yields admirable outcomes, with low rates of AAA-related mortality as long as 6 years after repair. Second, a diagnosis of AAA should immediately indicate modification of cardiovascular risk factors consistent with secondary prevention of cardiovascular events. The fact that more than half the patients in OVER were taking beta-blockers and aspirin and more than 40% were taking angiotensin-converting–enzyme inhibitors suggests that good medical therapy may forestall expected cardiovascular mortality. Reported cardiovascular medical therapy was better in the OVER study than in the DREAM and EVAR 1 trials and may be one factor that sustained the initial mortality benefit seen in OVER. Third, similar long-term outcomes now allow more patient preference–related decision making to be part of the process. In the absence of a significant difference in long-term mortality between the two types of repair, patients can weigh the value of open repair, a major operation with greater upfront morbidity and mortality, against that of endovascular repair, with its lower early-event rate but the need for indefinite radiologic surveillance.

Finally, one of the initial goals of studying this therapy was to extend AAA repair to patients for whom open repair is deemed unsafe yet who remain at risk for rupture. The EVAR 1 investigators studied 404 patients thought to be ineligible for surgery, randomly assigning them to either endovascular repair or expectant management.[12] During 4 years of follow-up, mortality was 68%, with no significant difference among the groups. These results further support the notion that aneurysm-related deaths represent a small portion of all-cause mortality and that the worse the underlying medical condition, the less likely the patient will die of an aneurysm-related cause.

Is the dream of endovascular repair over? First, it has substantially reduced the pain and suffering associated with AAA repair and rightly has overtaken open repair as the primary form of treatment. Second, these trials make clear that attention to other smoking-related illnesses

is warranted, since they represent the majority of causes of morbidity and mortality. Third, the results of the OVER study confirm that the patient population who should undergo AAA repair remains the same as it has been for the past 15 years. Thus, endovascular repair has neither expanded AAA repair to new populations nor reduced long-term mortality when compared with open repair. The dream of improving long-term survival and expanding the population that will benefit from AAA repair is seemingly over, but the reality of better procedural recovery for patients today is certainly a step forward.

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

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1. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery) developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. J Am Coll Cardiol 2007;50:1707-32.
2. Ashton HA, Buxton MJ, Day NE, et al. The Multicentre Aneurysm Screening Study (MASS) into the effect of abdominal aortic aneurysm screening on mortality in men: a randomised controlled trial. Lancet 2002;360:1531-9.
3. Lederle FA, Wilson SE, Johnson GR, et al. Immediate repair compared with surveillance of small abdominal aortic aneurysms. N Engl J Med 2002;346:1437-44.
4. Hirsch AT, Haskal ZJ, Hertzer NR, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation 2006;113(11):e463-e654.
5. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. Ann Vasc Surg 1991;5:491-9.
6. Harris PL. The highs and lows of endovascular aneurysm repair: the first two years of the Eurostar Registry. Ann R Coll Surg Engl 1999;81:161-5.
7. The United Kingdom EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1863-71.
8. De Bruin JL, Baas AF, Buth J, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1881-9.
9. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA 2009;302:1535-42.
10. Levin DC, Rao VM, Parker L, Frangos AJ, Sunshine JH. Endovascular repair vs open surgical repair of abdominal aortic aneurysms: comparative utilization trends from 2001 to 2006. J Am Coll Radiol 2009;6:506-9.
11. Lederle FA, Freischlag JA, Kyriakides TC, et al. Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. N Engl J Med 2012;367:1988-97.
12. The United Kingdom EVAR Trial Investigators. Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. N Engl J Med 2010;362:1872-80.

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ORIGINAL ARTICLE

Long-Term Comparison of Endovascular and Open Repair of Abdominal Aortic Aneurysm

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ABSTRACT

BACKGROUND

Whether elective endovascular repair of abdominal aortic aneurysm reduces long-term morbidity and mortality, as compared with traditional open repair, remains uncertain.

METHODS

We randomly assigned 881 patients with asymptomatic abdominal aortic aneurysms who were candidates for both procedures to either endovascular repair (444) or open repair (437) and followed them for up to 9 years (mean, 5.2). Patients were selected from 42 Veterans Affairs medical centers and were 49 years of age or older at the time of registration.

RESULTS

More than 95% of the patients underwent the assigned repair. For the primary outcome of all-cause mortality, 146 deaths occurred in each group (hazard ratio with endovascular repair versus open repair, 0.97; 95% confidence interval [CI], 0.77 to 1.22; P=0.81). The previously reported reduction in perioperative mortality with endovascular repair was sustained at 2 years (hazard ratio, 0.63; 95% CI, 0.40 to 0.98; P=0.04) and at 3 years (hazard ratio, 0.72; 95% CI, 0.51 to 1.00; P=0.05) but not thereafter. There were 10 aneurysm-related deaths in the endovascular-repair group (2.3%) versus 16 in the open-repair group (3.7%) (P=0.22). Six aneurysm ruptures were confirmed in the endovascular-repair group versus none in the open-repair group (P=0.03). A significant interaction was observed between age and type of treatment (P=0.006); survival was increased among patients under 70 years of age in the endovascular-repair group but tended to be better among those 70 years of age or older in the open-repair group.

CONCLUSIONS

Endovascular repair and open repair resulted in similar long-term survival. The perioperative survival advantage with endovascular repair was sustained for several years, but rupture after repair remained a concern. Endovascular repair led to increased long-term survival among younger patients but not among older patients, for whom a greater benefit from the endovascular approach had been expected. (Funded by the Department of Veterans Affairs Office of Research and Development; OVER ClinicalTrials.gov number, NCT00094575.)

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Each year, 40,000 patients in the United States undergo elective procedures to repair abdominal aortic aneurysms.[1] These procedures result in about 1250 perioperative deaths — more than for any other general or vascular surgical procedure, with the exception of colectomy.[2] Endovascular repair was introduced in the 1990s as a less invasive method than traditional open repair. Randomized trials have shown that endovascular repair reduces perioperative mortality,[3-5] but in the United Kingdom Endovascular Aneurysm Repair 1 (EVAR 1) trial[3] and the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial,[4] this advantage was lost within 2 years owing to excess late deaths in the endovascular-repair groups. In the Open versus Endovascular Repair (OVER) Veterans Affairs Cooperative Study, excess late deaths were not observed in the endovascular-repair group at 2 years.[5] We report here the long-term results of that study.

METHODS

STUDY DESIGN AND OVERSIGHT

The study design and methods have been described previously[5] and are briefly reviewed here. The study was designed, conducted, analyzed, and written by the authors, who also wrote the first draft and vouch for the data and analysis. The study 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 study was conducted in accordance with the protocol, available with the full text of this article at NEJM.org. The authors vouch for the accuracy and completeness of the data and analysis.

PATIENTS

Patients with abdominal aortic aneurysms for which repair was planned were eligible for the study if the aneurysm had a maximum external diameter of at least 5.0 cm, an associated iliac-artery aneurysm with a maximum diameter of at least 3.0 cm, or a maximum diameter of at least 4.5 cm plus either rapid enlargement (an increase of at least 0.7 cm in 6 months or 1.0 cm in 12 months) or a saccular appearance. Patients were excluded if they were not considered to be a candidate for either procedure, had previously undergone abdominal aortic surgery, needed urgent repair, or were unable or unwilling to give informed consent or to follow the protocol.

PROCEDURES

Patients were randomly assigned to open repair or endovascular repair with equal probability. Only endovascular-repair devices approved by the Food and Drug Administration were used in the study. The specific type of endovascular-repair devices 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. Though group assignments were of necessity unblinded, concealment of treatment assignments from site investigators and patients was maintained throughout randomization by means of telephone calls to the coordinating center, as described previously.[5] The protocol required that a study-approved vascular surgeon or interventional radiologist perform the aneurysm repair within 6 weeks after randomization.

Follow-up visits were scheduled at 1 month after aneurysm repair, at 6 and 12 months after enrollment, and then yearly. All follow-up visits after endovascular repair included computed tomography (CT) and plain radiography of the abdomen, whereas after open repair, CT alone was required at 1 year and at the end of the study. Patients were contacted by telephone monthly during the first 14 months after the repair and then annually midway between study visits to identify interim outcomes, and they were asked to maintain a log of all health care visits. Additional follow-up information was obtained by the coordinating center with the use of national data sets.

OUTCOMES

The primary outcome was long-term mortality from any cause. Short-term secondary outcomes have been reported previously.[5] Long-term secondary outcomes included prespecified subgroups of the primary outcome; secondary therapeutic procedures that resulted directly or indirectly from the initial procedure and that required a separate trip to the procedure suite (with each trip to the procedure suite counting as one secondary procedure), including any unplanned surgical procedures within 30 days after the initial procedure and any additional aortoiliac procedures at any time; post-repair hospitalizations; uncorrected aortoiliac abnormalities noted on imaging at the end of the study; and health-related quality-of-life factors, including erectile function.

Cause of death and secondary therapeutic procedures were adjudicated by an outcomes commit-

tee whose members were unaware of the group assignments. Aneurysm-related mortality was not a prespecified outcome because of the potential for ascertainment bias, but it is reported here for comparison with other trials. All deaths that occurred within 30 days after the repair or during the hospitalization for repair were considered to be related to the aneurysm, as were all late deaths adjudicated as having resulted directly or indirectly from the aneurysm or its treatment.

Health-related quality of life was assessed with the use of two brief questionnaires: the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the European Quality of Life–5 Dimensions (EQ-5D) instrument, which were completed at baseline and at follow-up visits. The SF-36 evaluates eight dimensions of health aggregated into two summary measures: a mental component score and a physical component score.[6] We also calculated the physical component score with deaths included.[7] The EQ-5D consists of a five-item questionnaire used to generate an index score, with U.S. population–based preference weights, and a visual-analogue scale.[8] Erectile function was assessed with the use of the previously validated International Index of Erectile Function (IIEF).[9] Questionnaires were completed by the patients and reviewed for completeness by study personnel.

Table 1. Characteristics of the Patients at the Time of Randomization.*

Characteristic	Endovascular Repair (N=444)	Open Repair (N=437)
Age — yr	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 — kg	89.9±16.8	89.7±17.8
Body-mass index‡		
Mean	28.6±5.2	28.7±5.6
≥35 — no. (%)	47 (10.6)	44 (10.1)
Smoking status — no. (%)		
Ever smoked§	428 (96.4)	413 (94.5)
Currently smokes	170 (38.3)	193 (44.2)
Medical 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)
Cancer other than skin cancer	83 (18.7)	70 (16.0)
Diabetes	100 (22.5)	100 (22.9)
Chronic obstructive lung disease	126 (28.4)	133 (30.4)
Hypertension	347 (78.2)	330 (75.5)
Blood pressure — mm Hg		
Systolic	133.6±18.7	133.0±18.8
Diastolic	75.8±10.9	74.3±10.6
Medications — no. (%)		
Beta-blocker	282 (63.5)	282 (64.5)
Aspirin	244 (55.0)	277 (63.4)
ACE inhibitor	192 (43.2)	180 (41.2)
Anticoagulant	44 (9.9)	34 (7.8)
Claudication — no. (%)	66 (14.9)	81 (18.5)

Table 1. (Continued.)

Characteristic	Endovascular Repair (N=444)	Open Repair (N=437)
Ankle–brachial index — no. (%)		
≤0.9 on at least one side	159 (35.8)	155 (35.5)
≤0.4 on at least one side	48 (10.8)	45 (10.3)
Maximum activity level — no. (%)		
Sedentary or mild	182 (41.0)	185 (42.3)
Moderate or vigorous	262 (59.0)	252 (57.7)
Serum creatinine — mg/dl	1.2±0.5	1.1±0.4
GFR less than 60 ml/min/1.73 m^2 — no. (%)¶	140 (31.5)	136 (31.1)
Surgical risk, RAND score — no. (%)‖		
Low	240 (54.1)	228 (52.2)
Intermediate	169 (38.1)	175 (40.0)
High	31 (7.0)	29 (6.6)
Family history of abdominal aortic aneurysm — no. (%)	70 (15.8)	51 (11.7)
Maximum diameter of aneurysm		
Mean diameter — cm	5.7±0.8	5.7±1.0
<5.5 cm — no. (%)	192 (43.2)	190 (43.5)
<5.0 cm — no. (%)	23 (5.2)	18 (4.1)
5.5–5.9 cm — no. (%)	133 (30.0)	123 (28.1)
6.0–6.9 cm — no. (%)	86 (19.4)	83 (19.0)
≥7.0 cm — no. (%)	33 (7.4)	41 (9.4)
Intended endovascular device — no. (%)		
Cook Zenith	166 (37.4)	175 (40.0)
Gore Excluder	177 (39.9)	150 (34.3)
Medtronic AneuRx	88 (19.8)	98 (22.4)
Other	13 (2.9)	14 (3.2)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. P>0.05 for all between-group comparisons of baseline characteristics except aspirin use (P=0.01). ACE denotes angiotensin-converting enzyme.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ "Ever smoked" was defined as having smoked more than 100 cigarettes over the person's lifetime.
¶ The glomerular filtration rate (GFR) was estimated with the use of the four-variable equation in the Modification of Diet in Renal Disease study.[12]
‖ For a description of the RAND criteria for surgical risk, in which higher scores denote higher risk,[5] see Table S1 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The study began in October 2002 and was reconfigured in 2005, as previously described.[5] For the revised plan, which included 5 years of enrollment plus 4 years of follow-up, we calculated that a sample of 872 patients would provide 80% power to detect a 25% relative reduction in mortality at a two-sided alpha level of 0.05. To reach this number, enrollment was continued for an additional 6 months, until April 2008, at three centers.

Data were analyzed according to the intention-to-treat principle. Estimates of cumulative event rates were calculated by means of the Kaplan–Meier method, and hazard ratios with confidence intervals were estimated by means of Cox proportional-hazards models.[10] The effect of treatment in prespecified subgroups was assessed by means of treatment–subgroup interactions in the Cox models. Variables were compared with the use of chi-square tests and t-tests. P values of less

than 0.05 were considered to indicate statistical significance; two-sided P values are reported. Statistical analyses were performed with the use of SAS software, version 9.1 (SAS Institute). Restricted mean survival (analogous to the area under the curve for a survival plot) was assessed with the use of the pseudo-mean values approach.[11] Longitudinal mixed-effects models, adjusted for baseline values, were used to compare the two groups with respect to quality-of-life measures. Treatment effect and change in quality-of-life measures over time were assessed in repeated-measures models (with unstructured covariance), with the assigned repair method and baseline measurements used as covariates.

RESULTS

PATIENTS

A total of 881 patients at 42 Veterans Affairs medical centers were randomly assigned to either endovascular repair (444) or open repair (437) and were followed for up to 9 years (mean, 5.2). Details of exclusions before randomization were described previously[5] and are shown in Figure S1 in the Supplementary Appendix, available at NEJM.org. Characteristics at the time of randomization were also described previously[5] and are shown in Table 1. The two groups of patients were similar, with no significant differences except that a greater proportion of the open-repair group used aspirin. The mean age of the study cohort was 70 years, and 99% of the patients were men; the mean maximum diameter of the abdominal aortic aneurysm was 5.7 cm. A total of 96% of the randomly assigned patients underwent the assigned repair; in another 2%, the assigned repair was attempted but not completed (Fig. S1 in the Supplementary Appendix).

At the end of the study, on October 15, 2011, there were 4578 patient-years of follow-up, and vital status was confirmed for all patients. Of patients alive at the end of the study, 93% had attended the study clinic during the final year, and telephone calls and databases were used to obtain follow-up data regarding secondary outcomes in another 6%. Throughout the study, the proportion of quality-of-life forms completed ranged from 85% of those possible for the EQ-5D (an indicator of the rate of study-visit attendance) to 67% for the IIEF (which some patients declined to complete, especially after previously noting erectile dysfunction).

MORTALITY AND RUPTURE

For the primary outcome of all-cause mortality, 146 deaths occurred in each group (hazard ratio with endovascular repair vs. open repair, 0.97; 95% confidence interval [CI], 0.77 to 1.22; P=0.81) (Fig. 1A and Table 2). As reported previously, perioperative mortality (death during hospitalization or within 30 days after the procedure) was lower in the endovascular-repair group than in the open-repair group (0.5% vs. 3.0%, P=0.004). In our earlier analysis, with 2-year results available for 80% of patients, the difference in mortality between the two groups was no longer significant at 2 years. In the current analysis, which includes all patients, the difference in mortality was significant at 2 years (hazard ratio with endovascular repair, 0.63; 95% CI, 0.40 to 0.98; P=0.04) and was of borderline significance at 3 years (hazard ratio, 0.72; 95% CI, 0.51 to 1.00; P=0.05) but not thereafter. The restricted mean survival was also not significantly different between the two groups at 5 years (P=0.13) and at 9 years (P=0.65).

Ten deaths (2 perioperative and 8 late) were determined to be aneurysm-related in the endovascular-repair group (2.3%), as compared with 16 deaths (13 perioperative and 3 late) in the open-repair group (3.7%; absolute difference, –1.4 percentage points; 95% CI, –3.7 to 0.8; P=0.22). Six aneurysm ruptures were confirmed in the endovascular-repair group (4 occurred more than 5 years after the repair, and 3 of the 6 were fatal), as compared with no ruptures in the open-repair group (P=0.03). Of the six patients with rupture, one had declined aneurysm repair after randomization, another had missed appointments for follow-up imaging studies for 3 years before the rupture, and a third patient declined treatment after graft migration and sac enlargement were diagnosed. One of the remaining three patients had undergone recent endovascular treatment of a proximal aortic dissection, and in the other two patients, large type 1 endoleaks were diagnosed at the time of rupture.

SECONDARY THERAPEUTIC PROCEDURES AND OTHER OUTCOMES

A total of 148 secondary therapeutic procedures were performed in 98 patients in the endovascular-repair group and 105 procedures were performed in 78 patients in the open-repair group (P=0.26 for the number of procedures and P=0.12 for the number of patients) (Table 2). Among the secondary procedures in the endovascular-repair group,

there were 100 endovascular procedures, 9 conversions to open repair (none of which resulted in death within 1 year), 19 other arterial procedures with an open component, 11 wound-related procedures, 6 amputations (1 during an arterial procedure), and 4 miscellaneous procedures. Among the secondary procedures in the open-repair group, there were 48 incisional hernia repairs, 15 endovascular procedures, 13 open arterial procedures, 11 laparotomies for bowel ischemia or obstruction, 7 amputations, 7 miscellaneous open procedures, and 4 wound-related procedures. The time to a secondary therapeutic procedure or death (Fig. 1B) was similar in the two groups throughout the study (hazard ratio for a secondary procedure or death with endovascular repair, 1.06; 95% CI, 0.87 to 1.28; P=0.57).

Several aortoiliac abnormalities remained untreated at the end of the study. Of the 298 patients in the endovascular group who were alive at the end of the study, 244 underwent CT within the preceding year; 3 of these patients were found to have an enlarged aneurysm sac, and 1 patient each had a kinked graft, graft migration, and an iliac-artery aneurysm greater than 3 cm in diameter. Of the 291 patients in the open-repair group who were alive at the end of the study, 195 underwent CT within the preceding year, which revealed iliac-artery dissection in 1 patient, an iliac-artery aneurysm greater than 3 cm in diameter in 2 patients, and a proximal abdominal aortic aneurysm greater than 4 cm in diameter in 1 patient.

The number of hospitalizations after the initial aneurysm repair was similar in the two groups (Table 2). More hospitalizations were determined to be aneurysm-related in the endovascular-repair group than in the open-repair group, but the difference was not significant.

Long-term mortality for prespecified subgroups of patients is shown in Figure 2. Survival was better with endovascular repair than with open repair among patients younger than 70 years of age (hazard ratio, 0.65; 95% CI, 0.43 to 0.98; P=0.04). Among those 70 years of age or older, survival was better with open repair than with endovascular repair, but this effect was of marginal significance (hazard ratio, 1.31; 95% CI, 0.99 to 1.73; P=0.06), with the result that the interaction between treatment group and age group was highly significant (P=0.006). In a post hoc analysis to further evaluate these findings, we examined survival plots and cause of death according to age group (Fig. S2a and S2b and Table S2 in the Supplementary Appendix). The between-group difference in mortality among the younger patients may be related to a difference in cancer-related deaths (Table S2 in the Supplementary Appendix). An interaction of marginal significance was also seen between type of treatment and date of randomization, with

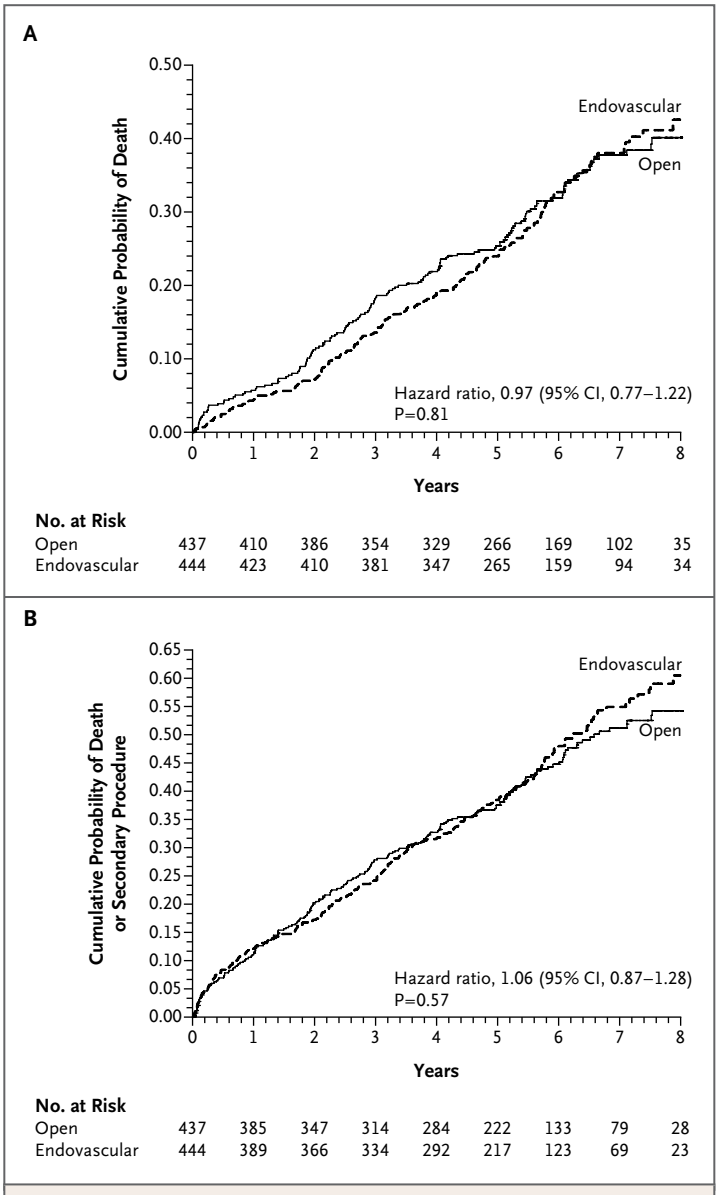

Figure 1. Kaplan–Meier Plots of the Cumulative Probability of Death or a Secondary Therapeutic Procedure, According to Type of Aneurysm Repair.

Panel A shows the cumulative probability of death from the time of randomization among patients with an abdominal aortic aneurysm who underwent endovascular repair as compared with those who underwent open repair. Panel B shows the cumulative probability of death or a secondary therapeutic procedure.

Table 2. Clinical Outcomes in the Two Treatment Groups.

Outcome	Endovascular Repair (N=444)	Open Repair (N=437)	P Value
All deaths — no. of patients (%)	146 (32.9)	146 (33.4)	0.81
Cause of death — no. of patients (%)			
Aneurysm-related cause	10 (2.3)	16 (3.7)	0.22
During hospitalization or within 30 days after repair	2 (0.5)	13 (3.0)	0.004
Cardiovascular cause not related to aneurysm	39 (8.8)	29 (6.6)	0.23
Cancer	39 (8.8)	48 (11.0)	0.27
Pneumonia or other infection	15 (3.4)	12 (2.8)	0.59
Chronic obstructive lung disease	5 (1.1)	13 (3.0)	0.05
Accident, homicide, or suicide	10 (2.3)	4 (0.9)	0.18
Other cause	15 (3.4)	9 (2.1)	0.23
Unknown cause	13 (2.9)	15 (3.4)	0.67
Aneurysm rupture	6 (1.4)	0	0.03
New or worsened claudication — no. of patients (%)	23 (5.2)	15 (3.4)	0.20
Secondary therapeutic procedures			
No. of patients (%)	98 (22.1)	78 (17.8)	0.12
No. of procedures	148	105	0.26
Hospitalizations after repair			
Total no. of hospitalizations	954	1040	0.08
Total no. of patients with one or more hospitalizations (%)	325 (73.2)	314 (71.9)	0.66
Hospitalizations related to aneurysm			
No. of hospitalizations	171	117	0.12
No. of patients (%)	95 (21.4)	78 (17.8)	0.19

the endovascular-repair group tending to fare relatively better in later years (P=0.054).

Survival after endovascular repair, as compared with open repair, tended to be worse when Medtronic AneuRx was the intended graft (P=0.06 for the interaction between treatment group and use of AneuRx vs. another device). This device had been used in 6 of the 10 patients with aneurysm-related deaths in the endovascular-repair group and in 2 of the 3 patients with nonfatal ruptures.

As shown in Figure 3, there were no significant differences between the two treatment groups in terms of health-related quality of life or erectile function.

DISCUSSION

In this long-term, multicenter, randomized trial involving patients with abdominal aortic aneurysm, there was no significant difference in the primary outcome of long-term all-cause mortality between the endovascular-repair group and the open-repair group. The perioperative survival advantage with endovascular repair was sustained for several years, after which there was no significant difference between the two groups. Endovascular repair led to improved long-term survival among patients younger than 70 years of age, but among older patients it tended to reduce survival.

Aneurysm rupture after repair was uncommon but occurred only in the endovascular-repair group, resulting in a significant between-group difference. We found no significant difference between the two groups with respect to number of secondary therapeutic procedures, number of postrepair hospitalizations, quality of life, or erectile dysfunction.

Much of the early enthusiasm for endovascular repair focused on the expected advantage among old or infirm patients who were not good candidates for open repair. Our finding that endovascular repair resulted in better outcomes among younger patients and in worse outcomes among older patients was therefore surprising.

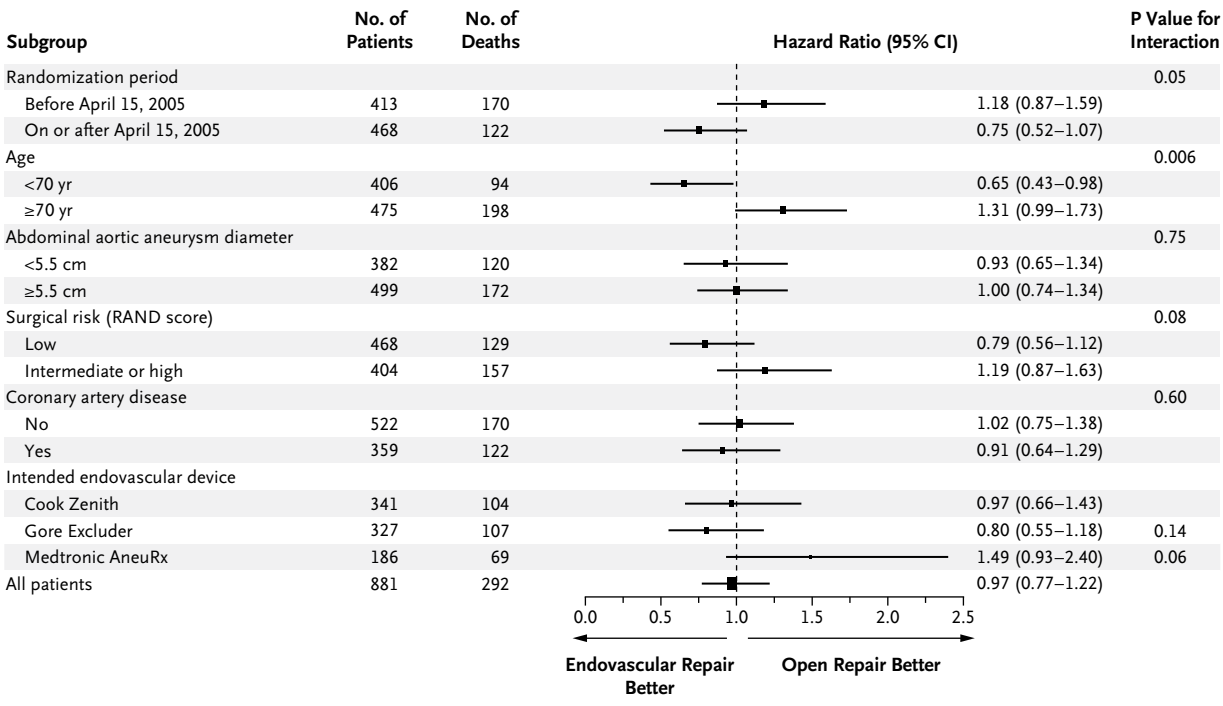

Figure 2. Hazard Ratios for Death, According to Baseline Characteristics.

The sizes of the black rectangles are proportional to the numbers of deaths in the subgroups. P values for the Gore Excluder and the Medtronic AneuRx devices are for the comparisons with the other two intended endovascular devices. CI denotes confidence interval.

The EVAR 1 study showed no interaction between age and treatment effect, though the data, as presented, did not allow an assessment of trends.[3] However, the EVAR 1 study also showed that the short-term benefit of endovascular repair was most pronounced among the patients who were most fit,[13] and long-term complications and reinterventions after endovascular repair were more common among older patients.[14]

The clinical implications of this age effect must be reconciled with our finding that late rupture occurred only in the endovascular-repair group. The procedure associated with late failures would seem to be less desirable for use in younger patients. The late-rupture rate in our study was low, however, with only 6 ruptures during 4576 patient-years of follow-up, which is less than one third the rate in the EVAR 1 study (25 ruptures, also all after endovascular repair, during 5309 patient-years of follow-up).[3] Furthermore, 4 of the 6 ruptures in our study, including 2 of 3 fatal ruptures, occurred in patients older than 70 years of age at study entry. Three of the 6 ruptures in our study occurred in patients who did not adhere to the recommended follow-up and endovascular procedures. Pending longer-term data, we therefore consider endovascular repair to be a reasonable option in patients younger than 70 years of age who are likely to adhere to medical advice.

We found that the rates of secondary therapeutic procedures were similar after endovascular repair and open repair, whereas in the EVAR 1 study, the rate of secondary procedures was much higher after endovascular repair.[3] However, in that study, "readmission data were not collected for abdominal hernias or other complications related to open repair," thus rendering the comparison unbalanced. As noted in our earlier report, repair of incisional hernia was the most common secondary therapeutic procedure after open repair, which was also the case in the DREAM trial.[4] In that trial, reinterventions began to differ significantly in favor of open repair after 4 years, whereas in our study, the two groups remained similar throughout the study in terms of the incidence of death or secondary therapeutic procedures.

The excess late deaths that resulted in loss of

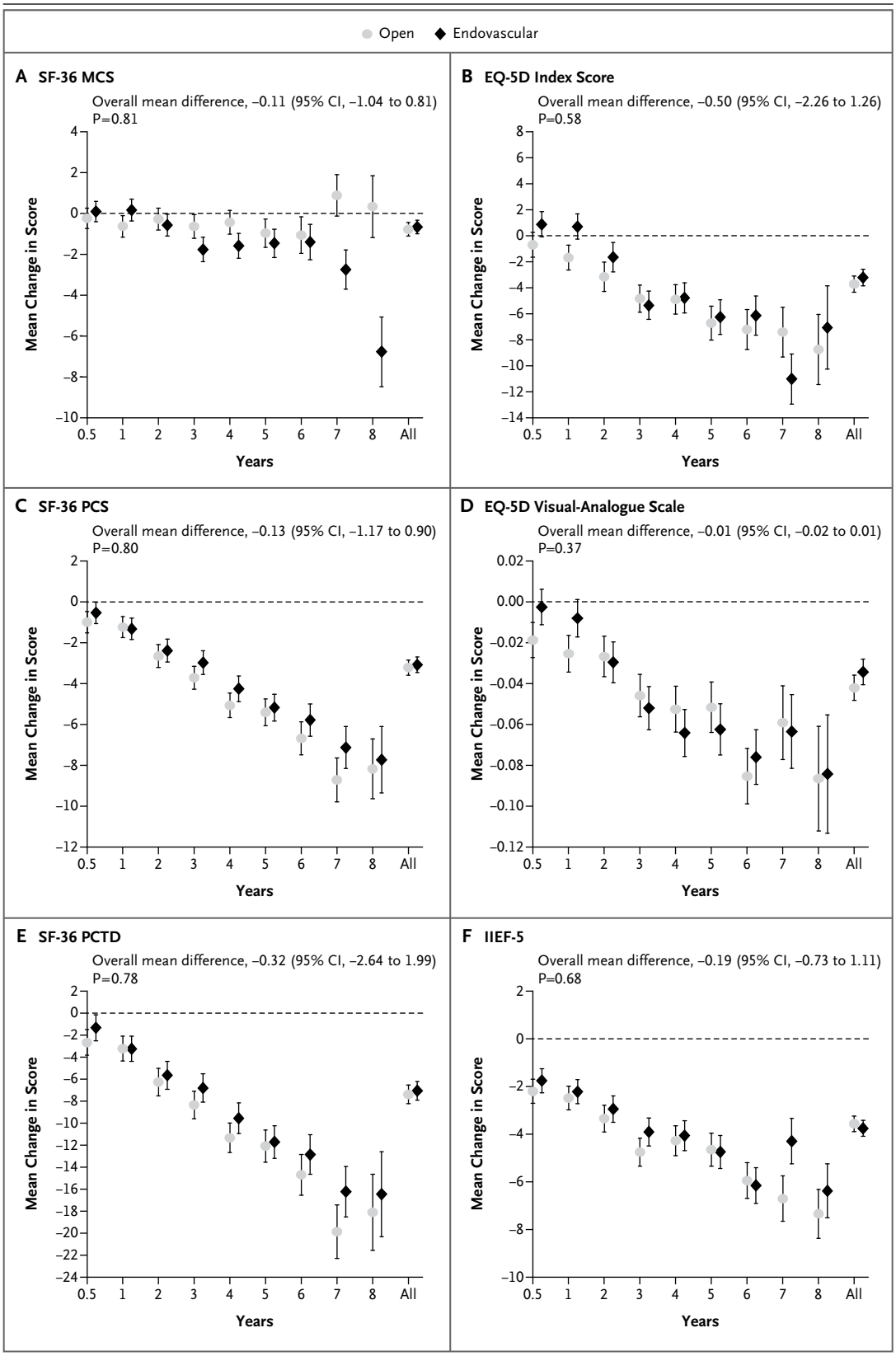

Figure 3 (facing page). Changes in Quality-of-Life Measures.

Data are least-squares mean (±SE) changes from baseline. Panels A, C, and E show changes in scores on the Medical Outcomes Study 36-Item Short-Form Health Survey for the mental component summary (SF-36 MCS), the physical component summary (SF-36 PCS), and the physical component transformed, with deaths included (SF-36 PCTD), respectively. Scores for these three measures range from 0 to 100, with higher scores indicating better health status. Panel B shows the European Quality of Life–5 Dimensions (EQ-5D) index scores, which range from 0 (death) to 1.0 (perfect health), and Panel D shows the EQ-5D visual-analogue scale, which ranges from 0 (worst health status) to 100 (best health status). Panel F shows the scores for the five-item International Index of Erectile Function (IIEF-5), in which scores range from 5 to 25, with higher scores indicating better erectile function. "All" denotes least-squares mean for all participants over all years of the study for which data were available.

the perioperative survival advantage in the endovascular-repair group occurred later in our study than in the EVAR 1 and DREAM trials, but they occurred nevertheless. Although this convergence of survival curves could be attributed to chance, its occurrence in all three studies argues otherwise. The EVAR 1 investigators attributed loss of the perioperative survival advantage in their study to late ruptures after endovascular repair.[3] In our study, there were only three fatal aneurysm ruptures, rendering this explanation inadequate. Furthermore, if loss of the perioperative survival advantage were due to late deaths attributable to endovascular repair, one would expect the survival curves to eventually cross and the endovascular-repair group to have worse long-term survival, but there is no evidence for this in any of the three studies. Another proposed explanation for the convergence of survival curves,[15] and perhaps the most likely one, is that the perioperative deaths after open repair tended to be among the patients who were the most frail, with the curves converging as deaths occurred in these frail patients in the endovascular-repair group.

Our results suggest that endovascular repair continues to improve and is now an acceptable alternative to open repair even when judged in terms of long-term survival. However, our results also indicate that late rupture remains a concern and that endovascular repair does not yet offer a long-term advantage over open repair, particularly among older patients, for whom such an advantage was originally expected.

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

REFERENCES

1. McPhee JT, Hill JS, Eslami MH. The impact of gender on presentation, therapy, and mortality of abdominal aortic aneurysm in the United States, 2001-2004. J Vasc Surg 2007;45:891-9.
2. Ghaferi AA, Birkmeyer JD, Dimick JB. Variation in hospital mortality associated with inpatient surgery. N Engl J Med 2009;361:1368-75.
3. The United Kingdom EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1863-71.
4. De Bruin JL, Baas AF, Buth J, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. N Engl J Med 2010;362:1881-9.
5. Lederle FA, Freischlag JA, Kyriakides TC, et al. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. JAMA 2009;302:1535-42.
6. Ware JE Jr. SF-36 Health Survey update (http://www.sf-36.org/tools/sf36.shtml).
7. Diehr P, Patrick DL, McDonell MB, Fihn SD. Accounting for deaths in longitudinal studies using the SF-36: the performance of the Physical Component Scale of the Short Form 36-item health survey and the PCTD. Med Care 2003;41:1065-73.
8. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203-20.
9. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Peña BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res 1999;11:319-26.
10. Kalbfleish JD, Prentice PL. The statistical analysis of failure time data. New York: Wiley, 1980.
11. Klein JP, Gerster M, Andersen PK, Tarima S, Perme MP. SAS and R functions to compute pseudo-values for censored data regression. Comput Methods Programs Biomed 2008;89:289-300.
12. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247-54. [Erratum, Ann Intern Med 2008;149:519.]
13. Brown LC, Greenhalgh RM, Howell S, Powell JT, Thompson SG. Patient fitness and survival after abdominal aortic aneurysm repair in patients from the UK EVAR trials. Br J Surg 2007;94:709-16.
14. Brown LC, Greenhalgh RM, Powell JT, Thompson SG. Use of baseline factors to predict complications and reinterventions after endovascular repair of abdominal aortic aneurysm. Br J Surg 2010;97:1207-17. [Erratum, Br J Surg 2011;98:162.]
15. Blankensteijn JD, de Jong SECA, Prinssen M, et al. Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. N Engl J Med 2005;352:2398-405.