From the Society for Vascular Surgery

Endovascular abdominal aortic aneurysm repair: Long-term outcome measures in patients at high-risk for open surgery

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Purpose: **The study was conducted to determine the outcome in the United States after endovascular repair (EVAR) of infrarenal abdominal aortic aneurysms (AAAs) in patients at high-risk for open surgery by using independently audited, high-compliance, chart-verified data sets, and to compare those results with open surgery.**

Methods: **High-risk was defined to match a recent European trial (EVAR2) and included age of ≥60 years with aneurysm size of ≥5.5 cm, plus at least one cardiac, pulmonary, or renal comorbidity. Data from five multicenter investigational device exemption clinical trials leading to Food and Drug Administration (FDA) approval were analyzed. Of 2216 EVAR patients, 565 met the high-risk criteria. Of 342 surgical controls (OPEN), 61 met high-risk criteria. Primary outcome comparisons included AAA-related death, all-cause death, and aneurysm rupture. Secondary measures were endoleak, AAA sac enlargement, and migration.**

Results: **Average age of the high-risk EVAR subset was 76 ± 7 years vs 74 ± 6 years OPEN ($P = 0.07$), mean EVAR AAA size was 6.4 ± 0.8 cm vs 6.6 ± 1.0 cm OPEN ($P = .33$), and average EVAR follow-up was 2.7 years vs 2.5 years OPEN. The 30-day operative mortality was 2.9% in EVAR vs 5.1% in OPEN ($P = .32$). The AAA-related death rate after EVAR was 3.0% at 1 year and 4.2% at 4 years compared with 5.1% at both time points after OPEN ($P = .58$). Overall survival at 4 years after EVAR was 56% vs 66% in OPEN ($P = .23$). After treatment, EVAR successfully prevented rupture in 99.5% at 1 year and in 97.2% at 4 years.**

Conclusions: **Endovascular repair of large infrarenal AAAs in anatomically suited high-surgical-risk patients using FDA-approved devices in the United States is safe and provides lasting protection from AAA-related mortality. EVAR mortality remained comparable with OPEN up to 4 years. The decision to treat AAAs in patients with advanced age and significant comorbidities must be individualized and carefully considered, but repair provides excellent protection from AAA-related death. (J Vasc Surg 2006;44:229-36.)**

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The Society for Vascular Surgery (SVS) established a database for endovascular aneurysm repair (EVAR) in 1998 to evaluate the 4-year outcome of patients with infrarenal abdominal aortic aneurysms (AAAs).[1,2] The database is populated with results from the five multicenter, controlled clinical trials used by the United States Food and Drug Administration (FDA) for clinical use approval of the AnCure (Guidant, Indianapolis, Ind) AneuRx (Medtronic, Minneapolis, Minn), Excluder (W. L. Gore & Assoc., Flagstaff, Ariz) PowerLink (Endologix, Irvine, Calif), and Zenith (Cook, Bloomington, Ind) endovascular grafts. Each of these investigational device exemption (IDE) trials compared EVAR with open surgical repair (OPEN); as required by the FDA, the accuracy of data collection was confirmed and verified by independent audit. The results of the individual trials and the overall SVS database have been previously published.[3-9]

A recent European randomized trial, EVAR Trial 2 (EVAR2) examined the safety and efficacy of EVAR in patients who would be considered high risk or unsuitable

candidates for open AAA repair.[10] This is an important analysis, since the relative benefit of EVAR compared with OPEN may be greatest in those patients at high risk for traditional surgery. Mortality results of EVAR2 (9% at 30 days and 64% at 4 years in the EVAR arm) caused concern that EVAR may offer no advantage compared with the natural history of untreated AAAs in high-risk patients. The purpose of the current analysis was to determine the short-term and 4-year outcome measures of EVAR in equivalent high-surgical-risk patients in the United States, using the most accurate and detailed data available, and to compare that with OPEN surgery in light of the natural history of untreated AAAs and the EVAR2 trial.

METHODS

Clinical data from the five US IDE clinical trials submitted by the manufacturers to the FDA for device approval are included in the AAA Database. The exact methods of each of these prospective analyses have been published.[3-8] To match EVAR2, high risk was defined as age ≥60 years, preprocedure aneurysm diameter ≥5.5 cm, *and* at least one of the following comorbidities: symptomatic congestive heart failure, valvular heart disease, cardiac arrhythmia, chronic obstructive pulmonary disease (COPD), chronic renal failure, or serum creatinine value of >2.6 mg/dL.[10,11] The pooled data from five US IDE trials contained 2558 patients. Selection criteria between EVAR and OPEN in these series were comparable, as reflected by the instructions for use of the devices. The only substantial difference among the studies was a greater neck angle exclusion threshold for the Zenith device. Of these, 565 EVAR patients and 61 OPEN patients met this high-risk definition. The remaining 1651 EVAR and 281 OPEN patients were considered normal risk.

The primary outcome measures of aneurysm repair were (1) operative mortality, defined as death during the initial hospitalization or death from any cause ≤30 days of the index procedure; (2) aneurysm-related mortality, defined as death from any cause ≤30 days of the index procedure, death ≤30 days of a secondary procedure or surgical conversion, or any death due to aneurysm rupture or graft complication; (3) all-cause mortality, and (4) aneurysm rupture after repair. Secondary outcome measures for endovascular grafts were endoleak, aneurysm sac enlargement, and endograft migration. Aneurysm sac enlargement was defined as an aneurysm diameter increase of ≥5 mm compared with predischarge. It is important to note that one manufacturer's protocol defined enlargement at >5 mm based on 30-day results rather than on predischarge imaging. Otherwise, increase in aneurysm size is defined as ≥5 mm from predischarge. Migration was defined as longitudinal movement >5 mm relative to anatomic landmarks determined at the time of the initial endovascular procedure. The 4-year mortality of the high-risk EVAR patient subset was also compared with the normal-risk group in the US IDE data set.

Statistical methods. Baseline characteristics of EVAR and OPEN were compared using the two-tailed *t* test for continuous variables and the χ^2 or Fisher exact, as necessary, for discrete/categoric data. Descriptive statistics are listed as mean ± standard deviation for continuous variables and percent (frequency) for categoric variables. Kaplan-Meier estimates, using the log-rank test, were used to compare the primary outcome between groups for freedom from death (ie, survival), aneurysm-related death, and rupture. Cox proportional hazards models were used to estimate hazard ratios and 95% confidence intervals. A hazard ratio <1 indicates a better outcome, on average, for patients in the EVAR group, whereas a value >1 indicates a worse outcome for patients in that group. Differences were considered significant if $P < .05$. Statistical analyses were performed by New England Research Institutes, Inc (NERI), in Watertown, Mass. All data were analyzed using SAS system software (SAS Institute, Cary, NC). All data figures were generated using S-PLUS (Insightful Corporation, Seattle, Wash).

Table I. Number of patients within each investigational device exemption trial who met the high-risk definition

	EVAR (n = 565)	*OPEN (n = 61)*
AnCure (Guidant)	111	25
AneuRx (Medtronic)	285	9
Excluder (WL Gore)	55	19
PowerLink (Endologix)	24	8
Zenith (Cook)	90	0

EVAR, Endovascular aneurysm repair; *OPEN,* open surgical aneurysm repair.

RESULTS

Patient population. The numbers of high-risk patients from each of the IDE clinical trial included in the AAA Database are summarized in Table I. Baseline demographic information and comorbid factors are listed in Table II. The only statistically significant difference between EVAR and OPEN groups before aneurysm treatment was gender (89% male in EVAR vs 67% OPEN, $P < .01$). EVAR patients were approximately 1.5 years older (75.7 vs 74.2 years, $P = .07$). OPEN patients were more likely to have COPD (71% vs 61%, $P = .13$) (Table III, *A*). EVAR and OPEN had comparable prevalence of prior myocardial infarction (41% EVAR, 38% OPEN), congestive heart failure (26% EVAR, 16% OPEN), coronary artery disease (70% EVAR, 67% OPEN), and renal insufficiency (7% EVAR, 8% OPEN). There was a trend towards more angina in the EVAR group (31% EVAR vs 19% OPEN, $P = .14$), but it was not statistically significant. There was no statistically significant difference in preoperative aneurysm size between EVAR and OPEN, with a mean aneurysm diameter 6.4 ± 0.8 cm in EVAR patients and 6.6 ± 1.0 cm in OPEN. Mean postoperative follow-up time for the EVAR group was 2.7 ± 1.7 years (maximum, 7.1 years) compared with 2.5 ± 1.7 years (maximum, 6.6 years) for OPEN.

Table II. Demographics and procedural information by treatment arm

	EVAR (n = 565) %	*OPEN (n = 61) %*	P*
Preoperative variables			
Age	75.7 ± 7.1 (60-96)	74.2 ± 6.2 (60-87)	.07
AAA diameter (mm)	64.2 ± 8.4 (55-110)	65.5 ± 9.7 (55-98)	.33
Gender (male)	89.2 (504/565)	67.2 (41/61)	<.0001
Race (white)	94.9 (534/565)	100 (52/52)	.09†
Myocardial infarction	41.2 (223/565)	37.7 (23/61)	.59
Cardiac revascularization	46.7 (222/475)	44.3 (27/61)	.72
Angina	31.3 (142/454)	19.4 (7/36)	.14
Cardiac valve disease	20 (38/190)	21.1 (11/52)	.85
Significant arrhythmia	45.1 (255/565)	32.8 (20/61)	.06
Congestive heart failure	25.8 (146/565)	16.4 (10/61)	.11
Coronary artery disease	69.5 (132/190)	67.3 (35/52)	.76
Hypertension	66.9 (378/565)	72.1 (44/61)	.41
Diabetes	13.8 (78/565)	16.4 (10/61)	.58
COPD	60.5 (342/565)	70.5 (43/61)	.13
Smoking	84.9 (480/565)	77.1 (47/61)	.10
Renal insufficiency	6.6 (37/565)	8.2 (5/61)	.63
Serum creatinine (mg/dL)	1.3 ± 0.9 (0.6-8.9)	1.3 ± 0.4 (0.8-2.3)	.79
Systolic blood pressure (mm Hg)	136.2 ± 23.9 (81-229)	138.5 ± 21.7 (110-188)	.69
Diastolic blood pressure (mmHg)	76.6 ± 11.3 (56-110)	80.6 ± 14.0 (52-100)	.27
Ankle-brachial index (left)	1.0 ± 0.2 (0.3-2.0)	1.0 ± 0.2 (0.6-1.6)	.97
Ankle-brachial index (right)	1.0 ± 0.2 (0.1-2.0)	1.0 ± 0.2 (0.6-1.6)	.86
Postoperative variables			
Hospital length of stay (days)	3.5 ± 4.7 (0-82)	9.7 ± 8.8 (0-59)	< .0001
Intensive care unit stay (hours)	20.9 ± 49.1 (0-664)	51.2 ± 52.2 (1-330)	.0008
General anesthesia	27.8 (142/510)	90.5 (38/42)‡	< .0001†
Blood product transfusion	21.4 (66/309)	64.7 (11/17)	< .0001†
Follow-up time (mean, years)	2.7 ± 1.7 (0-7.1)	2.5 ± 1.7 (0-6.6)	—
Follow-up time (median, years)	2.2	2.7	—

EVAR, Endovascular aneurysm repair; *OPEN,* open surgical aneurysm repair; *COPD,* chronic obstructive pulmonary disease.
Data are percentages or means ± SD (ranges).
**P* was calculated using *t* test for continuous variables and χ^2 test for categoric variables, unless otherwise specified.
†*P* was calculated using Fisher's exact test.
‡One patient received an epidural; 3 patients with missing data.

Primary outcome measures. Kaplan-Meier analyses of the primary end points, operative mortality, AAA-related mortality, all-cause mortality, and AAA rupture for EVAR patients extended to 4 years as shown in Fig 1, 2, and 3. There were no statistically significant differences among the various devices in primary outcome measures.

Operative mortality. The 30-day operative mortality for EVAR in this high-risk patient cohort was 2.9% compared with 5.1% for OPEN (hazard ratio, 0.541; 95% confidence interval, 0.1577 to 1.8572; $P = .32$). Use of general anesthesia (n = 142) did not affect mortality (2.8% general anesthesia, 2.7% other forms of anesthesia, log-rank $P = .945$).

AAA-related death. One AAA-related death occurred in the interval from 30 days to 1 year in the EVAR group and none in OPEN. The AAA-related death rate at 1 year was 3.0% for EVAR and 5.1% for OPEN ($P = .37$ by Kaplan-Meier log-rank test). Four additional AAA-related deaths occurred in the EVAR group from years 1 to 4. Thus, freedom from AAA-related death after EVAR was 97% at 30 days and 96% at 4 years by Kaplan-Meier analysis. After OPEN repair, freedom from AAA-related death was 95% at 30 days and remained at that level to 4 years (Fig 1) ($P = .58$).

All-cause mortality. No significant difference was found in all-cause mortality between EVAR and OPEN through the duration of this analysis. Four-year survival was 56% in EVAR and 66% in OPEN ($P = .23$), as seen in Fig 2. All-cause mortality at 4 years in the high-risk US IDE EVAR patients was also compared with the normal-risk US IDE EVAR patients. The high-risk EVAR mortality was twice that of the non-high-risk patients (44% vs 21%, $P < .0001$) (Fig 4).

Rupture. Seven postoperative AAA ruptures occurred in EVAR patients (1 at <30 days, 6 late) during 1523 patient-years of follow-up; all but one resulted in an AAA-related death. There was no statistical difference in freedom from postoperative aneurysm rupture between EVAR patients (99.5%) and OPEN patients (100%) at 1 year by Kaplan-Meier analysis (log-rank test, $P = .78$) (Fig 3). Freedom from rupture after EVAR was 97% at 4 years. The difference in rupture between EVAR and OPEN at 4 years was not significant ($P = .58$).

Secondary EVAR end points. There were 80 (14.2%) endoleaks reported at 30 days, 99 (17.5%) at 1 year, and 107 (18.9%) at 4 years in the EVAR group, but the incidence of endoleaks did not significantly vary over time. The distribution of endoleaks by type was not avail-

Table III. A, Distribution of comorbidities in the high-risk cohort

	EVAR n = 565 (%)	*OPEN n = 61 (%)*	P
Cardiac	342/565 (60.5)	29/61 (47.5)	.0498
Arrhythmia	255/565 (45.1)	20/61 (32.8)	.0649
Valvular heart disease	38/190 (20.0)	11/52 (21.2)	.8544
Congestive Heart Failure	146/565 (25.8)	10/61 (16.4)	.1051
Pulmonary (COPD)	342/565 (60.5)	43/61 (70.5)	.1288
Renal	37/565 (6.6)	5/61 (8.2)	.6250

EVAR, Endovascular aneurysm repair; *OPEN,* open surgical aneurysm repair.

Table III. B, Distribution of high-risk cohort by the number of comorbidity categories ($P = .46$)

	EVAR n = 565 (%)	*EVAR n = 565 (%)*
1 high-risk comorbidity	413 (73.1%)	46 (75.4%)
2 high-risk comorbidities	148 (26.2%)	14 (23.0%)
All 3 high-risk comorbidities	4 (0.7%)	1 (1.6%)

EVAR, Endovascular aneurysm repair; *OPEN,* open surgical aneurysm repair.

Table III. C, Comparison of comorbidities in high-risk cohort with EVAR2

	EVAR (US IDE) n = 565 (%)	*EVAR2[10] n = 166 (%)*
Cardiac	342/565 (60.5)	108/166 (65)
Pulmonary (COPD)	342/565 (60.5)	Not available
Mean FEV_1	Not available	1.6 L
Renal	37/565 (6.6)	Not available
Median creatinine	1.1 mg/dL	108μmol/L (1.2 mg/dL)

EVAR, Endovascular aneurysm repair; *IDE,* investigational device exemption; *COPD,* chronic obstructive pulmonary disease; *FEV_1,* forced expiratory volume in 1 second.

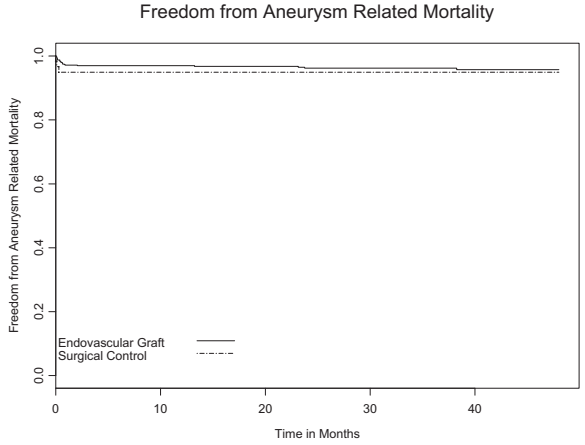
able. There were 11 (1.9%) AAA sac enlargements reported at 30 days, 26 (4.6%) at 1 year, and 62 (11%) at 4 years in EVAR. No endograft migrations were reported ≤30 days of implant in this high-risk EVAR subset. Endograft migration occurred in four patients (0.7%) at 1 year and in 15 patients (2.7%) at 4 years.

DISCUSSION

The Outcomes Committee of the Society for Vascular Surgery maintains the AAA Database, which is populated by data from controlled IDE clinical trials, to monitor the long-term safety and efficacy of EVAR. Each of the IDE trials was designed around standardized guidelines to study a single endograft device for purposes of FDA market approval. Minor variations among the trials were incorporated to address device-specific questions. Because there was no predetermined allocation of EVAR vs OPEN procedures, the proportion of OPEN patients who met high-risk criteria varied from 0% to 30% among the US IDE trials. Nonetheless, these unique, independently audited, high-compliance, chart-verified data sets related to AAAs allow accurate identification of patients who would be considered high-risk for open aneurysm repair.

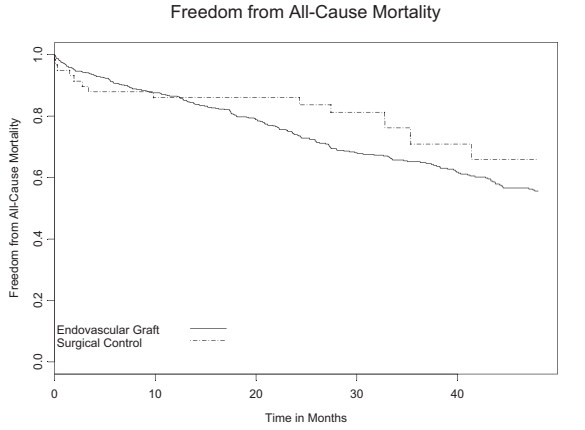
The nature of FDA studies provides similar long-term end points and high completeness of follow-up, resulting in high credibility of the EVAR and OPEN data in the US IDE trials. The results of individual IDE trials have been published and demonstrate safety and efficacy of EVAR across the full spectrum of inclusion criteria.[3-8] Application of the EVAR2 high-risk criteria to the US IDE trial data set identified 565 patients who were certainly more ill, overall, than the 1651 normal-risk participants (4-year mortality: 44% high risk, 21% normal risk; $P < .0001$) (Fig 4). However, despite fitting the EVAR2 definition of high risk, the US IDE mortality compares favorably with EVAR2 in short-term (30-day mortality: 2.9% US IDE, 9% EVAR2) and 4-year (44% US IDE, 64% EVAR2) results. We believe the US IDE results indicate that EVAR is safe and effective in most patients with advanced age, large aneurysms, and high-risk medical comorbidities.[10]

Previous single-center reports have shown EVAR to be a safe alternative to OPEN in high-risk patients and octogenarians.[12-14] Anderson et al[15] analyzed the New York Statewide Planning and Research Cooperative System (SPARCS) for EVAR and OPEN for the elective treatment of AAA from 2000 to 2002.[15] Over the 3-year study period, the authors identified an increase in incidence of hypertension, coronary artery disease, and hyperlipidemia in patients undergoing EVAR compared with OPEN; however, despite this increase in comorbidities over time, the perioperative mortality, postoperative complications, and length of stay were significantly lower for EVAR compared



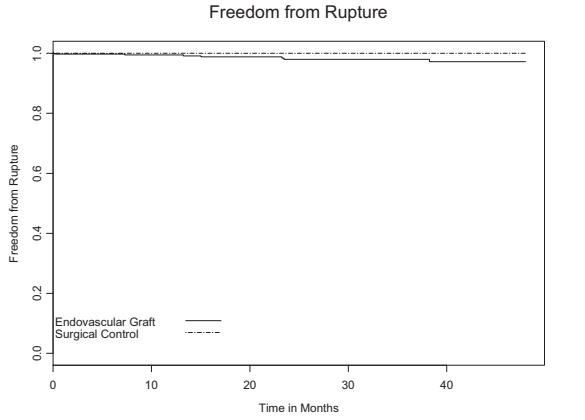
	0-30 d	*30 d-1 yr*	*1yr-2 yr*	*2 yr-3 yr*	*3 yr-4 yr*
EVAR					
# at risk	565	545	462	347	233
# of events	16	1	3	0	1
# censored	4	82	112	114	74
K-M estimate	0.9715	0.9697	0.9622	0.9622	0.9575
Standard error	0.00701	0.00724	0.00849	0.00849	0.00959
OPEN					
# at risk	61	55	46	38	27
# of events	3	0	0	0	0
# censored	3	9	8	11	16
K-M estimate	0.9494	0.9494	0.9494	0.9494	0.9494
Standard error	0.0285	0.0285	0.0285	0.0285	0.0285

Fig 1. Kaplan-Meier curve of freedom from aneurysm-related death ($P = .5787$).



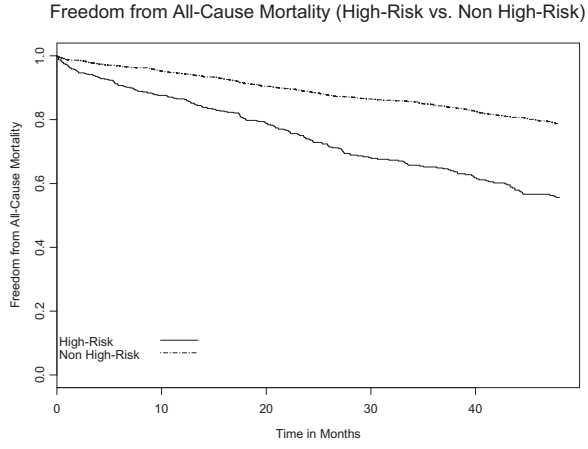
	0-30 d	*30 d-1 yr*	*1 yr-2 yr*	*2 yr-3 yr*	*3 yr-4 yr*
EVAR					
# at risk	565	545	462	347	233
# of events	16	59	64	35	30
# censored	4	24	51	79	45
K-M estimate	0.9715	0.8651	0.7397	0.6516	0.5560
Standard error	0.00701	0.0145	0.0191	0.0219	0.0247
OPEN					
# at risk	61	55	46	38	27
# of events	3	5	0	6	1
# censored	3	4	8	5	15
K-M estimate	0.9494	0.8604	0.8604	0.7092	0.6585
Standard error	0.0285	0.0459	0.0459	0.0677	0.0796

Fig 2. Kaplan-Meier curve of survival ($P = .2312$).



	0-30 d	*30 d-1 yr*	*1 d-2 yr*	*2 yr-3 yr*	*3 yr-4 yr*
EVAR					
# at risk	399	385	322	228	142
# of events	1	1	4	0	1
# censored	13	62	90	86	40
K-M estimate	0.9975	0.9946	0.9799	0.9799	0.9722
Standard error	0.00253	0.00385	0.00825	0.00825	0.0112
OPEN					
# at risk	17	15	12	11	7
# of events	0	0	0	0	0
# censored	2	3	1	4	2
K-M estimate	1.00	1.00	1.00	1.00	1.00
Standard error	0.00	0.00	0.00	0.00	0.00

Fig 3. Kaplan-Meier curve of postoperative abdominal aortic aneurysm rupture ($P = .5842$).



	0-30 d	*30 d-1 yr*	*1 d-2 yr*	*2 yr -3 yr*	*3 yr-4 yr*
High risk					
# at risk	565	545	462	347	233
# of events	16	59	64	35	30
# censored	4	24	51	79	45
K-M estimate	0.9715	0.8651	0.7397	0.6516	0.5560
Standard error	0.00701	0.0145	0.0191	0.0219	0.0247
Non high risk					
# at risk	1651	1623	1492	1307	1077
# of events	19	71	86	57	66
# censored	9	60	99	173	246
K-M estimate	0.9885	0.9447	0.8888	0.8471	0.7873
Standard error	0.00263	0.00567	0.00791	0.00928	0.0112

Fig 4. Kaplan-Meier curve of survival (high-risk EVAR vs. non high-risk EVAR) ($P < .0001$).

with OPEN. In our analysis of high-risk patients, the 2.9% 30-day mortality of EVAR did not reach statistical significance compared with the 5.1% mortality of OPEN, but our analysis was likely underpowered in the OPEN arm based on the criteria for high risk. The New York State experience was evaluated for 4770 patients,[15] whereas ours had the data of only 565 patients analyzed.

Various studies evaluating the natural history outcomes of patients who did not undergo surgery because they were deemed unsuitable for traditional open repair because of comorbid factors have confirmed a high incidence of AAA-related death.[16,17] In a prospective, multicenter observational study of rupture rates in patients unfit for surgery, Lederle et al[16] reported a 1-year rupture rate of 9.4% in patients with AAAs 5.5 to 5.9 cm in diameter, 19.1% for patients with AAAs 6.5 to 6.9 cm, and 32.5% for AAAs ≥7.0 cm. These remarkably high rates of death from AAA rupture were based on a 46% autopsy rate; thus, the true incidence of AAA-related death is almost certainly higher. With an average diameter of 6.4 cm, the US IDE trial high-risk EVAR group had a 1-year AAA-related mortality of 3.0%, dramatically less than natural history as reported by Lederle et al.

Conway et al[17] reported on 106 patients deemed unfit for open aneurysm repair due to comorbid factors. They identified AAA rupture as the cause of death at 3 years in 36% of AAAs 5.5 to 5.9 cm in diameter, 50% for AAAs 6.0 to 7.0 cm, and 55% for AAAs >7.0 cm. Jones et al[18] followed 50 high-risk patients who were turned down for open AAA repair. Death from AAA rupture at 3 years was reported in 28% for AAAs 5.0 to 5.9 cm and 41% for AAAs ≥6.0 cm. At 4 years, the current analysis of the US IDE EVAR cohort demonstrated AAA-related mortality of 4.3% in EVAR and 5.1% in OPEN compared with 40% to 50% in the two natural history studies.[17,18]

Given the results of these natural history studies, watchful waiting would seem an appropriate clinical recommendation only for those with the most extreme medical comorbidities, whereas the minimally invasive EVAR treatment, intuitively, should offer a relatively greater degree of benefit in those at high risk for open surgery. Results of EVAR2, however, raise questions about the appropriateness of EVAR over observation in high-risk patients with large AAAs.[10]

The EVAR2 trial is a study of 338 patients aged ≥60 years who had AAAs of at least 5.5 cm in diameter and who met high-surgical-risk criteria for open repair due to cardiac, pulmonary, or renal comorbidities. Patients in that trial were randomized to EVAR or no intervention. The 30-day mortality for EVAR in the EVAR2 trial was 9%. AAA-related mortality at 4 years was 14% for EVAR and 19% for no intervention (P = NS). Overall, 4-year survival was only 34% in EVAR and 38% in the no-intervention group. The authors concluded that EVAR "is not a safe procedure in such high-risk patients." Despite comparable age (76.8 years in EVAR2, 75.7 in US IDE), aneurysm size (6.4 cm EVAR2, 6.4 cm US IDE), high-risk entry thresholds (cardiac, pulmonary, and renal comorbidities), and incidence of these comorbidities in the two reports, the 30-day mortality for US IDE EVAR was less than one third that of the EVAR2 trial (2.7% vs 9%). Likewise, at 4 years, AAA-related mortality was markedly lower in US IDE EVAR patients at 4% compared with 14% in EVAR2. Indeed, the overall 4-year survival of 565 high-risk US IDE EVAR patients was markedly higher than the 166 patients in EVAR2 (56% US IDE EVAR vs 34% EVAR2). Given that the 95% confidence interval for EVAR in the US IDE Database is (0.5066, 0.6054) and that the EVAR2 mortality does not fall within this interval, the survival rate in US IDE EVAR is statistically significant, at a .05 level, compared with EVAR2.

There are at least two identifiable explanations of the large outcomes differences between the high-risk patients in US IDE EVAR trials and those in EVAR2. First, 14 patients in EVAR2 died preoperatively during the 57-day interval between randomization and repair. Thus, 52% of the perioperative deaths (14/27) and 19% of total deaths in the EVAR arm occurred preoperatively. Nine patients died from AAA rupture before their elective EVAR date, accounting for 45% of the 20 aneurysm-related deaths in the EVAR arm of EVAR2. Many of these deaths might not have occurred with a shorter interval before repair.

Second, the final decision to include a patient in EVAR2 was delegated to the individual providers at each hospital (surgeon, radiologist, anesthesiologist, and cardiologist) under a "pragmatism" guideline. Thus, not only was it necessary for a patient to meet one of the cardiac, pulmonary, or renal criteria, but the patients also had to fail the "pragmatism" test to be assigned to EVAR2. In our retrospective analysis of US IDE EVAR patients, a pragmatism analysis could not be applied, but the distribution of comorbidities is illustrated in Table III, *B*. Thus, although the EVAR2 and US IDE high-risk patients were equivalent in terms of age and AAA size, and the prevalence of cardiac, renal, and pulmonary risks was comparable (Table III, *C*), it is possible that EVAR2 patients were sicker, overall, than those analyzed in the current report. However, based upon published results of comorbidities, the US IDE criteria are more objective than EVAR2, as compared in Table III, *C*. The impact of the pragmatism test was not emphasized in the EVAR2 report, but this additional criterion is likely another major reason why 30-day mortality in EVAR2 was 9%. This was apparently an extremely ill group of patients, and it is clear from EVAR2 that there are patients who are far too ill for any form of AAA therapy. Objective analysis of comorbidities that would identify these patients should be further investigated.

All-cause mortality is an important consideration in the high surgical risk population. As noted, mortality at 4 years was 44% in this current high-risk EVAR analysis, 21% in the normal-risk US IDE EVAR patients, and 66% in EVAR2. Endovascular AAA repair brought about no net beneficial impact on all-cause mortality in EVAR2, and it was one of the few trials to be conducted using no intervention as the control group. Much has been made of the lack of mortality reduction in this trial, but review of the details provides a

possible explanation. In EVAR2, 27% of the deaths (20/74) in the EVAR arm were aneurysm-related, but six of the deaths occurred preoperatively, falsely inflating the AAA death rate in the treatment arm. In the no-treatment arm, 32% of the deaths (22/68) were aneurysm-related, but this may actually have been falsely low. Forty-seven patients in the no-treatment arm (22%) crossed over to surgery with very low mortality, thereby reducing the aneurysm-related death in the control arm. This clearly biased the results against EVAR in the intent-to-treat analysis. It would appear that the most convincing conclusion from EVAR2 is that large aortic aneurysms constitute a lethal disorder. Their conclusion regarding lack of all-cause mortality benefit between repair and no treatment should be questioned.

Compared with EVAR2, the US IDE EVAR trials in similarly high-risk patients provided protection against aneurysm-related death with low perioperative mortality. Roughly 30% of overall mortality in EVAR2 was AAA-related, whereas AAA-related deaths accounted for only 4% in US IDE patients. This large incremental difference in mortality does much to explain why EVAR2 4-year mortality was 66%, whereas the US trial 4-year overall mortality was 44%.

Our study has two levels of limitation. First is the low number of patients in the OPEN arm in the comparison of EVAR with OPEN in the US IDE data. With only 61 patients in the OPEN arm, our study was underpowered to identify a difference in mortality. The second level of limitation relates to comparing the results of our study with those of EVAR2. The control groups differ; we compared with OPEN surgery while EVAR2 compared with no treatment. Furthermore, it is difficult to compare the overall morbidity of our high-risk patients with those in EVAR2. Only a detailed evaluation of the cumulative comorbidities and the causes of death could resolve this question. Finally, the current analysis did not assess cost-effectiveness or quality-of-life issues that were addressed in EVAR2.

CONCLUSION

Analysis of EVAR outcomes in high-risk patients enrolled in US IDE trials indicates that this treatment is safe and effective, with results far superior to a recently published EVAR2 trial. Analysis to 4 years indicates that EVAR provides excellent protection from aneurysm rupture and AAA-related death, with no significant difference from open surgical controls. A thorough individualized risk/benefit analysis must be undertaken for each patient who fits the definition of high risk for surgery, but providers must remain aware of natural history studies indicating that AAA rupture and death is the likely fate when watchful waiting is chosen for patients with large AAAs. High-risk patients found to have an extremely short life expectancy from nonaneurysmal disorders may be appropriate candidates for watchful waiting. For the rest, in the presence of suitable aortic anatomy, EVAR may be the best treatment option.

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INVITED COMMENTARY

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The objectives of this article from Sicard et al are two-fold. First, it is meant to assess the benefit of elective endovascular aneurysm repair (EVAR) in patients at high-risk for open surgery and second, compare the obtained outcomes with those of the EVAR 2 trial published in *The Lancet* in 2005.[1] The conclusions of the current article were substantially different from those of the EVAR 2 report. The authors have made a commendable effort to explain the differences, and understandably, they try to convince the reader that their conclusion is the correct one.

What is the nature of the substantial differences in the main outcome events after EVAR in these two studies? The design of the current analysis is not straightforward. The baseline patient cohort came from five commercially sponsored nonrandomized investigational device exemption (IDE) studies, with inherently several unknown factors. The selection criteria to include a patient, although not specified, most likely varied between the different studies. Study protocols from device manufacturers have a natural tendency to avoid the selection of patients with an increased risk of postoperative complications, including death. Nevertheless, the authors were able to identify a group of patients at high operative risk.

The factors determining high-risk patients were probably not equally balanced between the different studies, and most important, no formal meta-analysis methodology was used. Crude minimal criteria, requiring the presence of (only) one comorbidity, sufficed to define a patient as high risk, which contrasted from the severity of the requirements for patient enrolment in EVAR 2.[2] The reader must be puzzled by finding out that a portion of these patients received open repair despite being considered unfit for open surgery. The details of why a patient was allocated to EVAR or open repair were not specified.

From a design point of view, the EVAR 2 trial is far superior. Supported by an independent governmental grant and with proper randomization of a large patient group between treatments, EVAR 2 is supposed to provide level I scientific evidence. The details were less transparent, however, and the fact that to date no straightforward generally accepted criteria exist to define the patient unfit for open repair caused some confusing observations.

In addition, some disturbing logistic problems occurred during the trial. Notably, the significant delay between randomization and treatment was at the expense of several ruptured aneurysms before the intervention. All weaknesses were detailed in the discussion of the present article. One of the other flaws in EVAR 2 was that a number of patients initially were misclassified, as these patients (crossing-over from watchful waiting to intervention) did tolerate a secondary AAA procedure well, including open repair in 12 patients.

Where does this leave us? After careful studying the present article in this journal and the report in *The Lancet,* it occurs that there is more than one category of high-risk patients. Considering the substantial difference in all-cause mortality after 4 years of follow-up, the average patient in the IDE studies was not nearly as unfit as most of the patients in EVAR 2. One should note that in unfit patients, not only the all-cause mortality but also the aneurysm-related mortality (including the one-month rate) proportionally increases.[3] Perhaps the severest problem of EVAR 2 was that many patients were too sick for even an endovascular procedure.

What can we learn from these two articles? For intermediately increased-risk patients, who represent large proportion in the average vascular surgical practice, the conclusions of the IDE derived data that EVAR may be the best treatment can be accepted. In patients with a very short life expectancy, for instance <1 year,[3] a policy of nonintervention, as suggested by the EVAR 2 reporters, definitely is the wiser option.

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