Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial

*EVAR trial participants**

Summary

Background Endovascular aneurysm repair (EVAR) to exclude abdominal aortic aneurysm (AAA) was introduced for patients of poor health status considered unfit for major surgery. We instigated EVAR trial 2 to identify whether EVAR improves survival compared with no intervention in patients unfit for open repair of aortic aneurysm.

Methods We did a randomised controlled trial of 338 patients aged 60 years or older who had aneurysms of at least 5·5 cm in diameter and who had been referred to one of 31 hospitals in the UK. We assigned patients to receive either EVAR (n=166) or no intervention (n=172). Our primary endpoint was all-cause mortality, with secondary endpoints of aneurysm-related mortality, health-related quality of life (HRQL), postoperative complications, and hospital costs. Analyses were by intention to treat.

Findings 197 patients underwent aneurysm repair (47 assigned no intervention) and 80% of patients adhered to protocol. The 30-day operative mortality in the EVAR group was 9% (13 of 150, 95% CI 5–15) and the no intervention group had a rupture rate of 9·0 per 100 person years (95% CI 6·0–13·5). By end of follow up 142 patients had died, 42 of aneurysm-related factors; overall mortality after 4 years was 64%. There was no significant difference between the EVAR group and the no intervention group for all-cause mortality (hazard ratio 1·21, 95% CI 0·87–1·69, p=0·25). There was no difference in aneurysm-related mortality. The mean hospital costs per patient over 4 years were UK£13 632 in the EVAR group and £4983 in the no intervention group (mean difference £8649, SE 1248), with no difference in HRQL scores.

Interpretation EVAR had a considerable 30-day operative mortality in patients already unfit for open repair of their aneurysm. EVAR did not improve survival over no intervention and was associated with a need for continued surveillance and reinterventions, at substantially increased cost. Ongoing follow-up and improved fitness of these patients is a priority.

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*Trial participants listed at end of EVAR trial 1[10]

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Introduction

The natural history of large abdominal aortic aneurysm (AAA) is progressive enlargement that can lead to rupture.[1] The risk of rupture can be as high as 25% per year for aneurysms with diameters greater than 6 cm.[2] Although open surgical repair[3] is a tried and tested procedure for patients considered fit enough to withstand major surgery, the best way to manage unfit patients with large AAA, for whom the survival rate at 2 years can be as low as 50% (unpublished data from UK Small Aneurysm Study, UK Small Aneurysm Study Participants, Imperial College, London, UK), remains unclear. Endovascular aneurysm repair (EVAR), a minimally invasive approach, was developed as a possible solution.[4,5] As the technology developed, EVAR has been used increasingly in patients judged fit for open repair, and results of trials[6,7] show that the 30-day mortality in such patients is less than 2%. Although registry data[8] suggest that 30-day mortality with EVAR is higher in unfit patients, the original use of the technique for unfit patients has not been rigorously examined.

The hypothesis underlying EVAR trial 2 was that, for unfit patients with an AAA of at least 5·5 cm in diameter, EVAR compared with no intervention would reduce the risk of aneurysm-related death from rupture and improve long-term survival and health-related quality of life (HRQL).

Methods

Patients and procedures

Between September, 1999, and December, 2003, we enrolled patients into a randomised controlled trial of individuals aged 60 years or older who had an aneurysm of at least 5·5 cm in diameter. We followed up all patients until Dec 31, 2004. Detailed methods for EVAR trial 2 have been described elsewhere.[9,10] The enrolment protocol and data collection methods are identical to those described for EVAR trial 1.[10] Patients were recruited from 31 of 41 eligible hospitals. We regarded hospitals as eligible when they had completed 20 EVAR procedures and submitted the data to the Registry for Endovascular Treatment of Aneurysms (RETA).[8] We expected all patients, irrespective of treatment allocation, to receive best medical treatment for comorbidities and annual computed tomography (CT) surveillance of their aneurysm. All patients provided written informed consent, and the study was approved by the North-West Multicentre Research Ethics Committee.

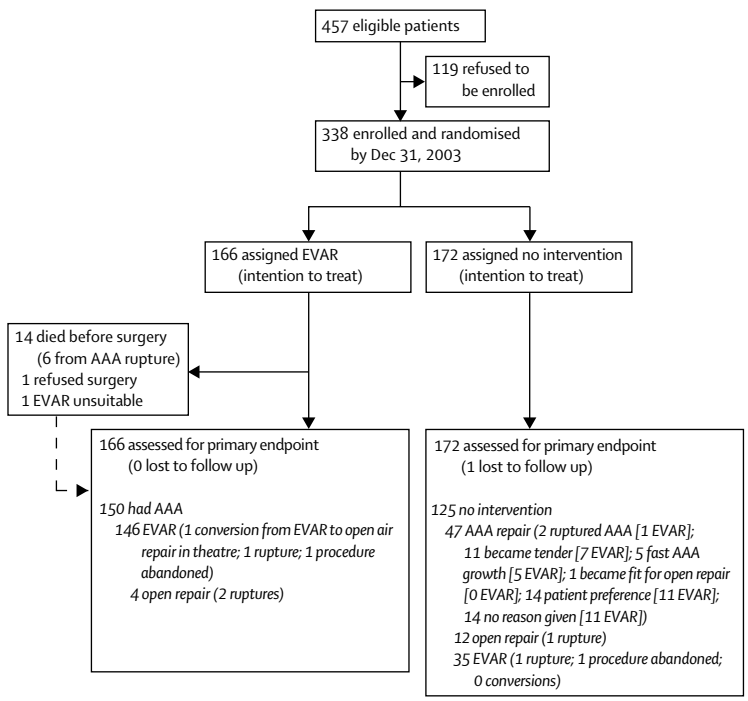


Figure 1: **Trial profile**

	EVAR (n=166)	No intervention (n=172)
Age (years) (mean, SD)	76·8 (6·2)	76·0 (6·7)
Sex (men)	141 (85%)	147 (85%)
Body-mass index (kg/m²) (mean, SD)	26·4 (4·92)	26·3 (4·4)
AAA diameter (cm) (median, IQR)	6·4 (6·0–7·4)	6·3 (6·0–7·0)
AAA deemed tender at randomisation	4 (2%)	8 (5%)
Diabetes	25 (15%)	22 (13%)
Current smokers	29 (17%)	28 (16%)
Past smokers	127 (77%)	132 (77%)
Never smoked	10 (6%)	12 (7%)
History of cardiac disease*	108 (65%)	125 (73%)
Aspirin use	96 (58%)	93 (54%)
Statin use	65 (39%)	68 (40%)
Systolic blood pressure (mm Hg) (mean, SD)	140 (20)	138 (23)
Diastolic blood pressure (mm Hg) (mean, SD)	80 (11)	79 (12)
Ankle-brachial pressure index (mean of both legs, SD)	0·98 (0·20)	0·97 (0·19)
FEV_1 (L) (mean, SD)	1·6 (0·6)	1·7 (0·7)
Serum creatinine (μmol/L) (median, IQR)	108 (91–135)	115 (93–145)
Serum cholesterol (mmol/L) (mean, SD)	4·9 (1·2)	4·9 (1·1)

Data are number (%) unless otherwise indicated. *Myocardial infarction, cardiac revascularisation, angina, cardiac valve disease, significant arrhythmia, or uncontrolled congestive cardiac failure.

Table 1: **Baseline characteristics**

Once enrolled, we anticipated that patients allocated to EVAR would receive their aneurysm repair within 30 days of randomisation. Thus, for this group, we obtained HRQL data with Short Form 36 (SF36) and EuroQol 5-D (EQ5D) at 1, 3, and 12 months after the operation. We assessed the no intervention group for HRQL at 2, 4, and 13 months from randomisation to account for the anticipated 1 month time to operation in the intervention group. The follow-up protocol for aneurysm growth, graft durability, secondary interventions, adverse events, and renal function was identical to that for EVAR trial 1.[10] Our primary endpoint was all-cause mortality, with secondary endpoints of aneurysm-related mortality, quality of life, postoperative complications, and hopsital costs. The methods we used to obtain resource use and cost estimations were the same as for EVAR trial 1.[10]

Statistical analysis

With an average follow-up of 3·3 years, sample size calculations indicated that for 90% power at the 5% significance level, 280 patients would be needed to detect a 10% difference in all-cause mortality per year (25% in the no intervention group *vs* 15% in the EVAR group; 146 deaths in total). The methods for statistical analyses were the same as for EVAR trial 1.[10] We used Cox regression modelling and χ^2 tests for comparisons between results of EVAR trial 1 and EVAR trial 2. All main analyses were by intention to treat, according to a predefined statistical analysis plan. For a post-hoc per protocol mortality analysis, we excluded patients who contravened their allocated treatment with censorship at the time of protocol violation.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Between September, 1999, and December, 2003, we identified 457 patients with an aneurysm of 5·5 cm in diameter or greater who were judged unfit for open repair.[10] The characteristics of the 119 patients who refused to be randomised (mean

	EVAR (n=166)	No intervention (n=172)	Hazard ratio from Cox regression model (95% CI; p)		
			Crude	Primary adjusted*	Secondary adjusted†
Aneurysm-related deaths‡	20	22	1·01 (0·55–1·84; 0·98)	1·00 (0·54–1·84; 1·00)	0·99 (0·53–1·84; 0·97)
Deaths from all causes	74	68	1·21 (0·87–1·69; 0·25)	1·21 (0·86–1·69; 0·27)	1·24 (0·88–1·75; 0·22)

*Adjusted for age, sex, FEV_1, AAA diameter, log (creatinine), and statin use. †Adjusted for variables in primary adjustment plus body-mass index, smoking, systolic blood pressure, and serum cholesterol. ‡Deaths within 30 days of surgery for AAA plus deaths with underlying cause given as ICD10 codes I713–19.

Table 2: **Aneurysm-related and all-cause mortality (intention-to-treat analysis)**

	EVAR	No intervention
Before operation (n=166 and 172, respectively)		
AAA rupture	6	21
Coronary heart disease	2	13
Stroke	1	3
Cancer, lung	0	2
Cancer, other	1	6
Respiratory	2	5
Renal	1	3
Other	1	2
Unknown	0	2
Total	14	57
<30 days after primary operation (n=150 and 47, respectively)		
Procedure related AAA (elective)	10	1
AAA rupture and emergency repair	3	0
Total	13	1
>30 days after primary operation (n=137 and 46, respectively)		
Procedure related AAA (elective)	1	0
Coronary heart disease	14	3
Stroke	1	0
Cancer, lung	4	1
Cancer, other	10	1
Respiratory	12	1
Other	5	3
Unknown	0	1
Total	47	10

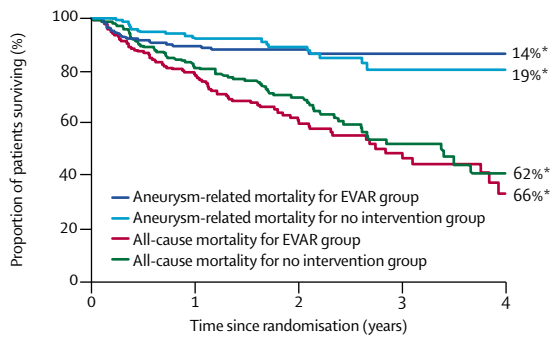
Table 3: **Causes of death by group**

age 77 years [SD 7], 86% male, median AAA diameter 6·5 cm [IQR 6·0–7·5]) did not differ from those of the patients who consented to randomisation (table 1). Patients who refused had a preference for EVAR (n=60), no intervention (n=58), or had unknown preference (n=1). Of those randomised, patients assigned EVAR who received surgery (n=150) did so in a median of 57 days (IQR 39–82). 144 of 166 (87%) of those patients had an endograft implanted successfully. 47 of 172 (27%) patients assigned no intervention underwent aneurysm exclusion, including 12 cases of open repair. Data are not available to assess whether there was any change in fitness for all 47 patients, though a few had been reassessed for fitness particularly if the aneurysm became tender, and known reasons for aneurysm repair are shown in figure 1. The median time from randomisation to aneurysm exclusion in these patients was 163 days (IQR 78–477).

Table 1 shows the baseline characteristics of the patients. It is noteworthy that about three-quarters of patients had symptomatic cardiac disease, the mean forced expiratory volume in 1 sec (FEV_1) was low at 1·7 L (SD 0·7), 14% (47 of 338) had diabetes, and the median creatinine concentration was 110 μmol/L (IQR 91–145), all worse than for patients entered into the parallel EVAR trial 1 for fit patients.[6] The extent of aspirin and statin use was low. By December, 2004, median follow-up was 2·4 years (IQR 1·6–3·6).

By Dec 31, 2004, 100% of patients had been followed up for 1 year, 62% for 2 years, 36% for 3 years, and 15% for 4 years. 142 patients died during follow-up, 42 (30%) from aneurysm-related causes (tables 2 and 3). Kaplan-Meier estimates indicate that overall mortality was 64% by 4 years. However, neither aneurysm-related mortality nor all-cause mortality differed between groups (crude hazard ratio, comparing the EVAR group with the intervention group, 1·01 and 1·21, respectively; table 2, figure 2). There were no significant interactions, for either all-cause or aneurysm-related mortality, for the effect of EVAR with age, sex, aneurysm diameter, or creatinine concentration (all p>0·1). In a post-hoc analysis, the follow up was divided into the first 6 months after randomisation and the period after those 6 months. The hazard ratios for aneurysm-related mortality comparing the EVAR and no intervention groups were 1·67 (95% CI 0·72–3·86) and 0·53 (0·20–1·39) in the two periods, respectively. The corresponding hazard ratios for all-cause mortality were 1·31 (0·70–2·45) and 1·18 (0·80–1·73).

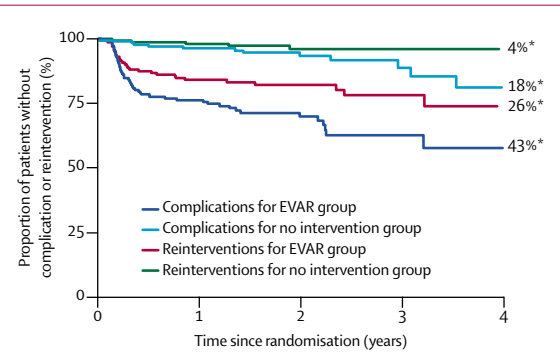
Causes of death are shown in table 3. The deaths from aneurysm rupture in the no intervention group were



Number at risk

No intervention	172	139	71	29	9
EVAR	166	129	58	23	6

Figure 2: **Kaplan-Meier curve of survival and survival free from aneurysm-related death**
*Mortality 4-year point estimates.



Number at risk for complications

No intervention	172	137	69	26	7
EVAR	166	105	47	14	5

Number at risk for reinterventions

No intervention	172	137	70	29	9
EVAR	166	115	55	20	7

Figure 3: **Kaplan-Meier curve of postoperative complications and reinterventions**
*4-year point estimates for patients with complications or reinterventions.

	Successful EVARs completed (n=178)†	
	Number of patients with complication	Number of patients with reintervention
Graft rupture (1)	1	1
Graft infection (1)	1	0
Graft migration (2)	2	0
Endoleak type 1 (11)‡	10	8
Endoleak type 3 (6)‡	5	3
Graft kinking (2)	1	1
Endotension (1)§	1	1
Endoleak type 2 (23)‡	17	3
Graft thrombosis (8)	7	5
Graft stenosis (0)	0	0
Distal embolisation from graft (0)	0	0
Renal infarction (2)	2	0
Anastomotic aneurysm (1)	1	1
Iliac dilatation (1)	1	0
Technical problem on graft insertion (1)	1	1
Other surgery required (8)	8	8
Total (68 complications in 58 patients)	58 of 178 (33%; 95% CI 26–40)	32 of 178 (18%; 95% CI 13–24)

*In some cases patients have had more than one type of complication. In these cases most serious complication has been used for classification. Complications are listed in order of severity. Total numbers of complications are given in brackets in first column. †181 EVARs attempted: one conversion in theatre, two procedures abandoned. ‡Type 1=presence of blood leaking either from top or bottom of graft; type 2=other arteries backbleeding into aortic sac; type 3=structural fault of graft or its limbs. §Continued sac expansion after repair without observed endoleak.

Table 4: **Postoperative complications* for all patients receiving EVAR (not intention to treat)**

matched by the rupture and operative deaths in the EVAR group. 32 ruptures were reported across both groups by Dec 31, 2004. Five of these 32 patients underwent attempted repair of whom two survived to 30 days. There were 23 ruptures in the no intervention group (crude rupture rate 9·0 per 100 person years, 95% CI 6·0–13·5). The aneurysms of nine patients in the EVAR group ruptured before receipt of elective treatment. The median time from randomisation to rupture was 98 days (range 6–767). The three longest delays of more than a year occurred in patients who were subsequently found to have problematic aortic anatomy that delayed their EVAR procedure, and the other six patients whose operations were delayed by less than a year were on waiting lists for their procedures or undergoing further fitness tests for comorbidities. We considered whether the excess of respiratory deaths in the EVAR group was attributable to the use of general anaesthesia. General anaesthesia was used in 83 of 166 (50%) patients in the EVAR group versus 27 of 172 (16%) in the no intervention group. EVAR was used in both groups of the trial in 181 patients of whom 96 (53%) had a general anaesthetic. There were eight respiratory deaths in the general anaesthetic group and five in the no general anaesthetic group (χ^2 test p=0·45).

In the EVAR group, the 30-day operative mortality was 13 of 150 (9%, 95% CI 5–15; table 3), significantly higher than the 1·7% 30-day mortality for EVAR in the EVAR 1 trial (p<0·0001).[6] If only elective cases were included, this operative mortality reduced to ten of 147 (7%, 3–12). All grafts used in the EVAR group were commercially available devices (87% bifurcated systems): 86 (59%) Zenith (Cook, Copenhagen, Denmark); 31 (21%) Talent (Medtronic, Minneapolis, MN, USA); ten (7%) Excluder (Gore, Flagstaff, AZ, USA); nine (6%) AneuRx (Medtronic); five (3%) Quantum (Cordis, Johnson and Johnson, Waterloo, Belgium); two (1%) Bard device (Bard, New Jersey, NJ, USA); one (<1%) Anson Aorfix (Lambard Medical, Oxford, UK); one (<1%) EVT (Guidant, Indianapolis, IN, USA); and one (<1%) Edwards Lifepath (Edwards Lifesciences, Saint-Prex, Switzerland). Compared with the fit patients in the EVAR group of EVAR trial 1,[10] there was a greater need in our patients for internal iliac artery embolisation (26 of 150 *vs* 58 of 532), blood products (mean 264 mL *vs* 164 mL), and renal dialysis (six of 150 *vs* five of 532), and the length of stay in hospital was longer (mean 12 days *vs* 10 days).

Since 20% of patients did not adhere to their allocated treatment, we did a post-hoc per-protocol analysis for mortality. The hazard ratio for all-cause mortality was 1·07 (0·75–1·52; p=0·70), which did not differ markedly

	EVAR: mean (SD) (number of patients)	No intervention: mean (SD) (number of patients)	Crude difference: mean (SE)	Difference adjusted for baseline score: mean (SE) (number of patients)	p
EQ5D weighted index score*					
Baseline	0·58 (0·31) (164)	0·63 (0·28) (171)	−0·05 (0·03)	Ref	
0–3 months	0·57 (0·28) (48)	0·56 (0·29) (92)	0·01 (0·05)	0·03 (0·05) (139)	0·51
3–12 months	0·64 (0·28) (122)	0·60 (0·26) (120)	0·04 (0·03)	0·06 (0·03) (241)	0·06
12–24 months	0·65 (0·24) (88)	0·60 (0·30) (68)	0·05 (0·04)	0·04 (0·04) (156)	0·30
SF36 physical component summary*					
Baseline	35·47 (6·63) (160)	35·12 (6·23) (171)	0·35 (0·71)	Ref	
0–3 months	33·96 (5·13) (46)	35·60 (5·70) (89)	−1·64 (1·00)	−1·86 (0·88) (134)	0·04
3–12 months	34·33 (6·10) (116)	35·12 (6·42) (111)	−0·78 (0·83)	−1·11 (0·77) (224)	0·15
12–24 months	34·54 (5·89) (71)	36·01 (6·92) (60)	−1·47 (1·12)	−0·64 (1·04) (130)	0·54
SF36 mental component summary*					
Baseline	45·13 (7·92) (160)	46·31 (6·97) (171)	−1·18 (0·82)	Ref	
0–3 months	45·76 (8·65) (46)	44·03 (7·78) (89)	1·73 (1·47)	2·30 (1·38) (134)	0·10
3–12 months	44·76 (7·21) (116)	44·84 (7·85) (111)	−0·08 (1·00)	0·94 (0·95) (224)	0·32
12–24 months	45·36 (7·20) (71)	44·67 (7·93) (60)	0·70 (1·32)	0·50 (1·29) (130)	0·70

*Higher scores indicate better quality of life.

Table 5: **Comparison of HRQL at different timepoints from randomisation by intention-to-treat groups**

from the analysis by intention to treat (table 2). Similarly, the hazard ratio for aneurysm-related mortality was 0·77 (0·41–1·45; p=0·43).

Analysis by intention to treat showed that by 4 years, 43% of patients in the EVAR group had had at least one postoperative complication compared with only 18% in the no intervention group (hazard ratio 5·3, 2·8–10·0; p<0·0001 [figure 3]). The overall reintervention rate was 11·5 per 100 person years in the EVAR group and 1·8 per 100 person years in the no intervention group, and by 4 years, 26% of patients in the EVAR group had needed at least one reintervention compared with only 4% in the no intervention group (hazard ratio 5·8, 2·4–14·0; p<0·0001 [figure 3]). The reintervention rate for the EVAR group of EVAR trial 2 (11·5 per 100 person years) seemed higher than that observed for patients in the EVAR group of EVAR trial 1 (6·9 per 100 person years),[10] but this finding was not significant (hazard ratio 1·4, 0·9–2·1; p=0·10).

The types of postoperative complications and the number of reinterventions that arose after EVAR are shown in table 4. There were three conversions to open repair after EVAR deployment, one during the primary theatre procedure, one more during the primary admission, and one after initial discharge from hospital. By Dec 31, 2004, 62 patients had developed a post-operative complication (58 after EVAR) and 37 had needed at least one reintervention (32 after EVAR). There were no deaths within 30 days of reintervention.

The baseline EQ5D scores in EVAR 2 (table 5) were substantially lower than for patients randomised in EVAR trial 1.[10] There were no clear and consistent differences in HRQL between the two groups at any time.

The mean discounted costs per patient of the primary procedure and of admission to hospital were UK£11 016 in the EVAR group versus £3518 for the no intervention group (table 6). The mean estimated discounted costs per patient over 4 years were £13 632 for the EVAR group and £4983 for the no intervention group (table 6). The resource use for surgical procedures in the 47 patients allocated to no intervention was similar to those who received EVAR in the EVAR group.

	EVAR (n=166)*	No intervention (n=172)*	Mean difference	SE of difference
Primary hospital admission				
Main procedure	7090	1990	5100	374
Hospital stay	3504	1421	2083	541
Other	422	107	315	89
Total	11 016	3518	7498	776
Secondary procedures, adverse events, scans				
Secondary AAA procedures	1530	849	681	897
Other adverse events	327	27	300	158
Outpatients/CT scan/ultrasound scan†	759	589	170	90
Total	2616	1465	1151	797
Total cost including 4-year follow up	13 632	4983	8649	1248

*150 of 166 patients received primary AAA repair in the EVAR group and 47 of 172 patients received primary AAA repair in the no intervention group. †Average number of outpatient follow-up appointments, CT and ultrasound scans estimated from a survey of trial centres.

Table 6: **Estimated costs (UK£) over 4 years of follow-up based on intention to treat**

Discussion

Our findings indicate that the patients we enrolled had significantly worse health than those studied in EVAR trial 1,[6,10] and show that EVAR is not a safe procedure in such high-risk patients. Concern remains about the medical treatment of these patients, since so few receive statins, which improve survival in patients with aneurysms.[11,12] The rupture rate we noted in the no intervention group, in patients with favourable anatomy in terms of neck dimensions and iliac involvement, is considerably lower than that noted in other prospective studies monitoring large aneurysm rupture.[2,13]

We noted no survival benefit (either all-cause or aneurysm-related) for EVAR compared with no intervention. The curves for aneurysm-related mortality in figure 2 did cross at about 2 years, however, raising the possibility of a late benefit for the EVAR group. Extended follow-up is needed to clarify any association, but given that only one third of these unfit patients are expected to live beyond 4 years, a clear difference is unlikely to emerge.

More than a quarter of patients assigned to no intervention for their aneurysm underwent aneurysm repair. Of these, 30% received surgery because of patient preference and 30% received surgery for unrecorded reasons, possibly because of surgeon preference. Such crossovers indicate the loss of equipoise that existed during the trial for some patients and for some clinicians who could not accept uncertainty of the efficacy of EVAR in this high-risk situation. Per-protocol analysis indicated that these crossovers did not alter the main conclusions of the trial.

There was a greater difference in hospital costs between the two groups in EVAR trial 2 than in EVAR trial 1 because in EVAR trial 2, the alternative to EVAR was no surgical intervention. However, we did not obtain information about the use of medication during follow-up, which might have led to an underestimation of total health-care costs. By December, 2004, 43% of patients in the EVAR group of EVAR trial 2 had had postoperative complications compared with 41% in EVAR trial 1. However, the secondary intervention rate for patients in the EVAR group of EVAR trial 2 seemed to be higher than that observed for fit patients in EVAR trial 1. Furthermore, there was no consistent HRQL benefit between the randomised groups of EVAR trial 2.

We intended EVAR trial 2 to be a pragmatic trial that reflected common practice. Although there was sometimes a lengthy interval between randomisation and surgery in the EVAR group, this delay perhaps reflects some of the difficulties encountered by doctors when managing this group of patients with complex medical histories and comorbidities. Despite this limitation and that of crossovers between the groups, we

have shown no survival benefit from endovascular aneurysm repair in patients unfit for open repair. EVAR is costly, has little effect on HRQL, and involves a continuing need for surveillance and reintervention. We do not therefore see a need to pursue cost-effectiveness modelling in EVAR trial 2 at this time. However, we have resources to monitor our patients until 2010, and this additional follow-up will indicate whether there is any change in outcome in the long term. In the meantime, the focus should be on improving fitness rather than early EVAR.

Conflict of interest statement

RMG has received research support from manufacturers of endovascular grafts—Cook, Boston Scientific, and Bard. These companies with W L Gore, Medtronic, and Edwards Lifesciences are major sponsors of the annual international Charing Cross Symposium. MJS has received research and consultancy funding from Medtronic and Boston Scientific. The other members of the writing committee declare that they have no conflict of interest.

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