Does EVAR Alter the Rate of Cardiovascular Events in Patients with Abdominal Aortic Aneurysm Considered Unfit for Open Repair? Results from the Randomised EVAR Trial 2

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Abstract Objectives: To investigate whether EndoVascular Aneurysm Repair (EVAR) influences the rate of cardiovascular events (fatal or non-fatal myocardial infarction or stroke) in patients with abdominal aortic aneurysm (AAA) considered unfit for open repair.
Design: Randomised controlled trial.
Materials: Between 1999 and 2004, 404 patients with large AAA considered unfit for open repair were randomised to EVAR or no surgical intervention across 33 UK hospitals and followed until July 2009.
Methods: The Customised Probability Index was used to determine fitness for each patient and Cox regression was used to compare time to first cardiovascular event between randomised groups and levels of fitness.
Results: During an average of 2.8 years of follow-up, 67 first cardiovascular events occurred with a non-significantly higher event rate in the EVAR group compared to the no intervention group (6.6 versus 5.1 events per 100 person years); adjusted hazard ratio 1.42 [95% CI 0.87–2.34], p = 0.156. There was no evidence to suggest that the hazard ratio between randomised groups changed with level of fitness (p = 0.378).
Introduction

The prevalence of abdominal aortic aneurysm (AAA) increases with age for both sexes and there is good evidence demonstrating an association between the incidence of cardiovascular disease and the development of AAA, although the pathology is thought to differ between the two disease processes. Possibly the most important environmental factor associated with the development of AAA is smoking where the relationship is even stronger than that seen between smoking and other forms of cardiovascular disease. Furthermore, a high proportion of patients with AAA have been shown to have clinically significant concomitant coronary artery and cerebrovascular disease.

In the early 1990s EndoVascular Aneurysm Repair (EVAR) was developed specifically for the treatment of patients who were not considered fit enough to undergo open surgical repair and, although the use of EVAR is now used more commonly in fitter patients, it still remains the only choice of elective intervention for the very unfit. Whether endovascular intervention is justified in these patients is currently being tested in the UK EVAR Trial 2 and mid-term results already have demonstrated that immediate endovascular repair does not provide any benefit in terms of mortality, quality of life or costs within the first 4 years after treatment. Final long-term results are due for release in 2010 but the provisional conclusions based on mid-term data suggest that optimising patient co-morbidities should be prioritised before considering endovascular repair. However, despite the mid-term results of EVAR Trial 2 demonstrating no benefit, and possible early harm, in patients undergoing EVAR, it remains a common treatment choice in these unfit patients.

Unfit patients are vulnerable to a number of co-morbidities but are at particularly high risk of cardiovascular events. Here, we use data from EVAR Trial 2 to investigate whether EVAR influences the rate of subsequent cardiovascular events (defined as fatal or non-fatal myocardial infarction (MI) or stroke) as it is possible that an increased rate of cardiovascular events could offset any potential survival benefit associated with aneurysm repair. Beyond this, we investigate whether the impact of EVAR versus no intervention differs across the range of fitness within the trial.

Materials and methods

The patients

The methods and mid-term results for EVAR Trial 2 have been published previously. Patients of both sexes aged at least 60 years with an aneurysm measuring at least 5.5 cm on computed tomography (CT) scan, deemed anatomically suitable for endovascular repair but anaesthetically unfit for an open repair were entered into EVAR Trial 2 and randomised to either EVAR or no surgical intervention. Full ethical approval for the trial was granted by the UK North West Multi-centre Research Ethics Committee (MREC 98/8/26 & 27) and the trials are registered with international trial number ISRCTN55703451. Patients were recruited from 33 UK hospitals between September 1999 and August 2004; this includes an additional 66 patients who were randomised between January and August 2004 who were not included in the planned mid-term analyses published in 2005. Patients are followed up annually by a dedicated local trial coordinator at each hospital, who reports prospectively on the events of MI and stroke. All patients have been flagged at the UK Office for National Statistics (ONS) for mortality with provision of death certificates coded according to The International Classification of Diseases – 10th Revision (ICD-10) and audited by a Trial Endpoints Committee. Follow-up data were included up to the time of analysis in July 2009, an average of 6.8 years after recruitment. Between 2007 and 2009, a trial auditor visited each hospital site to check the trial case record forms against the patient notes, to confirm the occurrence of reported adverse events, and to collect data on unreported events including MI and stroke. A total of 292 patient notes were available for inspection (72% of all randomised patients) with the remaining 28% unavailable in hospital archives or missing from medical records departments on the dates of audit. The audit confirmed all previously reported cardiovascular events and also identified 1 unreported non-fatal stroke; data for this event were retrieved for inclusion in the main trial database. UK hospitals work to the World Health Organisation criteria for these events and therefore events reported in discharge summaries and hospital notes were included, even when source documentation was not available at audit. The local policies on specific levels of enzymes, extent of ECG disturbance or other neurological criteria were not recorded but should be consistent within each hospital. Randomisation was stratified by hospital inferring that variation in definitions between hospitals should not have lead to any strong differences between randomised groups.

Definition of cardiovascular events

The primary outcome for the analysis was time from randomisation to first cardiovascular event defined as either fatal or non-fatal MI or stroke. In addition, the numbers of multiple events in patients were summated to calculate crude overall event rates.

Definition of fatal MI – Primary cause of death after adjudication of the death certificate assigned under ICD-10 myocardial infarction codes I210–I238.
**Assessment of patient fitness**

Previous research using data from EVAR Trial 1 (where fit patients were randomised to receive either open or endovascular repair) has used the Customised Probability Index (CPI) to investigate the role of fitness in patients undergoing AAA repair. A slightly modified version of the score was used based upon the data available in the EVAR Trials database as described previously. In brief, the CPI is a validated prognostic score for operative mortality after open AAA repair but for this analysis it was used as an indicator of fitness rather than a prognostic indicator for survival after open repair. It includes components for cardiac, respiratory and renal function as well as use of beta-blockade or statins. Possible scores range from -25 in the most fit to +57 in the least fit with higher scores indicating a higher risk of operative death after AAA repair. This modified score was applied to the patients in EVAR Trial 2 but split into tertiles (thirds) for the purpose of presentation. For 30 of the 404 patients, one score component was missing and linear regression was used to impute the missing component based upon CPI variables in the 373 patients with complete data. For one patient, more than one component was missing and this patient was excluded from the analysis investigating the impact of EVAR across the fitness spectrum.

**Statistical analysis**

The analysis was conducted according to a pre-defined statistical analysis plan and performed using Stata version 10 (Stata Corporation, Texas, USA). All patients were analysed within their randomised group according to the intention-to-treat principle. Given that some patients were still under standard annual follow-up and some had died or been lost to follow-up, the timing of events and censoring of patients was pre-defined according to the following rules.

For patients with an event recorded since randomisation:

- If the patient had a baseline/follow-up appointment or had been audited more than 18 months prior to the event, then the event was defined as the first event.

For patients without any event recorded, censoring occurred at the latest of these dates:

- for patients who are alive, the date of last follow-up appointment or the date of audit.
- for patients who are dead, the date of death (without mention of MI or stroke cause) was used providing the death occurred within 18 months after the last follow-up or date of audit. For patients dying more than 18 months after their last follow-up or date of audit, the date of follow-up or audit was used for censoring.

Cox regression modelling was used to compare time to first cardiovascular event between randomised groups. Crude hazard ratios were presented as well as ones adjusted for baseline age, sex, AAA diameter, body mass index, systolic blood pressure, serum total cholesterol, history of cardiac disease (defined as previous MI, angina, cardiac revascularisation, cardiac valve disease, significant arrhythmia or uncontrolled congestive cardiac failure), mean Ankle Brachial Pressure Index, Forced Expiration Volume in 1 s, log (serum creatinine), statin use, aspirin use, smoking status (current, past or never) and diabetes. Adjustment was performed using a propensity score developed from a logistic regression model using these covariates to predict randomised group. The propensity score was available for patients with complete data. 54 patients without a prognostic score due to missing covariates were incorporated into the adjusted model using the missing indicator method. Kaplan–Meier methods were used to display curves for survival without a cardiovascular event between randomised groups and fitness tertile groups.

To investigate whether the hazard ratio between EVAR and no intervention differed with fitness, a test for interaction was performed between randomised group and CPI score. The CPI score was included in the Cox model in continuous format but data were presented within tertile groups to indicate the magnitude of any effect.

**Results**

Between September 1999 and August 2004, a total of 404 patients were randomised, 197 to EVAR and 207 to no intervention. The baseline characteristics were very similar between randomised groups and with those published previously. The mean (SD) age and AAA diameter were 77 (6) years and 6.7 (1.0) cm respectively with 86% male. A large proportion of patients had a history of previous cardiac disease with a non-significantly higher percentage in the no intervention group (74%) when compared with the EVAR group (67%); Chi-squared test, p = 0.128. The use of
For the 25 non-fatal events, 11 were ascertained from the EVAR 2 trial, and 14 from the EVAR 1 trial. All 42 fatal events were ascertained from the death certificates. Compliance with randomised treatment was moderate (79%). In the group randomised to EVAR, 17 patients did not have an AAA repair and 5 had an elective or emergency open repair. In the group randomised to no intervention, 12 had an elective open repair and 51 had an elective EVAR at some point during follow-up.

Patients were followed for an average of 6.8 years after recruitment (unconditional follow-up) with only 2 patients lost to follow-up. There was a high attrition of follow-up due to patients being censored at death and time after non-fatal events being excluded (conditional follow-up). Thus, a total of 67 first cardiovascular events occurred during an average of 2.8 years of conditional follow-up and a breakdown of the type of events is given in Table 1. Of these 67 patients, 2 went on to have a second event and 1 had a third event generating a total of 70 events in an average of 2.8 years of follow-up; crude overall rate 6.1 [95% CI 4.7–7.6] events per 100 person years. In the EVAR group, 3 cardiovascular events were reported before the EVAR procedure and 10 occurred within 30 days of the EVAR, with the remaining 23 occurring more than 30 days after EVAR. In the no intervention group, 9 events occurred after AAA repair in the 63 patients having aneurysm repair against protocol (none within 30 days). For the 319 patients complying with their randomised allocation, 33 (19%) patients in the EVAR group and 22 (15%) patients in the no intervention group experienced a cardiovascular event during follow-up; adjusted Cox hazard ratio 1.07 [95% CI 0.60–1.91].

Table 2 presents the results of Cox regression modelling between randomised groups and Fig. 2 shows the Kaplan–Meier estimates up to the first 6 years after randomisation. The patients in the EVAR group experienced a higher rate of cardiovascular events, but this did not reach statistical significance, p = 0.156. The CPI score includes a component for cardiac disease so it was unsurprising that the rate of cardiovascular events tended to increase as fitness deteriorated (Fig. 3) but the test of interaction between randomised group and CPI score was non-significant with no particular trend for the Cox regression hazard ratios across the tertile groups (p = 0.378, Table 2).

The overall event rate was compared to that seen in EVAR Trial 1 of 1252 patients comparing EVAR with open repair in patients considered fit for open repair, where a total of 171 cardiovascular events had occurred during an average of 4.4 years of follow-up (crude rate 3.1 [95% CI 2.7–3.6] events per 100 person years). Unsurprisingly, patients in the EVAR 2 trial experienced a significantly higher rate of cardiovascular events than those in EVAR Trial 1; crude Cox regression hazard ratio 1.77 [95% CI 1.33–2.36] p < 0.001.

Discussion

Patients with aortic aneurysm are known to be at greater risk of mortality than the age and sex-matched population. Much of this increase is thought to be from cardiovascular disease and it has been shown to persist beyond repair of the aneurysm. As far as we are aware, this is the first published analysis of fatal and non-fatal cardiovascular events in unfit patients with AAA, although numerous studies have demonstrated a high cardiovascular event rate in patients with any kind of peripheral vascular disease and quote a 5-year risk of approximately 25%. Much of the literature on cardiovascular outcomes...
Table 2  Results from Cox regression model comparing time to first cardiovascular event between EVAR and no intervention for all patients and within tertiles of fitness in EVAR Trial 2.

<table>
<thead>
<tr>
<th>Fitness&lt;sup&gt;a&lt;/sup&gt; (CPI score missing in 1 patient)</th>
<th>EVAR</th>
<th>No intervention</th>
<th>Crude hazard ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Adjusted hazard ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p-Value from test of interaction in adjusted&lt;sup&gt;b&lt;/sup&gt; model</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>N = 197</td>
<td>N = 207</td>
<td>1.31 (0.81–2.12)</td>
<td>1.42 (0.87–2.34)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>N = 404</td>
<td>36/197 (6.6)</td>
<td>31/207 (5.1)</td>
<td>0.272 (0.156)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good fitness</td>
<td>N = 138</td>
<td>11/62 (5.8)</td>
<td>2.01 (0.80–5.07)</td>
<td>1.98 (0.75–5.24)</td>
<td>p = 0.378</td>
</tr>
<tr>
<td>N = 141</td>
<td>11/65 (5.8)</td>
<td>9/76 (3.5)</td>
<td>0.83 (0.38–1.84)</td>
<td>1.05 (0.45–2.42)</td>
<td>CPI score included in continuous format</td>
</tr>
<tr>
<td>Moderate fitness</td>
<td>N = 141</td>
<td>11/65 (5.8)</td>
<td>1.65 (0.69–3.93)</td>
<td>1.61 (0.67–3.87)</td>
<td>p = 0.378</td>
</tr>
<tr>
<td>Poor fitness</td>
<td>N = 124</td>
<td>8/55 (6.6)</td>
<td>1.65 (0.69–3.93)</td>
<td>1.61 (0.67–3.87)</td>
<td>p = 0.378</td>
</tr>
</tbody>
</table>

<sup>a</sup> Customised Probability Index (CPI) score used to classify patients into tertile groups of fitness but included in the adjusted Cox model in continuous format as an interaction term with randomised group.

<sup>b</sup> adjusted for age, sex, AAA diameter, body mass index, systolic blood pressure, cholesterol, cardiac disease (previous history of any of the following: myocardial infarction, angina, severe valve disease, significant arrhythmia, uncontrolled congestive cardiac failure), ankle brachial pressure index (mean of both legs), Forced expiration volume in 1 s, log(creatinine), statin use, aspirin use, smoking status and diabetes. Missing indicator method used to include 54 patients without a complete set of covariates.

summarizes cardiovascular mortality and morbidity in terms of relative and absolute percentage risks rather than rates per 100 person years so it is difficult to compare directly the results presented here with those in the general or high risk population. We have only identified one previous study which reported on cardiovascular event rates during long-term follow-up of (presumably fit) patients undergoing open aneurysm repair, where Kaplan–Meier estimates at 3 and 5 years were 10.3% and 14.9% respectively. The rates observed in the EVAR 2 trial were almost twice this, even though most of the interventions used the less invasive endovascular technique. Similarly, the rates observed in the EVAR 2 trial were almost twice those in EVAR Trial 1, where fit patients were randomised to either EVAR or open repair.

Use of optimal medical therapy was poor in the UK EVAR Trials, particularly in EVAR Trial 2 where use of anti-platelet and statin therapy should have been prescribed to all patients, unless contraindicated. Overall, only 47% of patients had baseline systolic blood pressure below the recommended maximum level of 140 mmHg and it seems likely that the high cardiovascular event rates seen in these patients could be reduced simply by a more rigorous application of medical therapy. In addition, outcomes might have been improved if referral to cardiac, renal and respiratory specialists had been more rigorously implemented. In some cases, optimisation of respiratory function may have lead to an improved prognosis in these sick patients as demonstrated in other research.

As anticipated, Table 2 and Fig. 3 demonstrate that the rate of cardiovascular events tends to increase as patient fitness deteriorates but the non-significant test of interaction with randomised group suggests that the impact of EVAR relative to no intervention is not being influenced strongly by patient fitness. All these patients have been deemed unfit for open repair and represent the extreme

![Figure 2](image1.png)  Kaplan–Meier estimates for time to first cardiovascular event stratified by randomised group.

![Figure 3](image2.png)  Kaplan–Meier estimates for time to first cardiovascular event coloured coded into green, orange and red for the most, moderately and least fit tertiles.
end of the spectrum of fitness with numerous other non-
cardiovascular factors influencing their classification as
unsuitable for open repair. In addition, trial protocol
guidelines recommended that any patient with myocardial
infarction or new onset of angina within the previous 3
months should not be considered for entry into the trial.

We acknowledge that there are limitations to this study.
First, it is possible that some non-fatal MI and stroke events
have not been reported if patients were referred to other
hospitals for treatment. Second, the ascertainment of
non-fatal events from death certificates is unconventional,
but allowed inclusion of a further 7 non-fatal events (10% of
the total) that occurred between last follow-up and death.
Third, clinical confirmation of non-fatal events according to
World Health Organisation (WHO) criteria was available for
just 44% of all events and it is possible that the rates pre-
sent here are an over-estimate of the event rate defined
according to WHO standards. However, the impact of these
limitations is reduced by the randomised nature of the study
design and the analysis of patients according to the inten-
tion-to-treat principle. Conversely, the overall compliance
with randomised group was only moderate in this trial (79%) with
30% of patients in the no intervention group eventually
crossing over to have elective AAA repair. Given that growth
of the AAA as well as changes in the fitness status of patients
after randomisation would have considerable bearing on the
decision to intervene for the aneurysm, the per protocol
results that are presented here are likely to be biased and
therefore are difficult to interpret. Nevertheless, they
confirm the intention-to-treat results with no significant
difference in event rates demonstrated between compliant
groups. Interestingly, there were no cardiovascular events
within 30 days of delayed aneurysm repair (n = 63), against
protocol, in the no intervention group as compared to 10
within 30 days of EVAR in the group randomised to EVAR. This
could reflect an improvement in fitness in the patients with
delayed AAA repair but also, it is possible that these patients
came from the fitter end of the spectrum thus allowing
consideration of AAA repair more readily.

In this study, we have investigated the impact of EVAR on
cardiocvascular event rates in unfit patients and shown that
there is only weak evidence to suggest a higher rate after
EVAR than surveillance alone. Moreover, Fig. 2 demonstrates
that most of the difference between groups was evident
after 4 years of follow-up, when there were few patients
remaining under follow-up. Nevertheless, these results lend
weight to the conclusions of our earlier publication,13 where
we suggested that optimisation of co-morbidities and
improvement of patient fitness should remain the goal in
these patients before aneurysm repair is considered.

Conflict of Interest

The authors have no conflicts of interest.

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A full list of EVAR Trial Participants is provided in Ref. 21.

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