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National Institute for Health Research

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Abstract

The UK EndoVascular Aneurysm Repair (EVAR) randomised controlled trials: long-term follow-up and cost-effectiveness analysis

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Background: Short-term survival benefits of endovascular aneurysm repair (EVAR) compared with open repair (OR) of intact abdominal aortic aneurysms have been shown in randomised trials, but this early survival benefit is soon lost. Survival benefit of EVAR was unclear at follow-up to 10 years.

Objective: To assess the long-term efficacy of EVAR against OR in patients deemed fit and suitable for both procedures (EVAR trial 1; EVAR-1); and against no intervention in patients unfit for OR (EVAR trial 2; EVAR-2). To appraise the long-term significance of type II endoleak and define criteria for intervention.

Design: Two national, multicentre randomised controlled trials: EVAR-1 and EVAR-2.

Setting: Patients were recruited from 37 hospitals in the UK between 1 September 1999 and 31 August 2004.

Participants: Men and women aged ≥ 60 years with an aneurysm of ≥ 5.5 cm (as identified by computed tomography scanning), anatomically suitable and fit for OR were randomly assigned 1 : 1 to either EVAR ($n = 626$) or OR ($n = 626$) in EVAR-1 using computer-generated sequences at the trial hub. Patients considered unfit were randomly assigned to EVAR ($n = 197$) or no intervention ($n = 207$) in EVAR-2. There was no blinding.

Interventions: EVAR, OR or no intervention.

Main outcome measures: The primary end points were total and aneurysm-related mortality until mid-2015 for both trials. Secondary outcomes for EVAR-1 were reinterventions, costs and cost-effectiveness.

Results: In EVAR-1, over a mean of 12.7 years (standard deviation 1.5 years; maximum 15.8 years), we recorded 9.3 deaths per 100 person-years in the EVAR group and 8.9 deaths per 100 person-years in the OR group [adjusted hazard ratio (HR) 1.11, 95% confidence interval (CI) 0.97 to 1.27; $p = 0.14$]. At 0–6 months after randomisation, patients in the EVAR group had a lower mortality (adjusted HR 0.61, 95% CI 0.37 to 1.02 for total mortality; HR 0.47, 95% CI 0.23 to 0.93 for aneurysm-related mortality; $p = 0.031$), but beyond 8 years of follow-up patients in the OR group had a significantly lower mortality (adjusted HR 1.25, 95% CI 1.00 to 1.56, $p = 0.048$ for total mortality; HR 5.82, 95% CI 1.64 to 20.65, $p = 0.0064$ for aneurysm-related mortality). The increased aneurysm-related mortality in the EVAR group after 8 years was mainly attributable to secondary aneurysm sac rupture, with increased cancer mortality

also observed in the EVAR group. Overall, aneurysm reintervention rates were higher in the EVAR group than in the OR group, 4.1 and 1.7 per 100 person-years, respectively ($p < 0.001$), with reinterventions occurring throughout follow-up. The mean difference in costs over 14 years was £3798 (95% CI £2338 to £5258). Economic modelling based on the outcomes of the EVAR-1 trial showed that the cost per quality-adjusted life-year gained over the patient's lifetime exceeds conventional thresholds used in the UK. In EVAR-2, patients died at the same rate in both groups, but there was suggestion of lower aneurysm mortality in those who actually underwent EVAR. Type II endoleak itself is not associated with a higher rate of mortality.

Limitations: Devices used were implanted between 1999 and 2004. Newer devices might have better results. Later follow-up imaging declined, particularly for OR patients. Methodology to capture reinterventions changed mainly to record linkage through the Hospital Episode Statistics administrative data set from 2009.

Conclusions: EVAR has an early survival benefit but an inferior late survival benefit compared with OR, which needs to be addressed by lifelong surveillance of EVAR and reintervention if necessary. EVAR does not prolong life in patients unfit for OR. Type II endoleak alone is relatively benign.

Future work: To find easier ways to monitor sac expansion to trigger timely reintervention.

Trial registration: Current Controlled Trials ISRCTN55703451.

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List of abbreviations

AAA	abdominal aortic aneurysm
ABPI	ankle–brachial pressure index
ACE	Anévrysme de l'aorte abdominale, Chirurgie versus Endoprothése
BMI	body mass index
CAG	Confidentiality Advisory Group
CI	confidence interval
CT	computed tomography
DMEC	Data Monitoring and Ethics Committee
DREAM	Dutch Randomised Endovascular Aneurysm Management
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQol-5 Dimensions
EVAR	endovascular aneurysm repair
EVAR-1	EVAR trial 1
EVAR-2	EVAR trial 2
HDU	high-dependency unit
HES	Hospital Episode Statistics
HR	hazard ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IFU	instructions for use
IPD	individual patient data
IPW	inverse probability weighting
ITT	intention to treat
M	missing values
MD	Doctor of Medicine
MI	myocardial infarction
MMP	matrix metalloproteinase
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OR	open repair
OVER	Open Versus Endovascular Repair
PhD	Doctor of Philosophy
QALY	quality-adjusted life-year
R&D	research and development
RCT	randomised controlled trial
SE	standard error
TMC	Trial Management Committee

Plain English summary

Abdominal aortic aneurysm is the swelling of the main artery of the body conducting blood down through the belly to the legs. Unfortunately this vessel, the aorta, can expand and burst. To prevent this, a big operation requiring open surgery has been used since 1951. Since the mid-1990s, it has been possible to offer patients a less invasive procedure by placing a device within the swollen aorta to strengthen it from within.

The problem is that we did not know how long these devices last and whether or not they can do the job as well as the open operation over many years.

Early results suggested that there was a lower risk of death associated with aneurysm repair using the new device than having the big open operation. After some 5–10 years, this early advantage was lost and so we followed up patients for up to 15 years to see what the end result would be.

We have found that the new device was not as durable after 8 years as the open operation and, based on this evidence, the device might not be considered value for money in the UK. This was partly because of inadequate follow-up and monitoring. We shall now recommend more regular assessment of the new method.

However, for patients who are not fit enough for open repair, although the length of life is not altered, there is some evidence that the new device prevents the aorta from bursting and is effective in that respect.

Scientific summary

Background

Abdominal aortic aneurysm is a common condition particularly affecting men aged > 60 years. In patients with aneurysms the aorta becomes dilated in the segment below the diaphragm. As the size of the aneurysm increases, the risk of rupture increases. Ruptured aneurysms are fatal in > 80% of cases. Currently, there is no proven medical therapy to cure or slow the growth of the aneurysm and surgical correction remains the only course of treatment. Many aneurysms are small (< 5.5 cm), and there is evidence that it is safe and less costly to monitor them using ultrasound until they grow to a size at which aneurysm repair can be considered; this size threshold is usually about 5.5 cm.

Currently, there are two main methods of correction, open repair (OR) and endovascular aneurysm repair (EVAR). OR is major, requires a lengthy convalescence of about 2–3 months and is associated with quite a high operative mortality (between 4% and 10%). However, the procedure is known to be very durable and the repair is likely to last for the rest of the patient's lifetime. EVAR is a minimally invasive technique that can be performed under a local anaesthetic as it requires only, at most, two small incisions in the groin to expose the femoral arteries, but can be done percutaneously. The stent graft system is then fed into the aorta via catheters and guide wires and then positioned and secured correctly above and below the aneurysmal segment of aorta. The location of the stent graft is imaged using radiological methods, with patients being exposed to relatively large doses of radiation and contrast agent. EVAR has a lower operative mortality and a faster recovery time, with less requirement for high-dependency care and a shorter hospital stay. However, this early survival benefit for EVAR is lost a number of years after repair, calling into question the durability of endovascular repair. Not all patients have aortic anatomy which permits EVAR, and the very long-term durability of endovascular repair beyond 8 years is unknown, as is the need for long-term post-repair surveillance and possible reintervention to correct graft-related complications.

In 1999, two randomised controlled trials (RCTs) [EVAR trial 1 (EVAR-1) and EVAR trial 2 (EVAR-2)] were set up to test the safety, efficacy and cost-effectiveness of endovascular repair in two different populations of patients. EVAR-1 randomised patients who were considered to be fit for both procedures to either EVAR or OR. EVAR-2 randomised patients who were considered to be unfit to undergo OR to EVAR or no intervention.

The two EVAR trials are now well placed to compare the long-term durability of EVAR up to 15 years. We previously reported follow-up for aneurysm-related and total mortality up to 8 years, at which point there was no difference between EVAR and OR in EVAR-1 and no difference in total mortality between EVAR and no repair in EVAR-2. There has been no previous trial with very long-term follow-up of EVAR or OR beyond this time.

Objectives

There were a number of objectives of this project. A primary aim was to present very long-term results, over up to 15 years, of EVAR-1 in terms of aneurysm-related and total mortality, cause of death, aneurysm-related reinterventions, costs and cost-effectiveness. Second, we combined results from EVAR-1 with three other international RCTs of EVAR compared with OR [the Dutch Randomised Endovascular Aneurysm Management (DREAM) trial, the Open Versus Endovascular Repair (OVER) trial and Anévrysme de l'aorte abdominale, Chirurgie versus Endoprothése (ACE)], providing a large sample size to enable a comprehensive investigation of potential subgroups that may benefit more from EVAR. From the combined

data we additionally investigated how significant the detection of a type II endoleak is in terms of subsequent mortality. To prevent future serious complications from arising, we investigated how monitoring the aneurysm sac diameter after EVAR could be used to identify high-risk patients. Our final aim was to report on aneurysm-related and total mortality results up to 15 years for the EVAR-2 trial.

Methods

The EVAR trials (EVAR-1 and EVAR-2) commenced recruitment on 1 September 1999 and closed recruitment on 31 August 2004. Patients were initially funded and followed up for perioperative and late death, graft-related complications, reinterventions and resource use until September 2009 (average follow-up 7 years). Ethics approval for extended follow-up beyond this time was from the North West Multicentre Research Ethics Committee, UK. From September 2009, patients in both trials were followed up until 30 June 2015 for mortality. All patients were flagged for mortality at the Office for National Statistics who supplied the central trial office with centrally coded death certificates, which were all reviewed by an independent Endpoint Committee without knowledge of trial or study group assignment.

Because of diminishing patient attendance for follow-up and imaging, patients in EVAR-1 were followed for graft-related reinterventions until 31 March 2015, also using record linkage to administrative data for hospital readmissions and reinterventions via Hospital Episode Statistics (HES). Reinterventions, now including incisional hernia repairs throughout the trial and other operative procedures preceding death, were checked with the trial centres, with 89% concordance between administrative and clinical site data. For this extended follow-up of patients, the grading of aneurysm-related reinterventions and the associated use of high-dependency or intensive care were obtained by questionnaire to the principal investigators at the trial centres. Graft-related complications for both trials were obtained directly using a new case record form for late follow-up.

Statistical analyses were carried out according to predefined statistical analysis plans with the primary analysis by randomised group, but analyses were also performed for per-protocol comparisons. Cox regression models were used to analyse all-cause and aneurysm-related mortality as well as graft-related reinterventions. For EVAR-1, aneurysm-related costs over the trial period were calculated from trial resource use, standard NHS unit costs and manufacturers' list prices. Cost-effectiveness of EVAR compared with OR was estimated over the lifetime of the patients using decision modelling. A Markov model was used to estimate the cost of surveillance, reinterventions, aneurysm-related deaths and other-cause deaths. The perspective was the UK NHS at 2014–15 prices. Health outcomes were measured in quality-adjusted life-years (QALYs). The base-case model was based primarily on the results of EVAR-1. Sensitivity analyses considered alternative scenarios. The probability that the intervention was cost-effective was estimated using Monte Carlo simulation.

A two-stage individual patient data (IPD) meta-analysis was performed to combine results from the four trials comparing EVAR with OR (EVAR-1, DREAM, OVER and ACE). Cox regression analyses were conducted separately within each trial and then hazard ratios (HRs) were pooled using random-effects meta-analysis with between-study heterogeneity estimated using the method of DerSimonian and Laird. The effect of type II endoleaks in EVAR-treated patients on subsequent survival was investigated by including the detection (and/or treatment) of a type II endoleak as a time-dependent covariate in a Cox model.

The association between the growth of a postoperative aneurysm sac and the risk of future complications was investigated by fitting a linear mixed model to repeated sac diameter measurements for patients undergoing EVAR in EVAR-1. Estimates of current sac diameter and rate of growth were then used in a subsequent Cox model, predicting future complications at landmark times of 2, 3 and 5 years post operation.

Results

EVAR trial 1 extended follow-up

From 1 September 1999 to 31 August 2004, we recruited 1252 patients to participate in EVAR-1; participants were equally and randomly assigned to the two treatment groups. By 30 June 2015, only four patients were lost to follow-up for mortality and 25 for reinterventions, with data now available from record linkage for 13 of 17 patients previously lost to mortality follow-up. For 13 individuals, a cause of death was established based only on a death certificate. Annual clinical follow-up with a computed tomography scan or duplex imaging reduced steadily over the period of the trial and was consistently lower in the OR group. Out of the 724 patients still under follow-up in September 2009, 655 (90%) were tracked with HES, with local clinical follow-up reported in 48 of 69 (70%) of the remaining patients. After publication of 30-day mortality results, 26 of the 37 trial centres remained in equipoise and continued recruitment into a separate study from 1 September 2004 to 15 June 2005, when the primary outcome results were published, with a further 175 patients not reported previously but now used in sensitivity analyses for mortality only.

During 9968 person-years of follow-up, 910 deaths occurred (101 of which were aneurysm related). Overall, aneurysm-related mortality was 1.1 deaths per 100 person-years in the EVAR group and 0.9 deaths per 100 person-years in the OR group [adjusted HR 1.31, 95% confidence interval (CI) 0.86 to 1.99; $p = 0.21$]. For total mortality, there were 9.3 deaths per 100 person-years in the EVAR group and 8.9 deaths per 100 person-years in the OR group (adjusted HR 1.11, 95% CI 0.97 to 1.27; $p = 0.14$). There was evidence of deviation from the proportional hazards assumption for aneurysm-related mortality ($p < 0.001$), with an early benefit of EVAR during the first 6 months, counteracted by an increase in aneurysm-related mortality beyond 4 years, the difference being most marked beyond 8 years (adjusted HR 5.82, 95% CI 1.64 to 20.65; $p = 0.006$). There was also evidence of deviation from the proportional hazards assumption for total mortality ($p = 0.02$), with an early benefit of EVAR during the first 6 months, similar mortality between the groups from 6 months to 8 years, but thereafter an increase in mortality in the EVAR group (adjusted HR 1.25, 95% CI 1.00 to 1.56; $p = 0.05$). Aneurysm-related mortality curves cross over between 6 and 8 years and total mortality curves diverge after 10 years. Sensitivity analyses including the additional 175 patients from the separate 2004–5 study yielded very similar results.

During 9715 person-years of follow-up, there were 258 graft-related reinterventions performed in 165 patients in the EVAR group and 105 graft-related reinterventions performed in 74 patients in the OR group, with rates to first reintervention of 4.1 and 1.7 per 100 person-years, respectively (adjusted HR 2.42, 95% CI 1.82 to 3.21; $p < 0.001$). The reintervention rate was significantly higher in the EVAR group for any reintervention and serious reinterventions in the first 4 years and for life-threatening reinterventions (including conversion to OR, repeat EVAR and treatment of graft infection) in the periods 6 months to 4 years and beyond 8 years. Even after 2 or 5 years without any life-threatening reintervention, new life-threatening reinterventions occurred at any time to 15 years of follow-up. The relative difference in reintervention rate between the groups was highest in the period 6 months to 4 years after randomisation, particularly for the most serious reinterventions.

Overall mean costs over 14 years, including aneurysm repair, aneurysm-related reinterventions, surveillance and follow-up, were £19,845 in the EVAR group and £16,307 in the OR group (mean difference £3538, 95% CI £2059 to £5018). Decision modelling based on EVAR-1 showed that the lifetime difference in cost was £3616 and the difference in QALYs was 0.018, with a cost per QALY of £202,776. The cost per QALY exceeds conventional thresholds used in the UK. If EVAR is to be considered a cost-effective use of NHS resources, it needs to demonstrate fewer reinterventions and fewer late aneurysm deaths than were observed in the EVAR trial.

EVAR trial 2 extended follow-up

Over up to 15 years' follow-up in EVAR-2, the EVAR group was associated with a significantly lower rate of aneurysm-related mortality than no repair. Overall aneurysm-related mortality was 3.2 deaths per 100 person-years in the EVAR group and 6.5 deaths per 100 person-years in the no-intervention group

(adjusted HR 0.55, 95% CI 0.34 to 0.90; $p = 0.018$). Whereas the EVAR group was not associated with a lower rate of death from any cause at any time during follow-up, as the majority of EVAR-2 patients had a limited life expectancy. There was no significant difference in life expectancy (restricted to 12 years of follow-up) between the groups (4.2 years in both the EVAR and the no-intervention groups; $p = 0.99$).

Individual patient data meta-analysis of four randomised controlled trials of endovascular aneurysm repair compared open repair

A total of 2783 patients, with 14,245 person-years of follow-up were included in the IPD meta-analysis with a median follow-up of 6.0, 6.0, 5.4 and 3.1 years for EVAR-1, DREAM, OVER and ACE, respectively. Overall, there was no difference in total mortality over the follow-up period of the trials (pooled HR 0.99, 95% CI 0.87 to 1.13). Between 0 and 6 months, mortality was lower for the EVAR groups with 46 deaths compared with 73 deaths for OR (pooled HR 0.61, 95% CI 0.42 to 0.89), with no evidence of heterogeneity between the trials. After this, the early advantage of the EVAR group was lost and the HRs moved (non-significantly) in the direction of OR. The findings for aneurysm-related mortality were similar in direction.

There were two subgroups of patients who appeared to have no early benefit (to 6 months) under EVAR compared with OR: patients with moderate renal dysfunction and those with coronary artery disease. For those with above-median estimated glomerular filtration rate (eGFR), the pooled HR was significantly in favour of EVAR and was 0.42 (95% CI 0.21 to 0.84), compared with the less favourable and non-significant pooled HR of 0.68 (95% CI 0.43 to 1.08) for those with worse renal function (interaction $p = 0.024$). Similarly, patients with coronary artery disease gained no early advantage of being in the EVAR group in comparison with patients without prior coronary artery disease (interaction $p = 0.047$).

Type II endoleaks and sac expansion

In the IPD meta-analysis, there was no overall evidence that type II endoleak in itself is associated with a higher rate of mortality, although, as previously shown, type II endoleak as part of the 'cluster' of complications is associated with secondary rupture. However, this suggests that it is other complications that are listed in the cluster that are important, and not type II endoleaks on their own. The cluster did define type II with sac expansion and it seems that sac expansion is the important factor here. A risk score developed to predict secondary rupture that used estimates of sac growth from a linear mixed model, was found to have good predictive accuracy (C-indices ranging from 0.755 to 0.846 depending on landmark time and prediction horizon chosen).

Conclusions and recommendations for research

Very long-term follow-up has shown that EVAR has an early survival benefit but an inferior late survival benefit compared with OR, which needs to be addressed by lifelong surveillance of EVAR and reintervention, if necessary. EVAR does not prolong life in patients unfit for OR and its role in those only marginally fit for OR merits further investigation. Type II endoleak alone is relatively benign, but when type II endoleak is associated with the so-called 'cluster' it is far from a benign condition.

Based on the long-term evidence from EVAR-1 and other RCTs, EVAR is more costly over the patient's lifetime. In order for EVAR to be considered effective and cost-effective, an area of further research is to find better ways to target reintervention of patients who are at risk of secondary rupture and avoid reintervention in patients at very low risk. Our early findings suggest that an algorithm could be developed based on annual measurements of aortic sac diameter only. This might have excellent predictive value for future rupture. If effective, it would need substantial validation on a separate cohort of patients.

Trial registration

This trial is registered as ISRCTN55703451.

National ethics approval for extended follow-up to 15 years was obtained from the North West Multicentre Research Ethics Committee (MREC) on 11 February 2011 (MREC reference number 98/8/26 for EVAR-1 and MREC reference number 98/8/27 for EVAR-2).

Funding

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Chapter 1 Introduction

Scientific background

Abdominal aortic aneurysm

Abdominal aortic aneurysm (AAA) is defined as a localised enlargement of the abdominal aorta, such that the diameter is > 3 cm or > 50% larger than the normal diameter.[1–3] It was recognised if an aneurysm is found in one site, there is an increased chance of one being found elsewhere in the arterial tree. The commonest by far is AAA and patients with it have increased chance of thoracic aortic aneurysm and also popliteal aneurysm. It was soon recognised that all of the arteries of patients with aneurysms are wider and the term 'dilating' arterial disease was used.[4] In addition, it was described as 'arteriomegaly'.[5] To support the concept that there were other causative factors of dilatation, diabetes mellitus was found in only 1% of 'dilating disease patients'.[4]

Epidemiology and risk factors

Abdominal aortic aneurysm is a common condition affecting particularly men aged > 60 years. In the second half of the twentieth century, there was a steady increase in mortality from aortic aneurysm in England and Wales.[6–8] According to population screening studies using ultrasonography, the prevalence of aortic aneurysm among 65-year-old men is 4%.[9] In the 65–74 years age group, the prevalence increases to 5% in men and to about one-third in women.[10] Following these reports, aneurysm screening programmes, usually of men aged 65 years, were implemented in several countries. These programmes have now reported a much lower prevalence of 1.9% in England and 1.7% in Sweden, respectively.[11,12] As well as the decline in incidence of clinically relevant aneurysms in men in England, Wales and Scotland, the age at which these aneurysms present has increased by 5–10 years.[13] Reports from other countries also show that aneurysm-related mortality is no longer increasing.[14–16]

Increasing age and male gender are known to be the strongest associated risk factors. Other risk factors associated with AAAs include smoking and ethnicity. The wall weakens as a result of loss of elastin and collagen[17] or fibrillin[18] and the dilating process associated with more inflammation.[19]

Age, sex and ethnicity

The risk of aneurysm increases dramatically after 60 years of age. Clinically relevant aneurysms (> 4 cm in diameter) are present in approximately 1% of men aged between 55 and 64 years, and the prevalence increases by 2–4% per decade thereafter.[20,21] In the UK, the rate of aneurysm in Caucasian men aged > 65 years is about 4.7%. Rupture of the aneurysm occurs in 1–3% of men aged ≥ 65 years, with a mortality rate of 70–95%. This equates to around 3000 deaths from rupture each year in men aged ≥ 65 years in England and Wales. Aneurysms are much less common in individuals of Asian and African descent. However, when adjusted for age, the rate of aneurysm-related mortality is higher among African Americans than in Caucasians.[22] Other studies have shown that the Asian population (men and women), who tend to be of smaller stature, are disadvantaged when being considered for endovascular aneurysm repair (EVAR), as the presence of smaller vessels is not conducive to easy deployment or long-term durability of the grafts.[23,24]

Abdominal aortic aneurysms are four to six times more common in men than in women.[25] In addition, aneurysms develop in women approximately a decade later than in men. However, there is evidence that for women the risk of rupture, growth rates and operative mortality are all higher.[25–30]

Smoking

Smoking has been found to be the principal risk factor for aneurysm formation, growth and rupture.[31,32] It is a much stronger risk factor than for coronary artery disease. The duration of exposure rather than the

level of exposure appears to determine the risk of the development of an aneurysm in men aged > 50 years. The slow decline of risk after the cessation of smoking and the higher relative risk for small compared with large aneurysms suggests that smoking is a direct causative factor.[32]

Other risk factors

Patients with aneurysms frequently have atherosclerosis, and numerous studies show an association with coronary heart disease and peripheral atherosclerosis.[33,34] A host of other risk factors, such as poor lung function,[35] hypertension and high cholesterol levels,[36,37] have been suggested to increase the risk of aneurysmal development, although there are conflicting reports in the current literature. A positive family history, especially in male first-degree relatives, is also associated with increased risk of aneurysm.[38,39] Studies suggest lower prevalence of diabetes for dilating (aneurysmal) disease, stenosing arterial disease and a protective role for diabetes on the development of aneurysms.[4] Diabetes has also been associated with slower aneurysm growth rates.[37,40,41]

To obtain insight into the pathological processes associated with the vascular remodelling that accompanies aortic dilatation, early work in our group compared the histological features and the activity of matrix metalloproteinases (MMPs) in aneurysm biopsies.[19] The histological feature most clearly associated with enlarging aneurysm diameter was a higher density of inflammatory cells in the adventitia. This inflammation was non-specific. We also identified gelatinase A (MMP-2) as the principal metallogelatinase in small aneurysms and an increasing activity of gelatinase B (MMP-9) in large aneurysms. This early work identified that the recruitment of inflammatory cells into the adventitia, with subsequent elaboration of metalloproteinases, including gelatinase B, may contribute to the rapid growth and rupture of larger aneurysms.

We also found that a strong interaction occurs between fibrillin genotype and blood pressure and that this contributes to the development of aneurysmal disease.[18] Marfan syndrome is a congenital disorder of connective tissue that is associated with various systemic complications, and the defective gene has been mapped to the fibrillin-1 (*FBN1*) gene on chromosome 15.[42]

Our group was also involved with early work exploring genetic variants of collagen III and AAA. Variations in collagen structure were recognised in Ehlers–Danlos syndrome type IV and could also be associated with a predisposition to aortic aneurysm. We reported, in 1991, that genetic variants of type III collagen may influence the extensile properties of the aortic wall and that mutations in the type III collagen gene may be associated with aortic aneurysms.[17] More specifically, variation at the haptoglobin locus could have a direct effect on the degradation of elastin in atherosclerotic aorta, whereas variation at the cholesteryl ester transfer protein locus could affect lipid metabolism and promote atherosclerosis. These results indicated that a gene on chromosome 16 was associated with aortic aneurysm.

Around the same time, Irizarry *et al.*[43] demonstrated the presence of interstitial collagenase [now known as matrix metalloproteinase 1 (MMP-1)] in specimens of AAAs and Curci *et al.*[44] reported that, because elastin represents a critical component of aortic wall structure and a matrix substrate for metalloelastases, human macrophage elastase may have a direct and singular role in the pathogenesis of aortic aneurysms.

Aneurysms result from chronic weakening of the arterial wall, and approximately 80% occur between the renal arteries and aortic bifurcation. Aneurysmal expansion can also be found in the suprarenal segment and can sometimes extend upwards into the thoracic segment of the aorta above the diaphragm or downwards beyond the aortic bifurcation into the common iliac arteries. When the aneurysm becomes large, it may be diagnosed by examining the abdomen of the supine patient and feeling for a large pulsatile mass. Large aneurysms in thin people are easy to detect, but the accuracy of the clinical examination is much reduced by obese body habitus and small aneurysm size.[45] There is also large variability in the interobserver sensitivity for detection of aneurysms, and even an experienced clinician may miss palpating an aneurysm in the presence of central obesity or abdominal distension.[46]

The majority of aneurysms are asymptomatic and, if undetected, the aortic dilatation can continue for many years. It can lead to catastrophic rupture, which is fatal in > 80% of cases. If left untreated, aneurysms have been known to grow to very large sizes, up to ≥ 15 cm, and, in rare cases, have ruptured at more modest diameters as small as 3–4 cm. Large and life-threatening aneurysms are preceded by a long period of subclinical growth in the diameter of the aneurysm (about 1.6 mm/year on average). Although diagnosis is usually incidental, expansion may become painful and lead to pulsating sensations in the abdomen or pain in the chest, lower back or groin.

The treatment options for asymptomatic aneurysms are conservative management, surveillance with a view to eventual repair and immediate repair. Repair is indicated if the aneurysm is > 5.5 cm, grows > 1 cm per year or is symptomatic (tender).[47,48] The successful management of the condition depends on the clinician finding the correct balance between careful surveillance of the aneurysm diameter until it enlarges to a point at which the risk of rupture is deemed to exceed the risk of death from elective surgery.

Detection and treatment of abdominal aortic aneurysm

Detection and screening

Owing to the asymptomatic nature of the disease, a considerable number of cases present as an emergency following a rupture, which has only a 10–20% survival rate.[49] The in-hospital survival rate for treating a ruptured aneurysm is just above 50%, but many patients never have the opportunity to undergo surgical intervention.[21]

As the condition is not always found early, population screening programmes have been set up. The basis for such programmes is the known increased risk of rupture for aneurysms > 5.5 cm, whereas neither open surgery[50,51] nor endovascular repair[52] is of benefit for aneurysms of 4.0–5.4 cm. Both of these aneurysms being more common in men, the number of women affected is much lower and, therefore, the real threshold of intervention could be lower in women, though trial data do not show this.[53]

The method of population screening is based on ultrasound. Duplex ultrasound scanning of the abdomen is safe, inexpensive and non-invasive. Ultrasound-based assessments quantify the maximal anterior–posterior and transverse diameter of the aorta. Among asymptomatic patients, ultrasound detects the presence of aneurysms accurately and reproducibly. Sensitivity and specificity are both close to 100% when compared with operative findings, making ultrasound an ideal test for mass screening.[54,55]

Ellis *et al.*[56] showed that variability can be 8 mm if a different operator or system is used, but 4 mm for the same operator and ultrasound system. In the UK Small Aneurysm Trial,[57] trained nurses had a reproducibility of 2 mm. The UK Small Aneurysm Trial[57] and Aneurysm Detection And Management (ADAM)[51] trial criterion of 5.5 cm was based on an outer-to-outer front-to-back ultrasound measurement. Scott *et al.*,[58] for UK screening, chose inner to inner.

However, when assessing aneurysm size, ultrasound is less precise than computed tomography (CT). Reproducible measurement of aneurysm size is important because it is the single component of prognosis and also because it provides a baseline to determine the aneurysm growth rate. An aneurysm growth rate of > 1 cm/year has been suggested as a threshold for surgery irrespective of size,[59] even though there is no evidence to suggest that the growth rate influences rupture risk independently of aneurysm size.

The efficiency of ultrasound-based screening in men aged ≥ 65 years has been very well demonstrated in population-based randomised controlled trials (RCTs) and subsequent meta-analyses.[60–67] The aneurysm-associated mortality rate, the number of ruptured aneurysms and the number of emergency operations can be reduced significantly by a single ultrasound examination in men over the age of 65 years. At the same time, there is a two- to threefold increase in the number of elective aneurysm operations. In the UK, The NHS Abdominal Aortic Aneurysm Screening Programme[68] was introduced after research and analysis of data from a number of randomised trials and existing local screening programmes in England that

showed a reduction in aneurysm-related mortality when men aged ≥ 65 years were offered ultrasound screening. The evidence was assessed by the UK National Screening Committee against a set of internationally recognised criteria that confirmed that screening all men aged ≥ 65 years saves lives. The programme is aimed at reducing deaths from ruptured aneurysms through early detection, appropriate monitoring and treatment. The introduction of aneurysm screening to men aged 65 years is estimated to reduce premature death from ruptured aneurysms by up to 50% over 10 years. The prevalence of aneurysms in men is three times higher than in women and, currently, there is no good evidence to support aneurysm screening in older women.

Investigation of abdominal aortic aneurysm for possible intervention

In the EVAR trials, CT was used to investigate the suitability of aneurysms for intervention. Initially, three-dimensional scanning was not well advanced, but the technique greatly improved with time, and with it the interpretation of the findings and sizing of the infrarenal aorta.

Follow-up after aneurysm repair

At the beginning of the EVAR trials, routine follow-up of AAAs, even annually, was not usual and patients with open repair (OR) were frequently discharged to primary care. Ultrasound gathered favour with relation to population screening and detection.

Intervention for aortic aneurysm

Intervention for aortic aneurysm depends on the size or diameter of the aneurysm and is a balance between the risk of rupture and the operative mortality for aneurysm repair. Appropriate patient selection and timing of repair for the aneurysm is based on identifying individuals at the greatest risk of aneurysm rupture. Patients undergoing surgical intervention have immediate perioperative risks that must be weighed against the low likelihood of rupture before death from other causes.[69]

Frequency of screening

Most people with aneurysms in the diameter range 3.0–5.5 cm are kept under review in surveillance programmes. There is consensus that very small aneurysms (3.0–3.9 cm) have a very small risk of rupture and, therefore, do not require surgical intervention. Most aneurysms initially measuring < 40 mm are very unlikely to expand to a size necessitating repair within 5 years,[70] and patients with aneurysms of this size should receive ultrasound surveillance at regular intervals. Over the last two decades longitudinal studies of patients with smaller aneurysms have provided insights into the ideal timing of repair and the need for, and frequency of, ultrasound surveillance if an expectant management strategy is followed. A Cochrane review summarising the results from four trials to date demonstrated no advantage to early repair (via open or endovascular surgery) for small aneurysms in the range 4.0–5.5 cm. A policy of ultrasound surveillance is also advised as the 'best care' for patients with asymptomatic aneurysms of this size.[48] Once the aneurysm reaches 5.5 cm (measured by duplex ultrasound in males) or the aneurysm growth rate exceeds 1 cm per year, it is recommended that a vascular surgeon review the patient immediately (or within 2 weeks) to prevent interval rupture. If fit enough for surgery the patients should be considered for elective surgical repair at this juncture. For females, a maximum aortic diameter of 5.0 cm, as measured by duplex ultrasound, is considered to be the point at which a referral to a vascular surgeon is mandated.

Treatment of abdominal aortic aneurysm once detected

Medical therapy

Patients diagnosed with AAA who do not meet the criteria for intervention at the time of the initial diagnosis should be managed conservatively based on the results of randomised trials. The criteria for intervention are an aneurysm diameter of < 5.5 cm, a growth rate of > 1 cm per year or a tender aneurysm.[50] However, the natural history of aneurysms is one of progressive expansion necessitating regular clinical evaluation and surveillance of aneurysm diameter to identify aneurysms that satisfy the criteria for justified intervention.

Medical therapies focus on the management of modifiable risk factors for aneurysm and cardiovascular disease with the goals of reducing the need for intervention as a result of aneurysm expansion or rupture, reducing morbidity and mortality associated with repair, and reducing cardiovascular morbidity and mortality.[71] Although many pharmacological therapies aimed at limiting aneurysm expansion and preventing rupture have been investigated, currently there is no proven focused therapy that reduces aneurysm growth. A systematic review and meta-analysis investigating the impact of a range of pharmaceutical agents (including beta-blockers, other antihypertensive therapies, antibiotics and anti-inflammatory agents including statins) demonstrated little evidence of reduction in aneurysm growth rates.[72] Among the factors associated with aneurysm expansion and rupture, smoking is the most important modifiable risk factor and smoking cessation is recommended for all patients with aneurysms.[73] Although reduced aneurysm expansion and rupture risk have not been clearly demonstrated among those who have stopped smoking, smoking cessation has other benefits. In addition, because aneurysm is regarded as a coronary risk equivalent, most guidelines recommend aspirin, statins and antiplatelet therapy for patients with aneurysms to reduce the risk of a future cardiovascular event. Other medical conditions, such as hypertension, should be treated as appropriate. In general, there is surprisingly little high-quality evidence on medical treatment for small aneurysms, especially in relation to the use of newer beta-blockers, angiotensin-converting enzyme inhibitors and statins.[74]

Open surgical repair

For patients whose AAA satisfies criteria for intervention, OR was regarded as the gold standard before these UK trials. It involves an incision of the abdomen to directly visualise the aortic aneurysm. Dubost *et al.* described how the technique involves access either through a transabdominal route or via a retroperitoneal approach.[75] During OR the aneurysmal portion of the aorta is replaced with a graft, usually made of DACRON® (Invista™, Wichita, KA, USA) or polytetrafluoroethylene.[76] The graft is sutured within the aorta. The DACRON is anastomosed to the aortic neck and either to the aortic bifurcation below (tube graft) or to the two iliac arteries (bifurcation device).

Recovery after OR is substantial and, in the UK, operative mortality has been reported to be 5.6%.[47] Immediately following surgery, patients can expect to spend 1–3 days in the intensive care unit (ICU), followed by 4–10 days on the hospital ward. After discharge, patients will take 3–6 months to fully recover their energy and return to their preoperative daily activities.

Advent of endovascular aortic repair

Before the advent of EVAR, OR was the only surgical treatment available for aortic aneurysms. In the spring of 1990, word came of a novel endovascular technique which was later reported in 1991 by Parodi *et al.* in Argentina.[77] However, it later transpired that Volodos *et al.* in the Ukraine (at the time of the Soviet Union), a student of Dotter, had already done such a procedure, unknown to the Western world.[78]

By 1996 it was evident that commercial EVAR devices would become available shortly. The urge was to learn the new device method, but it would require comparison with OR for those patients medically fit for OR, although Parodi *et al.*[77] had championed the method for those patients not fit enough for OR.

The EVAR trials [EVAR trial 1 (EVAR-1) and EVAR trial 2 (EVAR-2)] were set up to meet the above need and funded by the Health Technology Assessment (HTA) programme under the then director, Sir Miles Irving.

Even though a registry of devices was also introduced at about the same time,[79] this lacked the RCT discipline of comparison with the then alternative. Sir Miles Irving called for, and delivered, device funding by NHS subventions such that the only way to achieve funding was as part of the EVAR trials. The shorthand for the procedure was taken from these world-first trials: 'EVAR'.

A feature of the trials was for complete endorsement by the Vascular Surgical Society of Great Britain and Ireland and the British Society of Interventional Radiology. Together these societies recommended collaboration of both disciplines for the trial and together the societies founded the EVAR trial centres.

Endovascular aneurysm repair was seen as a minimally invasive option which involves the insertion of a stent graft into the lumen, effectively excluding the aneurysm from blood flow and minimising the risk of rupture. The concept of endograft is to deploy inside the aneurysm through femoral access to exclude the aneurysm sac from circulation. EVAR requires adequate aortic and iliac fixation sites for effective sealing and fixation. The first devices were assembled in the sterile operating room and deployed. There was inevitable delay before commercial higher-quality devices became available. The earliest systems used handmade stent grafts that allowed a repair to lie entirely within the abdominal aorta (aortoaortic graft). Subsequently, it was shown that the aortoaortic endovascular grafts were suitable for < 10% of patients and bifurcation systems were developed; these allowed a greater proportion of aneurysms to be managed by an endovascular method.[80] In-house systems were introduced in the UK that employed an aorto-uniiliac stent graft system made with the second side being occluded using a DACRON sac and stent and the procedure completed with a femoro–femoral crossover graft.[81,82] This left patients with two small incisions in the groin and minimum pain. These in-house systems were soon superseded as commerical higher-quality devices became available.

The imagined advantages of EVAR over OR included reduced operative time, avoidance of general anaesthesia, less trauma and postoperative pain, reduced hospital length of stay and use of intensive care facilities, reduced blood loss and reduced immediate postoperative mortality.

Post-surgical surveillance

The European Society for Vascular Surgery, in agreement with the EVAR protocol, recommends that all EVAR patients should undergo CT 30 days post procedure. If there is any endoleak, then further CT at 6 and 12 months is recommended. In patients with no early endoleak and stable or shrinking aneurysm, annual duplex ultrasound scanning is recommended. Any subsequent new endoleak or increase in aneurysm sac size should prompt more detailed imaging with CT.[83] Many clinicians now follow patients almost exclusively by ultrasound to measure maximum aneurysm diameter and obtain further imaging only if the sac fails to shrink or expands > 5 mm.

Currently, the European Society for Vascular Surgery recommends colour duplex ultrasound imaging at least once every 5 years following OR.[83] Imaging protocols following EVAR are controversial and currently the topic of much debate.

Endoleaks

The inability to obtain or maintain a secure seal between a vessel wall and a transluminally implanted intra-aneurysmal graft was a complication unique to the evolving technique of endovascular aneurysm exclusion. As the term 'leak' had long been associated with aneurysm rupture, the term 'endoleak' was proposed as a more definitive description of this phenomenon. White *et al.*[84] first proposed standardisation of the terminology describing this important sequela to endovascular aneurysm exclusion. This was important to facilitate uniform reporting of clinical trial data vital to the evaluation of this emerging technique.

Endoleaks represent the most common complication of EVAR and occur in 20–25% of patients.[85,86] They are frequently identified in late imaging follow-up and used to justify lifelong follow-up of these patients. If left untreated, endoleaks can lead to fatal ruptures.[87] There are five different types of endoleaks, all of which are characterised by persistent blood flow within the aneurysm sac but outside the stent graft.[88] The classification is determined by the source of vessels that causes the inflow into the sac. Type I endoleaks are leaks at the proximal aorta and stent graft (type IA) or leaks at the distal iliac and stent graft limb (type IB). Type II endoleaks are caused by retrograde flow through collateral vessels into the aneurysm sac. Type III endoleaks are holes, defects or separations in the stent graft material. Type IV endoleaks represent porous graft walls. Type V endoleaks have been described as being as result of endotension with an enlarging aneurysm sac without a visible endoleak.[89] Other complications that can occur after EVAR include device migration[90–92] and postoperative stent graft kinking.[93] CT angiography has been the most commonly used modality for follow-up after EVAR and is currently the best method for detecting endoleaks.

Clinical trials comparing endovascular aneurysm repair and open repair

We searched MEDLINE and EMBASE for all articles published from 1 January 2000 to 31 May 2016 using search terms '15 year follow-up of EVAR for intact abdominal aortic aneurysm', 'long-term elective repair', 'abdominal aortic aneurysm', 'minimally invasive surgery', 'vascular surgical procedures', 'endovascular surgery' and 'open surgery'.

EVAR trial 1, the first and largest randomised trial of endovascular aortic repair compared with OR of aortic aneurysms, began in 1999, alongside its sister trial EVAR-2, to evaluate the efficacy of endovascular repair in patients too frail to be considered for OR and compared best medical therapy with endovascular aortic repair.[94–96] A number of trials have now been undertaken to compare endovascular with OR, but EVAR-2 remains unique in addressing the question of whether or not endovascular repair is justified in patients in whom OR is not an option, usually on the grounds of poor anaesthetic fitness. Other randomised clinical trials with protocols like that of EVAR-1, comparing open and endovascular repair, followed in the Netherlands [the Dutch Randomised Endovascular Aneurysm Management (DREAM) trial],[97] USA [Open Versus Endovascular Repair (OVER) trial][98] and France (Anévrysme de l'aorte abdominale, Chirurgie versus Endoprothése; ACE).[99]

EVAR trial 1

Before the current report of late follow-up to 15 years, EVAR-1 offered the longest follow-up of any of the RCTs comparing EVAR with OR up to 10 years. Early 30-day results were reported in 2004,[100] mid-term results in 2005[101] and long-term follow-up over 8 years (median 6 years) in 2010.[94] Baseline characteristics were not significantly different between treatment groups. The perioperative (30-day) mortality was significantly lower for EVAR (1.8% vs. 4.3%). During 6904 person-years of follow-up, 524 deaths occurred, 76 of which were aneurysm related. Kaplan–Meier survival curves for all-cause mortality among the two cohorts converged at 2 years, demonstrating that the survival advantage favouring EVAR is lost. With regard to aneurysm-related mortality, Kaplan–Meier curves converged at 6 years because of endograft failure leading to late rupture-related mortality, increasing substantially in the EVAR group. Secondary outcomes including graft complications, reinterventions and costs favoured OR over the long term. Although there was a health-related quality of life (HRQoL) benefit with EVAR at 3 months, this benefit was lost at 1 year. Based on these findings, the EVAR-1 investigators concluded that, although EVAR offered lower operative mortality, there was no difference in total or aneurysm mortality. Furthermore, EVAR was associated with increased rates of complications, reinterventions and costs.

The Dutch Randomised Endovascular Aneurysm Management trial

One year after the start of EVAR-1, the DREAM trial, which used a similar protocol to EVAR-1, began enrolling patients from 26 centres in the Netherlands and four centres in Belgium. Three hundred and fifty-one patients whose maximum aneurysm diameter was > 5.0 cm and who were deemed to have acceptable risk for both procedures were randomised to undergo either open or endovascular repair. Operative mortality was reported in 2004, 2-year follow-up in 2005 and long-term follow-up in 2010.[97,102–104] The primary study outcomes were rates of death from any cause and reinterventions. The 30-day postoperative mortality was 1.2% after EVAR and 4.6% after OR. At 2 years post procedure, the cumulative rates of aneurysm-related death remained lower for EVAR than for OR (2.1% vs. 5.7%), a difference that was entirely attributable to the initial perioperative outcomes.[104] Survival curves for all-cause mortality converged at 1 year and, by the end of follow-up, all-cause mortality was equivalent between groups. As with the EVAR-1, the rates of graft-related complications and reinterventions were higher after EVAR.

The Open Versus Endovascular Repair trial

The OVER trial was the first RCT in the USA and enrolled patients between 2002 and 2008 from 42 Veterans Affairs Medical Centres. Again, trial design was based on that of EVAR-1 but only men were recruited. Eight hundred and eighty-one patients with an aneurysm of maximum diameter > 5.0 cm, an iliac aneurysm of diameter > 3.0 cm or an aneurysm of diameter > 4.5 cm and rapid enlargement

(> 0.5 mm in 6 months), were randomised to undergo either open or endovascular repair. Interim data analysis was reported in 2009 and long-term results in 2012.[98,105] The primary study outcomes were procedure failure, secondary therapeutic procedures, length of stay, quality of life, erectile dysfunction, major morbidity and death. The 30-day mortality was 0.5% after EVAR and 3.0% after OR. Survival curves converged at 2 years and over 9 years of follow-up, mortality rates were not significantly different between groups (7.0% EVAR vs. 9.8% OR). There were no differences between the two groups in major morbidity, procedure failure, secondary therapeutic procedures, aneurysm-related hospitalisations, HRQoL or erectile dysfunction. In this trial, incisional hernia was included as an OR-related complication. As a result, the rates of secondary intervention were found to be similar between groups (13.7% EVAR vs. 12.5% OR), with the majority of secondary procedures in the EVAR group as a result of endovascular revisions compared with repair of incisional hernia in the OR group.

The Anévrysme de l'aorte abdominale, Chirurgie versus Endoprothése trial

The fourth RCT, with a similar design to EVAR-1, was the ACE trial, which randomly assigned 316 patients with an aneurysm > 5.0 cm to EVAR or OR surgery.[99] As with the trials above, there were no significant differences in the cumulative survival or major adverse events rates at the 1 year' follow-up and at 3 years' follow-up. In contrast to the other three trials, operative mortality was also not significantly different (0.6% EVAR vs. 1.3% OR). The need for reintervention was higher in the EVAR group than in the OR group (16% vs. 2.4%).

EVAR trial 2

Unlike EVAR-1, EVAR-2 remains unique and its publication altered global practice. Endovascular repair of AAA was originally developed for patients who were considered to be physically ineligible for open surgical repair. Whereas the four previously described major RCTs enrolled patients who were physically fit enough to undergo either EVAR or OR, EVAR-2 enrolled patients who were too high risk for open surgical repair, randomising such unfit patients to EVAR or observation. The enrolment protocol and data collection methods were identical to those of EVAR-1.[106] Three hundred and thirty-eight patients were enrolled and randomised between September 1999 and December 2003.[107] After mid-term analysis on this cohort, an additional 66 patients were recruited for long-term follow-up, giving a total of 404 patients.[95] A total of 197 patients were randomised to EVAR while 207 were assigned to have no intervention. However, of the 207 patients in the observation arm, 70 eventually underwent some form of aneurysm repair attributable to rupture, rapid growth, symptomatic aneurysm or patient preference. Patients were followed for rates of death, graft-related complications and reinterventions, and costs up to the end of 2009. The 30-day operative mortality was 7.3% in the EVAR group. The overall rate of aneurysm rupture in the no-intervention group was 12.4 per 100 person-years. Aneurysm-related mortality was lower in the EVAR group, but this advantage did not result in any benefit in terms of total mortality. A total of 48% of patients who survived endovascular repair had graft-related complications, and 27% required reintervention within the first 6 years. During 8 years of follow-up, endovascular repair was considerably more expensive than no repair (cost difference £9826).

After the 10-year results of EVAR-2, the funding and enthusiasm for EVAR use in situation dropped as these HTA-funded trials had shown that no operation was not only giving false hope, unnecessary cost and no change in the expected date of death. The per-protocol analysis hinted at some benefit in patients who actually underwent EVAR.

Evidence outside the trials

Outside the evidence from these trials, Schermerhorn *et al.*[108] recently assessed perioperative and long-term survival, reinterventions and complications after EVAR compared with OR of AAA in propensity score-matched cohorts of Medicare beneficiaries who underwent repair during the period 2001–8 and were followed until 2009. The authors found that endovascular repair, compared with OR, was associated with early survival advantage that gradually decreased over time, with catch-up of mortality after 3 years. The rate of rupture after aneurysm repair was significantly higher under EVAR than OR.

A recent observational study from a single institution in Queensland, Australia,[109] reported no differences in 5-, 10- and 15-year survival rates between OR ($n = 982$, median follow-up 6.5 years) and EVAR ($n = 358$, median follow-up 4.0 years), but suffered from incomplete patient reporting. The EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair (EUROSTAR) database has reported that rate of secondary sac rupture after EVAR is low for the first 4 years, but after this time the rate appears to increase, particularly in those with known sac expansion.[110] A previous report from the EVAR trials defined a 'cluster' of findings (type I endoleak, type III endoleak, type II endoleak with sac expansion, kinking and migration), which was associated with secondary sac rupture with 67% risk of death.[111]

There has been no previous comprehensive report of very long-term follow-up of EVAR or OR beyond 10 years. EVAR-1 reported follow-up for aneurysm-related and total mortality for a period of 8 years,[94] at which point there was no difference between endovascular and open abdominal aneurysm repair and the problem of secondary sac rupture after EVAR, associated with 67% mortality, was just becoming apparent.[111] The original trial protocol stated that if concerns became apparent about the durability of EVAR, the trial should be extended to address this issue. In this report we present long-term results up to 15 years, of EVAR-1 in terms of aneurysm-related and total mortality, cause of death, aneurysm-related reinterventions and cost-effectiveness. We also report results up to 15 years for EVAR-2 in terms of overall mortality.

Rationale for follow-up from 10 years up to 15 years

In July 1999, the UK EVAR-1 and EVAR-2 trials were commissioned by the NHS research and development (R&D) HTA programme [now known as the National Institute for Health Research (NIHR) HTA programme]. The trials were funded for 4 years (from July 1999 to 2003), followed by a 2-year extension, which was granted to ensure that recruitment targets were met. Subsequently, long-term follow-up support was awarded for a further 5 years of follow-up until July 2010 (up to 10 years of follow-up). The trial objectives were to assess the safety and efficacy of EVAR against the established open surgical treatment in the management of large aneurysms of at least 5.5 cm diameter as measured using CT. Two trials were instigated: EVAR-1 would compare EVAR against OR in patients who were considered fit and suitable for both procedures and EVAR-2 would compare EVAR against no intervention for patients who were considered suitable for EVAR but unfit for OR. The primary outcome for both trials was mortality, with secondary outcomes of complications, reinterventions, HRQoL, adverse events, costs and cost-effectiveness.

In follow-up until December 2009, 27 sac ruptures had occurred after EVAR, carrying a 67% mortality rate. Type I endoleak, type III and type II with sac expansion, kinking and migration were identified as the 'cluster' of complications associated with these late EVAR secondary sac ruptures.[111] It is possible that the early aneurysm-related mortality benefit of EVAR is lost as a result of these late sac ruptures and death. If this trend were to continue, after 15 years, OR would have a lower aneurysm-related mortality than endovascular repair, even with every attempt made to intervene to correct known causes of sac expansion to reduce the risk of secondary rupture in EVAR patients. The possible future projection is shown graphically for EVAR-1 in *Figure 1*. The rationale for continuing follow-up to 15 years in EVAR-1 was to test this hypothesis. The primary outcome measure for the 15-year follow-up was aneurysm-related mortality and total mortality.

Our secondary outcomes included reinterventions (time to first reintervention, to first reintervention for a life-threatening problem and to first serious reintervention).

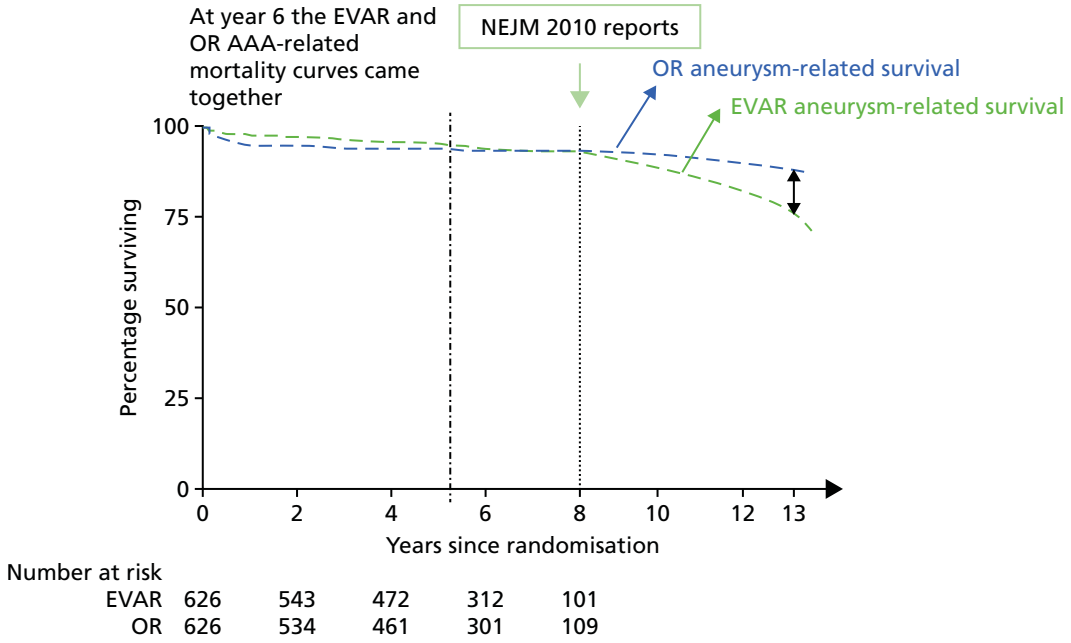


FIGURE 1 Projected aneurysm-related survival after 8 years of follow-up in EVAR-1 based on observed trends. NEJM, *New England Journal of Medicine*.

Other secondary outcomes included complications, cost and cost-effectiveness. The evaluation of cost-effectiveness of OR and EVAR after a 15-year time period is particularly pertinent because EVAR-related complications continue to occur many years after the original procedure. This objective required knowledge of continuing graft-related complications and use of hospital resources to the end of 2014.

Based on the 27 sac ruptures reported by Wyss *et al.*,[111] in 2010, it was hypothesised that sac growth after EVAR is associated with an increased risk of rupture and the presence of a significant complication or endoleak. It was therefore assumed that patterns of sac growth might predict the need for reintervention, even in the absence of a defined endoleak. A further outcome was therefore to investigate any association between sac growth (*Figure 2*) and secondary rupture, complication, endoleak and reintervention correction.

In 2012, there was a call with vignette (NIHR Evaluation, Trials and Studies Coordinating Centre – HTA) for addressing the question 'What is the optimal management strategy for type II endoleaks?' The then Director of the HTA programme, Professor Tom Walley, questioned whether or not the HTA-funded EVAR trials would produce data that could answer this question. The authors of the EVAR trials considered the Director's question and considered that an individual patient data (IPD) meta-analysis of EVAR-1, the DREAM trial, the OVER trial and ACE would produce much useful information and among it some on type II endoleaks. We informed the HTA programme that we would be able to address the question 'What is the optimal management strategy for type II endoleaks?' without requiring further data collection.

An IPD meta-analysis of four multicentre randomised trials of EVAR compared with OR was conducted to a prespecified analysis plan, reporting on mortality, aneurysm-related mortality and reinterventions.

Data from the IPD meta-analysis have been used to address the question of the management of type II endoleaks following EVAR.

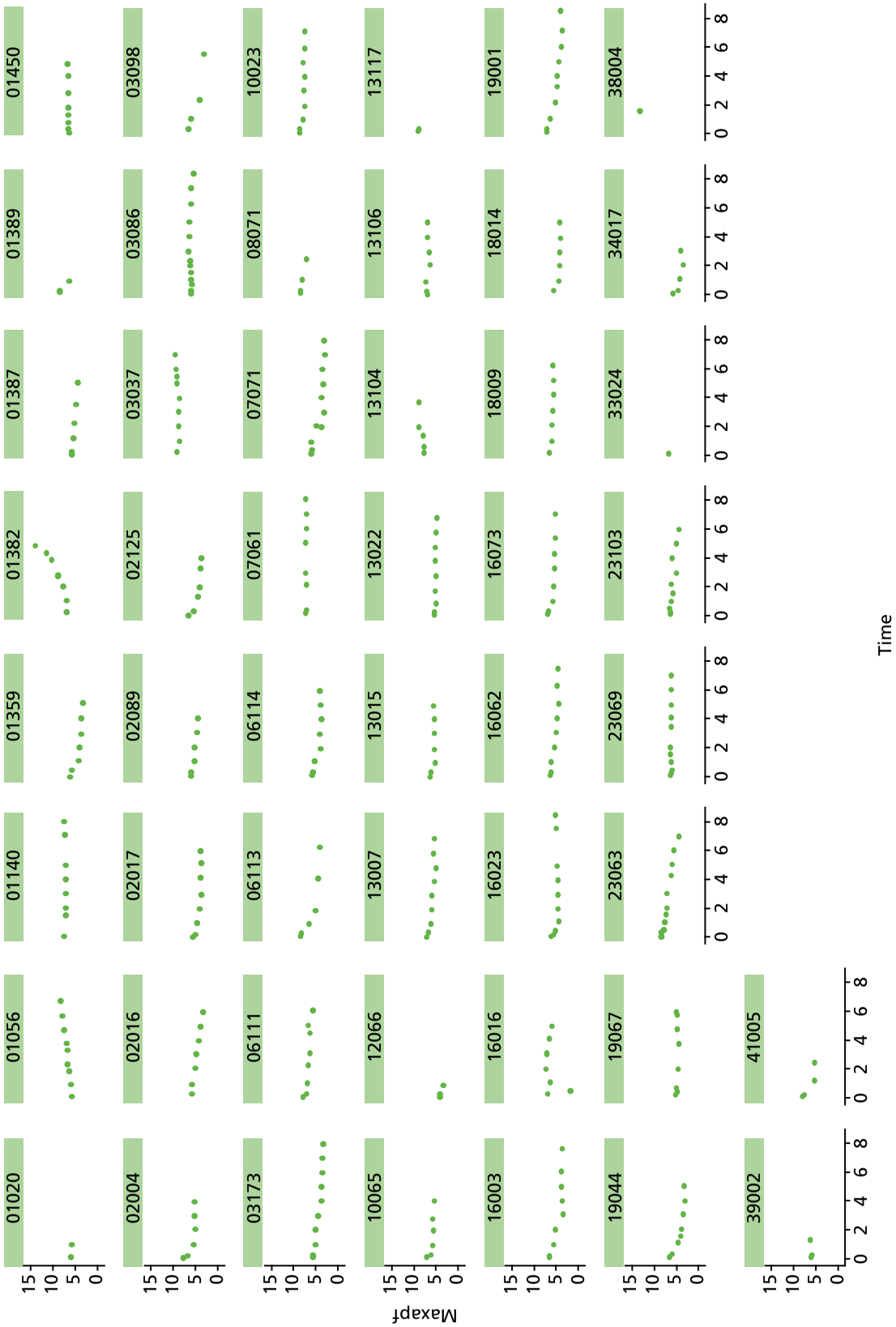


FIGURE 2 Change in sac diameter of a random selection of 50 patients (post-EVAR measurements only, preoperative measurements excluded). Graphs by ID.

Chapter 2 Methods

Detailed descriptions of the trial design, methodology and results after 10 years of follow-up have previously been reported, including an earlier HTA programme report which was published in February 2012.[96]

Participants

Men and women aged ≥ 60 years were enrolled into EVAR-1 between 1 September 1999 and 31 August 2004 from 37 hospitals in the UK. Twelve hundred and fifty-two patients whose maximum aortic aneurysm diameter was ≥ 5.5 cm, with aortic morphology compatible with endograft placement within the manufacturer's instructions for use (IFU) and who were deemed to have an acceptable risk of postoperative death for both procedures were randomised to undergo either OR or EVAR.

EVAR trial 2 was designed to address the question of whether or not endovascular repair reduces the rate of death among patients who were considered to be physically ineligible for OR. During the same time period, patients of both sexes who were at least 60 years of age with large aneurysms (≥ 5.5 cm in diameter) and who were deemed unfit for OR, were randomly assigned to undergo either EVAR or no repair.

Interventions

In EVAR-1, patients were randomised to undergo either OR or EVAR. In EVAR-2, patients were randomly assigned to undergo either EVAR or no repair.

Objectives

The objective was to follow up the world's first RCT of EVAR compared with OR with up to 15 years of follow-up; to reconvene the EVAR trial centres and brief them on the uncertainty of outcome versus OR in the very long term and to inform them of the risk of secondary rupture;[111] to re-establish a link via the new EVAR trial manager and identify and brief the current lead vascular surgeon and radiologist at each of the 37 trial centres; with funding for clinical trial data collection and results of CT scanning or other imaging, to identify the contacts for these purposes; and then to be in a position to achieve the 10–15 years of additional clinical follow-up for all alive patients from 1 September 2009.

Outcomes (measures)

Our primary outcome was aneurysm-related mortality and total mortality. Aneurysm-related mortality was defined as all deaths from aneurysm rupture before repair, within 30 days of the primary procedure, within 30 days of any reintervention attributable to the aneurysm, from other aneurysm-related causes (including graft infection or fistula), or from secondary aneurysm rupture after repair. Our secondary outcomes included reintervention (time to first reintervention, first reintervention for a life-threatening problem and first serious reintervention). Further secondary outcomes included complications, sac growth and risk of late complications, costs and cost-effectiveness.

For the primary mortality outcome, patients were followed up from 1 September 1999 to 30 June 2015 [using record linkage from the Office for National Statistics (ONS), with death classification based on death certificates and clinical information provided to the Endpoint Committee]. Patients were followed up for death (total and aneurysm related), dates as above, and for graft-related complications and reinterventions

from 1 September 2009 to 31 March 2015. For graft-related reinterventions between 1 September 2009 and 31 March 2015, follow-up was predominantly using record linkage to administrative data for hospital readmissions and reinterventions via Hospital Episode Statistics (HES).

Reinterventions, including incisional hernia repair throughout the trial and other operative procedures preceding death, were subsequently checked with the trial centres, with 89% concordance between administrative and clinical site data. Graft-related complications and reinterventions were also directly obtained from the trial centres with a new case record form for our follow-up between 1 September 2009 and 31 March 2015. The primary analysis compared rates of total mortality and aneurysm-related mortality to 30 June 2015; aneurysm-related mortality was adjudicated and confirmed by the Endpoint Committee.

Sample size

As of 1 September 2009, there were 711 patients with an average age of 80 years reported alive and under follow-up in EVAR-1 (357 and 354 in the EVAR and OR groups, respectively), and 96 patients with an average age of 82 years reported alive and under follow-up in EVAR-2 (50 and 46 in the EVAR and no-intervention groups, respectively). This gives 80% power at the 5% significance level to detect hazard ratios (HRs) of 1.25 and 1.83 during the extended follow-up periods in EVAR-1 and EVAR-2, respectively, assuming 10% to be still alive at the end of June 2015.

Randomisation and blinding

Randomisation was conducted using computer-generated sequences of randomly permuted blocks stratified by centre at the trial hub (Charing Cross Hospital). Patients in EVAR-1 were randomly allocated (1 : 1) to undergo either OR or endovascular repair. In EVAR-2, patients were randomly allocated (1 : 1) to undergo either EVAR or to have no intervention. There was no blinding in either trial.

Statistical methods

All analyses were performed according to a predefined statistical analysis plan and were based on the intention-to-treat (ITT) principle, with outcomes assessed from the time of randomisation. Cox regression modelling was used to compare total mortality, aneurysm-related mortality and time to first graft-related reintervention. Crude regression estimates were presented as well as ones adjusted for two sets of baseline covariates: primary adjustment for age, sex, aneurysm diameter, forced expiratory volume in 1 second, log-creatinine level and statin use; secondary adjustment for the primary covariates as well as body mass index (BMI), smoking status (current, past and never), systolic blood pressure and serum cholesterol level. For the graft-related reintervention analysis, additional secondary adjustment was made for top neck aortic diameter at the level of the lowest renal artery, neck length (distance between the lowest renal artery and the start of the aneurysm) and common iliac diameter (largest of both legs). The primary and secondary adjustment results were very similar and the latter are reported. Baseline data were almost complete, with 94% and 92% of patients in EVAR-1 and EVAR-2, respectively, having a complete set of covariates for the adjusted analyses. HRs were presented as the EVAR group relative to the OR group for EVAR-1 and the EVAR group relative to the no-intervention group for EVAR-2. Owing to non-proportional hazards during the first 8 years of follow-up,[94,95] data were analysed by splitting follow-up into four time periods: 0–6 months, 6 months–4 years, 4–8 years and > 8 years. HRs presented in these time periods help to explain the non-proportionality, but must be interpreted conditional on surviving up to the time point in question and are therefore dependent on how the randomised groups fared in the follow-up prior to the time period. Deviations from the proportional hazards assumption were assessed overall and within these periods by regressing scaled Schoenfeld residuals against log of time. Regression estimates are presented both unadjusted and adjusted for baseline covariates. Kaplan–Meier estimates were used to show survival probabilities up to

15 years in each group. Tests of interaction were performed for total mortality and aneurysm-related mortality between randomised group and sex, age and aneurysm diameter (the last two as continuous variables).

In EVAR-1, two sensitivity analyses were performed to allow inclusion of patients with missing covariates in the adjusted models: first, the missing indicator method[112] and, second, multiple imputation using chained equations that included terms for the event outcome and the estimate of the cumulative baseline hazard.[113–117]

In addition, a per-protocol analysis was performed in EVAR-1 on data from patients who had undergone their randomly assigned treatment. This analysis excluded patients who did not undergo aneurysm repair, those who underwent emergency repair, those in whom the repair was abandoned during surgery (i.e. the aorta was left unrepaired) and those who did not undergo the randomly assigned procedure.

In the EVAR-1 analysis, time to first reintervention analyses were conducted separately for any graft-related reintervention, any serious reintervention (see two or three stars in *Table 1*) and any life-threatening condition (see four or five stars in *Table 1*). The criteria used to censor individuals are provided in *Severity score for reinterventions*. Further analyses were also undertaken in patients without any reintervention between randomisation and 2 years and without any reintervention between randomisation and 5 years.

All analyses were carried out in Stata version 13 (StataCorp LP, College Station, TX, USA). The Data Monitoring and Ethics Committee (DMEC) approved the statistical analysis plan.

Methods used for very long-term follow-up and changes to protocol

Patients in both trials were followed up comprehensively for rates of perioperative and late death, graft-related complications, reinterventions and resource use until September 2009.[94]

By the end of the 10-year follow-up in September 2009, three of the participating centres had merged with other local participating centres into single NHS trusts (Leeds, Belfast and Glasgow). All the trial participants at four further centres that had recruited very small numbers of patients had died and so were also not included in late follow-up. A total of 31 centres therefore participated in late follow-up to 15 years. Ethics approval for extended patient follow-up was obtained on 16 February 2011 from the UK North West Multicentre Research Ethics Committee, which did not require patients to be reconsented for ongoing follow-up of the EVAR trials up to 15 years (reference number 98/8/26 for EVAR-1 and reference number 98/8/27 for EVAR-2). Patient consent for the ongoing audit of medical notes for follow-up was given by each patient before randomisation. The EVAR trials' extended follow-up for both trial 1 and trial 2 was to be based on a review of hospital notes and continued flagging with the Medical Research Information Service for date and cause of death. As with the earlier follow-up, a lead clinician and a local co-ordinator were identified at each of the centres. The co-ordinator was to be remunerated for annual data extraction of clinical information from patient hospital notes relating to aneurysm-related complications and reinterventions from routine hospital visits for surveillance of the aneurysm repair for 2010–14.

Very long-term follow-up for reinterventions: October 2009 to March 2015

For the current phase of very long-term follow-up, funding was not achieved until 26 April 2012 and the trial manager was appointed on 1 December 2012. There was a delay in the signing of contracts between Imperial College London and the NIHR. The collaboration agreement was a four-way agreement that included the University of Cambridge (statistics) and the University of York (cost-effectiveness). Final contracts were not signed until 28 August 2013. In addition, local R&D approval was required from the 32 NHS trusts (30 in England, one in Scotland and one in Northern Ireland). First contact with each of the NHS trust R&D offices was made by the trial manager in December 2012. This process was not completed until 28 January 2014. A new case record form (see *Appendix 1*) was designed with the expectation of

collecting data on complications and reinterventions retrospectively for 2010–12 from clinical notes review and then prospectively for a further 3 years. Imaging scans and reports were also gathered as well as information on adverse events such as strokes, myocardial infarctions (MIs), chronic renal failure and amputation.

Owing to the delays described above, prospective data collection did not start until late in 2013. After 1 year of data collection, it became clear that for EVAR-1 the majority of OR patients (72%) and some EVAR patients (32%) were no longer being followed up at the original trial centres and some hospital mergers had taken place leading to patients being followed up at non-trial hospitals. For EVAR-2, nearly all of the patients had died. At a meeting of the Data Management Subcommittee of the Trial Management Committee (TMC) on 4 November 2014, it was decided to obtain permission for record linkage follow-up for all English trial patients alive or lost to follow-up in September 2009, by obtaining administrative data for hospital readmissions and procedures for patients from EVAR-1 only. There were so few EVAR-2 patients surviving, that given the need to provide robust justification to obtain ethics approval for using administrative data, this option was not pursued for EVAR-2 patients.

Obtaining permission to do this was a two-stage procedure. As patients had not given consent for access to their routine hospital administrative data on enrolment during 1999–2004, we had to obtain ethics approval (section 251) from the Confidentiality Advisory Group (CAG) to enable disclosure of confidential patient information. This required a lengthy process to demonstrate our institution met the stringent information governance requirements. The application to the CAG was submitted on 23 September 2014 and approval was granted on 18 February 2015. The second part of the process involved an application for HES data, which was submitted on 19 February 2015. HES is a government data warehouse containing records of all patients, tracked by their unique NHS number, admitted to NHS hospitals in England and contains details of inpatient care, outpatient appointments and accident and emergency attendance records. HES data allowed us to obtain patient data on all hospital readmissions and procedures (with procedure coding) until 31 March 2015 for 655 of the 724 (90%) patients alive in September 2009, including 13 patients previously lost to follow-up. Only seven English patients evaded HES record linkage. All procedures identified via HES which were potentially related to the original aneurysm repair, including abdominal hernia repairs, were validated with the relevant trial centre or where possible with other non-trial hospitals. There was 89% concordance between administrative data and clinical site data.

Sixty-nine patients, including 62 in either Scotland or Northern Ireland, could not be followed up via HES, of whom 48 (70%) had local follow-up at the trial centre. These 48 patients included 8 out of 15 patients in Scotland, 38 out of 47 patients in Northern Ireland and two out of seven English patients who were unmatched by HES. There were no Welsh centres. This process of using complementary sources of information from record linkage with local validation increased the completeness of patient follow-up in EVAR-1 from 51% to 97%, with only 25 patients being lost to follow-up for reinterventions by 31 March 2015.

Given the time taken for this process, the NIHR agreed to the project end date being extended until 31 August 2016.

Severity score for reinterventions

There is no recognised reporting system for reintervention or reintervention severity, to facilitate allocation of resource use. Therefore, the grading of the severity of aneurysm-related reinterventions and the associated use of high dependency or intensive care (high-dependency unit; HDU/ICU) were obtained by a questionnaire that was sent to each of the principal investigators at the 32 trial centres. Thus the EVAR trials severity score obtained is shown in *Table 1*.

TABLE 1 Severity score for reinterventions and use of enhanced care

Reintervention category	Severity	Mean estimated days in HDU	Mean estimated days in ICU
Conversion to OR	*****	2.1	1.9
Reintervention for graft infection: OR	*****	2.9	2.9
Reintervention for graft infection: EVAR	*****	2.3	0.7
Reoperation of OR: OR	*****	2.5	2.7
Known aneurysmal extension above or below original graft: OR	*****	2.2	1.6
Known aneurysmal extension above or below original graft: EVAR	*****	1.3	0.5
Replacement stent graft	*****	1.5	0.6
Fenestrated EVAR	*****	1.7	0.3
Axillobifemoral bypass graft	*****	1.2	0.0
Added stent; proximal (type Ia endoleak) or distal (type Ib endoleak)	****	0.4	0.1
Staple or ligation: EVAR	***	0.5	0.0
Embolisation (of endoleak)	***	0.1	0.0
Sclerosis of endoleaks	***	0.1	0.0
Femorofemoral crossover graft	***	0.2	0.0
Distal limb procedure/revascularisation: OR	***	0.6	0.0
Distal limb procedure/revascularisation: EVAR	***	0.1	0.0
Amputation	***	0.3	0.0
Reintervention for thrombosis of graft limb: EVAR	**	0.6	0.2
Reintervention for thrombosis of graft limb: OR	**	0.6	0.2
Incisional hernia: OR	**	0.5	0.0
False femoral aneurysm: OR	**	0.1	0.0
Minor reintervention	*	0.0	0.0

Notes
Obtained from survey of trial site principal investigators.
Serious reinterventions are any reintervention with two or three stars.
Life-threatening reinterventions are any reintervention with four or five stars.

Reinterventions recorded during follow-up included those that took place during primary admission and subsequent admissions. Also included are previously ignored reinterventions for ORs [e.g. incisional hernias (see *Table 1* for full list of reinterventions recorded)]. The date of any reintervention during the primary admission was taken to be the mid-point between the date of admission and the date of discharge or in-hospital death. The censoring time for reinterventions was determined as follows:

- For all patients from Scotland and Northern Ireland and those from England unmatched in HES with a known follow-up in 2014/15, the date of their latest follow-up was used for censoring.
- For alive patients in Scotland and Northern Ireland and those from England unmatched in HES without a follow-up in 2014/15, the date of last follow-up or the date of audit of their notes was used for censoring.
- For all patients in England tracked via HES, censoring was taken as 31 March 2015, unless the date of death was earlier.

- For dead patients without a follow-up in 2014/15, the date of death was used for censoring, providing it occurred within the year after their last follow-up or date their notes were audited, otherwise these latter dates were used for censoring.

Very long-term follow-up for complications: October 2009 to March 2015

As administrative data do not report complications, only reinterventions, this meant that it would no longer be possible to conduct a comparison of complication rates by randomised group. Complication data were obtained in satisfactory numbers only for analysis of complication rate by time period in the group randomised to EVAR.

Complications were only obtained from the trial centres using the new case record form for late follow-up (see *Appendix 1*). The new case record form was designed to capture all information about the cluster of complications identified by Wyss *et al.*[111] as preceding rupture as well as all reinterventions over the whole 5-year follow-up period. Trial centres were reminded that all patients should continue in regular follow-up (the protocol specified annual follow-up including clinical, imaging and serum creatinine level assessment) and all patients, including lapsed follow-ups, should be recalled for a final clinical and imaging follow-up in 2014. As previously, the management of aneurysm-related complications was left to the discretion of the trial centre.

Very long-term follow-up for mortality: October 2009 to June 2015

Follow-up for mortality was unchanged throughout the trial and data for the date, place and cause of death from the ONS were obtained from September 2009 to June 2015. These data, together with information about reinterventions, were assessed by the Endpoint Committee, who were blinded to randomised group and trial in which the patient participated. The committee considered all events from both EVAR-1 and EVAR-2.

All death certificates were reviewed by an Endpoint Committee to agree cause of death (*Figure 3*). Aneurysm-related mortality was defined as all deaths (1) from aneurysm rupture before repair, (2) within 30 days of the primary procedure, (3) within 30 days of any reintervention attributable to the aneurysm, and (4) other aneurysm-related causes (including graft infection or fistula) or from secondary aneurysm rupture after repair. Deaths for which the underlying cause was attributed to *International Classification of Diseases*, Tenth Edition codes I713–719 were also classified as aneurysm related.

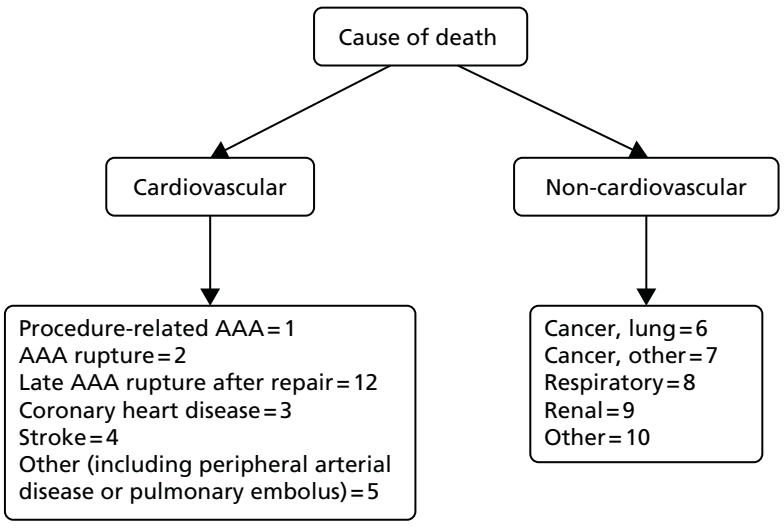


FIGURE 3 Classification of death codes assigned by the Endpoint Committee.

Imaging follow-up

The original EVAR trials protocol included annual imaging via a CT scanning to record the aneurysm sac diameter in EVAR patients and anastomosis diameter in OR patients. For the late follow-up, wherever CT scanning was performed as part of routine follow-up, images were copied for transfer to the trial co-ordinating centre. After 2010, many of the centres had reverted to using duplex ultrasound and the number of CT scans available was largely curtailed. Often with duplex scans the infrarenal maximum outer-to-outer anteroposterior diameter is recorded. For EVAR, crucially, maximum sac diameter is an essential finding. Endoleaks and other complications were noted from the imaging reports reflecting the opinion of the local NHS radiologist. All CT scans that were available were examined in the trial centre core laboratory by a skilled and trained vascular fellow to note known factors associated with eventual secondary sac rupture.

Additional 231 patients not included in earlier reports

After publication of the 30-day mortality results (not the primary outcome of the trial), 26 of the 37 centres remained in equipoise and wished to continue randomising patients until the primary outcome results (mortality after minimum 1-year follow-up from randomisation) were available. The chairperson of the DMEC approved this further recruitment, provided it was undertaken as a separate study, which could report on these later cases, with more experienced clinicians responsible particularly for EVAR. Two hundred and thirty-one additional patients were therefore randomised to a separate study between 1 September 2004 and the publication of mid-term results on 15 June 2005 and are being reported for the first time. One hundred and seventy-five patients were randomised to either OR or EVAR in EVAR-1 and 56 patients to either EVAR or no intervention in EVAR-2 (total 231 patients). Patient follow-up for mortality was the same as for the main EVAR-1 and EVAR-2 patients. In EVAR-1 this included a further 175 patients who have now been included in sensitivity analyses for mortality. Of these 175 patients, 88 patients were randomised to the EVAR arm of the study, of whom 70 were alive in September 2009. Eighty-seven patients were randomised to the OR arm of the study, of whom 66 were still alive in September 2009. For EVAR-2, 28 patients were randomised to EVAR, of whom 11 were alive in September 2009 and 28 patients were assigned to the no-intervention arm, of whom eight were alive in September 2009. The delays described above made it very challenging to obtain retrospective follow-up data for these 231 patients. Evaluation of data collection for these patients by the Data Management Subcommittee of the TMC on 30 June 2014 showed follow-up information on only one-third. Where available, we therefore focused on obtaining details of the primary operation for these additional patients. This information included (1) the preoperative diameter of the aneurysm; (2) the date of operation; (3) whether the patient had an EVAR or OR; and (4) if EVAR, which device was used. All of these additional 231 patients were registered with the Medical Research Information Service for mortality reporting. This allowed the 175 EVAR-1 patients to be included in sensitivity analysis for all-cause mortality, but little else, including the impact of later generation endografts on complication and reintervention rates.

Data management

All data transferred to the co-ordinating centre at Imperial College London were entered into the trial database by the trial manager based at Charing Cross Hospital. Data were handled in a secure way according to good clinical trial practice with due consideration for patient data confidentiality. The pre-existing database and new database for late follow-up were both stored securely on a dedicated, stand-alone (non-networked) computer system that was maintained in a locked office. The system was protected by strong passwords and advanced encryption standard (14 rounds and a 256-bit key). It was accessible only to the trial manager and the data manager. The trial manager was the only person responsible for data entry. Data entry errors were assessed by carrying out double data entry on a randomly selected 10% of patients. The case record form used for late follow-up is included in *Appendix 1*.

The approval for obtaining HES data was granted on the condition that all data received should be stored on the Imperial College Healthcare NHS Trust system accessible to only the trial manager. The reason for this stipulation was the lack of a satisfactory information governance toolkit assessment at Imperial College London which the NHS trust had in place. The information governance toolkit is a performance tool produced by the Health and Social Care Information Centre for the Department of Health. It draws together legal rules and central guidance and presents them in one place as a set of information governance requirements. Organisations are required to carry out self-assessments of their compliance against these requirements, which include management structures and responsibilities, confidentiality and data protection and information security. A realistic time scale for completion of a satisfactory toolkit assessment is therefore in the order of several months, and in 2015 very few universities had a satisfactory assessment in place. This requirement was the reason for the delay in obtaining HES data and was satisfactorily resolved as a result of our institutions partnership with the NHS trust.

Computed tomography images that were transferred anonymously to the trial co-ordinating centre were also treated with the same level of security and confidentiality. These were subsequently transferred to the dedicated research workstation in the core laboratory at Charing Cross Hospital.

Patient and public involvement

Patient and public involvement has been a prominent aspect in the EVAR-1 and EVAR-2, and never more so than when explaining to patients the difference of the methods offered at randomisation. During follow-up we were increasingly concerned that failure to carry out clinical and imaging annual assessments could be detrimental to patient outcomes. Thus, the trial manager visited every trial centre co-ordinator who was given a copy of the Wyss paper (2010)[111] to stress the need for ongoing follow-up and for this to be explained by them to patients.

In February 2015, we were granted approval to obtain confidential data on hospital admissions and procedures via HES. In June 2015, data were obtained for patients who were participants in EVAR-1 at hospitals in England and who had been lost to aneurysm-related follow-up. In order to obtain approval from the CAG we interviewed (face to face), trial patients at routine hospital visits. We explained to the patients that confidential records were held in a government database which stores information about all patient hospital visits in England. We asked them their view on access to confidential data from NHS and government records. All interviewed patients stated that they would be happy for us to access information in this way.

Organisational structure and committees

The late follow-up of the EVAR trials was managed centrally by the principal investigator (Professor Roger Greenhalgh), the trial manager (Dr Rajesh Patel) and Professor Janet Powell (co-applicant), who are based at the Charing Cross Hospital site of Imperial College London. Statistical expertise was provided by Dr Michael Sweeting (University of Cambridge) and costs and cost-effectiveness expertise were provided by Dr David Epstein who related to Professor Mark Sculpher (University of York).

Trial Management Committee

This committee was concerned with the day-to-day running of the trials and related to both the DMEC and the Trial Steering Committee. It was chaired by Professor Roger Greenhalgh and members included Professor Janet Powell (vascular biology), Dr Michael Sweeting (statistics), who related to Professor Simon Thompson, Dr David Epstein (health economics), Mr Colin Bicknell (vascular surgeon), Miss Regula Von-Allen (vascular surgeon), Mr Thomas Wyss (imaging core laboratory) and Dr Nick Burfitt

(interventional radiologist). Dr Rajesh Patel (trial manager) attended all meetings to update committee members on trial progress and highlight any problematic issues.

Data Monitoring and Ethics Committee

This committee was regularly updated on trial progress and the DMEC communicated with the Trial Steering Committee. The committee was chaired by Professor Gerry Fowkes and included Dr Robert Morgan from the British Society of Interventional Radiology and Professor Bruce Campbell from the National Institute for Health and Care Excellence (NICE).

Trial Steering Committee

This committee was chaired by Professor Richard Lilford (University of Birmingham) and included Roger Greenhalgh for the applicants and TMC, as well as Michael Wyatt (Newcastle), Simon Thompson (statistics) and Mark Sculpher (health economics). The role of the committee was to liaise between the DMEC and TMC and oversee any issues relating to the progress of the trials or needs for additional funding.

Endpoint Committee

This committee was chaired by Professor Janet Powell and included an independent vascular surgeon (Professor Alison Halliday) and a consultant cardiologist (Dr Simon Gibbs). All death certificates were centrally coded at the ONS and were reviewed by this committee in relation to any aneurysm-related procedures. All available data relating to the death and a primary underlying cause of death were classified according to the groupings presented in *Figure 3*, where death codes 1, 2 and 12 were classified as aneurysm related. Aneurysm-related deaths were defined as all deaths occurring within 30 days of the primary aneurysm repair or any reintervention for a graft-related complication unless over-ruled by post-mortem findings or a separate procedure (unrelated to the aneurysm) that took place between the aneurysm intervention and death (code 1); all deaths from rupture of an unrepaired aneurysm (code 2); and all deaths from rupture of a repaired aneurysm, usually endograft rupture (code 12). In addition, late complications of aneurysm repair, such as aortoduodenal fistula or bowel obstruction, were recorded as procedure-related deaths (code 1).

Chapter 3 Results for EVAR trial 1

Patients

From 1 September 1999 until 31 August 2004, we recruited 1252 patients to participate in this trial, who were equally, and randomly, assigned to the two treatment groups. There were no differences in baseline characteristics between the groups, mean age 74 years, 1135 men (*Table 2*).[101]

Baseline characteristics were compared between randomised groups and no differences were observed.

Patients were followed until 30 June 2015 (mean 12.7 years; median 12.4 years; minimum 1.8 years; maximum, 15.8 years); mean person-years observation to either death or end of the study was 8.0 years. By 30 June 2015 only four patients were lost to follow-up for mortality and 25 for reinterventions (this includes five patients in the EVAR group and 20 patients in the OR group), with data now available from record linkage for 13 of the 17 patients previously lost to mortality follow-up (*Figure 4*).

TABLE 2 Comparison of baseline characteristics in EVAR-1

Baseline characteristics by randomised group for EVAR trial 1		
Baseline characteristic[a]	**EVAR (*n* = 626)**	**OR (*n* = 626)**
Age (years)	74.1 (6.1) [0]	74.0 (6.1) [0]
Number of males (%)	565 (90) [0]	570 (91) [0]
AAA diameter (cm)	6.4 (0.9) [0]	6.5 (1.0) [1]
BMI (kg/m^2)	26.5 (4.6) [1]	26.5 (4.3) [6]
Diabetes (%)	61 (10) [2]	68 (11) [6]
Smoking status (%)	[1]	[1]
Current	134 (21)	136 (22)
Past	419 (67)	444 (71)
Never	72 (12)	45 (7)
History of cardiac disease[b] (%)	269 (43) [0]	261 (42) [0]
Systolic blood pressure (mmHg)	148 (22) [5]	147 (21) [2]
Diastolic blood pressure (mmHg)	82 (12) [7]	82 (13) [3]
ABPI (mean of both legs)	1.01 (0.18) [13]	1.03 (0.18) [27]
FEV_1 (l)	2.1 (0.7) [8]	2.2 (0.7) [4]
Serum creatinine level (μmol/l)[a]	102 (91–118) [1]	102 (90–120) [4]
Serum cholesterol level (mmol/l)	5.1 (1.2) [18]	5.1 (1.1) [25]
Statin use (%)	216 (35) [7]	224 (36) [3]
Aspirin use (%)	338 (54) [0]	325 (52) [0]

ABPI, ankle–brachial pressure index; FEV_1, forced expiratory volume in 1 second.

a Continuous variables presented as mean (standard deviation), apart from creatinine which is presented as median (interquartile range) as data were positively skewed. Categorical variables presented as number (%). Data in squared brackets indicate number of patients with missing data.

b Cardiac disease defined as previous history of any of the following: MI, angina, cardiac revascularisation, cardiac valve disease, significant arrhythmia or uncontrolled congestive cardiac failure.

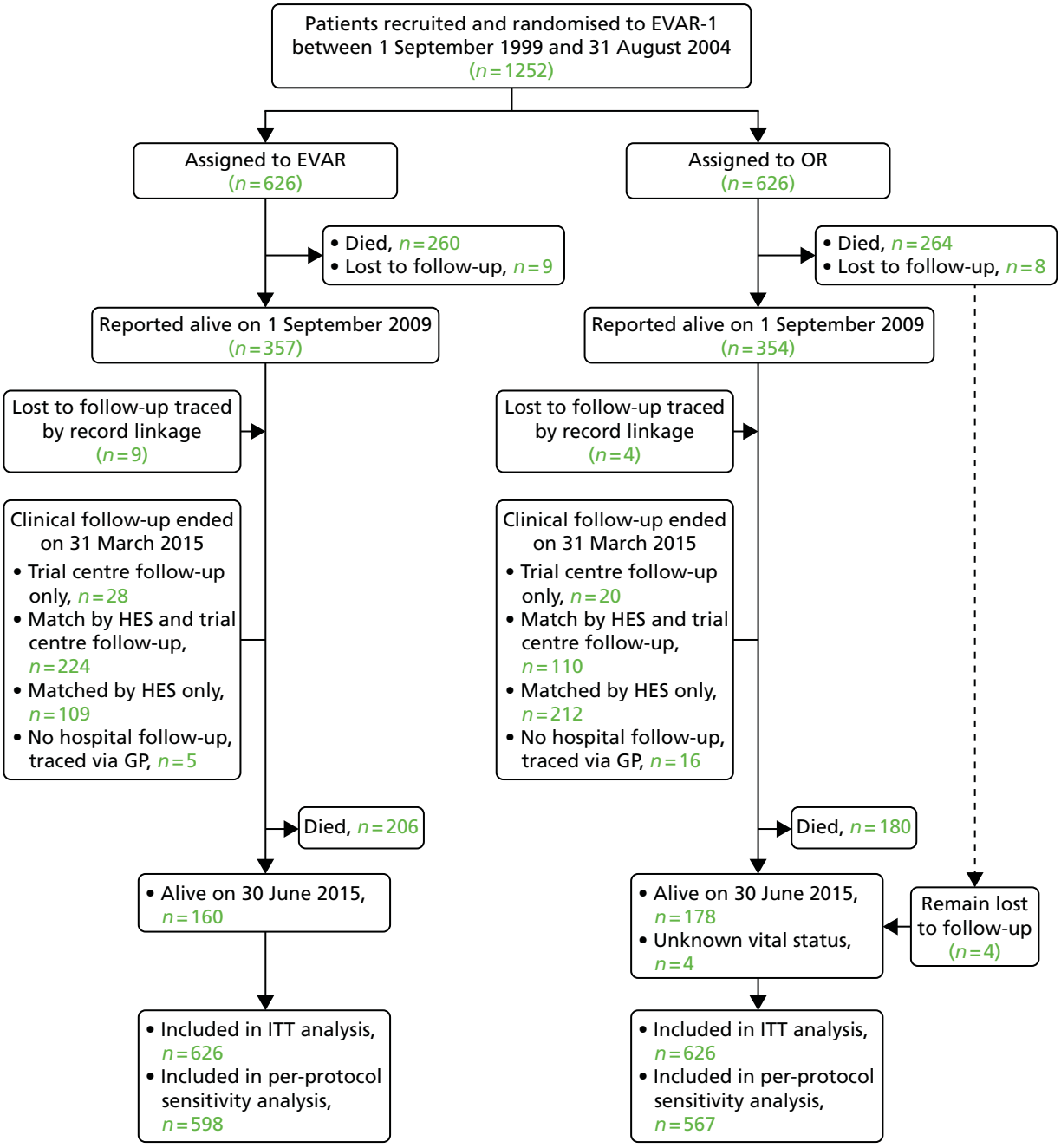


FIGURE 4 CONSORT diagram for mortality and reinterventions. GP, general practitioner.

For 13 individuals, a cause of death was established based only on a death certificate. Annual clinical follow-up with CT scanning or duplex imaging reduced steadily over the period of the trial and was consistently lower in the OR group (*Table 3*).

Over the course of follow-up, CT was carried out a median of six (interquartile range 3–8) times per patient in the EVAR group and three (interquartile range 1–6) times in the OR group. Of the patients who had not had death reported by 1 September 2009, 655 of 728 (90%) patients were tracked with HES, including 13 patients previously lost to follow-up, with local follow-up reported in 48 (70%) of the remaining patients (see *Figure 4*). After publication of the 30-day mortality results,[100] 26 of the 37 trial centres remained in equipoise and continued recruitment into a separate study from 1 September 2004 until 15 June 2005, when primary outcome results were published,[101] with a further 175 patients not reported previously but now used in sensitivity analyses for mortality only. Operative characteristics are shown for the 1252 patients in the EVAR-1 in *Table 4a* and the additional 175 patients in *Table 4b*.

TABLE 3 Computed tomography scanning and duplex imaging follow-up information for individuals who had survived and were still under follow-up to the end of each year since randomisation

	EVAR, *n*/*N* (%)		OR, *n*/*N* (%)	
Years since randomisation	CT	Duplex[a]	CT	Duplex[a]
< 1	532/581 (92)		55/566 (10)[b]	
1–2	448/543 (83)		414/534 (78)	
2–3	419/503 (83)		363/500 (73)	
3–4	354/474 (75)		306/464 (66)	
4–5	291/443 (66)		262/439 (60)	
5–6	271/409 (66)		221/399 (55)	
6–7	183/370 (49)	24/56 (43)	144/370 (39)	6/52 (12)
7–8	139/339 (41)	59/147 (40)	97/333 (29)	6/139 (4)
8–9	111/297 (37)	70/189 (37)	58/284 (20)	9/172 (5)
9–10	72/263 (27)	73/208 (35)	26/257 (10)	11/212 (5)
10–11	47/220 (21)	69/214 (32)	8/224 (4)	15/219 (7)
11–12	24/135 (18)	42/135 (31)	6/143 (4)	13/143 (9)
12–13	12/74 (16)	20/74 (27)	1/83 (1)	13/83 (16)
13–14	3/41 (7)	9/41 (22)	2/50 (4)	6/50 (12)
14–15	0/9 (0)	2/9 (22)	0/12 (0)	0/12 (0)

a Duplex ultrasound scans recorded on the case record form were recorded from only 2010 onwards, so the denominator includes only those whose follow-up had reached the end of 2010.
b Protocol stated that CT scanning should be performed 1 year postoperatively and annually thereafter.

TABLE 4a Comparison of baseline and operative characteristics by randomised group for 1252 patients in EVAR-1

Baseline characteristic[a]	EVAR (*n* = 626)	OR (*n* = 626)
Age (years)	74.1 (6.1)	74.0 (6.1)
Number of males (%)	565 (90)	570 (91)
Mean AAA diameter (cm)	6.4 (0.9)	6.5 (1.0)
Procedure received		
EVAR	598	31
OR	16	571
None	12 (all died before operation)	24 (including five who refused)
Unknown	0	0

a Continuous variables presented as mean (standard deviation).

TABLE 4b Comparison of baseline and operative characteristics by randomised group for the additional 175 patients in the separate study from 1 September 2004 to 15 June 2005

Baseline characteristic[a]	EVAR ($n = 88$)	OR ($n = 87$)
Age (years)	75.1 (5.9)	75.1 (5.9)
Number of males (%)	83 (94)	81 (93)
Mean AAA diameter (cm)	6.5 (1.1)	6.4 (0.8)
Procedure received		
EVAR	73	5
OR	3	61
None		3
Unknown	12	18

a Continuous variables presented as mean (standard deviation).

Note

Minimum baseline data were collected for this later (1 September 2004–15 June 2005) study and collection of clinical follow-up data was less comprehensive than for the main EVAR-1 trial. However, no patients were lost to follow-up for mortality reporting.

Aneurysm-related and total mortality

During 9968 person-years of follow-up, 910 deaths occurred, 101 of which were aneurysm related (*Table 5*). Overall aneurysm-related mortality was 1.1 deaths per 100 person-years in the EVAR group and 0.9 deaths per 100 person-years in the OR group [adjusted HR 1.31, 95% confidence interval (CI) 0.86 to 1.99; $p = 0.21$]. For total mortality, there were 9.3 deaths per 100 person-years in the EVAR group and

TABLE 5 Deaths from any cause and aneurysm-related causes, according to time since randomisation

	EVAR ($n = 626$) *n/N* (rate/100 person-years)	OR ($n = 626$) *n/N* (rate/100 person-years)	HR (95% CI)		*p*-value[b]
			Unadjusted	Adjusted[a]	
Total mortality					
All patients	466/626 (9.3)	444/626 (8.9)	1.05 (0.92 to 1.19)	1.11 (0.97 to 1.27)	0.14
Time since randomisation					
0–6 months	26/626 (8.5)	45/626 (15.0)	0.57 (0.35 to 0.92)	0.61 (0.37 to 1.02)	0.06
6 months–4 years	126/600 (6.7)	116/581 (6.3)	1.07 (0.83 to 1.38)	1.13 (0.87 to 1.47)	0.35
4–8 years	135/474 (8.3)	129/464 (8.0)	1.03 (0.81 to 1.31)	1.07 (0.83 to 1.37)	0.62
> 8 years	179/339 (14.9)	154/333 (12.7)	1.18 (0.95 to 1.47)	1.25 (1.00 to 1.56)	0.0484
Aneurysm-related death					
All patients	56/626 (1.1)	45/626 (0.9)	1.24 (0.84 to 1.83)	1.31 (0.86 to 1.99)	0.21
Time since randomisation					
0–6 months	14/626 (4.6)	30/626 (10.0)	0.46 (0.24 to 0.87)	0.47 (0.23 to 0.93)	0.0307
6 months–4 years	12/599 (0.6)	8/581 (0.4)	1.48 (0.60 to 3.62)	1.46 (0.56 to 3.83)	0.44
4–8 years	14/474 (0.9)	4/464 (0.2)	3.46 (1.14 to 10.52)	3.11 (0.99 to 9.72)	0.05
> 8 years	16/339 (1.3)	3/333 (0.2)	5.50 (1.60 to 18.89)	5.82 (1.64 to 20.65)	0.0064

a HRs were adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 second, log-creatinine level, statin use, BMI, smoking status, systolic blood pressure and total cholesterol level (77 individuals were excluded as a result of missing data).

b *p*-values were adjusted for covariates.

8.9 deaths per 100 person-years in the OR group (adjusted HR 1.11, 95% CI 0.97 to 1.27; $p = 0.14$). The results for the sensitivity analyses that included patients with missing baseline covariates were similar for aneurysm-related and total mortality (*Table 6*).

There was evidence of deviation from the proportional hazards assumption for aneurysm-related mortality ($p < 0.0001$), with an early benefit of EVAR during the first 6 months, counteracted by an increase in aneurysm-related mortality beyond 4 years, the difference being most marked after 8 years (adjusted HR 5.82, 95% CI 1.64 to 20.65; $p = 0.0064$) (see *Table 5*). There was also evidence of deviation from the proportional hazards assumption for total mortality ($p = 0.0232$), with an early benefit of EVAR during the first 6 months, similar mortality between the groups from 6 months to 8 years, but thereafter an increase in mortality in the EVAR group (adjusted HR 1.25, 95% CI 1.00 to 1.56; $p = 0.0484$) (see *Table 5*). Kaplan–Meier curves for aneurysm-related and total mortality are shown in *Figure 5*. Aneurysm-related mortality curves cross over between 6 and 8 years and total mortality curves diverge after 10 years. Median survival was 8.7 years and 8.3 years in the EVAR and OR groups, respectively (log-rank *p*-value 0.49). Sensitivity analyses, including the additional 175 patients from the separate 2004–5 study, yielded very similar results (*Figure 6*).

The full list of causes of death by time period are given in *Table 7*. Overall, there were 31 deaths from rupture after aneurysm repair in the EVAR group and five in the OR group. Two patients in the OR group had ruptures in 2010 and 2012 having refused operation. Overall, there was no evidence of a difference in cancer-related mortality between the groups (adjusted HR 1.09, 95% CI 0.84 to 1.40; $p = 0.53$), although there was some evidence of an increase in the EVAR group after 8 years (adjusted HR 1.87, 95% CI 1.19 to 2.96; $p = 0.007$) (*Figure 7* and *Table 8*).

Details of the primary cancer sites underlying mortality after 8 years are shown in *Table 9*.

TABLE 6 Sensitivity analyses accounting for missing baseline covariates

	HR (95% CI)		
	Complete-case analysis (secondary adjustment)	Missing indicator method (secondary adjustment)	Multiple imputation (secondary adjustment)
Any death			
All patients	1.11 (0.97 to 1.27)	1.08 (0.95 to 1.24)	1.09 (0.95 to 1.24)
Time since randomisation			
0–6 months	0.61 (0.37 to 1.02)	0.57 (0.35 to 0.93)	0.58 (0.36 to 0.95)
6 months–4 years	1.13 (0.87 to 1.47)	1.11 (0.86 to 1.43)	1.10 (0.85 to 1.41)
4–8 years	1.07 (0.83 to 1.37)	1.03 (0.81 to 1.31)	1.04 (0.81 to 1.32)
> 8 years	1.25 (1.00 to 1.56)	1.28 (1.03 to 1.59)	1.27 (1.02 to 1.58)
Aneurysm-related death			
All patients	1.31 (0.86 to 1.99)	1.28 (0.85 to 1.91)	1.29 (0.87 to 1.91)
Time since randomisation			
0–6 months	0.47 (0.23 to 0.93)	0.44 (0.23 to 0.84)	0.47 (0.25 to 0.89)
6 months–4 years	1.46 (0.56 to 3.83)	1.44 (0.56 to 3.68)	1.38 (0.56 to 3.42)
4–8 years	3.11 (0.99 to 9.72)	3.44 (1.12 to 10.53)	3.58 (1.17 to 10.94)
> 8 years	5.82 (1.64 to 20.65)	6.17 (1.75 to 21.74)	6.14 (1.75 to 21.57)

Note
HRs were adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 second, log-creatinine level, statin use, BMI, smoking status, systolic blood pressure and total cholesterol level.

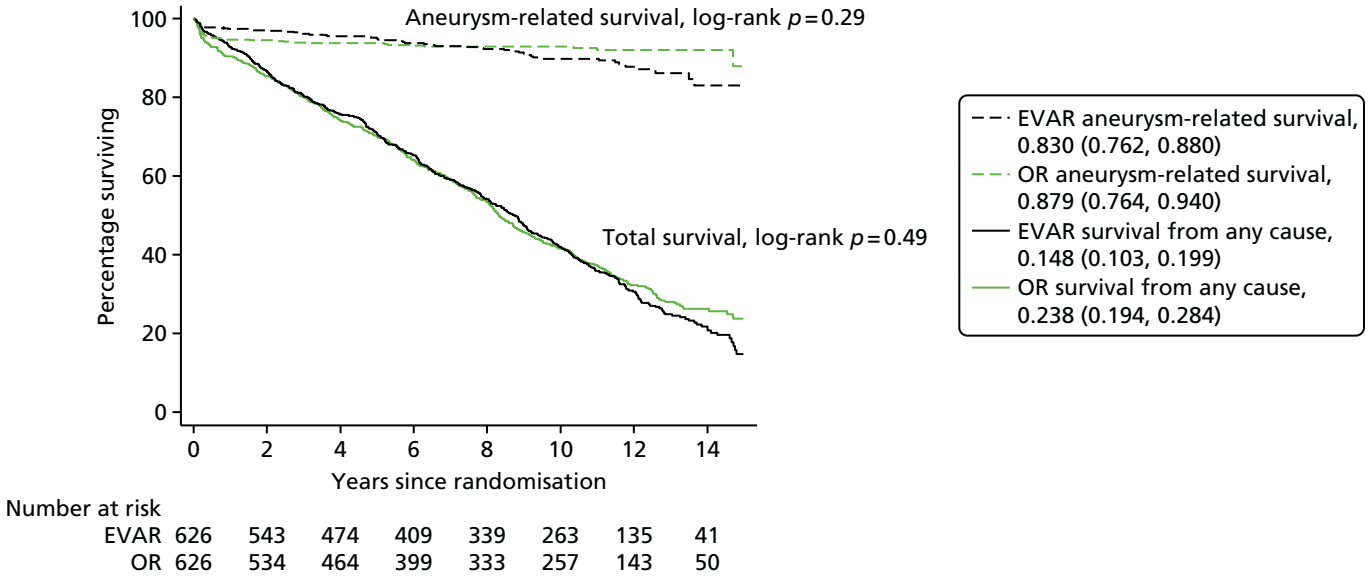


FIGURE 5 Kaplan–Meier estimates for total and aneurysm-related survival over a maximum of 15 years' follow-up.

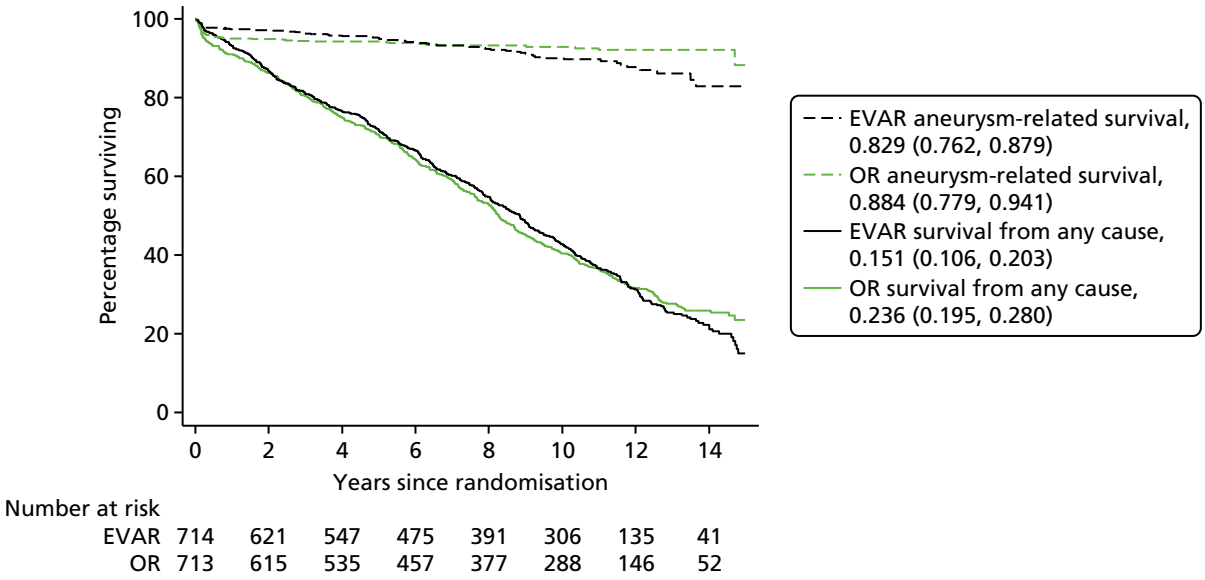


FIGURE 6 Kaplan–Meier estimates for total and aneurysm-related survival including the 175 additional patients randomised in a separate study from 1 September 2004 to 15 June 2005 (EVAR, $n = 88$; OR, $n = 87$) for sensitivity analysis.

TABLE 7 Causes of death by period since randomisation

Cause of death	EVAR, *n* (%)	OR, *n* (%)
Randomisation to 6 months	$n = 26$	$n = 45$
Aneurysm rupture before repair (primary)	5 (19)	5 (11)
Aneurysm related after repair	7 (27)	24 (53)
Aneurysm rupture after repair (secondary)	2 (8)	1 (2)
Coronary heart disease	4 (15)	4 (9)
Stroke	0 (0)	1 (2)
Other vascular disease	2 (8)	2 (4)
Cancer, lung	1 (4)	0 (0)
Cancer, other	2 (8)	0 (0)
Respiratory	0 (0)	5 (11)
Renal	2 (8)	0 (0)
Other	1 (4)	3 (7)
Unknown	0 (0)	0 (0)
6 months–4 years	$n = 126$	$n = 116$
Aneurysm rupture before repair (primary)	2 (2)	5 (4)
Aneurysm related after repair	2 (2)	2 (2)
Aneurysm rupture after repair (secondary)	8 (6)	1 (1)
Coronary heart disease	27 (22)	25 (22)

continued

TABLE 7 Causes of death by period since randomisation (*continued*)

Cause of death	EVAR, *n* (%)	OR, *n* (%)
Stroke	11 (9)	6 (5)
Other vascular disease	6 (5)	5 (4)
Cancer, lung	19 (15)	20 (17)
Cancer, other	20 (16)	29 (25)
Respiratory	10 (8)	16 (14)
Renal	4 (3)	1 (1)
Other	15 (12)	6 (5)
Unknown	2 (2)	0 (0)
4–8 years	*n* = 135	*n* = 129
Aneurysm rupture before repair (primary)	0 (0)	1 (1)
Aneurysm related after repair	6 (4)	2 (2)
Aneurysm rupture after repair (secondary)	8 (6)	1 (1)
Coronary heart disease	31 (23)	28 (22)
Stroke	16 (12)	12 (9)
Other vascular disease	7 (5)	7 (5)
Cancer, lung	12 (9)	16 (12)
Cancer, other	22 (16)	27 (21)
Respiratory	16 (12)	22 (17)
Renal	4 (3)	3 (2)
Other	13 (10)	10 (8)
Unknown	0 (0)	0 (0)
> 8 years	*n* = 179	*n* = 154
Aneurysm rupture before repair (primary)	0 (0)	1 (1)
Aneurysm related after repair	3 (2)	0 (0)
Aneurysm rupture after repair (secondary)	13 (7)	2 (1)
Coronary heart disease	33 (18)	35 (23)
Stroke	10 (6)	15 (10)
Other vascular disease	4 (2)	12 (8)
Cancer, lung	13 (7)	10 (6)
Cancer, other	37 (21)	21 (14)
Respiratory	29 (16)	30 (19)
Renal	5 (3)	4 (3)
Other	31 (17)	24 (16)
Unknown	1 (1)	0 (0)

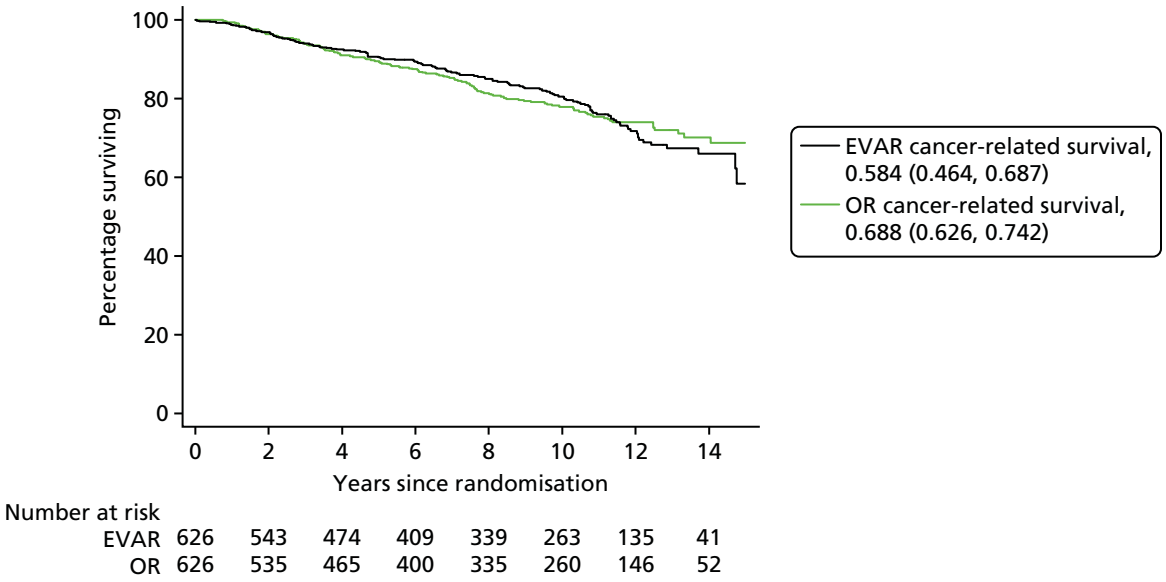


FIGURE 7 Kaplan–Meier estimates for cancer-related survival over a maximum of 15 years' follow-up.

TABLE 8 Deaths from cancer-related causes, according to time since randomisation

	EVAR ($n = 626$), n/N (rate/100 person-years)	OR ($n = 626$), n/N (rate/100 person-years)	HR (95% CI)		p-value[b]
			Unadjusted	Adjusted[a]	
Cancer-related death					
All patients	126/626 (2.5)	123/626 (2.5)	1.02 (0.80 to 1.31)	1.09 (0.84 to 1.40)	0.53
Time since randomisation					
0–4 years	42/626 (1.9)	49/626 (2.3)	0.85 (0.56 to 1.28)	0.90 (0.59 to 1.37)	0.63
4–8 years	34/474 (2.1)	43/464 (2.7)	0.78 (0.50 to 1.22)	0.76 (0.47 to 1.21)	0.24
> 8 years	50/339 (4.2)	31/333 (2.5)	1.65 (1.05 to 2.58)	1.87 (1.19 to 2.96)	0.007

a HRs were adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 second, log-creatinine level, statin use, BMI, smoking status, systolic blood pressure and total cholesterol level.
b p-values were adjusted for covariates.

TABLE 9 Cancer deaths after 8 years

Cancer site	EVAR, n	OR, n
Lung or pleura	13	11
Gastrointestinal or peritoneum	11	6
Genitourinary	14	11
Blood	6	2
Brain	1	0
Unspecified	5	1
Total	50	31

There was no evidence of significant interactions between the randomly assigned treatment and age, sex or aneurysm diameter for either aneurysm-related or total mortality ($p > 0.10$ for all comparisons).

Per-protocol analysis including 598 patients in the EVAR group who received elective EVAR and 567 patients in the OR group who received elective OR again showed strongly the benefit of EVAR during the first 6 months, counteracted by an increase in aneurysm-related mortality at all subsequent time periods (*Table 10*); the increase being proportionately greater than for the analysis by randomised group. Overall, aneurysm-related mortality was significantly higher in the EVAR group (1.0/100 person-years) than in the OR group (0.6/100 person-years) (adjusted HR 1.76, 95% CI 1.07 to 2.89; $p = 0.0263$). There was weak evidence that total mortality was higher in the EVAR group, at 9.1 per 100 person-years, than in the OR group, at 8.4 per 100 person-years (adjusted HR 1.14, 95% CI 0.99 to 1.31; $p = 0.07$).

Aneurysm-related reinterventions

During 9715 person-years of follow-up, there were 258 graft-related reinterventions performed in 165 patients in the EVAR group and 105 graft-related reinterventions performed in 74 patients in the OR group, with rates to first reintervention of 4.1 and 1.7 per 100 person-years, respectively (adjusted HR 2.42, 95% CI 1.82 to 3.21; $p < 0.0001$) (*Table 11*). The reintervention rate was significantly higher in the EVAR group for any reintervention and serious reinterventions in the first 4 years (*Figure 8a*, see *Table 11*) and for life-threatening reinterventions (including conversion to OR, repeat EVAR and treatment of graft infection), in the periods 6 months to 4 years and beyond 8 years (*Figure 8b*, see *Table 11*). Even after 2 years (*Figure 8c*) or 5 years (*Figure 8d*) without any life-threatening reintervention, new life-threatening reinterventions occurred at any time to 15 years of follow-up. The relative difference in reintervention rate

TABLE 10 Per-protocol analysis of deaths from any cause and aneurysm-related causes according to time since randomisation

	EVAR ($n = 598$), *n/N* (rate/100 person-years)	OR ($n = 567$), *n/N* (rate/100 person-years)	HR (95% CI)		*p*-value[b]
			Unadjusted	Adjusted[a]	
Any death					
All patients	443/598 (9.1)	391/567 (8.4)	1.10 (0.96 to 1.26)	1.14 (0.99 to 1.31)	0.07
Time since randomisation					
0–6 months	17/598 (5.8)	34/567 (12.4)	0.47 (0.26 to 0.83)	0.48 (0.26 to 0.90)	0.0224
6 months–4 years	120/581 (6.6)	95/533 (5.6)	1.19 (0.91 to 1.56)	1.21 (0.92 to 1.60)	0.17
4–8 years	130/461 (8.2)	121/437 (8.0)	1.02 (0.80 to 1.31)	1.05 (0.81 to 1.36)	0.71
> 8 years	176/331 (15.0)	141/314 (12.0)	1.26 (1.01 to 1.57)	1.30 (1.03 to 1.63)	0.0254
Aneurysm-related death					
All patients	49/598 (1.0)	29/567 (0.6)	1.62 (1.03 to 2.57)	1.76 (1.07 to 2.89)	0.0263
Time since randomisation					
0–6 months	9/598 (3.1)	23/567 (8.4)	0.37 (0.17 to 0.79)	0.36 (0.15 to 0.85)	0.0208
6 months–4 years	10/580 (0.6)	2/533 (0.1)	4.70 (1.03 to 21.46)	4.36 (0.92 to 20.67)	0.06
4–8 years	14/461 (0.9)	2/437 (0.1)	6.68 (1.52 to 29.40)	5.80 (1.29 to 26.08)	0.0220
> 8 years	16/331 (1.4)	2/314 (0.2)	8.27 (1.90 to 36.00)	9.43 (2.09 to 42.59)	0.0035

a HRs were adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 second, log-creatinine level, statin use, BMI, smoking status, systolic blood pressure and total cholesterol level (71 individuals were excluded as a result of missing data).
b *p*-values were adjusted for covariates.

TABLE 11 First reintervention from any relevant procedure, first serious reintervention and first life-threatening reintervention, according to time since randomisation

	EVAR ($n = 626$), n/N (rate/100 person-years)	OR ($n = 626$), n/N (rate/100 person-years)	HR (95% CI)		p-value[b]
			Unadjusted	Adjusted[a]	
Any reintervention					
All patients	164/626 (4.1)[c]	74/626 (1.7)	2.37 (1.80 to 3.12)	2.42 (1.82 to 3.21)	< 0.0001
Time since randomisation					
0–6 months	67/626 (23.7)	36/626 (12.5)	1.89 (1.26 to 2.83)	1.95 (1.28 to 2.98)	0.0020
6 months–4 years	56/536 (3.5)	9/559 (0.5)	6.81 (3.37 to 13.77)	6.29 (3.09 to 12.78)	< 0.0001
4–8 years	21/381 (1.6)	16/436 (1.1)	1.48 (0.77 to 2.84)	1.60 (0.81 to 3.15)	0.17
> 8 years	20/264 (2.3)	13/282 (1.3)	1.76 (0.88 to 3.54)	1.51 (0.71 to 3.19)	0.29
Any serious reintervention					
All patients	140/626 (3.3)	57/626 (1.3)	2.60 (1.91 to 3.54)	2.62 (1.90 to 3.61)	< 0.0001
Time since randomisation					
0–6 months	45/626 (15.5)	19/626 (6.5)	2.38 (1.39 to 4.06)	2.46 (1.39 to 4.33)	0.0019
6 months–4 years	52/557 (3.1)	8/570 (0.5)	6.93 (3.29 to 14.58)	6.45 (3.04 to 13.68)	< 0.0001
4–8 years	21/403 (1.5)	16/444 (1.1)	1.43 (0.75 to 2.74)	1.45 (0.73 to 2.88)	0.29
> 8 years	22/277 (2.5)	14/289 (1.4)	1.76 (0.90 to 3.44)	1.59 (0.78 to 3.26)	0.20
Life-threatening reintervention					
All patients	85/626 (1.9)	41/626 (0.9)	2.12 (1.46 to 3.08)	2.09 (1.42 to 3.08)	< 0.0002
Time since randomisation					
0–6 months	22/626 (7.4)	19/626 (6.5)	1.14 (0.62 to 2.11)	1.08 (0.57 to 2.08)	0.81
6 months–4 years	27/576 (1.5)	2/570 (0.1)	13.77 (3.27 to 57.92)	12.78 (3.01 to 54.23)	0.0006
4–8 years	15/434 (1.0)	11/450 (0.7)	1.41 (0.65 to 3.06)	1.41 (0.63 to 3.14)	0.40
> 8 years	21/302 (2.1)	9/300 (0.8)	2.50 (1.14 to 5.45)	2.44 (1.05 to 5.68)	0.0385

a HRs were adjusted for age, sex, maximum aneurysm diameter, forced expiratory volume in 1 second, log-creatinine level, statin use, BMI, smoking status, systolic blood pressure, total cholesterol level, top neck diameter, neck length and maximum common iliac diameter (91 individuals were excluded as a result of missing data).
b *p*-values were adjusted for covariates.
c Reinterventions were performed in 165 EVAR patients, but one reintervention is excluded from analyses because of the unknown time of the reintervention.

between the groups was highest in the period 6 months to 4 years after randomisation, particularly for the most serious reinterventions (see *Table 11*). A similar pattern, by time period, was observed for second and subsequent reinterventions (*Table 12*).

Discussion of EVAR trial 1

The most striking finding of these very long-term results is that both aneurysm-related and total mortality rates are greater in late follow-up for patients who were randomised to EVAR than those randomised to OR, although over the whole follow-up period the average total and aneurysm-related mortality rates were not significantly different between groups. The significant late divergence of the survival curves in favour of OR (see *Figure 5*) can be partly explained through greater contribution to late mortality from aneurysm-related and cancer deaths in the EVAR group, and the fact that these were elderly patients and the survival curves will inevitably start to converge in older ages.

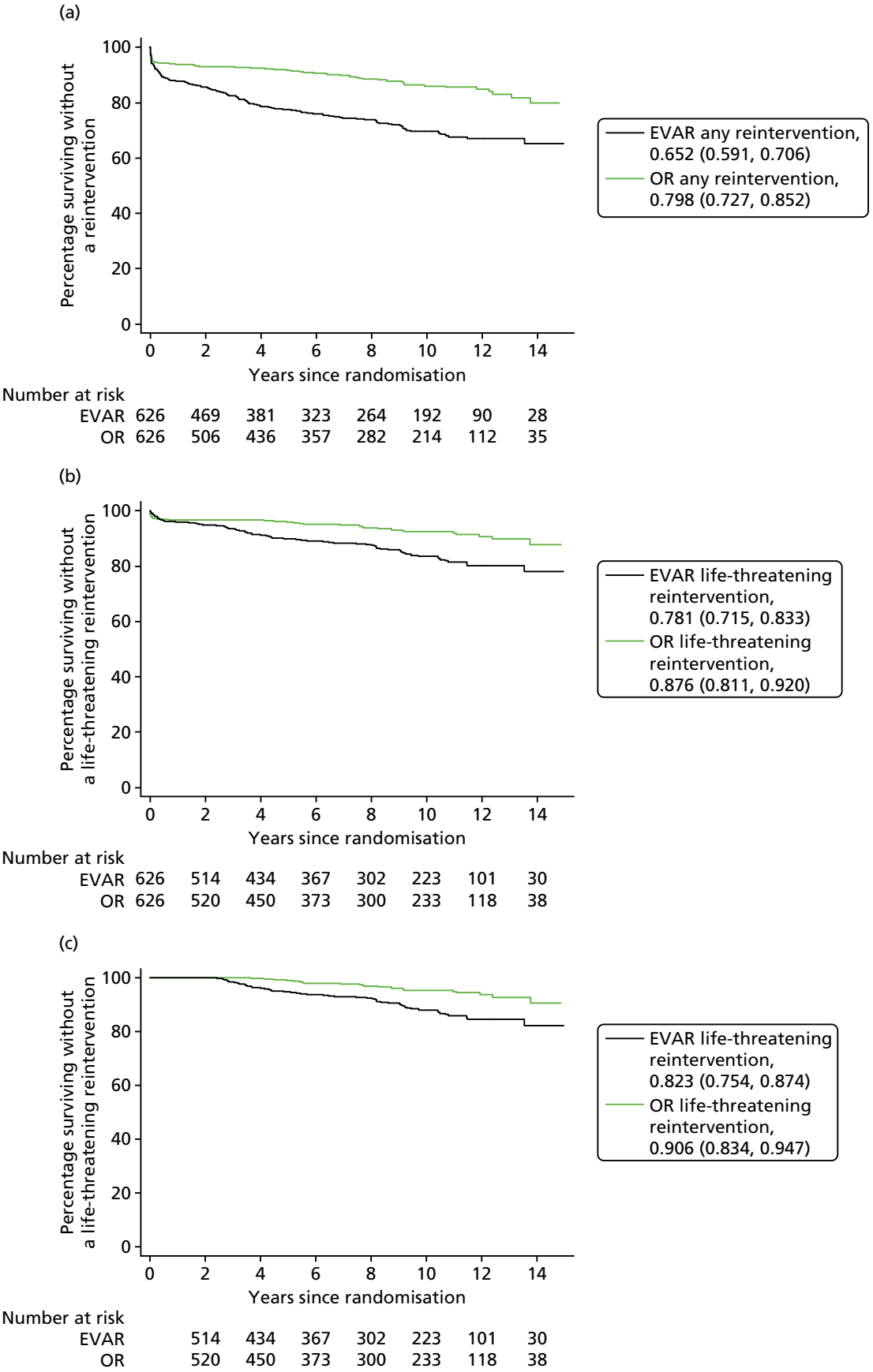


FIGURE 8 Kaplan–Meier estimates over a maximum of 15 years' follow-up for (a) the time to first reintervention; (b) the time to first life-threatening reintervention; (c) the time to first life-threatening reintervention for individuals who have survived 2 years free of a life-threatening reintervention; and (d) the time to first life-threatening reintervention for individuals who have survived 5 years free of a life-threatening reintervention. (*continued*)

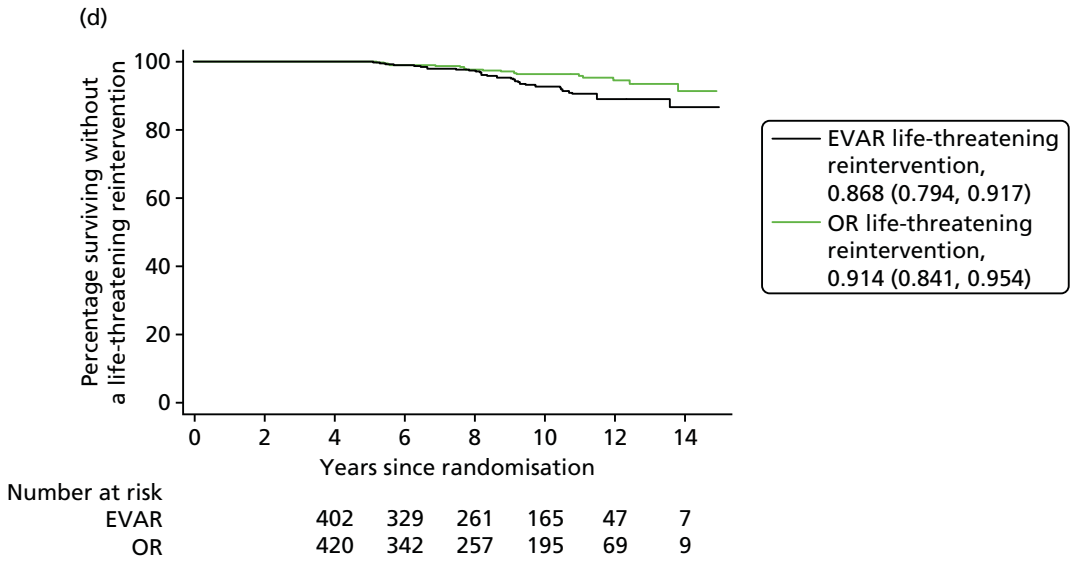


FIGURE 8 Kaplan–Meier estimates over a maximum of 15 years' follow-up for (a) the time to first reintervention; (b) the time to first life-threatening reintervention; (c) the time to first life-threatening reintervention for individuals who have survived 2 years free of a life-threatening reintervention; and (d) the time to first life-threatening reintervention for individuals who have survived 5 years free of a life-threatening reintervention.

TABLE 12 All reinterventions by randomised group and time epoch

Reintervention	EVAR, *n*	OR, *n*
0–6 months	*n* = 81	*n* = 36
First	67	36
Second	11	0
Third	2	0
Fourth	1	0
6 months–4 years	*n* = 73	*n* = 10
First	56	9
Second	12	1
Third	4	0
Fourth	1	0
4–8 years	*n* = 46	*n* = 35
First	21	16
Second	13	13
Third	9	4
Fourth	2	2
Fifth	1	0
> 8 years	*n* = 57	*n* = 24
First	20	13
Second	14	7
Third	10	3

continued

TABLE 12 All reinterventions by randomised group and time epoch (*continued*)

Reintervention	EVAR, *n*	OR, *n*
Fourth	7	1
Fifth	4	0
Sixth	2	0

Note
There was no evidence that calendar time of randomisation had any effect of the reintervention rate in 6 months–4 years, or any other epoch.

Total and aneurysm-related mortality were lower in patients who received EVAR in the first 6 months, but increased after 6 months' follow-up, leading to a significantly higher rate after 8 years' follow-up in EVAR than in those who received OR. After the first 6 months, the increased aneurysm-related deaths in the EVAR group were predominantly from secondary sac rupture. Over the whole duration of follow-up, two aneurysm-related deaths followed reintervention, but 31 of the others were from secondary sac rupture, partly attributable to a failure to have corrected underlying causes of sac expansion from endoleak.[111] In those patients allocated to OR, there were five secondary ruptures, of which four were in patients who received EVAR and the remaining secondary rupture occurred more than 8 years after OR.

Reinterventions occurred in both groups throughout follow-up, including those who were free from reintervention after 2 or even 5 years, but the rate of reintervention was higher in the EVAR group at all time periods. These late reinterventions included those with high severity score, indicating that there was never a safe period to abandon follow-up for patients with EVAR. However, in this trial, some patients were discharged from surveillance and, therefore, lost the option of planned reintervention. With an average age of 74 years at randomisation, there could have been pressing clinical reasons not to reintervene for some patients with long-term follow-up because of age and frailty. A criticism in earlier reports from this trial, that not all incision-related reinterventions following OR were reported, was remedied in this long-term follow-up.

Limitations of EVAR trial 1

Limitations of this trial include that devices used were implanted between 1999 and 2004 and newer devices may be expected to have better results[118] and imaging for sizing and placement of endografts has improved. The original trial protocol was for annual follow-up by CT, which was used in the early stages of the trial. However, in the later stages, many of the EVAR patients were followed up using ultrasonography. This change from CT to ultrasonography was influenced by increasing concern about radiation exposure.[119] Moreover, imaging follow-up declined over time, particularly for the OR patients. Consequently, reinterventions became less likely once surveillance ceased. Nor can we assume that follow-up practice is the same in the rest of the world as it is in the UK, where many patients were discharged from surveillance after several years. Since the EVAR group patients had more diligent follow-up than the OR patients, aneurysm-related mortality may have been underestimated in the OR group, although this does not affect our findings for total mortality. A further limitation is that, as a result of decreasing clinical follow-up at the original trial hospitals, the methodology to identify reinterventions changed after 2009 to predominantly using record linkage through the HES administrative data set, these reinterventions subsequently being validated at the trial hospitals. However, these data also captured data for patients whose care had moved to non-trial hospitals and recovered some patients previously lost to follow-up.

Patients prefer EVAR,[120] and today it is the method of choice for repair of AAA. EVAR devices improve constantly, and sizing and imaging for deployment is better than between 1999 and 2004: a corollary is that experience in OR is declining. However, aortas with aneurysmal disease continue to dilate, and in time a good device can leak or migrate and even an OR can rupture. Challenges in the future to maintain the initially superior results of being in the EVAR group include the need to halt the dilating disease process as well as devices which allow for this inevitable dilating process over the years. It is fortunate that the long-term results of this study can act as a benchmark against which new endovascular technologies for aneurysm repair can be compared at each time point. In the meantime, surveillance must be addressed in clinical guidelines: it should be diligent, regular, easy and avoid CT scanning where possible, perhaps concentrating on the sac diameter after EVAR either by ultrasonography or novel implantable sensor devices.[121–125]

Chapter 4 Costs: endovascular aneurysm repair compared with open repair over 15 years

Introduction

This chapter estimates the total cost per patient of each procedure over 15 years in patients who were suitable for EVAR and fit for OR. The costs for each patient include the index procedure, aneurysm-related reinterventions and surveillance, as received in EVAR-1. Other potentially related categories of acute and chronic health-care costs, such as MI, stroke, amputation, renal failure and cancer, are not included in this analysis, as data on health-care use for these reasons were not collected after 2009.

As this chapter presents a description of the data, rather than an economic evaluation, costs were not discounted. A full economic evaluation showing discounted costs and quality-adjusted life-years (QALYs) is presented in *Chapter 5*.

Methods

All resources in the current analysis were costed at 2014/15 prices. The follow-up is divided into two periods: (1) 1 September 1999–31 August 2009; and (2) 1 September 2009–31 March 2015. The method of costing is different for the two periods. During the first period (1999–2009), detailed hospital resource use data were available for the index procedure and aneurysm-related reinterventions for each patient from the case record forms. The same methodology is used here as in the previous publication,[94] the only difference being that, in the previous publication, these resources were costed at 2008/9 prices. In the current analysis, these same resources have been recosted using largely new unit costs at 2014/15 prices (*Table 13*).

Detailed hospital resource use data were not widely available from case record forms after 1 September 2009 because of loss to follow-up, especially in patients in the OR group. To supplement the trial data and information from hospital notes, data on hospital episodes for each patient from 1 September 2009 to 31 March 2015 were obtained from national NHS HES (see *Chapter 2* for the definition of the censoring date for reinterventions). Each episode was assigned a Hospital Resource Group code[127] and matched with the published national average cost of that episode.[126] A Hospital Resource Group is similar to a Diagnostic Resource Group. HES data did not include time in critical care. The TMC estimated the likely time in ICU and HDU for each type of procedure during the follow-up via a survey of all the centre principal investigators (see *Table 1*). These estimates were used to calculate the costs of critical care for each episode in the follow-up after 1 September 2009 using published national average costs.[126]

Surveillance was undertaken through attendance at vascular outpatient consultations, CT scanning and ultrasonography. These data were available for each patient in EVAR-1 over the entire period of follow-up (1999–2015) and these were costed at 2014/15 prices using national average costs.[126]

Hospital notes were searched over the full trial period for incisional hernia repair procedures. These are almost exclusively carried out after OR. These reinterventions were not included in previous publications,[94,101] but are included in this analysis and were costed by Hospital Resource Group at 2014/15 prices using national average costs.[126] Analysis is by ITT. Costs were converted to US dollars at purchasing power parities (£0.70 = US$1.00).[128] All data management and analysis was carried out in Stata version 13.

TABLE 13 Unit costs used in the analysis (2014/15 prices unless otherwise stated)

Resource	Unit cost (£)	Source	Reference
EVAR device	6558	Average selling price of the EVAR device (across all manufacturers) in the UK	Marianna Stellino, W.L. Gore and Associates, 14 October 2015, personal communication
Other consumables and accessories: EVAR	387 (at 2004 prices)	Survey of participating centres undertaken by the EVAR trials, May 2004	Brown *et al.*, 2012[96]
Graft: OR	240 (at 2004 prices)	Survey of participating centres undertaken by the EVAR trials, May 2004	Brown *et al.*, 2012[96]
Other consumables: OR	189 (at 2004 prices)	Survey of participating centres undertaken by the EVAR trials, May 2004	Brown *et al.*, 2012[96]
Blood products	140.02	National Blood Service	www.blood.co.uk (accessed November 2015)
Ultrasound	88	Ultrasound scanning	*NHS Reference Costs 2014 to 2015*[126]
CT	103	CT scanning	*NHS Reference Costs 2014 to 2015*[126]
Theatre time (per hour)	1139	NHS Scotland	Cost book 2014/15 R142X theatre services
Hospital stay (per day)	342	Day in ward, YR04Z endovascular repair, excess bed-day	*NHS Reference Costs 2014 to 2015*[126]
Critical care (per day)	1142	Activity-weighted average, adult critical care 0–6 organs supported	*NHS Reference Costs 2014 to 2015*[126]

Handling missing data

Because of staggered recruitment to the trial between 1 September 1999 and 31 August 2004, follow-up data were available at the censoring date for reinterventions on 31 March 2015 from between 11 to 15.5 years. The aim of this chapter is to estimate mean costs per patient over the full time horizon of the trial (i.e. 15 years). As not all patients have the full 15 years of follow-up, we need to try to understand the reasons for the missing data and handle the missing data accordingly.[129] In this chapter we assume that the missing data have a monotone pattern. This means in practice that all patients are assumed to have complete follow-up for costs (no missing data on surveillance or reinterventions) until their censoring date for reinterventions. This administrative censoring was handled in two ways: (1) using inverse probability weighting (IPW); and (2) multiple imputation.

Inverse probability weighting

In the first method, the administrative censoring was handled using IPW.[130] It was assumed that data were missing monotonically and missing completely at random. The following steps were taken in data management prior to implementation of the IPW programme:

1. The cost, $cost_{it}$, for patient i for each year t from date of randomisation ($t = 1 \ldots 14$) was calculated as the sum of the costs of interventions, reinterventions and surveillance during that year for that patient.
2. Patients who died before the index operation were assigned a cost of zero for all years up to the censoring date (if no other information is available).
3. If no interventions or surveillance were recorded in the trial or the HES data for a patient i in any year t before the censoring date ($t < Xi$), then $cost_{it}$ was assigned a value of zero (assumption of monotone missing cost data).
4. Any surveillance or reintervention apparently incurred on a date after the designated censoring date for that patient was assumed to be an error and reassigned to the last period before censoring for that patient (assumption of monotone missing cost data).

5. If a patient died, then $cost_{it}$ after the time of death ($t > X_{it}$) was assumed to be zero; this assumption ensures that the weighted cost includes both alive and dead individuals.
6. There were insufficient reinterventions in the final year to estimate reliable CIs; hence costs over 14 years are presented in this chapter.
7. Data were organised in the long format.

The IPW method sets up an indicator variable, d^*_{it}, which takes value 1 if the patient is dead or still in follow-up at time t, and zero otherwise. A Kaplan–Meier survival function is then calculated and used to estimate G^*_{it}, defined as the probability that patient i is still in follow-up or dead by time t. The probability G^* is estimated without explanatory covariates and hence assumes that data are missing completely at random. The weight w_{it} is then defined as d^*_{it}/G^*_{it}. This ensures that observations at the end of the trial (when there are fewer patients in follow-up) receive a greater weight in the analysis.

Weighted linear regression is carried out for each period t separately, where $cost_{it}$ is the dependent variable and $treat_i$ the independent variable. The coefficient β_t on the $treat_{it}$ variable is then interpreted as the difference in mean cost per patient at time t between the treatment groups. The difference in the total mean cost per patient over the full 14 years (taking account of administrative censoring) is the sum of the coefficients for each year, $\sum^{T=14}_{t=1}\beta_t$. CIs were estimated by bootstrap.[131]

Multiple imputation

In the second method, the administrative censoring was handled using multiple imputation.[129] It was assumed that data were missing monotonically and missing at random.

The following steps were taken in data management prior to imputation:

1. The cost, $cost_{it}$, for patient i for each year t from date of randomisation ($t = 1 \ldots 14$) was calculated as the sum of the costs of interventions, reinterventions and surveillance during that year for that patient.
2. Patients who died before the index operation were assigned a cost of zero for all years up to the censoring date (if no other information is available).
3. If no interventions or surveillance were recorded in the trial or the HES data for a patient i in any year t before the censoring date ($t < Xi$), then $cost_{it}$ was assigned a value of zero (assumption of monotone missing cost data).
4. Any surveillance or reintervention apparently incurred on a date after the designated censoring date for that patient was assumed to be an error and reassigned to the last period before censoring for that patient (assumption of monotone missing cost data).
5. Data were organised in the wide format.

Multiple imputation was undertaken using predictive mean matching, drawing on the five closest neighbours. Imputation was carried out separately for each randomised treatment group (by $treat_i$). Fifteen imputed data sets were created (missing values; $M = 15$). For each dependent variable with missing data ($cost_{it}$), a customised conditional prediction equation was built with the following independent variables, $died_{t+1}$, age_i, sex_i, $eq5ds_{i0}$, $cost_{i1}$ if $died_t == 0$, where $died_{t+1}$ is a binary indicator variable which takes value 1 if the patient died in the next period. This takes account that health-care costs are often higher in the months leading up to death. The variables age_i, sex_i, $eq5ds_{i0}$ are the age, gender and EuroQol-5 Dimensions (EQ-5D) index at baseline. The variable $cost_{i1}$ is the cost incurred in the first year. This takes account of the severity and complications incurred in the index procedure, which may predict subsequent need for health care. The conditional expression (if $died_t == 0$) restricts estimation of costs and imputation to the patients known to be alive at time t.

After imputation, the total cost per patient ($total\_cost_i$) was calculated passively as the sum of the $cost_{it}$ in each of the 14 years. If a patient died, then $cost_{it}$ after the time of death ($t > X_{it}$) was assumed to be zero.

Analysis was carried out using linear regression, which was used to estimate the difference in mean costs and standard errors (SEs) between the treatment groups, with $total\_cost_i$ as the dependent variable and $treat_i$ as the independent variable. Rubin's rule was applied to aggregate coefficients across the M data sets.

Results

Mean costs over 14 years estimated using inverse probability weighting

The cost results for the IPW method are shown in *Table 14 and Figure 9*. In the EVAR group there were 626 randomised patients, of whom 160 were alive on 30 June 2015. In the OR group, there were 626 randomised patients, of whom 181 were alive on 30 June 2015. Eleven patients in the EVAR group and 20 patients in the OR group did not receive any aneurysm repair and were assigned zero cost for the initial procedure. The overall difference in mean cost between the groups at 1 year is £2194. This difference increases gradually over 14 years to £3798 (95% CI £2338 to £5258). Most of this difference is as a result of the initial procedure cost and subsequent reinterventions.

Table 15 shows the estimates from the regression of total cost on treatment group, using Rubin's rules to aggregate coefficients over the $M = 15$ data sets. The estimated difference in mean cost per patient between the groups is £3757 (95% CI £2332 to £5182).

TABLE 14 Mean costs per patient of procedures and surveillance undertaken in EVAR-1, estimated using IPW

	Procedures and reinterventions (£)			Surveillance and imaging (£)			Total mean cost (£)		
Year	OR	EVAR	Difference	OR	EVAR	Difference	OR	EVAR	Difference
1	13,725	15,660	1935	218	405	187	13,857	16,051	2194
2	168	153	–15	188	200	12	334	340	5
3	0	281	281	168	177	9	152	445	293
4	45	382	337	142	154	12	173	525	352
5	106	214	108	113	128	15	205	332	127
6	92	160	68	100	113	13	179	265	87
7	69	123	53	66	88	22	129	206	77
8	241	112	–129	49	81	32	280	188	–92
9	101	288	187	35	77	43	130	357	226
10	125	199	73	17	62	45	140	255	115
11	56	320	264	12	55	43	66	362	296
12	43	166	123	12	41	29	53	198	144
13	78	0	–78	14	26	12	88	25	–63
14	81	114	32	12	14	3	89	126	37
Total mean	14,931	18,171	3240	1147	1622	475	15,876	19,674	3798
SE			666			23			745
95% CI			1934 to 4546			430 to 521			2338 to 5258

Note
Total mean cost may not correspond exactly to the row sum of procedures only and surveillance only because of the differences in the IPW in each case.

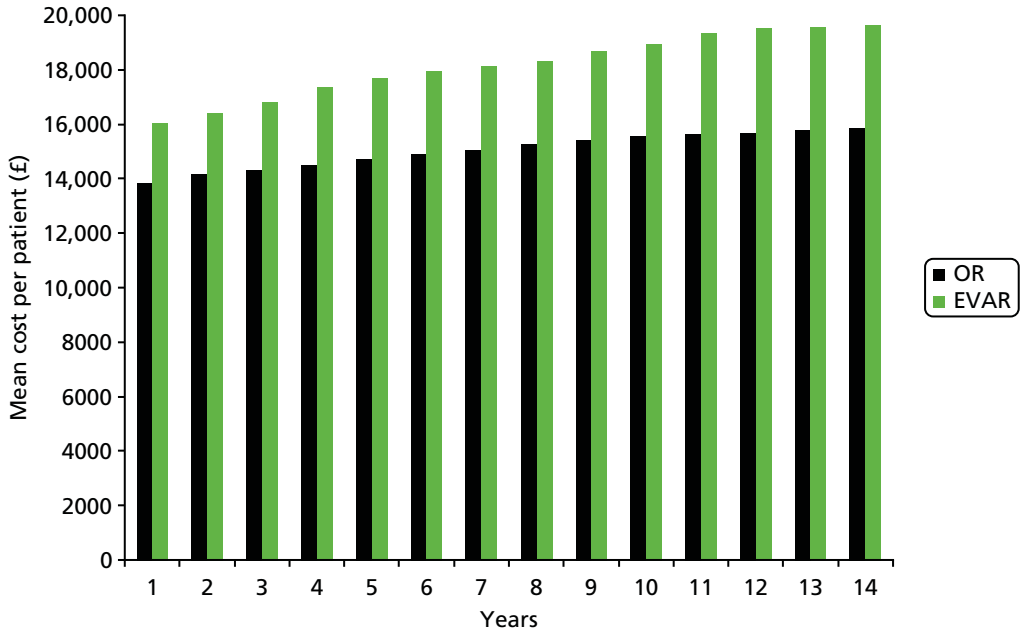


FIGURE 9 Evolution of mean cost (£) per patient in each treatment group over time. Mean cost over 14 years estimated using multiple imputation.

TABLE 15 Regression of total cost on treatment group using multiple imputation to handle missing values

	Mean	SE	*t*	*p*-value	95% CI
Treat	3757	726	5	0.000	2332 to 5182
Intercept	15,891	513	31	0.000	14,884 to 16,897

Discussion

This chapter has estimated mean costs per patient for EVAR and OR over 14 years follow-up. The estimate of the difference in mean costs between the treatment groups is robust to the method used for handling missing data. The difference in cost is £3798 (95% CI £2338 to £5258) under IPW and £3757 (95% CI £2332 to £5182) under multiple imputation.

The methods make different assumptions about the missing data mechanism. The IPW method assumes data are missing completely at random, that is, the probability of an observation being missing does not depend on observed or unobserved measurements. This may be reasonable if the data are administratively censored, where the censoring arises because of the (random) date of recruitment into the trial, rather than unplanned loss to follow-up. The multiple imputation method assumes that data are missing at random, that is, given the observed data, the probability of an observation being missing does not depend on the unobserved data. The high degree of similarity between the two estimates suggests that the missing completely at random assumption is reasonable in this case.

It is perhaps unsurprising that the two methods give similar results, because the number of missing data is modest in this study. This is because there is complete follow-up for reinterventions for 11.5 years (the end of randomisation until the closure of the trial) and data for reinterventions, were obtained from HES (and verified from hospital notes and trial documents).

Chapter 5 Cost-effectiveness of endovascular and open repair

Introduction

This chapter presents a cost-effectiveness model of EVAR compared with OR for aneurysm repair, in patients fit for OR and suitable for EVAR. Parameters are mainly based on the outcomes of EVAR-1. Nevertheless, 24% of the OR group are alive at 15 years; hence some assumptions about the rate of mortality beyond follow-up are needed.

Methods

Overview

A Markov model was constructed to compare costs and QALYs over the lifetime of aneurysm patients undergoing either OR or EVAR. The perspective is the UK NHS and the price year is 2014–15. The discount rate was 3.5% per annum. The structure of the model was the same as used in a previous publication,[132] with some minor changes to reflect the new data and analyses presented in this report.

There are three 'states': alive, dead from AAA-related causes, or dead from other causes. The cycle length is 6 months. Aneurysm repair (EVAR or OR) takes place during the first model cycle, incurring costs and reduced HRQoL compared with that in the general population.

Patients may die during the first 6 months from an AAA-related cause (mainly operative deaths) or other causes. During each subsequent 6-month cycle, the patient may die of aneurysm causes or other causes, whereas survivors undergo surveillance and may require surgical or endovascular reintervention. Reintervention incurs a cost and decrement in HRQoL during that 6-month cycle.

Patients have one surveillance visit (outpatient attendance and ultrasound) per year after EVAR and one every 5 years under OR. The parameters used in the base-case model are shown in *Table 16*.

Aneurysm-related mortality

The rates of aneurysm mortality during the trial follow-up period are taken from EVAR-1. The base-case model adheres, as far as possible, to the results of EVAR-1. The base case uses the ITT estimates from the RCT (see *Table 5*) and assumes no difference in aneurysm mortality after the RCT ends. Three sensitivity analyses are conducted using different assumptions about the relative rate of aneurysm mortality between the treatment groups. The first sensitivity analysis, scenario 1, assumes that the HR for aneurysm mortality observed at the end of the trial continues beyond the RCT. The second sensitivity analysis, scenario 2, assumes that the HR for aneurysm mortality after 4 years is equal to the lower limit of the 95% CI for the mean, rather than the central value, and no difference in aneurysm mortality after the RCT ends. A third sensitivity analysis, scenario 3, uses per-protocol estimates from the RCT (see *Table 10*) and assumes no difference in AAA after the RCT ends.

Deaths from other causes

The age-specific annual rates of non-aneurysm mortality (i.e. deaths from other causes) in the model are based on UK life tables for all-cause mortality in the general male population.[133] Approximately 90% of patients in EVAR-1 were male. The rates of non-aneurysm mortality are calibrated so that overall mortality after OR at 15 years estimated by the model is the same as that observed in EVAR-1, that is 23.8% survived up to 15 years. This is implemented in the model by a parameter representing the relative risk of

TABLE 16 Model parameters (base case)

Parameter	Variable	Parameter value	Mean	SE	LL	UL	Events	Patient-years at risk
Age at baseline	Age	74						
Years	Cyclelength	0.5						
One male	Gender	1						
Trial OCM compared with population OCM	SMR	1.175						
HR AAA deaths 0–6 months	HR_aaa_1	0.47	0.47		0.23	0.93		
HR 6 months–4 years	HR_aaa_2	1.46	1.46		0.56	3.83		
HR 4–8 years	HR_aaa_3	3.11	3.11		0.99	9.72		
HR > 8 years	HR_aaa_4	5.82	5.82		1.64	20.65		
HR after the end of the RCT	HR_aaa_5	1	1		0.36	2.62		
Absolute rate open AAA deaths 0–6 months	open_aaa_1	0.10					30	300
Absolute rate open AAA deaths 6 months–4 years	open_aaa_2	0.004					8	2000
Absolute rate open AAA deaths 4–8 years	open_aaa_3	0.002					4	2000
Absolute rate open AAA deaths > 8 years	open_aaa_4	0.002					3	1500
Costprocedure EVAR	evar_c_proc	15104	15104	345				
Costprocedure open	open_c_proc	14127	14127	449				
Costreintervention/ episode	c_reint	8670	8670	831				
Costsurveillance/ attendance	c_surv	227						
Number of surveillance/ year (OR)	s_open	0.2						
Number of surveillance/ year (EVAR)	s_evar	1						
Difference utility EVAR – OR 0–3 months	Diff_u_1a	0.0599	0.0599	0.0166				
Difference utility EVAR – OR 3–6 months	Diff_u_1b	0						
Difference utility EVAR – OR 6 months–4 years	Diff_u_2	0						
Difference utility EVAR – OR 4–8 years	Diff_u_3	0						
Difference utility EVAR – OR > 8 years	Diff_u_4	0						
Utility at baseline	u_0	0.804	0.804	0.021				
Decrement in utility after OR 0–3 months	open_u_1a	–0.0802	–0.0802	0.0119				

TABLE 16 Model parameters (base case) (*continued*)

Parameter	Variable	Parameter value	Mean	SE	LL	UL	Events	Patient-years at risk
Decrement in utility after OR 3–6 months	open_u_1b	–0.0802	–0.0802	0.0119				
Decrement in utility 6 months–4 years	open_u_2	0						
Decrement in utility 4–8 years	open_u_3	0						
Decrement in utility > 8 years	open_u_4	–0.01						
Decrement in utility 0–6 months after reintervention	reint_u	–0.0604	–0.0604	0.0258				
Decrement in utility 0–6 months before death	death_u	–0.149	–0.149	0.0166				
HR reinterventions 0–6 months	HR_reint_1	1.95	1.95		1.28	2.98		
HR 6 months–4 years	HR_reint_2	6.29	6.29		3.09	12.78		
HR 4–8 years	HR_reint_3	1.6	1.6		0.81	3.15		
HR > 8 years	HR_reint_4	1.51	1.51		0.71	3.13		
Absolute rate OR reinterventions 0–6 months	open_reint_1	0.125					36	288
Absolute rate OR reinterventions 6 months–4 years	open_reint_2	0.005					9	1800
Absolute rate OR reinterventions 4–8 years	open_reint_3	0.011					16	1454
Absolute rate OR reinterventions > 8 years	open_reint_4	0.013					13	1000
EVAR OCM compared with OR OCM	evar_excess	1.072						
Discountrate, year	discount	0.035						

LL, lower limit of the 95% CI; OCM, other-cause mortality; UL, upper limit of the 95% CI.

EVAR-1 patients, relative to the general population. In this case, the relative risk is 1.175 (see *Table 16*). The higher rate of mortality in the EVAR-1 population, relative to the general population of the same age, probably arises from the comorbidities and risk factors that usually are associated with development of an AAA.

The differences in all-cause survival between endovascular and OR observed in the RCT over the whole 15-year follow-up can mostly be explained by differences in aneurysm-caused deaths, although it has been suggested that there may have been more deaths from other causes in the EVAR group, in particular mid-term cardiovascular deaths[134] and cancer deaths after 8 years (see *Chapter 3*). The survival curves in the EVAR-1 trial were observed to converge at around 2–4 years (see *Figure 5*). To reproduce this catch-up in this model, the rates of non-aneurysm mortality after EVAR are set to be slightly greater for the first 2 years (HR 1.072). After 2 years these rates are assumed to be the same in both treatment groups.

Health-related quality of life

EVAR trial 1 collected HRQoL data in both groups using the EuroQol-5 Dimensions, three-level version, instrument up to 10 years. Extensive analyses of these data were undertaken as part of this study and are presented as a working paper.[135] Analysis of EQ-5D in EVAR-1 shows that HRQoL declines in the first 6 months relative to baseline in all patients and that EVAR patients have, on average, better HRQoL during this period than OR patients.[135] After 6 months from the initial operation there is no difference in mean EQ-5D score from baseline between the groups. However, HRQoL is impaired in the 6 months after a reintervention and in the 6 months prior to death (see *Table 16*).

Reinterventions

Survivors are at risk of reinterventions, which incur a hospital procedure cost and a decrement in HRQoL for 6 months. Reinterventions are those that were identified in EVAR-1 and include incisional hernia repair (mainly after OR) and aneurysm-related reinterventions such as stent graft replacement. The rates of reinterventions up to 15 years are taken from *Table 11* of this report. It is assumed in the model that there is no difference in the rate of reinterventions after the 15-year follow-up of the RCT.

Costs

Hospital costs of the procedures for EVAR and OR were estimated using the methods described in *Chapter 4*. The costs of surveillance using ultrasound were estimated from NHS unit costs.[126] The cost of a reintervention was estimated as the mean hospital reintervention cost from EVAR-1 using the methods described in *Chapter 4*.

Sensitivity analyses

In addition to the three sensitivity analyses described earlier, a further sensitivity analysis (scenario 4) was conducted using the parameters of the model used in the guidance on the use of endovascular stent grafts issued by NICE in 2009 (technology appraisal number 167).[136] The following parameters were assumed to apply for EVAR by this guidance: a HR for late aneurysm deaths of 1.5; a HR for reinterventions of 1.5; an annual cost of surveillance after EVAR of £56; and no difference in the initial procedure cost. Other input parameters are kept the same as the base case.

Probabilistic sensitivity analysis

All results are presented as the mean of 1000 Monte Carlo simulations of the model. Results were unaltered when tested using 5000 simulations. HRs were assigned a log-normal distribution, rates were assigned gamma distributions, the costs of the procedures were assigned normal distributions and the decrements in utility were assigned normal distributions. The normal distribution for modelling costs and utility is acceptable here as the sample size in EVAR-1 was large and the SEs of the means for these parameters are small. Therefore, the central limit theorem can be assumed to apply.

Results

Table 17 shows the results of the model. The base case assumes that there is no difference in aneurysm mortality beyond the end of the trial and no difference in reinterventions beyond the end of the trial. *Figure 10* shows the predicted survival curves under these assumptions. The curves cross at about 4 years for any-cause mortality. EVAR is not effective or cost-effective over the lifetime under the base-case assumptions, with greater overall health benefit, measured in QALYs, but also greater cost. The incremental cost-effectiveness ratio (ICER) is £202,776 per QALY.

Figure 11 shows the distribution of simulations from the probabilistic implementation of the base-case model. The difference in QALYs is highly skewed, with a long tail. This arises from the wide CIs around the HRs for aneurysm-related deaths. The probability that EVAR is cost-effective is 0.06 at a threshold of £20,000 per QALY and 0.19 at a threshold of £30,000 per QALY.

TABLE 17 Results of the cost-effectiveness analysis

	OR		EVAR		Difference			Probability that EVAR is cost-effective at a threshold of	
	Cost (£)	QALY	Cost (£)	QALY	Cost (£)	QALY	ICER	£20,000/QALY	£30,000/QALY
Base case	15,536	6.415	19,152	6.433	3616	0.018	202,776	0.063	0.191
Scenario 1	15,512	6.421	19,150	6.432	3638	0.011	330,555	0.051	0.65
Scenario 2	15,599	6.435	19,212	6.542	3653	0.107	34,026	0.223	0.480
Scenario 3	15,521	6.421	19,057	6.199	3554	–0.223	D–	0.003	0.015
Scenario 4	15,271	6.431	16,315	6.526	1044	0.095	10,929	0.702	0.763

D–, on average EVAR is more costly and less effective than OR.

Notes

Scenario 1: HR for aneurysm mortality observed at the end of the trial continues beyond the RCT.
Scenario 2: HR for aneurysm mortality after 4 years is equal to the lower limit of the 95% CI.
Scenario 3: per-protocol analysis.
Scenario 4: input parameters taken from NICE appraisal of endovascular stents in 2009 (technology appraisal number 167).[136]

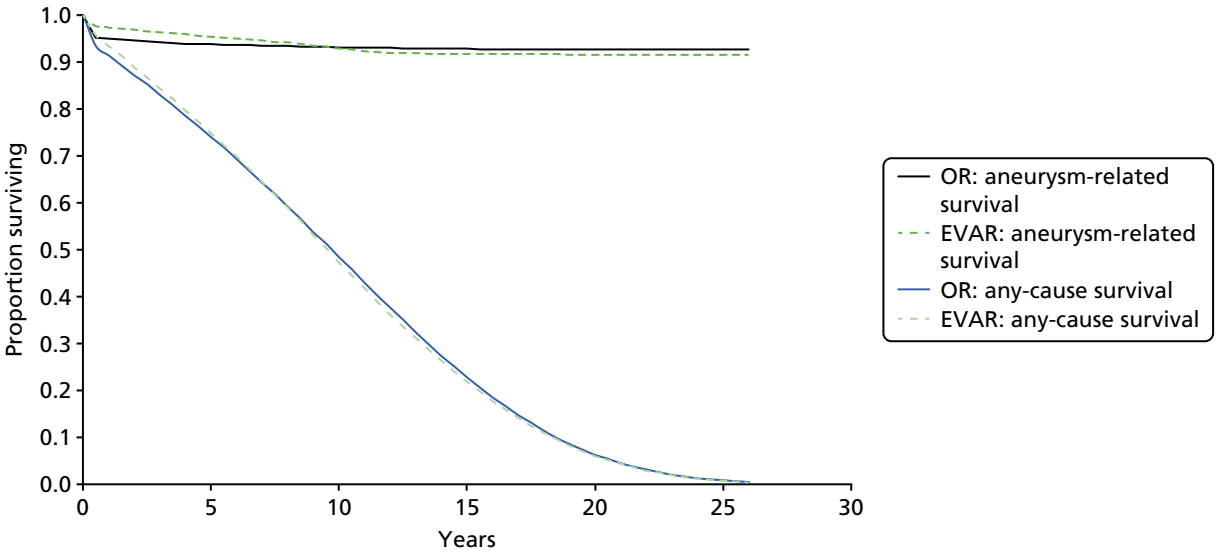


FIGURE 10 Predicted survival curves from the base-case model (deterministic implementation).

The first sensitivity analysis, scenario 1, assumes that the HR for aneurysm mortality observed at the end of the trial continues beyond the RCT. This makes EVAR somewhat less effective than the base case, but the results are not substantially different. The second sensitivity analysis, scenario 2, assumes that the HR for aneurysm mortality after 4 years is equal to the lower limit of the 95% CI for the mean (rather than the central value). Under this scenario, the ICER reduces to £34,026 per QALY. Under the per-protocol analysis, scenario 3, EVAR is more effective in the short term than in the base case, but there are more aneurysm-related deaths in the long term, and EVAR becomes less effective and more costly than OR over the lifetime. Scenario 4 applies the model input values used in the NICE final appraisal document. EVAR is considerably more effective than OR in this scenario and the ICER reduces to £11,088 per QALY. The probability that EVAR is cost-effective is 0.70 at £20,000 per QALY and 0.76 at £30,000 per QALY. *Figure 12* shows the cost-effectiveness acceptability curve for the base-case and sensitivity analyses.

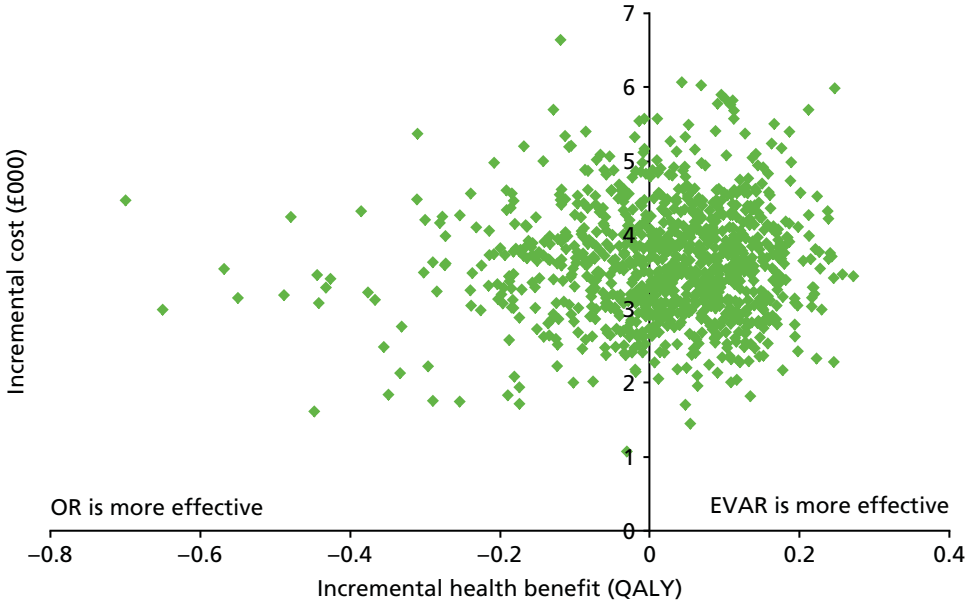


FIGURE 11 Cost-effectiveness plane (base-case model, probabilistic implementation).

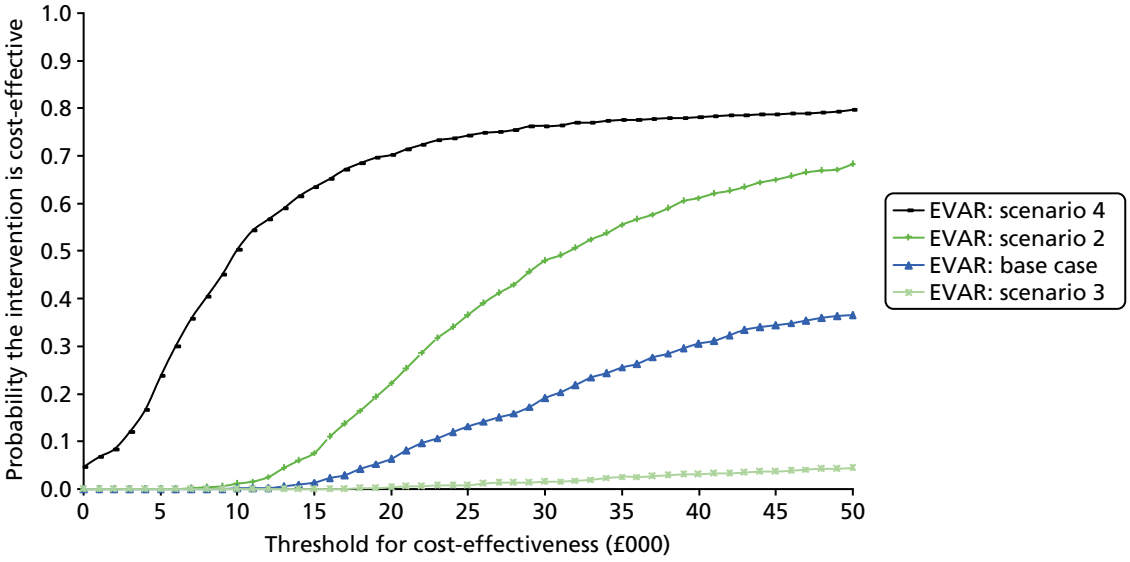


FIGURE 12 Cost-effectiveness acceptability curves for the base-case and sensitivity analyses. Note that the cost-effectiveness acceptability curve for scenario 1 is the same as the base case.

Discussion

The base-case model uses EVAR-1 data to inform outcomes within the trial follow-up and assumes that the rates of aneurysm mortality and reinterventions are the same as OR after the end of the trial. Under this model, EVAR showed greater overall health benefit but higher costs than OR. The initial benefit after EVAR was attenuated by late mortality and reinterventions, which are associated with a decrement in HRQoL. Over the lifetime of the patient, these two factors outweigh the initial gain in operative mortality and faster recovery from surgery. Lifetime costs are greater for EVAR because of the price of the stent graft, the need for surveillance and the need for reinterventions. The ICER in the base case is > £200,000 per QALY, considerably above the threshold of £20,000–30,000 per QALY that conventionally applies in the UK.

The base-case model is based closely on EVAR-1 during the first 15 years, which found that the initial gains in operative mortality were gradually lost over the longer term and that EVAR was associated with greater costs. EVAR might be considered cost-effective in certain scenarios. Scenario 2 assumes that late AAA mortality is lower than the base case. This might be plausible, but it is selective of the evidence. Given the trial data, it is equally likely that the 'true' HR for aneurysm mortality could be at the upper limit of the 95% CI, rather than at the lower limit.

The results shown here are similar to earlier estimates based on the 8-year data from EVAR-1.[132] The DREAM trial, based in the Netherlands, concluded that EVAR was not cost-effective even after 1 year.[137] The OVER trial, based in the USA, found that EVAR was effective and cost-effective at 2 years,[138] but this was in a lower-risk group and did not take account of late mortality or reinterventions.

The NICE appraisal of endovascular stent grafts (technology appraisal number 167) was conducted in 2009 when the 4-year results of EVAR-1 were known. The committee acknowledged the high internal validity of the EVAR trial but were concerned that the study did not properly reflect the performance of the latest generation of endovascular stents, which were thought to have improved since the trial recruitment period 1999–2004. Hence, NICE assumed more favourable outcomes for the later generation of EVAR devices than were reported in the trial. In particular, it assumed lower aneurysm-related mortality, fewer reinterventions, fewer resources used in the hospital stay and less cost for surveillance than observed in EVAR-1. Using these values in the current model, this scenario produced an ICER of £10,929 per QALY, which would be highly cost-effective at conventional thresholds used in the UK. These assumptions, as yet, are not supported by evidence from RCTs. Nevertheless, this modelling does show how EVAR would need to improve in order to be considered cost-effective. For example, EVAR might be cost-effective if ways could be found to monitor sac expansion to trigger more timely and better targeted reintervention and reduce late aneurysm deaths.

Chapter 6 Individual patient data meta-analysis of EVAR trial 1, the Dutch Randomised Endovascular Aneurysm Management trial, the Open versus Endovascular Repair trial and Anévrysme de l'aorte abdominale, Chirurgie versus Endoprothése trial

Introduction

Open repair of AAA was first introduced by Dubost *et al.* in 1951.[75] In the 1990s the less invasive EVAR was introduced and the first multicentre randomised trial of EVAR compared with OR was started in 1999 (EVAR-1), in the UK.[100] This was soon followed by other multicentre trials in Europe (the DREAM and ACE trials) and the OVER trial in the USA.[98,99,104]

Each of the randomised trials of EVAR compared with OR recruited patients (suitable for either OR or EVAR) with slightly different entry characteristics with respect to age, sex, aneurysm morphology and other demographics. The EVAR-1, DREAM and OVER trials all showed an early survival benefit for EVAR, whereas the ACE trial did not. This early survival benefit for EVAR was lost within 1–3 years for EVAR-1 and the DREAM trial, but not until later for the OVER trial.[94,98,104] This 'catch-up' in mortality has been noted in many other studies, including a Cochrane review and analyses of the Medicare database,[108,139] but no satisfactory explanation for this phenomenon has emerged (the Cochrane review was limited by not being able to report aneurysm-related mortality or subgroup analyses).[139] Each trial individually has been too small to investigate the reasons for this 'catch-up' mortality in the EVAR groups or to answer the much-discussed question of whether or not younger and fitter patients (or other subgroups) should be offered OR, which is considered more durable than EVAR.[140,141] This 'catch-up' in mortality needs to be avoided if EVAR is to outperform OR in the longer term. To try to address some of these issues, the four randomised trials agreed to pool their data for an IPD meta-analysis.

Methods

In July 2013, MEDLINE, EMBASE and clinical trial databases were searched for randomised trials comparing OR and EVAR of AAAs. The search terms used were AAA, aneurysm, endovascular, stent, open repair and randomised trial. From 275 reports, we identified four eligible trials reporting mid-term follow-up. The methods for these four multicentre trials included in this meta-analysis have been published previously.[94,102,105,106] EVAR-1 randomised 1252 patients (91% male), with an aneurysm diameter of > 5.5 cm, between September 1999 and August 2004 in the UK. The DREAM trial randomised 351 patients (92% male), with an aneurysm diameter of ≥ 5 cm, between November 2000 and December 2003 in the Netherlands and Belgium. The OVER trial randomised 881 patients (99% male), with an aneurysm diameter of ≥ 5.0 cm, between October 2002 and April 2008 at Veteran Affairs hospitals in the USA. The ACE trial randomised 306 patients (99% male), with an aneurysm diameter of > 5.0 cm, between March 2003 and March 2008 in France (seven patients withdrew consent before discharge). All patients were considered fit for open surgery under general anaesthesia and all trials used approved devices for EVAR, predominantly within the manufacturers' IFU, and followed up patients for a minimum of 3 years. Summary baseline characteristics for patients by trial are shown in *Table 18*.

TABLE 18 Baseline and post-randomisation characteristics of patients in the four trials

Baseline variable	EVAR-1 (*n* = 1252)	DREAM (*n* = 351)	OVER (*n* = 881)	ACE (*n* = 299)
Age (years), mean (SD)	74 (6.1)	70 (6.7)	70 (7.8)	69 (7.4)
Male sex, *n* (%)	1135 (91)	332 (92)	876 (99)	296 (99)
BMI (kg/m^2), mean (SD)	26.5 (4.5)	26.7 (4.7)	28.6 (5.4)	27.2 (3.5)
Smoking status,[a] *n* (%)				
Current	270 (22)	130 (37)	363 (41)	72 (24)
Ex	863 (69)	78 (22)	481 (55)	75 (25)
Diabetes, *n* (%)	128 (10)	35 (10)	200 (23)	49 (16)
Previous angina/MI, *n* (%)	492 (39)	153 (44)	268 (30)	115 (38)
ABPI, mean (SD)[b]	1.0 (0.18)	1.0 (0.16)	0.98 (0.18)	NA
Creatinine level (μmol/l), median (IQR)	102 (90–119)	95 (84–109)	97 (80–110)	93 (82–110)
EQ-5D score, mean (SD)	0.82 (0.12)	0.84 (0.11)	0.85 (0.09)	NA
AAA diameter (cm), mean (SD)	6.5 (0.9)	6.0 (0.9)	5.7 (0.9)	5.6 (0.7)
AAA neck length (cm), mean (SD)	2.8 (1.2)	2.5 (1.2)	2.6 (1.2)	2.8 (1.0)
AAA neck diameter (cm), mean (SD)	2.35 (0.30)	2.39 (0.33)	2.26 (0.35)	2.36 (0.33)
Post-randomisation parameters				
Time (days) from randomisation to repair,[c] median (IQR)	40 (1–576)	39 (3–209)	17 (0–290)	27 (1–203)
Repair in compliance with randomisation, %	93	96	96	93
Follow-up for mortality (years), median (IQR)	6.0 (3.9–7.3)	6.0 (5.0–6.8)	5.4 (4.1–6.8)	3.1 (2.1–3.4)
30-day operative mortality, *n*/*N* (%)				
EVAR	11/614 (1.8)	2/170 (1.2)	1/439 (0.2)	2/150 (1.3)
OR	26/602 (4.3)	5/173 (2.9)	8/429 (1.9)	1/147 (0.7)
Reintervention rate, *n*/person-years (rate per 100 person-years)				
EVAR	174/3381 (5.1)	77/906 (8.5)	155/2334 (6.6)	32/419 (7.6)
OR	64/3309 (1.9)	41/932 (4.4)	104/2276 (4.6)	10/408 (2.5)

ABPI, ankle–brachial pressure index; IQR, interquartile range; NA, not available; SD, standard deviation.
a Ex-smokers in the ACE and DREAM trials were defined as those smoking in the 10 years prior to randomisation.
b Mean and median ABPI were almost identical.
c For those who underwent aneurysm repair.

Notes
Between-trial differences observed for all baseline characteristics; $p < 0.001$ (Kruskal–Wallis test for continuous variables, Pearson's chi-squared test for categorical variables).
Drug therapy was recorded differently for each trial so that it is not reported.

The four data sets were merged based on fields available in the case record forms of the largest trial (EVAR-1), range checks were conducted and queries resolved with the individual trial co-ordinating centres. The common baseline variables across the trials were age, sex, history of smoking, diabetes, coronary artery disease (defined as previous stable or unstable angina or MI), BMI, maximum aneurysm diameter, proximal aortic neck length and diameter, ankle–brachial pressure index (ABPI) and creatinine level, used for estimated glomerular filtration rate (eGFR),[142] but without information on ethnicity. Each trial also contained some data about hypertension, which was included in a modified Wilkins cardiovascular survival risk score[143] (*Table 19*). The reporting of both drug use (including antiplatelet and lipid-lowering agents)

TABLE 19 Derivation of a cardiovascular risk score based on a modified version of Wilkins *et al.*[143]

	Blood pressure	Previous MI	Diabetes	Smoking (never/ex/current)	EVAR-1, *n*	DREAM, *n*	OVER, *n*	ACE, *n*
All optimal	SBP < 120 mmHg and DBP < 80 mmHg (ACE trial only: no hypertension)	No	No	Never	4 (0)	3 (1)	7 (1)	31 (10)
	AND	AND	AND					
One or more not optimal	SBP 120–139 mmHg or DBP 80–89 mmHg (ACE trial only: SBP controlled by one drug or DBP ≤ 90 mmHg)	No	No	Never/ex	173 (14)	40 (11)	182 (21)	15 (5)
	OR	AND	AND					
One or more elevated	SBP 140–159 mmHg or DBP 90–99 mmHg (ACE trial only: one hypertensive drug for both SBP and DBP)	No	No	Never/ex	232 (19)	44 (13)	75 (9)	49 (16)
	OR	AND	AND					
One major	SBP ≥ 160 mmHg or DBP ≥ 100 mmHg (ACE trial only: two or more hypertensive drugs for both SBP and DBP or uncontrollable)	Yes	Yes	Current	579 (46)	149 (43)	397 (45)	109 (36)
	OR	OR	OR					
Two or more majors	SBP ≥ 160 mmHg or DBP ≥ 100 mmHg (ACE trial only: two or more hypertensive drugs or uncontrollable)	Yes	Yes	Current	264 (21)	112 (32)	219 (25)	95 (32)
	AND/OR	AND/OR	AND/OR					

DBP, diastolic blood pressure; SBP, systolic blood pressure.

Note

Of the 2783 individuals in the IPD data set, four did not have complete data on blood pressure/blood pressure-lowering drugs or history of MI, diabetes or smoking status to enable a cardiovascular risk score to be calculated. The remaining 2779 individuals were distributed across the risk categories as shown.

and reinterventions was very different in the four trials (particularly intestinal and wound-related reinterventions following OR). The postoperative surveillance protocol was identical for both randomised groups in all trials, except for the DREAM trial, in which, after 2 years, surveillance was relaxed for the OR group. However, for complications, only endoleaks after EVAR were reported similarly across the trials; laparotomy-related complications were not.

Statistical analysis

The primary analyses considered the groups 'as randomised' within each trial. Mortality after randomisation was assessed at 30 days, in hospital and then at three defined time periods: 0–6 months, 6 months–4 years and > 4 years after randomisation. Aneurysm-related mortality included death from (1) primary aneurysm rupture, (2) within 30 days of aneurysm repair or any reintervention; and (3) rupture after repair. Given the different times between randomisation and aneurysm repair in the four trials (*Table 20*), aneurysm-related mortality was also assessed at 30 days, 31 days–3 years and > 3 years after aneurysm repair. Kaplan–Meier survival curves by randomised group were generated from the combined data from all four trials and the restricted mean life-years up to a certain time estimated by the area under the curve up to that time. Logistic regression was used to compare operative (30-day) and in-hospital mortality among patients who underwent repair, and Cox proportional hazards regression was used to compare total and aneurysm-related mortality and time to reintervention. A two-stage IPD meta-analysis was performed. First analyses were conducted separately within each trial and then pooled time-period-specific estimates were calculated using random-effects meta-analysis with between-study heterogeneity estimated using the method of DerSimonian and Laird.[144] The proportion of between-trial variability beyond that expected by chance was quantified using the I^2-statistic.[145] All analyses were then repeated adjusting for the following baseline covariates: age, sex, maximum aneurysm diameter and log-creatinine level.

The subgroups age, sex, eGFR, coronary artery disease, ABPI, the modified Wilkins cardiovascular survival risk score, maximum aneurysm diameter, proximal aneurysm neck diameter and neck length were assessed for differences in the effect of the EVAR and open strategies by including an interaction term between the subgroup and randomised group in a Cox regression model. Except for sex and coronary artery disease, all measures were entered as continuous variables to assess effect modification. Each interaction term was pooled across the trials using random-effects meta-analysis and its statistical significance assessed using a Wald test, taking the 5% level as significant. For presentation purposes only (and not for assessing significance), HRs are shown by dichotomising continuous measures at chosen cut-off points: age (72 years), eGFR (68.4), ABPI (0.9), cardiovascular risk score (2 major), maximum aneurysm diameter (5.9 cm), neck diameter (2.3 cm), neck length (2.5 cm), estimating the HRs within each subgroup and pooling these across studies.

The hazard of reintervention following aneurysm repair was analysed using an Anderson–Gill multiple failure time model.[146]

All analyses were performed using Stata statistical software, version 13.

Results

A total of 2783 patients, with 14,245 person-years of follow-up, were included in this meta-analysis: their baseline characteristics are shown in *Table 18*, with significant intertrial differences in all variables. Patients in EVAR-1 were older and had larger aneurysms than patients in the other trials. Nearly all patients in the OVER and EVAR-1 trials had a history of smoking, compared with about half the patients in the DREAM and ACE trials. Nearly all patients in the OVER and EVAR-1 trials had a history of smoking, compared with about half the patients in the DREAM and ACE trials, and patients in the OVER trial had the highest BMI and highest proportion of patients with diabetes. Summary post-randomisation characteristics of the trials

TABLE 20 Unadjusted and adjusted HRs for total mortality by time since randomisation

All-cause mortality	EVAR-1 ($n = 1252$), *n* deaths/*N* (rate/100 person-years)	DREAM ($n = 351$), *n* deaths/*N* (rate/100 person-years)	OVER ($n = 881$), *n* deaths/*N* (rate/100 person-years)	ACE ($n = 299$), *n* deaths/*N* (rate/100 person-years)	Pooled ($n = 2783$), *n* deaths/*N* (rate/100 person-years)
All patients					
EVAR	260/626 (7.5)	58/173 (6.2)	146/444 (6.3)	17/150 (4.1)	481/1393 (6.7)
OR	264/626 (7.7)	60/178 (6.2)	146/437 (6.4)	12/149 (2.9)	482/1390 (6.8)
Time since randomisation					
0–6 months					
EVAR	26/626 (8.5)	6/173 (7.1)	11/444 (5.0)	3/150 (4.6)	46/1393 (6.7)
OR	45/626 (15.0)	10/178 (11.6)	17/437 (8.0)	1/149 (1.4)	73/1390 (10.9)
6 months–4 years					
EVAR	125/599 (6.7)	33/167 (6.2)	73/433 (5.2)	13/146 (3.8)	244/1345 (5.9)
OR	116/581 (6.3)	25/168 (4.6)	78/420 (5.9)	10/146 (3.0)	229/1315 (5.7)
> 4 years					
EVAR	109/472 (8.4)	19/134 (6.0)	62/348 (8.6)	1/33 (17.7)	191/987 (8.2)
OR	103/461 (7.9)	25/143 (7.4)	51/331 (7.0)	1/23 (17.5)	180/958 (7.6)
Unadjusted HR (95% CI)					
All patients	0.98 (0.82 to 1.16)	1.01 (0.70 to 1.44)	0.98 (0.78 to 1.23)	1.52 (0.71 to 3.24)	0.99 (0.87 to 1.13)
Time since randomisation					
0–6 months	0.57 (0.35 to 0.92)	0.60 (0.22 to 1.66)	0.63 (0.29 to 1.34)	2.95 (0.31 to 28.40)	0.61 (0.42 to 0.89)*
6 months–4 years	1.06 (0.82 to 1.37)	1.36 (0.81 to 2.29)	0.89 (0.65 to 1.23)	1.25 (0.55 to 2.83)	1.04 (0.87 to 1.25)
> 4 years	1.06 (0.81 to 1.39)	0.81 (0.45 to 1.47)	1.23 (0.85 to 1.78)		1.07 (0.88 to 1.32)
	EVAR-1 ($n = 1246$)	**DREAM ($n = 339$)**	**OVER ($n = 881$)**	**ACE ($n = 281$)**	**Pooled ($n = 2747$)**
Adjusted HR (95% CI)[a]					
All patients	1.00 (0.84 to 1.19)	0.88 (0.61 to 1.27)	1.04 (0.82 to 1.31)	1.43 (0.63 to 3.22)	1.01 (0.89 to 1.14)
Time since randomisation					
0–6 months	0.58 (0.36 to 0.95)	0.42 (0.14 to 1.25)	0.62 (0.29 to 1.33)	[b]	0.57 (0.39 to 0.84)**
6 months–4 years	1.08 (0.84 to 1.40)	1.15 (0.68 to 1.95)	0.94 (0.69 to 1.30)	1.14 (0.49 to 2.68)	1.05 (0.87 to 1.26)
> 4 years	1.11 (0.85 to 1.46)	0.79 (0.43 to 1.44)	1.30 (0.89 to 1.90)	[b]	1.12 (0.91 to 1.38)

*$0.01 < p < 0.05$, **$0.001 < p < 0.01$, ***$p < 0.001$.
a Adjusted for age, sex, maximum aneurysm diameter and log-creatinine level.
b Too few events to estimate a HR.

also are given in *Table 18*. The median follow-up was 6.0, 6.0, 5.4 and 3.1 years, for EVAR-1, the DREAM, OVER and ACE trials, respectively, 5.5 years for the pooled data and compliance with randomised allocation was 93% or higher in all trials.

Total mortality

Over the follow-up of all four trials there were 481 deaths in the EVAR groups and 482 in the OR groups. Kaplan–Meier curves by randomised group for total mortality across all four trials are shown in *Figure 13*. Overall, there was no difference in total mortality over the follow-up period of the trial (pooled HR 0.99, 95% CI 0.87 to 1.13) (*Figure 14a* and see *Table 20*). Between 0 and 6 months mortality was lower for the EVAR groups, with 46 deaths, than for OR, with 73 deaths (HR 0.61, 95% CI 0.42 to 0.89), with no evidence of heterogeneity between the trials. The early survival advantage of EVAR in the first 6 months was largely attributable to the lower 30-day operative mortality for EVAR than with OR (unadjusted pooled odds ratio 0.40, 95% CI 0.22 to 0.73) (*Figure 14b*). After this, the early advantage of the EVAR group was lost and the HRs moved (non-significantly) in the direction of OR. Adjusted HRs were similar. By 5 years the estimated survival was 73.6% (95% CI 71.1% to 75.9%) in both the EVAR and OR groups with an expected 0.06 additional life-years in the EVAR group, corresponding to 23 days (95% CI –16 to 61 days; $p = 0.246$). The causes of death by each time period are shown in *Table 21*.

Aneurysm-related mortality

The findings for aneurysm-related mortality were similar in direction, with relative benefit for the EVAR groups 0–6 months after randomisation (25 aneurysm-related deaths vs. 55 in the OR groups; pooled unadjusted HR 0.44, 95% CI 0.26 to 0.76). In later time periods the results move in the direction of OR, 6 months–4 years and > 4 years, with pooled HRs of 1.43 (95% CI 0.61 to 3.34) and 2.29 (95% CI 0.49 to 10.85), respectively (*Figure 15*). For those who received aneurysm repair, analysis by time from repair showed a strong relative advantage for the EVAR group in the first 30 days, between 30 days and 3 years there was no difference between the groups, but after 3 years there was a significant relative advantage for the OR group, with three aneurysm-related deaths compared with 19 deaths in the EVAR groups (HR 5.16, 95% CI 1.49 to 17.89; $p = 0.010$) (*Table 22*).

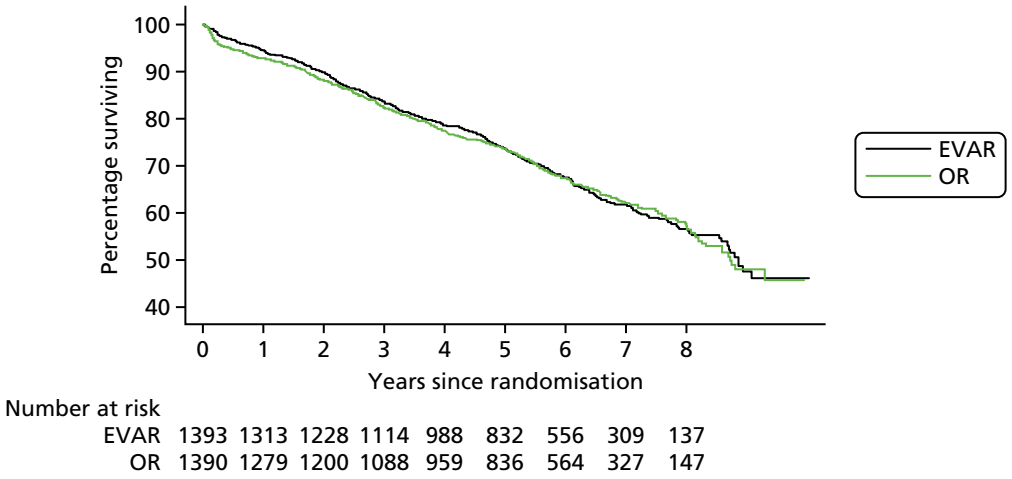


FIGURE 13 Kaplan–Meier survival curves for overall total mortality, by randomised group, for all four trials combined.

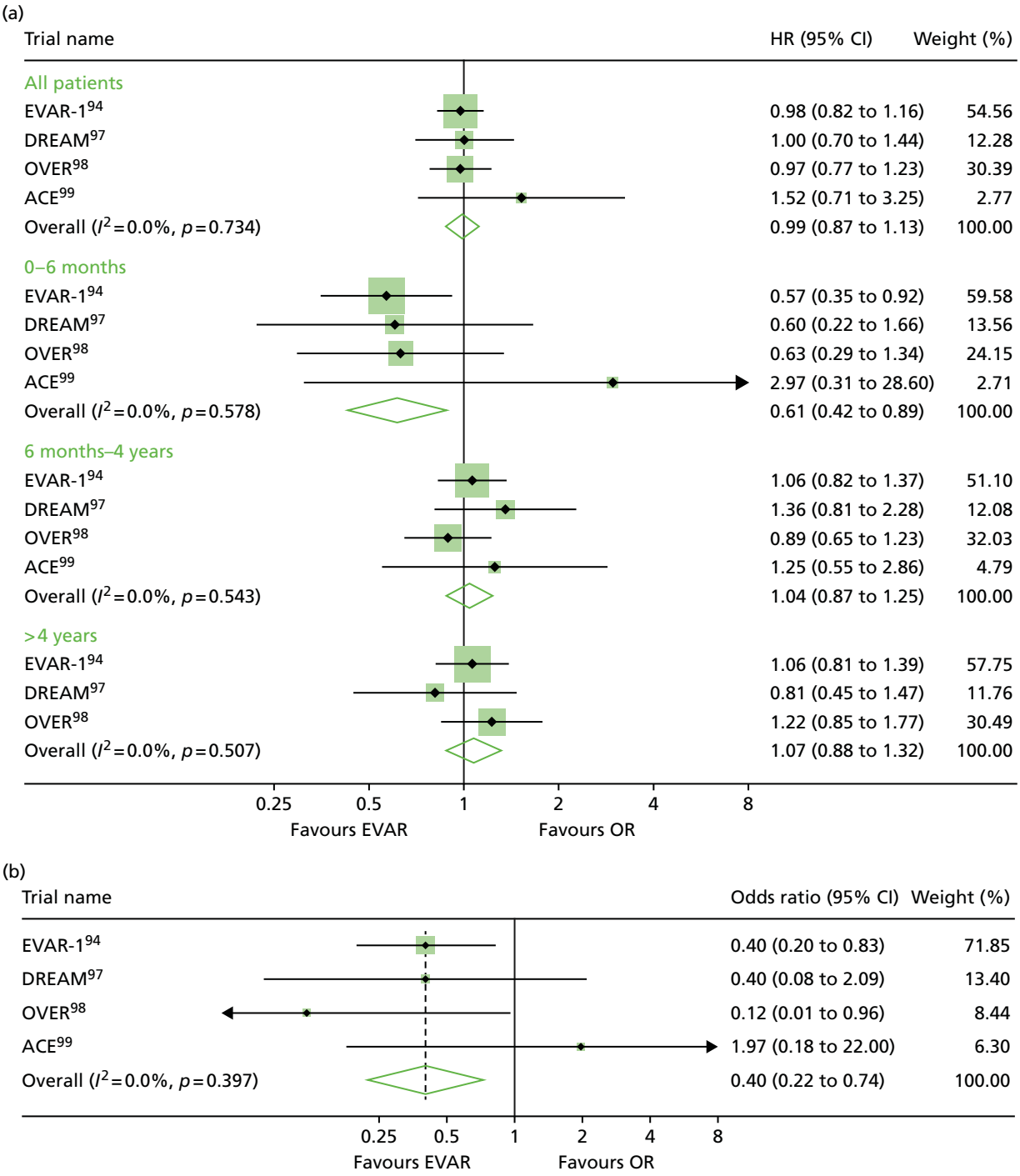


FIGURE 14 (a) Total mortality, overall and at 0–6 months, 6 months–4 years and > 4 years since randomisation, unadjusted HRs; and (b) mortality within 30 days of operation, showing odds ratio.

Total mortality by subgroups

There was no significant effect of age or sex on the relative effectiveness of EVAR in preventing deaths in any time period, including the first 6 months following randomisation (*Figure 16*). There were two subgroups of patients who appeared to have no early benefit (to 6 months) under EVAR compared with OR: patients with moderate renal dysfunction and those with coronary artery disease. For those with above-median eGFR, the pooled HR of 0.42 (95% CI 0.21 to 0.84) was significantly in favour of EVAR compared with the less favourable and non-significant pooled HR of 0.68 (95% CI 0.43 to 1.08) for those with worse renal function; therefore, the interaction between eGFR measure and treatment group was significant (interaction $p = 0.024$) (see *Figure 16*).

TABLE 21 Causes of death by randomised group and time since randomisation

	EVAR-1, *n* (%)		DREAM, *n* (%)		OVER, *n* (%)		ACE, *n* (%)	
Cause of death	EVAR (*n* = 26)	OR (*n* = 45)	EVAR (*n* = 6)	OR (*n* = 10)	EVAR (*n* = 11)	OR (*n* = 17)	EVAR (*n* = 3)	OR (*n* = 1)
0–6 months								
AAA related	14 (54)	30 (67)	3 (50)	10 (100)	5 (45)	14 (82)	3 (100)	1 (100)
MI/other cardiac	4 (15)	4 (9)	0 (0)	0 (0)	2 (18)	0 (0)	0 (0)	0 (0)
Stroke	0 (0)	1 (2)	0 (0)	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)
Other vascular	2 (8)	2 (4)	1 (17)	0 (0)	3 (27)	0 (0)	0 (0)	0 (0)
Cancer, lung	1 (4)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cancer, other	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)	3 (18)	0 (0)	0 (0)
Pulmonary	0 (0)	5 (11)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Renal	2 (8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	1 (4)	3 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	EVAR (*n* = 125)	OR (*n* = 116)	EVAR (*n* = 33)	OR (*n* = 25)	EVAR (*n* = 73)	OR (*n* = 78)	EVAR (*n* = 13)	OR (*n* = 10)
6 months–4 years								
AAA related	12 (10)	8 (7)	1 (3)	1 (4)	2 (3)	0 (0)	4 (31)	0 (0)
MI/other cardiac	27 (22)	25 (22)	8 (24)	6 (24)	16 (22)	15 (19)	2 (15)	4 (40)
Stroke	11 (9)	6 (5)	1 (3)	2 (8)	3 (4)	1 (1)	1 (8)	0 (0)
Other vascular	7 (6)	6 (5)	0 (0)	3 (12)	3 (4)	4 (5)	0 (0)	0 (0)
Cancer, lung	19 (15)	20 (17)	1 (3)	7 (28)	7 (10)	12 (15)	2 (15)	2 (20)
Cancer, other	20 (16)	29 (25)	12 (36)	2 (8)	18 (25)	15 (19)	2 (15)	1 (10)
Pulmonary	9 (7)	15 (13)	2 (6)	2 (8)	4 (5)	8 (10)	1 (8)	1 (10)
Renal	4 (3)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	1 (8)	1 (10)
Other	15 (12)	6 (5)	4 (12)	2 (8)	12 (16)	9 (12)	0 (0)	0 (0)
Unknown	1 (1)	0 (0)	4 (12)	2 (8)	8 (11)	13 (17)	0 (0)	1 (10)
	EVAR (*n* = 109)	OR (*n* = 103)	EVAR (*n* = 19)	OR (*n* = 25)	EVAR (*n* = 62)	OR (*n* = 51)	EVAR (*n* = 1)	OR (*n* = 1)
> 4 years								
AAA related	10 (9)	2 (2)	2 (11)	0 (0)	3 (5)	3 (6)	0 (0)	0 (0)
MI/other cardiac	28 (26)	26 (25)	6 (32)	9 (36)	15 (24)	10 (20)	0 (0)	0 (0)
Stroke	11 (10)	11 (11)	1 (5)	2 (8)	4 (6)	2 (4)	0 (0)	0 (0)
Other vascular	8 (7)	6 (6)	0 (0)	0 (0)	5 (8)	2 (4)	0 (0)	0 (0)
Cancer, lung	9 (8)	9 (9)	0 (0)	0 (0)	7 (11)	7 (14)	0 (0)	0 (0)
Cancer, other	14 (13)	20 (19)	4 (21)	7 (28)	7 (11)	11 (22)	0 (0)	0 (0)
Pulmonary	14 (13)	17 (17)	3 (16)	2 (8)	9 (15)	11 (22)	0 (0)	0 (0)
Renal	4 (4)	2 (2)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Other	11 (10)	10 (10)	3 (16)	1 (4)	5 (8)	1 (2)	0 (0)	0 (0)
Unknown	0 (0)	0 (0)	0 (0)	3 (12)	7 (11)	4 (8)	1 (100)	1 (100)

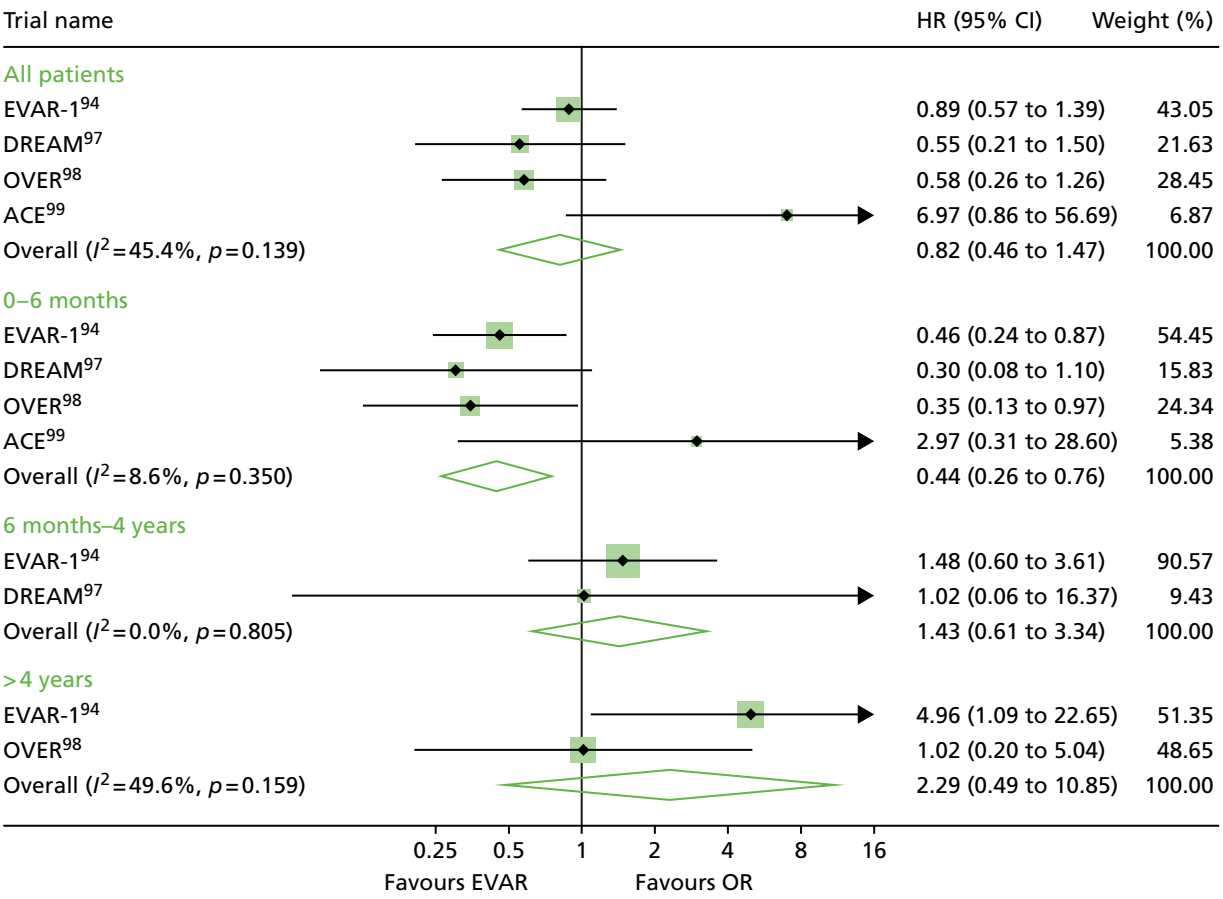


FIGURE 15 Aneurysm-related mortality, overall and at 0–6 months, 6 months–4 years and > 4 years since randomisation. Unadjusted HRs.

Similarly, patients with coronary artery disease gained no early advantage of being in the EVAR group, in comparison with patients without prior coronary artery disease (interaction $p = 0.047$) (*Figure 17*). None of the morphological aneurysm characteristics, smoking, diabetes or BMI was associated with mortality (*Figures 18* and *19*).

Baseline ABPI was not available for the ACE trial. In the other trials, patients with peripheral arterial disease (low ABPI of < 0.9) had a similar early survival advantage from being in the EVAR group as those with a ABPI of ≥ 0.9. However, in the 6 months to 4 years time period, for those with a ABPI of < 0.9, the OR group had the survival advantage (HR 1.67, 95% CI 1.12 to 2.49), in comparison with patients with a ABPI of > 0.9 (interaction $p = 0.022$). During the 6 months to 4 years time period, for those with a ABPI of < 0.9, total mortality was 9.6 and 5.7 per 100 person-years in the EVAR and OR groups, respectively, compared with 5.1 and 5.8 per 100 person-years, respectively, in the higher ABPI group. The cause of death in the two ABPI groups by time period is shown in *Table 23*. The operative mortality by subgroup shows that the highest mortality was in those with low ABPI (*Table 24*) and this group has higher aneurysm-related mortality throughout. Finally, a cardiovascular risk score was not discriminatory at any time period.

Complications and reinterventions

Complications (apart from endoleaks after EVAR) and reinterventions were reported heterogeneously across the four trials. The overall rates of reinterventions reported were higher in the EVAR group than in the OR group for all trials (see *Table 18*). The risk of reintervention by time period following aneurysm repair is shown in *Figure 20*, with substantial heterogeneity between trials for reinterventions recorded between 31 days and 3 years.

TABLE 22 Unadjusted and adjusted HRs for aneurysm-related mortality by time since operation for those who underwent surgery

Aneurysm-related mortality	EVAR-1 ($n = 1216$) *n* deaths/*N* (rate/100 person-years)	DREAM ($n = 343$) *n* deaths/*N* (rate/100 person-years)	OVER ($n = 868$) *n* deaths/*N* (rate/100 person-years)	ACE ($n = 297$) *n* deaths/*N* (rate/100 person-years)	Pooled ($n = 2724$) *n* deaths/*N* (rate/100 person-years)
All patients					
EVAR	31/614 (0.9)	6/170 (0.7)	9/439 (0.4)	7/150 (1.7)	53/1373 (0.8)
OR	32/602 (1.0)	10/173 (1.1)	13/429 (0.6)	1/147 (0.3)	56/1351 (0.8)
Time since operation					
0–30 days					
EVAR	11/614 (22.0)	2/170 (14.3)	1/439 (2.8)	2/150 (16.4)	16/1373 (14.2)
OR	26/602 (53.7)	5/173 (35.5)	8/429 (22.9)	1/147 (8.3)	40/1351 (36.5)
31 days–3 years					
EVAR	7/603 (0.4)	2/168 (0.4)	5/438 (0.4)	4/148 (1.1)	18/1357 (0.5)
OR	4/576 (0.3)	5/168 (1.1)	4/421 (0.3)	0/146 (0.0)	13/1311 (0.4)
> 3 years					
EVAR	13/498 (0.8)	2/140 (0.5)	3/380 (0.3)	1/78 (2.3)	19/1096 (0.6)
OR	2/484 (0.1)	0/146 (0.0)	1/352 (0.1)	0/72 (0.0)	3/1054 (0.1)
Unadjusted HR					
All patients	0.94 (0.57 to 1.54)	0.61 (0.22 to 1.68)	0.68 (0.29 to 1.59)	6.86 (0.84 to 55.78)	0.89 (0.51 to 1.56)
Time since operation					
0–30 days	0.41 (0.20 to 0.83)	0.40 (0.08 to 2.08)	0.12 (0.02 to 0.97)	1.97 (0.18 to 21.76)	0.41 (0.22 to 0.74)**
31 days–3 years	1.69 (0.50 to 5.77)	0.40 (0.08 to 2.08)	1.20 (0.32 to 4.47)	[a]–	1.07 (0.49 to 2.36)
> 3 years	6.35 (1.43 to 28.15)	[a]–	3.18 (0.33 to 30.64)	[a]–	5.16 (1.49 to 17.89)*
	EVAR-1 ($n = 1211$)	**DREAM ($n = 331$)**	**OVER ($n = 868$)**	**ACE ($n = 280$)**	**Pooled ($n = 2690$)**
Adjusted HR[b]					
All patients	0.97 (0.59 to 1.59)	0.44 (0.15 to 1.30)	0.71 (0.30 to 1.67)	[a]–	0.81 (0.55 to 1.21)
Time since operation					
0–30 days	0.42 (0.21 to 0.86)	0.21 (0.02 to 1.85)	0.13 (0.02 to 1.05)	[a]–	0.36 (0.19 to 0.67)**
31 days–3 years	1.82 (0.52 to 6.36)	0.32 (0.06 to 1.65)	1.13 (0.29 to 4.39)	[a]–	0.98 (0.38 to 2.55)
> 3 years	6.58 (1.48 to 29.21)	[a]–	3.19 (0.33 to 31.26)	[a]–	5.30 (1.52 to 18.46)**

*$0.01 < p < 0.05$, **$0.001 < p < 0.01$, ***$p < 0.001$.
a Too few events to estimate a HR.
b Adjusted for age, sex, maximum aneurysm diameter and log-creatinine level.

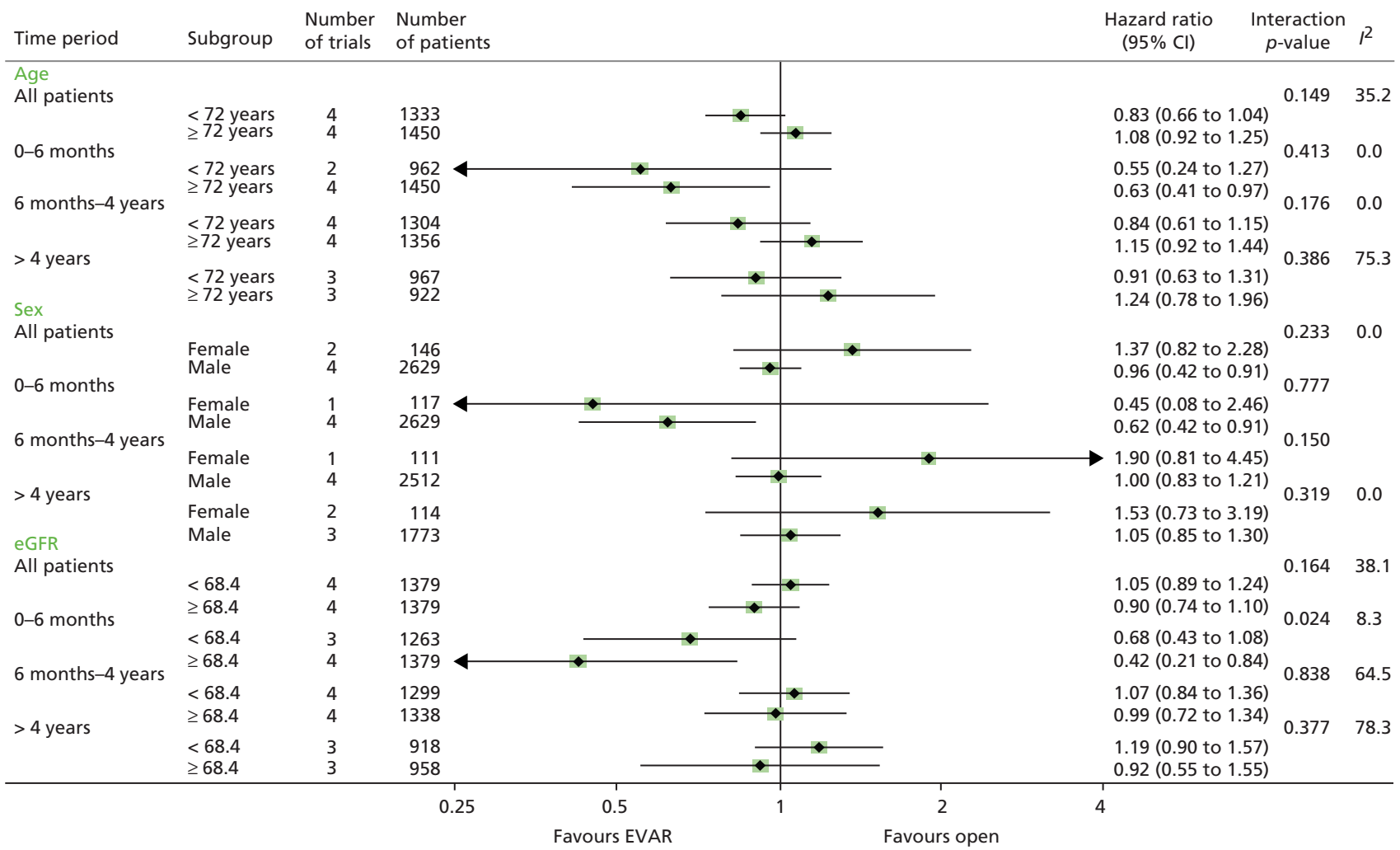


FIGURE 16 Unadjusted HRs for total mortality by subgroups of age, sex and eGFR: overall and at 0–6 months, 6 months–4 years and > 4 years since randomisation. Interaction *p*-value for age and eGFR calculated using the continuous measures (median eGFR 68.4). Not all trials contribute to the subgroup analyses or every time point.

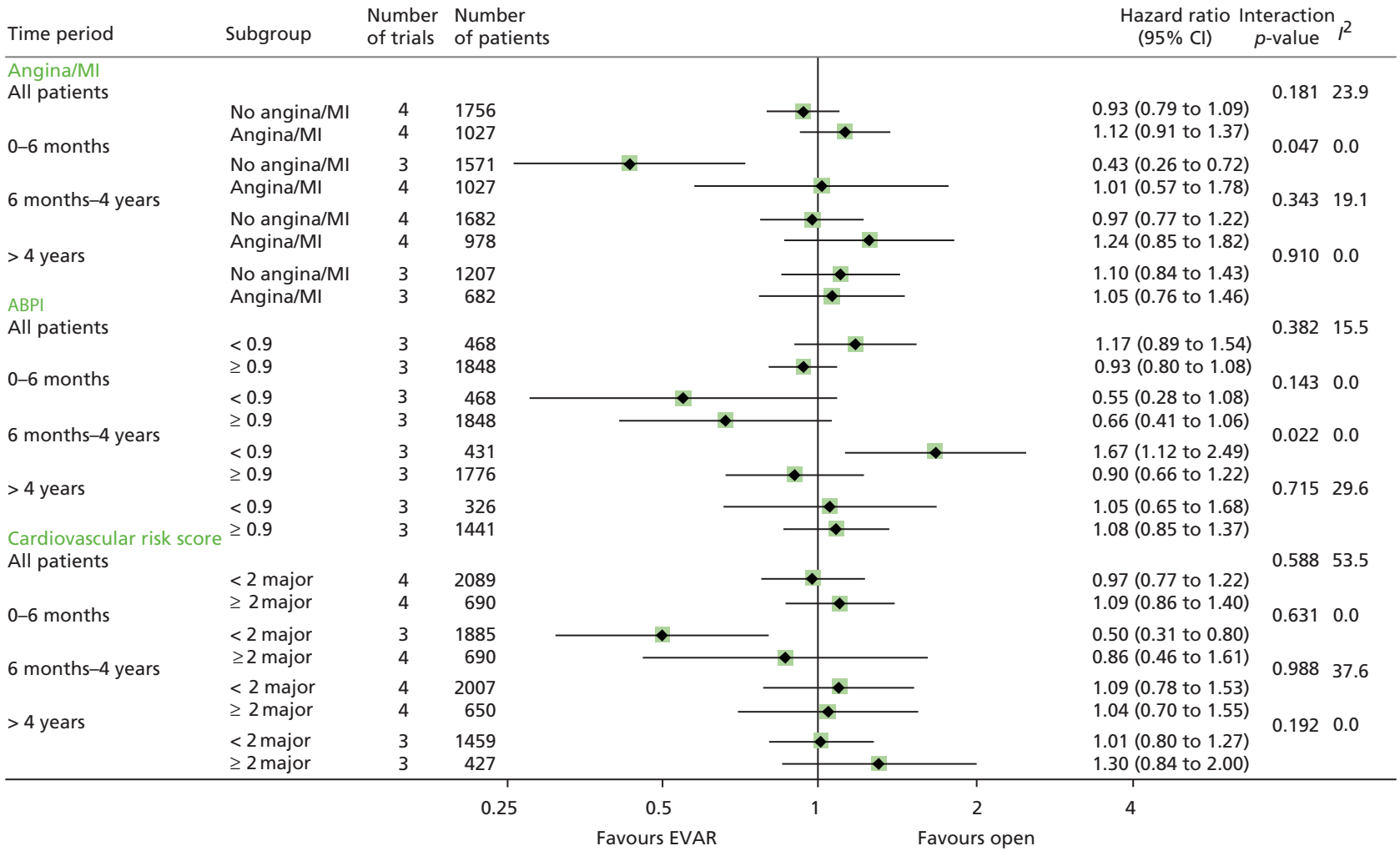


FIGURE 17 Unadjusted HRs for total mortality by subgroups of history of angina or MI, ABPI and cardiovascular risk score: overall and at 0–6 months, 6 months–4 years and > 4 years since randomisation. Interaction *p*-values for ABPI and cardiovascular risk score calculated using the continuous measures. Not all trials contribute to the subgroup analyses or every time point.

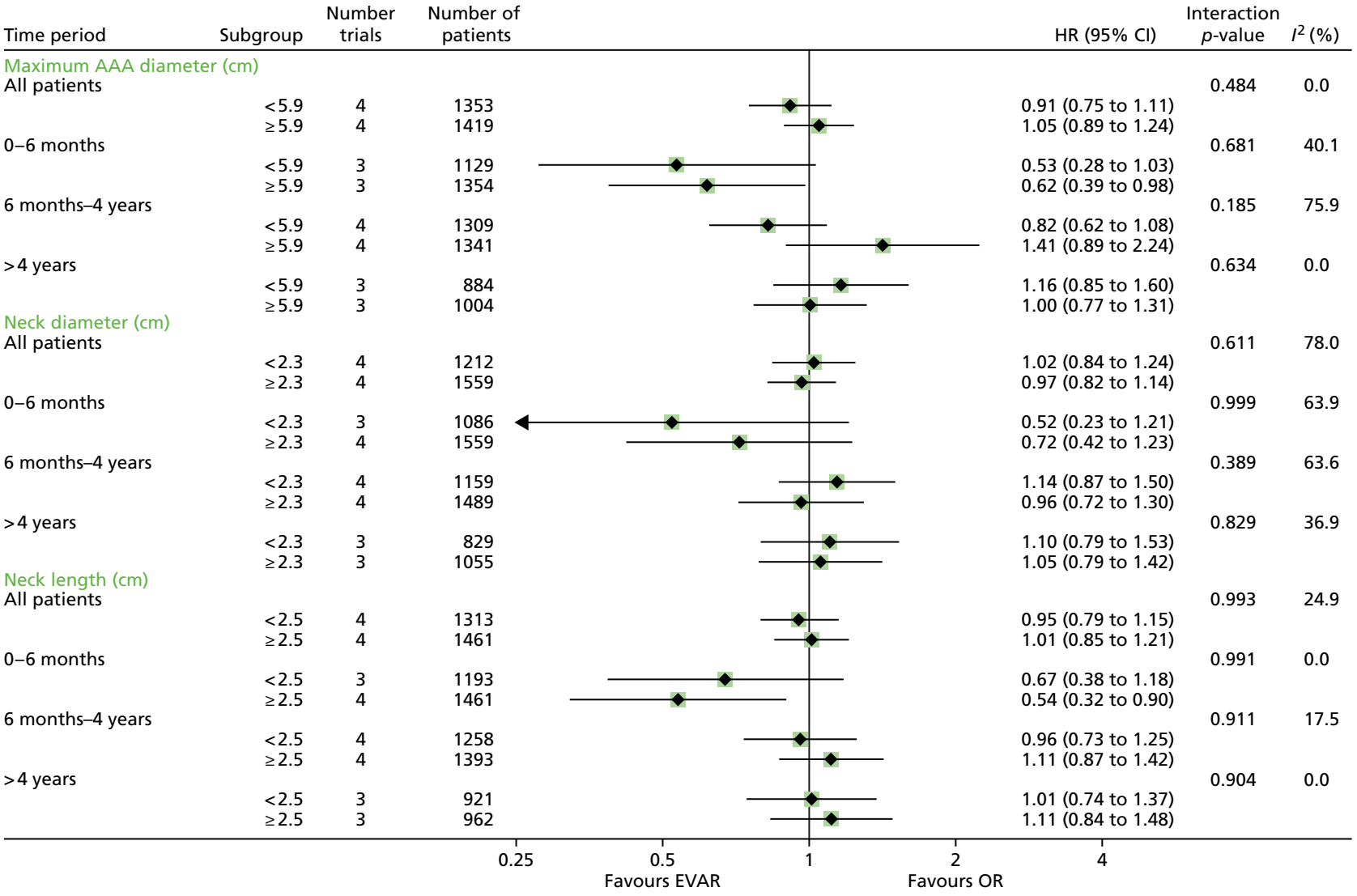


FIGURE 18 Unadjusted HRs for total mortality by subgroups of maximum AAA diameter, neck diameter and neck length: overall and at 0–6 months, 6 months–4 years and > 4 years since randomisation. Interaction *p*-values for maximum AAA diameter, neck diameter and neck length calculated using the continuous measures. The number of trials contributing to each analysis is shown.

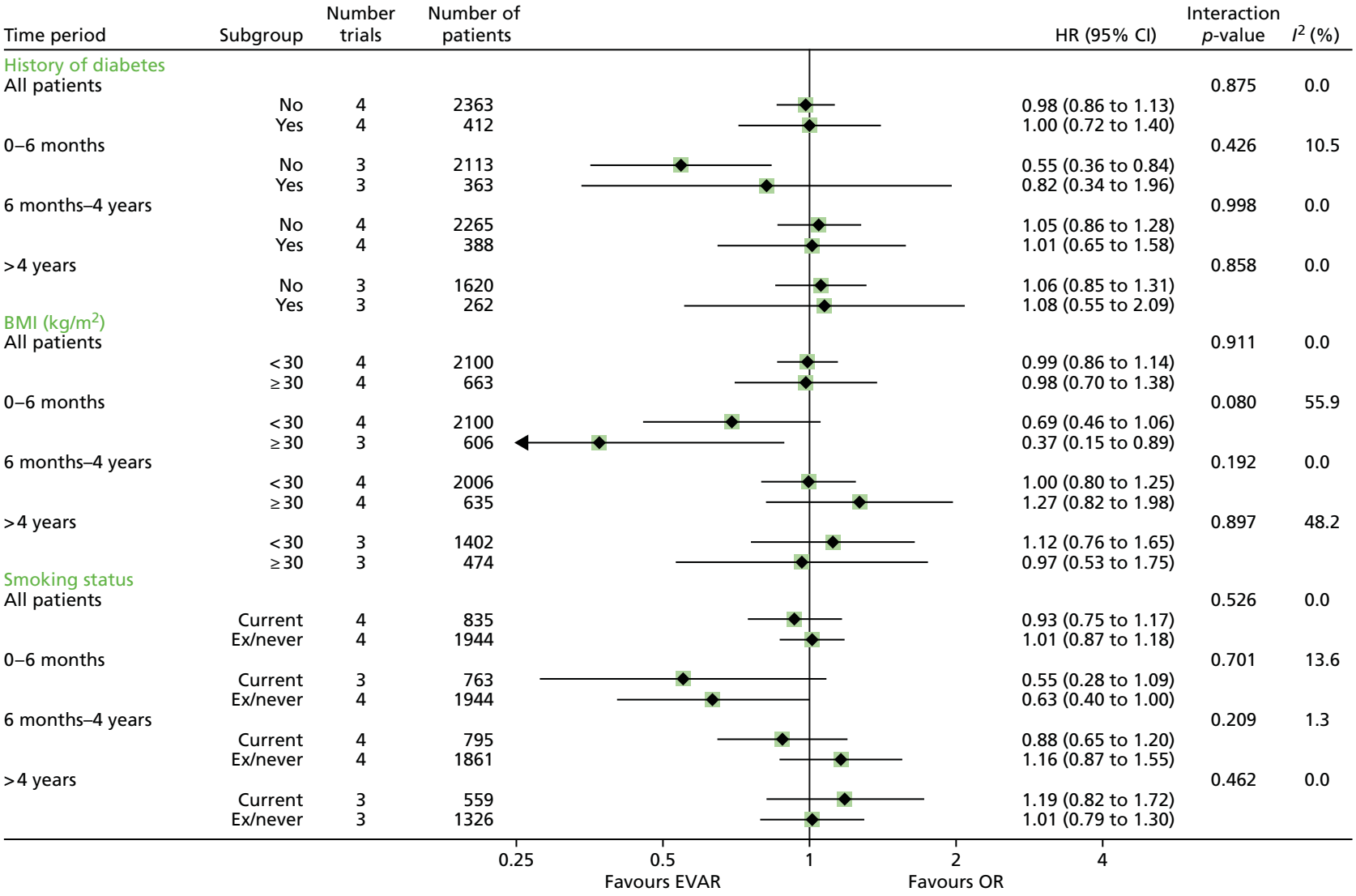


FIGURE 19 Unadjusted HRs for total mortality by subgroups of history of diabetes, BMI and smoking status: overall and at 0–6 months, 6 months–4 years and > 4 years since randomisation. Interaction *p*-values for BMI calculated using the continuous measures. The number of trials contributing to each analysis is shown.

TABLE 23 Causes of death by categorisation of baseline ABPI and time since randomisation

	ABPI < 0.9, *n*		ABPI ≥ 0.9, *n*	
Cause of death	**EVAR (*n* = 13)**	**OR (*n* = 23)**	**EVAR (*n* = 29)**	**OR (*n* = 43)**
0–6 months				
AAA related	7 (54)	18 (78)	15 (52)	30 (70)
MI/other cardiac	0 (0)	1 (4)	6 (21)	3 (7)
Stroke	0 (0)	0 (0)	1 (3)	1 (2)
Other vascular	4 (31)	2 (9)	2 (7)	0 (0)
Cancer, lung	1 (8)	0 (0)	1 (3)	0 (0)
Cancer, other	0 (0)	0 (0)	2 (7)	3 (7)
Pulmonary	0 (0)	2 (9)	0 (0)	0 (0)
Renal	1 (8)	0 (0)	1 (3)	0 (0)
Other	0 (0)	0 (0)	1 (3)	3 (7)
Unknown	0 (0)	0 (0)	0 (0)	0 (0)
	EVAR (*n* = 62)	**OR (*n* = 39)**	**EVAR (*n* = 149)**	**OR (*n* = 161)**
6 months–4 years				
AAA related	6 (10)	3 (8)	7 (5)	6 (4)
MI/other cardiac	15 (24)	10 (26)	33 (22)	31 (19)
Stroke	3 (5)	1 (3)	12 (8)	7 (4)
Other vascular	5 (8)	3 (8)	5 (3)	5 (3)
Cancer, lung	6 (10)	5 (13)	20 (13)	30 (19)
Cancer, other	8 (13)	10 (26)	40 (27)	34 (21)
Pulmonary	6 (10)	3 (8)	7 (5)	20 (12)
Renal	1 (2)	0 (0)	3 (2)	2 (1)
Other	7 (11)	2 (5)	17 (11)	14 (9)
Unknown	5 (8)	2 (5)	5 (3)	12 (7)
	EVAR (*n* = 35)	**OR (*n* = 36)**	**EVAR (*n* = 144)**	**OR (*n* = 131)**
> 4 years				
AAA related	3 (9)	4 (11)	12 (8)	1 (1)
MI/other cardiac	9 (26)	14 (39)	34 (24)	25 (19)
Stroke	2 (6)	4 (11)	13 (9)	10 (8)
Other vascular	4 (11)	3 (8)	8 (6)	4 (3)
Cancer, lung	0 (0)	0 (0)	14 (10)	16 (12)
Cancer, other	3 (9)	3 (8)	22 (15)	35 (27)
Pulmonary	7 (20)	3 (8)	19 (13)	23 (18)
Renal	0 (0)	2 (6)	4 (3)	1 (1)
Other	3 (9)	0 (0)	15 (10)	12 (9)
Unknown	4 (11)	3 (8)	3 (2)	4 (3)

TABLE 24 Operative mortality by subgroup level, for individuals who underwent an operation

Subgroup	Operative mortality, *n*/*N* (%)
Age (years)	
< 72	12/1311 (0.9)
≥ 72	44/1413 (3.1)
Sex	
Female	6/150 (4.0)
Male	50/2574 (1.9)
eGFR	
< 68.4	35/1341 (2.6)
≥ 68.4	20/1360 (1.5)
Angina/MI	
No angina/MI	35/1721 (2.0)
Angina/MI	21/1003 (2.1)
ABPI	
< 0.9	19/455 (4.2)
≥ 0.9	29/1813 (1.6)
Cardiovascular risk score	
< 2 major	43/2052 (2.1)
≥ 2 major	13/668 (2.0)
Maximum AAA diameter (cm)	
< 5.9	18/1330 (1.4)
≥ 5.9	37/1383 (2.7)
Neck diameter (cm)	
< 2.3	23/1191 (1.9)
≥ 2.3	33/1521 (2.2)
Neck length (cm)	
< 2.5	29/1284 (2.3)
≥ 2.5	27/1431 (1.9)
History of diabetes	
No	47/2317 (2.0)
Yes	9/399 (2.3)
BMI (km/m^2)	
< 30	44/2057 (2.1)
≥ 30	11/649 (1.7)
Smoking status	
Current	14/814 (1.7)
Ex/never	42/1906 (2.2)

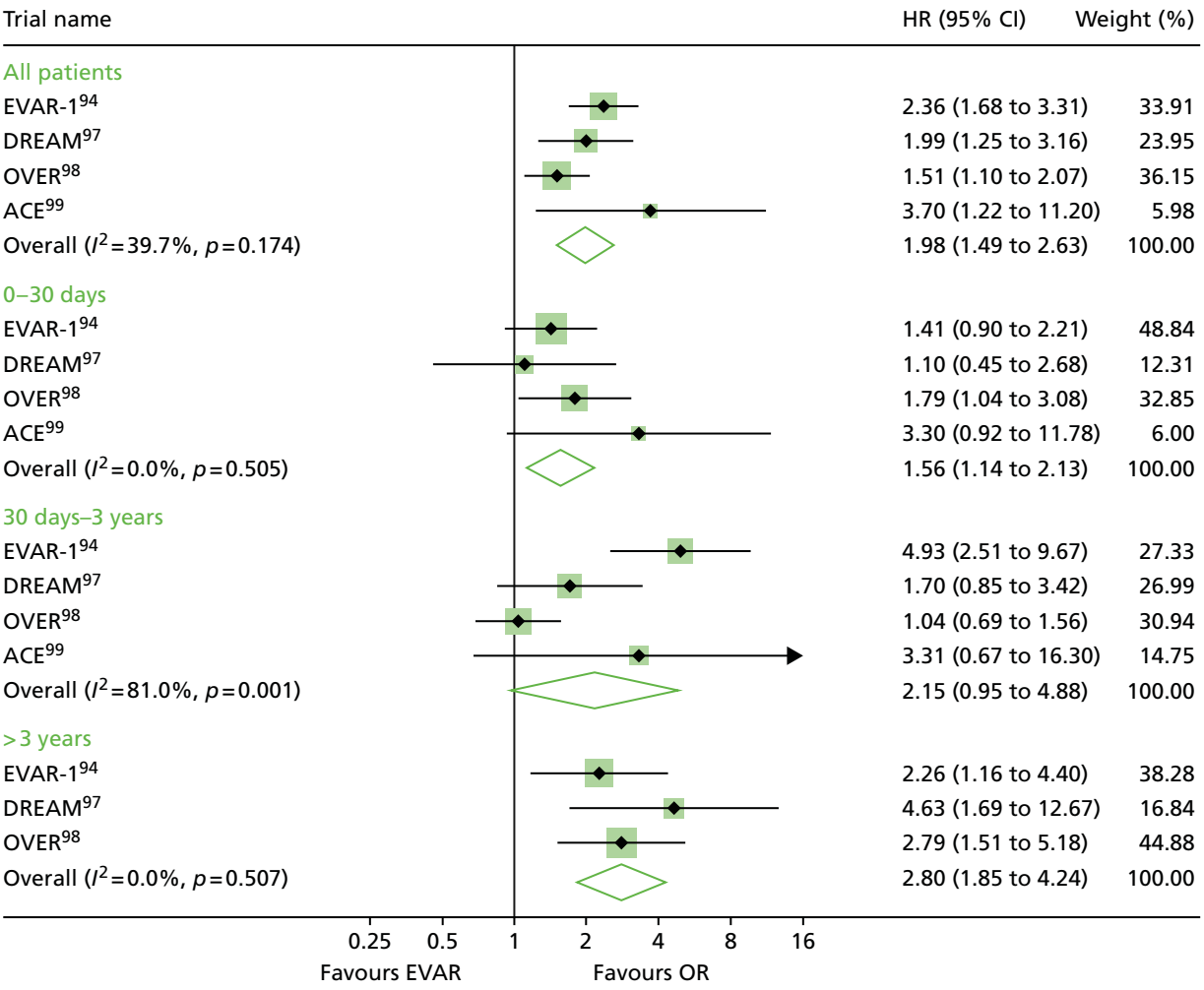


FIGURE 20 Hazard ratio for any reintervention by time period following aneurysm repair for 2718 subjects undergoing aneurysm repair (seven subjects missing follow-up for reinterventions after aneurysm repair). Note that the number of reinterventions reported here may differ slightly from those reported by the individual trial publications, particularly for the OVER trial where more reinterventions after EVAR-1 were included in their trial report. This difference is mainly attributable to the different ways in which reinterventions were categorised across the trials. For instance, amputations were included in reinterventions for the OVER trial, but placed in a separate category for all the other trials and this meta-analysis. Similarly, below knee reconstructions were included as OVER trial reinterventions, but were not included for the meta-analysis unless there was clear evidence that these procedures were aneurysm related.

There was no indication that complications following EVAR decreased with the year in which the trial commenced: these rates, together with types and numbers of complications, are reported in *Table 25*. The most common reported complication after EVAR was type II endoleak, which overall was reported 435 times in 325 of 2783 (12%) patients, with corrective reintervention being performed in 99 of 435 (23%) detected type II endoleaks. The second most common type of complication was type I endoleak, for which 79 of 120 (66%) patients received an early reintervention. Similarly, early correction of other serious EVAR-related complications was attempted only in less than two-thirds of cases. Secondary sac rupture was reported in 37 patients – 33 in the EVAR randomised groups (2.4% of patients) and four in the OR groups (0.3% of patients); although all four of these patients were treated with EVAR, for those with secondary rupture following treatment with EVAR, the median time to rupture was 3.5 years (*Figure 21*). Of these patients, 11 (30%) had a type I endoleak, of which seven were treated, seven (19%) had a type II endoleak, of which three were treated, two (5%) had a type III endoleak, of which one was treated, and nine had known graft migration. Nineteen (51%) patients had no endoleaks detected before secondary sac rupture and one further patient had a thoracic endograft for proximal aortic dissection 3 days earlier. The mean time between detection of the first endoleak and rupture was 1.8 years. The 30-day mortality rate following rupture was 62% ($n = 23$).

TABLE 25 Complications by trial, focusing on EVAR-related complications

	EVAR-1 (*n* = 1252)	DREAM[a] (*n* = 351)	OVER (*n* = 881)	ACE (*n* = 299)	Total (*n* = 2783)
Follow-up for complications, years mean (SD)	5.3 (2.5)	5.2 (2.2)	5.2 (2.1)	2.8 (1.1)	5.0 (2.4)
Rate of complications, *n*/person-years (rate per 100 person-years)					
EVAR	315/3381 (9.3)	125/906 (13.8)	209/2334 (9.0)	103/419 (24.6)	752/7040 (10.7)
OR	27/3309 (0.8)	7/932 (0.8)	13/2276 (0.6)	8/408 (2.0)	55/6925 (0.8)
Type of complication,[b] *n* (*n* treated)					
Type I endoleak	56 (35)	24 (17)	25 (19)	15 (8)	121 (79)
Type II endoleak	146 (39)	73 (12)	139 (38)	77 (10)	435 (99)
Type III endoleak	25 (15)	5 (1)	7 (7)	0 (0)	37 (23)
Type IV endoleak	0 (0)	0 (0)	5 (2)	0 (0)	5 (2)
Type V endoleak	0 (0)	0 (0)	11 (3)	5 (0)	16 (3)
Secondary rupture	27 (10)	2 (2)	5 (4)	3 (3)	37 (18)
Rate of secondary rupture after EVAR per 100 person-years	0.7	0.1	0.2	0.7	0.5

SD, standard deviation.
a After 2 years only complications with reinterventions were reported.
b Total number during primary admission and after discharge, allowing for patients to have recurring endoleaks. Generally, reinterventions during the primary stay were not linked to the complications of graft migration, graft thrombosis and graft infection, so that the total number of these complications receiving treatment cannot be reported.

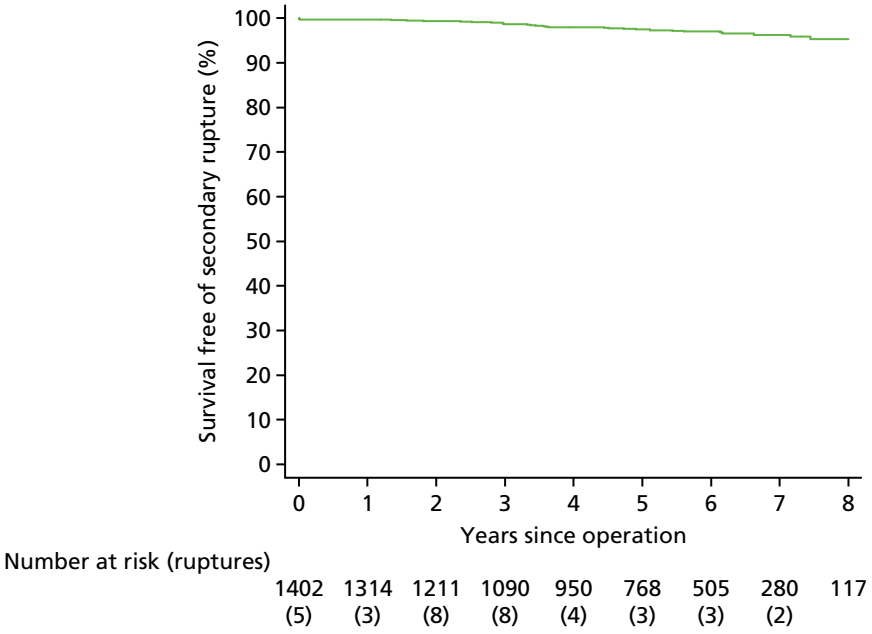


FIGURE 21 Time from repair to secondary rupture, in those who were treated with EVAR.

Discussion

These four randomised trials, in Europe and the USA, provide the best evidence for the early survival advantage offered by EVAR rather than OR. Patients prefer the less invasive method of AAA repair, EVAR, which has been widely adopted, and the majority of elective repairs are now performed using EVAR.[108,120,147] This meta-analysis, over a 5-year time horizon, confirms that overall there is an early survival advantage under EVAR, which is lost within 3 years of randomisation, so that the life-years saved from EVAR over a 5-year time period are minimal. Between 0 and 6 months after randomisation, total and aneurysm-related mortality were lower for the EVAR group, mainly because of the 2.5-fold lower operative mortality in this group. However, after this time period, the early EVAR group advantage was eroded progressively. By 3 years after aneurysm repair, aneurysm-related mortality was five times higher in the EVAR group (at this stage mainly because of secondary rupture or reinterventions), and this is likely to contribute to the 'catch-up' in mortality.

The next investigations focused on whether the early survival advantage was either maintained or lost in subgroups of patients categorised by their preoperative characteristics. Over a 5-year time horizon, there was no convincing evidence that being randomised to EVAR or OR resulted in differential survival between any subgroups of the population. This does not support the suggestion that younger and fitter patients with aortic morphology suitable for EVAR are likely to benefit from OR over 5 years.[140] However, differential effect modification was suggested in some subgroups (renal dysfunction, coronary artery disease) in the first 6 months and for those with peripheral arterial disease in the later 6 months–4 years time period, possibly caused by frailty effects.

Low ABPI was introduced as a measure of peripheral atherosclerosis[148] and is a marker of generalised atherosclerosis.[149] This subgroup had the highest pooled operative mortality, although the relative early advantage of EVAR was maintained. However, between 6 months and 4 years, fortunes reversed in favour of a survival advantage in the OR group, a pattern which indicates that those with low ABPI are another contributor to the 'catch-up' in mortality phenomenon.

All trials enrolled patients with evidence of moderate renal dysfunction, 35% of the overall enrolment having eGFR < 60 (chronic kidney disease stage 3 or above). For these patients, there was no evidence of a benefit from being randomised to EVAR (vs. OR), even in the first 6 months. These data are in agreement with an earlier observational study showing a high early postoperative event rate for patients with a low eGFR.[150] Whether or not renal function deteriorates more rapidly after either elective EVAR or OR of an AAA has been debated fiercely and less attention has been focused on improving the perioperative care.[151] Similarly, patients with known coronary artery disease had no evidence of an early survival advantage from being randomised to EVAR. Given that EVAR is less invasive than OR, these findings for the moderate renal dysfunction and coronary artery disease are surprising. Perhaps the stress of EVAR in these subgroups has been underestimated. It also is possible that those randomised to EVAR received less stringent preoperative evaluations, resulting in better perioperative care for the OR group with these comorbidities.

This study has several limitations that restrict its scope. First, all endografts were implanted between 1999 and 2008 using general anaesthesia, and today newer endografts are used, often implanted under local anaesthesia. Second, reporting standards for baseline characteristics (e.g. smoking, drugs) differed between trials. Third, the reporting of complications and reinterventions (aneurysm related and other cardiovascular) was very heterogeneous across the trials. Moreover, today it is recognised that type II endoleaks with sac enlargement can be dangerous[111] and that a type II endoleak might even hide a type I or type III endoleak. Fourth, at the time these trials recruited (1999–2008), no trial had a clear policy for reintervention in the presence of endoleaks after EVAR and even serious complications such as type I endoleak were not always corrected quickly, which may have contributed to the increasing aneurysm-related mortality rate in the EVAR group at ≥ 3 years after aneurysm repair.

The reintervention rate was consistently higher in the EVAR groups (see *Table 18*), although the data are heterogeneous and the largest trial did not report incision-related complications after OR. It would be reassuring to learn that by using more recent EVAR devices within IFU, coupled with more rigorous surveillance, the continuing aneurysm-related mortality in the EVAR group could be attenuated to minimise the 'catch-up' in mortality. To rely entirely on the introduction of new devices to prevent aneurysm-related mortality in the EVAR group, especially without adequate surveillance, may be unwise. Recent analyses of the Medicare database support this caution.[108]

In summary, this meta-analysis confirms the advantage of lower mortality in the EVAR group in the first 6 months and provides some new insight of how this early advantage of the EVAR group is eroded (aneurysm-related mortality and inclusion of those with peripheral arterial disease). Additionally, two subgroups were identified who do not have lower mortality under EVAR at any time, to suggest that these groups (moderate renal dysfunction and established coronary artery disease) may benefit from improved perioperative care, especially for EVAR. Surveillance must focus on reducing aneurysm-related deaths in the mid-term and longer term, particularly deaths resulting from reinterventions and secondary ruptures after EVAR.

Chapter 7 The significance of type II endoleaks following endovascular aneurysm repair: results from the individual patient data meta-analysis

There was a call with vignette (NIHR Evaluation, Trials and Studies Coordinating Centre – HTA 2012 – Interventional Procedures Panel) for possible funding on the management of endoleaks following EVAR.

In the vignette, the incidence of type II endoleak is shown to range from 0% to 17% 30 days post EVAR (decreasing to 1–8% at 6 months' follow-up).[152] It is also noted that current evidence on type II endoleak is insufficient to define criteria for intervention in isolated type II endoleak after EVAR.[153] In addition, the question of static sac size is raised.[154] Attempts have been made to classify diagnoses of management following endovascular thoracic and abdominal aortic repair.[155] Additionally, management of type II endoleak (preoperative vs. postoperative vs. expectant management) provided a summary of the known position in 2009[156] and a retrospective study with CT angiography evaluating the potential outcome of predictors in type II endoleak was also available in 2011.[157]

Type II endoleaks are a common complication of endovascular repair of AAA (EVAR). The sensitivity and specificity of the detection depends on the imaging modalities used for postoperative EVAR surveillance, with magnetic resonance imaging being described as the most sensitive method. Less sensitive but more commonly used is CT or duplex scanning, with or without contrast.

The natural history of type II endoleaks remains poorly understood and, as a result, the optimal management and long-term success of interventions are currently unknown. Studies regarding the significance of type II endoleak have shown mixed results. Some studies have shown that type II endoleaks are not associated with adverse outcomes, whereas other studies have shown that persistent type II endoleak is associated with aneurysm sac growth, increased risk of rupture, reintervention and need for conversion to OR.[158] However, most studies are in agreement that uncorrected type II endoleak may result in persistently elevated pressure in the sac without sac shrinkage.[159] There is a long-standing debate whether or not, in the absence of sac expansion, intervention is required for type II endoleaks and many are thought to resolve spontaneously. There is also a debate whether or not persistent type II endoleaks are in fact hidden type I endoleaks (with due required correction).

Individual patient data meta-analysis

This is described in *Chapter 6*. In the merging of the data from the four RCTs, for complications only endoleaks after EVAR were similar across the trials.

The hazard of reintervention following aneurysm repair was analysed using a multiple failure time model. In addition, for patients who received EVAR, mortality HRs were investigated in individuals without and with a detected/treated type II endoleak.

Results on type II endoleak from the individual patient data meta-analyses

For patients who received EVAR (including patients who were randomised to OR but crossed over), mortality HRs were investigated in individuals without and with a detected/treated type II endoleak. These analyses are no longer by randomised groups and are thus observational in nature. To investigate this, a three-level time-dependent categorical variable was created for each individual based on information from their first

detected type II endoleak. Specifically, follow-up for each individual was split into periods in which (1) no type II endoleak had been detected since randomisation; (2) the first type II endoleak had been detected but as yet was untreated; and (3) the first type II endoleak had been detected and treated. A Cox regression model was fitted from randomisation with this time-dependent exposure to assess the HRs of detected untreated and detected treated type II endoleaks in relation to no detected type II endoleaks.

Table 26 shows data from EVAR-1, DREAM, OVER and ACE, in terms of number of deaths and number of aneurysm-related deaths, and also pooled data. As can be seen in *Table 26*, there is no difference between patients with no detected type II endoleak and either untreated or treated type II endoleaks, unadjusted or adjusted for age, sex, aneurysm diameter and log-creatinine.

Overall, there was no evidence that a detected type II endoleak (either treated or untreated) was associated with worse overall survival, although results differed by trial (see *Table 26*). In EVAR-1, patients who had been treated for their type II endoleak had a higher hazard of mortality than patients with no detected type II endoleak, whereas patients with untreated type II endoleaks had a lower hazard. The converse was seen in the OVER trial, with the untreated type II endoleak patients having a higher mortality rate. These differences may be attributable to different decisions regarding who to treat in the two trial populations.

TABLE 26 Effects of treated and untreated type II endoleak on total mortality for patients who received EVAR in the four RCTs

Analysis	EVAR-1	DREAM	OVER	ACE	Pooled
Number contributing to analysis (*n* deaths/*n* AAA deaths)	*n* = 629 (255/32)	*n* = 171 (59/7)	*n* = 440 (143/8)	*n* = 163 (18/7)	*n* = 1403 (475/54)
Unadjusted					
No type II endoleak (reference)	1.00	1.00	1.00		1.00
Untreated type II endoleak	0.83 (0.57 to 1.21)	1.19 (0.61 to 2.30)	1.56 (1.05 to 2.32)	[a]	1.14 (0.75 to 1.76) $p = 0.538$; $I^2 = 61\%$
Treated type II endoleak	1.87 (1.14 to 3.08)	2.11 (0.65 to 6.84)	0.50 (0.18 to 1.37)	[a]	1.30 (0.56 to 3.03) $p = 0.546$; $I^2 = 65\%$
Any type II endoleak	1.03 (0.75 to 1.41)	1.31 (0.72 to 2.39)	1.26 (0.87 to 1.84)	[a]	1.14 (0.91 to 1.43) $p = 0.241$; $I^2 = 0\%$
Number contributing to analysis (*n* deaths/*n* AAA deaths)	*n* = 628 (255/32)	*n* = 165 (56/6)	*n* = 440 (143/8)	*n* = 154 (16/6)	*n* = 1387 (470/52)
Adjusted [b]					
No type II endoleak (reference)	1.00	1.00	1.00		1.00
Untreated type II endoleak	0.86 (0.59 to 1.26)	1.22 (0.63 to 2.38)	1.46 (0.97 to 2.19)	[a]	1.14 (0.79 to 1.62) $p = 0.488$; $I^2 = 44\%$
Treated type II endoleak	1.71 (1.04 to 2.84)	2.68 (0.81 to 8.88)	0.48 (0.18 to 1.32)	[a]	1.31 (0.54 to 3.17) $p = 0.549$; $I^2 = 67\%$
Any type II endoleak	1.04 (0.76 to 1.44)	1.38 (0.75 to 2.54)	1.19 (0.81 to 1.74)	[a]	1.14 (0.91 to 1.43) $p = 0.276$; $I^2 = 0\%$

a Too few events to estimate a HR.
b Adjusted for age, sex, aneurysm diameter and log-creatinine level.
Note
HRs (95% CI) shown in those with a detected type II endoleak and whether or not the endoleak was, as yet, treated or untreated.

Further analyses from the individual patient data meta-analysis restricting to endoleaks detected within the first 3 years

Further analyses were conducted to assess whether type II endoleaks detected within the first 3 years of randomisation were associated with a higher rate of mortality. The following results are based on the EVAR-treated patients only, therefore are subject to potential confounding (non-randomised) comparisons. Data on treated and untreated type II endoleaks from the four RCTs, restricted to endoleaks detected within the first 3 years, were used to define a time-dependent variable in a Cox regression model.

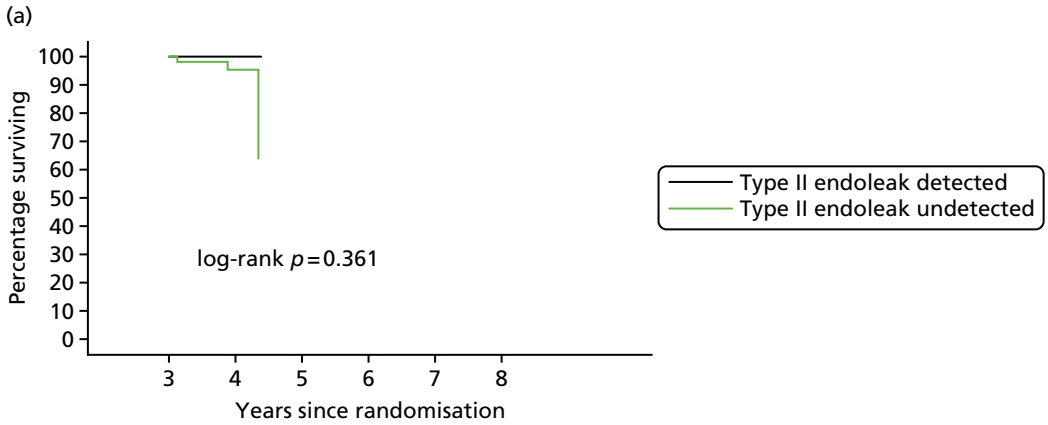
Figure 22 shows survival beyond 3 years for each trial, separated by those with and without detected type II endoleak. There were no significant differences between the two groups in terms of overall survival in any of the trials. The HRs for a detected type II endoleak (within the first 3 years) for both all-cause and aneurysm-related mortality are shown in *Table 27*. As with the individual trial results, the pooled estimates show no evidence of a substantial increase in either all-cause or aneurysm-related mortality following a detected type II endoleak within the first 3 years, for individuals who survive beyond 3 years. However, because of the small numbers aneurysm-related mortality could be assessed only within EVAR-1.

There was no overall evidence that type II endoleak (either treated or untreated) had a dramatic effect on subsequent survival.

Discussion

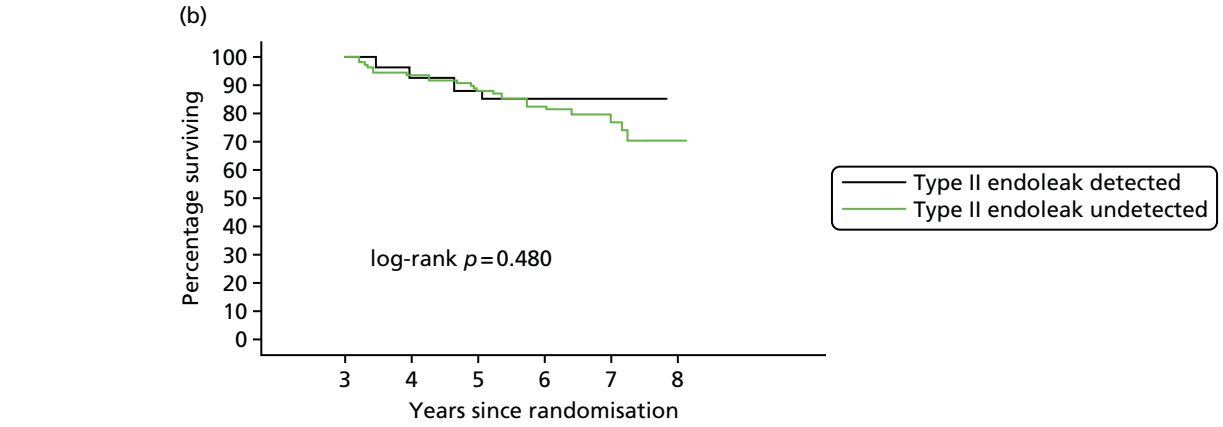
The pooled estimates show no evidence of a substantial increase in either all-cause or aneurysm-related mortality following a detected type II endoleak within the first 3 years, for individuals who survive beyond 3 years. However, as a result of small numbers, aneurysm-related mortality could be assessed only within EVAR-1.

As previously shown, type II endoleak as part of the 'cluster' of complications is associated with secondary rupture. However, this suggests that it is other complications that are listed in the cluster that are important and not type II endoleaks on their own. The 'cluster' did include type II endoleak with sac expansion in its definition and it seems that sac expansion is the important measure here.

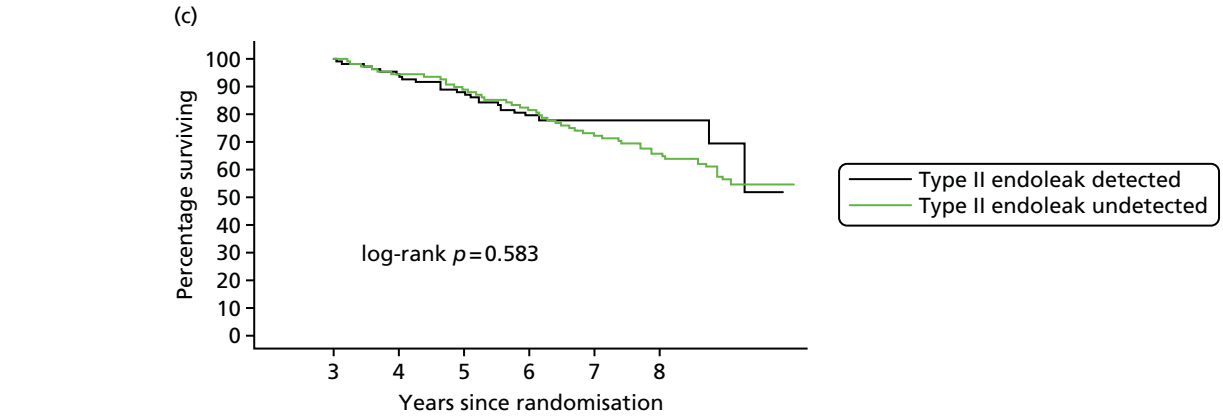


Number at risk						
Type II endoleak detected	22	6	0	0	0	0
Type II endoleak undetected	69	31	0	0	0	0

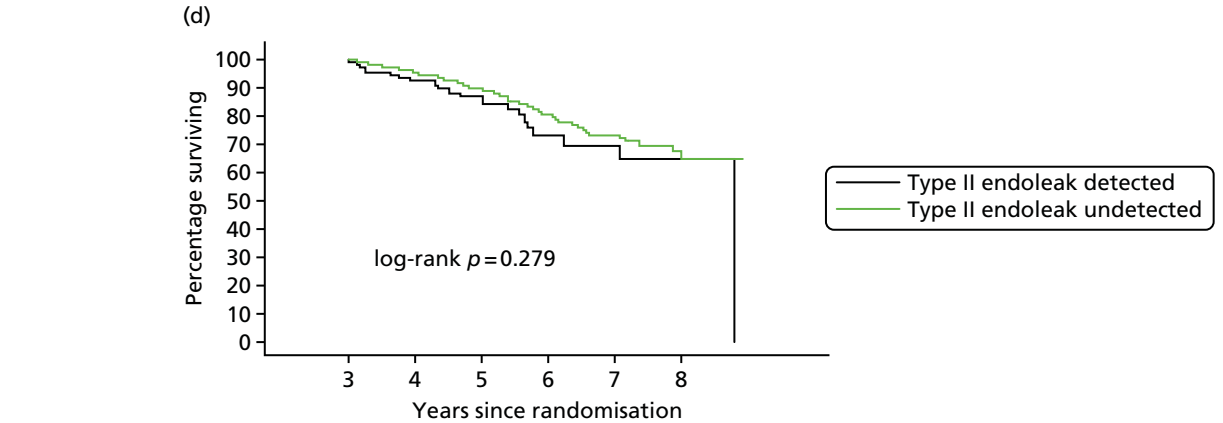
FIGURE 22 All-cause mortality for EVAR-operated patients surviving beyond 3 years, by whether or not a type-II endoleak is detected within the first 3 years. (a) ACE; (b) DREAM; (c) EVAR-1; and (d) OVER. (*continued*)



Number at risk						
Type II endoleak detected	26	24	23	16	9	0
Type II endoleak undetected	114	107	100	64	30	2



Number at risk						
Type II endoleak detected	101	94	89	57	26	14
Type II endoleak undetected	411	385	361	253	149	85



Number at risk						
Type II endoleak detected	88	76	51	27	16	8
Type II endoleak undetected	293	271	214	137	79	26

FIGURE 22 All-cause mortality for EVAR-operated patients surviving beyond 3 years, by whether or not a type-II endoleak is detected within the first 3 years. (a) ACE; (b) DREAM; (c) EVAR-1; and (d) OVER.

TABLE 27 Effects of type II endoleak on survival: unadjusted and adjusted HRs of mortality for individuals detected/not detected to have a type II endoleak within the first 3 years

	ACE ($n = 163$)	DREAM ($n = 171$)	EVAR-1 ($n = 629$)	OVER ($n = 440$)	Total ($n = 1403$)
Known type II endoleak before 3 years: yes, *n* (%)	35 (21)	36 (21)	120 (19)	102 (23)	293 (21)
Unadjusted					
Number surviving beyond 3 years and not censored (*n* deaths/*n* AAA deaths)	$n = 91$ (3/1)	$n = 140$ (28/2)	$n = 512$ (140/14)	$n = 381$ (84/3)	$n = 1124$ (255/20)
All-cause mortality: HR (95% CI) of type II endoleak on post 3-year survival		0.68 (0.24 to 1.97)	0.88 (0.56 to 1.38)	1.32 (0.80 to 2.18)	1.01 (0.74 to 1.39) $p = 0.935$; $I^2 = 0\%$
Aneurysm-related mortality: HR (95% CI) of type II endoleak on post 3-year survival			1.70 (0.53 to 5.41)		1.70 (0.53 to 5.41) $p = 0.373$
Adjusted					
Number surviving beyond 3 years and not censored (*n* deaths/*n* AAA deaths)	$n = 88$ (3/1)	$n = 135$ (26/2)	$n = 511$ (140/14)	$n = 381$ (84/3)	$n = 1115$ (253/20)
All-cause mortality: HR (95% CI) of type II endoleak on post 3-year survival		0.77 (0.26 to 2.28)	0.88 (0.56 to 1.39)	1.28 (0.77 to 2.13)	1.01 (0.73 to 1.40) $p = 0.936$; $I^2 = 0\%$
Aneurysm-related mortality: HR (95% CI) of type II endoleak on post 3-year survival			1.67 (0.50 to 5.60)		1.67 (0.50 to 5.60) $p = 0.405$

Notes
Restricting population to those who underwent and completed EVAR (ACE, $n = 163$; DREAM, $n = 171$; EVAR-1, $n = 629$; OVER, $n = 440$). The table below shows the number of individuals who have survived to 36 months, with and without a discovered type II endoleak. The HRs of having a type II endoleak on subsequent survival post 3 years are presented.

Additionally, it is often difficult to be sure exactly where an endoleak is occurring. With improved experience and imaging quality, the certainty that a type II endoleak actually is one and nothing more serious should be improving. The big fear is that a type II endoleak is 'a type I endoleak in disguise'. This is perhaps why the increase of sac diameter is such an important indicator of functionally important endoleak of one form or another.

Chapter 8 Modelling sac growth following elective endovascular aneurysm repair and associations with complications and secondary rupture

Introduction

Following elective EVAR surgery, the aneurysm sac should gradually shrink over time as the endograft diverts blood flow away from the aneurysm. It is important, however, to continue monitoring the sac over time, through repeat imaging, and the position of the endograft to allow early detection of serious complications such as endoleaks, which can lead to secondary rupture. In the EVAR trials, the follow-up protocol suggested CT imaging of the sac and EVAR device location initially at 1, 3 and 12 months postoperatively and then annually thereafter. In this chapter we investigate whether or not variables that are easily measured on a CT scan or ultrasound, such as the diameter of the sac, are (1) associated with the onset of a complication or secondary rupture and (2) can be used to accurately predict the occurrence of the event so that an appropriate imaging protocol can be set up or a reintervention can be planned. To achieve this it is first important to model and better understand the trajectory profile of sac diameters postoperatively. A suitable model of the sac trajectory over time can then be utilised to provide predictors of outcomes, such as the current predicted sac diameter or the current rate of growth (see *Figure 23* for an illustration).

Data

A total of 1656 patients were randomised in the EVAR trials prior to September 2004 (EVAR-1, $n = 1252$; EVAR-2, $n = 404$) (*Figure 24*). Of these patients, 847 underwent elective EVAR without conversion to OR (EVAR-1, $n = 623$; EVAR-2, $n = 224$). After excluding individuals who underwent no postoperative CT (one individual), whose sac diameter measurements were all missing (58 individuals) or who received a

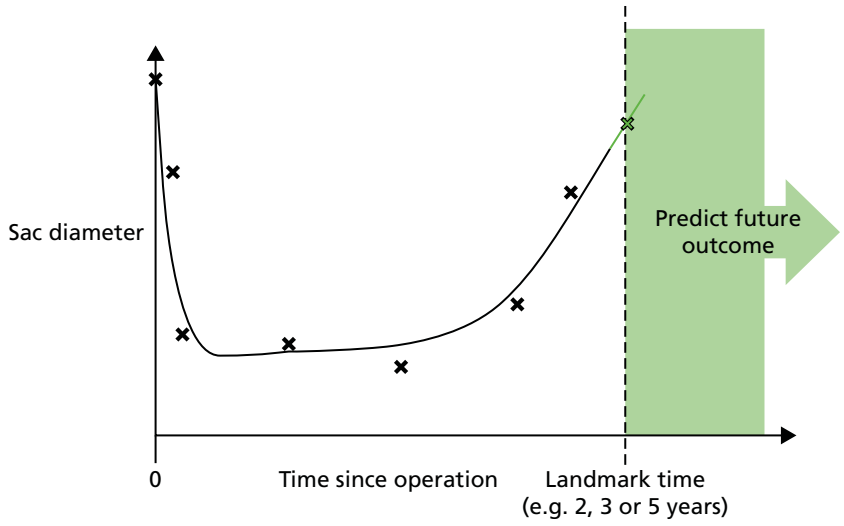


FIGURE 23 Illustration of a modelled sac trajectory (solid curve) using CT measurements taken over time (crosses). The model can be used to relate important aspects of the sac trajectory at the landmark time of prediction, such as (1) the current predicted diameter (green cross) and (2) the current rate of sac growth (green line).

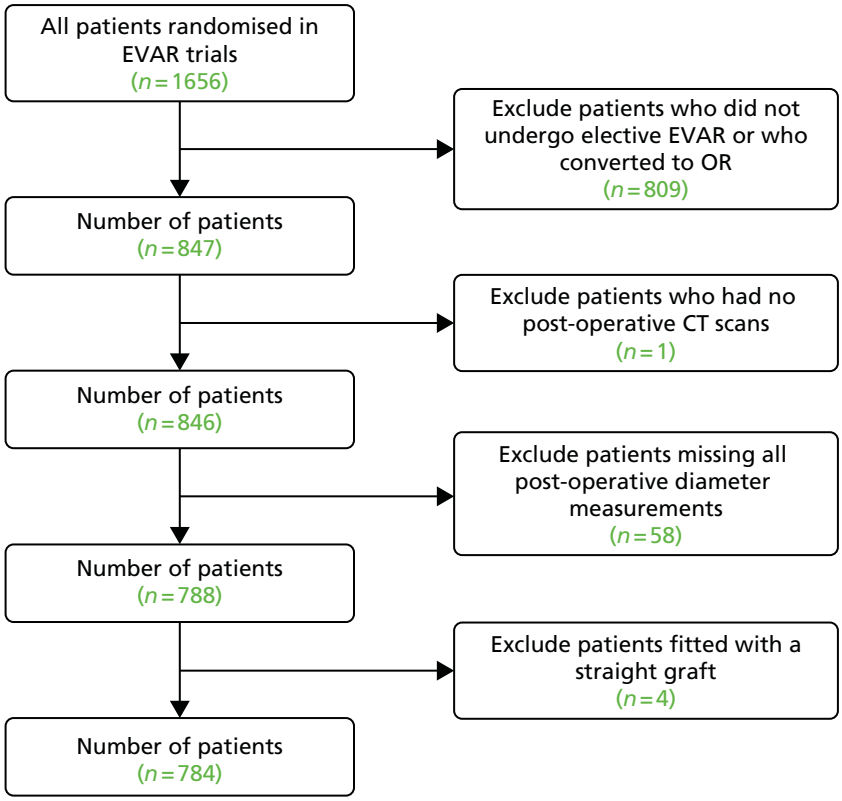


FIGURE 24 Flow diagram showing EVAR-1 and EVAR-2 patients used in the sac growth analysis.

straight graft (four individuals), the final analysis data set consisted of 784 individuals who underwent elective EVAR surgery, irrespective of their randomisation group.

Of these 784 individuals, 591 (75.4%) were from EVAR-1 and 193 (24.6%) were from EVAR-2. Six hundred and ninety-nine (89.2%) patients were male and the mean age was 75 years (range 54–94 years). Further patient characteristics are presented in *Table 28*.

Methods

Modelling sac diameter following elective endovascular aneurysm repair operation

Each individual provided a set of repeated sac diameter measurements. To model the sac trajectories over time and account for between-patient variation in the sac trajectories we use a mixed-effects model. First, we tried to capture the shape of the trajectory by finding a model from the class of fractional polynomial models that best fitted the relationship between sac diameter and follow-up time.[160] As is traditional with such a class of models, we allowed polynomial powers of time up to cubic terms (i.e. x, x^2 and x^3), a square root transformation ($x^{0.5}$), a log-transformation and the inverse polynomial and square root terms (e.g. powers –2, –1 and –0.5). Each power of time was assessed as both a fixed- and a random-effect term in a mixed-effects model and an independent variance covariance matrix was used for the random effects. A variable selection procedure was undertaken with the best fitting model (according to Akaike information criterion) chosen as the final model.

In addition to the chosen functional form of the sac trajectory over time, we also investigated including baseline covariates and linear time interactions in the mixed model in order to explain any heterogeneity in sac diameters and growth over time.

TABLE 28 Characteristics of the analysis population

	n = 785	Number missing (%)
Age, years	74.5 (6.4)	0 (0)
Sex (male), *n* (%)	699 (89.2)	0 (0)
Smoking status, *n* (%)		
Current	159 (20.3)	1 (0.1)
Past	548 (70.0)	
Never	76 (9.7)	
Trial, *n* (%)		
EVAR-1	591 (75.4)	0 (0)
EVAR-2	193 (24.6)	
Preoperative AAA size (cm)	6.5 (0.9)	0 (0)
Graft shape, *n* (%)		
Uni-iliac	57 (7.5)	20 (2.5)
Bi-iliac	707 (92.5)	
Graft manufacturer, *n* (%)		
Cook®/Zenith®	434 (55.9)	7 (0.9)
Medtronic/Talent®	231 (29.7)	
GORE®/EXCLUDER®	48 (6.2)	
Other	64 (8.2)	
Number of postoperative sac measurements	5.4 (2.7)	

Note
Mean (standard deviation) unless otherwise stated.

The final mixed-effects model was fitted once using all individuals and sac diameter measurements over follow-up to get accurate estimates of the fixed effects and variance components and in particular the long-term trajectory of sac diameter. Using these estimates, we then obtained predicted sac diameter measurements and rates of growth for each individual by calculating their empirical Bayes predicted random effects. This was done three times for each individual, corresponding to three landmark times at 2, 3 and 5 years in which predictions of future events are to be assessed, each time using only data available up to the landmark time in the calculation of the random effects.

Modelling future complications and reinterventions

We investigated modelling three possible future events:

1. any aneurysm-related complication except for sac expansion (see *Table 29* for a full list of complications)
2. any cluster complication[2], defined here to be any of the following: a type I endoleak, a type II endoleak (with sac expansion), a type III endoleak, migration, or kinking
3. secondary rupture.

TABLE 29 Aneurysm-related complications considered and those defined as a 'cluster' complication

Complication type	Cluster complication	Individuals reporting complication at least once, *n* (%)	Times complication reported during follow-up, *n*
Endoleak type I	Yes	78 (10)	93
Endoleak type II	Yes[a]	189 (24)	240
Endoleak type III	Yes	32 (4)	33
Migration	Yes	55 (7)	63
Kinking	Yes	29 (4)	33
Other	No	21 (3)	21
Thrombosis	No	45 (6)	48
Graft infection	No	4 (1)	4
False femoral aneurysm	No	3 (0)	3
Neck expansion	No	7 (1)	7
Renal failure	No	1 (0)	1
Anastomotic aneurysm	No	9 (1)	9
Rupture	No	13 (2)	14
Stent fracture	No	3 (0)	3
Renal infection	No	6 (1)	6
Unknown	No	1 (0)	1

a In this chapter, endoleak type II with or without sac expansion is defined as a cluster complication, in contrast to the definition in Wyss *et al.*[111]

For each event we considered three potential times at which a prediction was to be made (the landmark times) (see *Table 24*).

These times were chosen to be at 2, 3 and 5 years postoperatively. We fitted Cox proportional hazards regression models to individuals still at risk at each of the landmark times, taking the landmark time as the entry time into the model. The time until the first occurrence of the event following the landmark time was of primary interest. Individuals were censored at their last CT/US date that assessed the complications of interest (the full set of complications were assessed up to September 2009, whereas cluster complications were assessed up until March 2015). Non-fatal rupture events were obtained via clinical follow-up and from HES, whereas fatal rupture events were obtained from the ONS. Therefore, the censoring date for the analysis of rupture events occurred at the earliest of the last data extraction for HES or ONS.

Along with a set of baseline covariates, we also investigated two aspects of the sac trajectory as predictors of the outcome: (1) the current predicted sac diameter; and (2) the current predicted rate of growth. A naive, albeit simple, estimate of the current sac diameter is to take the last observed sac diameter measurement, an approach labelled 'last observation carried forward', whereas an 'observed' sac growth can be calculated by dividing the difference in an individual's last two measurements by the time elapsed. Alternatively, predictions of current sac diameter and current sac growth can be obtained from the fitted longitudinal model, which has the advantage of using all previous sac diameter measurements to derive a more precise estimate. The disadvantage of using predictions from a model is that they require some non-trivial calculations to be performed (e.g. using a computer program). Such an approach could, however, be easily facilitated through the development of a purpose-built web interface.

The predictive performance of the fitted Cox models at each landmark time was assessed in terms of predicting events occurring within 1, 2 or 5 years of the landmark time for any complication and cluster complication (the time horizon). As fewer rupture events were observed, ruptures were predicted within 5 or 10 years of the landmark time. A C-index was calculated and interpreted as the proportion of pairs of individuals in whom the ordering of the event times within the time horizon was correctly predicted. A C-index of 1.0 can be interpreted as perfect discrimination, whereas a value of 0.5 indicates that the model is predicting events no better than chance. To account for overoptimism, C-indices were calculated on a 10-fold cross-validated data set using nine-tenths of the data to fit the model and the remaining one-tenth to validate. Changes in C-index from a prediction model excluding any aspects of sac diameter were also calculated.

Results: pattern of sac growth over time

Table 30 shows the average number of sac diameter measurements per individual up until the landmark time of interest, and the number of individuals and complication events that occur after the landmark time contributing to the survival analysis.

A plot of the repeated sac diameter measurements over time for each individual is shown in *Figure 25*, stratified by those who did not or did experience a rupture during follow-up. The time trend appears to be non-linear, with an initial decrease in sac diameter followed by a flattening out for those who did not experience a rupture. The time trend in the group who ruptured is similar, but with an increase in sac diameter prior to rupture for some individuals. (Note that the time of rupture may not necessarily be immediately after the last sac diameter measurement as a result of some patients ceasing regular clinical imaging.)

After comparing all models with a linear time trend and up to two fractional polynomial terms, our final mixed-effects model contained linear, quadratic and square root powers of time with both fixed- and random-effects terms for each time component. *Figure 26* shows the population-averaged time trajectory for those with average or reference baseline covariates (see *Table 31* for specification of reference baseline covariates). Sac diameter initially tends to decrease sharply postoperatively, followed by a period of flattening out and then a gradual growth.

Table 31 shows the estimates for predictors of sac diameter and rate of growth from the final mixed-effects model (coefficients for the function of time and variance components are given in *Table 40*). Baseline age and sex were not included in the final model because they were not significantly associated with postoperative sac diameter after adjusting for preoperative AAA size. Larger preoperative AAA size was associated with larger postoperative sac diameters. Different rates of sac growth were observed for different graft shapes and graft manufacturers, with higher growth rates associated with the use of uni-iliac grafts and Medtronic/Talent® (Medtronic CardioVascular, Santa Rosa, CA, USA) and GORE®/EXCLUDER® (W.L. Gore and Associates, Flagstaff, AZ, USA) grafts relative to Cook®/Zenith® (Cook Medical, Bloomington, IN, USA) grafts.

TABLE 30 Numbers of sac measurements and events contributing to the mixed model and Cox model analyses

	Landmark time		
	2 years	3 years	5 years
Number of patients contributing to mixed model	784	784	784
Mean number of sac measurements prior to landmark time	2.8	3.5	4.6
Number at risk for any complication at landmark time	666	604	479
Number experiencing any complication after landmark time	136	100	50
Number at risk for cluster complications at landmark time	666	607	482
Number experiencing any cluster complication after landmark time	144	114	80
Number at risk for secondary rupture at landmark time	665	608	501
Number experiencing a fatal or non-fatal secondary rupture after landmark time	36	32	21

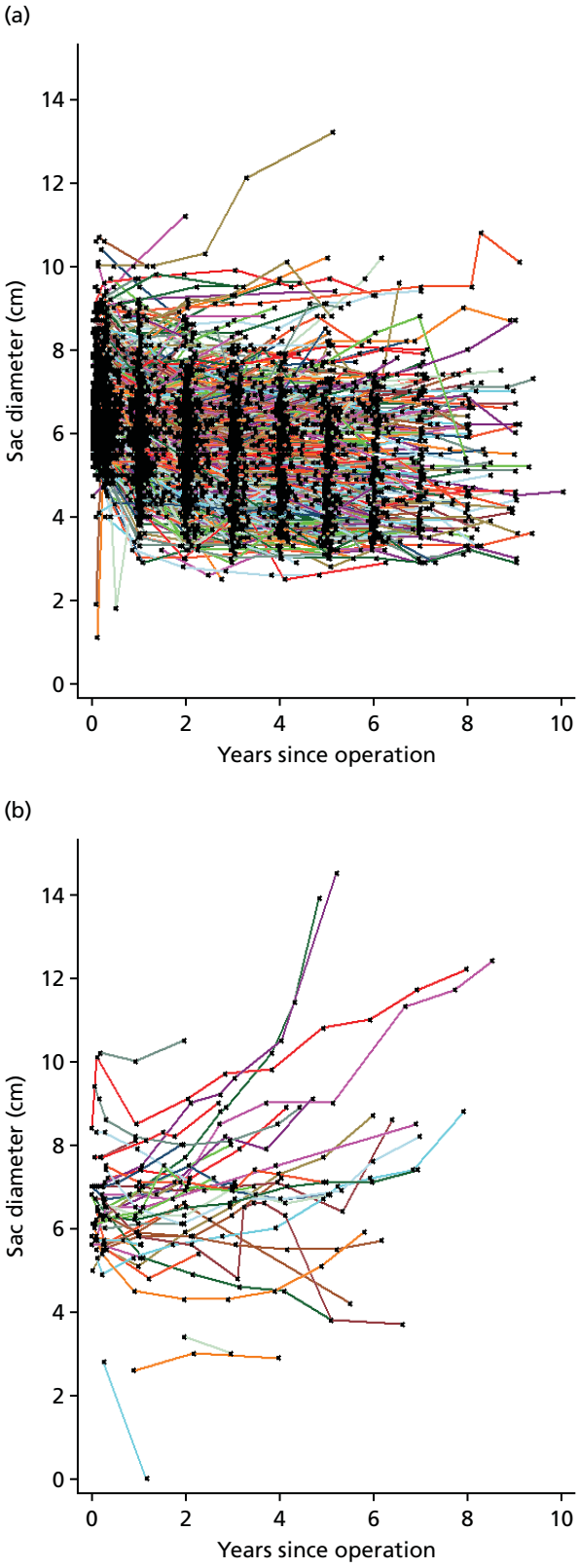


FIGURE 25 Repeated sac diameter measurements against time since operation for each individual. (a) Individuals who did not experience a rupture during follow-up; and (b) individuals who had a rupture event.

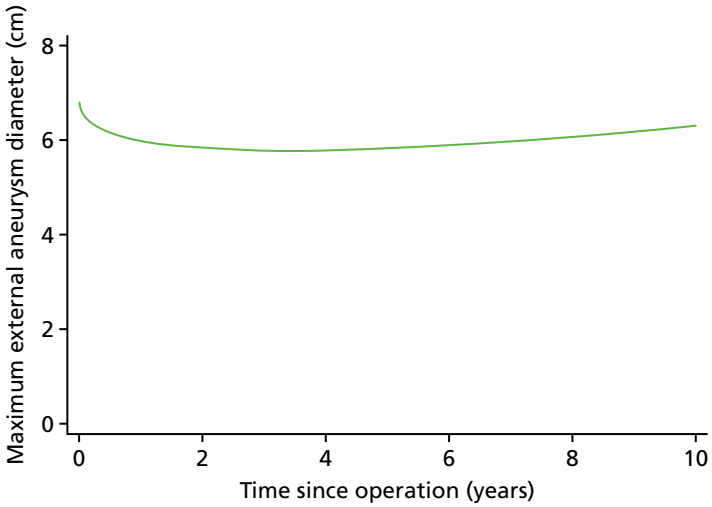


FIGURE 26 Population-averaged trajectory of postoperative sac diameter for an EVAR-1 individual with average preoperative AAA size, fitted with a uni-iliac, Cook/Zenith graft.

TABLE 31 Modelling of sac diameter measurements over time

	Change in mean sac diameter (cm) (95% CI)	*p*-value
Preoperative AAA size, per cm increase	0.937 (0.891 to 0.984)	< 0.001
Graft shape		
Uni-iliac	Reference	0.479
Bi-iliac/bifem	0.059 (–0.104 to 0.221)	
Graft manufacturer		
Cook/Zenith	Reference	0.799
Medtronic/Talent	–0.016 (–0.110 to 0.079)	
GORE/EXCLUDER	–0.047 (–0.231 to 0.137)	
Other	–0.074 (–0.231 to 0.084)	
Trial		
EVAR-1	Reference	< 0.001
EVAR-2	0.194 (0.095 to 0.293)	
	Change in rate of sac growth (cm/year) (95% CI)	***p*-value**
Graft shape		
Uni-iliac	Reference	0.015
Bi-iliac/bifem	–0.116 (–0.210 to –0.023)	
Graft manufacturer		
Cook/Zenith	Reference	< 0.001
Medtronic/Talent	0.191 (0.135 to 0.247)	
GORE/EXCLUDER	0.245 (0.139 to 0.351)	
Other	0.016 (–0.075 to 0.107)	

Note
Mean differences, 95% CIs and *p*-values are reported from a mixed model with fixed- and random-effect terms for the intercept, linear, quadratic and square root time, and fixed-effect terms for baseline covariates and their linear time interactions.

Figure 27 shows fitted sac diameter trajectories at the landmark times of 2, 3 and 5 years post operation for six patients with differing outcomes. Each trajectory has been fitted using only the sac diameter measurements available up to the landmark time. Also plotted are all observed sac diameter measurements, up to September 2009, for each patient. The patient who experiences a rupture after 12 years (see *Figure 27a*) has initially stable, then increasing, sac diameter measurements, which is reflected in the fitted trajectories at 2, 3 and 5 years. At 5 years the fitted curve detects the increase in sac diameter and upward trajectory in the observed measurements. Patients who experience stable or decreasing measurements tend to have similar fitted trajectories at the different landmark times.

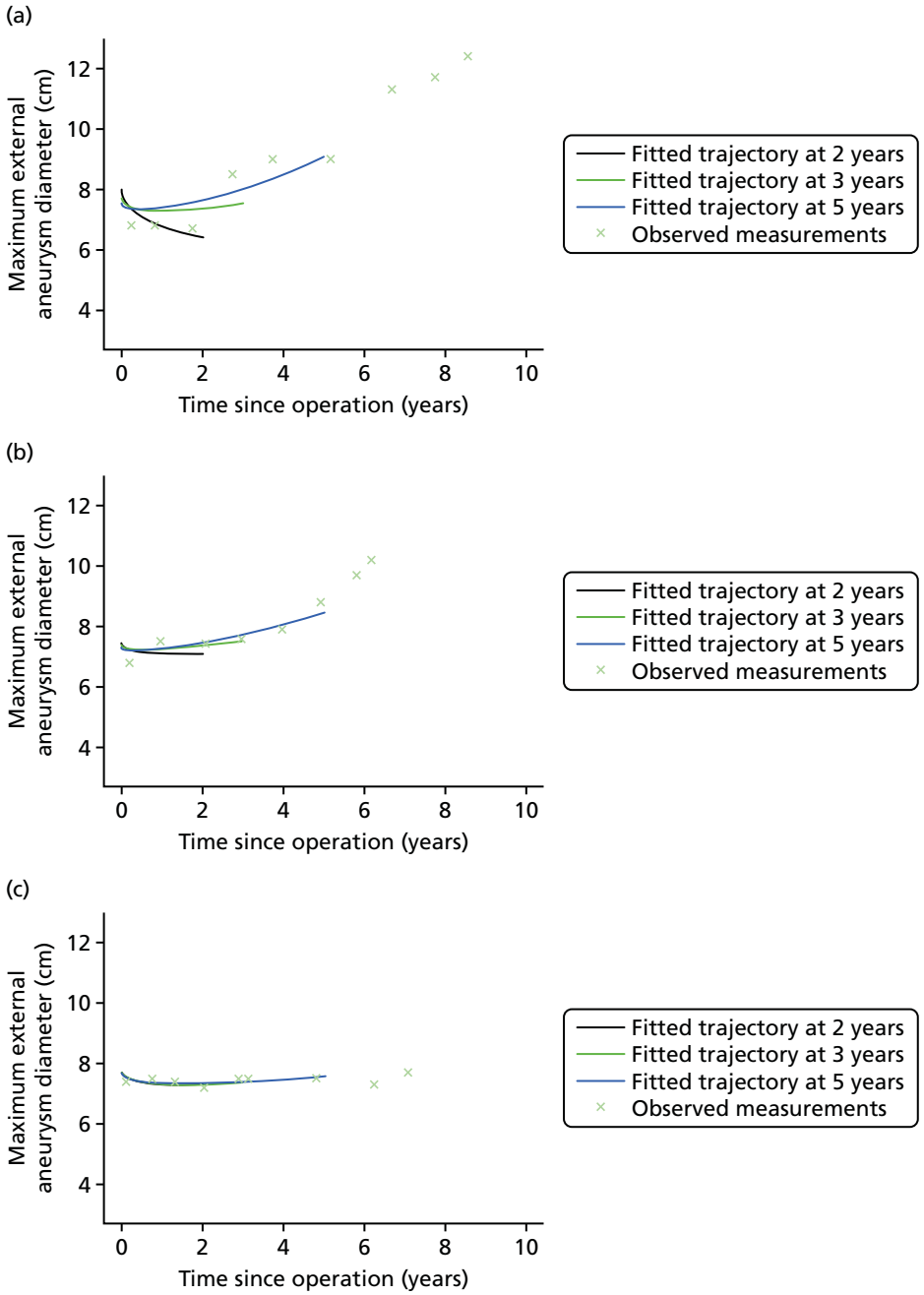


FIGURE 27 Postoperative sac diameter measurements for six individuals and their fitted trajectories using only past measurements at 2, 3 and 5 years. (a) Rupture at 12 years post operation; (b) type II endoleak at 6 years post operation; (c) type II endoleak at 0.1 years post operation; and (d–f) no post-operation complications. (*continued*)

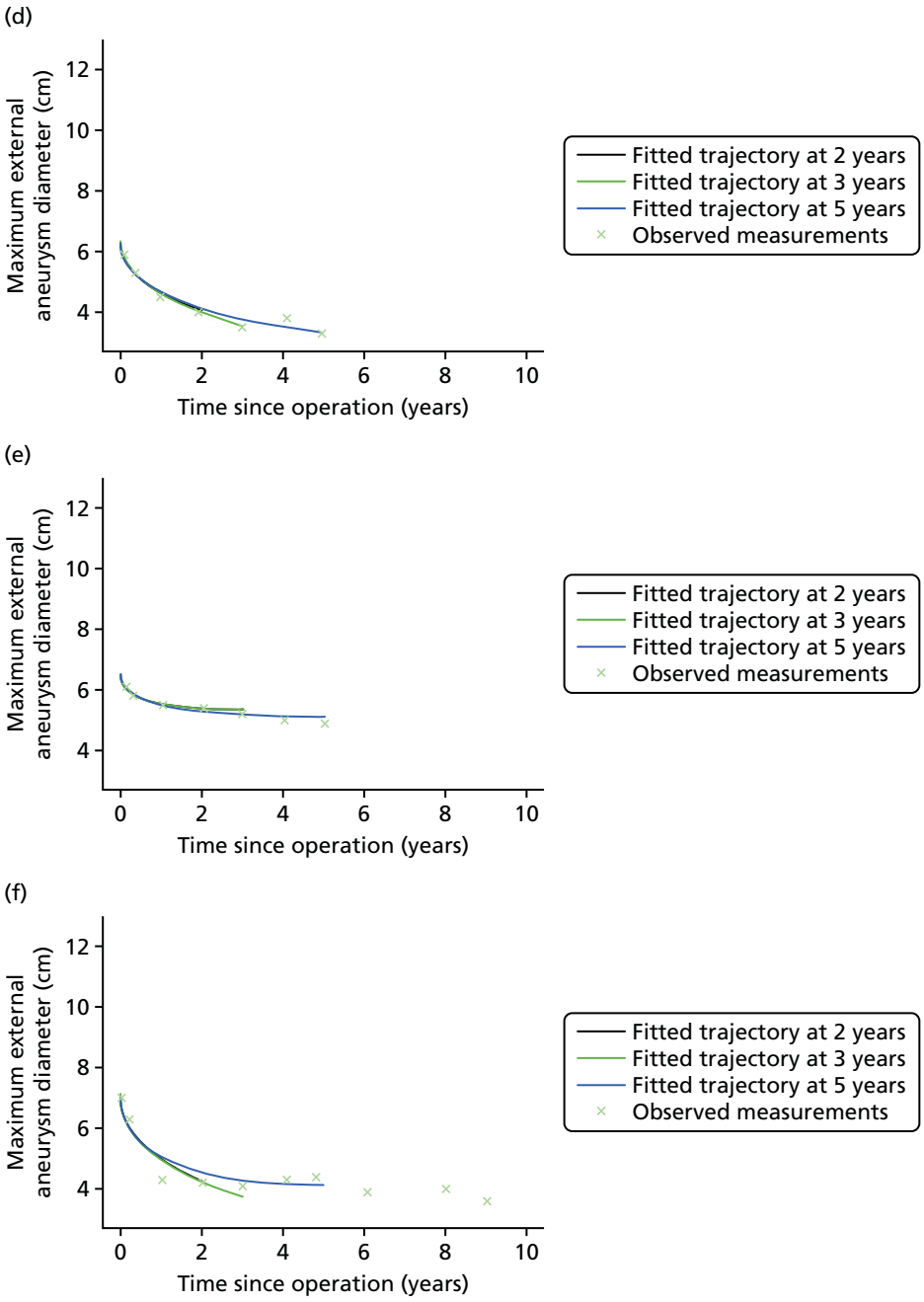


FIGURE 27 Postoperative sac diameter measurements for six individuals and their fitted trajectories using only past measurements at 2, 3 and 5 years. (a) Rupture at 12 years post operation; (b) type II endoleak at 6 years post operation; (c) type II endoleak at 0.1 years post operation; and (d–f) no post-operation complications.

Results: associations between aspects of sac trajectory and risk of future events

Any future complication

There were 315 first-time complications that occurred in 2846 person-years of observation (crude risk of 11.1 per 100 person-years, 95% CI 9.9 to 12.4). There were 666, 604 and 479 individuals still under follow-up at the landmark forecasting times of 2, 3 and 5 years post operation, respectively. In univariate survival analyses, at 2 and 3 years following operation, there was found to be an association between the following factors and a heightened risk of developing any future complication: larger preoperative AAA size; a Medtronic/Talent or other graft; larger current sac diameter; and a larger current rate of sac growth (both predicted from the linear

mixed model) (*Table 32*). However, after adjustment, only graft manufacturer remained statistically significant. At 5 years post operation, after adjustment, there were no variables that were convincingly associated with the risk of a future complication taking place.

Cluster complications

There were 288 first-time cluster complications that occurred in 3457 person-years of observation (crude risk of 8.3 per 100 person years, 95% CI 7.4 to 9.4). Stronger associations were observed with cluster complications (*Table 33*). At 2 and 3 years post operation, after adjustment for other potential confounders, graft manufacturer remained significantly associated with future complications, with Gore/Excluder grafts showing a fourfold lower risk than Cook/Zenith grafts (HR at 3 years = 0.26, 95% CI 0.08 to 0.86) and 'other' manufacturers estimated to have nearly double the risk as the Cook/Zenith grafts (HR at 3 years = 1.93, 95% CI 1.08 to 3.46). No other variables significantly predicted cluster complications at these time periods.

TABLE 32 Modelling survival for any complications

Landmark time	Univariate model,[a] HR (95% CI)	Multivariate model, HR (95% CI)
2 years post operation* (n = *638; number of events = 133)		
Age (years)	1.024 (0.996 to 1.052)	1.016 (0.988 to 1.045)
p-value	0.093	0.265
Preoperative AAA size (cm)	1.188 (1.003 to 1.407)	1.401 (0.837 to 2.345)
p-value	0.046	0.199
Graft shape		
Uni-iliac	Reference	Reference
Bi-iliac/bifem	0.719 (0.397 to 1.302)	0.900 (0.483 to 1.677)
p-value	0.276	0.740
Graft manufacturer		
Cook/Zenith	Reference	Reference
Medtronic/Talent	1.437 (0.982 to 2.102)	1.126 (0.719 to 1.764)
GORE/EXCLUDER	0.814 (0.352 to 1.883)	0.540 (0.220 to 1.329)
Other	2.420 (1.445 to 4.052)	2.158 (1.284 to 3.627)
p-value	0.004	0.008
Current sac diameter (cm)	1.226 (1.073 to 1.401)	0.834 (0.494 to 1.410)
p-value	0.003	0.498
Current rate of growth[b]	1.229 (1.054 to 1.433)	1.422 (0.915 to 2.211)
p-value	0.008	0.118
3 years post operation* (n = *583; number of events = 98)		
Age (years)	1.035 (1.002 to 1.069)	1.024 (0.990 to 1.059)
p-value	0.037	0.163
Preoperative AAA size (cm)	1.234 (1.022 to 1.490)	1.107 (0.679 to 1.807)
p-value	0.029	0.683

TABLE 32 Modelling survival for any complications (*continued*)

Landmark time	Univariate model,[a] HR (95% CI)	Multivariate model, HR (95% CI)
Graft shape		
Uni-iliac	Reference	Reference
Bi-iliac/bifem	1.450 (0.589 to 3.567)	1.824 (0.720 to 4.620)
p-value	0.419	0.205
Graft manufacturer		
Cook/Zenith	Reference	Reference
Medtronic/Talent	1.448 (0.934 to 2.245)	1.149 (0.694 to 1.904)
GORE/EXCLUDER	0.502 (0.156 to 1.616)	0.325 (0.096 to 1.101)
Other	2.124 (1.165 to 3.871)	1.828 (0.992 to 3.368)
p-value	0.024	0.038
Current sac diameter (cm)	1.295 (1.126 to 1.490)	1.123 (0.682 to 1.851)
p-value	< 0.001	0.648
Current rate of growth[b]	1.262 (1.060 to 1.502)	1.192 (0.707 to 2.011)
p-value	0.009	0.510
5 years post operation* (n = *467; number of events = 49)		
Age (years)	1.004 (0.959 to 1.052)	0.993 (0.946 to 1.043)
p-value	0.850	0.783
Preoperative AAA size (cm)	1.240 (0.957 to 1.608)	1.371 (0.906 to 2.074)
p-value	0.104	0.135
Graft shape		
Uni-iliac	Reference	Reference
Bi-iliac/bifem	0.990 (0.308 to 3.188)	1.169 (0.353 to 3.867)
p-value	0.987	0.799
Graft manufacturer		
Cook/Zenith	Reference	Reference
Medtronic/Talent	1.291 (0.700 to 2.380)	0.924 (0.486 to 1.757)
GORE/EXCLUDER	0.296 (0.040 to 2.192)	0.209 (0.028 to 1.566)
Other	1.394 (0.569 to 3.412)	1.287 (0.512 to 3.232)
p-value	0.436	0.420
Current sac diameter (cm)	1.239 (1.036 to 1.481)	0.939 (0.633 to 1.393)
p-value	0.019	0.756
Current rate of growth[b]	1.317 (1.024 to 1.695)	1.504 (0.919 to 2.463)
p-value	0.032	0.105

a Univariate analyses restricted to sample used for multivariate analyses.
b HRs for current rate of growth are given per approximate population standard deviation, 0.2 cm/year.

Note
HRs, 95% CIs and *p*-values are reported from univariate and multivariate Cox proportional hazards models.

TABLE 33 Modelling survival for cluster complications

Landmark time	Univariate model,[a] HR (95% CI)	Multivariate model, HR (95% CI)
2 years post operation (n = 639; number of events = 137)		
Age (years)	1.023 (0.996 to 1.051)	1.013 (0.986 to 1.042)
p-value	0.096	0.342
Preoperative AAA size (cm)	1.285 (1.090 to 1.516)	1.416 (0.854 to 2.347)
p-value	0.003	0.178
Graft shape		
Uni-iliac	Reference	Reference
Bi-iliac/bifem	0.912 (0.479 to 1.736)	1.161 (0.595 to 2.266)
p-value	0.778	0.661
Graft manufacturer		
Cook/Zenith	Reference	Reference
Medtronic/Talent	1.454 (0.999 to 2.117)	1.085 (0.698 to 1.686)
GORE/EXCLUDER	0.910 (0.394 to 2.103)	0.549 (0.224 to 1.349)
Other	2.711 (1.637 to 4.489)	2.450 (1.474 to 4.072)
p-value	0.001	0.001
Current sac diameter (cm)	1.350 (1.184 to 1.540)	0.916 (0.549 to 1.529)
p-value	< 0.001	0.737
Current rate of growth[b]	1.313 (1.126 to 1.532)	1.451 (0.938 to 2.245)
p-value	0.001	0.094
3 years post operation (n = 587; number of events = 108)		
Age (years)	1.025 (0.994 to 1.058)	1.008 (0.976 to 1.041)
p-value	0.117	0.648
Preoperative AAA size (cm)	1.315 (1.098 to 1.575)	1.232 (0.789 to 1.922)
p-value	0.003	0.359
Graft shape		
Uni-iliac	Reference	Reference
Bi-iliac/bifem	1.610 (0.656 to 3.953)	2.216 (0.879 to 5.585)
p-value	0.298	0.091
Graft manufacturer		
Cook/Zenith	Reference	Reference
Medtronic/Talent	1.325 (0.872 to 2.014)	0.852 (0.532 to 1.365)
GORE/EXCLUDER	0.519 (0.162 to 1.663)	0.256 (0.077 to 0.855)
Other	2.270 (1.276 to 4.035)	1.929 (1.076 to 3.459)
p-value	0.016	0.008
Current sac diameter (cm)	1.452 (1.268 to 1.663)	1.102 (0.699 to 1.738)
p-value	< 0.001	0.676
Current rate of growth[b]	1.439 (1.213 to 1.709)	1.493 (0.932 to 2.392)
p-value	< 0.001	< 0.001

TABLE 33 Modelling survival for cluster complications (*continued*)

Landmark time	Univariate model,[a] HR (95% CI)	Multivariate model, HR (95% CI)
5 years post operation* (n = *470; number of events = 75)		
Age (years)	1.014 (0.976 to 1.053)	0.987 (0.949 to 1.027)
p-value	0.481	0.523
Preoperative AAA size (cm)	1.399 (1.132 to 1.729)	1.012 (0.710 to 1.443)
p-value	0.002	0.948
Graft shape		
Uni-iliac	Reference	Reference
Bi-iliac/bifem	1.210 (0.442 to 3.315)	1.482 (0.531 to 4.137)
p-value	0.711	0.453
Graft manufacturer		
Cook/Zenith	Reference	Reference
Medtronic/Talent	1.183 (0.720 to 1.944)	0.709 (0.426 to 1.181)
Gore/Excluder	0.252 (0.035 to 1.839)	0.133 (0.018 to 0.977)
Other	1.583 (0.765 to 3.273)	1.334 (0.637 to 2.792)
p-value	0.279	0.083
Current sac diameter (cm)	1.629 (1.405 to 1.888)	1.586 (1.116 to 2.252)
p-value	< 0.001	0.010
Current rate of growth[b]	1.697 (1.389 to 2.072)	1.151 (0.774 to 1.712)
p-value	< 0.001	0.488

a Univariate analyses restricted to sample used for multivariate analyses.
b HRs for current rate of growth are given per approximate population standard deviation, 0.2 cm/year.
Note
HRs, 95% CIs and *p*-values are reported from univariate and multivariate Cox proportional hazards models.

At 5 years post operation, the graft manufacturer was no longer associated with the onset of future cluster complications, whereas there was some evidence that a larger sac diameter at 5 years was an important predictor. After adjusting for current sac diameter, the rate of sac growth was no longer found to be an independent risk factor, as sac diameter and rate of growth were highly correlated by 5 years ($\rho = 0.76$) (*Figure 28*).

Secondary rupture

There were 41 secondary rupture events that occurred in 5666 person-years of observation [crude rupture risk of 0.72 per 100-person years, 95% CI 0.53 to 0.98). Survival free of secondary rupture is shown in *Figure 29*. Owing to the small number of ruptures, only current sac diameter and rate of growth were investigated as potential predictors of rupture. Both were strongly associated with rupture events at all landmark times in univariate analyses, but only (modelled) rate of sac growth remained an independent risk factor when adjusting for each other (*Table 34*). For a 0.2 cm per year increase in growth rate the risk of secondary rupture increases substantially (HR at 5 years = 2.61, 95% CI 1.49 to 4.57), a finding that is consistent across follow-up.

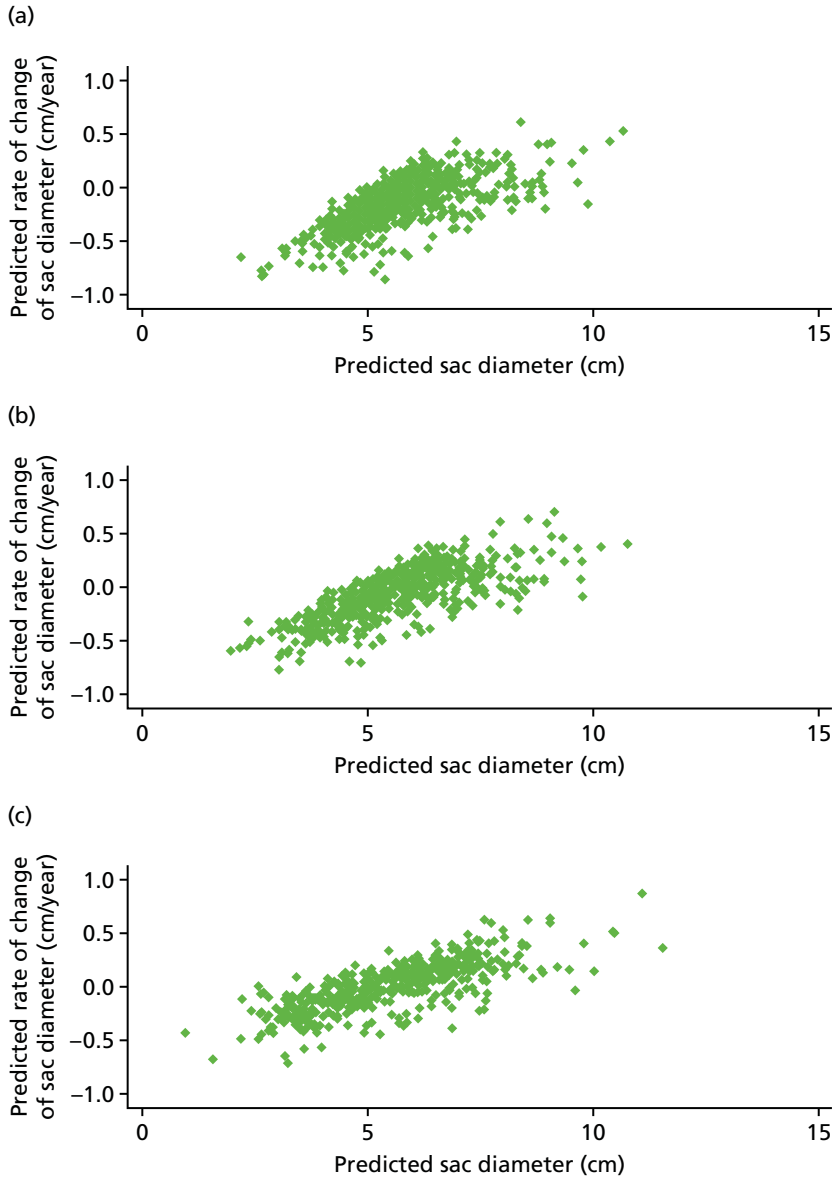


FIGURE 28 Predicted current rate of change against predicted current sac diameter using past measurements at 2, 3 and 5 years. Prediction at (a) 2 years; (b) 3 years; and (c) 5 years.

Results: predictive capabilities of a risk score

Predictive accuracy was assessed for any complication and any cluster complication in three models: model 1C included only baseline covariates (age, preoperative AAA size, graft shape and graft manufacturer); model 2C additionally included current sac diameter; and model 3C additionally included current sac diameter and rate of sac growth. The predictive accuracy measures, as estimated by the cross-validated C-index, are shown in *Tables 35* and *36* for any complication and any cluster complication, respectively. Very low C-indices of magnitude between 0.53 and 0.63 are observed, indicating that the models are unable to accurately identify individuals who will develop complications in the time horizons studied. For example, a C-index of 0.5 shows that the model is no more likely than chance (i.e. probability of 0.5) to identify out of a randomly chosen pair of individuals which one will suffer a complication first. Slight improvements are observed when sac diameter or rate of growth is included in the prediction model though the overall predictive accuracy remains low.

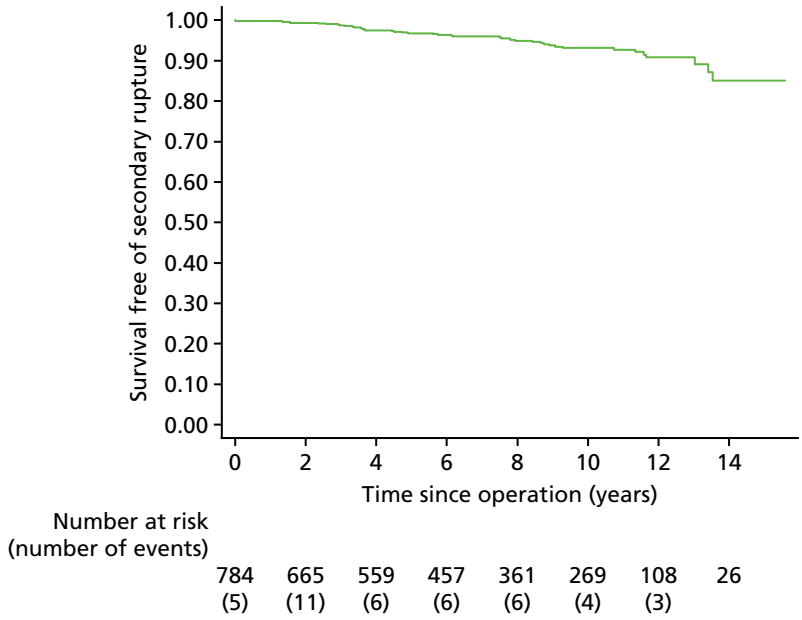


FIGURE 29 Survival free of death from secondary rupture for 785 EVAR-operated patients in EVAR-1 and EVAR-2.

TABLE 34 Modelling survival for rupture events

Landmark time		Univariate model, HR (95% CI)	Multivariate model, HR (95% CI)
2 years post operation ($n = 636$; number of events = 36)	Current sac diameter (cm)	1.673 (1.303 to 2.148)	1.160 (0.820 to 1.640)
	p-value	< 0.001	0.402
	Current rate of growth[a]	2.622 (1.847 to 3.723)	2.372 (1.559 to 3.611)
	p-value	< 0.001	< 0.001
3 years post operation ($n = 586$; number of events = 32)	Current sac diameter (cm)	2.033 (1.597 to 2.588)	1.270 (0.883 to 1.828)
	p-value	< 0.001	0.197
	Current rate of growth[a]	3.628 (2.550 to 5.163)	2.993 (1.897 to 4.722)
	p-value	< 0.001	< 0.001
5 years post operation ($n = 486$; number of events = 21)	Current sac diameter (cm)	2.407 (1.821 to 3.181)	1.516 (0.989 to 2.324)
	p-value	< 0.001	0.056
	Current rate of growth[a]	3.888 (2.625 to 5.758)	2.609 (1.488 to 4.574)
	p-value	< 0.001	0.001

a HRs for current rate of growth are given per approximate population standard deviation, 0.2 cm/year.

Note

HRs, 95% CIs and *p*-values are reported from univariate and multivariate Cox proportional hazards models.

TABLE 35 Cross-validated C-indices for prediction of any complication

Landmark time	Time horizon (number of events)	C-index (95% CI)		
		Model 1C	Model 2C	Model 3C
2 years	1 year ($n = 50$)	0.543 (0.482 to 0.604)	0.567 (0.505 to 0.629)	0.565 (0.503 to 0.626)
	2 years ($n = 79$)	0.562 (0.515 to 0.610)	0.587 (0.539 to 0.635)	0.575 (0.527 to 0.623)
	5 years ($n = 125$)	0.576 (0.537 to 0.615)	0.598 (0.559 to 0.637)	0.585 (0.546 to 0.625)
3 years	1 year ($n = 35$)	0.585 (0.518 to 0.652)	0.598 (0.532 to 0.665)	0.593 (0.526 to 0.660)
	2 years ($n = 56$)	0.578 (0.526 to 0.631)	0.612 (0.561 to 0.663)	0.607 (0.556 to 0.659)
	5 years ($n = 95$)	0.587 (0.542 to 0.631)	0.613 (0.569 to 0.657)	0.610 (0.566 to 0.654)
5 years	1 year ($n = 20$)	0.537 (0.455 to 0.620)	0.561 (0.474 to 0.620)	0.571 (0.485 to 0.657)
	2 years ($n = 36$)	0.563 (0.498 to 0.628)	0.566 (0.499 to 0.632)	0.567 (0.500 to 0.633)
	5 years ($n = 50$)	0.533 (0.471 to 0.595)	0.548 (0.482 to 0.613)	0.554 (0.490 to 0.619)

Note
Model 1C has baseline covariates only; model 2C has baseline covariates + current sac diameter; model 3C has baseline covariates + current sac diameter + current rate of growth.

TABLE 36 Cross-validated C-indices for prediction of cluster complications

Landmark time	Time horizon (number of events)	C-index (95% CI)		
		Model 1C	Model 2C	Model 3C
2 years	1 year ($n = 41$)	0.534 (0.470 to 0.599)	0.566 (0.502 to 0.630)	0.568 (0.504 to 0.631)
	2 years ($n = 68$)	0.550 (0.499 to 0.601)	0.589 (0.540 to 0.639)	0.582 (0.533 to 0.632)
	5 years ($n = 114$)	0.578 (0.539 to 0.618)	0.608 (0.569 to 0.647)	0.599 (0.559 to 0.638)
3 years	1 year ($n = 32$)	0.602 (0.537 to 0.667)	0.616 (0.550 to 0.683)	0.604 (0.535 to 0.673)
	2 years ($n = 47$)	0.580 (0.527 to 0.633)	0.625 (0.574 to 0.677)	0.617 (0.565 to 0.669)
	5 years ($n = 95$)	0.584 (0.541 to 0.628)	0.623 (0.581 to 0.666)	0.619 (0.577 to 0.662)
5 years	1 year ($n = 22$)	0.554 (0.468 to 0.640)	0.613 (0.523 to 0.704)	0.613 (0.523 to 0.704)
	2 years ($n = 40$)	0.573 (0.508 to 0.639)	0.611 (0.545 to 0.676)	0.610 (0.544 to 0.675)
	5 years ($n = 72$)	0.553 (0.496 to 0.668)	0.608 (0.552 to 0.665)	0.611 (0.554 to 0.668)

Note
Model 1C has baseline covariates only; model 2C has baseline covariates + current sac diameter; and model 3C has baseline covariates + current sac diameter + current rate of growth.

Five models were considered for predicting secondary rupture: 1R, using the last observed sac diameter measurement; 2R, using 'observed' sac growth, calculated by dividing the difference in an individual's last two measurements by the time elapsed; 3R, using model predicted current sac diameter only; 4R, using model predicted sac growth only; and 5R, using model predicted sac diameter and sac growth together. The predictive accuracy of each model at different prediction times and prediction intervals is shown in *Table 37*. The C-indices of the model with just model predicted sac diameter (model 3R) range from 0.71 to 0.78 and are similar to those of the model using the last observed measurement (model 1R). These increase to between 0.76 and 0.85 when predicted sac growth alone is included in the risk prediction model, which indicates relatively good predictive accuracy based on this measure alone. The model with 'observed' sac growth (model 2R) has the worst predictive performance in general, with C-indices ranging

TABLE 37 Cross-validated C-indices for prediction of ruptures

Landmark time	Time horizon (number of events)	C-index (95% CI)				
		Model 1R	Model 2R	Model 3R	Model 4R	Model 5R
2 years	5 years ($n = 14$)	0.732 (0.625 to 0.838)	0.606 (0.483 to 0.728)	0.733 (0.624 to 0.842)	0.796 (0.665 to 0.927)	0.798 (0.672 to 0.924)
	10 years ($n = 27$)	0.699 (0.610 to 0.787)	0.588 (0.488 to 0.688)	0.706 (0.616 to 0.796)	0.755 (0.649 to 0.861)	0.754 (0.651 to 0.856)
3 years	5 years ($n = 13$)	0.784 (0.686 to 0.881)	0.726 (0.604 to 0.848)	0.783 (0.681 to 0.884)	0.828 (0.718 to 0.938)	0.818 (0.709 to 0.927)
	10 years ($n = 25$)	0.744 (0.652 to 0.837)	0.709 (0.610 to 0.809)	0.743 (0.646 to 0.839)	0.776 (0.671 to 0.881)	0.768 (0.664 to 0.873)
5 years	5 years ($n = 12$)	0.768 (0.623 to 0.913)	0.611 (0.434 to 0.788)	0.772 (0.628 to 0.916)	0.846 (0.750 to 0.942)	0.817 (0.692 to 0.942)
	10 years ($n = 20$)	0.778 (0.654 to 0.901)	0.623 (0.470 to 0.775)	0.783 (0.660 to 0.907)	0.844 (0.757 to 0.930)	0.822 (0.715 to 0.928)

Note
Model 1R has last observation carried forward; model 2R has 'observed' current rate of growth; model 3R has current sac diameter; model 4R has current rate of growth; and model 5R has current sac diameter + current rate of growth.

from 0.59 to 0.73, indicating that precise measures of sac growth cannot be obtained from just two repeat measurements of sac diameter. The predictive capability of the model is not significantly enhanced when both predicted sac diameter and growth are included together (model 5R).

The relationship between sac growth and risk of rupture is further highlighted in *Table 38*, in which the proportion of rupture events that occur in a 5-year time period after the landmark time of interest is subdivided by categories of sac growth (< 0 mm/year, 0–2 mm/year, 2–4 mm/year and ≥ 4 mm/year). Individuals who are not censored in this 5-year time period are classified either as a case (a rupture event occurs within 5 years) or as a control (no rupture event occurs within the 5 years). For an individual, sac growth can be calculated using either a prediction from a fitted linear mixed model or an 'observed' growth, as described in the previous paragraph. The advantage of the first approach is that it should give a more accurate prediction of current sac growth as it is based on all past sac diameter measurements, whereas the latter approach will be more sensitive to measurement error of the sac, resulting in a wider variability in the estimated rates of growth. The advantage of the second approach, however, is that it can be easily calculated without the need for a computer algorithm. From *Table 38* it can be clearly seen that predicted sac growth is a relatively good predictor of risk of rupture, with a 15% or greater observed risk

TABLE 38 Relationship between predicted sac growth and proportion of rupture events that occur in a 5-year prediction interval (out of individuals who are not censored within the prediction interval)

Landmark time	Predicted or naive (observed)	Sac growth, *n*/*N* (%)			
		< 0 mm/year	0–2 mm/year	2–4 mm/year	≥ 4 mm/year
2 years	Predicted ($n = 14$)	4/529 (0.8)	4/177 (2.3)	9/39 (23.1)	2/6 (33.3)
	Observed ($n = 13$)	6/456 (1.3)	4/110 (3.6)	1/46 (2.2)	7/90 (7.8)
3 years	Predicted ($n = 13$)	3/433 (0.7)	4/232 (1.7)	7/79 (8.9)	5/11 (45.5)
	Observed ($n = 13$)	4/425 (0.9)	5/145 (3.5)	1/58 (1.7)	9/99 (9.1)
5 years	Predicted ($n = 12$)	1/341 (0.3)	4/267 (1.5)	4/115 (3.5)	5/34 (14.7)
	Observed ($n = 12$)	4/370 (1.1)	2/182 (1.1)	1/63 (1.6)	7/115 (6.1)

of rupture in individuals with predicted sac growth ≥ 4 mm per year compared with < 1% risk in individuals with predicted growth < 0 mm per year. Using an 'observed' growth rate, it is more difficult to discriminate between the high- and low-risk populations.

Finally, it may be useful to consider a sac growth cut-off point at which a clinician may choose to instigate further investigations or more detailed clinical imaging. The sensitivity (the proportion of future rupture cases that are correctly identified for further investigation) and the specificity (the proportion of cases that do not rupture that are not chosen for further investigation) of different growth rate cut-off points are shown in *Table 39*, based on rupture events (cases) and non-rupture events (controls) that occur within 5 years (excluding individuals who are censored during this time). Cut-off points that yield both sensitivity and specificity > 70% are highlighted. At 2 years, identifying individuals with any positive growth (> 0 mm/year) would result in 79% of the future rupture cases being identified, but at a cost of 28% of non-rupture cases also undergoing further investigation. If only individuals with > 1 mm per year predicted growth are chosen for further investigation, then only 68% of future ruptures (within 5 years) would be identified, although only 14% of non-rupture cases would be identified for further investigation. At 3 years post operation, sac growth can be more readily detected and the sensitivity to predict future ruptures is higher, 84% using a cut-off point of 0 mm per year and 79% using a cut-off point of 1 mm per year. But a cut-off point of 0 mm per year gives quite a low specificity, suggesting that any observed growth at this time point is not necessarily related to potential future rupture. Specificities at 5 years post operation are generally lower.

Conclusions/implications for imaging protocols following elective endovascular aneurysm repair

We have shown in this chapter that patterns of sac growth, if modelled correctly, can be useful predictors for future serious rupture events. Estimates of sac expansion should be derived from longitudinal modelling of the sac diameter trajectory, which accounts for all previous measurements and thus produces more accurate estimates of current sac growth. Naive estimates of growth based on the last two observed diameter measurements are too crude to be of practical use in a prediction model. The current sac diameter was not found to be an independent risk factor of rupture after accounting for the growth rate of the sac and the predictive accuracy of a model just using sac diameter was lower than a model that used sac growth.

Further work is planned to recommend clinical cut-off points for which high-risk individuals could be flagged for more comprehensive surveillance and imaging. This would require a careful consideration of an acceptable trade-off between ensuring a high sensitivity (correctly identifying those who will truly go on and rupture), while keeping 1 – specificity relatively low (i.e. not flagging too many individuals who will not rupture). For such cut-off points to be used in clinical practice will require (1) stringent validation on external data sources; (2) acceptance by the clinical community; and (3) software implementation to allow real-time decisions to be made. This could be coupled with developments in potential real-time monitoring of sac expansion.

TABLE 39 Sensitivity and specificity of using different cut-off points of sac growth for classifying those 'at risk' of rupture within the next 5 years (considering only individuals who are not censored within the prediction interval)

		Sensitivity (%)/specificity (%) cut-off point for further investigations: sac growth (mm/year)				
Landmark time	Predicted or naive (observed)	0	1	2	3	4
2 years	Predicted ($n = 14$)	79/72	68/86	58/95	26/99	11/99
	Observed ($n = 13$)	67/66	50/77	44/81	39/85	39/88
3 years	Predicted ($n = 13$)	84/58	79/76	63/89	42/97	26/99
	Observed ($n = 13$)	79/59	63/74	53/79	53/84	47/87
5 years	Predicted ($n = 12$)	93/46	86/62	64/81	43/92	36/96
	Observed ($n = 12$)	71/51	64/68	57/76	57/81	50/85

We have shown in these analyses that a decision threshold based on sac growth may not be constant over time because of the non-linear nature of the sac trajectory. At 2 years post operation any sac expansion is highly indicative of a possible future rupture event, whereas at 5 years post operation the majority of patients who were not observed to have a rupture also had non-negative growth rates (albeit sometimes close to zero). This finding suggests two things: first, that the cut-off point for further investigations could be raised slightly at 3 or 5 years post operation; and, second, that surveillance cannot stop at 2 years post operation in the face of a shrinking sac, as some sacs do not start to expand until after this time.

Developing a model to predict future complications or cluster complication was less successful, with none of the developed models providing high predictive accuracy. This could partly be due to the non-specific nature of the outcomes under consideration, particularly with respect to 'any complication', which was a composite outcome of 16 different aneurysm-related complications (see *Table 29*).

Limitations of this work are that there were relatively few rupture events (36 occurred beyond 2 years post operation). Therefore, the results may be overly optimistic and require validation using external data sources. C-indices were calculated using cross-validation in an attempt to mitigate this issue, but the sensitivities and specificities shown in *Table 39* could be overly optimistic. A further limitation of this work is that reinterventions that occurred before secondary rupture are ignored in the modelling. Patients with high sac expansion may therefore have undergone corrective procedures, resulting in a lower risk of subsequent rupture. This could have led us to underestimate the association between sac growth and rupture. Future analyses could therefore consider alternative end points such as aneurysm-related mortality or a composite end point of reintervention or secondary rupture.

In developing a model for describing sac trajectories over time, we found that grafts produced by different manufacturers behaved differently with respect to the rate of subsequent sac expansion. It should, however, be noted that these grafts were all first-generation grafts and the results are in no way indicative of today's newer-generation endovascular devices. Furthermore, some grafts may have been more widely used on more difficult aneurysms, which were then more likely to expand post operation (*Table 40*).

TABLE 40 Additional coefficients and variance components estimated from linear mixed-effects model

	Coefficient	*p*-value
Fixed effects		
Time (years)	0.300 (0.167 to 0.432)	< 0.001
Quadratic time	0.000 (–0.007 to 0.008)	0.905
Square root time	–1.116 (–1.285 to 0.947)	< 0.001
Between-person standard deviation		
Time	0.130 (0.088 to 0.191)	
Quadratic time	0.022 (0.019 to 0.027)	
Square root time	0.644 (0.594 to 0.698)	
Within-person (residual) standard deviation	0.383 (0.371 to 0.395)	

Chapter 9 Results from EVAR trial 2

The EVAR trial 2 patients and their follow-up

Between 1 September 1999 and 31 August 2004, 404 patients were recruited to participate in EVAR-2. A total of 197 patients were randomly assigned to the endovascular group and 207 were assigned to the no-intervention group. There were no significant differences between the two study groups with respect to baseline characteristics, mean age was 76.8 years and 347 (86%) were men (*Table 41*), but these patients were older and more physically frail than patients randomised to EVAR-1.[95]

Patients were followed for mortality until 30 June 2015 (mean 12.3 years, median 12.2 years); mean follow-up to either death or end of the study was 4.2 years. Mortality was from regular reports from NHS Digital, which were assessed by the Endpoint Committee in a consistent manner for all deaths reported between September 2009 and June 2015. Out of 98 patients still under follow-up in September 2009, 45 (46%) had local follow-up at the trial centre. In contrast to follow-up of EVAR-1 patients, the EVAR-2 patients were not tracked using the administrative database of HES from NHS Digital. The Consolidated Standards of Reporting Trials diagram is shown in *Figure 30*.

TABLE 41 Baseline characteristics of patients in EVAR-2

Baseline characteristics by randomised group for EVAR trial 2		
Baseline characteristic[a]	**EVAR (*n* = 197)**	**No intervention (*n* = 207)**
Age (years)	77.2 (6.3) [0]	76.4 (6.7) [0]
Number of males (%)	168 (85) [0]	179 (86) [0]
AAA diameter (cm)	6.8 (1.0) [0]	6.7 (1.0) [0]
BMI (kg/m^2)	26.4 (5.0) [1]	26.5 (4.4) [1]
Diabetes (%)	30 (15) [2]	29 (14) [2]
Smoking status (%)	[0]	[0]
Current	33 (17)	37 (18)
Past	152 (77)	156 (75)
Never	12 (6)	14 (7)
History of cardiac disease[b] (%)	132 (67) [0]	153 (74) [0]
Systolic blood pressure (mmHg)	140 (20) [0]	139 (23) [0]
Diastolic blood pressure (mmHg)	79 (12) [0]	79 (12) [3]
ABPI (mean of both legs)	0.99 (0.20) [10]	0.98 (0.19) [8]
Forced expiration volume in 1 second (l)	1.6 (0.6) [7]	1.7 (0.7) [4]
Serum creatinine (μmol/l)[a]	107 (90–134) [0]	112 (94–140) [2]
Serum cholesterol (mmol/l)	4.8 (1.2) [13]	4.8 (1.1) [7]
Statin use (%)	82 (42) [1]	86 (42) [0]
Aspirin use (%)	114 (58) [1]	114 (55) [0]

a Continuous variables are presented as mean (standard deviation), apart from creatinine which is presented as median (interquartile range) as data were positively skewed. Categorical variables presented as number (%). Data in squared brackets indicate number of patients with missing data.
b Cardiac disease is defined as previous history of any of the following: MI, angina, cardiac revascularisation, cardiac valve disease, significant arrhythmia or uncontrolled congestive cardiac failure.

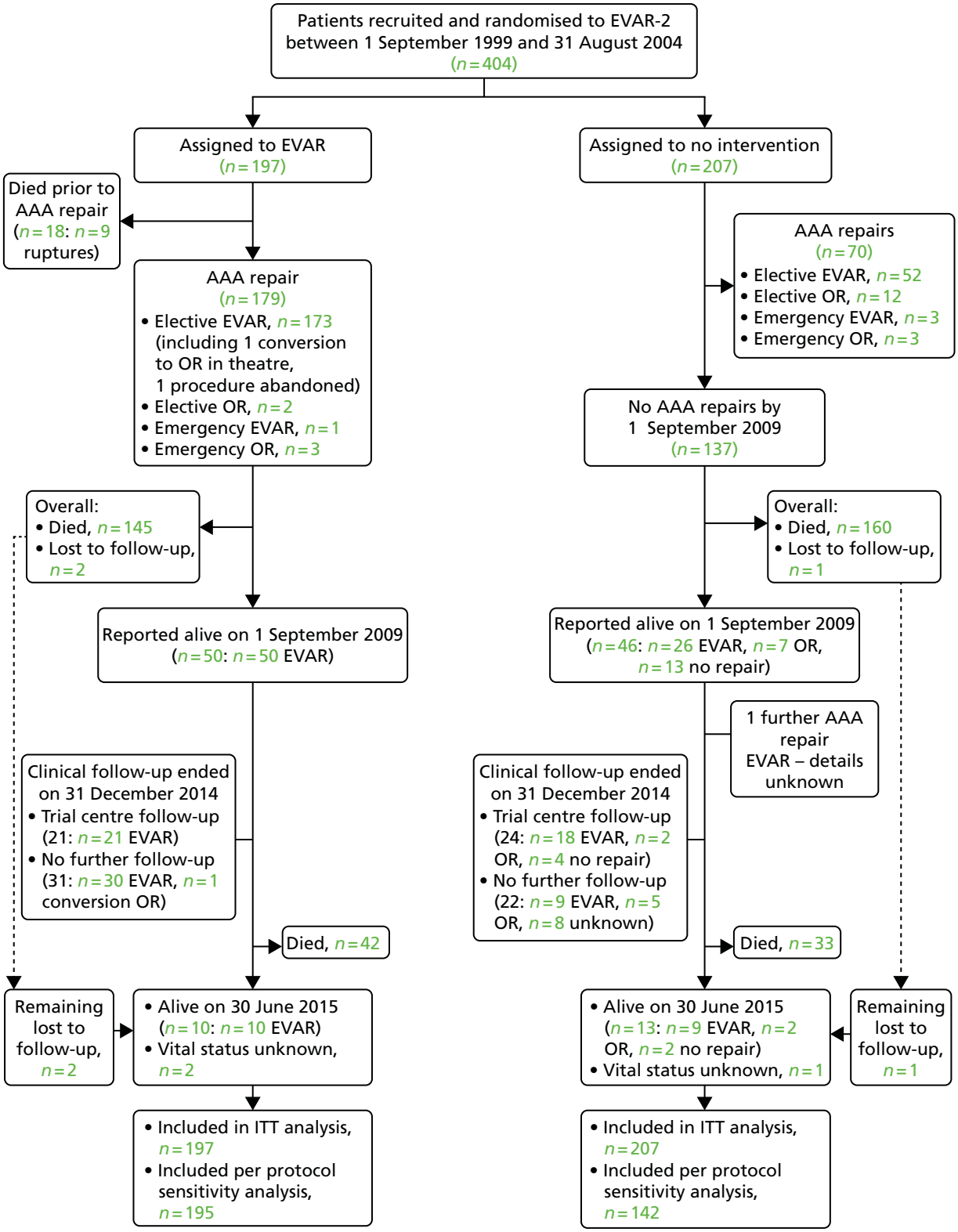


FIGURE 30 Consolidated Standards of Reporting Trials diagram: EVAR-2.

Long-term survival of patients randomised in the EVAR trial 2

After the 5- and 10-year results of EVAR-2 were known,[95,107] it has become increasingly recognised that there is a cohort of patients who have such a limited life expectancy or such extensive comorbidities that repair of an AAA should not be considered.[161,162] The difficulty is in defining carefully this group of patients. In EVAR-2, the participating clinicians appeared to have had good judgement in selecting patients for this trial: by 4 years < 40% of patients remained alive and by 8 years this had reduced to < 20%.[95] Nevertheless, the approximately 20% of patients who remain alive after 8 years were perhaps physically the fittest of all the patients enrolled in EVAR-2 and it is of interest to compare their very long-term survival both by ITT and per-protocol analysis. This starts to enable description of the patients who, although physically frail and ineligible for OR, may have many life-years ahead and might benefit from EVAR, particularly if conducted under local anaesthesia. Such information could be important for updating the guidelines for the management of physically frail patients with large aneurysms.

Aneurysm-related and total mortality

During 1713 person-years of follow-up, 381 deaths occurred and 84 of which were aneurysm related. Overall aneurysm-related mortality was 3.2 deaths per 100 person-years in the EVAR group and 6.5 deaths per 100 person-years in the no-intervention group (adjusted HR 0.55, 95% CI 0.34 to 0.90; $p = 0.018$). Beyond 8 years of follow-up, the rate of aneurysm-related mortality was very low, with two aneurysm-related deaths in the EVAR group (at 8.0 and 13.2 years after randomisation) and one aneurysm-related death in the no-intervention group (at 9.3 years after randomisation), with survival curves remaining parallel (*Figure 31*). However, at 8 years only 10 of 38 patients in the no-intervention group remained with an intact unrepaired aneurysm compared with 0 of 32 patients in the EVAR group.

For total mortality, there were 22.4 deaths per 100 person-years in the EVAR group and 22.1 deaths per 100 person-years in the no-intervention group. Beyond 8 years the number of deaths and mortality rate were similar in the two randomised groups. By 12 years of follow-up the estimated survival was 5.7% (95% CI 3.05 to 9.7%) in the EVAR group and 8.5% (95% CI% 5.2 to 12.9%) in the no-intervention group (see *Figure 31*). There was no significant difference in life expectancy (restricted to 12 years of follow-up), between the groups (4.2 years in both the EVAR and the no-intervention groups; $p = 0.99$).

Deaths according to time since randomisation are given in *Table 42*; deaths from any cause and aneurysm-related causes according to time since randomisation are given in *Table 43*; and the full causes of death by time period are given in *Table 44*. Overall, there were 16 deaths from aneurysm rupture in the EVAR group (13 procedure related and three secondary ruptures) and 53 in the no-intervention group (52 primary and one secondary rupture).

Aneurysm-related reinterventions

During 1663 person-years of follow-up, 54 graft-related reinterventions were performed in 38 patients in the EVAR group and 21 graft-related reinterventions were performed in 15 patients in the no-intervention group (*Table 45*). HRs for risk of a reintervention are shown in *Table 46* by time epoch. There was a significantly higher rate of reinterventions in the EVAR group in the 6 months following randomisation. Beyond 4 years the rate of reintervention was similar between the two groups, as a result of a decreasing rate in the EVAR group and a slightly increasing rate in the no-intervention group as surviving individuals among those who underwent aneurysm repair.

Further analysis was carried out to compare baseline characteristics between those who did not survive > 8 years and the 70 (17%) patients who did (*Table 47*). The patients who survived ≥ 8 years were younger, with higher BMI, lower creatinine levels and better lung function than patients who survived < 8 years. There was also a small difference in aneurysm diameter, with slightly smaller aneurysms in the long-term survivors.

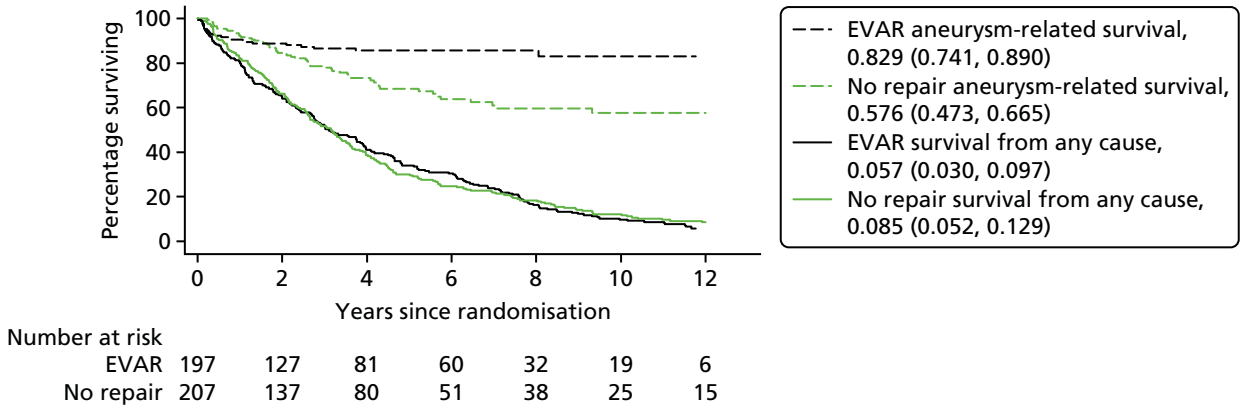


FIGURE 31 Kaplan–Meier estimates for total survival and aneurysm-related survival up to 12 years of follow-up. Twelve-year survival probabilities are reported in the key.

TABLE 42 Deaths according to time since randomisation

	EVAR ($n = 197$)	No repair ($n = 207$)
***Any death*, n (%)**		
All patients	187 (94.9)	194 (93.7)
Time of death, *n* (%)		
0–6 months	24 (13)	19 (10)
6 months–4 years	92 (49)	108 (56)
4–8 years	49 (26)	42 (22)
> 8 years	22 (12)	25 (13)
Cause of death, *n* (%)		
Procedure-related AAA	11 (6)	3 (2)
Procedure-related AAA rupture	13 (7)	53 (27)
Coronary heart disease	45 (24)	60 (31)
Stroke	4 (2)	5 (3)
Other (including PAD)	3 (2)	3 (2)
Cancer, lung	13 (7)	8 (4)
Cancer, other	27 (14)	20 (10)
Respiratory	47 (25)	18 (9)
Renal	3 (2)	4 (2)
Other	18 (10)	15 (8)
Secondary AAA rupture	3 (2)	1 (1)
Unknown	0 (0)	4 (2)

PAD, peripheral arterial disease.

Discussion of EVAR trial 2

Findings from these EVAR-2 results have shown that the benefit of EVAR in terms of aneurysm-related mortality persists throughout follow-up. However, although some patients (< 10%) survive to 12 years, either with or without aneurysm repair, the majority of EVAR-2 patients had a limited life expectancy, and hence at no time does aneurysm repair confer an overall survival benefit. Given the rather limited clinical and imaging follow-up of these patients beyond 8 years, aneurysm-related mortality could have been underestimated during the final few years of follow-up and, therefore, is a less reliable outcome for EVAR-2 than for EVAR-1 and the magnitude of the difference in aneurysm-related mortality appears to be unchanged between 8 and 12 years after randomisation. Our earlier interpretation, that it is advisable to take time to optimise patient fitness before considering EVAR, continues to hold up. By the end of patient follow-up at least 71 of 207 (34%) patients assigned to no intervention had undergone aneurysm repair. Some patients had their aneurysm repair many years after randomisation and over 12 years of follow-up there was no difference in either survival or average life-years between the randomised groups.

TABLE 43 Deaths from any cause and aneurysm-related causes, according to time since randomisation

	Treatment group, *n*/*N*		HR (95% CI)		
	EVAR (*n* = 197), *n*/*N* (rate/100 person-years)	No repair (*n* = 207), *n*/*N* (rate/100 person-years)	Unadjusted	Adjusted (primary, secondary)	*p*-value
Any death					
All patients	187/197 (22.4)	194/207 (22.1)	1.02 (0.84 to 1.25)	1.05 (0.85 to 1.30)	0.55
				1.07 (0.86 to 1.33)	
Time since randomisation					
0–6 months	24/197 (26.0)	19/207 (19.0)	1.38 (0.76 to 2.52)	1.48 (0.80 to 2.71)	0.41
				1.32 (0.68 to 2.54)	
6 months–4 years	92/173 (21.4)	108/188 (23.6)	0.90 (0.69 to 1.20)	0.96 (0.72 to 1.29)	0.92
				1.02 (0.75 to 1.37)	
4–8 years	49/81 (21.4)	42/80 (19.7)	1.09 (0.72 to 1.65)	1.01 (0.66 to 1.56)	0.82
				0.95 (0.60 to 1.50)	
> 8 years	22/32 (26.3)	25/38 (23.2)	1.15 (0.65 to 2.04)	1.24 (0.66 to 2.36)	0.70
				1.14 (0.59 to 2.20)	
Aneurysm-related death					
All patients	27/197 (3.2)	57/207 (6.5)	0.50 (0.32 to 0.80)	0.55 (0.34 to 0.88)	0.018
				0.55 (0.34 to 0.90)	
Time since randomisation					
0–6 months	15/197 (16.3)	9/207 (9.0)	1.82 (0.80 to 4.16)	1.93 (0.84 to 4.46)	0.19
				1.78 (0.75 to 4.21)	
6 months–4 years	10/173 (2.3)	35/188 (7.6)	0.31 (0.15 to 0.62)	0.33 (0.16 to 0.68)	0.0050
				0.34 (0.16 to 0.72)	
4–8 years	0/81 (0.0)	12/80 (5.6)	0	NC	NC
> 8 years	2/32 (2.4)	1/38 (0.9)	2.57 (0.23 to 28.45)	3.90 (0.14 to 108.15)	NC
				NC	
> 4 years	2/81 (0.6)	13/80 (4.0)	0.15 (0.03 to 0.68)	0.18 (0.04 to 0.80)	0.029
				0.17 (0.04 to 0.84)	

NC, not calculable (because of the small number of events).

Inspection of the baseline characteristics of the long-term survivors suggested 'the survival of the fittest' phenomenon. The long-term survivors had notably better baseline lung function than the remainder, which might have impacted on the ability of the long-term survivors to cope well with general anaesthesia. During the randomisation period, many of the EVAR procedures are likely to have been conducted under general anaesthesia, although today there is more widespread use of local anaesthesia in physically frail patients. The differences in creatinine levels may be of less significance, as with their younger age and higher BMI, the glomerular filtration rates might be quite similar for the long-term survivors and the remainder. Aneurysm diameter is an accepted indicator of the risk of cardiovascular mortality, so that the patients with lower baseline aneurysm diameter are likely to have been at lower risk of cardiovascular death.[163–165]

TABLE 44 Causes of death by period since randomisation

Cause of death	EVAR	No repair
Randomisation to 6 months	**n = *24***	**n = *19***
Primary-related AAA	8	1
Procedure-related AAA rupture	7	8
Coronary heart disease	2	5
Stroke	0	2
Other (including PAD)	0	0
Cancer, lung	1	0
Cancer, other	0	0
Respiratory	5	1
Renal	0	1
Other	1	1
Secondary AAA rupture	0	0
Unknown	0	0
6 months–4 years	**n = *92***	**n = *108***
Primary-related AAA	3	0
Procedure-related AAA rupture	6	35
Coronary heart disease	30	32
Stroke	3	2
Other (including PAD)	0	3
Cancer, lung	7	3
Cancer, other	14	11
Respiratory	19	9
Renal	2	3
Other	7	8
Secondary AAA rupture	1	0
Unknown	0	2
4–8 years	**n = *49***	**n = *41***
Primary-related AAA	0	3
Procedure-related AAA rupture	0	9
Coronary heart disease	11	12
Stroke	1	0
Other (including PAD)	0	0
Cancer, lung	4	4
Cancer, other	8	5

continued

TABLE 44 Causes of death by period since randomisation (*continued*)

Cause of death	EVAR	No repair
Respiratory	15	5
Renal	1	0
Other	9	3
Secondary AAA rupture	0	0
Unknown	0	0
> 8 years	**n = *22***	**n = *25***
Primary-related AAA	0	0
Procedure-related AAA rupture	0	0
Coronary heart disease	2	11
Stroke	0	1
Other (including PAD)	3	0
Cancer		
Cancer, lung	1	1
Cancer, other	5	4
Respiratory	8	3
Renal	0	0
Other	1	3
Secondary AAA rupture	2	1
Unknown	0	1

PAD, peripheral arterial disease.

Although longer follow-up shows benefits in terms of aneurysm-related mortality, primarily through prevention of late aneurysm rupture, patients in this trial had a limited life expectancy, regardless of whether the aneurysm was repaired or no intervention was performed. Life expectancy was estimated to be 4.2 years in both the EVAR and no-intervention groups. By 1 September 2009, only 98 patients had survived, and by 30 June 2015 only 23 patients were still alive. The clinical factors leading to the assessment that these patients were physically ineligible for OR seem likely to have contributed to a high subsequent rate of death from any cause. This rate was not influenced by assignment to EVAR.

Beyond 8 years of follow-up, there were no reinterventions recorded in the EVAR group and just three reinterventions in the group randomised to no repair. By September 2009 there were so few EVAR-2 patients surviving that, given the need to provide robust justification to obtain ethics approval for using administrative data, HES data were not pursued for EVAR-2 patients. In hindsight, this might have been a mistake. HES data may have allowed us to capture further primary aneurysm repairs as well as more reinterventions, including those carried out at non-trial hospitals, and better define the cause of late deaths. However, the main reason for the low number of reinterventions is the attrition as a result of high mortality in EVAR-2, leaving less time for graft-related complications to develop. Throughout the trial,

TABLE 45 Reintervention according to time since randomisation

	EVAR ($n = 197$)	No repair ($n = 207$)
Any reintervention		
All patients, *n* patients (*n* reinterventions)	38 (54)	15 (21)
Time of reintervention		
Randomisation to 6 months	26	6
6 months–4 years	20	8
4–8 years	8	4
> 8 years	0	3
Type of reintervention		
Added stent	18	4
Staple or ligation	0	0
Embolisation (of endoleak)	9	2
Sclerosis of endoleaks	0	0
Conversion to OR	1	2
Other	6	2
Known aneurysmal extension above or below original graft	0	1
Reintervention for thrombosis of graft limb	0	0
Reintervention for graft infection	0	1
Incisional hernia	0	0
False femoral aneurysm	0	1
Minor reintervention	2	1
Femorofemoral crossover graft	3	1
FEVAR	0	1
Axillobifemoral graft	0	0
Distal limb procedure/revascularisation	11	2
Reoperation of OR	1	0
Replacement stent graft	0	2
Further open abdominal surgery in primary admission	3	0
Amputation	0	0
Unknown	0	1

FEVAR, fenestrated endovascular aneurysm repair.

Note

Centres were asked to recall all patients for a final follow-up in 2014. Only 21 out of 52 patients in the EVAR group that were still alive in September 2009 had a follow-up. A total of 24 out of 46 patients in the OR group that were still alive in September 2009 had a follow-up visit.

TABLE 46 All reinterventions from any relevant procedure according to time since randomisation (analysed using the Anderson–Gill model)

	EVAR ($n = 197$) *n* unique reintervention episodes[a]/total *N* person-years (rate/100 person-years)	No intervention ($n = 207$) *n* unique reintervention episodes[a]/total *N* person-years (rate/100 person-years)	HR (95% CI) Unadjusted	Adjusted (primary,[a] secondary)	*p*-value
Any reintervention					
All patients	47/809 (5.8)	21/854 (2.5)	2.36 (1.28 to 4.37)	2.42 (1.31 to 4.48)	0.005
				2.54 (1.32 to 4.87)	
Time since randomisation					
0–6 months	23/91 (25.3)	6/100 (6.0)	4.10 (1.50 to 11.22)	4.31 (1.53 to 12.10)	0.004
				4.94 (1.65 to 14.81)	
6 months–4 years	16/418 (3.8)	8/451 (1.8)	2.17 (0.85 to 5.56)	2.15 (0.80 to 5.77)	0.077
				2.56 (0.90 to 7.29)	
> 4 years	8/300 (2.7)	7/303 (2.3)	1.12 (0.39 to 3.25)	1.15 (0.43 to 3.08)	0.99
				0.99 (0.29 to 3.36)	

a Reinterventions that occur on separate days (seven reinterventions occurred on the same day as another reintervention).

one might have expected a lower reintervention rate than in EVAR-1, as EVAR-2 patients were frailer and less fit. However, up to September 2009 patient fitness did not seem to have influenced the decision to intervene, with a similar reintervention rate in both EVAR groups of EVAR-1 and EVAR-2. In late follow-up from September 2009, in those patients that underwent endovascular repair (including a considerable number of patients in the no-intervention group that had aneurysm repair), it is likely that reinterventions, even when deemed necessary, may not have been performed because of physical frailty.

Like EVAR-1, EVAR-2 used principally early-generation endografts; later iterations of grafts would now be the commonly used. The long-term durability of these later iterations of endografts has not been evaluated, but it is hoped that they would be associated with lower rates of complications and reinterventions.

It is perhaps unsurprising that long-term survival is associated with younger age, smaller aneurysm and better lung function at baseline. It is thus likely that future selection for EVAR in the relatively frail might likely be influenced by age, size of aneurysm and respiratory status.

TABLE 47 Comparison of baseline characteristics for those individuals who survived ≥ 8 years after randomisation vs. those who did not in EVAR-2

Baseline characteristic[a]	Did not survive > 8 years ($n = 334$)	Survived ≥ 8 years ($n = 70$)	*p*-value[b]
Age (years)	77.2 (6.6) [0]	74.9 (6.0) [0]	0.0048
Number of males (%)	287 (86) [0]	60 (86) [0]	0.96
AAA diameter (cm)	6.7 (1.0) [0]	6.6 (1.1) [0]	0.021
BMI (kg/m^2)	26.2 (4.7) [2]	27.9 (4.7) [0]	0.0078
Diabetes (%)	47 (14) [3]	12 (17) [1]	0.50
Smoking status (%)	[0]	[0]	0.97
Current	58 (17)	12 (17)	
Past	255 (76)	53 (76)	
Never	21 (6)	5 (7)	
History of cardiac disease[c] (%)	233 (70) [0]	52 (74) [0]	0.45
Systolic blood pressure (mmHg)	139 (21) [0]	139 (24) [0]	0.93
Diastolic blood pressure (mmHg)	79 (12) [3]	80 (12) [0]	0.41
ABPI (mean of both legs)	0.98 (0.20) [24]	1.00 (0.21) [1]	0.59
Forced expiration volume in 1 second (l)	1.6 (0.7) [10]	1.9 (0.7) [1]	0.0047
Serum creatinine level (μmol/l)[a]	110 (94–141) [1]	105 (87–119) [1]	0.014
Serum cholesterol level (mmol/l)	4.8 (1.1) [19]	4.8 (1.3) [1]	0.97
Statin use (%)	138 (41) [1]	30 (43) [0]	0.83
Aspirin use (%)	186 (56) [1]	42 (60) [0]	0.53

a Continuous variables presented as mean (standard deviation), apart from serum creatinine level which is presented as median (interquartile range) as data were positively skewed. Categorical variables presented as number (%). Data in squared brackets indicate number of patients with missing data.
b *p*-value calculated from a Wilcoxon rank-sum non-parametric test for continuous variables and a chi-squared test for categorical variables.
c Cardiac disease is defined as previous history of any of the following: MI, angina, cardiac revascularisation, cardiac valve disease, significant arrhythmia or uncontrolled congestive cardiac failure.

Chapter 10 Conclusions and recommendations

Suggestions of possible implications on practice and local health-care delivery

EVAR trial 1 was performed in the UK as a collaborative venture between the two disciplines of vascular surgery and interventional radiology, which worked well for elective repair of the abdominal aorta by endovascular methods. Recruitment was ahead of schedule both because of this high-level national support for the EVAR trials and also because Sir Miles Irving linked NIHR funding of EVAR to subventions which were triggered only by randomisation with local freedom of choice of EVAR manufacturer device.

The results have been segmented into four periods: 0–6 months, 6 months–years, 4–8 years and > 8 years. From a benefit in mortality in favour of the EVAR group up to 6 months, beyond 4 years this was counterbalanced by an increase in aneurysm-related mortality, the difference being most marked after 8 years. In terms of total mortality, there was benefit in favour of EVAR during the first 6 months. Groups were similar between 6 months and 8 years, but after 8 years total mortality was significantly worse in the EVAR group than in the OR group.

Reinterventions were greater in the EVAR group throughout EVAR-1 in all periods, and there was never a time when there was evidence that the interventions were expected to be so low that follow-up surveillance could stop.

Despite warnings to the trial centres to recommend ongoing annual clinical follow-up and imaging, this fell away. Even though many centres switched from CT to ultrasound, this did not stop the reduction of enthusiasm to follow patients at this late stage.

In EVAR-2 after 10 years there was poor clinical follow-up and we did not use HES to track reinterventions. This was because the number of patients alive at that stage was very small. However, we had robust data on mortality and our evidence shows superior aneurysm-related mortality in favour of EVAR increasing with time, but there was no difference in the groups in terms of all-cause mortality.

The IPD meta-analysis confirms the advantage of lower mortality in the EVAR group in the first 6 months and provides some new insight of how this early advantage of the EVAR group is eroded (aneurysm-related mortality and inclusion of those with peripheral arterial disease). Additionally, we identified two subgroups in which mortality was not lower at any time, suggesting that these groups (patients with moderate renal dysfunction and established coronary artery disease) may benefit from improved perioperative care, especially if undergoing EVAR. Surveillance must focus on reducing aneurysm-related deaths in the mid-term and longer term, particularly deaths resulting from reinterventions and secondary ruptures after EVAR.

In the IPD meta-analysis there was no overall evidence that type II endoleak in itself is associated with a higher rate of mortality, although, as previously shown, type II endoleak as part of the ‘cluster’ of complications is associated with secondary rupture. However, this suggests that it is other complications that are listed in the ‘cluster’ that are sinister and not type II endoleaks alone. The ‘cluster’ included definition of the type II endoleak with sac expansion and it seems that sac expansion is the important factor here. The findings here on type II endoleak might suggest that the enthusiasm to correct type II endoleak when on its own is misplaced. On the other hand, when type II endoleak is associated the so-called ‘cluster’ it is far from a benign condition. In addition, type II endoleak can be wrongly diagnosed and a more severe endoleak, such as types IA or IB, can be at the root of the problem.

The mean difference in costs over 14 years was £3798 (95% CI of £2338 to £5258). Decision modelling based on EVAR-1 showed that the lifetime difference in cost was £3616 and the difference in QALYs was 0.018, with a cost per QALY of £202,776. The cost per QALY exceeds conventional thresholds used in the UK. The DREAM and ACE trials (conducted in the Netherlands and France, respectively) found similar results. If EVAR is to be considered a cost-effective use of NHS resources, it needs to demonstrate fewer reinterventions and fewer late aneurysm deaths than were observed in the EVAR trial.

Patterns of sac growth, if modelled correctly, can be useful predictors for future serious rupture events. Estimates of sac expansion should be derived from longitudinal modelling with a sac diameter trajectory, which accounts for all previous measurements and thus produces more accurate estimates of current sac growth. Naive estimates of growth based on the last two observed diameter measurements are too crude to be of critical use in a prediction model. The current sac diameter was not found to be an independent risk factor of rupture after accounting for the growth rate of the sac and the predictive accuracy of the model just using sac diameter was lower than a model that used sac growth.

Recommendations for future research

To pursue annual follow-up with appropriate imaging is the first priority, although a simple switch from annual CT scanning (with associated radiation exposure) to ultrasound is in itself not enough for follow-up to be continued adequately.

As EVAR is more costly over the patient's lifetime, an earlier discharge from secondary care to simple follow-up in primary care might be a worthwhile aim in the future. In order for EVAR to be considered effective and cost-effective, an area of further research is to find better ways to target reintervention of patients who are at risk of secondary rupture and avoid reintervention in patients at very low risk. Our early findings suggest that an algorithm could be developed based on annual measurements of aortic sac diameter only. This might have excellent predictive value for future rupture. If effective, it would need substantial validation on a separate cohort of patients.

The long-term findings of EVAR-2 present an ethical problem for consideration. Our evidence is that endovascular repair does not alter mortality from all causes in any way, but EVAR can lower aneurysm-related mortality. It is entirely possible that greater enthusiasm to perform endovascular repair may re-emerge and a view on the attitudes to this will become important.

The determination of which frail patients merit aortic repair needs further determination. We see early encouragement that such a cohort could be defined. It would need to be clinically tested. This may be the only realistic way that EVAR could become effective and cost-effective.

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These trials are a collaborative effort and their success is a result of the enormous enthusiasm and support from all of the committee members and participating centres. A full list of EVAR trial participants is given in *Appendix 2*.

Contributions of authors

Rajesh Patel drafted and compiled the report as trial manager, referring always to the other authors.

Janet T Powell critically reviewed the manuscript and added value at every stage.

Michael J Sweeting drafted all statistical methods as he performed all statistical analyses. He also drafted *Chapter 8* with **Jessica K Barrett** and critically reviewed the manuscript.

David M Epstein performed cost and cost-effectiveness analyses, and drafted *Chapters 4* and *5*.

Jessica K Barrett performed analysis for *Chapter 8* and co-drafted this chapter with **Michael J Sweeting**.

Roger M Greenhalgh had overall responsibility, co-ordination and supervision, with special responsibility for clinical issues, and he edited the report.

Publications

Brown LC, Epstein D, Manca A, Beard JD, Powell JT, Greenhalgh RM. The UK Endovascular Aneurysm Repair (EVAR) trials: design, methodology and progress. *Eur J Vasc Endovasc Surg* 2004;**27**:372–81.

EVAR Trial Participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. *Lancet* 2004;**364**:843–8.

EVAR Trial Participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet* 2005;**365**:2179–86.

EVAR Trial Participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet* 2005;**365**:2187–92.

Greenhalgh RM, Brown LC, Powell JT. High risk and unfit for open repair are not the same. *Eur J Vasc Endovasc Surg* 2007;**34**:154–5.

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.

Brown LC, Greenhalgh RM, Kwong GP, Powell JT, Thompson SG, Wyatt MG. Secondary interventions and mortality following endovascular aortic aneurysm repair: device-specific results from the UK EVAR trials. *Eur J Vasc Endovasc Surg* 2007;**34**:281–90.

Powell JT, Brown LC, Greenhalgh RM, Thompson SG. The rupture rate of large abdominal aortic aneurysms: is this modified by anatomical suitability for endovascular repair? *Ann Surg* 2008;**247**:173–9.

Epstein DM, Sculpher MJ, Manca A, Michaels J, Thompson SG, Brown LC, *et al.* Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm. *Br J Surg* 2008;**95**:183–90.

Rodway AD, Powell JT, Brown LC, Greenhalgh RM. Do abdominal aortic aneurysm necks increase in size faster after endovascular than open repair? *Eur J Vasc Endovasc Surg* 2008;**35**:685–93.

Brown LC, Brown EA, Greenhalgh RM, Powell JT, Thompson SG, on behalf of the UK EVAR Trial Participants. Renal function and abdominal aortic aneurysm: the impact of different management strategies on long-term renal function in the UK EndoVascular Aneurysm Repair (EVAR) Trials. *Ann Surg* 2010;**251**:966–75.

Brown LC, Greenhalgh RM, Thompson SG, Powell JT. 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. *Eur J Vasc Endovasc Surg* 2010;**39**:396–402.

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.

The UK EVAR Trial Investigators. Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. *N Engl J Med* 2010;**362**:1872–80.

The UK EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med* 2010;**362**:1863–71.

Wyss TR, Brown LC, Powell JT, Greenhalgh RM. Rate and predictability of graft rupture after endovascular and open abdominal aortic aneurysm repair: data from the EVAR Trials. *Ann Surg* 2010;**252**:805–12.

Brown LC, Thompson SG, Greenhalgh RM, Powell JT, on behalf of the EVAR Trial participants. Incidence of cardiovascular events and death after open or endovascular repair of abdominal aortic aneurysm: results from the randomised EVAR trial 1. *Br J Surg* 2011;**98**:935–42.

Epstein D, Sculpher MJ, Powell JT, Thompson SG, Brown LC, Greenhalgh RM. Long-term cost-effectiveness analysis of endovascular versus open repair for abdominal aortic aneurysm based on four randomized clinical trials. *Br J Surg* 2014;**101**:623–31.

Brown LC, Powell JT, Thompson SG, Epstein DM, Sculpher MJ, Greenhalgh RM. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy. *Health Technol Assess* 2012;**16**(9).

Wyss TR, Dick F, Brown LC, Greenhalgh RM. The influence of thrombus, calcification, angulation, and tortuosity of attachment sites on the time to the first graft-related complication after endovascular aneurysm repair. *J Vasc Surg* 2011;**54**:965–71.

Patel R, Sweeting MJ, Powell JT, Greenhalgh RM, for the EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm in 15-years follow-up of the UK endovascular aneurysm repair trial 1 (EVAR trial 1): a randomised controlled trial. *Lancet* 2016;**388**:2366–74.

Powell JT, Sweeting MJ, Ulug P, Blankensteijn JD, Lederle FA, Becquemin JP, Greenhalgh RM. Endovascular or open repair for abdominal aortic aneurysm over 5 years: Individual patient data meta-analysis from EVAR 1 DREAM, OVER and ACE trials. *Br J Surg* 2017;**104**:166–78.

Sweeting MJ, Patel R, Powell JT, Greenhalgh RM. Endovascular repair of abdominal aortic aneurysm in patients physically ineligible for open repair: very long-term follow-up in the EVAR-2 randomized controlled trial. *Ann Surg* 2017;**266**:713–19.

IMPROVE Trial Investigators. Comparative clinical effectiveness and cost effectiveness of endovascular strategy vs. open repair for ruptured abdominal aortic aneurysm: three year results of the IMPROVE randomised trial. *BMJ* 2017;**359**:4859.

Data sharing statement

Any requests for data should be sent to the corresponding author, Professor Roger Greenhalgh.

References

1. Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65 to 74 years. *Lancet* 1988;**2**:613–15. https://doi.org/10.1016/S0140-6736(88)90649-6
2. Sonesson B, Länne T, Hansen F, Sandgren T. Infrarenal aortic diameter in the healthy person. *Eur J Vasc Surg* 1994;**8**:89–95. https://doi.org/10.1016/S0950-821X(05)80127-6
3. Wanhainen A, Themudo R, Ahlstrom H, Lind L, Johansson L. Thoracic and abdominal aortic dimension in 70-year-old men and women – a population-based whole-body magnetic resonance imaging (MRI) study. *J Vasc Surg* 2008;**47**:504–12. https://doi.org/10.1016/j.jvs.2007.10.043
4. Greenhalgh RM, Rosengarten DS, Mervart I, Lewis B, Calnan JS, Martin P. Serum lipids and lipoproteins in peripheral vascular disease. *Lancet* 1971;**2**:947–50. https://doi.org/10.1016/S0140-6736(71)90269-8
5. Thomas ML. Arteriomegaly. *Br J Surg* 1971;**58**:690–4. https://doi.org/10.1002/bjs.1800580915
6. Fowkes FG, Macintyre CC, Ruckley CV. Increasing incidence of aortic aneurysms in England and Wales. *BMJ* 1989;**298**:33–5. https://doi.org/10.1136/bmj.298.6665.33
7. Filipovic M, Goldacre MJ, Roberts SE, Yeates D, Duncan ME, Cook-Mozaffari P. Trends in mortality and hospital admission rates for abdominal aortic aneurysm in England and Wales, 1979-1999. *Br J Surg* 2005;**92**:968–75. https://doi.org/10.1002/bjs.5118
8. Choke E, Vijaynagar B, Thompson J, Nasim A, Bown MJ, Sayers RD. Changing epidemiology of abdominal aortic aneurysms in England and Wales: older and more benign? *Circulation* 2012;**125**:1617–25. https://doi.org/10.1161/CIRCULATIONAHA.111.077503
9. Heather BP, Poskitt KR, Earnshaw JJ, Whyman M, Shaw E. Population screening reduces mortality rate from aortic aneurysm in men. *Br J Surg* 2000;**87**:750–3. https://doi.org/10.1046/j.1365-2168.2000.01476.x
10. Scott RA, Wilson NM, Ashton HA, Kay DN. Influence of screening on the incidence of ruptured abdominal aortic aneurysm: 5-year results of a randomized controlled study. *Br J Surg* 1995;**82**:1066–70. https://doi.org/10.1002/bjs.1800820821
11. Earnshaw JJ. Doubts and dilemmas over abdominal aortic aneurysm. *Br J Surg* 2011;**98**:607–8. https://doi.org/10.1002/bjs.7495
12. Svensjö S, Björck M, Gürtelschmid M, Djavani Gidlund K, Hellberg A, Wanhainen A. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease. *Circulation* 2011;**124**:1118–23. https://doi.org/10.1161/CIRCULATIONAHA.111.030379
13. Anjum A, Powell JT. Is the incidence of abdominal aortic aneurysm declining in the 21st century? Mortality and hospital admissions for England & Wales and Scotland. *Eur J Vasc Endovasc Surg* 2012;**43**:161–6. https://doi.org/10.1016/j.ejvs.2011.11.014
14. Schwarze ML, Shen Y, Hemmerich J, Dale W. Age-related trends in utilization and outcome of open and endovascular repair for abdominal aortic aneurysm in the United States, 2001-2006. *J Vasc Surg* 2009;**50**:722–9.e2. https://doi.org/10.1016/j.jvs.2009.05.010
15. Norman PE, Spilsbury K, Semmens JB. Falling rates of hospitalization and mortality from abdominal aortic aneurysms in Australia. *J Vasc Surg* 2011;**53**:274–7. https://doi.org/10.1016/j.jvs.2010.08.087

16. Sandiford P, Mosquera D, Bramley D. Trends in incidence and mortality from abdominal aortic aneurysm in New Zealand. *Br J Surg* 2011;**98**:645–51. https://doi.org/10.1002/bjs.7461

17. Powell JT, Adamson J, MacSweeney ST, Greenhalgh RM, Humphries SE, Henney A. Genetic variants of collagen III and abdominal aortic aneurysm. *Eur J Vasc Surg* 1991;**5**:145–8. https://doi.org/10.1016/S0950-821X(05)80679-6

18. Powell JT, MacSweeney ST, Greenhalgh RM, Turner RJ, Henney AM. Interaction between fibrillin genotype and blood pressure and the development of aneurysmal disease. *Ann N Y Acad Sci* 1996;**800**:198–207. https://doi.org/10.1111/j.1749-6632.1996.tb33310.x

19. Freestone T, Turner RJ, Coady A, Higman DJ, Greenhalgh RM, Powell JT. Inflammation and matrix metalloproteinases in the enlarging abdominal aortic-aneurysm. *Arterioscl Throm Vasc Biol* 1995;**15**:1145–51. https://doi.org/10.1161/01.ATV.15.8.1145

20. Singh K, Bønaa KH, Jacobsen BK, Bjørk L, Solberg S. Prevalence of and risk factors for abdominal aortic aneurysms in a population-based study: the Tromsø study. *Am J Epidemiol* 2001;**154**:236–44. https://doi.org/10.1093/aje/154.3.236

21. Powell JT, Greenhalgh RM. Clinical practice. Small abdominal aortic aneurysms. *N Engl J Med* 2003;**348**:1895–901. https://doi.org/10.1056/NEJMcp012641

22. Gillum RF. Epidemiology of aortic aneurysm in the United States. *J Clin Epidemiol* 1995;**48**:1289–98. https://doi.org/10.1016/0895-4356(95)00045-3

23. Masuda EM, Caps MT, Singh N, Yorita K, Schneider PA, Sato DT, *et al.* Effect of ethnicity on access and device complications during endovascular aneurysm repair. *J Vasc Surg* 2004;**40**:24–9. https://doi.org/10.1016/j.jvs.2004.02.035

24. Cheng SW, Ting AC, Ho P, Poon JT. Aortic aneurysm morphology in Asians: features affecting stent-graft application and design. *J Endovasc Ther* 2004;**11**:605–12. https://doi.org/10.1583/04-1268R.1

25. Lederle FA, Johnson GR, Wilson SE, Aneurysm Detection and Management Veterans Affairs Cooperative Study. Abdominal aortic aneurysm in women. *J Vasc Surg* 2001;**34**:122–6. https://doi.org/10.1067/mva.2001.115275

26. Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht H, *et al.* 2014 ESC guidelines on the diagnosis and treatment of aortic diseases. *Eur Heart J* 2014;**35**:2873–U2893. https://doi.org/10.1093/eurheartj/ehu281

27. Norman PE, Powell JT. Abdominal aortic aneurysm: the prognosis in women is worse than in men. *Circulation* 2007;**115**:2865–9. https://doi.org/10.1161/CIRCULATIONAHA.106.671859

28. Stenbaek J, Granath F, Swedenborg J. Outcome after abdominal aortic aneurysm repair. Difference between men and women. *Eur J Vasc Endovasc Surg* 2004;**28**:47–51. https://doi.org/10.1016/j.ejvs.2004.02.013

29. Mofidi R, Goldie VJ, Kelman J, Dawson AR, Murie JA, Chalmers RT. Influence of sex on expansion rate of abdominal aortic aneurysms. *Br J Surg* 2007;**94**:310–14. https://doi.org/10.1002/bjs.5573

30. Hultgren R, Granath F, Swedenborg J. Different disease profiles for women and men with abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2007;**33**:556–60. https://doi.org/10.1016/j.ejvs.2006.11.030

31. Wilmink TB, Quick CR, Day NE. The association between cigarette smoking and abdominal aortic aneurysms. *J Vasc Surg* 1999;**30**:1099–105. https://doi.org/10.1016/S0741-5214(99)70049-2

32. Lederle FA, Nelson DB, Joseph AM. Smokers' relative risk for aortic aneurysm compared with other smoking-related diseases: a systematic review. *J Vasc Surg* 2003;**38**:329–34. https://doi.org/10.1016/S0741-5214(03)00136-8

33. Golledge J, Norman PE. Atherosclerosis and abdominal aortic aneurysm: cause, response, or common risk factors? *Arterioscl Throm Vasc Biol* 2010;**30**:1075–7. https://doi.org/10.1161/ATVBAHA.110.206573

34. Cornuz J, Sidoti Pinto C, Tevaearai H, Egger M. Risk factors for asymptomatic abdominal aortic aneurysm: systematic review and meta-analysis of population-based screening studies. *Eur J Public Health* 2004;**14**:343–9. https://doi.org/10.1093/eurpub/14.4.343

35. Fowkes FG, Anandan CL, Lee AJ, Smith FB, Tzoulaki I, Rumley A. Reduced lung function in patients with abdominal aortic aneurysm is associated with activation of inflammation and hemostasis, not smoking or cardiovascular disease. *J Vasc Surg* 2006;**43**:474–80. https://doi.org/10.1016/j.jvs.2005.11.018

36. Vardulaki KA, Walker NM, Day NE, Duffy SW, Ashton HA, Scott RA. Quantifying the risks of hypertension, age, sex and smoking in patients with abdominal aortic aneurysm. *Br J Surg* 2000;**87**:195–200. https://doi.org/10.1046/j.1365-2168.2000.01353.x

37. Lederle FA, Johnson GR, Wilson SE, Chute EP, Littooy FN, Bandyk D, *et al.* Prevalence and associations of abdominal aortic aneurysm detected through screening. Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study Group. *Ann Intern Med* 1997;**126**:441–9. https://doi.org/10.7326/0003-4819-126-6-199703150-00004

38. Powell JT, Greenhalgh RM. Multifactorial inheritance of abdominal aortic aneurysm. *Eur J Vasc Surg* 1987;**1**:29–31. https://doi.org/10.1016/S0950-821X(87)80020-8

39. Larsson E, Granath F, Swedenborg J, Hultgren R. A population-based case–control study of the familial risk of abdominal aortic aneurysm. *J Vasc Surg* 2009;**49**:47–50. https://doi.org/10.1016/j.jvs.2008.08.012

40. Brady AR, Thompson SG, Fowkes FG, Greenhalgh RM, Powell JT, UK Small Aneurysm Trial Participants. Abdominal aortic aneurysm expansion: risk factors and time intervals for surveillance. *Circulation* 2004;**110**:16–21. https://doi.org/10.1161/01.CIR.0000133279.07468.9F

41. Mattes E, Davis TM, Yang D, Ridley D, Lund H, Norman PE. Prevalence of abdominal aortic aneurysms in men with diabetes. *Med J Aust* 1997;**166**:630–3.

42. Lee B, Godfrey M, Vitale E, Hori H, Mattei MG, Sarfarazi M, *et al.* Linkage of Marfan syndrome and a phenotypically related disorder to two different fibrillin genes. *Nature* 1991;**352**:330–4. https://doi.org/10.1038/352330a0

43. Irizarry E, Newman KM, Gandhi RH, Nackman GB, Halpern V, Wishner S, *et al.* Demonstration of interstitial collagenase in abdominal aortic aneurysm disease. *J Surg Res* 1993;**54**:571–4. https://doi.org/10.1006/jsre.1993.1087

44. Curci JA, Liao S, Huffman MD, Shapiro SD, Thompson RW. Expression and localization of macrophage elastase (matrix metalloproteinase-12) in abdominal aortic aneurysms. *J Clin Invest* 1998;**102**:1900–10. https://doi.org/10.1172/JCI2182

45. Fink HA, Lederle FA, Roth CS, Bowles CA, Nelson DB, Haas MA. The accuracy of physical examination to detect abdominal aortic aneurysm. *Arch Intern Med* 2000;**160**:833–6. https://doi.org/10.1001/archinte.160.6.833

46. US Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd edn. Baltimore, MD: Williams & Wilkins; 1996.

47. The UK Small Aneurysm Trial Participants. Mortality results for randomised controlled trial of early elective surgery or ultrasonographic surveillance for small abdominal aortic aneurysms. *Lancet* 1998;**352**:1649–55. https://doi.org/10.1016/S0140-6736(98)10137-X

48. Filardo G, Powell JT, Martinez MA, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. *Cochrane Database Syst Rev* 2015;**2**:CD001835. https://doi.org/10.1002/14651858.CD001835.pub4

49. Ingoldby CJ, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* 1986;**73**:551–3. https://doi.org/10.1002/bjs.1800730711

50. The UK Small Aneurysm Trial Participants. Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms. *New Engl J Med* 2002;**346**:1445–52. https://doi.org/10.1056/NEJMoa013527

51. Lederle FA, Johnson GR, Wilson SE, Chute EP, Hye RJ, Makaroun MS, *et al.* The aneurysm detection and management study screening program: validation cohort and final results. Aneurysm Detection and Management Veterans Affairs Cooperative Study Investigators. *Arch Intern Med* 2000;**160**:1425–30. https://doi.org/10.1001/archinte.160.10.1425

52. Ouriel K, Clair DG, Kent KC, Zarins CK, Positive Impact of Endovascular Options for treating Aneurysms Early (PIVOTAL) Investigators. Endovascular repair compared with surveillance for patients with small abdominal aortic aneurysms. *J Vasc Surg* 2010;**51**:1081–7. https://doi.org/10.1016/j.jvs.2009.10.113

53. Ulug P, Powell JT, Sweeting MJ, Bown MJ, Thompson SG, SWAN Collaborative Group. Meta-analysis of the current prevalence of screen-detected abdominal aortic aneurysm in women. *Br J Surg* 2016;**103**:1097–104. https://doi.org/10.1002/bjs.10225

54. Wilmink AB, Forshaw M, Quick CR, Hubbard CS, Day NE. Accuracy of serial screening for abdominal aortic aneurysms by ultrasound. *J Med Screen* 2002;**9**:125–7. https://doi.org/10.1136/jms.9.3.125

55. Lindholt JS, Vammen S, Juul S, Henneberg EW, Fasting H. The validity of ultrasonographic scanning as screening method for abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 1999;**17**:472–5. https://doi.org/10.1053/ejvs.1999.0835

56. Ellis M, Powell JT, Greenhalgh RM. Limitations of ultrasonography in surveillance of small abdominal aortic aneurysms. *Br J Surg* 1991;**78**:614–16. https://doi.org/10.1002/bjs.1800780529

57. The UK Small Aneurysm Trial Participants. The U.K. Small Aneurysm Trial: design, methods and progress. *Eur J Vasc Endovasc Surg* 1995;**9**:42–48. https://doi.org/10.1016/S1078-5884(05)80223-0

58. Scott RA, Vardulaki KA, Walker NM, Day NE, Duffy SW, Ashton HA. The long-term benefits of a single scan for abdominal aortic aneurysm (AAA) at age 65. *Eur J Vasc Endovasc Surg* 2001;**21**:535–40. https://doi.org/10.1053/ejvs.2001.1368

59. Lederle FA, Wilson SE, Johnson GR, Littooy FN, Acher C, Messina LM, *et al.* Design of the abdominal aortic Aneurysm Detection and Management Study. ADAM VA Cooperative Study Group. *J Vasc Surg* 1994;**20**:296–303. https://doi.org/10.1016/0741-5214(94)90019-1

60. Ashton HA, Gao L, Kim LG, Druce PS, Thompson SG, Scott RA. Fifteen-year follow-up of a randomized clinical trial of ultrasonographic screening for abdominal aortic aneurysms. *Br J Surg* 2007;**94**:696–701. https://doi.org/10.1002/bjs.5780

61. Lindholt JS, Juul S, Henneberg EW. High-risk and low-risk screening for abdominal aortic aneurysm both reduce aneurysm-related mortality. A stratified analysis from a single-centre randomised screening trial. *Eur J Vasc Endovasc Surg* 2007;**34**:53–8. https://doi.org/10.1016/j.ejvs.2006.12.031

62. Lindholt JS, Norman P. Screening for abdominal aortic aneurysm reduces overall mortality in men. A meta-analysis of the mid- and long-term effects of screening for abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2008;**36**:167–71. https://doi.org/10.1016/j.ejvs.2008.03.006

63. Lindholt JS, Sorensen J, Sogaard R, Henneberg EW. Long-term benefit and cost-effectiveness analysis of screening for abdominal aortic aneurysms from a randomized controlled trial. *Br J Surg* 2010;**97**:826–34. https://doi.org/10.1002/bjs.7001

64. Norman PE, Jamrozik K, Lawrence-Brown MM, Le MT, Spencer CA, Tuohy RJ, *et al.* Population based randomised controlled trial on impact of screening on mortality from abdominal aortic aneurysm. *BMJ* 2004;**329**:1259. https://doi.org/10.1136/bmj.38272.478438.55

65. Thompson SG, Ashton HA, Gao L, Scott RA, Multicentre Aneurysm Screening Study Group. Screening men for abdominal aortic aneurysm: 10 year mortality and cost effectiveness results from the randomised Multicentre Aneurysm Screening Study. *BMJ* 2009;**338**:b2307. https://doi.org/10.1136/bmj.b2307

66. Thompson SG, Ashton HA, Gao L, Buxton MJ, Scott RA, Multicentre Aneurysm Screening Study Group. Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening. *Br J Surg* 2012;**99**:1649–56. https://doi.org/10.1002/bjs.8897

67. Cosford PA, Leng GC. Screening for abdominal aortic aneurysm. *Cochrane Database Syst Rev* 2007;**2**:CD002945. https://doi.org/10.1002/14651858.CD002945.pub2

68. Davis M, Harris M, Earnshaw JJ. Implementation of the National Health Service Abdominal Aortic Aneurysm Screening Program in England. *J Vasc Surg* 2013;**57**:1440–1445. https://doi.org/10.1016/j.jvs.2012.10.114

69. Welch HG, Albertsen PC, Nease RF, Bubolz TA, Wasson JH. Estimating treatment benefits for the elderly: the effect of competing risks. *Ann Intern Med* 1996;**124**:577–84. https://doi.org/10.7326/0003-4819-124-6-199603150-00007

70. Vega de Ceniga M, Gomez R, Estallo L, Rodriguez L, Baquer M, Barba A. Growth rate and associated factors in small abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2006;**31**:231–6. https://doi.org/10.1016/j.ejvs.2005.10.007

71. Golledge J, Powell JT. Medical management of abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg* 2007;**34**:267–73. https://doi.org/10.1016/j.ejvs.2007.03.006

72. Guessous I, Periard D, Lorenzetti D, Cornuz J, Ghali WA. The efficacy of pharmacotherapy for decreasing the expansion rate of abdominal aortic aneurysms: a systematic review and meta-analysis. *PLOS ONE* 2008;**3**:e1895. https://doi.org/10.1371/journal.pone.0001895

73. Greenhalgh RM, Fowkes FG, Powell JT, Forbes JF, Ruckely CV. Smoking, lung function and the prognosis of abdominal aortic aneurysm. The UK Small Aneurysm Trial Participants. *Eur J Vasc Endovasc Surg* 2000;**19**:636–642. https://doi.org/10.1053/ejvs.2000.1066

74. Rughani G, Robertson L, Clarke M. Medical treatment for small abdominal aortic aneurysms. *Cochrane Database Syst Rev* 2012;**9**:CD009536. https://doi.org/10.1002/14651858.CD009536.pub2

75. Dubost C, Allary M, Oeconomos N. [Treatment of aortic aneurysms; removal of the aneurysm; re-establishment of continuity by grafts of preserved human aorta.] *Mem Acad Chir* 1951;**77**:381–3.

76. Prager MR, Hoblaj T, Nanobashvili J, Sporn E, Polterauer P, Wagner O, *et al.* Collagen- versus gelatine-coated Dacron versus stretch PTFE bifurcation grafts for aortoiliac occlusive disease: long-term results of a prospective, randomized multicenter trial. *Surgery* 2003;**134**:80–5. https://doi.org/10.1067/msy.2003.179

77. Parodi JC, Palmaz JC, Barone HD. Transfemoral intraluminal graft implantation for abdominal aortic aneurysms. *Ann Vasc Surg* 1991;**5**:491–9. https://doi.org/10.1007/BF02015271

78. Volodos NL, Karpovich IP, Troyan VI, Kalashnikova Yu V, Shekhanin VE, Ternyuk NE, *et al.* Clinical experience of the use of self-fixing synthetic prostheses for remote endoprosthetics of the thoracic and the abdominal aorta and iliac arteries through the femoral artery and as intraoperative endoprosthesis for aorta reconstruction. *VASA Suppl* 1991;**33**:93–5.

79. Harris PL, Buth J, Mialhe C, Myhre HO, Norgren L. The need for clinical trials of endovascular abdominal aortic aneurysm stent-graft repair: The EUROSTAR Project. EUROpean collaborators on Stent-graft Techniques for abdominal aortic Aneurysm Repair. *J Endovasc Surg* 1997;**4**:72–79. https://doi.org/10.1583/1074-6218(1997)004<0072:TNFCTO>2.0.CO;2

80. Andrews SM, Cuming R, Macsweeney ST, Barrett NK, Greenhalgh RM, Nott DM. Assessment of feasibility for endovascular prosthetic tube correction of aortic aneurysm. *Br J Surg* 1995;**82**:917–19. https://doi.org/10.1002/bjs.1800820720

81. Yusuf SW, Baker DM, Hind RE, Chuter TA, Whitaker SC, Wenham PW, *et al.* Endoluminal transfemoral abdominal aortic aneurysm repair with aorto-uni-iliac graft and femorofemoral bypass. *Br J Surg* 1995;**82**:916. https://doi.org/10.1002/bjs.1800820719

82. Nasim A, Thompson MM, Sayers RD, Bolia A, Bell PR. Endovascular repair of abdominal aortic aneurysm: an initial experience. *Br J Surg* 1996;**83**:516–19. https://doi.org/10.1002/bjs.1800830428

83. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, *et al.* Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *Eur J Vasc Endovasc Surg* 2011;**41**: S1–58. https://doi.org/10.1016/j.ejvs.2010.09.011

84. White GH, Yu W, May J, Chaufour X, Stephen MS. Endoleak as a complication of endoluminal grafting of abdominal aortic aneurysms: classification, incidence, diagnosis, and management. *J Endovasc Ther* 1997;**4**:152–68. https://doi.org/10.1177/152660289700400207

85. Veith FJ, Baum RA, Ohki T, Amor M, Adiseshiah M, Blankensteijn JD, *et al.* Nature and significance of endoleaks and endotension: summary of opinions expressed at an international conference. *J Vasc Surg* 2002;**35**:1029–35. https://doi.org/10.1067/mva.2002.123095

86. Hobo R, Buth J. Secondary interventions following endovascular abdominal aortic aneurysm repair using current endografts. A EUROSTAR report. *J Vasc Surg* 2006;**43**:896–902. https://doi.org/10.1016/j.jvs.2006.01.010

87. Schlosser FJ, Gusberg RJ, Dardik A, Lin PH, Verhagen HJ, Moll FL, *et al.* Aneurysm rupture after EVAR: can the ultimate failure be predicted? *Eur J Vasc Endovasc Surg* 2009;**37**:15–22. https://doi.org/10.1016/j.ejvs.2008.10.011

88. White GH, May J, Waugh RC, Chaufour X, Yu W. Type III and type IV endoleak: toward a complete definition of blood flow in the sac after endoluminal AAA repair. *J Endovasc Surg* 1998;**5**:305–9. https://doi.org/10.1583/1074-6218(1998)005<0305:TIATIE>2.0.CO;2

89. Rosen RJ, Green RM. Endoleak management following endovascular aneurysm repair. *J Vasc Interv Radiol* 2008;**19**:S37–43. https://doi.org/10.1016/j.jvir.2008.01.017

90. Chaikof EL, Blankensteijn JD, Harris PL, White GH, Zarins CK, Bernhard VM, *et al.* Reporting standards for endovascular aortic aneurysm repair. *J Vasc Surg* 2002;**35**:1048–60. https://doi.org/10.1067/mva.2002.123763

91. Tonnessen BH, Sternbergh WC, Money SR. Late problems at the proximal aortic neck: migration and dilation. *Semin Vasc Surg* 2004;**17**:288–93. https://doi.org/10.1053/j.semvascsurg.2004.09.005

92. Tonnessen BH, Sternbergh WC, Money SR. Mid- and long-term device migration after endovascular abdominal aortic aneurysm repair: a comparison of AneuRx and Zenith endografts. *J Vasc Surg* 2005;**42**:392–400. https://doi.org/10.1016/j.jvs.2005.05.040

93. Fransen GA, Desgranges P, Laheij RJ, Harris PL, Becquemin JP, EUROSTAR Collaborators. Frequency, predictive factors, and consequences of stent-graft kink following endovascular AAA repair. *J Endovasc Ther* 2003;**10**:913–18. https://doi.org/10.1177/152660280301000511

94. The UK EVAR Trial Investigators. Endovascular versus open repair of abdominal aortic aneurysm. *N Engl J Med* 2010;**362**:1863–71. https://doi.org/10.1056/NEJMoa0909305

95. The UK EVAR Trial Investigators. Endovascular repair of aortic aneurysm in patients physically ineligible for open repair. *N Engl J Med* 2010;**362**:1872–80. https://doi.org/10.1056/NEJMoa0911056

96. Brown LC, Powell JT, Thompson SG, Epstein DM, Sculpher MJ, Greenhalgh RM. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy. *Health Technol Assess* 2012;**16**(9). https://doi.org/10.3310/hta16090

97. De Bruin JL, Baas AF, Buth J, Prinssen M, Verhoeven EL, Cuypers PW, *et al.* Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. *N Engl J Med* 2010;**362**:1881–9. https://doi.org/10.1056/NEJMoa0909499

98. Lederle FA, Freischlag JA, Kyriakides TC, Matsumura JS, Padberg FT, Kohler TR, *et al.* Long-term comparison of endovascular and open repair of abdominal aortic aneurysm. *N Engl J Med* 2012;**367**:1988–97. https://doi.org/10.1056/NEJMoa1207481

99. Becquemin JP, Pillet JC, Lescalie F, Sapoval M, Goueffic Y, Lermusiaux P, *et al.* A randomized controlled trial of endovascular aneurysm repair versus open surgery for abdominal aortic aneurysms in low- to moderate-risk patients. *J Vasc Surg* 2011;**53**:1167–1173. https://doi.org/10.1016/j.jvs.2010.10.124

100. Greenhalgh RM, Brown LC, Kwong GP, Powell JT, Thompson SG, EVAR Trial Participants. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. *Lancet* 2004;**364**:843–8. https://doi.org/10.1016/S0140-6736(04)16979-1

101. EVAR Trial Participants. Endovascular aneurysm repair versus open repair in patients with abdominal aortic aneurysm (EVAR trial 1): randomised controlled trial. *Lancet* 2005;**365**:2179–86. https://doi.org/10.1016/S0140-6736(05)66627-5

102. Prinssen M, Buskens E, Blankensteijn JD. The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial. Background, design and methods. *J Cardiovasc Surg* 2002;**43**:379–84.

103. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, *et al.* A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2004;**351**:1607–18. https://doi.org/10.1056/NEJMoa042002

104. Blankensteijn JD, de Jong SE, Prinssen M, van der Ham AC, Buth J, van Sterkenburg SM, *et al.* Two-year outcomes after conventional or endovascular repair of abdominal aortic aneurysms. *N Engl J Med* 2005;**352**:2398–405. https://doi.org/10.1056/NEJMoa051255

105. Lederle FA, Freischlag JA, Kyriakides TC, Padberg FT Jr, Matsumura JS, Kohler TR. Outcomes following endovascular vs open repair of abdominal aortic aneurysm: a randomized trial. *JAMA* 2009;**302**:1535–42. https://doi.org/10.1001/jama.2009.1426

106. Brown LC, Epstein D, Manca A, Beard JD, Powell JT, Greenhalgh RM. The UK Endovascular Aneurysm Repair (EVAR) trials: design, methodology and progress. *Eur J Vasc Endovasc Surg* 2004;**27**:372–81. https://doi.org/10.1016/j.ejvs.2003.12.019

107. EVAR Trial Participants. Endovascular aneurysm repair and outcome in patients unfit for open repair of abdominal aortic aneurysm (EVAR trial 2): randomised controlled trial. *Lancet* 2005;**365**:2187–92. https://doi.org/10.1016/S0140-6736(05)66628-7

108. Schermerhorn ML, Buck DB, O'Malley AJ, Curran T, McCallum JC, Darling J, *et al.* Long-term outcomes of abdominal aortic aneurysm in the Medicare population. *N Engl J Med* 2015;**373**:328–38. https://doi.org/10.1056/NEJMoa1405778

109. Khashram M, Jenkins JS, Jenkins J, Kruger AJ, Boyne NS, Foster WJ, *et al.* Long-term outcomes and factors influencing late survival following elective abdominal aortic aneurysm repair: a 24-year experience. *Vascular* 2016;**24**:115–25. https://doi.org/10.1177/1708538115586682

110. Koole D, Moll FL, Buth J, Hobo R, Zandvoort HJ, Bots ML, *et al.* Annual rupture risk of abdominal aortic aneurysm enlargement without detectable endoleak after endovascular abdominal aortic repair. *J Vasc Surg* 2011;**54**:1614–22. https://doi.org/10.1016/j.jvs.2011.06.095

111. Wyss TR, Brown LC, Powell JT, Greenhalgh RM. Rate and predictability of graft rupture after endovascular and open abdominal aortic aneurysm repair: data from the EVAR Trials. *Ann Surg* 2010;**252**:805–12. https://doi.org/10.1097/SLA.0b013e3181fcb44a

112. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Stat Med* 2005;**24**:993–1007. https://doi.org/10.1002/sim.1981

113. Little R, Rubin D. *Statistical Analysis With Missing Data*. 2nd edn. Hoboken, NJ: John Wiley & Sons; 2002. https://doi.org/10.1002/9781119013563

114. Clark TG, Altman DG. Developing a prognostic model in the presence of missing data: an ovarian cancer case study. *J Clin Epidemiol* 2003;**56**:28–37. https://doi.org/10.1016/S0895-4356(02)00539-5

115. Royston P. Multiple imputation of missing values: update of ice. *Stata J* 2005;**5**:527–36.

116. Moons KG, Donders RA, Stijnen T, Harrell FE. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol* 2006;**59**:1092–101. https://doi.org/10.1016/j.jclinepi.2006.01.009

117. White IR, Royston P. Imputing missing covariate values for the Cox model. *Stat Med* 2009;**28**:1982–98. https://doi.org/10.1002/sim.3618

118. Verzini F, Isernia G, De Rango P, Simonte G, Parlani G, Loschi D, *et al.* Abdominal aortic endografting beyond the trials: a 15-year single-center experience comparing newer to older generation stent-grafts. *J Endovasc Ther* 2014;**21**:439–47. https://doi.org/10.1583/13-4599MR.1

119. Motaganahalli R, Martin A, Feliciano B, Murphy MP, Slaven J, Dalsing MC. Estimating the risk of solid organ malignancy in patients undergoing routine computed tomography scans after endovascular aneurysm repair. *J Vasc Surg* 2012;**56**:929–37. https://doi.org/10.1016/j.jvs.2012.02.061

120. Reise JA, Sheldon H, Earnshaw J, Naylor AR, Dick F, Powell JT, *et al.* Patient preference for surgical method of abdominal aortic aneurysm repair: postal survey. *Eur J Vasc Endovasc Surg* 2010;**39**:55–61. https://doi.org/10.1016/j.ejvs.2009.08.008

121. Ellozy SH, Carroccio A, Lookstein RA, Minor ME, Sheahan CM, Juta J, *et al.* First experience in human beings with a permanently implantable intrasac pressure transducer for monitoring endovascular repair of abdominal aortic aneurysms. *J Vasc Surg* 2004;**40**:405–12. https://doi.org/10.1016/j.jvs.2004.06.027

122. Ellozy SH, Carroccio A, Lookstein RA, Jacobs TS, Addis MD, Teodorescu VJ, *et al.* Abdominal aortic aneurysm sac shrinkage after endovascular aneurysm repair: correlation with chronic sac pressure measurement. *J Vasc Surg* 2006;**43**:2–7. https://doi.org/10.1016/j.jvs.2005.09.039

123. Milner R, Kasirajan K, Chaikof EL. Future of endograft surveillance. *Semin Vasc Surg* 2006;**19**:75–82. https://doi.org/10.1053/j.semvascsurg.2006.03.002

124. Ohki T, Ouriel K, Silveira PG, Katzen B, White R, Criado F, *et al.* Initial results of wireless pressure sensing for endovascular aneurysm repair: the APEX Trial – Acute Pressure Measurement to Confirm Aneurysm Sac Exclusion. *J Vasc Surg* 2007;**45**:236–42. https://doi.org/10.1016/j.jvs.2006.09.060

125. Kurosawa K, Ohta H, Sumi M, Ohki T. Physiologic monitoring data: will it change our follow-up paradigms? *Semin Vasc Surg* 2007;**20**:115–20. https://doi.org/10.1053/j.semvascsurg.2007.04.002

126. Department of Health. *NHS Reference Costs 2014 to 2015*. London: Department of Health; 2015.

127. NHS Digital. *HRG4+ 201415 Reference Costs Grouper User Manual*. London: NHS Digital; 2015.

128. Organisation for Economic Co-operation and Development. *Purchasing Power Parities for GDP and Related Indicators 2015*. 2015.

129. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *PharmacoEconomics* 2014;**32**:1157–70. https://doi.org/10.1007/s40273-014-0193-3

130. Willan AR, Lin DY, Manca A. Regression methods for cost-effectiveness analysis with censored data. *Stat Med* 2005;**24**:131–45. https://doi.org/10.1002/sim.1794

131. Efron B, Tibshirani R. *An Introduction to the Bootstrap*. New York, NY: Chapman & Hall; 1993. https://doi.org/10.1007/978-1-4899-4541-9

132. Epstein D, Sculpher MJ, Powell JT, Thompson SG, Brown LC, Greenhalgh RM. Long-term cost-effectiveness analysis of endovascular versus open repair for abdominal aortic aneurysm based on four randomized clinical trials. *Br J Surg* 2014;**101**:623–31. https://doi.org/10.1002/bjs.9464

133. Office for National Statistics. *National Life Tables, United Kingdom: 2012–2014*. URL: www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2015-09-23

134. Brown LC, Thompson SG, Greenhalgh RM, Powell JT, Endovascular Aneurysm Repair Trial Participants. Incidence of cardiovascular events and death after open or endovascular repair of abdominal aortic aneurysm in the randomized EVAR trial 1. *Br J Surg* 2011;**98**:935–42. https://doi.org/10.1002/bjs.7485

135. Epstein D. *Health Related Quality of Life After Surgical Repair of Asymptomatic Abdominal Aortic Aneurysms*. Granada: University of Granada; 2016.

136. National Institute for Health and Care Excellence. *Endovascular Stent–Grafts for the Treatment of Abdominal Aortic Aneurysms*. Technology appraisal guidance [TA167]. London: National Institute for Health and Care Excellence; 2009. URL: www.nice.org.uk/guidance/ta167 (accessed 1 December 2017)

137. Prinssen M, Buskens E, de Jong SE, Buth J, Mackaay AJ, van Sambeek MR, *et al.* Cost-effectiveness of conventional and endovascular repair of abdominal aortic aneurysms: results of a randomized trial. *J Vasc Surg* 2007;**46**:883–90. https://doi.org/10.1016/j.jvs.2007.07.033

138. Stroupe KT, Lederle FA, Matsumura JS, Kyriakides TC, Jonk YC, Ge L, *et al.* Cost-effectiveness of open versus endovascular repair of abdominal aortic aneurysm in the OVER trial. *J Vasc Surg* 2012;**56**:901–9. https://doi.org/10.1016/j.jvs.2012.01.086

139. Paravastu SC, Jayarajasingam R, Cottam R, Palfreyman SJ, Michaels JA, Thomas SM. Endovascular repair of abdominal aortic aneurysm. *Cochrane Database Syst Rev* 2014;**1**:CD004178. https://doi.org/10.1002/14651858.CD004178.pub2

140. Cronenwett JL. Endovascular aneurysm repair: important mid-term results. *Lancet* 2005;**365**:2156–8. https://doi.org/10.1016/S0140-6736(05)66629-9

141. Kontopodis N, Antoniou SA, Georgakarakos E, Ioannou CV. Endovascular vs open aneurysm repair in the young: systematic review and meta-analysis. *J Endovasc Ther* 2015;**22**:897–904. https://doi.org/10.1177/1526602815606937

142. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, *et al.* A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;**130**:461–70. https://doi.org/10.7326/0003-4819-130-6-199903160-00002

143. Wilkins JT, Ning H, Berry J, Zhao L, Dyer AR, Lloyd-Jones DM. Lifetime risk and years lived free of total cardiovascular disease. *JAMA* 2012;**308**:1795–801. https://doi.org/10.1001/jama.2012.14312

144. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–88. https://doi.org/10.1016/0197-2456(86)90046-2

145. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557–60. https://doi.org/10.1136/bmj.327.7414.557

146. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat* 1982;**10**:1100–20. https://doi.org/10.1214/aos/1176345976

147. Mani K, Björck M, Wanhainen A. Changes in the management of infrarenal abdominal aortic aneurysm disease in Sweden. *Br J Surg* 2013;**100**:638–44. https://doi.org/10.1002/bjs.9046

148. Sumner DS, Strandness DE. The relationship between calf blood flow and ankle blood pressure in patients with intermittent claudication. *Surgery* 1969;**65**:763–71.

149. Heald C, Fowkes F, Murray G, Price J. Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle/brachial index: systematic review. *Atherosclerosis* 2006;**189**:61–9. https://doi.org/10.1016/j.atherosclerosis.2006.03.011

150. Saratzis A, Sarafidis P, Melas N, Saratzis N, Kitas G. Impaired renal function is associated with mortality and morbidity after endovascular abdominal aortic aneurysm repair. *J Vasc Surg* 2013;**58**:879–85. https://doi.org/10.1016/j.jvs.2013.03.036

151. Chaikof EL, Brewster DC, Dalman RL, Makaroun MS, Illig KA, Sicard GA, *et al.* SVS practice guidelines for the care of patients with an abdominal aortic aneurysm: executive summary. *J Vasc Surg* 2009;**50**:880–96. https://doi.org/10.1016/j.jvs.2009.07.001

152. Gelfand DV, White GH, Wilson SE. Clinical significance of type II endoleak after endovascular repair of abdominal aortic aneurysm. *Ann Vasc Surg* 2006;**20**:69–74. https://doi.org/10.1007/s10016-005-9382-z

153. Karthikesalingam A, Thrumurthy SG, Jackson D, Choke E, Sayers, RD, Loftus IM, *et al.* Current evidence is insufficient to define an optimal threshold for intervention in isolated type II endoleak after endovascular aneurysm repair. *J Endovasc Ther* 2012;**19**:200–8. https://doi.org/10.1583/11-3762R.1

154. Patatas K, Ling L, Dunning J, Shrivastava V. Static sac size with a type II endoleak post-endovascular abdominal aortic aneurysm repair: surveillance or embolization? *Interact Cardiovasc Thorac Surg* 2012;**15**:462–6. https://doi.org/10.1093/icvts/ivs201

155. Cao P, De Rango P, Verzini F, Parlani G. Endoleak after endovascular aortic repair: classification, diagnosis and management following endovascular thoracic and abdominal aortic repair. *J Cardiovasc Surg* 2010;**51**:53–69.

156. Jonker FH, Aruny J, Muhs BE. Management of type II endoleaks: preoperative versus postoperative versus expectant management. *Semin Vasc Surg* 2009;**22**:165–71. https://doi.org/10.1053/j.semvascsurg.2009.07.008

157. Keedy AW, Yeh BM, Kohr JR, Hiramoto JS, Schneider DB, Breiman RS. Evaluation of potential outcome predictors in type II endoleak: a retrospective study with CT angiography feature analysis. *AJR Am J Roentgenol* 2011;**197**:234–40. https://doi.org/10.2214/AJR.10.4566

158. Brown A, Saggu GK, Bown MJ, Sayers RD, Sidloff DA. Type II endoleaks: challenges and solutions. *Vasc Health Risk Manag* 2016;**12**:53–63. https://doi.org/10.2147/VHRM.S81275

159. Gandhi RT, Bryce Y, Ganguli S, McWilliams J, Vatakencherry G. Management of type II endoleaks. *Endovascular Today* 2016;**15**:42–8.

160. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999;**28**:964–74. https://doi.org/10.1093/ije/28.5.964

161. Egorova N, Giacovelli JK, Gelijns A, Greco G, Moskowitz A, McKinsey J, *et al.* Defining high-risk patients for endovascular aneurysm repair. *J Vasc Surg* 2009;**50**:1271–9.e1. https://doi.org/10.1016/j.jvs.2009.06.061

162. De Martino RR, Goodney PP, Nolan BW, Robinson WP, Farber A, Patel VI, *et al.* Optimal selection of patients for elective abdominal aortic aneurysm repair based on life expectancy. *J Vasc Surg* 2013;**58**:589–95. https://doi.org/10.1016/j.jvs.2013.03.010

163. Brady AR, Fowkes FG, Thompson SG, Powell JT. Aortic aneurysm diameter and risk of cardiovascular mortality. *Arterioscler Thromb Vasc Biol* 2001;**21**:1203–7. https://doi.org/10.1161/hq0701.091999

164. Freiberg MS, Arnold AM, Newman AB, Edwards MS, Kraemer KL, Kuller LH. Abdominal aortic aneurysms, increasing infrarenal aortic diameter, and risk of total mortality and incident cardiovascular disease events: 10-year follow-up data from the Cardiovascular Health Study. *Circulation* 2008;**117**:1010–17. https://doi.org/10.1161/CIRCULATIONAHA.107.720219

165. Norman PE, Muller J, Golledge J. The cardiovascular and prognostic significance of the infrarenal aortic diameter. *J Vasc Surg* 2011;**54**:1817–20. https://doi.org/10.1016/j.jvs.2011.07.048

Appendix 1 Case record form

EVAR Trials 10-15 year follow up to December 2014

Together we are collecting data for the NIHR for the world first 15 year follow-up of EVAR v OR. 34 centres with designated investigators and coordinators will be named authors of the publication. Below is a 2014 simplified data collection form to collect as much as possible in one go. The most important data for EVAR/OR follow-up are aneurysm-related complications and reinterventions for the original repair either in radiology department or theatre.

Patient ID number ☐☐☐☐☐☐ Date of Birth (DD/MM/YY) ☐☐ ☐☐ ☐☐ Date of Data Extraction (DD/MM/YY) ☐☐ ☐☐ ☐☐

Aneurysm Trial Patient Follow-up after 2009? Yes ☐ No ☐

If yes tick which years - 2010 ☐ 2011 ☐ 2012 ☐ 2013 ☐ 2014 ☐

If No Why: Lost to follow-up ☐ Too Frail ☐ Patient Refused ☐

Patient Died ☐ Date of Death _____ Discharged from follow-up ☐ Date last seen _____

Annual Follow-Up

Complications from Notes: None (0) Endoleak Type I (1) Type II (2) Type III (3) Migration (4) Kinking (5) Sac expansion from baseline (mm)(6)

Year	Scan	Scan Type*	Complications Detected (1-6)	Date Detected (DD/MM/YY)	Complications Detected (1-6)	Date Detected (DD/MM/YY)	Complications Detected (1-6)	Date Detected (DD/MM/YY)
2010	Yes / No	CT/Duplex						
2011	Yes / No	CT/Duplex						
2012	Yes / No	CT/Duplex						
2013	Yes / No	CT/Duplex						
2014	Yes / No	CT/Duplex						

***If Duplex please attach scan report**

Reinterventions 2010–2014 for complications listed above

List of Methods: Added Stent (1) Staple (2) Embolisation (3) Sclerosis (4) Conversion to open repair (5) Other (6)

Date	Type of complication (1-6)	Reintervention Method (1-6)
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

OTHER ANEURYSM-RELATED COMPLICATIONS REPORTED

7. Known aneurysmal extension above or below original graft? Yes ☐ No ☐ Date _____
8. Thrombosis of graft limb? Yes ☐ No ☐ Date _____
9. Graft Infection? Yes ☐ No ☐ Date _____
10. During follow-up - Incisional Hernia Yes ☐ No ☐ Date _____
11. During follow-up - False Femoral Aneurysm Yes ☐ No ☐ Date _____

Intervention/Repair for above? Event (7-11) ☐ Date _____ Open or Endovascular Repair _____

Intervention/Repair for above? Event (7-11) ☐ Date _____ Open or Endovascular Repair _____

Intervention/Repair for above? Event (7-11) ☐ Date _____ Open or Endovascular Repair _____

Other Major Adverse Events During EVAR Trial Follow-Up		Date 1	Date 2	Date 3
Stroke	Yes ☐ No ☐	_____	_____	_____
Myocardial Infarction	Yes ☐ No ☐	_____	_____	_____
Major Amputation	Yes ☐ No ☐	_____	_____	_____
Renal Failure	Yes ☐ No ☐	_____	_____	_____
New Cancer Diagnosed	Yes ☐ No ☐	_____	ICD Code of cancer type _____	

Appendix 2 The UK EndoVascular Aneurysm Repair trial participants

Trial investigators

Grant applicants

RM Greenhalgh (principal investigator), JT Powell, MJ Sweeting, M Sculpher, D Epstein and CD Bicknell.

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Endpoint Committee

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Trial Manager (1999–2010)

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(Numbers in parentheses indicate the number of patients entered into both EVAR-1 and EVAR-2.)

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