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

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Scientific summary

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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).

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