The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy

LC Brown,[1] JT Powell,[1] SG Thompson,[2] DM Epstein,[3] MJ Sculpher[3] and RM Greenhalgh[1]*

[1]Vascular Surgery Research Group, Department of Surgery and Cancer, Imperial College London, Charing Cross Hospital, London, UK
[2]Medical Research Council Biostatistics Unit, Institute of Public Health, Cambridge, UK
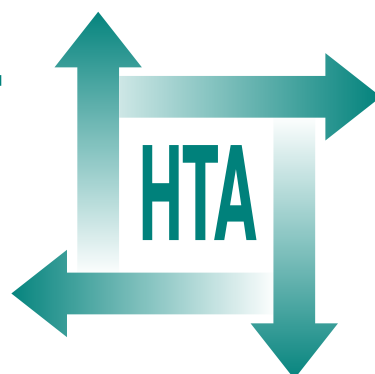[3]Centre for Health Economics, University of York, York, UK

*Corresponding author

Executive summary

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Executive summary

Background

Abdominal aortic aneurysm (AAA) is a condition in which the aorta becomes dilated in the segment below the diaphragm. In this region, the aorta normally measures about 1.5–2.5 cm in diameter but, with this condition, the diseased segment can grow up to much larger sizes and in extreme cases can rupture catastrophically, usually with fatal consequences (approximately 80% mortality). The prevalence of AAA (aortic diameter ≥ 3.0 cm) has been shown to be about 5% in men over the age of 65 years and tends to increase with age and be higher in smokers. The condition is far less common in women, with population studies showing a four- to fivefold greater prevalence in men. 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 four independent randomised trials have shown 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 and endovascular repair. Open surgical repair was first performed in the late 1950s and is still the most common method, but endovascular is catching up quickly. Open repair involves opening the abdominal cavity and repairing the aneurysm by suturing a Dacron tube graft inside the diseased section of aorta. This operation 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, once repaired, the procedure is known to be very durable and is likely to last for the rest of the patient's lifetime. More recently, endovascular aneurysm repair (EVAR) was developed in the early 1990s. This method is less invasive than open repair and can be performed under a local anaesthetic as it requires only two small incisions in the groin to expose the femoral arteries, which are downstream of the abdominal aorta. The stent–graft system is then fed into the aorta via catheters and guidewires, and then positioned and secured correctly above and below the aneurysmal segment of aorta. The location of the graft is imaged using radiological methods, with patients being exposed to relatively large doses of radiation and contrast agent. This new treatment appears to have a lower operative mortality and a faster recovery time, with less requirement for high-dependency care and a shorter hospital stay. However, not all patients have the aortic anatomy that permits application of EVAR, and the durability of endovascular repair does not appear to be as good as for open repair, with a need for post-repair surveillance and, sometimes, further, usually smaller, reinterventions to correct graft-related complications.

Most aneurysms are entirely asymptomatic and are detected only incidentally when patients are scanned for other conditions. However, in the UK, a national screening programme for AAA has been instigated for men aged 65 years and this is due to be rolled out nationally over the next 5 years. Randomised trials have shown that screening men for AAA is effective in terms of reducing the number of deaths from aneurysm rupture and appears to be highly cost-effective. The majority of screen-detected aneurysms tend to be small and need to be monitored until they reach 5.5 cm. At this point they are referred to local vascular centres for consideration of aneurysm repair and the pros and cons of open or endovascular repair need to be explained to the patient. Therefore, the EVAR trials were set up to compare these two repair methods to determine if one is superior to the other.

Objectives

Two trials were set up to test the safety, efficacy and cost-effectiveness of endovascular repair in two different populations of patients. EVAR trial 1 compares EVAR with open repair in patients who are considered to be fit for both procedures. EVAR trial 2 compares EVAR with no intervention in patients who are not considered to be fit enough to undergo the more invasive open repair procedure. The primary outcome for both trials was mortality (operative, all cause and aneurysm related) with secondary outcomes of graft-related complications and reinterventions, health-related quality of life, adverse events [myocardial infarction (MI), stroke, amputation and renal failure], renal function, costs and cost-effectiveness.

Methods

The EVAR trials are two randomised trials that were performed across 38 of 41 eligible UK centres. The trials commenced recruitment on 1 September 1999 and closed recruitment on 31 August 2004, with follow-up of all patients until the end of December 2009 (average follow-up 8 years). Patients of both sexes, aged at least 60 years, with an AAA diameter measuring at least 5.5 cm according to a computerised tomography scan and deemed anatomically suitable for an EVAR device were randomly allocated to (1) either EVAR or open repair in EVAR trial 1 for patients considered anaesthetically fit for open repair or (2) either EVAR or no intervention in EVAR trial 2 for patients considered unfit for open repair. Power calculations based upon the primary outcome of all-cause mortality indicated that a target of 900 patients was required for EVAR trial 1 and 280 for EVAR trial 2. Randomisation was performed centrally on a computer package using 1 : 1 ratio randomly permuted block sizes stratified by centre. Patients were recruited and followed up for all outcomes by dedicated local trial co-ordinators, who were all trained in trial protocol procedures. All patients were flagged for mortality at the Office for National Statistics, which supplied the central trial office with centrally coded death certificates, which were all reviewed by an independent Endpoints Committee without knowledge of randomised group. Quality of life was assessed using the European Quality of Life-5 Dimensions and Short Form questionnaire-36 items. The costs of the procedures were based upon a survey questionnaire that was sent to the participating trial centres in May 2004 requesting information on the costs of staff and consumables for each procedure in that centre. Cost-effectiveness was assessed using quality-adjusted life-years (QALYs). Patients were analysed according to predefined statistical analysis plans with the primary analysis by intention-to-treat randomised group but analyses were also performed for per-protocol comparisons. Logistic regression models were used to investigate operative mortality and Cox regression models were used to analyse all-cause and AAA-related mortality, as well as graft-related complications and reinterventions and cardiovascular events. All odds ratios (ORs) and hazard ratios (HRs) are presented as the EVAR group relative to the alternative treatment. Renal function was assessed using multilevel modelling.

Results

Recruitment targets were exceeded in both trials, with 1252 patients randomised into EVAR trial 1 (626 to EVAR) and 404 into EVAR trial 2 (197 to EVAR). Refusal rates were 24% and 26% in EVAR trials 1 and 2, respectively. Randomised groups were well balanced within each trial in terms of baseline characteristics, and compliance with randomised allocation was good in EVAR trial 1 (93%) and in the EVAR group of EVAR trial 2 (99%), but only moderate in the no-intervention group of EVAR trial 2 (69%). Follow-up was almost complete with only 20 patients lost to follow-up in terms of mortality (1%). There were differences in demographics and fitness between EVAR trial 1 and EVAR trial 2 patients: mean [standard deviation (SD)] ages were 74 (6.1) and 76 (6.5) years, respectively, and

mean (SD) AAA diameters were 6.4 (0.9) and 6.7 (1.0) cm, respectively, with a higher proportion of men in EVAR trial 1 (91% vs 86%).

In EVAR trial 1, 30-day operative mortality was 1.8% in the EVAR group compared with 4.3% in the open-repair group: adjusted OR 0.39 [95% confidence interval (CI) 0.18 to 0.87], $p = 0.02$. During a total of 6904 person-years of follow-up, a total of 524 deaths occurred (76 AAA related). Apart from an early advantage during the first 6 months in the EVAR group, there was no significant difference between the groups in terms of all-cause mortality by the end of follow-up, with 54% of patients surviving to 8 years: adjusted HR 1.03 (95% CI 0.86 to 1.23), $p = 0.72$. The EVAR group also demonstrated an early advantage in terms of AAA-related mortality, which was sustained for the first few years, but the benefit was lost by the end of the study, at least partially because of fatal endograft ruptures: adjusted HR 0.92 (95% CI 0.57 to 1.49), $p = 0.73$. There were no obvious differences in the number of medical adverse events between the groups; the EVAR group did appear to experience slightly lower rates of cardiovascular events (fatal and non-fatal MI and stroke) but this was not statistically significant. The rates of graft-related complications and reinterventions were substantially higher in the EVAR group: adjusted HRs 4.39 (95% CI 3.38 to 5.70), $p < 0.001$ and 2.86 (95% CI 2.08 to 3.94), $p < 0.001$, respectively. In terms of quality of life, the open-repair group had significantly lower physical functioning scores during the first 1–3 months, but no differences in scores were seen at 1 year. In a subset of 972 patients who survived beyond 1 year, long-term renal function decline could be compared between the randomised groups but no significant difference was evident. The mean costs of the initial procedures were £13,019 for EVAR and £11,842 for open repair: mean difference £1177 (95% CI –£374 to £2728). A decision model was constructed to extrapolate the 8-year trial results to estimate lifetime costs and QALYs. The difference in lifetime costs was £3519 (95% CI £1919 to £5053) higher with EVAR and there was only a very small difference in QALYs [–0.032 (95% CI –0.117 to 0.096) in favour of open repair, estimated by Monte Carlo simulation]. On average, EVAR was not found to be cost-effective compared with open repair but this finding was sensitive to alternative assumptions.

In EVAR trial 2, 30-day operative mortality was 7.3% in the EVAR group and the overall rate of aneurysm rupture in the no-intervention group was 12.4 (95% CI 9.6 to 16.2) per 100 person-years. During a total of 1413 person-years of follow-up, a total of 305 deaths occurred (78 AAA related). The EVAR group demonstrated a significant advantage in terms of AAA-related mortality but this became apparent only after 4 years: overall adjusted HR 0.53 (95% CI 0.32 to 0.89), $p = 0.02$. However, this advantage did not result in any benefit in terms of all-cause mortality, which was very high overall (82% mortality at 8 years, far higher than in EVAR trial 1): adjusted HR 0.99 (95% CI 0.78 to 1.27), $p = 0.97$. Per-protocol analyses suggested a stronger benefit in favour of the EVAR group but there was still no significant difference in all-cause mortality between the groups. There were no obvious differences in the number of medical adverse events between the groups; the EVAR group did appear to experience a higher rate of cardiovascular events (fatal and non-fatal MI and stroke) but this did not reach statistical significance ($p = 0.156$). The rates of graft-related complications and reinterventions were also high in EVAR trial 2 and very similar to the rates seen in EVAR trial 1. In terms of quality of life, there were no striking or consistent differences between the randomised groups at the three time points assessed (1, 3 and 12 months). In a subset of 222 patients who survived beyond 1 year, long-term renal function decline could be compared between the randomised groups and, although the rates of decline were slightly higher in the EVAR group, this difference did not achieve statistical significance ($p = 0.087$). Costs were considerably higher in the EVAR group: mean difference £10,596 (95% CI £8183 to £12,660). In a within-trial analysis, this translated into an incremental cost-effectiveness ratio (ICER) of about £265,000 per QALY. However, this ICER was reduced to about £35,000 per QALY when based upon an 8-year per-protocol analysis.

Analyses that combined the EVAR patients from both trials demonstrated that the presence of any of the following complications (endoleaks type 1, type 3 or type 2 with sac growth, migration or kinking)

were associated with a significantly increased risk of endograft rupture after EVAR (27 cases): adjusted HR 8.83 (95% CI 3.76 to 20.76), $p < 0.001$. In addition, older age and larger AAA diameter were both significantly associated with an increased risk of serious graft complications ($p = 0.04$ and $p < 0.001$, respectively) and reinterventions ($p = 0.03$ and $p < 0.001$, respectively). Furthermore, renal function appeared to decline faster prior to detection of a graft-related complication.

Conclusions

For patients with large AAA (≥ 5.5 cm) who are considered fit enough for open repair, EVAR offers a lower operative mortality, leading to a lower AAA-related mortality that is sustained for the first few years. However, a small but persistent occurrence of endograft ruptures leads to a convergence in the AAA-related mortality curves by 6 years such that there is no difference between the groups after 8 years of follow-up. Similarly, after 2 years of follow-up there was no difference in all-cause mortality, with cardiovascular mortality contributing to this 'mortality catch-up' phenomenon in the EVAR group. This suggests the need for improved medical therapy and more rigorous comorbidity optimisation protocols before and after any AAA repair.

Patients treated with EVAR experience significantly higher rates of graft-related complications and reinterventions with no apparent differences in quality of life. This, along with the need for continual post-EVAR surveillance, leads to an overall higher cost with EVAR, making it unlikely to be regarded as a cost-effective alternative to open repair according to current UK NHS funding thresholds. Today, newer devices are available and it is hoped that these will prove to be more durable.

For patients with large AAAs (≥ 5.5 cm), who are not considered fit enough for open repair, EVAR is effective in reducing the number of deaths from AAA rupture but this benefit does not become apparent for at least 4 years. This reduction in AAA-related mortality does not translate into any difference in all-cause mortality, as these patients experience high rates of mortality from multiple comorbidities. Therefore, life expectancy becomes an important factor when considering whether or not to treat a patient with EVAR in this situation. In addition, patients treated with EVAR are inconvenienced by the need for continued surveillance and are exposed to high rates of graft-related complications and reinterventions. Treatment with EVAR is far more costly and is unlikely to be regarded as a cost-effective treatment policy for these very unfit patients in whom management of comorbidities should perhaps be prioritised.

Trial registration

This trial is registered as ISRCTN 55703451.

Funding

Publication

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NIHR Health Technology Assessment programme

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