

Strategy of endovascular versus open repair for patients with clinical diagnosis of ruptured abdominal aortic aneurysm: the IMPROVE RCT

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Scientific summary

The IMPROVE RCT

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Background

Ruptured abdominal aortic aneurysm (AAA) remains a common vascular emergency in the older population, causing ≈ 6000 deaths each year in the UK. Without repair of the burst aorta, death is almost inevitable. More than half of people with ruptured aneurysms die before reaching hospital, and not all patients who reach hospital are offered a life-saving repair. Until the early part of this century, the only type of repair available was open surgical repair, which carried a very high mortality of $\approx 50\%$. The first published case showing the feasibility of using the less invasive endovascular repair was from Nottingham in 1994 (Yusuf SW, Whitaker SC, Chuter TA, Wenham PW, Hopkinson BR. Emergency endovascular repair of leaking aortic aneurysm. *Lancet* 1994;**344**:1645). By 2007, systematic reviews had been published to suggest that endovascular aneurysm repair (EVAR) could halve the operative mortality for ruptured aneurysms. By then, the number of centres in the UK that were experienced in using EVAR in the elective situation was sufficient to consider a randomised trial of emergency EVAR compared with open repair for ruptures.

Design

Because the applicability of EVAR is restricted by the morphology of the aorta, a trial of an endovascular strategy (EVAR if morphologically feasible, default open repair) compared with open repair was designed. Therefore, randomisation was carried out at the point of in-trial hospital diagnosis by a senior clinician, before a computerised tomography, which might delay transfer to theatre for emergency repair. To be able to join the trial, a centre had to have carried out at least five emergency EVARs with acceptable results. The sample size calculations indicated that a total of 300 participants in each group would be needed to have 90% power to show a significant reduction in 30-day operative mortality (the primary outcome measure) from 44.7% for open repair to 30.4% for the endovascular strategy group. It was also planned to follow up the participants for 12 months to allow us to carry out a cost-effectiveness evaluation.

Results

Between September 2009 and July 2013, 613 eligible participants with an in-hospital diagnosis of ruptured aneurysm were randomised: 316 to the endovascular strategy group and 297 to the open repair group. These 613 participants were derived from a total cohort of 1275 patients who were admitted with a clinical diagnosis of ruptured aneurysm at the 30 trial centres during the same period.

The 613 participants had a mean age of 77 years and a mean aortic diameter of 8.3 cm and included 133 women (22%). The diagnosis of rupture was later confirmed, using a core laboratory, in 536 out of 613 participants (87%; of these, 60% were morphologically suitable for EVAR); 22 participants had an acute symptomatic aneurysm, 46 participants had an asymptomatic aneurysm or other acute diagnosis, and only nine participants had no aortic aneurysm.

Overall 30-day mortality was 35.4% in the endovascular strategy group and 37.4% in the open repair group [unadjusted odds ratio (OR) 0.92, 95% confidence interval (CI) 0.66 to 1.28; $p = 0.62$], with similar results after adjustment for age, sex and Hardman index (an established morbidity score for ruptured aneurysms). There was weak evidence that the endovascular strategy was more effective in women than in men (interaction $p = 0.02$). Most participants (555/613; 91%) adhered to the trial protocol. Among the 502 participants with a proven rupture and for whom repair commenced, the 30-day mortality was 32% (84/259 participants) in the endovascular strategy group and 36% (87/243 participants) in the open repair

group (OR 0.86, 95% CI 0.59 to 1.24). The average hospital costs, including reinterventions, within the first 30 days of randomisation were similar between the randomised groups: mean £13,433 [standard deviation (SD) £10,354] and mean £14,619 (SD £12,353) for the endovascular strategy group and open repair group, respectively. At 30 days, some participants remained in hospital (28 in the endovascular strategy group, compared with 47 in the open repair group), but 94% of discharges in the endovascular strategy group were directly to home compared with 77% in the open repair group.

The recruited participants were also used in a large cohort analysis to identify factors, other than type of repair, that might be associated with postoperative survival (30-day mortality). The cohort analyses showed that shorter aneurysm neck length, admission at weekends and out of hours, and very low admission systolic blood pressures were all associated with higher operative mortality. In contrast, the use of EVAR under local, rather than general, anaesthesia was associated with much lower operative mortality (adjusted OR 0.27, 95% CI 0.10 to 0.70). An additional important factor that influenced 30-day mortality was the morphological parameter of aneurysm neck length. Operative mortality was much lower in the group of participants with aneurysm neck lengths of > 15 mm than in the group of participants with aneurysm neck lengths of < 15 mm, irrespective of whether endovascular or open repair was used. This is likely to be an important finding, which partly explains why observation series report much lower operative mortality for EVAR than for open repair: participants with long aneurysm necks are the most morphologically suitable for, and most likely to receive, EVAR.

At 1 year after randomisation, two participants in the open repair group had emigrated and had been lost to follow-up for mortality. All-cause mortality was 41.1% for the endovascular strategy group and 45.1% for the open repair group (OR 0.85, 95% CI 0.62 to 1.17; $p = 0.325$), with similar reintervention rates in each group (between 31 days and 1 year, there were 12 procedures involving 11 participants and 13 procedures involving nine participants in the endovascular and open repair groups, respectively). The average total hospital stay was 17 days in the endovascular strategy group and 26 days in the open repair group ($p < 0.001$). Among participants surviving rupture, the average utility score on the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), was higher in the endovascular strategy group than in the open repair group [mean differences of 0.087 (95% CI 0.017 to 0.158) and 0.068 (95% CI -0.004 to 0.140) at 3 months and 12 months, respectively]. There were indications that quality-adjusted life-years (QALYs) were higher and costs were lower for the endovascular strategy, combining to give an incremental net monetary benefit of £3877 (95% CI £253 to £7408) or €4356 (95% CI €284 to €8323) at a willingness-to-pay threshold of £30,000 per QALY.

Soon after completion of randomisation, it was estimated that $\approx 50\%$ of participants would remain alive at 3 years, and an application was made to extend participant follow-up for clinical effectiveness and cost-effectiveness evaluations to 3 years and to conduct individual patient data meta-analyses across the three recent European trials for the repair of ruptured aneurysm [Immediate Management of the Patient with Rupture: Open Versus Endovascular repair (IMPROVE), Amsterdam Acute Aneurysm trial (AJAX) (the Netherlands) and Endovasculaire versus Chirurgie dans les Anévrismes Rompus (ECAR) (France)] to 1 year. These meta-analyses all supported the main findings of the IMPROVE trial: no difference in mortality between the randomised groups at 1 year but more rapid participant recovery in the endovascular groups and the important effect of aneurysm neck length on 30-day mortality. IMPROVE was the only trial with full reporting to 3 years.

By 3 years after randomisation, a further two participants had emigrated and were lost to follow-up, this time in the endovascular strategy group. The mean participant follow-up was 4.9 years. Overall, there were 179 deaths (22.0 per 100 person-years) in the endovascular strategy group and 183 deaths (25.2 per 100 person-years) in the open repair group [hazard ratio (HR) 0.92, 95% CI 0.75 to 1.13; $p = 0.41$]. However, at 3 years, the survival curves had their widest separation, before converging again by 6 years, and for the prespecified mid-term period (3 months to 3 years) results favoured the endovascular strategy group (HR 0.57, 95% CI 0.36 to 0.90). At 3 years, mortality was 48% and 56% in the endovascular strategy group and the open repair group, respectively (OR 0.73, 95% CI 0.53 to 1.00; $p = 0.053$), with a more pronounced

effect for the endovascular strategy in the subgroup of 502 participants in whom repair was started for a proven rupture, in which the mortality rate was 42% and 54%, respectively (OR 0.62, 95% CI 0.43 to 0.89; $p = 0.009$). There was also weak evidence that the endovascular strategy was more effective in women than in men, but no such finding was observed for any other subgroup. In both randomised groups, there were continuing aneurysm-related reinterventions, the rate being non-significantly higher in the endovascular strategy group but the reinterventions being more severe in the open repair group. At 3 and 12 months, quality of life (QoL) was better in the endovascular strategy group but, by 3 years, there was no difference; mean EQ-5D-3L scores were 0.74 and 0.73 in the endovascular strategy group and open repair group, respectively. This was similar to the age- and sex-matched population. At 3 years, the endovascular strategy group had gained a mean of 0.166 QALYs (95% CI 0.002 to 0.311 QALYs; $p = 0.045$), the largest gains being for women and those with an admission Hardman index score of ≥ 2 . By 3 years, the average number of days in hospital for aneurysm-related care was 14.4 days and 20.5 days in the endovascular strategy group and open repair group, respectively, with a mean incremental cost of $-\pounds 2607$ (95% CI $-\pounds 5949$ to $\pounds 735$). The higher costs of open repair in primary admission had not been eroded by any excess of later aneurysm-related reinterventions in the endovascular strategy group. With survival, QoL and costs all favouring the endovascular strategy group at 3 years, there was an incremental net monetary benefit (INMB) of $\pounds 7833$ (95% CI $\pounds 1655$ to $\pounds 14,011$) for the endovascular strategy group, for a QALY valued at $\pounds 30,000$. The probability that the endovascular strategy is more cost-effective was $> 90\%$ at all realistic thresholds of willingness to pay for a QALY gain. Therefore, at 3 years, the endovascular strategy appeared to be both clinically effective and cost-effective.

The overall survival curves for patients admitted to hospitals with a diagnosis of ruptured aneurysm show a very steep attrition rate during the first 48 hours. However, all current risk scores, which may be used to select patients for surgery, are based on 30-day survival, a time period during which intensive care and several specialties other than vascular surgery contribute to patient care. Additionally, none of the available risk scores uses morphological data such as neck length. Additional funding was awarded to develop a risk score for 48-hour mortality in patients presenting with a ruptured aneurysm and to validate the score using external trials and observational cohorts. The developed model included the predictors of age, sex, haemoglobin, creatinine, systolic blood pressure, aneurysm neck length, neck angle and acute cardiac ischaemia. A simplified model that could be used at the bedside was also developed. The calibration slope was estimated as 1.08 (95% CI 0.81 to 1.35; $p = 0.54$) for the bedside score derived in the IMPROVE trial, indicating that both low and high predictions are well calibrated. The ability of the IMPROVE trial score to discriminate between patients who would and would not survive for 48 hours was reasonable, but not exceptional, with an area under receiver operating characteristic curve of 0.720 [standard error 0.025]. An external validation revealed that the score performed adequately in the ECAR trial and the Amsterdam cohort and did not perform well in AJAX or the Stockholm area cohort. Similarly, none of the previously published risk scores performed well in all of the different cohorts. The inability of risk scores to predict outcomes following emergency surgical repair with sufficient accuracy indicates that any risk score should be used only for either comparing different populations or adjusting population data, as the Hardman index was used in the IMPROVE trial. If the mortality risk of ruptured AAA repair cannot be predicted with sufficient accuracy, we suggest that the focus should shift to offering emergency repair to more patients and reducing the non-intervention rate.

Collaborative projects

The trial has also formed the basis for several collaborative projects. First was a Delphi consensus approach (vascular surgeons and emergency medicine physicians) to develop guidelines for the equitable and rapid transfer of patients with a clinical diagnosis of a ruptured AAA from district general hospitals to vascular centres, which resulted in the Royal College of Emergency Medicine Best Practice Guidelines. Second was a project to investigate whether or not missing QoL data were really missing at random. A third study compares the morphology of intact and ruptured AAAs to try and identify morphological features, other than maximum aortic diameter, which may be helpful in predicting aneurysms at the highest risk of rupture.

Fourth is a study of common iliac aneurysms, which may have an undilated contralateral iliac artery, to assess computational flow dynamic characteristics associated with the natural history of these little-studied aneurysms. The last two of these collaborative projects are still in progress and the transfer guidelines will be updated as part of the ongoing National Institute for Health and Care Excellence AAA review.

Conclusions

The primary outcome measure of the IMPROVE trial was mortality. Despite the lack of any significant difference in mortality (the primary outcome measure) between the randomised groups at 30 days and 1 year, by 3 years the story had changed. At 3 years, there was an interim mid-term survival benefit for the endovascular strategy, without an excess of aneurysm-related reinterventions. The more rapid recovery of the participants in the endovascular strategy group led to early gains in QoL. Together, these have led to an increase in QALYs for the endovascular strategy group, without additional costs compared with the open repair group. All of the outcomes favour the endovascular strategy, leading to it being highly likely that the endovascular strategy was cost-effective after 3 years.

The trial has also been the springboard for other important scientific projects including best practice guidelines for the transfer of patients with a suspected ruptured aneurysm into a vascular centre. Therefore, the results of this project should continue to influence the improvement of care for patients with a ruptured AAA.

Trial registration

This trial is registered as ISRCTN48334791 and NCT00746122.

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