Eur J Vasc Endovasc Surg (2015) 50, 297–302

REVIEW

Ruptured Aneurysm Trials: The Importance of Longer-term Outcomes and Meta-analysis for 1-year Mortality

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Objective: To assess current knowledge for the management of ruptured abdominal aortic aneurysm (AAA), based on the 1-year outcomes of 3 recent randomised trials.
Methods: An individual patient data meta-analysis of three recent randomised trials of endovascular versus open repair, including 817 patients, was conducted according to a pre-specified analysis plan, report all-cause mortality and re-interventions at 1 year after the index event.
Results: Mortality across the 3 trials at 1-year was 38.6% for the EVAR or endovascular strategy patient groups and 42.8% for the open repair groups, pooled odds ratio 0.84 (95% CI 0.63–1.11), $p = .209$. There was no evidence of heterogeneity in the odds ratios between trials. When the patients in the endovascular strategy group of the IMPROVE trial were restricted to those with proven rupture who were anatomically suitable for endovascular repair, the pooled odds ratio reduced slightly to 0.80 (95% CI 0.56–1.16), $p = .240$.
Conclusions: After 1 year there is a consistent but non-significant trend for lower mortality for EVAR or an endovascular strategy. Taken together with the recent gains in health economic outcomes demonstrated at 1 year in the IMPROVE trial, the evidence suggests that endovascular repair should be used more widely for ruptured aneurysms.

Article history: Received 10 April 2015, Accepted 10 April 2015, Available online 15 May 2015
Keywords: Ruptured abdominal aortic aneurysm, Meta-analysis

INTRODUCTION

The gold standard for surgical reporting standard is 30-day mortality. The French ECAR trial, which reports in this issue again shows that for ruptured abdominal aortic aneurysm (AAA) 30-day mortality is similar after either endovascular or open repair, echoing the recent AJAX and IMPROVE trials and confirmed in an individual patient meta-analysis.[1,2] For patients and health economies a longer-term perspective is needed.[3] Earlier this year the IMPROVE trial reported outcomes to 1 year.[4] There was no statistically significant difference in either overall mortality or AAA-related mortality between the randomised groups, although the estimate of overall mortality was numerically slightly lower for the endovascular strategy group: 41% versus 45% for open repair. ECAR also reports results to 1-year, again with a survival estimate that is numerically lower for the endovascular repair group albeit with no statistically significant difference in survival.[1]

Collaboration between the AJAX, ECAR, and IMPROVE trials (the Ruptured Aneurysm Trialists) also means that we can investigate the hypothesis that the numerically higher mortality in the open repair group of each trial would summate to a significant overall difference at 1 year after randomisation. The results of this individual patient meta-analysis are then discussed in the context of the total information available from the three trials.

METHODS

The methods for the three trials included in this meta-analysis have been published previously.[6–8] The AJAX trial (ISRCTN 66212637) randomised 116 patients, with a computed tomography (CT) scan showing probable rupture and patients being eligible for both open and endovascular aneurysm repair (EVAR), in three centres between 2004 and 2011, using a software-generated randomisation sequence provided by an independent clinical research unit, concealed in sealed envelopes for a 1:1 randomisation to either open or endovascular repair (aorto-uni-iliac grafts for endovascular repair). The ECAR trial (NCT 0057716)

[e] Full list in Appendix 1.

DOI of original article: http://dx.doi.org/10.1016/j.ejvs.2015.03.028

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http://dx.doi.org/10.1016/j.ejvs.2015.04.015

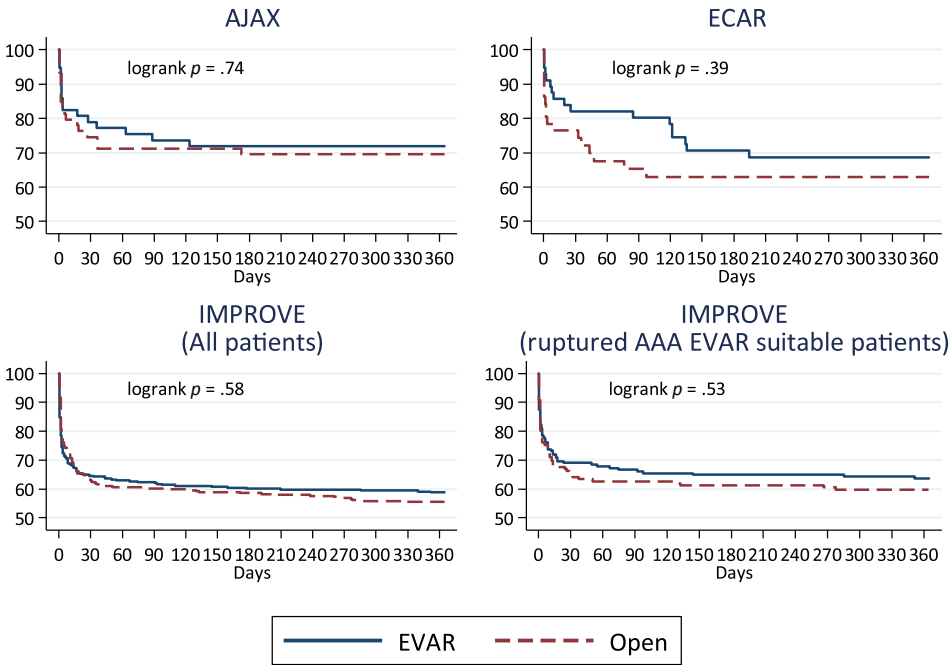

Figure 1. Survival to 1 year in the AJAX, ECAR, and IMPROVE randomised trials. The bottom right hand panel also shows data for the 308 IMPROVE trial patients with ruptured aorto-iliac aneurysm who were anatomically suitable for EVAR.

randomised 107 patients, with a CT scan showing confirmed rupture and an aortic anatomy suitable for endovascular repair and a systolic pressure of >80 mmHg, with treatment allocation by weekly rotation, in 14 centres between 2008 and 2012. The IMPROVE trial (ISRCTN 48334791) randomised 613 eligible patients with an in-hospital clinical diagnosis of ruptured aneurysm in 29 centres between 2009 and 2013, using an independent contractor providing telephone randomisation, with computer-generated assignation of patients in a 1:1 ratio, using variable block size and stratified by centre. For IMPROVE, patients were randomised before CT scan, and randomised to either an endovascular strategy (with open repair if endovascular repair was not anatomically feasible) or to open repair. All three trials were conducted with appropriate ethical approvals; information about these have been reported previously.[6–8] The three data sets were merged based on fields available in the case record forms of the largest trial (IMPROVE), range checks were conducted and queries resolved with the individual trial coordinating centres.

Unfortunately the data from the pilot Nottingham trial[9] could not be retrieved for the meta-analysis.

Statistical analysis

The primary analyses considered the groups "as randomised" within each trial, irrespective of the different trial designs and assessed mortality at 1 year after randomisation (for IMPROVE) and after admission (for AJAX and ECAR). The odds ratio of mortality for the endovascular strategy or EVAR versus open repair was estimated using logistic regression adjusting for trial as described previously.[2] Analyses were then repeated for odds ratios estimated from logistic regression models adjusted for age, sex, and Hardman index, a validated risk scoring system for ruptured aneurysms.[10] Patients lost to follow-up before 1-year were excluded from these analyses. Secondary analyses were conducted with the purpose of making the groups in the different trials more homogeneous. Only those patients with a ruptured AAA final diagnosis and considered suitable for EVAR were retained in the analyses. For AJAX and ECAR, suitability for EVAR was a prerequisite for inclusion in the trial. For the IMPROVE trial suitability for EVAR was defined as either local CT assessment of suitability or, if not assessed locally, a "within liberal Instructions For Use" definition from a core laboratory CT analysis was used.

RESULTS

Summary Kaplan—Meier curves for survival to 1 year for all three trials are shown in Fig. 1. All trials show a small non-significant numerically higher mortality estimate after open repair. The lower right-hand panel of Fig. 1 also shows the summary survival by randomised group for those patients from IMPROVE who had a confirmed rupture and were anatomically suitable for EVAR, a cohort more similar to the AJAX and ECAR cohorts. At 1 year the pooled mortality was 38.6% for EVAR/endovascular strategy and 42.8% for open repair.

For survival at 1-year after admission or randomisation, some patients had been lost to follow-up (AJAX 0, ECAR 17, IMPROVE 2). The remaining 817 patients have been included in an individual patient meta-analysis (Fig. 2A). The evidence from all three trials is homogeneous and hints at a slightly lower 1-year mortality after either EVAR or an endovascular strategy, although the pooled odds ratio is not

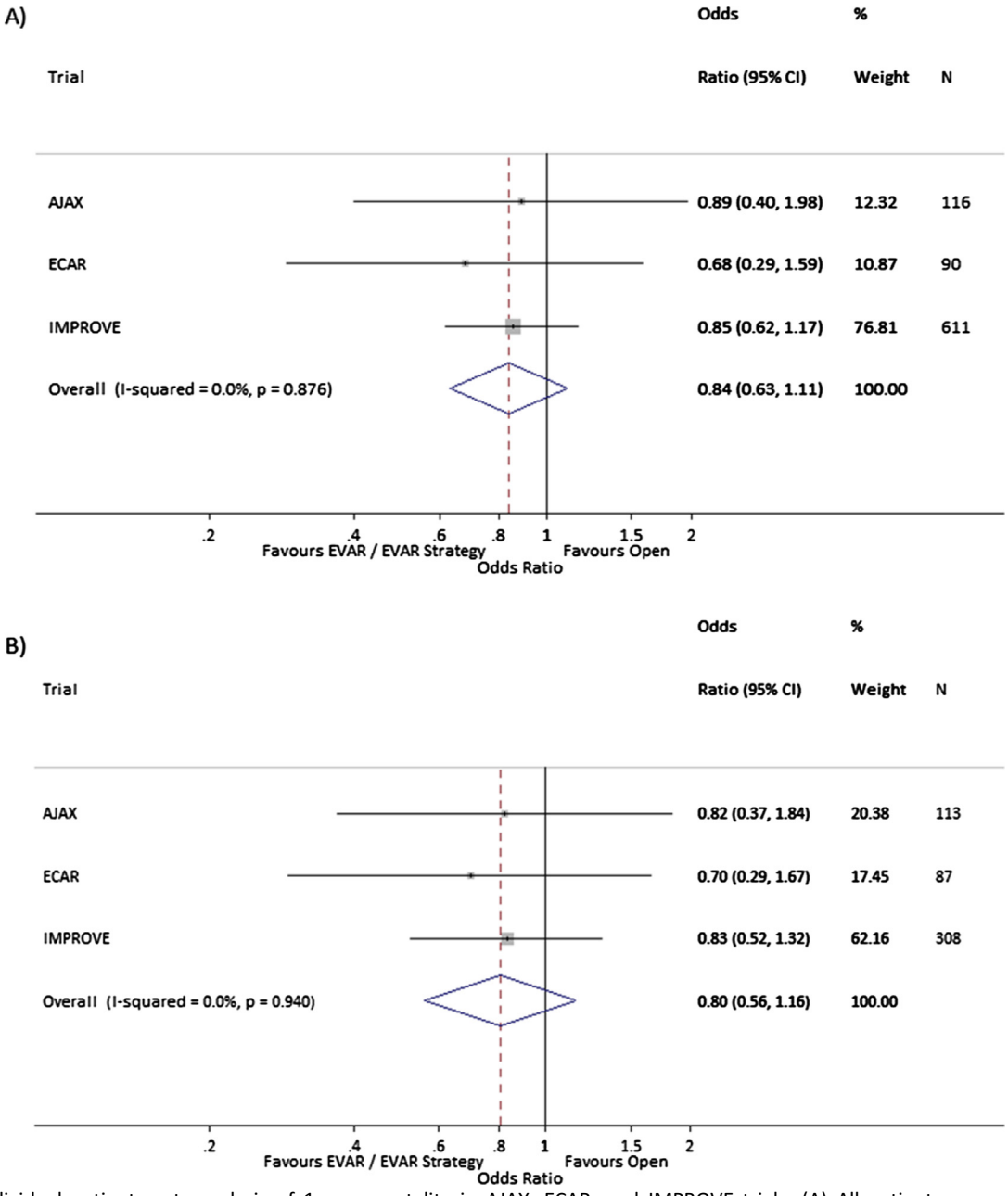

Figure 2. Individual patient meta-analysis of 1-year mortality in AJAX, ECAR, and IMPROVE trials. (A) All patients as randomised. (B) Patients with confirmed rupture who were anatomically suitable for EVAR.

statistically significant; 0.84 (95% CI 0.63−1.11), $p = .209$. The results are very similar after adjustment for age, sex, and Hardman index. When the analysis was restricted to consider only those patients who were considered anatomically suitable for EVAR and had confirmed rupture, the results were similar but the pooled odds ratio estimate now is slightly lower: 0.80 (95% CI 0.56 to 1.16), $p = .240$ (Fig. 2B).

The major open surgical AAA-related re-interventions which occurred between 30 days and 1 year are summarised in Table 1: only the IMPROVE trial reports such re-interventions in the open repair group. The reporting of endovascular and non-AAA related re-interventions were very different across the three trials and results cannot be summarised and therefore no formal meta-analysis of re-intervention rates is possible.

DISCUSSION

Open repair remains the most common intervention for ruptured AAA.[11,12] The early data from the randomised trials did not suggest that there was any important survival benefit for EVAR versus open repair, but the individual patient meta-analysis showed some heterogeneity.[2] At 1 year the results are much more homogeneous and consistent, although the small survival advantage for EVAR or an endovascular strategy is not statistically significant. These results follow the publication of the 1-year results of the

Table 1. Aneurysm-related complications requiring open surgery between 30 days and 1 year.

Randomised group	AJAX ($n = 116$)	ECAR followed to 1 year ($n = 90$)	IMPROVE ($n = 500$ ruptures followed to 1 year)
Open repair	None reported	None reported	7 (2 distal bypasses, 3 colonic resections 1 axillo-bifemoral graft)
EVAR/endovascular strategy[a]	2 conversions (1 for graft infection)	4 (1 conversion for graft infection, 1 conversion for endograft thrombosis, 1 axillo-bifemoral bypass and 1 redo cross-over graft)	3 (1 distal bypass, 1 colonic resection, 1 conversion to open repair for graft thrombosis)

[a] Endovascular strategy used in the IMPROVE trial as the randomised group to compare against Open repair.

ECAR trial and IMPROVE trials this year.[1,4] The AJAX trial published results to 6 months 2 years ago.[13]

The ECAR trial did not assess full health economic outcomes and patients were not followed up for quality of life. The AJAX trial assessed health economic outcomes to 6 months only. The IMPROVE trial has now reported health economic outcomes at 1 year and has identified gains for the endovascular strategy group.[4] For patients, full recovery (discharge back to home with return to normal quality of life, without any additional morbidity) is a key priority. The IMPROVE trial showed that average hospital stay was 17 days in the endovascular strategy group and 26 days in the open repair group and that at 3 months in the endovascular strategy group more patients had returned home and had a higher mean quality of life than in open repair group: recovery was faster in the endovascular strategy group.[4] The quality of life in the endovascular strategy group matched that of UK patients undergoing elective aneurysm repair at both 3 and 12 months.[14] Moreover, there was no evidence of a higher 1-year incidence of post-discharge AAA-related re-interventions in the endovascular strategy group. These findings translated into lower healthcare costs for the endovascular strategy over the first year following rupture, and with the gains in quality of life there is emerging evidence that an endovascular strategy is cost-effective in the UK for ruptured AAA.[4] Since, in sensitivity analyses, the findings of the cost-effectiveness analysis were robust to a variety of different assumptions including staffing levels in the operating theatre, the cost of devices, and including non-AAA related hospital admissions and interventions, it is likely that an endovascular strategy would also be cost-effective in many other healthcare systems. This is different from the findings of the Dutch AJAX trial,[5] perhaps because the IMPROVE trial included a much wider range of patients (more representative of the total ruptured AAA caseload).

If a new randomised trial was designed to show, with 90% power, that the 1-year mortality rate under EVAR was a relative 20% lower than under open repair (assuming 40% mortality under open and a 10% cross-over from both groups), the trial would need approximately 2,500 patients who were both anatomically suitable for EVAR and candidates for open repair. For a cohort of patients, without anatomical selection and a more modest mortality benefit for an endovascular strategy (relatively 15% lower than under open repair) a cohort of closer to 5,000 patients would be needed. This is unlikely to happen for several reasons. First the incidence of rupture is decreasing so if a trial recruiting 600 patients (IMPROVE) was a major challenge, the challenge of a trial of 2,500—5,000 patients would be even more formidable. The results for the trial with the widest range of patients (IMPROVE) already suggest patient benefit and cost-effectiveness at 1 year. The low re-intervention rate after emergency EVAR and cost-effectiveness of an endovascular strategy at 1 year will need confirmation at 3 years before any new trials can be fully informed: all three trials report a low rate of re-interventions after EVAR in the first year. Given the trends from current results there might be limited equipoise and enthusiasm for any new trials.

Perhaps more importantly, with gains for the endovascular approach being indicated with longer-term follow up, we need to identify how the results of endovascular repair can be improved, through fluid management, use of endovascular occlusion balloons, local anaesthesia, and other measures. It also is important to recognise that outside the pioneering vascular centres, open repair will be needed often for the 35—40% of patients who are not suitable for conventional EVAR and therefore have an intrinsically higher mortality risk.[15,16]

In summary, after three recent randomised trials and 1 year of patient follow-up the evidence suggests that although endovascular repair does not offer a significant survival advantage, endovascular repair should be used more widely. Nevertheless open repair must remain available for those unsuitable for conventional EVAR.

CONFLICT OF INTEREST

None.

FUNDING

This analysis was funded by the National Institute for Health Research Health Technology Assessment Programme (project number 07/37/64). The AJAX trial was supported by Netherlands Heart Foundation project 2002B197. The ECAR trial was supported by the French Ministry of Health. The IMPROVE trial was supported by UK Health Technology Assessment award 07/37/64. This individual patient meta-analysis was supported by a grant from the European Society of Vascular Surgery to Robert Hinchliffe.

APPENDIX 1. RUPTURED ANEURYSM TRIALISTS

AJAX Trial investigators

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