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Endovascular strategy or open repair for ruptured abdominal aortic aneurysm: one-year outcomes from the IMPROVE randomized trial

IMPROVE Trial Investigators†

Aims
To report the longer term outcomes following either a strategy of endovascular repair first or open repair of ruptured abdominal aortic aneurysm, which are necessary for both patient and clinical decision-making.

Methods and results
This pragmatic multicentre (29 UK and 1 Canada) trial randomized 613 patients with a clinical diagnosis of ruptured aneurysm: 316 to an endovascular first strategy (if aortic morphology is suitable, open repair if not) and 297 to open repair. The principal 1-year outcome was mortality; secondary outcomes were re-interventions, hospital discharge, health-related quality-of-life (QoL) (EQ-5D), costs, Quality-Adjusted-Life-Years (QALYs), and cost-effectiveness [incremental net benefit (INB)]. At 1 year, all-cause mortality was 41.1% for the endovascular strategy group and 45.1% for the open repair group, odds ratio 0.85 [95% confidence interval (CI) 0.62, 1.17], P = 0.325, with similar re-intervention rates in each group. The endovascular strategy group and open repair groups had average total hospital stays of 17 and 26 days, respectively, P < 0.001. Patients surviving rupture had higher average EQ-5D utility scores in the endovascular strategy vs. open repair groups, mean differences 0.087 (95% CI 0.017, 0.158), 0.068 (95% CI −0.004, 0.140) at 3 and 12 months, respectively. There were indications that QALYs were higher and costs lower for the endovascular first strategy, combining to give an INB of £3877 (95% CI £253, £7408) or €4356 (95% CI €284, €8323).

Conclusion
An endovascular first strategy for management of ruptured aneurysms does not offer a survival benefit over 1 year but offers patients faster discharge with better QoL and is cost-effective.

Clinical trial registration
ISRCTN 48334791.

Keywords
Aneurysm • Aorta • Rupture • Surgery • Stent grafts • Cost-effectiveness

Introduction
Ruptured abdominal aortic aneurysm (AAA) is fatal in over 80% of cases and operative mortality remains high in those who survive to undergo repair (42%).1 The majority of patients in Europe, the USA, and elsewhere is treated with open surgical repair rather than the less invasive endovascular aneurysm repair (EVAR)1–4 and emergency EVAR is not available, or not always available, in many centres.

Following a small pilot trial,5 three larger European randomized trials of endovascular vs. open repair of ruptured aneurysms were established, with the aim of testing the hypothesis that 30-day outcomes were better after either endovascular repair or an endovascular strategy: observational studies suggest that operative mortality after emergency endovascular repair is in the range of 16–36%, varying with haemodynamic stability.3,4 The conventional reporting standard for surgery is 30-day mortality and all three later randomized trials...
have reported this outcome recently. In the two smaller trials, which recruited a limited range of patients, who were fit for open repair and after CT scan deemed anatomically suitable for EVAR, 30-day mortality (20–25%) was similar in patients randomized to EVAR vs. open repair. The much larger IMPROVE trial, randomized patients at the point of in-hospital clinical diagnosis, when vascular teams were alerted, but before a CT scan had confirmed either the diagnosis or the anatomical suitability for EVAR. Randomization was to an endovascular strategy (EVAR wherever possible, with open repair for those anatomically unsuitable for standard EVAR) vs. open repair. The aim of this trial was to assess the clinical and cost-effectiveness of a preferential endovascular strategy for the management of suspected ruptured AAA. Again there was no 30-day survival benefit for the endovascular strategy, except perhaps in women, with overall mortality ~35%.

An editorial commentary on the 30-day outcomes of the IMPROVE trial emphasized correctly that modern intensive care permitted more patients to survive to 30 days, with many patients still being in hospital at 30 days, so that only an assessment of longer term outcomes, to 90 days and beyond, would provide the requisite evidence for both clinical and patient decision-making. This need for longer term data also is endorsed by a recent Cochrane review and the IDEAL recommendations. To the patients and their families involved in the design of the IMPROVE trial, the most important outcome was going home without major complications. Here we report the 1-year pre-specified outcomes from the IMPROVE trial.

Methods

Trial design

IMPROVE (Current Controlled Trials ISRCTN 48334791) is a multicentre trial of unselected patients with an in-hospital clinical diagnosis of ruptured AAA randomized to either an endovascular strategy of immediate CT scan and emergency EVAR if possible or to emergency open repair. Since patients were randomized before knowledge of whether the aortic anatomy was suitable for EVAR, open repair was the specified treatment for patients (35–40%) who were anatomically unsuitable for EVAR in the endovascular strategy group. In the open repair group, CT scan was not compulsory but was used in 90%. The trial methods and 30-day outcomes have been published and, together with the study protocol, and statistical analysis plan, are available from the trial web sites www.improvetrial.org www.imperial.ac.uk/medicine/improvetrial. Briefly, this trial was conducted in 29 British centres and 1 Canadian centre, with each centre retaining the credentialing criteria necessary for participation. Patients over 50 years with a clinical diagnosis of ruptured AAA or ruptured aorto-iliac aneurysm were eligible for inclusion, and 613 patients were randomized from September 2009 to July 2013. The trial guidelines for EVAR suitability were aneurysm neck diameter ≤32 mm, aneurysm neck length ≥10 mm, and neck angulation <60°. Since the diagnosis of rupture can be difficult, CT scans were reviewed later by experts in a core laboratory. There are no ESC guidelines for the management of ruptured AAA.

Randomization

The trial used central telephone computer-generated randomization (1:1), stratified by centre with variable block size. Since this was a surgical trial focusing on mortality there was no blinding.

Outcomes

The principal longer term outcome was all-cause mortality at 1 year and other 1 year measures included aneurysm-specific mortality, re-interventions, health-related quality-of-life (QoL), resource use, disposal (length of hospital stay and the patient-preferred outcome of discharge home, see Supplementary material online, Table S1), costs, and Quality-Adjusted-Life-Years (QALYs). We estimate cost-effectiveness by combining costs and QALYs to report incremental net benefit (INB). All-cause mortality in the UK was assessed through data linkage with the Office for National Statistics and locally in Canada. Trained local coordinators were responsible for the collection of prospective resource use data including re-interventions according to the trial case record form (during the primary admission and re-admissions with all interventions within 30 days classified as aneurysm related). The completeness of re-intervention and re-admission data was verified by monitoring and using an administrative dataset (Hospital Episode Statistics). The EuroQoL questionnaire (5-dimension 3-level version; EQ-5D), a generic measure of health-related QoL on a scale anchored at 0 (death) and 1 (perfect health), was administered at 3 and 12 months to patients discharged following ruptured AAA repair.

Detailed resource use and costs within 1 year of randomization were measured in accordance with international guidelines, and reported from a UK NHS and Personal Social Services perspective (see Supplementary material online, including unit costs, Table S2).

Ethical approval was provided by South-Central Berkshire Research Ethics Committee 08/H0505/173 (England and Wales), Scotland A Research Ethics Committee 08/MRE00/90 (Scotland), and the University of Western Ontario Health Sciences Research Ethics Board 17698 (Canada). There was a two-stage consent procedure, a brief initial consent and full post-operative consent. The National Information Governance Board ECC 4-03 (f) 2012 approved the collection of data for date and cause of death for patients without second post-operative consent.

Statistical analysis

The trial required the recruitment of 600 patients to show a 14% absolute difference in survival between the randomized groups with >90% power. Analyses were by intention-to-treat, with the principal sensitivity analysis restricted to the 502 patients with a confirmed diagnosis of rupture in whom repair was commenced, according to the prespecified analysis plan (www.improvetrial.org). The proportion surviving at 1-year post-randomization was compared between the randomized groups, using a Pearson’s χ² test without continuity correction, and odds ratios were reported using logistic regression before and after adjustment for sex, age (continuous measure), and Hardman Index (continuous, a validated scoring system for ruptured AAA). Kaplan–Meier survival curves were plotted after censoring at the end of follow-up or at 1 year, whichever came first, for overall and aneurysm-specific mortality and time to first re-intervention, using log-rank tests for between-group comparisons. As previously, we fitted a complier average causal effects model to estimate the potential effect of all patients adhering to trial protocol. Gray’s non-parametric test, accounting for competing risks, was used to compare the cumulative incidence of overall discharge (from index admission hospital and secondary hospital) and for discharge to home (time to discharge compared with Wilcoxon rank-sum test). For pre-specified subgroups (age, sex, and Hardman index), differences were assessed using logistic regression with a test of interaction; given the multiple tests performed an interaction test P-value of <0.01 was required to claim strong evidence of differences between subgroups. The EQ-5D utility index
score was calculated by combining the EQ-5D health profile of each patient with health state preference values from the UK general population. The resultant mean QoL utility scores at 3 and 12 months post-randomization were contrasted between the randomized groups, with unpaired t-tests. Quality-Adjusted-Life-Years up to 1 year were calculated by valuing each patient’s survival time by their QoL at 3 and 12 months according to the ‘area under the curve’ method. The study estimated INBs by valuing incremental QALYs at the recommended threshold for a QALY gain (£30 000) then subtracting the incremental costs from this with conversions into £ (€1.235) reported (see Supplementary material online, Appendix for details).

**Results**

One-year survival data were available for 611/613 patients randomized (Figure 1). Of the 613 patients, 536 had proven AAA rupture, and repair was started in 502 (see Figure 1). For the 77 patients without AAA rupture, 22 had acute, symptomatic AAA (with repair in 21), while of the 55 patients with discharge diagnoses unrelated to AAA 45 had co-existing asymptomatic AAA (mean diameter 6.9 cm) and 1 further patient had a thoracoabdominal aneurysm. Baseline characteristics were similar between the randomized groups (see Supplementary material online, Table S4); overall 480 (78%) were men, with mean (SD) age of 76.7 (7.6) years, aneurysm diameter of 8.4 (1.9) cm, and admission systolic blood pressure of 110 (32) mmHg.

After 1 year, 130 (41.1%) of patients in the endovascular strategy group had died vs. 133 (45.1%) in the open repair group, unadjusted odds ratio 0.85 [95% confidence interval (CI) 0.62, 1.17], \( P = 0.325 \). Adjusted results and those restricted to patients with ruptured AAA repair were similar, with odds ratios 0.86 (95% CI 0.62, 1.21) and 0.86 (0.59, 1.24), respectively. Almost half the deaths, in each group, occurred within 24 h and the majority occurred within 30 days (Table 1 and Figure 2A). At 1 year, AAA-related mortality (including all deaths within 30 days) in the endovascular strategy and open repair groups, respectively, was 33.9% and 39.3%, unadjusted odds ratio of 0.79 (95% CI 0.57, 1.10), \( P = 0.161 \) (see Supplementary material online, Figure S1). The subgroup analysis of 1-year mortality found weak evidence that the endovascular strategy was more effective in women than in men, ratio of odds ratio 0.41 (95% CI 0.18, 0.93), \( P = 0.034 \) (Figure 2B). Among ruptured aneurysm patients with repair

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**Figure 1** CONSORT diagram showing flow of patients through the trial. AAA, abdominal aortic aneurysm; rAAA, ruptured abdominal aortic aneurysm; 23% of ruptured abdominal aortic aneurysms were juxtarenal with an aortic neck length <10 mm,21 75% infra-renal, and 2% aorto-iliac.

*One hundred and forty-nine endovascular aneurysm repair and 110 open repair (27 open repairs in patients suitable for endovascular aneurysm repair, breach of protocol mainly for operational reasons, e.g. endovascular suite in use or inadequately staffed, 241 open repairs and 33 endovascular aneurysm repairs in breach of protocol, mainly for avoidance of general anaesthesia. *Follow-up pertains to endpoints other than mortality. *One patient mortality known to 30 days and one patient mortality known to 3 months. Case record form (CRF) captures re-interventions and re-admissions, and outpatient visits to the trial hospital.
started, the 1-year mortality was 98/259 (37.8%) in the endovascular strategy group and 104/241 (43.2%) in the open repair group, adjusted odds ratio 0.86 (95% CI 0.59, 1.24), \(P = 0.400\). The estimated unbiased causal odds ratio for a trial in which everyone adhered to the randomized policy was slightly lower: 0.78 (95% CI 0.49, 1.24).

Overall, the time to first AAA-related re-intervention was similar between the randomized groups, \(P = 0.701\) (log-rank test) (see Supplementary material online, Figure S2) and for the 502 ruptured AAA patients who underwent repair \(P = 0.674\) (log-rank test) (Figure 3, Table 1, details with reasons for re-interventions in Supplementary material online, Table S5). Between 31 days and 1 year, there were only 11 patients (4.2%, 12 procedures) with re-interventions in the endovascular group (including 5 endograft related, 1 revision of iliac limb of open repair, 1 limb ischaemia, and 1 colonic ischaemia) and 9 patients (3.7%, 13 procedures) in the open repair group (including 2 for limb ischaemia, 3 colonic ischaemia, 3 for continuing complications of earlier abdominal compartment syndrome, and 1 axillo-bifemoral bypass). Between hospital discharge and 1 year; there was only one AAA-related death, following open repair in the open repair group.

In the endovascular strategy group, 10 patients (3%) were transferred to a secondary hospital vs. 36 patients (12%) in the open repair group: at 30 days, 79 patients (13%) remained in hospital (49/79 in the open repair group). The average times to discharge from hospital (primary and secondary hospitals) were 17 (endovascular strategy group) and 26 days (open repair group), \(P < 0.001\); there was an indication of slightly higher cumulative incidence of discharge in the endovascular strategy group, \(P = 0.114\) (Figure 4A). There was strong evidence that a higher proportion of patients from the endovascular strategy group were discharged directly home from the primary hospital, \(P < 0.001\) (Figure 4B).

At 3 months, a higher proportion of patients in the endovascular strategy group reported ‘no problems’ on the physical health dimensions (mobility, self-care, and pain) of the EQ-5D QoL questionnaire, compared to the open repair group (see Supplementary material online, Table S6). The resultant EQ-5D mean utility scores were higher in the endovascular strategy vs. the open repair group; the mean differences for ruptured aneurysm AAA survivors were 0.087 (95% CI 0.017, 0.158; \(P = 0.015\)) and 0.068 (95% CI –0.004, 0.140; \(P = 0.063\)) at 3 and 12 months, respectively (Table 2 and Supplementary material online, Table S7). Average total costs (details in Supplementary material online, Table S8), which included the provision of both types of repair at all times, were less in the endovascular strategy (£16 394) vs. the open repair group (£18 723), with a mean incremental cost of £2329 (95% CI £5489, £922) (Table 2) or –£2617 (95% CI –£6167, £1036).

The QALY gain at 1 year for the endovascular strategy group was 0.052 (95% CI –0.005, 0.108), with similar results across subgroups.

### Table 1  Mortality for the 613 randomized patients, and numbers of re-interventions in the 502 ruptured abdominal aortic aneurysm patients with aneurysm repair started

<table>
<thead>
<tr>
<th>Variable</th>
<th>Missing</th>
<th>Endovascular strategy</th>
<th>Open repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>n = 316</td>
<td>112 (35.4%)</td>
<td>111 (37.4%)</td>
</tr>
<tr>
<td>Within 30 days</td>
<td>0</td>
<td>115 (36.4%)</td>
<td>114 (38.4%)</td>
</tr>
<tr>
<td>Before primary hospital discharge</td>
<td>0</td>
<td>115 (36.4%)</td>
<td>116 (39.1%)</td>
</tr>
<tr>
<td>Before overall hospital discharge</td>
<td>0</td>
<td>130 (41.1%)</td>
<td>133 (45.1%)</td>
</tr>
<tr>
<td>Within 1 year</td>
<td>2</td>
<td>2 (0.6%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Cause of death</td>
<td>2</td>
<td>AAA: 107 (33.9%)</td>
<td>116 (39.3%)</td>
</tr>
<tr>
<td>Myocardial disease</td>
<td></td>
<td>4 (1.3%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td></td>
<td>6 (1.9%)</td>
<td>4 (1.4%)</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td>4 (1.3%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Stroke and other vascular</td>
<td></td>
<td>7 (2.2%)</td>
<td>8 (2.7%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>2 (0.6%)</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Patients with re-interventions*</td>
<td>n = 259</td>
<td>55 (21.2%)</td>
<td>49 (20.2%)</td>
</tr>
<tr>
<td>AAA-related re-intervention</td>
<td>0</td>
<td>6 (2.3%)</td>
<td>11 (4.5%)</td>
</tr>
<tr>
<td>Non-AAA-related re-intervention</td>
<td>0</td>
<td>201 (77.6%)</td>
<td>187 (77.0%)</td>
</tr>
<tr>
<td>Number of re-interventions per-person*</td>
<td>0</td>
<td>42 (16.2%)</td>
<td>38 (15.6%)</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>11 (4.3%)</td>
<td>13 (5.4%)</td>
</tr>
<tr>
<td>2+</td>
<td></td>
<td>5 (1.9%)</td>
<td>5 (2.1%)</td>
</tr>
</tbody>
</table>

*Among 502 ruptured AAA patients with aneurysm repair started.
When the incremental costs and QALYs are represented on the cost-effectiveness plane, most (87%) of the estimates are in the quadrant that designates the endovascular strategy as ‘dominant’, with lower mean costs and higher mean QALYs (Figure 5). The INB of the endovascular strategy vs. open repair is positive at £3877 (95% CI £253, £7408) or €4788 (95% CI €312, €9149), a finding robust to a range of assumptions (see Supplementary material online, Tables S9 and 10, Figures S3 and S5), including increases in operating theatre staff and varying the costs of the EVAR device from £4000 to £10,000 (vs. £5700 in the base case) or additional interventions, Supplementary material online, Figure S5. The probability that the

![Figure 2](A) Kaplan-Meier estimates by randomized group, across all patients (log-rank test p = 0.325) and (B) 1-year mortality odds ratios for specified subgroups.
Discussion

Following repair of a ruptured AAA, it has been proposed that follow-up, to 90 days and beyond is necessary for patient and clinical decision-making. After 1 year, this trial has shown no significant survival benefit at any time-point for an endovascular strategy (using a standard EVAR device whenever anatomically and operationally possible, with open repair as a default option) vs. open repair. In contrast, there were gains for the endovascular strategy vs. the open repair group with respect to patient-preferred outcomes: faster discharge, more often to home, and QoL and overall the endovascular strategy was cost-effective.

Shock with systemic organ damage, rather than type of repair might result in the very high early mortality after ruptured AAA repair and many patients have prolonged hospital stays. There are other potential reasons why there was no difference in survival between the randomized groups. First, the operative mortality from open repair was lower than anticipated. Second, we now know that aortic anatomy, particularly aneurysm neck length, has an important influence on mortality and that those patients who are not candidates for standard EVAR (~40%) have the highest operative mortality, particularly for open repair, and that those anatomically suitable for EVAR have much lower mortality after either EVAR or open repair. The trial was designed to be inclusive and consider whether the availability of an endovascular service would improve the outcome of all patients with rupture, not just those anatomically suitable for EVAR. So inevitably the endovascular strategy group included a significant proportion of patients who had to be treated with open repair. Therefore, the findings suggesting faster recovery in the endovascular strategy group are notable; shorter overall hospital stay, a greater propensity to be discharged to home, and better early QoL than the open repair group. The between-group mean differences in QoL, 0.087 (3 months) and 0.068 (1 year), exceed the minimum clinically important difference of 0.03, although at 1 year, the mean difference was not statistically significant. The absolute EQ-5 utility scores of the endovascular strategy was more cost-effective was > 0.90 at all realistic thresholds of willingness to pay for a QALY gain (see Supplementary material online, Figure S4).

Figure 3  Time to first re-intervention for the 502 patients with repair of ruptured aneurysm started. Log-rank test $P = 0.674$.

Figure 4  Hospital discharge (A) Overall time to discharge from hospital and (B) time to discharge home from primary hospital.
Endovascular strategy or open repair

Table 2  Quality-of-life, total costs (£GBP), and cost-effectiveness outcomes up to 1 year

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Endovascular strategy</th>
<th>Open repair</th>
<th>Mean difference [95% CI] (£GBP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ-SD-ab at 3 months for ruptured AAA survivors</td>
<td>168 0.76 (0.24)</td>
<td>150 0.67 (0.32)</td>
<td>0.087 [0.017, 0.158]</td>
</tr>
<tr>
<td>EQ-SD-ab at 12 months for ruptured AAA survivors</td>
<td>161 0.77 (0.20)</td>
<td>140 0.71 (0.35)</td>
<td>0.068 [−0.004, 0.140]</td>
</tr>
<tr>
<td>QALY-ab for all randomized patients</td>
<td>316 0.40 (0.35)</td>
<td>297 0.35 (0.35)</td>
<td>0.052 [−0.005, 0.108]</td>
</tr>
<tr>
<td>Total cost (£GBP)</td>
<td>316 16 394 (19 543)</td>
<td>297 18 723 (20 599)</td>
<td>−2329 [−5489, 922]</td>
</tr>
<tr>
<td>Incremental net benefit ab,d [95% CI] (£GBP)</td>
<td>3877 [253, 7408]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5 Uncertainty in the mean cost (£GBP) and Quality-Adjusted-Life-Year differences and their joint distribution for endovascular strategy vs. open repair.

| Strategy group at 3 and 12 months (0.76 and 0.78) seemed slightly higher than those undergoing elective EVAR in the EVAR-1 trial (0.71 and 0.74, respectively), whereas the absolute scores of the open repair group (0.69 and 0.74) were similar to those undergoing elective open repair (0.67 and 0.75). In addition, in this trial, there was no evidence of a difference in re-interventions (including those for endoleaks) at any time during the first year after rupture and the risk of re-intervention for endoleak seems lower than the 10–23% range suggested in previous reports. The cost-effectiveness estimates remained robust to sensitivity analyses allowing for additional interventions. This is in contrast to the findings for elective repair, where in the first year AAA-related re-interventions were more common after EVAR and EVAR cost significantly more than open repair.

Limitations

First, this was a pragmatic trial and in those with ruptured AAA EVAR was started in only 58% in the endovascular group (with 27 EVAR-suitable patients receiving open repair for operational reasons) and 33 patients in the open repair group received EVAR (primarily because they were deemed unfit for general anaesthesia). Secondly, data completion was very good, including questionnaire responses, but any missing data were addressed with multiple imputation, which assumes that any systematic differences in outcomes can be explained by the variables included in the imputation model. Thirdly, there was no adjustment for testing of multiple hypotheses (except for subgroup analyses) but all reported outcomes were pre-specified. Fourthly, we did not adhere to the standard American guidelines for the reporting of complications and re-interventions, which are designed primarily for elective surgery. Finally, re-interventions and costs following EVAR for rupture may increase after 1 year and all patients will be followed-up for 3 years to address this.

Currently, only the Dutch AJAX trial has reported outcomes to beyond 30 days. There were no between-group differences in health-related QoL and endovascular repair was found not to be cost-effective. There were important distinctions between the IMPROVE and AJAX trials, which makes it difficult to interpret the different conclusions concerning QoL and cost-effectiveness; notably, the AJAX trial included a narrow range of hospitals and patients (recruited over many years and with few women), used aorto-uni-iliac devices (with subsequent femoro-femoral crossover grafting) for endovascular repair and applied unit costs from a single centre.

In summary, we present new effectiveness and cost-effectiveness evidence from a large, well-conducted randomized trial, conducted in the challenging circumstance of emergency patients requiring an immediate operation to avoid death. It was based on the randomization of unselected patients, including appropriate representation of women, to optimize the generalizability of the findings and all centres were accredited for providing EVAR in routine and emergency practice. Although the endovascular first strategy offers no survival benefit for patients with ruptured AAA, at up to 1 year, this within-trial report suggests that wider provision of emergency endovascular services is likely to be a cost-effective use of national healthcare systems.
Authors’ roles


Acknowledgement

IMPROVE trial investigators include the following:


Regional Principal Investigators (in order of site start date from earliest to most recent); numbers in parentheses indicate the number of patients entered into the trial:

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Supplementary material

Supplementary material is available at European Heart Journal online.

Funding

This trial was supported by UK Health Technology Assessment award 07/37/64. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the National Institute for Health Research, the National Health Service or the Department of Health. Funding to pay the Open Access publication charges for this article was provided by UK Health Technology Assessment award 07/37/64.

Conflict of interest: none declared.

Appendix

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