The effect of aortic morphology on peri-operative mortality of ruptured abdominal aortic aneurysm

IMPROVE Trial Investigators†

Aims
To investigate whether aneurysm shape and extent, which indicate whether a patient with ruptured abdominal aortic aneurysm (rAAA) is eligible for endovascular repair (EVAR), influence the outcome of both EVAR and open surgical repair.

Methods and results
The influence of six morphological parameters (maximum aortic diameter, aneurysm neck diameter, length and conicality, proximal neck angle, and maximum common iliac diameter) on mortality and reinterventions within 30 days was investigated in rAAA patients randomized before morphological assessment in the Immediate Management of the Patient with Rupture: Open Versus Endovascular strategies (IMPROVE) trial. Patients with a proven diagnosis of rAAA, who underwent repair and had their admission computerized tomography scan submitted to the core laboratory, were included. Among 458 patients (364 men, mean age 76 years), who had either EVAR (n = 177) or open repair (n = 281) started, there were 155 deaths and 88 re-interventions within 30 days of randomization analysed according to a pre-specified plan. The mean maximum aortic diameter was 8.6 cm. There were no substantial correlations between the six morphological variables. Aneurysm neck length was shorter in those undergoing open repair (vs. EVAR). Aneurysm neck length (mean 23.3, SD 16.1 mm) was inversely associated with mortality for open repair and overall: adjusted OR 0.72 (95% CI 0.57, 0.92) for each 16 mm (SD) increase in length. There were no convincing associations of morphological parameters with reinterventions.

Conclusion
Short aneurysm necks adversely influence mortality after open repair of rAAA and preclude conventional EVAR. This may help explain why observational studies, but not randomized trials, have shown an early survival benefit for EVAR.

Clinical trial registration:
ISRCTN 48334791.

Keywords
Aneurysm • Aorta • Imaging • Rupture • Surgery • Stent grafts

Introduction
Three recent randomized trials have shown that both endovascular and open repair of ruptured abdominal aortic aneurysms (rAAAs) can be performed with similar operative mortality, and this has been confirmed in a systematic review with meta-analysis. In contrast, systematic reviews of observational studies have shown a much lower operative mortality after endovascular repair vs. open repair. If large enough, randomized trials can investigate whether specific sub-groups of patients (by age, gender, and fitness) may derive particular benefit from either endovascular or open repair. However, aortic morphology, likely to be a key factor controlling the success of endovascular aneurysm repair (EVAR) for ruptured aneurysms, has not been investigated in detail previously. Aortic morphology also might be an important factor in open repair as suggested by a retrospective review of >200 cases of open repair for aneurysm rupture in a single Swiss centre.

Nearly, all patients with rAAA undergo computerized tomography (CT) scan, so that aortic morphology can be assessed rapidly. One liberal definition of suitability for endovascular repair, which has been used by laboratories for centralized assessment of CT scans, includes an aneurysm neck length ≥ 10 mm, neck...
diameter < 32 mm, and neck angle < 60°.² The Swiss study indicated that the 30-day mortality for open repair of patients outside this definition was increased by 8- to 9-fold compared with those within this definition,³ whereas a Dutch study found no difference.⁴ There are no previous reports of whether any specific morphological features (including maximum aneurysm diameter) influence the success of either EVAR or open repair and should be used to guide the type of emergency repair selected for individual patients.

Here, this issue of how aortic morphology influences outcome of ruptured aneurysm repair, after either EVAR or open repair, is addressed using data from the IMPROVE trial.² This also extends to exploring whether aortic morphology contributed to the surprising early finding of the IMPROVE trial that women appeared to benefit more from an endovascular strategy than men.² This was an important observation, since in general the mortality of women undergoing repair of a ruptured aneurysm is higher than in men.⁴,¹¹

Methods

In the IMPROVE trial,² 613 eligible patients, with an in-hospital clinical diagnosis of ruptured AAA, were randomized before anatomical suitability for EVAR had been ascertained, either to a strategy of EVAR if considered anatomically feasible or open repair. Patients who were randomized to the endovascular strategy group but following immediate CT scan were deemed to have an aortic anatomy unsuitable for EVAR were, by protocol, treated with open repair. The 613 patients derived from a total cohort of 1275 patients: half (352/672) of the non-randomized patients were moribund upon admission with repair considered futile, and died without aneurysm repair. Ethical approval for the participation in the IMPROVE trial of patients in England and Wales was from South-Central Berkshire Research Ethics Committee 08/H0505/173, in Scotland from Scotland A Research Ethics Committee 08/MRE00/90 and in Canada from University of Western Ontario Health Sciences Research Ethics Board 17698. This study included all patients randomized in the IMPROVE trial of patients in England and Wales was from South-Central Berkshire Research Ethics Committee 08/H0505/173, in Scotland from Scotland A Research Ethics Committee 08/MRE00/90 and in Canada from University of Western Ontario Health Sciences Research Ethics Board 17698. This study included all patients randomized in the IMPROVE trial,² with a confirmed diagnosis of ruptured AAA, a pre-operative CT scan available for core laboratory analysis and who received an operation to repair the rupture. This group consisted of 458 patients (364 men and 94 women) Figure 1. Groups were analysed according to operation received and not by randomized group (the open repair group contains those randomized to EVAR strategy who were found to be not anatomically suitable); hence, the results presented are observational and therefore careful control of potential confounding was required. There are no ESC guidelines for the management of ruptured AAA.

CT scans

General guidance on the CT scanning protocol to be used was provided in the IMPROVE Trial protocol, prior to site initiation. The guidance included suggested volumes of contrast to be used, extent of scan required, scan thickness, and acquisition delay (www.imperial.ac.uk/medicine/improvetrial). In a minority of CT scans, no radiographic contrast was used (due to patient contrast allergy or the presence of renal impairment). In these cases, only limited data were recorded from the CT scans.

Analysis of CT scan data

CT scans performed within the trial were analysed at St George’s Vascular Institute core laboratory using the St George’s Vascular Institute Protocol¹² to provide independent diagnosis of rupture and comprehensively characterize the aneurysm morphology. This protocol is accurate and reproducible with high levels of inter/intraobserver agreement.¹² The CT images were acquired in the DICOM (Digital Image and Communication in Medicine) format from the hospital archive. The DICOM files were transferred on anonymized CDs to the core lab and analysed using CT reconstruction software (3Surgery; 3Mensio Medical Imaging B.V., Blithoven, The Netherlands). After semi-automated 3D segmentation of the aorta, a central luminal line (CLL) was defined and installed, then multiplanar reformatted images were obtained in parallel (vessel stretched) and perpendicular (orthogonal) views. A baseline was then manually identified on the stretched vessel view at the level of the lowest renal artery to start the measurements. Lengths were measured along the CLL in the stretched vessel view as the distance between two predefined anatomical landmarks. Total (external wall to external wall), luminal, and non-luminal volumes were measured semi-automatically. The following standard definitions are made:

(i) Aneurysm neck: from the lowest renal artery to the first point of significant aneurysm dilatation.
(ii) Access vessels: common iliac artery (CIA) from the aortic bifurcation to the iliac bifurcation.

A detailed description of the other morphological definitions and measurements analysed may be found elsewhere.¹²

Outcomes

The primary outcome is mortality, with a secondary outcome of any reintervention, both within 30 days of randomization. Following the review of initial results, 24 h mortality also was assessed.

Statistical analysis

This was conducted according to a pre-specified plan, published on the trial web site http://www1.imperial.ac.uk/biosurgerysurgeticntechnology/clinical_trials_outcomes/vasculardisease/clinicaltrials/improvetrial/healthcare_professionals/resources/ before the data were inspected and analysed. As previously,² missing data were multiply imputed before analysis using chained equations (variables used for imputation are listed in Supplementary material online, Table S1). The analyses focused on repairs performed on aortas within and outside liberal instructions for use,¹ as well six morphological variables: maximum AAA diameter, aneurysm neck diameter at the distal renal artery, aneurysm neck length, neck conicality, proximal neck α-angulation, and maximum common iliac diameter. The proximal neck α-angulation was selected over the distal β-angulation used in IFU, because of clinician preference (α and β angles were correlated, r = 0.59). For neck conicality, the ratio of the most distal neck diameter measured (D1) to the diameter at the distal
renal artery (D2) relative to the centre line distance between these two levels (L) was used. The relative change per unit length is then calculated as (D1/D2-1)/L. Logistic regression models were fitted adjusting for pre-specified confounders (age, sex, Hardman index, lowest recorded systolic blood pressure, randomized group, and treatment commenced). A further model additionally adjusted the estimates for the effect of all the other morphological variables. For the IFU analysis, odds ratios, 95% confidence intervals and \(P\)-values (calculated using Wald’s test) are presented, with an additional sensitivity analysis to allow for the type of anaesthesia used for patients receiving EVAR. Each of the six morphological variables were considered as continuous covariates and odds ratios are reported based on a 1 SD increase to allow fair comparison of their relative importance. The interaction with sex was investigated in all models. Goodness of fit was assessed using the Hosmer–Lemeshow test, forming 10 equal-sized groups based on the predicted probabilities. All analyses were conducted using Stata statistical software, version 12 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX, USA: StataCorp LP).

### Results

The selection of the 458 patients for this analysis is shown in Figure 1 and their baseline characteristics, including aneurysm morphology measurements are shown in Table 1. Patients who commenced EVAR were on average older (\(P = 0.0032\)), more likely to have aortic anatomy within IFU (\(P < 0.001\)), had longer (\(P < 0.001\)) and less conical (\(P = 0.030\)) aneurysm necks and had larger common iliac arteries (\(P = 0.040\)). These differences were mainly attributed to patients who were not anatomically suitable for EVAR receiving open repair; full reasons for final treatment were reported previously. Ninety-five per cent limits of agreement of inter-observer variability in morphology measurements were assessed using Bland Altman plots (based on three independent observers): maximum aneurysm diameter ± 4 mm, neck diameter ± 2 mm, neck length ± 4 mm, and common iliac diameter ± 2 mm. There were no strong correlations between the six morphological variables. The aneurysm morphology was described as within liberal IFU in 58% patients; there were 155 deaths and 88 re-interventions within 30 days. As in previous series, the description of within liberal IFU from core laboratory aneurysm neck measurements was not concordant with local hospital definition of suitability for EVAR (Supplementary material online, Table S2). The distribution of maximum aneurysm diameter (at a mean systolic pressure of about 95 mmHg) is shown in Figure 2, displaying a steeper increase in the frequency of ruptures for aneurysm sizes >60 mm.

### Mortality

The association between aneurysm morphology and 30-day mortality is shown in Table 2, adjusting for the pre-specified confounders. Further adjustments for the other morphological measurements and a complete-case analysis gave similar results and are shown in Supplementary material online, Tables S3 and S4. There was no evidence of lack of fit in any of the complete-case analyses. Patients with aneurysm morphology within liberal IFU appeared to have

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the analysis population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>458</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>458</td>
</tr>
<tr>
<td>Hardman Index</td>
<td>405</td>
</tr>
<tr>
<td>Lowest pre-operative SBP, mmHg</td>
<td>429</td>
</tr>
<tr>
<td>Within liberal IFU, n (%)</td>
<td>389</td>
</tr>
<tr>
<td>Max aneurysm diameter (mm)</td>
<td>427</td>
</tr>
<tr>
<td>Aneurysm neck diameter at distal renal artery (mm)</td>
<td>374</td>
</tr>
<tr>
<td>Neck length (mm)</td>
<td>409</td>
</tr>
<tr>
<td>Conicality (% change per mm length)</td>
<td>361</td>
</tr>
<tr>
<td>Proximal neck angle (degrees)</td>
<td>406</td>
</tr>
<tr>
<td>Maximum common iliac diameter (mm)</td>
<td>404</td>
</tr>
</tbody>
</table>

Mean (SD) unless otherwise stated.
*Wilcoxon rank-sum test for continuous variables, Pearson \(x^2\) test for binary variables.

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**Figure 2** Distribution of maximum aneurysm diameters (at a mean systolic pressure of 95 mmHg).
Table 2  Aortic morphology and 30-day mortality (with multiple imputation for missing variables)

<table>
<thead>
<tr>
<th>Variable</th>
<th>EVAR commenced, 50 deaths, n = 177</th>
<th>Open commenced, 105 deaths, n = 281</th>
<th>Combineda, 155 deaths, n = 458</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>P-value</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Within liberal IFU (vs. outside)</td>
<td>0.72 (0.33, 1.61)</td>
<td>0.42</td>
<td>0.61 (0.35, 1.06)</td>
</tr>
<tr>
<td>Maximum AAA diameter (per 17 mm increase)</td>
<td>0.95 (0.66, 1.38)</td>
<td>0.80</td>
<td>0.83 (0.63, 1.10)</td>
</tr>
<tr>
<td>Aneurysm neck diameter at distal renal artery (per 4 mm increase)</td>
<td>1.18 (0.76, 1.82)</td>
<td>0.47</td>
<td>0.96 (0.69, 1.33)</td>
</tr>
<tr>
<td>Aneurysm neck length (per 16 mm increase)</td>
<td>0.83 (0.54, 1.26)</td>
<td>0.38</td>
<td>0.67 (0.49, 0.91)</td>
</tr>
<tr>
<td>Neck conicality (per 1.6% per mm change increase)</td>
<td>1.19 (0.63, 2.26)</td>
<td>0.60</td>
<td>1.17 (0.80, 1.70)</td>
</tr>
<tr>
<td>Proximal aneurysm neck (α) angulation (per 20° increase)</td>
<td>0.93 (0.63, 1.37)</td>
<td>0.70</td>
<td>0.85 (0.65, 1.11)</td>
</tr>
<tr>
<td>Maximum common iliac diameter (per 9 mm increase)</td>
<td>1.38 (0.93, 2.05)</td>
<td>0.11</td>
<td>1.09 (0.84, 1.41)</td>
</tr>
</tbody>
</table>

All models adjusted for age, sex, Hardman Index, lowest recorded systolic blood pressure, and randomized group. Odds ratios are presented per standard deviation increase of morphological parameter.

aAlso adjusted for operation commenced.

Figure 3  Distribution of aneurysm neck lengths in the complete cohort and stratified according to operation started and sex.
lower mortality for both EVAR and open repair, although overall this one-third reduction in mortality was only of borderline significance ($P = 0.054$). Further adjustment for type of anaesthesia used (general vs. local) gave a similar estimate for patients who commenced EVAR. Neck length, but none of the other morphological measurements, was associated with mortality; the odds ratio point estimate was more extreme in patients undergoing open repair than EVAR. Overall, for a 16 mm (one SD) increase in neck length, the adjusted odds ratio was 0.72 (95% CI 0.57, 0.92), $P = 0.009$.

The distribution of neck length was right skewed, with considerable numbers of patients having zero neck lengths, or juxtarenal aneurysms (Figure 3). The mortality results for patients by defined clinical categories of neck length are shown in Table 3 and Figure 4. Few patients with neck lengths <10 mm had EVAR started (Figure 3) and their mortality was high, but limited numbers could account for why neck length did not achieve statistical significance in this group (Table 2). For patients in whom open repair was started, the 30-day mortality increased steadily with decreasing neck length. For patients with neck lengths of $\geq 15$ mm, the mortality from EVAR and open repair appeared similar.

The strong inverse association between neck length and 30-day mortality did not appear to result from other potential confounders.

There was no evidence of those with shorter necks being more likely to have pre-operative shock or acute myocardial ischaemia, spending a longer time in theatre, or requiring post-operative renal replacement therapy (data not shown). Further, a post hoc comparison of supra-renal aortic diameter (measured 15 mm proximal to the proximal renal artery) and neck length showed little correlation between these measurements.

Similarly, 24 h mortality (79 deaths) increased with decreasing aneurysm neck length: for each 16 mm (one SD) increase in neck length; adjusted odds ratio 0.66 (95% CI 0.48, 0.90), $P = 0.008$.

Since outcomes after rupture in women are usually worse than those in men, we further investigated whether neck length might be influential. The distribution of several morphological parameters is different in men and women (Supplementary material online, Table S5). In particular, aneurysm neck length is different (Wilcoxon rank-sum test $P = 0.010$, Figure 3), as is common iliac diameter (mean 17.9 mm in women vs. 21.8 mm in men, with iliac aneurysm being more common in men). Thirty-day mortality for women and men, by categories of neck length, is shown in Table 3. A higher proportion of women than men presented with juxtarenal aneurysms: the proportion of women and men presenting with neck length 0–4 mm was 24% (20/84) and 12% (40/325), respectively. Women have similar or higher mortality than men for all neck lengths $<30$ mm. None of the tests of interaction by sex in the main analyses was statistically significant.

**Reinterventions**

This analysis included 412 patients after exclusion of those patients who either did not leave the operating theatre alive ($n = 41$) or had missing re-intervention data ($n = 5$). The need for one or more re-intervention within 30 days was not strongly associated with any of the morphological parameters, although there were associations of borderline statistical significance between both maximum aortic diameter and common iliac diameter and re-intervention (Table 4): data further adjusted for the other morphological measurements and complete-case analyses were similar and are shown in Supplementary material online, Tables S6 and S7.

**Discussion**

A single morphological parameter, aneurysm neck length, appears to have a significant influence on operative mortality following surgery for ruptured abdominal aortic aneurysm, independent of known confounders. As the aneurysm neck shortens, conventional EVAR...
becomes either impossible or, if attempted, carries a very high mortality rate. The strong, but previously unconsidered, relationship between short aneurysm neck length and high mortality after open repair explains why mortality after open repair remains high: many of these patients have juxtarenal aneurysms. Open juxtarenal aneurysm repair requires cross-clamping of the aorta above the renal arteries, with inevitable compromise of the visceral circulation, especially in shocked patients. In contrast, for longer aneurysm necks (~15 mm or more), infra-renal aortic clamps can be used for open repair, with operative mortality similar to that for EVAR (~25%).

Most ruptured aneurysms are very large even in the presence of hypotension, mean diameter 8.6 cm in this series, compared with at least 2 cm smaller in most elective repair series and a diameter of 2 cm or less in healthy infra-renal aorta. As the aneurysm increases in diameter, it might be expected that aneurysmal dilatation would extend both proximally and distally to involve a greater length of the aorta and diminish the proportion of patients within liberal IFU for EVAR (just 58% in this series). Increasing aneurysm diameter also increases the risk of complications and reinterventions after elective endovascular repair.

The emerging hypothesis that, for ruptured aneurysms, neck length is more important than the type of repair, needs to be tested in a separate large set of unselected patients. No such data set containing sufficient numbers of both EVAR and open repair patients could be identified. However, further credence concerning the key role of neck length comes from this IMPROVE data set by comparison of 30-day mortality by intention to treat (by randomized strategy group) and as treated (mimicking an observational study), with and without adjustment for neck length. The odds ratios for 30-day mortality by intention to treat (unadjusted), as treated

### Table 4: Aortic morphology and the risk of re-intervention within 30 days (with multiple imputation for missing variables) for 412 patients after exclusion of patients who either did not leave the operating theatre alive (n = 41) or had missing re-intervention data (n = 5)

<table>
<thead>
<tr>
<th>Variable</th>
<th>EVAR commenced (23 patients with re-interventions, n = 167)</th>
<th>Open commenced (65 patients with re-interventions, n = 245)</th>
<th>Combined* (88 patients with re-interventions, n = 412)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>Within IFU (vs. outside)</td>
<td>0.64 (0.24, 1.67)</td>
<td>0.95 (0.50, 1.81)</td>
<td>0.85 (0.50, 1.44)</td>
</tr>
<tr>
<td>Maximum AAA diameter (per 17 mm increase)</td>
<td>0.76 (0.45, 1.29)</td>
<td>0.80 (0.58, 1.11)</td>
<td>0.79 (0.60, 1.04)</td>
</tr>
<tr>
<td>Aneurysm neck diameter at distal renal artery (per 4 mm increase)</td>
<td>1.12 (0.65, 1.92)</td>
<td>1.20 (0.82, 1.77)</td>
<td>1.16 (0.85, 1.58)</td>
</tr>
<tr>
<td>Aneurysm neck length (per 16 mm increase)</td>
<td>0.89 (0.53, 1.51)</td>
<td>1.13 (0.80, 1.61)</td>
<td>1.06 (0.79, 1.41)</td>
</tr>
<tr>
<td>Neck conicality (per 1.6% per mm change increase)</td>
<td>1.01 (0.41, 2.50)</td>
<td>0.62 (0.38, 1.01)</td>
<td>0.70 (0.45, 1.10)</td>
</tr>
<tr>
<td>Proximal aneurysm neck (α) angulation (per 20° increase)</td>
<td>0.78 (0.45, 1.34)</td>
<td>1.14 (0.86, 1.52)</td>
<td>1.04 (0.81, 1.35)</td>
</tr>
<tr>
<td>Maximum common iliac diameter (per 9 mm increase)</td>
<td>1.47 (0.94, 2.30)</td>
<td>1.16 (0.88, 1.54)</td>
<td>1.24 (0.98, 1.57)</td>
</tr>
</tbody>
</table>

All models adjusted for age, sex, Hardman Index, lowest recorded systolic blood pressure, and randomized group. Odds ratios are presented per standard deviation increase of morphological parameter.

*Also adjusted for operation commenced.

This finding may help explain why population-level observational studies and meta-analyses of observational studies report that for ruptured aneurysm operative mortality for EVAR is about half that for open repair: the long aneurysm neck patients get EVAR and the short aneurysm neck patients get open repair. This follows earlier data from the EVAR-2 trial suggesting that the patients with shorter neck lengths have a much higher risk of rupture. Randomized trials, which compare patient groups with similar aortic morphology (particularly neck length) have failed to show any difference in operative mortality between EVAR and open repair.

The association of short aneurysm neck length with high operative mortality for ruptured aneurysm repair also partly may explain the worse outcomes in women than men: aneurysm neck length was shorter in women and a higher proportion of women than men have short aneurysm necks or juxtarenal aneurysms and open repair is associated with a very high mortality (Table 3). The women in this series also had common iliac morphology suitable for the seal of a distal EVAR limb in the common iliac artery, whereas in men this often might have to extend into the external iliac artery. Taken together, this might begin to explain why women, who are morphologically suitable for EVAR, appear to benefit more than men from an endovascular first strategy.
(unadjusted), and as treated (adjusted for neck length) were 0.87 (0.58, 1.32) P = 0.525, 0.63 (0.41, 0.97) P = 0.034, and 0.78 (0.50, 1.24) P = 0.298, respectively. The unadjusted as-treated estimate, which may be biased due to patient selection, shows a 30-day mortality benefit for EVAR, but after adjustment for aneurysm neck length there is no evidence of a difference between 30-day mortality after EVAR and open repair.

Findings from our analysis of how aneurysm morphology influenced early reintervention rates were less convincing probably because patient and events numbers were fewer; not all reinterventions were aneurysm specific and endoleaks are uncommon within the first 30 days. Maximum aortic diameter and common iliac diameter may emerge as important morphological parameters in analyses of longer term aneurysm-specific reinterventions. This would be consistent with the relevance of these two parameters in predicting complications after elective aneurysm repair.\(^{17,18}\)

In this era of endovascular therapy, these findings have important implications for reducing the operative mortality from ruptured aneurysm repair. First, these patients need to be treated in centres offering excellence in both endovascular and open repair. Second, future reporting of the outcome of ruptured aneurysm repair needs to be by category of neck length, for juxtarenal vs. localized infra-renal disease, with thoracoabdominal aneurysms reported separately. Third, endovascular techniques to repair short necked and juxtarenal aneurysms, including fenestrated or branched endografts, chimneys or snorkels as adjuncts to conventional EVAR and endovascular sealing technology, need to be developed and audited, to identify whether such innovations could lower operative mortality for this group of patients. Fourth, with aneurysm screening focusing largely on men, the proportion of women undergoing repair of ruptured aneurysm may increase and endografts designed for women, to increase the proportion eligible for endovascular repair, may be necessary to save lives.

In summary, aneurysm neck length rather than type of repair (endovascular or open) predicts the early survival from ruptured abdominal aortic aneurysm repair.

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**Supplementary material**

Supplementary material is available at European Heart Journal online.

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**Appendix**

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References


