

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Powell, JT; Hinchliffe, RJ; Thompson, MM; Sweeting, MJ; Ashleigh, R; Bell, R; Gomes, M; Greenhalgh, RM; Grieve, RJ; Heatley, F; Thompson, SG; Ulug, P (2013) Observations from the IMPROVE trial concerning the clinical care of patients with ruptured abdominal aortic aneurysm. *The British journal of surgery*, 101 (3). pp. 216-224. ISSN 0007-1323 DOI: <https://doi.org/10.1002/bjs.9410>

Downloaded from: <http://researchonline.lshtm.ac.uk/1635806/>

DOI: [10.1002/bjs.9410](https://doi.org/10.1002/bjs.9410)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

Observations from the IMPROVE trial concerning the clinical care of patients with ruptured abdominal aortic aneurysm

IMPROVE trial investigators*

Correspondence to: Professor J. T. Powell, Vascular Surgery Research Group, Imperial College (Charing Cross Campus), St Dunstan's Road, London W6 8RP, UK (e-mail: j.powell@imperial.ac.uk)

Background: Single-centre series of the management of patients with ruptured abdominal aortic aneurysm (AAA) are usually too small to identify clinical factors that could improve patient outcomes.

Methods: IMPROVE is a pragmatic, multicentre randomized clinical trial in which eligible patients with a clinical diagnosis of ruptured aneurysm were allocated to a strategy of endovascular aneurysm repair (EVAR) or to open repair. The influences of time and manner of hospital presentation, fluid volume status, type of anaesthesia, type of endovascular repair and time to aneurysm repair on 30-day mortality were investigated according to a prespecified plan, for the subgroup of patients with a proven diagnosis of ruptured or symptomatic AAA. Adjustment was made for potential confounding factors.

Results: Some 558 of 613 randomized patients had a symptomatic or ruptured aneurysm: diagnostic accuracy was 91.0 per cent. Patients randomized outside routine working hours had higher operative mortality (adjusted odds ratio (OR) 1.47, 95 per cent confidence interval 1.00 to 2.17). Mortality rates after primary and secondary presentation were similar. Lowest systolic blood pressure was strongly and independently associated with 30-day mortality (51 per cent among those with pressure below 70 mmHg). Patients who received EVAR under local anaesthesia alone had greatly reduced 30-day mortality compared with those who had general anaesthesia (adjusted OR 0.27, 0.10 to 0.70).

Conclusion: These findings suggest that the outcome of ruptured AAA might be improved by wider use of local anaesthesia for EVAR and that a minimum blood pressure of 70 mmHg is too low a threshold for permissive hypotension.

*Members of the writing committee and co-authors of this article are listed under the heading Contributors

Paper accepted 22 November 2013

Published online in Wiley Online Library (www.bjs.co.uk). DOI: 10.1002/bjs.9410

Introduction

Ruptured abdominal aortic aneurysm (AAA) is fatal without emergency surgical intervention. Although patients typically present with a cluster of characteristic symptoms, including collapse and back pain, in older people the differential diagnosis can be wide. Unlike myocardial infarction or stroke, the diagnosis cannot be made in the ambulance that brings most of these patients to hospital. Therefore, many patients still present in emergency departments of hospitals that do not offer emergency AAA repair. There is evidence that operative mortality after rupture is lower in larger-volume vascular centres¹ and that, in England, operative mortality for all types of emergency surgery is lower if patients present within working hours². However, even larger-volume centres cannot offer sufficiently sized

prospective case series in which to investigate hospital and clinical factors that may be associated with better patient outcomes. To date, the largest series³ on endovascular repair reported on 473 patients treated between 1998 and 2011 from centres in two countries. The supposed benefits of endovascular aneurysm repair (EVAR) in reducing operative mortality have been questioned recently, with a randomized trial⁴ of endovascular *versus* open repair for AAA rupture (all anatomically suitable for endovascular repair) showing no difference in operative mortality between the groups.

The Immediate Management of Patients with Ruptured Aneurysm: Open *Versus* Endovascular Repair (IMPROVE) trial (ISRCTN 48334791; <http://www.controlled-trials.com>) recruited eligible patients with a clinical diagnosis of AAA rupture between late 2009 and summer

2013. This prospective cohort was used to investigate the role of factors such as hospital presentation, time to surgery, fluid replacement therapy and type of anaesthesia on the early outcomes of emergency surgery. Patients whose initial diagnosis of rupture was unsubstantiated also provided insight into the range of differential diagnoses. The aim of this paper was to investigate the details of clinical practice that could be used to benefit future patients with ruptured AAA.

Methods

The detailed trial methodology and principal outcomes have been published elsewhere (<http://www.improvetrial.org>)^{5,6}. IMPROVE is a multicentre randomized trial designed to test the hypothesis that an endovascular strategy (immediate computed tomography (CT) and emergency EVAR if anatomically feasible) provides a survival advantage for patients with ruptured AAA compared with the standard treatment of emergency open repair (including CT at the clinicians' discretion). This trial was open to eligible centres in the UK and elsewhere. The eligibility of each centre to participate in the trial was determined by their clinical credentials, which included audited volumes of elective EVAR of at least 20 cases per year, of at least 50 aortic procedures, evidence of good interdisciplinary team working, team availability for at least 66 per cent of the week, rapid access to emergency CT (target 20 min), and audited experience of EVAR for ruptured and/or acute aneurysms (minimum of 5 procedures). Each centre nominated a lead clinician with Good Clinical Practice training (usually a surgeon or interventional radiologist), an emergency care physician and an anaesthetist (particularly for the training of junior staff).

All patients with a clinical diagnosis of ruptured AAA or ruptured aortoiliac aneurysm, made by a senior trial clinician, were eligible for inclusion, unless they were moribund and intervention was considered futile. The patient could be diagnosed and considered for randomization by either a senior member of the emergency team or a senior member of the vascular team at the trial hospital. In all cases, including hospital transfers, the patient had to be considered for randomization before CT findings had been assessed for EVAR suitability by the local intervention team. There were protocols for care in the emergency department, to minimize delays in recognizing the diagnosis, limiting unnecessary investigations, maintaining hypotensive haemostasis (target systolic pressure 70–80 mmHg) with a protocol of 250-ml fluid bolus resuscitation^{7,8}, and arranging prompt attention by the vascular team, irrespective of allocated treatment.

The minimum investigations included those necessary to obtain a Hardman index score⁹, electrocardiography, measurement of haemoglobin and creatinine levels, together with testing blood for cross-matching. The choice of anaesthesia, aortic stent-graft and open surgical approach (including site of aortic clamping) was at the discretion of the intervention team. All data were collected on electronic case report forms that were held in a central trial database and copies of admission CT were collected for analysis in the core laboratory at St George's Hospital, London.

Patients were excluded if they were younger than 50 years, had undergone AAA repair previously, had rupture of an isolated internal iliac aneurysm, had an aortocaval or aortoenteric fistula, had undergone recent assessment by aortic CT (were awaiting elective EVAR), or were known to have a connective tissue disorder (such as Marfan syndrome); those in whom intervention was considered futile (patient moribund) were also excluded.

The guidelines and protocols for the trial are available on the trial website (www.imperial.ac.uk/medicine/improvetrial)⁵. Ethical approval for the participation of patients in England and Wales was received from Berkshire National Research Ethics Service Committee, in Scotland from Scotland A Research Ethics Committee and in Canada from University of Western Ontario Health Sciences Research Ethics Board. Further approval for the use of routine data for patients lost to follow-up in England and Wales was obtained from the National Information Governance Board.

The diagnosis of AAA rupture for the purposes of the trial was made from one of the following findings: review of CT in the core laboratory (if this disagreed with local opinion, two further expert opinions were sought); observation of rupture at open repair; or death certificate, with or without post-mortem examination.

In the Amsterdam Acute Aneurysm (AJAX) trial⁴ the time taken for a patient to reach the operating theatre was on average 47–74 min, so routine working hours were defined by randomization as between 08.00 and 16.00 hours from Monday to Friday; out-of-hours comprised the remainder of the week.

Apart from the prespecified trial outcomes, a number of clinically driven hypotheses were generated by the trial management committee before data analysis. These included both preoperative and intraoperative factors. Specifically, it was hypothesized that, even when adjusted for Hardman index, age, sex, randomized group and aneurysm diameter: outcomes may be better for patients randomized within routine working hours; patients transferred from other hospitals to trial centres would have lower Hardman scores and better outcomes than those arriving

primarily at the trial centre; lowest blood pressure would not be associated with 30-day survival because overadministration of fluid and/or blood products is associated with higher mortality rates; general anaesthesia for endovascular repair may be associated with higher operative mortality compared with local anaesthesia; and centres treating larger numbers of ruptured AAA have more practised and skilled teams with improved patient survival rates.

Statistical analysis

A statistical analysis plan was published on the trial websites before any data were analysed. Continuous variables were analysed by means of the *t* test and categorical variables using the χ^2 test. Overall 30-day mortality rates were calculated from the time of randomization. Logistic regression was used to make primary adjustments for randomized group, age, sex, Hardman index and maximum aortic diameter, and secondary adjustment including other variables. Multiple imputation was used as necessary in the presence of missing values. The effect of routine working hours *versus* out-of-hours randomization on the effectiveness of the EVAR strategy was assessed by including an interaction term. Three patients had lowest systolic blood pressure below the limit of detection and their values were set to 33 mmHg (5 mmHg below the lowest recorded value). As these analyses were not specified in the original trial protocol and represent observational associations, the results must be interpreted with caution. Odds ratios (ORs) are presented with 95 per cent confidence intervals (c.i.).

Results

Clinical diagnostic accuracy

Of 613 eligible patients (600 from the UK and 13 from Canada), the diagnosis of rupture was confirmed in 536 patients and a further 22 underwent same-admission repair of a symptomatic aneurysm. This provided a cohort of 558 patients eligible for emergency or urgent aneurysm repair, 283 assigned to an endovascular strategy and 275 to open repair. A total of 55 patients had a discharge diagnosis that was not aneurysm-related, although 45 of these had an asymptomatic aneurysm. Clinical diagnostic accuracy was 91.0 per cent (558 of 613) for ruptured and symptomatic aneurysm, and 87.4 per cent (536 of 613) for ruptured aneurysm only. The most common other discharge diagnosis was a gastrointestinal disorder (15 of 55) followed by other vascular and genitourinary disorders (each 9 of 55). Four patients had a ruptured thoracic aortic

Table 1 Discharge diagnoses and incidental aneurysms in 55 patients without either ruptured or symptomatic abdominal aortic aneurysm

Diagnosis	Incidental AAA (n = 45)	No AAA (n = 10)
Ruptured thoracic aneurysm	4	0
Ischaemic heart disease	4	0
Other vascular	7	2
Genitourinary	5	4
Pulmonary	5	0
Gastrointestinal	11	4
Other	9	0

AAA, abdominal aortic aneurysm.

aneurysm and four had ischaemic heart disease (*Table 1*); there was a wide range of other discharge diagnoses.

Baseline data, operative details and mortality at 30 days after randomization

These data are summarized in *Table 2* for all 558 patients with ruptured or symptomatic AAA. The 30-day mortality rate was 35.7 per cent (101 of 283) in the endovascular strategy group and 39.3 per cent (108 of 275) in the open repair group. The effect of the primary adjustment variables (age, sex, Hardman index and maximum aortic diameter) is shown in *Table 3*: the expected prognostic value of the Hardman index is observed. The effect of other variables is shown in *Table 4*.

Time of presentation

Overall, patients randomized out-of-hours had a higher mortality risk (primary adjusted OR 1.47, 95 per cent c.i. 1.00 to 2.17; $P=0.048$), although this reduced to borderline significance after further adjustment for lowest recorded systolic pressure and volume of fluids administered (*Table 4*). There was also little evidence that the efficacy of the endovascular strategy *versus* open repair was different in patients randomized out-of-hours compared with those randomized in routine working hours (test of interaction, $P=0.100$).

Patient transfers: primary *versus* secondary presentation

The characteristics of patients with direct and secondary presentation to trial centres, including Hardman index, were similar, although a greater proportion of referred patients were randomized out-of-hours (*Table 5*). There was no difference in 30-day mortality between the 221 admitted directly to the trial centre *versus* the 335

Table 2 Baseline characteristics, operative details and 30-day mortality among 558 patients with ruptured or symptomatic abdominal aortic aneurysm

	No. of missing values	30-day mortality (n = 558)
Age (years)	0	
< 65		10 of 43 (23.3)
65–74		51 of 190 (26.8)
75–84		97 of 245 (39.6)
≥ 85		51 of 80 (63.8)
Sex	0	
F		59 of 117 (50.4)
M		150 of 441 (34.0)
Hardman index (0–5)	64	
0		27 of 148 (18.2)
1		96 of 234 (41.0)
2		48 of 88 (54.5)
≥ 3		13 of 24 (54.2)
Randomized group	0	
Endovascular strategy		101 of 283 (35.7)
Open repair		108 of 275 (39.3)
Maximum aortic diameter (cm)*	69	
< 7.0		42 of 104 (40.4)
7.0–7.9		41 of 99 (41.4)
8.0–8.9		45 of 116 (38.8)
9.0–9.9		30 of 94 (31.9)
≥ 10.0		22 of 76 (28.9)
Time of randomization	0	
Out-of-hours		144 of 362 (39.8)
Routine working hours		65 of 196 (33.2)
Presentation to hospital	2	
Direct		87 of 221 (39.4)
Transferred from another hospital		122 of 335 (36.4)
Lowest recorded systolic blood pressure (mmHg)†	35	
< 70		48 of 95 (50.5)
70–83		43 of 114 (37.7)
84–98		47 of 103 (45.6)
99–119		29 of 101 (28.7)
≥ 120		27 of 110 (24.5)
Total volume of i.v. fluids given before arrival in theatre (litres)‡	256	
≤ 0.5		21 of 63 (33.3)
0.6–1.0		52 of 124 (41.9)
1.1–2.0		31 of 72 (43.1)
≥ 2.1		21 of 43 (48.8)
Time from randomization to theatre (min)§	5	
< 25		49 of 128 (38.3)
25–44		46 of 136 (33.8)
45–69		43 of 117 (36.8)
≥ 70		34 of 118 (28.8)
Anaesthetic used for EVAR¶	4	
General		28 of 83 (33.7)
Local then general		9 of 30 (30.0)
Local only		9 of 69 (13.0)
Procedure received		
EVAR	9#	46 of 186 (24.7)
Aortouni-iliac		12 of 36 (33.3)
Bifurcated		29 of 135 (21.5)
Tube		1 of 6 (16.7)

Table 2 Continued

	No. of missing values	30-day mortality (n = 558)
EVAR converted to open		4 of 4 (100)
Open repair	37#	124 of 332 (37.3)
Aortouni-iliac		1 of 4 (25.0)
Bifurcated		14 of 54 (25.9)
Tube		87 of 237 (36.7)
No operation		35 of 36 (97.2)

Values in parentheses are percentages. *Includes diameter of common iliac aneurysm when ruptured observed here. †Lowest recorded between admission and entry to operating suite. ‡Any intravenous (i.v.) infusion including blood and blood products. §Only for 504 patients with ruptured abdominal aortic aneurysm who arrived at theatre alive. ¶Only for 186 patients who had endovascular aneurysm repair (EVAR). #Graft type missing.

Table 3 Adjusted effect of main variables on 30-day mortality in 558 patients

	Odds ratio	P†
Age (per 5-year increase)*	1.20 (1.04, 1.38)	0.015
Sex		
F	1.00	
M	0.72 (0.45, 1.14)	0.162
Hardman index (per 1-unit increase)	1.62 (1.26, 2.08)	< 0.001
Randomized group		
Open repair	1.00	
Endovascular strategy	0.89 (0.62, 1.28)	0.535
Maximum aortic diameter (per 1-cm increase)	0.94 (0.83, 1.06)	0.292

Values in parentheses are 95 per cent confidence intervals (c.i.). *Not full effect of age as dichotomized age included in Hardman index. Odds ratio of age (per 5-year increase) after exclusion of Hardman index from adjustment list was 1.37 (95 per cent c.i. 1.21 to 1.56) ($P < 0.001$). †Z test.

transferred from other hospitals (adjusted OR 0.76, 0.52 to 1.12).

Preoperative variables: fluids, blood pressure and time from randomization to operating suite

The volume of fluids administered before arrival in the operating theatre was recorded in only 302 patients. The relationship to lowest in-hospital preoperative measured systolic blood pressure is shown in *Fig. 1* for 296 patients who had both variables recorded. Patients were divided into quintiles according to the lowest recorded blood pressure before arrival in the operating theatre. There appeared to be a trend towards increasing fluids given with decreasing lowest recorded blood pressure; the effect of fluids administered on 30-day mortality was not significant in the multivariable adjusted model (*Table 4*). In contrast, the lowest systolic blood pressure recorded in hospital before operation (distribution in *Fig. 2a*) was

Table 4 Odds ratios for 30-day mortality with primary adjustment for age, sex, Hardman index, randomized group and maximum aneurysm diameter

	No. of patients*	Unadjusted odds ratio	Primary adjusted odds ratio¶	Secondary adjusted analysis#	
				Odds ratio	P††
Time of randomization	558				
Routine working hours		1.00	1.00	1.00	
Out-of-hours		1.33	1.47	1.40 (0.94, 2.08)	0.096
Presentation to hospital	556				
Primary		1.00	1.00	1.00	
Secondary		0.88	0.84	0.76 (0.52, 1.12)	0.170
Lowest recorded systolic blood pressure (per 10-mmHg increase)	558	0.87	0.87	0.88 (0.82, 0.94)	< 0.001
Total volume of i.v. fluids given before arrival in theatre (per 1-litre increase)	558	1.24	1.19	1.18 (0.86, 1.60)	0.289
Time from randomization to theatre (per quartile increase)†	499				
		0.89	0.89	0.93 (0.77, 1.11)	0.415
Anaesthetic used‡	182			<i>n</i> = 175**	
General		1.00	1.00	1.00	
Local then general		0.84	0.74	0.74 (0.25, 2.22)	0.596
Local only		0.29	0.25	0.27 (0.10, 0.70)	0.007
Graft type used‡	177			<i>n</i> = 175**	
Bifurcated		1.00	1.00	1.00	
Aortouni-iliac		1.83	1.79	1.46 (0.54, 3.94)	0.457
Tube		0.73	0.53	0.78 (0.07, 9.30)	0.843
Rate of patients with ruptured AAA presenting to centre (per patient per month increase)§	543	0.96	0.99	0.93 (0.65, 1.32)	0.674
Percentage of included patients (per 25 per cent increase)§	544	1.13	1.07	1.06 (0.86, 1.31)	0.591

Values in parentheses are 95 per cent confidence intervals. *Number used in analysis (multiply imputed data used for lowest recorded systolic blood pressure and volume of intravenous (i.v.) fluids given). †Includes only patients with ruptured abdominal aortic aneurysm (AAA) who reached the operating theatre alive; quartiles are shown in Table 2. ‡Only patients who had endovascular aneurysm repair (EVAR). §Excludes four centres with incomplete information on number not randomized. ¶Adjusted for core variables: age, sex, Hardman index, randomized group and maximum aortic diameter. #Adjusted for core variables, time of randomization, lowest recorded systolic blood pressure and total volume of i.v. fluids administered; **in patients who received EVAR, models were further adjusted for anaesthetic used and graft type. ††Z test.

Table 5 Comparison of baseline data for primary and secondary presentation at participating hospitals

	No. of missing values	Mode of arrival		P†
		Direct presentation (<i>n</i> = 221)	Transferred from another hospital (<i>n</i> = 335)	
Mean age (years)*	0	76.5(6.9)	76.5(7.9)	0.928
Sex ratio (M:F)	0	167:54	272:63	0.111‡
Hardman index	63			0.521‡
0		63 (32.0)	84 (28.4)	
1		96 (48.7)	138 (46.6)	
2		28 (14.2)	60 (20.3)	
≥ 3		10 (5.1)	14 (4.7)	
Lowest recorded systolic blood pressure before transfer to CT or theatre (mmHg)*	35	96.1(33.2)	93.6(27.4)	0.354
Maximum aortic diameter (cm)*	69	8.3(1.7)	8.4(1.6)	0.878
Randomized out-of-hours	0	127 (57.5)	233 (69.6)	0.004‡

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). CT, computed tomography. †t test, except ‡ χ^2 test.

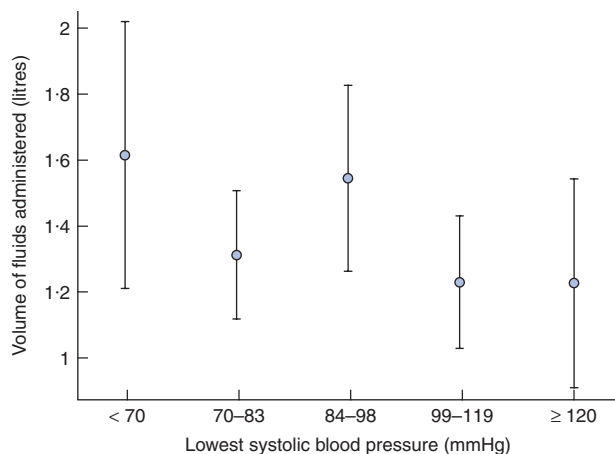


Fig. 1 Relationship between mean volume of fluids administered before arrival in the operating suite and lowest recorded systolic blood pressure, by quintiles of blood pressure, in 296 patients. Error bars represent 95 per cent confidence intervals

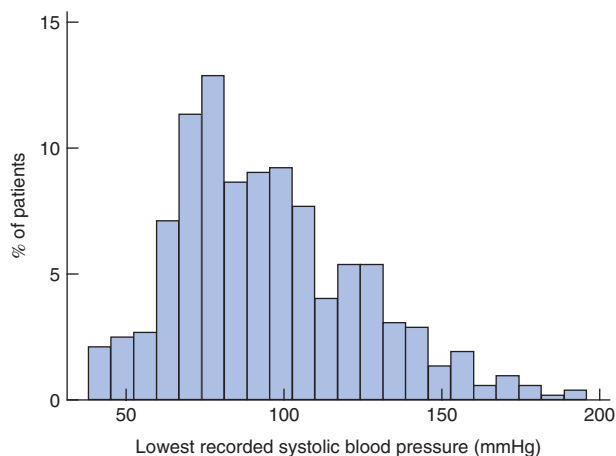
significantly associated with 30-day mortality, without any evidence of non-linearity (*Fig. 2b*). This association was independent of the volume of intravenous fluids administered: adjusted OR per 10-mmHg increase in blood pressure 0.88 (0.82 to 0.94). The 30-day mortality rate among patients with lowest systolic blood pressure above and below the threshold value of 70 mmHg was 34.1 and 51 per cent respectively. For 536 patients with confirmed rupture, the time from randomization to the operating suite was not associated with 30-day mortality ($P = 0.415$).

Operative variables

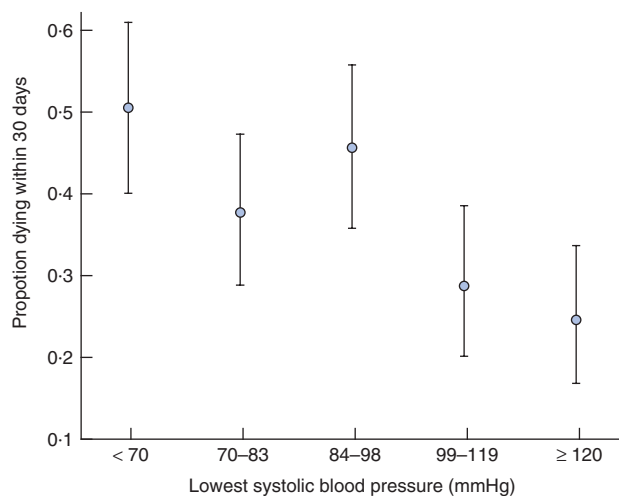
Overall, among the 186 patients who underwent EVAR, there appeared to be a substantially lower 30-day mortality associated with procedures conducted under local anaesthesia only. After adjustment, local anaesthesia was associated with a fourfold reduction in 30-day mortality (adjusted OR 0.27, 0.10 to 0.70; $P = 0.007$). Local anaesthesia was more commonly used with bifurcated graft configurations, whereas general anaesthesia was more frequently employed with aortouni-iliac configurations (*Table S1*, supporting information). Therefore, after adjustment for anaesthetic use, graft configuration was not associated with 30-day mortality (*Table 4*).

Centre volume and recruitment to the trial

The comprehensive logging of 652 non-recruited patients with ruptured aneurysm permitted assessment of the effect of centre volume and percentage recruitment to the trial



a Lowest systolic blood pressure



b Mortality in relation to blood pressure

Fig. 2 a Lowest recorded systolic blood pressures in 520 patients (three further patients had unrecordable blood pressure) and **b** effect of systolic blood pressure (lowest recorded) on probability of 30-day mortality. Error bars represent 95 per cent confidence intervals

on 30-day mortality. There was no evidence that 30-day mortality was influenced by either centre volume or the percentage of patients with ruptured aneurysm who were recruited (*Table 4*).

Discussion

These data from the IMPROVE trial have identified a number of areas of clinical practice that might benefit the everyday management of patients with ruptured aneurysm. The key clinical issues that might immediately affect patient survival concern the management of

preoperative blood pressure and the choice of anaesthesia for endovascular repair, in addition to the choice of endovascular reconstruction⁷.

Patients were entered into the trial on the basis of a clinical diagnosis of ruptured AAA made by a senior clinician. The trial therefore offered a unique opportunity to assess the accuracy of the in-hospital clinical diagnosis of ruptured AAA. Approximately one in ten patients with a clinically suspected ruptured AAA was found to have alternative pathology at either laparotomy or cross-sectional imaging, explaining their emergency presentation, even though the majority of these had an incidental AAA. Given that patients were diagnosed by an experienced clinician (and that some may have undergone ultrasound imaging or CT in another hospital), the diagnostic accuracy is likely to be significantly worse in everyday clinical practice. Therefore, it is reasonable to suggest that patients should not undergo attempted repair of a clinically suspected ruptured AAA without confirmatory imaging studies (usually CT). Interestingly, even 90 per cent of the patients randomized to open repair underwent preoperative CT⁶, suggesting that cross-sectional imaging is now part of routine clinical practice.

Although some patients require urgent treatment owing to haemodynamic decompensation (and pathways should be in place to facilitate rapid transfer), IMPROVE trial data suggest that, for most patients, there is sufficient time to permit confirmatory CT and appropriate further investigations⁶. Data from the present trial demonstrated that patients randomized to the endovascular strategy group had on average a delay of an additional 10 min between randomization and transfer to the operating room. This interval, although much shorter than the 30-min delay observed in the AJAX trial⁴, could be clinically significant as a number of patients due to receive endovascular repair eventually required open repair because of physiological deterioration. As most patients in the trial, irrespective of randomized group, underwent CT, the delay was most likely related to the challenging logistics of providing a 24/7 endovascular service. The IMPROVE trial results suggest that formalizing the patient pathway for EVAR might reduce the delay to definitive therapy.

Patients with ruptured AAA are increasingly being managed in large centralized vascular units. Consequently many patients with a clinical diagnosis of rupture are transferred from smaller hospitals. There was no evidence of inferior outcomes for patients transferred to the trial centres compared with those who presented directly, even after adjustment for Hardman index. This may be subject to confounding if only the most haemodynamically stable patients were accepted for transfer and there was

an increased percentage of transferred patients who were recruited out-of-hours. Such confounders underscore the need to use universally accepted criteria for transfer, and to develop local pathways to ensure that appropriate patients reach vascular centres rapidly^{10,11}.

Systolic blood pressure was found to be a useful and simple predictor of 30-day outcome. The Hardman index is more complicated, comprising five factors (not including systolic blood pressure) that reliably predict outcome; none of the five factors assessed shock directly. Other scoring systems, such as the Glasgow Aneurysm Score¹², include shock, but these are really designed for audit purposes rather than as prospective prognostic tools.

Recent publications^{3,7,13,14} on the management of ruptured AAA have suggested that intravenous fluid should be restricted (permissive hypotension, target systolic pressure 70–80 mmHg) to prevent further bleeding and optimize outcomes. In the present trial, the 30-day mortality rate was 51 per cent among patients with a lowest recorded systolic pressure of less than 70 mmHg and 34.1 per cent in those with a blood pressure above 70 mmHg. Systolic blood pressure was directly related to outcome in a linear fashion, with each 10-mmHg increase translating to a 13 per cent relative improvement in odds of survival. These data cannot give definitive guidance on the optimal systolic blood pressure in patients with ruptured AAA during the preoperative phase, but may suggest that the previously recommended threshold of 70 mmHg is too low, particularly in the older patient with other cardiovascular diseases and high cardiovascular resistance.

The IMPROVE trial centres were high-volume vascular centres and were credentialled to ensure that there was good team working and pathways of care for both open and endovascular surgery. There was no evidence of a significant difference in outcomes between the trial centres according to their recruitment rate.

The type of anaesthesia used for EVAR appeared to be important, with local anaesthesia associated with a significant fourfold survival benefit compared with general anaesthesia, even when adjusted for age, sex, Hardman index and other factors. Clearly this relationship exists only for EVAR but the potential benefit appears considerable. There are no other good clinical trial data to support local anaesthesia as the method of choice for endovascular repair of ruptured AAA, but authors with a large experience in this field advocate the use of local anaesthesia^{3,7}. The magnitude of the survival benefit in the IMPROVE trial data suggests that local anaesthesia should become first choice. General anaesthesia has significant haemodynamic consequences in patients with ruptured AAA and this may explain some of the effect.

Another important issue for clinical practice is whether aortouni-iliac or bifurcated endografts are better for treatment of ruptured AAA⁶. A *post hoc* analysis suggested that the 30-day mortality rate was higher in those who had aortouni-iliac endografts than in those who had bifurcated endografts: 33 per cent (12 of 36) *versus* 21.5 per cent (29 of 135) respectively. After adjustment, the higher mortality risk associated with aortouni-iliac endografts was not statistically significant (OR 1.46, 0.54 to 3.94; $P = 0.457$). This higher mortality rate from use of aortouni-iliac grafts has been confirmed by experienced single centres and a systematic review^{7,13,14}.

These analyses have a number of limitations. Foremost, they are observational and all the results need to be interpreted with care. Although the data have been adjusted for available factors, the analyses could still be confounded by patient selection. However, it is reassuring that the main findings, for example those for blood pressure and anaesthesia, are robust to different levels of adjustment for confounders (*Table 4*). The trial was pragmatic and, in an emergency setting, non-essential data such as fluid volume administration and adjunct clinical treatments were at the discretion of the local centre. Therefore, there are no additional details concerning type of anaesthesia used.

These analyses have raised a number of provocative issues, but all the results need to be interpreted with care. First, they suggest that CT should be recommended for all patients with suspected aneurysm rupture; only one patient in the IMPROVE trial died before completion of CT. Second, systolic blood pressure is an important prognostic marker for patients with ruptured AAA, and fluid replacement therapy is not an indicator of outcomes when data are adjusted for blood pressure. The lower the blood pressure, the higher the mortality risk; these results question whether the 70-mmHg threshold used for injured patients⁸ and the 70–80-mmHg threshold recommended for hypotensive haemostasis for ruptured aneurysm⁷ really should be used, particularly in an elderly cohort with aneurysm rupture. Third, it may be best to conduct endovascular repair under local anaesthesia wherever possible, although best-practice protocols remain to be defined. The benefits of local anaesthesia and the worse results of open repair out-of-hours suggest the need for more specialist anaesthesia services for patients with aneurysm rupture. Finally, a skilled multidisciplinary team to conduct emergency vascular surgery should be available throughout the week, to optimize results out-of-hours for ruptured aneurysms and other vascular emergencies such as acute limb ischaemia and trauma.

Contributors

Members of the writing committee and co-authors of this article are: J. T. Powell (Chair; Vascular Surgery Research Group, Imperial College, London, UK), R. J. Hinchliffe, M. M. Thompson (St George's Vascular Institute, St George's Hospital, London, UK), M. J. Sweeting (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK), R. Ashleigh (Department of Radiology, University Hospitals of South Manchester, Manchester, UK), R. Bell (Department of Vascular Surgery, Guy's and St Thomas's Hospital, London, UK), M. Gomes (Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK), R. M. Greenhalgh (Vascular Surgery Research Group, Imperial College, London, UK), R. J. Grieve (Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, UK), F. Heatley (Vascular Surgery Research Group, Imperial College, London, UK), S. G. Thompson (Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK) and P. Ulug (Vascular Surgery Research Group, Imperial College, London, UK).

Other contributors to the IMPROVE trial have been listed previously⁶.

Acknowledgements

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 Institutes of Health Research, the National Health Service or the Department of Health.

References

- Holt PJ, Poloniecki JD, Gerrard D, Loftus IM, Thompson MM. Meta-analysis and systematic review of the relationship between volume and outcome in abdominal aortic aneurysm surgery. *Br J Surg* 2007; **94**: 395–403.
- Symons NR, Moorthy K, Almoudaris AM, Bottle A, Aylin P, Vincent CA *et al.* Mortality in high-risk emergency general surgical admissions. *Br J Surg* 2013; **100**: 1318–1325.
- Mayer D, Aeschbacher S, Pfammatter T, Veith FJ, Norgren L, Magnuson A *et al.* Complete replacement of open repair for ruptured abdominal aortic aneurysms by endovascular aneurysm repair: a two-center 14-year experience. *Ann Surg* 2012; **256**: 688–695.
- Reimerink JJ, Hoornweg LL, Vahl AC, Wisselink W, van den Broek TA, Legemate DA *et al.*; Amsterdam Acute

- Aneurysm Trial Collaborators. Endovascular repair *versus* open repair of ruptured abdominal aortic aneurysms: a multicenter randomized controlled trial. *Ann Surg* 2013; **258**: 248–256.
- 5 Imperial College London. *Immediate Management of Patients with Ruptured aneurysm: Open Versus Endovascular Repair (IMPROVE)*. <http://www.imperial.ac.uk/medicine/improvetrial> [accessed 1 October 2013].
 - 6 IMPROVE trial investigators. Endovascular or open repair for ruptured abdominal aortic aneurysm: 30-day outcomes from the IMPROVE trial. *BMJ* 2014; **348**: f7661.
 - 7 Mayer D, Pfammatter T, Rancic Z, Hechelhammer L, Wilhelm M, Veith FJ *et al.* 10 years of emergency endovascular aneurysm repair for ruptured abdominal aortoiliac aneurysms: lessons learned. *Ann Surg* 2009; **249**: 510–515.
 - 8 Joint Royal Colleges Ambulance Liaison Committee. *Ambulance Service Clinical Practice Guidelines*; 2006. <http://www.jrcalc.org.uk/guidelines.html> [accessed 1 September 2013].
 - 9 Hardman DT, Fisher CM, Patel MI, Neale M, Chambers J, Lane R *et al.* Ruptured abdominal aortic aneurysms: who should be offered surgery? *J Vasc Surg* 1996; **23**: 123–129.
 - 10 Hinchliffe RJ, Ribbons T, Ulug P, Powell JT. Transfer of patients with ruptured abdominal aortic aneurysm from general hospitals to specialist vascular centres: results of a Delphi consensus study. *Emerg Med J* 2013; **30**: 483–486.
 - 11 College of Emergency Medicine. College Guidelines. <http://www.collemergencymed.ac.uk/Shop-Floor/Clinical%20Guidelines/> [accessed 1 September 2013].
 - 12 Samy AK, Murray G, MacBain G. Glasgow aneurysm score. *Cardiovasc Surg* 1994; **2**: 41–44.
 - 13 Dick F, Erdoes G, Opfermann P, Eberle B, Schmidli J, von Allmen RS. Delayed volume resuscitation during initial management of ruptured abdominal aortic aneurysm. *J Vasc Surg* 2013; **57**: 943–950.
 - 14 Karkos CD, Sutton AJ, Bown MJ, Sayers RD. A meta-analysis and metaregression analysis of factors influencing mortality after endovascular repair of ruptured abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg* 2011; **42**: 775–786.

Supporting information

Additional supporting information may be found in the online version of this article:

Table S1 Comparison of baseline data for patients undergoing endovascular repair with either general anaesthetic or local only (Word document)

Editor's commentary

AJAX and IMPROVE are indeed landmark trials that will help define optimal management of ruptured AAA for a generation. The authors and their funders are to be congratulated. And yet, both are negative trials: the primary endpoint (death at 30 days) was not better for the new treatment (EVAR) over standard management with open surgical repair (see Scientific Surgery for primary sources). Arguably, Collin and Murie were not so wrong when they called EVAR a failed experiment (*Br J Surg* 2001; **88**: 1281–1282), though the same challenge could be aimed at laparoscopic and, more recently, robotic abdominal surgery. But the results should be seen in the context of modern surgery, with progress from open to minimally invasive treatments, as expected by patients, for other quality of life benefits. The big question is a process one. For countries that do not have a coherent plan to deal with emergency AAA, should you invest in a process of vascular centralization to deliver an emergency EVAR service, or do you invest in population screening for AAA to reduce the rates of AAA rupture?

J. J. Earnshaw
Editor, *BJS*