

## A restrictive versus liberal transfusion strategy to prevent myocardial injury in patients undergoing surgery for fractured neck of femur: a feasibility randomised trial (RESULT-NOF)

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### Abstract

**Background:** The optimum transfusion strategy in patients with fractured neck of femur is uncertain, particularly if there is coexisting cardiovascular disease.

**Methods:** We conducted a prospective, single-centre, randomised feasibility trial of two transfusion strategies. We randomly assigned patients undergoing surgery for fractured neck of femur to a restrictive (haemoglobin, 70–90 g L<sup>-1</sup>) or liberal (haemoglobin, 90–110 g L<sup>-1</sup>) transfusion strategy throughout their hospitalisation. Feasibility outcomes included: enrolment rate, protocol compliance, difference in haemoglobin, and blood exposure. The primary clinical outcome was myocardial injury using troponin estimations. Secondary outcomes included major adverse cardiac events, post-operative complications, duration of hospitalisation, mortality, and quality of life.

**Results:** We enrolled 200 (22%) of 907 eligible patients, and 62 (31%) showed decreased haemoglobin (to 90 g L<sup>-1</sup> or less) and were thus exposed to the intervention. The overall protocol compliance was 81% in the liberal group and 64% in the restrictive group. Haemoglobin concentrations were similar preoperatively and at postoperative day 1 but lower in the restrictive group on day 2 (mean difference [MD], 7.0 g L<sup>-1</sup>; 95% confidence interval [CI], 1.6–12.4). Lowest haemoglobin within 30 days/before discharge was lower in the restrictive group (MD, 5.3 g L<sup>-1</sup>; 95% CI, 1.7–9.0). Overall, 58% of patients in the restrictive group received no transfusion compared with 4% in the liberal group (difference in proportion, 54.5%; 95% CI, 36.8–72.2). The proportion with the primary clinical outcome was 14/26 (54%, liberal) vs 24/34 (71%, restrictive), and the difference in proportion was –16.7% (95% CI, –41.3 to 7.8; P=0.18).

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**Conclusion:** A clinical trial of two transfusion strategies in hip fracture with a clinically relevant cardiac outcome is feasible.

**Clinical trial registration:** NCT03407573.

**Keywords:** anaemia; feasibility; hip fracture; myocardial injury; randomised controlled trial; surgery; transfusion

### Editor's key points

- Restrictive transfusion strategies have been shown to be equivalent or non-inferior in hospitalised patients.
- Feasibility trials have an important role in informing the viability and design of future definitive large trials.
- This study addresses the important features required to test the benefits and risks of a restrictive or liberal transfusion strategy in hip fracture surgery, and concludes that a large RCT can be successfully undertaken.

Epidemiological studies suggest that patient co-morbidities, including anaemia, are associated with increased rates of complications and death after surgery.<sup>1–3</sup> Anaemia may either reflect the severity of chronic disease or be the result of blood loss from injury or surgery, and may not have a causative relationship with poor outcomes. Patients commonly receive red cell transfusions to increase haemoglobin concentration with the belief that this may increase oxygen delivery to the tissues, particularly to the myocardium and improve clinical outcomes. Blood transfusion is associated with risks including fluid overload, immunosuppression, and consequent risks of infectious complications and cancer recurrence.<sup>4–8</sup> Donated blood is also a finite and costly resource.

Evidence generally supports restrictive transfusion strategies (i.e. a transfusion trigger of 70 g L<sup>-1</sup>) in stable hospitalised adult patients,<sup>9</sup> but the optimum transfusion threshold for surgical patients remains uncertain, particularly if there is coexisting cardiovascular disease (CVD).<sup>10</sup> The need for more evidence is highlighted in recommendations from the National Institute of Clinical Excellence (NICE) and the Association of Anaesthetists. Both of these guidelines recommend a restrictive transfusion practice, using 70 g L<sup>-1</sup> as the default threshold, but recommend caution and highlight that higher thresholds might be considered for patients with CVD. NICE recommended further research in this area was a priority.<sup>11</sup>

People undergoing surgery for fractured neck of femur (NOF) are often frail and older with multiple comorbidities,<sup>12</sup> including perioperative anaemia from fracture or surgery-induced bleeding.<sup>3,13,14</sup> There is a high prevalence of pre-existing CVD in this population,<sup>15,16</sup> and red cell transfusions are typically prescribed to prevent cardiac complications, improve mobilisation, and reduce length of hospitalisation.<sup>17–20</sup> Concerns exist that current practice guidelines may be inadequate in this setting. Findings of a recent Cochrane review of transfusion strategy in patients with hip fracture did not find evidence to support a liberal transfusion strategy but conceded that the overall quality of the evidence was low.<sup>21</sup> The largest study of transfusion strategy in this population used higher liberal and restrictive targets which were less relevant to current practice.<sup>22</sup> A recent UK survey suggested wide variation in perioperative transfusion practice among anaesthetists, surgeons, and perioperative

physicians<sup>23</sup> and a need for further studies to identify the optimum transfusion threshold in the perioperative period, particularly if there is coexisting CVD. The latest generation of cardiac troponin assays can detect myocardial necrosis with a high degree of precision and when measured after surgery the presence of necrosis correlates strongly with adverse outcomes.<sup>24</sup> Isolated postoperative elevations in troponin without symptoms or other clinical signs have similar associations with mortality as myocardial infarction (MI), which fulfils universal diagnostic criteria.

We conducted a prospective feasibility study of two red cell transfusion strategies in people admitted to hospital after a fractured NOF. The study aims were twofold:

1. To investigate the feasibility, in terms of recruitment, protocol compliance, and red cell transfusion, of conducting a randomised trial of liberal vs restrictive transfusion in patients with fractured NOF
2. To investigate the effect of transfusion strategy on the clinical outcomes of myocardial injury, other postoperative complications, mortality, duration of hospitalisation, and quality of life

## Methods

### Trial design and oversight

Restrictive vs Liberal Transfusion Strategy on Cardiac Patients Undergoing Surgery for Fractured NOF (RESULT-NOF) was a feasibility study of an open randomised trial of two transfusion strategies in people undergoing surgery for fractured NOF, conducted in a single NHS hospital in the UK. The study protocol was approved by a Scotland A Research Ethics Committee (Reference: 17/SS/0053) and registered with ClinicalTrials.gov (NCT03407573). Written consent was obtained from all study participants or, if they lacked capacity, their nearest relative or welfare attorney, in accordance with Scots Law. NHS Lothian and the University of Edinburgh acted as co-sponsors of the study ([www.accord.scot](http://www.accord.scot)). An independent data and safety committee met three times during the course of the study to review study outcomes.

### Participants

People aged 50 yr or older, within 48 h of admission to the Royal Infirmary of Edinburgh (RIE) with a fractured NOF, and who had not yet undergone surgery met inclusion criteria for enrolment to this study. Those who were receiving palliative care, who had received a blood transfusion before recruitment in same hospital admission, or who declined to give consent were excluded. Potential participants were identified directly from the orthopaedic wards, via daily screening of theatre lists, or transfers from the RIE Emergency Department (ED).

## Randomisation

Participants were randomly assigned 1:1 to either a restrictive or liberal transfusion strategy for the duration of their hospital stay or 30 days, whichever was sooner. A secure electronic internet-based randomisation system was used with a dynamically allocated block list (block sizes 4 and 6). The patient's clinical team and the hospital blood transfusion laboratory were informed of the patient's study status by the study team, having been concealed until that point, and that they were to be transfused according to the study protocol.

## Study procedure

Patients were enrolled preoperatively. A restrictive strategy was defined as a haemoglobin transfusion trigger of  $70 \text{ g L}^{-1}$  or less and a target haemoglobin range of  $70\text{--}90 \text{ g L}^{-1}$ . This was the target haemoglobin range recommended by UK guidelines. A liberal strategy was defined as a haemoglobin transfusion trigger of  $90 \text{ g L}^{-1}$  or less and a target haemoglobin range of  $90\text{--}110 \text{ g L}^{-1}$ . It was recommended that participants requiring transfusion should be transfused 1 unit of red blood cells and the haemoglobin rechecked until within the target range (Supplementary material). Physicians were able to transfuse participants in emergency or life-threatening situations (e.g. major haemorrhage). In these situations, the protocol was temporarily suspended until the situation was resolved and recorded as a protocol deviation.

At enrolment we collected baseline demographic data: age, sex, ethnicity, cardiovascular risk factors, pre-admission cardiac medications, Charlson comorbidity index, and ASA Physiological Status (ASA) classification. Cardiac risk factors were defined prospectively as a pre-existing diagnosis of the following: ischaemic heart disease, peripheral vascular disease, cerebrovascular disease, age older than 65 yr, diabetes, hypertension, or other cardiac disease. Measurement of baseline haemoglobin and plasma cardiac troponin I (cTnI) concentrations (ARCHITECT<sub>STAT</sub>; Abbott Laboratories, Abbott Park, IL, USA), and a 12-lead ECG were also performed.

Type of surgery, anaesthesia, surgical duration, and postoperative destination were recorded upon completion of surgery. Haemoglobin concentration measurement was obtained immediately after surgery in the recovery room using the HemoCue® Haemoglobin 201<sub>+</sub> system (HemoCue AB, Angelholm, Sweden). Further laboratory haemoglobin sampling was performed on postoperative days (POD) 1 and 2, then thereafter at the discretion of the clinical team. A further ECG was performed on POD 3. Blood samples were drawn by venepuncture into a vacuum tube and subsequently analysed in the central NHS laboratory.

The study cohort of interest was those participants whose haemoglobin decreased below a threshold plasma haemoglobin concentration of  $90 \text{ g L}^{-1}$  or less during their hospital admission as only these participants were exposed to the study intervention. From the time that an enrolled patient's haemoglobin decreased to  $90 \text{ g L}^{-1}$  or less, we measured troponin and haemoglobin on the first, second, and fifth days thereafter. Blood sampling and full outcome data were only collected in these participants; however, basic demographic and outcome data were collected for all participants enrolled. Serum troponin measurements obtained solely for the purpose of this research study were suppressed from clinical staff. A cardiology and an anaesthesia specialist trainee interpreted

all ECGs after recruitment was completed. Dynamic ischaemic ECG changes were considered either as new or progressive ECG changes consistent with ischaemia between admission and the third postoperative day.

Number and volume of blood transfusion, complications, and death within 30 days after surgery or before acute hospital discharge (whichever was sooner) were recorded. Participants were also contacted at 60 days after surgery to assess vital status and quality of life using the EuroQoL-5D (EQ-5D) tool.

All data were entered directly onto a secure, trial specific database using REDCap: Research Electronic Data Capture (Vanderbilt University, Nashville, TN, USA). This is a secure, fully audited password-protected platform, hosted on University of Edinburgh servers. All identifiable data were removed before extraction for analysis.

## Blinding

The clinical and research teams were not blinded to the intervention but were blinded to the primary outcome. The study statistician analysed data blinded from group allocation. The adjudicators who assessed ECGs and other data used to assess cardiovascular outcomes were also blinded.

## Outcomes

### Feasibility outcomes

The feasibility outcomes were the proportion of eligible patients recruited; protocol compliance; haemoglobin concentration distribution within 3 and 30 days of surgery (including nadir haemoglobin); red blood cell use within 5 days of anaemia, and within 30 days of surgery or hospital discharge. Three protocol deviations were prospectively defined as transfusion of red blood cells above the predefined transfusion trigger, transfusion without checking haemoglobin level and planned surgery postponed or not performed. All feasibility outcomes were measured between groups.

### Clinical outcomes

The primary outcome was postoperative myocardial injury defined as any serum cTnI concentration above the upper reference limit (URL) during the study period, measured using the ARCHITECT<sub>STAT</sub> high-sensitivity troponin I assay (Abbott Laboratories). The assay has a limit of detection of  $1.2 \text{ ng L}^{-1}$  and an interassay coefficient of variation of  $<10\%$  at  $4.7 \text{ ng L}^{-1}$ . The mean (standard deviation, sd) concentration for a healthy reference population is  $1.6 (3.1) \text{ ng L}^{-1}$ , and the 99th percentile URL for the whole population is 16 and  $34 \text{ ng L}^{-1}$  for women and men, respectively.<sup>25,26</sup>

Secondary outcomes were mortality at 30 and 60 days, acute kidney injury (Kidney Disease Improving Global Outcomes [KDIGO] definition), delirium, MI (universal definition), major adverse cardiac events (MACE), and postoperative complications. Definitions for postoperative complications are supplied in the Supplementary material. Other measured outcomes included: peak troponin concentration, area under a troponin-time curve, nadir haemoglobin within 30 days (or hospital discharge), hospital length of stay, discharge destination, hospital readmission, and EQ-5D at 60 days.

### Statistical analysis

Although no formal power calculation was made, it was estimated that 600 patients would be eligible for recruitment annually based on admission statistics to the RIE. Assuming a 50% refusal rate, a realistic target of 200 participants over a 1 yr period was established.

The statistical analysis was performed based on a pre-specified analysis plan. Continuous data were presented as mean (95% confidence interval [CI]), or median (inter-quartile range [IQR]) if non-normally distributed. Binary data were presented as frequency (%). Feasibility outcomes were reported as a difference between groups with corresponding 95% CI. Primary and secondary clinical outcomes were compared using a  $\chi^2$  or Fisher's exact test as appropriate and presented as a difference in proportions with corresponding 95% CIs. All analyses were based on a modified intention-to-treat (ITT) principle: we included all participants randomised into the RESULT-NOF study who become anaemic (haemoglobin, 90 g

L<sup>-1</sup> or less) during their treatment (and thus were exposed to the study intervention) and for whom outcome data were available. To assess the impact of missing follow-up cTnI measurements on the primary outcome, a sensitivity analysis was performed in which those who did not have the primary outcome but had at least one follow-up cTnI measurement missing were classified as having myocardial injury. Finally, an exploratory analysis was undertaken where the universal definitions applied to diagnose type 2 MI or myocardial injury, including an increase and decrease in troponin were applied.<sup>27</sup> All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

### Results

The study enrolment period ran from November 1, 2017 until January 31, 2019 when the 200th participant was recruited. The final patient follow-up was completed on April 31, 2019.

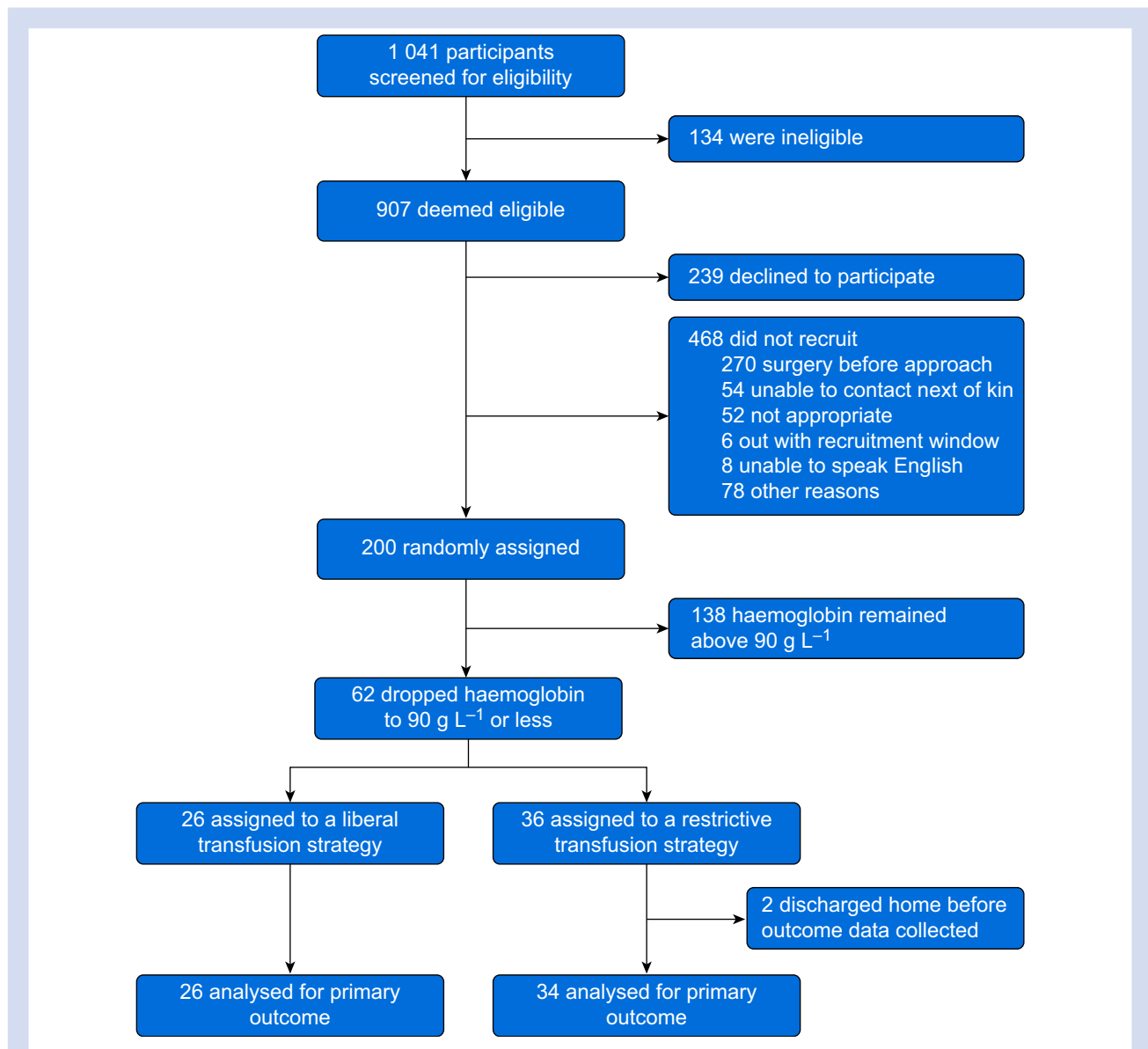


Fig. 1. Study recruitment flowchart.

## Participants

A flowchart summarising patient recruitment is outlined in Figure 1. A total of 1041 patients were screened, of whom 907 were eligible for recruitment and 200 (22%) participants were enrolled in the study. Sixty-two (31%) of 200 participants had a reduction in plasma haemoglobin concentration to 90 g L<sup>-1</sup> or less and were therefore exposed to the study intervention: 26 allocated to liberal and 36 to restrictive groups. All participants underwent surgery, reflecting current practice. Baseline patient characteristics are reported in Table 1. There was a higher prevalence of cardiovascular risk factors in participants who became anaemic compared with those who did not.

## Outcomes

### Feasibility outcomes

Feasibility outcomes are reported in Table 2. From 907 patients eligible for recruitment, 200 (22%) were recruited. The overall protocol compliance was 81% in the liberal group and 64% in the restrictive group. There was greater compliance to transfusion of red blood cells within the predefined trigger in the liberal compared with the restrictive group (difference, 25.6%; 95% CI, 7.1–44.1). Of the 18 participants transfused off-protocol, five were transfused in response to excessive bleeding in theatre and one was transfused in error after blood was prescribed for the wrong patient. There were minimal differences in haemoglobin concentration between liberal and restrictive groups preoperatively and at POD 1 with a larger difference at POD 2 (mean difference, 7.0 g L<sup>-1</sup>; 95% CI, 1.6–12.4; Table 2, Fig 2, and Supplementary Fig. S2). Lowest haemoglobin was lower in the restrictive group within 3 days of surgery (mean difference, 3.1 g L<sup>-1</sup>; 95% CI, -1.8 to 8.0) and within 30 days of surgery/hospital discharge (mean difference, 5.3; g L<sup>-1</sup>; 95% CI, 1.7–9.0). There was a difference in blood use between groups; 58% of participants in the restrictive group received no transfusion within 30 days of surgery/hospital discharge compared with only 4% in the liberal group (difference in proportions, 54.5%; 95% CI, 36.8–72.2).

### Primary outcome

Patient outcomes are summarised in Table 3. There was no statistically significant difference in the proportion of participants with the primary clinical outcome (54% in the liberal group vs 71% in the restrictive group; mean difference, -16.7%; 95% CI, -41.3–7.8;  $P=0.18$ ), or in the sensitivity analysis accounting for missing data. In the exploratory analysis using the universal definition of MI, the overall incidence of cardiac injury was smaller but with a similar pattern observed between groups (31% liberal vs 53% restrictive; mean difference, -22.2%; 95% CI, -46.6 to 2.2;  $P=0.086$ ) (Table 3).

In those compliant with the protocol, 12/21 (57%) had the primary clinical outcome in the restrictive arm and 12/21 (57%) in the liberal arm. Difference in proportions was 0.0% (95% CI, -29.9 to 29.9). We undertook a non-prespecified, *post hoc*, per-protocol analysis which did not demonstrate any difference in the primary outcome ( $P>0.99$ ).

### Secondary outcomes

The rate of ECG abnormalities was high: 57% in the liberal group vs 59% the restrictive group; however, only one MI was

**Table 1** Baseline patient characteristics

	Hb >90 g L <sup>-1</sup> during hospital stay N=138	Hb 90 g L <sup>-1</sup> or less during hospital stay	
		Liberal N=26	Restrictive N=36
Age, yr, mean (sd)	77 (11)	82 (11)	82 (11)
Female, n (%)	83 (60)	18 (69)	26 (72)
Charlson comorbidity index, mean (sd)	4.9 (1.9)	5.3 (1.7)	5.4 (1.8)
Cardiovascular risk factors, n (%) <sup>*</sup>	76 (55)	20 (77)	30 (86) <sup>†</sup>
Ischaemic heart disease	17 (22)	5 (25)	11 (37)
Other cardiac disease	26 (34)	6 (30)	6 (20)
Peripheral vascular disease	6 (8)	0 (0)	2 (7)
Cerebrovascular disease	13 (17)	7 (35)	8 (27)
One of: age >65 yr, diabetes mellitus, or hypertension	43 (57)	14 (70)	23 (77)
Type of surgery proposed, n (%)			
Total hip replacement	37 (27)	3 (12)	3 (8)
Hemiarthroplasty	53 (38)	10 (38)	13 (36)
Dynamic hip screw	37 (27)	10 (38)	12 (33)
Other <sup>‡</sup>	11 (8)	3 (12)	8 (22)
	N=137 <sup>§</sup>	Liberal N=26	Restrictive N=36
ASA physical status, n (%)			
1	10 (7)	0 (0)	0 (0)
2	59 (43)	6 (23)	10 (28)
3	59 (43)	15 (58)	23 (64)
4	8 (6)	5 (19)	3 (8)
5	1 (1)	0 (0)	0 (0)
Duration of surgery (min), mean (sd)	109 (27)	119 (38)	111 (36)
Type of anaesthesia, n (%)			
GA (regional technique)	16 (12)	3 (12)	7 (19)
Neuraxial blockade (regional technique)	100 (73)	20 (77)	25 (69)
GA and neuraxial blockade	15 (11)	2 (8)	2 (6)
Regional technique only	6 (4)	1 (4)	2 (6)
Postoperative destination, n (%)			
Trauma ward	135 (99)	26 (100)	34 (94)
ICU	0 (0)	0 (0)	1 (3)
HDU	2 (1)	0 (0)	1 (3)

ASA, American Society of Anesthesiologists; GA, general anaesthesia; Hb, haemoglobin; HDU, high dependency unit; sd, standard deviation.

<sup>\*</sup> More than one cardiovascular risk factor can be present.

<sup>†</sup> One participant had missing data on cardiovascular risk factors, denominator (N=35).

<sup>‡</sup> Cannulated screws, intertan nail, gamma nail.

<sup>§</sup> One participant withdrew before surgery.

diagnosed clinically in participants exposed to the intervention in the restrictive group. Rates of clinically diagnosed MACE were lower in the liberal group (8%) compared with the

Table 2 Feasibility outcomes

	Hb >90 g L <sup>-1</sup> during hospital stay (N=138)		Hb 90 g L <sup>-1</sup> or less during hospital stay		Difference (95% CI)*		
	N	Mean (SD)	Liberal (N=26)	Restrictive (N=36)			
Protocol compliance, n (%)							
Transfusion of red blood cells within the predefined transfusion trigger	–		24 (92)	24 (67)	25.6% (7.1–44.1)		
Transfusion with checking haemoglobin level	–		23 (88)	29 (81)	7.9% (–9.9 to 25.7)		
Patient had surgery	–		26 (100)	36 (100)	–		
<hr/>							
Haemoglobin concentration (g L <sup>-1</sup> )							
Preoperatively	138	130 (13)	26	115 (15)	36	120 (15)	–4.5 (–12.2 to 3.3)
Post-surgery	89	111 (14)	16	96 (14)	24	99 (17)	–2.6 (–12.8 to 7.6)
Postoperative day 1	137	113 (10)	26	90 (9)	36	92 (12)	–1.4 (–7.0 to 4.2)
Postoperative day 2	125	108 (11)	26	91 (9)	36	84 (11)	7.0 (1.6–12.4)
Nadir haemoglobin (g L <sup>-1</sup> )							
Within 3 days of surgery	135	107 (11)	26	85 (7)	35	82 (11)	3.1 (–1.8 to 8.0)
Within 30 days/before discharge	135	106 (11)	26	84 (6)	36	79 (8)	5.3 (1.7–9.0)
Number of units red blood cells transfused,† n (%)							
Within 5 days of anaemia, n (%)							
0		127 (100)		1 (4)		20 (57)	53.3 (35.3–71.3)
1		0 (0.0)		15 (58)		7 (20)	
2		0 (0.0)		8 (31)		7 (20)	
>2		0 (0.0)		2 (8)		1 (3)	
Missing		11		0		1	
Within 30 days/before discharge, n (%)							
0		133 (100)		1 (4)		21 (58)	54.5 (36.8–72.2)
1		0 (0.0)		14 (54)		5 (14)	
2		0 (0.0)		9 (35)		7 (19)	
>2		0 (0.0)		2 (8)		3 (8)	
Missing		5		0		0	
<hr/>							
Volume of red blood cells transfused (ml) in those with at least one unit transfused							
Within 5 days of anaemia	23	322 (300–608)	14	462 (326–579)	–		
Within 30 days/before discharge	23	327 (300–617)	13	575 (337–639)	–		

CI, confidence interval; Hb, haemoglobin; IQR, inter-quartile range; SD, standard deviation.

\* Difference in proportion or mean for Liberal minus Restrictive with 95% CI.

† Difference in proportions for 1 or more units of red blood cells transfused.

restrictive group (19%) (difference in proportion, –11.8%; 95% CI, –28.2 to 4.7;  $P=0.282$ ) but did not reach significance. There were no differences in other secondary clinical outcomes or mortality between groups (Table 3).

### Safety data

The rate of serious adverse events (SAE) was high in this group of patients with 15% (30/200) of patients suffering at least one or more SAE. Only one was possibly related to the study procedures, an episode of transfusion related circulatory overload in the restrictive group.

### Discussion

This study found that recruitment to a randomised trial of two transfusion strategies in a population of patients with a high prevalence of cardiovascular and other comorbidities was

feasible. Separation of groups by both haemoglobin concentration and blood usage was also demonstrated. Protocol compliance suggested that owing to clinical reasons and clinician beliefs, there was a difference in the rate of protocol deviations between liberal and restrictive groups, with a higher non-compliance rate in the restrictive arm. Use of a primary outcome based on detection of MI or myocardial injury using high-sensitivity troponin assay, measured after patients became anaemic, was also feasible. Although this study was not powered to detect a difference in clinical outcomes between groups, findings suggested a signal for an increased rate of myocardial injury associated with restrictive transfusion strategies, although it should be noted that the rate of pre-existing ischaemic heart disease was not evenly distributed between the groups (Table 1).

Concerns regarding the potential effect of severe anaemia on cardiac injury remain. A large study of two transfusion strategies in 2000 patients with fractured NOF published in

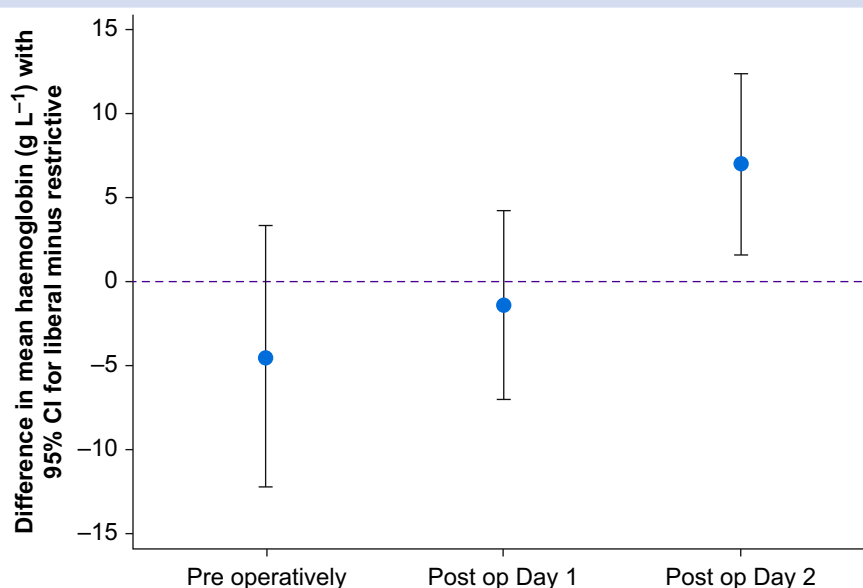


Fig. 2. Difference in mean haemoglobin between groups. CI, confidence interval.

2011 did not show a difference in a composite primary outcome of death or inability to walk unassisted across a room at 60 days.<sup>22</sup> This study reported the rate of acute coronary syndrome as a secondary outcome and observed no difference between groups. However, more recent systematic reviews of transfusion strategy in surgical patients have suggested that restrictive strategies are associated with increased rates of MI or MACE, particularly if there is pre-existing cardiac disease<sup>28,29</sup> and in patients undergoing surgery for fractured NOF.<sup>30</sup> One possible explanation is that the restrictive and liberal strategies used in earlier studies do not reflect current practice, which would consider a restrictive strategy to maintain haemoglobin between 70 and 90 g L<sup>-1</sup> and a liberal strategy at between 90 and 110 g L<sup>-1</sup>. A clinician survey undertaken in the UK by our group suggests continued uncertainty in managing anaemia in this group, particularly in the setting of cardiac disease.<sup>23</sup> Our findings are consistent with other recent trial data, including a small trial in vascular surgery and in transfusion-dependent patients with myelodysplasia which identified improvements in quality of life domains for participants in the liberal compared with restrictive arm.<sup>31</sup>

Other findings of our study were a high rate of co-existing CVD in this group, especially in those who were severely anaemic. This may account for protocol deviations among participants randomised to a restrictive strategy and may have represented clinical concern among clinicians, particularly as patients' haemoglobin levels decreased close to the restrictive trigger of 70 g L<sup>-1</sup>. Our study also suggested a high rate of post-operative cardiac complications in this group, particularly when modern high-sensitivity troponin assays are used routinely.

Strengths of this study are that it was a large feasibility trial that recruited within the planned time frame, with low rates of missing data or participants lost to follow-up. Participants in the liberal transfusion group had significantly higher exposure to blood, and there was a mean difference in haemoglobin

after POD 2, despite some issues with protocol compliance. High rates of cardiac complications and mortality suggest these would be patient-centred outcomes which could be studied in a future trial.

There were several weaknesses in the design which could be addressed in a refined protocol for a larger study. Firstly, 58% of eligible participants could not be recruited as they had already undergone surgery before the study team was able to approach them. This probably reflects quality improvement initiatives to expedite surgery and minimise the delay in operating on this group. It is possible that the more severely injured patients, and hence those with the greatest blood loss were excluded from the study for this reason, explaining the lower-than-anticipated rate of anaemia observed in this study. In this group, there are high rates of cognitive impairment (both acute and pre-existing) necessitating the need for proxy consent and introducing a further delay. Strategies to identify and recruit patients at an earlier stage in their inpatient admission could address these issues. The optimal transfusion threshold in older patients may also be different, and a future study should include a prespecified subgroup of older patients.

Although groups were balanced at the point of randomisation, only those who became anaemic (i.e. haemoglobin decreasing to 90 g L<sup>-1</sup> or less) were exposed to the study intervention and were part of the ITT analysis population, which resulted in some imbalance in patient characteristics in the restrictive and liberal groups. This study design has been used in previous studies of transfusion strategy, and we believe the imbalance between groups would have resolved with a larger sample size. A retrospective analysis of study data suggested that restricting recruitment to patients who were already anaemic (e.g. haemoglobin of 110 g L<sup>-1</sup> or less) would not have enriched the recruitment of patients whose haemoglobin later decreased to 90 g L<sup>-1</sup> or less.

Table 3 Clinical outcomes

	Hb >90 g L <sup>-1</sup> during hospital stay (N=138)		Hb 90 g L <sup>-1</sup> or less during hospital stay				Difference (95% CI)	P-value
			Liberal (N=26)		Restrictive (N=36)			
	N	n (%)	N	n (%)	N	n (%)		
Myocardial injury								
Primary outcome	–	NA	26	14 (54)	34	24 (71)	–16.7 (–41.3 to 7.8)	0.182
Sensitivity analysis	–	NA	26	17 (65)	36	27 (75)	–9.6 (–32.7 to 13.5)	0.410
Exploratory analysis	–	NA	26	8 (31)	34	18 (53)	–22.2 (–46.6 to 2.2)	0.086
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)		
Area under troponin time curve		NA	12	59 (26–84)	16	79 (33–234)	–	–
Troponin								
Baseline	129	6 (3–14)	23	13 (4–21)	34	13 (5–30)	–	–
Day 1	–	NA	22	17 (8–28)	30	45 (9–118)	–	–
Day 2	–	NA	24	14 (7–25)	27	26 (5–71)	–	–
Day 5	–	NA	15	12 (6–23)	20	18 (3–38)	–	–
Duration of hospitalisation in those discharged by day 30 (days)								
	129	8 (6–11)	20	10 (8–16)	30	12 (9–15)		
EQ-5D								
Health Index	108	0.6 (0.3–0.7)	21	0.6 (0.3–0.7)	28	0.6 (0.2–0.7)	–	–
VAS	110	70 (50–80)	20	55 (50–75)	27	65 (50–80)	–	–
	N	n (%)	N	n (%)	N	n (%)		
ECG on 3rd postoperative day								
Abnormal	119	50 (42)	23	13 (57)	32	19 (59)	–	–
Normal	119	69 (58)	23	10 (43)	32	13 (41)	–	–
Complications within 30 days/discharge								
MACE (clinically diagnosed)	135	4 (3)	26	2 (8)	36	7 (19)	–11.8 (–28.2 to 4.7)	0.282
Myocardial Infarction	135	0 (0)	26	0 (0)	36	1 (3)	–2.8 (–8.1 to 2.6)	1.000
New AKI	135	7 (5)	26	5 (19)	36	5 (14)	5.3 (–13.6 to 24.2)	0.729
Delirium	135	25 (19)	26	5 (19)	36	8 (22)	–3.0 (–23.3 to 17.4)	0.775
Infectious complications	135	18 (13)	26	8 (31)	36	13 (36)	–5.3 (–29.0 to 18.3)	0.661
Discharge destination								
Home	129	86 (67)	20	8 (40)	30	15 (50)	–	–
Other hospital	129	27 (21)	20	7 (35)	30	12 (40)	–	–
Nursing home	129	16 (12)	20	5 (25)	30	3 (10)	–	–
Mortality								
Within 30 days/discharge	135	0 (0)	26	1 (4)	36	2 (6)	–1.7 (–12.2 to 8.8)	1.000
Within 60 days	136	5 (4)	26	3 (12)	36	6 (17)	–5.1 (–22.4 to 12.2)	0.722

Difference in proportion for Liberal minus Restrictive with 95% CI and P-value from  $\chi^2$  or Fisher's exact test as appropriate.

AKI, acute kidney injury; CI, confidence interval; Hb, haemoglobin; IQR, inter-quartile range; MACE, major adverse cardiac events; NA, not applicable; sd, standard deviation; VAS, visual analogue scale.

Finally, protocol compliance is an area that would need to be improved in a larger study. The overall compliance of 70% observed in this study would need to be improved in a larger study. In studies of transfusion practice, some protocol deviations are inevitable as the protocol must be suspended in episodes of major haemorrhage. As many of these deviations occurred in the perioperative period, restricting the study intervention to the postoperative period could improve this. Clinician focus groups may also be useful to identify how the protocol could be adapted to improve adherence over an often protracted hospital stay with multiple clinical teams involved.

Our study confirms that older patients having surgery for hip fracture have a high rate of pre-existing cardiac disease and postoperative cardiac events, including troponin release. There is a high rate of anaemia and blood transfusion in this

population, and the optimum transfusion threshold is not known. A larger study of liberal vs restrictive transfusion practice with a clinically relevant cardiac outcome in this population is warranted and is feasible in an NHS hospital setting. The future design of such a trial could be informed by the findings of this study.

### Authors' contributions

Patient recruitment: SG, ABD, SC, NR, AMJM, TOW, DCR, MAG  
Research interventions: SG, ABD, SC, NR, AMJM, TOW, DCR, MAG

Data management and statistical analyses: JS, CK (in statistical advisory role).

Responsibility for the integrity of the manuscript: MAG



All authors contributed to the development of the study protocol and obtaining the research permissions. All authors contributed to the manuscript

## Declarations of interest

NLM has received consultancy, research grants, and speaker fees from manufacturers of cardiac troponin testing including Abbott Diagnostics, Roche, and Singulex. All other authors declare they have no conflicts of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2020.06.048>.

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