Randomised open-label trial comparing intravenous iron and an erythropoiesis-stimulating agent versus oral iron to treat preoperative anaemia in cardiac surgery (INITIATE trial)

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Randomised open-label trial comparing intravenous iron and an erythropoiesis-stimulating agent versus oral iron to treat preoperative anaemia in cardiac surgery

(INITIATE trial)

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ABSTRACT

Background Preoperative anaemia is a risk factor for adverse postoperative outcomes after cardiac surgery. Iron deficiency is a frequent cause of low preoperative haemoglobin. An effective treatment for preoperative anaemia associated with iron deficiency has not been determined.

Methods We conducted a single-centre, open-label, pragmatic randomised trial, enrolling 156 elective cardiac surgery patients who had low preoperative haemoglobin (100-130 g/L) with iron deficiency (serum ferritin <100 µg/L or transferrin saturation <30%) to compare intravenous ferric derisomaltose 1000 mg and darbepoetin 200 µg subcutaneously (intervention group) with oral ferrous sulphate 600 mg daily (control group). The primary outcome was transfusion of at least one unit of allogeneic red cells during surgery and within the following 5 days. Secondary outcomes included the change in haemoglobin level between randomisation and surgery, red cell transfusion volume, postoperative blood loss, pre-specified postoperative complications, length of hospital stay, and in-hospital death.

Results The odds of red cell transfusion were lower in the intervention group compared with the control group (adjusted OR 0.33. 95% CI: 0.15 to 0.75, P=0.008). Of the secondary outcomes, the only significant difference was the increase in haemoglobin between randomisation and surgery, intervention vs. control 9.5 g/L (95% CI: 6.8 to 12.2, P<0.001).

Conclusions In patients with a low preoperative haemoglobin and iron deficiency, preoperative treatment with a single dose of ferric derisomaltose and darbepoetin decreased the proportion of participants who received a perioperative blood transfusion as a consequence of a greater increase in haemoglobin compared to treatment with oral ferrous sulphate.
Keywords anaemia; cardiac surgery; intravenous iron; iron deficiency; preoperative;

transfusion

Trial registration ISRCTN Number: 41421863. EUDRACT number: 2011-003695-36
INTRODUCTION

Preoperative anaemia is associated with worse perioperative outcomes\(^1\). It was suggested fifty years ago that a randomised trial could be undertaken to determine whether outcomes could be improved by preoperative correction of anaemia\(^2\). This hope remains an open question, although several investigators have looked at ways to correct anaemia preoperatively. Correction of preoperative anaemia is considered to be one of the pillars of Patient Blood Management\(^3,4\). Unfortunately, the evidence to guide such recommendations remains scant or inconclusive\(^5\).

First reported in 2007\(^6\), the association between preoperative anaemia in cardiac surgery and increased postoperative complications has since been confirmed from large registries\(^7,8\). Preoperative anaemia is reported in approximately 20-30\%, and blood loss and red cell transfusion rates are higher in cardiac surgery than in other types of surgery\(^9\).

Serious wound and systemic infections\(^10\), renal failure, prolonged ventilation, low cardiac index, myocardial infarction, stroke and mortality\(^11\) have all been associated with transfusion after cardiac surgery, with mortality remaining significant after five years\(^12\).

We examined whether patients presenting for elective cardiac surgery with a haemoglobin between 100 g/l and 130 g/l treated with a combination of intravenous iron and a single dose of an erythropoiesis-stimulating agent can reduce the likelihood of needing a transfusion of red blood cells compared with the common practice of treating iron deficiency anaemia with oral iron tablets.
METHODS

Trial design and setting

This was a pragmatic, single-centre, open-label, randomised, superiority trial. It was conducted at a National Health Service (NHS) hospital which undertakes, annually, approximately 650 adult cardiac surgery procedures requiring cardiopulmonary bypass. We compared the treatment of low preoperative haemoglobin with reduced iron reserves in participants undergoing elective cardiac surgery, using either intravenous iron (ferric derisomaltose) plus an erythropoiesis-stimulating agent (darbepoetin) or oral iron supplementation alone with ferrous sulphate.

Participants

Patients undergoing first-time, elective cardiac surgery requiring standard median sternotomy were recruited. We screened blood results from samples taken at the initial outpatient consultation with the surgical team. Samples with haemoglobin in the range of 100 g/L to 130 g/L (inclusive) were highlighted to the laboratory to measure ferritin and transferrin saturation (TSAT)\textsuperscript{13}. Reduced iron reserves was defined as serum ferritin < 100 µg/L or TSAT < 30% provided the ferritin concentration was < 800 µg/L. By adopting a broader definition of iron deficiency, we aimed to capture all patients who might have benefitted from iron supplementation.

Patients were not eligible if they were unable to give informed consent; pregnant; participating in another clinical trial; receiving renal replacement therapy; receiving chemotherapy; suspected to have significant hepatic disease; had a contraindication to receive the study drugs, including active infection at the time of randomisation; or intending to refuse any blood transfusion.
We did not recruit patients if the procedure was planned to be minimally-invasive; hypothermic circulatory arrest was likely to be needed; or surgery was scheduled to be performed within two weeks of the outpatient attendance. Study information was posted to eligible patients who were then contacted by telephone, and those willing to participate in the trial were enrolled and asked to attend the hospital for randomisation.

**Randomisation**

After written informed consent was obtained, participants were randomly assigned to one of two groups – Intervention or Control. We used a web-based service to provide a concealed, computer-generated sequence of randomly permuted blocks of length 2 to 6, stratified by sex (male or female) and haemoglobin concentration (100–115 g/L or 116–130 g/L).

**Procedures**

Blood was taken to measure haemoglobin concentration (this value was used as the baseline to calculate the change between randomisation and surgery), reticulocyte count, electrolytes, creatinine, liver enzymes, C-reactive protein, thyroid function, serum vitamin B12, folate and erythropoietin. Serum was stored in liquid nitrogen and batched for duplicate measurements with the Hepcidin 25 (bioactive) HS ELISA RUO enzyme-linked immunosorbent assay (EIA 5782R, DRG Instruments, Marburg, Germany) according to the manufacturer’s instructions.

**Interventions**

On the day of randomisation, patients in the intervention arm were given ferric derisomaltose (previously known as iron isomaltoside, Monofer®) 1000 mg (or 20 mg/kg if
the patient weighed less than 50 kg) by intravenous infusion over 60 minutes. Darbepoetin (Aranesp®) 200 µg was given subcutaneously.

Participants in the control group were supplied with ferrous sulphate tablets and advised to start at a dose of 200 mg daily, increasing to 200 mg three times daily over several days, and reduce dosage to lessen any side effects. We asked the participants’ GP to manage the treatment of abnormal thyroid function or low serum vitamin B12 (< 220 pmol/L) or folate (< 7 nmol/L) and renew the prescription for ferrous sulphate (control participants only). The research nurse telephoned participants to confirm medication adherence and monitor any treatment side-effects.

**Timing of surgery**

Scheduling of surgery was determined by the surgical team, but we anticipated that this would be two to 10 weeks after randomisation and adjusted according to clinical priority.

**Masking**

Participation in the trial was denoted by a sticker on the outside of the patient’s medical records folder. Drugs administered at randomisation, clinical observations and correspondence relating to the trial were filed inside the folder. Neither the participants nor the clinical staff were masked to the treatment allocation, but transfusion decisions were made according to departmental protocols by staff not involved in the study.

**Intraoperative management**

Participants received comparable anaesthetic and surgical management as other patients not in the study. Clinical practices (e.g. intraoperative cell-salvage, tranexamic acid usage,
red cell transfusion trigger or fluid management) did not change throughout the duration of the trial.

In the haemodynamically stable, non-bleeding patient, the trigger for transfusion of allogeneic red cells was Hb ≤70 g/L. The practice of ‘single unit transfusion’ - only one unit of red cells was transfused at a time – was employed throughout. The haemoglobin level was recorded before the transfusion of each unit of red cells. In actively bleeding patients, both the transfusion trigger and treatment were left to the discretion of clinicians. Administration of other blood products to manage coagulopathy during and after surgery, was guided by point-of-care viscoelastic test of whole blood (ROTEM®) according to a locally agreed algorithm.

**Outcomes**

The primary outcome was the transfusion of at least one unit of allogeneic red cells from the start of surgery until the end of the fifth postoperative day.

Secondary outcomes are listed in Table S1 (see Supplementary Data). We also recorded patient-reported adverse symptoms after starting the randomised treatment (Table S5 – Supplementary Data).

**Sample size**

Local audit data revealed that in patients with preoperative haemoglobin concentration of 100-130 g/L, up to 80% were transfused at least one pack of red cells. We considered that a reduction in the absolute transfusion risk of 15% would be the minimum required to be clinically meaningful. To detect this difference with 80% power, we calculated that 302 participants were required, based on a two-tailed z-test, significance level 0.05 and 1:1 allocation. To account for dropouts, we planned to randomise 330 patients to each group.
**Interim analyses**

To compare rates of serious adverse events, a priori planned interim analyses were defined in the trial protocol to be performed after 100 and 200 participants had completed surgery. There were no meaningful differences in the rates of serious adverse events between the two groups after 100 patients. Due to a slower than predicted recruitment rate, we submitted a protocol amendment to perform an interim analysis after 150 participants had completed surgery. In accordance with CONSORT recommendations for binary outcomes in pragmatic trials\(^\text{15}\) we calculated the relative risk of transfusion and planned to halt the study if the odds ratio for transfusion in the intervention versus the control group was 0.46 or lower.

**Statistical analysis**

The statistical analysis plan (supplementary document “INITIATE SAP 1.0 signed”) was agreed and signed off by the Chief Investigator prior to analysis. Baseline, surgical and outcome variables were summarised using appropriate descriptive statistics. The primary outcome was analysed using a multivariable logistic regression model with intervention group, adjusted for the following covariates at baseline: CRP level, ferritin level, transferrin saturation and GFR level. All 156 participants who underwent surgery were included in the model on an intention-to-treat basis. The adjusted OR is presented as Intervention versus Control with its 95% confidence interval. The adjusted RR with its 95% confidence interval is also presented. The adjusted RR was obtained by fitting a Poisson regression model with robust standard errors with the same dependent variable and covariates\(^\text{16}\).

Appropriate multivariable regression models were fitted for the secondary outcomes (Tables S1 and S2 – see Supplementary Data) for which sufficient data were available:
logistic for secondary outcome 8; negative binomial for 2a, 3a, 4a and 5a; Cox for 12; and linear for 1, 2b, 3b, 4b, 5b, 6a and 6b. Secondary outcomes 7, 9, 10, 11 and 13 were relevant to an insufficient number of participants to fit any models. Covariates for the secondary outcome models were the same as for the primary outcome model. Specific model assumptions were checked and where the assumption of normality of residuals in linear regression was inappropriate, bootstrapping was used to calculate appropriate 95% confidence intervals and P values. All secondary outcome models were fitted for the 156 participants that underwent surgery, except 6a and 6b, which were fitted for 155 participants, due to missing data.

**Patient and public involvement**

The study design and protocol were informed by a series of meetings with local General Practitioners (GP) and patient groups. We will share the study results with the Sussex Heart Charity to disseminate to relevant patient groups.
RESULTS

Between April 2013 and September 2017, 2,151 outpatients were listed to undergo elective cardiac surgery of which 363 (16.9%) were eligible for the trial. The trial was stopped after the interim analysis showed that the odds ratio for transfusion in the intervention versus the control group was lower than 0.46. A total of 170 participants were randomised: 86 (50.6%) to the intervention group and 84 (49.4%) to the control group; 156 completed the trial.

There were 193 eligible patients who did not participate in the trial: 85 declined; 43 were in another study; 34 consulted the surgeon fewer than 2 weeks before surgery; 18 received treatment for anaemia off-study; 8 lacked sufficient capacity to give informed consent; and 5 could not be contacted in time to recruit into the study. The flow of participants through the stages of the trial is shown in Figure 1.

*insert Figure 1 here

Baseline characteristics

Baseline patient, surgery and haematological characteristics are shown in Table 1. The two groups were comparable with respect to major co-morbidities, baseline haemoglobin, iron status, haematinics and indicators of erythropoiesis. The interval between randomisation and surgery, operative risk (as measured by Euroscore II), types of surgery and duration of cardiopulmonary bypass were also similar.

*insert Table 1 here
Primary outcome

The primary outcome could be evaluated in 156 participants who underwent surgery. The odds of receiving a blood transfusion were significantly lower in the intervention compared to the control group (adjusted OR 0.33. 95% CI: 0.15 to 0.75, P=0.008). The adjusted risk ratio was 0.77 (95% CI: 0.63 to 0.94, P=0.010).

The proportion of participants who received any red cell transfusion was lower in the intervention group with an absolute difference in transfusion rate of 14.7% (Table 2).

Based on this difference, the number needed to treat with the intervention to have one less participant require transfusion is 6.8 (95% CI: 3.5 to 80).

*insert Table 2 here*

Secondary outcomes

Blood transfusion

Transfusion of red cells and other blood products are summarised in Table 2. While a greater proportion of control group participants received a transfusion of red cells within the first 5 days after surgery, there was no difference between the two groups for the number of packed RBCs given per participant. There was some evidence for a reduction in the volume of packed RBCs given in the intervention group, mean -212.2 (95% CI: -422.1 to -2.3) ml, P=0.047 (Table S2, secondary outcome 2b - see Supplementary Data).

Change in haemoglobin concentration

The median (IQR) haemoglobin increase in the intervention group was 12.0 g/L (7.0 to 17.0) compared to 0.0 g/L (-5.0 to 6.0) in the control group. The adjusted difference between the groups was 9.5 g/L (95% CI: 6.8 to 12.2, P<0.001). Despite treatment, haemoglobin level had dropped by the time of surgery in about 10% of participants in the intervention group and
50% in the control group (Figure 2). More participants attained a haemoglobin increase of 
≥10g/L after intravenous iron and darbepoetin (48/79; 61%) compared to oral iron (11/77; 
14%). Ferritin and TSAT increased after both treatments, although the increase was less 
after oral iron (Table S3 – see Supplementary Data). Deficiency of vitamin B12 (serum level 
<200 pg/ml) or folate (<24 ng/ml) was found in 5.8% and 1.9% of the patients respectively 
(Table S4 – see Supplementary Data).

The haemoglobin concentration of the participants at the time of routine measurement are 
shown in Figure 3.

*insert Figures 2 & 3 here

Postoperative complications

There were no differences in pre-specified clinical outcomes between the groups, although 
some endpoints were too infrequent to allow meaningful analysis. There were no 
thrombotic complications in either group, although four patients in the intervention group 
had perioperative embolic strokes. These were reviewed by the Safety Committee and 
considered to be related to the surgery. Three had severely atheromatous ascending aortas 
and the fourth had an unusually calcified aortic annulus making surgery to replace the valve 
difficult. Patient-reported symptoms and other adverse events are shown in Table S5 (see 
Supplementary Data).
DISCUSSION

We found that in a cohort of routine cardiac surgery patients with anaemia and iron
deficiency, red cell transfusion rate was lower after preoperative treatment with ferric
derisomaltose and darbepoetin compared with oral ferrous sulphate. A combination of
intravenous iron and erythropoiesis-stimulating agent resulted in a median 12.0 g/L
increase, while the group receiving oral iron showed no overall change in haemoglobin
concentration.

Many studies have adopted the WHO definition of anaemia to target interventions for
preoperative anaemia. We disagree with this approach in practice and in the design of this
trial: clinical decisions to transfuse red cells are not influenced by patient sex, and
transfusion-triggers used in routine clinical practice are not gender-specific\textsuperscript{17}. Our decision
to do this has been supported by subsequent consensus recommendations\textsuperscript{18}. We adopted a
liberal definition of iron-deficiency. In the context of predictable surgical blood loss of 500
mL or more this seemed reasonable.

Oral iron

Oral iron is widely regarded as the standard treatment of iron deficiency anaemia for
patients in the community. Yet, in several clinical scenarios, a greater increase in iron stores,
haemoglobin concentration or both is achieved after replacement with intravenous
compared with oral iron\textsuperscript{19, 20}. Oral iron supplementation relies on intestinal absorption of
iron, which is reduced when hepcidin concentration is elevated\textsuperscript{21}. Despite this, oral iron is
cheaper, logistically simpler, and remains the standard therapy for iron-deficiency.

The distribution of baseline hepcidin concentration was comparable in both groups in this
trial, with median hepcidin values at the upper limit of the non-anaemic reference range for
This suggests that the underlying cause of anaemia in around half of the patients is likely to have been due to inflammation or a combination of inflammation and iron deficiency. Impaired iron absorption could explain the differences in ferritin and TSAT increases from baseline. The relationship between hepcidin concentration and the erythropoiesis response requires further evaluation.

A higher incidence of side effects, which were predominantly gastrointestinal, was reported by patients who received iron orally (68% vs 45%). This is in keeping with the known side-effect profile of oral iron therapy. Based on the change in ferritin and TSAT, oral iron was able to increase iron stores, albeit only very slightly compared to giving iron intravenously. Newer formulations of oral iron may be more effective than ferrous sulphate and warrants wider recognition.

**Intravenous iron**

We administered a dose of 1000 mg of ferric derisomaltose which was, on average, 60-70% (higher for women) of the licensed maximal dose of 20 mg/kg for a single infusion. Although the fixed dose approach has its merits for simplicity in a trial context, dosing according to an individual’s calculated iron deficit might be a better approach to replenish iron stores.

Since we embarked on our trial, other investigators have evaluated intravenous iron alone to treat preoperative anaemia and found mean increases in haemoglobin (<10 g/L) that we would not consider clinically important.

**Erythropoiesis-stimulating agent**

Erythropoiesis would be expected to be enhanced by the addition of an erythropoiesis-stimulating agent. When we planned this trial, our aim was to enhance erythropoiesis in the intervention group. At the time, the proposal to combine an erythropoiesis-stimulating
agent with intravenous iron was rather unique as a treatment strategy for preoperative
anaemia. The use of erythropoietin to treat anaemia in chronic kidney disease had been
associated with thrombotic risks and we therefore planned to use only a single and
relatively low dose of an erythropoiesis stimulating agent. We chose darbepoetin, an agent that has not been reported for the treatment of
preoperative anaemia by other groups. The longer half-life of darbepoetin compared to
epoetin allowed us to simplify the treatment by administering a single dose and avoid
multiple hospital visits by the patients.

Biboulet et al. showed that the addition of erythropoietin to either intravenous or oral iron
increased haemoglobin concentration in anaemic patients awaiting major orthopaedic
surgery. As their patients were iron-replete before the start of treatment, the
haemoglobin increase after oral iron could be attributed largely to their use of three
preoperative doses of erythropoietin. Spahn et al. used only a single dose of erythropoietin
and intravenous iron, which were given the day before cardiac surgery. Although this
approach reduced the number of red cell units transfused after surgery, there was no
significant difference between treatment and control groups in the proportion of patients
who avoided any red cell transfusion.

In our study, haemoglobin concentration decreased between randomisation and surgery in
50% of patients in the oral iron group and 10% of the Intervention group. Data from other
trials also show that in a subset of patients receiving placebo or oral iron, haemoglobin
concentration can decrease further after randomisation.
Adverse surgical outcomes

The link between preoperative anaemia and poor operative outcomes remains to be clearly elucidated despite numerous observational studies demonstrating a correlation\textsuperscript{33-36}. Our study was not designed to examine this association. There were more strokes in the Intervention group, but our Safety Committee deemed these were unlikely to be caused by the study drugs. We did identify an increased incidence of the composite of serious complications in the intervention group, but this was one of many secondary endpoints.

Strengths and limitations of this study

The main strength of this study lies in its pragmatic design, comparing the standard treatment of low haemoglobin associated with iron deficiency to a treatment that could be implemented in most cardiac surgery units using drugs which have a good safety record. We chose a primary endpoint that is clinically appealing – the odds of avoiding any red cell transfusion.

Conducted in a single centre, the study has limited generalisability. However, we recruited over half of the patients who were eligible and the broad inclusion criteria enabled us to randomise most of patients who presented with a low haemoglobin for routine cardiac surgery.

The study was stopped following an interim analysis after just over half of the planned number of participants. Stopping the trial early poses the risk that the effects of the intervention on transfusion rate could be over-estimated. The open-label design could introduce a bias and exaggerate the benefits of the intervention. But we think this is unlikely, as clinical decisions that could influence red cell transfusion were based on objective criteria and taken by clinicians who were not involved with the trial. Moreover,
the participants comprised a minority of the caseload of the surgical unit over several years
and their clinical management during and after surgery was indistinguishable from other
patients. The haemoglobin values before the transfusion of each unit of red cell were
comparable in both groups (Table S6 – see Supplementary Data), providing reassurance that
bias was not a major problem.

We have not carried out a cost-benefit analysis. It might be argued that the costs of the
intervention would not be offset by the savings from reduced transfusion rates.

Furthermore, it could be argued that it was clinically irrelevant, at least in cardiac surgery,
where recent prospective studies have not detected adverse outcomes as a result of more
allogeneic transfusion37, 38. However, the latest guidelines from the Society of Thoracic
Surgeons continues to recommend a restrictive rather than a liberal approach to transfusion
as the latter confers no long-term benefits39. These criticisms would be more potent if at
one year from surgery, such a treatment strategy for this group rendered no important
benefits40.

CONCLUSION

We have shown that it is possible to increase preoperative haemoglobin levels and reduce
the risk of requiring blood transfusion in patients presenting for elective cardiac surgery
who have low haemoglobin levels associated with low iron reserves. Administration of
single doses of intravenous iron and subcutaneous darbepoetin can achieve this; oral iron
supplements cannot. Whether, ultimately, the association of preoperative anaemia with
poor postoperative outcomes can be ameliorated by interventions such as these remains
unanswered2.
Details of authors’ contributions

RK, NH, ML, JW and SN conceived and designed the study. FI, NS, CB and TC acquired the data. RK, NH, CJ, SB, JW, AH, TC and DHS analysed and interpreted the data. CJ and SB carried out the statistical analysis. RK, NH, CJ and SB drafted the manuscript. All authors critically revised the manuscript for intellectual content. RK and NH are guarantors and approved the final version. RK is the corresponding author and attests that all listed authors meet the authorship criteria and no others meeting the criteria have been omitted.

Acknowledgements

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Declaration of interests

All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

Pharmacosmos A/S (Holbaek, Denmark) supplied the ferric derisomaltose administered to participants in the study and funded the salary of a research nurse at the Clinical Research Facility at the Royal Sussex County Hospital for the duration of the study.
Data availability statement

The study protocol, de-identified participant data, and statistical analysis plan can be shared upon request. Please contact from the lead investigator (ORCID: 0000-0002-8598-9991).

Funding

The Royal College of Surgeons of England provided a research start-up grant; the Sussex Heart Charity donated equipment used in the trial; and Pharmacosmos A/S (Holbaek, Denmark) supplied the ferric derisomaltose and funded the salary of a research nurse for the duration of the study (from recruitment of the first until the final follow-up of the last participant - see Competing Interests). None of the funders or the study Sponsor (Brighton and Sussex University Hospital NHS Trust) had any role in the study design; in the collection, analysis and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Ethics and regulatory approval

Ethical and regulatory approval for the trial was given by the NHS Research Authority (London Bentham Committee, 2011) and the Medicines and Healthcare Regulatory Authority (2012). This trial was registered with EudraCT (2011-003696-36) and ISRCTN (41421863).
REFERENCES


16 Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. *American Journal of Epidemiology* 2004; **159**: 702-6


Figure 1 Flow of participants through the stages of the trial

Enrolment
- Screened for eligibility (n=2152)
  - Excluded (n=1982)
    - Hb not within range (n=1751)
    - Did not meet other inclusion criteria (n=38)
    - Declined to participate (n=85)
    - Not recruited for other reasons (n=108)
- Randomised (n=170)

Allocation
- Allocated to Control arm: Ferrous sulphate (n=84)
  - Received allocated intervention (n=84)
- Allocated to Intervention arm: Ferric derisomaltose and darbepoetin (n=86)
  - Received allocated intervention (n=85)
  - Did not receive allocated intervention (died before receiving intervention) (n=1)

Follow-up
- Lost to follow-up (n=7)
  - Did not undergo surgery (n=6)
  - Withdrew consent before surgery (n=1)
- Lost to follow-up (n=6)
  - Did not undergo surgery (n=5)
  - Withdrew consent before surgery (n=1)

Analysis
- Analysed for primary outcome (n=77)
  - Excluded from analysis (n=0)
- Analysed for primary outcome (n=79)
  - Excluded from analysis (n=0)
Figure 2. Cumulative percentage plot showing the change in haemoglobin between randomisation and surgery for participants in the intervention and control groups.

Cumulative percentage plot showing the change in haemoglobin between randomisation and surgery for participants in the intervention and control groups.

Hb level increased for less than 50% of participants in the control group compared to an increase in more than 85% of participants in the intervention group. This increase was greater than 10g/L for more than 50% of participants in the intervention group, whereas only around 15% of participants in the control group showed an increase this large.
Figure 3. Haemoglobin at randomisation, surgery, discharge and at 6-week follow-up by treatment groups

Box and whisker plots showing haemoglobin distribution at the four time points

- Randomisation
- Surgery
- Discharge
- 6 weeks follow up

Control
Intervention

Percntiles
10% 25% 50% 75% 90%
## Table 1 Patient, surgery and haematological baseline characteristics

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<th>Intervention (n=79)</th>
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<tr>
<td>Not diabetic</td>
<td>56 (72.7)</td>
<td>59 (74.7)</td>
</tr>
<tr>
<td>Diet- controlled</td>
<td>1 (1.3)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Oral therapy</td>
<td>7 (9.1)</td>
<td>6 (7.6)</td>
</tr>
<tr>
<td>Insulin</td>
<td>13 (16.9)</td>
<td>12 (15.2)</td>
</tr>
<tr>
<td>Renal function, eGFR (ml/min/1.73m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60</td>
<td>67 (87.0)</td>
<td>71 (89.9)</td>
</tr>
<tr>
<td>30-60</td>
<td>10 (13.0)</td>
<td>8 (10.1)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Euroscore II</td>
<td>2.04 (1.35-3.10)</td>
<td>2.33 (1.47-3.89)</td>
</tr>
<tr>
<td><strong>Surgical characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery within 2-10 weeks of randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>22 (28.6)</td>
<td>26 (32.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>55 (71.4)</td>
<td>53 (67.1)</td>
</tr>
<tr>
<td>Time between randomisation and surgery (days)</td>
<td>38 (24-77)</td>
<td>48 (29-84)</td>
</tr>
<tr>
<td><strong>Type of surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>27 (35.1)</td>
<td>33 (41.8)</td>
</tr>
<tr>
<td>CABG + Valve</td>
<td>14 (18.2)</td>
<td>13 (16.5)</td>
</tr>
<tr>
<td>Valve</td>
<td>36 (46.8)</td>
<td>33 (41.8)</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time (min)</td>
<td>92 (71-127)</td>
<td>88 (67-112)</td>
</tr>
<tr>
<td><strong>Haematological characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Control</strong></td>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Haemoglobin at randomisation (g/L)</td>
<td>124 (117-129)</td>
<td>120 (112-125)</td>
</tr>
<tr>
<td>Reticulocyte count (x10⁹/L)</td>
<td>60 (50-74)</td>
<td>54 (46-67)</td>
</tr>
<tr>
<td>Ferritin (µg/L)</td>
<td>66 (26-123)</td>
<td>60 (35-121)</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>16 (11-20)</td>
<td>17 (14-22)</td>
</tr>
<tr>
<td>Hepcidin (ng/ml)</td>
<td>21.5 (7.8-34.2)</td>
<td>17.0 (7.5-35.3)</td>
</tr>
<tr>
<td>Erythropoietin (U/L)</td>
<td>15.3 (12.2-18.6)</td>
<td>12.8 (9.2-19.2)</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml)</td>
<td>379 (291-470)</td>
<td>358 (284-485)</td>
</tr>
<tr>
<td>Folate (ng/ml)</td>
<td>9.0 (6.8-12.2)</td>
<td>8.3 (6.0-11.6)</td>
</tr>
<tr>
<td>TSH (mIU/L)</td>
<td>1.7 (1.3-2.7)</td>
<td>1.6 (1.2-2.7)</td>
</tr>
<tr>
<td>Thyroxine (pmol/L)</td>
<td>16.0 (14.3-18.4)</td>
<td>15.6 (14.1-17.2)</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>3.0 (1.6-7.0)</td>
<td>2.4 (1.0-5.3)</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>88 (77-109)</td>
<td>85 (76-102)</td>
</tr>
</tbody>
</table>

Data are reported as median (IQR) or number (%).

BMI = body mass index. eGFR= estimated glomerular filtration rate. Euroscore II = European System for Cardiac Operative Risk Evaluation. CABG=coronary artery bypass grafting. TSH = thyroid stimulating hormone.
Table 2. **Transfusion of red blood cells or other blood products**

<table>
<thead>
<tr>
<th></th>
<th>Control (n=77)</th>
<th>Intervention (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any RBC transfusion (Day 0-5)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>14 (18.2)</td>
<td>26 (32.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>63 (81.8)</td>
<td>53 (67.1)</td>
</tr>
<tr>
<td><strong>In transfused patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. RBC units</td>
<td>2 (2-4)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>RBC volume (ml)</td>
<td>604 (566-1145)</td>
<td>597 (314-1089)</td>
</tr>
<tr>
<td>Fresh frozen plasma volume (ml)</td>
<td>0 (0-0)</td>
<td>0 (0-0)</td>
</tr>
<tr>
<td>Cryoprecipitate volume (ml)</td>
<td>0 (0-400)</td>
<td>0 (0-400)</td>
</tr>
<tr>
<td>Platelets volume (ml)</td>
<td>0 (0-205)</td>
<td>0 (0-289)</td>
</tr>
</tbody>
</table>

Data are reported as median (IQR) or number (%). RBC=red blood cells.
Table 3. **Secondary outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (n=77)</th>
<th>Intervention (n=79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin change between randomisation and surgery (g/L)</td>
<td>0.0 (-5.0-6.0)</td>
<td>12.0 (7.0-17.0)</td>
</tr>
<tr>
<td>Postoperative blood loss* after 12 hours (ml)</td>
<td>425 (308-6580)</td>
<td>450 (325-675)</td>
</tr>
<tr>
<td>Postoperative blood loss* after 24 hours (ml)</td>
<td>600 (450-930)</td>
<td>650 (450-905)</td>
</tr>
<tr>
<td>Significant postoperative myocardial injury</td>
<td>2 (2.6)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>18 (23.4)</td>
<td>15 (19.0)</td>
</tr>
<tr>
<td>Re-sternotomy for bleeding within 24h of surgery</td>
<td>5 (6.5)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Delirium</td>
<td>6 (7.8)</td>
<td>7 (8.9)</td>
</tr>
<tr>
<td>Cerebral events &lt;24h</td>
<td>0 (0.0)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Length of postoperative hospital stay (days)</td>
<td>8 (5-13)</td>
<td>8 (6-11)</td>
</tr>
<tr>
<td>Composite adverse events Death/Stroke/RRT/IABP/Debridement</td>
<td>3 (3.9)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (2.6)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0)</td>
<td>4 (5.1)</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>2 (2.6)</td>
<td>3 (3.8)</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>1 (1.3)</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Surgical debridement</td>
<td>0 (0.0)</td>
<td>3 (3.8)</td>
</tr>
</tbody>
</table>

Data are reported as median (IQR) or number (%).

*n=76 for control group
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**Supplementary Material**
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