Intravenous iron to treat anaemia before cardiac surgery (ITACS): international, double blind, placebo controlled randomised trial

Paul S Myles,[1 2] Andrew A Klein,[3] Julian A Smith,[2 4] Sophia Wallace,[1 2] Andrew Forbes,[2] Silva Zavarsek,[5] Joel A Symons,[1 6] Robert A Baker,[7] Erica M Wood,[2 4] Zoe McQuilten,[1 2] David McGiffin,[1] Guy Christie-Taylor,[8] Chong Kee Soon,[9] Matthew T V Chan,[10] Catherine Martin,[2] Toby Richards[11]; on behalf of the Australian and New Zealand College of Anaesthetists Clinical Trials Network and the ITACS investigators

For numbered affiliations see end of the article

Correspondence to: PS Myles p.myles@alfred.org.au (ORCID 0000-0002-3324-5456)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2026;394:e100407
http://dx.doi.org/10.1136/bmj-2026-100407

Accepted: 21 July 2026

ABSTRACT

OBJECTIVE

To evaluate the effects of intravenous iron on red cell transfusion and recovery after cardiac surgery.

DESIGN

International, multicentre, double blind, placebo controlled randomised trial (ITACS).

SETTING

33 hospitals across 10 countries. Participants were enrolled between July 2016 and December 2023.

PARTICIPANTS

955 adults with anaemia undergoing elective cardiac surgery. Exclusion criteria included haemoglobinopathy or iron storage disorder, renal dialysis, and erythropoietin or intravenous iron given in the previous four weeks.

INTERVENTION

A computer generated program randomised participants to intravenous iron 1000 mg or placebo 1-26 weeks before surgery. Participants, clinicians, and data collectors were masked to the intervention.

MAIN OUTCOME MEASURES

The number of days alive and at home up to 90 days after surgery (primary outcome), red cell transfusion requirements and complications (secondary outcomes).

RESULTS

Of 2993 screened participants, 955 were enrolled and 921 of the eligible 939 modified intention-to-treat participants were assessed for the primary outcome. The median number of days alive and at home up to 90 days after surgery was 81.1 (interquartile range 74.8-83.7) in patients assigned to intravenous iron and 80.0 (69.5-83.6) in those receiving placebo (adjusted median difference 1.0 day, 95.4% confidence interval 0.0 to 2.1 days, P=0.041). Red cell transfusions were given to 262 patients (61.1%) in the iron group and 302 (68.2%) in the placebo group during their hospital stay (relative risk 0.90, 95% confidence interval 0.82 to 0.99, P=0.027). No differences were observed for major complications or length of hospital stay.

CONCLUSION

Among patients with anaemia undergoing elective cardiac surgery, preoperative intravenous iron was associated with a reduction in red cell transfusion and a small improvement in the number of days alive and at home in the first 90 days after surgery. Intravenous iron is an effective component of patient blood management in this setting.

TRIAL REGISTRATION

ClinicalTrials.gov NCT02632760.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Anaemia and blood transfusions are associated with an increased risk of complications and longer hospital stays after cardiac surgery

Preoperative intravenous iron supplementation increases haemoglobin and may reduce red cell transfusion, but evidence does not show improved patient centred outcomes or home days after cardiac surgery

WHAT THIS STUDY ADDS

This study shows that intravenous iron repletion in patients with anaemia before cardiac surgery increased preoperative haemoglobin concentration, reduced the need for red cell transfusion, and resulted in an extra day at home in the first 90 days after surgery

Intravenous iron saved approximately 44 units of blood products for every 100 patients treated

These benefits were similar in patients with or without demonstrable iron deficiency

Introduction

Preoperative anaemia affects a third of patients undergoing cardiac surgery and increases the risk of red cell transfusion.[1] Contemporary studies report approximately 20-50% of patients having cardiac surgery receive a blood transfusion.[1-3] Anaemia and blood transfusion are associated with increased complications, intensive care unit and hospital stay, and mortality after cardiac surgery.[3 4]

The most common cause of anaemia globally is iron deficiency,[5] and intravenous iron is a readily available and relatively inexpensive treatment option for patients in advance of major surgery. However, the safety, cost effectiveness, and impact on quality of life of intravenous iron supplementation in this setting are uncertain.[6 7] A 2024 systematic review of 14 clinical trials including 2043 patients undergoing cardiac surgery found that preoperative intravenous iron reduced the need for red cell transfusion from 53.4% to 40.2%, relative risk 0.77 (95% confidence interval (CI) 0.65 to 0.92). However, the study showed no beneficial effects on postoperative complications or any other patient centred outcomes.[2]

The ITACS (intravenous iron to treat anaemia before cardiac surgery) trial evaluated whether intravenous iron supplementation in patients with preoperative anaemia improves recovery and reduces complications,

enabling patients to have more time at home in the 90 days after cardiac surgery.

Methods

Trial design

We have previously published the design and rationale of the ITACS trial.[8] This was a multicentre, international, double blind, randomised, parallel group, placebo controlled pragmatic trial to assess whether intravenous iron was superior to placebo in patients with anaemia before cardiac surgery. We did not require evidence of iron deficiency as a cause of the anaemia. Patients were randomly assigned (1:1) to preoperative intravenous iron or matched placebo. The ethics committee at each site approved the study. Steering committee members vouch for the accuracy of the dataset and adherence to the protocol and analysis plan. The trial is registered at ClinicalTrials.gov (NCT02632760).

Participants

Eligible participants included men and women aged at least 18 years with anaemia (haemoglobin concentration <130 g/L) and with or without known iron deficiency. Participants were expected to undergo elective on-pump or off-pump cardiac surgery and were able to receive the trial drug 1-26 weeks before their planned operation. We modified our sex based haemoglobin inclusion criterion in the early phase of the trial because of growing criticism about a sex discriminatory criterion. We excluded patients undergoing transcatheter aortic valve implantation (but included patients who had their operation modified to either of these procedures after enrolment and randomisation), those with known or suspected haemoglobinopathy or iron storage disorder, those having renal dialysis, and those who received erythropoietin or intravenous iron in the previous four weeks. Complete details are reported in supplementary file S2. All patients provided written informed consent.

Randomisation and blinding

Randomisation was performed using a computer generated code that was accessed through a web based service. Group assignment was stratified by site, baseline haemoglobin (< or ≥100 g/L), and planned surgery (isolated coronary artery or single valve, or combined or other) using permuted blocks. The patients, anaesthetic and surgical teams, outcome assessors, and endpoint adjudicators were masked to group identity.

Intervention

The preparation of the study drug and its administration was done by unmasked study personnel or a hospital pharmacist not involved in any study evaluations. Preparation required drawing up the active drug or placebo (0.9% saline) into a black syringe and administration through a black (opaque) infusion line into a dedicated peripheral intravenous catheter (supplementary file S3),[8] and administered by slow intravenous push or infusion over 15-30 mins. We used one of two intravenous iron preparations according to country (supplementary file S1): ferric carboxymaltose (Vifor Pharma, Opfikon, Switzerland) or ferric derisomaltose also known as iron isomaltoside 1000 (Pharmacosmos A/S, Holbæk, Denmark), each 1000 mg, as a single dose infusion.[8] The effectiveness of patient masking was evaluated by asking patients to guess their group assignment on the eventual day of surgery.

Trial procedures

Patient demographic and perioperative data were recorded. The European System for Cardiac Operative Risk Evaluation II was used to indicate perioperative risk,[9] with higher scores indicating greater risk. All surgical, anaesthetic, and other perioperative clinical care, including investigations, were performed according to local practices. Red cell transfusion was recommended in line with established national and institutional guidelines.[4 10]

Blood samples were collected at baseline (before the intravenous study drug was administered) to measure haemoglobin and haematocrit, ferritin, transferrin and transferrin saturation, C reactive protein, and creatinine. Repeat blood tests were done on the day of surgery. If the baseline blood tests suggested that iron deficiency was an unlikely cause of the anaemia, additional blood testing was done to identify anaemia of chronic disease.[10 11] Measurement of serum phosphate was recommended on the day of surgery but not mandated.

Functional and quality of life questionnaires were completed at baseline, hospital admission, and during follow-up using the World Health Organization Disability Assessment Schedule 2 (WHODAS),[12] MacNew Heart Disease Health related Quality of Life,[13] and the EuroQol 5-dimension scale.[14] These questionnaires measured the participant's quality of life covering the domains of mobility, self-care, usual activities, pain or discomfort, anxiety or depression, and overall health state. Details of surgery, intensive care unit and hospital stay were recorded on the case report form.

Outcomes

We devised a statistical analysis plan with prespecified outcomes and published it on our publicly available trial website (www.itacs.org.au) before completion of the trial (supplementary file S4). We anticipated that some patients undergoing elective surgery would have a change in their health status, a change in the planned operation, or a change in their medical condition leading to cancellation of the operation. For these situations, the date of the change or cancellation of their original planned surgery was used as the intended date of surgery. These patients had their follow-ups to 90 days from that time so that their outcome data could be collected.

The primary outcome of the study was the number of days alive and at home up to 90 days after surgery (DAH_{90}).[15 16] DAH_{90} is a patient centred metric that encompasses the duration of hospital stay, additional days of any inpatient rehabilitation or readmission or both, and postoperative mortality. The calculation of DAH_{90} is detailed in the statistical analysis plan (supplementary file S4). In brief, DAH_{90} is calculated using the day and time of surgery as the starting point (day 0) and calculated as all days spent at home by the patient until day 90. A patient who dies within 90 days of surgery is scored as zero irrespective of whether they had spent some of that time at home. If the patient is discharged to a nursing facility or readmitted to hospital, the time spent in hospital because of readmission or that facility will be deducted in the DAH_{90} calculation (up to the limit of 90 days). Examples of DAH_{90} consistent with this definition are given in the protocol. Our case report form collected date (dd.mm.yyyy) and time (hh.mm) so that we could calculate DAH_{90} precisely, then we rounded it to fractions of a day for clinical relevance. Death within 90 days of surgery was recorded as zero days at home irrespective of whether patients had some time at home in that follow-up period.[12 15] We originally planned to measure our primary outcome up to 30 days after surgery (DAH_{30}) but recent clinical trials suggested a possible delayed response to the peak effect of intravenous iron, with readmissions beyond 30 days being a feature.[17 18] Therefore, we amended our primary outcome in December 2020.

The prespecified secondary outcomes were change in haemoglobin concentration from day of enrolment to day of surgery (preoperative response), correction of iron deficiency state (ferritin, transferrin saturation) from treatment to day of surgery, red cell transfusion (units), postoperative complications, 15 item quality of recovery scale,[19] intensive care unit and hospital stay, DAH_{30}, disability-free survival,[12] 90 day survival, and patient reported quality of life.[13 14] Adverse events were recorded (supplementary file S15). A cost effectiveness analysis is planned and will be published later.

Statistical analysis

DAH_{30} and DAH_{90} have a skewed distribution to the left with a small spike at day 0 owing to deaths in hospital.[15 16] The required sample size was obtained with simulations (B=10 000) by generating first hospital length of stay using a log-normal distribution, truncating DAH_{30} at 26 days, and finally computing DAH_{30} as 26 minus duration of hospital stay.[8] The log-normal distribution was calibrated to achieve a similar variability (standard deviation 8) and the median in the control arm was set to 17 days. A sample size of n=1000 has 93% and 81% power to detect a median increase of 1.5 and 1.25 days, respectively, using the Wilcoxon sum rank test; these proportions are comparable for DAH_{90}. After adjustment for 5% loss to follow-up and 10% crossover in the experimental arm, the trial had 94% power to detect a median difference of 1.45 days in DAH_{90}.

All patients were analysed in the groups to which they were assigned according to the intention-to-treat principle. For analysis of DAH_{90} we used a Wilcoxon rank sum test and quantile regression for estimating the treatment effect at the median DAH_{90}, adjusted for the randomisation stratification factors, and confidence interval (CI), with quantile regression considered the decisive analysis in case of discrepancy. CIs for the effect of intravenous iron on the median DAH_{90} or other relevant quantiles were obtained using bootstrapping with B=4000 replicates and centile based CIs. The nominal level 95% was slightly corrected (ie, 95.4% CI) to account for the two interim analyses.

Continuous secondary outcomes were analysed using multivariable linear regression. These analyses were adjusted for the baseline measurement of the outcome when available. Red cell transfusion units, DAH_{30}, and length of stay outcomes are summarised with medians and interquartile ranges and with estimated differences between medians and their 95% CIs computed through quantile regression. For quantile regression, death before discharge was set as the largest duration. Binary outcomes are expressed as risk ratios and standard 95% CIs using log-binomial regression or exact logistic regression to approximate these values when the number of events in either arm is fewer than five. In case of convergence issues with log-binomial regression, log-Poisson regression with robust standard errors was used. When possible, adjustment for region, baseline haemoglobin, and planned surgery—like the adjusted analysis for the primary outcome—were carried out in all the models to be consistent with the primary outcome analysis.

Because iron studies are not routine before cardiac surgery internationally, we prespecified iron deficiency in a subgroup analysis. Planned subgroup analyses assessed the effect of intravenous iron by patient age group, sex, surgery type, time from randomisation to operation (<4 weeks or ≥4 weeks), iron deficiency (ferritin <30 mg/dL or <100 mg/dL and C reactive protein >5 mg/L and/or transferrin saturation <20%),[11] haemoglobin strata (≤100, 101-120, ≥120 g/L), and study drug formulation. These analyses were conducted on the primary outcome using an interaction test in the corresponding quantile regression models. In post hoc analyses requested during the review process, variation in the treatment effect across the range of the continuous scaled subgroup variables (age, baseline haemoglobin, and time from iron infusion to surgery) was estimated from quantile regression models. These models are the main subgroup analyses of these variables and included interactions of treatment with the linear and quadratic terms of the subgroup variables, together with pointwise 95% CIs, and a Wald test for any treatment effect variation over the range of the subgroup variable obtained from bootstrapped standard errors (4000 bootstrap samples). Specific treatment effects are presented for the 10th, 25th,

50th, 75th, and 90th centiles of each subgroup variable, together with 95% CIs.

The full analysis code can be viewed at https://doi.org/10.26180/c.8534361. Analyses were conducted using Stata version 19.0.

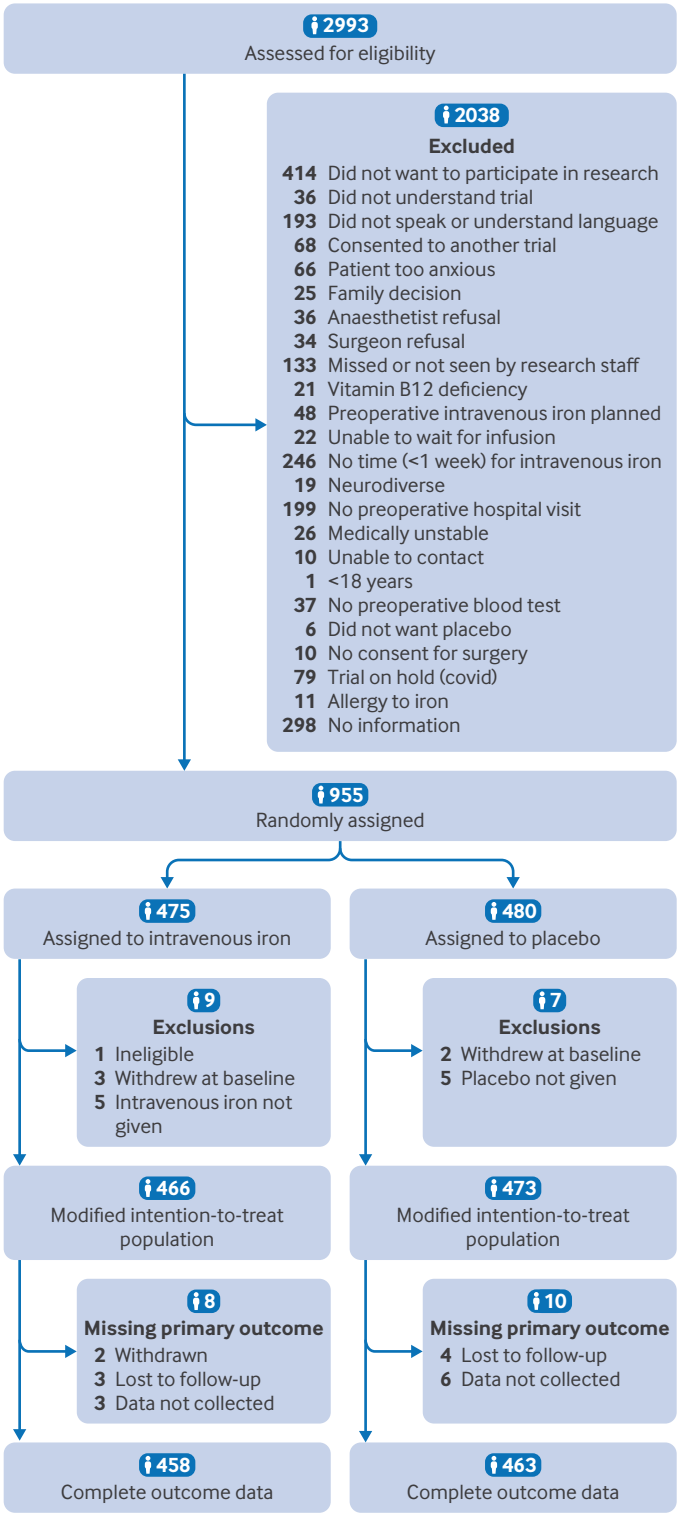

Fig 1 | CONSORT (Consolidated Standards of Reporting Trials) flowchart of ITACS (intravenous iron to treat anaemia before cardiac surgery) trial participants

Quality control and compliance checks

A steering committee provided oversight of the trial, a data quality committee monitored compliance and completeness of the data, and a data and safety monitoring committee advised on whether the trial should be stopped because of clear evidence of benefit or harm.[8] Interim analyses were planned after enrolment of 350 and 700 patients, adjusted according to an O'Brien and Fleming type I error spending function. The roles and responsibilities of each committee were defined by charters. Sites recruiting 35 or more participants were independently audited to review a random sample to verify eligibility criteria, patient consent, and outcomes using source documents. No discrepancies were identified during the audits.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research because this was not a requirement for ethics approval or funding at the initiation of the trial.

Results

The 33 participating centres from 10 countries in the ITACS trial enrolled patients between 15 July 2016 and 15 December 2023. Of 2993 screened patients, 955 were enrolled and randomly assigned: 475 to the intravenous iron group and 480 to the placebo group; 939 patients were included in the intention-to-treat population at baseline and 921 patients were assessed for the primary endpoint (fig 1). Patient masking to treatment group assignment was achieved (supplementary file S5).

The mean age of patients was 66 years, 60% were male, the median EuroSCORE was 1.7, and 472 (58.7%) of 804 trial participants tested had evidence of iron deficiency. The mean haemoglobin concentration was 119 g/L (standard deviation 12), the median ferritin concentration was 111 µg/L (interquartile range 48-243), and transferrin saturation was 18% (interquartile range 13-25%). Demographic, medical, and perioperative characteristics at baseline were similar between groups (table 1 and supplementary file S6). The median time from intravenous study drug administration to the day of surgery was 29.9 days (interquartile range 14.1-63.1 days) in the intravenous iron group and 27.9 days (12.9-58.1 days) in the placebo group. The median duration of surgery was 3.7 hours and the median postoperative mediastinal drain blood loss 450 mL in both groups (table 2). Fifteen patients (five in the iron group, 10 in the placebo group) received open label intravenous iron before surgery and 24 patients (seven in the iron group, 17 in the placebo group) in the 90 days after surgery (supplementary file S7).

Outcomes

The median number of days alive and at home up to 90 days after surgery was 81.1 (interquartile range 74.8-83.7) in patients assigned to intravenous iron

and 80.0 (69.5-83.6) in those receiving placebo (adjusted median difference 1.0 day, 95.4% CI 0.0 to 2.1, P=0.041; table 3). Supplementary file S8 gives details of each component of the outcome. Sixteen deaths (3.5%) occurred in the intravenous iron group and 22 (4.8%) in the placebo group up to 90 days after surgery. The increase in time at home was cumulative after discharge up to 90 days after surgery (supplementary files S9 and S10). The effect of intravenous iron was consistent before, during, and after the covid pandemic (supplementary file S11). On post hoc testing, the benefit of intravenous iron was most noticeable among patients with poorer recovery—one quarter of patients receiving placebo had DAH_{90} <70 whereas this figure was higher in the intravenous iron group (DAH_{90} <75; adjusted difference 6.1 days, 95% CI 1.9 to 8.9, P=0.005; table 4). When estimating DAH_{90} at the 10th, 25th, 50th, 75th, and 90th centiles simultaneously, marked variation was found in iron infusion versus placebo difference across the five quantiles (P=0.014), including comparing the intergroup difference at the 25th versus 50th centile (P=0.006). These exploratory results indicate that the beneficial effects of intravenous iron are greatest in those with poorer recovery (likely higher preoperative risk) profiles.

Figure 2 presents the subgroup analyses and supplementary files S12-S13 give the original prespecified and additional subgroup analyses. For the primary outcome, we found little evidence that the effect of intravenous iron varied across subgroups: patient age group (P=0.34), sex (P=0.47), surgery type (P=0.36), iron deficiency (P=0.88), haemoglobin strata (P=0.76), study drug formulation (P=0.32), and time from infusion to surgery (P=0.20). These results for age, haemoglobin, and time from infusion to surgery differed little from those when categorised according to the original statistical analysis plan (supplementary file S13).

On the day of surgery, a median 28.7 days after receiving the study drug, the haemoglobin concentration in patients in the iron group was significantly higher than in the placebo group (median difference 3.8 g/L, interquartile range 2.3-5.3), as was the ferritin concentration and transferrin saturation (all P<0.001). On post hoc testing, patients in the iron group were more likely to have their anaemia corrected by the day of surgery: 123 (27.0%) versus 76 (16.5%), risk difference 11.0% (95% CI 5.7 to 16.3), P<0.001. Red cell transfusions were given to 143 patients (33.3%) in the iron group and 189 patients (42.7%) in the placebo group intraoperatively (relative risk 0.79, 95% CI 0.67 to 0.92, P=0.003; table 2). The total number of red cell units transfused intraoperatively was 320 in the iron group and 470 in the placebo group.

The median QoR-15 (15 item quality of recovery score) score at three days after surgery was 101 (interquartile range 81-114) in the iron group and 97 (76-112) in the placebo group (P=0.062; table 3). Red cell transfusions were given to 262 patients (61.1%) in the iron group and 302 patients (68.2%) in the placebo group during their hospital stay (relative risk 0.90, 95% CI 0.82 to 0.99, P=0.027; table 3) with a number needed to treat of 14.6 (95% CI 7.7 to 125). The total number of red cell units transfused during hospital stays was 972 in the iron group and 1202 in the placebo group. Therefore, intravenous iron supplementation saved approximately 44 units of blood products for every 100 patients treated. For risk of red cell transfusion during the hospital stay, the effect of intravenous iron was consistent across subgroups (supplementary file S14). No significant difference was found in intensive care unit or hospital stay.

Table 1 | Characteristics of patients at study entry

Characteristics	Intravenous iron (n=466)	Placebo (n=473)
Personal characteristics		
Age (years), mean (SD)	65.9 (11.1)	66.0 (11.2)
Male sex	280 (60.1)	280 (59.2)
Race		
White	295 (63.3)	298 (63.0)
Asian	111 (23.8)	112 (23.7)
Indian or Pakistani	26 (5.6)	31 (6.6)
Black	7 (1.5)	5 (1.1)
Other	27 (5.8)	27 (5.7)
Risk and health status scores		
ASA physical status		
2	19 (4.1)	23 (4.9)
3	306 (65.8)	313 (66.2)
4	140 (30.1)	137 (29.0)
EuroSCORE II, median (IQR)	1.6 (1.0-3.0)	1.8 (1.1-3.1)
WHODAS score, median (IQR)	20 (15-27)	20 (15-26)
MacNew score, median (IQR)	139 (114-159)	138 (114-159)
EQ-5D-5L VAS, median (IQR)	70.0 (55-80)	70.0 (50-80)
Pre-existing medical conditions		
Heart failure	116 (25.1)	127 (27.3)
Previous myocardial infarction	136 (29.4)	104 (22.3)
Smoking history	183 (39.7)	202 (43.3)
Chronic lung disease	70 (15.2)	81 (17.4)
Diabetes	183 (39.6)	206 (44.2)
Preoperative drugs		
Oral iron treatment	41 (8.9)	48 (10.3)
Statin	334 (72.3)	339 (72.7)
ARB or ACE inhibitor	232 (50.2)	244 (52.4)
Beta blocker	275 (59.5)	271 (58.2)
Calcium channel blocker	132 (28.6)	115 (24.7)
Preoperative laboratory test		
Haemoglobin (g/L), mean (SD)	119.5 (11.5)	118.7 (11.9)
Ferritin (µg/L), median (IQR)	114 (47-242)	109 (50-245)
Transferrin (g/L), median (IQR)	2.6 (2.3-3.1)	2.6 (2.3-3.1)
Transferrin saturation (%), median (IQR)	19.0 (13.0-25.0)	18.0 (12.0-24.5)
Type of surgery		
Coronary artery bypass graft	171 (36.9)	181 (38.8)
Valve	159 (34.3)	174 (37.3)
Combined	66 (14.3)	64 (13.7)
Other*	33 (7.1)	24 (5.2)
No surgery	34 (7.3)	23 (4.9)
Creatinine baseline (µmol/L), median (IQR)	90.0 (72.0-110.0)	89.0 (72.0-112.0)

Data are numbers (%) unless stated otherwise. Denominators may vary because some patients did not undergo surgery.
ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; ASA=American Society of Anaesthesiologists; EQ-5D-5L=European Quality of Life: 5 dimensions 5 levels; IQR=interquartile range; MacNew=MacNew heart disease health-related quality of life; SD=standard deviation; WHODAS=12-Item World Health Organization Disability Assessment Schedule, which estimates amount of disability; scores of 24 or more indicate at least moderate disability.
*Other surgery includes septal defect repair, pulmonary thromboendarterectomy, and so forth.

Table 2 | Perioperative characteristics

Characteristics	Intravenous iron (n=466)	Placebo (n=473)	Difference (95% CI)	P value*
Day of surgery (preoperative)				
Haemoglobin (g/L), mean (SD)	120.7 (13.5)	116.3 (14.1)	3.8 (2.3 to 5.3)	<0.001
Ferritin (µg/L), median (IQR)	517 (267-816)	112 (56-232)	415 (371 to 478)	<0.001
Transferrin saturation (%), median (IQR)	28.0 (22.0-39.0)	19.0 (14.0-28.0)	7.4 (5.2 to 9.70)	<0.001
WHODAS score, median (IQR)	20.0 (15.0-28.0)	20.0 (15.0-27.0)	-0.4 (-1.1 to 0.4)	0.37
MacNew score, median (IQR)	141 (117-160)	138 (112-160)	—	—
EQ-5D-5L VAS, median (IQR)	70 (60-80)	70 (50-80)	-0.4 (-2.4 to 1.7)	0.71
Day of surgery (intraoperative)				
Total bypass time (min), median (IQR)	98 (74-135)	98 (75-135)	—	—
Lowest haemoglobin concentration during bypass, mean (SD)	82.0 (12.7)	79.5 (12.9)	—	—
Red cell transfusion	143 (33.3)	189 (42.7)	0.79 (0.67 to 0.92)	0.003
Red cell units, median (IQR)	0.0 (0.0-1.0)	0.0 (0.0-2.0)	0.0 (-5.1 to 5.1)	1.0
Platelets	107 (24.9)	101 (22.8)	—	—
Fresh frozen plasma	72 (16.8)	73 (16.5)	—	—
Total mediastinal drainage (mL), median (IQR)	450 (300-690)	450 (290-765)	—	—
Surgical time (min), median (IQR)	220 (177-273)	224 (180-273)	—	—

Data are numbers (%) unless stated otherwise. Denominators may vary because some patients did not undergo surgery.
CI=confidence interval; EQ-5D-5L=European Quality of Life: 5 dimensions 5 levels; IQR=interquartile range; MacNew=MacNew heart disease health-related quality of life; SD=standard deviation; WHODAS 12-Item World Health Organization Disability Assessment Schedule, which estimates amount of disability; scores of 24 or more indicate at least moderate disability; VAS=visual analogue scale; number of red cell units (bags) reported are only for those who received a transfusion intraoperatively.
*P values are calculated by χ^2 test or Wilcoxon rank sum test.

The rates of death, myocardial infarction, stroke, other cardiovascular events, and infections were comparable between groups at 30 days after surgery (table 3), but some evidence was observed of a reduced risk of respiratory infections in the iron group (supplementary file S15). Fewer patients in the iron group than in the placebo group received a red cell transfusion up to three months after surgery (59.1% and 67.1%, respectively; relative risk 0.88, 95% CI 0.80 to 0.97; P=0.011). Disability-free survival was 46.2% in the iron group and 40.2% in the placebo group at six months after surgery (relative risk 1.14, 95% CI 0.99 to 1.32, P=0.064; table 3). The WHODAS (disability) score was lower for patients in the iron group than for those in the placebo group at 30 days (P=0.015), but not at three months (P=0.15) or six months (P=0.69) after surgery (supplementary file S16). We observed no significant between group differences in quality of life assessed by the EQ-5D-5L (European Quality of Life: 5 dimensions 5 levels) questionnaire at 30 days, three months, and six months after surgery (supplementary file S16).

Adverse events

Except for hypophosphataemia, which occurred in approximately 20% of those tested on the day of admission for surgery (relative risk 16.3, 95% CI 5.1 to 51.5), the numbers of patients experiencing adverse events were similar between groups (supplementary file S15). We had no reports of anaphylaxis or transfusion reactions.

Sensitivity and per protocol analyses

The above results were not meaningfully affected after excluding 53 patients who were enrolled and received the intravenous study drug but did not undergo surgery (supplementary files S17-S21), or in a per protocol analysis (supplementary files S22-S25).

Discussion

Principal findings

In this international randomised controlled trial, we found that intravenous iron administered to patients with anaemia in the weeks before elective cardiac surgery increased the preoperative haemoglobin concentration and partly corrected anaemia, reduced red cell transfusions, and resulted in an extra day at home in the first 90 days after surgery. The increase in home days was larger in those with poor recovery profiles. Intravenous iron supplementation saved approximately 44 units of blood products for every 100 patients treated. These benefits were similar in patients with or without demonstrable iron deficiency and with both iron preparations. We did not find evidence of an increased risk of infection with intravenous iron. Intravenous iron was associated with an increased risk of hypophosphataemia but no other adverse effects. The effectiveness of perioperative phosphate supplementation in patients receiving intravenous iron has not yet been shown.

Even though more time at home after surgery is highly valued by patients,[20-22] we could question whether a one day difference is of clinical importance. However, we did observe a larger effect size (difference 9.0 days and 6.1 days) for the 10th and 25th centiles of home days, respectively, indicating that intravenous iron has a stronger effect in those with a poor recovery profile—that is, the 10-25% of patients likely to have multimorbidity and at greatest risk of postoperative complications.[23 24] DAH_{90} reflects patients' (and clinicians') primary aim of a healthy recovery free of serious complications and hospital readmissions, has been validated as a patient centred outcome in Australia,[15] Sweden,[16] Canada,[25] and the UK,[26] and is associated with reduced hospital costs.[16 27] The increase in time at home did not occur because of earlier hospital

Table 3 | Primary and secondary outcomes in ITACS trial

Outcome	Intravenous iron (n=466)	Placebo (n=473)	Estimate (95% CI*)	Effect measure	P value
Primary outcome					
Days at home at 90 days					
Median (IQR)	81.1 (74.8-83.7)	80.0 (69.5-83.6)	1.0 (0.0 to 2.1)	DMedian	0.04
Mean (SD)	73.7 (20.7)	70.1 (23.5)	—	—	—
Secondary outcomes					
In hospital†					
QoR-15 score day 3, median (IQR)	101.0 (81.0-114.0)	97.0 (76.0-112.0)	3.3 (-0.2 to 6.7)	Dmedian	0.06
Red cell transfusion	262 (61.1)	302 (68.2)	0.90 (0.82 to 0.99)	RR	0.027
Red cell transfusion (units), median (IQR)	1.0 (0.0-3.0)	2.0 (0.0-4.0)	-1.0 (-1.4 to -0.7)	Dmedian	<0.001
Intensive care unit readmission	21 (4.9)	32 (7.2)	0.68 (0.40 to 1.16)	RR	0.15
Hospital stay (days), median (IQR)	8.1 (6.2-11.0)	8.1 (6.2-11.3)	0.0 (-0.5 to 0.6)	Dmedian	0.95
30 days after surgery†					
Days at home, median (IQR)	21.7 (16.0-23.8)	20.9 (12.8-23.7)	0.1 (-0.3 to 1.3)	Dmedian	0.28
Myocardial infarction	13 (2.8)	13 (2.8)	1.02 (0.48 to 2.16)	RR	0.97
Stroke	9 (1.9)	16 (3.4)	0.57 (0.25 to 1.27)	RR	0.17
Other cardiovascular event‡	87 (18.8)	96 (20.6)	0.89 (0.69 to 1.15)	RR	0.39
Infection	105 (22.7)	124 (26.7)	0.84 (0.67 to 1.05)	RR	0.13
Thromboembolism	6 (1.3)	5 (1.1)	1.23 (0.38 to 3.97)	RR	0.73
Total ICU stay (hours), median (IQR)	42.0 (22.0-73.0)	45.5 (24.0-93.0)	-6.0 (-14.0 to 2.0)	Dmedian	0.20
30 day readmission	70 (15.2)	63 (13.6)	1.12 (0.82 to 1.53)	RR	0.49
Mortality	13 (2.8)	14 (3.0)	0.95 (0.45 to 1.99)	RR	0.88
Three months after surgery§					
Haemoglobin (g/L), median (IQR)	114.0 (106.0-124.0)	110.0 (102.0-119.0)	1.1 (-1.2 to 3.3)	Dmean	0.35
Red cell transfusion	267 (59.1)	308 (67.1)	0.88 (0.80 to 0.97)	IRR	0.01
90 day readmission§	118 (26.5)	114 (25.6)	1.04 (0.83 to 1.30)	RR	0.73
Mortality	16 (3.5)	22 (4.8)	0.74 (0.40 to 1.39)	RR	0.35
Six months after surgery§					
Mortality	20 (4.4)	31 (6.8)	0.66 (0.38 to 1.13)	RR	0.13
Disability-free survival¶	210 (46.2)	183 (40.2)	1.14 (0.99 to 1.32)	RR	0.06

Data are numbers (%) unless stated otherwise. Denominators may vary because some patients did not undergo surgery.
All analyses adjusted for randomisation stratification variables of baseline haemoglobin, surgery type, and sites grouped into three regions (1=Australia, New Zealand; 2=Malaysia, Hong Kong, Singapore; 3=Great Britain, Germany, Canada, South Africa, United Arab Emirates). Haemoglobin at three months was also adjusted for baseline value. The QoR-15 score (day 3) and haemoglobin at three months after surgery estimate were calculated using linear regression, with robust standard errors, giving a difference between treatment groups. Binary outcomes analysed using binary regression giving risk ratio estimate, except for red cell binary outcomes (in hospital and up to day 90), both of which failed to converge, therefore Poisson regression was used resulting in incidence rate ratio estimate. Quantile regression was used for primary and secondary skewed outcomes. CIs for iron effect on the median obtained by bootstrapping with 4000 replicates. For analysis of DAH_{90}, 95.4% CIs were used to account for two interim analyses. Statistical analysis plan required both Wilcoxon rank sum test and quantile regression for primary outcome, with quantile regression considered as the decisive analysis in case of discrepancy (Wilcoxon rank sum test result=0.007, no adjustment available). The skewed outcome red cell amount (units given) in hospital could not be analysed using bootstrapping for the CI so quantile regression was undertaken without bootstrapping but using robust standard errors to estimate the CI.
CI=confidence interval; Dmedian=difference in medians; Dmean=difference in means; IQR=interquartile range; IRR=incidence rate ratio; ITACS=intravenous iron to treat anaemia before cardiac surgery; QoR-15=15 item quality of recovery score; RR=risk ratio; SD=standard deviation.
*Except for primary outcome where CIs are 95.4%.
†Excludes those who did not undergo surgery (n=53), for which time of measurement was date of change or cancellation of original planned surgery.
‡Includes atrial fibrillation and heart block.
§Includes 30 day readmissions.
¶Disability defined by World Health Organization Disability Assessment Schedule score of 24 or more (ie, at least moderate disability).

discharge but was cumulative after discharge up to 90 days after surgery and included reduced time in hospital after any readmissions (supplementary file S8). A reduction in anaemia (higher haemoglobin) is likely to provide better overall health status. Most patients undergoing major surgery have many weeks or months of fatigue, sleep disturbance, and impaired physical and mental wellbeing, especially older patients ("post-hospitalisation syndrome").[28] Some of these effects are secondary to reduced iron stores and anaemia from perioperative blood loss (>1 L in cardiac surgery).

Table 4 | Distribution of adjusted median difference (95% CI) at selected quantiles in days alive and at home up to 90 days after surgery (DAH_{90})

DAH_{90}	10th centile	25th centile	50th centile	75th centile	90th centile
DAH_{90} iron*	50.0	74.8	81.1	83.7	85.0
DAH_{90} placebo*	34.0	69.5	80.0	83.6	84.8
DAH_{90} difference (95% CI)‡	9.0 (-5.2 to 21.8)	6.1 (1.9 to 8.9)	1.0 (0.0 to 2.0)†	0.2 (-0.1 to 1.0)	0.4 (-0.0 to 1.0)
P value‡	0.26	0.005	0.041	0.20	0.08

Comparison of difference between 25th and 10th centile was -2.9 (95% CI -9.3 to 15.2), P=0.75. Comparison of difference between 25th and 50th centile was 5.1 (1.3 to 7.5), P=0.006. Comparison of difference between 25th and 75th centile was 5.9 (1.6 to 8.4), P=0.006. Comparison of difference between 25th and 90th centile was 5.7 (1.5 to 8.4), P=0.006.
*Unadjusted quantile values.
†95.4% CI to account for interim analyses.
‡Adjusted for stratification variables, with CIs and P value from 4000 bootstrap replications of simultaneous quantile regression across all listed quantiles. Wald test (4 degrees of freedom) for variation in iron infusion versus placebo difference across DAH_{90} quantiles yielded P=0.014.

Level	Iron	Placebo	Difference (95% CI)	Interaction P value	Difference (95% CI)
Age, years*				**0.34**	
10th centile	82.37 (79.40 to 84.34)	81.70 (75.76 to 83.88)			0.65 (-0.50 to 2.38)
25th centile	82.77 (78.25 to 83.90)	81.74 (75.76 to 83.83)			0.46 (-0.66 to 1.49)
50th centile	81.91 (77.90 to 83.81)	81.75 (76.71to 83.83)			0.97 (-0.49 to 2.31)
75th centile	81.79 (76.87 to 83.80)	80.87 (72.86 to 83.75)			2.10 (-0.20 to 4.33)
90th centile	81.74 (76.00 to 83.75)	80.65 (71.69 to 83.73)			3.30 (-0.53 to 6.85)
Sex				**0.47**	
Male	81.80 (75.00 to 83.9)	80.70 (70.00 to 83.60)			1.07 (0.03 to 2.61)
Female	80.90 (74.80 to 82.9)	79.70 (68.00 to 83.10)			0.26 (-0.84 to 2.69)
Surgery				**0.36**	
CABG	81.80 (75.20 to 83.70)	81.80 (74.30 to 83.80)			-0.01 (-1.02 to 1.29)
Valve	80.90 (75.00 to 83.00)	78.90 (66.90 to 82.70)			1.94 (-0.01 to 4.68)
CABG and valve	79.80 (71.90 to 82.80)	78.20 (56.90 to 81.90)			2.04 (-1.95 to 8.89)
Other	80.70 (76.20 to 83.10)	78.00 (65.50 to 82.40)			2.82 (-1.44 to 12.75)
No surgery	90.00 (88.80 to 90.00)	90.00 (90.00 to 90.00)			
Iron deficiency				**0.88**	
Yes	80.70 (71.00 to 83.00)	79.50 (68.00 to 83.2)			1.21 (-1.55 to 2.90)
No	81.80 (76.70 to 83.70)	80.80 (71.70 to 83.6)			0.98 (-0.29 to 3.09)
Haemoglobin, g/L*				**0.76**	
10th centile	76.87 (62.00 to 80.98)	76.74 (57.00 to 81.94)			0.22 (-3.06 to 3.26)
25th centile	78.79 (61.93 to 82.87)	78.74 (59.50 to 82.98)			1.00 (-0.43 to 2.72)
50th centile	80.65 (71.93 to 82.89)	78.86 (66.78 to 83.11)			1.26 (0.10 to 2.61)
75th centile	80.90 (74.54 to 83.66)	79.33 (68.88 to 83.18)			1.29 (0.12 to 2.44)
90th centile	80.98 (74.76 to 83.70)	79.77 (68.88 to 83.60)			1.16 (-0.17 to 2.36)
Study drug				**0.32**	
Carboxymaltose	81.20 (75.00 to 83.70)	79.00 (66.00 to 83.10)			1.80 (0.05 to 3.39)
Isomaltoside	81.00 (74.70 to 83.80)	80.80 (72.70 to 83.70)			0.69 (-0.85 to 1.71)
Time from infusion to surgery, weeks*				**0.20**	
10th centile	80.82 (68.64 to 83.55)	74.00 (56.00 to 81.84)			1.79 (-0.32 to 3.21)
25th centile	81.80 (70.69 to 83.87)	79.70 (70.00 to 83.02)			1.69 (-0.19 to 3.01)
50th centile	80.89 (73.15 to 83.05)	79.79 (69.26 to 83.09)			1.43 (0.02 to 2.59)
75th centile	80.91 (74.71 to 83.37)	79.33 (69.53 to 82.98)			0.85 (-0.15 to 2.25)
90th centile	80.99 (74.76 to 83.53)	79.70 (69.53 to 82.98)			-0.09 (-1.15 to 2.03)
Country				**0.65**	
Australia	81.00 (73.00 to 83.10)	78.90 (62.50 to 83.10)			1.98 (-0.18 to 3.64)
Malaysia	81.80 (78.60 to 84.70)	81.70 (71.90 to 83.80)			0.31 (-1.81 to 3.93)
Great Britain	81.80 (76.90 to 83.80)	80.80 (75.80 to 83.60)			0.67 (-1.48 to 1.95)
Hong Kong	80.60 (70.40 to 82.20)	78.80 (75.10 to 81.90)			1.87 (-3.70 to 4.45)
New Zealand	81.90 (76.20 to 83.90)	81.10 (76.90 to 83.80)			1.00 (-4.74 to 4.26)
South Africa	81.90 (74.80 to 90.00)	72.80 (59.90 to 80.70)			7.70 (-0.93 to 18.31)
Germany	65.00 (31.90 to 82.10)	79.30 (57.00 to 83.00)			-12.44 (-41.83 to 18.12)
Singapore	83.70 (82.80 to 85.70)	82.80 (76.00 to 84.30)			–
United Arab Emirates	84.70 (80.90 to 84.90)	83.90 (79.10 to 84.80)			–
Canada	80.90 (80.90 to 80.90)	79.80 (75.80 to 83.80)			–

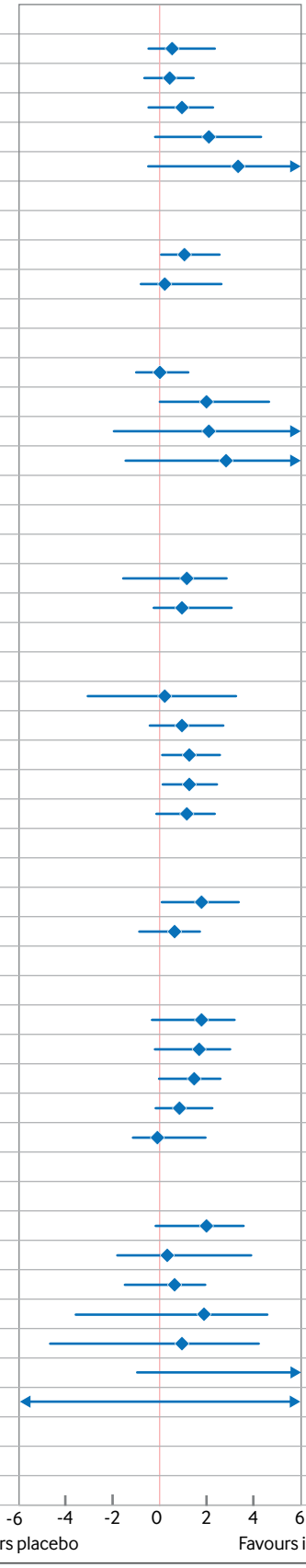

Fig 2 | Difference in number of days alive and at home up to 90 days after surgery associated with use of intravenous iron in selected subgroups. *Interaction P value for continuous subgroups is from a Wald test (2 degrees of freedom) for any linear or quadratic variation in treatment effect across full range of subgroup variables. CABG=coronary artery bypass graft; CI=confidence interval

The incidence of red cell transfusion in our study (60-70%) is consistent with previous studies showing a twofold or greater increase in patients with anaemia undergoing cardiac surgery.[4 29] Red cell transfusion is associated with worse outcomes after cardiac surgery.[3 4] The benefits of intravenous iron observed in our study are likely to be mediated by the reduction in red cell transfusion. A study of 847 442 patients undergoing cardiac surgery in the United States found that more than half of the 39% of patients receiving any red cell transfusion received only 1 unit. This single unit transfusion was associated with higher risk of stroke, renal failure, prolonged ventilation, and mortality compared with patients who did not receive a transfusion (risk adjusted, all P<0.001).[3]

International guidelines[4 5 7 30] recommend oral iron supplementation for patients with, or at risk of, anaemia before elective surgery, but include the option of intravenous iron treatment if surgery is expected within weeks (all conditional recommendations with limited certainty evidence). Given current intravenous iron formulations can provide a large (and safe) treatment dose in only 15 minutes,[5] and the positive findings observed in our trial, current guidelines should consider intravenous iron supplementation for patients with anaemia awaiting cardiac surgery.

Approximately 20-40% of patients undergoing cardiac surgery have anaemia, most of whom have an absolute or functional iron deficiency.[2 31] Iron depletion is common in patients with coronary artery disease[31] and heart failure,[18 32] and a high proportion of patients with anaemia undergoing cardiac surgery have iron deficiency.[33] A total of 70.5% (558/792) of our patients had a serum ferritin level less than 100 ng/mL or a transferrin saturation less than 20%, and very few had evidence of high iron stores. Intravenous iron effectively treats an absolute iron deficiency but can also overcome the functional deficiency seen in anaemia of chronic disease.[34] We undertook a prespecified subgroup analysis and could not find any evidence of a differential effect of intravenous iron in those with or without demonstrable iron deficiency. An individual patient data meta-analysis of four randomised trials comparing intravenous iron with placebo in patients with heart failure suggested that the benefits might be limited to those with a transferrin saturation less than 20%, regardless of their ferritin concentration.[32] Others have found that intravenous iron can reduce red cell transfusion in patients who are non-anaemic (mean preoperative haemoglobin 145 g/L, standard deviation 12) and having cardiac surgery.[2] Iron supplementation is likely to have other beneficial effects in addition to haematopoiesis, including mitochondrial function, muscle function, and mass.

Spahn and colleagues[35] conducted a single centre, randomised trial evaluating a preoperative treatment bundle that included subcutaneous erythropoietin alpha, intravenous iron (20 mg/kg), vitamin B_{12}, and folate administered the day before elective cardiac surgery in 505 patients with anaemia or isolated iron deficiency. These authors found the treatment bundle led to a 1 unit reduction in red cell transfusion in the treatment group (P=0.036). The study had limited follow-up and did not show any reduction in postoperative complications or other patient centred outcomes. The most recent systematic review of 14 clinical trials found that preoperative intravenous iron reduced the need for red cell transfusion by 23% (95% CI 8.0 to 35), irrespective of the presence of anaemia or iron deficiency. However, no beneficial effect on postoperative complications or any other patient centred outcomes was shown.[2]

Strengths and limitations

Key strengths of the ITACS trial include a low dropout rate and measurement of patient centred outcomes such as quality of recovery, days at home, and quality of life.[2 6] We used a pragmatic design that did not control other aspects of patient blood management, although we did require all sites to follow their local red cell transfusion guidelines. A one day difference in a 90 day recovery period was in itself a very small treatment effect. Some patients received open label intravenous iron before or after surgery. We enrolled patients with anaemia but did not require confirmation of absolute iron deficiency, accepting that some would have anaemia of chronic disease or a combination of both. The comparisons of our secondary and safety outcomes were not adjusted for multiplicity and so are prone to type I error. Finally, for some patients surgery was delayed or cancelled but the findings were robust in the sensitivity analyses.

Conclusion

We found that preoperative intravenous iron increased the number of days alive and at home in the first 90 days after surgery and was associated with a reduction in red cell transfusion in patients with anaemia undergoing elective cardiac surgery.

AUTHOR AFFILIATIONS

[1]Alfred Hospital, Melbourne, VIC, Australia
[2]Monash University, Melbourne, VIC, Australia
[3]Royal Papworth Hospital, Cambridge, UK
[4]Monash Health, Clayton, VIC, Australia
[5]Deakin University, Burwood, VIC, Australia
[6]University of Melbourne, Melbourne, VIC, Australia
[7]Flinders Medical Centre and Flinders University, Adelaide, SA, Australia
[8]Royal Adelaide Hospital, Adelaide, SA, Australia
[9]Institut Jantung Negara, Kuala Lumpur, Malaysia

[10]Chinese University of Hong Kong, Hong Kong Special Administrative Region, China

[11]School of Health, Sport & Bioscience, University of East London, London, UK

The authors are indebted to Adam Meehan (Research Path, Melbourne, Australia) for data management and construction of the web accessed electronic database. They thank Rob Carter, Stephane Heritier, and Keyvan Karkouti for their earlier contributions to the study, and Karen Goulding and the ANZCA Clinical Trials Network Coordinators for their diligence and collaboration.

Contributors: All authors of this paper meet the ICMJE criteria for authorship and contributed to the design and planning of the study. PSM, TR, and AAK conceived the trial, PSM was the chief investigator, PSM and SW were responsible for the day-to-day running of the trial. CM and AF did the statistical analysis. PSM wrote the first draft of the manuscript; all authors revised this draft. PSM is the guarantor of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. ANZCA Clinical Trials Network and ITACS investigators are listed in supplementary file S1.

Funding: The study was funded by the Australian National Health and Medical Research Council (NHMRC, ID1108049) and the Australian and New Zealand College of Anaesthetists (ANZCA, ID19/019). PSM, EMW, and ZM are supported by NHMRC investigator grants. AF and CM are supported by an NHMRC ideas grant. The study drug was provided at no cost from Vifor Pharma Management, Zurich, Switzerland (ferric carboxymaltose) and Pharmacosmos UK, Reading, UK (ferric derisomaltose or iron isomaltoside 1000). None of the funders had any influence on the study design, data collection, analysis, interpretation of results, manuscript preparation, or the decision to publish. All authors had full access to all data, including statistical reports and tables, and take full responsibility for the integrity of the data and the accuracy of the analysis.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Australian National Health and Medical Research Council and the Australian and New Zealand College of Anaesthetists for the submitted work. AAK or his institution has received educational grant funding or honoraria from Pharmacosmos and Fisher and Paykel. TR has received educational grant funding or honoraria from Pharmacosmos, Vifor Pharma, Acelity, Amgen, Medtronic, and Tiash. EMW has received institutional funding from Abbvie, Alexion, Amgen, Antengene, AstraZeneca, Beigene, Bristol Myers Squibb, Gilead, Janssen, Novartis, Roche, Sanofi, and Takeda. CKS received a speaker fee from Menarini, and travel expenses and speaker fee from Pharmacosmos.

Ethical approval: The trial was approved in Australia through the Alfred Health Human Research Ethics Committee (HREC/15/Alfred/88; local reference: project 605/15), and the ethics committee at each site approved the study. All participants provided written informed consent.

Data sharing: Study data are available at: https://doi.org/10.26180/c.8534361. Full analysis code can be viewed at: https://doi.org/10.26180/c.8534361.

Transparency: The corresponding author affirms that the manuscript is an honest, accurate, and transparent account of the review being reported; that no important aspects of the study has been omitted; and that any discrepancies from the review as planned (and, if relevant, registered), have been explained.

Dissemination to participants and related patient and public communities: All participants will receive information about the treatment group to which they were allocated, along with the main conclusions of the study. This information will be sent to their secure digital mailbox on publication.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Lau MPXL, Low CJW, Ling RR, et al. Preoperative anemia and anemia treatment in cardiac surgery: a systematic review and meta-analysis. *Can J Anaesth* 2024;71:127-42. doi:10.1007/s12630-023-02620-1
2 Hung KC, Chang LC, Ho CN, et al. Efficacy of intravenous iron supplementation in reducing transfusion risk following cardiac surgery: an updated meta-analysis of randomised controlled trials. *Br J Anaesth* 2024;133:1137-49. doi:10.1016/j.bja.2024.08.030
3 Ivascu Girardi N, Cushing MM, Evered LA, et al. Incidence and impact of a single-unit red blood cell transfusion: analysis of The Society of Thoracic Surgeons Database 2010-2019. *Ann Thorac Surg* 2023;115:1035-41. doi:10.1016/j.athoracsur.2022.11.037
4 Tibi P, McClure RS, Huang J, et al. STS/SCA/AmSECT/SABM Update to the clinical practice guidelines on patient blood management. *Ann Thorac Surg* 2021;112:981-1004. doi:10.1016/j.athoracsur.2021.03.033
5 Pasricha SR, Tye-Din J, Muckenthaler MU, et al. Iron deficiency. *Lancet* 2021;397:233-48. doi:10.1016/S0140-6736(20)32594-0
6 Elhenawy AM, Meyer SR, Bagshaw SM, et al. Role of preoperative intravenous iron therapy to correct anemia before major surgery: a systematic review and meta-analysis. *Syst Rev* 2021;10:36. doi:10.1186/s13643-021-01579-8
7 Casselman FPA, Lance MD, Ahmed A, et al. 2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery in collaboration with EBCP. *Eur J Cardiothorac Surg* 2025;67:ezae352. doi:10.1093/ejcts/ezae352
8 Myles PS, Richards T, Klein A, et al. Rationale and design of the intravenous iron for treatment of anemia before cardiac surgery trial. *Am Heart J* 2021;239:64-72. doi:10.1016/j.ahj.2021.05.008
9 Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. *Eur J Cardiothorac Surg* 2012;41:734-45. doi:10.1093/ejcts/ezs043
10 Kotzé A, Harris A, Baker C, et al. British Committee for Standards in Haematology guidelines on the identification and management of pre-operative anaemia. *Br J Haematol* 2015;171:322-31. doi:10.1111/bjh.13623
11 Muñoz M, Acheson AG, Bisbe E, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. *Anaesthesia* 2018;73:1418-31. doi:10.1111/anae.14358
12 Shulman MA, Myles PS, Chan MTV, et al. Measurement of disability-free survival after surgery. *Anesthesiology* 2015;122:524-36. doi:10.1097/ALN.0000000000000586
13 Höfer S, Lim L, Guyatt G, et al. The MacNew Heart Disease health-related quality of life instrument: a summary. *Health Qual Life Outcomes* 2004;2:3. doi:10.1186/1477-7525-2-3
14 EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199-208. doi:10.1016/0168-8510(90)90421-9
15 Myles PS, Shulman MA, Heritier S, et al. Validation of days at home as an outcome measure after surgery: a prospective cohort study in Australia. *BMJ Open* 2017;7:e015828. doi:10.1136/bmjopen-2017-015828
16 Bell M, Eriksson L, Svensson T, et al. Days at home after surgery: an integrated and efficient outcome measure for clinical trials and quality assurance. *EClinical Medicine* 2019;doi:10.1016/j.eclinm.2019.04.011
17 Richards T, Baikady RR, Clevenger B, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. *Lancet* 2020;396:1353-61. doi:10.1016/S0140-6736(20)31539-7
18 Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020;396:1895-904. doi:10.1016/S0140-6736(20)32339-4
19 Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332-40. doi:10.1097/ALN.0b013e318289b84b
20 Fried TR, Bradley EH, Towle VR, et al. Understanding the treatment preferences of seriously ill patients. *N Engl J Med* 2002;346:1061-6. doi:10.1056/NEJMsa012528
21 Burke LG, Orav EJ, Zheng J, et al. Healthy days at home: a novel population-based outcome measure. *Healthc (Amst)* 2020;8:100378. doi:10.1016/j.hjdsi.2019.100378
22 Groff AC, Colla CH, Lee TH. Days spent at home - a patient-centered goal and outcome. *N Engl J Med* 2016;375:1610-2. doi:10.1056/NEJMp1607206
23 Fowler AJ, Wahedally MAH, Abbott TEF, et al. Long-term disease interactions amongst surgical patients: a population cohort study. *Br J Anaesth* 2023;131:407-17. doi:10.1016/j.bja.2023.04.041
24 Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Crit Care* 2006;10:R81. doi:10.1186/cc4928
25 Jerath A, Austin PC, Wijeysundera DN. Days alive and out of hospital: validation of a patient-centered outcome for perioperative medicine. *Anesthesiology* 2019;131:84-93. doi:10.1097/ALN.0000000000002701

26 Spurling LJ, Moonesinghe SR, Oliver CM. Validation of the days alive and out of hospital outcome measure after emergency laparotomy: a retrospective cohort study. *Br J Anaesth* 2022;128:449-56. doi:10.1016/j.bja.2021.12.006

27 Reilly JR, Myles PS, Wong D, et al. Hospital costs and factors associated with days alive and at home after surgery (DAH. 30). *Med J Aust* 2022;217:311-7. doi:10.5694/mja2.51658

28 Krumholz HM. Post-hospital syndrome--an acquired, transient condition of generalized risk. *N Engl J Med* 2013;368:100-2. doi:10.1056/NEJMp1212324

29 Klein AA, Collier TJ, Brar MS, et al. The incidence and importance of anaemia in patients undergoing cardiac surgery in the UK—the first Association of Cardiothoracic Anaesthetists national audit. *Anaesthesia* 2016;71:627-35. doi:10.1111/anae.13423

30 Klompas AM, Hensley NB, Burt JM, et al. Practice Advisory on the Implementation of Preoperative Anemia Management: The Society of Cardiovascular Anesthesiologists and the Society for the Advancement of Patient Blood Management. *Anesth Analg* 2024. doi:10.1213/ANE.0000000000007321.

31 Jankowska EA, Wojtas K, Kasztura M, et al. Bone marrow iron depletion is common in patients with coronary artery disease. *Int J Cardiol* 2014;182c:517-22. doi:10.1016/j.ijcard.2014.10.006

32 Anker SD, Kirwan BA, van Veldhuisen DJ, et al. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail* 2018;20:125-33. doi:10.1002/ejhf.823

33 Klein AA, Chau M, Yeates JA, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. *Br J Anaesth* 2020;124:243-50. doi:10.1016/j.bja.2019.11.023

34 Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. *Hematology Am Soc Hematol Educ Program* 2010;2010:338-47. doi:10.1182/asheducation-2010.1.338

35 Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. *Lancet* 2019;393:2201-12. doi:10.1016/S0140-6736(18)32555-8

Supplementary file: Supplementary files