Rationale and design of the intravenous iron for treatment of anemia before cardiac surgery trial

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Background Approximately 20% to 30% of patients awaiting cardiac surgery are anemic. Anemia increases the likelihood of requiring a red cell transfusion and is associated with increased complications, intensive care, and hospital stay following surgery. Iron deficiency is the commonest cause of anemia and preoperative intravenous (IV) iron therapy thus may improve anemia and therefore patient outcome following cardiac surgery. We have initiated the intravenous iron for treatment of anemia before cardiac surgery (ITACS) Trial to test the hypothesis that in patients with anemia awaiting elective cardiac surgery, IV iron will reduce complications, and facilitate recovery after surgery.

Methods ITACS is a 1,000 patient, international randomized trial in patients with anemia undergoing elective cardiac surgery. The patients, health care providers, data collectors, and statistician are blinded to whether patients receive IV iron 1,000 mg, or placebo, at 1-26 weeks before their planned date of surgery. The primary endpoint is the number of days alive and at home up to 90 days after surgery.

Results To date, ITACS has enrolled 615 patients in 30 hospitals in 9 countries. Patient mean (SD) age is 66 (12) years, 63% are male, with a mean (SD) hemoglobin at baseline of 118 (12) g/L; 40% have evidence (ferritin <100 ng/mL and/or transferrin saturation <25%) suggestive of iron deficiency. Most (59%) patients have undergone coronary artery surgery with or without valve surgery.

Conclusions The ITACS Trial will be the largest study yet conducted to ascertain the benefits and risks of IV iron administration in anemic patients awaiting cardiac surgery. (Am Heart J 2021;239:64–72.)

Preoperative anemia is common (20% to 30%) in patients awaiting cardiac surgery and is associated with increased complications, intensive care unit (ICU) and hospital stay, and mortality.[1,2] The extent of anemia is worsened by hemodilution occurring with cardiopulmonary bypass and surgical bleeding (average blood loss 0.5-1.5 L). Further, the need for blood transfusion is greatly increased in anemic patients and is also associated with poor outcomes.[2,3] Approximately 40% of patients undergoing cardiac surgery receive a blood transfusion.[4,5]

Iron deficiency is the commonest cause of anemia worldwide and is very common in patients having coronary artery surgery.[6] Iron deficiency, of itself, is also independently associated with worse outcomes after surgery.[7] The traditional definition of iron deficiency anemia refers to depletion of the body's iron stores due to dietary deficiency or chronic blood loss—an absolute iron deficiency—and consequent anemia. Chronic disease and inflammation have a direct effect in the pathway of iron absorption and metabolism leading to a state of *functional* iron deficiency and if prolonged can lead to anemia of chronic disease.[9-11] Specifically, the iron regulatory protein hepcidin is upregulated, blocking path-

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ways of iron transport. This prevents iron absorption from the gut, further uptake by the reticuloendothelial system increases stores (ferritin), but distribution and transfer to the bone marrow is blocked.[8] Consequently, despite normal or even increased body iron stores (with normal ferritin levels), these are artifactual, and a state of functional iron deficiency exists. This is commonly seen in renal and cardiac disease and increasingly recognized as a cause for anemia in the surgical patient.[6,9,10] Importantly, intravenous (IV) iron can overcome this functional deficiency and may correct anemia.[11] Cardiac surgery patients are also at increased risk of inadequate iron stores, often defined by a serum ferritin <100 g/L,[12,13] which may not protect against postoperative anemia if there is excessive surgical bleeding.

IV iron therapy is effective in treating anemia in medical (heart failure, kidney disease), postpartum, and preoperative settings (orthopedic surgery, colon cancer resection, hysterectomy, hip/knee joint replacement).[9,14-17] A recent clinical trial in abdominal surgery reported that IV iron given preoperatively may reduce readmissions for complications in the postoperative period.[18] Cardiac surgery is different in that patients often have greater blood loss, and therefore increased susceptibility to anemia. Correction of iron deficiency in patients with cardiac disease can reduce hospital readmissions.[19] It is highly plausible that anemia correction with IV iron can improve patient outcome following cardiac surgery, but the current evidence is weak.[9,20] Furthermore, free iron mediates free radical production associated with organ damage[21] and may increase infection risk in surgery;[22] this balance between effective anemia correction and potential risk needs further research. A single-center trial reported that a combination of erythropoietin alpha, IV iron, folic acid, and vitamin B_{12} led to a 1-unit reduction in red cell transfusion in patients undergoing cardiac surgery,[12] but follow up was limited and there was no demonstrable clinical outcome benefit. Therefore, a definitive large trial is needed to determine if IV iron safely and effectively corrects preoperative anemia, and thus improves clinical recovery after cardiac surgery.[23]

Trial objectives

The primary aim of the intravenous iron for treatment of anemia before cardiac surgery (ITACS) trial is to assess whether IV iron improves patient recovery because of correction of preoperative iron deficiency anemia, reduced the need for blood transfusion and risk of complications, manifesting as earlier hospital discharge, lower mortality and reduced readmissions after surgery. We also aim to demonstrate that IV iron is cost-effective in this setting.

Study hypotheses

Primary: A single dose of IV iron in the weeks before surgery corrects anemia in patients undergoing elective cardiac surgery, and thereby improves patient recovery and their return to home when compared with placebo.

Secondary (Health Economics): Preoperative administration of IV iron will be "dominant" when compared with current practice – that is, it will both save money and improve health outcomes.

Trial design

The ITACS study is a multicenter, international, double-blind, randomized, parallel-group, controlled, pragmatic trial, with patients randomly assigned to either preoperative IV iron or matched placebo in patients with anemia awaiting elective cardiac surgery. This is an effectiveness trial[24,25]—some elements of the trial are deliberately left to the perioperative clinicians' discretion in order to reflect usual practice and maximize generalizability. The trial is registered at ClinicalTrials.gov, Identifier: NCT02632760.

Primary endpoint

The primary endpoint is the number of days alive and at home up to 90 days after surgery (DAH_{90}).[26,27] This endpoint, therefore, encompasses death, hospital stay, need for ongoing rehabilitation, and readmission(s). It reflects the personal, social, and economic benefits of a good recovery after surgery. Although we had originally planned to measure our primary endpoint up to 30 days after surgery,[26] recent clinical trials have indicated a possible delayed response to peak effect of IV iron, with readmissions beyond 30 days being a feature.[18,19]

Secondary endpoints

Secondary endpoints include (1) change in hemoglobin concentration from day of enrolment to day of surgery (preoperative response), (2) correction of iron deficiency state (ferritin, transferrin saturation) from treatment to day of surgery, (3) red cell transfusion (units), (4) postoperative complications, (5) 15-item quality of recovery scale,[28] (6) ICU and hospital stay (7) days alive and at home up to 30 days after surgery (DAH_{30}), (8) disability-free survival, from day of surgery to 6 months after surgery, (9) 90-day survival, (10) patient-reported quality of life using the MacNew Heart Disease Health-Related Quality of Life Questionnaire (MacNew)[29] up to the day of surgery, and EQ-5D[30] and the World Health Organization Disability Assessment Schedule 2.0 (WHODAS)[31] scales postoperatively up to 90 days after surgery.

Healthcare cost and cost offsets in each arm will be estimated using quality of life (EQ-5D)[30] questionnaire to derive incremental cost-effectiveness ratios (ICERs).

Table I. Specific inclusion and exclusion criteria

Inclusion criteria
Adult (≥18 years) with anemia (male or female Hb <130 g/L) expected to undergo elective on-pump or off-pump cardiac surgery, and able to receive trial drug 1-26 weeks prior to planned surgery.
Exclusion criteria
Transcatheter aortic valve implantation (TAVI) and other catheter laboratory interventional procedures
Pregnancy
Known hypersensitivity to study drug (ferric carboxymaltose, iron isomaltoside, or equivalent) or its excipients
Previously documented TSAT > 50%
Previously documented vitamin B_{12} or folate deficiency
Known or suspected hemoglobinopathy/thalassemia
Bone marrow disease
Hemochromatosis
Renal dialysis
Erythropoietin or IV iron in the previous 4 weeks

Note: Oral iron (tablets, capsules) therapy is not an exclusion criterion.

Methods

This trial is funded by the Australian National Health and Medical Research Council. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents. The organizational structure of the trial is provided in the Supplemental materials.

Sources of funding

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Patient population

ITACS is enrolling patients with anemia undergoing elective cardiac surgery (Table I). We will enroll a total of 1,000 patients in 29 participating sites in Australasia, Europe, Asia, South Africa, and Canada (details provided in the Supplemental materials). Centers must obtain institutional review board approval prior to enrolling patients and all patients must provide informed consent to participate in ITACS.

Assessment for eligibility

Patients on the waiting list for elective cardiac surgery patients are screened for eligibility. Patients with anemia are further reviewed and offered participation in the trial. Patients who are eligible but not recruited into the trial are recorded in a study log that includes the reasons for the lack of participation. Following informed consent, baseline blood tests are taken, and quality of life and other questionnaires are completed.

Allocation and randomization

After the patient's consent has been obtained, patients are randomly assigned (1:1) to groups via a web-based service using computer-generated code to either receive IV iron or placebo. Group assignment is stratified by site, baseline hemoglobin (< or ≥100 g/L), and planned surgery (isolated coronary artery or single valve surgery, or combined/other), using permuted blocks. ITACS is an intention-to-treat trial. Any participant who is enrolled and randomized to the treatment group is followed for the duration of the trial.

Measurements

As per guidelines,[13,23,32] we recommend that baseline (pre-IV study drug) blood sampling is done to measure serum hemoglobin and hematocrit, ferritin, transferrin and transferrin saturation, C-reactive protein, and crea-

Table II. Schedule for assessments during the trial

Schedule	Visit 1 Baseline	Visit 2 Day of surgery (preop)	Visit 3 Post-op Day 1	Visit 4 Post-op Day 3	Visit 5 Day of discharge	Visit 6 30 Day follow-up	Visit 7 90 Day follow-up	Visit 8 6 month follow-up
Entry criteria	X							
Blood tests (routine care) before IV study drug, then repeated: creatinine, Hb, platelets, WCC	X	X	X		X	X	X	
Ferritin, transferrin, Tsat, CRP	X							
If ferritin >30 ng/mL and normal CRP, or ferritin >100 ng/mL, include:								
Vitamin B_{12}, folate, reticulocyte count, liver and thyroid function tests		X						
Informed consent	X							
Medicare consent (Australia only)	X							
Randomization	X							
Study drug infusion	X							
Demographics, medical history	X							
Document blood product usage		X	X	X	X			
Questionnaires	X	X			X	X	X	X
Primary endpoint						X	X	
Secondary endpoints					X	X	X	X
QoR-15 scale				X				
Adverse events	X					X	X	
Safety endpoints						X	X	

Hb, hemoglobin; *WCC*, white cell count; *Tsat*, transferrin saturation; *CRP*, C-reactive protein; *QoR*, quality of recovery.

tinine. The full schedule of assessments is outlined in Table II, with a full list in the Supplemental materials.

On admission to hospital on the day of surgery, we recommend the patient has repeat blood tests along with blood group and screen, and health status questionnaires repeated. If the baseline blood test suggested that iron deficiency is an unlikely cause of the anemia (ferritin >30 ng/mL with a normal C-reactive protein, or ferritin >100 ng/mL with elevated C-reactive protein) then recommendations are that additional blood testing is done to measure hemoglobin, vitamin B_{12}, folate, reticulocyte count, liver enzymes, and thyroid hormone.[13,32] There are no other impacts on surgery or perioperative care. Details of surgery, postoperative recovery, hospital stay, and any complications are recorded on the case report form.

The WHODAS,[31] MACNEW,[29] and EQ-5D[30] are used to measure the participant's quality of life covering the domains of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and overall health state. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) is used to estimate operative risk.[33]

Definitions of endpoints

The primary endpoint, DAH_{90}, is calculated using mortality and hospitalization data from the date of the index surgery (= Day 0). Any patient death within 90 days of surgery is scored as zero irrespective of whether they had spent some of that time at home. For example, if a patient died on Day 5 after their surgery whilst still an inpatient, or Day 22 whilst at home, they would be assigned 0 days at home. If a patient was discharged from hospital on Day 6 after surgery but was subsequently readmitted for 7 days before their second hospital discharge, then they would be assigned 77 days at home. If a patient has complications and spends 16 days in hospital, and then is transferred to a nursing facility for rehabilitation, and spend 24 days there before finally being discharged to their own home, they would be assigned 50 days at home.[26,27] Home is considered to be the patient's normal place of residence or that of a family member, but not a rehabilitation or nursing home facility.

ICU stay includes the initial ICU admission and additional time following any ICU readmission up to 90 days after surgery. Hospital stay is calculated from the start (date, time) of surgery until actual hospital discharge. Hospital readmission days are totalled. Myocardial infarction, stroke, infections, and other complications are recorded as such if there is documentation in the clinical notes, or confirmation with laboratory testing or imaging. We recommend blood sampling for measurement of serum phosphate on the day of surgery.[34]

Surgical and anesthetic techniques, perioperative management

Preoperative demographic characteristics and details of each patient's medical and surgical history are recorded. All surgical and other perioperative clinical

care, including investigations, are according to local practices. All relevant factors are recorded in the trial case report form.

Transfusion practices

In accordance with the pragmatic nature of the trial, a transfusion protocol for red cells or other blood components is recommended in line with established national and institutional guidelines.[5,32] We are collecting relevant hemoglobin/hematocrit values during and after surgery, use of intraoperative cell salvage, postoperative mediastinal drainage (blood loss), and all blood transfusions in order to compare process of care measures to ensure that transfusion practices are comparable in the two groups.

Study medications and duration

The active drug being evaluated is one of two currently marketed IV iron preparations, ferric carboxymaltose, or iron (der)isomaltoside (details in the Supplemental materials), each 1,000 mg, independent of body weight. We will test for heterogeneity of effect of each of these iron preparations at the conclusion of the trial.

The preparation of the study drug administration is done by unblinded study personnel or a hospital pharmacist not involved in any study evaluations. This requires drawing up the active drug or placebo (0.9% saline) into a black syringe and administration via a black (opaque) infusion line into a dedicated peripheral IV catheter (Figure).[18] Following recruitment and at least 7 days preoperatively, a single dose administration of trial drug is given by slow IV push or infusion over 15-30 mins[9, 35]; further details are provided in a Procedures Manual. If an anaphylactic or other severe adverse event occurs, emergency unblinding can occur by contacting the trial coordination site at any time. The effectiveness of patient blinding is assessed on the day of surgery.

Study procedures, blinding, and follow-up

Iron or placebo administration and group identity are concealed from the surgeon, anesthesiologist, and all other clinicians caring for the patients. Patients, surgeons, and research staff collecting data and interviewing patients postoperatively are blind to treatment assignment.

Collection of data and compliance checks

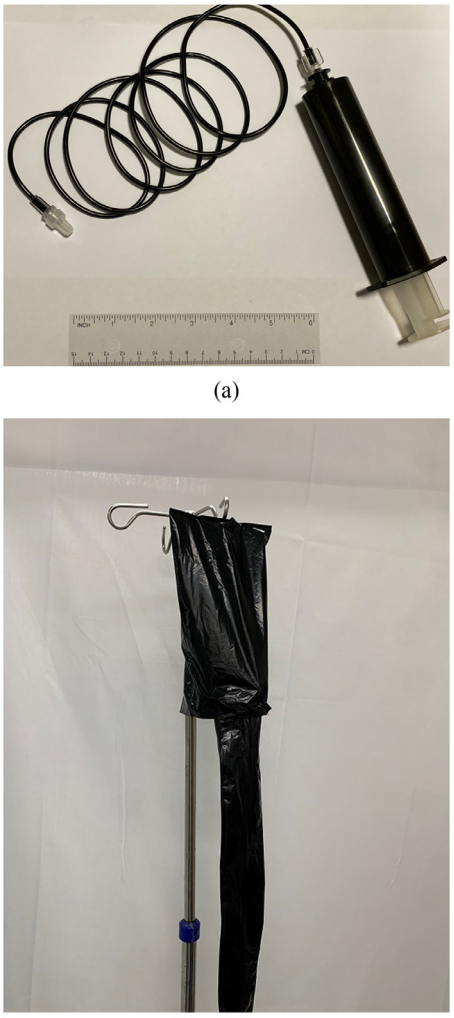
Data are collected by local research staff, and entered onto a paper case report form. All data are subsequently entered onto a database on the study website (www.itacs.org.au), where all data and processes are reviewed daily at the data management centre (see below). Data fields are checked and, in conjunction with the local site research staff, missing data or inconsistencies are corrected, before being automatically downloaded on to a confirmed database. All study personnel have 24-h access to the study coordinating center to resolve any questions that arise. A Data Quality Committee is monitoring data accuracy and completeness throughout the conduct of the trial.

Random audits of centers are being undertaken to access the accuracy and legitimacy of the trial data. Statistical monitoring for data completeness, data variance, and risk-appropriate endpoint rates is also done.

Handling cancellations or changes in surgical plan

It is anticipated that some elective surgical patients will have a change in their health status or options for treatment that will modify the planned operation after study enrolment (eg, from an open aortic valve replacement to a percutaneous procedure, or opting for an off-pump

Figure 1



(a)

(b)

Study drug delivery systems (**A**) ferric carboxymaltose study sites (supplier: Dispomed, Germany) or (**B**) iron isomaltoside sites.

rather than on-pump coronary procedure), or a change in medical condition that leads to a cancellation of the operation. For these situations, the date of the change or cancellation of their original planned surgery is used as the intended date of surgery. Such patients have their baseline assessments and (ideally) blood tests repeated for measurement of hemoglobin at or soon after this notification. They are also followed up to 90 days from this date in order to have their outcome data collected. Thus, they will have some relevant secondary endpoint data that can be included in the intention-to-treat and per-protocol analyses, but their recovery data will not be included in the analysis for the primary endpoint of the trial. Note that we may use some of the 30-day data in *post hoc* analyses.

Statistics

Sample size and power consideration

DAH_{30} and DAH_{90} have typically a skewed distribution to the left with a small spike at 0 due to deaths in hospital.[26,27] The required sample size was obtained by simulations (B=10,000) by generating the first hospital length of stay using a lognormal distribution, truncating DAH_{30} at 26 days (the maximum observed in our ATACAS trial[4]), and finally computing DAH_{30} as 26 minus length of stay. Such data are bimodal with a spike at 0 as the observed data. The lognormal distribution was calibrated to achieve a similar variability (SD=8) and the median in the control arm was set to 17 days. A sample size of n=1,000 has, respectively, 93%, and 81% power to detect a median increase of 1.5 and 1.25 days using the Wilcoxon sum rank test for the analysis; this is comparable for DAH_{90}. After adjustment for 5% loss to follow-up and 10% crossover in the experimental arm, the trial will still have 87% power to detect an increase in median of 1.5 days in DAH_{30}. For DAH_{90}, using the same logic but with a small increase in the proportion to 5% in the spike and a median DAH_{90} of 80, we have 95% power to detect a difference of 1.45 days using the Wilcoxon test and 85% power with median regression.

Statistical analysis

A statistical analysis plan will be finalized and be made publicly available before data lock and accessing the trial database to begin the final analyses. All patients who are randomly assigned to study drug administration will be considered as comprizing the intention-to-treat population for all primary, secondary, and safety analyses. Baseline characteristics of the two treatment groups will be tabulated using appropriate summary statistics.

For analysis of DAH_{90}, we will use a Wilcoxon rank-sum test, and quantile regression[24] for more complex modeling, such as adjusted analyses. The primary interest lies in the median but other quantiles might be considered. In total, 95% confidence intervals for the IV iron effect on the median DAH_{90} or other relevant quantiles will be obtained via bootstrapping.[24] The same principle will also be applied to DAH_{30}. Secondary functional outcomes (eg, EQ-5D[30]) will be analyzed using multivariable linear regression or ordinal logistic regression, as appropriate. A secondary analysis using median regression with site as a random effect will also be carried out to account for potential difference across sites. The effect of IV iron on binary outcomes will be tested using chi-squared tests, with the adjusted analysis carried out by log-binomial regression. Results will be expressed with risk ratios and 95% CI. Other secondary endpoints will be compared with Wilcoxon rank-sum and/or *t* tests, and Cox proportional hazards regression for time-to-event endpoints, as appropriate. As routine iron studies are not a common practice internationally, we prespecify iron deficiency in a subgroup analysis. Planned subgroup analyses will assess the effect IV iron by patient age group, sex, surgery type, iron deficiency (ferritin (<30 mg/dL, or ferritin <100 mg/dL and C-reactive protein >5 mg/L and/or transferrin saturation <20%),[13] hemoglobin strata (≤100, 101-120, ≥120 g/L) and study drug formulation. These analyses will be conducted on the primary endpoint via an interaction test in the corresponding quantile regression models.

Our first interim analysis was done after enrolment of 302 patients, and the second interim analysis is planned to occur after enrolment of 700 patients, adjusted according to the O'Brien and Fleming method.

Planned substudy

We are incorporating an observational study to better characterize anemia and iron deficiency detection, to identify those who may most benefit from IV iron before (any) surgery. Our substudy hypothesis is that the soluble transferrin receptor/log-ferritin ratio and reticulocyte hemoglobin content are superior to hemoglobin in monitoring response to IV iron therapy in patients undergoing elective cardiac surgery. Further, that these markers will correlate with hepcidin response, such that IV iron lowers hepcidin before surgery. In a subset (n=160) of patients, we are collecting blood for preoperative iron studies, C-reactive protein, and hepcidin levels; plus taking a sternal bone marrow sample during surgery for iron staining. The blood tests will be repeated on the day of operation, but before surgery, and on Day 3 after surgery.

Health economics

Economic appraisal in the context of trials is designed to answer one or both of two questions: (1) should we introduce a new initiative (the "value-for-money" or "allocative efficiency" question); and (2) if so, how best to design/implement it (the "technical efficiency" question). In this trial, we are focused on a technical efficiency question—not whether surgery should take place, but how best to provide it. More specifically, is the

inclusion of preoperative single-dose IV iron in patients with anemia a more cost-effective care pathway for elective cardiac surgery than current practice?

A trial-based economic evaluation will be undertaken from a health service funder's perspective to determine the value-for-money of IV iron infusion for the treatment of anemia prior to cardiac surgery in comparison with the standard care for Australian-based patients. The effectiveness of IV iron infusion will be directly informed by the ITACS trial in which IV iron is compared with standard care alone. The primary outcome measure for the economic evaluation will be quality-adjusted life years calculated based on utility weights (estimated by EQ-5D-5L) and life-years survived. Given the chosen perspective, costs related to health care including indexed hospitalization, postsurgical care (medical services, pharmaceutical use, hospital, and ambulance service, rehabilitation center, nursing home, allied health service, etc.) will be included. Postsurgery care up to 6 months for all Australian participants will be informed by case report form (any adverse events and rehospitalizations) complemented by data from Medicare (capturing outpatient care and medication use). All data will be collected after individual consent is obtained. All the costs will be expressed in Australian dollars valued in 2022. The resource use questionnaire will not be employed to reduce participant burden and minimize recall bias. In addition to estimating the ICER for quality-adjusted life-year gain, we will also estimate (1) "net cost per hospital stay"; (2) "net cost per patient alive at 90 days and out of hospital"; (3) "net cost per quality of life" using both clinical (WHODAS) and economic instruments (EQ-5D); and (4) the "net cost per mortality avoided." ICERs will be reported as both point and range estimates. Both costs and benefits will be discounted by 3% per annum. Extensive sensitivity analysis will be undertaken to investigate the robustness of the ICERs to variations in key cost, pathway, and outcome parameters in the trial and across sites. Results will be presented on the cost-effectiveness plane and an acceptability curve will also be plotted.

In addition to this trial-based economic analysis, economic modeling (ie, Markov model) will extend the trial horizon (6-months) to lifetime to simulate long-term costs and health benefits associated with IV iron prior to cardiac surgery. Further exploration of methods to cost outpatient care and medication use in non-Australian patients will also be conducted.

Adverse events

Anaphylactoid and other adverse drug reactions are very uncommon with the contemporary IV iron preparations.[36] Hypophosphatemia has been reported with the iron carboxymaltose preparation.[34] Safety data are being collected: (1) anaphylactoid reactions, (2) transfusion reactions, (3) cardiovascular events (myocardial infarction and stroke), (4) thromboembolism, (5) infection—surgical site, deep sternal wound, and other, (6) hypophosphatemia, and (7) adverse events.

Data safety and monitoring committee

The Data and Safety Monitoring Committee (DSMC) consists of a critical care physician/triallist (Chair), cardiac surgeon, cardiac anesthesiologist, hematologist, independent statistician, and a clinical pharmacologist. The DMSC consider the interim results and vote for continuation or stopping the trial. A majority vote of the DSMC to stop the trial will be communicated to the Steering Committee at the Trial Coordinating Center according to predetermined stopping rules (as above) and consideration of other relevant evidence.[37] To date, the DSMC has met on two occasions (an early safety/integrity review and an interim analysis at n=302) and the trial is continuing.

Current status of the trial

ITACS is currently recruiting patients in 27 centers within 9 countries and has randomized 615 patients as of April 2, 2021. Details of the study centers are provided in the Supplemental materials. Tables II and III report on characteristics of the first 615 patients enrolled in the trial; 40% have evidence (ferritin <100 ng/mL and/or transferrin saturation <25%) suggestive of iron deficiency. These data demonstrate a cohort of patients at the increased need for red cell transfusion and complications of cardiac surgery.

Limitations

ITACS is enrolling patients with anemia but not limited to those with proven iron deficiency. Although anemia is mostly detected before elective cardiac surgery, it is very uncommon for the cause of anemia to be elucidated through formal iron studies and other assessments, and in any case scheduling uncertainty often limits such efforts. Bone marrow iron depletion is common in patients with coronary artery disease,[6] and a high proportion of cardiac surgical patients with anemia have iron deficiency.[38] Furthermore, there is little agreement on how to diagnose functional iron deficiency. Iron studies are being done at the time of enrolment, and to date, we have found that 40% have evidence of iron deficiency. We are evaluating the effect of IV iron 1,000 mg, and not including erythropoietin because there are concerns it may increase risk of thrombosis, particularly in those with cardiac disease.[23] We acknowledge that a higher dose is likely to be needed in patients with severe iron deficiency anemia (a very small proportion of our cohort) or higher body weight to achieve a complete biological response and hemoglobin recovery.[39] We are enrolling patients expected to have their surgery 1-26 weeks later; the shorter duration may or may not provide sufficient time for a complete bone marrow response but this is likely to plateau within 14 days.[40] To date, our median

Table III. Baseline characteristics and types of surgery

Variable	
Baseline (prerandomization)	n=615
Patient age, mean (SD), years	66 (12)
Male sex	388 (63)
ASA physical status	22 (3.6)
2	407 (66)
3	186 (30)
4	118 (12)
Hemoglobin, mean (SD), g/L	106 (46-220)
Ferritin, median (IQR), ng/mL	2.7 (2.4-3.3)
Transferrin, median (IQR), g/L	18 (12-25)
Transferrin saturation, median (IQR), %	
At day of surgery	n=557
Heart failure	147 (25)
Previous myocardial infarction	168 (29)
Diabetes	240 (41)
Previous/current smoker	251 (43)
EuroSCORE II, median (IQR), %	1.9 (1.2-3.5)
Preoperative medications	296 (51)
ACE-inhibitor/ARB	342 (59)
Beta-blocker	149 (26)
Calcium channel blocker	428 (73)
Statin	53 (9.1)
Oral iron therapy	39 (39)
Time between study drug	25 (13-53)
administration and day of surgery,	239 (43)
days	192 (34)
mean (SD)	88 (16)
median (IQR)	40 (7)
Type of surgery	34 (6.2)
Isolated CABG	
Isolated valve repair/replacement	
Combined CABG-valve	
Other*	
Revision (redo) surgery	

No. (%) unless specified.
ASA, American Society of Anesthesiologists; *ACE*, angiotensin converting enzyme; *ARB*, angiotensin-receptor blocker; *CABG*, coronary artery bypass graft.
*Other surgery includes combined multiple valve, septal defect repair, pulmonary thromboendarterectomy, etc.

(IQR) time from randomization to surgery is 25 (13-53) days. Variation in blood transfusion practices is likely although the range is not expected to be very wide because of established guidelines; therefore a transfusion protocol is not mandated.[5, 32] We are collecting relevant data and using a pragmatic design to strengthen generalizability.

Conclusion

Anemia is common and a major risk factor for surgery. ITACS will be the largest randomized study yet conducted to ascertain the benefits and risks of IV iron administration in anemic patients awaiting cardiac surgery. A total of 615 (of 1,000) patients have been randomized to date, and the trial is expected to conclude in early 2022.

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Author contributions

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Declarations of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.05.008.

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