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Post-operative iron in cardiac surgery trial – a protocol for a randomised controlled trial

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ABSTRACT

INTRODUCTION. Anaemia is common after cardiac surgery and has a negative impact on rehabilitation and patient well-being. We aim to compare the efficacy of single, high-dose intravenous iron therapy versus oral iron supplementation to correct anaemia following open cardiac surgery.

METHODS. We present a randomised, active-control superiority trial. Adult patients with moderate anaemia (haemoglobin 5.0-6.8 mmol/l) on the first post-operative day after first-time, non-emergent cardiac surgery are eligible. After stratification by gender, 110 patients are randomised 1:1 to either single, high-dose intravenous iron therapy (20 mg/kg ferric derisomaltose) or oral iron supplementation (100 mg ferrous sulphate orally twice daily). The primary outcome measure at the four-week follow-up is the proportion of participants who are neither anaemic (haemoglobin < 8.1 mmol/l in men and < 7.5 mmol/l in women) nor have received allogeneic red blood cells since randomisation. Secondary outcome measures include changes in haemoglobin and iron biomarkers, exercise capacity, patient-reported outcome measures and cost of care at the four-week follow-up.

CONCLUSION. The results of the PICS trial may fundamentally alter future management of anaemia following cardiac surgery.

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Anaemia is a well-established independent risk factor for adverse cardiovascular events in the general population and particularly in patients with cardiovascular diseases. Prior to cardiac surgery, anaemia is present in approximately every fourth patient [1, 2]. Preoperative anaemia has been found to be a powerful predictor of adverse outcome after cardiac surgery [3]. At hospital discharge, anaemia is almost invariably present due to pre-existing anaemia, perioperative blood loss, blood sampling and inadequate nutritional intake [4]. Post-operative anaemia has been shown to prolong hospital stay and increase the rate of major adverse cardiovascular events [4]. Debilitating symptoms of anaemia like dyspnoea, fatigue and poor exercise tolerance represent serious obstacles to rehabilitation and patient well-being [4, 5]. Importantly, iron deficiency treatment has been shown to improve the well-being and physical performance of chronic heart failure patients, even in the absence of anaemia [6].

To the best of our knowledge, no internationally established recommendations cover the treatment of moderate anaemia following cardiac surgery despite the &;magnitude and importance of the problem. Whereas severe

post-operative anaemia is commonly treated with blood transfusions [7], moderate-to-mild anaemia is mostly corrected with oral iron supplementation. However, the effectiveness of oral iron after major surgery is limited due to poor absorption and considerable gastrointestinal side effects [8]. Post-operative anaemia therefore frequently persists for months [4].

Building evidence suggests that intravenous iron may be a safe, well-tolerated and effective alternative to oral iron [9]. Two randomised controlled trial have shown that a combination of intravenous iron with &;haemopoietic stimulation reduced the perioperative requirement of blood transfusion in cardiac surgery patients with preoperative anaemia and/or &;iron deficiency [10, 11]. Despite promising results in other surgical subspecialties, the overall evidence for intravenous iron treatment in cardiac surgery is of moderate quality regarding efficacy and safety [12]. The level of evidence in terms of patient-reported outcome measures is even considered low [12]. Well-designed studies are lacking that investigate the impact of targeted early intravenous iron therapy of anaemic cardiac surgery patients on haemoglobin levels, transfusion requirements, iron status, functional outcome and patient-reported outcome measures.

We aimed to evaluate the efficacy, safety and cost-effectiveness of single, high-dose intravenous iron therapy versus oral iron supplementation to correct anaemia following cardiac surgery.

METHODS

Study design

The objective of the PICS trial is to compare the efficacy of single, high-dose intravenous iron therapy versus oral iron supplementation for treatment of anaemia following cardiac surgery. PICS is an investigator-initiated, single-centre, randomised and stratified, parallel-group, active-controlled superiority trial including adult cardiac surgery patients with moderate post-operative anaemia. PICS enrols patients undergoing first-time non-emergent cardiac surgery with cardiopulmonary bypass at Aarhus University Hospital, Denmark. Eligible procedures are coronary artery bypass grafting, valve surgery or a combination of both. The addition of pulmonary vein ablation and/or occlusion of the left atrial appendage is permitted. Preoperative assessment includes complete blood count, reticulocyte count, plasma iron, ferritin, transferrin saturation, C-reactive protein, creatinine, vitamin B_{12} and folate. Patients are ineligible for the study if they have contraindications to intravenous iron treatment or an anticipated inability to complete all study assessments. The complete inclusion and exclusion criteria are outlined in **Table 1** and **Table 2**.

TABLE 1 Inclusion criteria.

Age ≥ 18 yrs
First-time, non-emergent cardiac surgery with cardiopulmonary bypass
CABG
Valve surgery
Combination of CABG and valve surgery
Addition of pulmonary vein ablation and/or occlusion of the left atrial appendage is permitted
Willing and able to provide written informed consent
Moderate anaemia on the first post-operative day: haemoglobin level 5.0-6.8 mmol/l

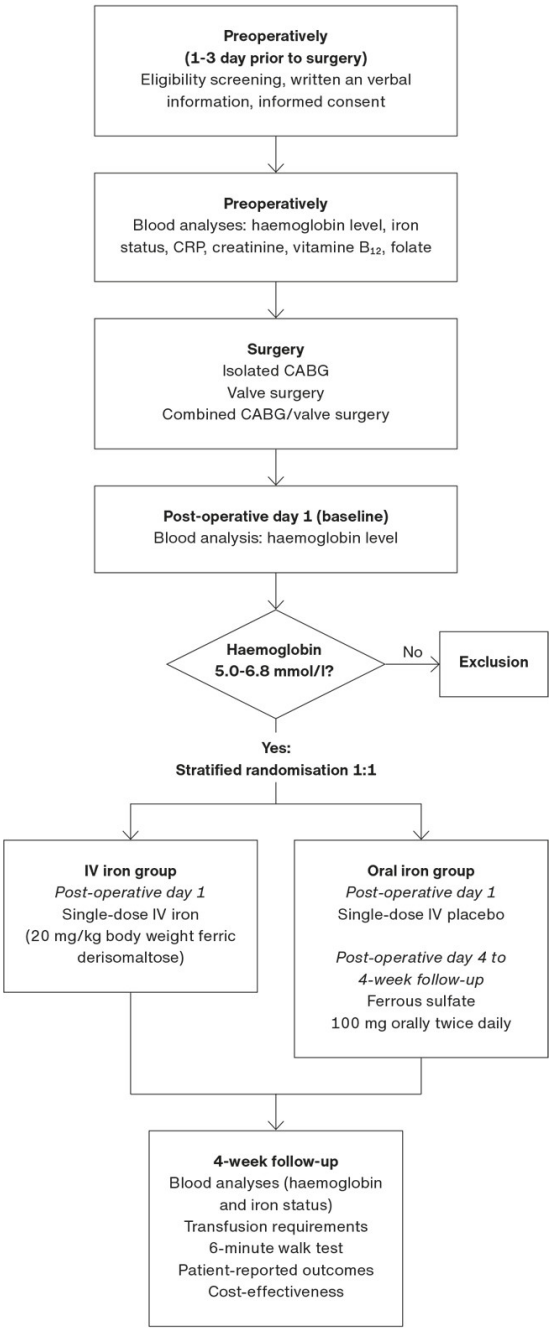
CABG = coronary artery bypass grafting.

TABLE 2 Exclusion criteria.

Contraindications to treatment with intravenous iron
Hypersensitivity to any iron formulation
History of iron overload or disturbances in iron utilisation, e.g., haemochromatosis, haemosiderosis or porphyria cutanea tarda
History of liver disease, e.g. cirrhosis
Multiple drug allergies or previous anaphylaxis
Severe asthma, eczema or other atopic allergy, rheumatoid arthritis or systemic lupus erythematosus
Severe active infection, e.g. endocarditis
Intravenous iron therapy within the 4 wks leading up to surgery
Untreated vitamin B_{12} or folate deficiency
Anticipated inability to perform a 6-min. walk test or to attend clinical follow-up
Anticipated post-operative length of stay in the intensive care unit > 48 h
Women of childbearing potential, pregnant and nursing women
Active participation in another interventional trial with potential impact on post-operative anaemia or exercise capacity

As most cardiac surgery patients are under the residual influence of sedatives or pain on the first post-operative day, they are considered unable to provide written informed consent. We therefore enrol patients preoperatively if they meet the first three inclusion criteria and no exclusion criteria. Only patients who meet the final inclusion criterion of moderate anaemia on the first post-operative day (haemoglobin 5.0-6.8 mmol/l) are randomly assigned to one of the two treatment groups (intravenous or oral iron) in a blinded fashion. Stratified permuted block randomisation with an allocation ratio of 1:1 is used. Randomisation is stratified for gender, as haemoglobin, blood volume and consequently transfusion requirements differ for men and women.&; We randomise via the interactive web-based Research Electronic Data Capture (REDCap) Randomisation Module at Aarhus University, Denmark [13]. All eligible patients not enrolled in the study are registered anonymously in a log list including the reason for lack of enrolment. The trial flow chart including study assessments is depicted in **Figure 1**.

FIGURE 1 Post-operative iron in cardiac surgery trial flow chart.



CABG = coronary artery bypass grafting; IV = intravenous.

Study intervention

Patients receive study intervention after randomisation on the first post-operative day. Patients in the intravenous iron group receive a single, high-dose intravenous infusion of 20 mg/kg body weight ferric derisomaltose 1000 (MonoFer, Pharmacosmos A/S, Holbæk, Denmark). Patients in the oral iron group receive placebo (0.9% sodium chloride, B. Braun Medical A/S, Frederiksberg, Denmark). The study drugs are prepared by study personnel who are not involved in any study assessments. We use dark non-transparent bags and black infusion lines (B. Braun Medical, Melsungen, Germany) to conceal the dark-brown appearance of ferric

derisomaltose. Participants and healthcare providers are kept unaware of treatment assignment until the fourth post-operative day.

On the fourth post-operative day, patients in the oral iron group are prescribed open-label oral ferrous sulphate 100 mg twice daily (Ferro Duretter, ACO, Upplands Väsby, Sweden), which is to be continued until the four-week follow-up. At this point, unblinding becomes inevitable for patients and caretakers as oral iron therapy results in black tarry stools. The high dosage of 100 mg ferrous sulphate twice daily on consecutive days is in accordance with Danish product characteristics recommendations [14].

Outcome measures

All patients are scheduled for a clinical follow-up visit four weeks after randomisation. Outcome assessors are blinded to treatment allocation. The primary outcome measure is defined as the proportion of participants at the four-week follow-up who are neither anaemic nor have received allogeneic red blood cells since randomisation. Post-operative anaemia is defined as haemoglobin < 8.1 mmol/l in men and < 7.5 mmol/l in women.

Secondary outcome measures include changes in laboratory variables (haemoglobin, reticulocyte count, iron, ferritin and transferrin saturation), red blood cell transfusion requirements, exercise capacity, patient-reported outcome measures and safety (adverse events/reactions). &; Data on cost of care are collected from randomisation until the four-week follow-up. Details needed to compare the cost-effectiveness of the strategies are outlined in a separate protocol using a mixed-method approach.&; Details of secondary outcome measures at the four-week clinical follow-up are listed in **Table 3**.

TABLE 3 Secondary outcome measures at the four-week clinical follow-up.

Change in haemoglobin levels since randomisation
Changes in reticulocyte count, iron, ferritin and transferrin saturation since baseline
Transfusion requirements: units of packed red blood cell units since randomisation
Dyspnoea as assessed by NYHA functional class [15]
Exercise capacity as assessed by 6-minute walk distance [16]
Fatigue as assessed by the Multidimensional Fatigue Inventory [17]
QoR as assessed with the QoR-9 questionnaire [18]
This 9-item instrument has a max. score of 18 and a min. score of 0
The questions were translated into Danish language using a forward and back translation method
Gastrointestinal symptoms during the week prior to follow-up as assessed by questionnaire including 5 dimensions[a] and 4 levels[b]
A final score is calculated by adding each item
Health-related QoL as assessed by the EQ-5D-5L [19]
Cost of care and cost-effectiveness at 4 wks after randomisation based on total hospital costs and costs of public care provided in the 4 following surgery
A cost-effectiveness analysis according to the intention-to-treat principle from a Danish health sector perspective

EQ-5D-5L = European QoL 5-dimension 5-level instrument; NYHA = New York Heart Association; QoL = Quality of Life; QoR = Quality of Recovery.
a) Nausea, constipation, diarrhoea, abdominal pain and bloating.
b) 0 = symptom has not been present; 1 = the symptom was present and resulted in mild discomfort; 2 = the symptom was present and resulted in moderate discomfort; 3 = the symptom was present and resulted in severe discomfort.

Statistical considerations

We hypothesise that single, high-dose intravenous iron therapy is superior to oral iron supplementation in the treatment of anaemia after cardiac surgery with regard to the composite primary endpoint. The hypothesis will be tested using a two-sided χ^2-test. The needed sample size was calculated based on the results from the PROTECT trial [20]. &;Given an absolute risk reduction (delta) of 28%, a significance level (alpha) of 0.05 and allowance for 10% attrition, recruiting 110 patients will provide 95% power to reject the null hypothesis.

For secondary outcome measures including laboratory testing, comparisons between continuous data will be

tested by use of unpaired t test or Mann-Whitney U test, as appropriate. Categorical data will be tested by use of χ^2-test or Fisher's exact test, as appropriate. Spearman rank correlation will be used to measure the strength of association between non-normally distributed variables with the denotation of correlation coefficient. All safety data are summarised descriptively.

The level of significance is set at $p \leq 0.05$; all tests will be two-sided. All statistical analyses will be done using &;&;STATA software version 16 or above (STATA Corp., College Station, TX, USA).

Organisation and ethical concerns

The study protocol has been approved by the Central Denmark Regional Committee on Health Research Ethics (10 November 2020, 1-10-72-221-20), the Danish Medicines Agency (29 October 2020, 2020090500) and the Danish Data Protection Agency (31 December 2020, 1-16-02-716-20). The trial is registered with EudraCT (Number: 2020-001389-12) and Clinical Trials (ID: NCT04608539). Furthermore, the PICS trial is conducted in accordance with the Declaration of Helsinki and monitored continuously by the Good Clinical Practice Unit at Aarhus University, Denmark. All patients provide informed written consent before participating. Decisions on study design, acquisition, analysis, interpretation or publication of data are exclusively retained by the authors who have initiated and designed the trial. Events are adjudicated by an independent adverse clinical event committee.

The target sample size of the current trial is 110 patients. Trial enrolment was initiated in May 2021 and is expected to be completed by March 2023. As of 17 May 2022, 126 patients have been screened for eligibility, 89 patients have been enrolled and 47 patients have been randomised.

International Committee of Medical Journal Editors Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analysed in this protocol article. The full study protocol, statistical analysis plan and informed consent form are available upon reasonable request.

Trial registration: EudraCT number: 2020-001389-12; Clinical Trials ID: NCT04608539.

DISCUSSION

Importance of the knowledge to be gained

The majority of cardiac surgery patients are discharged from hospital with significant anaemia and iron deficiency that result in debilitating symptoms and impede rehabilitation. Current standard oral iron therapy may require months and is associated with substantial side effects. The PICS trial determines whether a single, high dose of intravenous iron is more effective than oral iron in correcting anaemia after cardiac surgery. We aim to expand our understanding of the quality and obstacles of early recovery following cardiac surgery. Our results may potentially improve rehabilitation of cardiac surgery patients not only in Denmark but worldwide.

Study limitations

The inability to continue participant blinding during the weeks of follow-up due to the black discoloration of stools on oral iron treatment is considered a major limitation of the current trial. However, we consider open-label continuation of the study four days after randomisation acceptable, as the majority of blood transfusions (as part of the primary composite endpoint) are administered in the early post-operative period [20]. As participant blinding is impossible during follow-up, the patient-reported outcome measures must be regarded as exploratory. However, the remaining outcome assessment and data analysis will be performed blinded to treatment allocation.

CONCLUSION

The PICS trial is a randomised trial comparing single, high-dose intravenous iron treatment with conventional oral iron supplementation in patients with moderate anaemia following cardiac surgery. The aim is to determine whether this strategy translates into better clinical and patient-reported outcomes.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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