A one-shot solution for improved patient blood management in cardiac surgery?

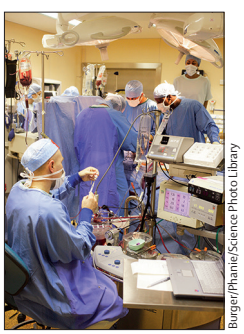
Preoperative anaemia and low intraoperative haemoglobin (Hb) concentration remain independent risk factors for serious adverse outcomes, including mortality and major morbidity in patients undergoing cardiac surgery.[1] However, effective therapies that reduce the incidence of these adverse events remain to be identified. Retrospective data and a recent prospective randomised controlled trial (RCT) suggest that red blood cell (RBC) transfusions might not adequately treat the mechanism of organ injury associated with anaemia[2,3] or that they might cause additional morbidity. Liberal RBC transfusion approaches more effectively restore Hb concentrations toward non-anaemic values, but transfusion of stored allogeneic RBCs does not correct the primary metabolic deficiencies associated with anaemia, nor does it restore iron homoeostasis. In *The Lancet*, evidence from a single-centre RCT by Donat Spahn and colleagues[4] suggests that a single preoperative treatment bundle consisting of subcutaneous erythropoietin alpha (EPO 40 000 IU), intravenous iron (20 mg/kg), subcutaneous vitamin B12, and oral folate is effective at restoring iron homoeostasis and reducing RBC transfusion rates in patients undergoing cardiac surgery (odds ratio 0·70 [95% CI 0·50–0·98] for each threshold of number of RBC transfusions, p=0·036).

This therapy resulted in an increase in postoperative reticulocyte count and postoperative Hb concentration, and a reduced amount of RBC transfusion in a cohort of patients with iron deficiency or anaemia. In view of the ongoing difficulty of optimally managing patients with anaemia in a timely and efficient manner, Spahn and colleagues' trial provides a simple and pragmatic approach to effectively treating iron deficiency anaemia in patients undergoing cardiac surgery. While clinical care bundles of therapy have been shown to be effective in management of acute care patients, this approach is limited in that the relative contribution of each component of the therapy cannot be individually assessed. For example, two previous studies have shown that a single dose of preoperative EPO and iron are more effective than iron alone at reducing RBC transfusion in patients undergoing cardiac surgery.[5,6]

While no increase in adverse events was identified in Spahn and colleagues' trial, the trial was not adequately powered to detect such changes. Data from larger trials of anaemia treatment in perioperative medicine are needed to address the broader question of whether or not such treatments can reduce associated serious adverse outcomes, including organ injury and mortality, or whether they might increase them. For example, with respect to acute kidney injury (AKI), many clinical studies have shown that the kidney is vulnerable to injury in anaemic patients undergoing cardiac surgery through a hypoxic mechanism or from free haemoglobin secondary to native RBC injury during surgery on cardiopulmonary bypass and/or present in donated blood. Pretreatment of anaemia could potentially reduce AKI, but the hypothesis that treating anaemia reduces hypoxia-induced organ injury, including AKI, remains to be fully assessed in adequately powered RCTs.

In addition, concerns about adverse effects related to EPO, including thrombosis, stroke, and mortality in medical patients,[7] especially when used in high doses or for prolonged periods, have tempered the use of EPO in clinical practice. Although the drugs and doses used in this study were not associated with increased thrombotic events, further evidence that EPO is both efficacious and safe in relatively small single-dose therapy will require additional large RCTs addressing the effect of treatment on serious adverse events.

The study by Spahn and colleagues[4] has some limitations. Despite the outcomes of recent systematic reviews and meta-analyses, the issue of safety associated with EPO and intravenous iron has not been fully addressed by the current or previously published studies.[8] The efficacy of monotherapy with intravenous iron is currently under investigation in larger RCTs (ITACS: NCT02632760, PREVENTT: NCT01692418). In addition, the routine use of vitamin B12 and folate, while relatively inexpensive and safe, makes it difficult to attribute the relative effect of EPO, iron, vitamin B12, and folate on the observed outcomes. The current study design does not answer the question of whether or not



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EPO is required above and beyond intravenous iron in cases of pure iron deficiency. This is an important issue as EPO is associated with additional adverse reactions and many clinicians argue that it is not necessary in the case of iron deficiency. Review of the literature comparing EPO plus iron with iron alone shows increased efficacy by adding EPO to iron in patients undergoing cardiac surgery and in patients with other medical conditions.[8] This positive effect of EPO is supported by the current study.

In summary, this new study provides evidence that pragmatic approaches to treating anaemia and iron deficiency can reduce the use of allogeneic RBC transfusion and increase postoperative Hb concentration. Whether such approaches can reduce adverse effects associated with anaemia in patients undergoing cardiac surgery remains to be confirmed. In addition, with the development of additional novel treatments of anaemia, including small peptide prolyl hydroxylase inhibitors,[9] ongoing trials will be needed to assess the relative efficacy and safety of both new and older therapies.

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Emergency general surgery: can we do better?

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In *The Lancet,* Carol Peden and colleagues[1] report a randomised trial of a quality improvement (QI) effort to enhance the outcomes of emergency abdominal surgery. The Enhanced Peri-Operative Care for High-risk patients (EPOCH) group attempted to implement a 37-element care bundle at 93 hospitals across the UK. National Health Service hospitals doing a substantial volume of emergency abdominal surgery and contributing to the National Emergency Laparotomy Audit were eligible for inclusion. The most frequently enrolled patients had intestinal obstruction or perforation. Institutional leaders in surgery, anaesthesia, and critical care worked with their QI teams with a primary objective to reduce 90-day mortality from 25% to 16%. Both the QI and usual care groups had a 90-day mortality of 16%. The QI group were more likely than the usual care group to have preoperative documentation of risk (66% *vs* 55%), to receive goal directed fluid therapy (59% *vs* 47%), and to have serum lactate measured at the end of surgery (60% *vs* 54%). However, secondary outcomes, including 180-day mortality, length of stay, and readmissions, also did not differ between the QI and usual care groups.

Foremost, the authors should be congratulated on accomplishing such a large-scale QI randomised

Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial

Donat R Spahn, Felix Schoenrath*, Gabriela H Spahn, Burkhardt Seifert, Philipp Stein, Oliver M Theusinger, Alexander Kaserer, Inga Hegemann, Axel Hofmann, Francesco Maisano, Volkmar Falk*

Summary

Background Anaemia and iron deficiency are frequent in patients scheduled for cardiac surgery. This study assessed whether immediate preoperative treatment could result in reduced perioperative red blood cell (RBC) transfusions and improved outcome.

Methods In this single-centre, randomised, double-blind, parallel-group controlled study, patients undergoing elective cardiac surgery with anaemia (n=253; haemoglobin concentration (Hb) <120 g/L in women and Hb <130 g/L in men) or isolated iron deficiency (n=252; ferritin <100 mcg/L, no anaemia) were enrolled. Participants were randomly assigned (1:1) with the use of a computer-generated range minimisation (allocation probability 0·8) to receive either placebo or combination treatment consisting of a slow infusion of 20 mg/kg ferric carboxymaltose, 40 000 U subcutaneous erythropoietin alpha, 1 mg subcutaneous vitamin B12, and 5 mg oral folic acid or placebo on the day before surgery. Primary outcome was the number of RBC transfusions during the first 7 days. This trial is registered with ClinicalTrials.gov, number NCT02031289.

Findings Between Jan 9, 2014, and July 19, 2017, 1006 patients were enrolled; 505 with anaemia or isolated iron deficiency and 501 in the registry. The combination treatment significantly reduced RBC transfusions from a median of one unit in the placebo group (IQR 0–3) to zero units in the treatment group (0–2, during the first 7 days (odds ratio 0·70 [95% CI 0·50–0·98] for each threshold of number of RBC transfusions, p=0·036) and until postoperative day 90 (p=0·018). Despite fewer RBC units transfused, patients in the treatment group had a higher haemoglobin concentration, higher reticulocyte count, and a higher reticulocyte haemoglobin content during the first 7 days (p≤0·001). Combined allogeneic transfusions were less in the treatment group (0 [IQR 0–2]) versus the placebo group (1 [0–3]) during the first 7 days (p=0·038) and until postoperative day 90 (p=0·019). 73 (30%) serious adverse events were reported in the treatment group group versus 79 (33%) in the placebo group.

Interpretation An ultra-short-term combination treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin B12, and oral folic acid reduced RBC and total allogeneic blood product transfusions in patients with preoperative anaemia or isolated iron deficiency undergoing elective cardiac surgery.

Funding Vifor Pharma and Swiss Foundation for Anaesthesia Research.

Introduction

Anaemia is frequent in patients scheduled for elective cardiac surgery and is associated with an increased number of red blood cell (RBC) transfusions and adverse clinical outcomes, including mortality.[1,2] Iron deficiency is of prime importance in many forms of anaemia.[3] In addition, iron plays a pivotal part in many processes involved in energy production and efficient organ function such as myocardial function.[4,5] Several expert groups therefore recommend treatment of iron deficiency preoperatively even if not yet associated with anaemia.[5,6] This could be of particular relevance in patients with impaired left ventricular function undergoing cardiac surgery because treatment of iron deficiency in patients with congestive heart failure has been shown to improve functional status within 4 weeks and to reduce the need for hospital admission and mortality.[7,8] Previous studies have shown that up to 37% of patients undergoing cardiac surgery were reported to be iron deficient, two-thirds of them without anaemia, and they received more RBC transfusions perioperatively than patients without iron deficiency.[9] A systematic assessment and treatment of anaemia and iron deficiency before cardiac surgery is currently lacking and not an integral part of the preoperative standard work-up in most health-care systems. This study addressed the hypothesis that an immediate preoperative treatment of anaemia or isolated iron deficiency could result in reduced perioperative RBC transfusions and in an improved perioperative outcome.

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Research in context

Evidence before this study

Anaemia and iron deficiency are frequent in patients scheduled for elective cardiac surgery and preoperative anaemia is associated with an increased rate of red blood cell (RBC) transfusions and adverse clinical outcomes. Iron deficiency is of prime importance in many forms of anaemia and iron plays a pivotal part in efficient organ function such as myocardial function. We searched MEDLINE from inception until May 30, 2018, including the search terms "anaemia", "preoperative", "iron deficiency", "cardiac", "surgery", "transfusion", "erythropoietin", and "iron" to identify studies assessing the effect of preoperative treatment of anaemia and iron deficiency in cardiac surgery. We identified one previous randomised trial in patients undergoing cardiac valve surgery in which a combination treatment with subcutaneous erythropoietin and intravenous iron the day prior to surgery resulted in a decrease in RBC transfusions.

Added value of this study

Our trial found that ultra-short-term (usually the day before surgery but on Friday in patients operated the next Monday) combination treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin B_{12}, and oral folic acid reduced the need for RBC and total allogeneic blood product transfusions in patients with preoperative anaemia or isolated iron deficiency undergoing elective cardiac surgery.

Implications of all the available evidence

Physicians should routinely measure haemoglobin and iron parameters in patients undergoing cardiac surgery and consider combination treatment of preoperative anaemia or iron deficiency even the day prior to surgery. This is of particular relevance since a growing percentage of elective cardiac surgery is done within a few days after an acute cardiac event.

Methods

Study design and participants

This was a single-centre, randomised, double-blind, parallel-group controlled study in patients undergoing elective cardiac surgery. Patients with anaemia (n=253; haemoglobin concentration (Hb) <120 g/L in women and Hb <130 g/L in men) or isolated iron deficiency (n=252; ferritin <100 mcg/L, no anaemia) were enrolled from University Hospital of Zürich (Zürich, Switzerland). Patients with anaemia and iron deficiency were stratified to the anaemia subgroup. In parallel, data from eligible patients without anaemia and without iron deficiency were entered prospectively into a registry. Adult patients scheduled for elective isolated coronary artery bypass grafting (CABG), valve surgery, and combined CABG and valve procedures were eligible for enrolment. All patients signed a written informed consent. Detailed eligibility and exclusion criteria are provided in the appendix.

See Online for appendix

The trial protocol was approved by the local ethics committee (KEK ZH 2013 number 0043) and registered online at ClinicalTrials.gov (NCT02031289). No formal data analysis or interim analysis was done before locking the database on Jan 24, 2018.

Randomisation and masking

Randomisation was done at the Clinical Trial Center of the University Hospital of Zurich. Patients with anaemia or isolated iron deficiency were randomly assigned (1:1) with the use of a computer-generated range minimisation (allocation probability 0·8) into placebo versus combination treatment. Randomisation was further stratified by the type of surgery, primary versus re-do operations, on-cardiopulmonary versus off-cardiopulmonary bypass operations, and presence versus absence of dual platelet inhibition in the anaemia and isolated iron deficiency group. Either iron or placebo (0·9% saline) were given intravenously via a black infusion set from behind a screen to assure blinding of the patient by a person not involved in data capturing or data entering.

Procedures

Patients were treated at the University Hospital of Zurich, Zürich, Switzerland. Combination treatment consisted of a slow (30 min) intravenous infusion of 20 mg/kg ferric carboxymaltose (maximum of 1000 mg, Ferinject®, Vifor (International) AG, St Gallen, Switzerland), 40 000 U subcutaneous erythropoietin α (Eprex®, Janssen-Cilag AG, Baar, Switzerland), 1 mg subcutaneous vitamin B_{12} (Vitarubin®-superconc, Streuli Pharma AG, Uznach, Switzerland), and 5 mg oral folic acid (acidum folicum, Streuli Pharma AG, Uznach, Switzerland). Additional placebo treatment consisted of two subcutaneous injections of 1 mL saline and an oral placebo. Patient's vital signs were monitored during and at least 15 min after drug application. Total acquisition costs of these drugs were 682 Swiss Francs (CHF) per patient. For the cost calculation the actual price of one RBC unit of 212·50 CHF was used. CHF and US$ were at approximate parity June 19, 2018.

Treatment was given on the day of anaesthetic evaluation (usually the day before the operation but on Friday in patients operated on the next Monday). Patients with intractable surgical bleeding resulting in massive transfusion (≥10 RBC transfusions per 24 h) and patients requiring intraoperative extracorporeal membrane oxygenation were excluded from the study.

Patients were treated according to the standards of the Institute of Anaesthesiology and the Department of Cardiovascular Surgery of the University Hospital of Zurich, Zurich, Switzerland, including the standard of applying compression stockings and, if bedridden,

additionally low molecular weight heparin preoperatively to patients. According to the Hospital Transfusion Guidelines an Hb transfusion trigger of less than 70–80 g/L was used intraoperatively and during the stay in intensive care, followed by an Hb <80 g/L on the regular ward. Secondary outcomes were recorded during the index hospitalisation and at the time of the first postoperative consultation with the referring cardiologist, which was scheduled at postoperative day 90.

Outcomes

The primary outcome was the number of RBC transfusions administered during the first 7 days (starting with the day of operation), until death or hospital discharge, whichever came first. Short-term (7 days) secondary outcomes were: acute kidney injury (increase of creatinine >50% *vs* preoperative value), infections requiring antibiotic treatment and perioperative course of Hb, reticulocyte count, reticulocyte Hb content, platelet and leucocyte counts, international normalised ratio, high-sensitivity troponin, creatinine, C-reactive protein, calculated RBC loss (preoperative RBC mass minus RBC mass at postoperative day 5 plus transfused RBC mass[10]) as well as tolerance of study drugs and placebo administration. Secondary outcomes at postoperative day 90 were: percentage of patients without any RBC transfusion, number of allogeneic blood products (RBC, plasma, platelets) administered, length of stay in intensive care and in hospital, duration of mechanical ventilation, major adverse cardiac and cerebrovascular events, new onset of atrial fibrillation, thrombotic and thromboembolic complications, mortality, product acquisition costs, and the occurrence of serious adverse events (list provided in the appendix pp 10–11).[10] Stroke was defined as a new and irreversible neurological deficit with a new lesion found in CT or MRI. Myocardial infarction was defined as an increase of high-sensitive troponin (>10 times 99th percentile of reference value) with documented obstruction of a coronary artery or bypass in coronary angiogram. In addition, the maximum troponin level measured at intensive care unit admission and on postoperative day 1 and postoperative day 2 was compared between groups. All available data were analysed.

Statistical analysis

The pre-specified primary analysis was the comparison of treatment and placebo groups using the two-sided Mann-Whitney test. Sample size calculation was based on the RBC transfusions observed in 2011 at the Department of Cardiovascular Surgery of the University Hospital of Zurich, Zurich, Switzerland in patients undergoing the targeted operations, assuming a reduction of one unit of RBC by treatment. A sample size of two times 250 study patients was calculated to yield an 80% power to detect such a difference at a significance level of 0·05. Effect size and heterogeneity of treatment are assessed using ordinal logistic regression with the primary outcome as dependent variable and treatment and subgroups anaemia versus isolated iron deficiency as factors. Model fit is assessed using deviance. Interactions are assessed using likelihood ratio test and information criteria Akaike information criterion and Bayesian information criterion. The effect of treatment is reported as odds ratio (OR) with 95% CI.

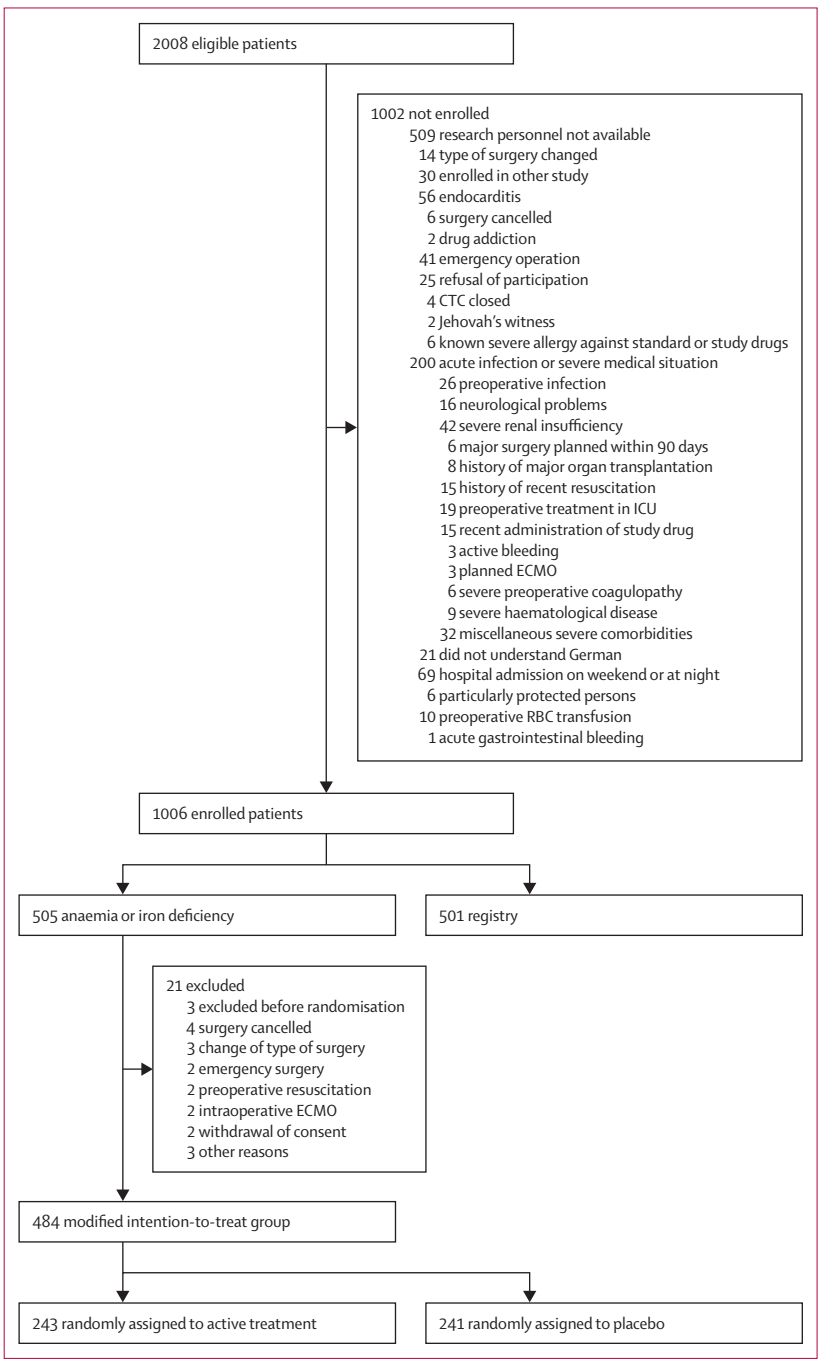

Figure 1: **Trial profile**
CTC=Clinical Trial Centre. ECMO=extra-corporeal membrane oxygenation.

	Treatment group (n=243)	Placebo group (n=241)
Age (years)	69 (11)	67 (12)
Women	85 (35%)	82 (34%)
Height (cm)	168 (9)	169 (10)
Weight (kg)	76 (15)	77 (16)
BMI (kg/m²)	27·1 (4·8)	26·9 (5·0)
EuroSCORE	4·5 (5·3)	4·2 (4·8)
Previous cardiac surgery	11 (5%)	8 (3%)
Dual platelet inhibition	39 (16%)	38 (16%)
Haemoglobin (g/L)	128 (15)	129 (15)
Reticulocyte count (G/L)	56 (23)	54 (22)
Reticulocyte haemoglobin (pg)	33 (3)	33 (3)
Ferritin (mcg/L)	149 (168)	156 (232)
Holotranscobalamine (pmol/L)	98 (63)	82 (48)
Folic acid in erythrocyte (mcg/L)	489 (269)	484 (281)
Creatinine (mmol/L)	89 (25)	89 (26)
eGFR (mL/min)	73 (20)	75 (21)
Platelet count (G/L)	240 (73)	227 (66)
hs Troponin (ng/L)	91 (265)	99 (273)
CRP (mg/L)	6·8 (12·1)	8·9 (20·6)
NT pro BNP (ng/L)	1292 (1992)	1532 (4675)
Systolic blood pressure (mm Hg)	131 (22)	130 (20)
Diastolic blood pressure (mm Hg)	72 (12)	70 (12)
Oxygen saturation (%)	96 (2)	97 (2)
Alcohol consumption	53 (22%)	49 (20%)
Smoking		
Former smoker	88 (36%)	78 (32%)
Current smoker	38 (16%)	53 (22%)
Hospital admission for CV disease in last 4 weeks	71 (29%)	65 (27%)
Angina at index hospital admission	111 (46%)	107 (45%)
Myocardial infarction		
History of myocardial infarction	21 (9%)	22 (9%)
Acute myocardial infarction	45 (19%)	41 (17%)
(Table 1 continues in next column)		

	Treatment group (n=243)	Placebo group (n=241)
(Continued from previous column)		
Infection		
Previous infection (4 weeks)	12 (5%)	13 (5%)
Acute infection (1 week)	11 (5%)	14 (6%)
Gastrointestinal disease		
History of gastrointestinal disease	12 (5%)	11 (5%)
Acute gastrointestinal disease	17 (7%)	19 (8%)
Kidney disease		
History of kidney disease	10 (4%)	12 (5%)
Acute kidney insufficiency	53 (22%)	51 (21%)
Liver disease		
History of liver disease	3 (1%)	2 (1%)
Acute liver disease	3 (1%)	2 (1%)
Malignant disease		
History of malignant disease	24 (10%)	15 (6%)
Acute malignancy	8 (3%)	8 (3%)
Operative characteristics		
Type of surgery		
CABG only	117 (48%)	106 (44%)
Off-pump	93 (38%)	85 (35%)
On-pump	24 (10%)	21 (9%)
Valve only	81 (33%)	89 (37%)
CABG valve combined	45 (19%)	46 (19%)

Data are reported as mean (SD) or number of patients (%). BMI=body-mass index. EuroSCORE=European System for Cardiac Operative Risk Evaluation. eGFR=estimated glomerular filtration rate. CRP=C-reactive protein. NT pro BNP=N-terminal pro brain natriuretic peptide. CV=cardiovascular. CABG=coronary artery bypass grafting.

Table 1: **Patient characteristics**

Continuous and count variables are reported as mean (SD) or median (IQR) and compared between groups using the Mann-Whitney test. Categorical variables are reported as frequency with percentage and compared between groups using the χ^2 test or Fisher's exact test as appropriate. Haematological variables at postoperative days 1, 3, and 5 were compared using the Mann-Whitney test for the mean of these three measurements. Maximal troponin concentrations of the day of operation and postoperative days 1 and 2 was compared between groups using the unpaired *t* test for logarithmically transformed data. Normal distribution within groups was assessed visually. The 95% CI for the ratio of geometric means was reported. For major adverse cardiac and cerebrovascular events and serious adverse events we additionally calculated OR with 95% CI. Statistical analyses were done by IBM SPSS Statistics 25 (IBM Corp, Armonk, NY, USA). p value less than 0·05 was considered to indicate statistical significance. All reported p values are two-sided and have not been adjusted for multiple testing (only one single primary outcome). All figures were designed using Prism 7 (GraphPad Software, La Jolla, CA, USA).

In this paper, we report the data from the randomised, double-blind, parallel-group controlled study comparing combination treatment with placebo in patients with preoperative anaemia or iron deficiency. Data from the parallel registry of non-anaemic, non-iron-deficient patients are not within the scope of this paper.

Funding

The study was funded by the Swiss Foundation for Anaesthesia Research, Zurich, Switzerland, a grant from Vifor Pharma, Glattbrugg, Switzerland (including provision of free of charge ferric carboxymaltose), and funds of the Institute of Anaesthesiology of the University Hospital of Zurich, Switzerland. None of the external granting institutions was involved in the design of the protocol, data analysis, writing of the manuscript, and the decision to submit. All authors had full access to data and vouch for their integrity.

	Treatment (n=243)	Placebo (n=241)	p value
RBC units transfused in first 7 days	..	..	0·036
Mean (SD)	1·5 (2·7)	1·9 (2·9)	..
Median (IQR)	0 (0–2)	1 (0–3)	..
Distribution, n (%)			
0	135 (56%)	114 (47%)	..
1	31 (13%)	27 (11%)	..
2	33 (14%)	38 (16%)	..
3	10 (4%)	23 (10%)	..
4	12 (5%)	11 (5%)	..
≥5	22 (9%)	28 (12%)	..
FFP units transfused in first 7 days	..	..	0·28
Mean (SD)	0·1 (1·1)	0·2 (1·7)	..
Median (IQR)	0 (0–0)	0 (0–0)	..
N (%)	5 (2%)	9 (4%)	..
Platelet concentrates units transfused in first 7 days	..	..	0·21
Mean (SD)	0·3 (1·1)	0·3 (1·2)	..
Median (IQR)	0 (0–0)	0 (0–0)	..
N (%)	27 (11%)	37 (15%)	..
Total units of allogeneic blood products, first 7 days	..	..	0·038
Mean (SD)	1·9 (4·5)	2·4 (5·0)	..
Median (IQR)	0 (0–2)	1 (0–3)	..
N of patients (%)	111 (46%)	129 (54%)	..
RBC units transfused in day 0 to POD 90	..	..	0·018
Mean (SD)	1·7 (3·2)	2·3 (3·3)	..
Median (IQR)	0 (0–2)	1 (0–3)	..
Distribution, n (%)			
0	129 (53%)	107 (44%)	..
1	28 (12%)	23 (10%)	..
2	37 (15%)	39 (16%)	..
3	13 (5%)	25 (10%)	..
4	12 (5%)	9 (4%)	..
≥5	24 (10%)	38 (16%)	..
(Continued from previous column)			
Fresh frozen plasma (FFP) units transfused, Day 0 to POD 90	..	..	0·19
Mean (SD)	0·1 (1·1)	0·2 (1·7)	..
Median (IQR)	0 (0–0)	0 (0–0)	..
N (%)	5 (2%)	10 (4%)	..
Platelet concentrates units transfused, day 0 to POD 90	..	..	0·21
Mean (SD)	0·3 (1·1)	0·3 (1·2)	..
Median (IQR)	0 (0–0)	0 (0–0)	..
N (%)	27 (11%)	37 (15%)	..
Total units of allogeneic blood products, day 0 to POD 90	..	..	0·019
Mean (SD)	2·2 (4·8)	2·8 (5·2)	..
Median (IQR)	0 (0–2)	1 (0–3)	..
N (%)	117 (48%)	136 (56%)	..
RBC acquisition costs in CHF, day 0 to POD 90	..	..	0·018
Mean (SD)	370 (674)	480 (704)	..
Median (IQR)	0 (0–425)	213 (0–638)	..
Total RBC transfusion cost including drug treatment in CHF, day 0 to POD 90	..	..	<0·0001
Mean (SD)	1052 (674)	480 (704)	..
Median (IQR)	682 (682–1107)	213 (0–638)	..

RBC=red blood cell. POD 90=day of first postoperative consultation with the referring cardiologist expected at postoperative day 90; effectively at a median of 98 days (IQR 90–112) after the day of surgery. CHF=Swiss Francs. For the cost calculation the actual price of one RBC unit of 213 CHF was used.

Table 2: **Transfusion outcome according to treatment**

Results

Between Jan 9, 2014, and July 19, 2017, 1006 patients were enrolled; 505 with anaemia or isolated iron deficiency and 501 in the registry. From 505 patients with anaemia or isolated iron deficiency, three were not randomly assigned, four were not operated, in three patients more complex surgery rendered patients ineligible, two required emergency surgery, two were resuscitated between enrolment and the planned surgery, two required intraoperative extra-corporeal membrane oxygenation, two withdrew consent, two were excluded for other reasons, and one was excluded for massive transfusion. This left 484 patients with anaemia or isolated iron deficiency (the sample) in the modified intention-to-treat group (figure 1, table 1, appendix p 4). The postoperative day 90 follow-up visit took place at a median of 98 postoperative days (IQR 90–112). Five patients (1%) were lost to follow-up and hence follow up was complete at 90 days for 99% of patients. Mean (SD) age of patients was 68 years (12), 35% were women, and the mean EuroSCORE was 4·3 (5·0).

Baseline patient characteristics, including haemoglobin and ferritin concentrations, were well balanced between treatment and placebo groups. In addition, the distribution of type of surgery and history of previous cardiac surgery was similar (table 1).

Combination treatment reduced RBC transfusions from one unit (IQR 0–3) to zero units (0–2; Mann-Whitney test p=0·036) during the first 7 days. Univariable ordinal regression yielded an OR of 0·70 (95% CI 0·50–0·98 for each threshold of number of RBC transfusions, p=0·036) for treatment versus placebo group (table 2).

Combination treatment also reduced RBC transfusions until postoperative day 90 (p=0·018; table 2). Despite fewer RBC units transfused, treated patients had a higher Hb concentration, higher reticulocyte count, and a

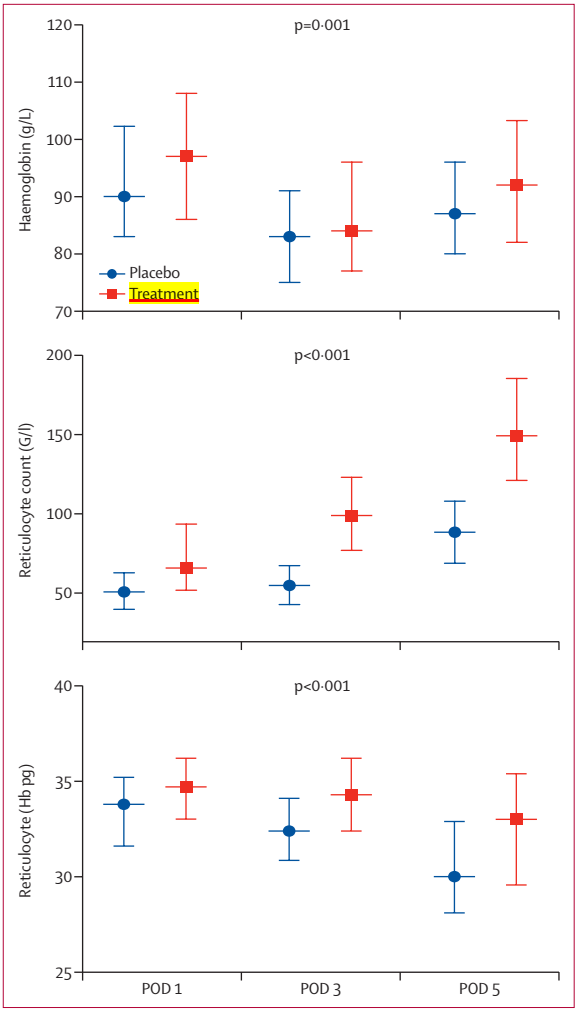

Figure 2: **Haemoglobin, reticulocyte count, and reticulocyte Hb content on postoperative days (POD) 1, 3, and 5 according to treatment**
p value between treatment and placebo. Data are median (IQR).
Hb=haemoglobin concentration.

higher reticulocyte Hb content during the first 7 days (figure 2). Fresh frozen plasma and platelet transfusions were similar during the first 7 days and until postoperative day 90 but the combined allogeneic transfusions were less in the treatment (0 units [IQR 0 to 2]) versus placebo group (1 unit [0 to 3]) during the first 7 days (p=0·038) and until POD 90 (p=0·019). RBC acquisition costs until postoperative day 90 were also less (p=0·018) in the treatment group (0 CHF [IQR 0–425]; 370 CHF [SD 674]) *vs* placebo group (213 CHF [0–638]; 480 CHF [SD 704]). However, total costs were higher in the treatment (682 CHF [IQR 682–1107]; 1052 CHF [674]) versus the placebo group (213 CHF [0–638]; 480 CHF [SD 704]; p<0·001; table 2). Secondary outcomes, including serious adverse events (73 participants in the treatment group [30%] *vs* 79 in the placebo group [33%]; p=0·56) and mortality at POD 90 (18 particpants in the treatment group [7%] *vs* 14 in the placebo group [6%]) were similar between treatment and placebo group (table 3). Only RBC loss was significantly lower in the treatment group (612 mL [IQR 438–915]) versus the placebo group (736 mL [IQR 527–1013]; p=0·001; table 3).

To address a possible heterogeneity in the effect of treatment, a multivariable ordinal logistic regression was done with the number of RBC transfusions during the first 7 days as dependent variable and treatment and subgroups anaemia versus isolated iron deficiency as factors ($p_{interaction}$=0·65). Consequently, there is no evidence for differences in the effect of treatment between subgroups.

21 (9%) participants in the placebo group and 23 (10%) in the treatment group experienced a major adverse cardiac and cerebrovascular events (OR 1·10 [95% CI 0·59–2·04]). 79 (33%) participants in the placebo group and 73 (30%) in the treatment group experienced a serious adverse event (OR 0·88 [95% CI 0·60–1·29]). The geometric mean of maximal troponin was also similar (geometric mean ratio 0·92; treatment *vs* placebo [95% CI 0·75–1·13]).

Baseline patient characteristics, including haemoglobin and ferritin concentrations, distribution of type of surgery, and history of previous cardiac surgery were well balanced between treatment and placebo group in the isolated iron deficiency subgroup (appendix p 4).

No significant reduction of RBC transfusions by combination treatment (0 units [IQR 0–1]) versus placebo (0 units [0–2]) could be shown. Univariable ordinal regression yielded an OR of 0·76 (95% CI 0·45–1·29) for each threshold of number of red blood cell transfusions; p=0·32 for treatment versus placebo group (appendix pp 5–6). FFP, platelet, and combined allogeneic transfusions were similar between groups during the first 7 days. Until postoperative day 90 combined allogeneic transfusions were also not different (0 units [IQR 0–2]) in the treatment group versus (0 units [0–2]) in the placebo group (p=0·13, appendix pp 5–6). Nevertheless, treated patients had a higher Hb concentration, higher reticulocyte count, and a higher reticulocyte Hb content during the first 7 days (figure 3). RBC acquisition costs until postoperative day 90 were similar (p=0·11) between groups (0 CHF [IQR 0–213] in the treatment group *vs* 0 CHF [0–425] in the placebo group). However, total costs were higher in the treatment group (682 CHF (IQR 682–895); 921 [SD 534]) than in the placebo group (0 CHF [0–425]; 357 [663]; appendix pp 5–6; p<0·001). Secondary outcomes were similar between groups except for a RBC loss, which was significantly lower (p=0·016) in the treatment group than in the placebo group (appendix p 7).

Baseline patient characteristics including haemoglobin and ferritin concentrations, distribution of type of surgery and history of previous cardiac surgery were well balanced between treatment and placebo groups in the anaemia subgroup (appendix p 4).

The combination treatment tended to reduce RBC transfusions from two units (IQR 0–3) to one units (0–3;

p=0·059). Univariable ordinal regression yielded an OR of 0·65 (95% CI 0·41–1·01) for each threshold of number of RBC transfusions (p=0·058 for treatment *vs* placebo group; appendix pp 5–6). FFP and platelet transfusions were similar during the first 7 days. Combined allogeneic transfusions tended to be lower during the first 7 days in the treatment group (one unit [IQR 0–3]) versus in the placebo group (two units [0–4]; p=0·054). Until postoperative day 90, combined allogeneic transfusions were one unit (IQR 0–3) in the treatment group and two units (0–4) in the placebo group (p=0·073, appendix pp 5–6). Treated patients had a higher Hb concentration, higher reticulocyte count, and a higher reticulocyte Hb content during the first 7 days (figure 3). RBC acquisition costs until POD 90 were similar (p=0·072) in the treatment (213 CHF [IQR 0–638]) and the placebo group (425 CHF [0–850]). However, total costs were higher in the treatment group (895 CHF [IQR 682–1320]; 1182 [SD 769]) than in the the placebo group (425 CHF [0–850]; 599 [SD 724]; p<0·001; appendix pp 5–6). Secondary outcomes were similar between groups except for a RBC loss which was significantly lower (p=0·011) in treated patients (appendix p 7).

Discussion

To the best of our knowledge, this is the first large scale prospective randomised controlled trial showing that an ultra-short-term combination treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin B_{12}, and oral folic acid reduces RBC and total allogeneic blood product transfusions in patients with preoperative anaemia or isolated iron deficiency undergoing elective cardiac surgery.

Ideally, erythropoietin is given days before a planned intervention since the earliest increase of the reticulocyte count can be expected only after 2 to 3 days.[11,12] For logistic reasons and monetary constraints within the health-care system this was not possible in the current study. Hence by design the treatment was only given the day before surgery. The co-administration of intravenous iron, subcutaneous erythropoietin alpha, and vitamin B_{12}, and oral folic acid apparently accelerated the haemopoietic response as evidenced by a significantly higher reticulocyte count and reticulocyte Hb content in treated patients, which was noted already at the first postoperative day and was observed at least until postoperative day 5 (figure 2). This is the most likely mechanism that resulted in reduced RBC transfusions (table 2).

A growing number of cardiac surgical patients are operated within a few days after an acute cardiac event.[13] Therefore, the finding that combined treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin B_{12}, and oral folic acid the day before surgery is efficacious is of particular relevance. Earlier treatment, whenever possible, remains desirable since an Hb increase of 10–15 g/L per week might be expected,[10,11,14,15] which could further decrease RBC transfusions. A longer

	Treatment group (n=243)	Placebo group (n=241)	p value
Patients transfused (≥1 RBC), first 7 days	108 (44%)	127 (53%)	0·084
Combined allogeneic transfusions (≥1 RBC or ≥1 TC or ≥1 FFP), first 7 days	111 (46%)	129 (54%)	0·10
Length of stay in ICU (days)	..	..	0·33
Mean (SD)	3·5 (7·8)	2·7 (5·2)	..
Median (IQR)	1 (0·9–2·0)	1 (0·9–2·0)	..
Length of stay in hospital (days)	..	..	0·73
Mean (SD)	12·0 (9·7)	12·3 (11·0)	..
Median (IQR)	8·8 (6·9–12·9)	8·9 (6·9–13·7)	..
Duration of mechanical ventilation (h)	..	..	0·95
Mean (SD)	28·1 (79·3)	20·8 (56·3)	..
Median (IQR)	5·7 (3·7–9·2)	5·5 (3·9–10·6)	..
MACCE	23 (10%)	21 (9%)	0·88
Allergy	5 (2%)	2 (1%)	0·45
Angina	4 (2%)	4 (2%)	1·00
Myocardial infarction	1 (0%)	6 (3%)	0·068
Maximum postoperative hs troponin until POD 2 (g/L)	..	..	0·40
Mean (SD)	1259 (2654)	1259 (2383)	..
Median (IQR)	571 (222–1110)	578 (293–1230)	..
Stroke	6 (3%)	6 (3%)	1·00
Acute kidney injury	22 (9%)	18 (8%)	0·62
Dialysis	15 (6%)	8 (3%)	0·20
Atrial fibrillation	43 (18%)	52 (22%)	0·30
Infection	88 (36%)	77 (32%)	0·34
Gastrointestinal disease	2 (1%)	2 (1%)	1·00
Laparotomy	0 (0%)	3 (1%)	0·12
New malignoma	0 (0%)	1 (0%)	0·50
Haemothorax	9 (4%)	13 (5%)	0·39
Rethoracotomy	12 (5%)	17 (7%)	0·35
Bleeding (other)	4 (2%)	3 (1%)	1·00
Thromboembolic event	2 (1%)	6 (3%)	0·18
Resuscitation	12 (5%)	13 (5%)	0·84
Serious adverse events	73 (30%)	79 (33%)	0·56
Death (first 7 days)	4 (2%)	7 (3%)	0·58
Death (day 0 to POD 90)	18 (7%)	14 (6%)	0·58

Data are n (%) unless otherwise stated. RBC=red blood cells. TC=thrombocytes. FFP=fresh frozen plasma. MACCE=major adverse cardiac and cerebrovascular events. MACCE were new stroke, myocardial infarction, or death until POD 90. POD 90=day of first postoperative consultation with the referring cardiologist expected at postoperative day 90; effectively at a median of 98 days (IQR 90–112) after the day of surgery. Allergy=appearance of any allergic reactions till POD 90. Angina=patients complaining of angina subjectively. Myocardial infarction=elevation of Troponin T, if preoperative troponin was in the normal range and confirmation of the occlusion of a coronary artery in radiological or postmortem examinations. Stroke=new onset of irreversible neurological impairments during hospital admission and confirmation of a new cerebral lesion in radiological examinations (CT, MRI) or postmortem examination. Acute kidney injury=>2-fold increase of creatinine compared with the preoperative value or oliguria (<0·5 mL/kg per h) over 12 h (RIFLE – I, AKIN 2). Dialysis=patients requiring a new renal replacement therapy based on the decision of the responsible physician. Atrial fibrillation=new onset of atrial fibrillation of at least 30 seconds and documented with an ECG; not accounted were atrial arrhythmias of a duration under 30 s or in patients requiring catecholamines. Infection=postoperative increase of inflammatory values leading to a prolonged hospital stay or requiring a specific therapy or microbial detection of the causal germ. Gastrointestinal disease=diagnosis of a new gastrointestinal disease. Laparotomy: patients requiring a laparotomy in the theatre during hospital stay. New malignoma=diagnosis of a new malignoma. Haematothorax=diagnosis of a haematothorax confirmed by radiological examinations. Rethoracotomy=patients requiring a rethoracotomy during hospital stay. Bleeding (other)=patients with other bleeding complications. Gastrointestinal bleedings were confirmed by endoscopy. Thromboembolic event=diagnosis of new thromboembolic events confirmed by radiological examinations (sonography, CT) during hospital stay or new documentation in patients records during the follow-up period. No elective screening of thromboembolic events was performed. Resuscitation=patients requiring cardio pulmonal resuscitation till POD 90.

Table 3: **Secondary outcomes according to treatment**

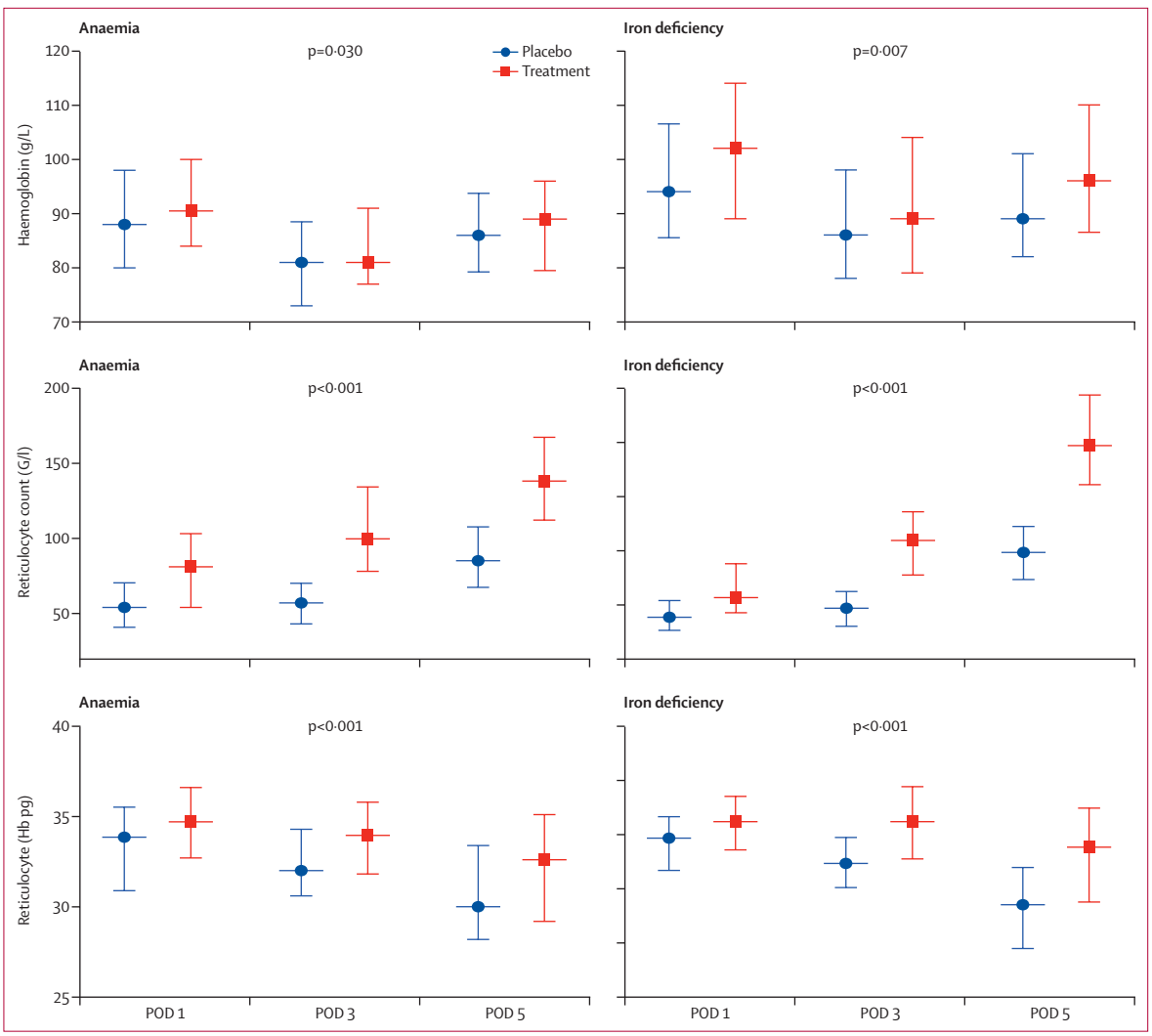

Figure 3: Haemoglobin, reticulocyte count, and reticulocyte Hb content on postoperative days (POD) 1, 3, and 5 in the anaemia and isolated iron deficiency sub-groups according to treatment

p value within subgroups between treatment and placebo. Data are median (IQR). Hb=haemoglobin concentration.

preoperative treatment period might also allow to initially treat iron deficiency anaemia with intravenous iron only, re-check the haemoglobin after 2 weeks[14] and only administer the combination treatment in patients with incomplete response. In patients with congestive heart failure and iron deficiency, intravenous iron treatment might be particularly beneficial since it was shown to improve New York Heart Association functional class already after 4 weeks.[7] Health-care providers globally need to work with clinicians to establish a sustainable framework, which allows fostering of treatment of anaemia before major surgery in an outpatient setting at a point in time when an intervention (such as erythropoietin, iron administration, or both) can be most effective.

Iron deficiency was defined by a ferritin less than 100 mcg/L. This is similar but more restrictive than in the study by Anker and colleagues[7] who showed that intravenous iron treatment improved the functional status and the clinical outcome of patients with heart failure and iron deficiency. Patients with atherosclerosis and undergoing CABG surgery are in a low grade inflammatory state,[5,16,17] which increases ferritin irrespective of the iron status—ie, higher values might still indicate iron deficiency. In future studies, iron deficiency might be more stringently defined by a combination of ferritin, transferrin saturation, hepcidin and eventually soluble transferrin receptor.

Anaemia is frequent in patients undergoing cardiac surgery.[1,2] In multiple retrospective studies an association with increased RBC transfusions and adverse clinical outcomes, such as increased length of hospital stay, acute kidney injury, and mortality has been found.[1,2] In this study we were able to significantly reduce RBC transfusions by the combination treatment from a median

of 1 to a median of 0 (table 2), which did not seem to affect the secondary clinical outcomes that were similar between groups (table 3). The most likely explanation for these findings is the study design. The study was not powered to show a difference for any of the secondary outcomes. In addition, surgery was undertaken before anaemia was effectively treated. Another important difference from previous studies is the fact that we did not compare transfused with non-transfused patients but patients with preoperative anaemia or isolated iron deficiency that either received a combination treatment or not, and in both groups about 50% of patients were transfused at any time (table 3). Finally, in a recent large prospective randomised trial comparing the application of a liberal versus a restrictive RBC transfusion trigger a similar difference in median RBC transfusions of 1 unit was found without differences in clinical secondary outcomes.[18] This might reiterate the call for earlier treatment of anaemia before major surgery in an outpatient setting allowing for a more timely and complete restauration of the RBC mass, which might lead to a greater reduction of RBC transfusions and eventually also to an improved clinical outcome. Only adequately powered future studies will allow to answer this question.

Also mortality was similar in both groups and numerically higher than the EuroSCORE (table 1). This is expected because the EuroSCORE predicts the in-hospital or 30-day mortality but 90-day mortality was assessed in this study, which is known to be higher.[19]

The relative efficacy of the combination treatment in terms of a reduction in RBC transfusions might appear higher in patients with preoperative anaemia than in patients with isolated iron deficiency (appendix pp 5–6). However, multivariable ordinal logistic regression did not find a significant difference. Nevertheless, a timely treatment of patients with iron deficiency scheduled for cardiac surgery with congestive heart failure might well be advantageous given the beneficial effect of intravenous iron on functional status and the clinical outcome.[7,8]

The efficacy of a short term treatment with erythropoietin in combination with intravenous iron has been previously shown in one small and potentially underpowered study in 74 anaemic patients undergoing surgery for valvular heart disease.[20] The current study confirms this finding in a larger cohort and expands it to patients undergoing CABG and combined CABG and valve surgery as well as to a combined anaemia or isolated iron deficiency group of patients.

Preoperative correction of anaemia and iron deficiency is an integral part of the concept of Patient Blood Management[6] and is recommended by major professional societies of cardiothoracic surgeons and anaesthesiologists.[21,22] Patient Blood Management goes beyond the treatment of preoperative anaemia and iron deficiency; it also comprises measures to reduce perioperative blood loss such as meticulous surgical haemostasis, advanced perioperative coagulation management restrictive transfusion thresholds,[18] and optimising anaemia tolerance. Although the success of this concept has been shown in a large general surgical patient population of more than 605 000 patients,[23,24] the benefit in cardiac surgery has so far only been shown in relatively small cohorts.[25] The results of this study underline that the immediate preoperative correction of anaemia and iron deficiency might result in a reduction of allogeneic RBC transfusions in patients undergoing cardiac surgery and hence could become an important part of Patient Blood Management.

The reduction of acquisition costs for RBC transfusion during the entire study period from a median of 213 CHF to 0 CHF was statistically significant (table 2). However, due to the acquisition costs of the combination treatment of 682 CHF, total costs of RBC transfusion were higher in the treatment group than in the placebo group (table 2). Acquisition costs of RBC transfusions underestimate the true cost of RBC transfusions significantly.[26] In surgery, these total costs have been estimated to be 685 CHF in Switzerland in an activity-based (including testing, administration, and infusion) cost calculation.[26] The true costs of the administration of intravenous iron, subcutaneous erythropoietin, and vitamin B_{12} are unknown but the ratio between total and acquisition costs are lower than with RBC transfusions.

This study has some important limitations. The sample size was calculated based on the transfusions administered to patients undergoing cardiac surgery in 2011 at the Department of Cardiovascular Surgery of the University Hospital of Zurich, Zurich, Switzerland, to show a difference in RBC transfusion in the combined anaemia or isolated iron deficiency group. The sample size therefore was underpowered to show a benefit in each subgroup. Particularly in the isolated iron deficiency subgroup, a distinctly larger study would be necessary to demonstrate efficacy; in part also due to the fact that these patients were not anaemic and hence their baseline risk of receiving an RBC transfusion was limited. However, there might be other benefits like a faster Hb recovery after surgery, as shown in cardiac[27] and non-cardiac surgery[15] but this was not addressed in this study. As the results of our study were drawn from a single centre, generalisability might be limited due to the patient collective from a single locality. Furthermore, only a limited number of health-care professionals were involved in patient's treatment. Future multicentre studies might overcome this limitation. There was no adjustment for multiple testing. p values for secondary outcomes and subgroup analyses hence should be interpreted with particular care. Finally, by study design a combination treatment was given and therefore it was not possible to assess the individual contribution of each of the four drugs administered. Future studies might be needed to answer this question. However, it might well be that the combination treatment is the key to success.

This study has also particular strengths. Due to the stratification, patients with preoperative anaemia or isolated iron deficiency were well balanced between the treatment and placebo groups (table 1). In addition, this study was also maximally blinded. The treatment was administered via a black tubing with the infusion bag covered and additionally placed behind a screen. The physician who administered the treatment was not involved in patient enrolment, patient treatment, nor data acquisition in any form. The physician responsible for data acquisition was unaware of group assignment of patients because the randomisation system alerted the physician responsible for treating patients via text message. Also, surgeons, intensive-care units specialists, and physicians on the postoperative ward were completely unaware of group assignment.

Increased iron requirements and limited external supply can lead to an iron deficiency and consecutively to an iron deficiency anaemia. Data from the UK show that more than 30% of all patients undergoing cardiac surgery are anaemic preoperatively. In almost 50% of these patients a functional iron deficiency was observed.[2] In chronic inflammation, frequently present in atherosclerotic patients, hepcidin decreases iron absorption and prevents iron recycling, resulting in an iron restricted erythropoiesis, despite normal iron stores (functional iron deficiency).[5] Preclinical data suggest that intravenous iron might slightly increase inflammatory markers. Catalysation of redox reactions or transcription of pro-inflammatory enzymes could play a part.[28] However, the mechanism of action is not fully understood and not supported by clinical perioperative data.[29] Despite the concerns about the effect of iron on infection and inflammation, intravenous iron had no effect on infection rates in intensive-care unit patients[30] and short term preoperative or early postoperative intravenous iron decreased perioperative infections.[31] The similar infection rate in the treatment and the placebo group in this study thus is in line with these findings.

Due to concerns about its pro-thrombotic and platelet-activating effects, erythropoietin is not licensed in some countries (eg, the UK) to treat patients with cardiovascular diseases. Sowade and colleagues[32] investigated the effect of preoperative erythropoietin therapy on platelets and haemostasis in patients undergoing cardiac surgery. They concluded that the preoperative erythropoietin therapy is not associated with an increased thromboembolic risk. In agreement with this finding, our study did not find any differences in thrombotic events between the placebo and the active treatment group. Thrombotic events occurred numerically even less often in the treatment group than in the placebo group. However, this study was not designed to investigate the safety of erythropoietin in patients undergoing cardiac surgery. Furthermore, preoperative erythropoietin administration has been shown to reduce the risk for acute kidney injury in patients undergoing cardiac surgery.[33] In addition, erythropoietin has been shown to reduce all-cause-mortality and end-stage renal disease in patients with acute kidney injury after coronary artery bypass grafting.[34] Based on odds ratios close to 1 for MACCE, SAEs, and maximum postoperative troponin level, adequately powered prospective randomised studies probably require several thousand patients to specifically confirm the safety of our combination treatment in cardiac surgery.

Ultra-short-term combination treatment with intravenous iron, subcutaneous erythropoietin alpha, vitamin B_{12}, and oral folic acid reduces RBC and total allogeneic blood product transfusions in patients with preoperative anaemia or isolated iron deficiency undergoing elective cardiac surgery.

Contributors

DRS, FS, GHS, BS, OMT, AH, and VF contributed to the study design. DRS, FS, GHS, PS, OMT, and AK contributed to the collection of data. BS did the data analyses. All authors contributed to interpretation of the data. DRS wrote the first draft of the manuscript. All authors provided critical revisions to the manuscript before seeing and approving the final version.

Declaration of interests

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Data sharing

For original deidentified individual patient data please contact donat.spahn@usz.ch. Data will be made available for a period of 5 years after the publication date.

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