

Intravenous iron supplementation treats anemia and reduces blood transfusion requirements in patients undergoing coronary artery bypass grafting—A prospective randomized trial

Hoda Shokri, Ihab Ali¹Departments of Anesthesiology and ¹Cardiothoracic Surgery, Ain Shams University, Cairo, Egypt

ABSTRACT

Study Objective: Preoperative anemia results in two- to sixfold increased incidence of perioperative blood transfusion requirements and reduced postoperative hemoglobin (Hb) level. This prospective study was designed to investigate the effect of preoperative intravenous infusion of iron on Hb levels, blood transfusion requirements, and incidence of postoperative adverse events in patients undergoing coronary artery bypass grafting.

Design: Prospective randomized trial.

Setting: Academic university hospital.

Patients: Eighty patients (52–67 years old) underwent coronary artery bypass grafting and received either iron therapy or saline infusion preoperatively.

Interventions: Patients were randomly allocated to iron or placebo groups. In the iron group, patients received a single intravenous dose of ferric carboxymaltose (1000 mg in 100 mL saline) infused slowly over 15 min 7 days before surgery. In placebo group, patients received a single intravenous dose of saline (100 mL saline) infused slowly over 15 min 7 days before surgery.

Measurements: Patients were followed up with regards to incidence of anemia, Hb level on admission, preoperatively, postoperatively, 1 week and 4 weeks after discharge, aortic cross-clamp time, the number of packed red blood cells (pRBCs) units, the percentage of reticulocytes pre–postoperatively and 1 week later, hospital stay and intensive care unit (ICU) stay length, and the incidence of postoperative complications.

Main Results: Iron therapy was associated with lower incidence of anemia 4 weeks after discharge ($P < 0.001$). Hb level was significantly higher in the iron group compared to the placebo group preoperatively and postoperatively, and 4 weeks after discharge ($P < 0.001$). Iron therapy resulted in shorter hospital and ICU stay ($P < 0.001$) and shorter aortic cross-clamp time, reduced pRBCs requirements postoperatively. Percentage of reticulocytes was significantly higher in placebo group than in iron group postoperatively and 1 week after discharge and the incidence of postoperative complications was similar to the placebo group.

Conclusions: Preoperative IV iron infusion is a safe and feasible way to manage preoperative anemia. Preoperative administration of IV iron is associated with a higher postoperative Hb level, shorter hospital and ICU stay, and reduced perioperative red blood cell transfusion requirements with insignificant difference in incidence of postoperative complications.

Keywords: Anemia, coronary artery bypass grafting, iron, placebo

Address for correspondence: Dr. Hoda Shokri, Ain Shams University, Cairo, Egypt.

E-mail: Drhoda10@yahoo.com

Submitted: 20-Aug-2020 **Revised:** 09-Jan-2021 **Accepted:** 06-Feb-2021 **Published:** 11-Apr-2022

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.aca_209_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Shokri H, Ali I. Intravenous iron supplementation treats anemia and reduces blood transfusion requirements in patients undergoing coronary artery bypass grafting—A prospective randomized trial. *Ann Card Anaesth* 2022;25:141-7.

INTRODUCTION

Coronary artery diseases are associated with morbidity and mortality in both developed and developing countries.^[1] Patients undergoing cardiac surgery along with cardiopulmonary bypass (CPB) may have excessive perioperative blood loss requiring red blood cell transfusions.^[1] The severity of preoperative anemia is considered an important predictor for perioperative blood transfusions, and it is associated with higher incidence of postoperative morbidity^[2] and 30-day mortality.^[3,4]

In many studies, it was assumed that 30% of anemic patients scheduled for cardiac surgery received more allogeneic blood transfusions than those with normal hemoglobin (Hb) levels.^[5] Preoperative anemia results in two- to sixfold increased incidence of perioperative blood transfusion and low postoperative Hb levels.^[6]

Hence, preoperative anemia is associated with complications, such as stroke, postoperative myocardial infarction, prolonged hospital or intensive care unit (ICU) stay, increased 30-day mortality, kidney injury, and transfusion induced lung injury.^[7,8] Perioperative anemia mostly concerns the ageing population, which is remarkably growing with increased risk of diabetes, myocardial diseases, and obesity, creating a progressive demand for coronary artery bypass grafting (CABG).^[9,10]

Therefore, perioperative blood Hb adjustment has been adopted to maximize Hb levels and reduce the risk of blood transfusion.^[11] Preoperative administration of intravenous iron is a promising and feasible alternative to blood transfusion for controlling preoperative anemia, which affects one in four patients scheduled for surgical procedures.^[12]

This prospective study was designed to investigate the effect of preoperative intravenous infusion of iron on incidence of anemia, Hb levels, red blood cell transfusion requirements, and incidence of postoperative adverse events as cardiac tamponade in patients undergoing elective CABG.

METHODS

Study design

This prospective, randomized, double-blind, parallel-group study was approved by the ethics committee of Ain Shams University. Eighty patients, aged from 52 to 67 years, undergoing elective CABG were recruited in this study. The study was carried out in the Cardiothoracic Academy of Ain Shams University from September 2019 to January

2020. Ethical approval was provided by the local ethics committee (FMASU R 03/2019) and informed consent was obtained from all parents. The trial was registered under the number Clinical trial.gov no. NCT04061655. Preoperative check-up was completed 3–4 weeks in advance and included patients' medical history, current medication use, body weight and height, physical examination, and hematologic parameters (Hb, hematocrit, reticulocytes, mean corpuscular Hb, mean corpuscular volume, mean corpuscular Hb concentration, iron indices (serum ferritin, transferrin saturation, and serum iron), other routine tests, coronary angiography, and echocardiography).

The inclusion criteria were aged 52–67 years old, elective CABG scheduled, eligibility to receive the study medication and clopidogrel interruption 10 days before surgery, and anemia defined as Hb less than 13 g/dL for men and 12 g/dL for women.

Patients' hypersensitivity to iron, history of hepatitis B or C or human immunodeficiency virus, folate or vitamin B12 deficiency, unstable angina, history of stroke in the last 6 months, Hb <8 g/dL, active severe infection, suspicion of acquired iron overload (ferritin >300 µg/L) or autologous blood transfusion in the previous month, pregnancy or nursing, impaired renal function (γ -creatinine >150 µmol/L, hemochromatosis or hemosiderosis), vitamin B12 or folic acid deficiency, and anemia from intestinal bleeding were not eligible to participate in the study.

A total of 80 patients were randomly allocated to either the iron group or placebo group using the concealed envelope method according to a computer-generated randomization code, with an allocation ratio 1:1. Opaque-sealed envelopes were prepared according to the randomization schedule. Patients of the iron group ($n = 40$) received a single intravenous dose of ferric carboxymaltose (Ferinject, Vifor Pharma Management, Zurich, Switzerland) (1000 mg in 100 mL saline) infused for 15 min 7 days before surgery. Patients of the placebo group ($n = 40$) received a single-dose infusion of 100 mL saline for 15 min 7 days before surgery (sodium chloride 9 mg/mL; Fresenius Kabi, Copenhagen, Denmark). To ensure blinding, all infusion syringes, infusion lines, and disposables were wrapped in aluminum foil by the pharmacist, who was unaware of the nature of the study, and the research team was blinded to the treatment allocation.

The anesthesia procedure was standardized, and surgeries were performed by the same surgical team. Premedication with midazolam was limited to a maximum of 0.05 mg/kg. Anesthesia was induced with 12 µg/kg fentanyl, 5–7 mg/

kg sodium thiopental, and 0.15 mg/kg pancuronium and was maintained with 1–2.0% isoflurane. Monitoring using invasive arterial blood pressure, pulse oximetry, central venous catheter, arterial blood gases, and nasopharyngeal temperature during surgery. Heart rate and blood pressure were maintained within 20% of baseline. For anticoagulation treatment, heparin 300 U/kg was administered into the right atrium to achieve an activated clotting time above 480 s. CPB was initially handled with nonocclusive roller pumps, membrane oxygenators, arterial line filtration, and cold blood-enriched hyperkalemic arrest. Next, the CPB circuit was primed with 1.8 L lactated Ringer's solution and 50 mL 20% mannitol. CPB included systemic hypothermia (esophageal temperature 28°C) during aortic cross-clamping, perfusion pressure between 60 and 80 mmHg, and pump flow rates of 2.2 L/min/m². Myocardial protection was accomplished with antegrade cold blood cardioplegia. A 32- μ m filter (Avecor Affinity, Minneapolis, MN, USA) was used in the arterial perfusion line. Toward the end of the operation, patients were warmed to 36–37°C. Following separation from the CPB, heparin was neutralized with protamine sulfate (1 mg protamine sulfate/100 U heparin) to achieve activated clotting time within 10% of baseline. Finally, all patients were transferred to the ICU after surgery. The primary endpoint included the effect of iron therapy on the incidence of anemia in each group 4 weeks after discharge. The secondary endpoints included measurement of the Hb level on admission, preoperatively, postoperatively, 1 week and 4 weeks after discharge, number of pRBCs units, percentage of reticulocytes preoperatively, postoperatively and 1 week later, hospital stay length, length of ICU stay, and incidence of postoperative complications including cerebrovascular stroke, prolonged ventilation (duration of mechanical ventilation >12–24 h), heart failure, cardiac tamponade, hospital mortality, infection (sepsis and pneumonia), myocardial infarction, and pericardial effusion.

Sample-size justification

The Power Calculations and Sample Size Software (PASS; NCSS, LLC, East Kaysville, UT, USA) showed that 80 patients, 40 per arm, were required considering a 5% dropout (power of 80%; alpha error at 5%). These calculations based on a previous study by Johansson *et al.*^[13] showed that among the treatment group, the percentage of nonanemics was 38% compared to 8% in the placebo group.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using STATA (Stata Corp LLC, TX, USA). Descriptive statistics were carried out for numerical parametric

data and are presented as mean \pm SD, whereas categorical data are presented as numbers and percentages. Variables such as demographic data and comorbidities were compared using the χ^2 test. *P* value less than 0.05 was considered significant.

RESULTS

The study was carried out in the Cardiothoracic Academy of Ain Shams University from September 2019 to January 2020. Ethical approval was provided by the local ethics committee (FMASU R 03/2019). The trial was registered under the number Clinical trial.gov no. NCT04061655.

A group of 80 patients were randomized [Figure 1], all were enrolled in our study without a single case of protocol violation, and their data were analyzed. The research team decided on the removal of patients from the study because of their clinical condition or violation of the protocol.

There was no significant difference in terms of demographic data, American Association of Anesthesiologists (ASA) status, comorbidities, and surgical data between the two study groups; aortic cross-clamp time was significantly shorter in iron group compared with placebo group, *P* < 0.001 [Table 1].

The intention-to-treat analysis of the primary outcome revealed an incidence of anemia 4 weeks after discharge of (13/40) 32% in patients receiving iron and (32/40) 80% in those receiving placebo (*P* < 0.001) [Table 2]. Hb level was significantly higher in the iron group compared to the placebo group preoperatively and postoperatively and 4 weeks after discharge (*P* < 0.001) [Table 2]. In contrast, Hb level was comparable between study groups on admission and 1 week after discharge (*P* = 0.397).

The amount of postoperative blood loss was similar between the study groups (*P* = 0.843).

Table 1: Demographic data of the studied patients

	Iron (n=40)	Placebo (n=40)	Tests	
			t/ χ^2	P
Patient demographics				
Age (years)	58.35 \pm 4.44	60.08 \pm 4.79	1.671	0.099
Sex			2.464	0.116
Female	22 (55%)	15 (37.5%)		
Male	18 (45%)	25 (62.5%)		
ASA			0.802	0.370
I	17 (42.5%)	21 (52.5%)		
II	23 (57.5%)	19 (47.5%)		
EF %	62.38 \pm 4.7	63.10 \pm 5.8	0.614	0.541
Total bypass (min)	126.4 \pm 9.5	123.28 \pm 8.36	1.560	0.123
Aortic cross-clamp time (min)	56.55 \pm 5.5	72.75 \pm 6.42	12.115	<0.001*

* significant, Data (age, ejection fraction [EF], total bypass time, and cross-clamp time) were presented as mean \pm SD, while sex and ASA were presented as percentage

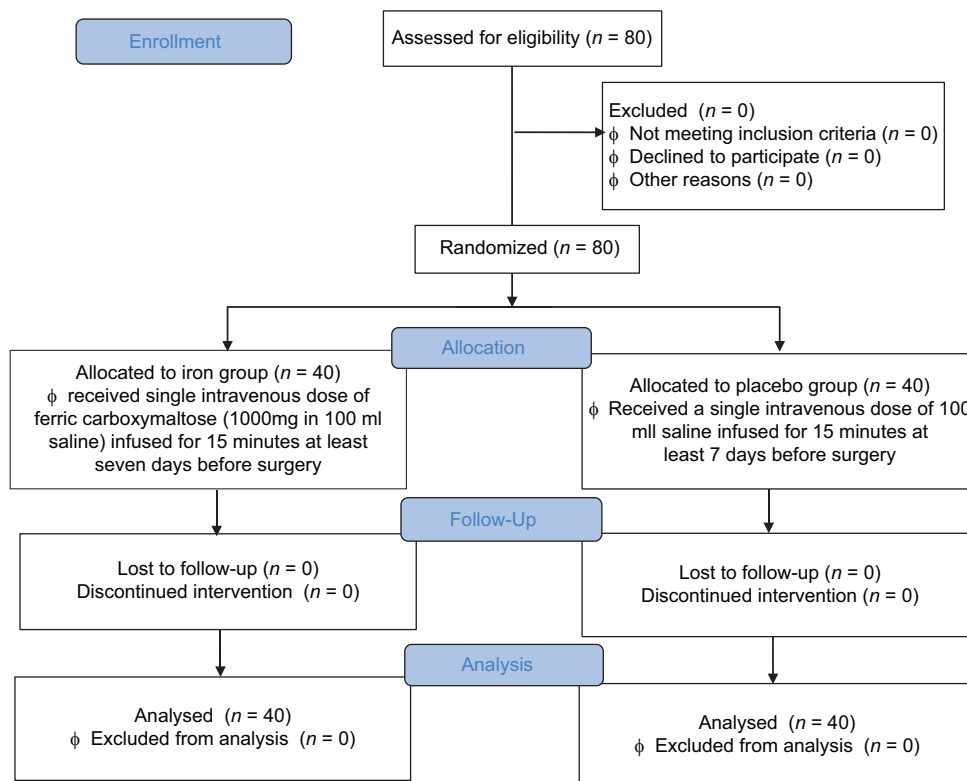


Figure 1: Study flow chart

Table 2: Hemoglobin levels, blood loss, and number of blood units: comparison between groups

	Iron (n=40)	Placebo (n=40)	Tests	
			t/ χ^2	P
Incidence of anemia 4 weeks after discharge	13 (32%)	32 (80%)	14.57	<0.001*
Postoperative blood loss (mL)	1239.4±172.43	1247.33±183.43	0.199	0.843
Number of pRBCs units given postoperatively	5 (12.5%)	22 (55%)	16.157	<0.001*
Hb (g/dL)				
On admission	9.52±0.84	9.77±0.74	1.650	0.103
Preoperative	12.76±0.88	10.03±0.83	9.086	<0.001*
Postoperative	9.1±0.63	7.55±0.6	11.257	<0.001*
One week after discharge	10.35±0.89	10.18±0.85	0.851	0.397
Four weeks after discharge	12.44±0.71	11.26±1.13	5.583	<0.001*

All data were presented as mean±SD except number of blood units which was presented as percentage. RBCs: red blood cells; Hb: hemoglobin.

*Highly significant

The number of pRBCs taken was significantly higher in the placebo group than in the iron group given postoperatively ($P < 0.001$) [Table 2].

The length of hospital stay and the ICU stay was significantly longer in the placebo group than in the iron group ($P < 0.001$) [Table 3].

There was no statistically significant difference regarding the incidence of adverse cardiovascular events such as atrial fibrillations and also the incidence of infection ($P = 0.531$ and $P = 0.456$, respectively) [Table 3].

There was no significant difference between the study groups in terms of prolonged ventilation ($P = 0.136$), mortality

rate ($P = 0.644$), heart failure ($P = 0.305$), and the incidence of stroke ($P = 0.314$) [Table 3]. The incidence of pericardial effusion and cardiac tamponade were similar between the two groups ($P = 0.556$ and $P = 1.00$, respectively).

Percentage of reticulocytes was comparable between the two study groups preoperatively ($P = 0.293$). However, percentage of reticulocytes was significantly higher in placebo group than in iron group postoperatively and 1 week after discharge ($P < 0.001$) [Table 4].

DISCUSSION

The results of this study showed that the preoperative management of anemia with intravenous iron therapy

Table 3: Postoperative complications: comparison between groups

	Iron (n=40)	Placebo (n=40)	Tests	
			t/ χ^2	P
Adverse cardiovascular events (myocardial infarction, atrial fibrillation)	5 (12.5%)	7 (17.5%)	0.392	0.531
Infection (sepsis and pneumonia)	3 (7.5%)	5 (12.5%)	0.556	0.456
Prolonged ventilation	2 (5%)	6 (15%)	2.222	0.136
Mortality rate	2 (5%)	3 (7.5%)	0.213	0.644
Heart failure	1 (2.5%)	3 (7.5%)	1.053	0.305
Stroke incidence	0 (0%)	1 (2.5%)	1.013	0.314
Length of hospital stay (days)	4.33±1	8.68±1.1	18.576	<0.001*
ICU stay (days)	1.28±0.45	2.23±0.95	3.408	<0.001*
Pericardial effusion	1 (2.5%)	2 (5%)	0.346	0.556
Cardiac tamponade	2 (5%)	2 (5%)	0.000	1.000

* significant, All data were presented as percentage except hospital stay length was presented as mean±SD

Table 4: Reticulocyte count: comparison between groups

Reticulocyte (%)	Iron (n=40)	Placebo (n=40)	t-Test	
			t	P
Preoperative	1.46±0.38	1.54±0.27	1.059	0.293
Postoperative	1.88±0.19	4.3±0.27	23.177	<0.001*
One week after discharge	1.72±0.52	7.96±0.41	59.598	<0.001*

* significant All data were presented as mean±SD

in patients undergoing CABG was associated with less incidence of postoperative anemia 4 weeks after discharge, increased Hb level preoperatively, postoperatively and 4 weeks after discharge, significant decrease in the postoperative packed RBC requirements, shorter hospital and ICU stay length, shorter aortic cross-clamp time, and insignificant difference as regard the incidence postoperative complications between the study groups. Percentage of reticulocytes was significantly higher in placebo group than in iron group postoperatively and 1 week after discharge.

Over the past 2 decades, a variety of blood conservation programs have been carried out to address the problem of preoperative anemia aiming to limit RBC transfusions.^[14]

An earlier systematic review showed that anti-fibrinolytic drugs decreased blood loss during surgery and consequently the need for RBC transfusions,^[15,16] although the drugs used to reduce blood loss may provoke hypercoagulation.^[17] Similarly, it was reported that erythropoiesis-stimulating agents are associated with thrombotic events.^[18] Thus, intravenous iron treatment is an effective intervention for preoperative anemia. However, definitive evidence is lacking.^[19,20]

In a previous randomized controlled trial, Johansson *et al.* compared iron isomaltoside to placebo regarding the ability to change Hb from baseline to 4 weeks in patients undergoing elective coronary artery bypass graft or valve replacement. The incidence of anemia was significantly less in the iron isomaltoside group compared to the placebo

group (P = 0.012), and the percentage of nonanemic patients at week 4 was significantly more pronounced in the iron isomaltoside group (38.5% vs. 8%; P < 0.05). The authors found that iron isomaltoside is safe and effective in prevention of anemia after cardiac surgery.^[13] The results of this study agreed with the findings of the current study.

In nonsurgical procedures, it has been reported that IV iron supplements effectively raise preoperative Hb values.^[21] Recent intravenous preparations, such as Venofer® (iron (III)-hydroxide sucrose), have been more tolerable.^[22]

IV iron therapy is more effective compared to oral iron and it has many advantages such as higher and prompt increase in Hb levels and rebuilding of body iron stores.^[23]

A study by Munoz *et al.* discussing the effect of perioperative intravenous iron for management of anemia and reducing transfusion requirements, they reported that intravenous iron therapy was safe and reduced the transfusion requirements and enhanced the recovery from postoperative anemia.^[24]

After review of literature, it was found that a single intravenous dose of ferric carboxymaltose (1000 mg) infused over 15 min (FCM, Ferinject) is a novel, easy treatment for rapid correction of anemia, particularly when oral therapy is either ineffective or intolerable.^[25]

A meta-analysis by Schack and colleagues^[26] investigated the effect of preoperative iron therapy on allogenic blood transfusion, postoperative Hb levels, length of hospital stay, mortality rate, and postoperative infections in acute major noncardiac surgeries. They also found that there was risk reduction of transfusion (P=0.0004) in seven studies. Postoperative mortality was reduced in the iron therapy group in a meta-analysis of four observational studies (P = 0.04); postoperative infection reduction was also detected in four studies.^[26] The findings of this study

support the results of the current study regarding the reduction of transfusion requirements.

In a recent study including 22,785 consecutive patients, the research team found that transfusion of 1 or 2 units of RBCs resulted in increased morbidity and mortality after cardiac surgery.^[27]

Habib and his colleagues^[28] noticed that in patients with preoperative hematocrit value of 42.6%, the mortality rate was 1.6% and increased to 3.6% in patients receiving RBC units. In cases of preoperative hematocrit value of 27.5%, the mortality rate increased to 7.5% and blood transfusion to 66.6%.

Zindrou and his colleagues^[29] stated that preoperative anemia was associated with a fourfold increase of the odds of postoperative complications, especially in valvular surgery and fivefold increase in the mortality rate in patients undergoing cardiac surgery.

A multicenter study including patients undergoing cardiac surgery showed that lower preoperative Hb levels were associated with an increased need for blood transfusion, higher mortality, and lengthy hospital stay.^[30] In addition, Hb levels below 13 g/dL caused worse outcomes. Furthermore, female patients with Hb levels below 12 g/dL scheduled for cardiac surgery, received more RBC units, and stayed in the hospital for longer. For this reason, we suggest that Hb < 13 g/dL is the trigger for the initiation of anemia treatment in patients of both sexes undergoing major surgery.^[30] These findings agreed with the results of the current study except for mortality.

Different from the findings of the current study, an earlier study by Garrido *et al.*,^[19] who studied the efficacy of iron therapy either oral or IV on the incidence of anemia and transfusion requirements in cardiac surgery, they found that iron supplementation was ineffective, a possible cause may be insufficient dose of iron therapy received or ineffective type of iron treatment given (3 doses of 100 mg IV iron (III)–hydroxide sucrose complex every 24 h pre–postoperatively).^[19]

In a study by Bisbe and his colleagues, they found that preoperative IV iron administration in anemic patients scheduled for major elective surgical procedure markedly increases postoperative Hb level and reduces the incidence of postoperative anemia.^[31] These findings support the results of the present study.

According to the International treatment guidelines, patients scheduled for elective surgery associated with an

expected blood loss of 500 mL or more must be screened for anemia 2 weeks prior to surgery and anemia should be treated with intravenous iron therapy.^[32]

In contrast to results of the present study, Richards *et al.*^[33] studied the efficacy of iron therapy use for patients undergoing major abdominal surgery; they showed that iron treatment raised Hb level but it did not reduce the need for postoperative blood transfusion or hospital stay length. This controversy may be due to the difference in the nature of the surgical procedure.

Limitations

This study was subjected to some limitations including the relatively small sample size. For this reason, further studies of a larger scale would be beneficial to support the findings of the current study regarding the clinical effect of iron therapy administered preoperatively on Hb levels of patients scheduled for elective CABG and to identify adverse events occurring at lower frequency. The adverse events have not been classified as serious or nonserious, recovering or nonrecovering.

CONCLUSION

Preoperative IV iron infusion was shown to be a safe and feasible way to manage preoperative anemia. The preoperative administration of IV iron was associated with higher preoperative and postoperative Hb levels that reduced the need for perioperative RBC transfusions and significantly shorter ICU and hospital stay length and insignificant difference regarding the incidence of postoperative complications between the study groups.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ozolina A, Strike E, Harlamovs V, Porite N. Excessive bleeding after cardiac surgery in adults: Reasons and management. *Acta Chir Latviensis* 2009;9:86–91.
2. Jans O, Jorgensen C, Kehlet H, Johansson PI, Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Role of preoperative anemia for risk of transfusion and postoperative morbidity in fast-track hip and knee arthroplasty. *Transfusion* 2014;54:717–26.
3. Wu WC, Schiffner TL, Henderson WG, Eaton CB, Poses RM, Utley G, *et al.* Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *JAMA* 2007;297:2481–8.
4. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal A, *et al.* Preoperative anaemia and postoperative outcomes

- in non-cardiac surgery: A retrospective cohort study. *Lancet* 2011;378:1396–407.
5. Basora M, Deulofeu R, Salazar F, Quinto L, Gomar C. Improved preoperative iron status assessment by soluble transferrin receptor in elderly patients undergoing knee and hip replacement. *Clin Lab Haematol* 2006;28:370–5.
 6. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, *et al*. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013;165:964–71.
 7. Nelson M, Green J, Spiess B, Kasirajan V, Nicolato P, Liu H, *et al*. Measurement of blood loss in cardiac surgery: Still too much. *Ann Thorac Surg* 2018;105:1176–81.
 8. Tzatzairis T, Vogiatzaki T, Kazakos K, Drosos G. Perioperative blood management strategies for patients undergoing total knee replacement: Where do we stand now? *World J Orthop* 2017;8:441–54.
 9. Goodnough LT, Shander A, Spivak JL, Waters JH, Friedman AJ, Carson JL, *et al*. Detection, evaluation, and management of anemia in the elective surgical patient. *Anesth Analg* 2005;101:1858–61.
 10. Theusinger OM, Leyvraz PF, Schanz U, Seifert B, Spahn DR. Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: Efficacy and limits: A prospective study. *Anesthesiology* 2007;107:923–7.
 11. Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anemia in geriatrics: A systematic review of the literature. *Am J Med* 2004;116:3S–10S.
 12. Beris P, Muñoz M, Garcia-Erce JA, Thomas D, Maniatis A, Van der Linden P. Perioperative anaemia management: Consensus statement on the role of intravenous iron. *Br J Anaesth* 2008;100:599–604.
 13. Johansson PI, Rasmussen AS, Thomsen LL. Intravenous iron isomaltoside 1000 (Monofer®) reduces postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination thereof: A randomized double-blind placebo-controlled clinical trial (the PROTECT trial). *Vox Sang* 2015;109:257–66.
 14. Nissenson AR, Goodnough LT, Dubois RW. Anemia: Not just an innocent bystander? *Arch Intern Med* 2003;163:1400–4.
 15. Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. *Cochrane Database Syst Rev* 2013;CD010245. doi: 10.1002/14651858.CD010245.pub2.
 16. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, *et al*. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2011;CD001886. doi: 10.1002/14651858.CD001886.pub3.
 17. Zufferey PJ, Miquet M, Quenet S, Martin P, Adam P, Albaladejo P, *et al*. Tranexamic acid in hip fracture surgery: A randomized controlled trial. *Br J Anaesth* 2010;104:23–30.
 18. Glaspy J. Thrombosis during therapy with erythropoiesis stimulating agents in cancer. In: Nowrousian M.R. (eds) *Recombinant Human Erythropoietin (rhEPO) in Clinical Oncology* 2008. https://doi.org/10.1007/978-3-211-69459-6_30.
 19. Garrido-Martin P, Nassar-Mansur MI, de la Llana-Ducros R, Virgos-Aller TM, Rodriguez Fortunez PM, Ávalos-Pinto R, *et al*. The effect of intravenous and oral iron administration on perioperative anaemia and transfusion requirements in patients undergoing elective cardiac surgery: A randomized clinical trial. *Interact Cardiovasc Thorac Surg* 2012;15:1013–8.
 20. Edwards TJ, Noble EJ, Durran A, Mellor N, Hosie KB. Randomized clinical trial of preoperative intravenous iron sucrose to reduce blood transfusion in anaemic patients after colorectal cancer surgery. *Br J Surg* 2009;96:1122–8.
 21. Kulnigg S, Stoinov S, Simanenkov V, Dudar LV, Karnafel W, Garcia LC, *et al*. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: The ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008;103:1182–92.
 22. Kosch M, Bahner U, Bettger H, Matzkies F, Teschner M, Schaefer RM. A randomized, controlled parallel-group trial on efficacy and safety of iron sucrose (Venofer) vs iron gluconate (Ferlecit) in haemodialysis patients treated with rHuEpo. *Nephrol Dial Transplant* 2001;16:1239–44.
 23. Lindgren S, Wikman O, Befrits R, Blom H, Eriksson A, Granno C, *et al*. Intravenous iron sucrose is superior to oral iron sulphate for correcting anaemia and restoring iron stores in IBD patients: A randomized, controlled, evaluator-blind, multicentre study. *Scand J Gastroenterol* 2009;44:838–45.
 24. Muñoz M, Gómez-Ramírez S, Martín-Montañez E, Pavia J, Cuenca J, García-Erce JA. Perioperative intravenous iron: An upfront therapy for treating anaemia and reducing transfusion requirements. *Nutr Hosp* 2012;27:1817–36.
 25. Moore RA, Gaskell H, Rose P, Allan J. Meta-analysis of efficacy and safety of intravenous ferric carboxymaltose (Ferinject) from clinical trial reports and published trial data. *BMC Blood Disord* 2011;11:4. doi: 10.1186/1471-2326-11-4.
 26. Schack A, Berkfors AA, Ekeloef S, Gögenur I, Burcharth J. The effect of perioperative iron therapy in acute major non-cardiac surgery on allogeneic blood transfusion and postoperative haemoglobin levels: A systematic review and meta-analysis. *World J Surg* 2019;43:1677–91.
 27. Paone G, Likosky DS, Brewer R, Theurer PF, Bell GF, Cogan CM, *et al*. Transfusion of 1 and 2 units of red blood cells is associated with increased morbidity and mortality. *Ann Thorac Surg* 2014;97:87–94.
 28. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A. Adverse effects of low haematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? *J Thorac Cardiovasc Surg* 2003;125:1438–50.
 29. Zindrou D, Taylor KM, Bagger JP. Preoperative haemoglobin concentration and mortality rate after coronary artery bypass surgery. *Lancet* 2002;359:1747–8.
 30. Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery—why, who, when, how? *Anaesthesia* 2019;74:49–57.
 31. Bisbe E, Garcia-Erce JA, Diez-Lobo AI, Muñoz M; Anaemia Working Group España. A multicentre comparative study on the efficacy of intravenous ferric carboxymaltose and iron sucrose for correcting preoperative anaemia in patients undergoing major elective surgery. *Br J Anaesth* 2011;107:477–8.
 32. Mueller MM, Van Remoortel H, Meybohm P. Patient blood management: Recommendations from the 2018 Frankfurt Consensus Conference. *JAMA* 2019;321:983–97.
 33. Richards T, Baikady RR, Clevenger D, Butcher A, Abey Siri S, Chau M. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTI): A randomized, double blinded controlled trial. *Lancet* 2020;396:1353–61.