Acta Anaesth. Bel., 2022, 73 (4): *235-239*

*Review*

# Iron deficiency in cardiac surgical patients

L. Hof[1], O. Old[1], A. U. Steinbicker[1], P. Meybohm[2], S. Choorapoikayil[1], K. Zacharowski[1]

[1]*Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Goethe University, Frankfurt, Germany;* [2]*Department of Anaesthesiology, Intensive Care, Emergency and Pain Medicine, University Hospital Wuerzburg, Wuerzburg, Germany.*

Corresponding author: Dr. Suma Choorapoikayil, Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy, University Hospital Frankfurt, Goethe University, 60590 Frankfurt, Germany. Tel.: +49-69-6301-5868; E-mail: Suma.Choorapoikayil@kgu.de

## *Abstract*

**Iron is an essential element and involved in a variety of metabolic processes including oxygen transport, cellular energy production, energy metabolism of heart muscles, brain function, cell growth and cell differentiation. Preoperative anaemia is an independent risk factor for poor outcome. Recently, iron deficiency was considered only in the context of anaemia. However, negative consequences of iron deficiency in the absence of anaemia have been described for patients undergoing cardiac surgery. To date, the benefit of intravenous iron supplementation in these patients has been controversially debated. In this review, we discuss the latest progress in studies of intravenous iron supplementation in iron deficient cardiac surgical patients.**

***Keywords:*** **Iron deficiency, anaemia, intravenous iron supplementation, hepcidin.**

Iron is an essential component of every living organism. In mammals, iron is incorporated into proteins in form of haeme complexes (haemoglobin, myoglobin, cytochrome proteins, myeloperoxidase, nitric oxide synthetase), nonhaeme complexes (flavin-iron enzymes, transferrin, ferritin), iron sulphur clusters (respiratory complexes I-III, coenzyme Q10, mitochondrial aconitase, DNA primase), or other functional groups such as hypoxia inducible factor prolyl hydroxylases[1,2]. Overall, iron plays a vital role in cellular energy production, energy metabolism of heart muscles, brain function, cell growth and cell differentiation[3,4]. In the human body, approximately 60-70% of iron is located in the haemoglobin molecule of the erythrocytes, equivalent to 2-2.5 g of 3-4 g of total iron[5], 20-25% is kept in iron stores and 10-15% is bound to myoglobin and enzymes of the oxidative metabolism[6]. Iron is continuously recycled from aged or non-functional erythrocytes by reticuloendothelial macrophages. The amount of iron absorbed from the dietary intake is low and ranges between 1-2 mg per day.

Hepcidin, firstly described in 2002[7], is a key player in iron homeostasis and has been studied extensively within the last years. Hepcidin is a hormone secreted by hepatocytes. It is a negative regulator of iron availability and inhibits the release of iron to the plasma. Expression of hepcidin is regulated by cytokines, plasma iron and hypoxia. Overexpression of hepcidin is associated with anaemia of chronic disease and suppression of hepcidin results in hemochromatosis with iron accumulation in vital organs[8].

The concentration of iron is tightly regulated to avoid toxicity. Systemic iron overload is often present in patients with haemochromatosis, thalassemia, congenital dyserythropoietic anaemia, sideroblastic anaemia, myelodysplastic syndromes or after high frequent intravenous iron supplementation[9]. If iron overload exceeds the binding capacity of transferrin, non-transferrin bound iron may lead to the generation of reactive oxygen species, resulting in oxidative damage and organ dysfunction. In addition, unbound iron can enter cells and thereby various tissues, in which it may accumulate and impair organ function. An association between iron overload and development of cirrhosis, cardiomyopathy, diabetes mellitus and other endocrinopathies has been reported[10-21]. Furthermore, iron overload as well as iron deficiency (ID) alter cardiac output.

In the heart, iron overload is associated with oxidant-mediated injury, interference with cardiac electrical function, and formation of fibrosis, whereas ID is known to be associated with an acute coronary syndrome, idiopathic pulmonary arterial hypertension, cyanotic congenital heart disease and heart failure symptoms[22-29].

Iron deficiency is a condition in which the availability of iron is reduced and iron dependent processes are severely compromised. Causes for ID are multifactorial and include low intake of dietary iron, increased iron requirements during growth, pregnancy, menstruation, infections, excessive blood loss during surgery or intake of medication that impair enterocyte iron uptake such as phosphate binders or antacids. Iron deficiency can be absolute or functional. In patients with absolute ID the storage pool of iron is reduced. Functional ID is caused by inflammatory processes associated with increased hepcidin expression leading to reduced iron absorption from the duodenum and reduced release of iron from iron stores.

Not long ago, ID was considered only in the context of iron deficiency anaemia. Anaemia is a well-known risk factor for adverse outcome in patients undergoing major non-cardiac and cardiac surgery. However, in recent years, the deleterious consequences of ID without anaemia have been studied in patients undergoing cardiac and vascular surgery, too[30-40]. It is important to note that ID may for example delay the recovery from postoperative anaemia. Klip et al examined the clinical association of ID and postoperative outcome in 1,506 patients with chronic heart failure (HF). The authors revealed that ID, but not anaemia, was an independent predictor for mortality (hazard ratio 1.42, 95% CI 1.14-1.77, p=0.002). Iron deficiency was associated with higher NYHA class, higher N-terminal pro-brain-type natriuretic peptide levels, lower mean corpuscular volume levels, and female sex (all $p<0.05$). Due to the study design it was not possible to assess iron status or haemoglobin levels over time[23]. Similar results were found by Jankowska et al. who investigated 546 patients with stable systolic HF. The authors showed that ID independent of anaemia was associated with poor outcome including death[30].

The effectiveness of intravenous iron supplementation in anaemic patients undergoing cardiac surgery have been shown[25,31,41-43]. It is noteworthy to mention that the iron-dependent maturation from erythroid-committed precursors to differentiated erythrocytes takes up to 4 to 6 days[44,45]. Therefore, the therapeutical effect of iron supplementation can presumably be expected after 5 to 7 days.

Yet, the clinical consequences of ID and effectiveness of intravenous iron supplementation are poorly characterized. Iron deficiency may not only lead to impaired erythropoiesis, but also to impaired oxidative metabolism, cellular energetics, and cellular immune mechanism[46-50]. Furthermore, ID is associated with reduced aerobic performance and physical condition.

Acute blood loss during surgery or trauma often require fluid substitution, which often leads to dilution and thus a reduced haemoglobin concentration in the blood. In patients with acute anaemia the heart rate and cardiac output increase whereas these compensatory mechanisms may be impaired in cardiovascular patients. Particularly, in patients with chronic HF even mild anaemia is associated with increased NYHA class, reduced functional capacity and survival[51]. In addition, several studies reported that an increased heart rate may increase the mortality rate in patients with ischemic heart disease[52,53]. Almost all cardiac surgical patients experience anaemia in the postoperative period[54], particularly patients with a prolonged stay at the intensive care unit[55,56]. Thus, the risk for postoperative complications increases in patients with impaired cardiac function. Iron deficiency in these patients is detrimental, because of the increased demand for erythropoiesis. However, the effectiveness of intravenous iron supplementation in cardiac surgery patients is highly debated[57-63]. Anker et al showed that supplementation of intravenous iron in patients with chronic HF and ID with or without anaemia improved symptoms, functional capacity, and the quality of life, whereas mortality rate was not decreased[25]. Brautaset Englund and colleagues revealed that intravenous iron supplementation only improved peak oxygen consumption and replenished iron stores in heart transplant recipients with a ferritin level < 30 µg/l, but not in patients with ferritin level < 100 µg/l[64]. In contrast, intravenous iron supplementation 3 months before transfemoral aortic valve implementation (TAVI) did not improve six-minute walk distance, handgrip strengths and NYHA class between the treated and untreated group[65]. Miles et al compared outcome data of patients undergoing cardiac surgery with and without ID. The authors found no difference in days alive and at home, ICU stay, readmission to hospital, health related quality of life scores, RBC transfusion or postoperative complications[66].

Diagnosis of ID can be challenging. The selection of parameters to diagnose ID varies between hospitals worldwide. The majority of hospitals use ferritin levels and transferrin saturation to diagnose ID. However, those parameters might not

be sufficient to diagnose ID in patients undergoing surgery, particularly in the context of inflammation or other comorbidities. The soluble transferrin receptor and the reticulocyte haemoglobin equivalent are valuable additional factors to diagnose ID. The formation of reticulocytes, the precursors of erythrocytes, is iron dependent; therefore, a reduced level of reticulocyte haemoglobin equivalent provides an early indicator for iron availability before changes in mean cell volume and haemoglobin levels occur. The ferritin cut-off values used to diagnose ID varies widely from 30 ng/ml for a person without inflammation compared with higher cut-off values of up to 300 ng/ml for a person with chronic inflammatory diseases such as cardiomyopathy, rheumathoid arthritis or inflammatory bowel disease such as M. Crohns disease. Therefore, iron supplementation can yield different results and findings of studies should be interpreted with caution. Blum et al assessed the impact of iron supplementation in iron-deficient-anaemic elderly patients (≥65 years of age) undergoing major surgery. The authors found that intravenous iron supplementation was associated with a significant reduction in RBC transfusion rate. Interestingly, the authors found a preoperative haemoglobin decrease of more than 0.6 g/dl in 55% of the non-anaemic, 46% of the anaemic and 45% of the iron-deficient-anaemic supplemented with intravenous iron. The authors hypothesize that the decrease in haemoglobin levels might be associated with a progressive decrement in bone marrow haematopoiesis, neo-adjuvant therapy, advancing age, or continuous blood loss, for example in patients with carcinomas. It is possible that iron supplementation mitigates a decrease in haemoglobin and the benefit of iron supplementation therapy in this patient group may not be defined by an increase in the haemoglobin value, but by the absence of a haemoglobin decrease[67].

Only a few studies assessed hepcidin levels after iron supplementation in patients undergoing (cardiac) surgery[54,68,69]. Song et al examined the impact of intravenous iron supplementation in 103 compared to 101 patients undergoing complex cardiac surgery. The authors showed that iron supplementation 3 days before surgery increased transferrin saturation and ferritin level throughout the postoperative period. However, no difference in the RBC transfusion requirement have been observed between the treated and untreated group. Interestingly, in the iron supplemented group, a 3-fold increase of hepcidin was observed and a raise in haemoglobin level was detected at postoperative day 10. Increased expression of hepcidin reduces iron mobilization and intestinal absorption, thereby restraining erythropoiesis[70]. Considering the fact that maturation of erythrocytes takes up to 6 days, an increase in haemoglobin would be visible a few days after iron supplementation at the earliest. This was also evident in the analysis by Song and colleagues. A rise in reticulocytes and haemoglobin was not noted until postoperative day 6. Therefore, a reduction in intraoperative RBC transfusion rate was very unlikely in the analysed patients[70].

Taken together, ID may be harmful in patients undergoing cardiac surgery. Corwin et al recommend that all cardiac surgery patients with ID should be supplemented with intravenous iron[71]. However, screening for the presence of ID is not current practice and significant knowledge gaps exist in our understanding when and how ID should be treated in patients undergoing cardiac surgery. Further research is required to study the effectiveness of preoperative intravenous iron supplementation in patients undergoing cardiac surgery. Special attention should be paid to confounding factors such as status of iron store, hepcidin level, age, comorbidities, blood transfusion thresholds, and volume of surgical blood loss.

*Disclosures:* The Department of Anaesthesiology, Intensive Care Medicine & Pain Therapy of the University Hospital Frankfurt, Goethe University received support from B. Braun Melsungen, CSL Behring, Fresenius Kabi, and Vifor Pharma for the implementation of Frankfurt‘s Patient Blood Management program. KZ has received honoraria for participation in advisory board meetings for Haemonetics and Vifor and received speaker fees from CSL Behring, Masimo, Pharmacosmos, Boston Scientific, Salus, iSEP, Edwards and GE Healthcare. He is the Principal Investigator of the EU-Horizon 2020 project ENVISION (Intelligent plug-and-play digital tool for real-time surveillance of COVID-19 patients and smart decision-making in Intensive Care Units) and Horizon Europe 2021 project COVend (Biomarker and AI-supported FX06 therapy to prevent progression from mild and moderate to severe stages of COVID-19). AUS is part of the DFG research group FerrOS (STE 1895/9-1, STE 1895/10-1), and receives a research grant from Pharmacosmos, Denmark, to perform a single-center prospective trial on preoperative anemia treatment. PM and/or the Department received research grants from the German Research Foundation (ME 3559/1-1, ME 3559/3-1), BMBF (01KG1815), BMG (ZMVI1-2520DAT10E); honoraria for scientific lectures from B. Braun Melsungen, Biotest AG, Vifor Pharma, CSL Behring, Pharmacosmos. The remaining authors have nothing to declare.

## References


1. Evstatiev R, Gasche C. Iron sensing and signalling. Gut. 2012;61(6):933-952.
2. Hurrell RF. Bioavailability of iron. European journal of clinical nutrition. 1997;51 Suppl 1:S4-8.
3. Cacoub P, Choukroun G, Cohen-Solal A, et al. Iron deficiency screening is a key issue in chronic inflammatory diseases: A call to action. Journal of internal medicine. 2022;292(4):542-556.
4. Wang CY, Babitt JL. Liver iron sensing and body iron homeostasis. Blood. 2019;133(1):18-29.
5. Ganz T. Erythrocytes and erythroblasts give up iron. Blood. 2018;132(19):2004-2005.
6. Andrea U Steinbicker 1, Martina U. Out of balance--systemic iron homeostasis in iron-related disorders Muckenthaler Nutrients. 2013 Aug 2;5(8):3034-61.
7. Nicolas G, Viatte L, Bennoun M, Beaumont C, Kahn A, Vaulont S. Hepcidin, a new iron regulatory peptide. Blood cells, molecules & diseases. 2002;29(3):327-335.
8. Nemeth E, Ganz T. Hepcidin-Ferroportin Interaction Controls Systemic Iron Homeostasis. International journal of molecular sciences. 2021;22(12).
9. Camaschella C, Nai A. Ineffective erythropoiesis and regulation of iron status in iron loading anaemias. British journal of haematology. 2016;172(4):512-523.
10. Milic S, Mikolasevic I, Orlic L, et al. The Role of Iron and Iron Overload in Chronic Liver Disease. Medical science monitor : international medical journal of experimental and clinical research. 2016;22:2144-2151.
11. Hilgard P, Gerken G. Liver cirrhosis as a consequence of iron overload caused by hereditary nonspherocytic hemolytic anemia. World journal of gastroenterology. 2005;11(8):1241-1244.
12. Kowdley KV. Iron Overload in Patients With Chronic Liver Disease. Gastroenterology & hepatology. 2016;12(11):695-698.
13. Ford ES, Cogswell ME. Diabetes and serum ferritin concentration among U.S. adults. Diabetes care. 1999;22(12):1978-1983.
14. Jiang R, Manson JE, Meigs JB, Ma J, Rifai N, Hu FB. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. Jama. 2004;291(6):711-717.
15. Simcox JA, McClain DA. Iron and diabetes risk. Cell metabolism. 2013;17(3):329-341.
16. Huang J, Jones D, Luo B, et al. Iron overload and diabetes risk: a shift from glucose to Fatty Acid oxidation and increased hepatic glucose production in a mouse model of hereditary hemochromatosis. Diabetes. 2011;60(1):80-87.
17. Gao H, Yang J, Pan W, Yang M. Iron Overload and the Risk of Diabetes in the General Population: Results of the Chinese Health and Nutrition Survey Cohort Study. Diabetes & metabolism journal. 2022;46(2):307-318.
18. Miranda MA, Lawson HA. Ironing out the Details: Untangling Dietary Iron and Genetic Background in Diabetes. Nutrients. 2018;10(10).
19. Kim MK, Lee JW, Baek KH, et al. Endocrinopathies in transfusion-associated iron overload. Clinical endocrinology. 2013;78(2):271-277.
20. Chirico V, Rigoli L, Lacquaniti A, et al. Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. European journal of haematology. 2015;94(5):404-412.
21. Atmakusuma TD, Hasibuan FD, Purnamasari D. The Correlation Between Iron Overload and Endocrine Function in Adult Transfusion-Dependent Beta-Thalassemia Patients with Growth Retardation. Journal of blood medicine. 2021;12:749-753.
22. Murphy CJ, Oudit GY. Iron-overload cardiomyopathy: pathophysiology, diagnosis, and treatment. Journal of cardiac failure. 2010;16(11):888-900.
23. Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. American heart journal. 2013;165(4):575-582.e573.
24. Comín-Colet J, Enjuanes C, González G, et al. Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. European journal of heart failure. 2013;15(10):1164-1172.
25. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. The New England journal of medicine. 2009;361(25):2436-2448.
26. von Haehling S, Jankowska EA, van Veldhuisen DJ, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. Nature reviews Cardiology. 2015;12(11):659-669.
27. Reinhold J, Papadopoulou C, Baral R, Vassiliou VS. Iron deficiency for prognosis in acute coronary syndrome - A systematic review and meta-analysis. International journal of cardiology. 2021;328:46-54.
28. Viethen T, Gerhardt F, Dumitrescu D, et al. Ferric carboxymaltose improves exercise capacity and quality of life in patients with pulmonary arterial hypertension and iron deficiency: a pilot study. International journal of cardiology. 2014;175(2):233-239.
29. Tay EL, Peset A, Papaphylactou M, et al. Replacement therapy for iron deficiency improves exercise capacity and quality of life in patients with cyanotic congenital heart disease and/or the Eisenmenger syndrome. International journal of cardiology. 2011;151(3):307-312.
30. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. European heart journal. 2010;31(15):1872-1880.
31. Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. Journal of the American College of Cardiology. 2011;58(12):1241-1251.
32. Parikh A, Natarajan S, Lipsitz SR, Katz SD. Iron deficiency in community-dwelling US adults with self-reported heart failure in the National Health and Nutrition Examination Survey III: prevalence and associations with anemia and inflammation. Circulation Heart failure. 2011;4(5):599-606.
33. Frise MC, Holdsworth DA, Sandhu MS, et al. Non-anemic iron deficiency predicts prolonged hospitalisation following surgical aortic valve replacement: a single-centre retrospective study. Journal of cardiothoracic surgery. 2022;17(1):157.
34. Immohr MB, Sugimura Y, Aubin H, et al. Iron deficiency does not impair the outcome after elective coronary artery bypass and aortic valve procedures. Journal of cardiac surgery. 2021;36(2):542-550.
35. Rössler J, Schoenrath F, Seifert B, et al. Iron deficiency is associated with higher mortality in patients undergoing cardiac surgery: a prospective study. British journal of anaesthesia. 2020;124(1):25-34.
36. Triphaus C, Judd L, Glaser P, et al. Effectiveness of Preoperative Iron Supplementation in Major Surgical Patients With Iron Deficiency: A Prospective Observational Study. Annals of surgery. 2021;274(3):e212-e219.
37. Gaudriot B, Oilleau JF, Kerforne T, et al. The impact of iron store on red blood cell transfusion: a multicentre prospective cohort study in cardiac surgery. BMC anesthesiology. 2022;22(1):74.
38. Gao P, Wang X, Zhang P, et al. Preoperative Iron Deficiency Is Associated With Increased Blood Transfusion in Infants Undergoing Cardiac Surgery. Frontiers in cardiovascular medicine. 2022;9:887535.
39. Kim HB, Shim JK, Ko SH, Kim HR, Lee CH, Kwak YL. Effect of iron deficiency without anaemia on days alive and out of hospital in patients undergoing valvular heart surgery. Anaesthesia. 2022;77(5):562-569.

40. Miles LF, Kunz SA, Na LH, Braat S, Burbury K, Story DA. Postoperative outcomes following cardiac surgery in non-anaemic iron-replete and iron-deficient patients - an exploratory study. Anaesthesia. 2018;73(4):450-458.
41. Piednoir P, Allou N, Driss F, et al. Preoperative iron deficiency increases transfusion requirements and fatigue in cardiac surgery patients: a prospective observational study. European journal of anaesthesiology. 2011;28(11):796-801.
42. Spahn DR, Schoenrath F, Spahn GH, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. Lancet (London, England). 2019;393(10187):2201-2212.
43. Evans CR, Jones R, Phillips G, Greene G, Phillips M, Morris-Clarke R. Observational study of pre-operative intravenous iron given to anaemic patients before elective cardiac surgery. Anaesthesia. 2021;76(5):639-646.
44. Besarab A, Hörl WH, Silverberg D. Iron metabolism, iron deficiency, thrombocytosis, and the cardiorenal anemia syndrome. The oncologist. 2009;14 Suppl 1:22-33.
45. Moras M, Lefevre SD, Ostuni MA. From Erythroblasts to Mature Red Blood Cells: Organelle Clearance in Mammals. Frontiers in physiology. 2017;8:1076.
46. Cairo G, Bernuzzi F, Recalcati S. A precious metal: Iron, an essential nutrient for all cells. Genes & nutrition. 2006;1(1):25-39.
47. Dunn LL, Suryo Rahmanto Y, Richardson DR. Iron uptake and metabolism in the new millennium. Trends in cell biology. 2007;17(2):93-100.
48. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. The Journal of nutrition. 2001;131(2s-2):568S-579S; discussion 580S.
49. Rouault TA, Tong WH. Iron-sulphur cluster biogenesis and mitochondrial iron homeostasis. Nature reviews Molecular cell biology. 2005;6(4):345-351.
50. Haas JD, Brownlie Tt. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. The Journal of nutrition. 2001;131(2s-2):676S-688S; discussion 688S-690S.
51. Szachniewicz J, Petruk-Kowalczyk J, Majda J, et al. Anaemia is an independent predictor of poor outcome in patients with chronic heart failure. International journal of cardiology. 2003;90(2-3):303-308.
52. Palatini P, Julius S. Elevated heart rate: a major risk factor for cardiovascular disease. Clinical and experimental hypertension (New York, NY : 1993). 2004;26(7-8):637-644.
53. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. American journal of hypertension. 2000;13(1 Pt 2):3s-10s.
54. Peters F, Ellermann I, Steinbicker AU. Intravenous Iron for Treatment of Anemia in the 3 Perisurgical Phases: A Review and Analysis of the Current Literature. Anesthesia and analgesia. 2018;126(4):1268-1282.
55. Koch CG, Reineks EZ, Tang AS, et al. Contemporary bloodletting in cardiac surgical care. The Annals of thoracic surgery. 2015;99(3):779-784.
56. Chant C, Wilson G, Friedrich JO. Anemia, transfusion, and phlebotomy practices in critically ill patients with prolonged ICU length of stay: a cohort study. Critical care (London, England). 2006;10(5):R140.
57. 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 sanguinis. 2015;109(3):257-266.
58. Xu H, Duan Y, Yuan X, Wu H, Sun H, Ji H. Intravenous Iron Versus Placebo in the Management of Postoperative Functional Iron Deficiency Anemia in Patients Undergoing Cardiac Valvular Surgery: A Prospective, Single-Blinded, Randomized Controlled Trial. Journal of cardiothoracic and vascular anesthesia. 2019;33(11):2941-2948.
59. Cladellas M, Farré N, Comín-Colet J, et al. Effects of preoperative intravenous erythropoietin plus iron on outcome in anemic patients after cardiac valve replacement. The American journal of cardiology. 2012;110(7):1021-1026.
60. Padmanabhan H, Siau K, Nevill AM, et al. Intravenous iron does not effectively correct preoperative anaemia in cardiac surgery: a pilot randomized controlled trial. Interactive cardiovascular and thoracic surgery. 2019;28(3):447-454.
61. Hogan M, Klein AA, Richards T. The impact of anaemia and intravenous iron replacement therapy on outcomes in cardiac surgery. European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery. 2015;47(2):218-226.
62. Yang SS, Al Kharusi L, Gosselin A, Chirico A, Baradari PG, Cameron MJ. Iron supplementation for patients undergoing cardiac surgery: a systematic review and meta-analysis of randomized controlled trials. Canadian journal of anaesthesia = Journal canadien d'anesthesie. 2022;69(1):129-139.
63. Klein AA, Chau M, Yeates JA, et al. Preoperative intravenous iron before cardiac surgery: a prospective multicentre feasibility study. British journal of anaesthesia. 2020;124(3):243-250.
64. Brautaset Englund KV, Østby CM, Rolid K, et al. Intravenous iron supplement for iron deficiency in cardiac transplant recipients (IronIC): A randomized clinical trial. The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation. 2021;40(5):359-367.
65. Kvaslerud AB, Bardan S, Andresen K, et al. Intravenous iron supplement for iron deficiency in patients with severe aortic stenosis scheduled for transcatheter aortic valve implantation: results of the IIISAS randomised trial. European journal of heart failure. 2022;24(7):1269-1279.
66. Miles LF, Pac Soo V, Braat S, et al. Associations between non-anaemic iron deficiency and outcomes following elective cardiac surgery (IDOCS): a prospective cohort study. The Lancet Haematology. 2022;9(7):e514-e522.
67. Blum LV, Zierentz P, Hof L, et al. The impact of intravenous iron supplementation in elderly patients undergoing major surgery. BMC geriatrics. 2022;22(1):293.
68. Assouline B, Benoliel A, Zamberg I, et al. Intravenous iron supplementation after liver surgery: Impact on anemia, iron, and hepcidin levels-a randomized controlled trial. Surgery. 2021;170(3):813-821.
69. Wittkamp C, Traeger L, Ellermann I, Eveslage M, Steinbicker AU. Hepcidin as a potential predictor for preoperative anemia treatment with intravenous iron-A retrospective pilot study. PloS one. 2018;13(8):e0201153.
70. Song JW, Soh S, Shim JK, et al. Effect of Perioperative Intravenous Iron Supplementation for Complex Cardiac Surgery on Transfusion Requirements: A Randomized, Double-blinded Placebo-controlled Trial. Annals of surgery. 2022;275(2):232-239.
71. Corwin HL, Shander A, Speiss B, et al. Management of Perioperative Iron Deficiency in Cardiac Surgery: A Modified RAND Delphi Study. The Annals of thoracic surgery. 2022;113(1):316-323.

doi.org/10.56126/73.4.28