

Effect of intravenous iron replacement therapy on exercise capacity in iron deficient anemic patients after cardiac surgery

Cinzia Nugara^{1,2}, Giuseppe Vitale¹, Giuseppa Caccamo¹, Silvia Sarullo³, Francesco Giallauria⁴, Antonino Di Franco⁵, Silvia Vitale⁶, Filippo M. Sarullo¹

¹Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital, Palermo, Italy; ²Biomedical Department of Internal Medicine and Specialities (DIBIMIS), University of Palermo, IRCSS Bonino Pulejo, Messina, Italy; ³University of Palermo, Cardiology Unit, Palermo, Italy; ⁴Department of Translational Medical Sciences, Division of Internal Medicine, Metabolic and Cardiac Rehabilitation Unit, University of Naples Federico II, Italy; ⁵Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York City, NY, USA; ⁶Medical Biotechnology and Molecular Medicine, University of Palermo, Italy

Correspondence: Filippo M. Sarullo, Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital, Via Messina Marine 197, 90121 Palermo, Italy.
Tel. +39.091.479263 - Fax: +39.09. 477625.
E-mail: fsarullo@neomedial.it

Keywords: Iron deficiency; anemia; cardiac surgery; exercise capacity; ferric carboxymaltose; ferric gluconate.

Contributions: FMS, contribution to work concept; CN, FMS, manuscript drafting; CN, GV, GC, SS, SV, contribution to data acquisition, analysis, and interpretation; ADF, FG, critically revised the manuscript. All the authors read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work ensuring integrity and accuracy.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Availability of data and materials: All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was not obtained from all individual participants included in the study due to retrospective study design.

Consent for publication: Not applicable.

Received for publication: 3 November 2019.

Accepted for publication: 2 January 2020.

©Copyright: the Author(s), 2020

Licensee PAGEPress, Italy

Monaldi Archives for Chest Disease 2020; 90:1196

doi: 10.4081/monaldi.2020.1196

This article is distributed under the terms of the Creative Commons Attribution Noncommercial License (by-nc 4.0) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Abstract

Iron deficiency (ID) is recognized as an important comorbidity in patients undergoing cardiac surgery; however, it still remains under-diagnosed and under-treated in clinical practice. This study aims at comparing efficacy and the effects on exercise capacity of intravenous ferric carboxymaltose (FCM) *versus* ferric gluconate (FG) in patients with ID anemia (IDA) resulting from cardiac surgery. We retrospectively analyzed data from our records of in-hospital patients with IDA after cardiac surgery undergoing cardiac rehabilitation. Group I was treated with FG, group II with FCM. Efficacy measures included changes (baseline *vs* discharge) in hemoglobin (Hb) and in distance traveled at six-minutes walking test (6MWT). Data from 74 in-patients (mean age 67.5±10.4 years, 43% women) were analyzed. At discharge, patients treated with FCM showed higher levels of Hb (11.1±1.2g/dl *vs* 10.2±1.1 g/dl; p=0.001), greater distance traveled at 6MWT (279.2±108.8 meters *vs* 236.3±72.7 meters; p=0.048), and lower in-hospital rehabilitation length of stay (20.3±7 *vs* 25.3±11.7 days; p=0.043) as compared to FG group. At multivariate analysis, the most powerful predictors of Hb increase >1 g/dl at discharge were transferrin levels (p=0.019) and treatment with FCM (p<0.001). FCM replacement therapy and iron serum levels were the most powerful predictors of 6MWT distance improvement (>100 meters) at discharge (p=0.13 and p=0.003, respectively). In patients with IDA following cardiac surgery, intravenous FCM is effective in restoring Hb levels and in improving exercise capacity after cardiac surgery.

Introduction

Patients undergoing cardiac surgery are at increased risk of excessive perioperative bleeding and increased blood product transfusion [1]. In the setting of patients undergoing surgery, anemia is present in a third of all patients [2], but it is more prevalent in cardiac surgery where it may be interest about 50% of patients [3].

Iron deficiency (ID) is increasingly recognized as an important comorbidity in patients undergoing cardiac surgery and it has been shown to be responsible of 29% of preoperative anemia [1]. ID reduces exercise capacity in patients with chronic heart failure

(CHF) but also in healthy volunteers [4-6]. Iron plays a crucial role in systemic oxygen (O₂) delivery and utilization [7]. Iron is also an obligate component of enzymes involved in cellular respiration, oxidative phosphorylation, vascular homeostasis, nitric oxide-generation, and the citric acid cycle [8]. Hence, cells with high energy demands, including skeletal and cardiomyocytes, are particularly sensitive to iron depletion [9].

The most rapid and effective method of correcting anemia is transfusing red blood cells; however, blood transfusion itself is not riskless [1]. In the specific setting of cardiac surgery, blood transfusions are associated with both infections and ischemic postoperative morbidity, longer hospital stay, increased early and late mortality and greater hospital costs [10]. On the other hand, prophylactic administration of red blood cells to correct anemia preoperatively leads to lower rates of intraoperative anemia and transfusion compared with intraoperative transfusions [11]. Treatment of perioperative anemia using oral or intravenous (IV) iron replacement therapy is safer, cheaper and relatively more convenient than blood transfusion.

The aim of the present study was to compare the efficacy and the impact on exercise capacity of IV ferric carboxymaltose (FCM) versus ferric gluconate (FG) in patients with ID anemia resulting from cardiac surgery.

Methods

A retrospective analysis of medical records of consecutive adult patients with anemia following cardiac surgery hospitalized, from January 2017 to December 2018, was completed at the Cardiovascular Rehabilitation Unit of Buccheri La Ferla Fatebenefratelli Hospital in Palermo, Italy.

Inclusion criteria were: Hb \leq 12 g/dl, ferritin \leq 100 ng/ml (or \leq 300 mg/ml if transferrin saturation [TSAT] \leq 20%), and left ventricle ejection fraction (LVEF) $>$ 50%. Exclusion criteria were age $<$ 18 years, pregnancy, iron therapy and/or blood transfusions in the 6 weeks prior to enrollment, allergy/intolerance to iron and inability to perform six-minutes walking test (6MWT).

A total of 74 patients met inclusion criteria and were divided into two groups:

- Group I: 35 patients treated with FG (dose: 125 mg/die IV);
- Group II: 39 patients treated with FCM (maximum dose: 1000 mg/week IV).

FCM before 2018 was not available in our center, therefore patients enrolled in 2017 had been treated with FG; those enrolled in 2018 with FCM.

The following variables have been collected and stored in a centralized database in a de-identified manner for both groups of patients:

- Demographics and baseline anthropometric and clinical data (date of birth, height, weight, body mass index; co-morbidities such as diabetes, chronic obstructive pulmonary disease, chronic renal failure as defined by estimated glomerular filtration rate (calculated with MDRD formula) [eGFR] $<$ 60 ml/min/1.73 m³; pharmacological treatment; LVEF; in-hospital length-of-stay);
- Biochemical data (NT-proBNP, hemoglobin, serum iron, transferrin and ferritin levels and TSAT), both at admission and at discharge (after iron replacement therapy).

All patients underwent 6MWT both at admission and at discharge to assess exercise capacity.

Efficacy measures included changes from baseline in Hb and in distance traveled at 6MWT.

Statistical analysis

Statistical analysis was performed using SAS JMP v.10 software package. Continuous variables are described as mean \pm standard deviation, or as median and interquartile range, in case of non-normal distribution. Categorical variables are expressed as number (percentages). Differences between groups were assessed by Student *t*-test, analysis of variance, or χ^2 -test, as appropriate. Contribution of baseline characteristics to study outcomes was assessed by univariate analysis and multivariable analysis. All derived cutoff values used for continuous variables have been chosen by means of receiver operating characteristic (ROC) curve analysis. Changes from baseline were tested by paired *t*-test or McNemar test, as appropriate. A *p*-value $<$ 0.05 was considered statistically significant; all tests were 2-tailed.

Results

Data from 74 patients (mean age 67.5 \pm 10.4 years, 43% women) were analyzed. Table 1 summarizes clinical and biochemical characteristics of the study population. No significant differences in demographics, drug therapy, type of surgery, LVEF and marital panel were observed between the 2 groups. Mean in-hospital length of treatment was 22.8 \pm 9.3 days. At baseline, patients treated with FCM had higher prevalence of chronic renal failure (59% vs 28%, *p* = 0.01) and higher levels of NT-proBNP (3848 pg/ml vs 1335 pg/ml, *p* = 0.006); no significant difference in functional capacity at admission was observed (176.8 \pm 114 meters in FCM group vs 173.7 \pm 73 meters in FG group; *p* = 0.88).

Patients treated with FCM had significantly lower in-hospital length-of-stay (20.3 \pm 7 vs 25.3 \pm 11.7 days, *p* = 0.043), greater distance walked at 6MWT at discharge than patients treated with FG (279.2 \pm 108.8 meters vs 236.3 \pm 72.7 meters, *p* = 0.048) and higher Δ distance (102.4 \pm 63 vs 62.6 \pm 48.8 meters, *p* = 0.003) (Figure 1, Table 2). At discharge, FCM-treated patients had lower NT-ProBNP levels (945 pg/ml vs 1272 pg/ml, *p* = 0.10), higher Hb levels (11.1 \pm 1.2 g/dl vs 10.2 \pm 1.1 g/dl, *p* = 0.001) (Figure 2, Table 2), and significant ($>$ 1 g/dl) changes in Hb levels (*p* $<$ 0.0001) as compared to FG group.

After adjusting for age, sex and eGFR, multivariate analysis showed that transferrin levels [1.01 (1.00-1.02) *p* = 0.028] and replacement therapy with FCM [8.22 (2.66-29.11), *p* $<$ 0.0002] were the most powerful predictors of Hb $>$ 1 g/dl at discharge. Finally, FCM replacement therapy and iron serum levels were the most important predictors of 6MWT distance improvement ($>$ 100 meters) at discharge (OR: 3.95, 1.31-13.06, *p* = 0.013 and OR: 0.92, 0.86-0.97, *p* = 0.003, respectively).

Discussion

Cardiac rehabilitation is the best strategy approaching pre and post cardiac surgery [12,13]. In cardiac rehabilitation setting, anemia is commonly diagnosed after cardiac surgery and is often associated with ID [14]. It is well known that anemia due to ID impairs O₂-carrying and tissue oxidative capacity, resulting in a diminished peak O₂ consumption and ability to endure submaximal exertion. Even in absence of anemia, ID can attenuate exercise performance [15].

ID is a treatable condition; however, it is still under-diagnosed and under-treated in clinical practice [16].

Several studies [4,17] demonstrated that IV iron loading improved exercise capacity and symptoms in patients with CHF and evidence of abnormal iron metabolism. In CHF, iron sucrose [18,19] and FCM [4] are the most adopted IV formulations for replacement therapy. Oral iron formulation is usually the first-line strategy; however, these supplementations may not be useful in all patients with IDA, since it is often poorly absorbed [4,20]. A recent study

suggests that FCM is an effective therapy in patients with IDA who have gastrointestinal disorders and has a safety profile comparable to other IV iron agents [21].

We conducted a single-center retrospective study of anemic patients after cardiac surgery and found that those treated with FCM had shorter in-hospital stay, greater improvement in Hb values and in distance walked at 6MWT than patients treated with FG. To the

Table 1. Clinical and biochemical characteristics of study population.

	Ferric gluconate (n=35)	Ferric carboxymaltose (n=39)	p
Age (years)	67 ± 11	68 ± 9	0.55
Females, n (%)	12 (34)	20 (51)	0.16
BMI, kg/m ²	28.8 ± 6	27.2 ± 6	0.25
CABG	8 (26)	8 (24)	0.99
Valvular surgery	23 (74)	25 (75)	0.99
Diabetes, n (%)	9 (25)	11 (28)	0.99
COPD, n (%)	9 (25)	8 (20)	0.78
Chronic renal failure, n (%)	10 (28)	23 (59)	0.01
Single antithrombotic therapy	23 (65)	22 (56)	0.47
Double antithrombotic therapy	1 (3)	2 (5)	0.99
Triple antithrombotic therapy	0 (0)	1 (2)	0.99
Vitamin K antagonists	19 (54)	19 (48)	0.64
NOACs	4 (11)	8 (20)	0.35
LVEF, % (IQR)	60 (48-60)	60 (55-60)	0.33
NT-proBNP, ng/ml, median (range)	1335 (764-3157)	3848 (1147-7241)	0.006
eGFR, ml/min/1.73 m ³	71 ± 21.8	60.7 ± 29.9	0.08
Hb, g/dl	9,5 ± 1	9,2 ± 1	0.19
Serum iron, µg/dl	35.5 ± 8.2	36.9 ± 12.5	0.58
Transferrin, mg/dl	235 ± 45	227.5 ± 57	0.51
Ferritin, ng/ml	375 ± 283	398 ± 376.8	0.76
Transferrin saturation, %	10.4 ± 2.8	10.4 ± 3.2	0.92
In-hospital length-of-stay, days	25.3 ± 11.7	20.3 ± 7	0.043

BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; Hb, Hemoglobin; LVEF, left ventricular ejection fraction; NOACs, new oral anticoagulants; NT-proBNP, N-terminal pro-hormone of brain natriuretic peptide.

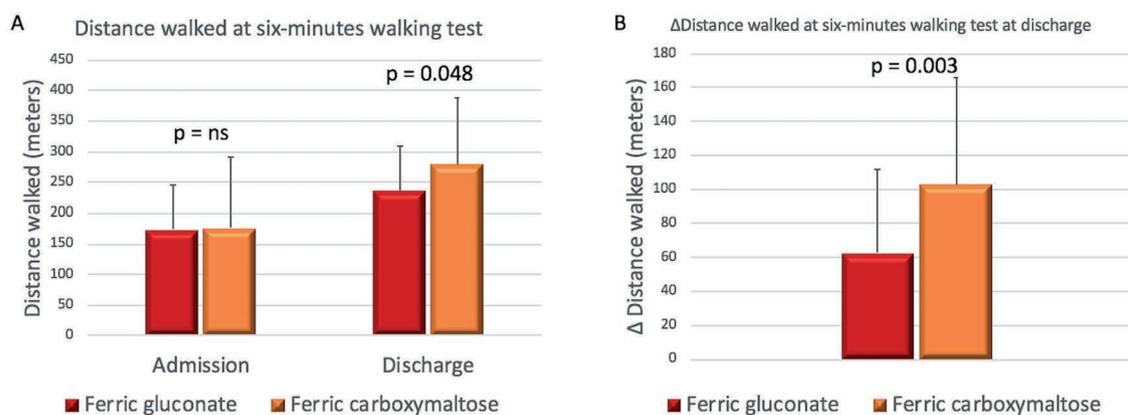


Figure 1. Distance walked at six-minutes walking test (A) and Δ distance at discharge (B) in patients treated with ferric gluconate and ferric carboxymaltose.

best of our knowledge, this is the first study evaluating exercise capacity in patients without CHF and IDA after cardiac surgery.

In a large sample size population of consecutive routine elective surgical patients who were having major orthopedic surgery, abdominal, and genitourinary surgery, and other surgeries, Khalafallah *et al.* [22] found that postoperative IV FCM is a feasible and pragmatic management approach. More recently, in anemic patients undergoing elective cardiac surgery, Padmanabahn *et al.* [23] observed no significant differences in Hb increments after IV or oral iron administration; however, it should be remarked that only a small proportion of patients had proven ID. Notably, no adverse events were reported in all studies [22,23].

Previous studies showed encouraging evidences for iron replacement therapy in patients with CHF and ID [4]. Van Veldhuisen *et al.* [4] reported that treatment with intravenous FCM improves iron stores and showed a favorable effect on peak VO₂. Ponikowsky *et al.* [24] found that treatment of symptomatic, iron-deficient CHF patients treated with FCM for more than 1 year, had sustainable improvement in functional capacity, symptoms, and quality of life. Interestingly, Viethen *et al.* [25] reported that parenteral iron supplementation with FCM significantly improves exercise capacity and quality of life and is well tolerated in patients with pulmonary hypertension and iron deficiency. These data highlight that there is solid evidence suggesting that iron replacement therapy exerts beneficial effects on exercise capacity and is proven to be safe in HF patients with iron deficiency. However, type, dose and duration of replacement therapy as well as the effect on mortality and hospitalization still remain to be ascertained.

In the present study, we divided our population with IDA after cardiac surgery in two groups of IV iron replacement treatment. Mean ejection fraction in our population was normal. According to the literature, patients treated with FCM showed greater reduction of NT-proBNP levels [19]. In our population, levels of the NT-proBNP at the baseline is greater in the FCM group, this data is probably correlated to lower eGFR that reflect a major neurohormonal activation. After treatment with FCM, we observed a significant reduction of NT-proBNP levels than FG group. We suppose that this result is correlated to the improvement of myocardial oxygenation and to the increase of Hb concentration that inhibiting the renin-angiotensin-aldosterone system reduce serum concentrations of NT-proBNP.

In the group treated with FCM we observed greater increase in hemoglobin values and in distance travelled at 6MWT at discharge. We did not observe any adverse events in both groups. Moreover, in our study, transferrin levels were predictors of increased

hemoglobin on discharge. It is well known that transferrin contributed about as much to the model as transferrin saturation that predicts the probability of treatment response. This might explain the good discriminative power of transferrin in iron deficiency diagnosis.

Our results suggest that FCM may be an appropriate alternative to more established parenteral iron therapies, allowing higher doses with each infusion and therefore fewer infusions to achieve repletion of iron stores and rapid Hb responses. Furthermore, patients treated with FCM showed lower in-hospital rehabilitation length of stay. Use of FCM, reducing hospital stays, reduces the costs and risks associated with prolonged hospitalization.

Our results show that treatment of iron deficiency is crucial and FCM is effective in achieving this goal. However, further studies are mandatory in order to evaluate the effects of FCM replacement therapy on long-term outcomes in IDA patients after cardiac surgery.

Study limitation

This study has a number of limitations. First, this is a retrospective, single center study. Moreover, an important limitation of this study is the small sample size. Finally, we had no control group with IDA not treated or treated with oral iron replacement

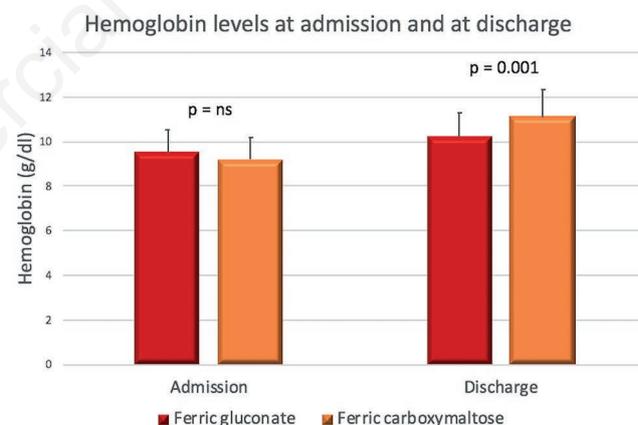


Figure 2. Hemoglobin levels at admission and at discharge in the two groups of patients.

Table 2. Hemoglobin and 6MWT parameters at discharge according to iron replacement therapy.

	Ferric gluconate (n=35)	Ferric carboxymaltose (n=39)	p
Distance at discharge (mt)	236.3 ± 72.7	279.2 ± 108.8	0.048
Distance at discharge (%Predicted)	50.9 ± 15.7	59.1 ± 19.7	0.052
Δ Distance at discharge	+62.6 ± 48.8	+ 102.4 ± 63	0.003
Δ Distance at discharge (%Predicted)	+13.8 ± 11.3	+ 22.12 ± 14.7	0.008
NT-ProBNP at discharge, median (range)	1272 (592-4146)	945 (487-1716)	0.10
Hb at discharge (g/dl)	10.2 ± 1.1	11.1 ± 1.2	0.001
Δ Hb	0.6 ± 0.9	1.9 ± 1.1	<0.0001
Hb >1 at discharge n (%)	11 (31)	31 (79)	<0.0001

Hb, hemoglobin.

therapy, because in our center all patients with IDA are treated with intravenous iron replacement therapy according to guidelines.

Conclusions

Diagnosis and treatment of iron deficiency anemia in adult surgical patients is important in order to improve outcomes in a cost-effective manner. Intravenous ferric carboxymaltose may be an effective therapy in this setting of patients and may improve exercise capacity after cardiac surgery. Further studies are necessary to confirm our preliminary data.

References

- Najafi M, Faraoni D. Hemoglobin optimization and transfusion strategies in patients undergoing cardiac surgery. *World J Cardiol* 2015;7:377-82.
- Musallam KM, Tamin HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011;378:1396-407.
- Loor G, Koch CG, Sabik JF III, et al. Implications and management of anemia in cardiac surgery: current state of knowledge. *J Thorac Cardiovasc Surg* 2012;144: 538-46.
- Van Veldhuisen DJ, Ponikowski P, van der Meer P, et al. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation* 2017;136:1374-83.
- Jankowska EA, von Haehling S, Anker SD, et al. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2013;34:816-29.
- Okonko DO, Mandal AK, Missouriis CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011;58:1241-51.
- Grote Beverborg N, Klip IT, Meijers WC, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail* 2018;11:e004519.
- Hass JD, Brownlie T 4th. Iron deficiency and reduced work capacity. *J Nutr* 2001;131:S676-88.
- Andrews NC. Disorders of iron metabolism. *N Eng J Med* 1999;341:1986-95.
- Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007;116:2544-52.
- Karkouti K, Wijeyesundera DN, Yau TM, et al. Advance targeted transfusion in anemic cardiac surgical patients for kidney protection: an unblinded randomized pilot clinical trial. *Anesthesiology* 2012;116:613-21.
- Pedretti RFE, Fattiroli F, Griffo R, et al. Cardiac Prevention and Rehabilitation “3.0”: From acute to chronic phase. Position Paper of the Italian Association for Cardiovascular Prevention and Rehabilitation (GICR-IACPR). *Monaldi Arch Chest Dis* 2018;88:1004.
- Doyle MP, Indraratna P, Tardo DT, et al. Safety and efficacy of aerobic exercise commenced early after cardiac surgery: A systematic review and meta-analysis. *Eur J Prev Cardiol* 2019;26:36-45.
- Tramarin R, Pistuddi V, Maresca L, et al. Patterns and determinants of functional and absolute iron deficiency in patients undergoing cardiac rehabilitation following heart surgery. *Eur J Prev Cardiol* 2017;24:799-807.
- Pozzo J, Fournier P, Delmas C, et al. Absolute iron deficiency without anaemia in patients with chronic systolic heart failure is associated with poorer functional capacity. *Arch Cardiovasc Dis* 2017;110:99-105.
- Ng O, Keeler BD, Mishra A, et al. Iron therapy for pre-operative anaemia. *Cochrane Database Syst Rev* 2015;12:CD011588.
- Miñana G, Cardells I, Palau P, et al. Changes in myocardial iron content following administration of intravenous iron (Myocardial-IRON): Study design. *Clin Cardiol* 2018;41:729-35.
- Rocha BML, Cunha GJL, Menezes Falcão LF, et al. The burden of iron deficiency in heart failure: Therapeutic Approach. *J Am Coll Cardiol* 2018;71:782-93.
- Toblli JE, Lombrana A, Duarte P, et al. Intravenous iron reduced NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007;50:1657-65.
- Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: The IRONOUT HF randomized clinical trial. *JAMA* 2017;317:1958-66. Erratum in: *JAMA* 2017;317:2453.
- Lichtenstein GR, Onken JE. Improved haemoglobin response with ferric carboxymaltose in patients with gastrointestinal-related iron-deficiency anemia versus oral iron. *Dig Dis Sci* 2018;63:3009-19.
- Khalafallah AA, Yan C, Al-Badri R, Robinson E, et al. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial. *Lancet Haematol* 2016;3:e415-25.
- Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;36:657-68.
- Padmanabhan H, Siau K, Nevill AM, et al. Intravenous iron does not effectively correct preoperative anaemia in cardiac surgery: a pilot randomized controlled trial. *Interact Cardiovasc Thorac Surg* 2018;28:447-54.
- 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. *Int J Cardiol* 2014;175:233-9.