Iron Deficiency in Patients with Heart Failure

Subjects: Cardiac & Cardiovascular Systems

Contributor: Andrew Sindone , Wolfram Doehner, MD, PhD , , Thibaud Damy , Peter Van Der Meer , Josep Comín-Colet

Iron deficiency (ID) is a comorbid condition frequently seen in patients with heart failure (HF). Iron has an important role in the transport of oxygen, and is also essential for skeletal and cardiac muscle, which depend on iron for oxygen storage and cellular energy production. Thus, ID *per se*, even without anaemia, can be harmful. In patients with HF, ID is associated with a poorer quality of life (QoL) and exercise capacity, and a higher risk of hospitalisations and mortality, even in the absence of anaemia.

chronic heart failure ferric carboxymaltose guidelines iron deficiency

1. Introduction

Heart failure (HF) impacts in the region of 26 million people across the world and due to the ageing population its prevalence is still increasing [1]. Although there have been advances to prevent and treat HF, it is still associated with substantial rates of mortality and morbidity as well as diminished patient quality of life (QoL) [1][2].

HF is defined as a syndrome characterised by cardinal symptoms, for example fatigue, breathlessness and ankle swelling, which may occur alongside signs including peripheral oedema, increased jugular venous pressure and crackles in the lung [3]. HF is caused be an abnormality of the heart, which may be functional and/or structural, resulting in increased pressure in the heart and/or a deficient cardiac output while resting and/or exercising [3].

Iron deficiency is an important and frequent comorbid condition in patients with HF [4][5][6][7][8][9]. In these patients, it independently predicts mortality and morbidity, and is also associated with impaired exercise capacity and reduced QoL [4][5][6][7][8][9]. The recently updated 2021 European Society of Cardiology (ESC) guidelines on HF acknowledge the importance of iron deficiency among patients with HF and also provide specific recommendations for diagnosing and appropriately treating the condition [3]. However, iron deficiency remains under-recognised and under-treated in clinical practice [10][11][12][13][14], likely due in part to a lack of practical guidance for clinicians that can be easily followed.

There are three main goals when treating patients with HF with reduced ejection fraction (HFrEF): (1) lessening mortality; (2) preventing recurrent hospitalisations due to HF worsening; and (3) improving functional capacity, clinical status and QoL [3]. Clinical trial evidence has shown that correcting iron deficiency with supplementary IV iron addresses two of the aforementioned treatment goals (reducing recurrent hospitalisations due to HF, and

improving HF symptoms, functional status, and QoL) [15][16][17][18]. Hence, correction of iron deficiency in patients with HFrEF is recommended to improve these clinical outcomes [3].

2. Role of Iron and the Impact of Iron Deficiency

Iron deficiency is a clinical condition where the available iron is inadequate to fulfil the needs of the body [19]. Iron has a critical role in the function of every cell in the human body [7]. As an essential component of respiratory chain proteins in mitochondria, iron is key for cellular energy generation [20]. While iron is most widely recognised for its role in the transport of oxygen as a vital constituent of haemoglobin (Hb), it also has a major role in non-haematopoietic tissues, such as cardiac and skeletal muscle, which are dependent on iron for oxygen storage, mitochondrial energy production and many other cellular processes [20][21] (**Figure 1**). Thus, iron deficiency *per se*, even in the absence of anaemia (i.e., at a normal Hb level), can be harmful. Experimental studies show that iron deficiency directly weakens the ability of human cardiomyocytes to contract in vitro, and that this can be corrected by iron repletion [22]. In patients who have chronic HF (CHF), iron deficiency can be associated with breathlessness on exertion, increased fatigue, reduced exercise capacity [7][23][24], poorer health-related QoL [25][26], worse HF symptoms, increased HF hospitalisation and higher mortality [5][27][28][29]. These adverse effects are independent of anaemia in patients who have HF and iron deficiency. Furthermore, anaemia does not affect these adverse outcomes in HF when corrected for iron deficiency and other prognostic markers, although patients with both iron deficiency and anaemia have worse outcomes [27][28][29]. Importantly, treatment of iron deficiency with intravenous (IV) iron is associated with improved functional status among patients with HF, even when Hb is normal [15][17][30].

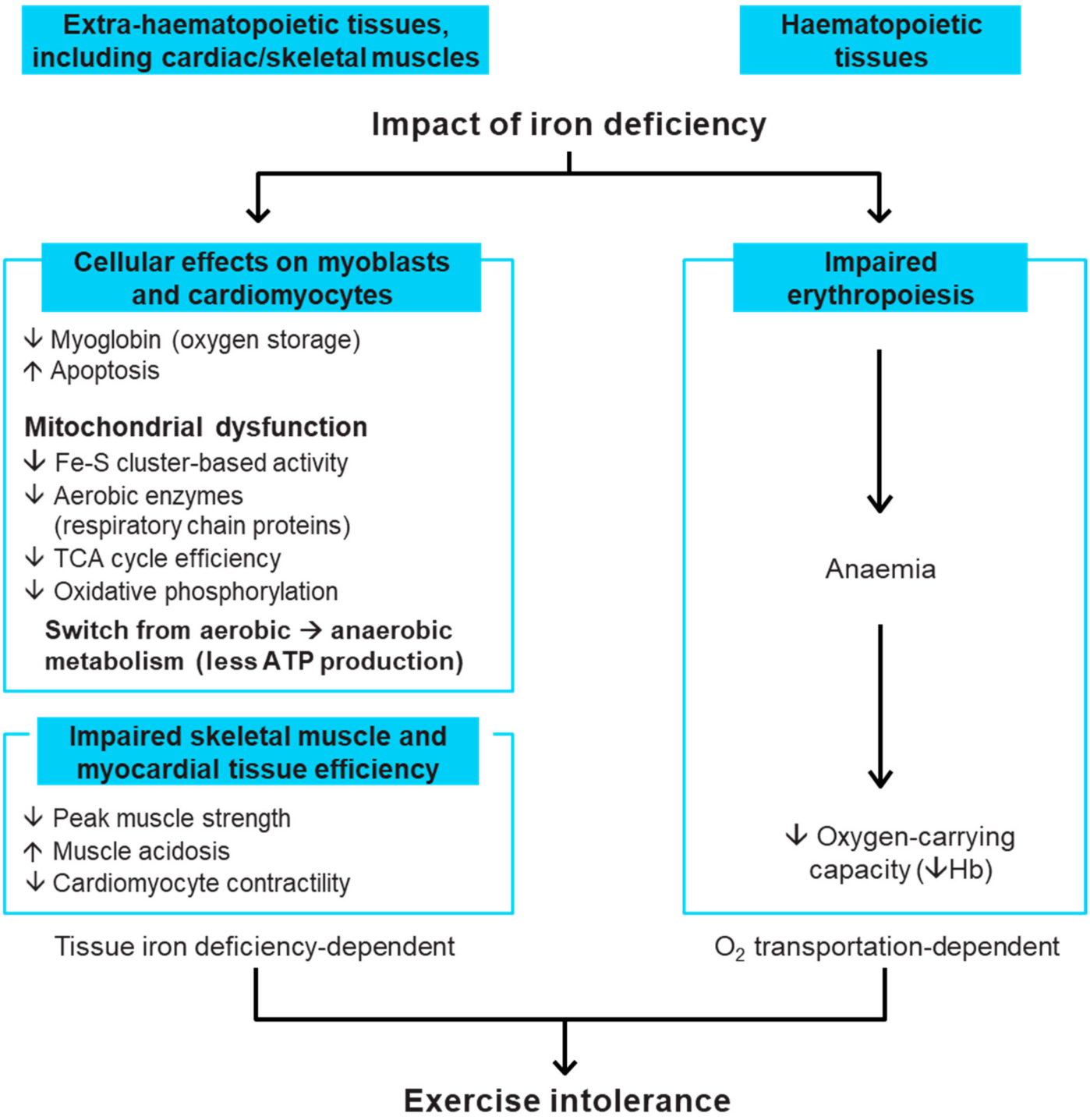

Figure 1. Role of iron in the body and detrimental impact of iron deficiency [20][21][31]. ATP, adenosine triphosphate; Fe-S, iron–sulphur; Hb, haemoglobin; TCA, tricarboxylic acid.

3. Iron Deficiency Prevalence in Patients with Heart Failure

Iron deficiency is one of the most commonly seen comorbid conditions in patients who have HF, with studies reporting that approximately 40−70% of patients with CHF have iron deficiency [5][7][32][33][34][35][36], regardless of their ejection fraction [9]. Iron deficiency also has a prevalence of up to 80% in patients with acute HF (AHF) [10][37].

Additionally, the prevalence of iron deficiency increases in severe HF (i.e., with higher New York Heart Association [NYHA] class [5]) and when anaemia is present [38].

4. Iron Deficiency Causes in Patients with Heart Failure

The aetiology of iron deficiency in HF is complex and multifactorial, with contradictory evidence on the precise cause(s) [29]. Factors that may contribute to iron deficiency include reduced appetite, co-administration of proton pump inhibitors, occult gastrointestinal blood loss and comorbidities such as chronic kidney disease and inflammatory activity [27][29][39][40]. The possible driving factors for iron deficiency in HF are summarised in **Figure 2**. Since hepcidin is tightly regulated by inflammatory activation as part of the antibacterial response mechanism and HF is a condition of increased inflammatory activation, patients with HF may have high levels of circulating hepcidin [29][41][42][43]. Hepcidin inhibits iron absorption by binding to ferroportin, causing sequestration of iron in the reticuloendothelial system and reducing the available useable iron [29]. There is some evidence that, as HF progresses and iron deficiency develops, the circulating hepcidin levels may become low in patients with CHF [43][44].

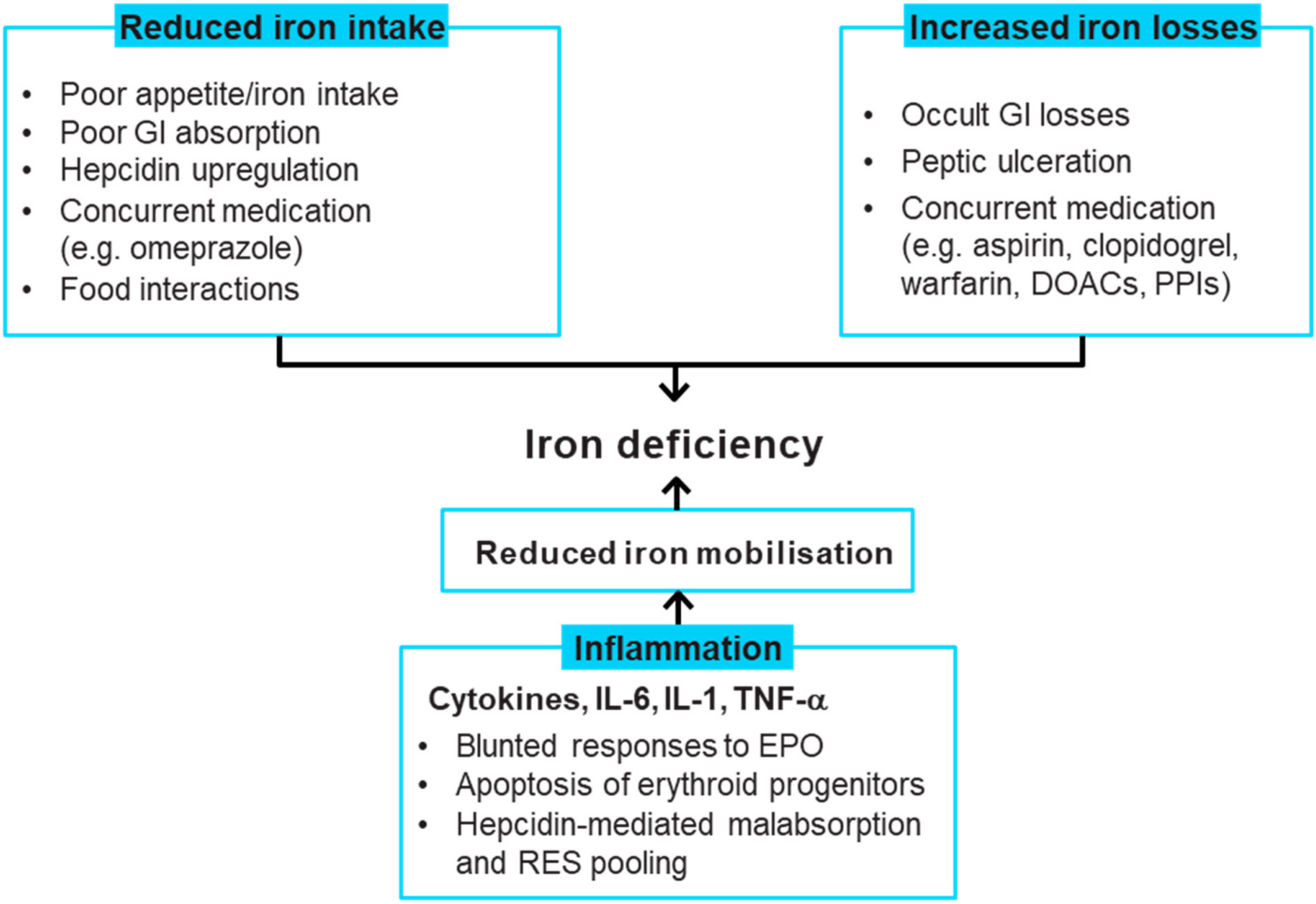

Figure 2. Causes of iron deficiency in heart failure [19][27][29][31][39][40][43][44][45][46]. DOAC, direct oral anticoagulant; EPO, erythropoietin; GI, gastrointestinal; IL, interleukin; PPI, proton-pump inhibitor; RES, reticuloendothelial

system; TNF-α, tumour necrosis factor alpha.

5. Recommendations for Correcting Iron Deficiency

The 2021 ESC HF guidelines recommend that IV FCM should be considered for the treatment of iron deficiency in:

- Symptomatic patients who have a left ventricular ejection fraction (LVEF) < 45% to alleviate symptoms, improve exercise capacity and QoL (recommendation class IIa, evidence level A)
- Pre- and post-discharge follow-up of patients hospitalised for AHF to improve symptoms and reduce rehospitalisation (recommendation class IIa, evidence level B)
- Symptomatic patients recently hospitalised for HF with LVEF < 50% to lessen the risk of HF hospitalisation (recommendation class IIa, evidence level B) [3].

These recommendations were determined from the results of the FAIR-HF, CONFIRM-HF, EFFECT-HF and AFFIRM-AHF trials described in more detail below [15][16][17][18]. A visualisation of the screening and treatment of iron deficiency with FCM across the HFrEF continuum is provided in **Figure 3**.

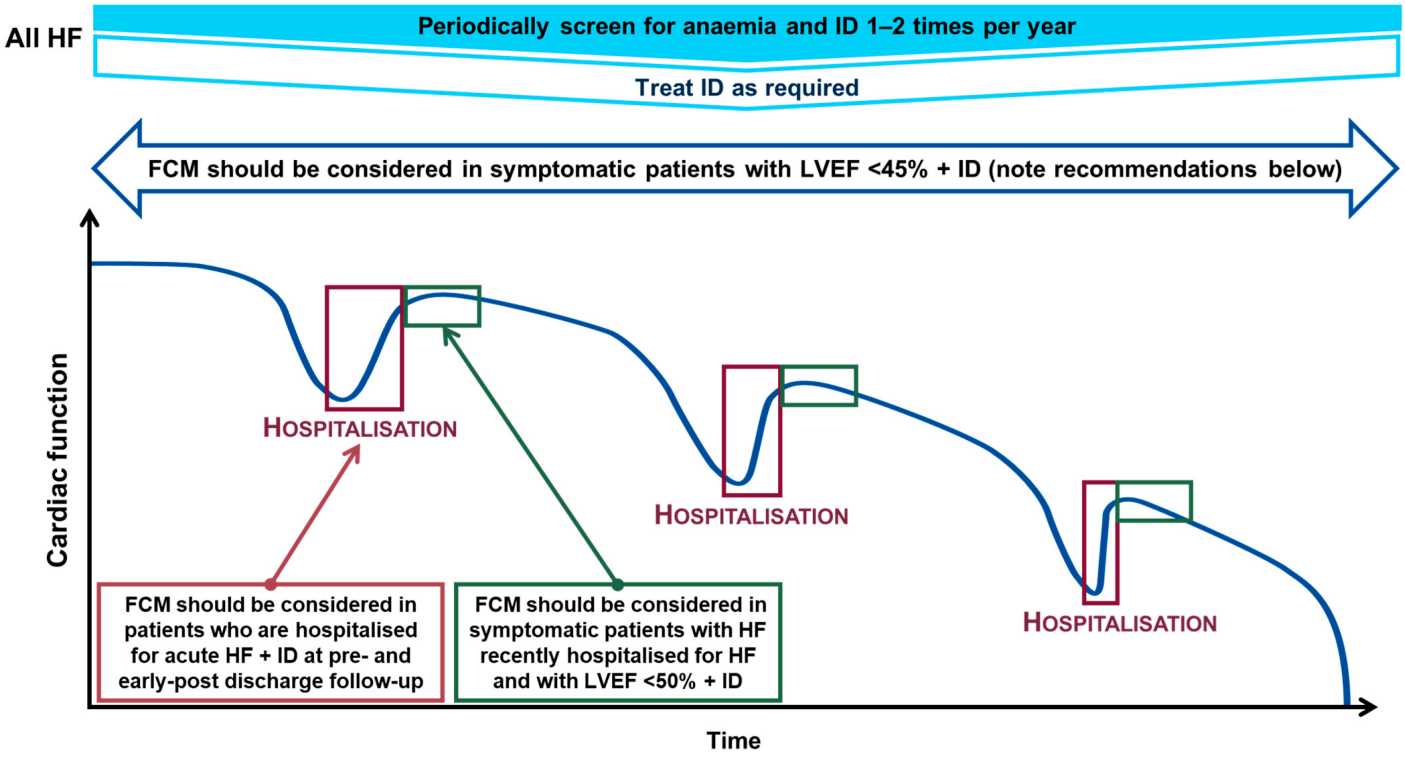

Figure 3. Screening and treatment of iron deficiency across the HFrEF continuum [3][47][48]. Iron deficiency determined by a ferritin <100 µg/L or TSAT <20% when ferritin is 100–299 µg/L; and anaemia determined by a Hb <13 g/dL in males and <12 g/dL in females. TSAT = (serum iron concentration/total iron-binding capacity) × 100. FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; LVEF, left ventricular ejection fraction; TSAT, transferrin saturation.

6. Evidence on the Therapeutic Management of Iron Deficiency

Ferric carboxymaltose (FCM), a precision-engineered nanomedicine with a characteristic clinical profile [49], is the most extensively studied IV iron in randomised controlled clinical trials of patients with CHF [15][16][17][18]. Therefore, the majority of the evidence-base for IV iron in HF applies to IV FCM and, as such, FCM is the only iron formulation specifically recommended for the treatment of iron deficiency in the 2021 ESC HF guidelines [3].

The largest randomised controlled trials to evaluate FCM in patients who were iron-deficient and had stable CHF (LVEF ≤ 45%) were the FAIR-HF [15], CONFIRM-HF [17], EFFECT-HF [18] and AFFIRM-AHF [16] studies. A summary of the designs and key efficacy and safety findings of these trials is shown in **Table 1**.

Table 1. Design and key results from the FAIR-HF, CONFIRM-HF, EFFECT-HF and AFFIRM-AHF clinical trials of IV FCM in patients with HFrEF who have iron deficiency.

	FAIR-HF [15]	CONFIRM-HF [17]	EFFECT-HF [18]	AFFIRM-AHF [16]
Design, duration and number of patients who received treatment per arm	Double-blind, placebo-controlled, randomised; 24 weeks FCM: 305 Placebo: 154	Double-blind, placebo-controlled, randomised; 52 weeks FCM: 152 Placebo: 152	Open-label, SoC-controlled, randomised; 24 weeks FCM: 88 SoC: 86	Double-blind, placebo-controlled, randomised; 52 weeks FCM: 559 Placebo: 551
Key inclusion criteria	NYHA class II (LVEF ≤ 40%) or III (LVEF ≤45%) Hb 9.5–13.5 g/dL ID (ferritin <100 µg/L or 100–299 µg/L + TSAT <20%)	NYHA class II/III (LVEF ≤ 45%) BNP >100 pg/mL and/or NT-proBNP >400 pg/ml Hb <15 g/dL ID (ferritin <100 µg/L or	NYHA class II/III (LVEF ≤ 45%) BNP >100 pg/mL and/or NT-proBNP >400 pg/ml Hb <15 g/dL ID (ferritin <100 µg/L or	Hospitalised for acute HF, treated with at least 40 mg IV furosemide (or equivalent) LVEF < 50% ID (ferritin <100 µg/L or

	FAIR-HF [15]	CONFIRM-HF [17]	EFFECT-HF [18]	AFFIRM-AHF [16]
		100–300 µg/L + TSAT < 20%)	100–300 µg/L + TSAT < 20%) Peak VO_2 10–20 mL/kg/min (reproducible)	100–299 µg/L + TSAT <20%)
Dosing regimen	Dose determined by Ganzoni formula [50] FCM equivalent to 200 mg iron/week for iron repletion then Q4W for maintenance	FCM equivalent to 500–3500 mg iron for iron repletion (baseline and Week 6); 500 mg iron for maintenance (Weeks 12, 24, 36) if iron deficiency still present	FCM equivalent to 500–1000 mg iron for iron repletion (baseline and Week 6) based on screening Hb and weight; only given at Week 6 if <70 kg and Hb <10 g/dL or ≥70 kg and Hb <14 g/dL; 500 mg iron for maintenance (Week 12) if iron deficiency still present	FCM equivalent to 500–1000 mg at baseline and Week 6 for iron repletion; 500 mg iron for maintenance at Weeks 12 and 24 for patients in whom ID persisted and for whom Hb was 8–15 g/dL
Mean cumulative iron dose/ total number of injections	NA/ Median 6 (3–7) during iron repletion phase	1500 mg/>75% of patients receiving FCM needed 2 injections maximum to correct and sustain iron parameters during the study	1204 mg/42% received 1, 55% received 2, and 3.3% received 3 FCM administrations	1352 mg/80% of patients received 1 or 2 FCM administrations during the treatment phase (i.e., up to

	FAIR-HF [15]	CONFIRM-HF [17]	EFFECT-HF [18]	AFFIRM-AHF [16]
				Week 24)
Treatment effect on iron-related parameters	FCM vs. placebo at Week 24 (mean ± SE) -Serum ferritin: 312 ± 13 vs. 74 ± 8 µg/L -TSAT: 29 ± 1 vs. 19 ± 1% -Hb: 130 ± 1 vs. 125 ± 1 g/L ($p < 0.001$ for all)	Mean treatment effect (baseline-adjusted) difference for FCM vs. placebo at Week 52: -Serum ferritin: 200 ± 19 µg/L -TSAT: 5.7 ± 1.2% -Hb: 1.0 ± 0.2 g/dL ($p < 0.001$ for all)	FCM vs. control (SoC) at Week 24: -Serum ferritin: 283 ± 150 vs. 79 µg/L -TSAT: 27 ± 8 vs. 20.2% -Hb: 13.9 ± 1.3 vs. 13.2 ± 1.4 g/dL ($p < 0.05$ for all)	Compared with placebo, serum ferritin and TSAT both rose with FCM by week 6 and continued to be significantly higher at week 52
Primary endpoint results	Changes in PGA and NYHA functional class at Week 24 for FCM vs. placebo -PGA: patients reported being much or moderately improved: 50% vs. 28% (OR 2.51; 95% CI, 1.75 to 3.61; $p < 0.001$) -NYHA functional class I/II: 47% vs. 30% placebo	LS means ± SE 6 MWT distance at Week 24 for FCM vs. placebo -18 ± 8 vs. −16 ± 8 metres (difference FCM vs. placebo: 33 ± 11 metres, $p = 0.002$)	Primary analysis LS means change from baseline in peak VO_2 at Week 24 for FCM vs. control (SoC) - −0.16 ± 0.387 vs. −1.19 ± 0.389 mL/min/kg ($p = 0.020$) Sensitivity analysis in which missing data were not imputed for control vs. control: - −0.16 ± 0.37 vs. −0.63 ± 0.38	Composite of total HF hospitalisations and CV deaths up to 52 weeks after randomisation for FCM vs. placebo: -293 primary events (57.2 per 100 patient-years) vs. 372 (72.5 per 100 patient-years) (RR: 0.79, 95% CI 0.62–1.01, $p = 0.059$) -Pre-COVID-19 sensitivity

	FAIR-HF [15]	CONFIRM-HF [17]	EFFECT-HF [18]	AFFIRM-AHF [16]
	(odds ratio for improvement by one class, 2.40; 95% CI, 1.55 to 3.71, $p < 0.001$)		mL/min/kg ($p = 0.23$)	analysis: 274 primary events (55.2 per 100 patient-years) vs. 363 (73.5 per 100 patient-years) (RR: 0.75, 95% CI 0.59–0.96, $p = 0.024$)
Key secondary endpoint results	Significant improvement ($p < 0.001$) with FCM vs. placebo in: -Self-reported PGA at Weeks 4 and 12 -6 MWT distance at Weeks 4, 12, and 24 -QoL (EQ-5D visual assessment) at Weeks 4, 12, and 24 -Overall KCCQ score at Weeks 4, 12, and 24	Significant improvements in PGA, NYHA class and 6 MWT with FCM vs. placebo: -PGA at Week 12 ($p = 0.035$) Week 24 ($p = 0.047$), Weeks 36 and 52 (both $p < 0.001$) -NYHA class at Week 24 ($p = 0.004$) and Weeks 36 and 52 (both $p < 0.001$) -6 MWT difference in changes at Week 36 (42 metres with 95% CI of 21–62, $p < 0.001$) and Week 52 (36 metres with 95% CI of 16–57, $p < 0.001$)	Significant improvements in NYHA class and PGA with FCM vs. control: -NYHA class at weeks 6, 12 and 24 (with imputation; all $p < 0.05$) -PGA at Weeks 12 and 24 (with imputation; $p < 0.05$) Note: effect of FCM vs. control on NYHA class and PGA without imputation (observed values) were similar	Total CV hospitalisations and CV deaths with FCM vs. placebo -370 vs. 451 (RR: 0·80, 95% CI 0·64–1.00, $p = 0.050$) CV deaths FCM vs. placebo -77 (14%) vs. 78 (14%) (HR: 0.96, 95% CI 0.70–1.32, $p = 0.81$) Significantly lower number HF hospitalisations with FCM vs. placebo -217 vs. 294 (RR 0.74; 95% CI 0.58–0.94, $p = 0.013$) Significant treatment benefits with IV FCM vs. placebo for time

	FAIR-HF [15]	CONFIRM-HF [17]	EFFECT-HF [18]	AFFIRM-AHF [16]
		-Fatigue score at Week 12 (p = 0.009), Week 24 (p = 0.002) and Week 36 (p < 0.001), and Week 52 (p = 0.002)		to first hospitalisation or CV death -181 (32%) vs. 209 (38%) (HR: 0.80, 95% CI 0.66–0.98, p = 0.030)
Safety endpoint results	FCM vs. placebo (incidence per 100 patient-years at risk) -All deaths: 3.4 % vs. 5.5% -Deaths with CV cause: 2.7% vs. 5.5% -Deaths, due to HF worsening: 0% vs. 4.1% -Hospitalisations with CV cause: 10.4% vs. 20.0% -Hospitalisations for worsening HF: 4.1% vs. 9.7%	FCM vs. placebo (incidence per 100 patient-years at risk) -All deaths: 8.9 % vs. 9.9% -Deaths with CV causes: 8.1% vs. 8.5% -Deaths, due to HF worsening: 3.0% vs. 2.1% -Hospitalisations, CV cause: 16.6% vs. 26.3% -Hospitalisations due to worsening HF: 7.6% vs. 19.4%	FCM vs. control (SoC) -All deaths: 0 (0%) vs. 4 (4.7%) -Hospitalisations: 37 (42.0%) vs. 21 (24.4%) ◦Due to worsening HF: 13 (14.8%) vs. 13 (15.1%) ◦Due to other CV reason: 13 (14.8%) vs. 3 (3.5%) ◦Due to non-CV reason: 11 (12.5%) vs. 4 (4.7%)	FCM vs. placebo -Serious adverse events: 250 (45%) vs. 282 (51%) -Cardiac disorder events: 224 (40%) patients with 391 events vs. 244 (44%) patients with 453 cardiac disorder events. -Treatment discontinued prematurely: 157 (28%) vs. 160 (29%) (modified intention-to-treat population)

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6 MWT, 6-minute walk test; AFFIRM-AHF, Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency; BNP, brain natriuretic peptide; CONFIRM-HF, Ferric Carboxymaltose evaluation in coMbination with chronic Heart Failure; CI, confidence interval; CV, cardiovascular; EFFECT-HF, Effect of Ferric Carboxymaltose on Exercise Capacity in

Patients With Iron Deficiency and Chronic Heart Failure; EQ-5D, EuroQol-5 Dimensions; FAIR-HF, Ferinject assessment in patients with IRon deficiency and chronic Heart Failure; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ID, iron deficiency; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LS, least squares; LVEF, left ventricular ejection fraction; NA, not available; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; PGA, patient global assessment; Q4W, every four weeks; OR, odds ratio; QoL, quality of life; RR, rate ratio; SE, standard error; SoC, standard of care; TSAT, transferrin saturation.

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