National Institute for Health and Care Excellence

Final

Chronic heart failure in adults: diagnosis and management

[C] Evidence review for IV iron therapy for heart failure

NICE guideline NG106

Evidence review underpinning recommendations 1.4.5 to 1.4.7 and recommendations for research in the NICE guideline

September 2025

Final

This evidence review was developed by NICE

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Contents

1. Intravenous iron therapy for chronic heart failure

1.1. Review question

What is the clinical and cost effectiveness of intravenous iron supplementation in adults with chronic heart failure and iron deficiency?

1.1.1. Introduction

Iron deficiency commonly occurs in heart failure, particularly in acute decompensations and is even more common in patients with coexisting CKD. It is associated with worse outcomes and has been an area of significant interest since the last guideline update, at which time insufficient evidence meant no recommendation was made. One of the postulated mechanisms for iron deficiency in the context of heart failure is malabsorption and therefore the mode of delivery of iron supplementation (oral versus intravenous) has also been an area of investigation. There are currently no specific quality standards addressing this area. Oral iron is poorly absorbed in people with heart failure with reduced ejection fraction, has considerable side effects and is not associated with any better outcome than placebo. Therefore, oral supplementation was not included in this review update. The aim of this review was to examine the clinical and cost effectiveness of intravenous iron supplementation in adults with iron deficiency and chronic heart failure, to provide recommendations for treatment and identify areas for future research. This will help determine if intravenous iron leads to better clinical outcomes, reduced hospitalisation if given in symptomatic people with reduced, mildly reduced or preserved ejection fraction and its cost effectiveness.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: • Adults diagnosed with heart failure who also have iron deficiency (defined by either serum ferritin < 100 ng/mL, or serum ferritin between 100-299 ng/mL if iron saturation (TSAT) < 20 %). • Patients stabilised on optimal medical therapy for heart failure (based on prevailing best practice at time of trial). Studies including an indirect population will only be included if ≥80% match the protocol criteria or there are subgroup data for the protocol population. Ongoing treatment after discharge for an acute episode of heart failure will be included. Exclusion: • Children • Acute heart failure in hospital • Heart failure due to right heart dysfunction (e.g., pulmonary pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies) High output heart failure • Adult congenital heart disease • Primary heart valve disease • Acute MI (within 3 months of the event)

Intervention	Inclusion • Intravenous (IV) iron supplementation. All IV iron formulations will be considered together. Exclusion • Oral iron supplementation
Comparison	Placebo or usual care
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • CV mortality (time-to-event) • Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value) • Unplanned hospitalisation or visits (all-cause) (time-to-event; including repeat events when reported) • Unplanned hospitalisation or visits (heart-failure-related) unplanned hospitalisation or visits (time-to-event; including repeat events when reported) • Improvement in exercise tolerance – 6-minute walk test or peak VO2 (continuous; change from baseline) o Both measures will be extracted where available; if neither is reported, other measures of exercise tolerance/functional capacity will be accepted. • Haemoglobin in anaemic patients (continuous; change from baseline) Adverse events (recorded as the number of people with at least one event, not the total number of events) • Withdrawal due to drug-related adverse events (dichotomous) • Hypophosphataemia (dichotomous) • Extravasation (dichotomous) • Anaphylaxis/hypersensitivity (dichotomous) • Hospitalisation for infection (dichotomous) o Sepsis, hospitalisation for pneumonia and infections categorised as serious adverse events will be included in this outcome. • Atrial fibrillation (dichotomous) Time points for analysis: o 3-12 months (pool all times ≥3 months, taking the closest to 12 months follow-up time from each study if multiple time points are reported within this range) o >12 months Exclude if follow-up < 3 months
Study design	Inclusion: • RCTs (randomised controlled trials) • Published systematic reviews of RCTs • Published network meta-analyses (NMAs) and individual participant data meta-analyses (IPDs). Exclusion: • Cross-over RCTs

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document (report E).

1.1.3.1. Literature search methods

The searches for the effectiveness evidence were run on 04/07/2024 and re-run on 09/01/2025. The following databases were searched: Cochrane Database of Systematic Reviews (CDSR) (Wiley); Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Embase (Ovid); MEDLINE ALL (Ovid); and Epistemonikos. Limits were applied to remove editorials, conference abstracts, empty registry entries and references not published in the English language. The National Guideline Centre (NGC) systematic review and randomised controlled trial search filters were used to limit to study types.

The searches for the cost effectiveness evidence (economic evaluations) were run on 12/02/2024 and re-run on 04/12/2024 and 13/01/2025. The following databases were searched: Embase (Ovid); MEDLINE ALL (Ovid); and INAHTA. Limits were applied to remove animal studies, editorials, conference abstracts, empty registry entries and references not published in the English language.

The searches for the cost effectiveness evidence (quality of life) were run on 25/07/2024 and re-run on 04/12/2024 and 13/01/2025. The following databases were searched: Embase (Ovid) and MEDLINE ALL (Ovid). Limits were applied to remove animal studies, editorials, conference abstracts, empty registry entries and references not published in the English language.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in Appendix B.

1.1.3.2. Review methods

Chronic heart failure is defined according to the following criteria:

- Symptoms (such as breathlessness, ankle swelling, and fatigue) with or without signs (such as elevated jugular venous pressure, pulmonary crackles, and peripheral oedema); and
- Elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion on imaging (such as pleural effusions, pulmonary oedema, ascites, lung comets); and
- Outpatient or stabilised after hospital admission.

However, for the purposes of this review, trials were not excluded on the basis of lacking corroboratory evidence from natriuretic peptides or imaging, as this would selectively exclude older trials. Although this would increase certainty in the population being correctly diagnosed, it would also reduce the size of the evidence base, including removing large trials previously included in the review. Therefore, including such trails was agreed to be appropriate.

Studies that were included and analysed in the previous update of the guideline and met the current protocol criteria were retained in this evidence review and pooled with newly identified studies where appropriate. The previously included studies were added to EPPI-reviewer and any data available for the additional outcomes that were not in the previous

protocol were also extracted. All outcomes were reassessed for risk of bias according to the Cochrane Risk of Bias 2 checklist for consistency with current methods.

The excluded studies from the previous update of the guideline were re-assessed against the current protocol. Two (Okonko 2008 and van Veldhuisen 2017) were added to the review due to usual care now being included as a comparator.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

A search was conducted for randomised trials, systematic reviews, network meta-analyses and individual participant data meta-analyses comparing the effectiveness of intravenous iron supplementation with placebo or usual care as treatment for patients with chronic heart failure and iron deficiency.

Twelve RCT studies (7 identified from the previous guideline review; 5 previously included and 2 previously excluded) reported in 27 papers were included in the review; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3). The included studies assessed a range of IV iron formulations and compared these to either placebo or usual care.

All included studies required participants to have symptomatic heart failure. Six of the studies (Anker 2025b, Kalra 2022a, Mentz 2023, Ponikowski 2015a, Van Veldhuisen 2017 and von Haehling 2024) specified prior heart-failure hospitalisation or elevated natriuretic peptides within the trial inclusion criteria, in accordance with the universal definition of heart failure, while the remaining 6 studies did not.

Two studies performed a pre-specified subgroup analysis based on iron saturation (Kalra 2022a and von Haehling 2024), and this was reported in addition to the overall pooled estimates in line with the review protocol. One study was identified where the population was people with preserved left ventricular ejection fraction (LVEF). Other included studies either did not report the LVEF of the participants or included people with reduced or mildly reduced LVEF.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J. All of the trials investigating intravenous iron versus placebo included in the previous update of this guideline were retained.

1.1.5. Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Anker 2009b [FAIR HF] Subsidiary studies: Anker 2009a Butler 2022 Comin-Colet 2013 Filippatos 2013	200 mg IV ferric carboxymaltose in a black syringe – weekly dosing until iron repletion was achieved followed by dosing every 4 weeks during maintenance Placebo - saline administered as an IV bolus injection of 4 ml (which is the amount of ferric carboxymaltose in a water solution for injection that is equivalent to 200 mg of iron) in a black syringe - weekly dosing until iron repletion was achieved followed by dosing every 4 weeks during maintenance	Ambulatory patients with NYHA class II-III; with LVEF 40% or less (with NYHA class II) or with LVEF 45% or less (with NYHA class III); haemoglobin level between 95 to 135 g per litre and iron deficiency. N= 459 Mean age (SD), intervention group: 67.8 (10.3) years Mean age (SD), comparison group: 67.4 (11.1) years Mean (SD) LVEF %, intervention group: 31.9 (5.5) Mean (SD) LVEF %, comparison group: 33 (6.1)	• All-cause mortality • Cardiovascular mortality • Health-related quality of life - KCCQ (overall summary score) • Health-related quality of life - EQ-5D index score • Hospitalisation for heart failure • 6-minute walk test • Haemoglobin in anaemic patients • Hospitalisation for infection Outcomes measured at 24 weeks follow-up	
Anker 2025b [FAIR HF2] Subsidiary studies: Anker 2025a	Ferric carboxymaltose initially up to 2000 mg during the first 2 visits at baseline and at week 4; the subsequent fixed maintenance doses of 500 mg were administered every 4 months unless the haemoglobin concentration exceeded 16 g/dL or the serum ferritin level exceeded 800 ng/m.	Chronic heart failure (NYHA class II-IV); with LVEF ≤ 45%, and evidence of serum iron deficiency (serum ferritin <100 ng/mL; or if transferrin saturation <20%, had a serum ferritin level between 100 ng/mL and 299 ng/mL); serum haemoglobin of 9.5 to 14.0 g/dL, and either current/recent admission to hospital due to heart failure or raised plasma concentrations of natriuretic	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • Health-related quality of life - EQ-5D index score • 6-minute walk test Outcomes measured at 12 and 36 weeks follow-up	

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (saline) administered at all visits	peptides (BNP > 100 pg/mL or NT-proBNP > 300 pg/mL) N=1105 Mean age (SD), intervention group: 70.1 (11.4) years Mean age (SD), comparison group: 69.7 (12.0) years Mean (SD) LVEF %, intervention group: NR Mean (SD) LVEF %, comparison group: NR		
Beck-da-Silva 2013 [IRON-HF] Subsidiary studies: Beck-da-Silva 2007	200 mg IV iron sucrose once a week for 5 weeks and placebo of oral presentation, three times a day, for 8 weeks Placebo – placebo of oral presentation, three times a day, for 8 weeks plus placebo of IV presentation once a week, for 5 weeks.	Outpatients followed at a HF clinic in a tertiary care hospital with NYHA class II-IV with LVEF <40%; haemoglobin between 9 and 12 g/dl; TSAT <20% and ferritin <500 µg/l and on stable baseline HF therapy. N=16 Mean age (SD), intervention group: 66.9 (8.3) years Mean age (SD), comparison group: 68.9 (10.1) years Mean (SD) LVEF %, intervention group: 25.2 (8.6) Mean (SD) LVEF %, comparison group: 30.7 (7.4)	• All-cause mortality Outcomes measured at 3 months follow-up	The study was terminated early due to poor recruitment

Study	Intervention and comparison	Population	Outcomes	Comments
Dhoot 2020	IV ferric carboxy-maltose administered in 0.9% normal saline bolus over 1 hour via drug infusion pump Standard of care (no further details reported)	Patients with symptomatic heart failure aged 18 to 65 years seen at a heart failure clinic with NHYA functional class II/III and iron deficiency. Baseline haemoglobin levels, mean (SD) were 11 (1.4) and 11.3 (0.9) mg/dl for IV iron and standard care respectively. N=70 Mean age (SD), intervention group: 51.0 (11.6) years Mean age (SD), comparison group: 54.8 (9.0) years Mean (SD) LVEF %, intervention group: 24.9 (5) Mean (SD) LVEF %, comparison group: 25.8 (5.5)	• Health-related quality of life – MLWHF • 6-minute walk test • Peak VO_2 • Haemoglobin in anaemic patients Outcomes measured at 24 weeks follow-up	
Kalra 2022a [IRONMAN] Subsidiary studies: Kalra 2022b Cleland 2024 Foley 2024	IV ferric derisomaltose provided 4 weeks after randomisation and every 4 weeks thereafter if ferritin was less than 100 mcg/L or if ferritin was ≤400 mcg/L and TSAT was <25% Usual care – patients were permitted to receive oral iron therapy at the investigator's discretion	Adults with new or established symptomatic heart failure (NYHA class II-IV) and evidence of iron deficiency (serum ferritin <100 µg/L or transferrin saturation <20%); LVEF ≤ 45%; and either current/recent admission to hospital due to heart failure or raised plasma concentrations of natriuretic peptides (NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in atrial fibrillation (or BNP >75 pg/mL or 300 pg/mL)). Haemoglobin levels >9g/dL and <14g/dL for men and <13g/dL for women. N=1137	• All-cause mortality • Cardiovascular mortality • Health-related quality of life – MLWHF • Health-related quality of life - EQ-5D index score • Hospitalisation (all-cause) • Hospitalisation (HF-related) • 6-minute walk test • Haemoglobin in anaemic patients • Hospitalisation for infection • Atrial fibrillation	

Study	Intervention and comparison	Population	Outcomes	Comments
		Median (IQR) age intervention group: 73.2 (66.7 to 80.1) years Median (IQR) age comparison group: 73.5 (67.1 to 79.1) years Median (IQR) LVEF %, intervention group: 32 (25 to 37) Median (IQR) LVEF %, comparison group: 35 (26 to 38)	Outcomes were measured at 4 months, and long-term follow-up was measured at a median of 2.7 years	
Martens 2021 [IRON-CRT] Subsidiary studies: Martens 2019	Intravenous iron in the form of intravenous ferric carboxymaltose diluted into 250mL NaCl 0.9% - dose range 500-2000 mg based on screening weight and haemoglobin. Maximal allowed dose of ferric carboxymaltose during one intravenous administration is 1000 mg/week, patients who require a dose of either 1500 or 2000 mg will receive a follow-up appointment after 1–2 weeks to receive the remaining dose Placebo - 250 ml NaCl 0.9% solution without ferric carboxymaltose. Patients also requiring an additional dose based on their body weight and haemoglobin levels also receive a second dosing appointment with infusion of placebo at that time	Adults with chronic heart failure with NYHA class II-IV and LVEF <45%; Haemoglobin <15g/dL; and presence of iron deficiency (ferritin < 100µg/L) with stable pharmacological therapy during the last 4 weeks (with the exception of diuretics) N=75 Mean age (SD), intervention group:72 (12) years Mean age (SD), comparison group: 73 (9) years Mean (SD) LVEF %, intervention group: 33 (8) Mean (SD) LVEF %, comparison group: 34 (7)	• Health-related quality of life - KCCQ • Peak VO_2 • All-cause mortality • Cardiovascular mortality • Heart failure-related hospitalisation Outcomes were measured at 3 months	

Study	Intervention and comparison	Population	Outcomes	Comments
Mentz 2023 [HEART-FID] Subsidiary studies: Mentz 2021 Nouhravesh 2024	Ferric carboxymaltose (FCM) + standard therapy for heart failure. FCM dosing was based on weight and was given in 2 doses separated by 7 days either as a continuous infusion or slow IV injection. FCM was administered every 6 months based on haemoglobin and iron indexes Placebo (no further details reported) + standard therapy for heart failure. Placebo dosing volume adjusted for weight to maintain blinding	Adults with chronic HF and NYHA functional class II to IV symptoms on maximally tolerated background therapy with LVEF ≤40% within 24 months or ≤30% within 36 months of screening, haemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 g/dL (males); ferritin <100 ng/mL or 100 to 300 ng/mL with TSAT <20% and documented hospitalisation for heart failure within 12 months of enrolment or elevated N-terminal-pro-brain natriuretic peptides (NT-proBNP >600 pg/ml or BNP >200 pg/mL for patients with sinus rhythm or NT-proBNP >1000 pg/ml or BNP >400 pg/mL for patients with atrial fibrillation). N=3065 Mean age (SD), intervention group: 68.6 (10.9) years Mean age (SD), comparison group: 68.6 (11.2) years Mean (SD) LVEF %, intervention group: 30.8 (7) Mean (SD) LVEF %, comparison group: 30.6 (7.3)	• All-cause mortality • Cardiovascular mortality • Hospitalisation for heart failure • 6-minute walk test • Hypophosphatemia • Anaphylaxis/hypersensitivity • Hospitalisation for infection Median duration of follow-up was 1.9 years, and follow-up occurred every 3 months	
Okonko 2008 [FERRIC-HF]	IV Iron sucrose with dosing based on weight. Participants received weekly treatment unless ferritin was ≥500 ng/ml	People aged 21 years and older with symptomatic CHF (NYHA class II or III); exercise limitation; haemoglobin <12.5 g/dl or 12.5 to 14.5 g/dl; ferritin <100 mcg/l or 100 to 300 mcg/l with TSAT	• All-cause mortality • Health-related quality of life - MLwHFQ • Peak VO_2 • All-cause hospitalisation	Identified from excluded studies in previous

Study	Intervention and comparison	Population	Outcomes	Comments
	and then at weeks 4, 8, 12 and 16. No treatment (no further details reported)	<20%; LVEF ≤45%; resting blood pressure ≤160/100 mm Hg; normal red cell folate and vitamin B12; and using maximally tolerated doses of optimal CHF therapy. N=35 Mean age (SD), intervention group: 64 (14) years Mean age (SD), comparison group: 62 (11) years Mean (SD) LVEF %, intervention group: 30 (7) Mean (SD) LVEF %, comparison group: 29 (6)	• Hospitalisation for heart failure • Haemoglobin in anaemic patients • Adverse events Outcomes measured at 18 weeks follow-up	update: now included due to usual care being permitted as a comparator
Ponikowski 2015a [CONFIRM-HF] Subsidiary studies: Butler 2022 Ponikowski 2014	Ferric carboxymaltose solution given as an undiluted bolus IV injection. Dose based on weight and haemoglobin value at screening. Doses were between 500 and 2000 mg during the therapy phase (up to week 6) and 500 mg during the maintenance phase Placebo – normal saline administered as per instructions for active therapy.	Stable ambulatory heart failure patients (NYHA class II or III) with LVEF ≤45%; elevated natriuretic peptides (BNP >100 pg/mL and/or NT-pro-BNP >400 pg/mL); presence of iron deficiency; haemoglobin <15 g/dL and capable of completing the 6-minute walk test. N=304 Mean age (SD), intervention group: 68.8 (9.5) years Mean age (SD), comparison group: 69.5 (9.3) years	• All-cause mortality • Cardiovascular mortality • Health-related quality of life – KCCQ • All-cause hospitalisation • Hospitalisation for heart failure • 6-minute walk test • Haemoglobin in anaemic patients • Withdrawal due to adverse drug-related events • Anaphylaxis/hypersensitivity Outcomes were measured at 6, 12, 24, 36, and 52 weeks follow-up	

Study	Intervention and comparison	Population	Outcomes	Comments
		Mean (SD) LVEF %, intervention group: 37.1 (7.5) Mean (SD) LVEF %, comparison group: 36.5 (7.3)		
Toblli 2007 Subsidiary studies: Toblli 2015 Toblli 2017	Iron sucrose complex administered via IV isotonic saline solution at a concentration of 200 mg/200 mll + conventional therapy for CHF. Treatment was followed for 5 consecutive weeks and after 6 months, participants received additional treatment if Hb decreased below 11 mg/dL or TSAT fell to 20% or less. Placebo - IV 200ml bag of isotonic saline solution 0.9% administered throughout 60 mins + conventional therapy for CHF. Treatment was followed for 5 consecutive weeks.	People with chronic heart failure, chronic renal failure, anaemia, and iron deficiency: LVEF ≤35%, NYHA functional class II to IV; Haemoglobin <12.5 g/dl for men and 11.5 <g/dl for women; serum ferritin <100 ng/ml and/or with transferrin saturation (TSAT) ≤20%; and creatinine clearance ≤90 ml/min). N=40 Mean age (SD), intervention group: 76 (7) years Mean age (SD), comparison group: 74 (8) years Mean (SD) LVEF %, intervention group: 31.3 (3.7) Mean (SD) LVEF %, comparison group: 30.8 (1.7)	• All-cause mortality • Cardiovascular mortality • Health-related quality of life – MLWHF • All-cause hospitalisation • Hospitalisation for heart failure • 6-minute walk test • Haemoglobin in anaemic patients The original study had a follow-up of 6 months and there was a long-term follow-up period of 1, 2, 3, 4 and 5 years.	
Van Veldhuisen 2017 [EFFECT-HF]	IV ferric-carboxymaltose delivered as an undiluted IV bolus injection or an infusion. Dosing at day 0 and week 6 was based on screening Hb and weight. At week 12, FCM was only administered if serum ferritin was <100 ng/mL or if	Adults with clinically stable mild to moderate chronic heart failure (NYHA class II to III) who were on optimal background therapy for heart failure; with LVEF ≤45%; haemoglobin <15g/dL, plasma brain natriuretic peptide concentration >100 pg/lL or N-terminal proBNP >400 pg/mL;	• All-cause mortality • All-cause hospitalisation • Hospitalisation due to heart failure Outcomes were followed up at 24 weeks.	Identified from excluded studies in previous update: now included due to usual care

Study	Intervention and comparison	Population	Outcomes	Comments
	ferritin was 100 to 300 ng/mL with TSAT <20%. Standard of care (no further details reported). Oral iron permitted.	decreased exercise capacity; and iron deficiency (serum ferritin <100 ng/mL or a serum ferritin of 100 to 300 ng/mL in combination with TSAT <20%). N=172 Mean age (SD), intervention group: 63 (12) years Mean age (SD), comparison group: 64 (11) years Mean (SD) LVEF %, intervention group: 33 (9) Mean (SD) LVEF %, comparison group: 31 (8)		being permitted as a comparator
von Haehling 2024 [FAIR-HFpEF]	1-2 sessions of intravenous ferric carboxymaltose 1000-2000 mg at baseline, 500-1000 mg at week 16 and 500-1000mg at week 32 Placebo - normal saline (no further details reported)	Adults with a diagnosis of heart failure (NYHA class II to III) with preserved ejection fraction (LVEF ≥45%) at screening, presence of iron deficiency (ferritin <100µg/L), haemoglobin >9.0 and ≤14.0 g/dL and treated with a diuretic Documented hospitalisation for heart failure within 12 months of enrolment or elevated NT-proBNP >300 pg/ml or BNP >100 pg/mL for patients with sinus rhythm or NT-proBNP >600 pg/ml or BNP >200 pg/mL for patients with atrial fibrillation). N=39	• All-cause mortality • All-cause hospitalisation • Withdrawal due to drug-adverse events • Health-related quality of life - KCCQ (overall summary score) • Health-related quality of life - EQ-5D-3L • 6-minute walk test Outcomes reported at 24 and 52 weeks. KCCQ, EQ-5D-3L, and 6-minute walk test reported at 24 weeks. All-cause mortality, all-cause hospitalisation, and withdrawal due to drug-adverse events reported at 52 weeks.	

Study	Intervention and comparison	Population	Outcomes	Comments
		Mean age (SD), intervention group: 76 (8.88) years Mean age (SD), comparison group: 79 (7.03) years Mean (SD) LVEF %, intervention group: 55.3 (6.5) Mean (SD) LVEF %, comparison group: 55,1 (7.8)		

BNP: B-type natriuretic peptides; CHF: Chronic heart failure; EQ-5D: EuroQoL 5-dimensions questionnaire; Hb: Haemoglobin; IQR: Interquartile range; IV: intravenous; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: Left ventricular ejection fraction; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; NaCl: Sodium chloride; NYHA: New York Health Association; SD: standard deviation; NT-proBNP: N-terminal pro-B-type natriuretic peptide level; SD: Standard deviation; TSAT: Transferrin saturation; VO2: Volume of oxygen consumption

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

1.1.6.1. Primary analysis: overall population

Table 3: Clinical evidence summary: Intravenous iron versus placebo or usual care (between 3-12 months)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with IV iron supplementation
All-cause mortality (HR) follow-up: mean 52 weeks	3366 (2 RCTs)	⊕⊕◯◯ Low[a,b]	HR 0.83 (0.66 to 1.04)	Not estimable	Not estimable
All-cause mortality follow-up: range 3 months to 12 months	4202 (9 RCTs)	⊕◯◯◯ Very low[a,b,c]	RR 0.79 (0.64 to 0.97)	93 per 1,000	20 fewer per 1,000 (34 fewer to 3 fewer)
Cardiovascular mortality (HR) follow-up: 52 weeks	3366 (2 RCTs)	⊕⊕◯◯ Low[a,b]	HR 0.86 (0.75 to 1.00)	Not estimable	Not estimable
Cardiovascular mortality follow-up: range 12 weeks to 52 weeks	835 (3 RCTs)	⊕◯◯◯ Very low[b,c]	RR 0.72 (0.38 to 1.38)	52 per 1,000	15 fewer per 1,000 (33 fewer to 20 more)
Minnesota Living With Heart Failure (MLWHF) (change and final values; score range from 0-105, lower scores are better) follow-up: range 12 weeks to 26 weeks	1278 (4 RCTs)	⊕◯◯◯ Very low[b,d,e]	-	The mean MLWHF change score was 47.0 and the final score was in one study was 3.0	MD 10.04 lower (18.31 lower to 1.78 lower)
Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (change scores; score range 0-100, higher scores are better) follow-up: range 24 weeks to 52 weeks	769 (4 RCTs)	⊕⊕⊕◯ Moderate[b]	-	The mean KCCQ OSS change from baseline was 2.02	MD 5.72 higher (3.18 higher to 8.26 higher)
Kansas City Cardiomyopathy Questionnaire (clinical summary score; score range 0-100, higher scores are better) follow-up: mean 24 weeks	760 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	-	The mean KCCQ clinical summary score change from baseline was 4.9	MD 5.1 higher (2.72 higher to 7.48 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with IV iron supplementation
EQ-5D index score (change scores; score range -0.59 to 1, higher scores are better) follow-up: range 24 weeks to 52 weeks	2716 (4 RCTs)	⊕◯◯◯ Very low[b,e]	-	The mean EQ-5D index score change from baseline was 0.45	MD 0.03 higher (0 lower to 0.06 higher)
EQ-5D-VAS (change scores; range 0-100, higher scores are better) follow-up: range 24 weeks to 52 weeks	673 (2 RCTs)	⊕⊕⊕⊕ High	-	The mean EQ-5D-VAS change from baseline was 2.4	MD 3.97 higher (1.51 higher to 6.42 higher)
Unplanned hospitalisation or visits (all-cause) (HR) follow-up: 52 weeks	301 (1 RCT)	⊕⊕⊕◯ Moderate[b]	HR 0.71 (0.45 to 1.12)	Not estimable	Not estimable
Unplanned hospitalisation or visits (all-cause) (rate ratio) follow-up: range 24 weeks to 52 weeks	760 (2 RCTs)	⊕⊕⊕◯ Moderate[b]	Rate ratio 0.66 (0.49 to 0.90)	410 per 1,000 person years	139 fewer per 1,000 person years (209 fewer to 41 fewer)[f]
Unplanned hospitalisation or visits (all-cause) (dichotomous) follow-up: range 18 weeks to 52 weeks	835 (4 RCTs)	⊕⊕◯◯ Low[b,c]	RR 0.66 (0.48 to 0.89)	220 per 1,000	75 fewer per 1,000 (115 fewer to 24 fewer)
Unplanned hospitalisation or visits (heart failure related) (HR) follow-up: 52 weeks	301 (1 RCT)	⊕⊕⊕◯ Moderate[b]	HR 0.39 (0.19 to 0.81)	Not estimable	Not estimable
Unplanned hospitalisation or visit (heart failure related) (rate ratio) follow-up: range 24 weeks to 52 weeks	3999 (4 RCTs)	⊕◯◯◯ Very low[b,c,e,g]	Rate ratio 0.62 (0.35 to 1.09)	215 per 1,000 person years	82 fewer per 1,000 person years (140 fewer to 19 more)[g]
Unplanned hospitalisation or visits (heart failure related) (dichotomous) follow-up: range 12 weeks to 52 weeks	822 (6 RCTs)	⊕◯◯◯ Very low[b,c,e]	RR 0.45 (0.18 to 1.14)	88 per 1,000	48 fewer per 1,000 (72 fewer to 2 more)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with IV iron supplementation
Improvement in exercise tolerance – 6-minute walk test (change scores and final values, higher scores are better) follow-up: range 18 weeks to 52 weeks	5308 (8 RCTs)	⊕⊕◯◯ Low[e]	-	The mean 6-minute walk distance change from baseline was -8.6 and mean final value was 301 metres	MD 25.44 higher (10.22 higher to 40.67 higher)
Improvement in exercise tolerance – peak VO2 [ml/kg/min] (change scores and final values, higher scores are better) follow-up: range 12 weeks to 24 weeks	176 (3 RCTs)	⊕⊕◯◯ Low[b,h]	-	The mean peak VO2 change from baseline was -0.6 and the final value in one study was 12.9 ml/kg/min	MD 1.77 higher (1 higher to 2.54 higher)
Haemoglobin in anaemic patients [g/dL] (change scores and final values, higher scores are better) follow-up: range 18 weeks to 52 weeks	1131 (5 RCTs)	⊕◯◯◯ Very low[b,e,i]	-	The mean haemoglobin change from baseline in in anaemic patients was 0.5 g/dL and the mean final value was 11.7 g/dl	MD 0.89 higher (0.44 higher to 1.35 higher)
Withdrawal due to drug-related adverse events follow-up: 52 weeks	39 (1 RCT)	⊕⊕◯◯ Low[b]	RR 3.50 (0.40 to 30.77)	48 per 1,000	119 more per 1,000 (29 fewer to 1,418 more)
Hypophosphataemia follow-up: 6 months	127 (1 RCT)	⊕⊕⊕◯ Moderate[a]	RR 5.60 (2.68 to 11.67)	103 per 1,000	474 more per 1,000 (173 more to 1,098 more)
Anaphylaxis/hypersensitivity follow-up: 24 weeks to 52 weeks	760 (2 RCTs)	⊕⊕⊕◯ Moderate[j]	Risk difference 0.00 (-0.01 to 0.01)	0 per 1,000	0 more per 1,000 (10 fewer to 10 more)[k]

CI: confidence interval; EQ-5D: EuroQoL 5-dimensions questionnaire; EQ-5D VAS: EuroQoL 5-dimensions questionnaire visual analogue scale; HR: Hazard ratio; IV: Intravenous; KCCQ OSS: Kansas City Cardiomyopathy Questionnaire overall summary score; MD: Mean difference; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; RCT: Randomised controlled trial; RR: Relative risk; VO2: Volume of oxygen consumption

a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: dose interruptions occurred in 564 participants (18.4%) and use of intravenous iron occurred outside the trial protocol in 31 participants in the intervention group and 104 participants in the placebo arm.

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x control group SD where no baseline values given) for continuous outcomes; MLWHFQ MID is 5; KCCQ MID is 5; EQ5D MID is 0.03; EQ VAS MID is 7.825; 6 minute walk test MID is 45.4; peak VO2 MID is 1.295; haemoglobin MID is 0.61.
c. Downgraded by 1 increment for indirectness due to the results being reported as number of events rather than in time-to-event format.
d. Downgraded by 1 increment for risk of bias due to concerns that varied between trials, including deviations from intended interventions, participants being aware of the assigned intervention, and lack of information about selection biases.
e. Downgraded by 1 increment if I2 41-60% and 2 increments if I2 >60%.f. Absolute difference calculated based on total event rates reported in the papers and total patient years of follow-up (assuming all patients completed follow-up, as person years not reported in all trials).
g. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies for reasons that varied between the trials, including no information provided regarding the allocation concealment in one trial and deviations from the intended intervention in another.
h. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies for reasons that varied between trials, including no pre-specified plan noted in one trial and participants being aware of the assigned intervention in another.
i. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies for reasons that varied between trials, including no pre-specified plan, participants being aware of the assigned intervention, deviations from the intended interventions, and unclear allocation concealment.
j. Downgraded by 1 increment for imprecision due to sample size being greater than 70, but less than 350.j. Absolute risk calculated from risk difference

Table 4: Clinical evidence summary: Intravenous iron versus placebo or usual care (over 12 months)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with IV iron
All-cause mortality (time-to-event) Follow-up: 1.9 years to 3 years	5307 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	HR 0.92 (0.83 to 1.03)	Not estimable	Not estimable
All-cause mortality (dichotomous) Follow-up: 1.9 years to 3 years	5347 (4 RCTs)	⊕⊕◯◯ Low[b,c]	RR 0.94 (0.86 to 1.03)	259 per 1,000	16 fewer per 1,000 (36 fewer to 8 more)
Cardiovascular mortality (time-to-event) Follow-up: 2.7 to 3 years	2242 (2 RCTs)	⊕⊕◯◯ Low[c,d]	HR 0.84 (0.68 to 1.03)	Not estimable	Not estimable
Cardiovascular mortality (dichotomous) Follow-up: 1.9 years to 3 years	5347 (4 RCTs)	⊕⊕◯◯ Low[b,c]	RR 0.88 (0.78 to 0.99)	181 per 1,000	22 fewer per 1,000 (40 fewer to 2 fewer)
Quality of Life: Minnesota Living with Heart Failure (change values) (range from 0 to 105, lower scores are better) Follow-up: 2.7 years	1137 (1 RCT)	⊕⊕◯◯ Low[c,d]	-	The mean MLWHF score was 42.7	MD 2.57 lower (6.73 lower to 1.59 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with IV iron
Quality of Life: EQ-5D index score (final values) (range from -0.59 to 1, higher scores are better) Follow-up: 2.7 years	1137 (1 RCT)	⊕⊕◯◯ Low[c,d]	-	The mean EQ-5D score was 0.55	MD 0.01 higher (0.03 lower to 0.05 higher)
Quality of Life: EQ-5D visual analogue scale (final values) (range: 0-100, higher scores are better) Follow-up: 2.7 years	1137 (1 RCT)	⊕⊕⊕◯ Moderate[d]	-	The mean EQ-5D VAS score was 59.4	MD 0.54 higher (2.86 lower to 3.94 higher)
Unplanned hospitalisations (all-cause; time-to-event) Follow-up: 2.7 years	1137 (1 RCT)	⊕⊕◯◯ Low[c,d]	HR 0.91 (0.79 to 1.05)	Not estimable	Not estimable
Unplanned hospitalisation (all-cause; rate ratio) Follow-up: 5 years	40 (1 RCT)	⊕⊕⊕◯ Moderate[e]	Rate ratio 0.15 (0.05 to 0.42)	270 per 1,000 person years	229 fewer per 1,000 person years (256 fewer to 157 fewer)[f]
Unplanned hospitalisations (all-cause; dichotomous) Follow-up: 2.7 years	1137 (1 RCT)	⊕◯◯◯ Very low[b,d,g]	RR 0.95 (0.87 to 1.03)	651 per 1,000	33 fewer per 1,000 (85 fewer to 20 more)
Unplanned hospitalisations (all-cause; dichotomous) Follow-up: 5 years	40 (1 RCT)	⊕◯◯◯ Very low[b,e,g]	RR 0.24 (0.10 to 0.58)	850 per 1,000	646 fewer per 1,000 (765 fewer to 357 fewer)
Unplanned hospitalisation (heart failure-related; rate ratio) Follow-up: 2.7 to 3 years	2242 (2 RCTs)	⊕⊕◯◯ Low[c,d]	Rate ratio 0.80 (0.66 to 0.97)	258 per 1,000 person years	52 fewer per 1,000 person years (88 fewer to 8 fewer)[h]
Unplanned hospitalisation (heart failure-related; dichotomous) Follow-up: 2.7 years	3065 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	RR 0.99 (0.87 to 1.13)	230 per 1,000	2 fewer per 1,000 (30 fewer to 30 more)
Unplanned hospitalisation (heart failure-related; dichotomous) Follow-up: 5 years	40 (1 RCT)	⊕◯◯◯ Very low[b,e,g]	RR 0.19 (0.06 to 0.54)	800 per 1,000	648 fewer per 1,000 (752 fewer to 368 fewer)
Improvement in exercise tolerance (6-minute walk test; final scores, higher scores are better)	193 (1 RCT)	⊕◯◯◯ Very low[c,i]	-	The mean 6MWD was 288.8 metres	MD 35.9 lower (74.41 lower to 2.61 higher)

Outcomes Follow-up	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo or usual care	Risk difference with IV iron
Follow-up: 2.7 years					
Withdrawal due to drug-related adverse event Follow-up: 56 weeks	301 (1 RCT)	⨁⨁◯◯ Low[c]	RR 0.74 (0.39 to 1.42)	126 per 1,000	33 fewer per 1,000 (77 fewer to 53 more)
Anaphylaxis/ Hypersensitivity Follow-up: 1.9 years	3065 (1 RCT)	⨁⨁⨁◯ Moderate[a]	Peto OR 7.41 (1.28 to 42.84)	0 per 1000	0 more per 1,000 (0 fewer to 10 more)[j]
Hospitalisation for infection Follow-up: 2.7 years	1137 (1 RCT)	⨁⨁◯◯ Low[c,d]	RR 0.70 (0.47 to 1.04)	93 per 1000	28 fewer per 1,000 (from 49 fewer to 4 more)
Hospitalisation for sepsis Follow-up: 1.9 years	3065 (1 RCT)	⨁⨁◯◯ Low[a,c]	RR 1.62 (0.81 to 3.22)	8 per 1,000	5 more per 1,000 (2 fewer to 19 more)
Atrial fibrillation Follow-up: 2.7 years	1127 (1 RCT)	⨁◯◯◯ Very low[c,d]	RR 1.65 (0.69 to 3.95)	14 per 1,000	9 more per 1,000 (4 fewer to 42 more)

6MWT: 6-minute walk test; CI: confidence interval; EQ-5D: EuroQoL 5-dimensions questionnaire; EQ-5D VAS: EuroQoL 5-dimensions questionnaire visual analogue scale; HR: Hazard ratio; IV: Intravenous; MD: Mean difference; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; OR: Odds ratio; RCT: Randomised controlled trial; RR: Relative risk; VO2: Volume of oxygen consumption

a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: dose interruptions occurred in 564 participants (18.4%) and use of intravenous iron occurred outside the trial protocol in 31 participants in the intervention group and 104 participants in the placebo arm.

b. Downgraded by 1 increment due to reporting as number of events.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes; MLWHFQ MID is 5; EQ5D MID is 0.03; EQ VAS MID is 11.9; 6 minute walk test MID is 68.25.

d. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context

e. Downgraded by 1 increment for risk of bias due to unclear allocation concealment.

f. Absolute difference calculated based on total event rates reported in the papers and total patient years of follow-up (assuming all patients completed follow-up, as person years not reported).

g. Downgraded by 2 increments for inconsistency due to unexplained heterogeneity (studies not pooled).

h. Absolute difference calculated based total event rates reported in the papers and total patient years of follow-up.

i. Downgraded by 2 increments for risk of bias due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context; and missing outcome data.

j. Absolute effect calculated from risk difference.

1.1.6.2. Sensitivity analysis: TSAT subgroups

Table 5: Clinical evidence summary: Intravenous iron versus placebo: TSAT subgroup analysis (3-12 months)

Outcome and strata	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with IV iron
Minnesota Living with Heart Failure (final scores) (range from 0 to 105, lower scores are better)					
TSAT <20%	841 (1 RCT) Follow-up: 4 months	⊕⊕◯◯ Low[a,b]	-	Mean final MLwHF score was 41.7	MD 3.0 lower (7.19 lower to 1.19 higher)
TSAT ≥20%	269 (1 RCT) Follow-up: 4 months	⊕⊕◯◯ Low[a,b]	-	Mean final MLwHF score was 35.0	MD 2.0 lower (7.97 lower to 3.97 higher)
Improvement in exercise tolerance: 6-minute walk test (final scores, higher scores are better)					
TSAT <20%	358 (2 RCTs) Follow-up: 4 to 12 months	⊕⊕⊕◯ Moderate[a]	-	Mean final 6MWD was 267 metres	MD 16.74 metres higher (7.94 lower to 41.41 higher)
TSAT ≥20%	156 (2 RCTs) Follow-up: 4 to 12 months	⊕⊕◯◯ Very low[a,b,c]	-	Mean final 6MWD was 324 metres	MD 3.84 metres higher (64.11 lower to 71.78 higher)

6MWT: 6-minute walk test; CI: confidence interval; IV: Intravenous; MD: Mean difference; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; RCT: Randomised controlled trial; TSAT: Transferrin saturation
a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes; MLWHFQ MID is 5; 6 minute walk test MID is 61.79.
c. Downgraded by 2 increments for inconsistency with I^2 >60%.

Table 6: Clinical evidence summary: Intravenous iron versus placebo: TSAT subgroup analysis (>12 months)

TSAT level	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with IV iron
All-cause mortality (time-to-event)					
TSAT <20%	841 (1 RCT) Follow-up: 2.7 years	⊕⊕◯◯ Low[a,b]	HR 0.92 (0.73 to 1.16)	Not estimable	Not estimable
TSAT ≥20%	269 (1 RCT) Follow-up: 2.7 years	⊕◯◯◯ Very low[a,b]	HR 1.30 (0.82 to 2.06)	Not estimable	Not estimable
All-cause mortality (dichotomous)					
TSAT <20%	858 (1 RCT) Follow-up: 2.7 years	⊕◯◯◯ Very low[a,b,c,d]	RR 0.88 (0.67 to 1.16)	357 per 1,000	43 fewer per 1,000 (118 fewer to 57 more)
TSAT ≥20%	269 (1 RCT) Follow-up: 2.7 years	⊕◯◯◯ Very low[a,b,d]	RR 1.18 (0.80 to 1.74)	258 per 1,000	46 more per 1,000 (52 fewer to 191 more)
Cardiovascular mortality (time-to-event)					
TSAT <20%	841 (1 RCT) Follow-up: 4 months	⊕⊕◯◯ Low[a,b]	HR 0.85 (0.64 to 1.13)	Not estimable	Not estimable
TSAT ≥20%	269 (1 RCT) Follow-up: 2.7 years	⊕◯◯◯ Very low[a,b]	HR 1.03 (0.59 to 1.81)	Not estimable	Not estimable
Cardiovascular mortality (dichotomous)					
TSAT <20%	858 (1 RCT) Follow-up: 2.7 years	⊕◯◯◯ Very low[a,b,d]	RR 0.85 (0.66 to 1.09)	255 per 1,000	38 fewer per 1,000 (87 fewer to 23 more)
TSAT ≥20%	269 (1 RCT) Follow-up: 4 months	⊕◯◯◯ Very low[a,b,d]	RR 0.95 (0.57 to 1.57)	188 per 1,000	9 fewer per 1,000 (81 fewer to 107 more)

TSAT level	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with IV iron
Hospitalisation for infection (time-to-event)					
TSAT <20%	841 (1 RCT) Follow-up: 2.7 years	⨁◯◯◯ Very low[a,b]	HR 0.70 (0.53 to 0.93)	Not estimable	Not estimable
TSAT ≥20%	269 (1 RCT) Follow-up:2.7 years	⨁◯◯◯ Very low[a,b]	HR 1.13 (0.69 to 1.86)	Not estimable	Not estimable

CI: confidence interval; HR: Hazard ratio; IV: Intravenous; MD: Mean difference; RCT: Randomised controlled trial; RR: Relative risk; TSAT: Transferrin saturation

a. *Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context.*

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes.

c. Downgraded by 1 increment if I^2 41-60% and 2 increments if I^2 >60%.

d. Downgraded by 1 increment for indirectness due reporting numbers of events.

See Appendix F for full GRADE tables.

1.1.7. Economic evidence

A single search was performed to identify economic evaluations of relevance to any of the questions in this guideline update that had been published since the last guideline. See the health economic review protocol in Appendix A and the literature search strategy in Appendix B. Further studies were identified through bibliography searching. A further 15 studies included previously in the guideline were re-assessed for applicability and quality.

1.1.7.1. Included studies

There are three economic studies included in this review question. These are summarised in the health economic evidence profile below (Table 7**)** and the health economic evidence tables in Appendix H.

1.1.7.2. Excluded studies

Nine economic studies relating to this review question were identified but were excluded. Three of these studies were selectively excluded due to the availability of more applicable evidence. These are listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in Appendix G.

1.1.8. Summary of included economic evidence

Table 7: Health economic evidence summary table: IV iron versus no iron treatment for iron deficiency in chronic heart failure

Study	Applicability and limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gutzwiller 2012 (United Kingdom)	Directly applicable[1] Potentially serious limitations[2]	• Within-trial analysis of FAIR-HF RCT Comparators: • No iron treatment • Iron repletion with ferric carboxymaltose IV bolus injection • 24 week follow-up	£149	0.037 QALYs	IV iron vs no iron treatment £3,977 per QALY gained	Probability Intervention 2 cost-effective (£20K/30K threshold): 99.66%/99.68% Univariate and probabilistic sensitivity analysis undertaken. Frequency and duration of hospitalisation, QALY difference, and cost of hospital day were the most influential parameters. None of the parameters tested resulted in an ICER above £20,000 per QALY gained.
Hofmarcher 2018 (Denmark, Finland, Norway and Sweden)	Partially applicable[3] Potentially serious limitations[4]	• Within-trial analysis of CONFIRM-HF Comparators: • No iron treatment • Iron repletion with IV administered ferric carboxymaltose • 52 week follow-up	Denmark -€298 -£228 Finland -€36 -£28 Norway -€484 -£371 Sweden -€379 -£290	0.050 QALYs	IV iron dominated no treatment in all four countries	Univariate analysis undertaken by changing the assumptions around what visit costs should be included for the cost of IV iron and different definitions of the rate of hospitalisations. IV iron remains cost effective based on an ICER of £20,000/QALY under all scenarios across all four countries.

Study	Applicability and limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Rognoni 2019 (Italy)	Partially applicable[5] Potentially serious limitations[6]	• Five health state Markov model, based on the four NYHA classes and death, with a one-week cycle length and 52 week time horizon using pooled data across 4 trials CONFIRM-HF, FIND-CKD trial, EFFICACY-HF and FAIR-HF as reported by Theidel 2017 (German setting) Comparators: • No iron treatment • Iron repletion with IV administered ferric carboxymaltose • 52 week follow-up	-€403 -£384	0.061	IV iron is dominant compared with no iron treatment	Deterministic sensitivity analysis: Multiple one-way scenarios were performed on resource use and costs. Variations in the weekly rate of hospitalisation for CHF was found to be the main driver of the results. Probabilistic sensitivity analysis showed IV iron to be dominant in all simulations.

Abbreviations: CHF: Chronic heart failure; FCM: ferric carboxymaltose; ICER=incremental cost-effectiveness ratio; IV: Intravenous; QALY=Quality-adjusted life-year; RCT=randomised controlled trial
1. NHS perspective. The FAIR-HF trial did not include British participants, but was mostly performed in European countries with a predominantly Caucasian population. This is unlikely to change the conclusions of cost-effectiveness.
2. Short time horizon may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators.
3. Nordic country perspective, utilities may not have been estimated in the most robust manner
4. Short time horizon may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators, combines data from FAIR-HF trial with different IV iron dosage strategies to inform utility estimates.
5. Italy healthcare perspective, which differs to the UK NHS.
6. Short time horizon, which may not capture full costs and effects of the intervention. Utilities based on NYHA class and does not consider utility decrements for hospitalisations

1.1.9. Economic model

This area was not prioritised for new cost-effectiveness analysis. No original economic modelling was completed for this review question.

1.1.10. Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 8: Unit costs of iron therapy

Resource	Unit Cost	Source
Ferric carboxymaltose 1000mg/20ml (50mg/1ml)	£154.23	BNF 2025
Ferric carboxymaltose 500mg/10ml (50mg/1ml)	£95.50	BNF 2025
Ferric derisomaltose (1000mg/10ml)	£169.50	BNF 2025
Ferric derisomaltose (500mg/5ml)	£84.75	BNF 2025
Ferric derisomaltose (100mg/1ml)	£16.95	BNF 2025

These costs were updated from the previous guideline update NG106 (2018). Costs were estimated based on drug costs, staff time, clinical space and transport based on the treatment protocol of the published clinical trials. Drug costs and staff time have been updated based on the latest published sources. Staff time was assumed to be the same as assumed in the 2018 update, including the assumption 30 minutes observation time was required for all regimens.

Staff costs are based on a band 6 nurse at a rate of £58 per hour (including qualifications) observing 2 patients at a time, PSSRU (2023).

The following costs have not been updated and were taken from Wilson (2013) cost analysis for pre-dialysis patients conducted at Kings college hospital.

- Clinic space - £5 per patient hour
- Clerical staff £3.28 per visit
- Transporting a patient to hospital: £45 for a return trip, it is assumed 10% of patients will require transport)
- Disposables were assumed to cost £5 per visit and included: Canula, needles, syringes, dressing, sodium chloride solution and IV giving set.

The doses reported in the clinical trials included in the clinical review were used to estimate the unit costs of intravenous iron.

- FAIR-HF:
    - Mid-point between the minimum and maximum number of visits (13 x 200mg) = £1,103
- CONFIRM-HF and EFFECT-HF
    - Mean dose based on 2 visits assuming 1000mg vial in the first visit followed by a follow up dose of 500mg vial in the second visit = £358

    - CONFIRM-HF mean dose 1500mg, EFFECT-HF mean dose 1204mg

- IRONMAN:

    - 2 doses of 1000mg across 2 visits = £464
      This is based on the mode (most frequent value) number of visits, since we were unable to calculate an exact average from how the number of visits was reported.

    - Based on a mean total dosage over the first year of 1978mg

- HEART-FID

    - Assume 2 doses of 1000mg across 2 visits based on a cumulative dose of 1809mg in year 1 = £417

Table 9: Cost analysis (list price)

Trial	Regimen				Drug cost (£)		Nurse time per infusion, minutes			Nurse cost (£) (b)		Other			Total (£)
	Drug	Iron mg/ vial	Vial/ visit	No. visits(d)	Cost per vial (a)	Total drug cost	Preparation	Infusion	Observation	Cost per visit	Total cost	Consumables	Transport	Admin time (c)	
FAIR-HF	Ferric Carboxymaltose	100	2	13	19	497	15	2	30	30	390	65	59	94	1103
CONFIRM-HF/EFFECT-HF	Ferric Carboxymaltose	1000	1	1	154	154	15	15	30	36	36	5	5	8	208
CONFIRM-HF/EFFECT-HF	Ferric Carboxymaltose	500	1	1	96	96	15	15	30	36	36	5	5	8	150
HEART-FID	Ferric Carboxymaltose	1000	1	2	154	308	15	15	30	36	73	10	9	17	417
IRONMAN	Ferric derisomaltose	1000	1	2	170	339	15	30	30	44	87	10	9	19	464

(a) BNF, October 2024
(b) PSSRU (2024) Unit costs of health and social care 2023
(c) Admin staff time and clinic space
(d) Over the trial follow-up period, although most people can achieve iron repletion after a single visit. Over the course of the trials, people can relapse and require more visits

1.1.11. Economic evidence statements

Three published cost-utility analyses were identified (Gutzwiller 2012, Hofmarcher 2018 and Rognoni 2019) comparing IV iron with no treatment.

- Two analysis (Hofmarcher 2018 and Rognoni 2019) based on CONFIRM-HF clinical trials found that IV iron was dominant over a 52 week time horizon. These were both partially applicable as conducted with a Scandinavian or Italian healthcare perspective.
- A directly applicable analysis conducted from the UK NHS perspective found that IV iron was cost-effective with a cost per QALY of £3,977 over a 24-week time horizon.

All the included studies were deemed as having potentially serious limitations due to the short time horizon.

1.1.12. The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

The committee considered all-cause mortality, cardiovascular mortality, health-related quality of life, unplanned hospitalisation, improvement in exercise, haemoglobin changes in anaemic patients, hypophosphatemia, anaphylaxis/ hypersensitivity, hospitalisation due to infection and withdrawal due to drug-related adverse events. For the purposes of decision making, all outcomes were rated as critical. For the current review, there were no available outcome data for extravasation.

Outcomes on all-cause mortality, cardiovascular mortality, and unplanned hospitalisation or visits (all-cause or heart failure-related) were preferred as time-to-event outcomes when reported in the papers. As these were not always reported as time-to-event values, the outcomes expressed as dichotomous values were also included. However, these outcomes were then downgraded once for indirectness.

Hypophosphatemia is relevant for ferric carboxymaltose but not for other IV iron formulations.

1.1.12.2. The quality of the evidence

Using the GRADE criteria, the confidence in the evidence ranged from high to very low. The evidence was commonly downgraded due to imprecision and risk of bias. For risk of bias this was often due to limited reporting of allocation concealment and concerns regarding deviations from the intended interventions. In terms of imprecision, unexplained heterogeneity defined by an I^2 value >40%, was present in the 3-12 month analysis for the following outcomes: Minnesota Living With Heart Failure, EQ-5D index score, heart failure and all cause hospitalisation (rate ratio), heart failure hospitalisation (dichotomous), 6-minute walk distance and change in haemoglobin. These factors reduced the committee's confidence in the findings.

1.1.12.3. Benefits and harms

Overall analysis results

One primary comparison was presented in the evidence: all intravenous iron formulations were grouped together and compared to placebo.

The committee noted that the main benefits of IV iron were seen for exercise tolerance and quality of life in the first year. Clinically important benefits were noted in the Minnesota Living with Heart Failure quality of life measure, the Kansas City Cardiomyopathy Questionnaire

overall summary score and clinical summary score, EQ-5D and improvement in exercise tolerance based on the 6-minute walk distance and peak VO_2 at 3-12 months.

The consistent improvement in these, with EQ-5D visual analogue scale being the only exception, was agreed to be of high importance to patients. People with heart failure who are often impacted by breathlessness, exhaustion and other reasons for reduced exercise capacity, which have implications for the ability to stay independent. Therefore, the evidence supports the use of IV iron to enable patients to achieve the best possible quality of life.

The committee noted that the lack of clear benefit for mortality was in line with their expectations, but were encouraged by the trend towards reduced mortality. They discussed the visual heterogeneity that was masked by imprecision. However, as the two studies that showed heterogeneity were small and had insufficient power to investigate this outcome this was agreed not to be important. Additionally, there was reassuring evidence for reduced hospitalisation, particularly in total heart failure related hospitalisations, where a clinically important reduction was seen. This evidence further supports a recommendation for IV iron. However, the committee's confidence in this evidence was reduced by inconsistency and particularly by the small benefit for hospitalisations seen in the largest trial (HEART-FID).

There was limited reporting of adverse events in the included studies, and most of the outcome estimates were too imprecise to inform recommendations. The large increased risk of hypophosphatemia in one small sub-study with ferric carboxymaltose (including less than 5% of the original trial population) was discussed. The committee were aware of the MHRA safety alert and SPC label update when discussing the clinical significance of IV iron induced hypophosphatemia attributable to ferric carboxymaltose. However, the evidence presented was not robust enough to draw conclusions and the committee noted that transient reductions in serum phosphate after IV iron would be expected to resolve spontaneously without resulting in adverse events in most cases.

The committee examined the data comparing outcomes at 3-12 months with those at >12 months and noted that, for most outcomes, there was no clear difference in effect estimates between the time points. However, there were less data at the longer follow-up time and therefore more uncertainty. There was some indication based on limited evidence that the benefits of IV iron may wane over time, and it was discussed that repeated doses may be required to maintain the benefit.

Heterogeneity

Several outcomes were informed by studies that had diverging results, with heterogeneity that could not be resolved by pre-specified subgroup analyses. The committee discussed subgroup data based on anaemia status, which suggested that the benefit in those with anaemia may be greater than those without. However, these analyses were not robust enough to be conclusive due to lack of available data.

Although it was agreed when developing the protocol that different iron dosing schedules would be pooled to maximise power in the meta-analysis, there were important differences between the trials in IV iron dosing that could have impacted on the effects. This could have a significant impact on the longevity of any benefits, which may require repeated intervention. However, despite the limitations around heterogeneity the pooled estimates still provide reasonable evidence of benefit in the first 12 months. The committee were aware of the varied IV iron schedules used in the trials but did not pre-specify this for subgroup analysis as there was no clear way of grouping the different regimens. The committee discussed whether any further guidance was needed about IV iron dosing schedules, however they agreed that each formulation has clear instructions on how to calculate the dose and that following these should be standard practice.

Population

The committee discussed what population IV iron should be recommended for. It was agreed that this would need to reflect the characteristics of the participants included in the clinical trials that informed the effectiveness estimates. Therefore, the recommendation for the use of IV iron is restricted to people with reduced ejection fraction and iron deficiency as defined by either TSAT <20%, which is the preferred measure due to being most accurate, or serum ferritin <100 ng/mL. In the experience of the committee, standard practice in this population should be to request both ferritin and TSAT at the same time. It was noted that ferritin is not always measured and has a minimum request interval (as this is uninformative if redone within 90 days). Therefore, if remeasurement is required within 90 days, TSAT can be requested.

The committee acknowledged the limitation of the iron deficiency definition including ferritin, which is an acute phase reactant and can be increased for other reasons such as infection or aging (due to the associated inflammatory response), potentially making it an unreliable marker of iron deficiency.

As only one small trial was available for the mildly reduced or preserved ejection fraction population, a research recommendation was made for this group to encourage further evidence-generation (Appendix K).

Chronic kidney disease (CKD)

The committee discussed that CKD patients often have high ferritin but also represent a substantial proportion of CHF with reduced ejection fraction patients. In CKD, IV iron is offered if ferritin <100 or TSAT <20%; both are measured and IV iron administered unless both are above the threshold.

TSAT subgroup data

The committee discussed the data that showed outcomes separately for TSAT subgroups. They observed that the most benefit of IV iron was seen in the TSAT 15-20% group, with less benefit for those with TSAT over 20% and under 15%. However, the number of participants in each of the subgroups were relatively small and only one study contributed data to each subgroup in most cases. Therefore, there was insufficient evidence to support such narrow eligibility criteria in the recommendation. It was discussed that the lack of benefit in those with TSAT <15% may not be because the IV iron supplementation is not effective, but rather because the outcome data are confounded by other pathologies.

Testing for iron status

The committee acknowledged that to assess the need for intravenous iron supplementation, people will need to have their iron status assessed. Therefore, they made a recommendation for the appropriate blood tests to be done, to include TSAT, serum ferritin and haemoglobin.

The committee highlighted the importance of considering alternative causes of iron deficiency anaemia when it is identified, but also the need to get the correct balance against over-investigating. They noted that investigations should only be done when true iron deficiency is present, and that alternative diagnoses to consider would include sepsis and pneumonia. A recommendation was made to ensure that consideration is given to investigation of alternative causes in cases where the iron deficiency anaemia may not be due to the chronic heart failure.

Summary

The committee agreed that there is sufficient evidence for people with reduced ejection fraction to support recommendations for assessing iron status and giving intravenous iron

supplementation when iron depletion is present based on the improvement in quality of life and exercise tolerance. However, the strength of the evidence is not currently sufficient to support strong recommendation for IV iron supplementation, therefore they recommended that clinicians consider it.

1.1.12.4. Cost effectiveness and resource use

The committee reviewed the economic evidence for ferric carboxymaltose compared with no treatment.

The only study with a UK perspective by Gutzwiller 2012 had only a 24-week follow up. The committee noted that the treatment regimen used within the FAIR-HF trial, on which the cost-effectiveness analysis is based, is not reflective of what would be seen in clinical practice and the more recent clinical trials. The FAIR-HF trial had between 11-15 treatment visits, whereas in clinical practice, people would receive larger dosages over fewer visit, usually maximum 2, so the expected cost would be lower making IV iron even more cost-effective.

The committee considered two further cost-effectiveness studies with a one-year time horizon and a non-UK healthcare perspective. Both analyses demonstrated IV iron therapy to be cost saving as it both improved quality of life and reduced costs as a result of fewer hospitalisations. These publications were both marked as partially applicable due to the difference in healthcare systems, although it is anticipated that IV therapy treatment would also be cost-effective in the UK setting.

The committee were concerned about the potential resource use associated with IV iron based on the frequency of dosing schedules used within the clinical trials. The clinical trials HEART-FID, CONFIRM-HF, EFFECT-HF and IRONMAN showed that, on average, most people receive two doses of treatment whilst a small proportion may require further doses. The committee expected that people would be seen for a maximum of two visits in clinical practice and considered this feasible.

The committee raised concerns on whether IV treatment would remain cost-effective in the long-term given that the cost-effectiveness evidence is restricted to one year. The committee highlighted that the HEART-FID found that IV iron had the most significant impact within the first three months, with its benefits largely disappearing after one year. However, the committee anticipated that the improvement in quality of life due to exercise tolerance and reduced hospitalisation, would likely offset the additional costs of treatment, which are usually only short term. The committee discussed that hospitalisation can be one of the greatest predicters of a patient's prognosis so any reduction in hospitalisation is likely to lead to longer term benefits.

The committee noted that only ferric carboxymaltose was included in the cost-effectiveness evidence presented. However, the clinical evidence shown in the IRONMAN study demonstrated similar efficacy for ferric derisomaltose. The unit costs based on list prices are comparable but ferric carboxymaltose can cause hypophosphatemia which is not expected to occur with ferric derisomaltose. Based on these discussion the committee expected that ferric derisomaltose would be another cost-effective option compared to no treatment.

Although IV iron has not been recommended by NICE before for people with heart failure, the European Society of Cardiology guidelines have already resulted in checking of iron status and IV iron prescription. Therefore, there is not expected to be a significant resource impact even a large proportion of patients with CHF also have iron deficiency.

The committee recommended a set of tests to identify people with anaemia in need of the treatment. Some concerns were raised at the additional resources required to provide the tests as it is not current practice to test for iron deficiency for people with HFrEF in primary

care. However, the committee agreed that it is important to target iron therapy on those patients that will benefit the most.

Overall, the committee discussed some concerns over the long-term efficacy of IV iron and the potential resource implications. Nevertheless, the committee concluded that the improvement in quality of life and reduction in hospitalisations would offset the additional costs, making IV iron cost-effective.

1.1.12.5. Other factors the committee took into account

To receive a TSAT level it is necessary to request 'iron studies' or an 'iron profile' test. It was agreed there may be a need to raise awareness of this.

The committee noted that the TSAT subgroup data came largely from the IRONMAN trial and that not all participants had TSAT levels measured. However, it was agreed that those with missing TSAT levels was low and balanced across the randomised groups – 15 missing in each group (2.6%).

It was discussed that after age 80 haemoglobin levels fall, so 'normal' levels, as for ferritin, are different in this cohort. However, this means they will not be disadvantaged as they would be more likely to be below the recommended threshold. Total serum iron and TSAT was noted to be the most accurate measurement for older adults. The evidence-base for IV iron to treat patients with HFrEF and iron deficiency was exclusively obtained in patients with haemoglobin range between 90 g/l and either 130-135 g/l for women, or 140-150 g/l for men. Thus the recommendation treatment with IV iron to these patients is restricted to the haemoglobin being within that range (for safety).

The committee considered where IV iron fits along the pathway with other pharmacological treatments for chronic heart failure with reduced ejection fraction. It was agreed that, when indicated, IV iron should be considered without a requirement for people to be optimised on the maximum tolerated doses of other pharmacological interventions.

When discussing the dosing regimes, it was also noted that the schedules including repeated doses used in the trials may not be feasible in clinical practice and do not reflect the current standard care, with a repeat dose generally only being given if symptoms are worsening. For example, repeated clinic attendance may not be practical for that often for older and/or frail patients and IV iron cannot currently be administered outside of a clinical setting because of the potential risks of extravasation or anaphylaxis, especially for the first dose.

Although the focus of the evidence review was not the frequency of testing, the committee discussed that this would depend on individual patient factors. They agreed that iron status and haemoglobin should be added to the clinical review.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.5 to 1.4.7.

1.1.13. References

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Appendices

Appendix A Review protocols

A.1 Review protocol for IV iron therapy for chronic heart failure

Field	Content
Review title	Intravenous iron therapy for chronic heart failure
Review question	What is the clinical and cost effectiveness of intravenous iron supplementation in adults with chronic heart failure and iron deficiency?
Objective	To update the evidence review on the clinical and cost effectiveness of iron supplementation in people with heart failure and iron deficiency.
Searches	Key papers: IRONMAN: Kalra PR, Cleland JGF, Petrie MC, Thomson EA, Kalra PA, Squire IB, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet 2022;400:2199–209. https://doi.org/10.1016/S0140-6736(22)02083-9 HEART-FID: Mentz RJ, Garg J, Rockhold FW, Butler J, De Pasquale CG, Ezekowitz JA, Lewis GD, O'Meara E, Ponikowski P, Troughton RW, et al; HEART-FID Investigators. Ferric carboxymaltose in heart failure with iron deficiency.N Engl J Med. 2023; 389:975–986. doi: 10.1056/NEJMoa2304968 The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by:

Field	Content
	• Date limitations – from 06.12.2017 (date of searches in 2018 update) • English language studies • Human studies Other searches: • Inclusion lists of relevant systematic reviews As this is a short update the searches will not be re-run. Committee members will be asked to identify any trials they are aware of that may be published after the search date, and the publication status of these will be checked later in development. NICE evidence surveillance is also active on this topic suite, so any new trials with the potential for a substantial impact on the guideline due to possible requirements to change recommendations, can also be included. Any evidence identified by surveillance that does not have a substantial impact will be added in future update. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Chronic heart failure with reduced ejection fraction
Population	**Inclusion**: • Adults diagnosed with heart failure who also have iron deficiency (defined by either serum ferritin < 100 ng/mL, or serum ferritin between 100-299 ng/mL if iron saturation (TSAT) < 20 %). • Patients stabilised on optimal medical therapy for heart failure (based on prevailing best practice at time of trial). Studies including an indirect population will only be included if ≥80% match the protocol criteria or there are subgroup data for the protocol population. Ongoing treatment after discharge for an acute episode of heart failure will be included. **Exclusion:** • Children • Acute heart failure in hospital • Heart failure due to right heart dysfunction (e.g., pulmonary pre-capillary pulmonary hypertension and primary right ventricular cardiomyopathies) • High output heart failure • Adult congenital heart disease

Field	Content
	• Primary heart valve disease • Acute MI (within 3 months of the event)
Intervention	**Inclusion** • Intravenous iron supplementation, including ferric carboxymaltose. All IV iron formulations will be considered together. **Exclusion** • Oral iron supplementation
Comparator	• Placebo or usual care
Types of study to be included	**Inclusion:** • RCTs • Published systematic reviews of RCTs • Published network meta-analyses (NMAs) and individual participant data meta-analyses (IPDs). **Exclusion:** • Cross-over RCTs
Other exclusion criteria	• Non-English language studies. • Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	This review will partially update NICE guideline NG106.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • All-cause mortality (time-to-event) • CV mortality (time-to-event) • Health-related quality of life (Minnesota Living With Heart Failure (MLWHF), the Kansas City Cardiomyopathy Questionnaire (KCCQ), or any validated score (continuous – change score preferred over final value) • Unplanned hospitalisation or visits (all-cause) (time-to-event; including repeat events when reported) • Unplanned hospitalisation or visits (heart-failure-related) unplanned hospitalisation or visits (time-to-event; including repeat events when reported) • Improvement in exercise tolerance – 6-minute walk test or peak VO_2 (continuous; change from baseline)

Field	Content
	○ Both measures will be extracted where available; if neither is reported, other measures of exercise tolerance/functional capacity will be accepted. • Haemoglobin in anaemic patients (continuous; change from baseline) Adverse events (recorded as the number of people with at least one event, not the total number of events) • Withdrawal due to drug-related adverse events (dichotomous) • Hypophosphataemia (dichotomous) • Extravasation (dichotomous) • Anaphylaxis/hypersensitivity (dichotomous) • Hospitalisation for infection (dichotomous) ○ Sepsis, hospitalisation for pneumonia and infections categorised as serious adverse events will be included in this outcome. • Atrial fibrillation (dichotomous) **Time points for analysis**: • 3-12 months (pool all times ³3 months, taking the closest to 12 months follow-up time from each study if multiple time points are reported within this range); • >12 months Exclude if follow-up <3 months The COMET database was searched for relevant core outcome sets and 2 consensus documents were identified and used to inform the protocol outcomes (https://onlinelibrary.wiley.com/doi/epdf/10.1093/eurjhf/hft095; and https://www.sciencedirect.com/science/article/pii/S2213177919307978?via%3Dihub). **Indirect outcome definitions** • If continuous data are not available, dichotomous outcome data for quality of life scales will be accepted but downgraded for outcome indirectness. For KCCQ this should be based on the threshold of an improvement of 5 points, which is the accepted MID. Only one threshold will be reported per study. Adverse events that are similar to the protocol definitions will be considered for inclusion and, if sufficiently similar, will be included but downgraded for outcome indirectness.

Field	Content
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0)
Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. • For time-to-event outcomes, if sufficient information is provided, hazard ratios will be reported but dichotomous data will also be extracted. Only one measure will be considered for decision making. This will be agreed with the committee taking into account the proportion of studies that report sufficient data to calculate the risk ratio and the hazard ratio, in order to maximise the available pooled data. If there are differences in effect estimates between the two measures, potential reasons for this will be considered in the interpretation of the evidence.

Field	Content	
	• Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 40% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. • The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
Analysis of sub-groups	**Subgroups that will be investigated regardless of heterogeneity** • Iron saturation (TSAT <20% vs TSAT ≥20%) The primary analysis will combine the evidence without stratification for iron saturation, and this subgroup data will also be explored, where possible, as a secondary analysis. **Subgroups that will be investigated if heterogeneity is present**: • Anaemia (present vs absent) • LVEF (preserved vs reduced/mildly reduced)	
Type and method of review	☑	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic

Field	Content		
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	February 2024		
Anticipated completion date	September 2025		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☑	☑
	Piloting of the study selection process	☑	☑
	Formal screening of search results against eligibility criteria	☑	☑
	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail		

Field	Content
	chfiatreatment@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
Review team members	From NICE: Dr Sharon Swain Mrs Eleanor Samarasekera Dr Lisa Miles Ms Annette Chalker Mr David Wonderling Mr Alfredo Mariani Ms Kirsty Luckham Ms Jemma Deane Mr Daniel Davies
Funding sources/sponsor	Development of this systematic review is being funded by NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10405
Other registration details	NA

Field	Content	
Reference/URL for published protocol	NA	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
Keywords	Heart failure; pharmacological; four pillars; ACE inhibitors; sacubitril valsartan; beta-blockers; mineralocorticoid receptor antagonists; SGLT2 inhibitors.	
Details of existing review of same topic by same authors	NA	
Current review status	☐	Ongoing
	☑	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	NA	
Details of final publication	www.nice.org.uk	

CHF: Chronic heart failure; COMET: Core outcome measures in effectiveness trials; EF: Ejection fraction; eGFR: estimated glomerular filtration rate; EPPI: Evidence for Policy & Practice Information Centre; ESC: European society of cardiology; GC: guideline committee; IV: intravenous; LVEF; Left ventricular MI: Myocardial infarction MID: minimally important difference; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; TSAT: Transferrin saturation; VO_2: Volume of oxygen consumption

A.2 Health economic review protocol

	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	Populations, interventions and comparators must be as specified in the clinical review protocol above. Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) Unpublished reports will not be considered unless submitted as part of a call for evidence. Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below. For questions being updated, the search will be run from December 2017, which was the cut-off date for the searches conducted for NICE guideline NG106.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2010, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published after 2010 that were included in the previous guideline will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).{NICE2014} Inclusion and exclusion criteria If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. Where there is discretion

	All questions – health economic evidence
	The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. Setting: UK NHS (most applicable). OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). OECD countries with predominantly private health insurance systems (for example, Switzerland). Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. Health economic study type: Cost–utility analysis (most applicable). Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). Comparative cost analysis. Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. Year of analysis: The more recent the study, the more applicable it will be. Studies published in 2010 or later (including any such studies included in the previous guideline) but that depend on unit costs and resource data entirely or predominantly from before 2010 will be rated as 'Not applicable'. Studies published before 2010 (including any such studies included in the previous guideline) will be excluded before being assessed for applicability and methodological limitations. Quality and relevance of effectiveness data used in the health economic analysis: The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

What is the clinical and cost effectiveness of intravenous iron supplementation in adults with chronic heart failure and iron deficiency?

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review.

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search terms for the population and intervention were compared to the searches for previous NICE guidance (NG106). Modifications were made to these original search strategies for the specifications in the review protocol.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results

- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies could not be applied in this search due to a database problem.

Date limits

A date limit of 1st December 2017 to current was applied, as stated in the review protocol from when searches were conducted for NG106.

Search filters and classifiers

Effectiveness searches

The National Guideline Centre (NGC) systematic review and randomised controlled trial search filters were applied in MEDLINE and Embase.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

The National Guideline Centre (NGC) Quality of Life filter was applied in MEDLINE and Embase strategies.

Key decisions

The effectiveness search strategy was developed to find evidence for the specified population and intervention.

The cost-effectiveness searches used population only terminology.

Searches were adapted to suit different database functionality and were re-run as originally written.

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	4th July 2024	Wiley	Issue 7 of 12, July 2024	1
Cochrane Central Register of Controlled Trials (CENTRAL)	4th July 2024	Wiley	Issue 7 of 12, July 2024	102
Embase	4th July 2024	Ovid	Embase 1974 to 2024 July 03	372
MEDLINE	4th July 2024	Ovid	Ovid MEDLINE(R) ALL 1946 to July 03, 2024	205
Epistemonikos	4th July 2024	Epistemonikos	4/07/2024	153

Re-run search results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Database of Systematic Reviews (CDSR)	9th January 2025	Wiley	Issue 1 of 12, January 2025	0
Cochrane Central Register of Controlled Trials (CENTRAL)	9th January 2025	Wiley	Issue 12 of 12, December 2024	15
Embase	9th January 2025	Ovid	Embase <1974 to 2025 January 07>	55
MEDLINE	9th January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to	26

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
			January 06, 2025>	
Epistemonikos	9th January 2025	Epistemonikos	9/01/2025	45

Search strategy history

Database name: Cochrane Database of Systematic Reviews (CDSR)

Searches		
ID	Search	Hits
#1	MeSH descriptor: [Heart Failure] explode all trees	14584
#2	MeSH descriptor: [Cardiomyopathy, Dilated] this term only	672
#3	MeSH descriptor: [Shock, Cardiogenic] this term only	485
#4	MeSH descriptor: [Ventricular Dysfunction] explode all trees	2918
#5	MeSH descriptor: [Cardiac Output, Low] this term only	457
#6	(((heart or cardia* or cardio* or myocard* or ventric*) near/2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still"))):ti	19762
#7	(((congestive or acute or decompensat* or chronic or left) NEAR/2 "heart failure")):ti,ab,kw	15954
#8	(((cardia* or cardio*) NEAR/2 (renal or reno) NEAR/2 syndrome*)):ti,ab,kw	95
#9	((cardiorenal NEAR/2 syndrome*)):ti,ab,kw	172
#10	(((cardiac or heart) NEAR/2 (edema* or oedema*))):ti,ab,kw	254
#11	(((dilated or congestive or idiopathic) NEAR/2 cardiomyopath*)):ti,ab,kw	1422
#12	(((cardiogenic or cardiocirculatory) NEAR/2 (shock or collapse))):ti,ab,kw	1681
#13	((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) NEAR/2 (failure* or insufficien* or dysfunction*))):ti,ab,kw	7175
#14	(((mid range or mild* or minimal* or normal or preserved or reduced) NEAR/3 (ejection fraction or EF or LVEF))):ti,ab,kw	5613
#15	((HFnEF or HFmrEF or HFpEF or HFrEF or lvsd)):ti,ab,kw	2623
#16	(((low or subnormal or depressed) NEAR/2 (cardiac NEAR/2 output))):ti,ab,kw	804
#17	((forward NEAR/2 failure*)):ti,ab,kw	197
#18	{or #1-#17}	35824
#19	MeSH descriptor: [Iron Compounds] explode all trees	3003
#20	MeSH descriptor: [Iron] this term only	3235

Searches
#21 ((alvofer or anaemex or colliron or cosmofer or dexferrum or dexiron or dextrafer or dextran or diafer or driken or eiseninject or faremio or fenate or fer or feraheme or fercayl or ferion or feriv or fermed or ferric or ferridextran or ferriferous or ferrinemia or ferrisaccharate or ferrisat or ferrivenin or ferrodex* or ferrologic or ferroprol or ferrosoferric or ferrous or ferrovin or ferrum or ferumoxytol or ferinject* or ferritin* or fervetag or fesin or hemafer or hibiron or idafer or iron or ironcrose or imferdex or imferon or impheron or imposil or infed or infufer or injectafer or ironate or iroprem or isofer or jerndextran or jilazo or iviron or magnetite or monofar or monofer or monoferric or monoferro or monover or nefrofer or nephroferol or ns32 or "ns 32" or proferdex or proferrin or referen or renegy or reoxyl or sucrofer or sucroven or uniferon or veniron or venofer or venotrix or "xi 921" or xi921)):ti,ab,kw 16541
#22 {or #19-#21} 17627
#23 #18 AND #22 483
#24 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 524201
#25 #23 NOT #24 362
#26 conference:pt 245616
#27 #25 NOT #26 with Publication Year from 2017 to 2024, in Trials 102
#28 #25 NOT #26 with Cochrane Library publication date Between Dec 2017 and Jul 2024, in Cochrane Reviews 1

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches
ID Search Hits
#1 MeSH descriptor: [Heart Failure] explode all trees 14584
#2 MeSH descriptor: [Cardiomyopathy, Dilated] this term only 672
#3 MeSH descriptor: [Shock, Cardiogenic] this term only 485
#4 MeSH descriptor: [Ventricular Dysfunction] explode all trees 2918
#5 MeSH descriptor: [Cardiac Output, Low] this term only 457
#6 (((heart or cardia* or cardio* or myocard* or ventric*) near/2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still"))):ti 19762
#7 (((congestive or acute or decompensat* or chronic or left) NEAR/2 "heart failure")):ti,ab,kw 15954
#8 (((cardia* or cardio*) NEAR/2 (renal or reno) NEAR/2 syndrome*)):ti,ab,kw 95
#9 ((cardiorenal NEAR/2 syndrome*)):ti,ab,kw 172
#10 (((cardiac or heart) NEAR/2 (edema* or oedema*))):ti,ab,kw 254

Searches
#11 (((dilated or congestive or idiopathic) NEAR/2 cardiomyopath*)):ti,ab,kw 1422
#12 (((cardiogenic or cardiocirculatory) NEAR/2 (shock or collapse))):ti,ab,kw 1681
#13 ((("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) NEAR/2 (failure* or insufficien* or dysfunction*))):ti,ab,kw 7175
#14 (((mid range or mild* or minimal* or normal or preserved or reduced) NEAR/3 (ejection fraction or EF or LVEF))):ti,ab,kw 5613
#15 ((HFnEF or HFmrEF or HFpEF or HFrEF or lvsd)):ti,ab,kw 2623
#16 (((low or subnormal or depressed) NEAR/2 (cardiac NEAR/2 output))):ti,ab,kw 804
#17 ((forward NEAR/2 failure*)):ti,ab,kw 197
#18 {or #1-#17} 35824
#19 MeSH descriptor: [Iron Compounds] explode all trees 3003
#20 MeSH descriptor: [Iron] this term only 3235
#21 ((alvofer or anaemex or colliron or cosmofer or dexferrum or dexiron or dextrafer or dextran or diafer or driken or eiseninject or faremio or fenate or fer or feraheme or fercayl or ferion or feriv or fermed or ferric or ferridextran or ferriferous or ferrinemia or ferrisaccharate or ferrisat or ferrivenin or ferrodex* or ferrologic or ferroprol or ferrosoferric or ferrous or ferrovin or ferrum or ferumoxytol or ferinject* or ferritin* or fervetag or fesin or hemafer or hibiron or idafer or iron or ironcrose or imferdex or imferon or impheron or imposil or infed or infufer or injectafer or ironate or iroprem or isofer or jerndextran or jilazo or iviron or magnetite or monofar or monofer or monoferric or monoferro or monover or nefrofer or nephroferol or ns32 or "ns 32" or proferdex or proferrin or referen or renegy or reoxyl or sucrofer or sucroven or uniferon or veniron or venofer or venotrix or "xi 921" or xi921)):ti,ab,kw 16541
#22 {or #19-#21} 17627
#23 #18 AND #22 483
#24 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 524201
#25 #23 NOT #24 362
#26 conference:pt 245616
#27 #25 NOT #26 with Publication Year from 2017 to 2024, in Trials 102
#28 #25 NOT #26 with Cochrane Library publication date Between Dec 2017 and Jul 2024, in Cochrane Reviews 1

Database name: Embase

Searches
1 heart failure/ or acute heart failure/ or cardiogenic shock/ or cardiopulmonary insufficiency/ or cardiorenal syndrome/ or exp diastolic dysfunction/ or forward heart failure/ or exp systolic dysfunction/ 422402
2 exp congestive heart failure/ 131428
3 heart ventricle failure/ or exp heart left ventricle failure/ 43221
4 dilated cardiomyopathy/ 2631
5 ((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 176606
6 ((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 124973
7 ((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 750
8 (cardiorenal adj2 syndrome*).tw. 2402
9 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1643
10 ((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 35968
11 ((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 29948
12 (("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 83144
13 ((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 52743
14 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw. 20772
15 ((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 6312
16 (forward adj2 failure*).tw. 128
17 or/1-16 631932
18 iron/ 206899
19 iron derivative/4686
20 ferric carboxymaltose/2400
21 iron dextran/ 2889
22 iron isomaltose/ 400
23 iron saccharate/ 2095
24 (alvofer or anaemex or colliron or cosmofer or dexferrum or dexiron or dextrafer or dextran or diafer or driken or eiseninject or faremio or fenate or fer or feraheme or fercayl or ferion or feriv or fermed or ferric or ferridextran or ferriferous or ferrinemia or ferrisaccharate or ferrisat or ferrivenin or ferrodex* or ferrologic or ferroprol or ferrosoferric or ferrous or ferrovin or ferrum or ferumoxytol or ferinject* or ferritin* or fervetag or fesin or hemafer or hibiron or idafer or iron or ironcrose or imferdex or imferon or impheron or imposil or infed or infufer or injectafer or ironate or iroprem or isofer or jerndextran or jilazo or iviron or magnetite or monofar or monofer or monoferric or monoferro or monover or nefrofer or nephroferol or ns32 or "ns 32" or proferdex or proferrin or referen or renegy or reoxyl or sucrofer or sucroven or uniferon or veniron or venofer or venotrix or "xi 921" or xi921).tw. 381772

Searches		
25	or/18-24	454792
26	17 and 25	6990
27	random*.ti,ab.	2086158
28	factorial*.ti,ab.	49732
29	(crossover* or cross over*).ti,ab.	130937
30	((doubl* or singl*) adj blind*).ti,ab.	284557
31	(assign* or allocat* or volunteer* or placebo*).ti,ab.	1322485
32	crossover procedure/	78564
33	single blind procedure/	55316
34	randomized controlled trial/	829416
35	double blind procedure/	220679
36	or/27-35	3069782
37	Systematic review/	474106
38	Meta-Analysis/	320655
39	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.	394002
40	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.	498040
41	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.	71090
42	(search strategy or search criteria or systematic search or study selection or data extraction).ab.	110749
43	(search* adj4 literature).ab.	136710
44	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.	497101
45	cochrane.jw.	25141
46	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.	7633
47	or/37-46	1020728
48	36 or 47	3786701
49	26 and 48	1013
50	limit 49 to english language	984
51	letter.pt. or letter/	1336008
52	note.pt.	991512
53	editorial.pt.	811094
54	(letter or comment*).ti.	246564
55	or/51-54	3200544
56	randomized controlled trial/ or random*.ti,ab.	2205660
57	55 not 56	3165032
58	50 not 57	979
59	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5986621

Searches
60 58 not 59 658
61 limit 60 to dc=20171201-20240731 372

Database name: MEDLINE

Searches
1 exp Heart Failure/ 154613
2 Cardiomyopathy, Dilated/ 17536
3 Shock, Cardiogenic/ 11313
4 exp Ventricular Dysfunction/ 44479
5 Cardiac Output, Low/ 5622
6 ((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 115762
7 ((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 77525
8 ((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 343
9 (cardiorenal adj2 syndrome*).tw. 1387
10 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1243
11 ((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 22588
12 ((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 15990
13 (("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 44840
14 ((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 24362
15 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw. 9155
16 ((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 4145
17 (forward adj2 failure*).tw. 78
18 or/1-17 303057
19 exp Iron Compounds/ 72499
20 Iron/ 109125
21 (alvofer or anaemex or colliron or cosmofer or dexferrum or dexiron or dextrafer or dextran or diafer or driken or eiseninject or faremio or fenate or fer or feraheme or fercayl or ferion or feriv or fermed or ferric or ferridextran or ferriferous or ferrinemia or ferrisaccharate or ferrisat or ferrivenin or ferrodex* or ferrologic or ferroprol or ferrosoferric or ferrous or ferrovin or ferrum or ferumoxytol or ferinject* or ferritin* or fervetag or fesin or hemafer or hibiron or idafer or iron or ironcrose or imferdex or imferon or impheron or imposil or infed or infufer or injectafer or ironate or iroprem or isofer or jerndextran or jilazo or iviron or magnetite or monofar or monofer or monoferric or monoferro or monover or nefrofer or nephroferol or ns32 or "ns 32" or proferdex or proferrin or referen or renegy or reoxyl or sucrofer or

Searches
sucroven or uniferon or veniron or venofer or venotrix or "xi 921" or xi921).tw. 316080
22 or/19-21 381540
23 18 and 22 3117
24 Randomized Controlled Trial/ 616258
25 controlled clinical trial.pt. 95564
26 randomi#ed.ti,ab. 843104
27 placebo.ab. 249612
28 randomly.ti,ab. 437581
29 Clinical Trials as topic.sh. 202739
30 trial.ti. 312527
31 or/24-30 1670608
32 Meta-Analysis/ 203538
33 exp Meta-Analysis as Topic/ 30173
34 (meta analy* or metanaly* or metaanaly* or meta regression).ti,ab. 311812
35 ((systematic* or evidence*) adj3 (review* or overview*)).ti,ab. 416796
36 (reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab. 57847
37 (search strategy or search criteria or systematic search or study selection or data extraction).ab. 92875
38 (search* adj4 literature).ab. 109479
39 (medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab. 410550
40 cochrane.jw. 16752
41 ((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab. 4107
42 or/32-41 772446
43 31 or 42 2263603
44 23 and 43 472
45 limit 44 to english language 445
46 letter/ 1260937
47 editorial/ 697319
48 news/ 226042
49 exp historical article/ 411878
50 Anecdotes as Topic/ 4747
51 comment/ 1037657
52 (letter or comment*).ti. 201347
53 or/46-52 2932661
54 randomized controlled trial/ or random*.ti,ab. 1660017
55 53 not 54 2906471

Searches		
56	45 not 55	442
57	limit 56 to ed=20171201-20240731	170
58	limit 56 to dt=20171201-20240731	192
59	or/57-58	205

Database name: Epistemonikos

Searches
Search 1
1 title:("heart failure" OR "heart-failure") AND title:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 44
2 abstract:("heart failure" OR "heart-failure") AND abstract:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 53
Search 2
3 title:(HFnEF OR HFmrEF OR HFpEF OR HFrEF OR lvsd) AND title:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron

Searches
OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 3
4 abstract:(HFnEF OR HFmrEF OR HFpEF OR HFrEF OR lvsd) AND abstract:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 10
Search 3
5 title:("left ventricular" OR "left-ventricular" OR "left ventricle" OR "left-ventricle" OR lv OR systolic* OR diastolic*) AND title:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 0
6 abstract:("left ventricular" OR "left-ventricular" OR "left ventricle" OR "left-ventricle" OR lv OR systolic* OR diastolic*) AND abstract:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR

Searches
jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 26
Search 4
7 title:("cardiorenal syndrome" OR "cardio-renal syndrome" OR "cardiac edema" OR "cardiac oedema" OR "heart edema" OR "heart oedema") AND title:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 0
8 abstract:("cardiorenal syndrome" OR "cardio-renal syndrome" OR "cardiac edema" OR "cardiac oedema" OR "heart edema" OR "heart oedema") AND abstract:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 0
Search 5
9 title:(cardiomyopath*) AND title:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron

Searches
OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 2 10 abstract:(cardiomyopath*) AND abstract:(alvofer OR anaemex OR colliron OR cosmofer OR dexferrum OR dexiron OR dextrafer OR dextran OR diafer OR driken OR eiseninject OR faremio OR fenate OR fer OR feraheme OR fercayl OR ferion OR feriv OR fermed OR ferric OR ferridextran OR ferriferous OR ferrinemia OR ferrisaccharate OR ferrisat OR ferrivenin OR ferrodex* OR ferrologic OR ferroprol OR ferrosoferric OR ferrous OR ferrovin OR ferrum OR ferumoxytol OR ferinject* OR ferritin* OR fervetag OR fesin OR hemafer OR hibiron OR idafer OR iron OR ironcrose OR imferdex OR imferon OR impheron OR imposil OR infed OR infufer OR injectafer OR ironate OR iroprem OR isofer OR jerndextran OR jilazo OR iviron OR magnetite OR monofar OR monofer OR monoferric OR monoferro OR monover OR nefrofer OR nephroferol OR ns32 OR "ns 32" OR "ns-32" OR proferdex OR proferrin OR referen OR renegy OR reoxyl OR sucrofer OR sucroven OR uniferon OR veniron OR venofer OR venotrix OR "xi 921" OR "xi-921" OR xi921) 15 Total 153 Limited from 2017-current; publication type: systematic review; Cochrane review: no; Systematic Review Question: all

Additional search methods

Studies identified in the previous update of this guideline and from systematic review reference lists were also added to the items retrieved.

Cost-effectiveness searches

Database results – Economic Evaluations

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	12th February 2024	Ovid	Embase <1974 to 2024 February 09>	4631
MEDLINE	12th February 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to February 09, 2024>	1799

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
HTA	12th February 2024	CRD	Up to 2018	8
NHS Economic Evaluation Database (NHS EED) (legacy database)	12th February 2024	CRD	Up to 2015	0
INAHTA	12th February 2024	INAHTA	12/02/2024	91

Database results – Quality of Life

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	25th July 2024	Ovid	Embase <1974 to 2024 July 24>	4213
MEDLINE	25th July 2024	Ovid	Ovid MEDLINE(R) ALL 1946 to July 24, 2024	2546

Re-run search results – Economic Evaluations – Update 1

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	4th December 2024	Ovid	Embase <1974 to 2024 December 03>	921
MEDLINE	4th December 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to December 02, 2024>	273

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
INAHTA	4th December 2024	INAHTA	4/12/2024	25

HTA AND NHS EED are legacy databases and were not re-run due as no new records have been added

Re-run search results – Economic Evaluations – Update 2

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	13th January 2025	Ovid	Embase <1974 to 2025 January 10>	112
MEDLINE	13th January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 10, 2025>	56
INAHTA	13th January 2025	INAHTA	13/01/2025	28

HTA AND NHS EED are legacy databases and were not re-run due as no new records have been added

Re-run search results – Quality of Life – Update 1

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	4th December 2024	Ovid	Embase <1974 to 2024 December 03>	187
MEDLINE	4th December 2024	Ovid	Ovid MEDLINE(R) ALL <1946 to December 02, 2024>	104

Re-run search results – Quality of Life – Update 2

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	13th January 2025	Ovid	Embase <1974 to 2025 January 10>	43
MEDLINE	13th January 2025	Ovid	Ovid MEDLINE(R) ALL <1946 to January 10, 2025>	29

Search strategy history

Database name: Embase economic evaluation

Searches
1 heart failure/ or acute heart failure/ or cardiogenic shock/ or cardiopulmonary insufficiency/ or cardiorenal syndrome/ or exp diastolic dysfunction/ or forward heart failure/ or exp systolic dysfunction/ 408023
2 exp congestive heart failure/ 127929
3 heart ventricle failure/ or exp heart left ventricle failure/ 42366
4 dilated cardiomyopathy/ 1707
5 ((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 172522
6 ((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 122466
7 ((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 732
8 (cardiorenal adj2 syndrome*).tw. 2306
9 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1605
10 ((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 35276
11 ((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 28677
12 (("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 81493
13 ((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 50358
14 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw. 19634
15 ((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 6190

Searches	
16	(forward adj2 failure*).tw. 126
17	or/1-16 613437
18	Health economics/ 36277
19	exp health care cost/ 348767
20	exp Fee/ 44635
21	exp Budget/ 34309
22	Funding/ 81371
23	budget*.ti,ab. 48615
24	cost*.ti. 198234
25	(economic* or pharmaco?economic*).ti. 78306
26	(price* or pricing*).ti,ab. 75356
27	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. 296991
28	(financ* or fee or fees).ti,ab. 234068
29	(value adj2 (money or monetary)).ti,ab. 4233
30	or/18-29 1088021
31	17 and 30 19541
32	limit 31 to english language 18944
33	Nonhuman/ not human/ 5382202
34	32 not 33 18821
35	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5832293
36	34 not 35 12844
37	(letter or editorial).pt. 2103817
38	36 not 37 11605
39	limit 38 to dc=20171201-20240229 4631

Database name: Medline economic evaluation

Searches	
1	exp Heart Failure/ 151655
2	Cardiomyopathy, Dilated/ 17386
3	Shock, Cardiogenic/ 11068
4	exp Ventricular Dysfunction/ 43989
5	Cardiac Output, Low/ 5620
6	((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 113028
7	((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 76267
8	((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 339

Searches
9 (cardiorenal adj2 syndrome*).tw. 1334
10 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1229
11 ((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 22225
12 ((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 15449
13 (("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 44123
14 ((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 23261
15 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw. 8567
16 ((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 4107
17 (forward adj2 failure*).tw. 77
18 or/1-17 297032
19 Economics/ 27523
20 Value of life/ 5821
21 exp "Costs and Cost Analysis"/ 268686
22 exp Economics, Hospital/ 25795
23 exp Economics, Medical/ 14419
24 Economics, Nursing/ 4013
25 Economics, Pharmaceutical/ 3125
26 exp "Fees and Charges"/ 31453
27 exp Budgets/ 14189
28 budget*.ti,ab. 36835
29 cost*.ti. 147915
30 (economic* or pharmaco?economic*).ti. 62859
31 (price* or pricing*).ti,ab. 55101
32 (cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab. 216581
33 (financ* or fee or fees).ti,ab. 166449
34 (value adj2 (money or monetary)).ti,ab. 3136
35 or/19-34 754861
36 18 and 35 5374
37 limit 36 to english language 5088
38 animals/ not humans/ 5160739
39 37 not 38 5054
40 limit 39 to (letter or historical article or comment or editorial or news or case reports) 351
41 39 not 40 4703
42 limit 41 to ed=20171201-20240229 1516
43 limit 41 to dt=20171201-20240229 1616
44 42 or 43 1799

Database name: HTA economic evaluation

Searches		
Line	Search	Hits
1	MeSH DESCRIPTOR heart failure EXPLODE ALL TREES	832
2	MeSH DESCRIPTOR Cardiomyopathy, Dilated	23
3	MeSH DESCRIPTOR Shock, Cardiogenic	23
4	MeSH DESCRIPTOR Ventricular Dysfunction EXPLODE ALL TREES	165
5	MeSH DESCRIPTOR Cardiac Output, Low	24
6	(((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or stand still))):TI	786
7	(((congestive or acute or decompensat* or chronic or left) adj2 heart failure))	741
8	(((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*))	1
9	((cardiorenal adj2 syndrome*))	0
10	(((cardiac or heart) adj2 (edema* or oedema*)))	2
11	(((dilated or congestive or idiopathic) adj2 cardiomyopath*))	48
12	(((cardiogenic or cardiocirculatory) adj2 (shock or collapse)))	78
13	(((left ventricular or left ventricle or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)))	203
14	(((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)))	52
15	((HFnEF or HFmrEF or HFpEF or HFrEF or lvsd))	21
16	(((low or subnormal or depressed) adj2 (cardiac adj2 output)))	23
17	((forward adj2 failure*))	0
18	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1516
19	* IN NHSEED	17613
20	#18 AND #19	434
21	* IN HTA	17351
22	#18 AND #21	260
23	* FROM 2017 TO 2024	506
24	#20 AND #23	0
25	#22 AND #23	8

Database name: INAHTA economic evaluation

Searches		
Line	Query	Hits
20	#19 AND #18	91
19	* FROM 2017 TO 2024	4504

Searches
18 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 411
17 (forward) AND (failure*) 4
16 (low or subnormal or depressed) AND (cardiac output) 6
15 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd) 4
14 (mid range or mild* or minimal* or normal or preserved or reduced) AND (ejection fraction or EF or LVEF) 30
13 ("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) AND (failure* or insufficien* or dysfunction*) 88
12 (cardiogenic or cardiocirculatory) AND (shock or collapse) 19
11 (dilated or congestive or idiopathic) AND (cardiomyopath*) 15
10 (cardiac or heart) AND (edema* or oedema*) 11
9 (cardiorenal) AND (syndrome*) 0
8 (cardia* or cardio*) AND (renal or reno) AND (syndrome*) 3
7 (congestive or acute or decompensat* or chronic or left) AND ("heart failure") 220
6 (heart or cardia* or cardio* or myocard* or ventric*)[Title] AND (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")[Title] 219
5 "Cardiac Output, Low"[mh] 3
4 "Ventricular Dysfunction"[mhe] 31
3 "Shock, Cardiogenic"[mh] 9
2 "Cardiomyopathy, Dilated"[mh] 5
1 "Heart Failure"[mhe] 222

Database name: Embase Quality of Life

Searches
1 heart failure/ or acute heart failure/ or cardiogenic shock/ or cardiopulmonary insufficiency/ or cardiorenal syndrome/ or exp diastolic dysfunction/ or forward heart failure/ or exp systolic dysfunction/ 425492
2 exp congestive heart failure/ 132098
3 heart ventricle failure/ or exp heart left ventricle failure/ 43359
4 dilated cardiomyopathy/ 2734
5 ((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 177876
6 ((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 125543
7 ((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 751
8 (cardiorenal adj2 syndrome*).tw. 2413
9 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1649

Searches		
10	((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw.	36128
11	((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw.	30219
12	(("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw.	83514
13	((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw.	53242
14	(HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw.	20999
15	((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw.	6339
16	(forward adj2 failure*).tw.	129
17	or/1-16	636045
18	quality adjusted life year/	38081
19	quality of life index/	3307
20	short form 12/ or short form 20/ or short form 36/ or short form 8/	53248
21	sickness impact profile/	2414
22	(quality adj2 (wellbeing or well being)).ti,ab.	4300
23	sickness impact profile.ti,ab.	1252
24	disability adjusted life.ti,ab.	7479
25	(qal* or qtime* or qwb* or daly*).ti,ab.	37019
26	(euroqol* or eq5d* or eq 5*).ti,ab.	33319
27	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.	142937
28	(health utility* or utility score* or disutilit* or utility value*).ti,ab.	10493
29	(hui or hui1 or hui2 or hui3).ti,ab.	3375
30	(health* year* equivalent* or hye or hyes).ti,ab.	210
31	discrete choice*.ti,ab.	5215
32	rosser.ti,ab.	145
33	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.	18387
34	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.	53543
35	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.	532
36	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.	13992
37	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.	1678
38	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.	5346
39	or/18-38	294233
40	17 and 39	7697
41	limit 40 to english language	7556
42	Nonhuman/ not human/	5499187
43	41 not 42	7515

Searches
44 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5991243
45 43 not 44 4363
46 (letter or editorial).pt. 2151720
47 45 not 46 4213

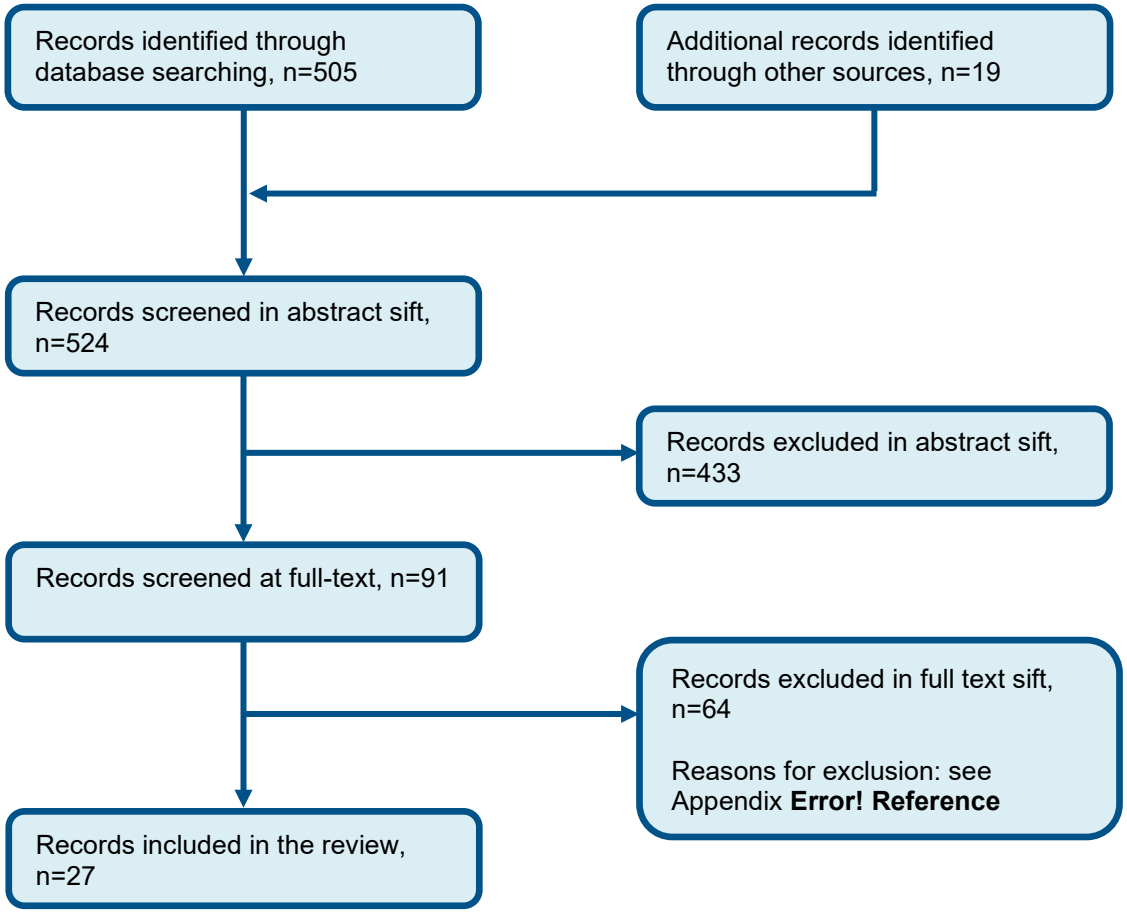
Database name: Medline Quality of Life

Searches
1 exp Heart Failure/ 154898
2 Cardiomyopathy, Dilated/ 17552
3 Shock, Cardiogenic/ 11354
4 exp Ventricular Dysfunction/ 44539
5 Cardiac Output, Low/ 5624
6 ((heart or cardia* or cardio* or myocard* or ventric*) adj2 (failure* or decompensat* or incompetenc* or insufficien* or dysfunction* or "stand still")).ti. 116177
7 ((congestive or acute or decompensat* or chronic or left) adj2 "heart failure").tw. 77705
8 ((cardia* or cardio*) adj2 (renal or reno) adj2 syndrome*).tw. 344
9 (cardiorenal adj2 syndrome*).tw. 1393
10 ((cardiac or heart) adj2 (edema* or oedema*)).tw. 1245
11 ((dilated or congestive or idiopathic) adj2 cardiomyopath*).tw. 22625
12 ((cardiogenic or cardiocirculatory) adj2 (shock or collapse)).tw. 16063
13 (("left ventricular" or "left ventricle" or lv or systolic* or diastolic*) adj2 (failure* or insufficien* or dysfunction*)).tw. 44962
14 ((mid range or mild* or minimal* or normal or preserved or reduced) adj3 (ejection fraction or EF or LVEF)).tw. 24530
15 (HFnEF or HFmrEF or HFpEF or HFrEF or lvsd).tw. 9242
16 ((low or subnormal or depressed) adj2 (cardiac adj2 output)).tw. 4154
17 (forward adj2 failure*).tw. 78
18 or/1-17 303908
19 quality-adjusted life years/ 16609
20 sickness impact profile/ 7337
21 (quality adj2 (wellbeing or well being)).ti,ab. 3238
22 sickness impact profile.ti,ab. 1089
23 disability adjusted life.ti,ab. 6213
24 (qal* or qtime* or qwb* or daly*).ti,ab. 21833
25 (euroqol* or eq5d* or eq 5*).ti,ab. 18468
26 (qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab. 80463
27 (health utility* or utility score* or disutilit* or utility value*).ti,ab. 5869

Searches
28 (hui or hui1 or hui2 or hui3).ti,ab. 2105
29 (health* year* equivalent* or hye or hyes).ti,ab. 86
30 discrete choice*.ti,ab. 3659
31 rosser.ti,ab. 111
32 (willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab. 12305
33 (sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab. 32728
34 (sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab. 458
35 (sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab. 8739
36 (sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab. 1004
37 (sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab. 4065
38 or/19-37 171196
39 18 and 38 2674
40 limit 39 to english language 2588
41 animals/ not humans/ 5207441
42 40 not 41 2582
43 limit 42 to (letter or historical article or comment or editorial or news or case reports) 36
44 42 not 43 2546

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of intravenous iron for chronic heart failure



Appendix D Effectiveness evidence

Anker, 2009

Bibliographic Reference	Anker, SD; Colet, JC; Filippatos, G; Willenheimer, R; Dickstein, K; Drexler, H; L?scher, TF; Mori, C; von Eisenhart Rothe, B; Pocock, S; Poole-Wilson, PA; Ponikowski, P; Rationale and design of Ferinject assessment in patients with IRon deficiency and chronic Heart Failure (FAIR-HF) study: a randomized, placebo-controlled study of intravenous iron supplementation in patients with and without anaemia.; European journal of heart failure; 2009; vol. 11 (no. 11); 1084-1091

Study details

Secondary publication of another included study- see primary study for details	Anker, 2009b (primary study)
Other publications associated with this study included in review	Comin-Colet, 2013, Filippatos, 2013,

Trial name / registration number	FAIR-HF/ NCT00520780
Inclusion criteria	NYHA Class II-III due to stable symptomatic CHF and all of the following Two weeks without cardiac hospitalisation Patients in NYHA II: acute care admission or emergency room visit for worsening heart failure within 24 months prior to start of treatment On optimal pharmacological treatment which includes a diuretic, a beta-blocker, and/or an ACE-inhibitor or ARB as determined by the investigator, unless contraindicated or not tolerated No dose changes of heart failure drugs during the last 2 weeks (exception: diuretics) No introduction of a new heart failure drug class during the last 4 weeks LVEF ≤40% for patients in NYHA II and LVEF ≤45% in NYHA III Hb: 9.5-13.5 g/dL Evidence of absolute or functional iron deficiency: screening ferritin < 100ng/mL or 100-300 ng/mL when TSAT < 20% Patient must be able to perform the 6 minute walk test according to investigator judgment

Exclusion criteria	Known active infection, C-reactive protein >20 mg/L, clinically significant bleeding, active malignancy ALT or AST >3 x upper limit of normal Anaemia due to reasons other than iron deficiency (ie haemoglobinopathy) Immunosuppressive therapy or renal dialysis History of erythropoietin, i.v. or oral iron therapy, and blood transfusion in previous 12 weeks and/or such therapy planned within the next 6 months Unstable angina pectoris, clinically significant uncorrected valvular disease or left ventricular outflow obstruction, obstructive cardiomyopathy Acute myocardial infarction or acute coronary syndrome, transient ischaemic attack or stroke within the last 3 months Coronary-artery bypass graft, percutaneous intervention (e.g. cardiac, cerebrovascular, aortic; diagnostic catheters are allowed) or major surgery, including thoracic and cardiac surgery, within the last 3 months

Anker, 2009

Bibliographic Reference	Anker, SD; Comin Colet, J; Filippatos, G; Willenheimer, R; Dickstein, K; Drexler, H; L?scher, TF; Bart, B; Banasiak, W; Niegowska, J; Kirwan, BA; Mori, C; von Eisenhart Rothe, B; Pocock, SJ; Poole-Wilson, PA; Ponikowski, P; Ferric

carboxymaltose in patients with heart failure and iron deficiency.; The New England journal of medicine; 2009; vol. 361 (no. 25); 2436-2448

Study details

Secondary publication of another included study- see primary study for details	
Other publications associated with this study included in review	Anker, 2009a, Comin-Colet, 2013, and Filippatos, 2013
Trial name / registration number	FAIR- HF/ NCT00520780
Study location	Argentina, Czech Republic, Germany, Greece, Italy, Norway, Poland, Romania, Russia, Spain, Ukraine (75 study sites)

Study setting	Study sites
Study dates	25 June 2007 to 31 December 2008
Sources of funding	Sponsored by Vifor Pharma
Inclusion criteria	See Anker, 2009a
Exclusion criteria	See Anker, 2009a
Recruitment / selection of participants	Patients were selected if they were ambulatory with NYHA class II-III, with LVEF 40% or less (with NYHA class II) or with LVEF 45% or less (with NYHA class III), haemoglobin level between 95 to 135 g per litre and iron deficiency.
Intervention(s)	Intravenous ferric carboxymaltose (200mg) administered in a black syringe. Dosing frequency was weekly until iron repletion was achieved and then every four weeks during maintenance. If the ferritin level exceeded 800 µg per litre or was between 500 and 800 µg per litre with a transferrin saturation of >50%, or if the haemoglobin level was higher than 160 g per litre, ferric carboxymaltose was discontinued and placebo was given instead.

Population subgroups	Tests for interaction were performed as part of a subgroup analysis. Those with anaemia and those without anaemia.
Comparator	Placebo (saline) administered as an intravenous bolus injection of 4 ml (which is the amount of ferric carboxymaltose in a water solution for injection that is equivalent to 200 mg of iron) in a black syringe. Dosing frequency was weekly until iron repletion was achieved and then every 4 weeks during the maintenance phase.
Number of participants	459 patients
Duration of follow-up	24 weeks
Indirectness	None

Study arms

Intravenous ferric carboxymaltose (200mg) (N = 304)

Placebo (N = 155)

Characteristics

Arm-level characteristics

Characteristic	Intravenous ferric carboxymaltose (200mg) (N = 304)	Placebo (N = 155)
% Female Sample size	n = 159 ; % = 52.3	n = 85 ; % = 54.8
Age Mean (SD)	67.8 (10.3)	67.4 (11.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 303 ; % = 99.7	n = 155 ; % = 100
NYHA class	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Intravenous ferric carboxymaltose (200mg) (N = 304)	Placebo (N = 155)
Sample size		
Class II Sample size	n = 53 ; % = 17.4	n = 29 ; % = 18.7
Class III Sample size	n = 251 ; % = 82.6	n = 126 ; % = 81.3
Heart failure aetiology No of events	n = NA ; % = NA	n = NA ; % = NA
LVEF Mean (SD)	31.9 (5.5)	33 (6.1)
Atrial fibrillation No of events	n = 94 ; % = 30.9	n = 44 ; % = 28.4

Characteristic	Intravenous ferric carboxymaltose (200mg) (N = 304)	Placebo (N = 155)
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Diuretic Sample size	n = 280 ; % = 92.1	n = 140 ; % = 90.3
ACE inhibitor or ARB Sample size	n = 281 ; % = 92.4	n = 141 ; % = 91
Digitalis glycoside Sample size	n = 46 ; % = 15.1	n = 25 ; % = 16.1
Beta-blocker Sample size	n = 262 ; % = 86.2	n = 129 ; % = 83.2
Transferrin saturation (%)	17.7 (12.6)	16.7 (8.4)

Characteristic	Intravenous ferric carboxymaltose (200mg) (N = 304)	Placebo (N = 155)
Mean (SD)		
Haemoglobin Mean (SD)	119 (13)	119 (14)
Ferritin Mean (SD)	52.5 (54.5)	60.1 (66.5)

Outcomes

Study timepoints

Baseline

24 week

Dichotomous outcomes

Outcome	Intravenous ferric carboxymaltose (200mg), Baseline, N = 304	Intravenous ferric carboxymaltose (200mg), 24 week, N = 305	Placebo, Baseline, N = 155	Placebo, 24 week, N = 154
All-cause mortality No of events	n = NA ; % = NA	n = 5 ; % = 3.4	n = NA ; % = NA	n = 4 ; % = 5.5
Death due to cardiovascular causes No of events	n = NA ; % = NA	n = 4 ; % = 2.7	n = NA ; % = NA	n = 4 ; % = 5.5
Hospitalisation for worsening heart failure No of events	n = NA ; % = NA	n = 6 ; % = 4.1	n = NA ; % = NA	n = 7 ; % = 9.7
Unplanned hospitalisation (all-cause)	n = NA ; % = NA	n = 28 ; % = NR	n = NA ; % = NA	n = 22 ; % = NR

Outcome	Intravenous ferric carboxymaltose (200mg), Baseline, N = 304	Intravenous ferric carboxymaltose (200mg), 24 week, N = 305	Placebo, Baseline, N = 155	Placebo, 24 week, N = 154
No of events				
Anaphylaxis/ hypersensitivity No of events	n = NR ; % = NR	n = 0 ; % = 0	n = NR ; % = NR	n = 0 ; % = 0

All-cause mortality - Polarity - Lower values are better

Mortality due to cardiovascular causes - Polarity - Lower values are better

Hospitalisation for any cardiovascular causes - Polarity - Lower values are better

Hospitalisation for worsening heart failure - Polarity - Lower values are better

First hospitalisation - Polarity - Lower values are better

Anaphylaxis/hypersensitivity - Polarity - Lower values are better

Continuous outcomes - between group differences

Outcome	Intravenous ferric carboxymaltose (200mg) vs Placebo, 24 week, N2 = 155, N1 = 304
Kansas City Cardiomyopathy Questionnaire Mean Study-Treatment Effect (change score) Mean (SE)	7 (2)
6-minute walk test Mean Study-Treatment Effect (change score) Mean (SE)	35 (8)
EQ-5D Visual Analogue Scale Mean Study-Treatment effect (change score) Mean (SD)	7 (2)

Kansas City Cardiomyopathy Questionnaire - Polarity - Higher values are better

6-minute walk test - Polarity - Higher values are better

EQ-5D Visual Analogue Scale - Polarity - Higher values are better

Continuous outcome

Outcome	Intravenous ferric carboxymaltose (200mg), Baseline, N = 155	Intravenous ferric carboxymaltose (200mg), 24 week, N = 155	Placebo, Baseline, N = 77	Placebo, 24 week, N = 77
Haemoglobin, final value Adjusted (reported as g/L in full text) (g/dL) Anaemic cohort numbers per group from Fillipatos, 2013 Mean (SE)	NR (NR)	12.7 (0.1)	NR (NR)	11.8 (0.2)

Haemoglobin - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: All-cause mortality-Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time-to-event.)*

Dichotomous outcomes: Mortality due to cardiovascular causes-Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time-to-event.)*

Continuous outcomes: EQ-5D Visual Analogue Scale- Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire: Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-minute walk test: Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Hospitalisation for worsening heart failure: Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time-to-event.)*

Dichotomous outcomes: First hospitalisation: Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time-to-event.)*

Continuous outcome: Haemoglobin final scores in anaemic cohort-Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as final value rather than a change value)*

Dichotomous outcomes: Anaphylaxis/hypersensitivity-Intravenous ferric carboxymaltose (200mg) versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Anker, 2025

Bibliographic Reference	Anker, Stefan D; Friede, Tim; Butler, Javed; Talha, Khawaja M; Diek, Monika; Nosko, Anna; Placzek, Marius; Hasenfus, Gerd; Ponikowski, Piotr; Karakas, Mahir; Rationale and design of the FAIR-HF2-DZHK05 trial: Ferric carboxymaltose assessment of morbidity and mortality in patients with iron deficiency and chronic heart failure.; European journal of heart failure; 2025

Study details

Secondary publication of another included study- see primary study for details	Rationale and design paper used as background for Anker (2025) Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency: The FAIR-HF2 DZHK05 Randomized Clinical Trial. JAMA doi:10.1001/jama.2025.38
Other publications associated with this study included in review	Primary study: Anker (2025) Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency: The FAIR-HF2 DZHK05 Randomized Clinical Trial. JAMA doi:10.1001/jama.2025.38
Trial name / registration number	FAIR HF2 NCT03036462

Anker, 2025

Bibliographic Reference	Anker, Stefan D; Friede, Tim; Butler, Javed; Talha, Khawaja M; Placzek, Marius; Diek, Monika; Nosko, Anna; Stas, Adriane; Kluge, Stefan; Jarczak, Dominik; deHeer, Geraldine; Rybczynski, Meike; Bayes-Genis, Antoni; Bohm, Michael; Coats, Andrew

J S; Edelmann, Frank; Filippatos, Gerasimos; Hasenfus, Gerd; Haverkamp, Wilhelm; Lainscak, Mitja; Landmesser, Ulf; Macdougall, Iain C; Merkely, Bela; Pieske, Burkert M; Pinto, Fausto J; Rassaf, Tienush; Visser-Rogers, Jennifer K; Rosano, Giuseppe; Volterrani, Maurizio; von Haehling, Stephan; Anker, Markus S; Doehner, Wolfram; Ince, Huseyin; Koehler, Friedrich; Savarese, Gianluigi; Khan, Muhammad Shahzeb; Rauch-Krohnert, Ursula; Gori, Tommaso; Trenkwalder, Teresa; Akin, Ibrahim; Paitazoglou, Christina; Kobielusz-Gembala, Iwona; Kuthi, Luca; Frey, Norbert; Licka, Manuela; Kaab, Stefan; Laugwitz, Karl-Ludwig; Ponikowski, Piotr; Karakas, Mahir; Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency: The FAIR-HF2 DZHK05 Randomized Clinical Trial.; JAMA; 2025

Study details

Secondary publication of another included study- see primary study for details	Primary paper
Other publications associated with this study included in review	Rationale/design paper: Anker (2025) Rationale and design of the FAIR-HF2-DZHK05 trial: Ferric carboxymaltose assessment of morbidity and mortality in patients with iron deficiency and chronic heart failure. European journal of heart failure
Trial name / registration number	FAIR HF2 NCT03036462
Study type	Randomised controlled trial (RCT)
Study location	Multicentre study, 6 countries in Europe.
Study setting	Clinical setting. 70 clinic sites in 6 European countries
Study dates	Screening and enrolment between Between March 7, 2017, and November 29, 2023.

Sources of funding	German Center for Cardiovascular Research (Deutsches Zentrum für Herz-Kreislauf-Forschung eV), CSL Vifor (an unrestricted scientific grant and free provision of 0.9% saline and ferric carboxymaltose), and the German Heart Foundation (Deutsche Herzstiftung eV).
Inclusion criteria	Patients had chronic heart failure with reduced ejection fraction for at least 3 months, a left ventricular ejection fraction of 45% or less, and evidence of serum iron deficiency (had a serum ferritin level <100 ng/mL; or if transferrin saturation was <20%, had a serum ferritin level between 100 ng/mL and 299 ng/mL). At the time of screening, eligible patients were considered (1) restabilized and eligible for hospital discharge within 24 hours, (2) as stable and ambulatory among those with a heart failure hospitalization within the past 12 months, or (3) as stable and ambulatory with elevated natriuretic peptide levels. Inclusion criteria: 1.Patients aged at least 18 years 2. Patients with chronic HF present for at least 12 months 3. Confirmed presence of ID (ferritin < 100 ng/mL or ferritin 100 – 299 ng/mL with TSAT < 20 %) 4. Serum haemoglobin of 9.5 to 14.0 g/dL 5. At time of screening considered re-stabilised and planned for discharge within next 24 hours, or stable ambulatory with a HF hospitalisation in the past 6 months, or stable ambulatory with BNP > 100 pg/mL or NT-proBNP > 300 pg/mL or MR-proANP > 120 pmol/L 6. LVEF ≤ 45 % (documented within the last 12 months prior to screening), NYHA class II/III 7. Patients with CRT devices and patients with indication to CRT therapy can be included 8. Females/Males who agree to comply with the applicable contraceptive requirements of the protocol 9. Non-pregnant, non-lactating females 10. Ability to understand the patient information and to personally sign and date the informed consent to participate in the study, before completing any study related procedures. 11. The patient is co-operative and available for the entire study. 12. Provided written informed consent
Exclusion criteria	1. Hypersensitivity to the active substance, to FCM or any of its excipients 2. Known serious hypersensitivity to other parenteral iron products 3. Anaemia not attributed to iron deficiency, e.g. other microcytic anaemia 4. Evidence of iron overload or disturbances in the utilisation of iron 5. History of severe asthma, eczema or other atopic allergy 6. History of immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) 7. Acute or chronic bacterial infection 8. Presence of a deficiency for vitamin B12 and/or serum folate (if present, this needs to be corrected before rescreening) 9. Treatment with an erythropoietin stimulating agent (ESA), any i.v. iron and/or a blood transfusion in the previous 6 weeks prior to randomisation 10. Oral iron therapy at doses > 100 mg/day in the week prior to randomisation 11. History of acquired iron overload 12. Current use of renal replacement therapy 13. Patient at an immediate need of

	transfusion or Hb ≥ 14.0 g/dL 14. Documented LVEF > 50 % within the last 12 months (in this case, LVEF measurement has to be repeated at screening and document a LVEF ≤ 45 %). 15. Chronic liver disease (including active hepatitis) and/or screening alanine transaminase or aspartate transaminase above 3 times the upper limit of the normal range 16. History of hepatic dysfunction (in particular Porphyria Cutanea Tarda (PCT)) 17. Patients with known hepatitis B surface antigen positivity and/or hepatitis C virus ribonucleic acid positivity or with known seropositivity to human immunodeficiency virus (no routine testing within trial) 18. Clinical evidence of current malignancy with exception of basal cell or squamous cell carcinoma of the skin, and cervical intraepithelial neoplasia 19. Currently receiving systemic chemotherapy and/or radiotherapy 20. Unstable angina pectoris as judged by the Investigator; severe valvular or left ventricular outflow obstruction disease needing intervention; atrial fibrillation/flutter with a mean ventricular response rate at rest > 120 beats per minute during screening/ baseline visit 21. Acute myocardial infarction within the last 3 months or unstable Angina pectoris within the last 4 weeks prior to randomisation 22. Coronary-artery bypass graft, coronary percutaneous intervention (diagnostic catheters are allowed) or major surgery, including thoracic and cardiac surgery, within the last 4 weeks prior to randomisation 23. Current or relevant history of physical or psychiatric illness, any medical disorder that may require treatment or make the patient unlikely to fully complete the clinical trial 24. Participation in a clinical trial or use of an IMP within 30 days or five times the half-life of the IMP - whichever is longer - prior to receiving the first dose within this study 25. Positive urine pregnancy test at screening or positive serum pregnancy test before the first treatment or is breast feeding 26. Patient is not willing to use adequate contraceptive precautions during the study and for up to 5 days after the last scheduled dose of IMP 27. Evidence in the patient's medical history or in the medical examination that might influence either the safety of the patient or the absorption, distribution, metabolism or excretion of the IMP product under investigation
Recruitment / selection of participants	From multiple clinical sites in 6 countries. Screening to meet inclusion criteria before being enrolled and randomised.
Intervention(s)	Dose/regimen followed European Medicines Agency summary of product characteristics based on haemoglobin concentration and bodyweight. Intravenous iron (ferric carboxymaltose) initially administered up to a maximum dose of 2000 mg during the first 2 visits at baseline and at week 4; the subsequent fixed maintenance doses of 500 mg were administered every 4 months unless the haemoglobin concentration exceeded 16 g/dL or the serum ferritin level exceeded 800 ng/mL.
Population subgroups	Iron saturation (TSAT <20% vs TSAT ≥20%) explored for 3 primary endpoints.

Comparator	Saline was administered at all visits for patients in the placebo group.
Number of participants	1105 randomised.
Duration of follow-up	The median duration of follow-up was 16.6 months (IQR, 7.9-29.9 months).
Method of analysis	ITT analysis
Additional comments	The analysis of the primary end points related to time to cardiovascular death or first heart failure hospitalization (in the full population and in the population of patients with a transferrin saturation <20% at baseline) was performed using the Cox proportional hazards model (adjusted for stratification variables of the randomization) to derive hazard ratios (HRs) with 95% CIs. The analysis for the primary end point of total (first and recurrent) heart failure hospitalisations was based on the semiparametric regression model for the mean and rate functions of recurrent events proposed by Lin et al14 (adjusted for stratification variables of the randomization) and reported as rate ratios (RRs) with 95% CIs. Recurrent event outcomes were illustrated by cumulative incidence functions and time to event outcomes were illustrated by Kaplan-Meier curves and stratified by treatment group.

Study arms

Intravenous iron supplementation (ferric carboxymaltose) (N = 558)

Intravenous iron supplementation. Ferric carboxymaltose initially administered up to a maximum dose of 2000 mg during the first 2 visits at baseline and at week 4; the subsequent fixed maintenance doses of 500 mg were administered every 4 months unless the haemoglobin concentration exceeded 16 g/dL or the serum ferritin level exceeded 800 ng/m.

Placebo (N = 547)

Saline was administered at all visits for patients in the placebo group.

Characteristics

Arm-level characteristics

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 558)	Placebo (N = 547)
% Female Sample size	n = 199 ; % = 35.7	n = 169 ; % = 30.9
Age Mean (SD)	70.1 (11.4)	69.7 (12)
Ethnicity Sample size	n = NR	n = NR
NYHA class - Class II Sample size	n = 369 ; % = 66.1	n = 359 ; % = 65.6
NYHA class - Class III Sample size	n = 186 ; % = 33.3	n = 184 ; % = 33.6
NYHA class - class IV Sample size	n = 1 ; % = 0.2	n = 3 ; % = 0.6
Heart failure aetiology - Ischemic cause of cardiomyopathy Sample size	n = 428 ; % = 76.7	n = 430 ; % = 78.6

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 558)	Placebo (N = 547)
LVEF Sample size	n = NR	n = NR
Atrial fibrillation Sample size	n = 282 ; % = 50.5	n = 290 ; % = 53
Background (non-randomised) heart failure medications - ACEi Sample size	n = 240 ; % = 43	n = 215 ; % = 39.3
Background (non-randomised) heart failure medications - ARB Sample size	n = 100 ; % = 17.9	n = 90 ; % = 16.5
Background (non-randomised) heart failure medications - ARNI Sample size	n = 200 ; % = 35.8	n = 219 ; % = 40
Background (non-randomised) heart failure medications - BB Sample size	n = 504 ; % = 90.3	n = 512 ; % = 93.6
Background (non-randomised) heart failure medications - MRA Sample size	n = 386 ; % = 69.2	n = 393 ; % = 71.9

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 558)	Placebo (N = 547)
Background (non-randomised) heart failure medications - SGLT2i Sample size	n = 130 ; % = 23.3	n = 131 ; % = 24
Transferrin saturation (%) Mean (SD)	18.6 (9.3)	17.9 (9)
Haemoglobin Mean (SD)	12.5 (1.1)	12.4 (1.1)
Ferritin Mean (SD)	72 (52)	74 (58)
Anaemia Sample size	n = NR	n = NR

Outcomes

Study timepoints

- 16.6 month
- 36 month
- 12 month

Contrast outcomes

Outcome	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 16.6 month, N2 = 558, N1 = 547	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 36 month, N2 = 558, N1 = 547	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 12 month, N2 = 558, N1 = 547
All-cause mortality Hazard ratio/95% CI	NR	0.94 (0.72 to 1.24)	NR
Cardiovascular mortality Hazard ratio/95% CI	NR	0.8 (0.55 to 1.14)	NR
Unplanned hospitalisation or visits (HF related) (total (first and recurrent) hospitalizations for heart failure) Rate ratio (rate per 100 patient years) Custom value	0.80 (0.60-1.06)	NR	NR
Health-related quality of life (EQ-5D) Change score, range -0.59 to 1-1 Mean (95% CI)	NR	NR	0.03 (0.01 to 0.06)
Improvement in exercise tolerance (6-minute walk test) Change score Mean (95% CI)	NR	NR	10.7 (-1.44 to 22.9)

All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (HF related) (total (first and recurrent) hospitalizations for heart failure) - Polarity - Lower values are better
Health-related quality of life (EQ-5D) - Polarity - Higher values are better
Improvement in exercise tolerance (6-minute walk test) - Polarity - Higher values are better

Dichotomous outcomes

Outcome	Intravenous iron supplementation (ferric carboxymaltose), 16.6 month, N = 558	Intravenous iron supplementation (ferric carboxymaltose), 36 month, N = 558	Intravenous iron supplementation (ferric carboxymaltose), 12 month, N = NR	Placebo, 16.6 month, N = 547	Placebo, 36 month, N = 547	Placebo, 12 month, N = NR
• **Unplanned hospitalisation or visits (HF related) (Total HF hospitalisations)** (no of occurrences (for reference only)) First and recurrent HF hospitalisations No of events	n = 264 ; % = 47.3	n = NR ; % = NR	n = NR ; % = NR	n = 320 ; % = 58.5	n = NR ; % = NR	n = NR ; % = NR
All-cause mortality No of events	n = NR ; % = NR	n = 104 ; % = 9	n = NR ; % = NR	n = NR ; % = NR	n = 111 ; % = 10	n = NR ; % = NR
Cardiovascular mortality No of events	n = NR ; % = NR	n = 54 ; % = 5.8	n = NR ; % = NR	n = NR ; % = NR	n = 65 ; % = 7.5	n = NR ; % = NR

• Unplanned hospitalisation or visits (HF related) (Total HF hospitalisations) - Polarity - Lower values are better
All-cause mortality - Polarity - Lower values are better
Cardiovascular mortality - Polarity - Lower values are better

Continuous outcomes

Outcome	Intravenous iron supplementation (ferric carboxymaltose), 12 month, N = 558	Placebo, 12 month, N = 547
Health-related quality of life (EQ-5D) Change score, range -0.59 to 1-1 Mean (SD)	0.02 (0.18)	-0.02 (0.19)
Improvement in exercise tolerance (6-minute walk test) Change score Mean (SD)	27.2 (91.1)	19.7 (84.7)

Health-related quality of life (EQ-5D) - Polarity - Higher values are better
Improvement in exercise tolerance (6-minute walk test) - Polarity - Higher values are better
Arm based data for EQ-5D and 6MWT for reference.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All-cause mortality-Hazard Ratio- FUP 36 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Cardiovascular mortality- Hazard Ratio-FUP 36 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits(HF related) (total(first and recurrent) hospitalizations for HF)-Rate ratio - FUP 16.6 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness as not a TTE outcome)*

Health-related quality of life(EQ-5D)-MD- FUP 12 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Improvement in exercise tolerance (6-minute walk test)-MD -FUP 12 Mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (HF related) (Total HF hospitalisations)-No of occurrences-FUP 16.6 Mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome directness as not a TTE outcome)*

All-cause mortality-Events-FUP 36 Mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not a TTE outcome)*

Cardiovascular mortality-Events-FUP 36 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome indirectness because not a TTE outcome)*

Health-related quality of life (EQ-5D)-Mean (SD) - FUP 12 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Improvement in exercise tolerance (6-minute walk test)-Mean SD- FUP 12 mo

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Beck-da-Silva, 2013

Bibliographic Reference	Beck-da-Silva, L; Piardi, D; Soder, S; Rohde, LE; Pereira-Barretto, AC; de Albuquerque, D; Bocchi, E; Vilas-Boas, F; Moura, LZ; Montera, MW; Rassi, S; Clausell, N; IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia.; International journal of cardiology; 2013; vol. 168 (no. 4); 3439-3442

Study details

Secondary publication of another included study- see primary study for details	NA

Other publications associated with this study included in review	Beck-da-Silva, 2007
Trial name / registration number	IRON-HF [NCT00386126]
Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Not reported - report states that participants were ambulatory
Study dates	Unclear. The published protocol states that the first participant was planned to be enrolled in August 2006 and the last participant was expected to finish in July 2007.
Sources of funding	Altana Pharma
Inclusion criteria	18 years of age or older

	Outpatients followed at a HF clinic in a tertiary care hospital with clinical diagnosis of HF for at least 3 months before study entry NYHA functional class II IV, who are able to perform ergospirometry Documentation of LVEF <40% within the last 6 months Adequate baseline therapy for HF based on patient's functional class (β- blockers, ACE inhibitors irrespective of functional class except if contra-indications,digoxin, espironolactone if NYHA class III or IV) Stable baseline HF therapy with same doses of medications and no intent to increase doses for the following 3 months Haemoglobin ≤12 g/dl and ≥9 g/dl Transferrin saturation <20% and ferritin <500 µg/l Ability to provide written informed consent
Exclusion criteria	Any clinically overt bleeding: gastrointestinal bleeding, hypermenorrhea, history of peptic ulcer without evidence of healing or inflammatory intestinal diseases. Uncorrected hypothyroidism Other inflammatory, neoplastic or infectious disease

	Serum creatinine >1.5 mg/dl
	Previous intolerance to oral elemental iron compounds
	HF due to alcoholic cardiomyopathy, current regular drinker of alcoholic beverages or HF due to peripartum cardiomyopathy
	Recent admission for decompensated HF (last month)
	Recent myocardial revascularization procedures (last 3 months)
	Recent ACS, stroke or TIA (last 3 months)
	Active or metastatic neoplastic disease with life expectancy of less than a year
	Patients in heart transplantation list
	Patients that had participated in any other clinical trial or study within the last month
	Pregnant or lactating women
	Pre-menopausal women that are not using any effective method of contraception
	Patients using prohibited medications or that have not yet accomplished the washout period
	Patients currently participating in cardiovascular rehabilitation programs

	Patients with pacemakers, implanted defibrillators or cardiac resynchronization therapy
Recruitment / selection of participants	Not reported
Intervention(s)	Iron Sucrose 200 mg intravenously, once a week, in 30 min infusions, for 5 weeks plus placebo of oral presentation, three times a day, for 8 weeks.
Population subgroups	Report stated that *a priori* subgroup analysis was conducted for transferrin saturation > or < 20%. However, this was not reported. Abstract states that all participants had anaemia and preserved renal function
Comparator	Placebo of oral presentation, three times a day, for 8 weeks plus placebo of IV presentation once a week, for 5 weeks.
Number of participants	23 participants were randomized: IV iron n=10, oral iron n=7; placebo n=6.
Duration of follow-up	3 months

Indirectness	Directly applicable
Method of analysis	ITT analysis No further information provided
Additional comments	The study was terminated due to poor recruitment. The protocol stated that other outcomes of interest would be assessed including HR-QoL and hospitalisation for heart failure. However, these were not reported in the primary publication. Change in oxygen maximal consumption was reported, however, an appropriate measure of variance was not provided, and therefore this was not extracted.

Study arms

Intravenous iron supplementation (Iron sucrose IV) (N = 10)

In addition to oral placebo

Placebo (N = 6)

Placebo provided in oral and IV forms

Characteristics

Arm-level characteristics

Characteristic	Intravenous iron supplementation (Iron sucrose IV) (N = 10)	Placebo (N = 6)
% Female Reported as %males and calculated to %females by analyst Sample size	n = 3 ; % = 33.3	n = 2 ; % = 33.3
Age (years) Mean (SD)	66.9 (8.3)	68.9 (10.1)
Ethnicity Nominal	NR	NR
NYHA class Nominal	NR	NR

Characteristic	Intravenous iron supplementation (Iron sucrose IV) (N = 10)	Placebo (N = 6)
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Ischaemic Sample size	n = 2 ; % = 22.2	n = 4 ; % = 66.7
Idiopathic Sample size	n = 2 ; % = 22.2	n = 1 ; % = 16.7
Alcohol Sample size	n = 1 ; % = 11.1	n = 0 ; % = 0
Hypertensive Sample size	n = 2 ; % = 22	n = 1 ; % = 16.7
Chagas	n = 2 ; % = 22.2	n = 0 ; % = 0

Characteristic	Intravenous iron supplementation (Iron sucrose IV) (N = 10)	Placebo (N = 6)
Sample size		
Other Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Diabetes mellitus Sample size	n = 3 ; % = 33.3	n = 2 ; % = 33.3
LVEF Mean (SD)	25.2 (8.6)	30.7 (7.4)
Atrial fibrillation Sample size	n = 2 ; % = 22.2	n = 3 ; % = 50
Background (non-randomised) heart failure medications Nominal	NR	NR

Characteristic	Intravenous iron supplementation (Iron sucrose IV) (N = 10)	Placebo (N = 6)
Device therapy Nominal	NR	NR
Transferrin saturation (%) Mean (SD)	18.9 (9.7)	13.5 (5.8)
Haemoglobin (g/dL) Mean (SD)	11.2 (0.6)	10.9 (0.7)
Ferritin (µl) Mean (SD)	185 (146)	95 (128)
Anaemia Sample size	n = 10 ; % = 100	n = 6 ; % = 100

Outcomes

Study timepoints

3 month

Outcomes - arm based

Outcome	Intravenous iron supplementation (Iron sucrose IV), 3 month, N = 10	Placebo, 3 month, N = 6
All-cause mortality No of events	n = 2 ; % = 20	n = 1 ; % = 16.7

All-cause mortality - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All-cause mortality - No. of Events - Iron sucrose IV v Placebo - t3

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome being reported as number of events rather than time-to-event.)*

Beck-da-Silva, 2007

Bibliographic Reference	Beck-da-Silva, L; Rohde, LE; Pereira-Barretto, AC; de Albuquerque, D; Bocchi, E; Vilas-Boas, F; Moura, LZ; Montera, MW; Rassi, S; Clausell, N; Rationale and design of the IRON-HF study: a randomized trial to assess the effects of iron supplementation in heart failure patients with anemia.; Journal of cardiac failure; 2007; vol. 13 (no. 1); 14-17

Study details

Secondary publication of	Beck-da-Silva, 2013

another included study- see primary study for details	
Other publications associated with this study included in review	NA

Butler, 2022

Bibliographic Reference	Butler, Javed; Khan, Muhammad Shahzeb; Friede, Tim; Jankowska, Ewa A; Fabien, Vincent; Goehring, Udo-Michael; Dorigotti, Fabio; Metra, Marco; Pina, Ileana L; Coats, Andrew J S; Rosano, Giuseppe; Comin-Colet, Josep; Van Veldhuisen, Dirk J; Filippatos, Gerasimos S; Anker, Stefan D; Ponikowski, Piotr; Health status improvement with ferric carboxymaltose in heart failure with reduced ejection fraction and iron deficiency.; European journal of heart failure; 2022; vol. 24 (no. 5); 821-832

Study details

Secondary publication of another included study- see primary study for details	Pooled results from Ponikowski, 2015 and Anker, 2009
Other publications associated with this study included in review	Ponikowski, 2015 and Anker, 2009
Trial name / registration number	NA
Study location	Anker, 2009: Argentina, Czech Republic, Germany, Greece, Italy, Norway, Poland, Romania, Russia, Spain, Ukraine (75 study sites) Ponikowski, 2015: Unclear
Study setting	Study sites

Study dates	See Anker, 2009 and Ponikowski, 2015
Sources of funding	Vifor Pharma
Inclusion criteria	Ambulatory systolic CHF patients with iron deficiency
Exclusion criteria	Not specified
Recruitment / selection of participants	Selected from CONFIRM-HF and FAIR-HF
Intervention(s)	FAIR-HF intervention: Intravenous ferric carboxymaltose (200mg). Dosing frequency was weekly until iron repletion was achieved and then every four weeks during maintenance. CONFIRM-HF intervention: Ferric carboxymaltose solution given as an undiluted bolus IV injection of 10 or 20 mL (equivalent to 500 or 1000 mg of iron, respectively) and was administered over at least one minute. Dose was administered based on participant weight and Hb value at screening. Doses were between 500 and 2000 mg during the therapy phase (baseline to week 6) and 500 mg during the maintenance phase.
Population subgroups	NA

Comparator	Placebo
Number of participants	760 participants
Duration of follow-up	12 and 24 weeks
Indirectness	None
Additional comments	KCCQ overall score at 24 weeks (LS mean (SD)): FCM pool = 11.4 (18.7) Placebo pool= 5.7 (15.0) KCCQ clinical summary score at 24 weeks (LS mean (SD)): FCM pool = 10.0 (18.5) Placebo pool = 4.9 (14.9)

	KCCQ total summary score at 24 weeks (LS mean (SD)): FCM pool = 10.9 (19.4) Placebo pool = 4.8 (16.7)

Study arms

Intravenous ferric carboxymaltose (FCM) pool (N = 454)

Placebo pool (N = 306)

Characteristics

Arm-level characteristics

Characteristic	Intravenous ferric carboxymaltose (FCM) pool (N = 454)	Placebo pool (N = 306)
% Female Sample size	n = 226 ; % = 49.8	n = 159 ; % = 52
Age Mean (SD)	67.8 (10.1)	68.2 (10.4)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White European ethnicity Sample size	n = 452 ; % = 99.6	n = 305 ; % = 99.7
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
Class III	n = 321 ; % = 70.7	n = 186 ; % = 60.8

Characteristic	Intravenous ferric carboxymaltose (FCM) pool (N = 454)	Placebo pool (N = 306)
Sample size		
Heart failure aetiology Ischaemic heart failure Sample size	n = 370 ; % = 81.5	n = 249 ; % = 81.4
LVEF Mean (SD)	33.6 (6.7)	34.7 (6.9)
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
ARNI or SLGT2 inhibitors Sample size	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Intravenous ferric carboxymaltose (FCM) pool (N = 454)	Placebo pool (N = 306)
ACEI or ARB or ARNI Sample size	n = 423 ; % = 93.2	n = 283 ; % = 92.5
Beta-blocker Sample size	n = 393 ; % = 86.6	n = 267 ; % = 87.3
Aldosterone antagonist Sample size	n = 237 ; % = 52.2	n = 147 ; % = 48
Triple therapy Sample size	n = 194 ; % = 42.7	n = 122 ; % = 39.9
Transferrin saturation (%) Mean (SD)	18.15 (14.5)	17.4 (8.3)
Haemoglobin	12.1 (1.3)	12.2 (1.4)

Characteristic	Intravenous ferric carboxymaltose (FCM) pool (N = 454)	Placebo pool (N = 306)
Mean (SD)		
Ferritin Mean (SD)	54 (52.6)	58.6 (55.6)

Outcomes

Study timepoints

Baseline

24 week

12 week

Continuous outcomes

Outcome	Intravenous ferric carboxymaltose (FCM) pool vs Placebo pool, Baseline, N2 = 306, N1 = 454	Intravenous ferric carboxymaltose (FCM) pool vs Placebo pool, 24 week, N2 = 306, N1 = 454	Intravenous ferric carboxymaltose (FCM) pool vs Placebo pool, 12 week, N2 = 306, N1 = 454
Kansas City Cardiomyopathy Questionnaire (overall summary score) Least square mean difference Mean (95% CI)	NA (NA to NA)	4.45 (2.19 to 6.72)	4.36 (2.14 to 6.59)
Kansas City Cardiomyopathy Questionnaire (clinical summary score) Least square mean difference Mean (95% CI)	NA (NA to NA)	4.29 (2.05 to 6.53)	4.01 (1.82 to 6.2)
Kansas City Cardiomyopathy Questionnaire (total symptom score) Least square mean difference	NA (NA to NA)	5.23 (2.87 to 7.59)	4.78 (2.43 to 7.14)

Outcome	Intravenous ferric carboxymaltose (FCM) pool vs Placebo pool, Baseline, N2 = 306, N1 = 454	Intravenous ferric carboxymaltose (FCM) pool vs Placebo pool, 24 week, N2 = 306, N1 = 454	Intravenous ferric carboxymaltose (FCM) pool vs Placebo pool, 12 week, N2 = 306, N1 = 454
Mean (95% CI)			

Kansas City Cardiomyopathy Questionnaire (overall summary score) - Polarity - Higher values are better

Kansas City Cardiomyopathy Questionnaire (clinical summary score) - Polarity - Higher values are better

Kansas City Cardiomyopathy Questionnaire (total symptom score) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (overall summary score): Intravenous ferric carboxymaltose (FCM) pool versus Placebo pool at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (clinical summary score)-Intravenous ferric carboxymaltose (FCM) pool versus Placebo pool at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (total symptom score)-Intravenous ferric carboxymaltose (FCM) pool versus Placebo pool at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (overall summary score)-Intravenous ferric carboxymaltose (FCM) pool versus Placebo pool at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (clinical summary score)-Intravenous ferric carboxymaltose (FCM) pool versus Placebo pool at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (total symptom score)-Intravenous ferric carboxymaltose (FCM) pool versus Placebo pool at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Cleland, 2024

Bibliographic Reference	Cleland, John G F; Kalra, Philip A; Pellicori, Pierpaolo; Graham, Fraser J; Foley, Paul W X; Squire, Iain B; Cowburn, Peter J; Seed, Alison; Clark, Andrew L; Szwejkowski, Ben; Banerjee, Prithwish; Cooke, Justin; Francis, Mark; Clifford, Piers; Wong, Aaron; Petrie, Colin; McMurray, John J V; Thomson, Elizabeth A; Wetherall, Kirsty; Robertson, Michele; Ford, Ian; Kalra, Paul R; Intravenous iron for heart failure, iron deficiency definitions, and clinical response: the IRONMAN trial.; European heart journal; 2024; vol. 45 (no. 16); 1410-1426

Study details

Secondary publication of another included study- see primary study for details	Kalra, 2022a and Kalra, 2022b (primary)
Other publications associated with this study included in review	Kalra, 2022a and Kalra, 2022b (primary)

Trial name / registration number	IRONMAN/ NCT02642562

Study arms

intravenous ferric derisomaltose (N = 569)

Usual care (N = 568)

Outcomes

Study timepoints

Baseline

4 month

Continuous outcome

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
Haemoglobin change Mean (95% CI)	NA (NA to NA)	NA (NA to NA)
TSAT less than or equal to 10% Mean (95% CI)	11.4 (10.6 to 12.2)	1.4 (1 to 1.8)
TSAT >10 less than or equal to 15% Mean (95% CI)	12.1 (11.1 to 12.8)	0.4 (0.1 to 0.7)
TSAT >15 to <20 % Mean (95% CI)	12.3 (11.5 to 12.9)	0.5 (0.2 to 0.8)
TSAT greater than or equal to 20% Mean (95% CI)	12.6 (11.8 to 13.1)	0.3 (0.1 to 0.6)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
Moderate anaemia Mean (95% CI)	10.9 (10.3 to 11.5)	0.8 (0.5 to 1.1)
Mild anaemia Mean (95% CI)	12.3 (11.8 to 12.6)	0.8 (0.5 to 1)
None Mean (95% CI)	13.1 (12.7 to 13.6)	0.3 (0 to 0.6)
Minnesota Living with Heart Failure Questionnaire (overall) Difference at 4 months Mean (95% CI)	NA (NA to NA)	NA (NA to NA)
TSAT less than or equal to 10% Mean (95% CI)	51 (31 to 68)	-3 (-11 to 5)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
TSAT >10 less than or equal to 15 Mean (95% CI)	43 (26 to 61)	-3 (-10 to 4)
TSAT >15 to <20 % Mean (95% CI)	41 (22 to 66)	-3 (-10 to 4)
TSAT greater than or equal to 20% Mean (95% CI)	36 (19 to 58)	-2 (-8 to 4)
Moderate anaemia Mean (95% CI)	49 (29 to 66)	-7 (-13 to -2)
Mild anaemia Mean (95% CI)	42 (24 to 58)	-3 (-9 to 3)
None	39 (19 to 60)	1 (-5 to 6)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
Mean (95% CI)		
6 minute walk test Difference usual care vs FDI Mean (95% CI)	NA (NA to NA)	NA (NA to NA)
TSAT less than or equal to 10% Mean (95% CI)	240 (142 to 335)	9 (-39 to 57)
TSAT >10 less than or equal to 15 Mean (95% CI)	288 (174 to 351)	12 (-41 to 65)
TSAT >15 to <20 % Mean (95% CI)	259 (173 to 330)	1 (-45 to 47)
TSAT greater than or equal to 20%	300 (204 to 365)	-27 (-71 to 16)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
Mean (95% CI)		
Moderate anaemia Mean (95% CI)	235 (149 to 322)	-19 (-57 to 18)
Mild anaemia Mean (95% CI)	270 (180 to 361)	27 (-17 to 71)
None Mean (95% CI)	300 (201 to 370)	2 (-38 to 43)
All-cause mortality Hazard ratio/95% CI	NA (NA to NA)	NA (NA to NA)
TSAT less than or equal to 10% Hazard ratio/95% CI	NA (NA to NA)	0.96 (0.66 to 1.4)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
TSAT >10 less than or equal to 15 Hazard ratio/95% CI	NA (NA to NA)	1.13 (0.75 to 1.7)
TSAT >15 to <20 % Hazard ratio/95% CI	NA (NA to NA)	0.69 (0.45 to 1.06)
TSAT greater than or equal to 20% Hazard ratio/95% CI	NA (NA to NA)	1.3 (0.82 to 2.05)
Moderate anaemia Hazard ratio/95% CI	NA (NA to NA)	0.91 (0.68 to 1.21)
Mild anaemia Hazard ratio/95% CI	NA (NA to NA)	0.8 (0.54 to 1.2)
None	NA (NA to NA)	1.29 (0.86 to 1.94)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
Hazard ratio/95% CI		
CV mortality Hazard ratio/95% CI	NA (NA to NA)	NA (NA to NA)
TSAT less than or equal to 10% Hazard ratio/95% CI	NA (NA to NA)	0.9 (0.56 to 1.45)
TSAT >10 less than or equal to 15 Hazard ratio/95% CI	NA (NA to NA)	1.05 (0.64 to 1.7)
TSAT >15 to <20 % Hazard ratio/95% CI	NA (NA to NA)	0.63 (0.38 to 1.05)
TSAT greater than or equal to 20% Hazard ratio/95% CI	NA (NA to NA)	1.03 (0.59 to 1.82)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 568, N1 = 569	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 568, N1 = 569
Moderate anaemia Hazard ratio/95% CI	NA (NA to NA)	0.93 (0.61 to 1.42)
Mild anaemia Hazard ratio/95% CI	NA (NA to NA)	0.52 (0.25 to 1.08)
None Hazard ratio/95% CI	NA (NA to NA)	0.89 (0.45 to 1.76)

Haemoglobin change - Polarity - Higher values are better

Minnesota Living with Heart Failure Questionnaire (overall) - Polarity - Lower values are better

6 minute walk test - Polarity - Higher values are better

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Dichotomous outcomes

Outcome	intravenous ferric derisomaltose, Baseline, N = 569	intravenous ferric derisomaltose, 4 month, N = 569	Usual care, Baseline, N = 568	Usual care, 4 month, N = 568
All-cause mortality No of events	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA
TSAT less than or equal to 10% No of events	n = NA ; % = NA	n = NR ; % = 38.5	n = NA ; % = NA	n = NR ; % = 40.8
TSAT >10 less than or equal to 15 No of events	n = NA ; % = NA	n = NR ; % = 32.1	n = NA ; % = NA	n = NR ; % = 29.6
TSAT >15 to <20 % No of events	n = NA ; % = NA	n = NR ; % = 27.6	n = NA ; % = NA	n = NR ; % = 36.8

Outcome	intravenous ferric derisomaltose, Baseline, N = 569	intravenous ferric derisomaltose, 4 month, N = 569	Usual care, Baseline, N = 568	Usual care, 4 month, N = 568
TSAT greater than or equal to 20% No of events	n = NA ; % = NA	n = NR ; % = 30.5	n = NA ; % = NA	n = NR ; % = 25.8
Moderate anaemia No of events	n = NA ; % = NA	n = NR ; % = 41.1	n = NA ; % = NA	n = NR ; % = 48.1
Mild anaemia No of events	n = NA ; % = NA	n = NR ; % = 25.5	n = NA ; % = NA	n = NR ; % = 29.4
None No of events	n = NA ; % = NA	n = NR ; % = 29.1	n = NA ; % = NA	n = NR ; % = 22.2
CV mortality No of events	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA	n = NA ; % = NA

Outcome	intravenous ferric derisomaltose, Baseline, N = 569	intravenous ferric derisomaltose, 4 month, N = 569	Usual care, Baseline, N = 568	Usual care, 4 month, N = 568
TSAT less than or equal to 10% No of events	n = NA ; % = NA	n = NR ; % = 23.8	n = NA ; % = NA	n = NR ; % = 26.8
TSAT >10 less than or equal to 15 No of events	n = NA ; % = NA	n = NR ; % = 21.8	n = NA ; % = NA	n = NR ; % = 21.8
TSAT >15 to <20 % No of events	n = NA ; % = NA	n = NR ; % = 18.9	n = NA ; % = NA	n = NR ; % = 27.8
TSAT greater than or equal to 20% No of events	n = NA ; % = NA	n = NR ; % = 17.7	n = NA ; % = NA	n = NR ; % = 18.8
Moderate anaemia	n = NA ; % = NA	n = NR ; % = 26.8	n = NA ; % = NA	n = NR ; % = 35

Outcome	intravenous ferric derisomaltose, Baseline, N = 569	intravenous ferric derisomaltose, 4 month, N = 569	Usual care, Baseline, N = 568	Usual care, 4 month, N = 568
No of events				
Mild anaemia No of events	n = NA ; % = NA	n = NR ; % = 18.1	n = NA ; % = NA	n = NR ; % = 21.3
None No of events	n = NA ; % = NA	n = NR ; % = 16.9	n = NA ; % = NA	n = NR ; % = 14.9

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous outcome: Haemoglobin change- TSAT less than or equal to 10%: Intravenous ferric derisomaltose versus Usual care

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: TSAT >10 less than or equal to 15%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: TSAT >15 to <20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: Moderate anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Haemoglobin change: None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): TSAT >10 less than or equal to 15-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): TSAT >15 to<20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): Moderate anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: Minnesota Living with Heart Failure Questionnaire (overall): None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: TSAT >10 less than or equal to 15-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: TSAT >15 to <20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: Moderate anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: 6-minute walk test: None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: TSAT >10 less than or equal to 15-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: TSAT >15 to <20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: Moderate anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: All-cause mortality: None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: TSAT >10 less than or equal to 15-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: TSAT >15 to <20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: Moderate anaemia- Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: CV mortality: None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: All-cause mortality: TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-cause mortality: TSAT >10 less than or equal to 15-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-cause mortality: TSAT>15 to <20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-cause mortality: TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-cause mortality: Moderate anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-cause mortality: Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-cause mortality: None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: TSAT less than or equal to 10%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: TSAT >10 less than or equal to 15-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: TSAT >15 to <20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: TSAT greater than or equal to 20%-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Indirectly applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: Moderate anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: Mild anaemia-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: CV mortality: None-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Comin-Colet, 2013

Bibliographic Reference	Comin-Colet, J; Lainscak, M; Dickstein, K; Filippatos, GS; Johnson, P; L?scher, TF; Mori, C; Willenheimer, R; Ponikowski, P; Anker, SD; The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study.; European heart journal; 2013; vol. 34 (no. 1); 30-38

Study details

Secondary publication of another included study- see primary study for details	Secondary publication, Anker, 2009b
Other publications associated with this study included in review	Anker, 2009a, Anker, 2009b, and Filippatos, 2013
Trial name / registration number	FAIR-HF
Indirectness	None

Study arms

Ferric carboxymaltose (N = 304)

Placebo (N = 155)

Outcomes

Study timepoints

24 week

Continuous outcomes

Outcome	Ferric carboxymaltose, Baseline, N = 220	Ferric carboxymaltose, 24 week, N = 220	Placebo, Baseline, N = 220	Placebo, 24 week, N = 221
Kansas City Cardiomyopathy Questionnaire - Overall summary score Mean (SEM) Custom value	52± 1	12.8 ± 1.3	53 ±1	6.2 ± 1.5

Outcome	Ferric carboxymaltose, Baseline, N = 220	Ferric carboxymaltose, 24 week, N = 220	Placebo, Baseline, N = 220	Placebo, 24 week, N = 221
EQ-5D - Visual Analogue Scale Mean (SEM) (change score) Custom value	54 ±1	9.1 ± 1.0	54 ±1	3.4 ± 1.6
EQ-5D index score change from baseline Mean (SEM) calculated from values reported as index score multiplied by 100 Mean (SE)	0.68 ±0.01	0.066 (0.012)	0.69 ±0.01	-0.01 (0.018)
Kansas City Cardiomyopathy Questionnaire Clinical summary score Custom value	55 ±1	11.4 ±1.3 (36.8±4.9)	55 ±1	4.2 ±1.5 (12.6±3.7)

Kansas City Cardiomyopathy Questionnaire - Overall summary score - Polarity - Higher values are better

EQ-5D - Visual Analogue Scale - Polarity - Higher values are better

EQ-5D index score - Polarity - Higher values are better

Kansas City Cardiomyopathy Questionnaire - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: Kansas City Cardiomyopathy Questionnaire -Overall summary score: Anaemic versus Non-anaemic at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: EQ-5D- Visual Analogue Scale- Anaemic versus Non-anaemic at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: EQ-5D index score: Ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Kansas City Cardiomyopathy Questionnaire: Overall summary score: Baseline value-Ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: EQ-5D-Visual Analogue Scale-Baseline value-Ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: EQ-5D index score: Baseline values-Ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Kansas City Cardiomyopathy Questionnaire-Ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Dhoot, 2020

Bibliographic Reference	Dhoot, Sandip; Mittal, Sanjay; Singh, Simar Pal; Patel, Vishal; Kasliwal, Ravi R; Mehta, Varshil; Effect of ferric-carboxy maltose on oxygen kinetics and functional status in heart failure patients with iron deficiency.; Future science OA; 2020; vol. 6 (no. 5); fso467

Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial name / registration number	Not specified

Study location	India
Study setting	Heart failure clinic at Medanta Hospital
Study dates	June 2016 to June 2018
Sources of funding	Not specified
Inclusion criteria	Patients symptomatic chronic heart failure (NYHA functional class II/III) Between the ages of 18-65 years Iron deficiency Seen at the Heart Failure Clinic Medanta Hospital, Gurgaon over a 2 year period
Exclusion criteria	Those with severe anaemia (Hb<8 g/dl, requiring blood transfusion within 30 days) Chronic liver disease Vitamin B12 deficiency (<200 pg/dL) Serum folate deficiency (nmol/l) And/or any other severe cardiac disorder

Recruitment / selection of participants	Recruitment from Heart Failure Clinic Medanta Hospital
Intervention(s)	Intravenous ferric carboxy-maltose was administered to subjects in 0.9% normal saline bolus over 1 hour via drug infusion pump. Dose not specified.
Population subgroups	Not applicable
Comparator	Standard of care (no further details reported)
Number of participants	70 participants
Duration of follow-up	24 weeks
Indirectness	None

Additional comments	No serious side effects were noted during this study. There was no mortality or decompensated heart failure or severe hypersensitivity reaction to FCM. Minor side effects reported were constipation, abdominal discomfort, headache, metallic taste, myalgia and nausea, which were likely not due to FCM. There was no significant difference among two groups

Study arms

Intravenous ferric-carboxy maltose (N = 35)

Intravenous ferric-carboxy maltose

Standard of care (N = 35)

Standard of care

Characteristics

Arm-level characteristics

Characteristic	Intravenous ferric-carboxy maltose (N = 35)	Standard of care (N = 35)
Age Mean (SD)	51 (11.6)	54.8 (9)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
Class II Sample size	n = 26 ; % = 74.3	n = 30 ; % = 85.7
Class III Sample size	n = 9 ; % = 25.7	n = 5 ; % = 14.3
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Cornary artery disease	n = NA ; % = 31.4	n = NA ; % = 68.6

Characteristic	Intravenous ferric-carboxy maltose (N = 35)	Standard of care (N = 35)
Sample size		
LVEF Mean (SD)	24.9 (5)	25.8 (5.5)
Haemoglobin (mg/dl) Mean (SD)	11 (1.4)	11.3 (0.9)
Ferritin Mean (SD)	40.1 (27.2)	45.5 (35.1)

Outcomes

Study timepoints

12 week

Continuous outcomes

Outcome	Intravenous ferric-carboxy maltose, Baseline, N = 35	Intravenous ferric-carboxy maltose, 12 week, N = 35	Standard of care, Baseline, N = 35	Standard of care, 12 week, N = 35
Minnesota Living with Heart Failure Questionnaire MLHFQ- final scores Mean (SD)	46.9 (15.7)	34.7 (13)	47.9 (15.1)	41.9 (13.2)
6-minute walk test Distance covered in metres (final score) Mean (SD)	431 (64.79)	502.1 (70)	418 (46.9)	455.5 (52.3)
Peak VO2 (ml/kg/min) final score Mean (SD)	12.1 (3.1)	14.9 (3.4)	12.1 (3)	12.9 (3)
Serum haemoglobin (mg/dL)	11 (1.4)	12.5 (1.2)	11.3 (0.9)	12.2 (1.3)

Outcome	Intravenous ferric-carboxy maltose, Baseline, N = 35	Intravenous ferric-carboxy maltose, 12 week, N = 35	Standard of care, Baseline, N = 35	Standard of care, 12 week, N = 35
final score Mean (SD)				

Minnesota Living with Heart Failure Questionnaire - Polarity - Lower values are better
6-minute walk test - Polarity - Higher values are better

Peak VO2 - Polarity - Higher values are better

Serum haemoglobin - Polarity – Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous outcomes: Minnesota Living with Heart Failure Questionnaire: Intravenous ferric-carboxy maltose versus Standard of care at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to no pre-specified plan noted and noted baseline characteristic differences between the intervention and control arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-minute walk test: Intravenous ferric-carboxy maltose versus Standard of care at12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to no pre-specified plan noted and noted baseline characteristic differences between the intervention and control arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Peak VO2: Intravenous ferric-carboxy maltose versus Standard of care at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to no pre-specified plan noted and noted baseline characteristic differences between the intervention and control arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Serum haemoglobin: Intravenous ferric-carboxy maltose versus Standard of care at 12 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(High risk of bias due to no pre-specified plan noted and noted baseline characteristic differences between the intervention and control arms.)*
Overall bias and Directness	Overall Directness	Directly applicable

Filippatos, 2013

Bibliographic Reference	Filippatos, G; Farmakis, D; Colet, JC; Dickstein, K; L?scher, TF; Willenheimer, R; Parissis, J; Gaudesius, G; Mori, C; von Eisenhart Rothe, B; Greenlaw, N; Ford, I; Ponikowski, P; Anker, SD; Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial.; European journal of heart failure; 2013; vol. 15 (no. 11); 1267-1276

Study details

Secondary publication of another included study- see primary study for details	Secondary publication- Anker, 2009b is primary study
Other publications associated with this study included in review	Anker, 2009a, Anker, 2009b, and Comin-Colet, 2013
Trial name / registration number	FAIR-HF
Additional comments	Total FCM anaemic patients = 156 Total Placebo anaemic patients = 76 Total FCM non-anaemic patients = 149

	Total Placebo non-anaemic patients = 78

Study arms

IV ferric carboxymaltose (N = 304)

Administered as an IV push injection at a dose equivalent to 200 mg iron weekly until achievement of iron repletion (correction phase) and then every 4 weeks thereafter (maintenance phase)

Placebo (N = 155)

Placebo

Outcomes

Study timepoints

- 24 week

Dichotomous outcomes

Outcome	IV ferric carboxymaltose, 24 week, N = 304	Placebo, 24 week, N = 155
All-cause mortality No of events	n = 5 ; % = NR	n = 4 ; % = NR
All-cause mortality - Anaemic No of events	n = 4 ; % = NR	n = 3 ; % = NR
All-cause mortality - Non-anaemic	n = 1 ; % = NR	n = 1 ; % = NR

Outcome	IV ferric carboxymaltose, 24 week, N = 304	Placebo, 24 week, N = 155
No of events		
Cardiovascular death No of events	n = 4 ; % = NR	n = 4 ; % = NR
Cardiovascular death - Anaemic No of events	n = 3 ; % = NR	n = 3 ; % = NR
Cardiovascular death - Non-anaemic No of events	n = 1 ; % = NR	n = 1 ; % = NR
Hospitalisation for any cardiovascular reason No of events	n = 15 ; % = NR	n = 14 ; % = NR
Hospitalisation for any cardiovascular reason - Anaemic No of events	n = 7 ; % = NR	n = 9 ; % = NR
Hospitalisation for any cardiovascular reason - Non-anaemic No of events	n = 8 ; % = NR	n = 5 ; % = NR

All-cause mortality - Polarity - Lower values are better
Cardiovascular death - Polarity - Lower values are better
Hospitalisation for any cardiovascular reason - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: All-cause mortality: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: All-cause mortality: Anaemic: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: All-cause mortality: Non-anaemic: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: Cardiovascular death: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: Cardiovascular death: Anaemic: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: Cardiovascular death: Non-anaemic: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: Hospitalisation for any cardiovascular reason: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: Hospitalisation for any cardiovascular reason: Anaemic: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Dichotomous outcomes: Hospitalisation for any cardiovascular reason: Non-anaemic: IV ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events.)*

Foley, 2024

Bibliographic Reference	Foley, Paul W; Kalra, Paul R; Cleland, John G F; Petrie, Mark C; Kalra, Philip A; Squire, Ian; Campbell, Philip; Chapman, Callum; Donnelly, Patrick; Graham, Fraser; Hannah, Andrew; Lang, Ninian N; Matthews, Iain; Leslie, Stephen J; Pellicori, Pierpaolo; Piper, Sue; Ray, Robin; Savage, Hernry O; Spencer, Chales; Walsh, John; Wong, Yuk-Ki; Ford, Ian; Effect of correcting iron deficiency on the risk of serious infection in heart failure: Insights from the IRONMAN trial.; European journal of heart failure; 2024

Study details

Secondary publication of another included study- see primary study for details	Primary study = Kalra, 2022a
Other publications associated with this study included in review	Kalra, 2022b (EPPI: 15739433) and Cleland, 2024 (EPPI: 15739520)
Trial name / registration number	IRONMAN/ NCT02642562
Population subgroups	Baseline TSAT <20% vs ≥20% and number of infection events (no infections, first events, or recurrent events)

Study arms

Intravenous ferric derisomaltose (N = 569)

Usual care (N = 568)

Outcomes

Study timepoints

Baseline

2.7 year

Dichotomous Outcomes

Outcome	Intravenous ferric derisomaltose, Baseline, N = 569	Intravenous ferric derisomaltose, 2.7 year, N = 569	Usual care, Baseline, N = 568	Usual care, 2.7 year, N = 568
Hospitalisation with infection as the main cause First infection events No of events	n = NA ; % = NA	n = 111 ; % = 20	n = NA ; % = NA	n = 140 ; % = 25
Hospitalisation with infection as the main cause Recurrent events No of events	n = NA ; % = NA	n = 189 ; % = 13	n = NA ; % = NA	n = 223 ; % = 15

Hospitalisation with infection as the main cause (first infection events) - Polarity - Lower values are better

Hospitalisation with infection as the main cause (Recurrent events) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes-Hospitalisation with infection as the main cause: Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Kalra, 2022

Bibliographic Reference	Kalra, Paul R; Cleland, John G F; Petrie, Mark C; Thomson, Elizabeth A; Kalra, Philip A; Squire, Iain B; Ahmed, Fozia Z; Al-Mohammad, Abdallah; Cowburn, Peter J; Foley, Paul W X; Graham, Fraser J; Japp, Alan G; Lane, Rebecca E; Lang, Ninian N; Ludman, Andrew J; Macdougall, Iain C; Pellicori, Pierpaolo; Ray, Robin; Robertson, Michele; Seed, Alison; Ford, Ian; Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial.; Lancet (London, England); 2022; vol. 400 (no. 10369); 2199-2209

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Kalra, 2022b (EPPI: 15739433) and Cleland, 2024 (EPPI: 15739520)
Trial name / registration number	IRONMAN/ NCT02642562
Study type	Randomised controlled trial (RCT)
Study location	United Kingdom
Study setting	Hospital sites
Study dates	25 August 2016 to 15 October 2021

Sources of funding	The study was funded by the British Heart Foundation (grant award CS/15/1/31175) and Pharmacosmos.
Inclusion criteria	Aged 18 years or older with new or established symptomatic heart failure Evidence of iron deficiency (serum ferritin <100 µg/L or transferrin saturation <20%) Left ventricular ejection fraction of 45% or less within the preceding 24 months Either current or recent (within 6 months) admission to hospital due to heart failure or, for patients not fulfilling either of these criteria, have raised plasma concentrations of natriuretic peptides (NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in atrial fibrillation, or BNP >75 ng/L in sinus rhythm or >300 ng/L in atrial fibrillation).
Exclusion criteria	Patients had a serum ferritin concentrations greater than 400 µg/L or haemoglobin concentration less than 9 g/dL. Men with haemoglobin concentration of more than 14 g/dL and women with a haemoglobin concentration of more than 13 g/dL.
Recruitment / selection of participants	Recruited from current or recent hospital admission or outpatient with an elevated NT-proBNP or BNP
Intervention(s)	Intravenous ferric derisomaltose- Patients assigned to ferric derisomaltose had their estimated iron deficit determined on the basis of haemoglobin value and bodyweight. Patients attended a trial visit 4 weeks after randomisation and every 4

	months thereafter. Investigators gave intravenous ferric derisomaltose at trial visits if ferritin was less than 100 µg/L or if ferritin was 400 µg/L or less and transferrin saturation was less than 25%.Specific dose not provided.
Comparator	Usual care- Patients were permitted to receive oral iron therapy at the investigator's discretion, although this was not actively encouraged.
Number of participants	1137 participants were randomly assigned
Duration of follow-up	Median 2.7 years
Indirectness	
Method of analysis	ITT analysis
Additional comments	Full inclusion and exclusion criteria listed in Kalra, 2022b

Study arms

intravenous ferric derisomaltose (N = 569)

Usual care (N = 568)

Characteristics

Arm-level characteristics

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
% Female Sample size	n = 142 ; % = 25	n = 158 ; % = 28
Age Median (IQR)	73.2 (66.7 to 80.1)	73.5 (67.1 to 79.1)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
White Sample size	n = 519 ; % = 91	n = 524 ; % = 92
Black Sample size	n = 12 ; % = 2	n = 7 ; % = 1
Asian Sample size	n = 35 ; % = 6	n = 31 ; % = 5
Other Sample size	n = 3 ; % = 1	n = 6 ; % = 1
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class II	n = 328 ; % = 58	n = 320 ; % = 56

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
Sample size		
NYHA class III Sample size	n = 230 ; % = 40	n = 238 ; % = 42
NYHA class IV Sample size	n = 11 ; % = 2	n = 10 ; % = 2
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Ischaemic Sample size	n = 331 ; % = 58	n = 316 ; % = 56
Non-ischaemic Sample size	n = 177 ; % = 31	n = 196 ; % = 35

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
Unknown Sample size	n = 61 ; % = 11	n = 56 ; % = 10
LVEF Median (IQR)	32 (25 to 37)	35 (26 to 38)
Atrial fibrillation No of events	n = 284 ; % = 50	n = 250 ; % = 44
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Loop diuretic Sample size	n = 458 ; % = 80	n = 468 ; % = 82
Angiotensin converting enzyme inhibitor	n = 271 ; % = 48	n = 281 ; % = 49

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
Sample size		
Angiotensin-receptor blocker Sample size	n = 90 ; % = 16	n = 113 ; % = 20
Sacubitril-valsartan Sample size	n = 130 ; % = 23	n = 110 ; % = 19
Angiotensin-converting enzyme inhibitor, angiotensin-receptor blocker or sacubitril-valsartan Sample size	n = 468 ; % = 85	n = 498 ; % = 88
Beta-blocker Sample size	n = 500 ; % = 88	n = 509 ; % = 90
Mineralocorticoid receptor antagonist	n = 325 ; % = 57	n = 307 ; % = 54

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
Sample size		
Digoxin Sample size	n = 70 ; % = 12	n = 65 ; % = 11
Any glucose lowering medication Sample size	n = 223 ; % = 39	n = 239 ; % = 42
Insulin Sample size	n = 80 ; % = 14	n = 101 ; % = 18
Sodium-glucose cotransporter-2 inhibitor Sample size	n = 15 ; % = 3	n = 14 ; % = 2
Device therapy Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	intravenous ferric derisomaltose (N = 569)	Usual care (N = 568)
Implantable cardioverter-defribillator Sample size	n = 91 ; % = 16	n = 72 ; % = 13
Cardiac resynchronisation therapy Sample size	n = 125 ; % = 22	n = 118 ; % = 21
Transferrin saturation (%) Median (IQR)	15 (11 to 20)	15 (10 to 19)
Haemoglobin Median (IQR)	12.1 (11.2 to 12.8)	12.1 (11.2 to 12.9)
Ferritin Median (IQR)	49 (30 to 86)	50 (30 to 85)

Outcomes

Study timepoints

Baseline

2.7 year

4 month

Dichotomous outcomes

Outcome	intravenous ferric derisomaltose, Baseline, N = 569	intravenous ferric derisomaltose, 2.7 year, N = 569	intravenous ferric derisomaltose, 4 month, N = 569	Usual care, Baseline, N = 568	Usual care, 2.7 year, N = 568	Usual care, 4 month, N = 568
All-cause mortality No of events	n = NR ; % = NR	n = 184 ; % = 32	n = NR ; % = NR	n = NR ; % = NR	n = 193 ; % = 34	n = NR ; % = NR
Cardiovascular death	n = NR ; % = NR	n = 119 ; % = 21	n = NR ; % = NR	n = NR ; % = NR	n = 138 ; % = 24	n = NR ; % = NR

Outcome	intravenous ferric derisomaltose, Baseline, N = 569	intravenous ferric derisomaltose, 2.7 year, N = 569	intravenous ferric derisomaltose, 4 month, N = 569	Usual care, Baseline, N = 568	Usual care, 2.7 year, N = 568	Usual care, 4 month, N = 568
No of events						
All-Cause Hospitalisation No of events	n = NR ; % = NR	n = 351 ; % = 62	n = NR ; % = NR	n = NR ; % = NR	n = 370 ; % = 65	n = NR ; % = NR
Cardiovascular hospital admission No of events	n = NR ; % = NR	n = 254 ; % = 45	n = NR ; % = NR	n = NR ; % = NR	n = 273 ; % = 48	n = NR ; % = NR
Hospitalisation due to infection No of events	n = NA ; % = NA	n = 175 ; % = NR	n = NA ; % = NA	n = NA ; % = NA	n = 213 ; % = NR	n = NA ; % = NA

All-cause mortality - Polarity - Lower values are better

Cardiovascular death - Polarity - Lower values are better

All-Cause Hospitalisation - Polarity - Lower values are better

Cardiovascular hospital admission - Polarity - Lower values are better

Hospitalisation due to infection - Polarity - Lower values are better

Hazard ratios

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 569, N1 = 568	intravenous ferric derisomaltose vs Usual care, 2.7 year, N2 = 569, N1 = 568	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 569, N1 = 568
All-cause mortality Hazard ratio/95% CI	NA (NA to NA)	0.95 (0.78 to 1.17)	NA (NA to NA)
Cardiovascular death Hazard ratio/95% CI	NA (NA to NA)	0.86 (0.67 to 1.1)	NA (NA to NA)
All-Cause Hospitalisation Hazard ratio/95% CI	NA (NA to NA)	0.91 (0.79 to 1.05)	NA (NA to NA)

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 569, N1 = 568	intravenous ferric derisomaltose vs Usual care, 2.7 year, N2 = 569, N1 = 568	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 569, N1 = 568
Cardiovascular hospital admission Hazard ratio/95% CI	NA (NA to NA)	0.9 (0.76 to 1.07)	NA (NA to NA)
Hospitalisation due to infection Rate ratio (95%CI) Custom value	NA	0.82 (0.62 to 1.08)	NA

All-cause mortality - Polarity - Lower values are better
Cardiovascular death - Polarity - Lower values are better
All-Cause Hospitalisation - Polarity - Lower values are better
Cardiovascular hospital admission - Polarity - Lower values are better
Hospitalisation due to infection - Polarity - Lower values are better
Continuous outcomes

Outcome	intravenous ferric derisomaltose vs Usual care, Baseline, N2 = 569, N1 = 568	intravenous ferric derisomaltose vs Usual care, 4 month, N2 = 569, N1 = 568	intravenous ferric derisomaltose vs Usual care, 20 months, N2 = 569, N1 = 568
Overall score of Minnesota Living with Heart Failure questionnaire Estimated mean difference Mean (95% CI)	NA (NA to NA)	-3.33 (-6.67 to 0)	-2.57 (-6.72 to 1.59)
6 min walk distance (m) Mean difference Mean (95% CI)	NA (NA to NA)	-1.6 (-28.2 to 24.9)	-35.9 (-74.4 to 2.64)
EQ-5D index Mean difference Mean (95% CI)	NA (NA to NA)	0.01 (-0.02 to 0.04)	0.01 (-0.03 to 0.05)

Overall score of Minnesota Living with Heart Failure questionnaire at 4 months - Polarity - Lower values are better
Overall score of Minnesota Living with Heart Failure questionnaire at 20 months - Polarity - Lower values are better
6 min walk distance (m) at 4 months - Polarity - Higher values are better
EQ-5D index at 4 months - Polarity - Higher values are better

EQ-5D index at 20 months - Polarity - Higher values are better

Adverse events

Outcome	intravenous ferric derisomaltose, 2.7 year, N = 559	intravenous ferric derisomaltose, 4 month, N = 559	Usual care, 2.7 year, N = 568	Usual care, 4 month, N = 568
Atrial fibrillation No of events	n = 13	*NA*	n = 8	*NA*

Atrial fibrillation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: All-cause mortality: Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to participants and people delivering the intervention were aware of the assigned intervention and due to issues with adherence of the intervention (due to Covid pandemic).)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: Cardiovascular death- Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: All-Cause Hospitalisation- Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: Cardiovascular hospital admission- Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to number of event data provided instead of hazard ratios)*

Dichotomous outcomes: Hospitalisation due to infection-Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: All-cause mortality: Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular death: Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: All-Cause Hospitalisation-Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Cardiovascular hospital admission-Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Hazard ratios: Hospitalisation due to infection-Intravenous ferric derisomaltose versus Usual care at 2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Partially applicable *(Value reported as a rate ratio)*

Continuous outcomes: Overall score of Minnesota Living with Heart Failure questionnaire at 4 months: Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Overall score of Minnesota Living with Heart Failure questionnaire at 20 months: Intravenous ferric derisomaltose versus Usual care at 20 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-min walk distance (m) at 4 months: Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-min walk distance (m) at 20 months: Intravenous ferric derisomaltose versus Usual care at 20 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context; and high rate of missing data for the reported outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: EQ-5D index at 4 months: Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: EQ-5D index at 20 months: Intravenous ferric derisomaltose versus Usual care at 20 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Overall score of Minnesota Living with Heart Failure questionnaire-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-min walk distance(m)-Intravenous ferric derisomaltose versus Usual care at 4 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Atrial fibrillation-2.7 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Deviations from intended interventions: Unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context)*
Overall bias and Directness	Overall Directness	Directly applicable

Kalra, 2022

Bibliographic Reference	Kalra, Paul R; Cleland, John Gf; Petrie, Mark C; Ahmed, Fozia Z; Foley, Paul Wx; Kalra, Philip A; Lang, Ninian N; Lane, Rebecca E; Macdougall, Iain C; Pellicori, Pierpaolo; Pope, Michael T B; Robertson, Michele; Squire, Iain B; Thomson, Elizabeth A; Ford, Ian; Rationale and design of a randomised trial of intravenous iron in patients with heart failure.; Heart (British Cardiac Society); 2022; vol. 108 (no. 24); 1979-1985

Study details

Secondary publication of another included study- see primary study for details	Rationale for Kalra, 2022 and Cleland, 2024
Other publications associated with this study included in review	Kalra, 2022 and Cleland, 204

Trial name / registration number	IRONMAN/ NCT02642562
Study location	See primary study
Study setting	See primary study
Study dates	See primary study
Sources of funding	See primary study
Inclusion criteria	Age 18 years or older Left ventricular ejection fraction (LVEF) ≥45% within the last 2 years using any conventional imaging modality (most recent assessment) NYHA class II-IV Iron deficient (defined as transferrin saturation (TSAT) <20% and/or ferritin <100 micrograms/litre Evidence of being in a higher risk heart failure group Current or recent (within 6 months) hospitalisation for heart failure

	Outpatients with NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in atrial fibrillation (or BNP >75 pg/mL or 300 pg/ mL, respectively) Able and willing to provide informed consent
Exclusion criteria	Haemoglobin <9 g/dL or 13 g/dL in women or >14g/dL in men Ferritin >400ug/L eGFR <15 mL/min/1.73 m2 (MDRD/CKD-EPI) Already planned to receive intravenous iron Likely to need or already receiving erythropoiesis-stimulating agents Blood transfusion in the previous 3 months or active clinically relevant bleeding in the investigator's opinion or known or suspected gastrointestinal malignancy. Planned cardiac surgery or revascularisation Any major vascular event in the previous 3 months, including type 1 myocardial infarction, cerebrovascular accident, major cardiovascular surgery or percutaneous coronary intervention. Awaiting or treated by cardiac transplantation or left ventricular assist device

	Active infection (if the patient has significant ongoing infection, recruitment should be postponed until it has resolved or been controlled). Any disease other than heart failure with a life expectancy of <2 years Pregnancy, breast feeding or childbearing potential in the absence of effective contraception Contraindication to intravenous iron according to contemporary Summary of Product Characteristics including hypersensitivity to Monofer ® or any of its excipients; known serious hypersensitivity to other parenteral iron products; anaemia due to causes other than iron deficiency (eg, haemolytic anaemia); iron overload or disturbances in utilisation of iron (eg, haemochromatosis and haemosiderosis); and decompensated liver disease Participation in another intervention study involving a drug or device within the past 90 days (coenrolment in observational studies is permitted)
Recruitment / selection of participants	See primary study
Intervention(s)	See primary study
Population subgroups	See primary study

Comparator	See primary study
Number of participants	See primary study
Duration of follow-up	See primary study
Indirectness	See primary study
Additional comments	

Martens, 2021

Bibliographic Reference	Martens, Pieter; Dupont, Matthias; Dauw, Jeroen; Nijst, Petra; Herbots, Lieven; Dendale, Paul; Vandervoort, Pieter; Bruckers, Liesbeth; Tang, Wai Hong Wilson; Mullens, Wilfried; The effect of intravenous ferric carboxymaltose on cardiac reverse remodelling following cardiac resynchronization therapy-the IRON-CRT trial.; European heart journal; 2021; vol. 42 (no. 48); 4905-4914

Study details

Secondary publication of another included study- see primary study for details	Primary study
Other publications associated with this study included in review	Martens, 2019 (rationale and design)
Trial name / registration number	IRON-CRT/ NCT03380520
Study location	Belgium
Study setting	Hospital setting

Study dates	November 2017 to June 2019
Sources of funding	Research Foundation Flanders (grant number: 1127917N) and unrestricted research grant from Vifor Pharma
Inclusion criteria	See Martens 2019
Exclusion criteria	See Martens 2019
Recruitment / selection of participants	Not specified
Intervention(s)	IV ferric carboxymaltose diluted into 250mL NaCl 0.9%. Based on screening weight and screening haemoglobin, patients will require a dose of ferric carboxymaltose ranging between 500 to 2000mg. Maximal allowed dose of ferric carboxymaltose during one intravenous administration is 1000 mg/week, patients who require a dose of either 1500 or 2000 mg will receive a follow-up appointment after 1–2 weeks to receive the remaining dose
Population subgroups	TSAT
Comparator	Placebo (250 ml NaCl 0.9% solution without ferric carboxymaltose). Patients also requiring an additional dose based on their body weight and haemoglobin levels also receive a second dosing appointment with infusion of placebo at that time

Number of participants	75 participants
Duration of follow-up	3 months
Indirectness	Some outcomes reported in a manner that is not in accordance with the protocol.

Study arms

IV ferric carboxymaltose (N = 37)

Placebo (N = 38)

Characteristics

Arm-level characteristics

Characteristic	IV ferric carboxymaltose (N = 37)	Placebo (N = 38)
Age Mean (SD)	72 (12)	73 (9)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class - Class II Sample size	n = 22 ; % = 59	n = 19 ; % = 50
NYHA class - Class III Sample size	n = 15 ; % = 41	n = 19 ; % = 50
Heart failure aetiology No of events	n = 19 ; % = 51	n = 24 ; % = 63
LVEF	33 (8)	34 (7)

Characteristic	IV ferric carboxymaltose (N = 37)	Placebo (N = 38)
Mean (SD)		
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - ACEI/ARB/ARNI Sample size	n = 34 ; % = 92	n = 33 ; % = 87
Background (non-randomised) heart failure medications - ARNI Sample size	n = 20 ; % = 54	n = 18 ; % = 47
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 37 ; % = 100	n = 37 ; % = 97
Background (non-randomised) heart failure medications - MRA Sample size	n = 30 ; % = 81	n = 29 ; % = 76

Characteristic	IV ferric carboxymaltose (N = 37)	Placebo (N = 38)
Background (non-randomised) heart failure medications - Loop diuretics Sample size	n = 20 ; % = 54	n = 21 ; % = 55
Device therapy Sample size	n = NA ; % = NA	n = NA ; % = NA
Device therapy - CRT-D Sample size	n = 23 ; % = 62	n = 19 ; % = 50
Transferrin saturation (%) Mean (SD)	18.8 (6)	19.4 (7)
Haemoglobin Mean (SD)	13.3 (1.2)	13.1 (1.3)
Ferritin	82 (38 to 106)	81 (43 to 99)

Characteristic	IV ferric carboxymaltose (N = 37)	Placebo (N = 38)
Median (IQR)		

Outcomes

Study timepoints

Baseline

3 month

Continuous Outcomes

Outcome	IV ferric carboxymaltose, Baseline, N = 37	IV ferric carboxymaltose, 3 month, N = 37	Placebo, Baseline, N = 38	Placebo, 3 month, N = 35
Kansas City Cardiomyopathy Questionnaire	NA (NA to NA)	5.51 (1.2 to 9.82)	NA (NA to NA)	-2.72 (-7.29 to 1.84)

Outcome	IV ferric carboxymaltose, Baseline, N = 37	IV ferric carboxymaltose, 3 month, N = 37	Placebo, Baseline, N = 38	Placebo, 3 month, N = 35
change score Mean (95% CI)				
Peak VO2 change score Mean (SD)	NA (NA)	0.87 (2.44)	NA (NA)	-0.5 (2.59)

Kansas City Cardiomyopathy Questionnaire - Polarity - Higher values are better
Peak VO2 - Polarity - Higher values are better

Dichotomous Outcomes

Outcome	IV ferric carboxymaltose, Baseline, N = 37	IV ferric carboxymaltose, 3 month, N = 37	Placebo, Baseline, N = 38	Placebo, 3 month, N = 38
All-cause mortality	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 3 ; % = 8

Outcome	IV ferric carboxymaltose, Baseline, N = 37	IV ferric carboxymaltose, 3 month, N = 37	Placebo, Baseline, N = 38	Placebo, 3 month, N = 38
No of events				
Cardiovascular mortality No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 2 ; % = 5
Heart failure-related hospitalisation No of events	n = NA ; % = NA	n = 1 ; % = 3	n = NA ; % = NA	n = 4 ; % = 11

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

Heart failure-related hospitalisation - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Continuous Outcomes: Kansas City Cardiomyopathy Questionnaire: IV ferric carboxymaltose versus Placebo at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Reported as final values rather than change values)*

Continuous Outcomes: Peak VO2: IV ferric carboxymaltose versus Placebo at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Reported as final values rather than change values)*

Dichotomous Outcomes: All-cause mortality: IV ferric carboxymaltose versus Placebo at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Reported as dichotomous values rather than time-to-event)*

Dichotomous Outcomes: Cardiovascular mortality: IV ferric carboxymaltose versus Placebo at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Reported as dichotomous values rather than time-to-event)*

Dichotomous Outcomes: Heart failure-related hospitalisation: IV ferric carboxymaltose versus Placebo at 3 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Reported as dichotomous values rather than time-to-event)*

Martens, 2019

Bibliographic Reference	Martens, Pieter; Dupont, Matthias; Dauw, Jeroen; Somers, Frauke; Herbots, Lieven; Timmermans, Philippe; Verwerft, Jan; Mullens, Wilfried; Rationale and design of the IRON-CRT trial: effect of intravenous ferric carboxymaltose on reverse remodelling following cardiac resynchronization therapy.; ESC heart failure; 2019; vol. 6 (no. 6); 1208-1215

Study details

Secondary publication of another included	Rationale for Martens, 2021

study- see primary study for details	
Other publications associated with this study included in review	Martens, 2021
Trial name / registration number	IRON-CRT/ NCT03380520
Study location	Belgium
Study setting	Hospital
Study dates	See primary study
Sources of funding	See primary study

Inclusion criteria	Patients with chronic heart failure and implantation of cardiac resynchronization therapy for more than 6 months ago and presence of iron deficiency (ferritin <100 micrograms/L, irrespective of TSAT or ferritine between 100 and 300 micrograms/L with TSAT <20%) and presence of incomplete reverse remodelling (LVEF <45%) Age ≥18 years Obtained informed consent Stable pharmacological therapy of heart failure during the last 4 weeks (with the exception of diuretics) At least 98% bivacing the last 6 months
Exclusion criteria	A TSAT >45% Haemoglobin >15 g/dL at inclusion Planned cardiovascular hospitalisation during study period Known hypersensitivity to Injectafer Known active infection, CRP >20mg/L, clinically significant bleeding, and active malignancy Chronic liver disease and/or screening ALT or AST above three times the upper limit of the normal range Immunosuppressive therapy or renal dialysis (current or planned within the next 6 months)

	History of erythropoietin, IV or oral iron therapy, and blood transfusion in previous 12 weeks and/or such therapy planned within the next 6 months. Unstable angina pectoris as judged by the investigator, clinically significant uncorrected valvular disease or left ventricular outflow obstruction, obstructive cardiomyopathy, poorly controlled fast atrial fibrillation or flutter, and poorly controlled symptomatic bradyarrhythmias or tachyarrhythmias. Acute myocardial infarction or acute coronary syndrome, transient ischaemic attack, or stroke within the last 3 months Coronary artery bypass graft, percutaneous intervention (e.g. cardiac, cerebrovascular, and aortic, diagnostic catheters are allowed), or major surgery, including thoracic and cardiac surgery, within the last 3 months Inability to fully comprehend and/or perform study procedures in the investigator's opinion Vitamin B12 and/or serum folate deficiency according to the laboratory (re-screening is possible after substitution therapy) Pregnancy or lactation Participation in another clinical trial within previous 30 days and/or anticipated participation in another trial during this study
Recruitment / selection of participants	See primary study

Intervention(s)	Ferric carboxymaltose diluted into 250mL NaCl 0.9%. Based on screening weight and screening haemoglobin, patients will require a dose of ferric carboxymaltose ranging between 500 to 2000mg. Maximal allowed dose of ferric carboxymaltose during one intravenous administration is 1000 mg/week, patients who require a dose of either 1500 or 2000 mg will receive a follow-up appointment after 1–2 weeks to receive the remaining dose
Population subgroups	See primary study
Comparator	Placebo (250 ml NaCl 0.9% solution without ferric carboxymaltose). Patients also requiring an additional dose based on their body weight and haemoglobin levels also receive a second dosing appointment with infusion of placebo at that time
Number of participants	See primary study
Duration of follow-up	See primary study
Indirectness	NA

Mentz, 2021

Bibliographic Reference	Mentz, Robert J; Ambrosy, Andrew P; Ezekowitz, Justin A; Lewis, Gregory D; Butler, Javed; Wong, Yee Weng; De Pasquale, Carmine G; Troughton, Richard W; O'Meara, Eileen; Rockhold, Frank W; Garg, Jyostna; Samsky, Marc D; Leloudis, Dianne; Dugan, Michael; Mundy, Linda M; Hernandez, Adrian F; Randomized Placebo-Controlled Trial of Ferric Carboxymaltose in Heart Failure With Iron Deficiency: Rationale and Design.; Circulation. Heart failure; 2021; vol. 14 (no. 5); e008100

Study details

Secondary publication of another included study- see primary study for details	Mentz, Robert J, Garg, Jyotsna, Rockhold, Frank W et al. (2023) Ferric Carboxymaltose in Heart Failure with Iron Deficiency. The New England journal of medicine 389(11): 975-986
Other publications associated with this study included in review	Nouhravesh, Nina, Garg, Jyotsna, Rockhold, Frank W et al. (2024) Characterization of serum phosphate levels over time with intravenous ferric carboxymaltose versus placebo as treatment for heart failure with reduced ejection fraction and iron deficiency: An exploratory prospective substudy from HEART-FID. European journal of heart failure

Mentz, 2023

Bibliographic Reference	Mentz, Robert J; Garg, Jyotsna; Rockhold, Frank W; Butler, Javed; De Pasquale, Carmine G; Ezekowitz, Justin A; Lewis, Gregory D; O'Meara, Eileen; Ponikowski, Piotr; Troughton, Richard W; Wong, Yee Weng; She, Lilin; Harrington, Josephine; Adamczyk, Robert; Blackman, Nicole; Hernandez, Adrian F; Ferric Carboxymaltose in Heart Failure with Iron Deficiency.; The New England journal of medicine; 2023; vol. 389 (no. 11); 975-986

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	Nouhravesh, Nina, Garg, Jyotsna, Rockhold, Frank W et al. (2024) Characterization of serum phosphate levels over time with intravenous ferric carboxymaltose versus placebo as treatment for heart failure with reduced ejection fraction and iron deficiency: An exploratory prospective substudy from HEART-FID. European journal of heart failure Mentz, Robert J, Ambrosy, Andrew P, Ezekowitz, Justin A et al. (2021) Randomized Placebo-Controlled Trial of Ferric Carboxymaltose in Heart Failure With Iron Deficiency: Rationale and Design. Circulation. Heart failure 14(5): e008100

Trial name / registration number	HEART-FID [NCT03037931]
Study type	Randomised controlled trial (RCT)
Study location	North America, Australia, New Zealand, and Eastern Europe
Study setting	Unclear - patients were described as ambulatory
Study dates	Participants were screened between March 217 and November 2021, and follow-up data were collected through February 2023.
Sources of funding	American Regent, a Daiichi Sankyo Group company
Inclusion criteria	≥18 years of age Chronic HF with New York Heart Association functional class II to IV symptoms on maximally tolerated background therapy for ≥2 weeks before randomization EF ≤40% within 24 months or ≤30% within 36 months of screening Haemoglobin >9.0 g/dL and <13.5 g/dL (females) or <15.0 g/dL (males)

	Ferritin <100 ng/mL or 100 to 300 ng/mL with a transferrin saturation <20% Documented HF hospitalization within 12 months of enrolment or elevated N-terminal-pro-brain natriuretic peptide within 90 days of randomization
Exclusion criteria	Known hypersensitivity to any component of FCM History of acquired iron overload Received intravenous iron therapy or a blood transfusion (within 3 months) Have active gastrointestinal bleeding Screening ferritin <15 ng/mL without an appropriate medical evaluation within the past 3 months
Recruitment / selection of participants	Not reported
Intervention(s)	Ferric carboxymaltose in addition to standard therapy for heart failure. Dosing was based on weight (≥50 v <50 kg), and was given in 2 doses separated by 7 days. FCM was given either as a continuous infusion or a slow intravenous injection. Patients weighing >50 kg received 750 mg FCM, and for patients weighing <50 kg, the dose was adjusted to 15 g/kg. FCM was administered every 6 months on the basis of haemoglobin and iron indexes.

	Three participants did not receive FCM, and dose interruptions occurred in 300 participants. The median number of injections during follow-up was 6 (IQR 4 to 10). At the day 180 visit, 1008 of 1232 patients (81.8%) who had received the trial drug did not require additional iron-replacement therapy due to adequate iron indexes and haemoglobin levels. Use of intravenous iron outside the trial protocol occurred in 31 participants.
Population subgroups	Inclusion criteria included an LVEF of ≤40%, and therefore all participants had LVrEF Data were reported separately for presence of anaemia, however, this was only for a composite outcome that was not included in the protocol, and therefore it was not extracted.
Comparator	Placebo (no further details reported) in addition to standard therapy for heart failure. Placebo dosing volume was adjusted for weight to maintain blinding. Placebo was administered every 6 months on the basis of haemoglobin and iron indexes. Does interruptions occurred in 264 participants. The median number of injections during follow-up was 6 (IQR 4 to 10). Use of intravenous iron outside the trial protocol occurred in 104 participants.
Number of participants	8195 participants were screened and 3065 were enrolled and underwent randomisation. Of 1532 participants assigned to FCM, 7 were lost of follow-up and 48 withdrew consent for follow-up. Of 1533 participants assigned to placebo, 4 were lost to follow-up and 41 withdrew consent.

Duration of follow-up	Follow-up occurred every 3 months with assigned treatment administered every 6 months. Participants were followed for the duration of the trial, regardless of adherence. The median duration of follow-up was 1.9 years (IQR 1.3 to 3.0 years).
Indirectness	Directly applicable
Method of analysis	ITT analysis Described as all patients randomized to a treatment group in the study regardless of compliance with the study medication and participants were analysed as randomised.
Additional comments	NA

Study arms

Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)

Treatment in addition to standard therapy for heart failure

Placebo (N = 1533)

Treatment in addition to standard therapy for heart failure

Characteristics

Arm-level characteristics

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
% Female Sample size	n = 506 ; % = 33	n = 531 ; % = 34.6
Age (years) Mean (SD)	68.6 (10.9)	68.6 (11.2)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
White Sample size	n = 1324 ; % = 86.4	n = 1325 ; % = 86.4
Black Sample size	n = 162 ; % = 10.6	n = 160 ; % = 10.4
Asian Sample size	n = 19 ; % = 1.2	n = 21 ; % = 1.4
Other Sample size	n = 27 ; % = 1.8	n = 27 ; % = 1.8
Hispanic or Latino ethnnic group Sample size	n = 85 ; % = 5.5	n = 100 ; % = 6.5

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class II Sample size	n = 797 ; % = 52	n = 820 ; % = 53.5
NYHA class III Sample size	n = 711 ; % = 46.4	n = 692 ; % = 45.2
NYHA class IV Sample size	n = 22 ; % = 1.4	n = 19 ; % = 1.2
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
Ischaemic Sample size	n = 938 ; % = 61.2	n = 899 ; % = 58.7
LVEF (%) Mean (SD)	30.8 (7)	30.6 (7.3)
Atrial fibrillation Atrial fibrillation/flutter Sample size	n = 676 ; % = 44.1	n = 664 ; % = 43.3
Background (non-randomised) heart failure medications Sample size	n = NR ; % = NR	n = NR ; % = NR
ACE-inhibitor or ARB Sample size	n = 901 ; % = 58.8	n = 923 ; % = 60.3

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
Sacubitril-valsartan Sample size	n = 461 ; % = 30.1	n = 448 ; % = 29.2
Beta blocker Sample size	n = 1415 ; % = 92.4	n = 1418 ; % = 92.6
Mineralocorticoid receptor antagonist Sample size	n = 858 ; % = 56	n = 847 ; % = 55.3
SGLT2 inhibitor Sample size	n = 118 ; % = 7.7	n = 111 ; % = 7.2
Device therapy Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
Implantable cardioverter-defibrillator Sample size	n = 495 ; % = 32.3	n = 484 ; % = 31.6
Cardiac-resynchronization therapy Sample size	n = 230 ; % = 15	n = 232 ; % = 15.1
Transferrin saturation (%) (%) Based on 151 participants with data in the FCM arm and 1517 participant with data in the placebo arm Mean (SD)	23.9 (11.2)	23 (10.3)
Haemoglobin (g/dL) Based on 151 participants with data in the FCM arm and 1521 participants with data in the placebo arm Mean (SD)	12.6 (1.4)	12.5 (1.4)

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 1532)	Placebo (N = 1533)
Ferritin (µg/L) Serum ferritin. Data from 1517 participants in the FCM arm and 1526 participants in the placebo arm Sample size	n = 56 ; % = 47.3	n = 57.3 ; % = 51.4
Anaemia Iron-deficiency anaemia. Based on 1515 participants in the FCM arm and 1521 participants in the placebo arm Sample size	n = 858 ; % = 56.6	n = 900 ; % = 59.2

Outcomes

Study timepoints

Baseline

12 month

Longer-term follow-up (median 1.9 years)

Outcomes - contrast

Outcome	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Baseline, N2 = NA, N1 = NA	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 12 month, N2 = 1533, N1 = 1532	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Longer-term follow-up (median 1.9 years), N2 = 1533, N1 = 1532
All-cause mortality Hazard ratio/95% CI	NA (NA to NA)	0.82 (0.65 to 1.05)	0.9 (0.78 to 1.05)
Cardiovascular mortality Confidence intervals relate to 96% confidence intervals as opposed to 95% confidence intervals. SE calculated by analyst based on z score of 2.05	NA (NA to NA)	0.86 (0.72 to 1.03)	NA (NA to NA)

Outcome	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Baseline, N2 = NA, N1 = NA	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 12 month, N2 = 1533, N1 = 1532	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Longer-term follow-up (median 1.9 years), N2 = 1533, N1 = 1532
Hazard ratio/95% CI			
Cardiovascular mortality Confidence intervals relate to 96% confidence intervals as opposed to 95% confidence intervals. SE calculated by analyst based on z score of 2.05 Mean (SE)	NA (NA)	0.86 (0.0756)	NA (NA)

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

Outcomes - arm based

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 1532	Intravenous iron supplementation (ferric carboxymaltose), 12 month, N = 1532	Intravenous iron supplementation (ferric carboxymaltose), Longer-term follow-up (median 1.9 years), N = 1532	Placebo, Baseline, N = 1533	Placebo, 12 month, N = 1533	Placebo, Longer-term follow-up (median 1.9 years), N = 1533
All-cause mortality No of events	n = NA ; % = NA	n = 131 ; % = 8.6	n = 361 ; % = 23.6	n = NA ; % = NA	n = 158 ; % = 10.3	n = 376 ; % = 24.5
Cardiovascular mortality No of events	n = NA ; % = NA	n = NA ; % = NA	n = 251 ; % = 16.4	n = NA ; % = NA	n = NA ; % = NA	n = 275 ; % = 17.9
Unplanned hospitalisation or visits (heart-failure-related) Defined as hospitalization for heart failure	n = NA ; % = NA	n = 297 ; % = 19.4	n = 351 ; % = 22.9	n = NA ; % = NA	n = 332 ; % = 21.7	n = 353 ; % = 23

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 1532	Intravenous iron supplementation (ferric carboxymaltose), 12 month, N = 1532	Intravenous iron supplementation (ferric carboxymaltose), Longer-term follow-up (median 1.9 years), N = 1532	Placebo, Baseline, N = 1533	Placebo, 12 month, N = 1533	Placebo, Longer-term follow-up (median 1.9 years), N = 1533
No of events						
Improvement in exercise tolerance – 6-minute walk test (m) 12-month outcome reported as change from baseline Sample size	n = 1531 ; % = 99.9	n = 1159 ; % = 75.7	n = NA ; % = NA	n = 1531 ; % = 99.9	n = 1118 ; % = 72.9	n = NA ; % = NA
Improvement in exercise tolerance – 6-minute walk test (m)	273.9 (109.7)	5 (71)	NA (NA)	274.7 (109.4)	4 (72)	NA (NA)

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 1532	Intravenous iron supplementation (ferric carboxymaltose), 12 month, N = 1532	Intravenous iron supplementation (ferric carboxymaltose), Longer-term follow-up (median 1.9 years), N = 1532	Placebo, Baseline, N = 1533	Placebo, 12 month, N = 1533	Placebo, Longer-term follow-up (median 1.9 years), N = 1533
12-month outcome reported as change from baseline Mean (SD)						
Hypersensitivity No of events	n = NA ; % = NA	n = NA ; % = NA	n = 5 ; % = 0.3	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0
Hospitalisation for infection Defined as sepsis No of events	n = NA ; % = NA	n = NA ; % = NA	n = 21 ; % = 1.4	n = NA ; % = NA	n = NA ; % = NA	n = 13 ; % = 0.8

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (heart-failure-related) - Polarity - Lower values are better

Improvement in exercise tolerance – 6-minute walk test - Polarity - Higher values are better

Hypersensitivity - Polarity - Lower values are better

Hospitalisation for infection - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All-cause mortality - TTE - Ferric carboxymaltose v Placebo - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality - TTE - Ferric carboxymaltose v Placebo - longer-term follow-up (median 1.9years)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Directly applicable

Cardiovascular mortality - TTE - Ferric carboxymaltose v Placebo - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality - No. of Events - Ferric carboxymaltose v Placebo - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

All-cause mortality - No. of Events - Ferric carboxymaltose v Placebo- longer-term follow-up (median1.9 years)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Cardiovascular mortality - No. of Events - Ferric carboxymaltose v Placebo - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Unplanned hospitalisation or visits (heart-failure-related) - No. of events - Ferric carboxymaltose v Placebo - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Unplanned hospitalisation or visits (heart-failure-related) - No. of events - Ferric carboxymaltose v Placebo - Longer-term follow-up (median 1.9 years)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Improvement in exercise tolerance - Ferric carboxymaltose v Placebo - t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Directly applicable

Hypersensitivity - No. of events - Ferric carboxymaltose v Placebo - Longer-term follow-up (median 1.9 years)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Hospitalisation for infection - No. of events - Ferric carboxymaltose v Placebo - Longer-term follow-up (median 1.9 years)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(There were serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Directly applicable

Nouhravesh, 2024

Bibliographic Reference	Nouhravesh, Nina; Garg, Jyotsna; Rockhold, Frank W; De Pasquale, Carmine G; O'Meara, Eileen; Lewis, Gregory D; Butler, Javed; Harrington, Josephine; Ezekowitz, Justin A; Ponikowski, Piotr; Troughton, Richard W; Wong, Yee Weng; Blackman, Nicole; Numan, Syed; Adamczyk, Robert; Hernandez, Adrian F; Mentz, Robert J; Characterization of serum phosphate levels over time with intravenous ferric carboxymaltose versus placebo as treatment for heart failure with reduced ejection fraction and iron deficiency: An exploratory prospective substudy from HEART-FID.; European journal of heart failure; 2024

Study details

Secondary publication of another included study- see primary study for details	Mentz, Robert J, Garg, Jyotsna, Rockhold, Frank W et al. (2023) Ferric Carboxymaltose in Heart Failure with Iron Deficiency. The New England journal of medicine 389(11): 975-986
Other publications associated with this study included in review	Mentz, Robert J, Ambrosy, Andrew P, Ezekowitz, Justin A et al. (2021) Randomized Placebo-Controlled Trial of Ferric Carboxymaltose in Heart Failure With Iron Deficiency: Rationale and Design. Circulation. Heart failure 14(5): e008100
Exclusion criteria	In addition to the main study exclusion criteria, there were the following substudy exclusion criteria:

	History of primary hypophosphataemia disorder (for example X-linked hypophosphataemia) Baseline serum phosphate <2.5mg/dl Untreated primary hyperparathyroidism

Study arms

Intravenous iron supplementation (ferric carboxymaltose) (N = 62)

Treatment in addition to standard therapy for heart failure. Participants were a subset of the HEART-FID study where 1533 participants were randomised to the arm.

Placebo (N = 71)

Treatment in addition to standard therapy for heart failure. Participants were a subset of the HEART-FID study where 1532 participants were randomised to the arm.

Characteristics

Arm-level characteristics

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 62)	Placebo (N = 71)
% Female Sample size	n = 26 ; % = 41.9	n = 29 ; % = 40.8
Age Median (IQR)	71.7 (66.9 to 75.8)	65.8 (58.4 to 74.5)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Black Sample size	n = 1 ; % = 1.6	n = 4 ; % = 5.6
Pacific Islander Sample size	n = 1 ; % = 1.6	n = 0 ; % = 0

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 62)	Placebo (N = 71)
White Sample size	n = 60 ; % = 96.8	n = 67 ; % = 94.4
Hispanic or Latino Sample size	n = 4 ; % = 6.5	n = 2 ; % = 2.8
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class II Sample size	n = 25 ; % = 40.3	n = 27 ; % = 38
NYHA class III Sample size	n = 35 ; % = 56.5	n = 43 ; % = 60.6
NYHA class IV	n = 2 ; % = 3.2	n = 1 ; % = 1.4

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 62)	Placebo (N = 71)
Sample size		
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Ischaemic Sample size	n = 38 ; % = 61.3	n = 40 ; % = 56.3
Non-ischaemic Sample size	n = 23 ; % = 37.1	n = 28 ; % = 39.4
Unknown Sample size	n = 1 ; % = 1.6	n = 3 ; % = 4.2
LVEF Sample size	n = NA ; % = NA	n = NA ; % = NA

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 62)	Placebo (N = 71)
≤20 percent Sample size	n = 2 ; % = 3.2	n = 5 ; % = 7
>20 and <=30 percent Sample size	n = 10 ; % = 16.1	n = 13 ; % = 18.3
>30 and <=40 percent Sample size	n = 50 ; % = 80.6	n = 53 ; % = 74.6
Atrial fibrillation Nominal	NR	NR
Background (non-randomised) heart failure medications Nominal	NR	NR

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 62)	Placebo (N = 71)
Device therapy Nominal	NR	NR
Transferrin saturation (%) Mean (SD)	27.4 (11.9)	20.8 (8.9)
Haemoglobin Nominal	NR	NR
Ferritin (µg/L) Sample size	n = 55.9 ; % = 42.5	n = 48.6 ; % = 38.5
Anaemia Nominal	NR	NR

Outcomes

Study timepoints

6 month

Outcomes - arm based

Outcome	Intravenous iron supplementation (ferric carboxymaltose), 6 month, N = 59	Placebo, 6 month, N = 68
Hypophosphataemia Defined as serum phosphate <0.8mmol/L No of events	n = 34 ; % = 57.6	n = 7 ; % = 10.3

Hypophosphataemia - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Hypophosphataemia - No. of events - Ferric carboxymaltose v Placebo - t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The number of participants who entered the substudy from the primary study was low. There were also serious concerns around deviations from intended interventions as dose interruptions occurred in 564 participants (18.4%). Additionally, use of intravenous iron also occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.)*
Overall bias and Directness	Overall Directness	Directly applicable

Okonko, 2008

Bibliographic Reference	Okonko, Darlington O; Grzeslo, Agnieszka; Witkowski, Tomasz; Mandal, Amit K J; Slater, Robert M; Roughton, Michael; Foldes, Gabor; Thum, Thomas; Majda, Jacek; Banasiak, Waldemar; Missouris, Constantinos G; Poole-Wilson, Philip A; Anker, Stefan D; Ponikowski, Piotr; Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients

with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial.; Journal of the American College of Cardiology; 2008; vol. 51 (no. 2); 103-12

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	FERRIC-HF/ NCT00125996

Study location	United Kingdom and Poland
Study setting	Treatment centres
Study dates	Not specified
Sources of funding	Not specified
Inclusion criteria	Patients were 21 years or older Symptomatic CHF (New York Heart Association [NYHA] functional class II or III) Exercise limitation as evidenced by a reproducible pVO2/kg ≤18ml/kg/min during screening Average of 2 screenings Hb concentrations (<12.5 g/dl (anemic group) or 12.5 to 14.5 g/dl (nonanemic group)) Ferritin <100 microgram/l or between 100 to 300 microgram/l with a transferrin saturation (TSAT) <20% Left ventricular ejection fraction ≤45% measured within the preceding 6 months using echocardiography or magnetic resonance imaging Use of maximally tolerated doses of optimal CHF therapy for at least 4 weeks before recruitment and without dose changes for at least 2 weeks

	Resting blood pressure ≤160/100mm Hg Normal red cell folate and Vitamin B12 (according to local laboratory reference ranges)
Exclusion criteria	The use of erythropoietin, iron (oral or IV), or blood transfusion within the previous 30 days History of acquired iron overload or hemochromatosis (or a first relative with hemochromatosis) Earlier hypersensitivity to parental iron preparations or a history of allergic disorders Active infection Bleeding Malignancy or haemolytic anaemia Presence of any condition that precluded exercise testing (such as decompensated heart failure, significant musculoskeletal disease, unstable angina pectoris, obstructive cardiomyopathy, severe uncorrected valvular disease, or uncontrolled brady- or tachyarrhythmias, concurrent immunosuppressive or renal replacement therapy, or chronic liver disease (alanine transaminase >3 times the upper limit of the normal range)
Recruitment / selection of participants	Not specified

Intervention(s)	IV iron sucrose provided as a solution for IV infusion in 5 ml ampules (20mg iron/ml). The treatment group received iron weekly (therapeutic phase) unless ferritin was ≥500 ng/ml and then at weeks 4, 8, 12 and 16 (maintenance phase). The total dose of iron was estimated as body weight (kg) x 2.4 x (15 - patients' Hb [g/dl]) + 500 mg (for stores). Each dose was administered as 200-mg aliquots in 50 ml normal saline infused over 30 min. A test infusion (10 ml over 10 min) was performed before the first treatment. Patients were observed for drug reactions for up to 1 hour after all visits.
Population subgroups	Anaemic cohort and non-anaemic cohort
Comparator	No treatment (no further details reported)
Number of participants	35 patients
Duration of follow-up	18 weeks
Indirectness	None
Additional comments	Intention-to-treat

Study arms

IV iron sucrose (N = 24)

IV iron sucrose

Usual care (N = 11)

No treatment

Characteristics

Arm-level characteristics

Characteristic	IV iron sucrose (N = 24)	Usual care (N = 11)
Age Mean (SD)	64 (14)	62 (11)

Characteristic	IV iron sucrose (N = 24)	Usual care (N = 11)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
Caucasian Sample size	n = 21 ; % = 88	n = 10 ; % = 91
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
Class II Sample size	n = 13 ; % = 54	n = 6 ; % = 55
Class III Sample size	n = 11 ; % = 46	n = 5 ; % = 45
Heart failure aetiology	n = NA ; % = NA	n = NA ; % = NA

Characteristic	IV iron sucrose (N = 24)	Usual care (N = 11)
Sample size		
Ischemic aetiology Sample size	n = 18 ; % = 75	n = 8 ; % = 73
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Diuretics Sample size	n = 17 ; % = 71	n = 8 ; % = 73
ACE inhibitors Sample size	n = 18 ; % = 75	n = 8 ; % = 73
Angiotensin II antagonists Sample size	n = 5 ; % = 21	n = 2 ; % = 18

Characteristic	IV iron sucrose (N = 24)	Usual care (N = 11)
Beta-blockers Sample size	n = 20 ; % = 83	n = 11 ; % = 100
Spironolactone Sample size	n = 11 ; % = 46	n = 6 ; % = 55
Digoxin Sample size	n = 6 ; % = 25	n = 2 ; % = 18
Transferrin saturation (%) Mean (SD)	20 (8)	21 (9)
Haemoglobin Mean (SD)	12.6 (1.2)	12.1 (1)
Ferritin	62 (37)	88 (62)

Characteristic	IV iron sucrose (N = 24)	Usual care (N = 11)
Mean (SD)		

Outcomes

Study timepoints

Baseline

18 week

Dichotomous outcomes - anaemic cohort

Outcome	IV iron sucrose , Baseline, N = 12	IV iron sucrose , 18 week, N = 12	Usual care, Baseline, N = 6	Usual care, 18 week, N = 6
Death No of events	n = NA ; % = NA	n = 1 ; % = NR	n = NA ; % = NA	n = 0 ; % = NR

Outcome	IV iron sucrose , Baseline, N = 12	IV iron sucrose , 18 week, N = 12	Usual care, Baseline, N = 6	Usual care, 18 week, N = 6
Hospitalisation No of events	n = NA ; % = NA	n = 2 ; % = NR	n = NA ; % = NA	n = 2 ; % = NR

Death - Polarity - Lower values are better

Hospitalisation - Polarity - Lower values are better

Dichotomous outcomes- non-anaemic cohort

Outcome	IV iron sucrose , Baseline, N = 12	IV iron sucrose , 18 week, N = 12	Usual care, Baseline, N = 5	Usual care, 18 week, N = 5
Hospitalisation No of events	n = NA ; % = NA	n = 1 ; % = NR	n = NA ; % = NA	n = 1 ; % = NR

Hospitalisation - Polarity - Lower values are better

Continuous outcomes- anaemic cohort

Outcome	IV iron sucrose , Baseline, N = 12	IV iron sucrose , 18 week, N = 12	Usual care, Baseline, N = 6	Usual care, 18 week, N = 6
Peak VO2 (ml/kg/min) Change at 18 weeks Mean (SD)	12.9 (2.8)	2.8 (3.2)	14.7 (3.6)	-1.1 (0.9)
Haemoglobin (g/dL) Changes at 18 weeks Mean (SD)	11.7 (1)	0.5 (1.5)	11.4 (0.7)	0.6 (1.1)

Peak VO2 - Polarity - Higher values are better
Haemoglobin - Polarity - Higher values are better

Continuous outcomes- non-anaemic cohort

Outcome	IV iron sucrose , Baseline, N = 12	IV iron sucrose , 18 week, N = 12	Usual care, Baseline, N = 5	Usual care, 18 week, N = 5
Peak VO2 (ml/kg/min) Changes at 18 weeks Mean (SD)	14.9 (2.2)	-0.3 (1.9)	13.6 (2.4)	0.1 (0.8)
Haemoglobin (g/dL) Changes at 18 weeks Mean (SD)	13.6 (0.6)	0.2 (0.7)	13.1 (0.3)	0.2 (0.8)

Peak VO2 - Polarity - Higher values are better
Haemoglobin - Polarity - Higher values are better

Dichotomous outcomes- total population

Outcome	IV iron sucrose , Baseline, N = 24	IV iron sucrose , 18 week, N = 24	Usual care, Baseline, N = 11	Usual care, 18 week, N = 11
Death No of events	n = NA ; % = NA	n = 1 ; % = 4	n = NA ; % = NA	n = 0 ; % = 0
All-cause hospitalisation No of events	*empty data*	n = 3	*empty data*	n = 3
Heart-failure related hospitalisation No of events	*empty data*	n = 1	*empty data*	n = 2

Death - Polarity - Lower values are better

All-cause hospitalisation - Polarity - Lower values are better

Heart-failure related hospitalisation - Polarity - Lower values are better

Continuous outcomes- total population

Outcome	IV iron sucrose , Baseline, N = 20	IV iron sucrose , 18 week, N = 20	Usual care, Baseline, N = 11	Usual care, 18 week, N = 11
Changes in peak VO2 (ml/kg/min) Mean (SD)	13.9 (2.7)	1.5 (2.7)	14.2 (3)	-0.7 (1.4)
Changes in Minnesota Living with Heart Failure Questionnaire Mean (SD)	41 (22)	-10 (18)	46 (18)	3 (19)
Changes in haemoglobin (g/dL) Mean (SD)	12.6 (1.2)	0.5 (1.2)	12.2 (1)	0.4 (0.9)

Changes in peak VO2 - Polarity - Higher values are better

Changes in Minnesota Living with Heart Failure Questionnaire - Polarity - Lower values are better

Changes in haemoglobin - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: Anaemic cohort: Death: IV iron sucrose versus No treatment at18 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Dichotomous outcomes: Anaemic cohort: Hospitalisation-IV iron sucrose versus No treatment at week 18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Dichotomous outcomes: Non-anaemic cohort: Hospitalisation: IV iron sucrose versus No treatment at week 18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Continuous outcomes: Anaemic cohort: Changes in peak VO2: IV iron sucrose versus No treatment at week18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Non-anaemic cohort: Changes in peak VO2: IV iron sucrose versus No treatment at week18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Non-anaemic cohort: Changes in haemoglobin: IV iron sucrose versus No treatment at week 18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Total population: Death: IV iron sucrose versus No treatment at work18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Continuous outcomes: Total population: Changes in Minnesota Living with Heart Failure Questionnaire: IV iron sucrose versus No treatment at week18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Total population: Changes in haemoglobin: IV iron sucrose versus No treatment at week18

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: anaemic cohort: Changes in haemoglobin: IV iron sucrose versus No treatment at 18 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Total population: Changes in peak VO2: IV iron sucrose versus No treatment at 18 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Dichotomous outcomes: Total population: All-cause hospitalisation

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Dichotomous outcomes: Total population: Heart-failure related hospitalisation

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information about balanced interventions and participants being aware of the assigned intervention)*
Overall bias and Directness	Overall Directness	Partially applicable *(Outcome reported as number of events rather than time to event)*

Ponikowski, 2015

Bibliographic Reference	Ponikowski, P; van Veldhuisen, DJ; Comin-Colet, J; Ertl, G; Komajda, M; Mareev, V; McDonagh, T; Parkhomenko, A; Tavazzi, L; Levesque, V; Mori, C; Roubert, B; Filippatos, G; Ruschitzka, F; Anker, SD; Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency?.; European heart journal; 2015; vol. 36 (no. 11); 657-668

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA
Trial name / registration number	CONFIRM-HF [NCT01453608]
Study type	Randomised controlled trial (RCT)
Study location	Austria, Italy, Poland, Portugal, Russia, Spain, Sweden, UK, Ukraine
Study setting	Unclear. Report states that participants were ambulatory
Study dates	Participants were enrolled between September 2011 and February 2013

Sources of funding	Vifor Pharma Ltd.
Inclusion criteria	Stable ambulatory HF patients in New York Heart Association (NYHA) class II or III Left ventricular ejection fraction (LVEF) ≤45% Elevated natriuretic peptides (brain natriuretic peptide >100 pg/mL and/or N-terminal-pro-brain natriuretic peptide >400 pg/mL) Presence of ID [defined as serum ferritin level <100 ng/ mL, or between 100 and 300 ng/mL if transferrin saturation (TSAT) <20%] Haemoglobin (Hb) <15 g/dL Participant capable of completing the 6 min walk test
Exclusion criteria	Participants with an immediate need for transfusion Uncontrolled Hypertension Infection Clinical evidence of current malignancy

	Significantly impaired liver or renal function
Recruitment / selection of participants	Not reported
Intervention(s)	Ferric carboxymaltose solution given as an undiluted bolus IV injection of 10 or 20 mL (equivalent to 500 or 1000 mg of iron, respectively) and was administered over at least one minute. Dose was administered based on participant weight and Hb value at screening. Doses were between 500 and 2000 mg during the therapy phase (baseline to week 6) and 500 mg during the maintenance phase.
Population subgroups	Subgroup analysis was presented for LVEF ≥40% and <40%, however, all participants had LVEF ≤45% (see inclusion criteria). Therefore all participants were either LVrEF or LVmrEF. Subgroup analysis was presented for haemoglobin ≥12 g/dl and <12 g/dl, however, all participants had haemoglobin <15 g/dL.
Comparator	Normal saline [0.9% (w/v) NaCl] administered as placebo as per instructions for active therapy.
Number of participants	589 participants were screened, and 304 were randomised. Of 152 participants allocated to FCM, 123 participants completed the trial. Of 152 participants allocated to placebo, 128 completed the trial.

Duration of follow-up	6, 12, 24, 36, and 52 weeks
Indirectness	Study judged as directly applicable Haemoglobin in anaemic patients judged as partially direct as it is unclear how many participants had anaemia as the inclusion criteria included people with haemoglobin 15 g/dL
Method of analysis	ITT analysis ITT analysis - performed on the full-analysis set (FAS), including all subjects who were randomized and in whom investigational drug treatment was started, and with efficacy data returned. Subjects were analysed according to the treatment group to which they were randomly assigned. ANCOVA repeated measure models were used for the analysis of the continuous secondary end-points variables. Time-to-event analyses were conducted using Kaplan–Meier estimators and log-rank tests. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were obtained from the proportional hazard ratio models. Other Safety analyses by summary statistics were performed on all subjects who received at least one dose of investigational drug or placebo. Follow up for collection of key safety information was until 30 days after the end of the study. Subjects were analysed according to the treatment they actually received.

Additional comments	None

Study arms

Intravenous iron supplementation (ferric carboxymaltose) (N = 152)

Placebo (N = 152)

Saline

Characteristics

Arm-level characteristics

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 152)	Placebo (N = 152)
% Female Sample size	n = 67 ; % = 45	n = 74 ; % = 49
Age Mean (SD)	68.8 (9.5)	69.5 (9.3)
Ethnicity Sample size	n = NA ; % = NA	n = NA ; % = NA
White Sample size	n = 149 ; % = 99	n = 150 ; % = 99
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class II	n = 80 ; % = 53	n = 91 ; % = 60

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 152)	Placebo (N = 152)
Sample size		
NYHA class III Sample size	n = 70 ; % = 47	n = 60 ; % = 40
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Ischamic cause of heart failure Sample size	n = 125 ; % = 83	n = 126 ; % = 83
LVEF (%) Mean (SD)	37.1 (7.5)	36.5 (7.3)
Atrial fibrillation Sample size	n = 66 ; % = 44	n = 73 ; % = 48

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 152)	Placebo (N = 152)
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Diuretic Sample size	n = 132 ; % = 88	n = 139 ; % = 92
ACE inhibitor Sample size	n = 116 ; % = 77	n = 118 ; % = 78
ARB Sample size	n = 34 ; % = 23	n = 37 ; % = 25
Digitalis glycoside Sample size	n = 29 ; % = 19	n = 40 ; % = 27

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 152)	Placebo (N = 152)
Beta-blocker Sample size	n = 133 ; % = 89	n = 139 ; % = 92
Device therapy Nominal	NR	NR
Transferrin saturation (%) Mean (SD)	20.2 (17.6)	18.2 (8.1)
Haemoglobin (g/dL) Mean (SD)	12.37 (1.41)	12.42 (1.3)
Ferritin (ng/mL) Mean (SD)	57 (48.4)	57.1 (41.6)
Anaemia	NA	NA

Characteristic	Intravenous iron supplementation (ferric carboxymaltose) (N = 152)	Placebo (N = 152)
Nominal		

Outcomes

Study timepoints

Baseline

52 week

56 week (Reported safety data were from 30 days after the end of the study)

Contrast-level outcome data

Outcome	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Baseline, N2 = 151, N1 = 150	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 52 week, N2 = 151, N1 = 150	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 56 week, N2 = 151, N1 = 150
All-cause mortality Hazard ratio/95% CI	NR (NR to NR)	0.89 (0.41 to 1.93)	NR (NR to NR)
Cardiovascular mortality Defined as death for any cardiovascular reason Hazard ratio/95% CI	NR (NR to NR)	0.96 (0.42 to 2.16)	NR (NR to NR)
Unplanned hospitalisation or visits (all-cause) Defined as hospitalisations Hazard ratio/95% CI	NR (NR to NR)	0.71 (0.45 to 1.12)	NR (NR to NR)
Unplanned hospitalisation or visits	NR (NR to NR)	0.39 (0.19 to 0.82)	NR (NR to NR)

Outcome	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Baseline, N2 = 151, N1 = 150	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 52 week, N2 = 151, N1 = 150	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 56 week, N2 = 151, N1 = 150
(heart-failure-related) Hospitalisations due to worsening HF Hazard ratio/95% CI			

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (all-cause) - Polarity - Lower values are better

Unplanned hospitalisation or visits (heart-failure-related) - Polarity - Lower values are better

Arm-level outcome data

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
All-cause mortality No of events	n = NA ; % = NA	n = 12 ; % = 8	n = NA ; % = NA	n = NA ; % = NA	n = 14 ; % = 9.3	n = NA ; % = NA
Cardiovascular mortality Defined as death for any cardiovascular reason No of events	n = NA ; % = NA	n = 11 ; % = 7.3	n = NA ; % = NA	n = NA ; % = NA	n = 12 ; % = 7.9	n = NA ; % = NA
HRQoL - Kansas City Cardiomyopathy Questionnaire (KCCQ) Change from baseline. Overall score ranges from 0 to 100 Sample size	n = 150 ; % = 100	n = 114 ; % = 76	n = NR ; % = NR	n = 151 ; % = 100	n = 106 ; % = 70.2	n = NR ; % = NR

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
HRQoL - Kansas City Cardiomyopathy Questionnaire (KCCQ) Change from baseline. Overall score ranges from 0 to 100 Mean (95% CI)	NA (NA to NA)	6.8 (4.4 to 9.2)	NR (NR to NR)	NA (NA to NA)	2.3 (-0.2 to 4.8)	NR (NR to NR)
HRQoL - Kansas City Cardiomyopathy Questionnaire (KCCQ) Change from baseline. Overall score ranges from 0 to 100 Mean (SD)	59 (17.3)	NA (NA)	NR (NR)	58.8 (17.9)	NA (NA)	NR (NR)

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
HRQOL - European Quality of Life-5 Dimensions (EQ-5D) Visual Analogue Scale Change from baseline. Overall score ranges from 0 to 100 Sample size	n = 150 ; % = 100	n = 114 ; % = 76	n = NR ; % = NR	n = 151 ; % = 100	n = 106 ; % = 70.2	n = NR ; % = NR
HRQOL - European Quality of Life-5 Dimensions (EQ-5D) Visual Analogue Scale Change from baseline. Overall score ranges from 0 to 100 Mean (95% CI)	NA (NA to NA)	7 (4.7 to 9.4)	NR (NR to NR)	NA (NA to NA)	4.4 (2 to 6.9)	NR (NR to NR)

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
HRQOL - European Quality of Life-5 Dimensions (EQ-5D) Visual Analogue Scale Change from baseline. Overall score ranges from 0 to 100 Mean (SD)	54.7 (15)	NA (NA)	NR (NR)	54.1 (16.3)	NA (NA)	NR (NR)
Unplanned hospitalisation or visits (all causes) Defined as hospitalisations No of events	n = NA ; % = NA	n = 46 ; % = 30.7	n = NA ; % = NA	n = NA ; % = NA	n = 69 ; % = 45.7	n = NA ; % = NA
Unplanned hospitalisation or visits (heart-failure-related)	n = NA ; % = NA	n = 10 ; % = 6.7	n = NA ; % = NA	n = NA ; % = NA	n = 32 ; % = 21.2	n = NA ; % = NA

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
Hospitalisations due to worsening HF No of events						
Improvement in exercise tolerance – 6-minute walk test (meters) Adjusted LS mean - Change from baseline Sample size	n = 150 ; % = 100	n = 125 ; % = 83.3	n = NR ; % = NR	n = 151 ; % = 100	n = 121 ; % = 80.1	n = NR ; % = NR
Improvement in exercise tolerance – 6-minute walk test (meters)	NA (NA to NA)	14 (-1 to 29)	NR (NR to NR)	NA (NA to NA)	-22 (-37 to -7)	NR (NR to NR)

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
Adjusted LS mean - Change from baseline Mean (95% CI)						
Improvement in exercise tolerance – 6-minute walk test (meters) Adjusted LS mean - Change from baseline Mean (SD)	288 (98)	NA (NA)	NR (NR)	302 (97)	NA (NA)	NR (NR)
Withdrawal due to adverse events No of events	n = NA ; % = NA	n = NA ; % = NA	n = 14 ; % = 9.2	n = NA ; % = NA	n = NA ; % = NA	n = 19 ; % = 12.5

Outcome	Intravenous iron supplementation (ferric carboxymaltose), Baseline, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 52 week, N = 150	Intravenous iron supplementation (ferric carboxymaltose), 56 week, N = 150	Placebo, Baseline, N = 151	Placebo, 52 week, N = 151	Placebo, 56 week, N = 151
Anaphylaxis/hypersensitivity Defined as severe allergic reactions No of events	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = NA ; % = NA	n = 0 ; % = 0

All-cause mortality - Polarity - Lower values are better

Cardiovascular mortality - Polarity - Lower values are better

HRQoL - Kansas City Cardiomyopathy Questionnaire (KCCQ) - Polarity - Higher values are better

HRQOL - European Quality of Life-5 Dimensions (EQ-5D) Visual Analogue Scale - Polarity - Higher values are better

Unplanned hospitalisation or visits (all causes) - Polarity - Lower values are better

Unplanned hospitalisation or visits (heart-failure-related) - Polarity - Lower values are better

Improvement in exercise tolerance – 6-minute walk test - Polarity - Higher values are better

Withdrawal due to adverse events - Polarity - Lower values are better

Anaphylaxis/hypersensitivity - Polarity - Lower values are better

Continuous outcome

Outcome	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, Baseline, N2 = 152, N1 = 152	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 52 week, N2 = 106, N1 = 114	Intravenous iron supplementation (ferric carboxymaltose) vs Placebo, 56 week, N2 = NA, N1 = NA
EQ-5D-VAS change score Custom value	NA	2.6 (-0.7 to 5.9)	NA

EQ-5D-VAS - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All-cause mortality - TTE - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Cardiovascular mortality - TTE - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (all-cause) - TTE - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (heart-failure-related) - TTE - ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality - No. of Events - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable (Outcome reported as number of events rather than time to event)

Cardiovascular mortality - No. of Events - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Outcome reported as number of events rather than time to event)

HRQoL - KCCQ - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

HRQoL - EQ-5D - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (all causes) - No. of Events - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable (Outcome reported as number of events rather than time to event)

Unplanned hospitalisation or visits (heart-failure-related) - No. of Events - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable (Outcome reported as number of events rather than time to event)

6-minute walk test - Ferric carboxymaltose v Placebo - t52

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Withdrawal due to adverse events - No. of Events - Ferric carboxymaltose v Placebo - t56

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Anaphylaxis/hypersensitivity - No. of Events - Ferric carboxymaltose v Placebo - t56

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcome: EQ-5D-VAS: Intravenous iron supplementation (ferric carboxymaltose) versus Placebo at 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Toblli, 2017

Bibliographic Reference	Toblli, J.E.; Di Gennaro, F.P.; Long-term effect of intravenous iron on overall survival and hospitalization in patients with heart failure with reduced ejection fraction, iron deficiency and mild renal impairment: An open-label 5-year follow up observation; Journal of Clinical and Diagnostic Research; 2017; vol. 11 (no. 11); oc18-oc24

Study details

Secondary publication of another included study- see primary study for details	Toblli, JE, Lombra?a, A, Duarte, P et al. (2007) Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. Journal of the American College of Cardiology 50(17): 1657-1665
Other publications associated with this study included in review	Toblli, JE; Di Gennaro, F; Rivas, C (2015) Changes in Echocardiographic Parameters in Iron Deficiency Patients with Heart Failure and Chronic Kidney Disease Treated with Intravenous Iron. Heart, lung & circulation 24(7): 686-695

Study arms

Intravenous iron supplementation (Iron sucrose) (N = 20)

Treatment in addition to conventional therapy for CHF

Placebo (N = 20)

Treatment in addition to to conventional therapy for CHF

Outcomes

Study timepoints

1 year

5 year

Arm-level outcomes

Outcome	Intravenous iron supplementation (Iron sucrose), 1 year, N = 20	Intravenous iron supplementation (Iron sucrose), 5 year, N = 20	Placebo, 1 year, N = 20	Placebo, 5 year, N = 20
All-cause mortality No of events	n = 1 ; % = 5	n = 4 ; % = 20	n = 4 ; % = 20	n = 11 ; % = 55

Outcome	Intravenous iron supplementation (Iron sucrose), 1 year, N = 20	Intravenous iron supplementation (Iron sucrose), 5 year, N = 20	Placebo, 1 year, N = 20	Placebo, 5 year, N = 20
CV mortality No of events	n = NR ; % = NR	n = 2 ; % = 10	n = NR ; % = NR	n = 6 ; % = 30
Unplanned hospitalisation or visits (all-cause) No of events	n = 2 ; % = 10	n = 4 ; % = 20	n = 10 ; % = 50	n = 17 ; % = 85
Unplanned hospitalisation or visits (heart-failure-related) No of events	n = NR ; % = NR	n = 3 ; % = 15	n = NR ; % = NR	n = 16 ; % = 80

All-cause mortality - Polarity - Lower values are better

CV mortality - Polarity - Lower values are better

Unplanned hospitalisation or visits (all-cause) - Polarity - Lower values are better

Unplanned hospitalisation or visits (heart-failure-related) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

All-cause mortality - No. of Events - Iron sucrose v Placebo - 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events rather than time to event)*

All-cause mortality - No- of Events - Iron sucrose v Placebo - 5 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events rather than time to event)*

CV mortality - No. Of Events - Iron sucrose v Placebo - 5 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events rather than time to event)*

Unplanned hospitalisation or visits (all-cause) - No. Of Events - Iron sucrose v Placebo - 1 year

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events rather than time to event)*

Unplanned hospitalisation or visits (all-cause) - No. Of Events - Iron sucrose v Placebo - 5 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events rather than time to event)*

Unplanned hospitalisation or visits (heart-failure-related) - No. Of Events - Iron sucrose v Placebo - 5 years

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to outcome reported as number of events rather than time to event)*

Toblli, 2015

Bibliographic Reference	Toblli, JE; Di Gennaro, F; Rivas, C; Changes in Echocardiographic Parameters in Iron Deficiency Patients with Heart Failure and Chronic Kidney Disease Treated with Intravenous Iron.; Heart, lung & circulation; 2015; vol. 24 (no. 7); 686-695

Study details

Secondary publication of another included	Toblli, 2007

study- see primary study for details	
Other publications associated with this study included in review	Toblli, 2017

Toblli, 2007

Bibliographic Reference	Toblli, JE; Lombra?a, A; Duarte, P; Di Gennaro, F; Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency.; Journal of the American College of Cardiology; 2007; vol. 50 (no. 17); 1657-1665

Study details

Secondary publication of	NA

another included study- see primary study for details	
Other publications associated with this study included in review	Toblli, 2017 and Toblli, 2015
Trial name / registration number	NCT02392910
Study type	Randomised controlled trial (RCT)
Study location	Argentina
Study setting	Not reported
Study dates	Not reported
Sources of funding	Not reported

Inclusion criteria	Diagnosis of chronic heart failure, chronic renal failure, anaemia, and iron deficiency: LV ejection fraction (EF) ≤35% New York Heart Association (NYHA) functional class II to IV Anaemia with an iron deficiency defined by Hb <12.5 g/dl for men and 11.5 <g/dl for women, and some of the following: serum ferritin <100 ng/ml and/or with transferrin saturation (TSAT) ≤20% Creatinine clearance ≤90 ml/min
Exclusion criteria	Haemodialysis therapy Anaemia not due to iron deficiency available for erythropoiesis NYHA functional class I History of allergy to the iron supplements Acute bacterial infections, parasitism known in the 4 previous weeks, and neoplasm Chronic digestive diseases Hypothyroidism Congenital cardiopathies

	Receiving iron supplements in the 4 previous weeks Receiving rhEPO in the 4 previous weeks History of hospitalization during the 4 weeks before enrolment into the study
Recruitment / selection of participants	Participants were consecutive patients from the general population that spontaneously consulted the outpatient's office at the cardiology section at the Hospital Aleman Buenos Aires.
Intervention(s)	Participants received IV isotonic saline solution 0.9% containing 200 mg/200 ml of iron sucrose complex. Each infusion was administered throughout 60 minutes. Treatment was followed for 5 consecutive weeks. Following the initial 6-month study, participants were monitored and received additional treatment if Hb decreased below 11 gm /dL or TSAT fell to 20% or less.
Population subgroups	All participants had anaemia according to inclusion criteria All participants had HFrEF according to inclusion criteria
Comparator	Participants received an IV 200ml bag of isotonic saline solution 0.9% administered throughout 60 mins. Treatment was followed for 5 consecutive weeks. Participants did not receive IV iron, oral iron, or placebo injections after the end of the 6-month study period.

Number of participants	40 participants were recruited and randomized to treatment. It appeared that participants who were lost to follow-up had died.
Duration of follow-up	The original trial had a follow-up of 6 months, and there was a long-term follow-up period of 1, 2, 3, 4 and 5 years.
Indirectness	Directly applicable
Method of analysis	Other Method of analysis was unclear
Additional comments	Toblli 2015 was a secondary publication where an additional 20 participants were allocated to treatment. The results from the initial 40 people are reported in Toblli 2007 and Toblli 2017 were extracted.

Study arms

Intravenous iron supplementation (Iron sucrose) (N = 20)

Treatment in addition to conventional therapy for the management of the CHF

Placebo (N = 20)

Treatment in addition to conventional therapy for the management of the CHF

Characteristics

Arm-level characteristics

Characteristic	Intravenous iron supplementation (Iron sucrose) (N = 20)	Placebo (N = 20)
% Female Sample size	n = 7 ; % = 35	n = 8 ; % = 40
Age (years) Mean (SD)	76 (7)	74 (8)
Ethnicity Nominal	NR	NR

Characteristic	Intravenous iron supplementation (Iron sucrose) (N = 20)	Placebo (N = 20)
NYHA class Mean (SD)	2.9 (0.7)	2.9 (0.6)
Heart failure aetiology Sample size	n = NA ; % = NA	n = NA ; % = NA
Coronary artery disease Sample size	n = 12 ; % = 60	n = 13 ; % = 65
Cardiomyopathy Sample size	n = 5 ; % = 25	n = 4 ; % = 20
Hypertension Sample size	n = 2 ; % = 10	n = 3 ; % = 15
Aortic valve disease	n = 1 ; % = 5	n = 0 ; % = 0

Characteristic	Intravenous iron supplementation (Iron sucrose) (N = 20)	Placebo (N = 20)
Sample size		
LVEF Reported as EF (%) Mean (SD)	31.3 (3.7)	30.8 (1.7)
Atrial fibrillation Sample size	n = 4 ; % = 20	n = 4 ; % = 20
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Diuretics Sample size	n = 19 ; % = 95	n = 19 ; % = 95
ACE inhibitors Sample size	n = 19 ; % = 95	n = 20 ; % = 100

Characteristic	Intravenous iron supplementation (Iron sucrose) (N = 20)	Placebo (N = 20)
AT1 receptor blockers Sample size	n = 5 ; % = 25	n = 4 ; % = 20
Beta-blockers Sample size	n = 20 ; % = 100	n = 20 ; % = 100
Vasodilators (nitrites) Sample size	n = 5 ; % = 25	n = 6 ; % = 30
Digoxin Sample size	n = 13 ; % = 65	n = 12 ; % = 60
Aspirin Sample size	n = 15 ; % = 75	n = 14 ; % = 70
Device therapy	NR	NR

Characteristic	Intravenous iron supplementation (Iron sucrose) (N = 20)	Placebo (N = 20)
Nominal		
Transferrin saturation (%) Mean (SD)	0.2 (0.01)	0.2 (0.01)
Haemoglobin (g/dL) Mean (SD)	10.3 (0.6)	10.2 (0.5)
Ferritin (ng/mL) Mean (SD)	73 (29.9)	70.6 (21.4)
Anaemia Report states that all participants had anaemia Sample size	n = 20 ; % = 100	n = 20 ; % = 100

Outcomes

Study timepoints

Baseline

6 month

Arm-based outcomes

Outcome	Intravenous iron supplementation (Iron sucrose), Baseline, N = 20	Intravenous iron supplementation (Iron sucrose), 6 month, N = 20	Placebo, Baseline, N = 20	Placebo, 6 month, N = 20
Health-related quality of life (Minnesota Living With Heart Failure (MLWHF) Final values Mean (SD)	60 (5)	41 (7)	58 (6)	59 (8)
Unplanned hospitalisation or visits (heart-failure-related)	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 5 ; % = 25

Outcome	Intravenous iron supplementation (Iron sucrose), Baseline, N = 20	Intravenous iron supplementation (Iron sucrose), 6 month, N = 20	Placebo, Baseline, N = 20	Placebo, 6 month, N = 20
No of events				
Improvement in exercise tolerance – 6-minute walk test (meters) Final values Mean (SD)	192.3 (60.9)	240.1 (51.2)	190.7 (56.1)	184.5 (58.5)
Haemoglobin in anaemic patients (g/dL) Final values Mean (SD)	10.3 (0.6)	11.8 (0.7)	10.2 (0.5)	9.8 (0.6)

Health-related quality of life (Minnesota Living With Heart Failure (MLWHF) - Polarity - Lower values are better

Unplanned hospitalisation or visits (heart-failure-related) - Polarity - Lower values are better

Improvement in exercise tolerance – 6-minute walk test - Polarity - Higher values are better

Haemoglobin in anaemic patients - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

HR-QoL - MLWHF - Iron sucrose v Placebo - 6months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Unplanned hospitalisation or visits (heart-failure-related) - No. of Events - Iron sucrose v Placebo - 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable (Partially applicable due to outcome reported as number of events rather than time to event)

6-minute walk test - Iron sucrose v Placebo - 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

Haemoglobin - Iron sucrose v Placebo - 6 months

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of information around allocation concealment)*
Overall bias and Directness	Overall Directness	Directly applicable

van Veldhuisen, 2017

Bibliographic Reference	van Veldhuisen, DJ; Ponikowski, P; van der Meer, P; Metra, M; Böhm, M; Doletsky, A; Voors, AA; Macdougall, IC; Anker, SD; Roubert, B; et, al.; Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Chronic Heart Failure and Iron Deficiency; Circulation; 2017; vol. 136 (no. 15); 1374-1383

Study details

Secondary publication of another included	Not applicable

study- see primary study for details	
Other publications associated with this study included in review	Not applicable
Trial name / registration number	EFFECT-HF
Study location	28 sites across 9 countries (Australia, Belgium, France, Germany, Italy, the Netherlands, Poland, Russia, and Spain).
Study setting	Participating study centre
Study dates	Not specified
Sources of funding	The study was sponsored by Vifor Pharma, Switzerland.
Inclusion criteria	Patients were 18 years or older

	Had clinically stable mild to moderate chronic heart failure- New York Heart Association (NYHA) class II-III. Were on optimal background therapy for heart failure for 4 or more weeks and with no dose changes in the last 2 weeks. Left ventricular ejection fraction is less than equal to 45% and had to be performed in less than or equal to 3 months of screening and more than 3 after stable beta-blocker therapy or device implantation (in particular cardiac resynchronization therapy) Plasma brain natriuretic peptide (BNP) concentration at baseline had to be >100 pg/mL or N-terminal (NT) proBNP had to be >400 pg/mL Patients were required to have a decreased exercise capacity (shown by a reproducible peak VO2 of 10 to 20 mL/kg/min. Patients need to have documented iron deficiency (defined as serum ferritin <100 ng/mL or a serum ferritin of 100 to 300 ng/mL in combination with transferrin saturation (TSAT) <20%).
Exclusion criteria	Patients had known sensitivity to FCM Had a history of iron overload or received erythropoiesis-stimulating agents, intravenous iron therapy and/or blood transfusions in the 6 weeks before randomisation Subjects with an immediate need of blood transfusion or Hb >15 g/dL Patients who had undergone an exercise training program in the previous 3 months or those planned in the next 6 months, as well as those with active bacterial infection, those with serious liver disease (transaminase >3 times the upper limit)

	A known vitamin B12 or serum folate deficiency or a known human immunodeficiency virus or hepatitis B or C infection Patients with clinical evidence of current malignancy and on renal dialysis Patients with unstable angina pectoris, severe valvular disease, or left ventricular outflow tract obstruction Patients with atrial fibrillation or flutter with a ventricular response rate of >100 beats per minute at rest Patients with recent (< 3 months) acute coronary syndrome, coronary artery bypass surgery, percutaneous coronary interventions, transient ischemic attack, or stroke, Women who were pregnant or without adequate contraception Subjects with recent participation in another study or with low body weight (<35 kg)
Recruitment / selection of participants	Not specified
Intervention(s)	Intravenous FCM (Mean administered dose was 1204mg ±391 mg).
Population subgroups	Not applicable

Comparator	Standard of care (no further details reported). Oral iron permitted.
Number of participants	172 participants
Duration of follow-up	24 weeks
Indirectness	None
Additional comments	Intention to treat analysis and per protocol analysis available

Study arms

Intravenous ferric-carboxy maltose (N = 86)

IV iron (ferric-carboxy maltose)

Standard of care (N = 86)

Standard of care

Characteristics

Arm-level characteristics

Characteristic	Intravenous ferric-carboxy maltose (N = 86)	Standard of care (N = 86)
Age Mean (SD)	63 (12)	64 (11)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA Class II Sample size	n = 61 ; % = 71	n = 54 ; % = 63
NYHA Class III	n = 25 ; % = 29	n = 32 ; % = 37

Characteristic	Intravenous ferric-carboxy maltose (N = 86)	Standard of care (N = 86)
Sample size		
LVEF Mean (SD)	33 (9)	31 (8)
Atrial fibrillation Sample size	n = 35 ; % = 41	n = 41 ; % = 48
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
ACE-inhibitors Sample size	n = 81 ; % = 94	n = 77 ; % = 90
Beta-blockers Sample size	n = 84 ; % = 98	n = 85 ; % = 98

Characteristic	Intravenous ferric-carboxy maltose (N = 86)	Standard of care (N = 86)
Diuretics Sample size	n = 80 ; % = 93	n = 82 ; % = 95
MRA Sample size	n = 58 ; % = 67	n = 62 ; % = 72
Device therapy Sample size	n = NA ; % = NA	n = NA ; % = NA
Implantable cardioverter defibrillator Sample size	n = 25 ; % = 29	n = 33 ; % = 38
Cardiac-resynchronization therapy Sample size	n = 11 ; % = 13	n = 11 ; % = 13
Transferrin saturation (%)	17.3%	18,1%

Characteristic	Intravenous ferric-carboxy maltose (N = 86)	Standard of care (N = 86)
Custom value		
Haemoglobin Mean (SD)	12.9 (1.3)	13 (1.5)
Ferritin Median (IQR)	48 (NA to NA)	53 (NA to NA)

Outcomes

Study timepoints

24 week

Dichotomous outcomes

Outcome	Intravenous ferric-carboxy maltose, 24 week, N = 86	Standard of care, 24 week, N = 86
Number of deaths No of events	n = 0 ; % = NR	n = 4 ; % = NR
Total hospitalisations (Worsening heart failure) No of events	n = 13 ; % = NR	n = 13 ; % = NR

Number of deaths - Polarity - Lower values are better

Total hospitalisations (Worsening heart failure) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous outcomes: Death: Intravenous ferric-carboxy maltose vs. Standard of care at week 24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information provided about allocation concealment)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to the outcome being reported as number of events rather than time to event.)*

Dichotomous outcomes: Total hospitalisations (Worsening heart failure): Intravenous ferric-carboxy maltose vs. Standard of care at week 24

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Some concerns for risk of bias due to no information provided about allocation concealment)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(Indirectly applicable)*

von Haehling, 2024

Bibliographic Reference	von Haehling, Stephan; Doehner, Wolfram; Evertz, Ruben; Garfias-Veitl, Tania; Derad, Carlotta; Diek, Monika; Karakas, Mahir; Birkemeyer, Ralf; Fillippatos, Gerasimos; Lainscak, Mitja; Butler, Javed; Ponikowski, Piotr; Bohm, Michael; Friede, Tim; Anker, Stefan D; Ferric carboxymaltose and exercise capacity in heart failure with preserved ejection fraction and iron deficiency: the FAIR-HFpEF trial.; European heart journal; 2024; vol. 45 (no. 37); 3789-3800

Study details

Secondary publication of another included study- see primary study for details	NA
Other publications associated with this study included in review	NA

Trial name / registration number	FAIR-HFpEF/ NCT03074591
Study location	Germany
Study setting	
Study dates	NS
Sources of funding	Vifor Pharma (Switzerland)
Inclusion criteria	Aged 18 years or older Have a clinical diagnosis of heart failure with preserved ejection fraction with LVEF ≥45% at screening or within 6 months prior to planned randomisation Ambulatory for at least 7 days with NYHA class II or III at time of randomisation Treated with a diuretic Presence of atrial fibrillation at screening or randomisation is allowed in 2 out of 4 patients (calculated per centre) Presence of one of the following criteria:

	Hospitalisation with a diagnosis of HF within 12 months prior to randomisation Raised plasma levels of natriuretic peptides in patients with sinus rhythm (i.e. in patients without AF: NT-proBNP >300 pg/mL or BNP >100 pg/mL or MR-proANP >120 pmol/L; in patients with AF: NT-proBNP >600 pg/mL or BNP >200 pg/mL or MR-proANP >250 pmol/ Evidence of diastolic function at screening or randomisation Haemoglobin >9.0 g/dL and ≤14.0 g/dL (at screening) ID with ferritin <100 ng/mL or ferritin 100-299 plus TSAT <20% at screening 6-minute walking distance at baseline <450 m (average of the last 2 documented tests within 8 weeks prior to planned randomisation that also need to be within 20% of each other)
Exclusion criteria	Any prior echocardiography measurement of LVEF <40% Clinical signs and symptoms of infection including fever >38 degrees Celsius Use of IV iron erythropoietin or blood transfusions within the previous 60 days Use of concurrent immunosuppressive therapy History of acquired iron overload or haemochromatosis (or a first relative with with haemochromatosis)

	Known hypersensitivity to FCM or any other IV iron product Known bleeding or haemolytic anaemia Presence of any condition that precludes exercise testing, such as decompensated HF, significant musculoskeletal disease, unstable angina pectoris, obstructive cardiomyopathy, severe uncorrected valvular disease, or uncontrolled brady-arrhythmias or tachy-arrhythmias Probable alternative diagnoses that in the opinion of the investigator could account for the patients' HF symptoms such as severe obesity, primary pulmonary hypertension, or chronic obstructive pulmonary disease (COPD), hence, patients with severe COPD or with a body mass index ≥40 kg/m2 Presence of uncontrolled atrial fibrillation with resting heart rate >110/min Presence of uncontrolled hypertension with blood pressure >160/100 mm Hg Renal replacement therapy Concurrent therapy with an erythropoiesis stimulating agent Known active malignancy Known HIV or active hepatitis infection Pregnancy

	Patients, who may be dependent on the sponsor, the investigator of the trial sites, have to be excluded from the trial Lack of willingness to to storage and disclosure of pseudonymous disease data in the context of the clinical trial Participation in another clinical trial within the previous 30 days Inability to fully comprehend and/or perform study procedures (in the investigator's opinion) Persons staying at an institution due to order by a national body or a court of law.
Recruitment / selection of participants	Not specified
Intervention(s)	Intravenous ferric carboxymaltose - Treatment provided after randomisation at baseline in 1–2 sessions (1000–2000 mg FCM or saline) as well as at week 16 (500–1000 mg) and at week 32 (500–1000 mg). Treatment according to randomisation at weeks 16 and 32 unless ferritin was >800 ng/mL, or when ferritin was > 500 ng/mL with TSAT > 50%, or when haemoglobin was > 16.0 g/dL at any stage during follow-up (in which case saline had to be given).
Population subgroups	Sex, ischaemic aetiology of HF, NYHA class, glomerular filtration rate, and haematinics at baseline
Comparator	Placebo - normal saline (no further details reported)

Number of participants	39 participants
Duration of follow-up	24 weeks and 52 weeks
Indirectness	NA

Study arms

Intravenous ferric carboxymaltose (N = 18)

1-2 sessions at baseline with 1000-2000mg FCM and at week 16 (500-1000mg FCM) and at week 32 (500-1000mg)

Placebo (N = 21)

Characteristics

Arm-level characteristics

Characteristic	Intravenous ferric carboxymaltose (N = 18)	Placebo (N = 21)
% Female Sample size	n = 10 ; % = 56	n = 14 ; % = 67
Age Mean (SD)	76 (8.88)	79 (7.03)
NYHA class Sample size	n = NA ; % = NA	n = NA ; % = NA
NYHA class - Class II Sample size	n = 11 ; % = 61	n = 10 ; % = 48
NYHA class - Class III Sample size	n = 7 ; % = 39	n = 11 ; % = 52
LVEF	55.3 (6.5)	55.1 (7.8)

Characteristic	Intravenous ferric carboxymaltose (N = 18)	Placebo (N = 21)
Mean (SD)		
Atrial fibrillation No of events	n = 10 ; % = 56	n = 10 ; % = 48
Background (non-randomised) heart failure medications Sample size	n = NA ; % = NA	n = NA ; % = NA
Background (non-randomised) heart failure medications - ACE inhibitor Sample size	n = 6 ; % = 33	n = 13 ; % = 62
Background (non-randomised) heart failure medications - ARB Sample size	n = 5 ; % = 28	n = 6 ; % = 29
Background (non-randomised) heart failure medications - ARNI Sample size	n = 2 ; % = 11	n = 0 ; % = 0

Characteristic	Intravenous ferric carboxymaltose (N = 18)	Placebo (N = 21)
Background (non-randomised) heart failure medications - Beta-blocker Sample size	n = 13 ; % = 72	n = 16 ; % = 76
Background (non-randomised) heart failure medications - Calcium antagonist Sample size	n = 3 ; % = 17	n = 7 ; % = 33
Background (non-randomised) heart failure medications - MRA Sample size	n = 2 ; % = 11	n = 7 ; % = 33
Background (non-randomised) heart failure medications - SGLT2i Sample size	n = 1 ; % = 6	n = 4 ; % = 19
Background (non-randomised) heart failure medications - Any other anti-diabetic Sample size	n = 6 ; % = 33	n = 7 ; % = 33

Characteristic	Intravenous ferric carboxymaltose (N = 18)	Placebo (N = 21)
Background (non-randomised) heart failure medications - Loop diuretic Sample size	n = 15 ; % = 83	n = 14 ; % = 67
Background (non-randomised) heart failure medications - Insulin Sample size	n = 3 ; % = 17	n = 3 ; % = 14
Background (non-randomised) heart failure medications - Allopurinol Sample size	n = 8 ; % = 44	n = 5 ; % = 24
Background (non-randomised) heart failure medications - Proton-pump inhibitor Sample size	n = 7 ; % = 39	n = 11 ; % = 52
Background (non-randomised) heart failure medications - Cholesterol-lowering drug Sample size	n = 10 ; % = 56	n = 16 ; % = 76

Characteristic	Intravenous ferric carboxymaltose (N = 18)	Placebo (N = 21)
Background (non-randomised) heart failure medications - Any anti-platelet Sample size	n = 7 ; % = 39	n = 10 ; % = 48
Background (non-randomised) heart failure medications - Any anticoagulant Sample size	n = 9 ; % = 50	n = 10 ; % = 48
Transferrin saturation (%) Mean (95% CI)	19.9 (13.8 to 24.8)	16 (14 to 21)
Haemoglobin Custom value	12 (11.4 to 12.8)	12.9 (11.7 to 13.2)
Ferritin Custom value	44 (23 to 72)	50 (24 to 94)

Outcomes

Study timepoints

Baseline

52 week

24 week

Dichotomous Outcomes

Outcome	Intravenous ferric carboxymaltose, 52 week, N = 18	Placebo, 52 week, N = 21
Death No of events	n = 0 ; % = 0	n = 0 ; % = 0
All-cause hospitalisation No of events	n = 4 ; % = NR	n = 16 ; % = NR

Outcome	Intravenous ferric carboxymaltose, 52 week, N = 18	Placebo, 52 week, N = 21
Withdrawal due to drug-adverse events No of events	n = 3 ; % = NR	n = 1 ; % = NR

Continuous outcomes

Outcome	Intravenous ferric carboxymaltose vs Placebo, Baseline, N2 = 18, N1 = 21	Intravenous ferric carboxymaltose vs Placebo, 52 week, N2 = 14, N1 = 12	Intravenous ferric carboxymaltose vs Placebo, 24 week, N2 = 15, N1 = 16
Kansas City Cardiomyopathy Questionnaire (overall summary score) mean difference Mean (95% CI)	NA (NA to NA)	NA (NA to NA)	6.5 (-3.8 to 16.7)
EQ-5D-3L	NA (NA to NA)	NA (NA to NA)	-0.03 (-0.14 to 0.09)

Outcome	Intravenous ferric carboxymaltose vs Placebo, Baseline, N2 = 18, N1 = 21	Intravenous ferric carboxymaltose vs Placebo, 52 week, N2 = 14, N1 = 12	Intravenous ferric carboxymaltose vs Placebo, 24 week, N2 = 15, N1 = 16
change score Mean (95% CI)			
6-minute walk test distance (m) (change score) Custom value	NA	13 ±23 (mean±SEM)	49± 22 (mean ±SEM)
6-minute walk test distance (m) (change score) Mean (95% CI)	NA (NA to NA)	NA (NA to NA)	49 (5.1 to 93)
Haemoglobin change score Mean (95% CI)	NA (NA to NA)	NA (NA to NA)	0.93 (0.1 to 1.76)

Kansas City Cardiomyopathy Questionnaire (overall summary score) - Polarity - Higher values are better

EQ-5D-3L - Polarity – Higher values are better

6-minute walk test – Polarity – Higher values are better

Haemoglobin - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Dichotomous Outcomes: Death: Intravenous ferric carboxymaltose versus Placebo at 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partially applicable *(Partially applicable due to the outcome being reported as number of events rather than time to event.)*

Dichotomous Outcomes: All-cause hospitalisation: Intravenous ferric carboxymaltose verus Placebo at 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Partiallyy applicable *(Partially applicable due to the outcome being reported as number of events rather than time to event.)*

Dichotomous Outcomes: Withdrawal due to drug-adverse events: Intravenous ferric carboxymaltose versus Placebo at 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Kansas City Cardiomyopathy Questionnaire (overall summary score): Intravenous ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: EQ-5D-3L: Intravenous ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-minute walk test: Intravenous ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: Haemoglobin: Intravenous ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-minute walk test-Mean(SEM): Intravenous ferric carboxymaltose versus Placebo at 52 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous outcomes: 6-minute walk test: Mean (SEM): Intravenous ferric carboxymaltose versus Placebo at 24 weeks

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E Forest plots

E.1 Intravenous iron versus placebo or usual care: 3-12 months

Figure 2: All-cause mortality (time-to-event)

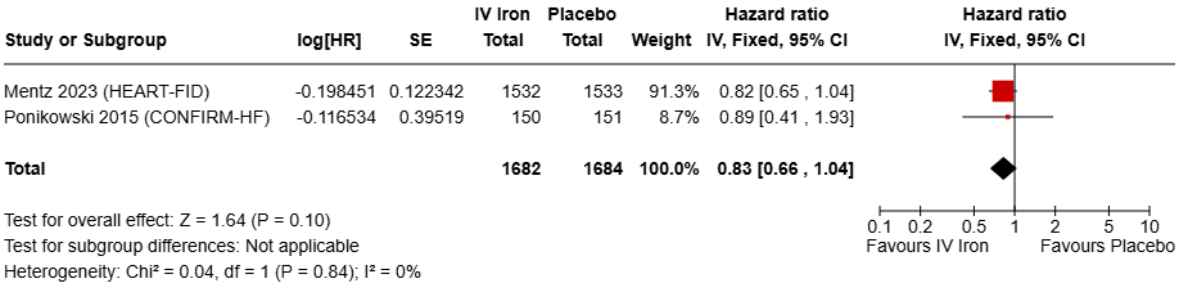


Figure 3: All-cause mortality (dichotomous)

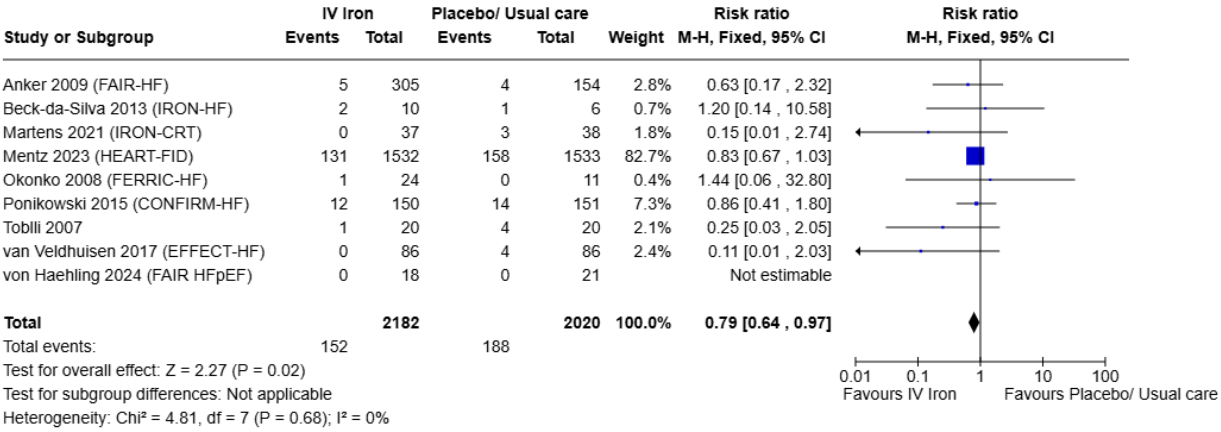


Figure 4: Cardiovascular mortality (time-to-event)

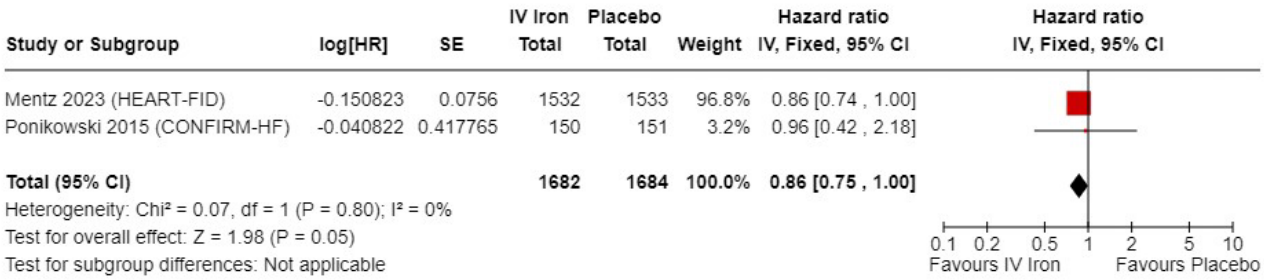


Figure 5: Cardiovascular mortality (dichotomous)

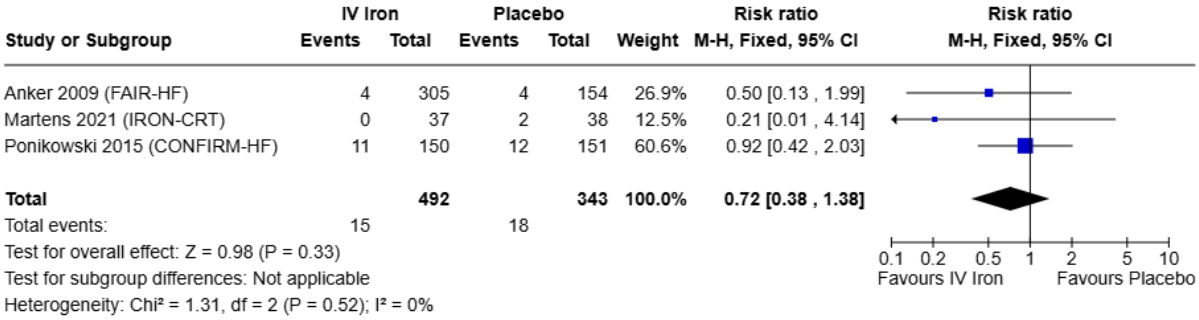
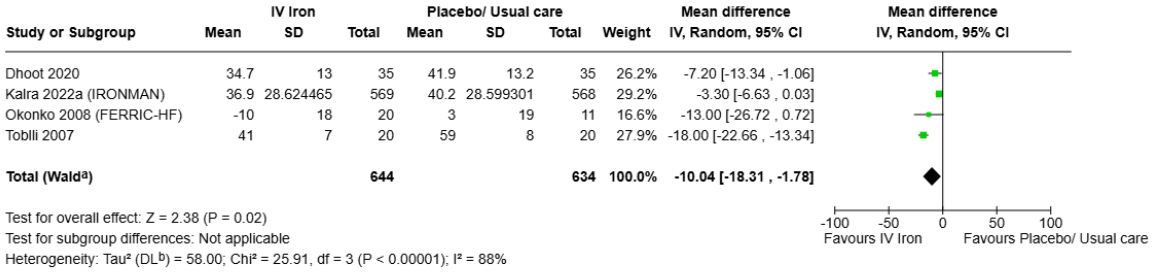


Figure 6: Minnesota Living with Heart Failure (score range 0-105; lower values are better) (change scores and final scores)



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 7: Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (score range 0-100; higher values are better) (change scores)

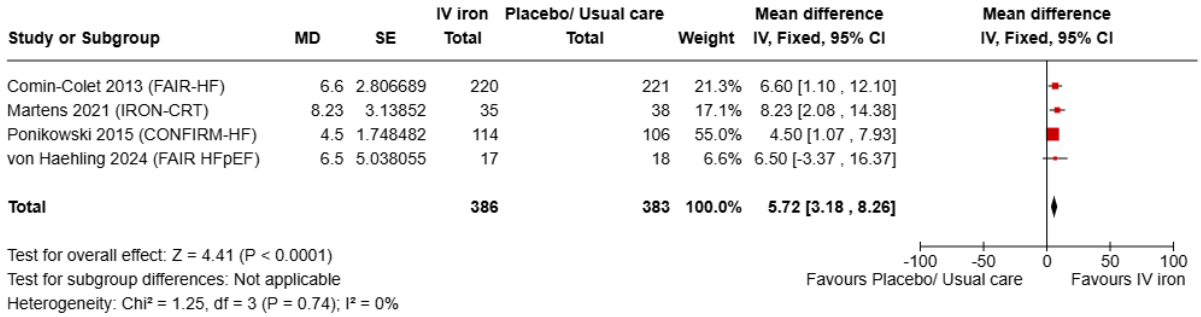
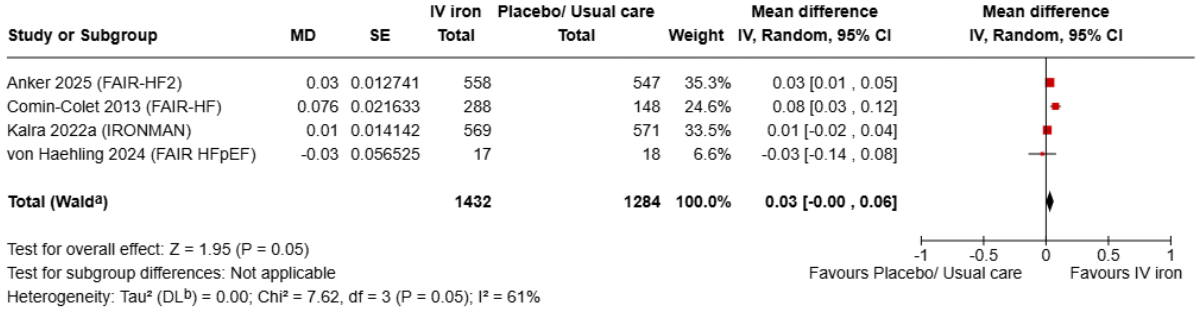


Figure 8: Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (score range from 0 to 100; higher values are better) (change score)

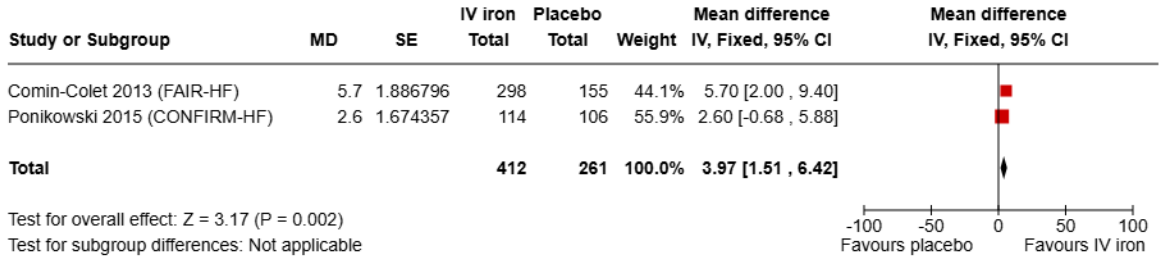
Figure 9: Health-related quality of life- EQ-5D index scores (score range -0.59 to 1; higher values are better) (change scores and final scores)



Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[b]) = 0.00; Chi² = 7.62, df = 3 (P = 0.05); I² = 61%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by DerSimonian and Laird method.

Figure 10: Health-related quality of life- EQ-5D VAS (score range 0 to 100; higher values are better) (change scores)



Test for overall effect: Z = 3.17 (P = 0.002)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 1.51, df = 1 (P = 0.22); I² = 34%

Figure 11: All-cause unplanned hospitalisations or visits (time to first hospitalisation)

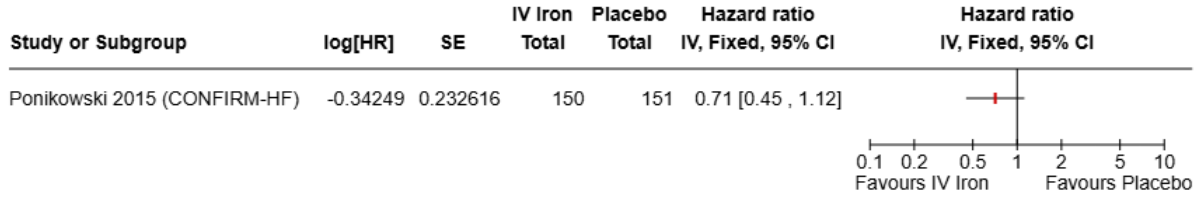
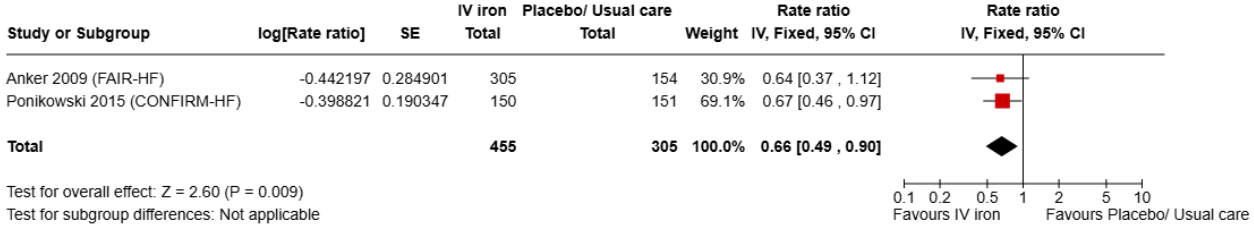


Figure 12: All-cause unplanned hospitalisations or visits (total number of all-cause hospitalisations, including repeat events; rate ratio)



Test for overall effect: Z = 2.60 (P = 0.009)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.90); I² = 0%

Figure 13: All-cause unplanned hospitalisations or visits (number of patients with at least one all-cause hospitalisation) (dichotomous)

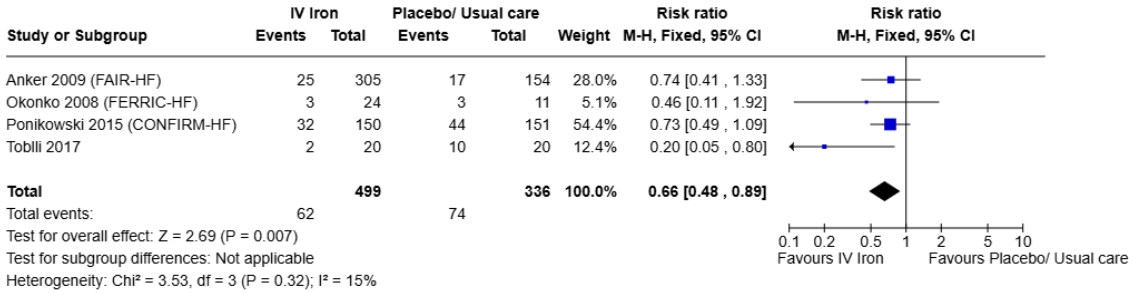


Figure 14: Heart failure-related unplanned hospitalisations or visits (time to first heart-failure hospitalisation)

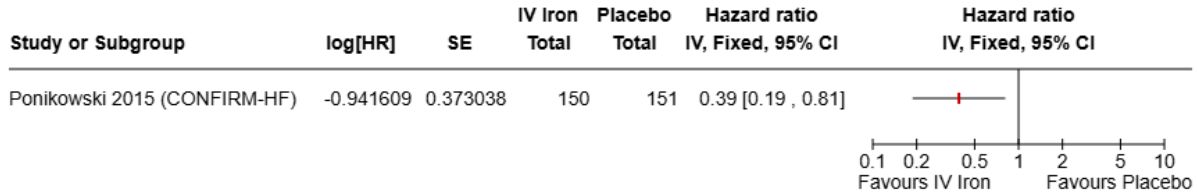
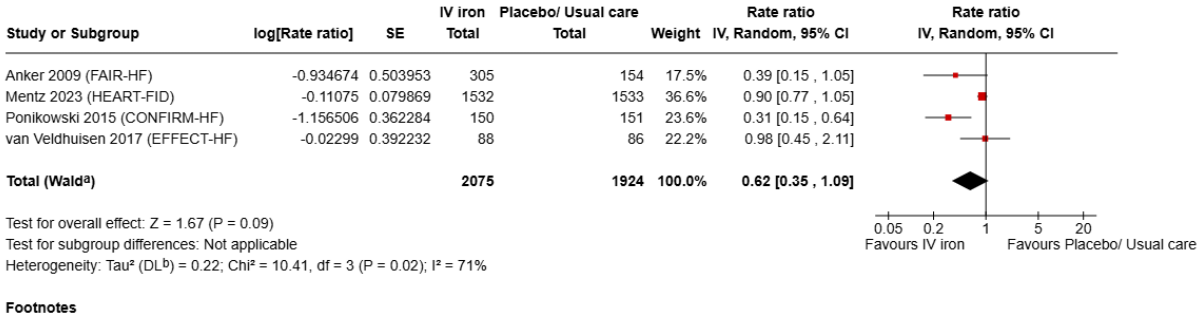


Figure 15: Heart failure-related unplanned hospitalisations or visits (total number of heart-failure hospitalisations, including repeat events) (rate ratio)

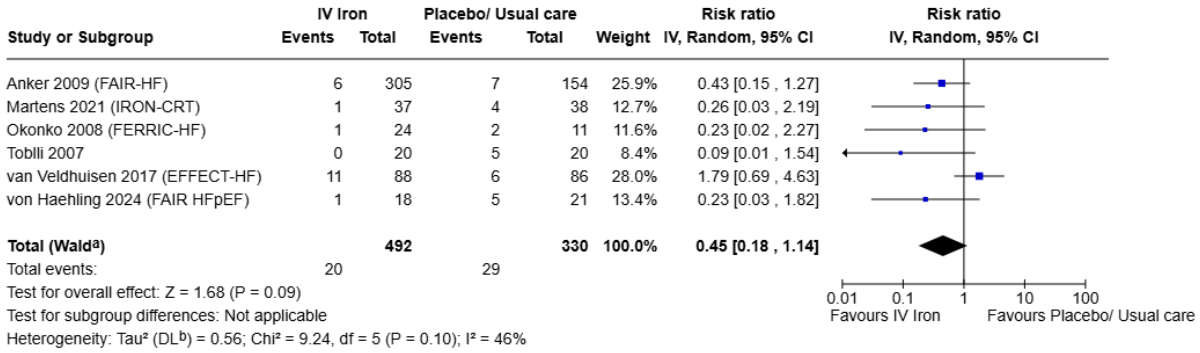


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 16: Heart failure-related unplanned hospitalisations or visits (number of patients with at least one heart-failure hospitalisation) (dichotomous)

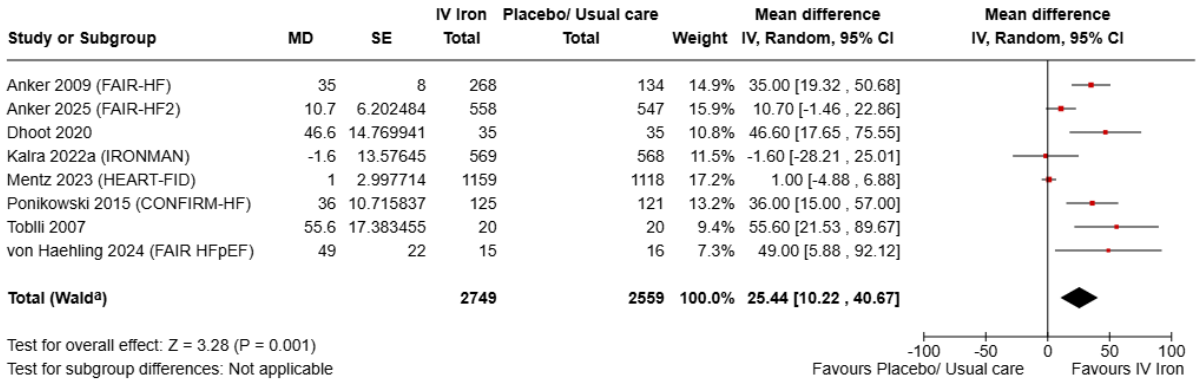


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 17: Improvement in exercise tolerance: 6-minute walk test (higher values are better) (change scores and final scores)



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 18: Improvement in exercise tolerance: peak VO_2 (ml/kg/min) (higher values are better) (change scores and final values)

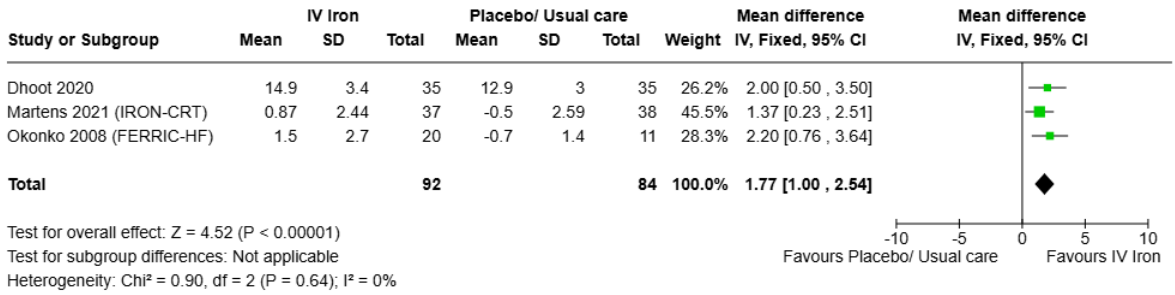
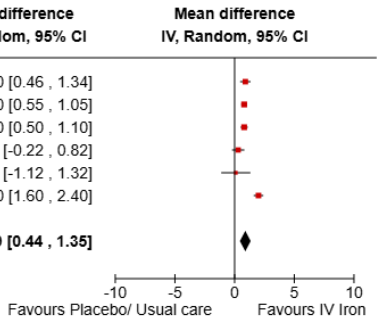


Figure 19: Haemoglobin in anaemic patients (g/dL) (higher values are better) (change scores and final values)

Study or Subgroup	MD	SE	IV Iron Total	Placebo/ Usual care Total	Weight	Mean difference IV, Random, 95% CI
Anker 2009 (anaemic cohort) (FAIR-HF)	0.9	0.223607	155	77	17.7%	0.90 [0.46 , 1.34]
Cleland 2024 (IRONMAN)[a]	0.8	0.127107	188	160	19.9%	0.80 [0.55 , 1.05]
Cleland 2024 (IRONMAN)[b]	0.8	0.152624	209	214	19.4%	0.80 [0.50 , 1.10]
Dhoot 2020	0.3	0.264035	35	35	16.6%	0.30 [-0.22 , 0.82]
Okonko 2008 (anaemic cohort) (FERRIC-HF)	0.1	0.623832	12	6	8.3%	0.10 [-1.12 , 1.32]
Toblli 2007	2	0.206155	20	20	18.1%	2.00 [1.60 , 2.40]
Total (Wald[c])			**619**	**512**	**100.0%**	**0.89 [0.44 , 1.35]**



Test for overall effect: Z = 3.87 (P = 0.0001)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (DL[d]) = 0.25; Chi² = 36.19, df = 5 (P < 0.00001); I² = 86%

Footnotes
[a]Mild anaemia subgroup
[b]Moderate anaemia subgroup
[c]CI calculated by Wald-type method.
[d]Tau² calculated by DerSimonian and Laird method.

Figure 20: Withdrawal due to adverse events

Study or Subgroup	IV iron Events	IV iron Total	Placebo Events	Placebo Total	Risk ratio M-H, Fixed, 95% CI
von Haehling 2024 (FAIR HFpEF)	3	18	1	21	3.50 [0.40 , 30.77]

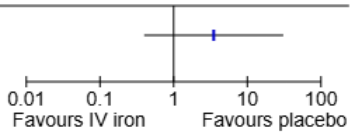


Figure 21: Hypophosphatemia (dichotomous)

Study or Subgroup	IV iron Events	IV iron Total	Placebo Events	Placebo Total	Risk ratio M-H, Fixed, 95% CI
Nouhravesh 2024 (HEART-FID)	34	59	7	68	5.60 [2.68 , 11.67]

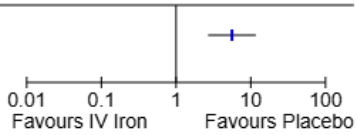
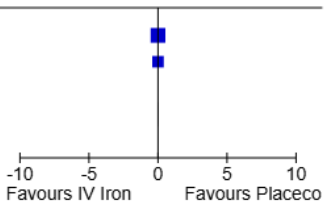


Figure 22: Anaphylaxis/ hypersensitivity (dichotomous)

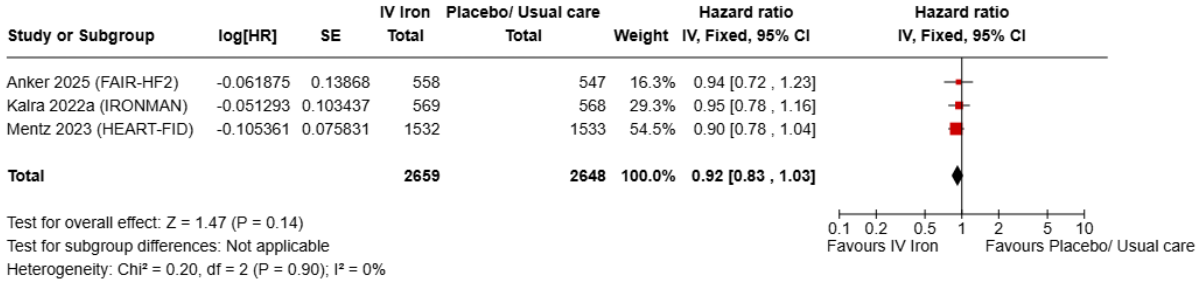
Study or Subgroup	IV Iron Events	IV Iron Total	Placebo Events	Placebo Total	Weight	Risk difference M-H, Fixed, 95% CI
Anker 2009 (FAIR-HF)	0	305	0	154	57.6%	0.00 [-0.01 , 0.01]
Ponikowski 2015 (CONFIRM-HF)	0	150	0	151	42.4%	0.00 [-0.01 , 0.01]
Total		**455**		**305**	**100.0%**	**0.00 [-0.01 , 0.01]**
Total events:	0		0			



Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%

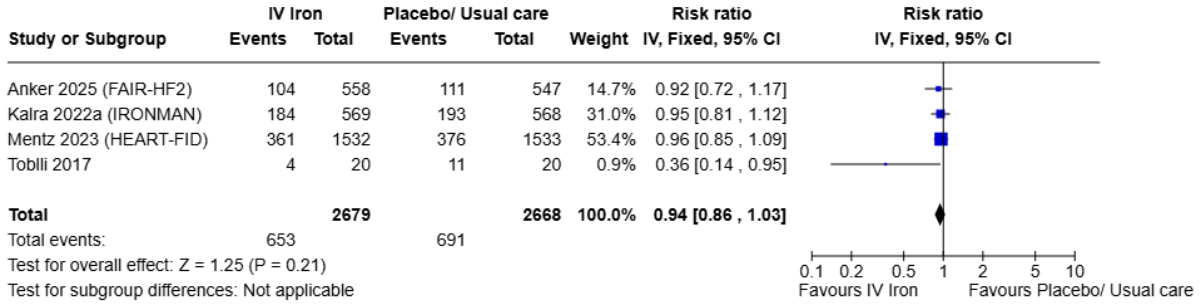
E.2 Intravenous iron versus placebo or usual care: >12 months

Figure 23: All-cause mortality (time-to-event)



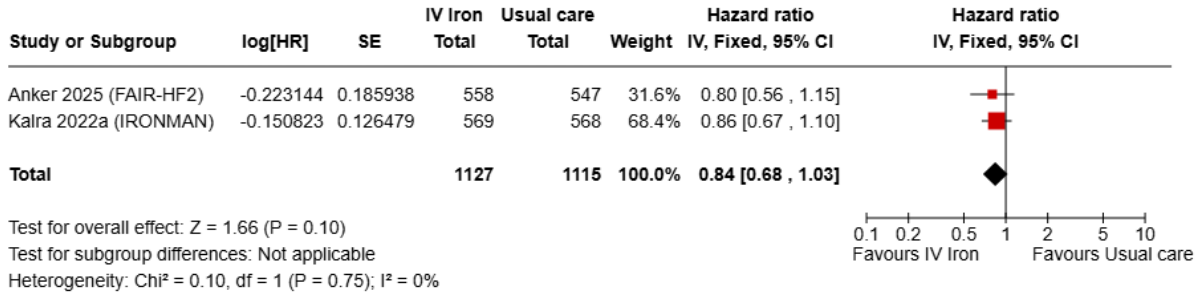
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.20, df = 2 (P = 0.90); I² = 0%

Figure 24: All-cause mortality (dichotomous)



Test for overall effect: Z = 1.25 (P = 0.21)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 3.91, df = 3 (P = 0.27); I² = 23%

Figure 25: Cardiovascular mortality (time-to-event)



Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%

Figure 26: Cardiovascular mortality (dichotomous)

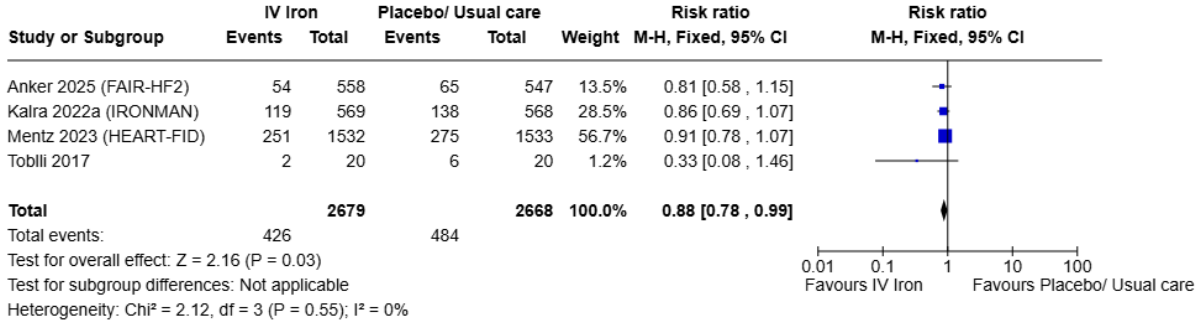


Figure 27: Health-related quality of life: Minnesota Living with Heart Failure (score range 0-105) (lower scores are better) (final values)

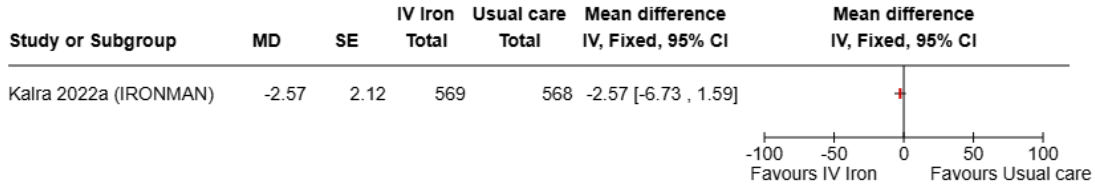


Figure 28: Health-related quality of life: EQ-5D index (score ranges -0.59 to 1;higher scores are better) (final values)

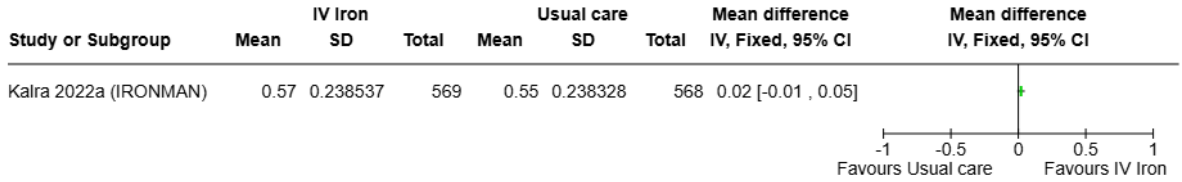


Figure 29: All-cause unplanned hospitalisation or visits (time-to-event)

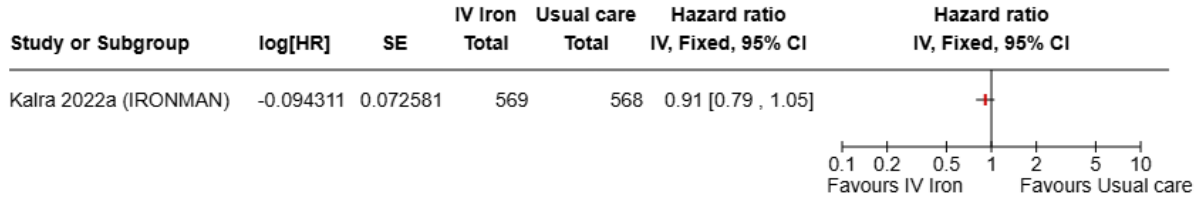


Figure 30: All-cause unplanned hospitalisation or visits (dichotomous)

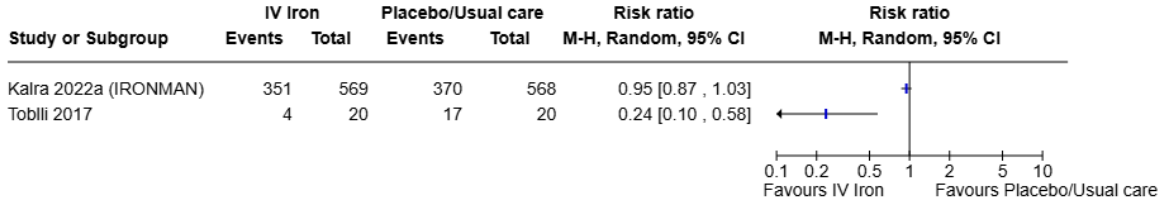


Figure 31: Heart failure-related unplanned hospitalisation or visits (rate ratio)

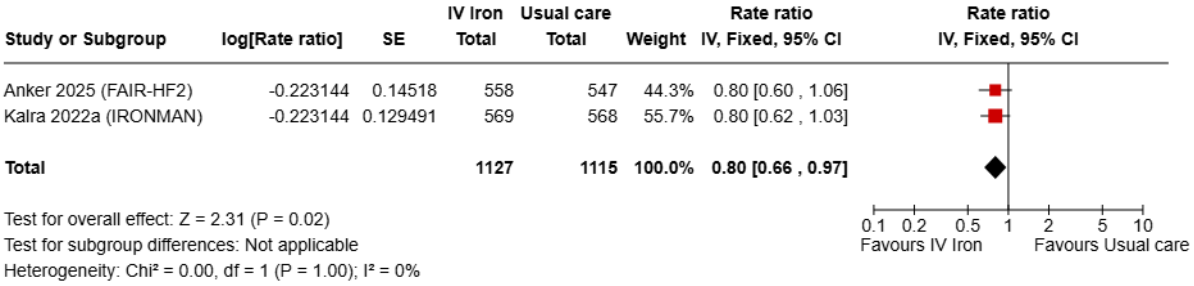


Figure 32: Heart failure-related unplanned hospitalisation or visits (dichotomous)

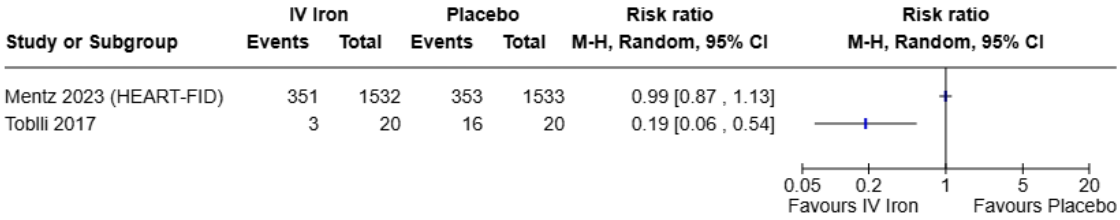


Figure 24: Improvement in exercise tolerance – 6-minute walk distance (higher scores are better) (final scores)

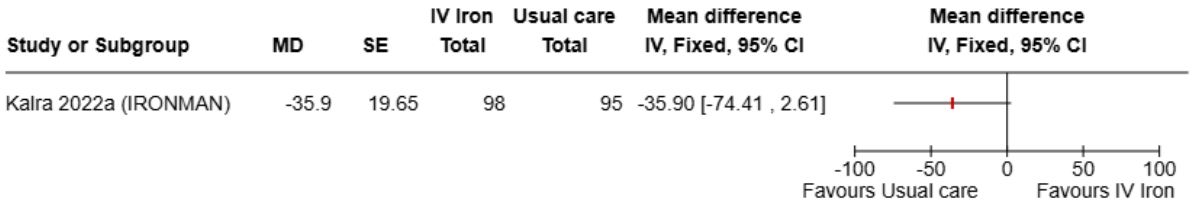


Figure 25: Withdrawal due to drug-related adverse events (dichotomous)

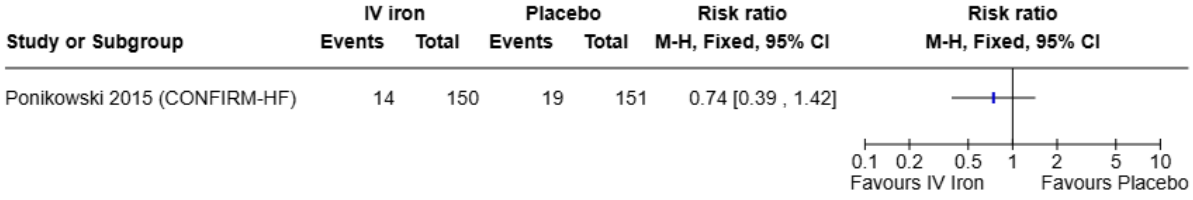


Figure 26: Anaphylaxis/hypersensitivity (dichotomous)

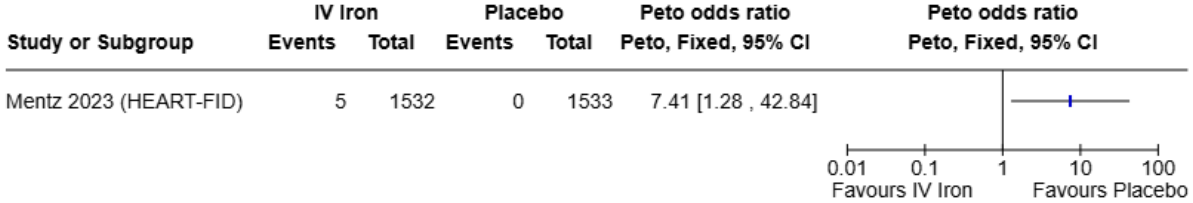


Figure 27: Hospitalisation for infection (dichotomous)

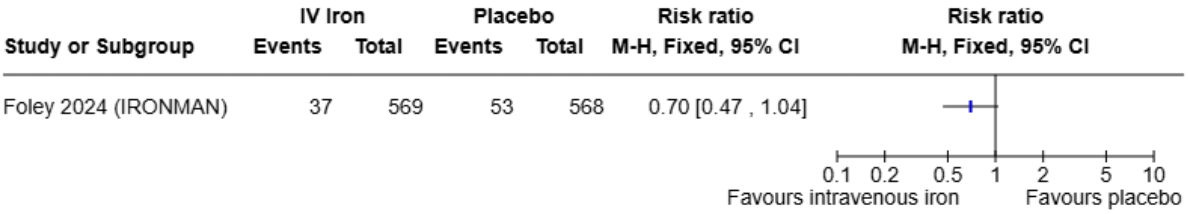


Figure 28: Hospitalisation for sepsis (dichotomous)

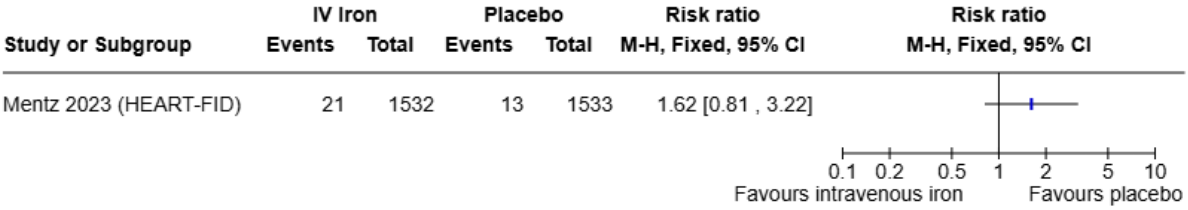
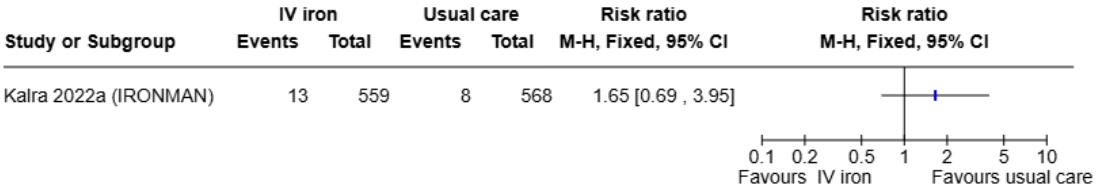


Figure 29: Atrial fibrillation (dichotomous)



E.3 Intravenous iron versus placebo (TSAT subgroups)

E.3.1 3-12 months

Figure 39: Health-related quality of life- Minnesota Living with Heart Failure (score ranges from 0-105) (lower scores are better) (change scores) (3-12 months) by TSAT level

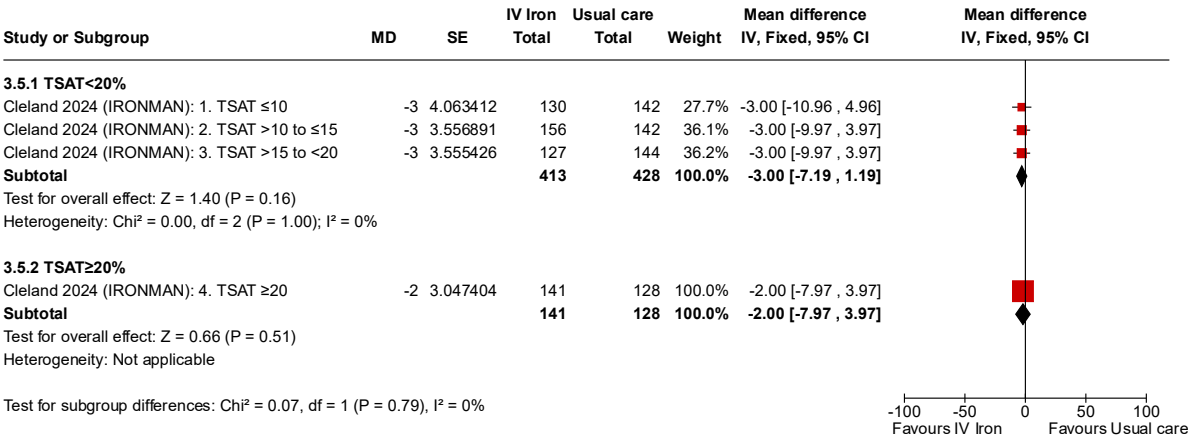
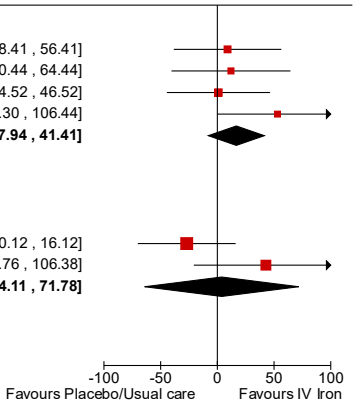


Figure 40: Improvement in exercise tolerance- 6-minute walk test (change scores) (higher values are better) (3-12 months) by TSAT level

Study or Subgroup	MD	SE	IV Iron Total	Placebo/Usual Care Total	Weight	Mean difference IV, Random, 95% CI
3.6.1 TSAT<20%						
Cleland 2024 (IRONMAN): 1. TSAT ≤10	9	24.190903	50	51	27.1%	9.00 [-38.41 , 56.41]
Cleland 2024 (IRONMAN): 2. TSAT >10 to ≤15	12	26.756764	65	52	22.1%	12.00 [-40.44 , 64.44]
Cleland 2024 (IRONMAN): 3. TSAT >15 to <20	1	23.222852	58	59	29.4%	1.00 [-44.52 , 46.52]
von Haehling 2024 (FAIR HFpEF) TSAT <20%	53.07	27.228613	9	14	21.4%	53.07 [-0.30 , 106.44]
Subtotal (Wald[a])			**182**	**176**	**100.0%**	**16.74 [-7.94 , 41.41]**
Test for overall effect: Z = 1.33 (P = 0.18)						
Heterogeneity: Tau² (REML[b]) = 0.00; Chi² = 2.37, df = 3 (P = 0.50); I² = 0%						
3.6.2 TSAT≥20%						
Cleland 2024 (IRONMAN): 4. TSAT ≥20	-27	21.999657	79	61	55.8%	-27.00 [-70.12 , 16.12]
von Haehling 2024 (FAIR HFpEF) TSAT ≥20%	42.81	32.43213	9	7	44.2%	42.81 [-20.76 , 106.38]
Subtotal (Wald[a])			**88**	**68**	**100.0%**	**3.84 [-64.11 , 71.78]**
Test for overall effect: Z = 0.11 (P = 0.91)						
Heterogeneity: Tau² (REML[b]) = 1668.80; Chi² = 3.17, df = 1 (P = 0.07); I² = 68%						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%						



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

E.3.2 >12 months

Figure 41: All-cause mortality (time-to-event): 3-12 months follow-up by TSAT level

Study or Subgroup	log[HR]	SE	IV Iron Total	Usual care Total	Weight	Hazard ratio IV, Fixed, 95% CI
3.1.1 TSAT <20%						
Cleland 2024 (IRONMAN): 1. TSAT ≤10	-0.040822	0.191837	130	142	38.2%	0.96 [0.66 , 1.40]
Cleland 2024 (IRONMAN): 2. TSAT >10 to ≤15	0.122218	0.208756	156	142	32.3%	1.13 [0.75 , 1.70]
Cleland 2024 (IRONMAN): 3. TSAT >15 to <20	-0.371064	0.218569	127	144	29.5%	0.69 [0.45 , 1.06]
Subtotal			**413**	**428**	**100.0%**	**0.92 [0.73 , 1.16]**
Test for overall effect: Z = 0.72 (P = 0.47)						
Heterogeneity: Chi² = 2.75, df = 2 (P = 0.25); I² = 27%						
3.1.2 TSAT ≥20%						
Cleland 2024 (IRONMAN): 4. TSAT ≥20	0.262364	0.233752	141	128	100.0%	1.30 [0.82 , 2.06]
Subtotal			**141**	**128**	**100.0%**	**1.30 [0.82 , 2.06]**
Test for overall effect: Z = 1.12 (P = 0.26)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 1.76, df = 1 (P = 0.18), I² = 43.2%						

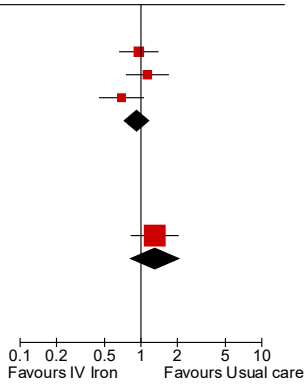
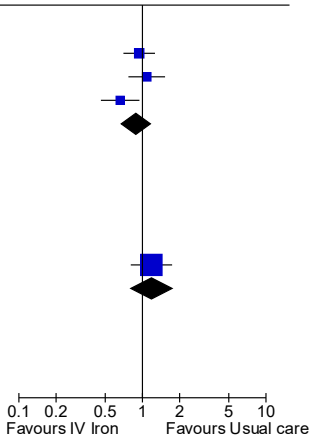


Figure 42: All-cause mortality (dichotomous): 3-12 months follow-up by TSAT level

Study or Subgroup	IV Iron Events	IV Iron Total	Usual care Events	Usual care Total	Weight	Risk ratio IV, Random, 95% CI
3.2.1 TSAT <20%						
Cleland 2024 (IRONMAN): 1. TSAT ≤10	50	130	58	142	37.1%	0.94 [0.70 , 1.26]
Cleland 2024 (IRONMAN): 2. TSAT >10 to ≤15	50	156	42	142	32.3%	1.08 [0.77 , 1.52]
Cleland 2024 (IRONMAN): 3. TSAT >15 to <20	35	144	53	144	30.6%	0.66 [0.46 , 0.95]
Subtotal (Wald[a])		**430**		**428**	**100.0%**	**0.88 [0.67 , 1.16]**
Total events:	135		153			
Test for overall effect: Z = 0.89 (P = 0.37)						
Heterogeneity: Tau² (REML[b]) = 0.03; Chi² = 4.07, df = 2 (P = 0.13); I² = 51%						
3.2.2 TSAT ≥20%						
Cleland 2024 (IRONMAN): 4. TSAT ≥20	43	141	33	128	100.0%	1.18 [0.80 , 1.74]
Subtotal		**141**		**128**	**100.0%**	**1.18 [0.80 , 1.74]**
Total events:	43		33			
Test for overall effect: Z = 0.85 (P = 0.39)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 1.46, df = 1 (P = 0.23), I² = 31.7%						



Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Figure 30: Cardiovascular mortality (time-to-event): 3-12 months follow-up by TSAT level

Study or Subgroup	log[HR]	SE	IV Iron Total	Usual care Total	Weight	Hazard ratio IV, Fixed, 95% CI
3.3.1 TSAT<20%						
Cleland 2024 (IRONMAN): 1. TSAT ≤10	-0.105361	0.242704	130	142	35.4%	0.90 [0.56 , 1.45]
Cleland 2024 (IRONMAN): 2. TSAT >10 to ≤15	0.04879	0.249218	156	142	33.6%	1.05 [0.64 , 1.71]
Cleland 2024 (IRONMAN): 3. TSAT >15 to <20	-0.462035	0.259284	127	144	31.0%	0.63 [0.38 , 1.05]
Subtotal			**413**	**428**	**100.0%**	**0.85 [0.64 , 1.13]**
Test for overall effect: Z = 1.14 (P = 0.26)						
Heterogeneity: Chi² = 2.11, df = 2 (P = 0.35); I² = 5%						
3.3.2 TSAT≥20%						
Cleland 2024 (IRONMAN): 4. TSAT ≥20	0.029559	0.28737	141	128	100.0%	1.03 [0.59 , 1.81]
Subtotal			**141**	**128**	**100.0%**	**1.03 [0.59 , 1.81]**
Test for overall effect: Z = 0.10 (P = 0.92)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%						

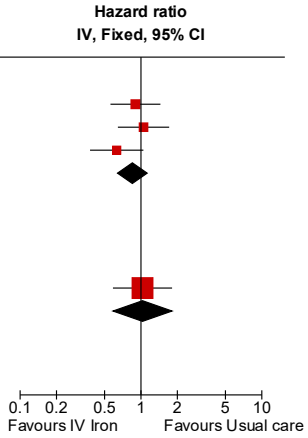


Figure 31: Cardiovascular mortality (dichotomous): 3- 12 months follow-up by TSAT level

Study or Subgroup	IV Iron Events	IV Iron Total	Usual care Events	Usual care Total	Weight	Risk ratio M-H, Fixed, 95% CI
3.4.1 TSAT<20%						
Cleland 2024 (IRONMAN): 1. TSAT ≤10	31	130	38	142	34.2%	0.89 [0.59 , 1.34]
Cleland 2024 (IRONMAN): 2. TSAT >10 to ≤15	34	156	31	142	30.5%	1.00 [0.65 , 1.54]
Cleland 2024 (IRONMAN): 3. TSAT >15 to <20	24	127	40	144	35.3%	0.68 [0.44 , 1.06]
Subtotal		**413**		**428**	**100.0%**	**0.85 [0.66 , 1.09]**
Total events:	89		109			
Test for overall effect: Z = 1.30 (P = 0.19)						
Heterogeneity: Chi² = 1.54, df = 2 (P = 0.46); I² = 0%						
3.4.2 TSAT≥20%						
Cleland 2024 (IRONMAN): 4. TSAT ≥20	25	141	24	128	100.0%	0.95 [0.57 , 1.57]
Subtotal		**141**		**128**	**100.0%**	**0.95 [0.57 , 1.57]**
Total events:	25		24			
Test for overall effect: Z = 0.22 (P = 0.83)						
Heterogeneity: Not applicable						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						

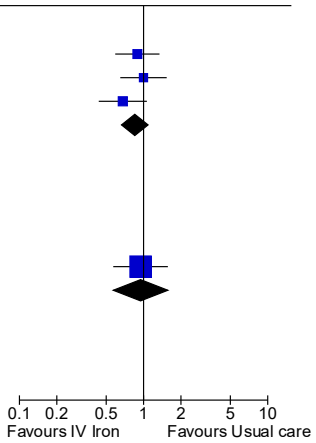
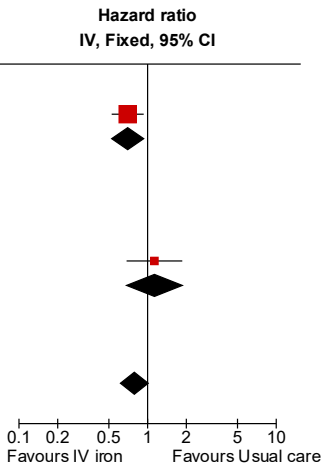


Figure 32: Intravenous iron versus placebo in chronic heart failure: Subgroup analysis- Hospitalisation for infection (time-to-event) (>12 months) by TSAT level

Study or Subgroup	log[HR]	SE	IV iron Total	Usual care Total	Weight	Hazard ratio IV, Fixed, 95% CI
3.8.1 TSAT <20%						
Foley 2024 (IRONMAN) TSAT <20%	-0.356675	0.146177	413	428	75.2%	0.70 [0.53 , 0.93]
Subtotal			**413**	**428**	**75.2%**	**0.70 [0.53 , 0.93]**
Test for overall effect: Z = 2.44 (P = 0.01)						
Heterogeneity: Not applicable						
3.8.2 TSAT ≥20%						
Foley 2024 (IRONMAN) TSAT ≥20%	0.122218	0.254342	141	128	24.8%	1.13 [0.69 , 1.86]
Subtotal			**141**	**128**	**24.8%**	**1.13 [0.69 , 1.86]**
Test for overall effect: Z = 0.48 (P = 0.63)						
Heterogeneity: Not applicable						
Total			**554**	**556**	**100.0%**	**0.79 [0.61 , 1.01]**
Test for overall effect: Z = 1.88 (P = 0.06)						
Test for subgroup differences: Chi² = 2.66, df = 1 (P = 0.10), I² = 62.5%						
Heterogeneity: Chi² = 2.66, df = 1 (P = 0.10); I² = 62%						



Appendix F GRADE tables

Table 10: Clinical evidence profile: intravenous iron versus placebo (3-12 months follow-up)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: mean 52 weeks)												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1682	1684	**HR 0.83** (0.66 to 1.04)	-	⨁⨁◯◯ Low[a,b]	CRITICAL
All-cause mortality (follow-up: range 3 months to 12 months)												
9	randomised trials	serious[a]	not serious	serious[c]	serious[b]	none	152/2182 (7.0%)	188/2020 (9.3%)	**RR 0.79** (0.64 to 0.97)	**20 fewer per 1,000** (from 34 fewer to 3 fewer)	⨁◯◯◯ Very low[a,b,c]	CRITICAL
Cardiovascular mortality (HR) (follow-up: 52 weeks)												
2	randomised trials	serious[a]	not serious	not serious	serious[b]	none	1682	1684	**HR 0.86** (0.75 to 1.00)	-	⨁⨁◯◯ Low[a,b]	CRITICAL
Cardiovascular mortality (follow-up: range 12 weeks to 52 weeks)												
3	randomised trials	not serious	not serious	serious[c]	very serious[b]	none	15/492 (3.0%)	18/343 (5.2%)	**RR 0.72** (0.38 to 1.38)	**15 fewer per 1,000** (from 33 fewer to 20 more)	⨁◯◯◯ Very low[b,c]	CRITICAL
Health-related quality of life - Minnesota Living With Heart Failure (MLWHF) (change and final values) (score range from 0-105, lower scores are better) (follow-up: range 12 weeks to 26 weeks)												
4	randomised trials	serious[d]	very serious[e]	not serious	serious[b]	none	644	634	-	MD **10.04 lower** (18.31 lower to 1.78 lower)	⨁◯◯◯ Very low[b,d,e]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
Health-related quality of life - Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (change scores) (score range 0-100, higher scores are better) (follow-up: range 24 weeks to 52 weeks)												
4	randomised trials	not serious	not serious	not serious	serious[b]	none	386	383	-	MD **5.72 higher** (3.18 higher to 8.26 higher)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Health-related quality of life - Kansas City Cardiomyopathy Questionnaire clinical summary score (change score) (score range 0-100, higher scores are better) (follow-up: mean 24 weeks)												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	454	306	-	MD **5.1 higher** (2.72 higher to 7.48 higher)	⨁⨁⨁◯ Moderate[b]	CRITICAL
Health-related quality of life - EQ5D index score (change scores) (score range -0.59 to 1, higher scores are better) (follow-up: range 24 weeks to 52 weeks; Scale from: -0.59 to 1)												
4	randomised trials	not serious	very serious[a]	not serious	serious[b]	none	1432	1284	-	MD **0.03 higher** (0 to 0.06 higher)	⨁◯◯◯ Very low[b,e]	CRITICAL
Health-related quality of life - EQ-5D-VAS (change scores) (range 0-100, higher scores are better) (follow-up: range 24 weeks to 52 weeks)												
2	randomised trials	not serious	not serious	not serious	not serious	none	412	261	-	MD **3.97 higher** (1.51 higher to 6.42 higher)	⨁⨁⨁⨁ High	CRITICAL
Unplanned hospitalisation or visits (all-cause) (HR) (follow-up: 52 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	150	151	**HR 0.71** (0.45 to 1.12)	**-**	⨁⨁⨁◯ Moderate[b]	CRITICAL
Unplanned hospitalisation or visits (all-cause) (rate ratio) (follow-up: range 24 weeks to 52 weeks)												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	455	305	**Rate ratio 0.66** (0.49 to 0.90)	**139 fewer per 1000 patient(s) per years** (from 209 fewer to 41 fewer)[f]	⨁⨁⨁◯ Moderate[b]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
Unplanned hospitalisation or visits (all-cause) (dichotomous) (follow-up: range 18 weeks to 52 weeks)												
4	randomised trials	not serious	not serious	serious[c]	serious[b]	none	62/499 (12.4%)	74/336 (22.0%)	**RR 0.66** (0.48 to 0.89)	**75 fewer per 1,000** (from 115 fewer to 24 fewer)	⨁⨁◯◯ Low[b,c]	CRITICAL
Unplanned hospitalisation or visits (heart failure related) (HR) (follow-up: 52 weeks)												
1	randomised trials	not serious	not serious	not serious	serious[b]	none	150	151	**HR 0.39** (0.19 to 0.81)	-	⨁⨁⨁◯ Moderate[b]	CRITICAL
Unplanned hospitalisation or visit (heart failure related) (rate ratio) (follow-up: range 24 weeks to 52 weeks)												
4	randomised trials	serious[g]	very serious[e]	serious[c]	serious[b]	none	2075	1924	**Rate ratio 0.62** (0.35 to 1.09)	**82 fewer per 1000 patient(s) per years** (from 140 fewer to 19 more)[f]	⨁◯◯◯ Very low[b,c,e,g]	CRITICAL
Unplanned hospitalisation or visits (heart failure related) (dichotomous) (follow-up: range 12 weeks to 52 weeks)												
6	randomised trials	not serious	serious[e]	serious[c]	serious[b]	none	20/492 (4.1%)	29/330 (8.8%)	**RR 0.45** (0.18 to 1.14)	**48 fewer per 1,000** (from 72 fewer to 12 more)	⨁◯◯◯ Very low[b,c,e]	CRITICAL
Improvement in exercise tolerance – 6-minute walk test (change scores and final values, higher scores better) (follow-up: range 18 to 52 weeks)												
8	randomised trials	not serious	very serious[e]	not serious	not serious	none	2749	2559	-	MD **25.44 higher** (10.22 higher to 40.67 higher)	⨁⨁◯◯ Low[e]	CRITICAL
Improvement in exercise tolerance – peak VO2 [ml/kg/min] (change scores and final values, higher scores are better) (follow-up: range 12 weeks to 24 weeks)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo or usual care	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[h]	not serious	not serious	serious[b]	none	92	84	-	MD **1.77 higher** (1 higher to 2.54 higher)	⨁⨁◯◯ Low[b,h]	CRITICAL
Haemoglobin in anaemic patients [g/dL] (change scores and final values, higher scores are better) (follow-up: range 18 weeks to 52 weeks)												
5	randomised trials	serious[i]	very serious[e]	not serious	serious[b]	none	760	660	-	MD **0.89 higher** (0.44 higher to 1.35 higher)	⨁◯◯◯ Very low[b,e,i]	CRITICAL
Withdrawal due to drug-related adverse events (follow-up: 52 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	3/18 (16.7%)	1/21 (4.8%)	**RR 3.50** (0.40 to 30.77)	**119 more per 1,000** (from 29 fewer to 1,000 more)	⨁⨁◯◯ Low[b]	CRITICAL
Hypophosphataemia (follow-up: 6 months)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	34/59 (57.6%)	7/68 (10.3%)	**RR 5.60** (2.68 to 11.67)	**474 more per 1,000** (from 173 more to 1,000 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Anaphylaxis/hypersensitivity (follow-up: range 24 weeks to 52 weeks)												
2	randomised trials	not serious	not serious	not serious	serious[j]	none	0/455 (0.0%)	0/305 (0.0%)	**Risk difference 0.00** (-0.01 to 0.01)	**0 fewer per 1,000** (from 10 fewer to 10 more)[k]	⨁⨁⨁◯ Moderate[j]	CRITICAL

ARB: Angiotensin receptor antagonist / blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; CI: confidence interval; HF: Heart failure; HR: Hazard ratio
a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: dose interruptions occurred in 564 participants (18.4%) and use of intravenous iron occurred outside the trial protocol in 31 participants in the FCM group and 104 participants in the placebo arm.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x control group SD where no baseline values given) for continuous outcomes; MLWHFQ MID is 5; KCCQ MID is 5; EQ5D MID is 0.03; EQ VAS MID is 7.825; 6 minute walk test MID is 45.4; peak VO2 MID is 1.295; haemoglobin MID is 0.61.

c. Downgraded by 1 increment for indirectness due to the results being reported as number of events rather than in time-to-event format.
d. Downgraded by 1 increment for risk of bias due to concerns that varied between trials, including deviations from intended interventions, participants being aware of the assigned intervention, and lack of information about selection biases.
e. Downgraded by 1 increment if I2 41-60% and 2 increments if I2 >60%.
f. Absolute difference calculated based on total event rates reported in the papers and total patient years of follow-up (assuming all patients completed follow-up, as person years not reported in all trials).
g. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies for reasons that varied between the trials, including no information provided regarding the allocation concealment in one trial and deviations from the intended intervention in another.
h. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies for reasons that varied between trials, including no pre-specified plan noted in one trial and participants being aware of the assigned intervention in another.
i. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies for reasons that varied between trials, including no pre-specified plan, participants being aware of the assigned intervention, deviations from the intended interventions, and unclear allocation concealment.
j. Downgraded by 1 increment for imprecision due to sample size being greater than 70, but less than 350.
k. Absolute effect calculated from risk difference.

Table 11: Clinical evidence profile: intravenous iron versus placebo (>12 months follow-up)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (HR) (follow-up: range 1.9 years to 3 years)												
3	randomised trials	serious[a]	not serious	not serious	not serious	none	-/2659	-/2648	**HR 0.92** (0.83 to 1.03)	-	⨁⨁⨁◯ Moderate[a]	CRITICAL
All-cause mortality (dichotomous) (follow-up: range 1.9 years to 3 years)												
4	randomised trials	not serious	not serious	serious[b]	serious[c]	none	653/2679 (24.4%)	691/2668 (25.9%)	**RR 0.94** (0.86 to 1.03)	**16 fewer per 1,000** (from 36 fewer to 8 more)	⨁⨁◯◯ Low[b,c]	CRITICAL
Cardiovascular mortality (HR) (follow-up: range 2.7 years to 3 years)												
2	randomised trials	serious[d]	not serious	not serious	serious[c]	none	-/1127	-/1115	**HR 0.84** (0.68 to 1.03)	-	⨁⨁◯◯ Low[c,d]	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo	Relative (95% CI)	Absolute (95% CI)		
Cardiovascular mortality (dichotomous) (follow-up: range 1.9 years to 3 years)												
4	randomised trials	not serious	not serious	serious[b]	serious[c]	none	426/2679 (15.9%)	484/2668 (18.1%)	**RR 0.88** (0.78 to 0.99)	**22 fewer per 1,000** (from 40 fewer to 2 fewer)	⨁⨁◯◯ Low[b,c]	CRITICAL
Health-related quality of life - Minnesota Living with Heart Failure (MLWHF) (final value) (score range from 0 to 105, lower scores are better) (follow-up: 2.7 years)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	569	568	-	MD **2.57 lower** (6.73 lower to 1.59 higher)	⨁⨁◯◯ Low[c,d]	CRITICAL
Health-related quality of life- EQ-5D index score (final values) (score range -0.59 to 1, higher scores are better) (follow-up: mean 2.7 years)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	569	568	-	MD **0.01 higher** (0.03 lower to 0.05 higher)	⨁⨁◯◯ Low[c,d]	CRITICAL
Health-related quality of life - EQ-5D VAS (final values) (score range 1-100, higher scores are better) (follow-up: mean 2.7 years)												
1	randomised trials	serious[d]	not serious	not serious	not serious	none	569	568	-	MD **0.54 higher** (2.86 lower to 3.94 higher)	⨁⨁⨁◯ Moderate[d]	CRITICAL
Unplanned hospitalisation or visits (all-cause) (HR) (follow-up: mean 2.7 years)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	-/569	-/568	**HR 0.91** (0.79 to 1.05)	-	⨁⨁◯◯ Low[c,d]	CRITICAL
Unplanned hospitalisation or visit (all-cause) (rate ratio) (follow-up: 5 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[e]	not serious	not serious	not serious	none	0/20	0/20	**Rate ratio 0.15** (0.05 to 0.42)	**229 fewer per 1000 patient(s) per years** (from 256 fewer to 157 fewer)[f]	⨁⨁⨁◯ Moderate[e]	CRITICAL
Unplanned hospitalisation or visits (all-cause) (dichotomous) (follow-up: mean 2.7 years)												
1	randomised trials	serious[d]	serious[g]	serious[b]	not serious	none	351/569 (61.7%)	370/568 (65.1%)	**RR 0.95** (0.87 to 1.03)	**33 fewer per 1,000** (from 85 fewer to 20 more)	⨁◯◯◯ Very low[b,d,g]	CRITICAL
Unplanned hospitalisation or visit (all-cause) (dichotomous) (follow-up: 5 years)												
1	randomised trials	serious[e]	serious[g]	serious[b]	not serious	none	4/20 (20.0%)	17/20 (85.0%)	**RR 0.24** (0.10 to 0.58)	**646 fewer per 1,000** (from 765 fewer to 357 fewer)	⨁◯◯◯ Very low[b,e,g]	CRITICAL
Unplanned hospitalisation or visits (heart failure related) (rate ratio) (follow-up: range 2.7 to 3 years)												
2	randomised trials	serious[d]	not serious	not serious	serious[c]	none	-/1127	-/1115	**Rate ratio 0.80** (0.66 to 0.97)	**52 fewer per 1000 patient(s) per years** (from 88 fewer to 8 fewer)[f]	⨁⨁◯◯ Low[c,d]	
Unplanned hospitalisation or visits (heart failure-related) (dichotomous)												
1	randomised trials	serious[a]	serious[g]	serious[b]	not serious	none	351/1532 (22.9%)	353/1533 (23.0%)	**RR 0.99** (0.87 to 1.13)	**2 fewer per 1,000** (from 30 fewer to 30 more)	⨁◯◯◯ Very low[a,b,g]	CRITICAL
Unplanned hospitalisation or visit (heart failure-related) (dichotomous) (follow-up: 5 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[e]	serious[g]	serious[b]	not serious	none	3/20 (15.0%)	16/20 (80.0%)	**RR 0.19** (0.06 to 0.54)	**648 fewer per 1,000** (from 752 fewer to 368 fewer)	⨁◯◯◯ Very low[b,e,g]	CRITICAL
Improvement in exercise tolerance - 6-minute walk distance (final scores, higher scores are better) (follow-up: 2.7 years)												
1	randomised trials	very serious[h]	not serious	not serious	serious[c]	none	98	95	-	MD **35.9 metres lower** (74.41 lower to 2.61 higher)	⨁◯◯◯ Very low[c,h]	CRITICAL
Withdrawal due to drug-related adverse events (follow-up: 56 weeks)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	14/150 (9.3%)	19/151 (12.6%)	**RR 0.74** (0.39 to 1.42)	**33 fewer per 1,000** (from 77 fewer to 53 more)	⨁⨁◯◯ Low[c]	CRITICAL
Anaphylaxis/ hypersensitivity (follow-up: 1.9 years)												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	5/1532 (0.3%)	0/1533 (0.0%)	**Peto odds ratio 7.41** (1.28 to 42.84)	**0 fewer per 1,000** (from 0 fewer to 10 more)[i]	⨁⨁⨁◯ Moderate[a]	CRITICAL
Hospitalisation for infection (follow-up: mean 2.7 years)												
1	randomised trials	serious[d]	not serious	not serious	serious[c]	none	37/569 (6.5%)	53/568 (9.3%)	**RR 0.70** (0.47 to 1.04)	**28 fewer per 1,000** (from 49 fewer to 4 more)[i]	⨁⨁◯◯ Low[c,d]	CRITICAL
Hospitalisation for sepsis (dichotomous) (follow-up: mean 1.9 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV iron supplementation	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	21/1532 (1.4%)	13/1533 (0.8%)	**RR 1.62** (0.81 to 3.22)	**5 more per 1,000** (from 2 fewer to 19 more)	⨁⨁◯◯ Low[a,c]	CRITICAL
Atrial fibrillation (follow-up: median 2.7 years)												
1	randomised trials	serious[d]	not serious	not serious	very serious[c]	none	13/559 (2.3%)	8/568 (1.4%)	**RR 1.65** (0.69 to 3.95)	**9 more per 1,000** (from 4 fewer to 42 more)	⨁◯◯◯ Very low[c,d]	CRITICAL

CI: confidence interval; EQ-5D: EuroQoL 5-dimensions questionnaire; EQ-5D VAS: EuroQoL 5-dimensions questionnaire visual analogue scale; HR: Hazard ratio; IV: Intravenous; MD: Mean difference; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; OR: Odds ratio; RR: Relative risk

a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: dose interruptions occurred in 564 participants (18.4%) and use of intravenous iron occurred outside the trial protocol in 31 participants in the intervention group and 104 participants in the placebo arm.
b. Downgraded by 1 increment due to reporting as number of events.
c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes; MLWHFQ MID is 5; EQ5D MID is 0.03; EQ VAS MID is 11.9; 6 minute walk test MID is 68.25.
d. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context
e. Downgraded by 1 increment for risk of bias due to unclear allocation concealment.
f. Absolute difference calculated based on person years of follow-up reported in the paper.
g. Downgraded by 2 increments for inconsistency due to unexplained heterogeneity (studies not pooled).
h. Downgraded by 2 increments for risk of bias due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context; and missing outcome data.
i. Absolute effect calculated from risk difference.

Table 12: Clinical evidence profile: Intravenous iron versus placebo: Subgroup analysis by TSAT level (3-12 months follow-up)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous iron	placebo	Relative (95% CI)	Absolute (95% CI)		
Health-related quality of life - Minnesota Living with Heart Failure (change score) (score range from 0-105, lower scores are better) - TSAT <20% (follow-up: 4 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous iron	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	413	428	-	MD **3 lower** (7.19 lower to 1.19 higher)	⨁⨁⨁◯ Low[a,b]	CRITICAL
Health-related quality of life - Minnesota Living with Heart Failure (change score) (score range from 0-105, lower scores are better) - TSAT greater than or equal to 20% (follow-up: 4 months)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	141	128	-	MD **2 lower** (7.97 lower to 3.97 higher)	⨁⨁⨁◯ Low[a,b]	CRITICAL
Improvement in exercise- 6-minute walk test (change scores, higher scores are better)- TSAT <20% (follow-up: range 4 months to 12 months)												
2	randomised trials	serious[a]	not serious	not serious	not serious	none	182	176	-	MD **16.74 higher** (7.94 lower to 41.41 higher)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Improvement in exercise- 6-minute walk test (change scores) - TSAT greater than or equal to 20% (follow-up: range 4 months to 12 months)												
2	randomised trials	serious[a]	very serious[c]	not serious	very serious[b]	none	88	68	-	MD **3.84 higher** (64.11 lower to 71.78 higher)	⨁◯◯◯ Very low[a,c]	CRITICAL

CI: confidence interval; IV: Intravenous; MD: Mean difference; MLWHFQ: Minnesota Living With Heart Failure Questionnaire; TSAT: Transferrin saturation
a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context.
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes; MLWHFQ MID is 5; 6 minute walk test MID is 61.79.
c. Downgraded by 2 increments for inconsistency with I2 >60%.

Table 13: Clinical evidence profile: Intravenous iron versus placebo: Subgroup analysis by TSAT level (>12 months follow-up)

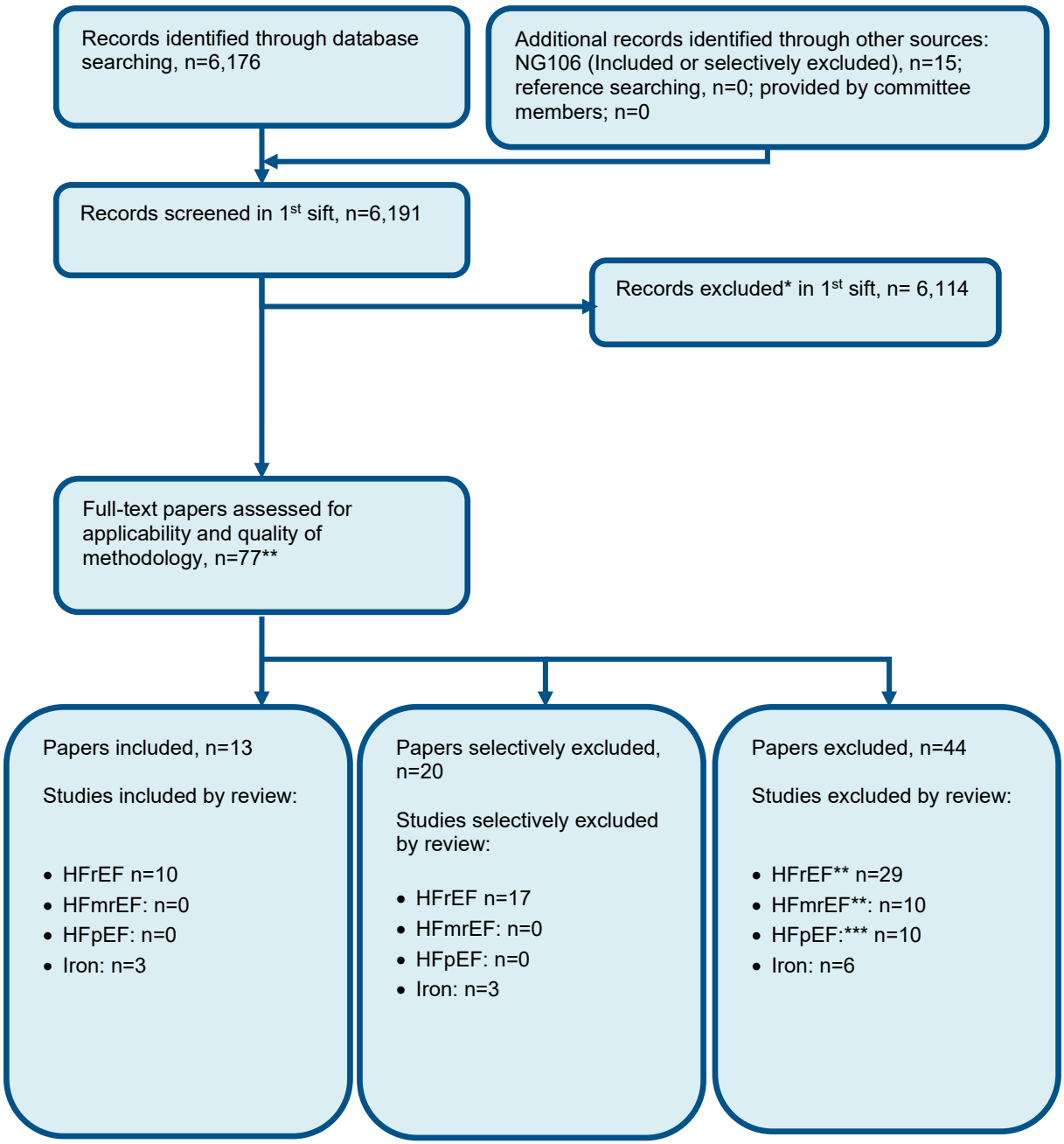
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous iron	placebo	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (time-to-event) - TSAT <20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	413	418	**HR 0.92** (0.73 to 1.16)	-	⨁⨁◯◯ Low[a,b]	CRITICAL
All-cause mortality (time-to-event) - TSAT greater than or equal to 20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	-/141	-/128	**HR 1.30** (0.82 to 2.06)	-	⨁⨁◯◯ Low[a,b]	CRITICAL
All-cause mortality (dichotomous) - TSAT <20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	serious[c]	serious[d]	serious[b]	none	135/430 (31.4%)	153/428 (35.7%)	**RR 0.88** (0.67 to 1.16)	**43 fewer per 1,000** (from 118 fewer to 57 more)	⨁◯◯◯ Very low[a,b,c,d]	CRITICAL
All-cause mortality (dichotomous) - TSAT greater than or equal to 20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b]	none	43/141 (30.5%)	33/128 (25.8%)	**RR 1.18** (0.80 to 1.74)	**46 more per 1,000** (from 52 fewer to 191 more)	⨁◯◯◯ Very low[a,b,d]	CRITICAL
Cardiovascular mortality (time-to-event) - TSAT <20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	413	428	**HR 0.85** (0.64 to 1.13)	-	⨁⨁◯◯ Low[a,b]	CRITICAL
Cardiovascular mortality (time-to-event) - TSAT greater than or equal to 20% (follow-up: 2.7 years)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intravenous iron	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	-/141	-/128	**HR 1.03** (0.59 to 1.81)	-	⨁◯◯◯ Very low[a,b]	CRITICAL
Cardiovascular mortality (dichotomous)- TSAT <20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	not serious	serious[d]	serious[b]	none	89/413 (21.5%)	109/428 (25.5%)	**RR 0.85** (0.66 to 1.09)	**38 fewer per 1,000** (from 87 fewer to 23 more)	⨁◯◯◯ Very low[a,b,d]	CRITICAL
Cardiovascular mortality (dichotomous)- TSAT greater than or equal to 20% (follow-up: 2.7 years)												
1	randomised trials	serious[a]	not serious	serious[d]	very serious[b]	none	25/141 (17.7%)	24/128 (18.8%)	**RR 0.95** (0.57 to 1.57)	**9 fewer per 1,000** (from 81 fewer to 107 more)	⨁◯◯◯ Very low[a,b,d]	CRITICAL
Hospitalisation for infection- TSAT <20% (follow-up: median 2.7 years)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	413	428	**HR 0.70** (0.53 to 0.93)	-	⨁⨁◯◯ Low[b,e]	CRITICAL
Hospitalisation for infection- TSAT greater than or equal to 20% (follow-up: median 2.7 years)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	141	128	**HR 1.13** (0.69 to 1.86)	-	⨁◯◯◯ Very low[b,e]	CRITICAL

CI: confidence interval; HR: Hazard ratio; IV: Intravenous; MD: Mean difference; RR: Relative risk; TSAT: Transferrin saturation
a. Downgraded by 1 increment for risk of bias in >50% of the weight of the included studies due to deviations from intended interventions: unblinded and 17% of usual care group received IV iron but no information about whether this was due to the trial context
b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. The MIDs were 0.8 to 1.25 for dichotomous outcomes or 0.5 x median baseline SD (or 0.5 x median control group SD where no baseline values given) for continuous outcomes.
c. Downgraded by 1 increment if I2 41-60% and 2 increments if I2 >60%.
d. Downgraded by 1 increment for indirectness due reporting numbers of events.

Appendix G Economic evidence study selection

Figure 33: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
**1 study was identified that met both the HFrEF and HFmrEF population criteria
*** the same 10 studies were reviewed for both the HFmrEF and HFpEF populations
.

Appendix H Economic evidence tables

Table 14: Health economic evidence study extraction table: Gutzwiller 2012

Section	Details for Gutzwiller et al. 2012
Study details	**Economic analysis type:** Cost-utility analysis. **Model type** Simple model based on one clinical trial **Country setting:** UK **Perspective:** NHS **Time horizon/Follow-up**: 24 weeks **Treatment duration:** Maximum 24 weeks **Discount rate per year:** not applicable due to short time horizon
Interventions	**Intervention 1:** No iron treatment - placebo (saline solution) arm in FAIR-HF trial. **Intervention 2:** Iron repletion with ferric carboxymaltose (FCM) administered as an IV bolus injection - 4mL equivalent to 200mg of iron until repletion was achieved. Patients receive one injection per week until iron repletion achieved (correction phase). Subsequently, an injection was given every 4 weeks (maintenance phase).
Population	**Population:** Iron-deficient CHF patients (NYHA class II or III) with or without anaemia **Patient characteristics** Sample size = 459 Mean age: Intervention 1= 67.4 (SD: 11.1) Intervention 2= 67.8 (SD: 10.3) Male: Intervention 1= 45.2% Intervention 2= 47.7%
Costs included	**Currency & cost year:** 2009 Pounds sterling **Cost components incorporated:** Drug, drug administration (no wastage), and hospitalisation for CHF. Cost of adverse events were not taken into account (no clinically relevant differences)
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY
Data Sources	**Health outcomes:** QALYs were calculated using patient-level utility data collected at baseline and at 4, 12 and 24 weeks (within-trial analysis of FAIR-HF) **Quality-of-life weights:** EQ-5D UK tariff. **Costs and/or resource use:** NHS Reference costs 2008-2009, BNF 2011, PSSRU 2007, Falkirk & District Royal Infirmary 2006.
Results: costs	**Total costs (mean per patient):** Intervention 1: £619 Intervention 2: £768 Incremental (2−1): £149 (95% CI: NR; p=NR)

Section	Details for Gutzwiller et al. 2012
Results: health outcomes	**QALYs (mean per patient):** Intervention 1: 0.298 Intervention 2: 0.336 Incremental (2−1): 0.037 (95% CI: 0.017-0.06; p=NR)
Results: cost effectiveness	**ICER (Intervention 2 versus Intervention 1):** £3,977 per QALY gained (pa) 95% CI: NR Probability Intervention 2 cost-effective (£20K/30K threshold): 99.66%/99.68%
Results: Uncertainty	**Deterministic:** Univariate sensitivity analysis varying the mean duration of hospitalisations for CHF in the UK; the cost of a hospital day by ±30%; drug costs by ±10% as no confidence intervals were available for these parameters. Further varied QALY difference; proportional reduction in hospitalisation days; frequency of hospitalisation in placebo group on basis of confidence intervals. Results ranged from dominance of IV iron strategy to £12,482 per QALY gained. Frequency and duration of hospitalisation, QALY difference, and cost of hospital day were the most influential parameters. Further variations were calculation of results considering only cases with complete data on utilities; calculation of costs via NYHA class approach; calculation of utilities using EQ-5D VAS scale scores. None of the parameters tested resulted in an ICER above £20,000 per QALY gained. **Probabilistic:** Mean costs for FCM £790 (range: £548 to £1,847), for placebo £618 (range £332 to £1002), mean effect of 0.038 QALYs (range -0.006 to 0.085). Probability Intervention 2 cost-effective (£20K/30K threshold): 99.66%/99.68%
Health inequalities assessment	NR
Comments	**Source of funding:** Vifor Pharma Ltd, Switzerland. **Other:** The FAIR-HF trial did not include British participants but was mostly performed in European countries with a predominantly Caucasian population. This is unlikely to change the conclusions of cost-effectiveness.
Rating: Applicability (Directly/ partially/ not)	Directly applicable NHS perspective
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations: Short time horizon may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators.

Abbreviations: CI= confidence interval; DA=deterministic analysis; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; PSS= Personal Social Services; QALY=quality-adjusted life-year; RCT=randomised controlled trial.

Table 15: Health economic evidence study extraction table: Hofmarcher 2018

Section	Details for Hofmarcher et al. 2018
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Within-trial analysis of CONFIRM-HF **Country setting:** Denmark, Finland, Norway and Sweden **Perspective:** Health care **Time horizon/Follow-up**: 52 weeks **Treatment duration:** 52 weeks **Discount rate per year:** Not applicable due to short time horizon
Interventions	**Intervention 1: No treatment:** Placebo arm from CONFIRM-HF clinical trial **Intervention 2: IV iron:** Iron repletion with ferric carboxymaltose (FCM) Initial dose based on weight and haemoglobin level from 500mg up to 1500mg, based on the initial allocation of patients in the CONFIRM-HF trial across the 6 dosing combinations. If more than 1000mg is required a second dose is given after at least one week, in the CONFIRM-HF trial the second dose was administered at 6 weeks. Patients assessed for iron deficiency at weeks 12, 24 and 36 weeks. 18.9% of patients from CONFIRM-HF still had iron deficiency. Analysis assumed half of these patients would require total dose of 1500mg, a quarter would require 500mg and the final quarter would require 1000mg. This differs slightly from the CONFIRM-HF protocol in which all patients with iron deficiency at weeks 12,24 and 36 received 500mg IV iron.
Population	**Population:** Adults with chronic heart failure (NYHA class II or III) and with iron deficiency. **Patient characteristics** Sample size = 304 Mean age = 69 Male = 53%
Costs included	**Currency & cost year:** 2017 Euros (presented here as 2017 UK pounds – converted using IMF Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx) based on Finland **Cost components incorporated:** Drug, administration visit, hospitalisation for HF and diagnostic test. Adverse events were not included because they were similar across both treatment arms
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY
Data Sources	**Effectiveness data:** Utility values measured with the EuroQoL Visual Analogue Scale (EQ-VAS) within the CONFIRM-HF clinical trial at baseline and at weeks 6, 12, 24, 36, and 52. To conform with the preferred EQ-5D measure for calculating QALYs. The values from CONFIRM-HF were mapped from EQ-VAS to EQ-5D data by using FAIR-HF study EQ-5D values and using the relationship between the two values to combine it with the EQ-VAS based value from the CONFIRM-HF trial. **Quality-of-life weights:** EQ-VAS and EQ-5D UK tariff, levels used were not specified. **Costs and/or resource use:** Drug cost from Vifor Pharma Nordiska, Stockholm, Sweden, national unit costs were based on the Nordic diagnosis related groups (DRG).

Section	Details for Hofmarcher et al. 2018
Results: costs	**Total costs (per patient):** **Denmark** Intervention 1: €1,381 Intervention 2: €1,082 Incremental (2−1):- €298 (95% CI: NR; p=NR) **Finland** Intervention 1: €997 Intervention 2: €961 Incremental (2−1): -€36 (95% CI: NR; p=NR) **Norway** Intervention 1: €1,759 Intervention 2: €1,275 Incremental (2−1):- €484 (95% CI: NR; p=NR) **Sweden** Intervention 1: €1,447 Intervention 2: €1,068 Incremental (2−1):- €379 (95% CI: NR; p=NR)
Results: health outcomes	**QALYs (per patient):** Intervention 1: NR Intervention 2: NR Incremental difference: 0.050 (95% CI: NR; p=NR)
Results: cost effectiveness	**Incremental cost-effectiveness ratios (Intervention 2 versus Intervention 1:** **Denmark** Intervention 2 (IV iron) is dominant **Finland** Intervention 2 (IV iron) is dominant **Norway** Intervention 2 (IV iron) is dominant **Sweden** Intervention 2 (IV iron) is dominant 95% CI: NR
Results: Uncertainty	**Deterministic:** Univariate sensitivity analysis varying the assumptions around what visit costs were included as part of intervention 2 (iron therapy) and whether there was a difference in the hospitalisation rate, a mean annual rate of 0.17 hospitalisations in the IV iron group and 0.34 in the placebo group based on CONFIRM-HF. Additionally some of the base case values used in the model were varied based on the 95% confidence interval. In the base case it was

Section	Details for Hofmarcher et al. 2018
	assumed IV iron could be administered as part of a routine appointment and so would not require an additional visit. When additional cost of appointment for IV therapy administration or for diagnostic tests to monitor iron levels, IV therapy remained dominant compared to no treatment in Denmark, Norway and Sweden. In Finland the ICER was €6,192 when visits for administering treatment were included and €1,472 when the cost of diagnostic tests were included. When no difference in hospitalisation was assumed IV iron was no longer dominant and had an ICER of €7,485 in Denmark, €9,007 in Finland, 7,458 in Norway and €6,517 in Sweden. IV iron remained dominant compared with placebo in Sweden and Norway when assumptions around the dosage administered, whether hospitalisation rate was based on all cause or worsening heart failure, price of IV iron was varied by 20%, median patient was used or utility values were based on the upper or lower of the 95% confidence interval for EQ-5D or if the EQ-VAS values were used. When all patients are assumed to receive the highest dose of 1,500mg of IV iron, in Denmark the ICER becomes €1,022, in all other scenarios changing the base case values IV iron remains dominant. In Finland the ICER is most sensitive to a change in the dosage patients are assumed to receive with the maximum ICER due to a change in parameter value being €8,324 when it is assumed all patients receive a dosage of 1,500mg. **Probabilistic:** Not reported
Health inequalities assessment	NR
Comments	**Source of funding:** Vifor Pharma Nordiska **Other:** IV iron is dominant compared to placebo in all countries under the base case assumptions. The results in Finland were most sensitive to the changes in assumptions due to the higher costs associated with visits for treatment and hospitalisation. However, the ICER still remained below €10,000 per QALY in all scenarios with a maximum ICER of €9,007 per QALY when no difference in hospitalisations was assumed.
Rating: Applicability (Directly/ partially/ not)	Partially applicable Nordic country perspective, utilities may not have been estimated in the most robust manner
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations. Short time horizon, may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators, combines data from FAIR-HF trial with different IV iron dosage strategies to inform utility estimates.

Abbreviations: CI= confidence interval; DA=deterministic analysis; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; PSS= Personal Social Services; QALY=quality-adjusted life-year; RCT=randomised controlled trial.

Table 16: Health economic evidence study extraction table: Rognoni 2019

Section	Details for Rognoni et al. 2019
Study details	**Economic analysis type:** Cost-utility analysis. **Model type:** Cohort Markov **Country setting:** Italy **Perspective:** Italian healthcare only direct healthcare costs included **Time horizon/Follow-up:** 1 year **Treatment duration:** 1 year **Discount rate per year:** Not discounted
Interventions	**Intervention 1:** Placebo **Intervention 2:** IV iron: Iron repletion with IV administered ferric carboxymaltose,
Population	**Population:** Adults with heart failure and iron deficiency **Cohort settings:** Patients distributed across NYHA classes, 33% patients start in NYHA class II and 67% start in NYHA class III Start age: Not reported Male: Not reported
Costs included	**Currency & cost year:** 2018 Euros (presented here as 2018 UK pounds – converted using IMF Purchasing Power Parities: https://eppi.ioe.ac.uk/costconversion/default.aspx) **Cost components incorporated:** Drug, hospitalisation costs, Monitoring, outpatient services and CHF treatments by NYHA class
Outcomes included	**Primary health outcome(s) in economic analysis:** QALY **Key events modelled /analysed:** deaths, change in NYHA class
Data Sources	**Effectiveness data:** Pooled data across 4 trials CONFIRM-HF, FIND-CKD trial, EFFICACY-HF and FAIR-HF as reported by Theidel 2017 **Baseline / epidemiological data:** Theidel 2017. **Quality-of-life weights:** sourced from two studies: Gohler 2009 EQ-5D weighted by population United states 31%, Western Europe 52%, Latin America 14% and KIRSCH 2000 EQ-5D using time trade off instrument. **Costs and/or resource use:** Resource use based on patients across 5 Italian hospitals in the Lombardy region with expertise in CHF. Resource use was separated for each NYHA class (severity level). Drug costs sourced from Federfarma (2019) Italian pharmaceutical database. Healthcare resources for each NYHA class was estimated through diagnosis-related group reimbursement rates for hospitalisations and regional tariff values for outpatient services.
Results: costs	**Total mean costs (per patient):** Intervention 1 (Placebo): €3,699 Intervention 2 (IV iron): €3,296 Incremental (2−1): -€403 (-£383.73) (95% CI: NR; p=NR)
Results: health outcomes	Over the time horizon of 1 year the model estimated an average **Life years (per patient):** Intervention 1: 0.956 Intervention 2: 0.974 Incremental (2−1): 0.018 (95% CI: NR; p=NR) **QALYs (per patient):**

Section	Details for Rognoni et al. 2019
	Intervention 1: 0.642 Intervention 2: 0.703 Incremental (2−1): 0.061 (95% CI: NR; p=NR)
Results: cost effectiveness	**Incremental cost-effectiveness ratios:** 2 vs 1: Intervention 2 is dominant 95% CI: NR
Results: Uncertainty	**Deterministic**: Multiple one-way scenarios were performed on the main model parameters which included varying parameters by 50% such as weekly costs for visits, other hospital admissions and other outpatient services by NYHA class. Variations in the weekly rate of hospitalisation for CHF was found to be the main driver of the results. The most pessimistic scenario of assuming a weekly rate of hospitalisation of 0.01 for CHF for those in the IV iron arm was still considered cost-effective based on a threshold of €20,000/QALY with an ICER of €16,167 (£15,394). The base case was based on the Theidel et al. 2017 RCT and assumed a hospitalisation rate of 0.001 for IV iron and 0.0026 for placebo. **Probabilistic:** IV iron dominant in all simulations
Health inequalities assessment	NR
Comments	**Source of funding:** Vifor Pharma Italia Srl
Rating: Applicability (Directly/ partially/ not)	Partially applicable Italy healthcare perspective, which differs to the UK NHS.
Rating: Quality/ limitations (Minor/ potentially serious/ very serious)	Potentially serious limitations Short time horizon, which may not capture full costs and effects of the intervention. Lack of detailed medical resource use data. Within-trial analysis and so does not reflect full body of available evidence for all comparators, combines data from FAIR-HF trial with different FCM dosage strategies to inform utility estimates.

Abbreviations: CI= confidence interval; DA=deterministic analysis; ICER=incremental cost-effectiveness ratio; PSA=probabilistic sensitivity analysis; NA=not applicable; NR=not reported; PSS= Personal Social Services; QALY=quality-adjusted life-year; RCT=randomised controlled trial.

Appendix I Health economic model

This question was not prioritised for health economic modelling

Appendix J Excluded studies

J.1 Clinical evidence studies

Table 17: Studies excluded from the clinical review

Study	Reason for exclusion
Ahmed, A, Ansari, HA, Ali, M et al. (2024) Effect of intravenous iron supplementation on patients with heart failure and iron deficiency: an updated metanalysis. Journal of the American College of Cardiology 83(13): 752	- Conference abstract
Ahmed, Mushood, Shafiq, Aimen, Javaid, Hira et al. (2024) Intravenous iron therapy for heart failure and iron deficiency: An updated meta-analysis of randomized clinical trials. ESC heart failure	- Systematic review used as source of primary studies *SR retrieved during reruns; all studies already identified in initial search*
Anker, Stefan D, Khan, Muhammad Shahzeb, Butler, Javed et al. (2023) Effect of intravenous iron replacement on recurrent heart failure hospitalizations and cardiovascular mortality in patients with heart failure and iron deficiency: A Bayesian meta-analysis. European journal of heart failure 25(7): 1080-1090	- Systematic review used as source of primary studies *No outcomes protocol outcomes reported: composite endpoint of recurrent HF hospitalisations and cardiovascular death only*
Anker, Stefan D, Kirwan, Bridget-Anne, van Veldhuisen, Dirk J et al. (2018) Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. European journal of heart failure 20(1): 125-133	- Review article but not a systematic review
Anker, Stefan D, Ponikowski, Piotr, Khan, Muhammad Shahzeb et al. (2022) Responder analysis for improvement in 6-min walk test with ferric carboxymaltose in patients with heart failure with reduced ejection fraction and iron deficiency. European journal of heart failure 24(5): 833-842	- Secondary publication of an included study that does not provide any additional relevant information
Arutyunov, G.P., Bylova, N.A., Ivleva, A.Y. et al. (2009) The safety of intravenous (IV) ferric carboxymaltose versus IV iron sucrose in patients with chronic heart failure (CHF) and chronic kidney disease (CKD) with iron deficiency (ID). European Journal of Heart Failure, Supplement 8(suppl2): ii71	- Conference abstract
Awad, Ahmed K, Abdelgalil, Mahmoud Shaban, Gonnah, Ahmed R et al. (2024) Intravenous iron for acute and chronic heart failure with reduced ejection fraction (HFrEF) patients with iron deficiency: An updated systematic review and meta-analysis. Clinical medicine (London, England) 24(3): 100211	- Systematic review indirectly matches the review protocol: used as source of primary studies *includes acute heart failure and outcome definitions unclear*
Barry, A. and Ellis, U. (2020) Impact of correcting iron deficiency on quality of life in	- Conference abstract

Study	Reason for exclusion
heart failure with reduced ejection fraction: a systematic review and meta-analysis. Can. J. Cardiol. 36(10): S66-S67	
Beale, Anna L, Warren, Josephine Lillian, Roberts, Nia et al. (2019) Iron deficiency in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Open heart 6(1): e001012	- Systematic review used as source of primary studies *Insufficient reporting of primary trials characteristics and risk of bias.*
Bhatia, Kirtipal, Sabharwal, Basera, Gupta, Kartik et al. (2024) Clinical outcomes of intravenous iron therapy in patients with heart failure and iron deficiency: Meta-analysis and trial sequential analysis of randomized clinical trials. Journal of cardiology 83(2): 105-112	- Systematic review used as source of primary studies *Insufficient reporting of primary trials characteristics and risk of bias.*
Cleland, John G F, Pellicori, Pierpaolo, Graham, Fraser J et al. (2024) Adjudication of Hospitalizations and Deaths in the IRONMAN Trial of Intravenous Iron for Heart Failure. Journal of the American College of Cardiology 84(18): 1704-1717	- Secondary publication of an included study that does not provide any additional relevant information
Dalal, Jamshed; Katekhaye, Vijay; Jain, Rishi (2017) Effect of ferric carboxymaltose on hospitalization and mortality outcomes in chronic heart failure: A meta-analysis. Indian heart journal 69(6): 736-741	- Systematic review used as source of primary studies *Insufficient search strategy; multiple relevant trials not identified*
Dinatolo, Elisabetta, Dasseni, Nicolo, Metra, Marco et al. (2018) Iron deficiency in heart failure. Journal of cardiovascular medicine (Hagerstown, Md.) 19(12): 706-716	- Review article but not a systematic review
Dugan, C., Peeling, P., Burden, R. et al. (2024) Efficacy of iron supplementation on physical capacity in non-anaemic iron-deficient individuals: protocol for an individual patient data meta-analysis. Systematic Reviews 13(1): 182	- Protocol for a study not yet published
Filippatos, Gerasimos, Ponikowski, Piotr, Farmakis, Dimitrios et al. (2023) Association Between Hemoglobin Levels and Efficacy of Intravenous Ferric Carboxymaltose in Patients With Acute Heart Failure and Iron Deficiency: An AFFIRM-AHF Subgroup Analysis. Circulation 147(22): 1640-1653	- Population not relevant to this review protocol *Acute heart failure*
Graham, Fraser J, Pellicori, Pierpaolo, Ford, Ian et al. (2021) Intravenous iron for heart failure with evidence of iron deficiency: a meta-analysis of randomised trials. Clinical research in cardiology : official journal of the German Cardiac Society 110(8): 1299-1307	- Systematic review used as source of primary studies *Recent relevant trials not captured due to search date.*
Graham, Fraser J, Pellicori, Pierpaolo, Kalra, Paul R et al. (2023) Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. European journal of heart failure 25(4): 528-537	- Systematic review used as source of primary studies *Insufficient reporting of primary trial characteristics and risk of bias*

Study	Reason for exclusion
Gutzwiller, FS, Pfeil, AM, Comin-Colet, J et al. (2013) Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis. International journal of cardiology 168(4): 3878-3883	- Secondary publication of an included study that does not provide any additional relevant information *Listed as an included paper in 2018 update, but did not provide any data*
Hamed, Mohamed, Elseidy, Sheref A, Ahmed, Asmaa et al. (2023) Intravenous iron therapy among patients with heart failure and iron deficiency: An updated meta-analysis of randomized controlled trials. Heliyon 9(6): e17245	- Systematic review used as source of primary studies *Rate data combined with dichotomous data in analysis*
Hamza, Mohammad, Sattar, Yasar, Manasrah, Nouraldeen et al. (2023) Meta-Analysis of Efficacy and Safety of Intravenous Iron in Patients With Iron Deficiency and Heart Failure With Reduced Ejection Fraction. The American journal of cardiology 202: 119-130	- Systematic review used as source of primary studies *Indirectly matches the protocol, pools chronic and acute heart failure and non-randomised with RCTs.*
Harrington, Josephine, Mentz, Robert J, Rockhold, Frank W et al. (2024) Hierarchical End Points in Prior Heart Failure Trials and the HEART-FID Trial. Circulation. Heart failure 17(2): e010676	- Study does not contain any outcome data relevant to this review protocol
Harrington, Josephine, Mentz, Robert J, Rockhold, Frank W et al. (2023) Baseline characteristics of patients in the randomized study to investigate the efficacy and safety of ferric carboxymaltose as treatment for heart failure with iron deficiency: HEART-FID trial. American heart journal 266: 25-31	- Secondary publication of an included study that does not provide any additional relevant information
Huang, Kevin W; Bilgrami, Nazar L; Hare, David L (2022) Iron Deficiency in Heart Failure Patients and Benefits of Iron Replacement on Clinical Outcomes Including Comorbid Depression. Heart, lung & circulation 31(3): 313-326	- Systematic review indirectly matches the review protocol: used as source of primary studies *Recent relevant trials not captured due to search date.*
Ismahel, Hassan and Ismahel, Nadeen (2021) Iron replacement therapy in heart failure: a literature review. The Egyptian heart journal : (EHJ) : official bulletin of the Egyptian Society of Cardiology 73(1): 85	- Review article but not a systematic review
Jankowska, Ewa A, Kirwan, Bridget-Anne, Kosiborod, Mikhail et al. (2021) The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study. European heart journal 42(31): 3011-3020	- Population not relevant to this review protocol *Acute heart failure*
Karakas, M. (2019) Effect of ferric carboxymaltose on LVEF as assessed by cardiac MRI in patients with chronic heart failure and iron deficiency: A randomized, double-	- Conference abstract

Study	Reason for exclusion
blinded, placebo-controlled, dual-center trial. European Journal of Heart Failure 21(supplement1): 176	
Khan, Muhammad Shahzeb, Usman, Muhammad Shariq, von Haehling, Stephan et al. (2020) Ferric carboxymaltose for the treatment of iron-deficient heart failure patients: a systematic review and meta-analysis. ESC heart failure 7(6): 3392-3400	- Systematic review used as source of primary studies *Recent relevant trials not captured due to search date.*
Kotit, Susy (2024) Benefits of intravenous iron supplementation in heart failure. Global cardiology science & practice 2024(2): e202410	- Review article but not a systematic review
Macdougall, Iain C, Ponikowski, Piotr, Stack, Austin G et al. (2023) Ferric Carboxymaltose in Iron-Deficient Patients with Hospitalized Heart Failure and Reduced Kidney Function. Clinical journal of the American Society of Nephrology : CJASN 18(9): 1124-1134	- Population not relevant to this review protocol *Acute heart failure*
Marques, Pedro, Vasques-Novoa, Francisco, Matias, Paula et al. (2024) Influence of iron deficiency definition on the efficacy of intravenous iron in heart failure: a meta-analysis of randomized trials. Clinical research in cardiology : official journal of the German Cardiac Society	- Systematic review used as source of primary studies *Only reports composite outcome. Insufficient details on included studies*
Martens, Pieter, Augusto, Silvio Nunes Jr, Mullens, Wilfried et al. (2024) Meta-Analysis and Metaregression of the Treatment Effect of Intravenous Iron in Iron-Deficient Heart Failure. JACC. Heart failure 12(3): 525-536	- Systematic review used as source of primary studies *Insufficient details on included studies and unclear statistical methods*
Martens, Pieter, Dupont, Matthias, Dauw, Jeroen et al. (2022) The effect of intravenous ferric carboxymaltose on right ventricular function - insights from the IRON-CRT trial. European journal of heart failure 24(6): 1106-1113	- Duration of follow up <3 months *Follow-up is 8 weeks*
Mhanna, Mohammed, Sauer, Michael C, Al-Abdouh, Ahmad et al. (2024) Intravenous iron therapy for patients with iron deficiency and heart failure: a systematic review and meta-analysis of randomized controlled trials. Proceedings (Baylor University. Medical Center) 37(3): 466-476	- Systematic review used as source of primary studies *Indirectly matches the protocol: pools acute and chronic heart failure. Insufficient reporting of primary trial risk of bias.*
Mocarski, ME, Vallakati, M, Patel, V et al. (2024) Efficacy of intravenous iron in patients with heart failure with reduced ejection fraction: an updated meta-analysis. Journal of the American College of Cardiology 83(13): 745	- Conference abstract
Mollace, Annachiara, Macri, Roberta, Mollace, Rocco et al. (2022) Effect of Ferric Carboxymaltose Supplementation in Patients with Heart Failure with Preserved Ejection	- Duration of follow up <3 months *Follow-up is 8 weeks*

Study	Reason for exclusion
Fraction: Role of Attenuated Oxidative Stress and Improved Endothelial Function. Nutrients 14(23)	
Mototani, Rena, Watanabe, Atsuyuki, Kuno, Toshiki et al. (2023) Effect of intravenous iron-carbohydrate complexes in patients with heart failure with reduced ejection fraction and iron deficiency: A meta-analysis of randomized controlled trials. Hellenic journal of cardiology : HJC = Hellenike kardiologike epitheorese 72: 67-69	- Study design not relevant to this review protocol
Ogugua, Fredrick M, Aguilar, Francisco A, Gamam, Abdulrahman et al. (2023) Treating Iron Deficiency (ID) Anemia in Heart Failure (HF) Patients with IV Iron: A Meta-Analysis. Cureus 15(7): e41895	- Systematic review used as source of primary studies *Recent relevant trials not captured due to search date.*
Okonko, Darlington O, Jouhra, Fadi, Abu-Own, Huda et al. (2019) Effect of ferric carboxymaltose on calculated plasma volume status and clinical congestion: a FAIR-HF substudy. ESC heart failure 6(4): 621-628	- Secondary publication of an included study that does not provide any additional relevant information
Oli, P.R., Shrestha, D.B., Shikhrakar, S. et al. (2023) Intravenous iron therapy for iron deficiency in patients with heart failure: An updated systematic review and meta-analysis. Health Sciences Review 9: 100131	- Systematic review used as source of primary studies *Insufficient reporting of primary trial risk of bias*
Osman, M., Syed, M., Balla, S. et al. (2021) A Meta-analysis of Intravenous Iron Therapy for Patients With Iron Deficiency and Heart Failure. American Journal of Cardiology 141: 152-153	- Full text paper not available
Padda, Inderbir, Sebastian, Sneha Annie, Fabian, Daniel et al. (2024) The Efficacy and Safety of Ferric Carboxymaltose in Heart Failure with Reduced Ejection Fraction and Iron Deficiency: An Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. Diseases (Basel, Switzerland) 12(12)	- Systematic review used as source of primary studies *SR retrieved during reruns; all studies already identified in the initial search*
Ponikowski, P., Macdougall, I., Bohm, M. et al. (2017) Impact of intravenous ferric carboxymaltose iron therapy on symptoms and functionality in iron-deficient patients with heart failure with reduced ejection fraction and renal dysfunction: An individualpatient data metaanalysis of 4 randomized, double-blind trials. Nephrology Dialysis Transplantation: iii581-iii582	- Conference abstract
Ponikowski, P., Macdougall, I.C., Bohm, M. et al. (2017) An individual patient data meta-analysis of outcomes in 4 randomized double-blind trials of iron-deficient patients with HFrEF and renal dysfunction treated with IV ferric carboxymaltose. European Journal of Heart Failure: 190	- Conference abstract

Study	Reason for exclusion
Ponikowski, P, Filippatos, G, Colet, JC et al. (2015) The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. European journal of heart failure 17(3): 329-339	- Secondary publication of an included study that does not provide any additional relevant information
Ponikowski, Piotr, Kirwan, Bridget-Anne, Anker, Stefan D et al. (2019) Rationale and design of the AFFIRM-AHF trial: a randomised, double-blind, placebo-controlled trial comparing the effect of intravenous ferric carboxymaltose on hospitalisations and mortality in iron-deficient patients admitted for acute heart failure. European journal of heart failure 21(12): 1651-1658	- Population not relevant to this review protocol *Acute heart failure*
Ponikowski, Piotr, Mentz, Robert J, Hernandez, Adrian F et al. (2023) Efficacy of ferric carboxymaltose in heart failure with iron deficiency: an individual patient data meta-analysis. European heart journal 44(48): 5077-5091	- Systematic review used as source of primary studies
Rangwala, Burhanuddin Sohail, Zuhair, Varisha, Mustafa, Muhammad Saqlain et al. (2024) Ferric carboxymaltose for iron deficiency in patients with heart failure: a systematic review and meta-analysis. Future science OA 10(1): 2367956	- Systematic review used as source of primary studies *SR retrieved during reruns; all studies already identified in initial search*
Ray, Robin, Ford, Ian, Cleland, John G F et al. (2024) The Impact of Ferric Derisomaltose on Cardiovascular and Noncardiovascular Events in Patients With Anemia, Iron Deficiency, and Heart Failure With Reduced Ejection Fraction. Journal of cardiac failure 30(5): 682-690	- Secondary publication of an included study that does not provide any additional relevant information
Reinhold, Johannes, Burra, Vyas, Corballis, Natasha et al. (2023) Effects of Intravenous Iron Replacement Therapy on Cardiovascular Outcomes in Patients with Heart Failure: A Systematic Review and Meta-Analysis. Journal of cardiovascular development and disease 10(3)	- Systematic review used as source of primary studies *Insufficient reporting of primary trial characteristics and risk of bias*
Salah, Husam M, Savarese, Gianluigi, Rosano, Giuseppe M C et al. (2023) Intravenous iron infusion in patients with heart failure: a systematic review and study-level meta-analysis. ESC heart failure 10(2): 1473-1480	- Systematic review used as source of primary studies *Indirectly matches the protocol; pools acute and chronic heart failure. Insufficient reporting of primary trial risk of bias*
Sephien, Andrew, Dayto, Denisse Camille, Reljic, Tea et al. (2024) Efficacy of Intravenous Iron in Patients with Heart Failure with Reduced Ejection Fraction and Iron Deficiency: A Systematic Review and Meta-Analysis of Randomized Control Trials. American journal of cardiovascular drugs : drugs, devices, and other interventions 24(2): 285-302	- Systematic review used as source of primary studies *Insufficient reporting of outcome data*

Study	Reason for exclusion
Silverberg, D S, Wexler, D, Sheps, D et al. (2001) The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. Journal of the American College of Cardiology 37(7): 1775-80	- Study does not contain an intervention relevant to this review protocol *Erythropoietin combined with intravenous iron*
Sindone, Andrew; Doehner, Wolfram; Comin-Colet, Josep (2023) Systematic review and meta-analysis of intravenous iron-carbohydrate complexes in HFrEF patients with iron deficiency. ESC heart failure 10(1): 44-56	- Systematic review used as source of primary studies *Insufficient reporting of primary trial data; odds ratios only without events*
Taha, Amira Mohamed, Elsaeidy, Ahmed Saad, Nada, Sarah A et al. (2024) Efficacy of Intravenous Ferric Carboxymaltose in Heart Failure Patients with Iron Deficiency Anemia: A Meta-analysis of 6271 Patients. Clinical drug investigation 44(12): 879-896	- Systematic review used as source of primary studies *SR retrieved during reruns; all studies already identified in initial search*
Techasatian, Witina, Nishimura, Yoshito, Tanariyakul, Manasawee et al. (2023) Intravenous Iron for Heart Failure: Updated Systematic Review and Meta-Analysis. Angiology: 33197231213181	- Systematic review used as source of primary studies *Insufficient detail on included studies*
Turgeon, Ricky D, Barry, Arden R, Hawkins, Nathaniel M et al. (2021) Pharmacotherapy for heart failure with reduced ejection fraction and health-related quality of life: a systematic review and meta-analysis. European journal of heart failure 23(4): 578-589	- Systematic review used as source of primary studies *Recent relevant trials not captured due to search date.*
Vukadinovic, Davor, Abdin, Amr, Emrich, Insa et al. (2023) Efficacy and safety of intravenous iron repletion in patients with heart failure: a systematic review and meta-analysis. Clinical research in cardiology : official journal of the German Cardiac Society 112(7): 954-966	- Systematic review used as source of primary studies *Insufficient search strategy*
Wang, Haiming, Li, Yanhua, Zhou, Jingjing et al. (2024) Impact of Intravenous Iron in patients with heart failure and Iron Deficiency: an updated Meta-analysis of Randomized controlled trials. BMC cardiovascular disorders 24(1): 695	- Study not reported in English
Wong, C., Ng, A., Lau, J. et al. (2016) Early responses to intravenous iron therapy in patients with chronic heart failure and iron deficiency. Heart Lung and Circulation 25(supplement2): 107	- Conference abstract
Yamani, Naser, Ahmed, Aymen, Gosain, Priyanka et al. (2021) Effect of iron supplementation in patients with heart failure and iron deficiency: A systematic review and meta-analysis. International journal of cardiology. Heart & vasculature 36: 100871	- Systematic review does not contain sufficient detail for included studies: used as source of primary studies

Study	Reason for exclusion
Yeo, Tee Joo, Yeo, Poh Shuan Daniel, Hadi, Farid Abdul et al. (2018) Single-dose intravenous iron in Southeast Asian heart failure patients: A pilot randomized placebo-controlled study (PRACTICE-ASIA-HF). ESC heart failure 5(2): 344-353	- Population not relevant to this review protocol *Acute heart failure*
Zhang, Junyi, Hu, Shengda, Jiang, Yufeng et al. (2020) Efficacy and safety of iron therapy in patients with chronic heart failure and iron deficiency: a systematic review and meta-analysis based on 15 randomised controlled trials. Postgraduate medical journal 96(1142): 766-776	- Systematic review used as source of primary studies *Outcomes reported as odds ratios and raw data not provided*
Zhou, Xiang, Xu, Weiting, Xu, Youjia et al. (2019) Iron Supplementation Improves Cardiovascular Outcomes in Patients with Heart Failure. The American journal of medicine 132(8): 955-963	- Systematic review used as source of primary studies *Recent trials not captured due to search date.*

J.2 Health Economic studies

Table 18: Studies excluded from the health economic review

Reference	Reason for exclusion
Bourguignon, Sandrine, Faller, Mathilde, Champs, Francois-Olivier et al. (2019) Budget impact of intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency in France. ESC heart failure 6(3): 559-569	- Not economic evaluation *Budget Impact model, no quality of life included*
Brock, Elisabeth, Moschovitis, Giorgio, Maeder, Micha T et al. (2022) Budget Impact of Intravenous Iron Therapy with Ferric Carboxymaltose in Patients with Chronic Heart Failure with Reduced Ejection Fraction (HFrEF) and Iron Deficiency in Switzerland. PharmacoEconomics - open 6(5): 735-743	- Not economic evaluation *Budget Impact model, no quality of life included*
Comín-Colet, Josep, Rubio-Rodríguez, Darío, Rubio-Terrés, Carlos et al. (2015) A Cost-effectiveness Analysis of Ferric Carboxymaltose in Patients With Iron Deficiency and Chronic Heart Failure in Spain. Revista Española de Cardiología (English Edition) 68(10): 846-851	- Selectively Exclude - A more applicable UK analysis was available *This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis (Gutzwiller et al. 2012) was available based on the same trial, this study was selectively excluded.*
Hofmarcher, Thomas and Borg, Sixten (2015) Cost-effectiveness analysis of ferric carboxymaltose in iron-deficient patients with chronic heart failure in Sweden. Journal of Medical Economics 18(7): 492-501	- Selectively Exclude - A more applicable UK analysis was available *This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK*

Reference	Reason for exclusion
	analysis (Gutzwiller et al. 2012) was available based on the same trial, this study was selectively excluded.
Lim, Eun-A, Sohn, Hyun-Soon, Lee, Haeyoung et al. (2014) Cost-utility of ferric carboxymaltose (Ferinject®) for iron-deficiency anemia patients with chronic heart failure in South Korea. Cost Effectiveness and Resource Allocation 12(1): 19	- Selectively Exclude - A more applicable UK analysis was available *This study was assessed as partially applicable with potentially serious limitations. However, given that a more applicable UK analysis (Gutzwiller et al. 2012) was available based on the same trial, this study was selectively excluded.*
Lim, G.B. (2021) Cost-effective benefit of iron-replacement therapy. Nature Reviews Cardiology 18(9): 611	- Exclude - full paper not accessible
McEwan, Phil, Ponikowski, Piotr, Davis, Jason A et al. (2021) Ferric carboxymaltose for the treatment of iron deficiency in heart failure: a multinational cost-effectiveness analysis utilising AFFIRM-AHF. European journal of heart failure 23(10): 1687-1697	- Population not relevant to this review protocol Acute heart failure
Pollock R, Kalra PR, Mcmurray JJV, Graham FJ, Pellicori P, Cleland JGF et al. Ferric derisomaltose versus usual care in patients with heart failure, reduced ejection fraction, and iron deficiency: a short-term UK cost-utility analysis based on the IRONMAN RCT. European Heart Journal. 2024; 45(Supplement_1)	- Exclude – Abstract presentation *Full study not yet available*
Rezapour, Aziz, Souresrafil, Aghdas, Shamsaei, Monireh et al. (2023) Economic evaluation of ferric carboxymaltose compared with placebo in iron-deficient patients with heart failure: a systematic review. International journal of clinical pharmacy 45(3): 566-576	- Exclude - review of economic evaluations
Theidel, U., Vaatainen, S., Martikainen, J. et al. (2017) Budget impact of intravenous iron therapy with ferric carboxymaltose in patients with chronic heart failure and iron deficiency in Germany. ESC heart failure 4(3): 274-281	- Not economic evaluation *Budget Impact model, no quality of life included*

Appendix K Recommendation for research – full details

K.1 Recommendation for research

What is the clinical and cost effectiveness of intravenous iron supplementation in adults with iron deficiency chronic heart failure with mildly reduced or preserved ejection fraction?

K.1.1 Why this is important

Iron deficiency is common among people with chronic heart failure and intravenous (IV) iron supplementation has been increasingly implemented in the management of iron deficiency among those with reduced ejection fraction in recent years. The review identified sufficient evidence in this population. However, there was limited evidence on the benefits and harms in those with mildly reduced or preserved ejection fraction. Therefore, it is important to investigate the use of IV iron in these groups to determine whether they may also obtain benefits from this intervention.

K.1.2 Rationale for the recommendation for research

Importance to 'patients' or the population	Little is known about the benefits and harms associated with intravenous iron supplementation for those with mildly reduced or preserved ejection fraction. If found to be effective in these population, intravenous iron could improve outcomes and quality of life, including by improved exercise capacity, reduction in fatigue, and reduced unplanned heart failure-related hospitalisation.
Relevance to NICE guidance	Intravenous iron supplementation has been considered in this guideline and there is a lack of data on safety and efficacy in these populations. Therefore, evidence to answer this research question could inform future updates of the guideline to extend the recommendations beyond those with reduced ejection fraction, to advise on whether it is appropriate to offer intravenous iron supplementation for those with mildly reduced or preserved ejection fraction.
Relevance to the NHS	The outcome could affect the treatment for iron deficiency in people with chronic heart failure and mildly reduced or preserved ejection fraction provided by the NHS. This will help determine if intravenous iron leads to better clinical outcomes, reduced hospitalisation if given in symptomatic people with mildly reduced or preserved ejection fraction and its cost effectiveness. Sufficient clinical space will be required to deliver the intervention.
National priorities	Not applicable
Current evidence base	Limited evidence was identified investigating intravenous iron supplementation for those with mildly reduced or preserved ejection fraction. Clinicians may apply the reduced ejection fraction guidance in these populations in the absence of evidence.
Equality considerations	No specific equality considerations were identified. The committee noted throughout the guideline that older people are generally excluded from trials but form a large proportion of those treated in clinical practice. Therefore, research should aim to include these people where possible.

K.1.3 Modified PICO table

Population	Inclusion:

	• Adults diagnosed with heart failure with mildly reduced or preserved ejection fraction, who also have iron deficiency (defined by transferrin saturation (TSAT) < 20 %). Stratify by LVEF: • 41-49% (mildly reduced) • ≥50% (preserved) Exclusion: • Children • Acute heart failure in hospital • Acute myocardial infarction (within 3 months of the event) • Adult congenital heart disease • Primary heart valve disease
Intervention	Intravenous iron supplementation sufficient to correct iron deficiency
Comparator	Placebo or usual care
Outcomes	• All-cause mortality • Cardiovascular mortality • Health-related quality of life (such as, Kansas City Cardiomyopathy Questionnaire) • Unplanned hospitalisation or visits • Improvement in exercise tolerance – 6-minute walk test • Withdrawal due to drug-related adverse events • Hypophosphatemia • Extravasation • Anaphylaxis/hypersensitivity • Hospitalisation for infection • Atrial fibrillation
Study design	Randomised controlled trial
Timeframe	>12 months (with assessments at 3, 6 and 12 to check ferritin, transferrin saturation and haemoglobin).
Additional information	Subgroup analysis: • Anaemia (present vs absent)