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REVIEW

Systematic review and meta-analysis of intravenous iron-carbohydrate complexes in HFrEF patients with iron deficiency

Andrew Sindone[1†], Wolfram Doehner[2†] and Josep Comin-Colet[3*†]

[1]*Heart Failure Unit and Department of Cardiac Rehabilitation, Concord Hospital, Sydney, Australia;* [2]*Berlin Institute of Health Center for Regenerative Therapies (BCRT) and Department of Cardiology (Virchow Klinikum), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité – Universitätsmedizin Berlin, Berlin, Germany; and* [3]*Cardiology Department, Bellvitge University Hospital, IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain*

Abstract

Iron deficiency (ID) is a common co-morbidity in patients with heart failure (HF). The present meta-analysis evaluates the effect of intravenous (IV) iron-carbohydrate complex supplementation in patients with HF with reduced ejection fraction (HFrEF) and ID/iron deficiency anaemia (IDA). Randomized controlled trials (RCTs) comparing IV iron-carbohydrate complexes with placebo/standard of care in patients with HFrEF with ID/IDA were identified using Embase (from 1957) and PubMed (from 1989) databases through 25 May 2021. Twelve RCTs including 2381 patients were included in this analysis. The majority (90.8%) of patients receiving IV iron-carbohydrate therapy were administered ferric carboxymaltose (FCM); 7.5% received iron sucrose and 1.6% received iron isomaltoside. IV iron-carbohydrate therapy significantly reduced hospitalization for worsening HF [0.53 (0.42–0.65); $P < 0.0001$] and first hospitalization for worsening HF or death [0.75 (0.59–0.95); $P = 0.016$], but did not significantly impact all-cause mortality, compared with control. IV iron-carbohydrate therapy significantly improved functional and exercise capacity compared with the control. There was no significant difference in outcome between IV iron-carbohydrate formulations when similar endpoints were measured. No significant difference in adverse events (AE) was observed between the treatment groups. IV iron-carbohydrate therapy resulted in improvements in a range of clinical outcomes and increased functional and exercise capacity, whereas AEs were not significantly different between IV iron-carbohydrate and placebo/standard of care arms. These findings align with the European Society of Cardiology's 2021 HF guidelines, which recommend the consideration of FCM in symptomatic patients with a left ventricular ejection fraction $< 45\%$ and ID.

Keywords Heart failure with reduced ejection fraction; Iron deficiency/iron deficiency anaemia; IV iron-carbohydrate complexes; Ferric carboxymaltose

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**Correspondence to: Josep Comin-Colet, Cardiology Department, Bellvitge University Hospital, IDIBELL, University of Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain. Email: josepcomin@gmail.com*
†Andrew Sindone, Wolfram Doehner, and Josep Comin-Colet contributed equally.

Introduction

Iron deficiency (ID) is a common co-morbidity in heart failure (HF), with the prevalence increasing with HF severity.[1–3] In stable chronic HF, ID has been estimated to occur in 30–50% of patients.[2] The causes underlying ID in HF are likely to be multifactorial and may include reduced gastrointestinal (GI) iron absorption as a result of inflammation, reduced absorption due to hepcidin upregulation, GI blood flow and mucosal oedema, increased GI blood loss, proteinuria arising from comorbid chronic renal disease, concomitant medications that reduce iron absorption, including anticoagulant therapy, and decreased iron intake due to poor nutrition or loss of appetite.[3–6]

For many years, the impact of ID on the worsening of cardiovascular (CV) diseases and in the development of anaemia has been underestimated.[1] Our increasing understanding of ID in patients with chronic diseases with underlying inflammation has led to the realization that patients with HF, among other diseases, are at an increased risk of developing

ID.[7] Furthermore, ID is associated with HF severity as assessed by New York Heart Association (NYHA) functional class and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels.[5] ID is a key factor in the reduced exercise capacity, fatigue, symptomatic worsening of HF, and increased hospitalizations observed in patients with HF.[2] Although therapeutic options to improve exercise capacity are limited, targeting ID has been demonstrated to provide functional benefits to these patients.[8,9] Consistent with this concept, it has been shown that ID has important prognostic and quality of life (QoL) implications[6,8] and is associated with adverse outcomes (independent of anaemia) in patients with HF.[10]

The 2021 European Society of Cardiology (ESC) HF guidelines advocate the optimal management of underlying diseases and co-morbidities, including ID, in patients with HF with reduced ejection fraction (HFrEF). In keeping with the importance of the optimal management of co-morbidities, the ESC HF guidelines recommend that 'all patients with HF are periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT. The detection of anaemia and/or iron deficiency should prompt appropriate investigation to define their cause'.[11]

ID is typically treated with oral iron or intravenous (IV) iron-carbohydrate supplementation.[2] Although oral iron supplementation in patients with HFrEF has not been shown to be of benefit and is not recommended by the 2021 ESC HF guidelines, IV iron-carbohydrate therapy has demonstrated efficacy and safety across a range of randomized controlled trials (RCTs).[8,9,11–20] However, each IV iron-carbohydrate complex has a different formulation, meaning that each has distinct pharmacokinetic properties.[21,22] Based on the results of RCTs evaluating ferric carboxymaltose (FCM), the 2021 ESC HF guidelines recommend the use of FCM to improve symptoms, exercise capacity, and QoL in patients with HFrEF and ID.[11]

This meta-analysis aims to evaluate the efficacy and safety of IV iron-carbohydrate complexes compared with placebo/standard of care in patients with HFrEF and ID/IDA by assessing clinically meaningful endpoints, symptomatic improvement, exercise capacity, QoL scores, and safety signals.

Methods

Search strategy

A comprehensive review of the published literature was conducted per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23] Searches were conducted on Embase (from 1957) and PubMed (from 1989) databases through 25 May 2021. The search was restricted to RCTs of IV iron-carbohydrate complexes administered to adult HFrEF patients with ID/IDA. The search terms used are listed in full in the Appendix.

Study inclusion criteria

Each publication retrieved from the literature search was assessed manually for eligibility with use of the full-text publication in English. Only those publications from completed RCTs that evaluated therapy with IV iron-carbohydrate complexes in adult patients with HFrEF, irrespective of the trial endpoints and results, were considered eligible for further review.

Study exclusion criteria

Published reports were excluded based on the following criteria: (i) studies reporting data from sub-analyses or sub-studies of the main parent study and hence including a patient population already evaluated as part of the parent study; (ii) any publication related to oral iron use, case reports, case series, non-randomized uncontrolled studies, literature reviews, editorials, or pharmacoeconomic studies evaluating cost-effectiveness of IV iron-carbohydrate complex use; (iii) publications from studies not conducted in the population of interest or that enrolled a mixed population of patients with HFrEF and patients with HF with preserved ejection fraction; (iv) only articles in English with full-text availability were selected and reviewed; and (v) conference abstracts were excluded due to the lack of a peer-reviewed publication process.

Study definitions

Study endpoints considered to determine the effectiveness and safety of IV iron-carbohydrate therapy in adult patients with HFrEF included:

- The effect of IV iron-carbohydrate therapy on rates of hospitalization and death
- Symptomatic improvement defined by evaluation of cardiac parameters, including NYHA class and left ventricular ejection fraction (LVEF)
- Patient-reported outcome measures evaluating QoL, such as Patient Global Assessment (PGA), Kansas City Cardiomyopathy Questionnaire (KCCQ), EuroQol 5D (EQ-5D), and Minnesota Living with Heart Failure Questionnaire (MLHFQ)
- Functional health improvement outcome measures of increase in exercise capacity defined as change in 6-min walk test (6MWT) and peak maximal oxygen capacity (VO_2)
- The effect of IV iron-carbohydrate therapy on adverse events (AEs) and serious adverse events (SAEs)

- Serum biomarker measures of treatment, that is, levels of NT-proBNP, serum ferritin, transferrin saturation (TSAT), haemoglobin (Hb), C-reactive protein (CRP), and measures of renal function [creatinine clearance (CrCl)]

Statistical analysis

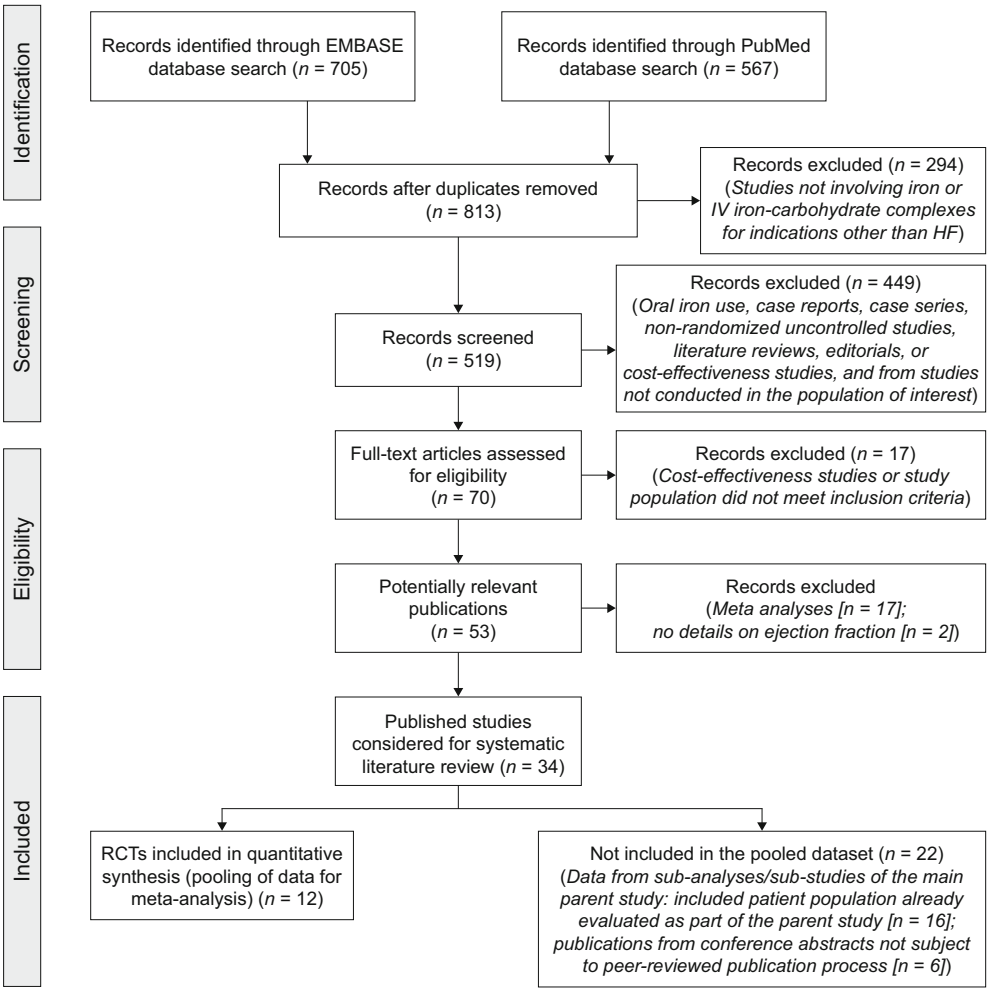
Dichotomous variables were analysed using odds ratio (OR) with 95% confidence interval (CI), whereas continuous data were analysed using weighted mean difference (WMD) and 95% CI. Statistical heterogeneity across the studies was evaluated using the chi-square-based *Q*-test. A random-effects model was used to calculate the pooled effect when significant heterogeneity was identified ($P < 0.10$ for the *Q*-test). If significant heterogeneity was not identified, a fixed-effects model was applied. The evaluated data are presented as forest plots to present the treatment effect and show the favourable treatment arm following administration of IV iron-carbohydrate complex therapy or control (placebo/standard of care). Publication bias was assessed using Begg's funnel plot and Egger's test (publication bias was considered absent if Egger's test *P* value > 0.05) when a minimum of three studies were available. If publication bias was detected, the publication in question was removed from the dataset and the dataset was re-examined for that endpoint. All statistical analyses were performed using R version 4.0.2. The pooled effect was considered significant if $P < 0.05$. For endpoints in which more than one IV iron-carbohydrate formulation was investigated, a sensitivity analysis was conducted.

Results

Screening of published studies

Searches of Embase and PubMed identified 705 and 567 publications, respectively. Of 1272 retrieved search results,

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



813 publications were identified as unique. Following the assessment of publications in accordance with the inclusion/exclusion criteria, 34 publications evaluating the efficacy and safety profile of IV iron-carbohydrate therapy in adult patients with HFrEF and ID/IDA were identified. In total, 12 RCTs were identified. Twenty-two of the 34 publications were not included in the pooled dataset; 16 publications included sub-studies and/or sub-analyses, and six publications were conference abstracts and were not subject to peer review. The screening process of the published literature is depicted in *Figure 1*. Details of the 12 RCTs included in the meta-analysis are presented in *Table S1*.

Pooled data were used to evaluate the effectiveness of therapy with IV iron-carbohydrate complexes on hospitalizations and deaths, in addition to improvement of cardiac function, exercise capacity, QoL parameters, serum markers, and safety signals in patients with HFrEF and ID/IDA.

Quantitative synthesis of RCTs identified for the meta-analysis

The 12 RCTs identified in this meta-analysis included 2381 patients assigned to either IV iron-carbohydrate therapy or placebo/standard of care (IV iron-carbohydrate therapy, 1277; placebo/standard of care, 1104).[8,9,14–19,24–27] Baseline characteristics of the patients are presented in *Table 1*. Of the patients included in the meta-analysis who received IV iron-carbohydrate therapy, 1160 (90.8%) received FCM, 96 (7.5%) received iron sucrose, and 21 (1.6%) received iron isomaltoside. For the 10 studies that provided sufficient dosing information (two studies either did not provide dosing details or provided only minimal information, on the basis of which calculation of the mean cumulative dose was not possible), the mean cumulative dose of IV iron-carbohydrate ranged from 929 to 2000 mg, with the duration of follow-up ranging from 2 to 52 weeks. The dosing scheme for IV iron-carbohydrate in each of the 12 RCTs is detailed in *Table S1*.

Effect of IV iron-carbohydrate complexes on hospitalizations and mortality

IV iron-carbohydrate therapy resulted in significant reductions in hospitalization for worsening HF [OR (95% CI) = 0.53 (0.42–0.65); $P < 0.0001$] and the composite endpoint of first hospitalization for worsening HF or death [OR (95% CI) = 0.75 (0.59–0.95); $P = 0.016$] (*Figure 2A and 2B*). No significant changes in risk were noted for all-cause mortality [OR (95% CI) = 0.60 (0.33–1.09); *Figure 2C*], death due to CV causes [OR (95% CI) = 0.89 (0.66–1.21)], death due to worsening HF [OR (95% CI) = 0.46 (0.18–1.17)], hospitalization for any cause [OR (95% CI) = 0.85 (0.26–2.76)] or hospitalization due to CV causes [OR (95% CI) = 1.00 (0.27–3.77)]. Publication bias was assessed for each endpoint using Begg's funnel plot and Egger's test (except for the endpoint first hospitalization for worsening HF or death due to the number of studies available). For the endpoints assessed, Begg's funnel plot and Egger's test showed no significant publication bias.

Sensitivity analyses were performed on the endpoints of all-cause mortality or hospitalization for worsening HF, the only endpoints assessed with more than one IV iron-carbohydrate complex, to assess differences between IV iron-carbohydrate formulations and outcome. These analyses demonstrated no differences in outcomes between FCM and iron sucrose for either all-cause mortality or hospitalization for worsening HF (data not shown).

Effect of IV iron-carbohydrate complexes on the symptomatic improvement of HF and exercise capacity

Significant differences in mean NYHA score [WMD (95% CI) = −1.0 (−1.5 to −0.5); $P < 0.0001$] and LVEF [WMD (95% CI) = 4.9 (1.2–8.6); $P < 0.0087$] were demonstrated between IV iron-carbohydrate complexes and control therapy (*Figure 3A and 3B*).

Furthermore, significant improvements in the mean 6MWT [WMD (95% CI) = 36.1 (34.2–38.0); $P < 0.0001$] and mean peak VO_2 [WMD (95% CI) = 2.0 (0.8–3.1); $P = 0.0007$] were observed with IV iron-carbohydrate therapy compared with control (*Figure 3C and 3D*).

For all endpoints used to assess the symptomatic improvement of HF and exercise capacity, Begg's funnel plot and Egger's test showed no significant publication bias.

Effect of IV iron-carbohydrate complexes on serum markers

Significant decreases in the mean levels of NT-proBNP [WMD (95% CI) = −358.9 (−430.0 to −287.8); $P < 0.0001$] and CRP [WMD (95% CI) = −4.7 (−6.3 to −3.1); $P < 0.0001$] were observed with IV iron-carbohydrate therapy compared with control therapy in the pooled data set. Increases in mean serum ferritin levels [WMD (95% CI) = 169.4 (113.8–224.9); $P < 0.0001$], percentage TSAT [WMD (95% CI) = 6.0 (2.5–9.4); $P = 0.0008$], Hb [WMD (95% CI) = 1.1 (0.5–1.8); $P = 0.001$], and CrCl levels [WMD (95% CI) = 11.72 (8.08–15.36); $P < 0.0001$] were noted in the IV iron-carbohydrate arm when compared with the control arm (*Figure S1*). Begg's funnel plot and Egger's test showed no significant publication

Table 1 Baseline characteristics of patients in the 12 RCTs included in the meta-analysis

Publication (year)	Study name (*N*)[a]	IV iron-carbohydrate, n (% of total study population)		Placebo, *n* (% of total study population)		Duration of follow-up
		Anaemic	Non-anaemic	Anaemic	Non-anaemic	
Silverberg *et al*. (2001)[24]	(*N* = 32)	16 (50.0)	0 (0)	16 (50.0)	0 (0)	35.6 ± 2.7 weeks (8.2 ± 2.7 months; 5–12 months)[b]
Toblli *et al*. (2007)[16]	(*N* = 40)	20 (50.0)	0 (0)	20 (50.0)	0 (0/0)	25 weeks
Okonko *et a*l. (2008)[18]	FERRIC-HF (*N* = 35)[c]	12 (34.3)	12 (34.3)	6 (17.1)	5 (14.3)	18 weeks
Anker *et al*. (2009)[8,35]	FAIR-HF (*N* = 459)	155 (33.7)	149 (32.5)	77 (16.8)	78 (17.0)	24 weeks
Beck-da-Silva *et al*. (2013)[19]	IRON-HF (*N* = 16)	10 (62.5)	0 (0)	6 (37.5)	0 (0)	13 weeks
Ponikowski *et al*. (2015)[9]	CONFIRM-HF (*N* = 301)	NA	NA	NA	NA	52 weeks
Toblli *et al*. (2015)[17]	(*N* = 60)	30 (50.0)	0 (0)	30 (50.0)	0 (0)	25 weeks
van Veldhuisen (2017)[14]	EFFECT-HF (*N* = 172)	NA	NA	NA	NA	24 weeks
Charles-Edwards *et al*. (2019)[e26]	FERRIC-HF II (*N* = 40)	11 (27.5)	10 (25.0)	9 (22.5)	10 (25.0)	2 weeks
Dhoot *et al*. (2020)[25]	FCM-HF-IN (*N* = 70)	NA	NA	NA	NA	12 weeks
Núñez *et al*. (2020)[e27]	Myocardial-IRON (*N* = 53)	10 (18.9)	17 (32.1)	6 (11.3)	20 (37.7)	4 weeks
Ponikowski *et al*. (2020)[15]	AFFIRM-AHF (*N* = 1108)	292 (26.4)	266 (24.0)	312 (28.2)	238 (21.5)	52 weeks

IV, intravenous; NA, not applicable; RCT, randomized controlled trial; TSAT, transferrin saturation.
[a]*N* = total number of patients treated with IV iron-carbohydrate therapy or placebo at baseline.
[b]As disclosed in the publication.
[c]Baseline characteristics as disclosed in the publication for the 35 patients randomized to treatment arms. End of study population (*n* = 30) used for endpoint analyses.
[d]Refers to median values. For all other studies, data represented as mean ± standard deviation unless otherwise indicated.
[e]Values are median (interquartile range).

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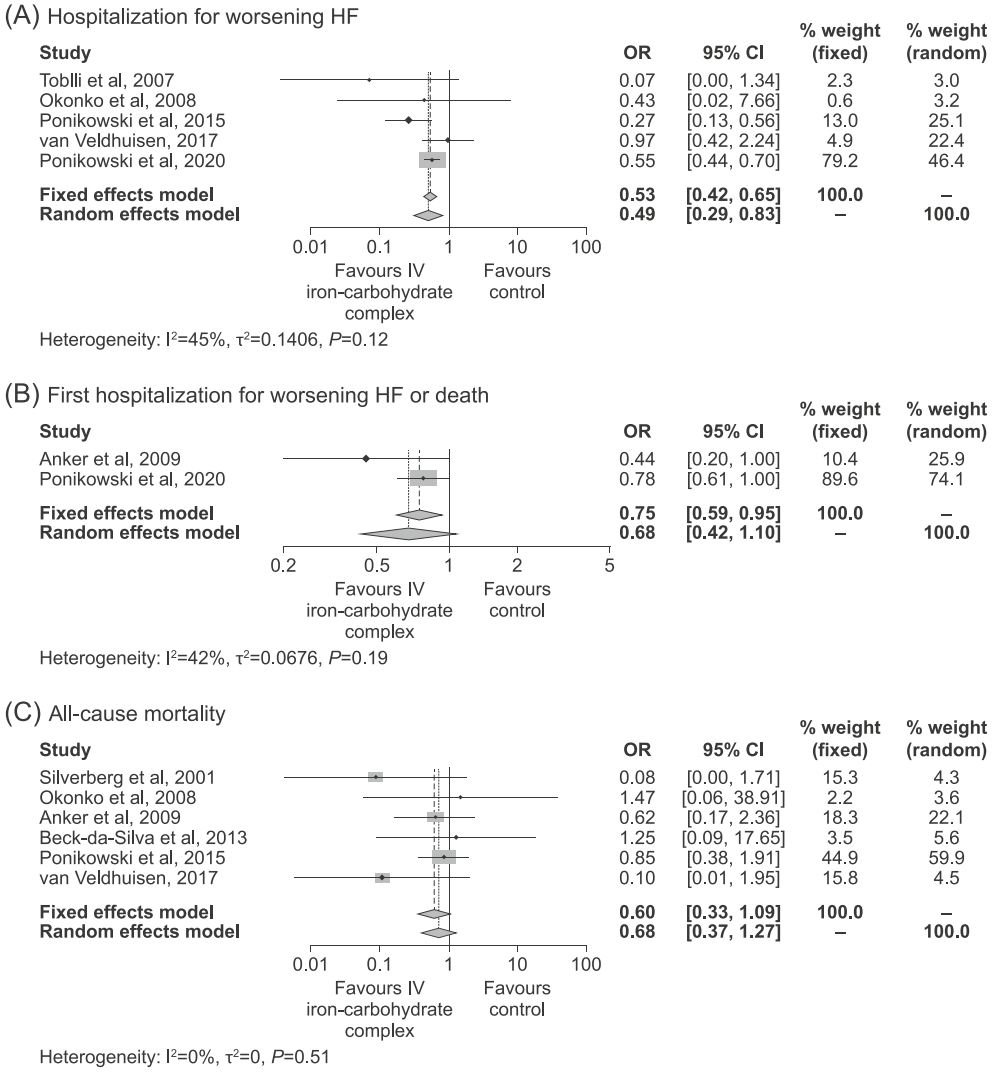
Table 1 (continued)

Publication (year)	Serum ferritin (ng/mL)		TSAT (%)		Haemoglobin (g/dL)	
	IV iron-carbohydrate	Placebo	IV iron-carbohydrate	Placebo	IV iron-carbohydrate	Placebo
Silverberg *et al*. (2001)[24]	221.4 ± 165.1	264.0 ± 162.5	25.1 ± 12.9	22.5 ± 16.7	10.3 ± 1.2	10.9 ± 0.8
Toblli *et al*. (2007)[16]	73.0 ± 29.9	70.6 ± 21.4	0.2 ± 0.01	0.2 ± 0.01	10.3 ± 0.6	10.2 ± 0.5
Okonko *et a*l. (2008)[18]	62 ± 37	88 ± 62	20 ± 8	21 ± 9	12.6 ± 1.2	12.2 ± 1.0
Anker *et al*. (2009)[8,35]	52.5 ± 54.5	60.1 ± 66.5	17.7 ± 12.6	16.7 ± 8.4	11.9 ± 1.3	11.9 ± 1.4
Beck-da-Silva *et al*. (2013)[19]	185 ± 146	95 ± 128	18.9 ± 9.7	13.5 ± 5.8	11.2 ± 0.6	10.9 ± 0.7
Ponikowski *et al*. (2015)[9]	57.0 ± 48.4	57.1 ± 41.6	20.2 ± 17.6	18.2 ± 8.1	12.37 ± 1.41	12.42 ± 1.3
Toblli *et al*. (2015)[17]	70.6 ± 24.9	68.4 ± 18.3	19.2 ± 1.8	19.2 ± 1.9	10.1 ± 0.8	10.1 ± 0.6
van Veldhuisen (2017)[14]	48[d]	53[d]	17.3[d]	18.1[d]	12.9 ± 1.3	13.0 ± 1.5
Charles-Edwards *et al*. (2019)[e26]	34 (18–50)	59 (39–79)	21 ± 8	18 ± 10	13.0 ± 1.5	12.8 ± 2.0
Dhoot *et al*. (2020)[25]	40.1 ± 27.2	45.5 ± 35.1	NA	NA	11.4 ± 1.4	11.3 ± 0.9
Núñez *et al*. (2020)[e27]	73.0 (56–126)	47.8 (23–114)	15.7 (12.0–19.2)	15.4 (9.6–20.0)	13.1 (11.9–13.4)	13.4 (12.7–14.6)
Ponikowski *et al*. (2020)[15]	83.9 ± 62.2	88.5 ± 68.6	15.2 ± 8.3	14.2 ± 7.5	12.3 ± 1.6	12.1 ± 1.6

IV, intravenous; NA, not applicable; RCT, randomized controlled trial; TSAT, transferrin saturation.
[a]*N* = total number of patients treated with IV iron-carbohydrate therapy or placebo at baseline.
[b]As disclosed in the publication.
[c]Baseline characteristics as disclosed in the publication for the 35 patients randomized to treatment arms. End of study population (*n* = 30) used for endpoint analyses.
[d]Refers to median values. For all other studies, data represented as mean ± standard deviation unless otherwise indicated.
[e]Values are median (interquartile range).

Figure 2 Comparison of IV iron-carbohydrate complex therapy compared with control therapy on hospitalization rates and mortality in patients with HFrEF and ID/IDA. (A) Hospitalization for worsening HF. (B) First hospitalization for worsening HF or death. (C) All-cause mortality.



bias for the serum markers analysed (due to the number of studies available, NT-proBNP and CrCl were not assessed for publication bias).

Effect of IV iron-carbohydrate complexes on QoL

Significant differences in the mean KCCQ score [WMD (95% CI) = 7.0 (6.7–7.3); $P < 0.0001$] and mean MLHFQ score [WMD (95% CI) = −13.5 (22.0 to −5.0); $P = 0.0018$] between the IV iron-carbohydrate arm and the control arm were observed, with both scores favouring treatment with IV iron-carbohydrate therapy (*Figure 4A and 4B*). Begg's funnel plot and Egger's test showed no significant publication bias for MLHFQ score (due to the number of studies available, KCCQ was not assessed for publication bias).

Effect of IV iron-carbohydrate complexes on AEs and SAEs

Of the 785 patients randomized to IV iron-carbohydrate therapy (from the five studies that provided AE data), 494 (62.9%) patients reported at least one AE as compared with 486 (63.6%) of the 764 patients randomized to control. A total of 1817 AEs were reported in the IV iron-carbohydrate arm compared with 1872 AEs from the control arm. The difference between IV iron-carbohydrate and control arms was not statistically significant with either the fixed-effect or random-effect models for total AEs [OR (95% CI) = 0.98 (0.79, 1.22); $P = 0.50$] (*Figure 5A*).

Reported AEs were also stratified by system organ class (SOC) across the studies pooled for the analyses. Significantly fewer patients in the IV iron-carbohydrate complex arm compared with the control arm reported at least one AE for

Figure 3 Comparison of effects of IV iron-carbohydrate complexes compared with control therapy on symptomatic improvement (A, LVEF and B, NYHA score) and exercise capacity (C, 6MWT and D, peak VO_2) in patients with HFrEF and ID/IDA.

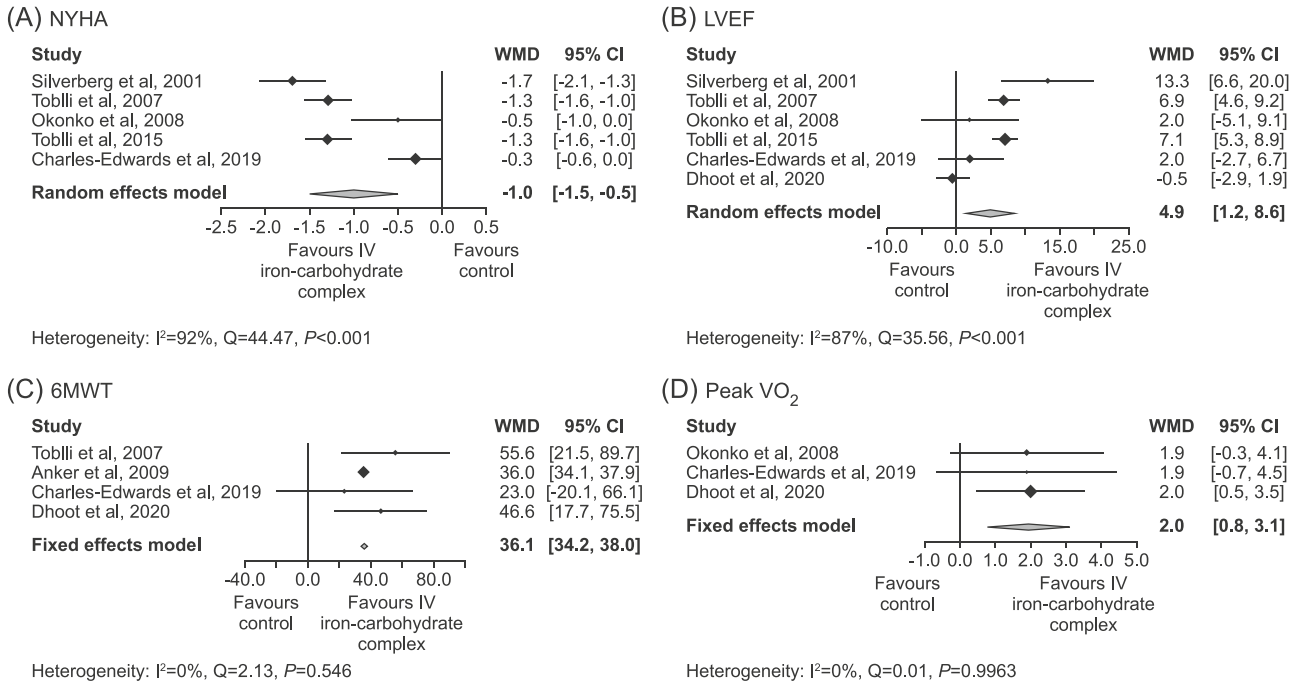
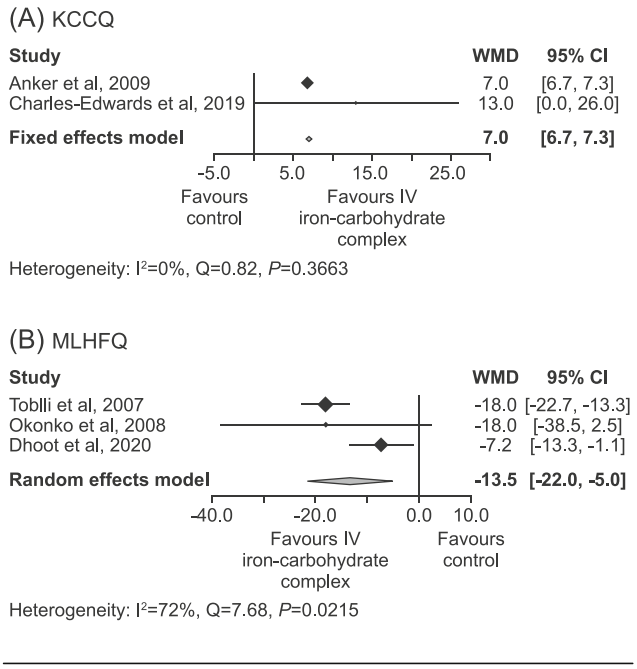


Figure 4 Comparison of effects of IV iron-carbohydrate complexes compared with control therapy on QoL measures in patients with HFrEF and ID/IDA. (A) KCCQ and (B) MLHFQ scores.

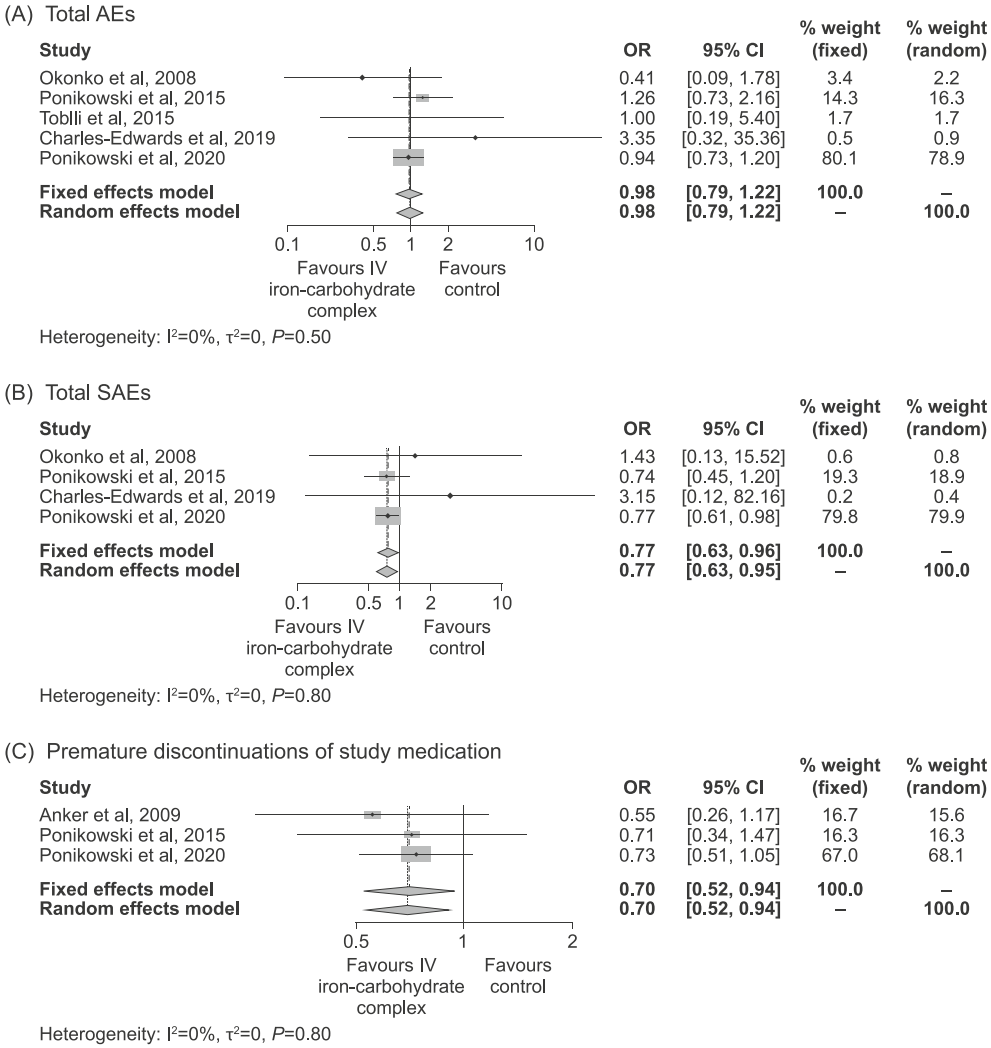


events coded to the cardiac disorder, respiratory, thoracic, and mediastinal disorder, and metabolism and nutrition disorder SOCs. However, no significant differences were observed in the number of patients reporting at least one AE in the IV iron-carbohydrate arm and the control arm for the gastrointestinal disorder, infection or infestation, investigation, nervous system disorder, vascular disorder, skin and subcutaneous tissue disorder, and musculoskeletal disorder SOCs. The pooled analysis favoured the control group for events coded to the general disorder or injection site condition SOC.

The incidence of SAEs was lower in the IV iron-carbohydrate group (616 events in 297 patients) than in the control group (738 events in 336 patients) [OR (95% CI) = 0.77 (0.63, 0.96); *P* = 0.0175] (*Figure 5B*). Fewer numbers of premature discontinuations of study medication were reported in the IV iron-carbohydrate arm (91 of the 1016 patients randomized to IV iron-carbohydrate from three studies) compared with the control arm (112 of the 857 patients randomized to control from three studies) [OR (95% CI) = 0.70 (0.52, 0.94); *P* = 0.0172] (*Figure 5C*).

No significant publication bias was found using Begg's funnel plot and Egger's tests for any of the safety parameters analysed.

Figure 5 Comparison of effects of IV iron-carbohydrate complexes compared with control therapy on (A) AEs and (B) SAEs, and on (C) premature discontinuation of study medication in patients with HFrEF and ID/IDA.



Discussion

The main result from this meta-analysis was that IV iron-carbohydrate therapy significantly reduced the rate of hospitalizations for worsening HF while also decreasing the rate of the endpoint first hospitalization for worsening HF or death, compared with control therapy. IV iron-carbohydrate therapy also improved HFrEF symptoms with the concurrent improvement of cardiac function as demonstrated by improved LVEF and NYHA score. Furthermore, when compared to control, IV iron-carbohydrate therapy improved exercise capacity as demonstrated by the 6MWT and peak VO_2 values. IV iron-carbohydrate therapy also significantly improved the levels of serum biomarkers in patients with HFrEF. Decreases in the mean levels of NT-proBNP and CRP and increases in mean serum ferritin levels, percentage TSAT, Hb, and CrCl were identified in the IV iron-carbohydrate arm when compared with the control arm. In addition, IV iron-carbohydrate therapy resulted in improved patient-reported QoL outcomes as demonstrated by both the KCCQ and MLHFQ scores. Although no significant effect of IV iron-carbohydrate therapy was identified for all-cause mortality, a non-significant trend was observed. For the endpoints in which the effect of more than one IV iron-carbohydrate formulation was assessed, sensitivity analyses were performed. These analyses did not identify a difference in outcome between FCM and iron sucrose for either all-cause mortality or hospitalization for worsening HF. There was no difference in the number of AEs between the IV iron-carbohydrate complex and the control arms; however,

there were significantly fewer SAEs and premature discontinuations from study medication in the IV iron-carbohydrate arm compared with the control arm.

Previous meta-analyses conducted by Zhou *et al*.[28] and Zhang *et al*.[29] of RCTs including patients with HF, regardless of LVEF, found that iron supplementation (oral or IV) improved HF hospitalization rates, cardiac function, and QoL, but did not impact on mortality rates. A more recent meta-analysis conducted by Yamani *et al*.[30] separately examined oral and IV iron supplementation and found that IV iron-carbohydrate supplementation significantly reduced overall and HF hospitalizations compared with control. Consistent with these previous meta-analyses, the present study found that IV iron-carbohydrate therapy reduced the rates of hospitalization for worsening HF and also first hospitalization for worsening HF or death, but did not significantly alter the rate of all-cause mortality. Consistency among the results of these previous meta-analyses and those presented here, despite varying search strategies resulting in the inclusion of different RCTs with varying criteria for patient enrolment, provides strength to the finding that IV iron-carbohydrate therapy is beneficial to patients with HFrEF and ID/IDA across several clinically relevant endpoints.

The 2021 ESC guidelines recommend that 'all patients with HF are regularly screened for anaemia and iron deficiency with full blood count, serum ferritin concentration, and TSAT. The detection of anaemia and/or iron deficiency should prompt appropriate investigation to define their cause'. In terms of ID treatment, the 2021 ESC guidelines state that 'intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF $<$ 45% and iron deficiency, defined as serum ferritin $<$ 100 ng/mL or serum ferritin 100–299 ng/mL with TSAT $<$ 20%, to alleviate HF symptoms, improve exercise capacity and QoL'.[11] Though at present only FCM is recommended by the ESC guidelines due to the volume of supporting data for this iron-carbohydrate formulation, further adequately powered RCTs may support the use of other formulations for the treatment of ID in patients with HFrEF. The outcomes of the present meta-analysis, in which 90.8% of patients received FCM, are aligned with the recommendations of the 2021 ESC HF guidelines.

There are several limitations of the present study. The RCTs in this analysis included patients who received different formulations and doses of IV iron-carbohydrate complexes, with varying study designs and protocols. Sensitivity analyses as part of the present meta-analysis were limited by the number of common endpoints shared between RCTs assessing different IV iron-carbohydrate formulations. Furthermore, different comparators were used between trials, with IV iron-carbohydrate complexes compared with either placebo or standard of care. In addition, whereas IV iron-carbohydrate therapy was assessed compared with placebo or standard of care, IV iron-carbohydrate therapy was not directly assessed against oral iron supplementation. Such an analysis would be of interest but would require further RCTs assessing IV iron-carbohydrate therapy compared with oral iron supplementation in head-to-head studies.

IV iron-carbohydrate preparations bypass GI absorption and the nanoparticulate iron-carbohydrate complexes are engineered to be taken up and processed by macrophages in order to replenish the body's internal iron stores.[31] The pharmacological properties of the IV iron-carbohydrate preparations are dependent on the specific chemical composition and physical structure of the nanoparticles. Unlike typical small chemical molecules or biotechnology-derived medicinal products, the entire non-biological complex drug (as with iron-carbohydrate preparations) forms the active pharmaceutical ingredient.[22] IV iron-carbohydrate preparations are colloidal suspensions consisting of iron-carbohydrate nanoparticles that share similar core chemistry, but differ from one another in the size of the core, and in the identity and density of the carbohydrate shell.[21] Due to the complexity of these nanomedicines, even subtle changes in production, storage, and handling can influence the safety and effectiveness of the end product.[32] As such, a tightly regulated manufacturing process is required for the production of IV iron-carbohydrate complexes.[22]

IV iron-carbohydrate complexes are engineered to deliver high doses of iron in a relatively short time in a form that is stable, non-reactive, and non-toxic.[33] To achieve this, IV iron-carbohydrate complexes behave as pro-drugs that require metabolism to become an 'active' drug. The carbohydrate shell of these complexes acts as a ligand, determining the clearance rate and biodistribution of the iron-carbohydrate complex.[34] Following release of the iron from the carbohydrate shell, iron is incorporated by ferritin into intracellular iron stores or taken up by transferrin.[21,34] Given the inherent properties of the various IV iron-carbohydrate complexes, each should be treated as a distinct clinical entity, with head-to-head studies required to evaluate equivalence between different formulations.

In conclusion, the results of the meta-analysis presented here demonstrate the ability of IV iron-carbohydrate therapy to improve meaningful clinical outcomes, including functional capacity, risk of hospitalization, and QoL in patients with HFrEF. Surrogate measures of HF severity were also improved, including cardiac function, NT-proBNP, and peak VO_2 with IV iron-carbohydrate complexes compared with control. Furthermore, a good safety profile was observed for IV iron-carbohydrate therapy as AEs were not significantly different between IV iron-carbohydrate and control arms. In fact, SAEs and premature discontinuation of study medication were lower in the IV iron-carbohydrate arm compared with the control arm. Of note, across the RCTs included in this meta-analysis, 90.8% of patients received FCM; as such, the findings presented here were largely based on RCTs evaluating one IV iron-carbohydrate formula-

tion. The findings of the present meta-analysis support the recommendation for the treatment of patients with HFrEF and ID/IDA with FCM in the recently updated ESC HF guidelines.

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Conflict of interest

AS has received honoraria, speaker fees, and consultancy fees, is a member of advisory boards, or has appeared on expert panels for Amgen, Aspen, AstraZeneca, Bayer, Biotronik, Boehringer Ingelheim, Bristol Myers Squibb, Menarini, Merck Sharp and Dohm, Mylan, Novartis, Otsuka, Pfizer, Sanofi, Servier, and Vifor Pharma. WD has received presenter honoraria and fees for consulting or advisory activities from Aimediq, Bayer, Boehringer Ingelheim, Lilly, Medtronic, Pfizer, Sanofi-Aventis, Sphingotec, and Vifor Pharma and research support from Boehringer Ingelheim, Vifor Pharma, and ZS Pharma. JCC has received honoraria, speaker fees, consultancy fees, and unrestricted research grants, is a member of advisory boards, or has appeared on expert panels for AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Menarini, Novartis, Otsuka, Pfizer, Sanofi, Servier, and Vifor Pharma.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of the 12 RCTs identified in the systematic literature review of adult patients with HFrEF treated with IV iron-carbohydrate therapy.

Figure S1. Comparison of effects of IV iron-carbohydrate complexes compared with control therapy on serum markers in patients with HFrEF and ID/IDA. **A.** NT-proBNP, **B.** CRP, **C.** serum ferritin, **D.** TSAT, **E.** Hb, and **F.** CrCl.

Appendix

Full search terms

Embase

- (('ferric carboxymaltose'/exp OR 'ferric carboxymaltose') OR 'ferinject' OR 'injectafer') AND ('heart failure with reduced ejection fraction' OR 'reduced ejection fraction' OR 'systolic heart failure' OR 'hfref' OR 'heart failure')
- ('heart failure with reduced ejection fraction' OR 'reduced ejection fraction' OR 'systolic heart failure' OR 'hfref' OR 'heart failure') AND ('venofer' OR 'iron sucrose' OR 'iron saccharate')
- (('heart failure with reduced ejection fraction'/exp OR 'heart failure with reduced ejection fraction') OR 'heart failure') AND ('iron isomaltose' OR 'ferumoxytol' OR 'intravenous iron')

PubMed

- ("ferric carboxymaltose" OR "FCM" OR "ferinject") AND ("heart failure with reduced ejection fraction" OR "reduced ejection fraction" OR "systolic heart failure" OR "heart failure" OR "HFrEF")
- ("venofer" OR "iron sucrose") AND ("heart failure with reduced ejection fraction" OR "reduced ejection fraction" OR "systolic heart failure" OR "heart failure" OR "HFrEF")
- ("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("iron"[MeSH Terms] OR "iron"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- ("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("iron"[MeSH Terms] OR "iron"[All Fields]) AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- ("intraveneous"[All Fields] OR "intraveneously"[All Fields] OR "intravenous"[All Fields] OR "intravenously"[All Fields]) AND ("iron"[MeSH Terms] OR "iron"[All Fields]) AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) AND ("reduce"[All Fields] OR "reduced"[All Fields] OR "reduces"[All Fields] OR "reducing"[All Fields]) AND ("eject"[All Fields] OR "ejected"[All Fields] OR "ejecting"[All Fields] OR

"ejection"[All Fields] OR "ejectional"[All Fields] OR "ejections"[All Fields] OR "ejects"[All Fields]) AND ("dose fractionation, radiation"[MeSH Terms] OR ("dose"[All Fields] AND "fractionation"[All Fields] AND "radiation"[All Fields]) OR "radiation dose fractionation"[All Fields] OR "fractionation"[All Fields] OR "chemical fractionation"[MeSH Terms] OR ("chemical"[All Fields] AND "fractionation"[All Fields]) OR "chemical fractionation"[All Fields] OR "fraction"[All Fields] OR "fractions"[All Fields] OR "fractionate"[All Fields] OR "fractionated"[All Fields] OR "fractionates"[All Fields] OR "fractionating"[All Fields] OR "fractionationed"[All Fields] OR "fractionations"[All Fields] OR "fractionator"[All Fields] OR "fractionators"[All Fields] OR "fractioned"[All Fields] OR "fractioning"[All Fields] OR "fractionized"[All Fields] OR "fractions"[All Fields])

- ferumoxytol and chronic heart failure with reduced ejection fraction
- ("ferrosoferric oxide"[MeSH Terms] OR ("ferrosoferric"[All Fields] AND "oxide"[All Fields]) OR "ferrosoferric oxide"[All Fields] OR "ferumoxytol"[All Fields]) AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- ("ferrosoferric oxide"[MeSH Terms] OR ("ferrosoferric"[All Fields] AND "oxide"[All Fields]) OR "ferrosoferric oxide"[All Fields] OR "ferumoxytol"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- ("iron isomaltoside 1000"[Supplementary Concept] OR "iron isomaltoside 1000"[All Fields] OR "iron isomaltoside"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- iron isomaltoside and heart failure with reduced ejection fraction
- "ferric"[All Fields] AND "derisomaltose"[All Fields] AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- "ferric"[All Fields] AND "derisomaltose"[All Fields] AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])
- "Monofer"[All Fields] AND ("chronic"[All Fields] OR "chronical"[All Fields] OR "chronically"[All Fields] OR "chronicities"[All Fields] OR "chronicity"[All Fields] OR "chronicization"[All Fields] OR "chronics"[All Fields]) AND ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields])

References

1. Ebner N, von Haehling S. Iron deficiency in heart failure: A practical guide. *Nutrients*. 2013; **5**: 3730–3739.
2. Rocha BML, Cunha GJL, Menezes Falcão LF. The burden of iron deficiency in heart failure: Therapeutic approach. *J Am Coll Cardiol*. 2018; **71**: 782–793.
3. Anand IS, Gupta P. Anemia and iron deficiency in heart failure. *Circulation*. 2018; **138**: 80–98.
4. McDonagh T, Macdougall IC. Iron therapy for the treatment of iron deficiency in chronic heart failure: Intravenous or oral? *Eur J Heart Fail*. 2015; **17**: 248–262.
5. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: An international pooled analysis. *Am Heart J*. 2013; **165**: 575–582.e3.
6. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: Diagnostic dilemmas and therapeutic perspectives. *Eur Heart J*. 2013; **34**: 816–829.
7. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: An overview. *JACC Heart Fail*. 2019; **7**: 36–46.
8. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan B-A, Mori C, von Eisenhart RB, Pocock SJ, Poole-Wilson PA, Ponikowski P, FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med*. 2009; **361**: 2436–2448.
9. 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. *Eur Heart J*. 2015; **36**: 657–668.
10. Marchi G, Busti F, Vianello A, Girelli D. Anemia and iron deficiency in heart failure: Extending evidences from chronic to acute setting. *Intern Emerg Med*. 2021; **16**: 167–170.
11. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; **42**: 3599–3726.
12. Lewis GD, Malhotra R, Hernandez AF, McNulty SE, Smith A, Felker GM, Tang WHW, LaRue SJ, Redfield MM, Semigran MJ, Givertz MM, Van Buren P, Whellan D, Anstrom KJ, Shah MR, Desvigne-Nickens P, Butler J, Braunwald E, for the NHLBI Heart Failure Clinical Research Network. Effect of oral iron repletion on exercise capacity in patients

with heart failure with reduced ejection fraction and iron deficiency: The IRONOUT HF randomized clinical trial. *JAMA*. 2017; **317**: 1958–1966.
13. Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Lüscher 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. *Eur Heart J*. 2013; **34**: 30–38.
14. van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, Voors AA, Macdougall IC, Anker SD, Roubert B, Zakin L, Cohen-Solal A, EFFECT-HF Investigators. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation*. 2017; **136**: 1374–1383.
15. Ponikowski P, Kirwan B-A, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA, AFFIRM-AHF investigators. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: A multicentre, double-blind, randomised, controlled trial. *Lancet Lond Engl*. 2020; **396**: 1895–1904.
16. Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol*. 2007; **50**: 1657–1665.
17. 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 Circ*. 2015; **24**: 686–695.
18. Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. 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. *J Am Coll Cardiol*. 2008; **51**: 103–112.
19. 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. *Int J Cardiol*. 2013; **168**: 3439–3442.
20. Jankowska EA, Kirwan B-A, Kosiborod M, Butler J, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Filippatos G, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Friede T, Fabien V, Dorigotti F, Pocock S, Ponikowski P. 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. *Eur Heart J*. 2021: ehab234.
21. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol JASN*. 2004; 15 Suppl 2: S93–S98.
22. Gaspar RS, Silva-Lima B, Magro F, Alcobia A, da Costa FL, Feio J. Non-biological complex drugs (NBCDs): Complex pharmaceuticals in need of individual robust clinical assessment before any therapeutic equivalence decision. *Front Med*. 2020; **7**: 590527.
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med*. 2009; **6**: e1000097.
24. Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: A randomized controlled study. *J Am Coll Cardiol*. 2001; **37**: 1775–1780.
25. Dhoot S, Mittal S, Singh SP, Patel V, Kasliwal RR, Mehta V. Effect of ferric-carboxy maltose on oxygen kinetics and functional status in heart failure patients with iron deficiency. *Future Sci OA*. 2020; **6**: FSO467.
26. Charles-Edwards G, Amaral N, Sleigh A, Ayis S, Catibog N, McDonagh T, Monaghan M, Amin-Youssef G, Kemp GJ, Shah AM, Okonko DO. Effect of iron isomaltoside on skeletal muscle energetics in patients with chronic heart failure and iron deficiency. *Circulation*. 2019; **139**: 2386–2398.
27. Núñez J, Miñana G, Cardells I, Palau P, Llàcer P, Fácila L, Almenar L, López-Lereu MP, Monmeneu JV, Amiguet M, González J, Serrano A, Montagud V, López-Vilella R, Valero E, García-Blas S, Bodí V, de la Espriella-Juan R, Lupón J, Navarro J, Górriz JL, Sanchis J, Chorro FJ, Comín-Colet J, Bayés-Genís A, Myocardial-IRON Investigators. Noninvasive imaging estimation of myocardial iron repletion following administration of intravenous iron: The myocardial-IRON trial. *J Am Heart Assoc*. 2020; **9**: e014254.
28. Zhou X, Xu W, Xu Y, Qian Z. Iron supplementation improves cardiovascular outcomes in patients with heart failure. *Am J Med*. 2019; **132**: 955–963.
29. Zhang J, Hu S, Jiang Y, Zhou Y. 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. *Postgrad Med J*. 2020; **96**: 766–776.
30. Yamani N, Ahmed A, Gosain P, Fatima K, Shaikh AT, Qamar H, Shahid I, Arshad MS, Almas T, Figueredo V. Effect of iron supplementation in patients with heart failure and iron deficiency: A systematic review and meta-analysis. *IJC Heart Vasc*. 2021; **36**: 100871.
31. Martin-Malo A, Borchard G, Flühmann B, Mori C, Silverberg D, Jankowska EA. Differences between intravenous iron products: Focus on treatment of iron deficiency in chronic heart failure patients. *ESC Heart Fail*. 2019; **6**: 241–253.
32. Nikravesh N, Borchard G, Hofmann H, Philipp E, Flühmann B, Wick P. Factors influencing safety and efficacy of intravenous iron-carbohydrate nanomedicines: From production to clinical practice. *Nanomedicine Nanotechnol Biol Med*. 2020; **26**: 102178.
33. Neiser S, Koskenkorva TS, Schwarz K, Wilhelm M, Burckhardt S. Assessment of dextran antigenicity of intravenous iron preparations with enzyme-linked immunosorbent assay (ELISA). *Int J Mol Sci*. 2016; **17**: E1185.
34. Koskenkorva-Frank TS, Weiss G, Koppenol WH, Burckhardt S. The complex interplay of iron metabolism, reactive oxygen species, and reactive nitrogen species: Insights into the potential of various iron therapies to induce oxidative and nitrosative stress. *Free Radic Biol Med*. 2013; **65**: 1174–1194.
35. Filippatos G, Farmakis D, Comin Colet J, Dickstein K, Lüscher TF, Willenheimer R, Parissis J, Gaudesius G, Mori C, von Eisenhart RB, 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. *Eur J Heart Fail*. 2013; **15**: 1267–1276.