Meta-Analysis and Metaregression of the Treatment Effect of Intravenous Iron in Iron-Deficient Heart Failure

Meta-analysis and meta-regression of the treatment effect of intravenous iron in iron deficient heart failure

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Word count text: 3299

References: 32

Figures: 3

Tables: 1

Supplemental figures: 7

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Abstract

Background

Guidelines recommend that intravenous iron should be considered to improve symptoms of heart failure (HF) and reduce the risk for HF-admissions in patients after acute HF.

Objective

To analyze the effect of intravenous iron on cardiovascular (CV)-death and HF-admissions in a broad population of HF-patients with iron deficiency and the relation with baseline TSAT.

Methods

A systematic review of all published randomized controlled trials (RCTs) assessing the effect of intravenous iron in patients with iron deficiency and heart failure between the 1st of January 2000 and August 26 2023 was performed. The overall treatment effect was estimated using a fixed effect model for: (1) CV-death, (2) CV-death and HF-admission, (3) first HF-admission and (4) total HF admissions. Meta-regression through a mixed effect model was used to explore the impact of baseline TSAT in case of heterogeneity amongst trial results.

Results

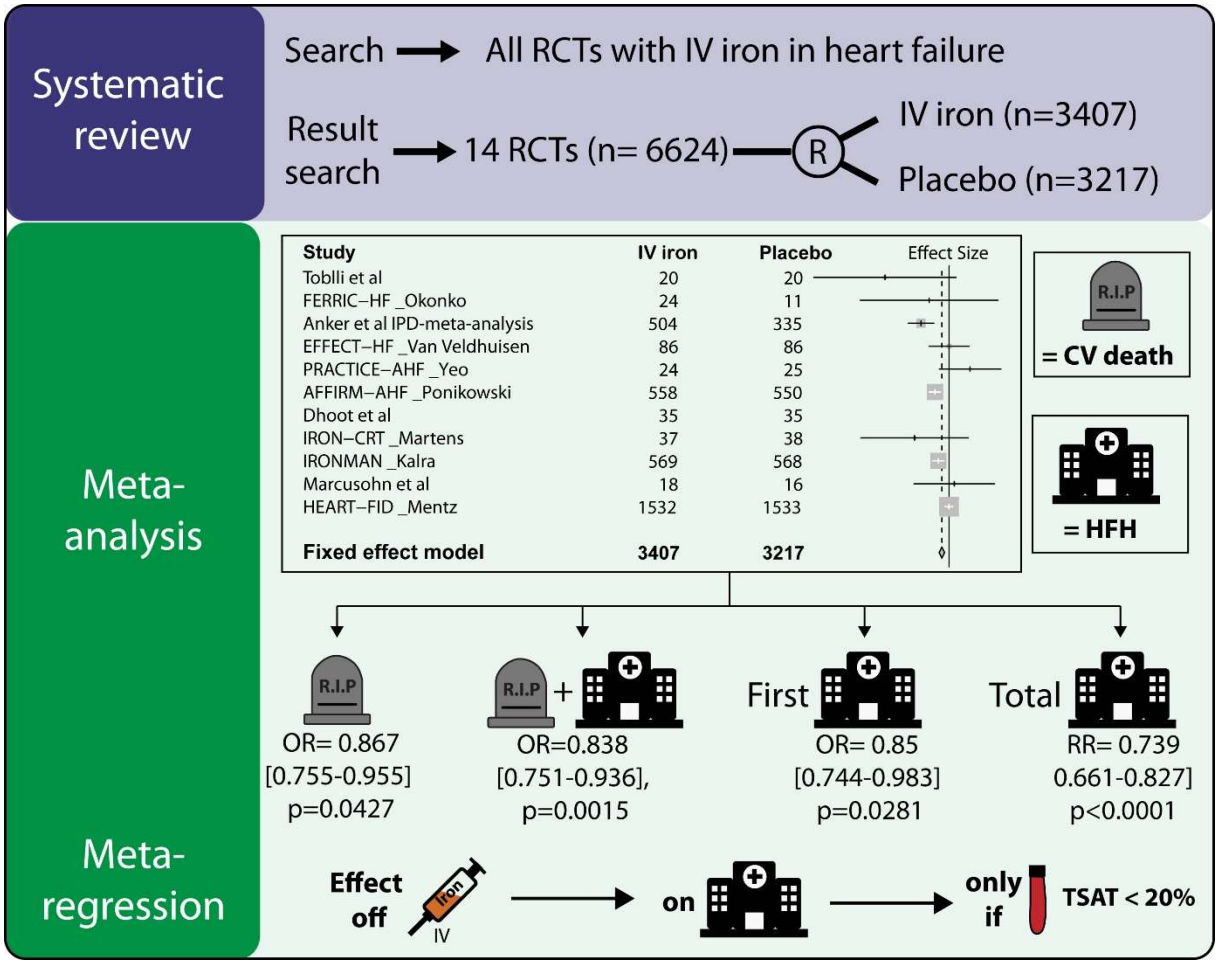
A total of 14 RCTs were identified in the systematic review and retained in the meta-analysis. Including aggregate level data on 6624 HF-patients of whom 3407 were randomized to intravenous iron and 3217 were randomized to placebo. Treatment with intravenous iron resulted in a lower risk for CV-death (Odds Ratio [OR]=0.867, 95%CI=[0.755-0.955], p=0.0427), combined CV-death and HF-admission (OR=0.838 95%CI=[0.751-0.936], p=0.0015), first HF-admission (OR= 0.855, 95%CI=[0.744-0.983], p=0.0281) and total HF-admissions (Rate ratio= 0.739, 95%CI=[0.661-0.827], p<0.0001). Significant heterogeneity amongst trial result was observed for first and total HF-admissions. Meta-regression suggested that some of the heterogeneity was related to the baseline TSAT of the enrolled population, with trials enrolling patients with lower TSAT exhibiting a large effect size on HF-related events.

Conclusion

The totality of data suggest that treatment with intravenous iron reduces both CV-death and HF-related events in a broad population with HF. A lower baseline TSAT might be important for the effect on HF-related events.

Key words: heart failure, iron deficiency, meta-analysis, evidence based medicine

VISUAL ABSTRACT



ABBREVIATIONS

CV= cardiovascular

LVEF= left ventricular ejection fraction

HF= heart failure

HFH= heart failure hospitalization

IPD= individual participant data

PICOTS= Participant, Intervention, Comparator, Outcome, Time and Study-design

RCT= randomized controlled trial

TSAT= transferrin saturation

INTRODUCTION

Iron deficiency is common in heart failure affecting around 40-50% of patients with chronic stable heart failure and up to 80% of patients with acute heart failure (AHF).[1-3] Randomized controlled trials have established a causal effect of iron deficiency showing that iron deficiency results in worse functional status and clinical outcome.[4-7] As a result guidelines recommend the use of intravenous iron for the improvement in functional status in patients with iron deficiency and a left ventricular ejection fraction (LVEF) < 45% or to reduce heart failure hospitalizations (HFH) in patients recently admitted for AHF with a LVEF<50%.[8] Since the writing of that guideline recommendation, the result of the IRONMAN trial suggested a benefit on HFH, although the trial was affected by the COVID-pandemic.[9] More recently the HEART-FID trial did not show a significant effect of ferric carboxymaltose on the composite of mortality, HFH and 6-minute walking distance using a pre-defined 99% confidence interval.[10] However the HEART-FID trial does illustrate a benefit of ferric carboxymaltose on this primary composite endpoint using a classic 95% confidence interval, as used in all other randomized controlled trials with intravenous iron. As a result there is residual uncertainty about the overall benefit of intravenous iron on hard clinical outcome include cardiovascular (CV) mortality or HFH. Additionally, some concerns have been raised in the recent years with the current definition of iron deficiency, as patients with a baseline TSAT>20% have a more benign disease trajectory, do not exhibit iron deficiency on bone marrow staining and exhibit potentially diminished treatment response to intravenous iron.[11-15] The goal of the current meta-analysis is two-fold: (1) to determine the overall treatment effect of intravenous iron on hard clinical outcome based on all randomized control trial data in heart failure and (2) to assess the impact of baseline TSAT on the benefit of intravenous iron using all aggregate level data from all randomized controlled trials with intravenous iron.

METHODS

Systematic review

The analytic plan and the search strategy used in the systematic review and meta-analysis were registered prior to data extraction and data analysis in the PROSPERO database. Using OVID we searched MEDLINE and Embase using a PICOTS (Participant, Intervention, Comparator, Outcome, Time and Study-design) search strategy consisting of subject headings and multiple posting terms (supplemental figure 1). The search was restricted to randomized controlled trials and trials published in English between January 2000 and

August 2023 using search filter options. Inclusion criteria for the search were aligned with previous reports of meta-analysis of randomized controlled trials for intravenous iron in heart failure.[16] In brief, randomized controlled trials investigating the effect of intravenous iron in comparison to placebo in patients with iron deficiency and heart failure was performed. There was no restriction in regard to the type of intravenous iron formulation, the definition used to define iron deficiency or the type of heart failure including baseline LVEF, NT-proBNP cut-offs for enrollment and degree of baseline functional limitation per New York Heart Association Class. Trials with oral iron or in cardiac transplant recipients were excluded. Two investigators (PM and SNA) independently performed the data search using the pre-defined analytic plan. Data extraction was performed according to a standardized data extraction sheet. If there was failure of data extraction consensus a third independent reviewer was sought. The risk for within trial bias was assessed using the Version 2 of the Cochrane risk-of-bias tool for randomized controlled trials. The primary efficacy endpoints for data extraction included (1) CV-mortality, (2) the combined endpoint of CV-death with HFH and (3) first HFH and (4) total HFH.

Meta-analysis and statistical analysis

All analysis were performed using R-studio. For the estimation of the overall treatment effect across trials a fixed effect model was used as the primary efficacy model. This to avoid attributing disproportional weight to smaller (generally more positive) randomized controlled trials as occurs in random effect models. For dichotomous first events the effect size estimate was an Odds-Ratio (OR) with accompanying 95% confidence interval and a rate ratio (RR) with accompanying 95% confidence interval for recurrent events. Treatment effect modification was explored on the primary efficacy model by IV-iron formulation. For sake of data analysis (and due to small numbers), trials with IV iron compounds other than ferric carboxymaltose (ferric derisomaltose, ferric gluconate and iron sucrose) were combined, to determine treatment effect modification by trials using ferric carboxymaltose compounds vs non- ferric carboxymaltose compounds. Heterogeneity was assessed using the I^2-statistic, with <25% indicating low, 25-50% low-moderate, 50-75% moderate-high and >75% high heterogeneity amongst trial results. The analysis was run through an custom made R-package (Oxford University). Sensitivity analysis of the primary efficacy analysis (which uses events solely on a binary basis) were performed to account for the differential follow-up times (time to event data). Two methods were used: First, for trials reporting a hazard ratios (HR) and 95% CI for time to first event

endpoints, a direct pooling approach with inverse variance weighing was used to determine an overall treatment effect (reported an overall HR and 95% CI). A second approach was used as most smaller trials did not provide time to event data precluding to generation of an overall HR. This approach consisted of running the primary efficacy model separately for trials with a follow-up duration ≤ 24 weeks and > 24 weeks. Between trial heterogeneity was explored using the dmetar and find.outliers R-package. Influences analysis was performed to assess the impact of between trial heterogeneity on the overall estimated treatment effect and visualized using Baujat plots. For endpoints with significant heterogeneity defined as an I^2 above 50% and significant test for heterogeneity it was pre-defined in the analysis plan to explore the impact of baseline TSAT on the treatment effect of intravenous iron across different trials through mixed-effect meta-regression.

RESULTS

Trials and population

A total of 14 randomized controlled trials were identified and included in the meta-analysis (see supplemental figure 2).[4-7, 9-11, 17-22] The baseline features of the 14 trials are reflected in table 1. For data extraction purposes the 2017 individual participant data (IPD) analysis from Anker et al was used to extract data from the FER-CARS-01, FAIR-HF, EFFICACY-HF and CONFIRM-HF trial as this paper also reported recurrent events.[11] Supplemental figure 3 gives an overview of the risk-of-bias tool for randomized trials version 2 assessment, indicating overall good methodologic quality of the trials retained in the meta-analysis. The current meta-analysis includes aggregate level data from 6624 participants of whom 3407 were randomized to intravenous iron and 3217 to placebo (or standard of care). The follow-up duration of the trials ranged from 12 weeks to 140 weeks. A total of 7 of the 11 trials had a mean follow-up of less or equal to 24 weeks, while the remainder of the trials had a follow-up of more than 24 weeks. Most trials included patients with heart failure with a reduced ejection fraction. Iron deficiency was most often defined as a ferritin <100 ng/ml or a ferritin 100-300 ng/ml if TSAT was <20% (see table 1). Most trials had an entry LVEF-criteria of <45%. The used iron formulations included two trials with iron sucrose, nine trials using ferric carboxymaltose, one trial using both iron sucrose and ferric carboxymaltose, one trial using ferric derisomaltose and one trial using ferric gluconate. All trials were placebo-controlled, but in some trials also the placebo-arm was defined as the standard of care arm, nevertheless placebo arms were all very similar.

Outcomes and treatment effect estimates

The current meta-analysis contains aggregate level data on a total of 979 CV-death events, 1903 combined CV-death with HFH events, 937 first HFH events and 1902 total HFH events. Assuming a modest treatment effect of 15% relative risk reduction for intravenous iron on all events, the current meta-analysis would provide 72%, 94%, 70% and 94% power to detect a significant treatment effect on the aforementioned endpoints respectively and would provide >99% power to detect a larger treatment effect of 25% relative risk reduction for all aforementioned endpoints. Figure 1 illustrates the Forest plots with treatment effect estimation from the fixed effect model for the endpoints (A) CV-death, (B) CV-death or HFH, (C) first HFH and (D) total HFH. Treatment with intravenous iron had a borderline significant effect on CV-mortality, with an OR= 0.867 (95% CI=[0.755-0.995], p=0.0427), without any indication for heterogeneity amongst the trial results as indicated by the I^2 of 0% (test for heterogeneity: p=0.6386, figure 1 panel A). Treatment with intravenous iron had a significant effect on the combined endpoint CV-mortality and HFH, with an OR= 0.838 (95% CI=[0.751-0.935], p=0.0015), with mild to moderate heterogeneity as indicated by the I^2 of 44.8% (test for heterogeneity: p=0.0699, figure 1 panel B). Treatment with intravenous iron had a significant effect on both first (OR=0.855, 95% CI=[0.744-0.983], p=0.0281) and recurrent (RR=0.739, 95% CI=[0.661-0.827], p<0.001) HFH. Albeit with significant heterogeneity amongst trial results as indicated by an I^2 of 60.3% and I^2 of 75.6% (both test for heterogeneity p<0.0137, figure 1 panel C and D). No treatment interaction was found for trial using ferric carboxymaltose vs non-ferric carboxymaltose compounds for CV-mortality (p-interaction= 0.6697), CV-mortality and HFH (p-interaction= 0.8003), first HFH (p-interaction= 0.9822), total HFH (p-interaction= 0.8003).

Sensitivity analysis

Similar treatment effect estimates as the primary efficacy model were obtained in a sensitivity analysis using a random effects model (supplemental figure 4) for CV-death, however for the endpoints containing HFH, the treatment effect estimations were proportionally larger in the random effect models (CVD-death and HFH: OR=0.781, 95% CI=[0.630-0.970]; first HFH: OR=0.774, 95% CI=[0.542-1.105] and total HFH: RR=0.668, 95% CI=[0.459-0.973]) in comparison to the fixed model due to attributing more weight to trials other than HEART-FID. To account for differential follow-up times in the different trials, a pooled estimate of the HR was given for trials reporting HR for time to first event endpoints (CV-death, CV-death + HFH,

and first HFH). The results are reflected in supplemental figure 5, showing a similar significant effect of IV iron on CV-death, CV-death + HFH, and first HFH. Additionally a sensitivity analysis similar to the primary efficacy analysis was performed for trials with ≤24 weeks follow-up or > 24 weeks follow-up, which are reflected in supplemental figure 6 and 7, again showing a similar effect size of reducing CV-death, CV-death + HFH, and HFH in both trials with shorter or longer follow-up.

Heterogeneity exploration for the treatment effect on heart failure admission

For the endpoint first HFH and total HFH potential causes of heterogeneity were assessed given the presence of a larger I^2 and significant test for heterogeneity. Figure 2 plots the overall contribution of the individual trials to the overall treatment effect (Y-axis) versus the overall contribution to the observed heterogeneity (X-axis). Both the Anker et al IPD-meta-analysis and the HEART-FID are significant sources of heterogeneity for the overall treatment effect estimation, with the Anker et al IPD-meta-analysis suggesting a more positive effect on HFH-events and the HEART-FID trial suggesting more neutral effects on HFH-events. Given the well-established concern of the current definition of iron deficiency employed in heart failure, the impact of baseline TSAT on the overall treatment effect was assessed through mixed effect meta-regression. Figure 3 represents a bubble plot of the treatment effect of the individual trials (Y-axis) according to the baseline mean TSAT (X-axis), with bubble size representing the individual trial weight from the fixed effect model for both first HFH (panel A) and total HFH (panel B). Figure 3 illustrates that in general trials with a baseline TSAT ≤ 20% have treatment effect estimates indicating a reduction in HFH events while a higher TSAT did not, explaining some of the heterogeneity induced by the HEART-FID trial that had a significantly higher baseline TSAT as indicated by table 1 and figure 3.

DISCUSSION

This meta-analysis provides important novel information about the cumulative benefit of intravenous iron on hard clinical endpoints in patients with heart failure, allowing practicing physician and other entities (drug approval agencies, guideline committees, governments) to get an appropriate treatment effect estimation of the benefit of intravenous iron, based on the totality of all data generated in heart failure (trials predominantly with LVEF<45%). Our meta-analysis shows that there is a modest (OR=0.867, 95%CI=[0.755-0.995]) but

significant effect on CV-mortality without heterogeneity across the different randomized controlled trials, a finding consistent in time to event sensitivity analysis.

While IRONMAN, HEART-FID and other trials in suggested a 15% lower rate mortality, none of these trials were individually powered to assess CV mortality and most confidence interval all just contained one. The larger number of CV-events in this analysis leads to a smaller confidence interval while the magnitude of the treatment effect is the same as previously suggested. Our meta-analysis also confirms previous reports and primary assessment of individual randomized controlled trials, showing that intravenous iron significantly reduces HFH events, both first and total HFH and its composite with CV-death. In comparison to a previous meta-analysis excluding the largest trial up to this point (HEAR-FID), the effect size estimates in the fixed effect model were somewhat smaller with proportional treatment effects indicated a 15-25% lower odds/risk for HFH-events.[16] This smaller effect-size was also recently documented in a meta-analysis by Ponikowski etal, showing a 16% lower risk for total HFH. This meta-analysis however only included CONFIRM-HF, HEART-FID and AFFIRM-AHF and include a total of 4475 patients, which is sizably smaller than the current meta-analysis looking at the totality of data in 6624 patients. Therefore this meta-analysis contains a third more patients, this larger sample size is important because the larger number of events will determine the uncertainty (reflected as a 95%CI) around any treatment effect. The somewhat lower treatment effect in this analysis stem from the primary mode of estimating of the overall treatment effect of intravenous iron. Our analysis uses a fixed effect model that attributes weight of the individual trials according to the events of the trial. Because the largest trial to date (HEART-FID) had the most neutral effect of HFH, such analytic approach seems appropriate to avoid overestimation of a treatment effect by attributing more weight to smaller (generally more positive) randomized controlled trials. Despite using this more conservative approach, there is a clear sign that intravenous iron reduces both CV-death and HFH-events. This is important as primary analysis of both the IRONMAN and AFFIRM-AHF trial were affected by the COVID-pandemic and the HEART-FID trial used a non-classic 99% CI. The current meta-analysis therefore provides more clarity about the total benefit of intravenous iron. The results of both the primary fixed effect analysis and the random effect sensitivity analysis are in line with one and another indicating that intravenous iron indeed reduces both CV-death and HFH events. We did not observe treatment effect modification by the trials using ferric carboxymaltose vs other compounds. Additionally the treatment effect sizes seem to be similar in trials with shorter and longer follow-up. This indicates that the beneficial effect of intravenous

already occurs relative early. This is in line with a previous randomized controlled trial (Myocardial iron trial) showing change in myocardial function and structure measured by MRI in as early as 7 days.

A challenge however for the interpretation of the effect on HFH events is the presence of significant heterogeneity. The presence of heterogeneity implies that it is less appropriate to indistinctively apply the overall pooled treatment effect estimate (OR=0.855 for first HFH and RR=0.739 for total HFH) across all trials. Exploration of the heterogeneity for the endpoints with significant heterogeneity (first HFH and total HFH) indicated that both the HEART-FID trial and the Anker et al IPD-meta-analysis contributed significantly to the overall heterogeneity. The Anker et al IPD-meta-analysis generally gives a more positive treatment effect of IV iron on first and total HFH events. A potential source of some of this heterogeneity could be related to the fact that this report contains data from smaller, earlier (generally more positive) and not individually published studies including FER-CARS-001 or EFFICACY-HF. However the Anker et al IPD meta-analysis, which had individual participant data, also clearly documented that patients with a TSAT>20.1% had not benefit with intravenous iron. The HEART-FID trial on the other hand exhibits a more neutral effect on first HFH and total HFH. This is important as in the fixed effect model the HEART-FID trial weighs the strongest in the effect size estimation. Because the patients enrolled in the HEART-FID trial had a significantly higher TSAT in comparison to all other randomized controlled trials with intravenous iron, we performed meta-regression to understand the impact of baseline TSAT in regard to the benefit of intravenous iron on HFH events. This analysis indicates that for HFH events, trials enrolling patients in the lower spectrum of TSAT (eg ≤20%) had a more pronounced benefit on HFH events (figure 3). This data is in line with the Anker et al IPD-meta-analysis showing that ambulatory patients with a TSAT>20.1% did not benefit from ferric carboxymaltose and in line with the IPD meta-analysis from Ponikowski indicating that patients with a TSAT< 20% had a significant benefit on the combined endpoint of CV-death and total HFH (HR=0.86, 95%CI=[0.67-1.00], p=0.046). Therefore most patients in the HEART-FID trial did not seem to benefit from intravenous iron as they had a TSAT>20%. The HEART-FID trial solely enrolled patients with stable outpatient heart failure, which often leads to diagnosis of iron deficiency with a higher TSAT in comparison to iron deficiency in acute heart failure. Some caution should be applied when interpreting these meta-regression results, as using aggregate level data could lead to ecological bias, making assumptions on the individual participant level harder. Nevertheless, this analysis is supported by IPD-meta-analysis data,

indicating that it is perhaps time that the field of heart failure move to redefine the definition of iron deficiency in heart failure, making a low TSAT<20% an essential element for selection of patients for therapy.

It is interesting that baseline TSAT influences the benefit on HFH-events , while no heterogeneity is observed for CV-death. This might be a chance finding as for instance the evidence of a CV-death benefit is only small as indicated by the p-value= 0.0427. However this observation might have some biological basis. It is well known that congestion such as occurring in AHF leads to less bioavailability of iron through reticulo-endothelial cell clustering.[23, 24] The bio-available iron is reflected by the iron present in the circulation in its free form (serum iron) or bound to transferrin (reflected by the TSAT).[15] In episodes of AHF, TSAT significantly drops. The heart is strongly iron dependent, as iron is an essential cofactor for most energetic processes in the heart.[25-27] Neuro-hormonal activation as occurs in heart failure might actually worsen myocardial iron deficiency.[28] The IRON-CRT trial showed that a low TSAT was important for short-term improvement in myocardial function with IV iron and treatment with intravenous iron can improve myocardial iron reserve and function as early as 7 days.[5, 29, 30] Indeed it is very likely that especially patients with a low TSAT benefit from intravenous iron, as iron injected into the bloodstream will immediately re-saturate transferrin, potentially leading to a replenishment of myocardial and skeletal muscle iron content generating resilience towards future AHF events. Perhaps patients with relatively saturated transferrin at baseline might benefit less from the immediate replenishment of transferrin through intravenous iron, explaining some of the heterogeneity in HFH-events. Potentially the effects of IV iron on CVD-death are more reflected by what the chronic iron reserve is, than necessary the short-term iron availably as reflected by TSAT or serum iron. More detailed analysis looking at definition of iron deficiency in heart failure could further help to unravel the relation between iron parameters and the effect on outcome.

CONCLUSION

Intravenous iron in patients with heart failure leads to a reduction in both CV-death and HFH-related events. For HFH related events the baseline TSAT might play a role in the overall treatment benefit.

CLINICAL PERSPECTIVE

This meta-analysis provide a pooled treatment effect estimate of intravenous iron showing a beneficial effect on cardiovascular mortality and heart failure readmissions. This meta-analysis includes all available randomized controlled trial data available with different intravenous iron compounds.

TRANSLATIONAL OUTLOOK

Observational studies have implicated predominantly a low TSAT in the pathophysiology of iron deficiency in heart failure. The current analysis supports the use of intravenous iron mainly in patients with a TSAT<20%. Future efforts are necessary to re-define iron deficiency in heart failure allowing for the most efficient allocation of intravenous iron towards patients benefiting from the intervention.

Table 1: Design features of trials identified in the systematic review and retained in the meta-analysis.

Parameter	Toblli et al	FERRIC-HF Okonko et al	FER-CARS-01	FAIR-HF Anker et al	EFFICACY-HF	CONFIRM-HF Ponikowski et al.	EFFECT-HF Van Veldhuisen et al
Year	2007	2008	2017*	2009	2017*	2015	2017
Sample size (I/P)	40 (20:20)	35 (24:11)	62 (30:27:15)**	459 (304:155)	34 (20:14)	301 (150:151)	174 (86:86)
Iron intervention	Iron sucrose	Iron sucrose	FCM / iron sucrose	FCM	FCM	FCM	FCM
Randomized	yes	yes	yes	yes	yes	yes	yes
Double blind	yes	no	unknown	yes	unknown	yes	yes
Definition iron deficiency	F<100 or T<20%	F<100 or T<20% + F 100-300	unknow	F<100 or T<20% + F 100-300	F<100 or T<20% + F 100-300	F<100 or T<20% + F 100-300	F<100 or T<20% + F 100-300
Main inclusion criteria	LVEF ≤ 35% NYHA II-IV Anemia	LVEF ≤ 45% NYHA II-III Hb ≤ 14.5	LVEF ≤ 45% NYHA II-III eGFR< 60	LVEF ≤ 45% NYHA II-III Hb ≤ 9.5-13.5	LVEF ≤ 45% NYHA II-III	LVEF ≤ 45% NYHA II-III Hb < 15	LVEF ≤ 45% NYHA II-III Hb < 15
Age (years)	75	63	63*				64
LVEF							
Hb (g/dl)	10.3±0.6	12.6±1.2	12.1±1.3*				12.9±1.3
Ferritin (µg/L)	73±30	62±37	56.8±54*				48
TSAT (%)	20±1	20±8	18±12*				17
Follow-up duration (weeks)	24	18	31*				24
HF-events reported	+	+	+*				+
CV-death reported	-	+	+*				+

Explanation: * Aggregate level data from the IPD-meta-analysis from Anker et al was used to extract data jointly for FER-CARS-01, FAIR-HF, EFFICACY-HF, and CONFIRM-HF. **Abbrevations:** I= intervention, p= placebo, FCM= ferric carboxymaltose, F= ferritin, T= Transferrin saturation, LVEF= left ventricular ejection fraction, NYHA= New York Heart Association class, Hb=hemoglobin, TSAT= transferrin saturation, HF= heart failure, CV= cardiovascular

Table 1: Design features of trials identified in the systematic review and retained in the meta-analysis - continued

Parameter	PRACTICE ASIA-HF, Yeo et al	AFFIRM-AHF Ponikowski et al	Dhoot et al	IRON-CRT Martens et al	IRONMAN Kalra et al	Marcusohn et al	HEART-FID Mentz et al
Year	2018	2020	2020	2021	2022	2022	2023
Sample size (I/P)	49 (24:25)	1108 (558:550)	70 (35:35)	75 (37:38)	1137 (569:568)	34 (18:16)	3065 (1532:1533)
Iron intervention	FCM	FCM	FCM	FCM	Ferric derisomaltose	Ferric gluconate	FCM
Randomized	yes	yes	yes	yes	yes	yes	yes
Double blind	no	yes	no	yes	no	no	yes
Definition iron deficiency	T<20% and F<300	F<100 or T<20% + F 100-300	F<100 or T<20% + F 100-300	F<100 or T<20% + F 100-300	F<100 or T<20% + F <400	F<100 or T<20% + F 100-300	F<100 or T<20% + F 100-300
Main inclusion criteria	AHF Hb < 14 All LVEF	AHF, NT-proBNP↑ LVEF<50% Hb 8-15	NYHA II or III Hb > 8	CRT > 6mo LVEF<45% NYHA≥II Hb<15	LVEF ≤ 45% AHF < 6 or NT-proBNP↑ Hb 9-14	AHF and NT-proBNP↑ Hb 8–14 All LVEF	LVEF ≤ 40% AHF<12 or NT-proBNP↑ Hb 9-13.5
Age (years)	63	71	53	73	73	71.5	68.6
Hb (g/dl)	11.6±1.9	12.3±1.6	11±4	13.3±1.2	12.1 (11.2-12.8)	11.9 (10.6-12.5)	12.6±1.4
Ferritin (µg/L)	91±80	84±62	40±27	82±57	49 (30-86)	93 (53-161)	56.6±49
TSAT (%)	16±10	15±8	unknown	18.8±6.5	15 (11-20)	12.9 (9.8-15.2)	23.4±10.8
Follow-up duration	12	52	12	13	140 (94-187)	12	99 (68-156
HF-events reported	+	+	+	+	+	+	+
CV-death reported	+	+	+	+	+	-	+

FIGURE CAPTIONS

Figure 1: Overall estimation of treatment effect of intravenous iron for various endpoints

Explanation: Panel A represents cardiovascular death, panel B represents time to first event being cardiovascular death or heart failure admission, panel C represent time to first heart failure events and panel D represents total heart failure admissions. **Abbreviations:** CV= cardiovascular, HFH= heart failure hospitalization, OR= odds ratio, RR= rate ratio, CI= confidence interval

Figure 2: Baujat plots for first HFH and total HFH

Explanation: Panel A represents first hospitalization and panel B represents total heart failure admissions. **Abbreviations:** HFH= heart failure hospitalization,

Figure 3: Bubble plots from mixed effect model of baseline TSAT vs treatment effect

Explanation: Green area indicates are of trials with beneficial treatment effect and TSAT≤20%. Panel A represents first hospitalization and panel B represents total heart failure admissions. **Abbreviations:** HFH= heart failure hospitalization, TSAT= transferrin saturation.

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