REVIEW PAPER

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Efficacy and safety of intravenous iron therapy in heart failure patients with iron deficiency: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction. Heart failure is a diverse life-threatening condition with complex biology and demanding therapeutic goals. Even when anemic patients are excluded, up to 59% of heart failure patients have low ferritin levels, making them especially vulnerable to iron deficiency. We aim to explore the benefits and safety of intravenous iron therapy among patients with heart failure and iron deficiency.

Material and methods. We have searched the literature on PubMed (MEDLINE), Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (WoS), and EMBASE until 31st August, 2023. We

used RevMan V. 5.4 to pool dichotomous data using a risk ratio (RR) with a 95% confidence interval (CI). This review has been registered and published in PROSPERO (CRD42023471419)
Results. Fourteen randomized controlled trials with 6,626 patients were included. The intravenous iron group was favored over the control group in reducing hospital admissions for heart failure (first event) (RR= 0.83, 95% CI 0.71 to 0.97; p = 0.02) and (total events) (RR= 0.81, 95% CI 0.74 to 0.89; p < 0.0001). Also, the iron group had a 21% lower risk in terms of cardiovascular death and hospital admission for heart failure (number of events, rate per 100 patients in a year) (RR= 0.79, 95% CI 0.74 to 0.85; p < 0.00001). Concerning the adverse events, both ferric carboxymaltose and ferric derisomaltose showed a beneficial effect in reducing the cardiac disorder (RR= 0.81, 95% CI 0.76 to 0.87; p <0.0001), and (RR= 0.82, 95% CI 0.71 to 0.95; p = 0.009), respectively.
Conclusions. Intravenous iron infusion in patients with heart failure has a favorable safety profile. It reduces total hospitalizations for heart failure and cardiovascular mortality, with no effect on all-cause mortality, cardiovascular mortality alone, or first-time hospitalization for heart failure.

Introduction

Heart failure (HF) is a multifaceted, life-threatening syndrome with a complex pathophysiology and challenging management goals. HF is a clinical syndrome characterized by symptoms and/or signs resulting from structural and/or functional cardiac abnormalities. This condition is confirmed by elevated levels of natriuretic peptides and/or objective evidence of pulmonary or systemic congestion. [1]. In 2017, The Global Burden of Disease report stated that 64.3 million people live with HF worldwide [2]. According to more recent estimates, one to three percent of individuals in low-income nations are believed to have HF. However, this incidence is expected to rise due to advancements in both diagnosis and treatment options that extend the lives of HF patients. In contrast, the incidence of HF has steadily declined over the past few decades, with an estimated 1–20 cases per 1,000 individuals identified annually [3].

Even after excluding anemic individuals, up to 59% of HF patients exhibit low ferritin levels, rendering them particularly susceptible to iron deficiency [4]. While the precise etiology of iron deficiency remains elusive, it has been suggested that increased iron depletion (due to gastrointestinal bleeding), reduced iron intake, absorption, and systemic bioavailability may contribute to the development of the disease [4]. It is crucial to note that iron deficiency in HF patients can manifest as either absolute (total body iron is decreased) or functional (total body iron is normal or increased). In the latter form, iron becomes sequestered in storage tissues (such as the liver), transferring insufficient amounts to the myocardium to meet its needs [5].

The activation of the neuroendocrine system can downregulate the messenger ribonucleic acid (mRNA) expression of Transferrin Receptor 1, leading to increased secretion of aldosterone and norepinephrine. Consequently, this downregulation can hinder iron uptake by cardiomyocytes [6]. The insufficient supply of iron to the myocardium gives rise to a condition known as myocardial iron deficiency, characterized by poor mitochondrial structure and function, oxidative stress, and increased detrimental cardiac remodeling [7]. Regardless of whether the iron deficiency is absolute or functional, it is associated with a poor prognosis in HF and has been demonstrated to be a robust and independent predictor of mortality [8].

Therefore, studies have aimed to evaluate the effectiveness of intravenous (IV) iron therapy in improving the condition of HF patients with iron deficiency. Among these, a multicenter randomized controlled trial (RCT) known as the CONFIRM-HF study, published in 2015, demonstrated the superiority of IV ferric carboxymaltose over placebo in ameliorating several outcomes, including functional capacity, symptoms, quality of life, martial deficiency, and hospitalization risks [9]. Other RCTs, such as the AFFIRM-AHF study, found that IV ferric carboxymaltose effectively lowers the risk of HF hospitalization among stabilized patients with iron deficiency and left ventricular ejection fraction < 50% after discharge from acute episodes, later corroborating these findings [10].

However, some results were not as positive. For example, the recent HEART-FID trial found no statistically significant difference in a hierarchical endpoint including mortality, HF hospitalizations, and six-minute walk distance between ambulatory HF patients with reduced ejection fraction and iron deficiency who took either ferric carboxymaltose or placebo [11], narrowly missing its prespecified target despite the large sample size.

In light of the ongoing controversy and inconsistency in the existing literature, we undertook a comprehensive systematic review and meta-analysis to evaluate the entirety of data derived from RCTs concerning the efficacy and safety of intravenous iron therapy in patients with HF and iron deficiency. The findings from our study hold substantial therapeutic implications.

Methods.

Protocol Registration

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12] and the Cochrane Handbook for systematic reviews and meta-analyses [13]. The review was registered and published in PROSPERO on 10th November 2023 under the ID CRD42023471419.

Data Sources & Search Strategy.

We have searched the literature on PubMed (MEDLINE), Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science (WoS), and EMBASE until 31st August 2023. We adjusted the search terms and keywords for each database; the results are presented in (**Table S1**).

Eligibility Criteria and Study Selection.

We included studies that followed the following PICOS criteria:

- Population (patients with HF and iron deficiency, no age criterion);
- Intervention (IV iron);
- Comparison (placebo or standard care);
- Outcomes:
  - Primary outcomes are (cardiovascular mortality, all-cause mortality, Hospital admission for heart failure (first event), hospital admission for heart failure (total event), cardiovascular death and hospital admission for heart failure (number of events, rate per 100 patients in a year), hospital admission for heart failure (number of events, rate per 100 patients in a year).
  - Secondary outcomes included adverse events: cardiac disorder, gastrointestinal disorder, injection site condition, infection, nervous system disorder, respiratory, thoracic, or mediastinal disorder, vascular disorder, any adverse effect, any serious adverse event, any adverse event leading to withdrawal, abnormal lab test, vital signs, or physical finding. Studies included were parallel RCTs.

Papers that met any of the following criteria were excluded: (1) non-original studies (e.g., book chapters, reviews, comments, letters to the editor, guidelines); (2) any other study design except RCTs; (3) studies involving duplicate or overlapping datasets; (4) non-human and in vitro experiments; and (5) studies not reported in English.

Study Selection.

We utilized the Covidence web tool to conduct the review. After eliminating duplicates, all obtained records were independently assessed by four authors. During the initial eligibility criteria full-text screening, the full texts of the records were reviewed by four authors. Any disagreements were resolved through discussion and consensus with a senior author.

Data Extraction.

After acquiring the full texts of relevant publications, we conducted a pilot extraction to effectively organize the data extraction sheet. The Excel-based data extraction sheet is divided into three sections.

The first part encompasses the summary characteristics of the included studies, such as the name of the first author, year of publication, country, follow-up period, population, iron preparation, comparator, iron dosing strategy, definition of iron deficiency, inclusion criteria, and primary outcome.

The second part consists of baseline information about the participants, covering race, The New York Heart Association (NYHA) class, age, gender, N-terminal prohormone of brain natri-

uretic peptide (NT-proBNP), B-type natriuretic peptide (BNP), left ventricular (LV) ejection fraction, 6-minute walk test distance (6MWT), systolic and diastolic blood pressure, hemoglobin, serum ferritin, transferrin saturation, estimated glomerular filtration rate (eGFR), phosphorus, hospital admissions for heart failure, de novo (new) hospital admissions for heart failure, comorbidities (atrial fibrillation (AF), acute coronary syndrome (ACS), hypertension, diabetes, chronic kidney disease (CKD), anemia, dyslipidemia), and medications (implantable cardioverter–defibrillator (ICD), cardiac resynchronization therapy (CRT), angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), sacubitril–valsartan, ACE inhibitor, ARB, beta-blocker, mineralocorticoid receptor antagonist (MRA), digoxin, sodium-glucose cotransporter-2 (SGLT2) inhibitor, loop diuretic, insulin, and any other glucose-lowering medication). Finally, the third part covers outcomes data. Four reviewers (A.R., O.A., A.A., and I.U.) were responsible for data extraction, and any discrepancies were resolved through discussion and agreement with a senior author.

Risk of Bias and Certainty of Evidence.

Four reviewers (A.R., O.A., A.A., and I.U.) independently assessed the quality of the studies using the Cochrane RoB2 method [14]. Any disagreements were resolved through discussion with a senior author. Simultaneously, two reviewers (M.A. and B.A.) employed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria [15, 16] to assess the certainty of evidence. A consensus was reached to resolve any disagreements.

Statistical Analysis.

The statistical analysis was performed using RevMan v5.3 software (15). For dichotomous outcomes, we calculated the risk ratio (RR), and for continuous outcomes, we computed the mean difference (MD), both presented with a 95% confidence interval (CI) under the fixed-effects model. In cases of significant heterogeneity, we applied the random-effects model. Heterogeneity was assessed using the Chi-square and I-square tests; the Chi-square test determined the presence of heterogeneity, and the I-square test gauged its extent. As per the Cochrane Handbook (chapter nine) [17], an I-square exceeding 50% signified significant heterogeneity, while a Chi-square test with an alpha level below 0.1 indicated considerable heterogeneity.

We performed a subgroup analysis based on (i) chronic or acute heart failure and (ii) type of iron preparation. Furthermore, trial sequential analysis was employed to validate desired or undesired intervention effects by analyzing data from ongoing trials. Sensitivity analysis was also conducted to assess the impact of alternative assumptions or analyses on the pre-specified research questions. In essence, sensitivity analysis aims to evaluate the validity and certainty of the primary methodological or analytic strategy. Finally, if at least 10 studies were reported in the outcome, the asymmetry analysis was performed to determine the publication bias by visual inspection of the funnel plot of the studies, and Egger's test confirmed the results [18]. A p-value ≤ 0.05 was considered statistically significant for all tests.

Results

Study selection

Our database search yielded 2740 studies. After duplicate removal, we screened the remaining 1225 Studies, and only 35 were eligible for full-text retrieval. Only 14 studies met our inclusion criteria and were included in our review [9–11, 19–29] (**Figure 1**).

Study characteristics

Our included studies reported the data of a total of 6,626 patients who were assigned to IV iron as the intervention group (3,408 patients) or the control group (3,218 patients). The mean age of the Intervention group was 68.4 ± 4.95, and 68.1 ± 5.89 for the control group. Nine studies were single-centered, while the rest were multicenter studies. The follow-up duration ranged from two weeks to 2.7 years. The included studies' summary and detailed patient baseline characteristics are described in (**Table 1** and **2**), respectively [9–11, 19–29].

Risk of bias

The risk of bias assessment for each outcome is depicted in **Figure 2**. Overall, most included stud-

ies exhibited a low risk of bias across all assessed domains. Notably, two studies raised some concerns regarding bias (Karla et al. 2022: the data leading to this result was not analyzed as per the pre-specified analysis plan; Ponikowski et al. 2015: there is no evidence that the result was unaffected by missing outcomes, and the missingness in the outcome could be dependent on its true value). A GRADE evidence profile outlines The certainty of evidence (**Table 3**).

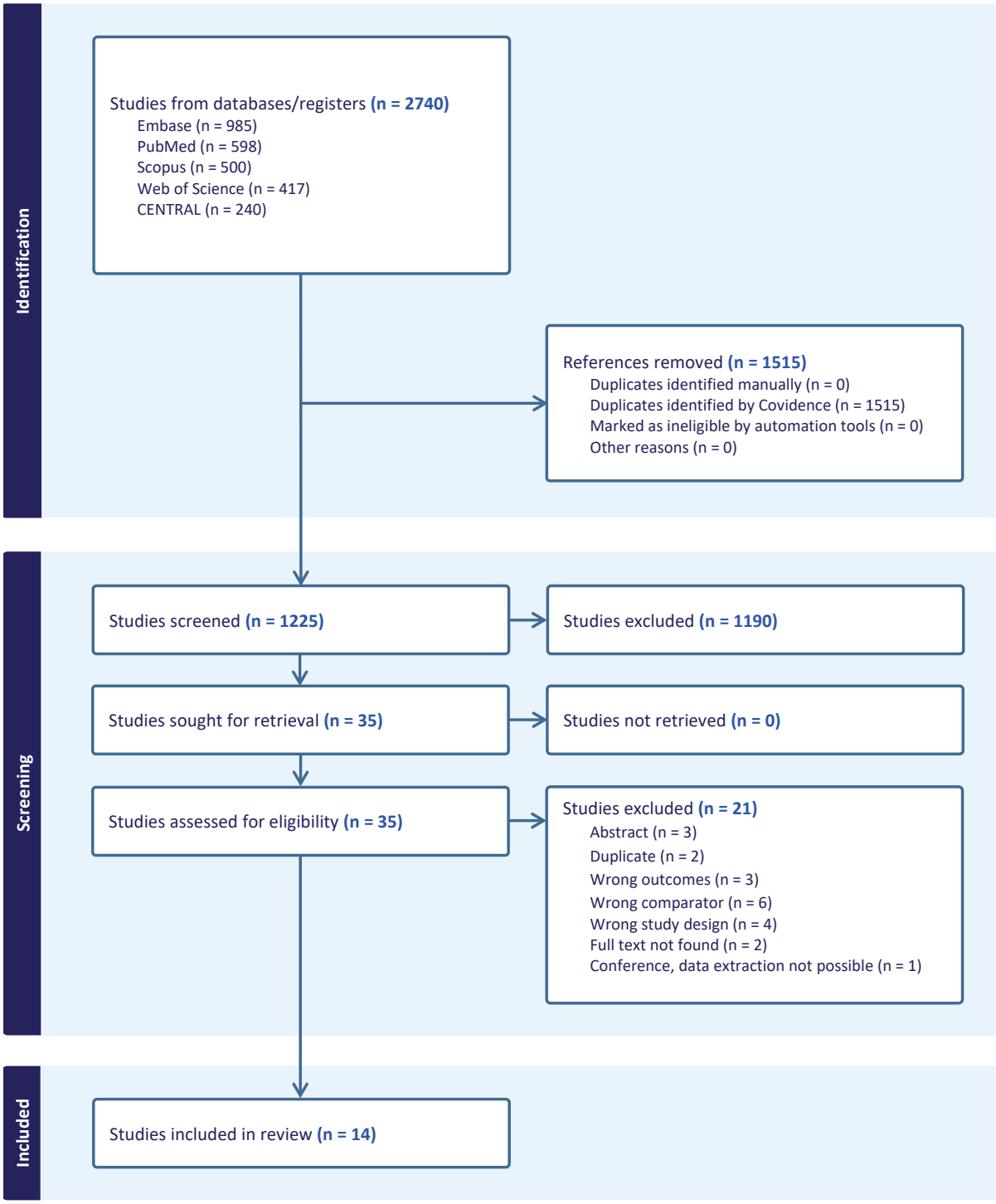

Figure 1. PRISMA chart showing the research strategy and inclusion and exclusion criteria.

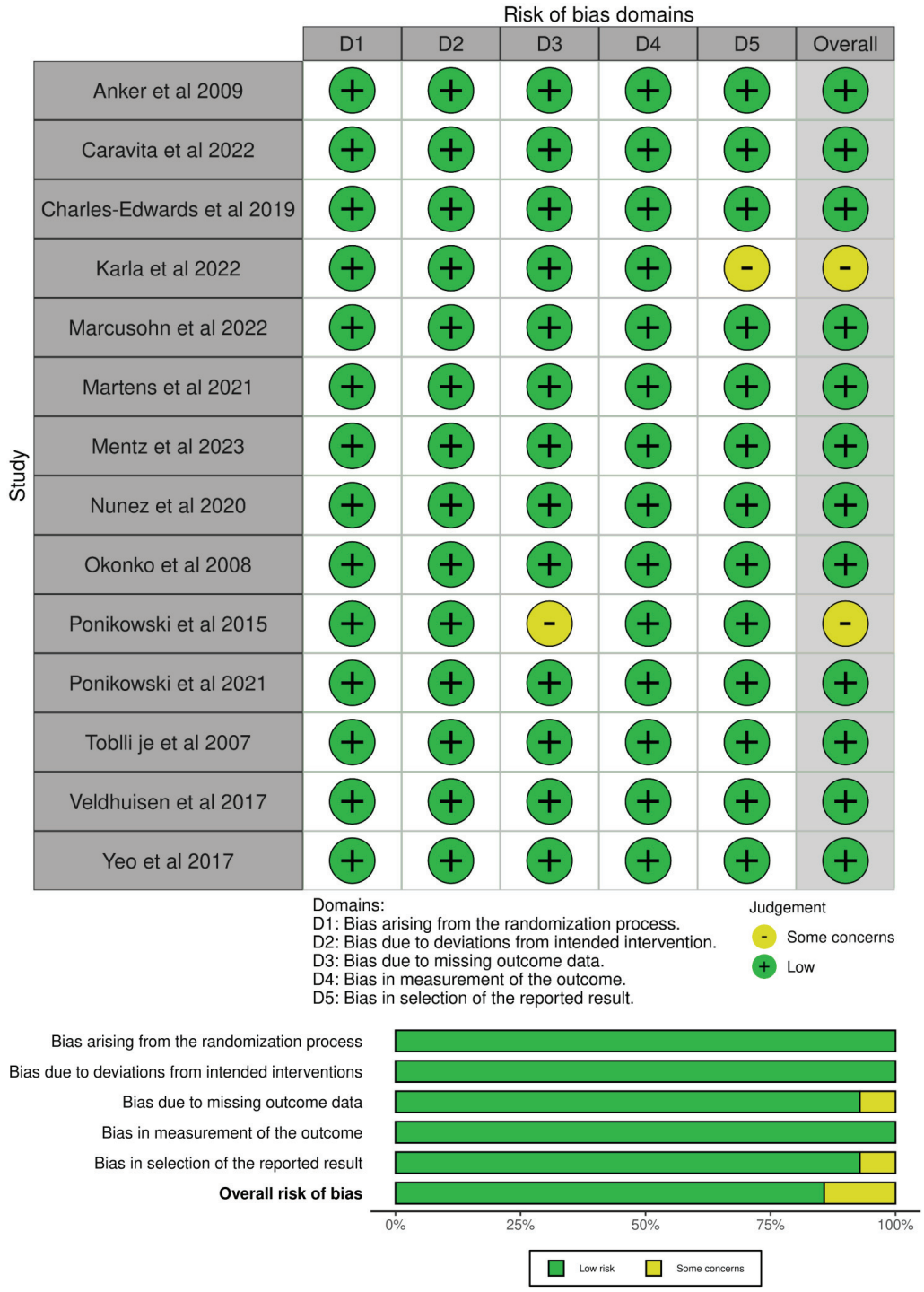

Figure 2. Risk of bias assessment is represented in traffic light and summary plots according to the Cochrane risk-of-bias tool, created using robvis.

Table 1. The summary of the included studies.

Ref.	Study	Year	Population	Comparison	Iron preparation	Iron dosing strategy	Country	Follow-up (week)	Iron deficiency	Definition of iron deficiency	Inclusion criteria	Primary outcome
[20]	Nunez et al	2020	Patients with stable chronic HF, left ventricular ejection fraction (LVEF) <50%, and ID (serum ferritin <100 lg/L	Placebo	Ferric Carboxymaltose	20-mL perfusion (equivalent to 1000 mg of iron)	Spain	30 days	Yes	ID (serum ferritin <100 lg/L [absolute ID] or 100–299 lg/L with transferrin saturation [TSAT] <20%	– Patients with ambulatory chronic heart failure Older than 18 years – Patients in NYHA class II-III on optimal background therapy – Elevated natriuretic peptides levels – Iron deficiency defined as: serum ferritin level <100 µg/L informed consent for participation in the study	Myocardial iron content
[21]	Okonko et al	2008	Anemic and Nonanemic Patients with Symptomatic Chronic Heart Failure and Iron Deficiency	Control	Iron sucrose	100mg at 0, 4, 8, 12 and 16 weeks	UK & Poland	18 weeks	Yes	Hb concentrations < 12.5 g/dl	– Age ≥ 21 years. – symptomatic CHF (New York Heart Association [NYHA] functional class II or III – Hb concentrations < 12.5 g/dl (anemic group) or 12.5 to 14.5 g/dl (nonanemic group) – Ferritin <100 µg/l or between 100 g/l and 300 µg/l – left ventricular ejection fraction ≤ 45%	Change in absolute pVO2 (ml/min) from baseline to week 18
[9]	Ponikowski et al	2015	Stable ambulatory HF patients	Placebo	Ferric Carboxymaltose	FCM doses were between 500 and 2000 mg iron FCM at each of Weeks 12, 24, and 36.	9 countries	24 weeks	Yes	Serum ferritin level ,100 ng/ mL, or between 100 and 300 ng/mL	– Iron deficient subjects with stable chronic heart failure – Reduced left ventricular ejection fraction Capable of completing 6-minute walk test. – At least 18 years of age.	Change in six-minute walk test
[10]	Ponikowski et al	2021	Patients With Acute Heart Failure	Placebo	Ferric Carboxymaltose	intravenously shortly before discharge and the second dose was administered at week 6 (visit three).	121 sites in Europe, South America, and Singapore	52 weeks	Yes	Iron deficient defined as serum ferritin <100 ng/mL or 100 ng/mL ≤ serum ferritin ≤299 ng/mL if TSAT <20%	– Hospitalised for an episode of acute heart failure (AHF) – Subject is iron deficient defined as serum ferritin <100 ng/mL. – Left ventricular ejection fraction <50% – Male or female aged ≥18 years old.	HF Hospitalizations and CV Death
[22]	Toblli je et al	2007	Anemic Patients with Chronic Heart Failure and Renal Insufficiency	Placebo	Iron sucrose	200 mg weekly	Argentina	6 months	Yes	Anemia with an iron deficit defined by Hb < 12.5 g/dl for men and < 11.5 g/dl for women.	– LV ejection fraction (EF) ≤ 35% – New York Heart Association (NYHA) functional class II to IV – anemia with an iron deficit defined by Hb < 12.5 g/dl	NT-pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) levels in a group of anemic patients with chronic heart failure (CHF) and chronic renal failure (CRF) receiving intravenous iron therapy.
[23]	Veldhuisen et al	2017	Patients with systolic HF (left ventricular ejection fraction ≤45%)	Placebo	Ferric Carboxymaltose	Infusions of 10 or 20 mL and Subjects will receive ferric carboxymaltose intravenously on Day 0, Week 6, and Week 12	Netherlands	24 weeks	Yes	Patients with Hb ≤14 g/dL	– Iron deficient subjects with stable chronic heart failure (CHF) – (NYHA II-III) on optimal background therapy for CHF – At least 18 years of age and	Effect of IV ferric carboxymaltose on exercise capacity, physical functioning and quality of life in patients with iron deficiency and chronic heart failure.
[24]	Yeo et al	2018	Asian patients with heart failure (HF)	Placebo	Ferric Carboxymaltose	1000mg intravenous Ferric Carboxymaltose	Singapore	12 weeks	Yes	Serum ferritin <300 ng/mL if transferrin saturation is <20%)	– Patients hospitalized for HF Capable of completing the 6MWT. – Screening TSAT <20%, Serum Ferritin <300 ng/mL and Hb≤14 g/dL – At least 21 years of age	Change in 6MWT distance over time

Ref.	Study	Year	Population	Comparison	Iron preparation	Iron dosing strategy	Country	Follow-up (week)	Iron deficiency	Definition of iron deficiency	Inclusion criteria	Primary outcome
[25]	Anker et al. (FAIR-HF)	2009	Patients who had chronic heart failure, left ventricular ejection fraction	Placebo	IV Ferric Carboxymaltose	4 ml weekly then every 4 weeks	Argentina, Czech Republic, Greece, Italy, Norway, Poland, Romania, Russia, Spain, Ukraine, and Germany	24 weeks	Yes	Serum ferritin level < 100 µg per liter when the transferrin saturation was <20%.	– patients who had chronic heart failure of New York Heart Association (NYHA) class II or III – Left ventricular ejection fraction of 40% or less a – hemoglobin level at the screening visit between 95 and 135 g per liter, and iron deficiency.	Patient Global Assessment and NYHA functional class, both at week 24.
[26]	Caravita et al.	2022	Patients with heart failure, reduced left ventricular ejection fraction, anemia	Placebo	IV ferric carboxymaltose	Intravenous ferric carboxymaltose or saline placebo was administered every 3 weeks.	Italy	2 weeks	Yes	Increase in ferritin, transferrin saturation, hepcidin, and by a reduction of soluble transferrin receptor.	– consecutive clinically stable patients with chronic HF that presented a left ventricular ejection fraction ≤45%, – anemia (haemoglobin 9–12 g/dl in women or 9–13 g/dl in men) – iron deficiency (serum ferritin <100 µg/L).	Chemoreflex sensitivity cardiorespiratory sleep study, symptom assessment and cardiopulmonary exercise test
[27]	Charles-Edwards et al. (FERRIC-HF II)	2019	Patients of chronic Heart Failure and Iron Deficiency	Placebo	Iron Isomaltoside	Iron (III) isomaltoside 1000 added to 100 mL of sterile 0.9% saline for infusions.	United Kingdom	2 Weeks	Yes	-	– Age ≥30 years – stable symptomatic chronic HF (New York Heart Association [NYHA] III and left ventricular ejection fraction [LVEF] ≤45%. – Use of optimal HF drugs for ≥4 weeks without dose changes.	The primary end point of PCr t 1/2 at 2 weeks.
[28]	Karla et al. (IRONMAN)	2022	Patients of heart failure with iron deficiency	Usual care	Intravenous ferric derisomaltose	Intravenous ferric derisomaltose doses depend on the bodyweight range	United Kingdom	2·7 years (IQR 1·8–3·6).	Yes	Ferritin level of <100 ng per milliliter or a level of 100 to 300 ng per milliliter with a transferrin saturation of <20%)	– Adults ≥18 years with heart failure – left ventricular ejection fraction of 40% or less. – hemoglobin level greater than 9.0 g per deciliter.	All hospital admissions for heart failure and cardiovascular death
[11]	Mentz et al. (HEART-FID)	2023	Patients of Heart Failure with Iron Deficiency	Placebo	IV Ferric Carboxymaltose	Dosing was weight-based; two doses separated by 7 days.	USA, Canada, NewZealand	12 months	Yes	Iron deficiency (serum ferritin <100 µg/L or transferrin saturation <20%)	– Aged 18 years or older, with new or established symptomatic heart failure, – Evidence of iron deficiency – Left ventricular ejection fraction of 45%.	Recurrent hospital admissions for heart failure and cardiovascular death.
[29]	Martens et al. (IRON-CRT)	2021	Symptomatic HFrEF patients with iron deficiency and a persistently reduced left ventricular ejection fraction <45%)	Standard care	IV Ferric Carboxymaltose	Calculated based on screened weight.	Belgium	3 months	Yes	Defined as a serum ferritin <100 ng/mL or serum ferritin between 100 and 300 ng/mL if transferrin saturation (TSAT) was <20%.	– Aged >_18 years, (ii) had – Stable heart failure at least 4 weeks – Received CRT as part of their treatment plan for HFrEF – Association (NYHA) class >_II – Had iron deficiency	Change in LVEF from baseline to 3-month.
[19]	Marcusohn et al.	2022	Patients With Iron Deficiency Hospitalized due to Acute Heart Failure	Optimal medical therapy	IV Sodium Ferric Gluconate Complex	Patients in the treatment group received 3–5 doses of IV SGFC 125 mg.	Palestine	24 weeks	Yes	Ferritin levels ,100 ng/mL or ferritin 100–300 ng/mL with transferrin saturation ,20%.	– Hemoglobin levels of 8–14 mg/dL on admission. – Ferritin levels ,100 ng/mL or ferritin 100–300 ng/mL with transferrin saturation – N-terminal pro–B-type natriuretic peptide (NT-proBNP) level 300 pg/mL. – Treatment with IV loop diuretics.	Change in distance during a 6-minute walk test (6MWT) from baseline to 12 and 24 weeks after initial assessment.

Table 2. Baseline characteristics, continuous data is reported as mean(SD) for FE/Control; and categorical data is reported as event (Total) for FE/Control.

Study	Nunez et al.	Okonko et al.	Ponikowski et al.	Toblli et al.	Ponikowski et al	Veldhuisen et al.	Yeo et al.	Anker et al. (FAIR-HF)	Caravita et al.	Charles-Edwards et al. (FERRIC-HF II)	Karla et al. (IRONMAN)	Mentz et al. (HEART-FID)	Martens et al. (IRON-CRT)	Marcusohn et al.
Year	2020	2008	2015	2007	2021	2017	2018	2009	2022	2019	2022	2023	2021	2022
Race (FE/Control)		Caucasian 21(88%)	White 149(99%)		White 528 Asian 26 Other 4		Chinese 10 Indian 3 Malay 10 Other 1	White 303(99.7%)		White 17(81%)	White 519 Black 12 Asian 35 Other 3	White 1324 Black 162 Asian 19 Other 27		
		Caucasian 10(91%)	White 150(99%)		White 523 Asian 22 Other 5		Chinese 15 Indian 4 Malay 6 Other 0	White 155(100%)		White 14(74%)	White: 524, Black: 7, Asian: 31, Other: 6	White: 1325, Black: 160, Asian: 21, Other: 27		
NYHA	II , III	II , III	II , III		I, II, III, IV	II , III		II , III	III	III	II, III, IV	II, III, IV	II, III	
N	27/26	24/11	150/151	20/20	558/550	86/86	24/25	304/155	38/20	21/19	569/568	1532/1533	37/38	18/16
Age	71.5(10.2)/ 72.3(9.4)	64(14)/ 62(11)	68.8(9.5)/ 69.5(9.3)	76(7)/ 74(8)	71.2(10.8)/ 70.9(11.1)	63(12)/ 64(11)	61.1(10.8)/ 64(10)	67.8(10.3)/ 67.4(11.1)	71(10)/ 71(10)	70(12)/62(13)	73.33(9.96)/ 73.23(8.92)	68.6(10.9)/ 68.6(11.2)	72(12)/ 73(9)	70.07(9.81)/ 75.67(9.75)
Male	21(27)/ 19(26)	17(24)/ 8(11)	83(150)/ 77(151)		314(558)/ 300(550)	60(86)/ 69(86)	18(24)/ 20(25)	145(304)/ 70(155)	30(38)/ 16(20)	16(21)/13(19)	427(569)/ 410(568)	1026(1532)/ 1002(1533)	26(37)/ 25(38)	12(18)/ 11(16)
BMI (kg/m2)		26(5)/ 28(5)	28.3(4.6)/ 29.1(5.7)	28.7(3.3)/ 29(3.4)	28.1(5.6)/ 28(5.7)	27.5(5)/ 26.9(4.4)28		28(4.8)/ 28.1(5.1)	26(4.6)/ 26.8(5.2)	29(4)/30(7)	28.6(5.9)/ 28.5(5.8)		27(5)/ 27(5)	
NYHA II	24(27)/ 26(26)	13(24)/ 6(11)	80(150)/ 91(151)		255(558)/ 240(550)	61(86)/ 54(86)		53(304)/ 29(155)		9(21)/10(19)	328(569)/ 320(568)	797(1532)/ 820(1532)	22(37)/ 19(38)	
NYHA III	3(27)/ 0(26)	11(24)/ 5(11)	70(150)/ 60(151)		272(558)/ 277(550)	25(86)/ 32(86)		251(304)/ 126(155)			230(569)/ 238(568)	711(1532)/ 692(1532)	15(37)/ 19(38)	
NYHA IV					16(558)/ 22(550)						11(569)/ 10(568)	22(1532)/ 19(1532)		
NT-proBNP (pg/mL)	1932(1451.1)/ 1630(1299.6)		2511(5006)/ 2600(4555)	255.9(124.6)/ 267.5(114.9)	5217.3(3974)/ 5388(4392.7)	1576/ 1469				1261.7(1438.2)/ 507.67(519.83)		1752.4(1842.4)/ 1672.5(1612.9)	1831(2057.6)/ 1525(1107.1)	
BNP (pg/mL)			772(995)/ 770(995)		1195(678.6)/ 1320.7(856.3)	491/ 460			638(798)/ 549(490)					8707.7(7689.8)/ 4166.7(4199)
LVEF	39.5(9)/ 37.3(8.6)	30(7)/ 29(6)	37.1(7.5)/ 36.5(7.3)		32.6(9.6)/ 32.7(10)	33(9)/ 31(8)	38.8(17.5)/ 33.2(14.8)	31.9(5.5)/ 33(6.1)	35(7)/ 35(8)	37(8)/ 37(8)	31.33(8.9)/ 33(8.9)	30.8(7)/ 30.6(7.3)	33(8)/ 34(7)	31.67(28.15)/ 42(24.38)
6-min walk test distance	272(48.5)/ 281(89.41)		288(98)/ 302(97)	192.3(60.9)/ 190.7(56.1)			252.4(122.7)/ 242.6(66.8)	274(105)/ 269(109)		324(79)/ 313(67)		273.9(109.7)/ 274.7(109.4)		216.3(82.78)/ 224.93(96.56)
SBP (mm Hg)	119.3(18.)/ 128(25.9)	120(22)/ 116(18)	125(14)/ 124(13)	139.7(8.2)/ 138.8(8.3)	119.8(15.2)/ 119.7(15.6)			126(15)/ 126(15)		124(16)/ 122(17)	119(19.3)/ 119.33(20.1)		121(15)/ 115(15)	
DBP (mm Hg)		69(9)/ 70(9)	75(8)/ 75(8)	74.4(9.6)/ 73.4(7.5)	72.6(10.3)/ 71.9(9.9)			77(9)/ 76(10)		73(10)/ 71(14)				
Hemoglobin (g/dl)	12.8(1.2)/ 13.6(1.49)	12.6(1.2)/ 12.2(1)	12.37(141)/ 12.42(1.3)	10.3(0.6)/ 10.2(0.5)	12.3(1.6)/ 12·1(1.6)	12.9(1.3)/ 13(1.5)	11.6(1.9)/ 13.1(1.3)	11.9(1.3)/ 11.9(1.4)		130(15)/ 128(20)	12.(1.2)/ 12.1(1.3)	12.6(1.4)/ 12.5(1.4)	13.3(1.2)/ 13.1(1.3)	11.73(1.36)/ 11.36(1.86)
Serum ferritin	85(54.8)/ 61.6(71.3)	62(37)/ 88(62)	57(48.4)/ 57.1(41.6)	73(29.9)/ 70.6(21.4)	83·9(62.2)/ 88.5(68.6)	48/ 53	91.4(80.4)/ 84.1(63.7)	52.5(54.5)/ 60.1(66.5)		34(25.5)/ 59(32.04)	55(41.6)/ 55(40.9)	56(47.3)/ 57.3(51.4)	75.3(52.4)/ 74.3(43.1)	102.33(92.5)/ 114(99.2)
Transferrin saturation	15.6(5.6)/ 15(8.2)	20(8)/ 21(9)	20.2(17.6)/ 18.2(8.1)	0.2(0.01)/ 0.2(0.01)	15.2(8.3)/ 14.2(7.5)	17.3/ 18.1	15.7(10.1)/ 13.9(6.8)	17.7(12.6)/ 16.7(8.4)		21(8)/ 18(10)	15.3(6.7)/ 14.7(6.7)	23.9(11.2)/ 23(10.3)	18.8(6)/ 19.4(7)	12.3(4.3)/ 13.6(5.4)
Ferritin <100 ng/mL			136(150)/ 133(151)		408(558)/ 380(550)									
eGFR <60 mL/min per 1·73 m²					292(558)/ 288(550)							288(801)/ 278(752)		

Study	Nunez et al.	Okonko et al.	Ponikowski et al.	Toblli et al.	Ponikowski et al	Veldhuisen et al.	Yeo et al.	Anker et al. (FAIR-HF)	Caravita et al.	Charles-Edwards et al. (FERRIC-HF II)	Karla et al. (IRONMAN)	Mentz et al. (HEART-FID)	Martens et al. (IRON-CRT)	Marcusohn et al.
Year	2020	2008	2015	2007	2021	2017	2018	2009	2022	2019	2022	2023	2021	2022
eGFR mL/min per 1·73 m²	60.2(16.7)/ 64.1(23.8)		66.4(21.7)/ 63.5(209)					63.8(21.2)/ 64.8(25.3)			57.2(12.2)/ 52.2(22.9)		56(25)/ 51(22)	
Atrial fibrillation	10(27)/ 14(26)		66(150)/ 73(151)		314(558)/ 305(550)	35(86)/ 41(86)		94(304)/ 44(155)	8(38)/ 7(20)	6(21)/ 4(19)	284(569)/ 250(568)	223(676)/ 240(664)		10(18)/ 5(16)
ACS			90(150)/ 90(151)		229(558)/ 213(550)	58(86)/ 55(86)	12(24)/ 13(25)		27(38)/ 13(20)		292(569)/ 285(568)			
Hypertension	22(27)/ 16(26)	12(24)/ 5(11)	130(151)/ 130(151)	2(20)/ 3(20)	468(558)/ 471(550)	62(86)/ 56(86)	21(24)/ 18(25)	243(304)/ 128(155)		13(21)/ 13(19)	297(569)/ 315(568)		32(37)/ 37(38)	17(18)/ 15(16)
Diabetes	15(27)/ 14(26)	8(24)/ 4(11)	38(150)/ 45(151)		227(558)/ 243(550)	26(86)/ 32(86)	15(24)/ 15(25)	93(304)/ 37(155)		10(21)/ 10(19)	252(569)/ 269(568)	246(694)/ 264(691)	17(37)/ 19(38)	11(18)/ 12(16)
CKD	8(27)/ 7(26)				222(558)/ 227(550)							178(424)/ 191(400)		12(18)/ 12(16)
Anemia	10(27)/ 6(26)				292(558)/ 312(550)					11(21)/ 9(19)		306(858)/ 339(900)		
Dyslipidaemia	18(27)/ 16(26)	7(24)/ 5(11)	98(150)/ 98(151)		300(558)/ 292(550)		20(24)/ 20(25)	144(304)/ 70(155)		7(21)/ 7(19)				16(18)/ 14(16)
ICD					67(558)/ 64(550)	25(86)/ 33(86)			23(38)/ 16(20)		91(569)/ 72(568)	495(1532)/ 484(1532)		
CRT					33(558)/ 30(550)	11(86)/ 11(86)			12(38)/ 6(20)		125(569)/ 118(568)	230(1532)/ 232(1532)	23(37)/ 19(38)	
ACE inhibitor/ ARB						81(86)/ 77(86)		281(304)/ 141(155)		16(21)/ 17(19)		901(1532)/ 923(1530)	34(37)/ 33(38)	
Sacubitril–valsartan	10(27)/ 8(26)										130(569)/ 110(568)	461(1532)/ 448(1532)		
ACE inhibitor	7(27)/ 6(26)	18(24)/ 8(11)	116(150)/ 118(151)	19(20)/ 20(20)	293(558)/ 283(550)		11(24)/ 8(25)		21(38)/ 10(20)		271(569)/ 281(568)			
ARB	5(27)/ 4(26)	5(24)/ 2(11)	34(150)/ 37(151)	5(20)/ 4(20)	97(558)/ 100(550)		8(24)/ 5(25)		12(38)/ 5(20)		90(569)/ 113(568)			
Beta-blocker	25(27)/ 21(26)	20(24)/ 11(11)	133(150)/ 139(151)	20(20)/ 20(20)	453(558)/ 461(550)	84(86)/ 85(86)	24(24)/ 20(25)	262(304)/ 129(155)	34(38)/ 20(20)	18(21)/ 16(19)	500(569)/ 509(568)	1415(1532)/ 1418(1532)	37(37)/ 37(38)	
antimineralocorticoid		11(24)/ 6(11)			376(558)/ 352(550)	58(86)/ 62(86)	7(24)/ 10(25)		20(38)/ 11(20)		325(569)/ 307(568)	858(1532)/ 847(1532)	30(37)/ 29(38)	
Digoxin	1(27)/ 4(26)	6(24)/ 2(11)	29(150)/ 40(151)	13(20)/ 12(20)	83(558)/ 101(550)			46(304)/ 25(155)		6(21)/ 4(19)	70(569)/ 65(568)			
SGLT2 inhibitor											15(569)/ 14(568)	118(1532)/ 111(1532)		
Loop diuretic	25(27)/ 24(26)		132(150)/ 139(151)		483(558)/ 465(550)		21(24)/ 23(25)		34(38)/ 15(20)	14(21)/ 12(19)	458(569)/ 468(568)		20(37)/ 21(38)	
Insulin			18(150)/ 20(151)					27(304)/ 9(155)			80(569)/ 101(568)			
Other Glucose loweing medication								49(304)/ 22(155)	18(38)/ 9(20)		223(569)/ 239(568)			

Abbreviations: ACE-angiotensin-converting enzyme; ACS-acute coronary syndrome; CKD-chronic kidney disease; CRT-cardiac resynchronization therapy; DBP-diastolic blood pressure ; ICD-implantable cardioverter-defibrillator; LVEF-left ventricle ejection fraction; SBP-systolic blood pressure; SGLT2-sodium-glucose transport protein 2.
reported as median

Table 3. GRADE evidence profile.

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsis-tency	Indirect-ness	Impre-cision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo or Standard Care	With IV Iron		Risk with Placebo or Standard Care	Risk difference with IV Iron
Cardiovascular Mortality											
6145 (6 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	509/2994 (17.0%)	462/3151 (14.7%)	***RR 0.90*** *(0.80 to 1.01)*	170 per 1,000	***17 fewer per 1,000*** *(from 34 fewer to 2 more)*
All cause mortality											
5281 (8 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	376/2557 (14.7%)	336/2724 (12.3%)	***RR 0.88*** *(0.78 to 1.01)*	147 per 1,000	***18 fewer per 1,000*** *(from 32 fewer to 1 more)*
Hospital admission for heart failure (first event)											
2813 (5 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	451/1326 (34.0%)	393/1487 (26.4%)	***RR 0.85*** *(0.77 to 0.95)*	340 per 1,000	***51 fewer per 1,000*** *(from 78 fewer to 17 fewer)*
Hospital admission for heart failure (total events)											
5978 (7 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	877/2912 (30.1%)	707/3066 (23.1%)	***RR 0.80*** *(0.73 to 0.86)*	301 per 1,000	***60 fewer per 1,000*** *(from 81 fewer to 42 fewer)*
CVD death and hospital admission for heart failure (number of events) rater per 100 patient year											
2704 (3 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	799/1273 (62.8%)	649/1431 (45.4%)	***RR 0.79*** *(0.74 to 0.85)*	628 per 1,000	***132 fewer per 1,000*** *(from 163 fewer to 94 fewer)*
Hospital admission for heart failure (number of events) rater per 100 patient year											
2704 (3 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	617/1273 (48.5%)	478/1431 (33.4%)	***RR 0.76*** *(0.70 to 0.83)*	485 per 1,000	***116 fewer per 1,000*** *(from 145 fewer to 82 fewer)*
6-min. walk distance at follow up											
4820 (8 RCTs)	not serious	very serious[a]	not serious	not serious	none	⊕⊕◯◯ Low	2341	2479	-	*The mean 6-min. walk distance at follow up was **0***	*MD **23.56 higher** (21.42 higher to 25.71 higher)*
Change in 6-min. walk distance from baseline											
3865 (4 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	1858	2007	-	*The mean change in 6-min. walk distance from baseline was **0***	*MD **2.34 higher** (0.69 higher to 4 higher)*
Any adverse effect											
343 (2 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ Low	116/170 (68.2%)	124/173 (71.7%)	***RR 1.06*** *(0.94 to 1.20)*	682 per 1,000	***41 more per 1,000*** *(from 41 fewer to 136 more)*
Any seriious adverse event											
2748 (7 RCTs)	not serious	not serious	not serious	not serious	none	⊕⊕⊕⊕ High	771/1363 (56.6%)	707/1385 (51.0%)	***RR 0.91*** *(0.85 to 0.97)*	566 per 1,000	***51 fewer per 1,000*** *(from 85 fewer to 17 fewer)*
Any adverse event leading to withdrawal											
344 (2 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ Low	19/171 (11.1%)	14/173 (8.1%)	***RR 0.74*** *(0.38 to 1.42)*	111 per 1,000	***29 fewer per 1,000*** *(from 69 fewer to 47 more)*
Abnormal lab test, vital sign or physical finding											
763 (2 RCTs)	not serious	not serious	not serious	very serious[b]	none	⊕⊕◯◯ Low	2/306 (0.7%)	1/457 (0.2%)	***RR 0.50*** *(0.05 to 5.46)*	7 per 1,000	***3 fewer per 1,000*** *(from 6 fewer to 29 more)*

CI: confidence interval; MD: mean difference; RR: risk ratio
Explanations:
a. I square test > 90%
b. Low number of events < 300 events.

Primary Outcomes

Overall analysis

A. Cardiovascular mortality

There was an insignificant risk ratio between the IV iron group and control (RR = 0.90, 95% CI 0.80 to 1.01; p = 0.07, n = 7), with no heterogeneity (I^2 = 0%, p = 0.84) **(Figure 3a and Figure 4).**

B. All-cause mortality

There was an insignificant risk ratio between the IV iron group and control (RR = 0.88, 95% CI 0.78 to 1.01; p = 0.06, n = 6), with no heterogeneity (I^2 = 0%, p = 0.47) **(Figure 3b and Figure 4).**

C. Hospital admission for heart failure (first event)

There was a significant risk ratio between the IV iron group and control (RR = 0.92, 95% CI 0.84 to 1.00; p = 0.04, n = 3), with moderate heterogeneity (I^2 = 44%, p = 0.12) **(Figure 3c and Figure 4)**. Heterogeneity reduced when excluding Mentz et al., and results remained significant in favor of IV iron (RR = 0.85, 95% CI 0.77 to 0.95; p = 0.004), with moderate heterogeneity (I^2 = 29%, p = 0.23).

D. Hospital admission for heart failure (total event)

IV iron group had lower hospital admissions than the control group (RR = 0.78, 95% CI 0.72 to 0.85; p < 0.00001, n = 2), with moderate heterogeneity (I^2 = 55%, p = 0.03). Heterogeneity was reduced by excluding Ponikowiski et al., and the results remained significant in favor of the IV iron group (RR = 0.80, 95% CI 0.73 to 0.86; p < 0.0001), with moderate heterogeneity (I^2 = 30%, p = 0.20) **(Figure 3d and Figure 4).**

E. Cardiovascular death and hospital admission for heart failure (number of events, rate per 100 patients in a year)

IV iron group was favored over the control group (RR = 0.81, 95% CI 0.76 to 0.87; p < 0.00001, n = 6), with high heterogeneity (I^2 = 63%, p = 0.04). Heterogeneity was reduced by excluding Mentz et al., and the results remained significant in favor of the IV iron group (RR = 0.79, 95% CI 0.74 to 0.85; p < 0.00001, n = 5), with no heterogeneity (I^2 = 0%, p = 0.58) **(Figure 3e and Figure 4).**

F. Hospital admission for heart failure (number of events, rate per 100 patients in a year)

IV iron group was favored over the control group (RR = 0.75, 95% CI 0.68 to 0.81; p < 0.00001, n = 5), with moderate heterogeneity (I^2 = 38%, p = 0.19). Heterogeneity was reduced by excluding Ponikowiski et al., and the results remained significant in favor of the IV iron group (RR = 0.76, 95% CI 0.70 to 0.83; p < 0.00001, n = 4), with no heterogeneity (I^2 = 0%, p = 0.46) **(Figure 3f and Figure 4).**

Subgroup analysis of main outcomes

Subgroup analysis according to chronic or acute heart failure

In cardiovascular mortality, neither acute or chronic conditions showed significant differences with no heterogeneity observed (RR = 0.89, 95% CI 0.78 to 1.01; p = 0.06, n = 1), and (RR = 0.97, 95% CI 0.73 to 1.30; p = 0.85, n = 5), respectively (**Figure S1**).

In all-cause mortality, groups of chronic conditions hovered around significance, while overall results were insignificant (RR = 0.88, 95% CI 0.77 to 1.00; p = 0.05, n = 6), with no heterogeneity (I^2 = 0%, p = 0.55) (**Figure S2**).

For hospital admission for heart failure (first event), the chronic heart failure group showed only significant preferences toward iron after removing HEART-FID due to heterogeneity (RR = 0.85, 95% CI 0.73 to 0.98; p = 0.03, n = 4), heterogeneity (I^2 = 56%, p = 0.1). (**Figure S3**).

In terms of total hospital admission for heart failure, in both acute and chronic conditions, iron was effective in reducing the total events (RR = 0.80, 95% CI 0.72 to 0.89; p < 0.0001, n = 5), heterogeneity (I^2 = 63%, p = 0.02), reduced by removing Ponikowski 2015 (I^2 = 32%, p = 0.21), and (RR = 0.73, 95% CI 0.64 to 0.83; p < 0.001), respectively (**Figure S4**).

Similar results were obtained for both drugs for CVD death and hospital admission for heart failure (number of events) rater per 100 patient-year [chronic heart failure (RR = 0.84, 95% CI 0.77 to 0.92; p < 0.0001, n = 3), heterogeneity (I^2 = 75%, p = 0.02), reduced by removing HEART-FID (I^2 = 0%, p = 0.44); acute heart failure (RR = 0.78, 95% CI 0.70 to 0.86; p < 0.0001, n = 1)], and hospital admission for heart failure (number of events)

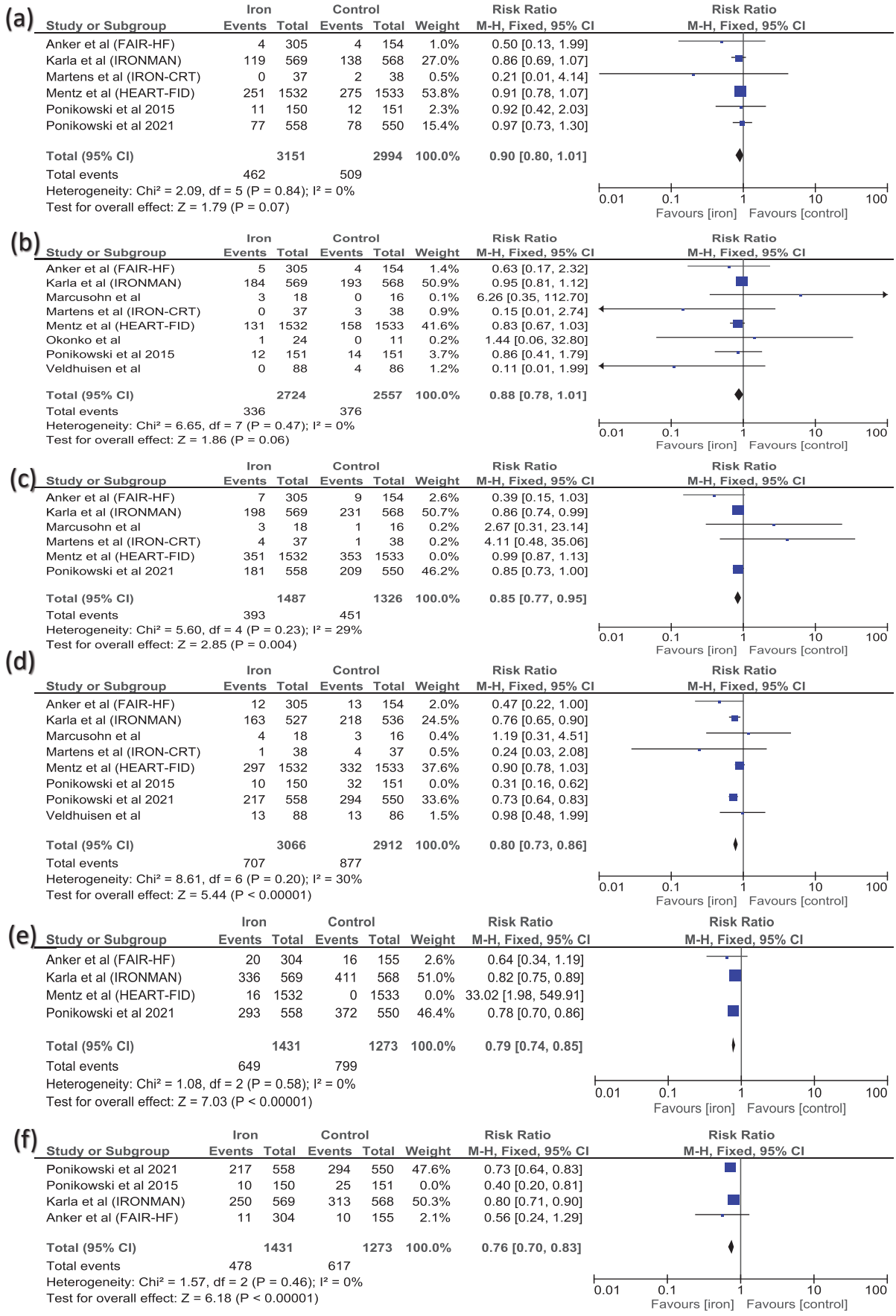

Figure 3. Forest plots examining the cardiovascular outcomes of intravenous iron infusion in patients with heart failure: (a) cardiovascular mortality; (b) all-cause mortality; (c) hospital admission for heart failure (first event); (d) hospital admission for heart failure (total event); (e) cardiovascular death and hospital admission for heart failure (number of events, rate per 100 patients in a year); (f) hospital admission for heart failure (number of events, rate per 100 patients in a year).

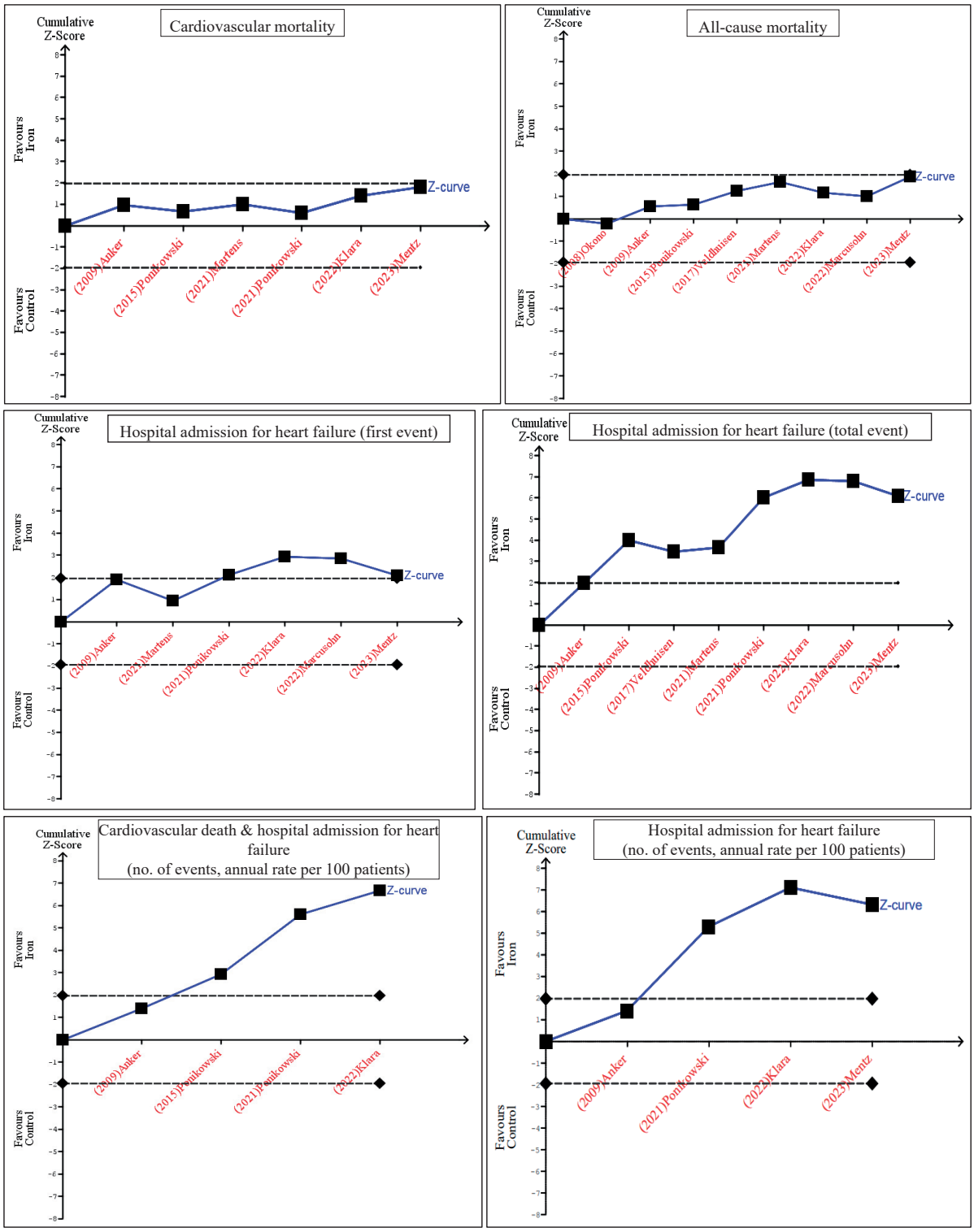

Figure 4. Sequential analysis for the main outcomes, cardiovascular mortality; all-cause mortality; hospital admission for heart failure (first event); hospital admission for heart failure (total event); cardiovascular death and hospital admission for heart failure (number of events, rate per 100 patients in a year); hospital admission for heart failure (number of events, rate per 100 patients in a year).

rater per 100 patient-year [chronic heart failure (RR = 0.76, 95% CI 0.68 to 0.86; p < 0.0001, n = 3), heterogeneity (I^2 = 54%, p = 0.22), reduced by removing Ponikowski 2015 (I^2 = 0%, p = 0.41); acute heart failure (RR = 0.73, 95% CI 0.64 to 0.83; p < 0.0001), n = 2] (**Figure S5 and Figure S6**).

Subgroup analysis according to the iron preparation

In cardiovascular mortality, neither Ferric carboxymaltose nor ferric derisomaltose showed significant preferences with no heterogeneity observed (RR = 0.92, 95% CI 0.80 to 1.05; p = 0.20, n = 5), and (RR = 0.86, 95% CI 0.69 to 1.07; p = 0.17, n = 1), respectively (**Figure S7**).

In all-cause mortality, despite overall results being insignificant, only the ferric carboxymaltose group significantly favored iron over the control (RR = 0.80, 95% CI 0.65 to 0.98; p = 0.03, n = 5), with no heterogeneity (I^2 = 0%, p = 0.50). Ferric derisomaltose and sodium ferric gluconate complex results were insignificant (**Figure S8**).

For hospital admission for heart failure (first event), ferric carboxymaltose (only after removing HEART-FID due to heterogeneity) and ferric derisomaltose showed a significant reduction in hospital admissions (RR = 0.84, 95% CI 0.72 to 0.99; p = 0.03, n = 4), heterogeneity (I^2 = 56%, p = 0.1, and were not reduced after removing HEART-FID, neither influencing the results), and (RR = 0.86, 95% CI 0.74 to 0.99; p = 0.04, n = 3). respectively (**Figure S9**).

In terms of total hospital admission for heart failure, ferric carboxymaltose and ferric derisomaltose results were effective in reducing the total events (RR = 0.78, 95% CI 0.71 to 0.86; p < 0.001, n = 6), heterogeneity (I^2 = 67%, p = 0.01), reduced by removing Ponikowski 2015 (I^2 = 50%, p = 0.09), and (RR = 0.76, 95% CI 0.65 to 0.90; p = 0.001, n = 5), respectively (**Figure S10**).

Similar results were obtained for both drugs for CVD death and hospital admission for heart failure (number of events) rater per 100 patient-year [ferric carboxymaltose (RR = 0.81, 95% CI 0.73 to 0.89; p < 0.001, n = 3), heterogeneity (I^2 = 75%, p = 0.02), reduced by removing HEART-FID (I^2 = 0%, p = 0.54); ferric derisomaltose (RR = 0.82, 95% CI 0.75 to 0.89; p < 0.0001), n = 1], and hospital admission for heart failure (number of events) rater per 100 patient-year [ferric carboxymaltose (RR = 0.73, 95% CI 0.61 to 0.79; p < 0.0001), n = 3, heterogeneity (I^2 = 35%, p = 0.22), reduced by removing Ponikowski 2015 (I^2 = 0%, p = 0.54); ferric derisomaltose (RR = 0.80, 95% CI 0.71 to 0.90; p < 0.0001), n = 2] (**Figure S11 and Figure S12**).

Adverse effects

Overall analysis

A. Cardiac disorder

IV iron group had fewer cardiac disorders than the control group (RR = 0.81, 95% CI 0.76 to 0.87; p < 0.00001, n = 7), with high heterogeneity (I^2 = 66%, p = 0.01). Heterogeneity was reduced by excluding Anker et al., and the results remained significant in favor of the IV iron group (RR = 0.84, 95% CI 0.78 to 0.90; p < 0.00001, n = 6), with no heterogeneity (I^2 = 0%, p = 0.65) (**Figure 5a)**.

B. Gastrointestinal disorder

There were no significant results between the IV iron and control groups (RR = 0.94, 95% CI 0.68 to 1.29; p = 0.69, n = 6), with no high heterogeneity (I^2 = 0%, p = 0.52) **(Figure 5b**).

C. Injection site condition

There were no significant results between the IV iron and control groups (RR = 1.12, 95% CI 0.79 to 1.59; p = 0.56, n = 3), with no high heterogeneity (I^2 = 0%, p = 0.59) (**Figure 5c)**.

D. Infection

There were no significant results between the IV iron and control groups (RR = 0.88, 95% CI 0.73 to 1.07; p = 0.20, n = 2), with no high heterogeneity (I^2 = 0%, p = 0.49) (**Figure 5d)**.

E. Nervous system, disorder

There were no significant results between the IV iron and control groups (RR = 1.16, 95% CI 0.81 to 1.66; p = 0.41, n = 6), with no high heterogeneity (I^2 = 0%, p = 0.86) (**Figure 5e)**.

F. Respiratory, thoracic, or mediastinal disorder

There were no significant results between the IV iron and control groups (RR = 0.76, 95% CI 0.55 to 1.05; p = 0.10, n = 5), with moderate heterogeneity (I^2 = 40%, p = 0.15). Heterogeneity was reduced by excluding Okonko et al., and the results remained insignificant (RR = 0.81, 95% CI 0.58 to 1.12; p = 0.21, n = 4), with low heterogeneity (I^2 = 20%, p = 0.29) (**Figure 5f)**.

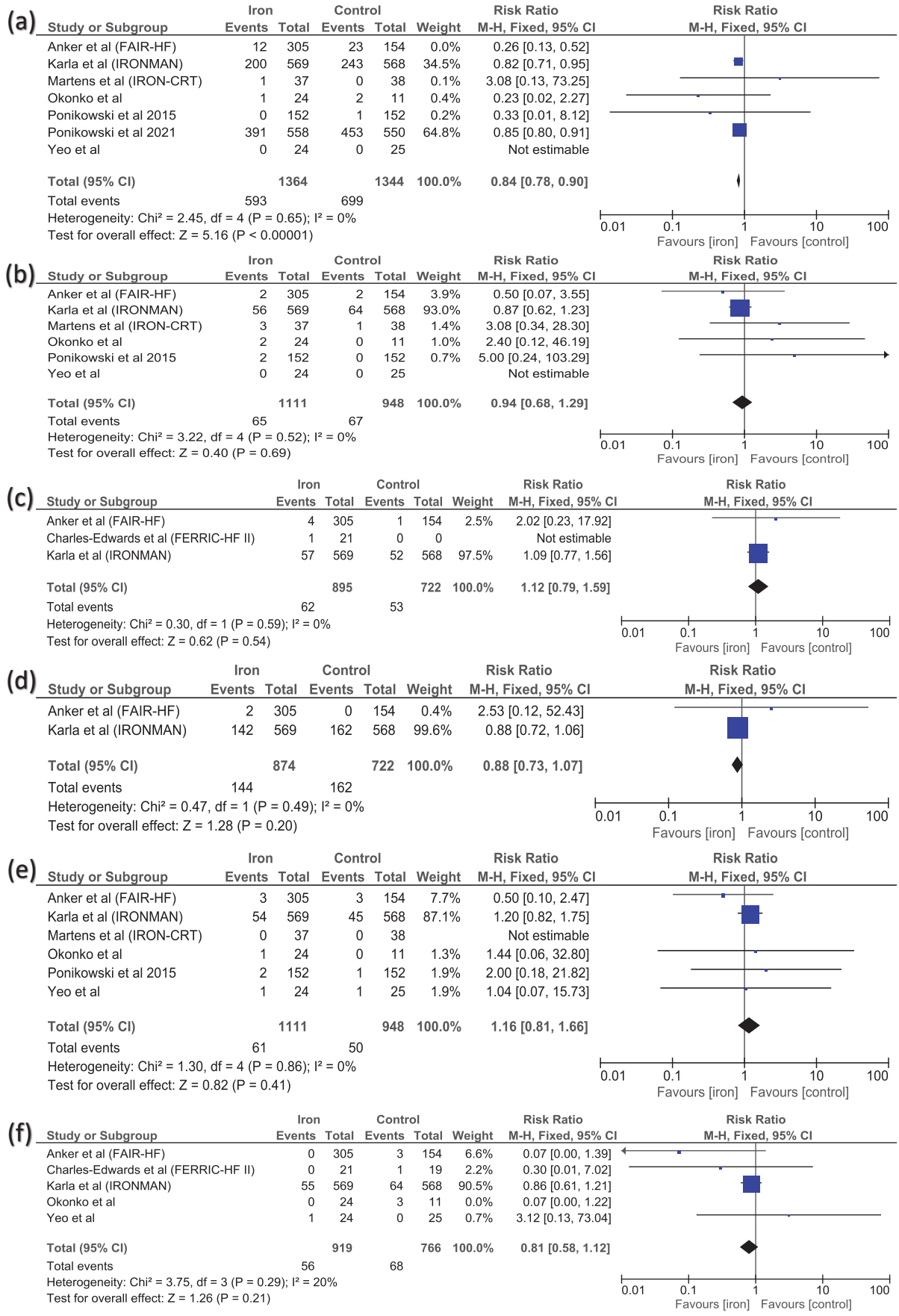

Figure 5. Forest plots examining the adverse effects of intravenous iron infusion in patients with heart failure: (a) cardiac disorder; (b) gastrointestinal disorder; (c) Injection site condition; (d) Infection; (e) nervous system disorder; (f) respiratory, thoracic, or mediastinal disorder.

G. Vascular disorder

There were no significant results between the IV iron and control groups (RR = 0.83, 95% CI 0.55 to 1.27; p = 0.40, n = 4), with no high heterogeneity (I^2 = 0%, p = 0.86) (**Figure 6a**).

H. Any adverse effect

There were no significant results between the IV iron and control groups (RR = 1.09, 95% CI 0.96 to 1.24; p = 0.17, n = 3), with low heterogeneity (I^2 = 25%, p = 0.26). Heterogeneity was reduced by excluding Martens et al. insignificant (RR = 1.06, 95% CI 0.94 to 1.20; p = 0.35, n = 2), with low heterogeneity (I^2 = 0%, p = 0.38) (**Figure 6b**).

I. Any serious adverse event

There were no significant results between the IV iron and control groups (RR = 0.98, 95% CI 0.93 to 1.03; p = 0.37, n = 8), with moderate heterogeneity (I^2 = 54%, p = 0.06). Heterogeneity was reduced by excluding Mentz et al., and the results were altered in favor of IV iron group (RR = 0.91, 95% CI 0.85 to 0.97; p = 0.003, n = 7), with no heterogeneity (I^2 = 0%, p = 0.66) **(Figure 6c)**.

J. Any adverse event leading to withdrawal

There were no significant results between the IV iron and control groups (RR = 0.74, 95% CI 0.38 to 1.42; p = 0.36, n = 2), and heterogeneity analysis was not applicable (**Figure 6d)**.

K. Abnormal lab test, vital signs, or physical finding

There were no significant results between the IV iron and control groups (RR = 0.50, 95% CI 0.05 to 5.46; p = 0.57, n = 2), and heterogeneity analysis was not applicable (**Figure 6e)**.

Subgroup analysis for the adverse effects

Subgroup analysis according to chronic or acute heart failure

Concerning the adverse events, iron reduced cardiac disorders in chronic and acute heart failure despite the lack of studies on the latter (**Figure S13**). Also, iron effectively reduced the serious adverse events in acute heart failure (RR = 0.87, 95% CI 0.77 to 0.99; p = 0.03, n = 6). In the case of chronic heart failure, the results became significant only after removing HEART-FID due to heterogeneity (I^2 = 52%, p = 0.08) that had the highest number of events (RR = 0.93% CI 0.87 to 1.00; p = 0.04, n = 5) without heterogeneity (I^2 = 0%, p = 0.72) (**Figure S14**).

Moreover, regarding respiratory, thoracic or mediastinum disorder, we observed a moderate heterogeneity in the chronic heart failure group (I^2 = 50%, p = 0.11) which was resolved by removing the IRONMAN study and resulted in altering both the overall and chronic heart failure results (RR = 0.23, 95% CI 0.07 to 0.75; p = 0.01, n = 5), low heterogeneity (I^2 = 32%, p = 0.27), and (RR = 0.10, 95% CI 0.02 to 0.54; p = 0.007, n = 4), without heterogeneity (I^2 = 0%, p = 0.75). These results may highlight the importance of iron injections in reducing the serious adverse effects of chronic and acute cases and those related to respiratory, thoracic or mediastinum disorders in chronic cases (**Figure S15**).

No significant differences were observed in acute or chronic conditions in gastrointestinal, nervous system, or vascular disorders (**Figures S16, S17, S18**). It was not possible to subgroup these outcomes: injection site condition, infection, any adverse effect, any adverse event leading to withdrawal, abnormal lab tests, and vital signs or physical findings.

Subgroup analysis according to the iron preparation

Concerning the adverse events, both ferric carboxymaltose and ferric derisomaltose showed a beneficial effect in reducing the cardiac disorder (RR = 0.81, 95% CI 0.76 to 0.87; p < 0.0001, n = 4), and (RR = 0.82, 95% CI 0.71 to 0.95; p = 0.009, n = 1), respectively. Heterogeneity was resolved in the ferric carboxymaltose group by removing FAIR-HF without altering the results. Iron sucrose did not show any significance regarding cardiac disorders; however, it included only one study with an overall small sample size (**Figure S19**).

Moreover, in terms of the presence of any serious adverse effect, despite the insignificant results overall, that was altered when we removed HEART-FID, which resulted in making only ferric carboxymaltose (compared with derisomaltose, iron isomaltoside, and iron sucrose) ferric shows significant reduction (RR = 0.86, 95% CI 0.77 to 0.97; p = 0.01, n = 5) with no heterogeneity. Hence, overall results also became significant (RR = 0.91, 95% CI 0.85 to 0.97; p = 0.009, n = 8) (**Figure S20**).

All formulation results were comparable, and they did not significantly influence gastrointestinal disorder, injection site condition, infection, nervous system disorder, respiratory, thoracic or mediastinum disorder, vascular disorder, any adverse effect, any adverse event leading to withdrawal and abnormal lab test, vital sign or physical finding (**Figures S20–S29**).

Discussion

The current body of evidence shows that IV ferric carboxymaltose treatment reduces the risk of hospital admission for the first and total events of HF worsening. Moreover, it is associated with a lower risk of the combination of cardiovascular death and HF hospitalization (number of events,

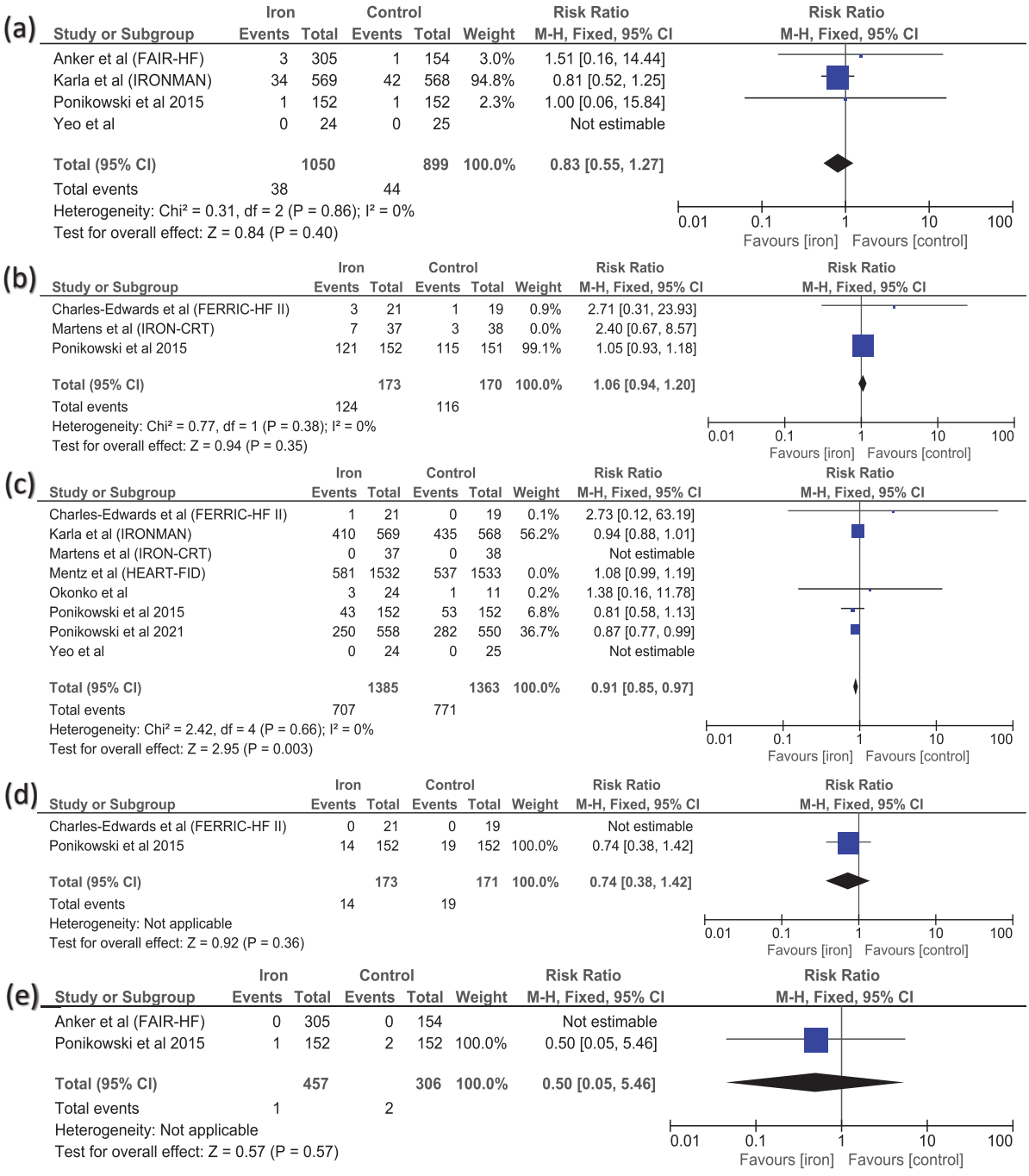

Figure 6. Forest plots examining the adverse effects of intravenous iron infusion in patients with heart failure: (a) vascular disorder; (b) any adverse effect; (c) any serious adverse event; (d) any adverse event leading to withdrawal; (e) abnormal lab tests, vital signs, or physical finding.

rate per 100 patients in a year). However, ferric carboxymaltose does not affect all-cause mortality or cardiovascular mortality. Regarding safety, patients treated with iron therapy experienced fewer cardiac adverse effects than controls. At the same time, they displayed no additional risks of other adverse effects. Our findings confirmed what was previously shown by systematic reviews and meta-analyses, which reported the effectiveness of IV iron supplementation in reducing hospitalization and the combined endpoint of death and hospitalization for decompensated HF [30–32].

Events of acute decompensation are the primary cause of hospital admission for heart failure. According to its mechanism, HF decompensation represents the situation in which neurohormonal signaling, preload, afterload, and intrinsic inotropy are all out of balance, and compensated HF has reached this point [33]. Ventricular filling pressure elevation, venous and arterial congestion, vasoconstriction, and inotropy depression could result from this. Inotropy depression presents clinically as acute symptoms and congestion indicators that necessitate immediate, typically IV, therapy [33]. It has been demonstrated that iron deficiency, whether absolute or functional, can enhance the processes leading to decompensated heart failure by aggravating cardiac congestion, supporting unfavorable cardiac remodeling, and reducing myocardial inotropy. Thus, greater sensitivity to sympathetic stimulation has been observed in iron-deficient mice with cardiac hypertrophy [34]. This may favor peripheral vasoconstriction, a major element in the pathogenesis of HF decompensation by worsening central (i.e., cardiopulmonary) congestion [33].

Iron deficiency may weaken the heart's defenses against oxidative stress because iron is a co-factor for anti-oxidative enzymes. This phenomenon has been linked to the cardiac remodeling process during heart failure [35]. Cardiac remodeling is a deleterious process in HF that leads to cardiac dysfunction with subsequent symptoms of exacerbation [36]. In line with this, experimental evidence has shown that myocardial iron deficiency aggravates acute myocardial ischemia as well as post-ischemic remodeling, which worsens the clinical outcomes of myocardial infarction-associated HF [37]. Moreover, iron deficiency impairs the contractility and relaxation of human cardiomyocytes by downregulating RyR2 channels and suppressing SERCA pump activity [38, 39]. This would then change the inotropy, which would aggravate systolic dysfunction and increase the risk of heart failure decompensation. Conversely, rodents supplemented with IV ferric carboxymaltose had normal Ca2+ signaling again [38]. Therefore, we can assume that iron replacement therapy can reverse the harmful effects of systemic iron deficiency and myocardial iron deficiency on cardiac function in the context of HF, inducing disease control and lesser susceptibility to acute symptomatic events that require hospitalization.

Notably, the latest months have seen progress in research on the impact of IV supplementation in heart failure, which warrants discussion. Further analysis of data from the IRONMAN trial [28] suggested that patients with anemia or with low transferrin saturation (even with adequate ferritin) benefit the most from intravenous iron supplementation [40]. Improved response in patients with low transferrin saturation was also highlighted in a recent meta-analysis by Martens et al. [41]. Furthermore, IRONMAN investigators showed data that indicate a general increase in resilience due to iron supplementation, with effect seen in hospitalizations for both cardiac and non-cardiovascular indications [42]. It is also noteworthy that further evidence for the beneficial influence of intravenous iron in patients with heart failure and preserved ejection fraction emerged from the FAIR-HFpEF trial, which demonstrated a benefit in 6-minute walking test distance [43]. The interplay between ejection fraction and the capacity to utilize and store iron appears as an interesting research topic.

Notably, the combined outcome of cardiovascular mortality and hospitalizations was decreased in the IV iron group, likely due to the reduced odds of HF hospitalization. Nevertheless, iron therapy had no effects on cardiovascular or all-cause mortality. Notably, both AFFIRM-AHF and HEART FID trials showed that supplementation with IV iron does not impact the risk of cardiovascular death. The positive effects of iron therapy in reducing mortality were noted in the IRONMAN study. All of these three studies were conducted during the COVID-19 pandemic, which could have a major influence on the effect of treatment, as the authors disclosed it. Especially in the context of COVID-19, HF population has witnessed a substantial reduction in hospitalizations and an increase in in-hospital mortality [44]. Moreover, in the HEART FID trial, iron

supplementation did not benefit in reducing cardiovascular hospitalizations. Here too, the authors reported possible interference of the COVID-19 pandemic with the treatment outcomes. Further studies outside of COVID-19 are needed to confirm the previous findings [45, 46].

Ferric carboxymaltose demonstrated good tolerability in clinical trials involving patients with iron deficiency. Most adverse events associated with its use were mild to moderate in severity. Commonly reported side effects included headache, dizziness, nausea, abdominal pain, constipation, diarrhea, rash, and injection-site reactions [47]. According to our analysis, we affirm that FC has a good safety profile in HF patients who are iron deficient as it did not increase the risk for any particular side effects relatively. It reduces the risk for cardiovascular side effects. Moreover, we observed that iron injections may reduce any adverse severe event for acute and chronic conditions, and respiratory, thoracic, or mediastinal disorders for chronic conditions mainly. This encourages further investigation of IV ferric carboxymaltose in large-scale studies.

Our study aligens with the newly published meta-analyses, Mhanna et al. conducted a systematic review and meta-analysis analyzing data from 14 RCTs involving 6,614 patients. The study demonstrated that IV iron therapy significantly improved quality of life and the 6-minute walk test compared to standard care, although it did not significantly affect left ventricular ejection fraction. [48] Awad et al. data from 18 RCTs found significant improvements in quality of life, as indicated by Kansas City Cardiomyopathy Questionnaire (KCCQ) scores, and enhanced clinical outcomes, including increased serum ferritin and hemoglobin levels. While all-cause hospitalizations and heart failure-related deaths showed no significant difference, IV iron therapy reduced hospitalizations due to heart failure. [49] Sephien et al. found that IV iron therapy was associated with a significant improvement in quality of life and a notable reduction in first heart failure hospitalizations. However, there was no significant change in all-cause mortality [50].

Implications for future research and clinical practice

The transition from inpatient to outpatient care is a vulnerable period for HF patients, particularly the elderly and those with comorbidities [51]. Additionally, HF hospitalization is associated with an elevated risk of mortality [52]. From an economic standpoint, HF hospitalizations are considered costly, with mean HF-specific inpatient costs in the USA ranging from $10,737 to $17,830 per hospitalization [53].

While recent HF treatments have demonstrated mortality reduction benefits, their impact on hospitalization rates remains neutral [51]. Preventing iron deficiency through iron supplementation can mitigate the risk of HF-related hospitalizations. Notably, IV iron therapy is safe and effective for HF patients, irrespective of anemia. This is because iron deficiency in HF patients can be functional, selectively affecting the myocardium—a condition known as myocardial iron deficiency, which is challenging to diagnose. Consequently, even patients with normal iron levels may benefit from iron therapy.

Therefore, it may become an integral part of routine treatment strategies aimed at preventing decompensation events. However, the promising benefits of IV iron supplementation in patients with HF must be carefully weighed against the potential safety concerns associated with iron overload [54]. IV iron administration introduces substantial amounts of non-transferrin-bound iron, bypassing hepatic regulatory mechanisms, which can lead to iron overload. Most published studies have utilized IV iron sucrose (with a maximum dose of 200 mg per session) or ferric carboxymaltose (with a maximum dose of 1000 mg per week) [55]. Due to gut wall edema, oral iron preparations, typically containing Fe^{2} , have been associated with poor absorption, a high incidence of side effects (affecting up to 40% of patients), and the necessity for up to six months of intake to restore iron stores [55].

On the other hand, unlike the IV form, oral iron absorption is tightly regulated by the effects of hepcidin; thereby, it can rarely lead to iron excess [54]. Oral iron can improve cardiac function, as measured by changes in left ventricular ejection fraction, among HF patients with iron deficiency, according to a recent meta-analysis of four RCTs (n = 582 patients); exercise capacity did not significantly increase [56]. Oral iron supplementation is more practical than IV ferric carboxymaltose due to higher availability and cheaper costs, making the former option worthy of greater inves-

tigation [24]. This points to the need for further research comparing the effects of IV and oral iron on HF-related outcomes.

Notably, the European Cardiology Society heart failure guidelines (2023 update; Recommendation Table 5) indicate that IV should be used to reduce the risk of hospitalization and increase quality of life in patients with iron deficiency and symptomatic heart failure with at least mild reduction of ejection fraction [57]. It is supposed that further extension of this recommendation might follow to include patients with preserved ejection fraction or additional comments on symptoms or the optimal way of diagnosing iron deficiency.

Strengths and limitations

This systematic review and meta-analysis represent the most updated study assessing the safety and efficacy profile of IV ferric carboxymaltose among heart failure patients. Similar work was previously conducted by Zhou et al. in 2019 [32] and Osman et al. in 2021 [31]. However, significant studies have been published since then, such as IRONMAN, HEART-FID, and AFFIRM-AHF, phase 3 RCTs. More recently, Reinhold et al. in 2023 [30], explored the effects of IV iron replacement therapy on cardiovascular outcomes in HF patients. Notably, their focus was solely on efficacy outcomes, lacking examination of safety-related outcomes, which are highly interesting. Our study incorporated updated data from 14 RCTs, involving 6,626 patients, some of which were large-scale, multicenter, double-blind studies.

Concerning the limitations, firstly, not all included studies maintained optimal methodological quality, with some being open-label or single-blind and/or having few participants. Secondly, due to incomplete information, we did not assess the impact of iron supplementation on cardiac function-related outcomes such as left ventricular ejection fraction, HF symptoms (e.g., dyspnea), quality of life, and cardiorespiratory performance. Thirdly, the included studies did not achieve the long-term follow-up needed to identify IV iron-based therapy's benefits fully. Fourthly, comparing the effects of different iron-based treatments (e.g., infused doses and used molecules) was impossible. Regarding iron preparation, most of the included studies covered only ferric carboxymaltose and ferric derisomaltose, both showing good efficacy and a comparable safety profile. However, there is a need for additional studies exploring the outcomes of other iron-based supplementations, including iron isomaltoside, iron sucrose, and sodium ferric gluconate complex, as the number of patients who received these treatments in the included studies was very small, hence insufficient to indicate any differences.

Conclusions

IV iron infusion is an effective option to reduce hospitalization episodes and cardiovascular mortality among HF patients. Additionally, it is a safe and well-tolerable treatment that can be given to this group of patients as an adjuvant therapy to traditional medications. Nevertheless, further studies are still required to confirm the clinical advantages of iron-based supplementations in the context of HF.

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List of Abbreviations: heart failure (HF), intravenous (IV), randomized controlled trial (RCT), mean difference (MD), confidence interval (CI), risk ratio (RR).

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Consent for publication: not applicable.

Availability of data and material: all data generated or analysed during this study are included in this published article.

Authors' contributions. MAazm: conceptualization and methodology. AR, OA, AA, IU, MAazm and BA: investigation and data curation. MAzid: formal analysis. YK and MAzid: Writing – Original Draft. BA: Supervision. MT: Project administration. MAazm, MAzid, MT and BA: Writing – Review & Editing. All authors read and approved the final content.

Conflict of interest statement
The authors declare no conflict of interest.

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Supplementary data

Table S1. Search strategy. ("Heart failure" OR "Cardiac Failure" OR " Heart Decompensation" OR "Myocardial Failure" OR "HFrEF" OR "HF" OR "HFpEF") AND ("intravenous iron" OR "ferric carboxymaltose" OR "iron derisomaltose" OR "iron supplementation" OR "iron therapy" OR "iron sucrose" OR "iron isomaltoside" OR "ferric gluconate"). Date/ 31/08/2023

Database	Search terms	Search field	Search results
Pubmed	("Heart failure" OR "Cardiac Failure" OR " Heart Decompensation" OR "Myocardial Failure" OR "HFrEF" OR "HF" OR "HFpEF") AND ("intravenous iron" OR "**ferric** carboxymaltose" OR "iron derisomaltose" OR "iron supplementation" OR "iron therapy" OR "iron sucrose" OR "iron isomaltoside" OR "ferric gluconate")	All Field	598
Cochrane	("Heart failure" OR "Cardiac Failure" OR " Heart Decompensation" OR "Myocardial Failure" OR "HFrEF" OR "HF" OR "HFpEF") AND ("intravenous iron" OR "ferric carboxymaltose" OR "iron derisomaltose" OR "iron supplementation" OR "iron therapy" OR "iron sucrose" OR "iron isomaltoside" OR "ferric gluconate")	Title, Abstract, Keywords	245
WOS	("Heart failure" OR "Cardiac Failure" OR " Heart Decompensation" OR "Myocardial Failure" OR "HFrEF" OR "HF" OR "HFpEF") AND ("intravenous iron" OR "ferric carboxymaltose" OR "iron derisomaltose" OR "iron supplementation" OR "iron therapy" OR "iron sucrose" OR "iron isomaltoside" OR "ferric gluconate")	Abstract	417
SCOPUS	("Heart failure" OR "Cardiac Failure" OR " Heart Decompensation" OR "Myocardial Failure" OR "HFrEF" OR "HF" OR "HFpEF") AND ("intravenous iron" OR "ferric carboxymaltose" OR "iron derisomaltose" OR "iron supplementation" OR "iron therapy" OR "iron sucrose" OR "iron isomaltoside" OR "ferric gluconate")	Abstract	500
EMBASE	Session Results ..... No. Query Results — Results — Date #3. #1 AND #2 — 985 — 31 Aug 2023 #2. 'intravenous iron':ti,ab,kw OR 'ferric carboxymaltose':ti,ab,kw OR 'iron derisomaltose':ti,ab,kw OR 'iron supplementation':ti,ab,kw OR 'iron therapy':ti,ab,kw OR 'iron sucrose':ti,ab,kw OR 'iron isomaltoside':ti,ab,kw OR 'ferric gluconate':ti,ab,kw — 14,830 — 31 Aug 2023 #1. 'cardiac failure':ti,ab,kw OR 'heart failure':ti,ab,kw OR 'myocardial failure':ti,ab,kw OR hfref:ti,ab,kw OR hf:ti,ab,kw OR hfpef:ti,ab,kw — 431,302 — 31 Aug 2023	All Field	985

Figure S1. Subgroup analysis according to chronic or acute heart failure for cardiovascular mortality.

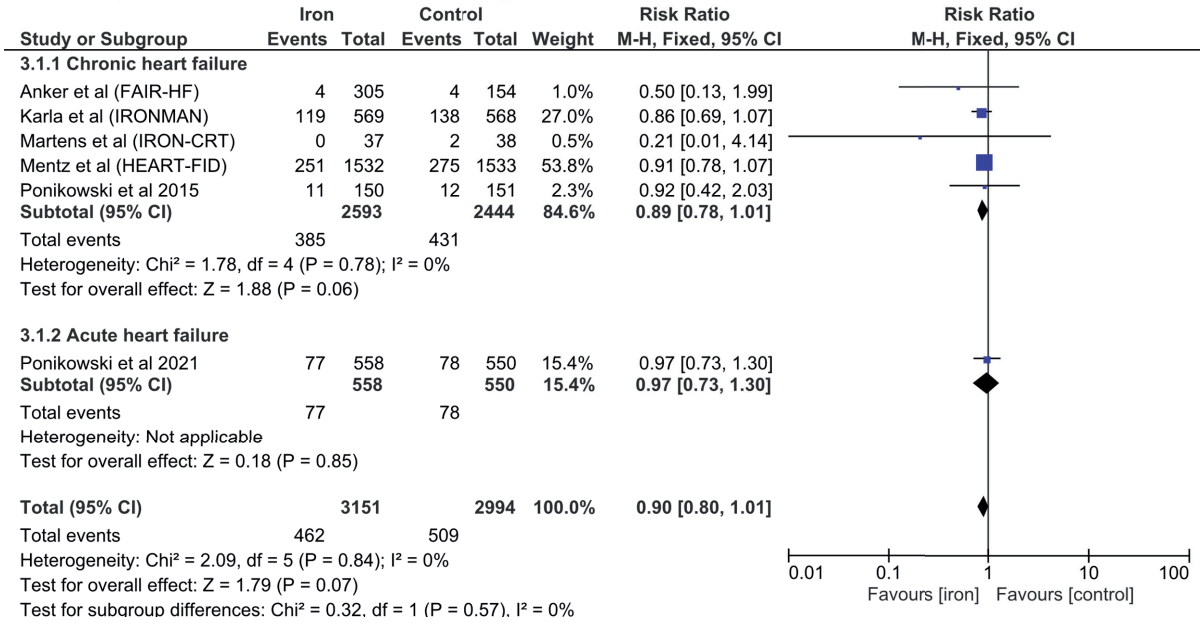

Figure S2. Subgroup analysis according to chronic or acute heart failure for all-cause mortality.

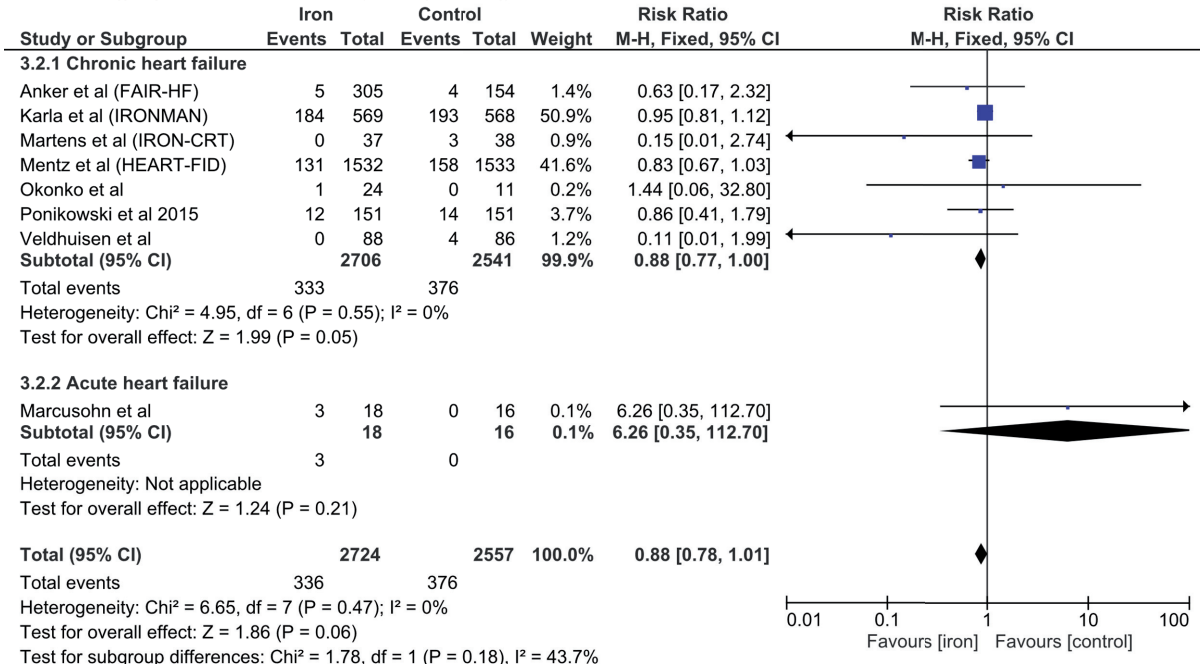

Figure S3. Subgroup analysis according to chronic or acute heart failure for Hospital admission for heart failure (first event).

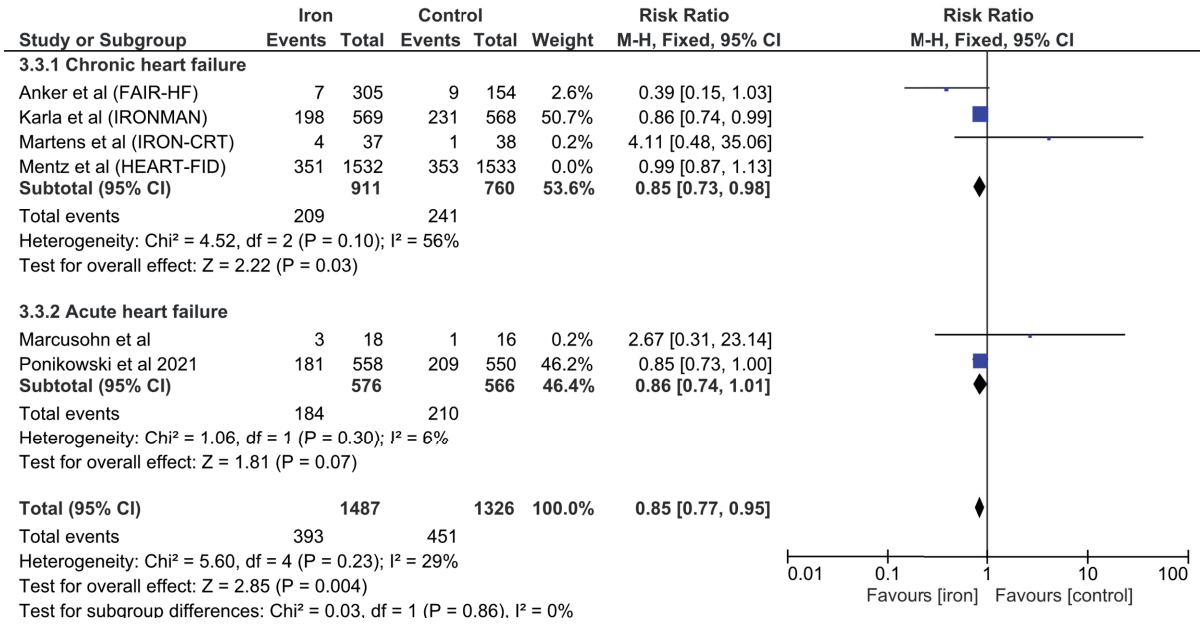

Figure S4. Subgroup analysis according to chronic or acute heart failure for Hospital admission for heart failure (total event).

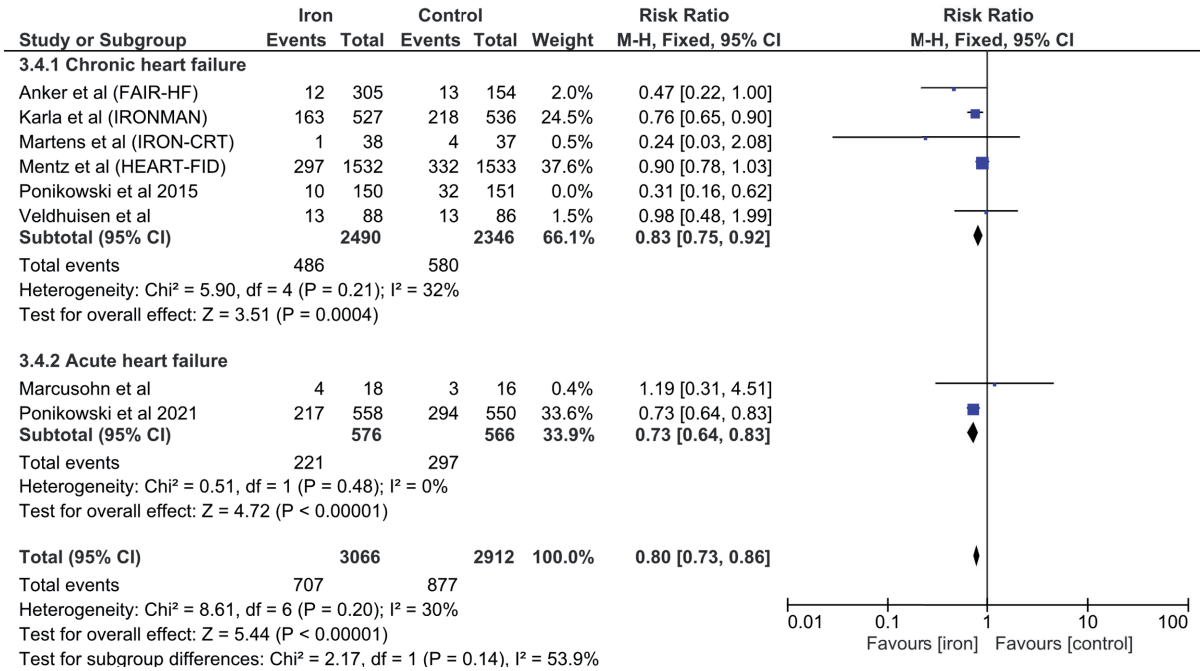

Figure S5. Subgroup analysis according to chronic or acute heart failure for cardiovascular death and hospital admission for heart failure (number of events) rater per 100 patient-year.

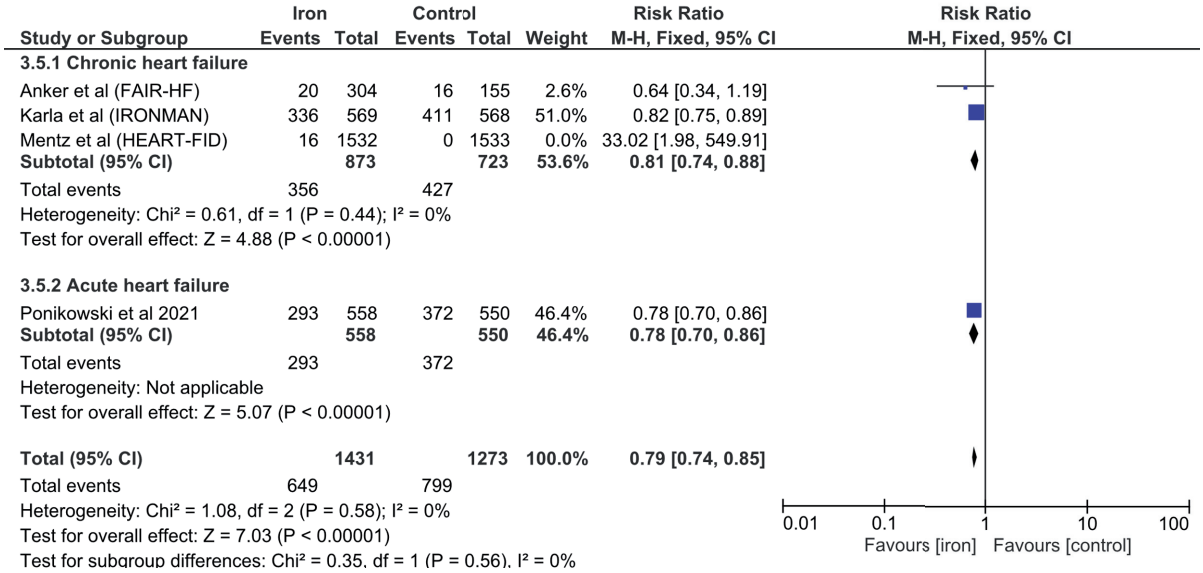

Figure S6. Subgroup analysis according to chronic or acute heart failure for hospital admission for heart failure (number of events) rater per 100 patient-year.

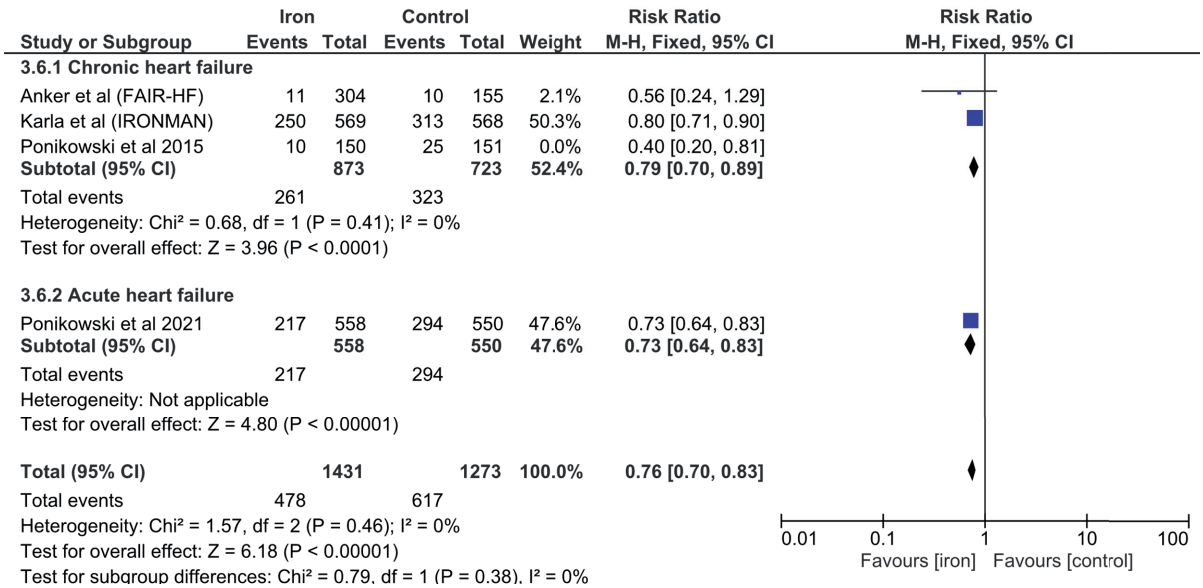

Figure S7. Subgroup analysis according to the iron preparation for cardiovascular mortality.

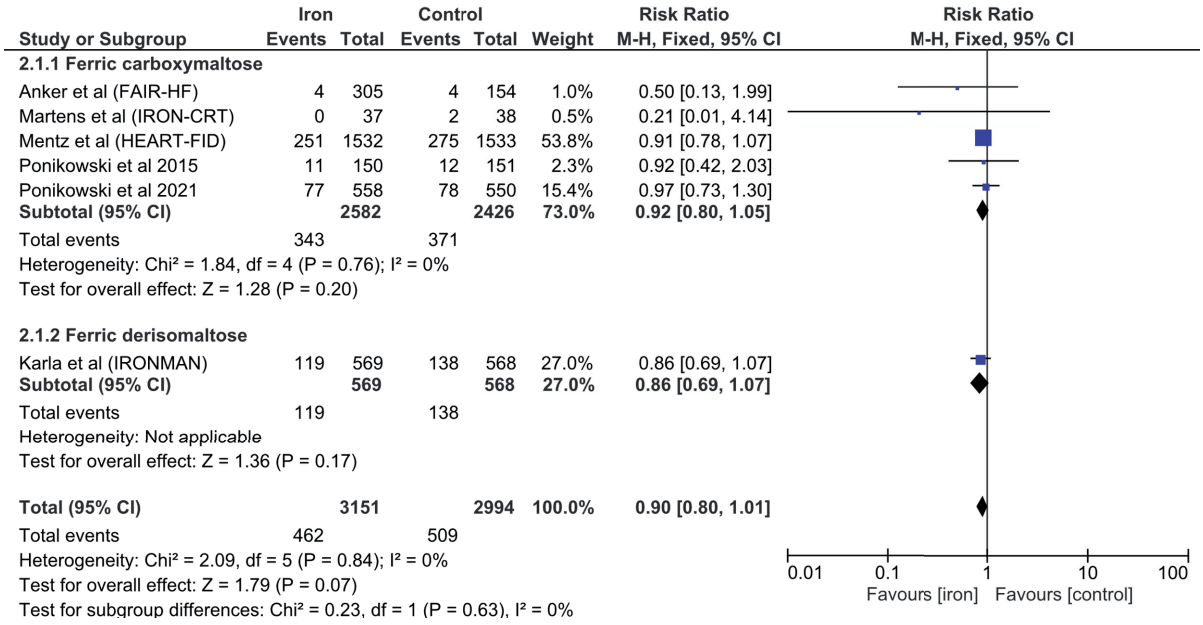

Figure S8. Subgroup analysis according to the iron preparation for all cause mortality.

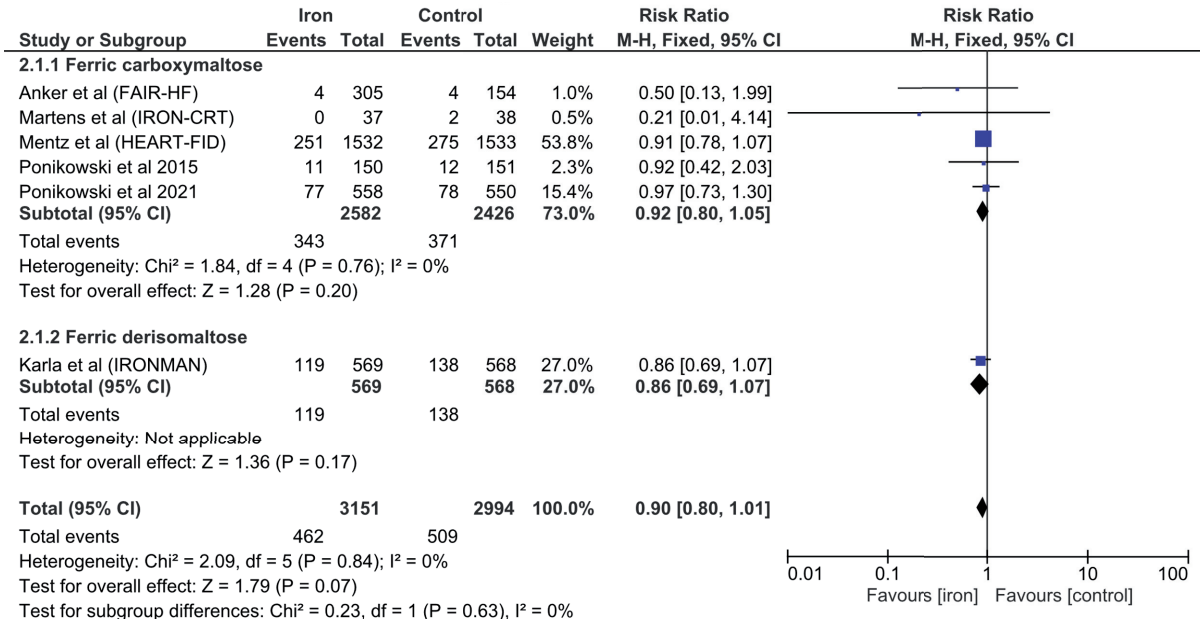

Figure S9. Subgroup analysis according to the iron preparation for hospital admission for heart failure (first event).

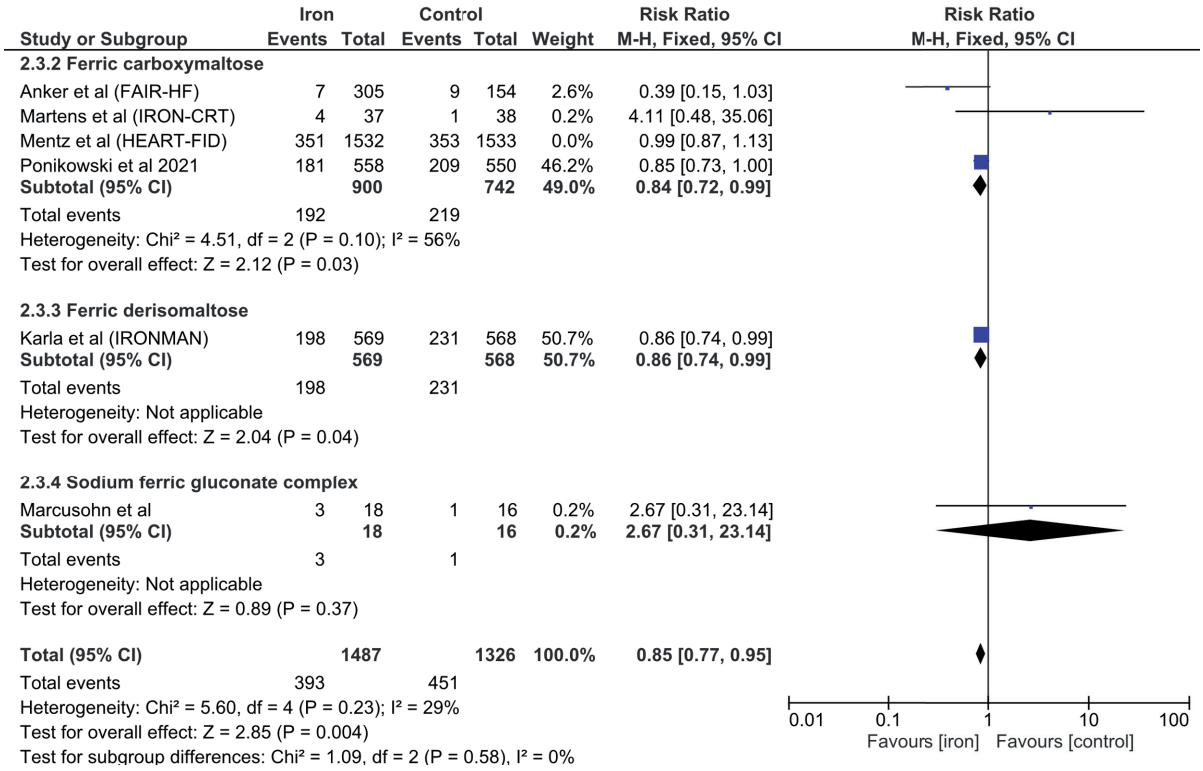

Figure S10. Subgroup analysis according to the iron preparation for hospital admission for heart failure (total event).

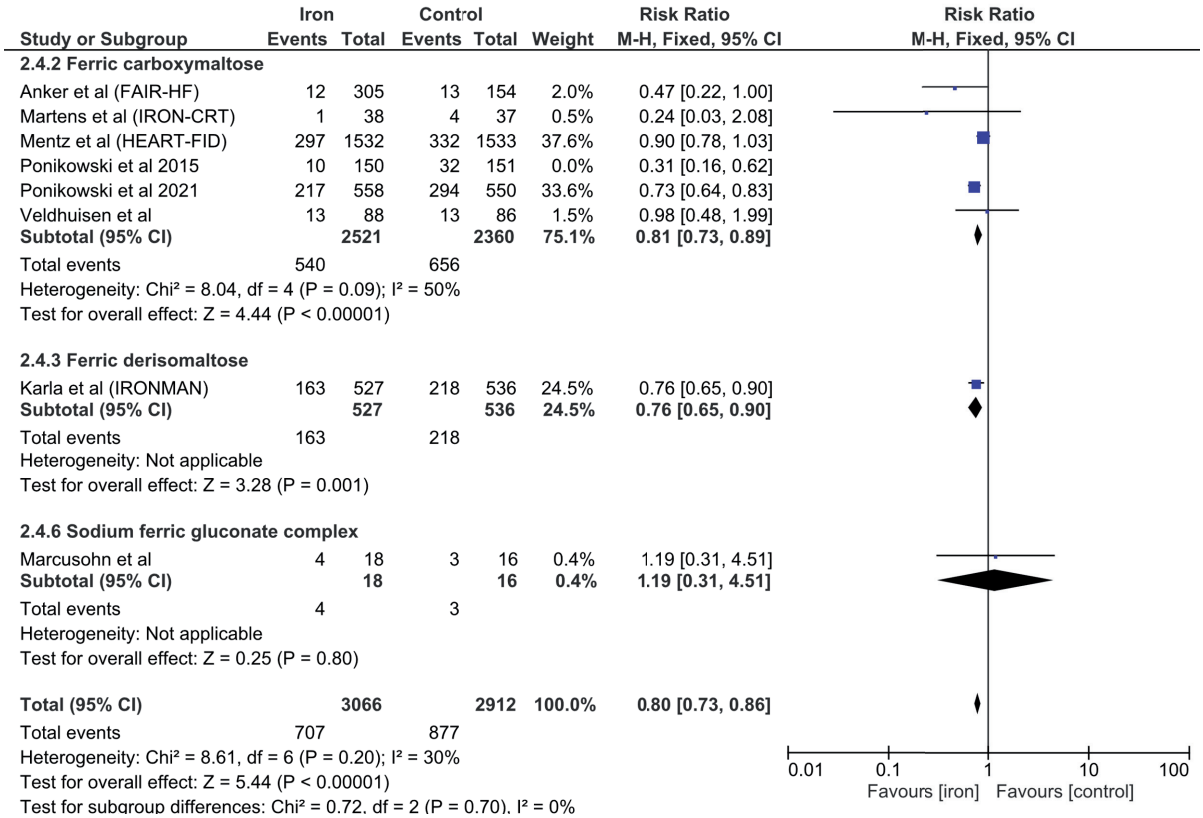

Figure S11. Subgroup analysis according to the iron preparation for cardiovascular death and hospital admission for heart failure (number of events) rater per 100 patient year.

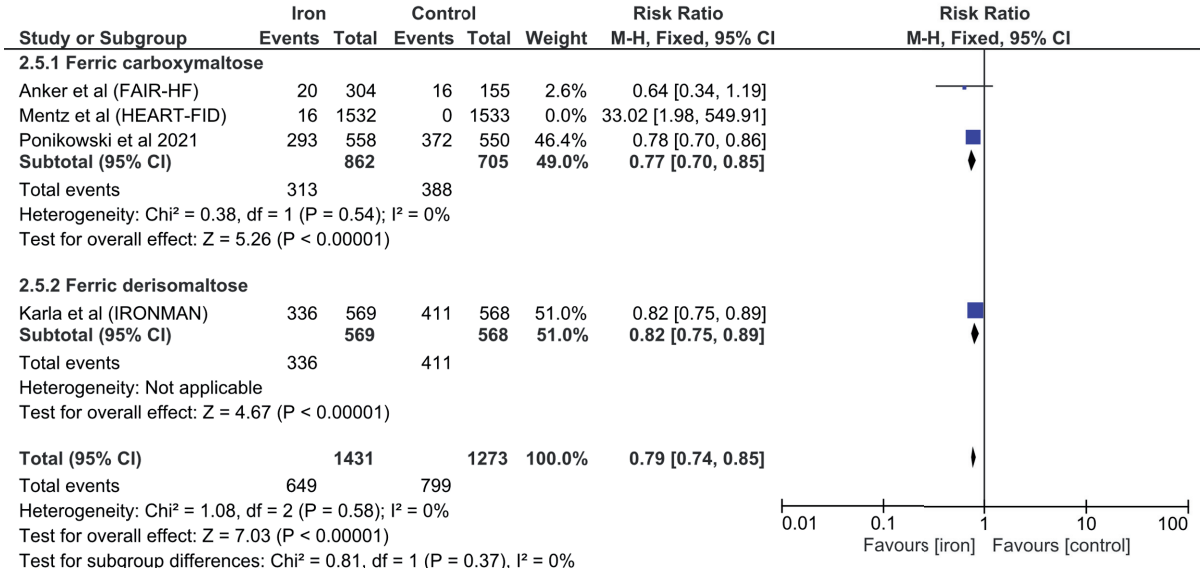

Figure S12. Subgroup analysis according to the iron preparation for hospital admission for heart failure (number of events) rater per 100 patient year.

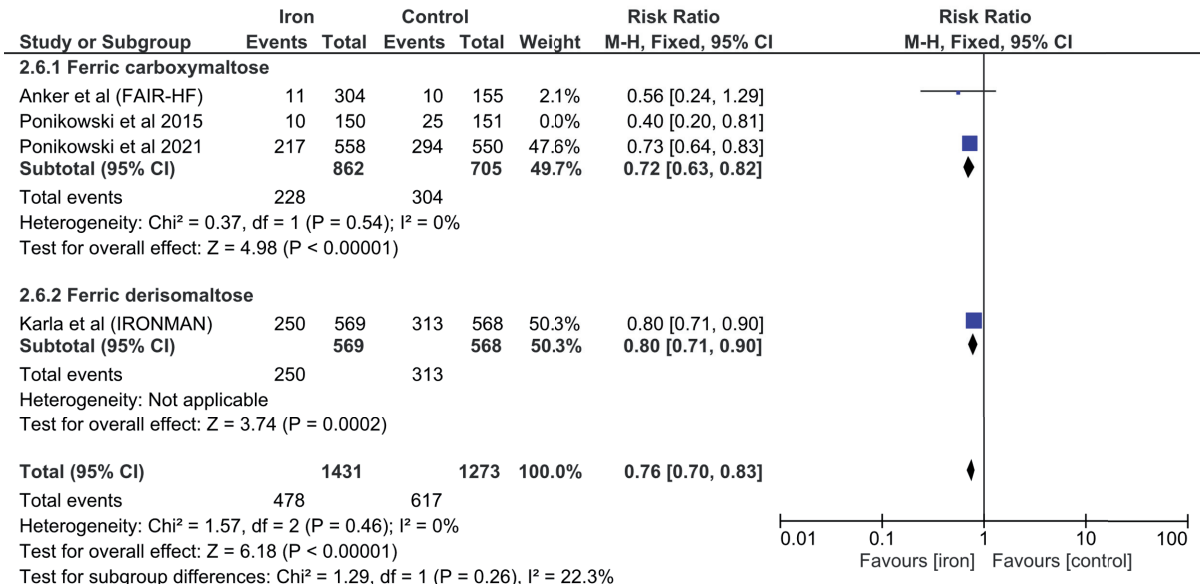

Figure S13. Subgroup analysis according to chronic or acute heart failure for cardiac disorder.

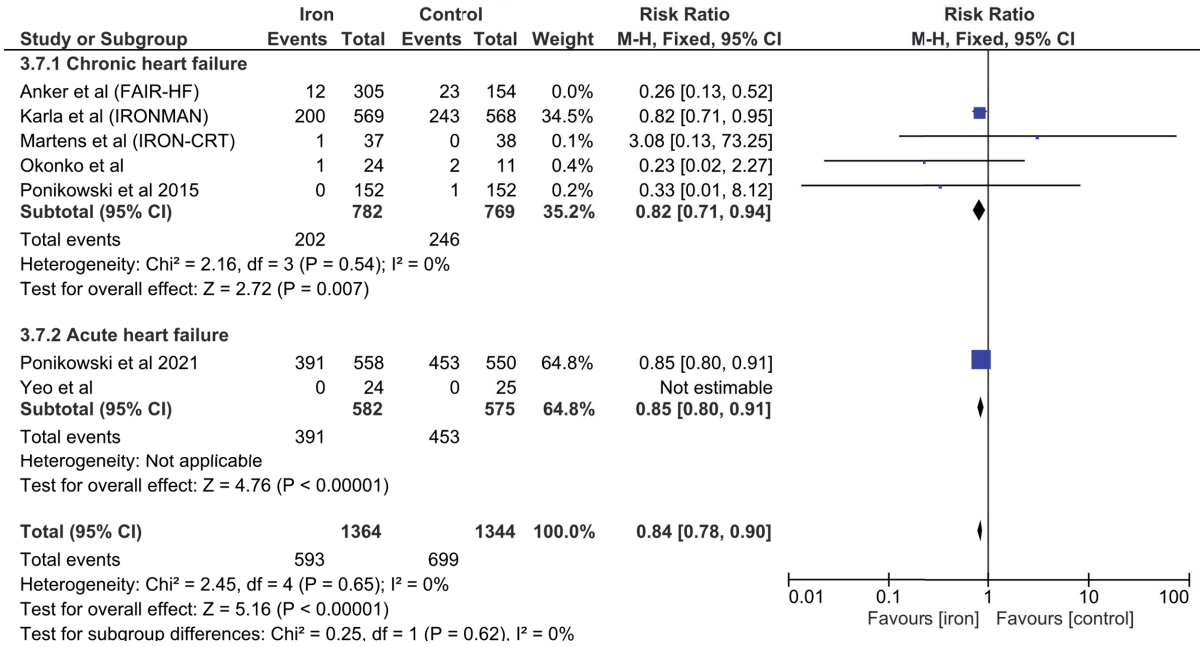

Figure S14. Subgroup analysis according to chronic or acute heart failure for any serious adverse event.

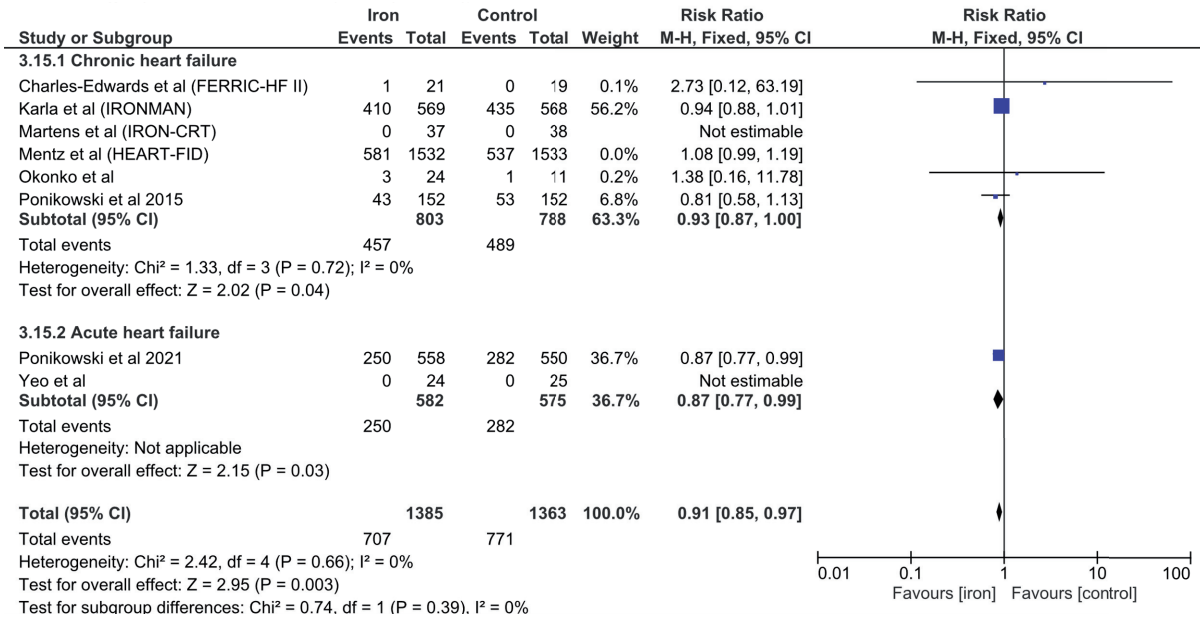

Figure S15. Subgroup analysis according to chronic or acute heart failure for respiratory, thoracic, or mediastinum disorder.

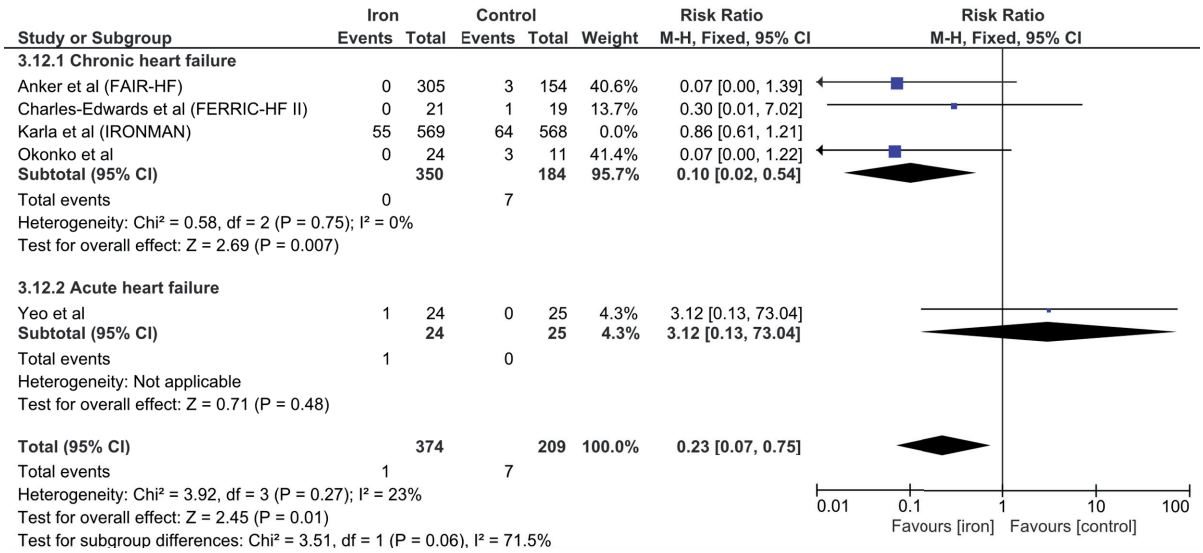

Figure S16. Subgroup analysis according to chronic or acute heart failure for gastrointestinal tract disorder.

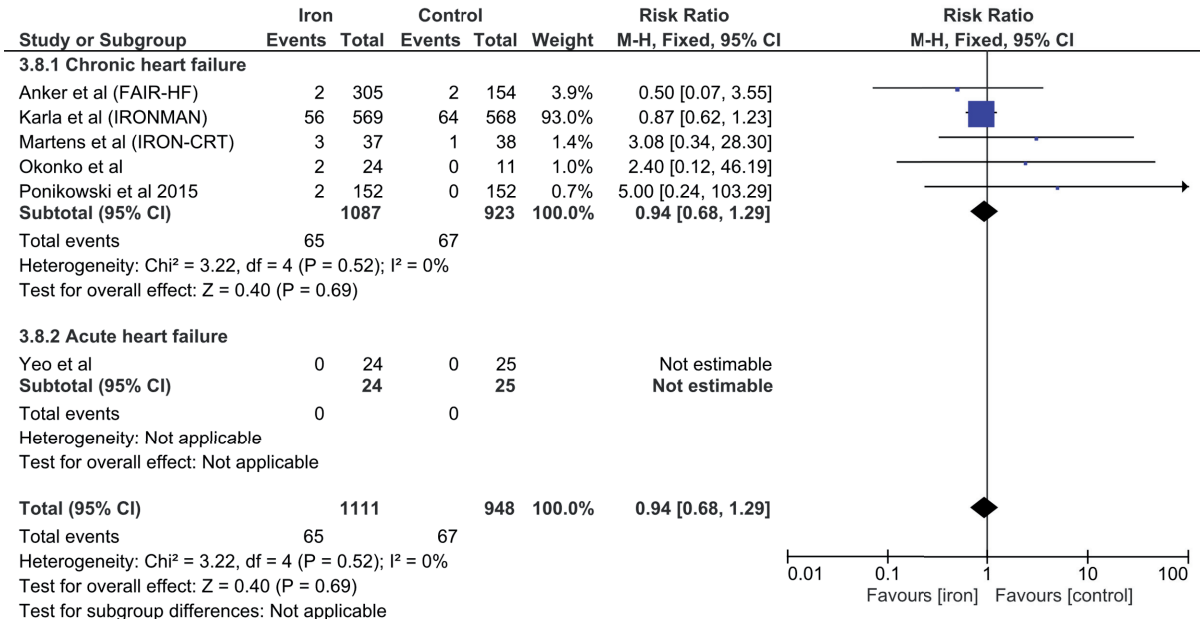

Figure S17. Subgroup analysis according to chronic or acute heart failure for nerves system disorder.

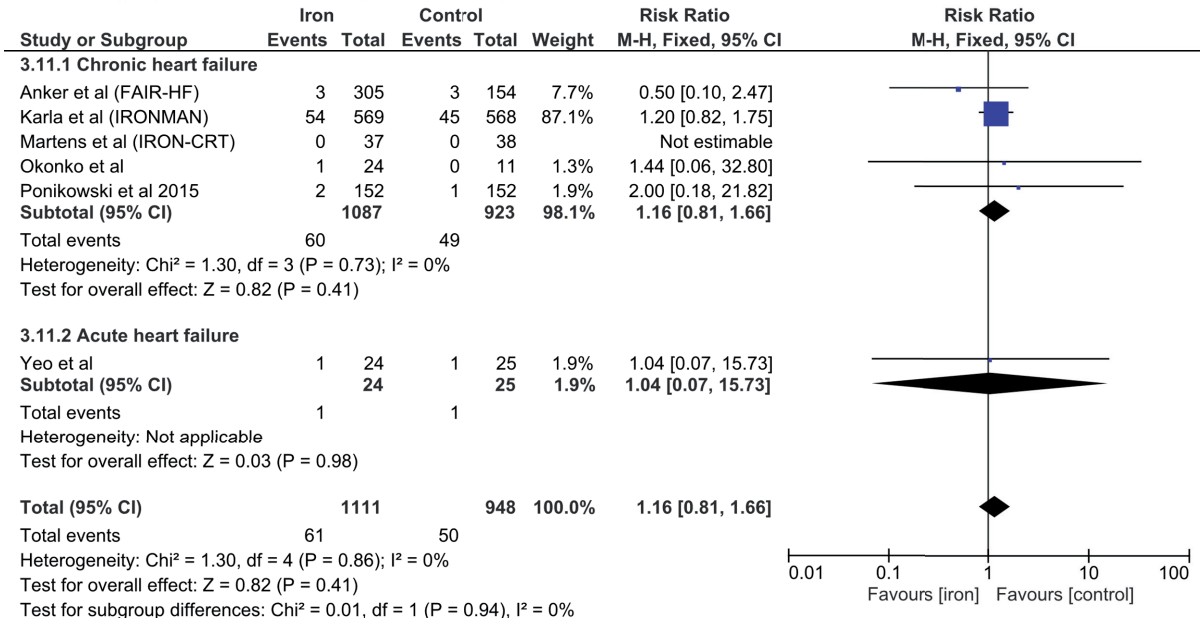

Figure S18. Subgroup analysis according to chronic or acute heart failure for vascular disorder.

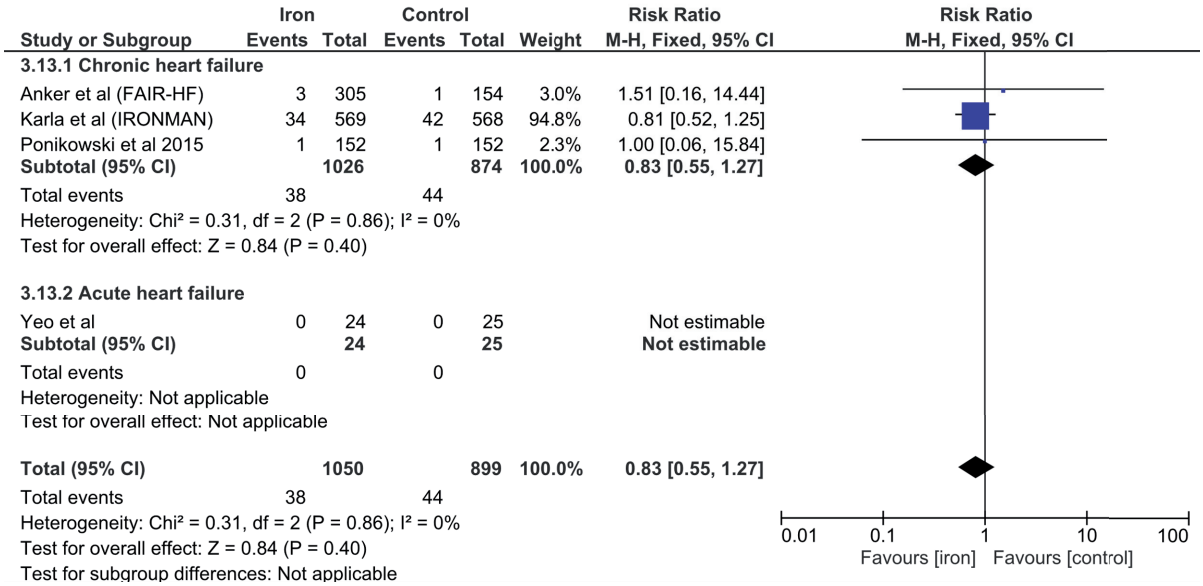

Figure S19. Subgroup analysis according to the iron preparation for cardiac disorder

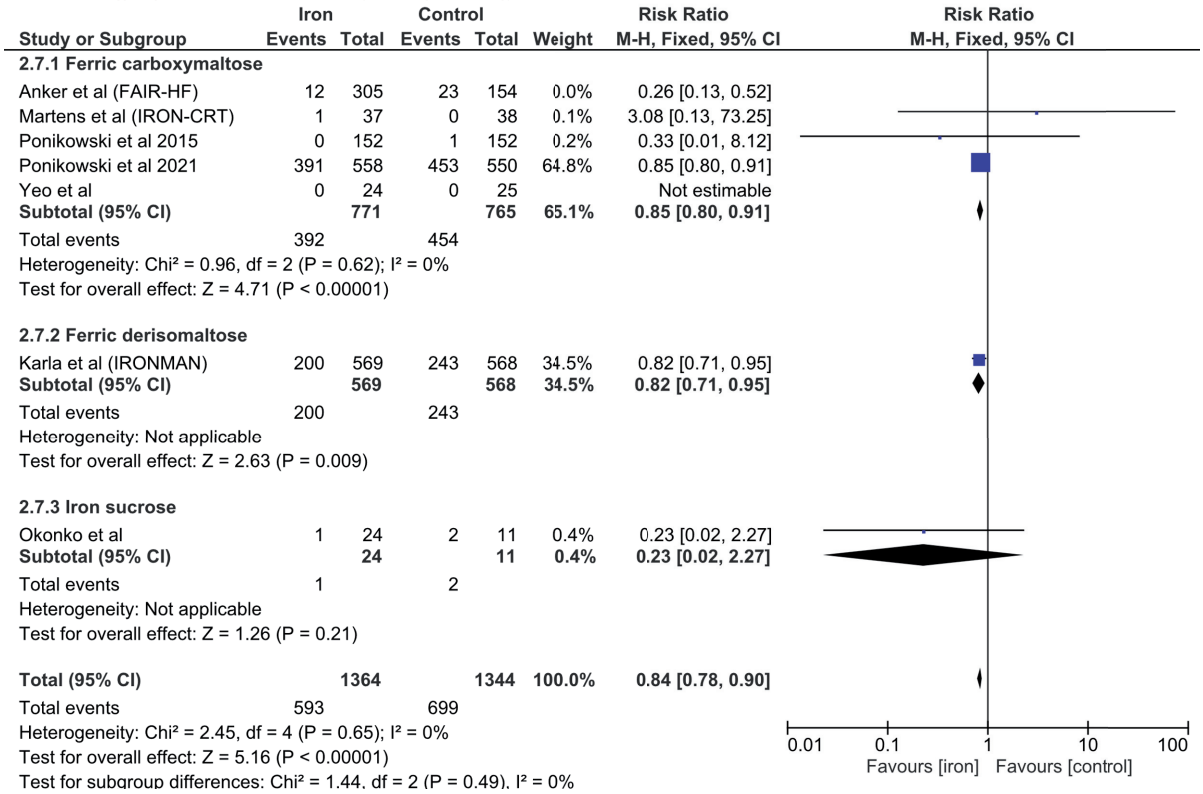

Figure S20. Subgroup analysis according to the iron preparation for any serious adverse effect.

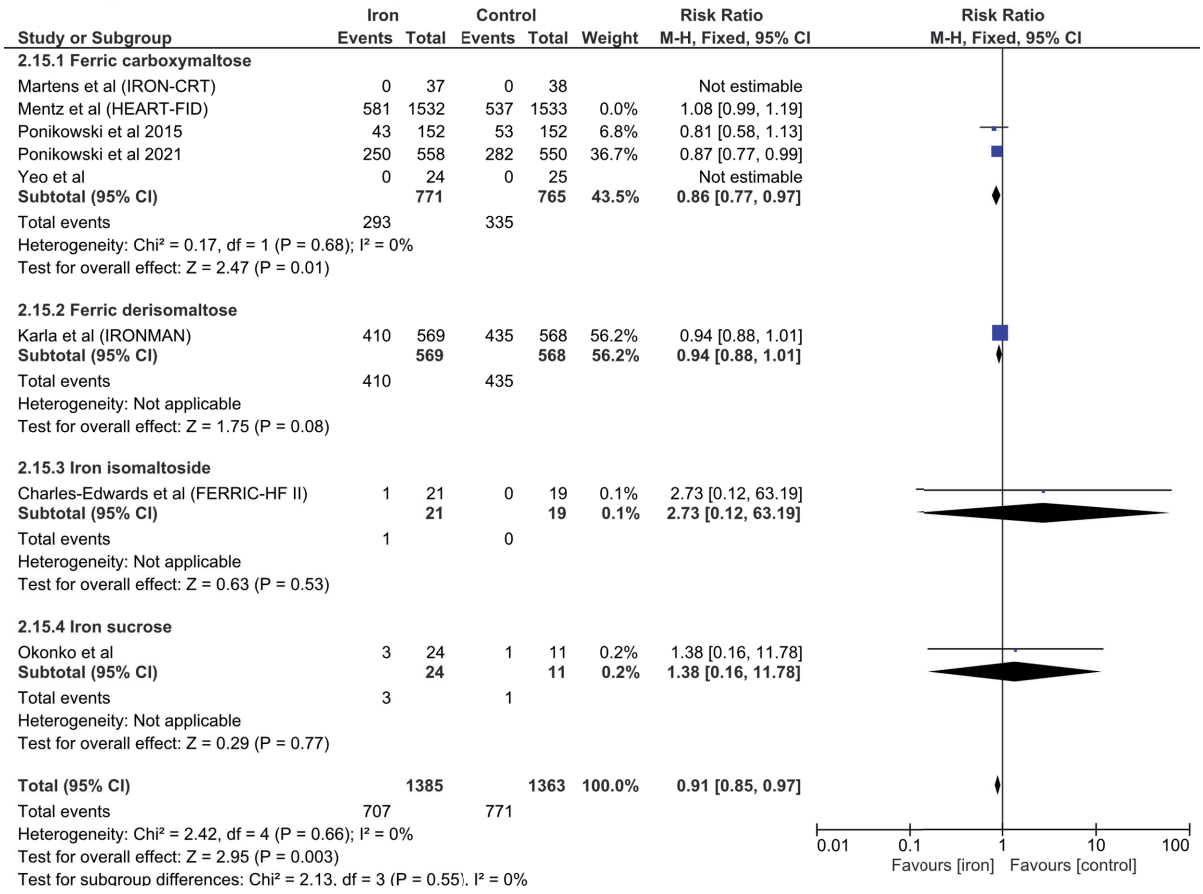

Figure S21. Subgroup analysis according to the iron preparation for any gastrointestinal tract disorder.

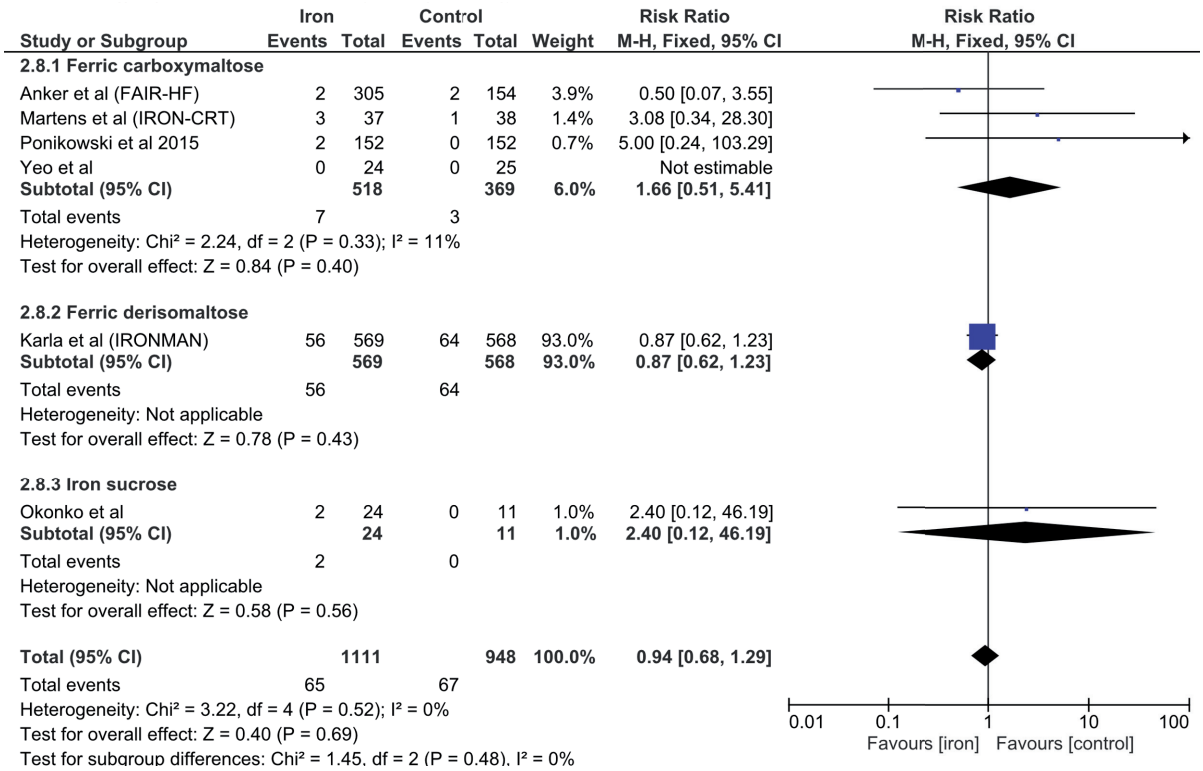

Figure S22. Subgroup analysis according to the iron preparation for injection site condition

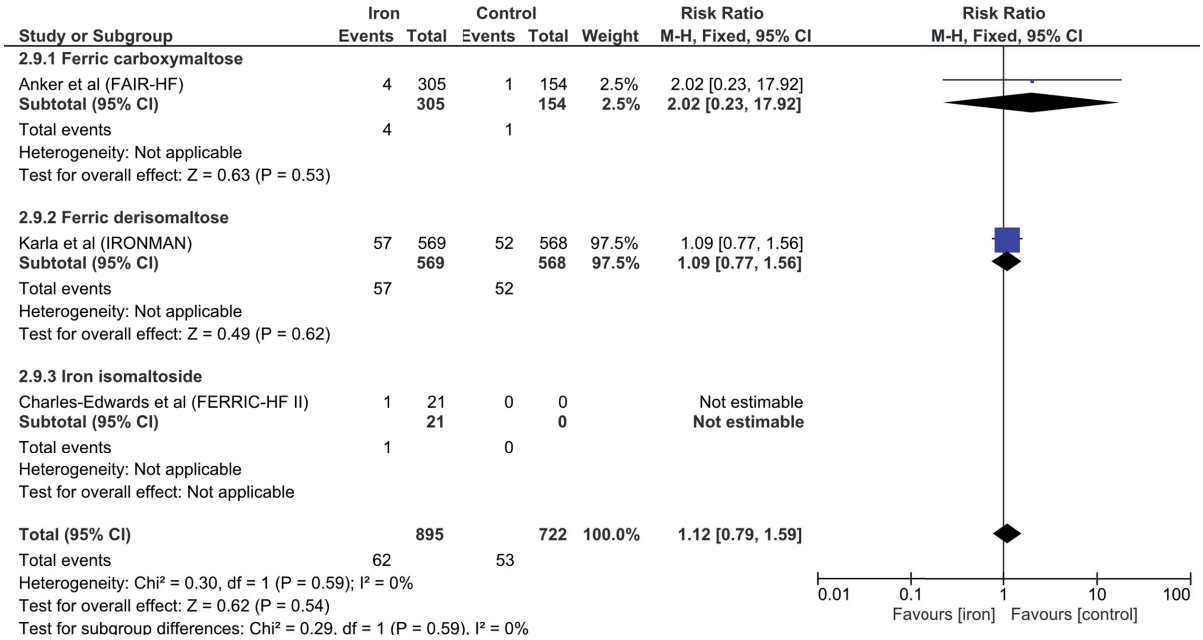

Figure S23. Subgroup analysis according to the iron preparation for infection.

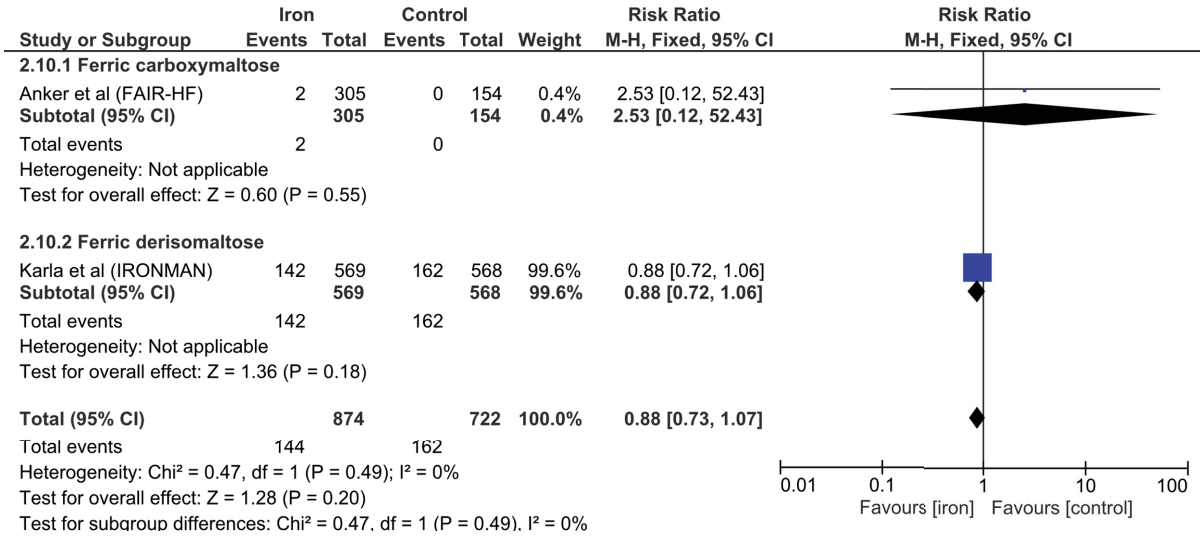

Figure S24. Subgroup analysis according to the iron preparation for nerves system disorder.

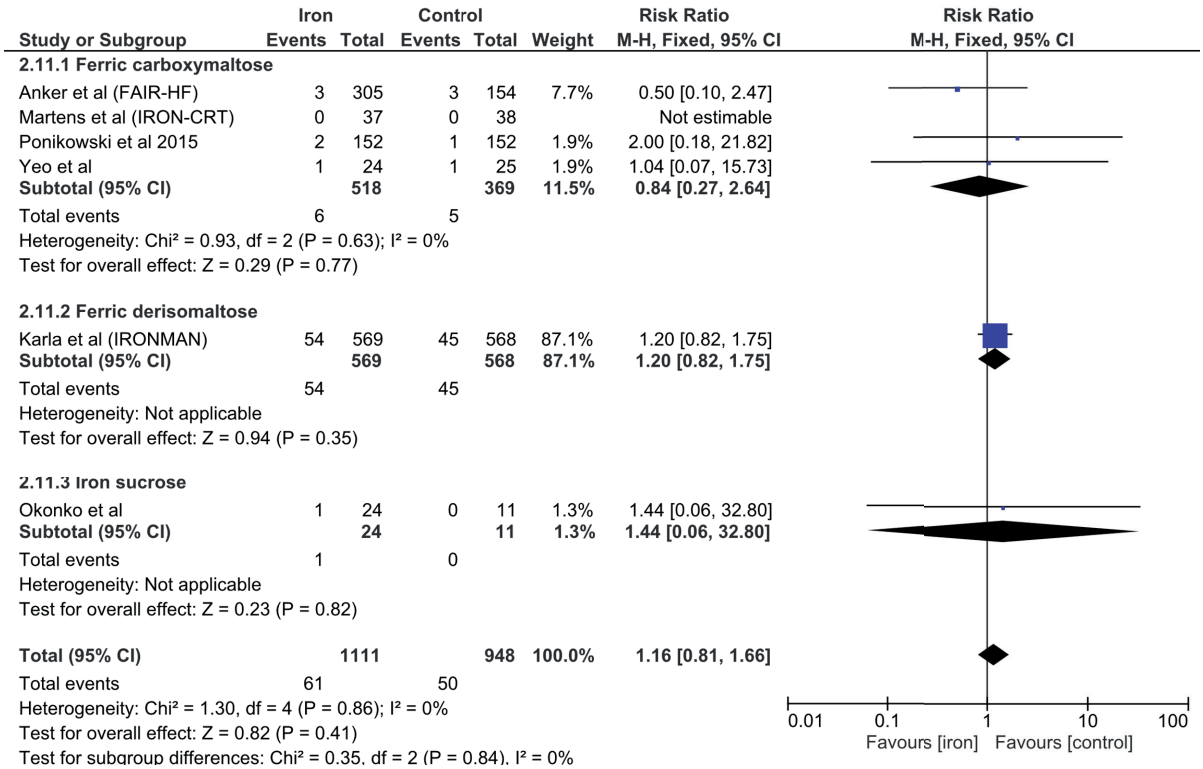

Figure S25. Subgroup analysis according to the iron preparation for respiratory, thoracic or mediastinum disorder.

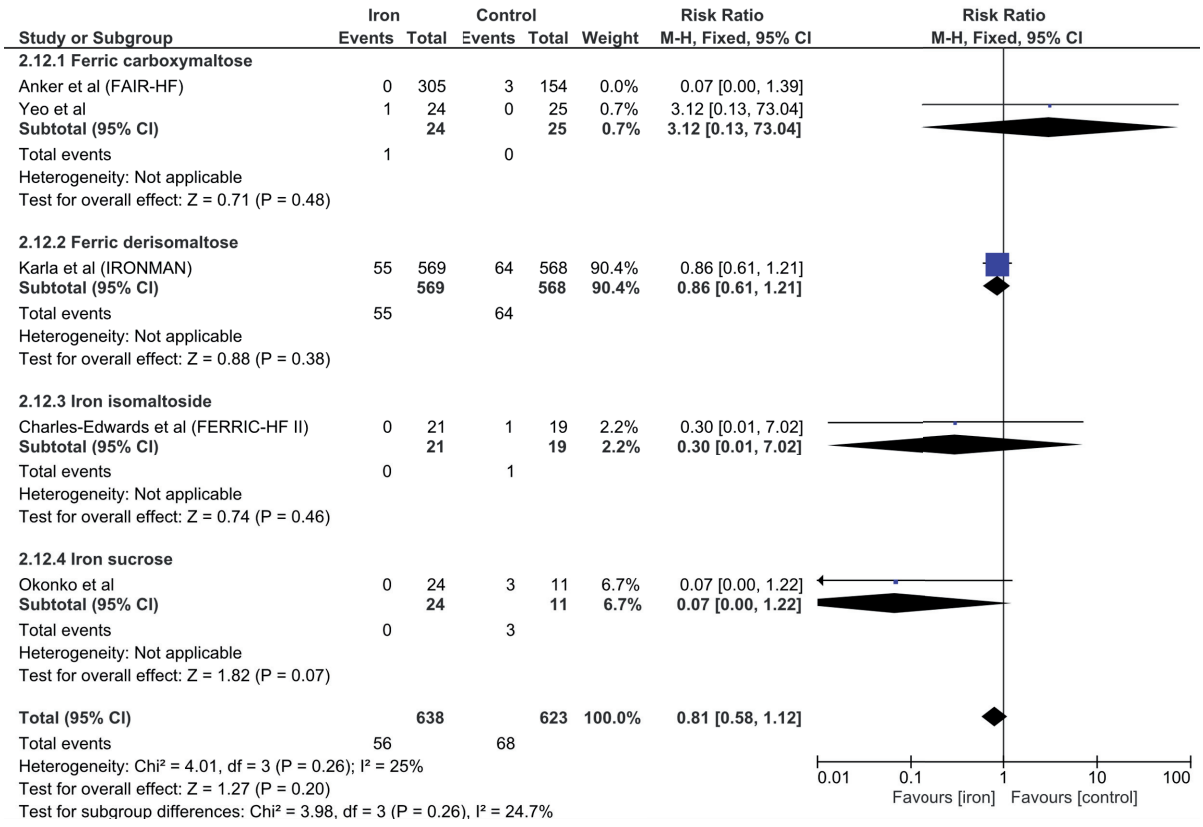

Figure S26. Subgroup analysis according to the iron preparation for vascular disorder.

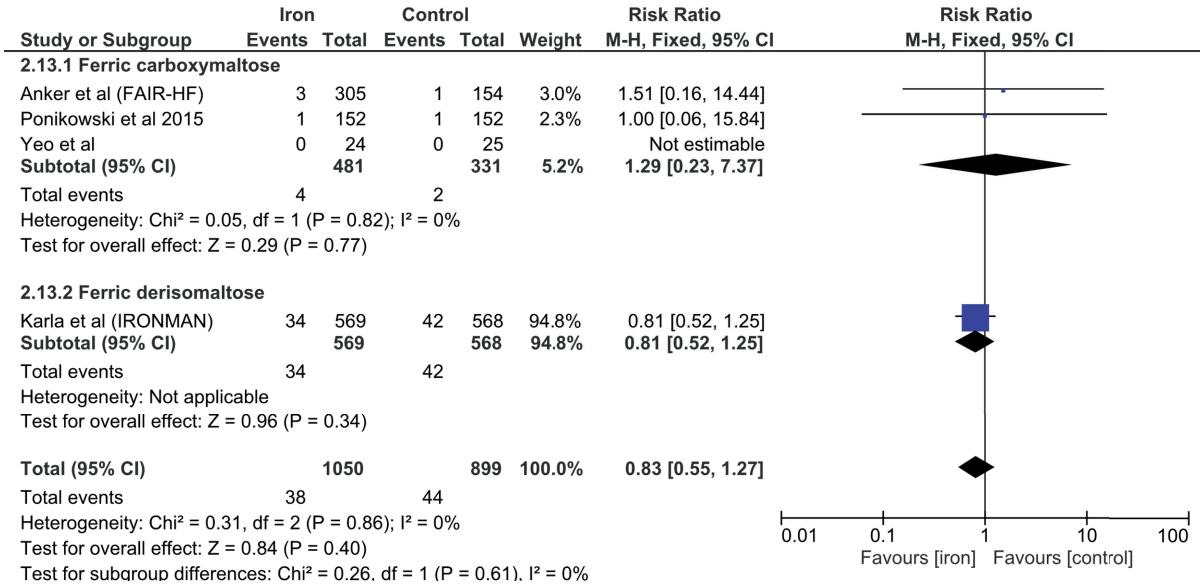

Figure S27. Subgroup analysis according to the iron preparation for any adverse effect.

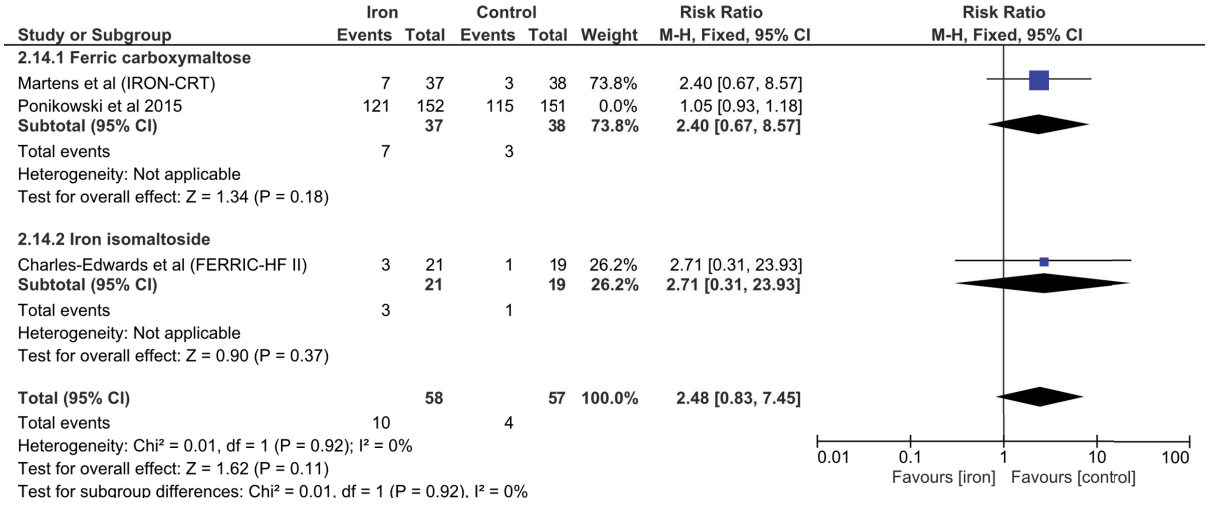

Figure S28. Subgroup analysis according to the iron preparation for any adverse event leading to withdrawal.

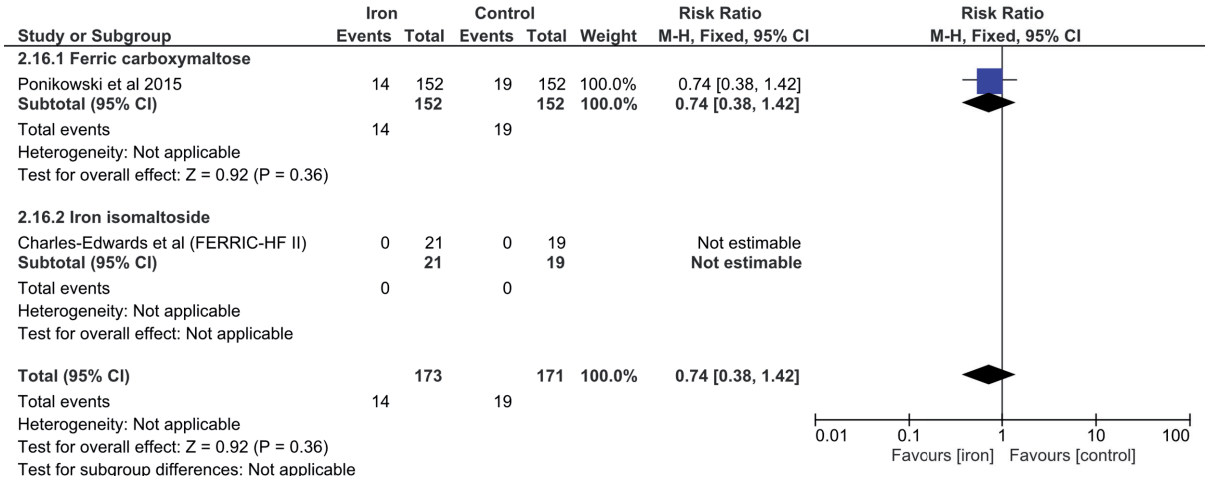

Figure S29. Subgroup analysis according to the iron preparation for abnormal lab test, vital sign or physical finding