European Journal of Heart Failure (2016) **18**, 786–795
doi:10.1002/ejhf.473

REVIEW

Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials

Ewa A. Jankowska[1,2]*, Michał Tkaczyszyn[1,2], Tomasz Suchocki[3], Marcin Drozd[1,2], Stephan von Haehling[4], Wolfram Doehner[5,6], Waldemar Banasiak[2], Gerasimos Filippatos[7], Stefan D. Anker[4], and Piotr Ponikowski[2,8]

[1]Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland; [2]Cardiology Department, Centre for Heart Diseases, Military Hospital, Wroclaw, Poland; [3]Biostatistics Group, Department of Genetics, Wroclaw University of Environmental and Life Sciences, Wroclaw, Poland; [4]Division of Innovative Clinical Trials, Department of Cardiology & Pulmonology, University Medicine Göttingen (UMG), Göttingen, Germany; [5]Department of Cardiology, Virchow Klinikum, Charite – Universitätsmedizin, Berlin, Germany; [6]Center for Stroke Research Berlin, Charite – Universitätsmedizin, Berlin, Germany; [7]Heart Failure Unit, Department of Cardiology, Athens University Hospital Attikon, Athens, Greece; and [8]Department of Heart Diseases, Wroclaw Medical University, Wroclaw, Poland

Received 27 August 2015; revised 6 November 2015; accepted 6 December 2015; online publish-ahead-of-print 28 January 2016

The aim of this study was to assess the net clinical and prognostic effects of intravenous (i.v.) iron therapy in patients with systolic heart failure (HF) and iron deficiency (ID). We performed an aggregate data meta-analysis (random effects model) of randomized controlled trials that evaluated the effects of i.v. iron therapy in iron-deficient patients with systolic HF. We searched electronic databases up to September 2014. We identified five trials which fulfilled the inclusion criteria (509 patients received i.v. iron therapy in comparison with 342 controls). Intravenous iron therapy has been shown to reduce the risk of the combined endpoint of all-cause death or cardiovascular hospitalization [odds ratio (OR) 0.44, 95% confidence interval (CI) 0.30–0.64, $P < 0.0001$], and the combined endpoint of cardiovascular death or hospitalization for worsening HF (OR 0.39, 95% CI 0.24–0.63, $P = 0.0001$). Intravenous iron therapy resulted in a reduction in NYHA class (data are reported as a mean net effect with 95% CIs for all continuous variables) (−0.54 class, 95% CI −0.87 to −0.21, $P = 0.001$); an increase in 6-min walking test distance (+31 m, 95% CI 18–43, $P < 0.0001$); and an improvement in quality of life [Kansas City Cardiomyopathy Questionnaire (KCCQ) score +5.5 points, 95% CI 2.8–8.3, $P < 0.0001$; European Quality of Life–5 Dimensions (EQ-5D) score +4.1 points, 95% CI 0.8–7.3, $P = 0.01$; Minnesota Living With Heart Failure Questionnaire (MLHFQ) score −19 points, 95% CI:−23 to −16, $P < 0.0001$; and Patient Global Assessment (PGA) +0.70 points, 95% CI 0.31–1.09, $P = 0004$]. The evidence indicates that i.v. iron therapy in iron-deficient patients with systolic HF improves outcomes, exercise capacity, and quality of life, and alleviates HF symptoms.

Keywords Heart failure • Iron deficiency • Intravenous iron • Anaemia • Outcomes • Meta-analysis

Introduction

Iron deficiency (ID) is a common co-morbidity found in 50% of patients with stable heart failure (HF).[1] ID constitutes the most frequent cause of anaemia in patients with HF,[2,3] but, most importantly, ID occurs in ~46% of non-anaemic patients with stable systolic HF.[1]

The presence of ID, regardless of concomitant anaemia, has been shown to worsen symptoms and to impair exercise capacity and quality of life (QoL) of patients with systolic HF.[1,4–8] Iron-deficient patients with HF (both anaemics and non-anaemics) are characterized by high mortality and increased rates of urgent hospitalizations due to HF progression.[1,4]

The gathered experimental and clinical evidence provided the basis to consider ID as a potential therapeutic target in patients with HF.[3,7,9–17] Indeed, in recent years, several studies have investigated the effects of intravenous (i.v.) iron therapy in iron-deficient patients with HF,[18–21] including the FAIR-HF[22] and CONFIRM-HF[23] trials encompassing >450 and >300 patients, respectively.

*Corresponding author: Laboratory for Applied Research on Cardiovascular System, Department of Heart Diseases, Wroclaw Medical University, Centre for Heart Diseases, Military Hospital, ul. Weigla 5, 50–981 Wroclaw, Poland. Tel/Fax: +48 261 660 661, Email: ewa.jankowska@umed.wroc.pl

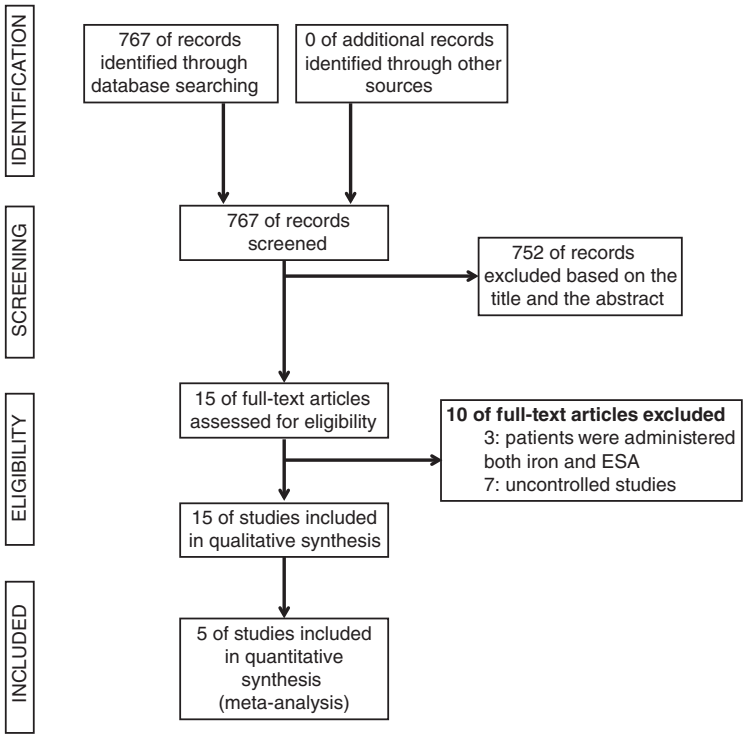

Figure 1 Search algorithm according to the PRISMA 2009 flow diagram.[43] ESA, erythropoiesis-stimulating agent.

The aim of our study was to summarize the evidence in the form of a meta-analysis of all randomized controlled trials that investigated the effects of i.v. iron therapy in iron-deficient patients with systolic HF (also analysed separately in anaemic and non-anaemic subjects).

Methods

Search strategy and study selection

We performed an aggregate data meta-analysis of randomized controlled trials regarding i.v. iron therapy in patients with systolic HF and ID.

One reviewer (M.T.) identified relevant English-language studies published between 1 January 1950 and 30 September 2014, by searching the US National Library of Medicine via PubMed records, Embase, Cochrane databases, Web of Science, FDA.gov, and ClinicalTrials.gov. The complete combined PubMed query (created using the PubMed Advanced Search Builder) was: '[(heart failure) AND (iron deficiency OR iron therapy OR iron supplementation OR iron repletion OR intravenous iron OR ferric carboxymaltose OR iron sucrose)]'. No other search restrictions or filters were applied. All potentially eligible studies were considered for review, irrespective of pre-defined primary outcomes. A manual search of reference lists of important review articles and previously conducted meta-analyses[3,7,10,11] regarding i.v. iron therapy in patients with HF was also performed. Only original clinical trial publications were included in this meta-analysis, and additional papers presenting further subanalyses of primary data were omitted to avoid data duplication.

Inclusion criteria in this meta-analysis comprised at least a single-blind randomized controlled trial regarding i.v. iron therapy without erythropoiesis-stimulating agents (ESAs) in patients with systolic HF. Systolic HF was defined as an left ventricular ejection fraction (LVEF) of ≤45%.

Data extraction and quality assessment

Based on published full-text articles of five included studies and supplementary content available online, two reviewers (E.A.J. and M.T.), independently of each other, extracted the following data for two study arms (i.v. iron vs. control group).

(i) Clinical events reported at the end of follow-up: (a) all-cause death; (b) cardiovascular death; (c) all-cause death or cardiovascular hospitalization (combined endpoint); (d) cardiovascular death or hospitalization for worsening HF; and (e) HF hospitalization.

(ii) Change from baseline to the end of follow-up in continuous variables: (a) European Quality of Life–5 Dimensions (EQ-5D) visual analogue scale;[24] (b) Kansas City Cardiomyopathy Questionnaire (KCCQ) score;[25] (c) Minnesota Living With Heart Failure Questionnaire (MLHFQ) score;[26] (d) Patient Global Assessment (PGA) on a 7-point scale [a patient's declaration regarding the change of his/her medical condition since enrolment was assigned the following scores: −3 ('is much worse'), −2 ('is moderately worse'), −1 ('is a little worse'), 0 ('is unchanged'), 1 ('has improved a little'), 2 ('has moderately improved'), and 3 ('has much improved'), and patients who died were assigned −4 points points];[22] (e) NYHA functional class; (f) 6-min walking test (6MWT) distance; and (g) LVEF.

Table 1 Comparison of studies included in the meta-analysis

	Toblli et al. (2007)[18]	Okonko et al. (2008)[19] FERRIC-HF study	Anker et al. (2009)[22] FAIR-HF study	Beck-da-Silva et al. (2013)[20] IRON-HF study	Ponikowski et al. (2015)[23] CONFIRM-HF study
Design					
Major inclusion criteria regarding HF diagnosis and its severity	LVEF ≤35%, NYHA II–IV, CrCl <90 mL/min	LVEF ≤45%, NYHA class II–III, peak VO_2 ≤ 18 mL/min/kg,	LVEF ≤40% and NYHA class II, LVEF ≤45% and NYHA class III	LVEF <40%, NYHA class II–IV	LVEF ≤45%, NYHA class II or III, BNP >100 pg/mL and/or NT-proBNP >400 pg/mL
Major inclusion criteria regarding Hb concentration	Hb <12.5 g/dL for men, and Hb <11.5 g/dL for women	Hb <12.5 g/dL (anaemic group) or Hb 12.5–14.5 g/dL (non-anaemic group)	Hb 9.5–13.5 g/dL	Hb ≥9.0 and ≤12.0 g/dL	Hb <15.0 g/dL
Major inclusion criteria regarding iron status	Ferritin <100 ng/mL or TSAT ≤20%	Ferritin <100 μg/L, or ferritin 100–300 μg/L with TSAT <20%	Ferritin <100 μg/L or 100–299 μg/L with TSAT <20%	TSAT <20% and ferritin <500 μg/L	Ferritin <100 ng/mL, or 100–300 ng/mL if TSAT <20%
Centres	Single centre	Double centre (Poland and UK)	Multicentre, multinational	Multicentre	Multicentre, multinational
Randomization	Yes, 1:1	Yes, 2:1	Yes, 2:1	Yes	Yes, 1:1
Comparator	Placebo	Placebo	Placebo	Placebo	Placebo
Blinding	Double-blinded	Observer-blinded	Double-blinded	Double-blinded	Double-blinded
Iron compound	ISC	ISC	FCM	ISC	FCM
Iron dosing rules	200 mg of i.v. iron weekly	Correction phase: 200 mg of iron i.v. weekly until ferritin ≥500 microgram/L Maintenance phase: 200 mg of iron i.v. every 4 weeks	Correction phase: 200 mg of i.v. iron weekly until repletion dose is achieved. Maintenance phase: 200 mg of i.v. iron every 4 weeks. Iron repletion total dose: calculated using Ganzoni formula[42]	Iron sucrose 200 mg i.v. once a week.	Correction phase: 500–2000 mg (dosed at baseline and week 6) Maintenance phase: 500 mg at each of weeks 12, 24, and 36, if ID was still present
Applied i.v. iron dose in a treatment arm	Total iron dose: 1000 mg	1433 ± 365 mg	Mean total dose: 1850 mg	Total iron dose: 1000 mg	Mean and median total dose was 1500 mg of iron during the 1-year study period
Treatment time	5 weeks	16 weeks	Max 24 weeks	5 weeks	Max 36 weeks
Follow-up (assessments)	5 months following the treatment phase	2 weeks after the cessation of the therapy	Up to week 24–26	Up to 3 months	Up to week 52
Endpoints: events					
All-cause death	+[a]	+	+	+	+
Cardiovascular death	–	–	+	–	+
All-cause death or cardiovascular hospitalization	–	+	+	–	+
Cardiovascular death or hospitalization for worsening HF	–	–	+	–	+
HF hospitalization	+	+	+	–	+
Endpoints: parameters					
PGA	–	+	+	–	+
NYHA class	+	+	+	–	+
6MWT distance	Data not suitable for meta–analysis[b]	–	+	–	+
EQ-5D score	–	–	+	–	+
KCCQ score	–	–	+	–	+
MLHFQ score	+	+	–	–	–
LVEF	+[c]	+	–	–	–

Table 1 Continued

Baseline characteristics of studied groups according to the assigned treatment/placebo	Toblli *et al.* (2007)[18]		Okonko *et al.* (2008)[19] FERRIC-HF study		Anker *et al.* (2009)[22] FAIR-HF study		Beck-da-Silva *et al.* (2013)[20] IRON-HF study		Ponikowski *et al.* (2015)[23] CONFIRM-HF study	
	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo	Treatment	Placebo
Number of patients randomized	20	20	24	11	304[d]	155[d]	10	6	150	151
No. of patients who completed the study (= reached endpoint)	20	20	20	10	278	135	–[e]	–[e]	123	128
Age (years)	76 ± 7	74 ± 8	64 ± 14	62 ± 11	68 ± 10	67 ± 11	67 ± 8	69 ± 10	69 ± 10	70 ± 9
Female sex (%)	–[e]	–[e]	29	27	52	55	33	33	45	49
NT-proBNP (pg/mL)	256 ± 125	268 ± 115	–[e]	–[e]	–[e]	–[e]	–[e]	–[e]	2511 ± 5006	2600 ± 4555
LVEF (%)	31 ± 4	31 ± 2	30 ± 7	29 ± 6	32 ± 6	33 ± 6	25 ± 9	31 ± 7	37 ± 8	37 ± 7
NYHA class	2.9 ± 0.7	2.9 ± 0.6	2.5 ± 0.5[f]	2.5 ± 0.5[f]	2.8 ± 0.4[f]	2.8 ± 0.4[f]	No data	No data	2.5 ± 0.5[f]	2.4 ± 0.5[f]
Ischaemic HF aetiology (%)	60	65	75	73	80.6	79.4	22.2	66.7	83	83
Ferritin (μg/L)	73 ± 30	71 ± 21	62 ± 37	88 ± 62	53 ± 55	60 ± 67	185 ± 146	95 ± 128	57 ± 48	57 ± 42
TSAT	20 ± 1	20 ± 1	20 ± 8	21 ± 9	18 ± 13	17 ± 8	19 ± 10	14 ± 6	20 ± 18	18 ± 8
Haemoglobin (g/dL)	10.3 ± 0.6	10.2 ± 0.5	12.6 ± 1.2	12.2 ± 1.0	11.9 ± 1.3	11.9 ± 1.4	11.2 ± 0.6	10.9 ± 0.7	12.37 ± 1.41	12.42 ± 1.30
Anaemia (%)	100	100	50	55	65	61	100	100	53	48

Continuous variables are presented as a mean ± standard deviation of the mean.

CrCl, creatinine clearance; EQ-5D, European Quality of Life–5 Dimensions; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; ISC, iron sucrose; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living With Heart Failure Questionnaire; 6MWT, 6-min walking test; peak VO_2, peak oxygen consumption; PGA, Patient Global Assessment; TSAT, transferrin saturation.

[a] Given zero events in both the iron and placebo arm, this study was excluded from the analysis.

[b] Complete data (mean ± SD) regarding the change from baseline not available for the treatment and control arms separately

[c] Indirect data from the meta-analysis of Kapoor *et al.*[11]

[d] 304 patients were randomized to FCM but one patient assigned to the placebo group received FCM instead and therefore the number of patients treated was 305.

[e] No data available in the paper or additional materials online.

[f] Mean NYHA class as a continuous variable was calculated by the authors of this meta-analysis.

Table 2 Risk of bias assessment in the studies included in the meta-analysis according to the Cochrane Collaboration's tool for assessing risk of bias[27]

Study	Source of bias						
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Toblli *et al.* (2007)	(+)	(?)	(+)	(+)	(+)	(?)	(?)
Okonko *et al.* (2008)	(+)	(?)	(−)	(−)	(+)	(+)	(−)
Anker *et al.* (2009)	(+)	(+)	(+)	(+)	(+)	(+)	(?)
Beck-da-Silva *et al.* (2013)	(+)	(?)	(+)	(+)	(?)	(−)	(−)
Ponikowski *et al.* (2015)	(+)	(+)	(+)	(+)	(+)	(+)	(?)

(+) Low risk of bias; (−) high risk of bias; (?) unclear risk of bias.

All analyses were performed: (i) in all patients with systolic HF; (ii) only in anaemic subjects; and (iii) only in non-anaemic subjects.

Risk of bias assessment in the five trials included in this meta-analysis was assessed using the Cochrane Collaboration's tool.[27] We evaluated the following bias domains: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and researchers), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting)[27] (*Table 2*).

Statistical analyses

Dichotomous variables (events: all-cause death, cardiovascular death, all-cause death or cardiovascular hospitalization, cardiovascular death or hospitalization for worsening HF, HF hospitalization) were analysed by calculating the odds ratio (OR) statistics with 95% confidence intervals (95% CIs) as the measure of an effect of i.v. iron therapy compared with the control group.

Continuous variables (EQ-5D score, KCCQ score, PGA, MLHFQ score, NYHA class, 6MWT distance, and LVEF) were analysed by calculating a mean difference (MD) with a standard deviation (SD) of the mean as the measure of an effect of i.v. iron therapy compared with the control group. The mean change was calculated between a value at the end of the study and a baseline value. Due to the specific characteristics of the PGA scale, which in fact reflects a self-reported change of a patient's medical condition since enrolment, we considered the score from −4 to 3 points analogous to the change from baseline calculated for other continuous variables.[22]

We calculated pooled estimates of the MD and pooled estimates of the OR using a random effects model,[28] and the *P*-value <0.05 was considered statistically significant.

For the assessment of heterogeneity between the studies included in this meta-analysis, we used Q Cochran and I^2 statistics, and the *P*-value of <0.10 was considered statistically significant.[29]

All analyses were performed using R software version 3.0.3[30] and the STATISTICA 12 data analysis software system (StatSoft Inc.).

Results

Characteristics of studies included in the meta-analysis

Based on an initial search with the review of article titles and abstracts, 15 potentially eligible studies were identified and retrieved for detailed review based on full-text articles (*Figure 1*). The primary literature search was repeated by the second reviewer (E.A.J.) blinded to the results of initial study selection, and the same list of 15 studies was obtained. Among the 15 trials identified, in 7 of them there was no control group, and in 3 studies patients were receiving a combination of i.v. iron and ESA therapy.

Five eligible randomized controlled trials[18−20,22,23] yielding a total number of 851 patients with HF (509 receiving i.v. iron) were finally included in this meta-analysis. General characteristics of analysed studies are summarized in *Table 1*. Of note, in the study of Beck-da-Silva *et al.*,[20] there were three arms [iron sucrose (ISC) i.v. and placebo p.o. vs. ferrous sulfate p.o. and placebo i.v. vs. placebo i.v. and placebo p.o.], and in the analyses reported here we included only two arms, namely ISC i.v. and placebo p.o. vs. placebo i.v. and placebo p.o.

Four studies were double-blind[18,20,22,23] and one study[19] was open-label and observer-blinded only. All studies enrolled patients with HF with reduced LVEF only, and the cut-off for LVEF at inclusion varied from ≤35% to ≤45%. In two papers,[18,20] only anaemic patients were investigated (for the definition of anaemia in these studies, see *Table 1*). In three published studies,[19,22,23] available data were also extracted separately for anaemic and non-anaemic enrollees. In the study of Okonko *et al.*,[19] anaemia was defined as haemoglobin <12.5 g/dL. Regarding FAIR-HF and CONFIRM-HF trials, we applied the definition of anaemia established by the World Health Organization.[31] The definitions of ID applied in particular studies are provided in *Table 1*. In two studies,[22,23] the i.v. iron preparation was ferric carboxymaltose (FCM; the number of patients receiving active treatment = 455) and in three[18−20] it was ISC (the number of patients receiving active treatment = 54).

The availability of particular variables included in the meta-analyses of the five selected studies is summarized in *Table 1*.

In the FAIR-HF study,[22] one anaemic patient randomly assigned to the placebo group received FCM instead—in analyses regarding continuous and dichotomous (events) variables this patient was included in the placebo (according to randomization) and active treatment arm (according to the therapy received), respectively. No event analysed in this meta-analysis occurred in the aforementioned patient.

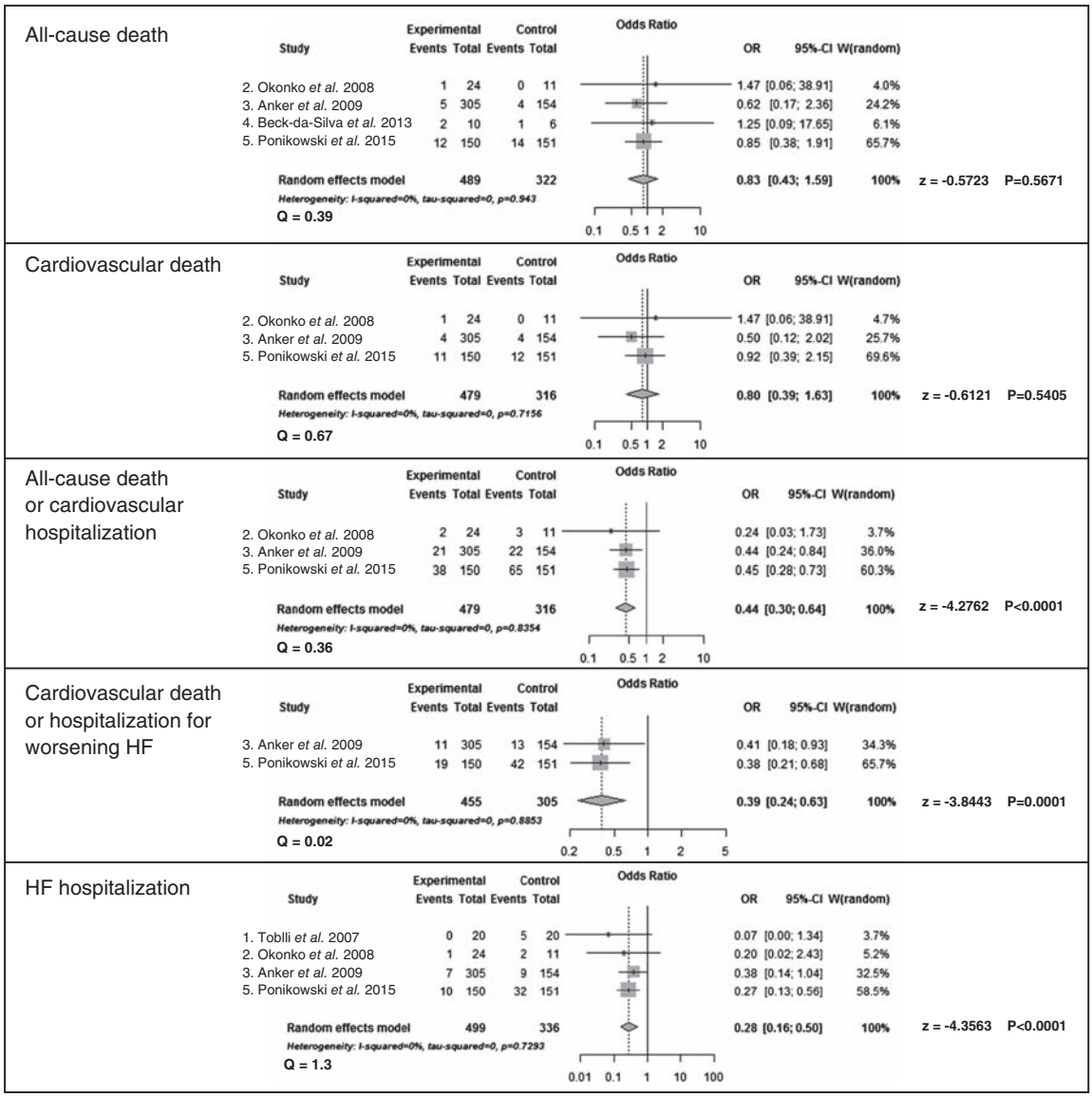

Figure 2 Effects of intravenous iron therapy on outcomes in patients with systolic heart failure (HF) and iron deficiency. CI, confidence interval, HF, heart failure; OR, odds ratio.

Effects of intravenous iron therapy in all patients with systolic heart failure

Intravenous iron therapy in patients with systolic HF and ID has been shown to reduce the risk of the combined endpoint of all-cause death or cardiovascular hospitalization, the risk of the combined endpoint of cardiovascular death or hospitalization for worsening HF, and the risk of HF hospitalization (*Figure 2*). The analysis revealed, however, no effect on either all-cause or cardiovascular mortality, which may be due to a low number of reported deaths [$n = 20$ (4%) vs. $n = 19$ (6%) for those treated vs. not treated with i.v. iron] and relatively short follow-up (*Figure 2*).

Parenteral iron therapy resulted in an improvement in exercise capacity (as reflected by a longer 6MWT distance), an alleviation of HF symptoms (a reduction in NYHA class; *Figure 3*), and an improvement in QoL as assessed using not only questionnaires specific for HF (KCCQ score and MLHFQ score) but also those reflecting patients' general medical condition (EQ-5D score and PGA) (*Figure 4*).

Effects of intravenous iron therapy in anaemic patients with systolic heart failure

In patients with systolic HF, ID, and anaemia, i.v. iron therapy has been shown to reduce the risk of combined all-cause death or cardiovascular hospitalization, combined cardiovascular death or

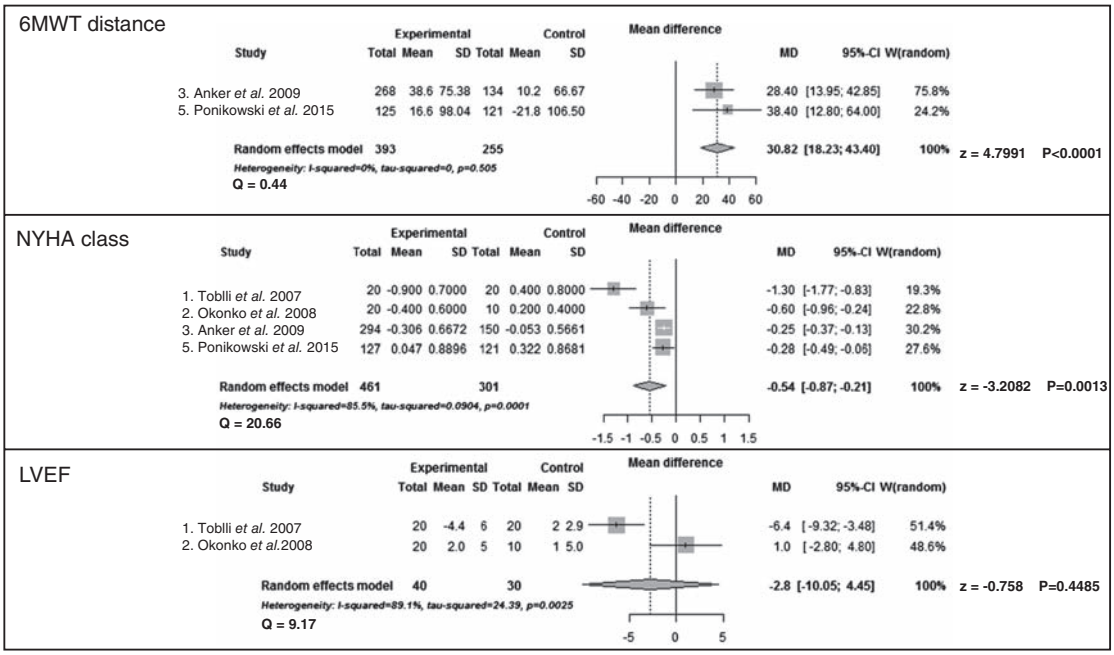

Figure 3 Effects of intravenous iron therapy on exercise capacity [6-min walking test (6MWT) distance], symptoms (NYHA class), and LVEF in patients with systolic heart failure and iron deficiency. CI, confidence interval, MD, mean difference, SD, standard deviation.

hospitalization for worsening HF, and the risk of HF hospitalization (Supplementary material online, *Figure S1*). There was no effect demonstrated on either all-cause or cardiovascular mortality (Supplementary material online, *Figure S1*).

Regarding exercise capacity, HF symptoms, and QoL in the anaemic subgroup, iron therapy resulted in an increase in 6MWT distance, the reduction in NYHA class (Supplementary material online, *Figure S2*), and an improvement in KCCQ score, EQ-5D score, and PGA (Supplementary material online, *Figure S3*).

Effects of intravenous iron therapy in non-anaemic patients with systolic heart failure

In the subgroup without co-existent anaemia, i.v. iron therapy has been demonstrated to reduce the risk of combined all-cause death or cardiovascular hospitalization, and borderline reduce the risk of HF hospitalization (Supplementary material online, *Figure S4*). There was no effect demonstrated on either all-cause or cardiovascular death (Supplementary material online, *Figure S4*). Further, in non-anaemic patients, iron therapy resulted in an increase in 6MWT distance, and the reduction in NYHA class (Supplementary material online, *Figure S5*). Regarding QoL, the treatment resulted in an improvement in PGA (Supplementary material online, *Figure S6*).

Discussion

In our meta-analysis we have demonstrated that i.v. iron therapy applied in iron-deficient patients with systolic HF, regardless of concomitant anaemia, improves outcomes, alleviates HF symptoms, and improves exercise capacity and QoL. This evidence strengthens previous data in favour of treating such patients with i.v. iron.

Regarding the most clinically relevant endpoint, i.e. all-cause death, we have found no differences in mortality rates between patients treated vs. not treated with i.v. iron, which was also demonstrated across all studies included in this meta-analysis.[18–20,22,23] This statement was valid for both all-cause and cardiovascular deaths, as well as for non-anaemic and anaemic subjects. However, it might result from the fact that the power of the analysis was not high enough to reveal statistically significant differences in mortality, due to a relatively low number of reported all-cause deaths [$n = 20$ (4.1%) vs. $n = 19$ (5.9%)] and cardiovascular deaths only [$n = 16$ (3.3%) vs. $n = 16$ (5.1%)] for those treated vs. not treated with i.v. iron, respectively. Therefore, we cannot clearly conclude about the impact of i.v. iron on either all-cause or cardiovascular mortality in iron-deficient patients with systolic HF.

There is no doubt that recurrent HF hospitalizations constitute a growing serious problem of contemporary management of patients with HF.[32–35] Our meta-analysis has revealed that i.v. iron therapy reduces the risk of HF hospitalization in iron-deficient patients with systolic HF. The reduction of hospitalization rates was seen not only in anaemic patients, but also borderline in non-anaemic subjects. In other hands, our meta-analysis provides the basis to consider i.v. iron therapy as a novel and advantageous intervention which has been able to prevent a substantial number of HF hospitalizations in patients with systolic HF.

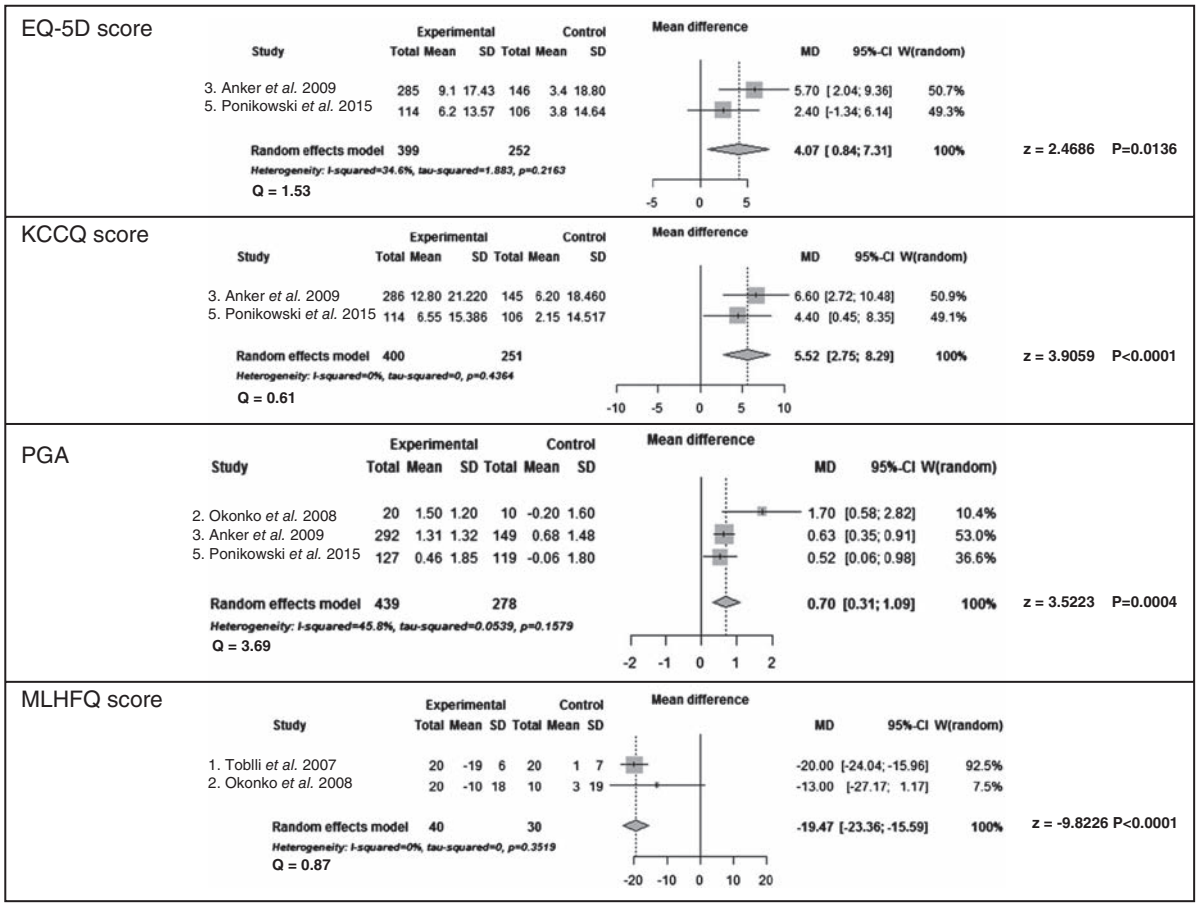

Figure 4 Effects of intravenous iron therapy on quality of life in patients with systolic heart failure and iron deficiency. CI, confidence interval, EQ-5D, European Quality of Life–5 Dimensions, KCCQ, Kansas City Cardiomyopathy Questionnaire; MD, mean differeence, MLHFQ Minnesota Living With Heart Failure Questionnaire; PGA, Patient Global Assessment; SD, standard deviation.

In the traditional approach, the beneficial effects of i.v. iron therapy were seen in patients with systolic HF and iron deficiency anaemia (IDA).[7] Surprisingly, although anaemia is considered as a common and ominous co-morbidity in HF,[36] its treatment remains challenging.[37] Erythropoiesis-stimulating agents did not bring benefits in anaemic patients with systolic symptomatic HF, and even appeared to be harmful, increasing the risk of thrombo-embolic events in these patients (RED-HF trial).[38] Therefore, i.v. iron therapy remains the only evidence-based therapy for IDA in patients with HF. In our analyses, such treatment can also can improve clinical outcomes and alleviate HF symptoms.

Most importantly, iron-deficient patients with a preserved haemoglobin level also benefit from i.v. iron therapy regarding clinical outcomes, HF symptoms, and QoL. Our analyses are in favour of the concept that ID itself should be considered as an important therapeutic target in HF,[1,3,5–7,9,39,40] and there is an effective intervention which can normalize iron status along with clinical benefits.

The limitations of this meta-analysis should be considered. Although all studies included patients with systolic HF with ID, the inclusion criteria were not identical in all papers. In some studies, additional clinical criteria such us reduced peak oxygen consumption,[19] high circulating natriuretic peptides,[23] or at least mild renal dysfunction[18] were required. Also, the analyzed studies had different treatment protocols, different iron compounds (ISC or FCM) and dosing, as well as different duration of i.v. iron therapy (from 5 to 36 weeks) and further clinical follow-up (for details see *Table 1*). Also we need to emphasize that the results of the meta-analysis were driven mainly by two studies,[22,23] where patients with systolic HF were treated with i.v. FCM (454 patients) in an active treatment arm. Importantly, it needs to be acknowledged that results of meta-analyses regarding emerging modern therapies can be influenced by the publication bias,[41] and further large-scale clinical trials are needed not only to establish the optimal dosing of iron in HF but also to confirm the impact of such therapy on clinical outcome endpoints. In conclusion, cumulative evidence from five published studies indicates that both IDA and ID itself should be considered as clinically important targets for i.v. iron therapy in patients with systolic HF.

Funding

This research was financially supported by the National Science Centre (Kraków, Poland) grant allocated on the basis of the decision number DEC-2012/05/E/NZ5/00590.

Conflict of interest: Wroclaw Medical University received an unrestricted grant from Vifor Pharma. E.A.J. reports grants and personal fees from Vifor Pharma. M.D. reports personal fees from Vifor Pharma. S.v.H. reports receiving consulting honoraria from Thermo Fisher, Solartium Dietetics, Professional Dietetics, Pfizer, Respicardia, and Vifor Pharma, grants from Vifor Pharma, payments for manuscript preparation from Solartium Dietetics and Vifor Pharma, payment for development of educational presentations from the Heart Failure Association of the European Society of Cardiology, and travel/accommodation/meeting expenses unrelated to the activities listed from Novartis Pharma. W.D. reports grants and personal fees from Vifor Pharma. W.B. reports personal fees from Vifor Pharma. G.F. was a member of the Steering and Clinical Endpoint Committee of trials sponsored by Vifor Pharma Ltd. S.D.A. reports grants and personal fees from Vifor Pharma, and is supported by grants of the German Cardiac Research Center (DZHK). P.P. reports grants and personal fees from Vifor Pharma, and personal fees from AMGEN.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Effects of intravenous iron therapy on outcomes in anaemic patients with systolic heart failure and iron deficiency.

Figure S2. Effects of intravenous iron therapy on exercise capacity and symptoms in anaemic patients with systolic heart failure and iron deficiency.

Figure S3. Effects of intravenous iron therapy on quality of life in anaemic patients with systolic heart failure and iron deficiency.

Figure S4. Effects of intravenous iron therapy on outcomes in iron-deficient patients with systolic heart failure without concomitant anaemia.

Figure S5. Effects of intravenous iron therapy on exercise capacity and symptoms in iron-deficient patients with systolic heart failure without concomitant anaemia.

Figure S6. Effects of intravenous iron therapy on quality of life in iron-deficient patients with systolic heart failure without concomitant anaemia.

References

1. Klip IT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W, Lok DJ, Rosentryt P, Torrens A, Polonski L, van Veldhuisen DJ, van der Meer P, Jankowska EA. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013;**165**:575–582.e3.
2. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, Tsagalou EP, Maroulidis GD, Alexopoulos GP, Kanakakis JE, Anastasiou-Nana MI. Etiology of anemia in patients with advanced heart failure. *J Am Coll Cardiol* 2006;**48**:2485–2489.
3. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2013;**34**:816–829.
4. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010;**31**:1872–80.
5. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, von Haehling S, Doehner W, Banasiak W, Polonski L, Filippatos G, Anker SD, Ponikowski P. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail* 2011;**17**:899–906.
6. Enjuanes C, Klip IT, Bruguera J, Cladellas M, Ponikowski P, Banasiak W, van Veldhuisen DJ, van der Meer P, Jankowska EA, Comín-Colet J. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. *Int J Cardiol* 2014;**174**:268–275.
7. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. *Nat Rev Cardiol* 2011;**8**:485–493.
8. Yeo TJ, Yeo PS, Ching-Chiew Wong R, Ong HY, Leong KT, Jaufeerally F, Sim D, Santhanakrishnan R, Lim SL, M Y Chan M, Chai P, Low AF, Ling LH, Ng TP, Richards AM, Lam CS. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance and prognosis. *Eur J Heart Fail* 2014;**16**:1125–1132.
9. Jankowska EA, Malyszko J, Ardehali H, Koc-Zorawska E, Banasiak W, von Haehling S, Macdougall IC, Weiss G, McMurray JJ, Anker SD, Gheorghiade M, Ponikowski P. Iron status in patients with chronic heart failure. *Eur Heart J* 2013;**34**:827–834.
10. Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail* 2012;**14**:423–429.
11. Kapoor M, Schleinitz MD, Gemignani A, Wu WC. Outcomes of patients with chronic heart failure and iron deficiency treated with intravenous iron: a meta-analysis. *Cardiovasc Hematol Disord Drug Targets* 2013;**13**:35–44.
12. Habedank D, Meyer FJ, Hetzer R, Anker SD, Ewert R. Relation of respiratory muscle strength, cachexia and survival in severe chronic heart failure. *J Cachexia Sarcopenia Muscle* 2013;**4**:277–285.
13. Josiak K, Jankowska EA, Piepoli MF, Banasiak W, Ponikowski P. Skeletal myopathy in patients with chronic heart failure: significance of anabolic–androgenic hormones. *J Cachexia Sarcopenia Muscle* 2014;**5**:287–296.
14. Khawaja T, Chokshi A, Ji R, Kato TS, Xu K, Zizola C, Wu C, Forman DE, Ota T, Kennel P, Takayama H, Naka Y, George I, Mancini D, Schulze CP. Ventricular assist device implantation improves skeletal muscle function, oxidative capacity, and growth hormone/insulin-like growth factor-1 axis signaling in patients with advanced heart failure. *J Cachexia Sarcopenia Muscle* 2014;**5**:297–305.
15. Klip IT, Jankowska EA, Enjuanes C, Voors AA, Banasiak W, Bruguera J, Rozentryt P, Polonski L, van Veldhuisen DJ, Ponikowski P, Comin-Colet J, van der Meer P. The additive burden of iron deficiency in the cardiorenal–anaemia axis: scope of a problem and its consequences. *Eur J Heart Fail* 2014;**16**:655–662.
16. Filippatos G, Farmakis D, Colet JC, Dickstein K, Lüscher TF, Willenheimer R, Parissis J, Gaudesius G, Mori C, von Eisenhart Rothe B, Greenlaw N, Ford I, Ponikowski P, Anker SD. Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial. *Eur J Heart Fail* 2013;**15**:1267–1276.
17. Van Craenenbroeck EM, Conraads VM, Greenlaw N, Gaudesius G, Mori C, Ponikowski P, Anker SD. The effect of intravenous ferric carboxymaltose on red cell distribution width: a subanalysis of the FAIR-HF study. *Eur J Heart Fail* 2013;**15**:756–762.
18. Toblli JE, Lombraña A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007;**50**:1657–1665.
19. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008;**51**:103–112.
20. Beck-da-Silva L, Piardi D, Soder S, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, Moura LZ, Montera MW, Rassi S, Clausell N. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. *Int J Cardiol* 2013;**168**:3439–3442.
21. Comín-Colet J, Ruiz S, Cladellas M, Rizzo M, Torres A, Bruguera J. A pilot evaluation of the long-term effect of combined therapy with intravenous iron sucrose and erythropoietin in elderly patients with advanced chronic heart failure and cardio-renal anemia syndrome: influence on neurohormonal activation and clinical outcomes. *J Card Fail* 2009;**15**:727–735.
22. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Lüscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart

Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–2448.
23. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;**36**: 657–668.
24. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;**33**:337–343.
25. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. *J Am Coll Cardiol* 2000;**35**:1245–1255.
26. Rector TS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure, part 2: content, reliability and validity of a new measure, the Minnesota Living with Heart Failure Questionnaire. *Heart Fail* 1987;**198–209**.
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;**7**:177–188.
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558.
30. R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2013.
31. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser* 1968;**405**:5–37.
32. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, Fruhwald F, Gullestad L, Logeart D, Fabbri G, Urso R, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors AA, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013;**15**:808–817.
33. Gheorghiade M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for heart failure: problems and perspectives. *J Am Coll Cardiol* 2013; **61**:391–403.
34. Cowie MR, Anker SD, Cleland JG, Felker GM, Filippatos F, Jaarsma T, Jourdain P, Knight E, Massie B, Ponikowski P, López-Sendón J. Improving care for patients with acute heart failure: before, during and after hospitalization. *ESC Heart Fail* 2014;**1**:110–145.
35. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Siswanto BB, Karen Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. *ESC Heart Faile* 2014;**1**:4–25.
36. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol* 2008;**52**: 818–227.
37. von Haehling S, Anker MS, Jankowska EA, Ponikowski P, Anker SD. Anemia in chronic heart failure: can we treat? What to treat? *Heart Fail Rev* 2012;**17**:203–210.
38. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJ, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van Veldhuisen DJ; RED-HF Committees; RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013;**368**:1210–1219.
39. Clark AL, Pellicori P. Clinical trials update from the European Society of Cardiology meeting 2014: PARADIGM-HF, CONFIRM-HF, SIGNIFY, atrial fibrillation, beta-blockers and heart failure, and vagal stimulation in heart failure. *ESC Heart Fail* 2014;**1**:82–86.
40. Cohen-Solal A, Damy T, Terbah M, Kerebel S, Baguet JP, Hanon O, Zannad F, Laperche T, Leclercq C, Concas V, Duvillié L, Darné B, Anker S, Mebazaa A. High prevalence of iron deficiency in patients with acute decompensated heart failure. *Eur J Heart Fail* 2014;**16**:984–991.
41. Dickersin K. The existence of publication bias and risk factors for its occurrence. *JAMA* 1990;**263**:1385–1389.
42. Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. *Schweiz Med Wochenschr* 1970;**100**:301–303.
43. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *PLoS Med* 2009;**6**:e1000097.