Intravenous ferric carboxymaltose in iron-deficient chronic heart failure patients with and without anaemia: a subanalysis of the FAIR-HF trial

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Aims
Therapy with i.v. iron in patients with chronic heart failure (CHF) and iron deficiency (ID) improves symptoms, functional capacity, and quality of life. We sought to investigate whether these beneficial outcomes are independent of anaemia.

Methods and results
FAIR-HF randomized 459 patients with CHF [NYHA class II or III, LVEF ≤ 40% (NYHA II) or ≤ 45% (NYHA III)] and ID to i.v. iron as ferric carboxymaltose (FCM) or placebo in a 2:1 ratio. We analysed the efficacy and safety according to the presence or absence of anaemia (haemoglobin ≤ 120 g/L) at baseline. Of 459 patients, 232 had anaemia at baseline (51%). The effect of FCM on the primary endpoints of self-reported Patient Global Assessment (PGA) and NYHA class at week 24 was similar in patients with and without anaemia [odds ratio (OR) for improvement, 2.48 vs. 2.60, \( P = 0.97 \) for PGA and 1.90 vs. 3.39, \( P = 0.51 \) for NYHA]. Results were also similar for the secondary endpoints, including PGA and NYHA at weeks 4 and 12, 6 min walk test distance, Kansas City Cardiomyopathy Questionnaire overall score, and European Quality of Life-5 Dimensions Visual Analogue Scale at most time points. Regarding safety, no differences were noticed in the rates of death or first hospitalization between FCM and placebo both in anaemic and in non-anaemic patients.

Conclusions
Treatment of ID with FCM in patients with CHF is equally efficacious and shows a similar favourable safety profile irrespective of anaemia. Iron status should be assessed in symptomatic CHF patients both with and without anaemia and treatment of ID should be considered.

Keywords
Anaemia • Iron deficiency • Heart failure • Intravenous iron • Ferric carboxymaltose

Introduction
Anaemia represents a frequent co-morbidity, an indicator of more advanced disease, and an independent predictor of prognosis in patients with chronic heart failure (CHF).¹,² The prevalence of anaemia in CHF ranges between 10% and 50%, depending on the severity of CHF and the applied haemoglobin (Hb) cut-offs.³ Moreover, anaemia is associated with reduced functional capacity, worse quality of life, increased...
prevalence of other co-morbidities, such as renal dysfunction and diabetes mellitus, and ultimately worse prognosis.\(^1,^2\)

The aetiology of anaemia in CHF is multifactorial and involves several mechanisms such as blunted erythropoietin production, erythropoietin resistance, iron deficiency, and defective iron utilization resulting from neurohormonal and inflammatory activation, renal dysfunction, and renin–angiotensin–aldosterone system inhibition.\(^3\)–\(^4\)

Thus, both erythropoiesis-stimulating agents (ESAs) and iron repletion have emerged as potential therapeutic modalities in CHF.

While earlier placebo-controlled studies suggested a potentially beneficial effect of administration of ESAs on exercise capacity and quality of life, because of the results of the ‘Reduction of Events with Darbepoetin alfa in Heart Failure’ (RED-HF) trial, the use of ESAs in CHF patients with mild to moderate anaemia is no longer supported.\(^5\) Iron deficiency, on the other hand, is found in approximately one-third of CHF patients, even in the absence of anaemia, and is independently associated with adverse outcomes.\(^6\) The recent FAIR-HF (‘Ferinject\(^6\) Assessment in patients with IRon deficiency and chronic Heart Failure’) trial showed that treatment of iron deficiency with i.v. ferric carboxymaltose (FCM) in CHF patients with NYHA class II or III and impaired LV systolic function improved symptoms, functional capacity, and quality of life at week 24.\(^7\)\(^8\) Interestingly, the beneficial effects of FCM on the study’s primary endpoints, namely the self-reported Patient Global Assessment (PGA) and NYHA class, were irrespective of the presence of anaemia. Similar results were earlier reported by the smaller Ferric Iron Sucrose in Heart Failure (FERRIC-HF) trial testing i.v. iron sucrose for 16 weeks, although in this trial the benefits were more pronounced in anaemic patients.\(^9\)

In order to reach a deeper understanding on the interaction among iron deficiency, anaemia, and iron supplementation therapy in CHF, we sought to evaluate the effects of i.v. FCM in CHF patients with iron deficiency seen in FAIR-HF according to the presence or absence of anaemia at baseline.

**Methods**

The methodology of the FAIR-HF trial has been described in detail elsewhere.\(^7\)\(^8\) In summary, 459 ambulatory patients with CHF, NYHA class II or III, impaired LVEF (≤40% for NYHA II or ≤45% for NYHA III), iron deficiency (serum ferritin <100 μg/L or 100–299 μg/L if transferrin saturation (TSAT) <20%), and a haemoglobin (Hb) level of 95–135 g/L were randomized to i.v. iron as FCM or placebo (saline) in a 2:1 ratio. The required total iron dose for correcting iron deficiency was calculated according to the Ganzoni formula that calculates iron deficit using body weight, target and actual Hb levels, and iron stores; FCM was administered as an i.v. push injection at a dose equivalent to 200 mg iron weekly until achievement of iron repletion (correction phase) and then every 4 weeks thereafter (maintenance phase).

The primary endpoints were the self-reported PGA and NYHA class (adjusted for baseline class) at week 24. Secondary efficacy endpoints were the PGA and NYHA class at weeks 4 and 12, as well as the 6 min walk test (6MWT) distance, the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, and the European Quality of Life-5 Dimensions (EQ-5D) Visual Analogue Scale (VAS) at weeks 4, 12, and 24 (all adjusted for baseline values). Both for the overall KCCQ and the EQ-5D VAS, scores range from 0 to 100, with higher scores indicating better quality of life.\(^10\)\(^11\) Safety endpoints included any serious and non-serious adverse events, as well as hospitalizations and deaths up to week 26.

In the present pre-specified subanalysis, we compared baseline demographics, clinical profiles, and main laboratory measurements of anaemic with those of non-anaemic patients, and analysed the trial’s efficacy and safety endpoints according to the presence or absence of anaemia. Anaemia was defined as a haemoglobin concentration of ≤120 g/L.

**Statistical analysis**

Baseline data are described using mean (SD) or median (lower quartile, upper quartile) for continuous variables depending on the distribution of the data, or number (percentage) for categorical variables. Differences between the anaemic and non-anaemic groups at baseline were tested using analysis of variance (ANOVA) or Kruskal–Wallis test for the continuous variables depending on the distribution of the data, and Pearson’s \(\chi^2\) test or Fisher’s exact test for the categorical variables.

In subgroups of patients with and without anaemia separately, NYHA and PGA outcomes were analysed using proportional odds models at 4, 12, and 24 weeks with the estimated odds ratio (OR), and the OR 95% confidence intervals (CIs) for a better outcome in the FCM group compared with placebo and \(P\)-values were reported.\(^12\) Tests for interaction between anaemic and non-anaemic patients were carried out in a joint model including anaemic and non-anaemic patients. Results for the NYHA endpoint are adjusted for baseline NYHA. Similar analyses within the subgroups of patients with and without anaemia separately were carried out for a variety of subgroups, with the interaction between subgroup and treatment effect analysed within the proportional odds model. 6MWT distance, KCCQ (overall score), and EQ-5D VAS were analysed as continuous variables within the subgroups of patients with and without anaemia separately, with treatment effects on changes from baseline at 4, 12, and 24 evaluated in a repeated-measures model adjusted for baseline value. Least square mean changes from baseline and their standard errors were displayed graphically.

Cox proportional hazards models were used to compare risk of the safety outcomes by the treatment received. All statistical analyses were performed using SAS software version 9.1 or higher (SAS Institute).

**Results**

**Baseline characteristics**

Overall, 232 of 459 patients had anaemia at baseline (51%). Patients’ demographics, clinical profile, and main laboratory values according to anaemia status and the treatment arm are presented in Table 1. Besides a significantly lower Hb level and iron-related parameters (\(P < 0.001\)), patients with anaemia were more frequently female (\(P = 0.01\)), had a decreased 6MWT distance (\(P < 0.001\)), and their renal function was lower (\(P < 0.001\)). On the other hand, anaemic patients showed a less frequent history of ischaemic CHF (\(P = 0.035\)) and previous myocardial infarction compared with patients without anaemia (\(P = 0.001\)).
**Table 1  Baseline demographics, clinical characteristics, and main laboratory measurements of the study population according to the presence or absence of anaemia at baseline and treatment arm (ferric carboxymaltose or placebo)**

|                                | Anaemic (n = 232) | Placebo (n = 227) | Non-anaemic (n = 227) | Placebo (n = 78) |
|--------------------------------|-------------------|-------------------|-----------------------|-----------------|
|                                | FCM (n = 155)     | Placebo (n = 77)  | FCM (n = 149)         | Placebo (n = 78) |
| Age, years                     | 68.2 (10.7)       | 67.9 (11.2)       | 67.5 (9.9)            | 67.0 (11.2)     |
| Female, n (%)                  | 92 (59.4%)        | 45 (58.4%)        | 67 (45.0%)            | 40 (51.3%)      |
| Caucasian, n (%)               | 154 (99.4%)       | 77 (100.0%)       | 149 (100.0%)          | 78 (100.0%)     |
| NYHA class II, n (%)           | 22 (14.2%)        | 13 (16.9%)        | 31 (20.8%)            | 16 (20.5%)      |
| NYHA class III, n (%)          | 133 (85.8%)       | 64 (83.1%)        | 118 (79.2%)           | 62 (79.5%)      |
| Ejection fraction, %           | 31.8 (5.8)        | 32.6 (6.5)        | 32.1 (5.2)            | 33.4 (5.6)      |
| Body weight, kg                | 75.9 (15.5)       | 77.5 (16.2)       | 78.0 (12.7)           | 77.7 (16.5)     |
| Body mass index, kg/m²         | 28.1 (5.3)        | 28.2 (5.2)        | 27.9 (4.1)            | 28.0 (5.0)      |
| Systolic blood pressure, mmHg  | 126 (15)          | 127 (14)          | 126 (15)              | 126 (15)        |
| Diastolic blood pressure, mmHg | 77 (10)           | 77 (10)           | 77 (9)                | 75 (10)         |
| Pulse rate, b.p.m.             | 71 (12)           | 71 (13)           | 70 (11)               | 73 (11)         |
| 6 min walk test distance, m    | 251 (96)          | 251 (117)         | 297 (108)             | 287 (98)        |
| Ischaemic, n (%)               | 119 (76.8%)       | 58 (73.5%)        | 126 (84.6%)           | 65 (83.3%)      |
| Cardiovascular risk factor     |                   |                   |                       |                 |
| Hypertension, treated with drugs, n (%) | 123 (79.4%)  | 59 (76.6%)        | 120 (80.5%)           | 69 (88.5%)      |
| Dyslipidaemia, treated with drugs, n (%) | 66 (42.6%)  | 38 (49.4%)        | 78 (52.3%)            | 32 (41.0%)      |
| Diabetes mellitus, n (%)       | 51 (32.9%)        | 16 (20.8%)        | 42 (28.2%)            | 21 (26.9%)      |
| History of AF, n (%)           | 52 (33.5%)        | 25 (32.5%)        | 42 (28.2%)            | 19 (24.4%)      |
| Medical history                |                   |                   |                       |                 |
| Previous myocardial infarction, n (%) | 74 (47.7%)  | 39 (50.6%)        | 94 (63.1%)            | 51 (65.4%)      |
| Known angina pectoris, n (%)   | 84 (54.2%)        | 38 (49.4%)        | 87 (58.4%)            | 51 (65.4%)      |
| Previous stroke, n (%)         | 12 (7.7%)         | 5 (6.5%)          | 12 (8.1%)             | 4 (5.1%)        |
| Previous CABG, n (%)           | 17 (11.0%)        | 7 (9.1%)          | 17 (11.4%)            | 6 (7.7%)        |
| Previous PTCA, n (%)           | 19 (12.3%)        | 11 (14.3%)        | 26 (17.4%)            | 9 (11.5%)       |
| Laboratory measurements        |                   |                   |                       |                 |
| Haemoglobin, g/L               | 109 (8)           | 108 (8)           | 129 (7)               | 130 (9)         |
| Red blood cell count, 10¹²/L   | 4.0 (0.5)         | 4.0 (0.4)         | 4.3 (0.4)             | 4.4 (0.4)       |
| Mean corpuscular volume, fl    | 89.4 (7.9)        | 90.6 (7.3)        | 93.9 (7.6)            | 92.7 (6.0)      |
| Iron, μmol/L                   | 12.7 (16.1)       | 9.3 (4.4)         | 13.4 (5.6)            | 13.9 (6.0)      |
| Serum ferritin, μg/L           | 51.3 (62.9)       | 59.2 (68.4)       | 53.7 (44.4)           | 60.9 (65.0)     |
| Transferrin, g/L               | 3.01 (0.54)       | 2.95 (0.58)       | 2.91 (0.48)           | 2.83 (0.43)     |
| Transferrin saturation, %      | 16.6 (15.6)       | 13.5 (7.4)        | 18.8 (8.4)            | 19.8 (8.1)      |
| Folate (folic acid), nmol/L    | 18.2 (10.4)       | 16.6 (8.5)        | 16.6 (8.0)            | 15.5 (8.0)      |
| Vitamin B12, pmol/L            | 289 (132)         | 299 (126)         | 282 (128)             | 293 (129)       |
| Creatinine, μmol/L             | 110 (60)          | 114 (69)          | 101 (35)              | 99 (35)         |
| Blood urea nitrogen, mg/dL     | 25.4 (13.1)       | 27.1 (16.0)       | 22.5 (10.9)           | 23.1 (11.3)     |
| Estimated glomerular filtration rate, mL/min | 61.9 (22.6) | 61.7 (26.5)       | 65.8 (19.6)           | 67.9 (23.9)     |
| Potassium, mmol/L              | 4.63 (0.64)       | 4.57 (0.52)       | 4.66 (0.59)           | 4.58 (0.53)     |
| Sodium, mmol/L                 | 141 (3)           | 140 (3)           | 141 (3)               | 141 (3)         |
| Total bilirubin, μmol/L         | 9.9 (7.4)         | 9.9 (5.9)         | 11.0 (5.6)            | 11.1 (6.3)      |
| Alanine aminotransferase, U/L   | 20.4 (11.7)       | 17.9 (7.5)        | 20.7 (12.9)           | 19.7 (8.7)      |
| Aspartate aminotransferase, U/L | 23.2 (10.4)      | 22.4 (7.0)        | 22.9 (10.5)           | 22.4 (7.4)      |
| Uric acid, mmol/L              | 0.38 (0.13)       | 0.40 (0.14)       | 0.37 (0.12)           | 0.40 (0.11)     |
| C-reactive protein, mg/L        | 7.62 (4.55)       | 9.71 (4.36)       | 7.30 (6.07)           | 8.47 (6.35)     |
| Concomitant treatment          |                   |                   |                       |                 |
| Diuretics, n (%)               | 141 (91.0%)       | 69 (89.6%)        | 139 (93.3%)           | 71 (91.0%)      |
| Agents blocking renin–angiotensin system, n (%) | 140 (90.3%)  | 69 (89.6%)        | 141 (94.6%)           | 72 (92.3%)      |
| Beta-blockers, n (%)           | 132 (85.2%)       | 64 (83.1%)        | 130 (87.2%)           | 65 (83.3%)      |
| Cardiac glycosides, n (%)      | 24 (15.5%)        | 14 (18.2%)        | 22 (14.8%)            | 11 (14.1%)      |
| Antiarrythmics, class I and III, n (%) | 20 (12.9%) | 5 (6.5%)          | 17 (11.4%)            | 6 (7.7%)        |
Efficacy endpoints

The primary endpoints of self-reported PGA and NYHA class at week 24 were significantly improved by FCM therapy independently of the presence or absence of anaemia (Figure 1). Specifically, more patients reported improvement and fewer patients reported worsening or no change in their condition at week 24 in the FCM arm compared with placebo, both in anaemic and in non-anaemic patients; the OR and 95% CI for a better rank in PGA were 2.48 (1.49–4.14), \( P < 0.001 \), for anaemic patients and 2.60 (1.55–4.35), \( P < 0.001 \) for non-anaemic patients (interaction \( P = 0.98 \)). Similarly,

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Table I Continued

|                              | Anaemic (n = 232) | Non-anaemic (n = 227) |
|------------------------------|-------------------|-----------------------|
|                              | FCM (n = 155)     | Placebo (n = 77)      | FCM (n = 149) | Placebo (n = 78) |
| Antplatelet agents, n (%)    | 100 (64.5%)       | 47 (61.0%)            | 89 (59.7%)    | 50 (64.1%)       |
| Anticoagulant agents, n (%)  | 35 (22.6%)        | 11 (14.3%)            | 32 (21.5%)    | 11 (14.1%)       |
| Insulin and analogues, n (%) | 18 (11.6%)        | 4 (5.2%)              | 9 (6.0%)      | 5 (6.4%)         |
| Oral hypoglycaemic agents, n | 27 (17.4%)        | 9 (11.7%)             | 22 (14.8%)    | 13 (16.7%)       |
| Lipid-lowering agents, n (%) | 61 (39.4%)        | 35 (45.5%)            | 81 (54.4%)    | 37 (47.4%)       |

Continuous variables are expressed as mean (standard deviation) and categorical variables as number of cases (percentage).
CABG, coronary artery bypass grafting; FCM, ferric carboxymaltose; PTCA, percutaneous transluminal coronary angioplasty.

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Figure 1  Self-reported Patient Global Assessment (PGA) and NYHA class at week 24 according to the presence or absence of anaemia at baseline and treatment arm [ferric carboxymaltose (FCM) or placebo].
NYHA class, adjusted for baseline class, was better at week 24 in the FCM arm compared with placebo, both in anaemic and in non-anaemic patients; the OR and 95% CI for improvement by one class were 1.90 (1.06–3.40), \( P = 0.03 \) for anaemic and 3.39 (1.70–6.75), \( P < 0.001 \) for non-anaemic patients (interaction \( P = 0.51 \)).

Regarding the trial’s secondary efficacy endpoints, self-reported PGA scores at weeks 4 and 12 were also significantly better in the FCM arm both in anaemic and in non-anaemic patients (FCM vs. placebo, \( P < 0.001 \) for both anaemic and non-anaemic patients, interaction \( P = 0.56 \) and \( P = 0.19 \) for PGA at week 4 and 12, respectively), and the same applied to NYHA class at week 4 (FCM vs. placebo, \( P = 0.002 \) for anaemic and \( P = 0.02 \) for non-anaemic patients, interaction \( P = 0.66 \), and at week 12 (FCM vs. placebo, \( P < 0.001 \) for anaemic and \( P = 0.004 \) for non-anaemic patients, interaction \( P = 0.34 \), Figure 2). Furthermore, 6MWT distance was significantly increased in the FCM arm both in patients with and in those without anaemia at weeks 4, 12, and 24 (FCM vs. placebo, \( P < 0.001 \), \( P < 0.001 \), and \( P < 0.01 \) for weeks 4, 12, and 24 in anaemic patients, and \( P = 0.04 \), \( P = 0.002 \), and \( P < 0.001 \) respectively in non-anaemic patients, interaction \( P = 0.42 \), \( P = 0.49 \), and \( P = 0.55 \), respectively, Figure 3). Regarding the quality of life questionnaires, both the EQ-5D VAS and the KCCQ overall summary score were significantly better in the FCM arm, in both anaemic and non-anaemic patients, at weeks 4, 12, and 24, with the exception of EQ-5D VAS at week 12 in the non-anaemic group (EQ-5D VAS, FCM vs. placebo, \( P = 0.004 \), \( P < 0.001 \), and \( P = 0.02 \) for weeks 4, 12, and 24 in anaemic patients, and \( P = 0.002 \), \( P = 0.18 \), and \( P < 0.01 \) in non-anaemic patients, interaction \( P = 0.79 \), \( P = 0.07 \), and \( P = 0.91 \), respectively; KCCQ, FCM vs. placebo, \( P < 0.001 \), \( P < 0.001 \), and \( P = 0.009 \) for weeks 4, 12, and 24 in anaemic patients, and \( P < 0.01 \), \( P = 0.03 \), and \( P = 0.02 \) in non-anaemic patients, interaction \( P = 0.27 \), \( P = 0.16 \), and \( P = 0.59 \), Figure 4).

**Safety endpoints**

The safety endpoints and the investigator-reported adverse events are shown in Table 2. Up to week 26, a total of 30 (13%) patients died or were hospitalized in the anaemia group [18 (12%) in the FCM arm and 12 (16%) in the placebo arm, \( P = 0.28 \)] and 19 (8%) patients, interaction \( P = 0.42 \), \( P = 0.49 \), and \( P = 0.55 \), respectively, Figure 3).
in the non-anaemic group [12 (8%) in the FCM arm and 7 (9%) in the placebo arm, \( P = 0.79 \)]. In patients with anaemia, FCM therapy was followed by significantly lower rates of death due to worsening HF (\( P = 0.013 \)) and hospitalization for any cardiovascular reason (\( P = 0.026 \)) compared with placebo, and there was also a weak trend towards a lower rate of hospitalization for any cardiovascular reason or death (\( P = 0.094 \)). In contrast, the rates of death or hospitalization did not differ between the FCM and the placebo arm in the non-anaemic group. Regarding the investigator-reported serious adverse events (SAEs), FCM therapy in patients with anaemia was followed by lower rates of cardiac disorders (\( P = 0.035 \)) and of thoracic, respiratory, or mediastinal disorders (\( P = 0.013 \)) compared with placebo. No differences in SAEs were encountered between the FCM and placebo arms in patients without anaemia.

Dosage

In the FCM group, the mean total dose administered was 1850 mg of iron during the 24-week treatment period. The median total iron dose to correct the iron deficiency during the correction phase was 1000 mg, and the median cumulative maintenance dose an additional 1000 mg. Neither the mean correction dose nor the mean maintenance iron dose considerably differed between the anaemic and the non-anaemic group (Table 3) (Supplementary material, Table S1).

Discussion

In the FAIR-HF trial study population, 51% of CHF patients, with NYHA class II or III symptoms, impaired LVEF, and iron deficiency had anaemia, defined as a Hb concentration of \( \leq 120 \) g/L. In line with previous reports,\(^{1,13}\) patients with anaemia were more frequently female, had worse functional status, higher incidence of NYHA class III, decreased distance in the 6MWT, and impaired renal function compared with those without anaemia. Interestingly, the previously observed beneficial effects of i.v. FCM therapy on patients’ symptoms, functional capacity, and quality of life\(^8\) were found to be independent of the presence or absence of anaemia at baseline, and these positive effects were consistent across all predefined subgroups. In addition, the overall safety profile of the drug was similar in patients with and those without anaemia.

Chronic anaemia is followed by tissue hypoxia due to decreased red cell production and reduced oxygen-carrying capacity of the blood. This causes an adaptive cardiovascular response, characterized by increased cardiac output, cardiac remodelling with ventricular hypertrophy and dilatation, and afterload reduction. Despite those compensatory reactions, it seems that the normal heart copes well with chronic anaemia without developing cardiac failure or evident LV dysfunction, even with low Hb levels and even in elderly individuals.\(^{14}\) This may not be the case in CHF patients, in which the functional reserve and the adaptation abilities of the cardiovascular system are obviously impaired. Anaemia has been associated with adverse prognosis in CHF. In a meta-analysis of 34 studies comprising 153 180 CHF patients, anaemia was associated with an almost double crude mortality risk and a 1.5 times higher adjusted mortality risk at 6 months (crude OR, 1.96; adjusted hazard ratio, 1.46).\(^1\) However, whether treatment of chronic anaemia in CHF patients is associated with better outcome remains controversial.

Several mechanisms are involved in the pathophysiology of anaemia in CHF, including blunted erythropoietin production and/or erythropoietin resistance, further bone marrow dysfunction, gastrointestinal blood losses, and haemodilution.\(^{2,15}\) but, in the majority of patients, iron deficiency seems to play a role.\(^6\) The use of
ESAs in CHF was initially received with enthusiasm as early small clinical studies showed improvement in surrogates of functional status, quality of life, and cardiac performance, but evidence on prognosis remained inconclusive until the very recent release of the RED-HF trial. The trial showed that ESAs did not reduce death from any cause or hospitalization for worsening HF when given in CHF with mild to moderate anaemia, while it increased the risk of thrombo-embolic events. Moreover, two large trials of ESAs in chronic kidney disease showed an increased risk of death or stroke, and therefore raised safety concerns.

Besides being a cause of anaemia in CHF, iron deficiency seems to be frequent in CHF and is associated with worse prognosis regardless of the presence of anaemia. The prevalence of iron deficiency in CHF varies widely, from 5% to 73%, depending on the population studied and the methods used to define iron deficiency. In a group of 546 CHF patients, iron deficiency was encountered in 57% of patients with anaemia but also in 32% of those without anaemia (37% overall prevalence), while it was independently associated with reduced event-free survival at 36 months.

**Figure 4** European Quality of Life-5 Dimensions Visual Analogue (EQ-5D VAS) and Kansas City Cardiomyopathy Questionnaire overall summary score (KCCQ OSS) according to the presence or absence of anaemia at baseline and treatment arm [ferric carboxymaltose (FCM) or placebo].
Besides being an integral component of Hb, the iron-containing oxygen transport protein in the red blood cells plays a critical role in cellular function. Among others, iron-containing proteins are also involved in oxygen storage (myoglobin) and cellular energy production in skeletal muscles. Accordingly, iron deficiency in humans has been associated with reduced exercise capacity and maximal...
Guidelines, it has been suggested that treatment with i.v. iron should be obtained in these patients by measuring serum ferritin concentrations and in combination with TSAT. In both European and Australian settings, functional iron deficiency may also be present in the context of a chronic inflammatory disease such as CHF. Pro-inflammatory cytokines, particularly interleukin-6, up-regulate the synthesis of hepcidin, the key systemic iron-regulatory hormone, which regulates intestinal iron absorption and tissue iron distribution by inducing degradation of the cellular iron exporter ferroportin. 33

In the present study, besides the amelioration of patients’ symptoms as depicted by the primary endpoints of self-reported PGA and NYHA class, iron therapy also had positive effects on quality of life and exercise capacity. Moreover, these beneficial effects were encountered as early as at week 4 and persisted throughout the follow-up period until week 24.

In conclusion, treatment of iron deficiency with i.v. FCM in NYHA class II or III CHF patients with impaired LV systolic function shows a good safety profile, and is well tolerated and rewarding in terms of symptoms, exercise capacity, and quality of life, regardless of the presence of anaemia. A reliable evaluation of the iron status can be obtained in these patients by measuring serum ferritin concentrations and in combination with TSAT. In both European and Australian Guidelines, it has been suggested that treatment with i.v. iron should be considered in iron-deficient patients. The better understanding of iron metabolism in CHF and other chronic diseases and the evaluation of iron deficiency as a therapeutic target merit further investigation. Two ongoing studies (EFFIC-HF and CONFIRM-HF) investigate the effect of i.v. iron on exercise capacity, physical functioning, and quality of life in patients with iron deficiency and CHF.

Supplementary material

Supplementary material is available at European Journal of Heart Failure online.

Conflicts of interest: S.D.A., P.P., J.C.C., G.F., R.W., K.D., and T.L. are members of the FAIR-HF steering committee. S.D.A. P.P., and R.W. are consultants and have received honoraria for speaking for Vifor Pharma Ltd and Amgen, Inc. S.D.A. has received honoraria for speaking for Roche Pharma and Teva. J.C.C., G.F., and T.L. have received honoraria for speaking for Vifor Pharma Ltd. C.M. and B.E.R. are employees of Vifor Pharma Ltd and hold stock in Galenica Ltd. G.G. is an employee of Vifor Pharma Ltd. I.F. and N.G. have received research funding from Vifor Pharma Ltd for the analysis of the FAIR-HF data set. D.F. and J.P. have no conflict of interest.

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