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ARTICLE

Iron deficiency in heart failure with preserved ejection fraction: rationale and design of the FAIR-HFpEF trial

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Abstract

Background: Iron deficiency is highly prevalent in patients with heart failure and has well established diagnostic criteria. Its occurrence is associated with reduced quality of life, exercise capacity and increased hospitalization rates and mortality. The clinical efficacy of treating iron deficiency has not been tested in patients with heart failure with preserved ejection fraction (HFpEF).

Methods: The FAIR-HFpEF trial aims to enroll patients with HFpEF, reduced exercise capacity and iron deficiency (defined as serum ferritin <100 ng/mL or serum ferritin 100-299 ng/mL with transferrin saturation <20%). Patients will be treated in a multi-center, double-blind, randomized clinical trial with intravenous ferric carboxymaltose (FCM) at doses aimed to replenish iron stores *vs.* placebo. The primary endpoint is the difference in exercise capacity from baseline to week 24 as assessed by the 6-minute walk test. Secondary endpoints include health-related quality of life assessments such as the Kansas City Cardiomyopathy Questionnaire, the European Quality of Life-5 Dimensions questionnaire and global function tests.

Conclusions: The FAIR-HFpEF trial is designed to investigate the effect of intravenous iron repletion in iron deficient patients with HFpEF using FCM.

Key words heart failure, preserved ejection fraction, exercise capacity, iron deficiency.

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Introduction

Heart failure (HF) affects millions of patients worldwide and is a major cause of death in the elderly.[1,2] Co-morbidities are numerous and have relevant impact on symptoms, quality of life and outcomes. Following the large FAIR-HF and CONFIRM-HF trials,[3,4] the European Society of Cardiology (ESC),[2] and other international bodies recommend the treatment of iron deficiency (ID) intravenously using ferric carboxymaltose (FCM) in symptomatic patients with HF with reduced ejection fraction (HFrEF) and ID [defined as serum ferritin <100 ng/mL or serum ferritin 100-299 ng/mL with transferrin saturation (TSAT) <20%] to *alleviate HF symptoms, improve exercise capacity and quality of life*. Most recent evidence for this group of patients has been added by publication of the IRONMAN trial in late 2022 using ferric derisomaltose in patients with HFrEF and ID.[5] The AFFIRM-AHF trial has helped to extend recommendations for the use of FCM to symptomatic HF patients recently hospitalized for worsening HF with either reduced or mildly reduced ejection fraction (HFmrEF) with left ventricular ejection fraction (LVEF) ≤50% and ID. Altogether, treatment of ID using FCM has been deemed safe and cost-effective.[6]

ESC and the joint guidelines of the American College of Cardiology, the American Heart Association and the Heart Failure

Association of America recommend to diagnose ID using the aforementioned cut-off values for ferritin and TSAT in all patients with HF across the entire spectrum of LVEF.[2,7] Apart from high prevalence values of ID in patients with HFrEF and HFmrEF, several analyses have shown similar trends for patients with HF with preserved ejection fraction (HFpEF). A recent meta-analysis of 15 studies has shown an ID prevalence of 59% among these patients.[8] The presence of ID in patients with HFpEF leads to reduced exercise capacity as evidenced by a lower peak oxygen consumption during exercise, by reduced 6-minute walk test distance (6MWTD), reduced health-related quality of life, or reduced functional status as determined by dyspnea class.[9] In this meta-analysis, the authors failed to detect an impact of ID on death or hospitalization rates.[8]

No clinical trial has validated the applicability of the ESC criteria of ID so far in patients with HFpEF using intravenous iron. We designed the multi-center, double-blind, randomized FAIR-HFpEF trial to study the effectiveness of FCM in iron deficient patients with HFpEF on exercise capacity as assessed using the 6MWTD.

Materials and Methods

Study design

Trial structure

The FAIR-HFpEF trial is a prospective, multi-center, 1:1 randomized, double-blind, parallel, controlled trial of intravenous FCM compared to placebo (saline) designed to study the effect on exercise tolerance, symptoms and quality of life in patients with HFpEF and ID with and without anemia. The trial is conducted as an investigator-initiated trial in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice. Funding is provided by Vifor Pharma, Switzerland. An independent ethics committee approved the protocol at every participating center. All subjects provide written informed consent. The trial is registered at clinicaltrials.gov (NCT03074591).

Study participants

The FAIR-HFpEF trial aims to recruit men and women aged ≥18 years who have chronic HFpEF and reduced exercise capacity, New York Heart Association functional class II-III symptoms, treatment with a diuretic, raised natriuretic peptide levels or a history of hospitalization with a diagnosis of HF within 12 months prior to randomization, and an LVEF ≥45% as measured by echocardiographic or magnetic resonance imaging within 6 months prior to randomization. Reduced exercise capacity at baseline is defined as a 6MWTD <450 m, measured as average of the last 2 documented tests within 8 weeks prior to planned randomization that also need to be within 20% of each other. Subjects are required to have ID at screening, defined as ferritin <100 ng/mL or ferritin 100-299 plus TSAT <20%. At randomization, patients are required to have evidence of diastolic dysfunction as assessed using echocardiography. The full list of inclusion criteria is provided in Table 1. The target number of patients to be randomized

Table 1. Obligatory inclusion criteria.

Inclusion criteria
- Patient is willing to participate and provides written informed consent
- Age ≥18 years
- Clinical diagnosis of HFpEF with LVEF ≥45% at screening or within 6 months prior to planned randomization (assessed by echocardiography or magnetic resonance imaging)
- Ambulatory for at least 7 days with NYHA class II or III at time of randomization (the screening visit can take place at the end of a hospitalization)
- Treated with a diuretic
- Presence of AF is allowed in 2 out of 4 patients (calculated per center)
- At screening or randomization, presence of one of the following criteria:
a) hospitalization with a diagnosis of HF within 12 months prior to planned randomization
b) raised plasma levels of natriuretic peptides in a patient with sinus rhythm (*i.e.* in patients without AF: NT-proBNP >300 pg/mL or BNP >100 pg/mL or MR-proANP >120 pmol/L; in patients with AF: NT-proBNP >600 pg/mL or BNP >200 pg/mL or MR-proANP >250 pmol/L)
- Evidence of diastolic dysfunction at screening or randomization, defined as:
a) E/E' >13
b) LA width ≥38 mm
c) LA length ≥50 mm
d) LA area ≥20 cm^2
e) LA volume ≥55 mL
f) LA volume index >28 mL/m^2
- Hemoglobin >9.0 g/dL and ≤14.0 g/dL (at screening)
- ID with ferritin <100 ng/mL or ferritin 100-299 ng/mL plus TSAT <20 % (at screening);
- 6MWTD at baseline <450 m (average of the last 2 documented tests within 8 weeks prior to planned randomization that also need to be within 20% of each other)

HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; AF, atrial fibrillation; HF, heart failure; LA, left atrium; ID, iron deficiency; TSAT, transferrin saturation; 6MWTD, 6-minute walk test distance.

given the original protocol was 100 anemic and 100 non-anemic patients with HFpEF, *i.e.* 200 patients in total. Enrolment, however, proved to be more difficult than expected and was further hampered by the COVID-19 pandemic that led to termination of enrolment in November 2022 after 42 patients being included.

Major exclusion criteria embrace any prior echo LVEF measurement <40%, clinical signs of infection or the use of intravenous iron, erythropoietin or blood transfusions within 60 days prior to enrolment. A complete list of exclusion criteria is provided in Table 2.

Study visits and follow-up

Patients will attend clinic within two weeks prior to the first dose of study medication to evaluate their eligibility for the study (Figure 1). Laboratory data used for determination of eligibility at the baseline visit must not be older than 7 days. Patients will sign the informed consent document before any study-specific procedures are performed. After this enrolment, blood samples will be taken. The results of these evaluations will be checked at the baseline visit to confirm eligibility according to the inclusion and exclusion criteria. Table 3 provides the full list of assessments performed during screening.

After baseline assessments, eligible patients will be randomized in a 1:1 ratio to receive intravenous FCM or placebo/saline (normal saline: 0.9% w/v NaCl) by unblinded investigators. In the FCM group, FCM will be administered according to the dosing schedule detailed in Table 4. In the placebo/saline group, patients will receive the equivalent number of normal saline infusions.

Study related assessments (including 6MWT, patient global assessment, quality of life questionnaires and NYHA class) will be performed by blinded investigators at baseline (visit 2), and visits 3 (week 8±3 days), 4 (week 16±1 week), 5 (week 24±1 week), 6 (week 32±2 weeks), and 7 (week 52±2 weeks). At assessment visits, a clinical examination and study related tests will be performed. Blood samples will be taken and stored for later assessment of cardiovascular and neurohormonal blood markers as well as characteristics of iron metabolism and immune status [baseline (visit 2), and visits 3, 4, 5, 6, and 7].

To keep the study double-blind (FCM is a dark brown solution), certain study procedures are to be performed by un-blinded independent personnel at the site. The un-blinded study personnel will perform the following study procedures:

i. Drug accountability
ii. Prepare and administer infusions (in black syringe and behind curtain to keep patient blinded).
iii. Monitor patients for elevated iron parameters or hemoglobin levels and proceed according to stopping rule below. Procedures are decided by the un-blinded physician.
In case of elevated levels of ferritin >800 ng/mL, or ferritin

Table 2. The following exclusion criteria are obligatory. Exclusions *e.g.* pregnancies have to be explained.

Exclusion criteria
- Unable to sign informed consent
- Any prior echocardiography measurement of LVEF <40%
- Clinical signs and symptoms of infection including fever >38°C
- Use of intravenous iron, erythropoietin, or blood transfusions within the previous 60 days
- Use of concurrent immunosuppressive therapy
- History of acquired iron overload or haemochromatosis (or a first relative with haemochromatosis)
- Known hypersensitivity to FCM or any other intravenous iron product
- Known bleeding or hemolytic anemia
- Presence of any condition that precludes exercise testing, such as decompensated HF, significant musculoskeletal disease, unstable angina pectoris, obstructive cardiomyopathy, severe uncorrected valvular disease, or uncontrolled brady-arrhythmias or tachy-arrhythmias
- Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms such as severe obesity, primary pulmonary hypertension, or COPD; hence, patients with the following are excluded: a) severe COPD, *i.e.* with known FEV1<50%, requiring home oxygen therapy, or on chronic oral steroid therapy b) body mass index ≥40.0 kg/m2
- Presence of uncontrolled atrial fibrillation with resting heart rate >110/min
- Presence of uncontrolled hypertension with blood pressure >160/100 mm Hg
- Renal replacement therapy
- Concurrent therapy with an erythropoiesis stimulating agent
- Known active malignancy
- Known HIV or active hepatitis infection
- Pregnancy
- Patients, who may be dependent on the sponsor, the investigator or the trial sites, have to be excluded from the trial
- Lack of willingness to storage and disclosure of pseudonymous disease data in the context of the clinical trial
- Participation in another clinical trial within previous 30 days and/or anticipated participation in another trial during this study
- Inability to fully comprehend and/or perform study procedures in the investigator's opinion
- Persons staying at an institution due to order by a national body or a court of law

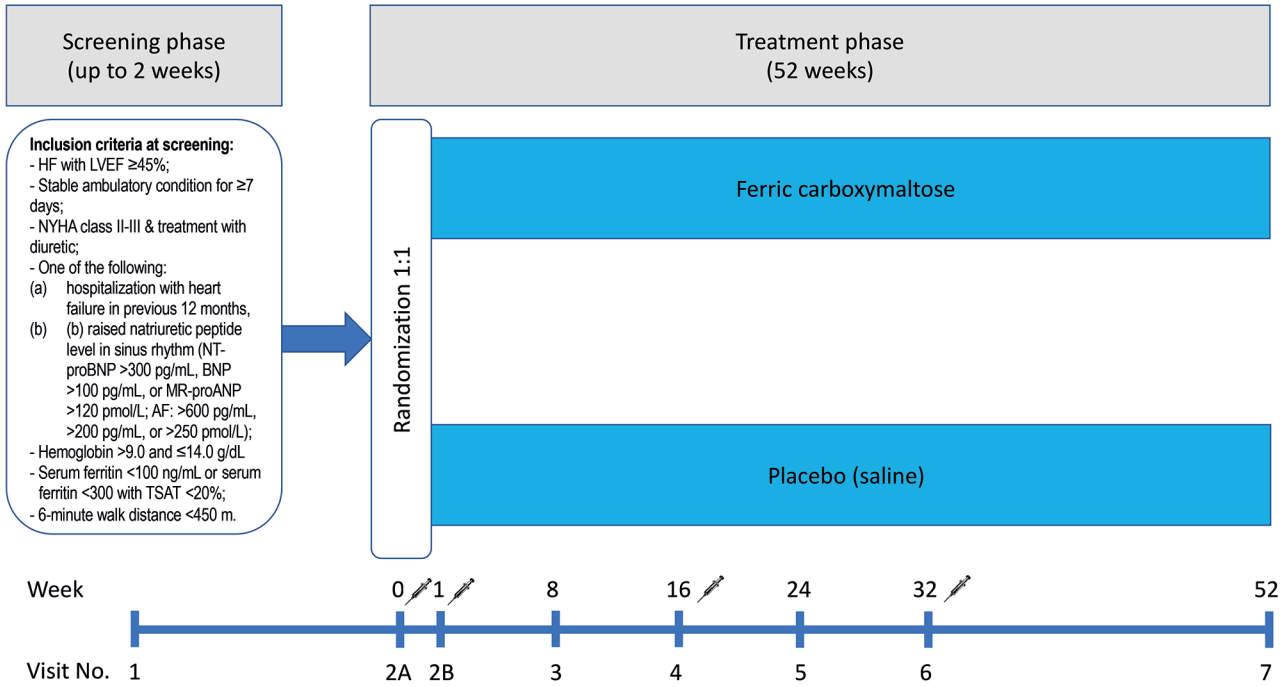
LVEF, left ventricular ejection fraction; FMC, ferric carboxymaltose; HF, heart failure; COPD, chronic obstructive pulmonary disease.

>500 ng/mL when TSAT is >50%, or hemoglobin >16 g/dL at any stage, FCM treatment has to be discontinued and placebo/saline is to be given instead. In this case, ferritin, TSAT and hemoglobin should be re-checked at the next visit, and these visits should coincide with planned dosing visits and/or assessment visits. Once ferritin has dropped to <400 ng/mL,

Table 3. Procedures performed during the first screening visit.

Assignment of subject identification number
- Conformance with inclusion/exclusion criteria (blood samples will be taken, for evaluation at the baseline visit before randomization)
- At least two hemoglobin values are to be obtained on site during the screening period. The mean of two values will be used for determination of eligibility and iron deficit. The time between these hemoglobin analyses can be 2 to 7 days. The later of the two hemoglobin values may not be older than 7 days at the baseline visit; it can also be obtained on the day of the baseline visit
- Recording of demographic data and baseline characteristics (year of birth, height, race and gender). In addition, socio-economic data (employment status, reason for unemployment, health insurance status) will be recorded
- Medical and surgical history (past five years or onset of chronic HF, whichever is longer)
- Prior medication history during the 12 weeks before screening
- Vital signs (blood pressure, pulse rate, body weight and waist-hip ratio)
- Clinical chemistry
- Hematology
- Vitamin B12 and serum folate status. In case of deficiencies, the patient is to receive substitution with preparations of Vitamin B12 and/or folate. In this case the patient can be re-screened using the same subject identification number
- Iron status
- Neurohormonal and inflammatory markers
- Urine pregnancy test (for female patients of childbearing potential)
- NYHA classification

HF, heart failure; NYHA, New York Heart Association.



AF, atrial fibrillation; BNP, B-type natriuretic peptide; HF, heart failure; LVEF, left ventricular ejection fraction; NT-probnp, N-terminal pro B-type natriuretic peptide; MR-proanp, mid-regional pro atrial natriuretic peptide; NYHA, New York Heart Association; TSAT, transferrin saturation. Since a single dose of FCM must not exceed 1000 mg, visit 2B is a dosing visit for patients who require more than 1000 mg of FCM for iron store repletion. A syringe symbol marks a dosing visit.

Figure 1. Design of the FAIR-HFpEF trial.

and TSAT to <45%, and hemoglobin to <16 g/dL, treatment with FCM is to be reinstituted. In case severe anemia develops (*i.e.* hemoglobin ≤9 g/dL), the patient is to discontinue treatment but remain in the study and further management of anemia is at the investigator's discretion. The study duration for all patients enrolled is 52 weeks (including follow-up for adverse events). All patients will be followed according to protocol and will receive double-blind iron repletion therapy or placebo/saline.

Primary and secondary endpoints

The primary endpoint is the change in exercise capacity from baseline to visit 5 (week 24±1 week) as assessed by the change in 6MWTD. This change will be assessed as the difference of the 6MWTD in meters from baseline to visit 5. For each subject the 6MWTD will be assessed by the same assessor throughout the study whenever possible.

Health-related quality of life (HRQoL) will be assessed using the HRQoL questionnaire which combines the European Quality of Life - 5 Dimensions (EQ-5D) questionnaire as a generic instrument with a disease-specific cardiology instrument: the *Kansas City Cardiomyopathy Questionnaire* (KCCQ). A complete list of endpoints is given in Table 5.

Sample size calculation and statistical analysis

A sample size of 86 patients per group gives a power of 90% for a two-sample t-test at the usual one-sided level of 2.5% if the standardized mean difference (Cohen's d) is 0.50.

Table 4. Dosing schedule in the FAIR-HFpEF trial.

Visit	Total ferric carboxymaltose, mg			
	Weight <70 kg		Weight ≥70 kg	
	Hb <10 g/dL	≥10 Hb ≤14 g/dL	Hb <10 g/dL	≥10 Hb ≤14 g/dL
2A	1000	1000	1000	1000
2B	500	-	1000	500
3	-	-	-	-
4	500*	500*	500*	500*
5	-	-	-	-
6	500*	500*	500*	500*
7	-	-	-	-

HB, hemoglobin. *If required, *i.e.* if serum ferritin <300 ng/mL.

Table 5. Complete list of endpoints in the FAIR-HFpEF trial.

Primary endpoint	- Change in exercise capacity from baseline (visit 2A) to visit 5 as assessed by the 6MWTD
Secondary endpoints	- Change in 6MWTD (in meters) from baseline (visit 2A) to visit 3, 4, 6, and 7, respectively - PGA assessment at visit 3, 4, 5, 6, and 7; - Change in NYHA functional class from baseline (visit 2A) to visit 3, 4, 5, 6, and 7, respectively - Change in plasma levels of blood parameters of kidney function and inflammation between baseline (visit 2A) and visits 3, 4, 5, 6, and 7 - Change in quality-of-life assessments (EQ-5D, KCCQ) from baseline (visit 2A) to the respective assessment timepoint at visit 3, 4, 5, 6, and 7 - Rate of recurrent HF hospitalizations and death*
Tertiary endpoints	- Resource use and costs associated with the treatment with intravenous FCM compared with placebo/saline: a. *medication, generic name (date of prescription, dose); b. ambulatory care contacts (not exclusively study related); c. examinations and procedures performed; d. emergency room visits / day clinic visits; e. hospitalizations (number, duration, reason); f. other health care services; g. days of work lost.
Safety endpoints	- Frequency, severity, and relationship to treatment for all adverse and serious adverse events (including deaths and hospitalizations with date-change – all to be adjudicated) - Observation of episodes of anaphylactoid reactions or symptomatic hypotension after IV iron infusion - Differences in vital signs (systolic and diastolic blood pressure, heart rate), body weight, waist-to-hip-ratio, alanine transaminase, urea, eGFR and creatinine from baseline to visit 7 - Number and duration of hospitalizations (total, for cardiovascular conditions, for worsening HF)

6MWTD, 6-minute walking test; PGA, patient global assessment; NYHA, New York Heart Association; HF, heart failure; FCM, ferric carboxymaltose; IV, intravenous; eGFR, estimated glomerular filtration rate.
*Given the lower than planned number of enrolled patients, these endpoints are considered exploratory and, as applicable, for safety considerations only.

Accounting for 10% dropout (which is supported by findings in the FAIR-HF and CONFIRM-HF trials) we aim to recruit 100 patients per group (*i.e.* 200 patients in total). The sample size calculation was carried out using nQuery Advisor 7.0 (Statistical Solutions Ltd., Cork, Ireland)

The primary endpoint (change in the 6MWTD from baseline to visit 5) will be analyzed using a mixed model repeated measures approach adjusted presence of atrial fibrillation, anemia, visit and baseline 6MWTD. Standard procedures for reporting of adverse events will be used. Adverse events will be summarized as frequencies and percentages by intervention group. Secondary endpoints: The analyses of continuous secondary endpoints will follow the same lines as the analysis of the primary endpoint. Patient global assessment scores at all visits will be compared between both groups using chi-square tests or Fisher's exact tests, when appropriate. The change in NYHA class from baseline to the respective visit in the FCM group will be tested using the Bowker symmetry test. Mixed effects proportional odds models will be used to adjust patient global assessment scores at all visits and NYHA class change from baseline to all visits for covariates.

Discussion

The FAIR-HFpEF trial is designed to investigate the effect of intravenous iron repletion in iron deficient patients with HFpEF using FCM. The primary endpoint is the change in exercise capacity from baseline to week 24 as assessed in a 6-min-walking test. The 6-min-walking test measures the distance an individual is able to walk, in meters, over a total of six minutes on a hard, flat surface. The goal is to walk as far as possible in six minutes to give an assessment of exercise tolerability. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway (*e.g.* hospital corridor). The 6MWTD provides an information about a patient's exercise capacity during usual daytime (submaximal) activities and thus provides a different measure than the peak oxygen consumption measured during spiroergometry, which assesses exercise capacity during maximal effort.

A recent systematic review has highlighted our difficulties at altering exercise capacity in patients with HF.[10] In patients with HFrEF, most guideline-recommended therapies approved on grounds of improving morbidity and mortality, failed to show any benefit at increasing 6MWTD or peak oxygen consumption (VO_2). This is true for angiotensin-converting enzyme (ACE) inhibitors, the angiotensin-neprilysin inhibitor (ARNI) sacubitril/valsartan, beta-blockers, mineralocorticoid-receptor antagonists, and the sodium-glucose co-transporter 2 (SGLT2) inhibitors dapagliflozin and empagliflozin. Only ivabradine proved beneficial in this regard.[10,11] The situation in HFpEF is similar. Even though the *Perindopril in Elderly People with Chronic Heart Failure* trial showed improvements in NYHA class and 6MWTD in the perindopril group of HFpEF patients,[12] it missed its primary endpoint, making the analysis of secondary endpoints difficult. Other trials of ACE inhibitors in patients with HFpEF have all failed to show improvements in exercise capacity as have other trials of standard medications used in HFrEF. For dapagliflozin a modest improvement in 6MWTD was reported (with no adjustment for informed missingness of data),[13] however, similar effects have not been reproduced with empagliflozin (EMPERIAL-Preserved/Reduced trials)[14] or dapagliflozin (DETERMINE-Preserved/Reduced trials),[15,16] when such adjustments indeed were made. The only means to effectively improve exercise capacity in both HFrEF and HFpEF is exercise training,[17-21] as a number of intervention trials have helped to improve exercise capacity using different protocols.

When it comes to improving HRQoL, the situation is slightly better. In HFrEF, the ARNI sacubitril/valsartan and the SGLT2 inhibitors dapagliflozin and empagliflozin have shown some beneficial effect. In the PARADIGM-HF trial of sacubitril/valsartan *vs.* placebo,[22] HRQoL was assessed using the KCCQ score, which showed significantly slower worsening in the sacubitril/valsartan as compared to the control group that received enalapril. In HFpEF, the PARAGON-HF trial showed a similar pattern,[23] but since the trial missed its primary endpoint, secondary endpoints can only be interpreted with caution. Several HRQoL assessment tests are frequently used in clinical trials in HF. The KCCQ is a self-administered, disease-specific instrument for measuring HRQoL in patients with chronic HF regardless of etiology. It is a 23-item questionnaire that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.[24] The answers that subjects give to the KCCQ's questions are used to calculate scores in ten scales. The EQ-5D, on the other hand, is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can take one of three responses, and a visual analogue scale for subjects' health state. The responses record three levels of severity: 1 = no problems; 2 = some or moderate problems; and 3 = extreme problems; within a particular EQ-5D dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state (for example 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems with mobility and self-care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression). Ambiguous values (*e.g.* 2 boxes ticked for a single dimension) should be treated as missing.

In HFrEF, treatment of ID using FCM was shown to improve HRQoL. The FAIR-HF trial,[3] published in 2009, showed improvements in KCCQ and EQ-5D, statistically significant already after 4 weeks of follow-up, with the effect lasting up to the end of the trial at 24 weeks. A similar pattern was reproduced in the CONFIRM-HF trial out to 52 weeks of follow-up. More recent data confirm that replenishing iron stores in patients with HFrEF reduces hospitalizations rates, but the effect on survival is negligible.[25] Intravenous treatment with different iron-carbohydrate complexes like FCM is considered well tolerated and safe.[26] Even more, replenishing of iron stores cannot be achieved in patients with HF using oral iron products, because of gastrointestinal adverse effects and of minute amounts of iron being absorbed across the gut wall in patients with HF.[27]

Conclusions

No such data are available for HFpEF even though the prevalence of ID overlaps strongly. The FAIR-HFpEF trial will be the largest trial conducted so far to assess the impact of FCM on ID treatment in patients with HFpEF. The results of the trial may help to identify the correct cut-off for the diagnosis of ID in patients with HFpEF and to establish a novel therapeutic avenue to improve exercise capacity and HRQoL in affected patients.

We have to acknowledge that our study has limitations. First, only male patients with LVEF ≤40% were included, so these findings may be not applied to female patients and to patients with HF with preserved ejection fraction. Second, although we tried to homogenize the sample, the number of patients that were included in the matching analysis was limited, making the sample size small. Third, although both trials have been prospectively conducted, follow-up was not analyzed in our study to determine if these body composition and muscle strength alterations would lead to worse outcomes in a long term. Finally, we cannot exclude that there may be differences in the correction of peak VO_2 between cycle ergometer and treadmill.

Conflict of interest

SvH has been a paid consultant for and/or received honoraria payments from AstraZeneca, Bayer, Boehringer Ingelheim, BRAHMS, Chugai, Grünenthal, Helsinn, Hexal, Novartis, Novo Nordisk, Pharmacosmos, Respicardia, Roche, Servier, Sorin, and Vifor. SvH reports research support from Amgen, Boehringer Ingelheim, IMI, and the German Center for Cardiovascular Research (DZHK). WD reports consulting fees from Aimediq, Bayer, Boehringer Ingelheim, Boston Scientific, Lilly, Medtronic, Pfizer, Sanofi-Aventis, Sphingotec, Vifor Pharma, travel support from Pharmacosmos, and research support to the Institute from EU (Horizon2020), German ministry of Education and Research, German Center for Cardiovascular Research, Boehringer Ingelheim, from Vifor Pharma related to this trial, and ZS Pharma. MK reports consulting fees and honoraria payments within the last 3 years from Adrenomed, 4TEEN4 Pharmaceuticals, Pharmacosmos, Sphingotec, and CSLVifor, all not related to the submitted work. MK reports research support within the last 3 years from the German Research Foundation (DFG), the German ministry of Education and Research (BMBF), the German Center for Cardiovascular Research (DZHK), the European Union (Horizon 2020), the Else Kroener-Fresenius Foundation (EKFS Clinician Scientist Professorship), Adrenomed AG, and CSL Vifor, all not related to the submitted work. TF reports personal fees for statistical consultancies (including data monitoring committees) from Actimed, Bayer, BiosenseWebster, BMS, Coherex Medical, CSL Behring, Enanta, Fresenius Kabi, Galapagos, IQVIA, Janssen, KyowaKirin, LivaNova, Minoryx, Novartis, r-connect, Recardio, Relaxera, Roche, Servier, Viatris and Vifor; all outside the submitted work. SDA reports grants and personal fees from Vifor and Abbott Vascular, and personal fees for consultancies, trial committee work and/or lectures from Actimed, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Bioventrix, Brahms, Cardiac Dimensions, Cardior, Cordio, CVRx, Edwards, Farraday, Impulse Dynamics, Janssen, Novartis, Occlutech, Pfizer, Respicardia, Servier, Vectorious, and V-Wave, and declares that he is named co-inventor of two patent applications regarding MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents.

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References

1. Lainščak M, Milinković I, Polovina M, et al. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP Heart Failure Long-Term Registry; European Society of Cardiology Heart Failure Long-Term Registry Investigators Group. Eur J Heart Fail 2020;22:92-102.
2. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022;24:4-131.
3. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436-48.
4. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. Eur Heart J 2015;36:657-68.
5. Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. Lancet 2022;400:2199-209.
6. McEwan P, Harrison C, Binnie R, et al. Impact of ferric carboxymaltose for iron deficiency at discharge after heart failure hospitalisation: a European multinational economic evaluation. Eur J Heart Fail 2023;25:389-98.
7. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. J Am Coll Cardiol 2022;79:e263-421.
8. Beale AL, Warren JL, Roberts N, Meyer P, Townsend NP, Kaye D. Iron deficiency in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Open Heart 2019;6:e001012
9. Bekfani T, Pellicori P, Morris D, et al. Iron deficiency in patients with heart failure with preserved ejection fraction and its association with reduced exercise capacity, muscle strength and quality of life. Clin Res Cardiol 2019;108:203-11.
10. von Haehling S, Arzt M, Doehner W, et al. Improving exercise capacity and quality of life using non-invasive heart failure treat-

ments: evidence from clinical trials. Eur J Heart Fail 2021;23:92-113.
11. Volterrani M, Cice G, Caminiti G, et al. Effect of carvedilol, ivabradine or their combination on exercise capacity in patients with heart failure (the CARVIVA HF trial). Int J Cardiol 2011;151:218-24.
12. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006:2338-45.
13. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med 2021;27:1954-60.
14. Abraham WT, Lindenfeld J, Ponikowski P, et al. Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. Eur Heart J 2021;42:700-10.
15. AstraZeneca. DETERMINE-preserved. Dapagliflozin effect on exercise capacity using a 6-minute walk test in patients with heart failure with preserved ejection fraction. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03877224. Accessed on: 24 February 2023.
16. AstraZeneca. DETERMINE-reduced. Dapagliflozin effect on exercise capacity using a 6-minute walk test in patients with heart failure with reduced ejection fraction. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03877237. Accessed on: 24 February 2023.
17. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659-67.
18. Edelmann F, Gelbrich G, Düngen HD, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol 2011;58:1780-91.
19. Smart NA, Haluska B, Jeffriess L, Leung D. Exercise training in heart failure with preserved systolic function: a randomized controlled trial of the effects on cardiac function and functional capacity. Congest Heart Fail 2012;18:295-301.
20. Kitzman DW, Brubaker PH, Herrington DM, et al. Effect of endurance exercise training on endothelial function and arterial stiffness in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. J Am Coll Cardiol 2013;62:584-92.
21. Kitzman DW, Brubaker P, Morgan T, et al. Effect of caloric restriction or aerobic exercise training on peak oxygen consumption and quality of life in obese older patients with heart failure with preserved ejection fraction: a randomized clinical trial. JAMA 2016;315:36-46.
22. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.
23. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-20.
24. 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;35:1245-55.
25. Salah HM, Savarese G, Rosano GMC, Ambrosy AP, Mentz RJ, Fudim M. Intravenous iron infusion in patients with heart failure: a systematic review and study-level meta-analysis. ESC Heart Fail 2023;10:1473-80.
26. Sindone A, Doehner W, Comin-Colet J. Systematic review and meta-analysis of intravenous iron-carbohydrate complexes in HFrEF patients with iron deficiency. ESC Heart Fail 2023;10:44-56.
27. Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. JAMA 2017;317:1958-66. Erratum in: JAMA 2017;317:2453.