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Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

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Recent developments in the management of chronic heart failure in patients with an impaired left ventricular ejection fraction have changed the natural history of this clinical syndrome and improved patients' outcomes.\(^1,2\) However, the normal daily activities of many patients with heart failure remain restricted; they report symptoms of fatigue and dyspnea.

**Table 1. Baseline Demographic and Clinical Characteristics of the Study Patients in the Intention-to-Treat Population, According to Study Group.**

| Variable                                    | Ferric Carboxymaltose (N=304) | Placebo (N=155) |
|---------------------------------------------|-------------------------------|-----------------|
| Age — yr                                    | 67.8±10.3                     | 67.4±11.1       |
| Female sex — no. (%)                        | 159 (52.3)                    | 85 (54.8)       |
| White race — no. (%)                        | 303 (99.7)                    | 155 (100.0)     |
| NYHA class — no. (%)                        |                               |                 |
| II                                          | 53 (17.4)                     | 29 (18.7)       |
| III                                         | 251 (82.6)                    | 126 (81.3)      |
| Left ventricular ejection fraction — %      | 31.9±5.5                      | 33.0±6.1        |
| Body weight — kg                            | 77.0±14.2                     | 77.6±16.3       |
| Body-mass index‡                            | 28.0±4.8                      | 28.1±5.1        |
| Blood pressure — mm Hg                      |                               |                 |
| Systolic                                    | 126±15                        | 126±15          |
| Diastolic                                    | 77±9                          | 76±10           |
| Pulse — beats/min                           | 71±11                         | 72±12           |
| 6-Minute walk test distance — m             | 274±105                       | 269±109         |
| Ischemic cause of heart failure — no. (%)   | 245 (80.6)                    | 123 (79.4)      |
| Cardiovascular risk factor — no. (%)        |                               |                 |
| Hypertension, treated with drugs            | 243 (79.9)                    | 128 (82.6)      |
| Dyslipidemia, treated with drugs            | 144 (47.4)                    | 70 (45.2)       |
| Diabetes mellitus                           | 93 (30.6)                     | 37 (23.9)       |
| Atrial fibrillation                         | 94 (30.9)                     | 44 (28.4)       |
| Medical history — no. (%)                   |                               |                 |
| Myocardial infarction                       | 168 (55.3)                    | 90 (58.1)       |
| Angina pectoris                             | 171 (56.3)                    | 89 (57.4)       |
| Stroke                                      | 24 (7.9)                      | 9 (5.8)         |
| Coronary revascularization                  | 64 (21.1)                     | 31 (20.0)       |
| Laboratory measurements                     |                               |                 |
| Hemoglobin — g/liter                        | 119±13                        | 119±14          |
| Mean corpuscular volume — μm³               | 91.6±8.1                      | 91.7±6.7        |
| Serum ferritin — μg/liter                   | 52.5±54.5                     | 60.1±66.5       |
| Transferrin saturation — %§§               | 17.7±12.6                     | 16.7±8.4        |
| C-reactive protein — mg/liter               | 7.46±5.34                     | 9.12±5.48       |
| Sodium — mmol/liter                         | 141±3                         | 141±3           |
| Potassium — mmol/liter                      | 4.65±0.61                     | 4.58±0.52       |
| Alanine aminotransferase — U/liter          | 20.5±12.3                     | 18.8±8.1        |
| Aspartate aminotransferase — U/liter        | 23.1±10.4                     | 22.4±7.2        |
| Creatinine — mg/dl                          | 1.2±0.6                       | 1.2±0.6         |
| Estimated glomerular filtration rate — ml/min/1.73 m² of body-surface area¶¶ | 63.8±21.2 | 64.8±25.3 |
that adversely affect their quality of life, leading to high morbidity.\textsuperscript{3,4} Therapeutic options to improve functional capacity in patients with heart failure are limited, and novel therapies are needed.

Numerous mechanisms unrelated to hemodynamic dysfunction may underlie impaired exercise tolerance in patients with chronic heart failure. Among them, inadequate oxygen supply and impaired oxygen use by skeletal muscle during exercise contribute to poor clinical status.\textsuperscript{5,6} In addition, anemia may aggravate symptoms in patients with heart failure.\textsuperscript{7} Targeting these abnormalities may confer functional benefits to such patients.

Iron plays a key role in oxygen uptake, transport, and storage, as well as oxidative metabolism in the skeletal muscle; it also is involved in erythropoiesis.\textsuperscript{8,9} Traditionally, iron deficiency has been considered to have clinical consequences only in the presence of anemia. Alternatively, a reduced hemoglobin level can be viewed as the end result of a process beginning with the gradual depletion of iron stores or defective iron absorption and the reduced availability of iron recycled in the reticuloendothelial system.\textsuperscript{9,10} Four small studies showed that the correction of iron deficiency with the use of intravenous iron in patients with chronic heart failure may result in clinical benefits.\textsuperscript{16-19} In one of these studies,\textsuperscript{17} the symptomatic benefit was similar in patients with anemia and those without anemia. We designed our randomized, double-blind study, called the Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF) trial, to determine whether the correction of iron deficiency with the use of intravenous iron (ferric carboxymaltose) confers symptomatic benefits in patients with chronic heart failure.

**METHODS**

**TRIAL DESIGN AND OVERSIGHT**

From June 25, 2007, through December 31, 2008, a total of 459 eligible patients were enrolled from 75 sites in 11 countries (Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The study design has been

| Concomitant treatment | Ferric Carboxymaltose (N = 304) | Placebo (N = 155) |
|-----------------------|-------------------------------|-----------------|
| Diuretic              | 280 (92.1)                    | 140 (90.3)      |
| ACE inhibitor or ARB  | 281 (92.4)                    | 141 (91.0)      |
| Digitalis glycoside   | 46 (15.1)                     | 25 (16.1)       |
| Beta-blocker          | 262 (86.2)                    | 129 (83.2)      |
| Antiplatelet therapy  | 189 (62.2)                    | 97 (62.6)       |
| Anticoagulant therapy | 67 (22.0)                     | 22 (14.2)       |
| Lipid-lowering therapy| 142 (46.7)                    | 72 (46.5)       |
| Insulin               | 27 (8.9)                      | 9 (5.8)         |
| Oral hypoglycemic agent | 49 (16.1)                | 22 (14.2)       |

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and NYHA New York Heart Association.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The percent transferrin saturation was calculated as iron (in micromoles per liter) ÷ transferrin (in grams per liter) × 25.1.
¶ The estimated glomerular filtration rate was calculated by the central laboratory according to the Modification of Diet in Renal Disease formula: 186 × (serum creatinine [in micromoles per liter] ÷ 88.4)\textsuperscript{−1.154} × age (in years)\textsuperscript{−0.203} × 1.21 (if patient is black) × 0.742 (if patient is female).
The protocol was approved by the institutional review board at each participating center, and the trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and local and national regulations. Written informed consent was provided by all patients before any study-related procedures were performed.

The trial was designed, implemented, and overseen by the FAIR-HF Executive Committee, together with representatives of the sponsor, Vifor Pharma (Glattbrugg, Switzerland). ClinStar (Moscow) was responsible for on-site monitoring of sites in Russia and Ukraine. Kendle (Munich, Germany) was responsible for on-site monitoring in other countries, in addition to data collection and data management. SOCAR Research (Nyon, Switzerland) was responsible for data analysis. Analyses were performed independently of the sponsor, according to a predefined plan of statistical analysis. The medical statistics unit at the London School of Hygiene and Tropical Medicine performed the same analyses, separately, with identical results. The manuscript was prepared and submitted for publication by the FAIR-HF Executive Committee. An independent data and safety monitoring board reviewed the safety data on an ongoing basis. The authors had access to the study data and vouch for the accuracy and completeness of the reported data and analyses.

RECRUITMENT AND FOLLOW-UP OF STUDY PATIENTS

Eligible subjects included ambulatory patients who had chronic heart failure of New York Heart Association (NYHA) class II or III, a left ventricular ejection fraction of 40% or less (for patients in NYHA class II) or 45% or less (for patients in NYHA class III), a hemoglobin level at the screening visit between 95 and 135 g per liter, and iron deficiency. The presence or absence of iron deficiency was determined on the basis of results received from the central laboratory. Iron deficiency was diagnosed when the serum ferritin level was less than 100 μg per liter or was between 100 and 299 μg per liter when the transferrin saturation was less than 20%. Patients were excluded if they had uncontrolled hypertension, other clinically significant heart disease, inflammation, or clinically significantly impaired liver or renal function.

RANDOMIZATION

Before the iron-correction phase was begun, a clinical history, physical examination, 6-minute walk test results, and 12-lead electrocardiogram were obtained for each patient. We also performed assessments of the health-related quality of life in all patients. Using a central interactive voice-response system, we randomly assigned eligible patients, in a 2:1 ratio, to receive either ferric carboxymaltose (provided by Vifor Pharma) or placebo (normal saline).
The total iron dose required for iron repletion was calculated at baseline, according to Ganzoni's formula and the mean of the two hemoglobin values obtained during the screening period. The ferric carboxymaltose or saline was administered as an intravenous bolus injection of 4 ml (which is the amount of ferric carboxymaltose in a water solution for injection that is equivalent to 200 mg of iron). The dosing frequency was weekly until iron repletion was achieved (the correction phase) and then every 4 weeks during the maintenance phase, which started at week 8 or week 12, depending on the required iron-repletion dose.

Because ferric carboxymaltose is a dark-brown solution that is easily distinguishable from the saline placebo, study personnel responsible for the preparation and administration of the study drug (including at least one physician) were aware of the group assignments and therefore were not involved in any study assessments. To ensure that patients were unaware of the study drug they were receiving, black syringes were used to administer the study treatment and a curtain (or something similar) was used to shield the injection site from the patient's view.

The central laboratory sent results regarding measures of iron metabolism and hemoglobin...
only to the study personnel who were aware of the group assignments. These persons were responsible for evaluating for the presence of elevated iron-metabolism measurements or severe anemia and for implementing the following procedures, as defined in the protocol. If the ferritin level exceeded 800 μg per liter or was between 500 and 800 μg per liter with a transferrin saturation of more than 50%, or if the hemoglobin level was higher than 160 g per liter, ferric carboxymaltose was discontinued and placebo was given instead. In this case, the ferritin, transferrin saturation, and hemoglobin levels were reassessed. After the ferritin level had dropped to less than 400 μg per liter, the transferrin saturation to under 45%, and the hemoglobin level to less than 160 g per liter, treatment with ferric carboxymaltose could be restarted. If severe anemia (hemoglobin level, ≤90 g per liter) developed, the study treatment was permanently discontinued. The follow-up of such patients continued, and further management of anemia was performed at the investigator’s discretion.

In addition to the dosing visits, at weeks 4, 12, 24, and 26, patients were assessed for efficacy and safety.

**Primary and Secondary End Points**

The primary end points were the self-reported Patient Global Assessment (Fig. 2 in the Supplementary Appendix) and NYHA functional class (adjusted for the class at baseline) at week 24. Secondary end points included the self-reported Patient Global Assessment and NYHA functional class at week 4 and week 12, as well as the distance on the 6-minute walk test and the overall score on the Kansas City Cardiomyopathy questionnaire (on which the overall score ranges from 0 to 100, with higher scores indicating better health) (Panel D), and the change in the overall score on the Kansas City Cardiomyopathy questionnaire (on which the overall score ranges from 0 to 100, with higher scores indicating better health) (Panel E). The data in Panels A and B are odds ratios, for the ferric carboxymaltose (FCM) group as compared with the placebo group and shown on a log2 scale, of being in a better assessment category (Panel A) or NYHA functional class (Panel B). In both panels, for data on the self-reported Patient Global Assessment that were missing for patients known to be alive and not in the hospital at each time point, the last available assessment was used. Patients who were hospitalized at each time point were given an assessment of much worse (in Panel A) or an NYHA class of IV (in Panel B). Patients who died before week 24 were categorized as dead (in Panel B, corresponding to NYHA class V). Data were not included for patients who were known to be alive at the time point but had no previous data. For Panel A, the odds ratios at week 4 and week 12 are 3.44 (95% confidence interval [CI], 2.34 to 5.07) and 3.19 (95% CI, 2.20 to 4.63). In Panel B, the odds ratios at week 4 and week 12 are 3.96 (95% CI, 1.98 to 7.93) and 3.42 (95% CI, 2.04 to 5.72). Panels C, D, and E show the mean (±SE) changes in the variable at weeks 4, 12, and 24. In those panels, the P values are for the comparison between the two study groups, and the I bars denote the standard error.

**Statistical Analysis**

Data analysis for efficacy was performed according to the intention-to-treat principle for each assigned study group. The planned sample size of 402 patients — 268 in the ferric carboxymaltose group and 134 in the placebo group — was calculated on the basis of assumptions that the study would have a statistical power of 90% (with a two-sided alpha of 0.025) to detect a mean difference in the NYHA class of 0.50 and in the self-reported Patient Global Assessment ranking of 0.90 (the primary end points) between the two study groups. Assuming that 10% of patients would not complete the week 24 visit, the planned sample size was increased to 442. Both primary end points were compared between the two study groups by
A Self-Reported Patient Global Assessment

|                | Placebo | Better | FCM | Better | Placebo | Better | FCM | Better |
|----------------|---------|--------|-----|--------|---------|--------|-----|--------|
|                | 0.5     | 0.0    | 0.5 | 0.0    | 0.5     | 0.0    | 0.5 | 0.0    |

Odds Ratio (95% CI)

|                | Placebo | Better | FCM | Better | Placebo | Better | FCM | Better |
|----------------|---------|--------|-----|--------|---------|--------|-----|--------|
|                | 0.0     | 0.0    | 0.0 | 0.0    | 0.0     | 0.0    | 0.0 | 0.0    |

B NYHA Functional Class

|                | Placebo | Better | FCM | Better | Placebo | Better | FCM | Better |
|----------------|---------|--------|-----|--------|---------|--------|-----|--------|
|                | 0.0     | 0.0    | 0.0 | 0.0    | 0.0     | 0.0    | 0.0 | 0.0    |

C 6-Minute-Walk Test

|                | Placebo | Better | FCM | Better | Placebo | Better | FCM | Better |
|----------------|---------|--------|-----|--------|---------|--------|-----|--------|
|                | 0.0     | 0.0    | 0.0 | 0.0    | 0.0     | 0.0    | 0.0 | 0.0    |

D EQ-5D Visual Analog Scale

|                | Placebo | Better | FCM | Better | Placebo | Better | FCM | Better |
|----------------|---------|--------|-----|--------|---------|--------|-----|--------|
|                | 0.0     | 0.0    | 0.0 | 0.0    | 0.0     | 0.0    | 0.0 | 0.0    |

E Kansas City Cardiomyopathy Questionnaire

|                | Placebo | Better | FCM | Better | Placebo | Better | FCM | Better |
|----------------|---------|--------|-----|--------|---------|--------|-----|--------|
|                | 0.0     | 0.0    | 0.0 | 0.0    | 0.0     | 0.0    | 0.0 | 0.0    |
means of polytomous regression. For data on the NYHA class, the model was adjusted for the baseline value. The alpha value was adjusted according to the method of Benjamini and Hochberg.

Missing data on the NYHA class and the self-reported Patient Global Assessment were imputed from data collected during the previous follow-up visit, according to the last-observation-carried-forward method, for patients who were known to be alive and not hospitalized at the time of the assessment. For hospitalized patients, a missing NYHA class was assigned as class IV and a missing self-reported Patient Global Assessment was assigned as “much worse.” For patients who had died, a missing NYHA class was assigned as class V and a missing self-reported Patient Global Assessment was assigned as “died.” The analysis regarding the primary end points was restricted to data for patients who had at least one valid self-reported Patient Global Assessment or NYHA value, respectively, during the follow-up period.

For the continuous variables, changes from the baseline value and values at weeks 4, 12, and 24 were compared between the ferric carboxymaltose group and the placebo group by comparing the means within each of the two study groups at each visit with the use of a model for repeated measures adjusted for baseline values. For categorical end points, differences in the distribution for each of the two study groups were tested by means of ordered polytomous regression. Tests for interaction were performed as part of the subgroup analysis regarding the primary end points by adding an interaction term to the ordered polytomous regression model. Cox proportional-hazards regression models were used to estimate the hazard ratios for safety outcomes on the basis of the treatment received. Event rates are reported per person-year at risk. All analyses were conducted with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE STUDY PATIENTS

The clinical characteristics of 459 patients are presented in Table 1. A total of 304 patients were randomly assigned to receive ferric carboxymaltose and 155 to receive placebo. The two groups were similar with respect to the baseline clinical and laboratory characteristics and the use of cardiovascular medications at the time of enrollment.

FOLLOW-UP

Of the 304 patients assigned to receive ferric carboxymaltose, 26 (8.6%) did not complete the 24 weeks of follow-up; of these 26, 5 had died and 21 had withdrawn (Fig. 1 in the Supplementary Appendix). Of the 155 patients assigned to receive placebo, 20 (12.9%) did not complete the 24 weeks of follow-up; of these 20, 4 had died and 16 had withdrawn.

PRIMARY END POINTS

The self-reported Patient Global Assessment at week 24 was improved in the ferric carboxymaltose group, with 50% of patients reporting that they were much or moderately improved, as compared with 28% of patients in the placebo group (odds ratio for being in a better rank, 2.51; 95% confidence interval [CI], 1.75 to 3.61; P<0.001) (Fig. 1A). Similarly, the NYHA functional class at week 24, after adjustment for the baseline value was improved in the ferric carboxymaltose group, with 47% having an NYHA functional class I or II, as compared with 30% in the placebo group (odds ratio for improvement by one class, 2.40; 95% CI, 1.55 to 3.71; P<0.001) (Fig. 1B).

SECONDARY END POINTS

The use of ferric carboxymaltose, as compared with placebo, significantly improved the self-reported Patient Global Assessment and NYHA class at weeks 4 and 12 (P<0.001 for all comparisons) (Fig. 2A and 2B, and Fig. 3 and 4 in the Supplementary Appendix). Significant improvements were also seen in the distance on the 6-minute walk test and in the quality of life, as evaluated by the EQ-5D visual assessment score and the overall Kansas City Cardiomyopathy score, at weeks 4, 12, and 24 (P<0.001 for all comparisons) (Fig. 2C, 2D, and 2E).

SUBGROUP ANALYSES

A consistent benefit regarding the two primary end points was observed in all prespecified subgroups (Fig. 3). The treatment effect was similar in patients with anemia and in those without anemia (prospectively defined as a hemoglobin level ≤120 g per liter at baseline).

SAFETY AND BIOCHEMICAL ANALYSES

Survival status was available for all patients through at least week 24. The rates of death, hospitalization, and serious and nonserious adverse events reported
by the investigators were similar in the two study groups (Table 2). There was a trend toward a lower rate of first hospitalization for any cardiovascular reason among patients receiving ferric carboxymaltose as compared with those receiving placebo (hazard ratio, 0.53; 95% CI, 0.25 to 1.09; P=0.08).

The hazard ratio for death or first hospitalization for any cardiovascular reason among patients who received ferric carboxymaltose as compared with those who received placebo was 0.61 (95% CI, 0.32 to 1.18; P=0.14).

Data on serious and nonserious adverse events are also shown in Table 2, and in Table 1 in the Supplementary Appendix. The study treatment was stopped prematurely in 16 (5.3%) of the 304 patients assigned to receive ferric carboxymaltose...
and in 14 (9.0%) of the 155 patients assigned to receive placebo. No severe allergic reactions related to the study treatment were reported. Of the patients treated with ferric carboxymaltose, injection-site discoloration was reported for four patients and injection-site pain for two patients.

Laboratory values for ferritin, transferrin saturation, and hemoglobin at week 24 were significantly different between the two study groups (P<0.001 for all comparisons) (Table 3). The mean (±SE) difference in the ferritin level (adjusted for baseline) between patients receiving ferric carboxymaltose and those receiving placebo was 243±17 μg per liter at week 4, 188±15 μg per liter at week 12, and 246±20 μg per liter at week 24 (P<0.001 for all comparisons). The corresponding mean differences in the hemoglobin level were 6.6±1.1, 10.6±1.3, and 5.9±1.5 g per liter, respectively (P<0.001 for all comparisons), and the corresponding mean differences in the mean corpuscular volume of erythrocytes were 1.5±0.4, 2.4±0.5, and 2.7±0.7 μm³, respectively (all P<0.001). The mean difference in the hemoglobin level at week 24 (adjusted for baseline) between the ferric carboxymaltose group and the placebo group was not significant among patients who did not have anemia at baseline (2.4±2.0 g per liter, P=0.21) but was significant among patients who had anemia at baseline (9.1±2.2 g per liter, P<0.001). The mean difference in estimated glomerular filtration rate (adjusted for baseline) between patients receiving

| End Point or Event                          | Ferric Carboxymaltose (N = 305) | Placebo (N = 154) | P Value |
|--------------------------------------------|----------------------------------|-------------------|---------|
| Safety end point                           | No. of End Points or Serious Adverse/Any Adverse Events | No. of Patients with End Point or Event (incidence/100 patient-yr at risk) | No. of End Points or Serious Adverse/Any Adverse Events | No. of Patients with End Point or Event (incidence/100 patient-yr at risk) | P Value |
| Death                                      | 5 (3.4)                          | 4 (5.5)           | 0.47    |
| Death due to cardiovascular causes         | 4 (2.7)                          | 4 (5.5)           | 0.31    |
| Death due to worsening heart failure       | 0 (0)                            | 3 (4.1)           |         |
| First hospitalization                      | 28 (17.7)                        | 22 (14.8)         | 0.30    |
| Hospitalization for any cardiovascular cause | 16 (10.4)                     | 18 (20.0)         | 0.08    |
| Hospitalization for worsening heart failure | 7 (4.1)                          | 9 (9.7)           | 0.11    |
| Any hospitalization or death               | 33 (21.2)                        | 26 (27.7)         | 0.38    |
| Hospitalization for any cardiovascular cause or death | 21 (13.9)                     | 22 (22.9)         | 0.14    |
| First hospitalization for worsening heart failure or death | 12 (7.5)                          | 13 (13.9)         | 0.15    |

Table 2. Safety End Points and Serious and Nonserious Adverse Events, According to Study Treatment Received.*

* Adverse events are classified on the basis of the system organ classes of the Medical Dictionary for Regulatory Activities. Events that were reported in more than 4% of all the study patients are listed here. One patient who had been randomly assigned to the placebo group received ferric carboxymaltose.
ferric carboxymaltose and those receiving placebo was 3.8±1.8 ml per minute (P=0.03). There were no significant differences between the two study groups with respect to adverse-event reporting based on chemical values and other hematologic laboratory test results.

**DISCUSSION**

Treatment with ferric carboxymaltose for 24 weeks in patients who had chronic heart failure and iron deficiency with or without anemia improved symptoms, functional capacity, and the quality of life. Our study also showed that treatment with ferric carboxymaltose was not associated with an unacceptable side-effect or adverse-event profile.

Our study showed improvement with ferric carboxymaltose in the two primary end points: the self-reported Patient Global Assessment and the NYHA class at 24 weeks. The benefit was evident after 4 weeks and was maintained throughout the study period. These results were consistent across all prespecified subgroups and were confirmed by the observed improvements in distance on the 6-minute walk test distance and in scores on the health-related quality-of-life questionnaires.

Our patient population was identified on the basis of laboratory biomarkers, ferritin, transferrin saturation, and hemoglobin. These variables were also used to calculate the iron-repletion dose and to guide decisions about continuation or interruption of ferric carboxymaltose. In that sense, the trial is a double-blind treatment trial that used guidance based on blood-sample data for study-treatment initiation and monitoring. The study results suggest that in the assessment of ambulatory patients with symptomatic heart failure and systolic dysfunction, laboratory investigations to detect iron deficiency may be useful in routine practice to decide whether symptom management, by means of treatment with intravenous iron, is indicated.

The dose needed to correct iron deficiency was calculated according to Ganzoni's formula and was provided over a period between 3 and 7 weeks (a median of six injections) during the correction phase. We required that iron was given in doses of 200 mg per application and that the dosing frequency was weekly during the correction phase and monthly during the maintenance phase. The results of our study are applicable only to this dosing regimen. Treatment approaches involv-
ing higher doses and higher ferritin thresholds for the interruption of therapy are untested in patients with heart failure.

The treatment with ferric carboxymaltose was beneficial to both patients with anemia and those without anemia. This suggests that iron deficiency is a valid independent therapeutic target. Iron metabolism in patients with chronic illness merits a more detailed investigation to unravel the reasons why the correction of iron deficiency can result in symptomatic improvements even in the absence of a change in hemoglobin. Our results are consistent with those from four small studies that were performed with the use of a different preparation of intravenous iron.\(^{16-19}\) One of these studies\(^ {15}\) recruited a subgroup of patients without anemia who had even higher hemoglobin levels than our patients (i.e., 125 to 145 g per liter). We do not know the limit of the hemoglobin up to which iron deficiency is pathophysiological important. On the basis of our current findings, we cannot recommend treatment with ferric carboxymaltose for patients who have chronic heart failure, iron deficiency, and a hemoglobin level above 135 g per liter, but such therapy is an area of interest for future research.

In conclusion, in stable, symptomatic, ambulatory patients with chronic heart failure, an impaired left ventricular ejection fraction, and iron deficiency, treatment with ferric carboxymaltose over a 24-week period improves symptoms, physical performance, and the quality of life and has acceptable side-effect and adverse-event profiles. The benefit was seen in anemia and in those without anemia.

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 APPENDIX

The members of the FAIR-HF study group are as follows: Executive Committee: S.D. Anker (chair), P. Ponikowski (cochair), K. Dickstein, G.S. Filippatos, T.E. Lüscher, R. Willenheimer, J. Comin Colet, H. Drexler (deceased), P.A. Poole-Wilson (deceased); and Data Safety and Monitoring Board: R.P. Wikström (chair), J. Lubes. The FAIR-HF site investigators and institutions were as follows (with numbers of recruited patients per country in parentheses): Argentina (6): J.H. Altamirano, Instituto de Investigaciones Cardiológicas Prof. Dr. Alberto C. Taquini, Buenos Aires; S.V. Rodríguez, Instituto de Diagnóstico Cardiovascular La Plata, Buenos Aires; Czech Republic (17): J. Spinar, Fakultní Nemocnice Brno, Brno; J. Povolný, Oblastní Nemocnice Kladno, Kladno; J. Bělohlávek, Všeobecná Fakultní Nemocnice, Prague; Z. Pulich, Fakultní Thomayerova Nemocnice, Prague; J. Horák, Fakultní Nemocnice Kralovské Vinohrady, Prague; Germany (11): S. Anker, Charité Berlin, Campus Virchow-Klinikum, Berlin; D. Wolf, CardioSec Clinical Research, Erfurt; M. Natour, Praxis Dr. M. Natour and M. Durak, Heidelberg; Öster (11): A. Manolitsa, General Hospital of Voula Askliption, Athens; J. Nanas, Alexandras General Hospital, Athens; D. Tremiliosinos, University Hospital of Athens Attikon, Athens; D. Alenopoulou, University Hospital of Patras, Patras; Italy (11): M. Volterrani, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Pisana, Rome; G. Vescovo, Unità Locale Socio Sanitaria 6 Ospedale San Bortolo, Vicenza; Norway (2): K. Dickstein, Stavanger Helseforskningsst, Stavanger; Poland (60): M. Mysliwiec, Wojewódzki Szpital Specjalistyczny im K. Dłuskiego, Białystok; M. Ogorek, Samodzielny Szpital Wojewódzki im M. Kopernika, Piotrków Trybunalski; P. Staneta, Niepubliczny zakład Opieki Zdrowotnej Specjalistyczna Przychodnia Lekarska, Medikard, Plock; J. Niegowska, Centrum Medyczne, Telmont Centrum Medyczne, Sp. z o.O., Warsaw; M. Dłuzniewski, Wojewódzki Szpital Bródnowski, Warsaw; P. Ponikowski, 4 Wojskowy Szpital Kliniczny z Polikliniką, Wrocław; L. Polonski, Śląskie Centrum Chorob Serca, Zabrze; Romania (16): M. Radu, Spitalul Clinic de Urgenta Brasov, Brasov; C.E. Macarie, Institutul de Boli Cardiovasculare Prof. Dr. C.C. Iliescu, Bucharest; G.A. Dan, Spitalul Clinic Colentina, Bucharest; P.I. Kikeli, Societatea Civila Medicaa Procardia Medica, Targu Mureș; Russia (200): E.S. Pasechnik, State Institution of Healthcare Kazuzhskaya Regional Hospital, Kaluga; A.A. Eremenko, Russian Scientific Center of Surgery of the Russian Academy of Medical Sciences, Moscow; A.A. Gorbachenkov, Central Clinical Hospital of Civil Aviation of the Ministry of Transport of the Russian Federation, Moscow; A.E. Bragina, City Clinical Hospital 61, Moscow; A.Y. Ileva, Outpatient Clinic 3 of President of the Russian Federation Ministry, Moscow; B.Y. Bart, Russian State Medical University, Outpatient Diagnostic Consulting Center 1, Moscow; G.P. Arutyunov, City Clinical Hospital 4, Moscow; R.A. Khokhlov, Voronezhsky Regional Hospital 1, Voronezh; S.N. Tereschenko, City Clinical Hospital 33, Nizhniy Novgorod; V.E. Olyenikov, State Institution of Healthcare Regional Clinical Hospital, Penza; N.A. Koziolova, Permsky Regional Hospital of War Veterans, Perm; D.V. Duplyakov, State Institute of Healthcare Regional Cardiology Dispensary of Samara, Samara; A.A. Petrov, Leningrad Regional Clinical Hospital, St. Petersburg; D.U. Butko, International Clinic and Hospital Medem, St. Petersburg; M.Y. Sitnikova, Research Institute of Cardiology, St. Petersburg; O.A. Berkovich, St. Petersburg State Medical
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