ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

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ABSTRACT

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BACKGROUND

Iron deficiency may impair aerobic performance. This study aimed to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve symptoms in patients who had heart failure, reduced left ventricular ejection fraction, and iron deficiency, either with or without anemia.

METHODS

We enrolled 459 patients with chronic heart failure of New York Heart Association (NYHA) functional class II or III, a left ventricular ejection fraction of 40% or less (for patients with NYHA class II) or 45% or less (for NYHA class III), iron deficiency (ferritin level <100 μg per liter or between 100 and 299 μg per liter, if the transferrin saturation was <20%), and a hemoglobin level of 95 to 135 g per liter. Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of intravenous iron (ferric carboxymaltose) or saline (placebo). The primary end points were the self-reported Patient Global Assessment and NYHA functional class, both at week 24. Secondary end points included the distance walked in 6 minutes and the health-related quality of life.

RESULTS

Among the patients receiving ferric carboxymaltose, 50% reported being much or moderately improved, as compared with 28% of patients receiving placebo, according to the Patient Global Assessment (odds ratio for improvement, 2.51; 95% confidence interval [CI], 1.75 to 3.61). Among the patients assigned to ferric carboxymaltose, 47% had an NYHA functional class I or II at week 24, as compared with 30% of patients assigned to placebo (odds ratio for improvement by one class, 2.40; 95% CI, 1.55 to 3.71). Results were similar in patients with anemia and those without anemia. Significant improvements were seen with ferric carboxymaltose in the distance on the 6-minute walk test and quality-of-life assessments. The rates of death, adverse events, and serious adverse events were similar in the two study groups.

CONCLUSIONS

Treatment with intravenous ferric carboxymaltose in patients with chronic heart failure and iron deficiency, with or without anemia, improves symptoms, functional capacity, and quality of life; the side-effect profile is acceptable. (ClinicalTrials.gov number, NCT00520780.)

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 that adversely affect their quality of life, leading to high morbidity.[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.[5,6] In addition, anemia may aggravate symptoms in patients with heart failure.[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.[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.[9,10] Iron deficiency in patients with or without anemia attenuates aerobic performance and is accompanied by reports of fatigue and exercise intolerance.[11] The repletion of iron in patients who have iron deficiency without heart failure improves cognitive, symptomatic, and exercise performance.[12,13]

Recently, it has been recognized that patients with heart failure may be prone to the development of iron deficiency as a consequence of a depletion of iron stores or defective iron absorption and the reduced availability of iron recycled in the reticuloendothelial system.[14,15] 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.[16-19] In one of these studies,[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 published previously.[20] 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 defi-

ciency 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 satura-tion was less than 20%. Patients were excluded if they had uncontrolled hypertension, other clini-cally significant heart disease, inflammation, or clinically significantly impaired liver or renal function.

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

Table 1. (Continued.)

	Ferric Carboxymaltose (N=304)	Placebo (N=155)
Concomitant treatment — no. (%)		
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) $^{-1.154}$ × age (in years) $^{-0.203}$ × 1.21 (if patient is black) × 0.742 (if patient is female).

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).

STUDY THERAPY AND BLINDING

The total iron dose required for iron repletion was calculated at baseline, according to Ganzoni's formula[21] 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 (hemo-

globin 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[22] (on which the overall score ranges from 0 to 100, with a higher score indicating a better quality of life) and the European Quality of Life–5 Dimensions (EQ-5D) Visual Analog Scale[23] (on which the score ranges from 0 to 100, with a higher score indicating better health) at weeks 4, 12, and 24 (all adjusted for the baseline data).

Safety end points were serious and nonserious adverse events, hospitalization, and death, as assessed up to week 26. Standardized definitions for the causes of death and hospitalization were developed by members of the FAIR-HF Executive Committee and were supplied to all investigators.[20]
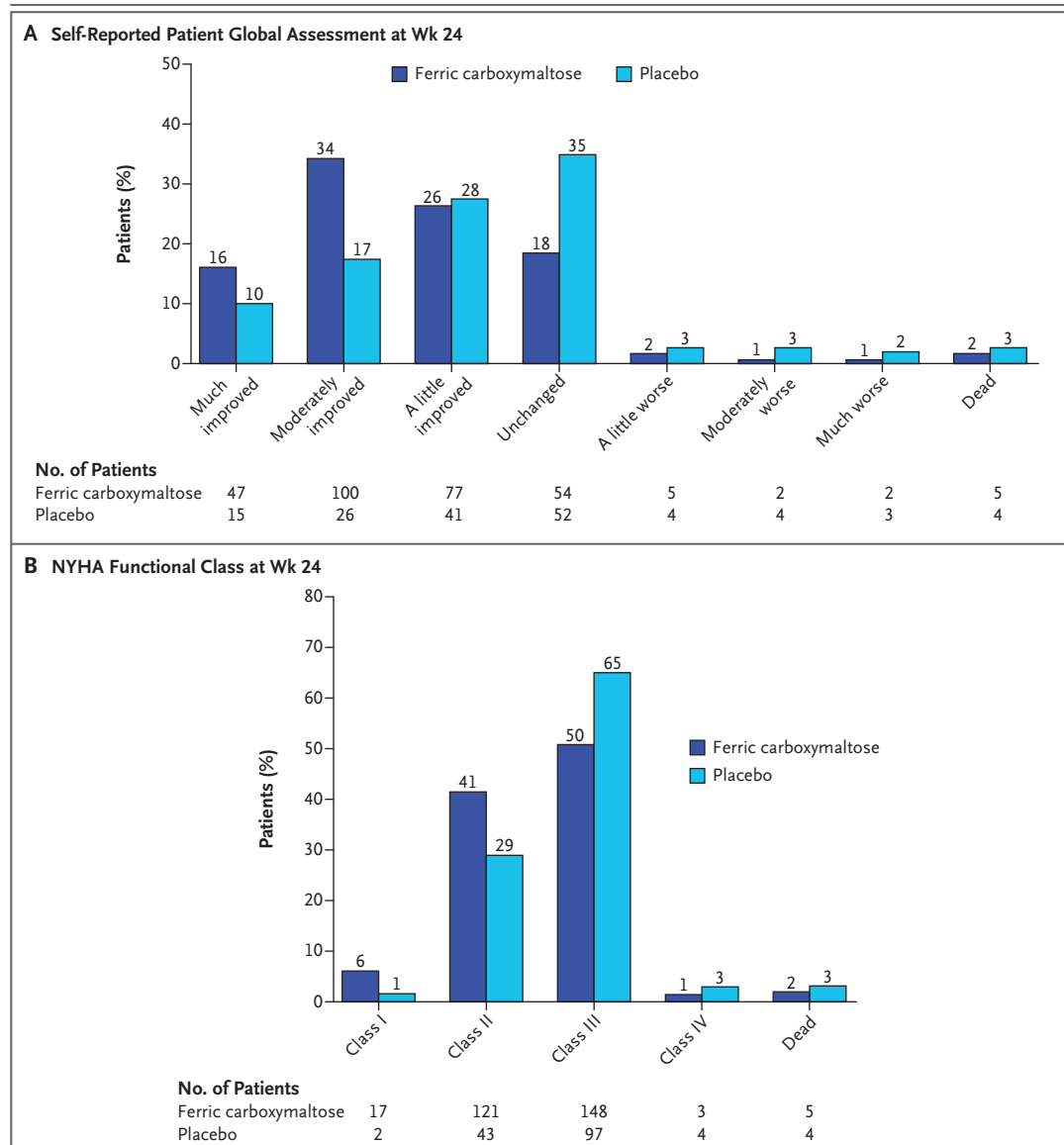
STATISTICAL ANALYSIS

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 means of polytomous regression.[24] For data on the NYHA class, the model was adjusted for the base-

line value. The alpha value was adjusted according to the method of Benjamini and Hochberg.[25]

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

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Figure 1 (facing page). Self-Reported Patient Global Assessment and New York Heart Association (NYHA) Functional Class at Week 24, According to Assigned Study Treatment.

Panel A shows the data regarding the self-reported Patient Global Assessment, and Panel B, data regarding the NYHA functional class. The odds ratio for an improvement in the self-reported Patient Global Assessment with ferric carboxymaltose as compared with placebo was 2.51 (95% confidence interval [CI], 1.75 to 3.61; P<0.001). Data on the self-reported Patient Global Assessment were missing for 30 patients known to be alive and not in the hospital at week 24 (18 receiving ferric carboxymaltose and 12 receiving placebo); for these patients, the last available assessment was used as the assessment for week 24. The two patients who were hospitalized at 24 weeks (both receiving ferric carboxymaltose) were assigned an assessment of much worse. The 9 patients who died before week 24 (5 who had been receiving ferric carboxymaltose and 4 who had been receiving placebo) were categorized as dead. Panel A does not include 12 patients in the ferric carboxymaltose group and 6 in the placebo group who were known to be alive at week 24 but who had no data on the self-reported Patient Global Assessment at any time during the study. The odds ratio for an improved NYHA class with ferric carboxymaltose as compared with placebo was 2.40 (95% CI, 1.55 to 3.71; P<0.001). Data on the NYHA class were missing for 28 patients known to be alive and not in the hospital at week 24 (16 receiving ferric carboxymaltose and 12 receiving placebo); for these patients, the last available NYHA classification was used as the classification for week 24. The 2 patients who were hospitalized at 24 weeks (both receiving ferric carboxymaltose) were considered to have NYHA class IV. The 9 patients who died before week 24 (5 who had been receiving ferric carboxymaltose and 4 who had been receiving placebo) were categorized as being dead (having NYHA class V). The data in Panel B do not include data for 10 patients in the ferric carboxymaltose group and 5 in the placebo group who were known to be alive at week 24 but who had no data on the NYHA functional class at any time during the study. In both panels, percentages may not sum to 100 because of rounding.

A Self-Reported Patient Global Assessment at Wk 24

No. of Patients	Much improved	Moderately improved	A little improved	Unchanged	A little worse	Moderately worse	Much worse	Dead
Ferric carboxymaltose	47	100	77	54	5	2	2	5
Placebo	15	26	41	52	4	4	3	4

B NYHA Functional Class at Wk 24

No. of Patients	Class I	Class II	Class III	Class IV	Dead
Ferric carboxymaltose	17	121	148	3	5
Placebo	2	43	97	4	4

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 ran-

domly 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).
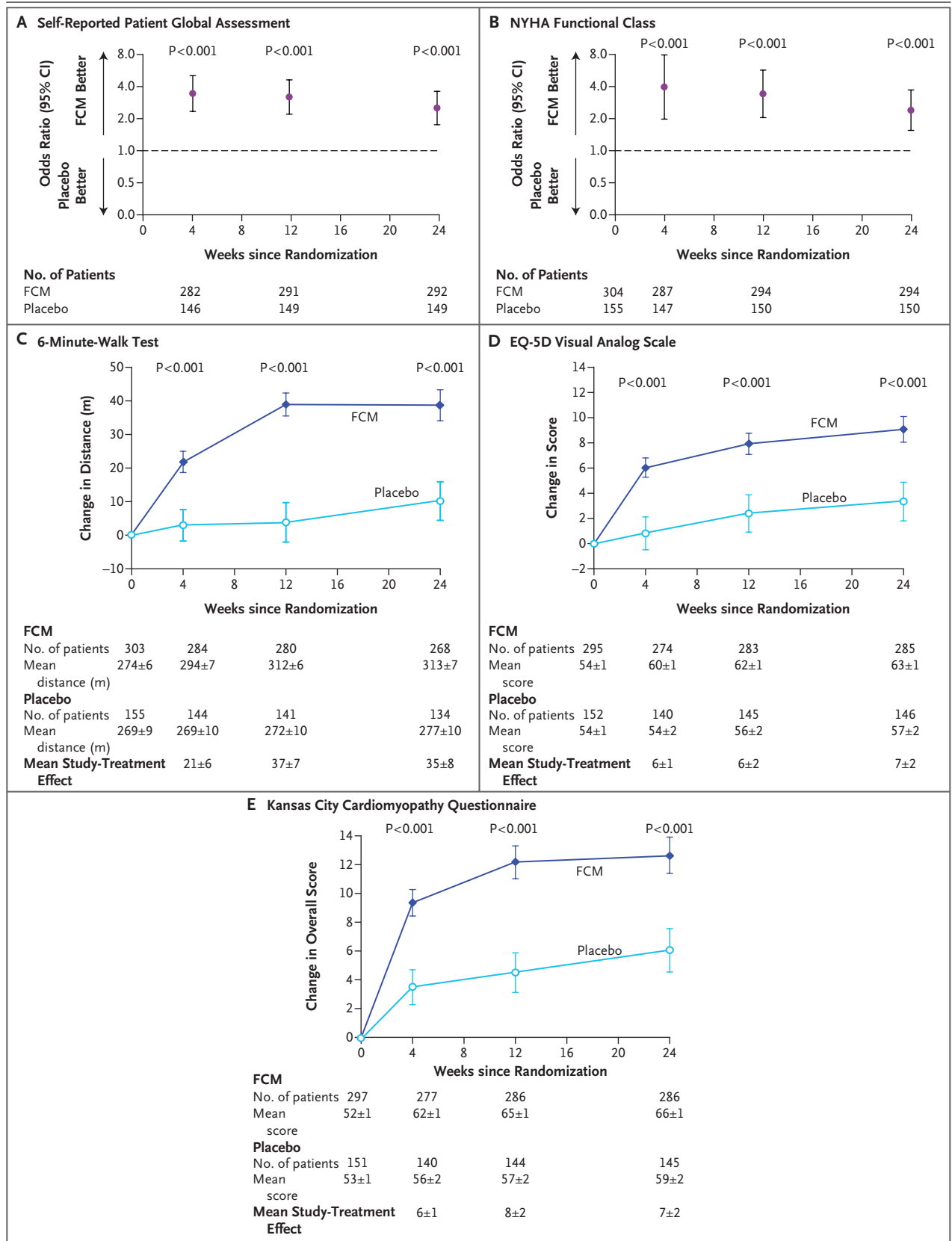
Figure 2 (facing page). Main Secondary Outcomes during the Study, According to Assigned Study Treatment.

Shown are data across the study period for the self-reported Patient Global Assessment (Panel A), the New York Heart Association (NYHA) functional class (Panel B), change in distance on the 6-minute walk test (Panel C), the change in the score on the European Quality of Life–5 Dimensions (EQ-5D) Visual Analog Scale (on which the 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 a higher score indicating a better quality of life) (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 $\log_2$ 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.

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
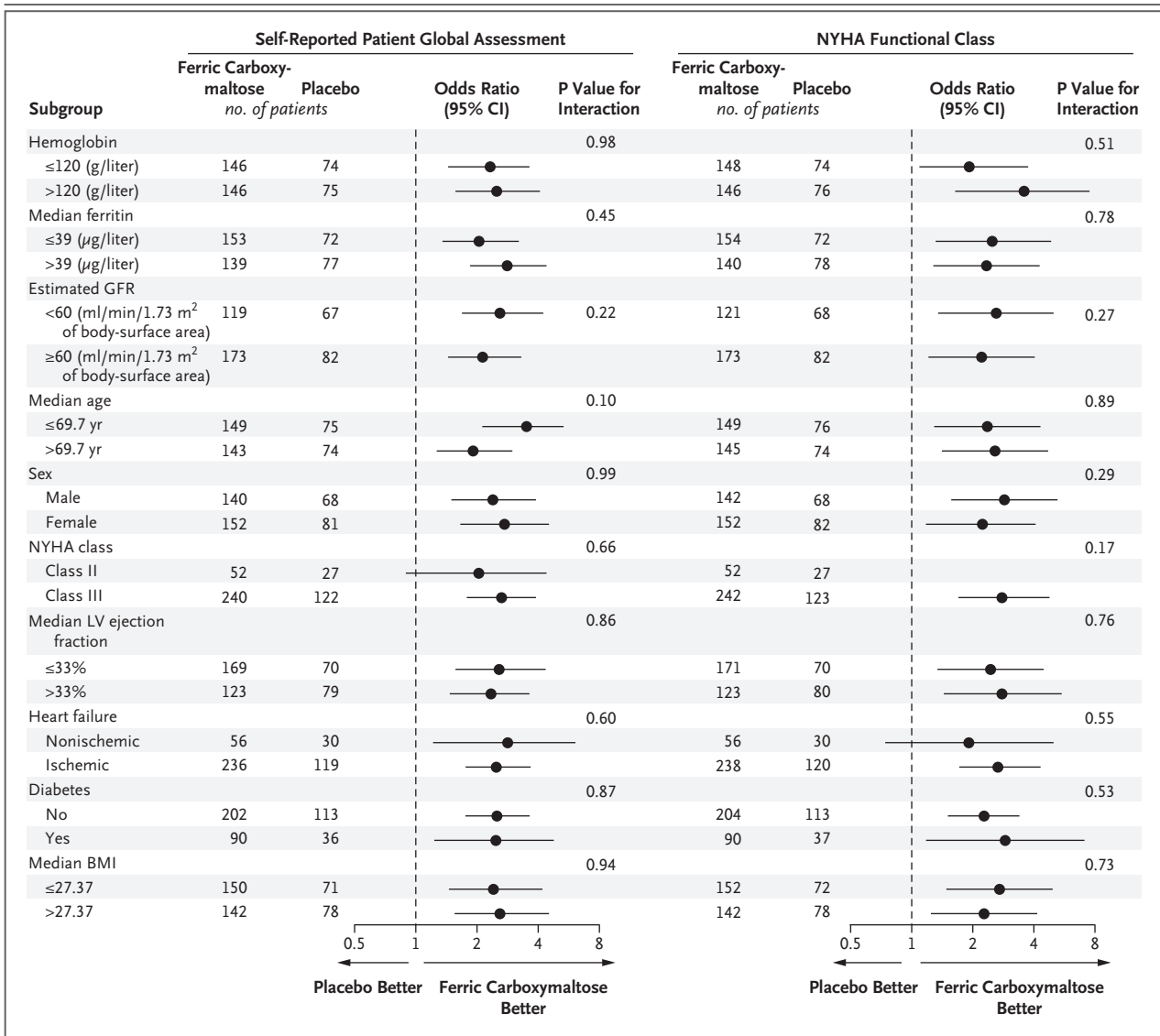
A Self-Reported Patient Global Assessment

No. of Patients

FCM	282	291		292
Placebo	146	149		149

B NYHA Functional Class

No. of Patients

FCM	304	287	294	294
Placebo	155	147	150	150

C 6-Minute-Walk Test

FCM

No. of patients	303	284	280	268
Mean distance (m)	274±6	294±7	312±6	313±7

Placebo

No. of patients	155	144	141	134
Mean distance (m)	269±9	269±10	272±10	277±10
Mean Study-Treatment Effect		21±6	37±7	35±8

D EQ-5D Visual Analog Scale

FCM

No. of patients	295	274	283	285
Mean score	54±1	60±1	62±1	63±1

Placebo

No. of patients	152	140	145	146
Mean score	54±1	54±2	56±2	57±2
Mean Study-Treatment Effect		6±1	6±2	7±2

E Kansas City Cardiomyopathy Questionnaire

FCM

No. of patients	297	277	286	286
Mean score	52±1	62±1	65±1	66±1

Placebo

No. of patients	151	140	144	145
Mean score	53±1	56±2	57±2	59±2
Mean Study-Treatment Effect		6±1	8±2	7±2

Subgroup	Self-Reported Patient Global Assessment				NYHA Functional Class			
	Ferric Carboxymaltose	Placebo	Odds Ratio (95% CI)	P Value for Interaction	Ferric Carboxymaltose	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients				no. of patients			
Hemoglobin				0.98				0.51
≤120 (g/liter)	146	74			148	74		
>120 (g/liter)	146	75			146	76		
Median ferritin				0.45				0.78
≤39 (μg/liter)	153	72			154	72		
>39 (μg/liter)	139	77			140	78		
Estimated GFR				0.22				0.27
<60 (ml/min/1.73 m² of body-surface area)	119	67			121	68		
≥60 (ml/min/1.73 m² of body-surface area)	173	82			173	82		
Median age				0.10				0.89
≤69.7 yr	149	75			149	76		
>69.7 yr	143	74			145	74		
Sex				0.99				0.29
Male	140	68			142	68		
Female	152	81			152	82		
NYHA class				0.66				0.17
Class II	52	27			52	27		
Class III	240	122			242	123		
Median LV ejection fraction				0.86				0.76
≤33%	169	70			171	70		
>33%	123	79			123	80		
Heart failure				0.60				0.55
Nonischemic	56	30			56	30		
Ischemic	236	119			238	120		
Diabetes				0.87				0.53
No	202	113			204	113		
Yes	90	36			90	37		
Median BMI				0.94				0.73
≤27.37	150	71			152	72		
>27.37	142	78			142	78		

0.5   1   2   4   8
Placebo Better ← | → Ferric Carboxymaltose Better

0.5   1   2   4   8
Placebo Better ← | → Ferric Carboxymaltose Better

Figure 3. Self-Reported Patient Global Assessment and New York Heart Association (NYHA) Functional Class in Predefined Subgroups, According to Assigned Study Treatment.

The number of patients in each subgroup for whom data were available is shown. The odds ratios are given for the ferric carboxymaltose group, as compared with the placebo group, on a $\log_2$ scale. For the results regarding the NYHA functional class in the subgroup of patients with heart failure of NYHA class II, one patient receiving ferric carboxymaltose had improvement to NYHA class I and two patients receiving placebo had a worsening to NYHA class III. The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. CI denotes confidence interval, GFR glomerular filtration rate, and LV left ventricular.

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

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

End Point or Event	Ferric Carboxymaltose (N=305)		Placebo (N=154)		P Value
	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)	
Safety end point					
Death	5	5 (3.4)	4	4 (5.5)	0.47
Death due to cardiovascular causes	4	4 (2.7)	4	4 (5.5)	0.31
Death due to worsening heart failure	0	0	3	3 (4.1)	
First hospitalization	28	25 (17.7)	22	17 (24.8)	0.30
Hospitalization for any cardiovascular cause	16	15 (10.4)	18	14 (20.0)	0.08
Hospitalization for worsening heart failure	7	6 (4.1)	9	7 (9.7)	0.11
Any hospitalization or death	33	30 (21.2)	26	19 (27.7)	0.38
Hospitalization for any cardiovascular cause or death	21	20 (13.9)	22	16 (22.9)	0.14
First hospitalization for worsening heart failure or death	12	11 (7.5)	13	10 (13.9)	0.15
Investigator-reported adverse event					
Cardiac disorder	12/46	38 (27.6)	23/49	33 (50.2)	0.01
Gastrointestinal disorder	2/29	24 (16.9)	2/7	5 (6.9)	0.06
General disorder or injection-site condition	4/28	23 (16.2)	1/6	6 (8.3)	0.14
Injection-site pain or discoloration	0/6	6 (4.1)	0/0	0	
Infection or infestation	2/56	50 (37.0)	0/32	24 (35.8)	0.97
Abnormal laboratory test, vital sign, or physical finding	0/63	32 (23.0)	0/10	10 (14.0)	0.17
Nervous system disorder	3/29	22 (15.6)	3/20	14 (20.3)	0.44
Respiratory, thoracic, or mediastinal disorder	0/9	9 (6.2)	3/13	10 (14.2)	0.06
Vascular disorder	3/24	20 (14.0)	1/13	11 (15.7)	0.80

* 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.

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 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.

Table 3. Levels of Iron-Metabolism Markers and Hemoglobin at Week 24 According to Study Treatment.*

Variable	Ferric Carboxymaltose (N=305)	Placebo (N=154)	P Value
All patients			
Ferritin (µg/liter)	312±13	74±8	<0.001
Transferrin saturation (%)†	29±1	19±1	<0.001
Hemoglobin (g/liter)	130±1	125±1	<0.001
Mean corpuscular volume (µm³)	97±0	94±1	<0.001
Patients with anemia (hemoglobin ≤120 g/liter)			
Ferritin (µg/liter)	275±18	68±11	<0.001
Transferrin saturation (%)†	29±1	17±1	<0.001
Hemoglobin (g/liter)	127±1	118±2	<0.001
Mean corpuscular volume (µm³)	98±1	93±1	<0.001
Patients without anemia (hemoglobin >120 g/liter)			
Ferritin (µg/liter)	349±19	80±11	<0.001
Transferrin saturation (%)†	30±1	22±1	<0.001
Hemoglobin (g/liter)	133±1	132±1	0.21
Mean corpuscular volume (µm³)	96±1	95±1	0.91

* Plus–minus values are means ±SE. The P value is for the mean treatment effect, adjusted for the baseline value. One patient who had been randomly assigned to the placebo group received ferric carboxymaltose.
† The percent transferrin saturation was calculated as iron (in micromoles per liter) ÷ transferrin (in grams per liter) × 25.1.

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[21] 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 involving 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 hemoglobin up to which iron deficiency is pathophysiologically 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 patients with anemia and in those without anemia.

APPENDIX

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