The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 14, 2023 VOL. 389 NO. 11

Ferric Carboxymaltose in Heart Failure with Iron Deficiency

Robert J. Mentz, M.D., Jyotsna Garg, M.S., Frank W. Rockhold, Ph.D., Javed Butler, M.D., M.P.H., M.B.A., Carmine G. De Pasquale, B.M., B.S., Justin A. Ezekowitz, M.B., B.Ch., Gregory D. Lewis, M.D., Eileen O'Meara, M.D., Piotr Ponikowski, M.D., Richard W. Troughton, M.B., Ch.B., Yee Weng Wong, M.B., B.S., Lilin She, Ph.D., Josephine Harrington, M.D., Robert Adamczyk, Pharm.D., Nicole Blackman, Ph.D., and Adrian F. Hernandez, M.D., M.H.S., for the HEART-FID Investigators*

ABSTRACT

BACKGROUND

Ferric carboxymaltose therapy reduces symptoms and improves quality of life in patients who have heart failure with a reduced ejection fraction and iron deficiency. Additional evidence about the effects of ferric carboxymaltose on clinical events is needed.

METHODS

In this double-blind, randomized trial, we assigned ambulatory patients with heart failure, a left ventricular ejection fraction of 40% or less, and iron deficiency, in a 1:1 ratio, to receive intravenous ferric carboxymaltose or placebo, in addition to standard therapy for heart failure. Ferric carboxymaltose or placebo was given every 6 months as needed on the basis of iron indexes and hemoglobin levels. The primary outcome was a hierarchical composite of death within 12 months after randomization, hospitalizations for heart failure within 12 months after randomization, or change from baseline to 6 months in the 6-minute walk distance. The significance level was set at 0.01.

RESULTS

We enrolled 3065 patients, of whom 1532 were randomly assigned to the ferric carboxymaltose group and 1533 to the placebo group. Death by month 12 occurred in 131 patients (8.6%) in the ferric carboxymaltose group and 158 (10.3%) in the placebo group; a total of 297 and 332 hospitalizations for heart failure, respectively, occurred by month 12; and the mean (±SD) change from baseline to 6 months in the 6-minute walk distance was 8±60 and 4±59 m, respectively (Wilcoxon–Mann–Whitney P=0.02; unmatched win ratio, 1.10; 99% confidence interval, 0.99 to 1.23). Repeated dosing of ferric carboxymaltose appeared to be safe with an acceptable adverse-event profile in the majority of patients. The number of patients with serious adverse events occurring during the treatment period was similar in the two groups (413 patients [27.0%] in the ferric carboxymaltose group and 401 [26.2%] in the placebo group).

CONCLUSIONS

Among ambulatory patients who had heart failure with a reduced ejection fraction and iron deficiency, there was no apparent difference between ferric carboxymaltose and placebo with respect to the hierarchical composite of death, hospitalizations for heart failure, or 6-minute walk distance. (Funded by American Regent, a Daiichi Sankyo Group company; HEART-FID ClinicalTrials.gov number, NCT03037931.)

From the Division of Cardiology, Department of Medicine (R.J.M., J.H., A.F.H.), and the Department of Biostatistics and Bioinformatics (F.W.R.), Duke University School of Medicine, and Duke Clinical Research Institute (R.J.M., J.G., F.W.R., L.S., J.H., A.F.H.) — both in Durham, NC; Baylor Scott and White Research Institute, Dallas (J.B.); the Department of Medicine, University of Mississippi, Jackson (J.B.); Flinders Medical Centre, Flinders University, Adelaide, SA (C.G.D.P.), and the Department of Cardiology, Prince Charles Hospital and Faculty of Medicine, University of Queensland, Brisbane (Y.W.W.) — both in Australia; Canadian VIGOUR Centre, University of Alberta, Edmonton (J.A.E.), and Montreal Heart Institute and Université de Montréal, Montreal (E.O.) — both in Canada; the Cardiology Division and Cardiovascular Research Center, Massachusetts General Hospital, Boston (G.D.L.); the Center for Heart Diseases, University Hospital, Wroclaw Medical University, Wroclaw, Poland (P.P.); Christchurch Heart Institute, University of Otago, Christchurch, New Zealand (R.W.T.); the Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN (Y.W.W.); and American Regent, Shirley, NY (R.A., N.B.). Dr. Mentz can be contacted at robert.mentz@duke.edu or at the Division of Cardiology, Department of Medicine, Duke University School of Medicine, 40 Duke Medicine Cir., Durham, NC 27710.

*A list of the collaborators in the HEART-FID trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 26, 2023, at NEJM.org.

N Engl J Med 2023;389:975-86.
DOI: 10.1056/NEJMoa2304968

CME at NEJM.org

In patients with heart failure, iron deficiency is common and is associated with worse symptoms and outcomes than those in patients with heart failure without iron deficiency.[1-4] The IRONOUT HF trial showed that oral iron therapy did not improve exercise capacity in patients who had heart failure with a reduced ejection fraction and iron deficiency,[5] and guidelines do not recommend the use of oral iron therapy in such patients.[6] In contrast, other trials showed that intravenous ferric carboxymaltose treatment improved the quality of life and functional capacity in patients who had heart failure with a reduced ejection fraction and iron deficiency.[7-9]

A Quick Take is available at NEJM.org

The AFFIRM-AHF trial compared ferric carboxymaltose with placebo with respect to cardiovascular death and total hospitalizations for heart failure in 1132 patients hospitalized with acute heart failure, a left ventricular ejection fraction of less than 50%, and iron deficiency; the rate ratio (ferric carboxymaltose vs. placebo) was 0.79 (95% confidence interval [CI], 0.62 to 1.01; P=0.059).[10] The IRONMAN trial, which assessed a different intravenous iron formulation (ferric derisomaltose), showed findings similar to those in the AFFIRM-AHF trial (rate ratio, 0.82; 95% CI, 0.66 to 1.02; P=0.070).[11] The conduct of these trials was affected by the coronavirus disease 2019 (Covid-19) pandemic, and prespecified analyses suggested that intravenous iron reduced hospitalizations for heart failure. A meta-analysis of trials of intravenous iron therapy that included 3773 patients with heart failure and iron deficiency showed that intravenous iron appeared to be associated with reduced hospitalizations for heart failure without an effect on mortality.[12] We designed the Ferric Carboxymaltose in Heart Failure with Iron Deficiency (HEART-FID) trial with a hierarchical composite outcome (death, hospitalization for heart failure, and 6-minute walk distance) to assess whether the incidence of death and hospitalization for heart failure would be lower and improvement in the 6-minute walk distance greater with ferric carboxymaltose therapy than with placebo in patients with heart failure with a reduced ejection fraction and iron deficiency.

Methods

Trial Design

The design of this double-blind, randomized, placebo-controlled, event-driven trial has been reported elsewhere.[13] The protocol and statistical analysis plan are available with the full text of this article at NEJM.org. An ethics committee at each center approved the trial, and all the patients provided written informed consent. The trial was sponsored by American Regent, a Daiichi Sankyo Group company, with coordination by the Duke Clinical Research Institute (DCRI). The sponsor, the DCRI, and the steering committee participated in the design of the trial and in the interpretation of data. Data were managed and analyzed by the DCRI, independent of the sponsor. An independent data and safety monitoring committee reviewed data approximately every 6 months. The first author drafted the original manuscript, which was reviewed and edited by all the authors. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Eligible patients were adults (≥18 years of age) with heart failure, a left ventricular ejection fraction of 40% or less, a hemoglobin level greater than 9.0 g per deciliter and either less than 13.5 g per deciliter (in women) or less than 15.0 g per deciliter (in men), iron deficiency (defined as a ferritin level of <100 ng per milliliter or a level of 100 to 300 ng per milliliter with a transferrin saturation of <20%), and either hospitalization for heart failure within the previous 12 months or an elevated natriuretic peptide level. This definition of iron deficiency was based on previous studies.[7,8] Detailed eligibility criteria are provided in the Supplementary Appendix (available at NEJM.org).

Trial Procedures

Patients who met the eligibility criteria were randomly assigned, in a 1:1 ratio, to receive intravenous ferric carboxymaltose or placebo, in addition to usual therapy for heart failure, with stratifica-

tion according to region of enrollment. Dosing was weight-based; two doses separated by 7 days were administered, as detailed in the protocol. Follow-up occurred every 3 months, with ferric carboxymaltose or placebo administered every 6 months on the basis of hemoglobin and iron indexes. Patients were followed for the duration of the trial, regardless of adherence.

TRIAL OUTCOMES

The primary outcome was a hierarchical composite of death within 12 months after randomization, hospitalizations for heart failure within 12 months after randomization, or change in the 6-minute walk distance from baseline (the day of randomization) to 6 months, as detailed in the Supplementary Appendix. The main secondary outcome was a composite of cardiovascular death or hospitalization for heart failure over the duration of follow-up (the interval between random assignment of the first patient and month 12 after assignment of the last patient), as assessed in a time-to-first-event analysis. We assessed four additional secondary outcomes: the change in 6-minute walk distance from baseline to 12 months, a composite of cardiovascular death or intervention for worsening heart failure during follow-up, a composite of cardiovascular death or cardiovascular hospitalization during follow-up, and cardiovascular death during follow-up. Deaths and cardiovascular hospitalizations were adjudicated by an independent committee at the DCRI whose members were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

The trial design allowed for sufficient power for analysis of the primary and main secondary outcomes. As previously reported[13] and as detailed in the statistical analysis plan, we estimated that a sample size of 3014 patients would provide the trial with 90% power to detect a difference between the trial groups in the primary outcome, at a two-sided significance level of 0.01, assuming a 2.5% annual loss to follow-up and 15% of patients missing data on the 6-minute walk distance at 6 months. For the main secondary outcome, the anticipated hazard ratio was set at 0.80. We calculated that with 1500 patients per group and 771 events, the trial would have 90% power to reject the null hypothesis at an overall two-sided significance level of 0.05.

After accounting for one interim analysis (with a significance level of 0.0001), the final analysis of the primary outcome used a two-sided significance level of 0.0099. This significance level fulfilled a special protocol agreement with the Food and Drug Administration that permitted the assessment of efficacy on the basis of a single randomized trial. In order to preserve an overall type I error rate of 0.05, the two-sided alpha level for the main secondary outcome was modified to 0.0399.

The primary analysis was performed according to the intention-to-treat principle and included data collected through the end of follow-up from patients who underwent randomization, as detailed in the Supplementary Appendix and the statistical analysis plan. In brief, for the primary end point, each patient in each trial group was ranked on the basis of the occurrence of death at 12 months, hospitalizations for heart failure at 12 months, or change in the 6-minute walk distance from baseline to 6 months, according to the prespecified hierarchy. In the main comparison of the primary outcome, we used the nonparametric Wilcoxon–Mann–Whitney test to sum the ranks of patients in each trial group and to compare the sums between the two groups. The main comparison relied on the use of a multiple imputation model with a Markov chain Monte Carlo algorithm. In addition to the main comparison, we calculated the overall unmatched win ratio, as assessed across 20 imputed data sets (with imputation of data on the 6-minute walk distance as specified in the statistical analysis plan), along with its 99% confidence interval. We calculated the overall unmatched win ratio within each of the 20 imputed data sets by adding all the wins in the ferric carboxymaltose group and dividing the sum by all the wins in the placebo group. Wins were determined by a comparison of the rank of each patient in the ferric carboxymaltose group with the rank of each patient in the placebo group according to the hierarchical primary outcome. The patient with a better rank with respect to death at 12 months was considered to have won that comparison. If both patients had the same rank, the outcome was considered a tie, and the patients were further compared

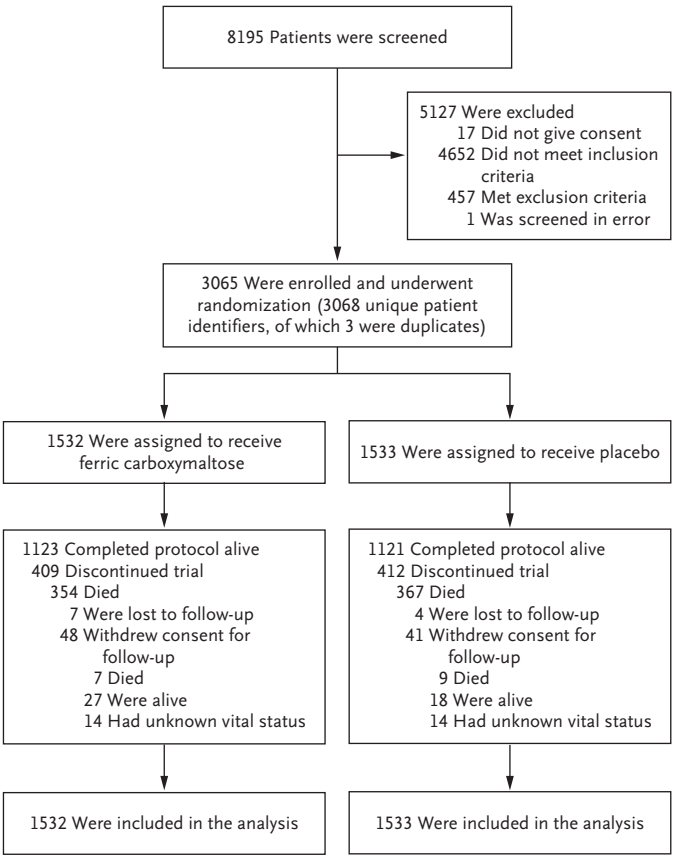


Figure 1. Screening, Randomization, and Follow-up.

with respect to heart failure hospitalizations at 12 months. If the outcome of that comparison was a tie, the patients were subsequently compared with respect to the change in the 6-minute walk distance between baseline and 6 months. We combined the 20 win ratios obtained from the 20 imputed data sets using Rubin's rule[14] to obtain the overall unmatched win ratio.[15]

The main secondary outcome was a composite of cardiovascular death or hospitalization for heart failure over the duration of follow-up, as assessed in a time-to-first-event analysis. The four additional secondary outcomes, assessed in time-to-first-event analyses, were evaluated throughout follow-up and were tested in the order listed in the statistical analysis plan with use of a Cox proportional hazards model that included region as a stratification factor with prespecified covariates. These secondary outcomes were analyzed without adjustment for multiplicity. Results are reported as point estimates and 96% confidence intervals, and the widths of these confidence intervals should not be used to infer definitive treatment effects for the secondary outcomes. Proportional hazard assumptions were examined, and missing data were handled as detailed in the statistical analysis plan. A cumulative incidence function was created to assess the effect of the competing risk of noncardiovascular death on the main secondary outcome. Prespecified subgroup analyses were performed for the main secondary outcome. We analyzed the mean change in the 6-minute walk distance from baseline to 12 months using linear regression and adjusting for the walk distance at baseline. Prespecified analyses were performed in patients with 10-m and 20-m changes in the 6-minute walk distance. All analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS AND FOLLOW-UP

Between March 2017 and November 2021, a total of 8195 patients were screened for eligibility. We enrolled 3065 patients, of whom 1532 were randomly assigned to the ferric carboxymaltose group and 1533 to the placebo group (Fig. 1). Reasons for ineligibility are shown in Table S1 in the Supplementary Appendix. Baseline characteristics appeared to be similar in the two groups (Table 1 and Table S2).

Follow-up data were collected through February 6, 2023. Overall, 48 patients in the ferric carboxymaltose group and 41 patients in the placebo group withdrew consent for follow-up; the vital status at the end of the trial was known for all but 28 patients (14 patients in each group) who withdrew consent (Fig. 1). Seven patients in the ferric carboxymaltose group and 4 patients in the placebo group were lost to follow-up. The median duration of follow-up was 1.9 years (interquartile range, 1.3 to 3.0).

DOSING AND IRON INDEXES

Three patients in the ferric carboxymaltose group and 1 patient in the placebo group did not receive the assigned agent. Dose interruptions (i.e., missed injections) occurred in 564 patients (18.4%) — 300 patients in the ferric carboxymaltose group,

Table 1. Characteristics of the Patients at Baseline.*

Characteristics	Ferric Carboxymaltose (N=1532)	Placebo (N=1533)
Age — yr	68.6±10.9	68.6±11.2
Female sex — no. (%)	506 (33.0)	531 (34.6)
Race — no. (%)†		
White	1324 (86.4)	1325 (86.4)
Black	162 (10.6)	160 (10.4)
Asian	19 (1.2)	21 (1.4)
Other	27 (1.8)	27 (1.8)
Hispanic or Latino ethnic group — no. (%)†	85 (5.5)	100 (6.5)
Geographic region — no. (%)		
North America	721 (47.1)	721 (47.0)
Asia Pacific	105 (6.9)	105 (6.8)
Europe	706 (46.1)	707 (46.1)
NYHA functional class at screening — no./total no. (%)		
II	797/1532 (52.0)	820/1532 (53.5)
III	711/1532 (46.4)	692/1532 (45.2)
IV	22/1532 (1.4)	19/1532 (1.2)
Clinical features of heart failure		
Left ventricular ejection fraction		
Mean — %	30.8±7.0	30.6±7.3
No. of patients with data	1532	1532
NT-proBNP level		
Median (IQR) — pg/ml	1485.5 (727.1–3044.5)	1423.6 (710.0–2883.8)
No. of patients with data	1518	1526
6-minute walk distance		
Mean — m	273.9±109.7	274.7±109.4
No. of patients with data	1531	1531
Laboratory values		
Hemoglobin level		
Mean — g/dl	12.6±1.4	12.5±1.4
No. of patients with data	1515	1521
Serum ferritin level		
Mean — μg/liter	56.0±47.3	57.3±51.4
No. of patients with data	1517	1526
Transferrin saturation		
Mean — %	23.9±11.2	23.0±10.3
No. of patients with data	1515	1517
Device and medications — no./total no. (%)		
Implantable cardioverter–defibrillator	495/1532 (32.3)	484/1532 (31.6)
Cardiac resynchronization therapy	230/1532 (15.0)	232/1532 (15.1)
ACE inhibitor or ARB	901/1532 (58.8)	923/1530 (60.3)
Sacubitril–valsartan	461/1532 (30.1)	448/1532 (29.2)
Beta-blocker	1415/1532 (92.4)	1418/1532 (92.6)
Mineralocorticoid receptor antagonist	858/1532 (56.0)	847/1532 (55.3)
SGLT2 inhibitor	118/1532 (7.7)	111/1532 (7.2)

* Plus–minus values are mean ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, IQR interquartile range, NT-proBNP N-terminal pro–B-type natriuretic peptide, NYHA New York Heart Association, and SGLT2 sodium–glucose cotransporter 2.
† Race and ethnic group were reported by the patient.

and 264 in the placebo group. The median number of injections during follow-up was 6 (interquartile range, 4 to 10) and was the same in both groups. At the day 180 visit, 1008 of 1232 patients (81.8%) in the ferric carboxymaltose group who had received the trial drug did not require additional iron-replacement therapy at this visit owing to adequate iron indexes and hemoglobin values (Table S3). Use of intravenous iron outside the trial protocol occurred in 31 patients in the ferric carboxymaltose group and 104 patients in the placebo group. Iron indexes at baseline and follow-up are provided in Figure S1.

PRIMARY OUTCOME

At 12 months, death had occurred in 131 patients (8.6%) in the ferric carboxymaltose group and in 158 (10.3%) in the placebo group; there were 297 and 332 total hospitalizations for heart failure, respectively, by 12 months; and the mean (±SD) change in the 6-minute walk distance from baseline to 6 months was 8±60 and 4±59 m, respectively (overall P=0.02) (Table 2). The unmatched win ratio for the hierarchical composite outcome in the ferric carboxymaltose group as compared with the placebo group was 1.10 (99% CI, 0.99 to 1.23) (Fig. 2). Table S4 provides data on the 6-minute walk distance at 6 months without imputation, as well as reasons for missing data. Figure S2 shows the change from baseline to 6 months in the 6-minute walk distance, and Figure S3 provides the cumulative distribution of this change. Results of prespecified sensitivity analyses that included different imputation methods appeared to be consistent with those of the primary analysis (Table S5). Because more than half the patients underwent randomization after March 2020, the censoring of data after the onset of the Covid-19 pandemic would have excluded the majority of follow-up data from the analyses.

SECONDARY OUTCOMES

During the follow-up period, cardiovascular death or hospitalization for heart failure (main secondary outcome) occurred in 475 patients (31.0%) in the ferric carboxymaltose group and in 494 patients (32.2%) in the placebo group (hazard ratio, 0.93; 96% CI, 0.81 to 1.06) (Table 2 and Fig. 2). The cumulative incidence function appeared to be similar to the Kaplan–Meier plots. The effect of ferric carboxymaltose seemed to be generally consistent across subgroups (Fig. 3); there was evidence of potential heterogeneity according to age, sex, renal insufficiency, and cause of heart failure.

The mean (±SD) change in the 6-minute walk distance from baseline to 12 months was 5±71 m in the ferric carboxymaltose group and 4±72 m in the placebo group (Fig. S2). Additional secondary outcomes are provided in Table 2, Figures S4 to S6, and Table S6. In prespecified analyses, the odds of an improvement of 10 m in the 6-minute walk distance from baseline to 6 months and from baseline to 12 months were higher with ferric carboxymaltose than with placebo; the odds of an improvement of 20 m from baseline to each time point were also higher with ferric carboxymaltose (Table S7).

SAFETY

Death from any cause during the follow-up period, a prespecified exploratory outcome, occurred in 361 patients (23.6%) in the ferric carboxymaltose group and in 376 patients (24.5%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.78 to 1.05); the hazard ratio for death from any cause through month 12 was 0.82 (95% CI, 0.65 to 1.05). Serious adverse events occurred in 581 patients (37.9%) in the ferric carboxymaltose group and in 537 patients (35.0%) in the placebo group. The number of patients with a serious adverse event occurring during the treatment period was similar in the two groups (413 patients [27.0%] in the ferric carboxymaltose group and 401 [26.2%] in the placebo group). The most common serious adverse events that occurred during the treatment period are summarized in Table S8. One event, which occurred in the ferric carboxymaltose group, was classified as hypophosphatemia and was considered by the investigator to be unrelated to the trial drug; the event resolved, and ferric carboxymaltose was continued (Table S9). Seven adverse events that occurred in the ferric carboxymaltose group during the treatment period were classified as angioedema (two events) or hypersensitivity (five events). Of the two events classified as angioedema, one event — facial edema of moderate severity — was assessed as probably related to ferric carboxymaltose, and

Table 2. Primary and Secondary Outcomes.*

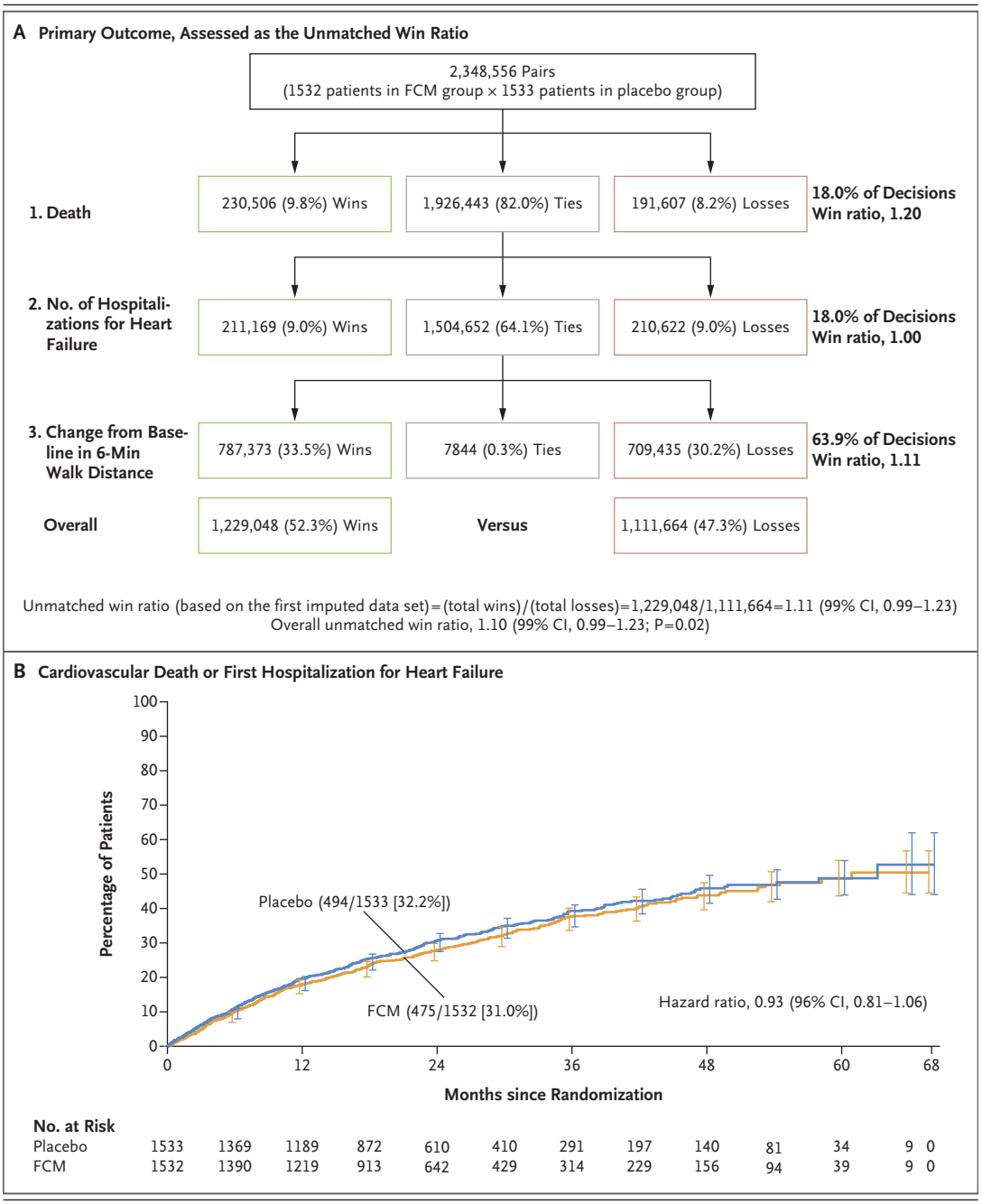
Outcome	Ferric Carboxymaltose (N=1532)	Placebo (N=1533)
Primary outcome		
Death by 12 mo — no. (%)	131 (8.6)	158 (10.3)
Hospitalizations for heart failure by 12 mo — total no.	297	332
Change in 6-minute walk distance from baseline to 6 mo — m	8±60	4±59
Overall unmatched win ratio (99% CI)	1.10 (0.99–1.23)†	—
Secondary outcomes		
Cardiovascular death or first hospitalization for heart failure during follow-up‡		
Patients — no. (%)		
Either outcome	475 (31.0)	494 (32.2)
Cardiovascular death	124 (8.1)	141 (9.2)
Hospitalization for heart failure	351 (22.9)	353 (23.0)
Events — no. per 100 patient-yr	16.0	17.3
Hazard ratio (96% CI)	0.93 (0.81–1.06)§	—
Cardiovascular death or intervention for worsening heart failure during follow-up‡		
Patients — no. (%)	487 (31.8)	500 (32.6)
Events — no. per 100 patient-yr	16.5	17.6
Hazard ratio (96% CI)	0.94 (0.83–1.07)§	—
Cardiovascular death or cardiovascular hospitalization during follow-up‡		
Patients — no. (%)	570 (37.2)	592 (38.6)
Events — no. per 100 patient-yr	20.4	22.1
Hazard ratio (96% CI)	0.92 (0.82–1.04)§	—
Cardiovascular death during follow-up‡		
Patients with event — no. (%)	251 (16.4)	275 (17.9)
Events — no. per 100 patient-yr	7.2	8.2
Hazard ratio (96% CI)	0.86 (0.72–1.03)§	—

* Plus–minus values are mean ±SD. For all but the primary outcome and the composite of cardiovascular death or first hospitalization for heart failure (main secondary outcome), the widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects.
† The unmatched win ratio, as assessed across 20 imputed data sets (with imputation of data on the 6-minute walk distance as specified in the statistical analysis plan) was calculated by adding all the wins in the ferric carboxymaltose group and dividing the sum by all the wins in the placebo group. P=0.02 for the comparison of the ferric carboxymaltose group with the placebo group.
‡ Follow-up was defined as the interval between random assignment of the first patient and month 12 after random assignment of the last patient.
§ Hazard ratios show the risk in the ferric carboxymaltose group relative to the risk in the placebo group and were calculated with time-to-first-event analyses using Cox proportional hazard models, with region as a stratification factor and with adjustment for age; sex; ejection fraction; NYHA functional class; cause of heart failure (ischemic vs. nonischemic); levels of NT-proBNP, hemoglobin, and ferritin; transferrin saturation; estimated glomerular filtration rate; and body-mass index. Confidence intervals for the hazard ratios are based on the Wald statistic at a two-sided alpha of 0.04.

the event resolved after oral therapy. Of the five hypersensitivity events, three were assessed as probably related to ferric carboxymaltose (of which one was assessed as severe), and all five events resolved.

DISCUSSION

In the HEART-FID trial, we assessed the long-term safety and efficacy of ferric carboxymaltose in patients who had heart failure with a reduced



ejection fraction and iron deficiency. We found no apparent difference between the ferric carboxymaltose group and the placebo group with respect to the primary outcome — a hierarchical composite that included death, hospitalizations for heart failure, or change in 6-minute walk distance. Results of prespecified sensitivity and supportive analyses appeared to be consistent with results of the primary analysis.

For the primary outcome, the component win ratios for the first imputed data set (provided here as an example) were 1.20 for death within 12 months after randomization (18.0% of decisions), 1.00 for hospitalization for heart failure within 12 months after randomization (18.0% of decisions), and 1.11 for change in the 6-minute walk distance between baseline and 6 months (63.9% of decisions). For the main secondary

Figure 2 (facing page). Primary Outcome, Assessed as the Unmatched Win Ratio, and Main Secondary Outcome.

Panel A shows the unmatched win ratio, as assessed in the first data set, and the overall unmatched win ratio, as assessed across 20 imputed data sets (with imputation of data on the 6-minute walk distance as specified in the statistical analysis plan), for the composite primary hierarchical outcome that consisted of death at 12 months, hospitalizations for heart failure at 12 months, or change in 6-minute walk distance from baseline to 6 months, in a comparison of the ferric carboxymaltose (FCM) group with the placebo group. Component win ratios for the first imputed data set have been provided as an example. For the calculation of the win ratios, all the patients were ranked from lowest to highest with respect to each component of the primary outcome, as specified in section 5.1 of the statistical analysis plan (see also section 8.6 of the protocol). Wins were determined by comparing the rank of each patient in the ferric carboxymaltose group with the rank of each patient in the placebo group according to the hierarchical primary outcome. The patient with a better rank with respect to death at 12 months was considered to have won that comparison. If both patients had the same rank, the outcome was considered a tie, and the patients were further compared with respect to heart failure hospitalizations at 12 months. If the outcome of that comparison was a tie, the patients were subsequently compared with respect to the change in the 6-minute walk distance between baseline and 6 months. Panel B shows Kaplan–Meier curves for cardiovascular death or first hospitalization for heart failure (main secondary outcome) in the ferric carboxymaltose and placebo groups. I bars indicate 96% confidence intervals (CIs).

outcome, a composite of cardiovascular death or first hospitalization for heart failure over the duration of follow-up, the number of events appeared to be similar in the ferric carboxymaltose and placebo groups (16.0 and 17.3 events per 100 patient-years, respectively). In contrast to the findings in the AFFIRM-AHF trial,[10] which suggested a reduction in recurrent hospitalization for heart failure but not a reduction in cardiovascular mortality with ferric carboxymaltose as compared with placebo, we observed no apparent difference in hospitalization for heart failure between the trial groups. The IRONMAN trial[11] suggested a reduction in recurrent hospitalization for heart failure with ferric derisomaltose as compared with usual care, and the hazard ratio for cardiovascular death (0.86; 95% CI, 0.67 to 1.10) was similar to the hazard ratio in the HEART-FID trial.

The lack of a long-term reduction in hospitalizations for heart failure in our trial was unexpected. Several factors may be responsible for this finding. The patient population in our trial was a lower-risk population than the population with acute heart failure in the AFFIRM-AHF trial (all patients enrolled while hospitalized) and the IRONMAN trial (15% of patients enrolled while hospitalized). Among patients who received placebo, the rate of cardiovascular death or first hospitalization for heart failure was 47.1 events per 100 patient-years in the AFFIRM-AHF trial as compared with 17.3 events per 100 patient-years in the HEART-FID trial. The relatively high use of evidence-based medications (including sacubitril–valsartan) in the HEART-FID trial may have affected the rate. In addition, although the HEART-FID trial used criteria for iron deficiency that have consistently been used in previous trials of ferric carboxymaltose, debate about the criteria remains.[16] Of note, more recent studies and scientific statements have suggested that heart-failure outcomes may be more closely related to a transferrin saturation of less than 20%, as well as to other criteria that do not rely on ferritin levels.[16-18] The mean transferrin saturation at baseline was higher in the HEART-FID trial than in previous trials.[7-11] The dose of ferric carboxymaltose and the timing of its administration also differed from those in the AFFIRM-AHF trial. The Covid-19 pandemic may have affected hospitalizations, given that the majority of patients in the HEART-FID trial were enrolled during the pandemic.

In comparison with findings in previous studies, the treatment effect of ferric carboxymaltose on the 6-minute walk distance was modest.[7] In the HEART-FID trial, the mean change from baseline at 6 months was 8 m in the ferric carboxymaltose group and 4 m in the placebo group. Of note, the imputation methods in our trial differed from those in past trials, yet prespecified sensitivity analyses confirmed the internal consistency of the results. The 6-minute walk distance was assessed more frequently in the CONFIRM-HF trial[8] than in our trial. With more recruiting sites and less frequent evaluations in the HEART-FID trial, there may have been more heterogeneity among patients and trial sites. Similar to the HEART-FID trial, the IRONMAN trial did not show a significant difference between the trial groups in the 6-minute walk

Subgroup	Ferric Carboxymaltose	Placebo	Hazard Ratio (96% CI)
	no. of patients with events/total no.		
Age			
≥65 yr	299/1024	340/1008	0.82 (0.70–0.97)
<65 yr	176/508	154/525	1.16 (0.92–1.45)
Sex			
Male	338/1026	370/1002	0.86 (0.74–1.00)
Female	137/506	124/531	1.11 (0.86–1.43)
Region			
North America	300/721	310/721	0.91 (0.77–1.08)
Asia Pacific	29/105	37/105	0.77 (0.46–1.28)
Europe	146/706	147/707	1.00 (0.78–1.27)
Race			
White	378/1324	387/1325	0.94 (0.81–1.09)
Black	81/162	83/160	0.96 (0.70–1.32)
Other	16/46	24/48	0.59 (0.30–1.14)
Body-mass index			
<25.0	102/347	111/330	0.90 (0.68–1.19)
25.0 to <30.0	153/583	158/601	0.94 (0.75–1.19)
≥30.0	220/602	225/601	0.93 (0.76–1.13)
Atrial fibrillation			
No	252/853	252/863	0.96 (0.80–1.15)
Yes	223/676	240/664	0.89 (0.74–1.08)
Diabetes mellitus			
No	229/838	230/841	0.96 (0.79–1.16)
Yes	246/694	264/691	0.90 (0.75–1.08)
NYHA functional class			
III and IV	235/733	248/711	0.89 (0.74–1.08)
I and II	240/799	246/821	0.95 (0.79–1.14)
Heart-failure hospitalization within past 12 mo			
No	69/205	77/210	0.83 (0.59–1.16)
Yes	264/783	287/759	0.84 (0.70–1.00)
Chronic renal insufficiency			
No	297/1094	294/1119	1.02 (0.86–1.20)
Yes	178/424	191/400	0.81 (0.66–1.01)
Heart-failure cause			
Nonischemic	178/594	182/633	1.03 (0.83–1.28)
Ischemic	297/938	312/899	0.86 (0.73–1.02)
NT-proBNP			
≤1462 pg/ml	154/743	174/780	0.85 (0.67–1.06)
>1462 pg/ml	314/775	316/746	0.98 (0.83–1.15)
Ejection fraction			
≤32%	315/766	319/788	0.99 (0.84–1.16)
>32%	160/766	175/744	0.85 (0.68–1.06)
Estimated eGFR			
<60 ml/min/1.73 m^2	288/801	278/752	0.94 (0.79–1.12)
≥60 ml/min/1.73 m^2	160/667	181/713	0.93 (0.74–1.16)
Ferritin level			
<100 μg/liter	419/1362	427/1353	0.93 (0.81–1.08)
≥100 to 300 μg/liter with TSAT <20%	21/51	28/51	0.69 (0.38–1.26)
Iron-deficiency anemia			
No	164/657	149/621	1.04 (0.83–1.32)
Yes	306/858	339/900	0.89 (0.76–1.05)

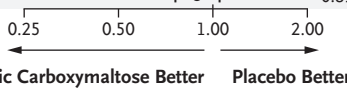


Figure 3 (facing page). Hazard Ratios for the Main Secondary Outcome in Prespecified Subgroups.

Shown are hazard ratios for the composite of cardiovascular death or first hospitalization for heart failure (main secondary outcome) in the ferric carboxymaltose group as compared with the placebo group, according to subgroups prespecified in the statistical analysis plan. The widths of 96% confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. Race was reported by the patient. The body-mass index is the weight in kilograms divided by the square of the height in meters. eGFR denotes estimated glomerular filtration rate, NT-proBNP N-terminal pro–B-type natriuretic peptide, NYHA New York Heart Association, and TSAT transferrin saturation.

distance.[11] Functional status may be limited by factors other than iron deficiency (e.g., deconditioning, frailty, and arthritis).[19] However, prespecified analyses showed that the odds of a 10-m or 20-m improvement in the 6-minute walk distance from baseline were more than 20% higher with ferric carboxymaltose than with placebo; some subgroups of patients may have had a larger response to ferric carboxymaltose.

The HEART-FID trial provides long-term data on the safety of repeated infusions of ferric carboxymaltose. The incidence of serious adverse events appeared to be similar in the trial groups. However, in the ferric carboxymaltose group, there were five hypersensitivity events (three events were assessed as probably related to the trial drug, one of which was a severe event) and two angioedema events (one of which was assessed as probably related to the trial drug and was moderate in severity). A previous trial showed short-term hypophosphatemia with ferric carboxymaltose treatment,[20] but long-term adverse events were not observed in the HEART-FID trial.

Guidelines provide a class 2a recommendation for the use of intravenous iron to improve functional status and quality of life in patients who have heart failure with iron deficiency[6,21]; European Society of Cardiology guidelines provide a class 2a recommendation for giving intravenous ferric carboxymaltose to recently hospitalized patients in order to reduce the risk of rehospitalization.[21] The 2017 guideline from the American College of Cardiology, American Heart Association, and Heart Failure Society of America indicated that outcome trials were needed before a strong recommendation could be provided.[22] The totality of evidence from past trials that assessed symptomatic or functional status,[7-9] combined with recent outcome trials,[10,11] which now include the HEART-FID trial, provide information about the safety profile of intravenous iron and effects on clinical outcomes.

Our trial has limitations. Some data on the 6-minute walk distance at follow-up were missing, but the number of patients with missing data was similar in the two groups, and results of sensitivity analyses with various methods of imputation appeared to be consistent with results of the primary analysis. Sodium–glucose cotransporter 2 inhibitors were used at baseline by 8% of patients, and future research will need to assess the use of ferric carboxymaltose with concomitant treatment. The majority of patients were enrolled during the Covid-19 pandemic, and whether the pandemic influenced the results is difficult to discern. Further evidence about the treatment of iron deficiency in patients with heart failure with an ejection fraction of more than 50% is needed.

We found that among ambulatory patients who had heart failure with a reduced ejection fraction and iron deficiency, there was no apparent difference between ferric carboxymaltose and placebo with respect to the hierarchical composite of death, hospitalizations for heart failure, and 6-minute walk distance.

Supported by American Regent, a Daiichi Sankyo Group company.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010;31:1872-80.
2. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. Eur Heart J 2013;34:816-29.
3. Del Pinto R, Ferri C. Iron deficiency in heart failure: diagnosis and clinical implications. Eur Heart J Suppl 2022;24:Suppl I:I-96–I-99.
4. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: an overview. JACC Heart Fail 2019;7:36-46.
5. 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.
6. Writing Committee Members, ACC/AHA Joint Committee Members. 2022 AHA/ACC/HFSA guideline for the management of heart failure. J Card Fail 2022;28(5):e1-e167.
7. 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.
8. 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.
9. van Veldhuisen DJ, Ponikowski P, van der Meer P, et al. Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. Circulation 2017;136:1374-83.
10. Ponikowski P, Kirwan B-A, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet 2020;396:1895-904.
11. 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.
12. Graham FJ, Pellicori P, Kalra PR, Ford I, Bruzzese D, Cleland JGF. Intravenous iron in patients with heart failure and iron deficiency: an updated meta-analysis. Eur J Heart Fail 2023;25:528-37.
13. Mentz RJ, Ambrosy AP, Ezekowitz JA, et al. Randomized placebo-controlled trial of ferric carboxymaltose in heart failure with iron deficiency: rationale and design. Circ Heart Fail 2021;14(5):e008100.
14. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987.
15. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33:176-82.
16. Masini G, Graham FJ, Pellicori P, et al. Criteria for iron deficiency in patients with heart failure. J Am Coll Cardiol 2022;79:341-51.
17. Grote Beverborg N, Klip IT, Meijers WC, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. Circ Heart Fail 2018;11(2):e004519.
18. Beavers CJ, Ambrosy AP, Butler J, et al. Iron deficiency in heart failure: a scientific statement from the Heart Failure Society of America. J Card Fail 2023;29:1059-77.
19. Psotka MA, Abraham WT, Fiuzat M, et al. Functional and symptomatic clinical trial endpoints: the HFC-ARC Scientific Expert Panel. JACC Heart Fail 2022;10:889-901.
20. Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. JAMA 2020;323:432-43.
21. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599-726.
22. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Card Fail 2017;23:628-51.