

# Ferric Carboxymaltose in Iron-Deficient Patients with Hospitalized Heart Failure and Reduced Kidney Function

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## Abstract

**Background** Reduced kidney function is common among patients with heart failure. In patients with heart failure and/or kidney disease, iron deficiency is an independent predictor of adverse outcomes. In the AFFIRM-AHF trial, patients with acute heart failure with iron deficiency treated with intravenous ferric carboxymaltose demonstrated reduced risk of heart failure hospitalization, with improved quality of life. We aimed to further characterize the impact of ferric carboxymaltose among patients with coexisting kidney impairment.

**Methods** The double-blind, placebo-controlled AFFIRM-AHF trial randomized 1132 stabilized adults with acute heart failure (left ventricular ejection fraction <50%) and iron deficiency. Patients on dialysis were excluded. The primary end point was a composite of total heart failure hospitalizations and cardiovascular death during the 52-week follow-up period. Additional end points included cardiovascular hospitalizations, total heart failure hospitalizations, and days lost to heart failure hospitalizations or cardiovascular death. For this subgroup analysis, patients were stratified according to baseline eGFR.

**Results** Overall, 60% of patients had an eGFR <60 ml/min per 1.73 m<sup>2</sup> (the lower eGFR subgroup). These patients were significantly older, more likely to be female and to have ischemic heart failure, and had higher baseline serum phosphate levels and higher rates of anemia. For all end points, event rates were higher in the lower eGFR group. In the lower eGFR group, the annualized event rates for the primary composite outcome were 68.96 and 86.30 per 100 patient-years in the ferric carboxymaltose and placebo arms, respectively (rate ratio, 0.76; 95% confidence interval, 0.54 to 1.06). The treatment effect was similar in the higher eGFR subgroup (rate ratio, 0.65; 95% confidence interval, 0.42 to 1.02;  $P_{\text{interaction}} = 0.60$ ). A similar pattern was observed for all end points ( $P_{\text{interaction}} > 0.05$ ).

**Conclusions** In a cohort of patients with acute heart failure, left ventricular ejection fraction <50%, and iron deficiency, the safety and efficacy of ferric carboxymaltose were consistent across a range of eGFR values.

**Clinical Trial registry name and registration number** Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency (Affirm-AHF), [NCT02937454](https://clinicaltrials.gov/ct2/show/study/NCT02937454).

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## Introduction

Reduced kidney function is common among patients with heart failure, with some reported prevalence rates of >60%.<sup>1</sup> Kidney impairment is associated with adverse clinical outcomes, including hospitalization for heart failure rates and reduced patient survival.<sup>1–4</sup> Both conditions predispose patients to iron deficiency, with many patients affected by all three conditions simultaneously, frequently termed *cardiorenal iron deficiency syndrome*.<sup>5–9</sup> In stable, chronic heart failure, the prevalence of iron deficiency approaches 30%–50% and even higher in the setting of acute heart failure (70%–80%).<sup>10,11</sup>

Iron deficiency independently predicts poor outcomes in heart failure and kidney disease.<sup>5,11</sup> In the setting of heart failure, iron deficiency is associated with reduced exercise capacity, lower quality of life, higher rates of hospitalization for heart failure, and shortened survival.<sup>6,12–17</sup> Iron repletion with intravenous ferric carboxymaltose has been shown to improve symptoms and functional health in patients with heart failure and iron deficiency.<sup>18–22</sup>

AFFIRM-AHF (A Randomised, Double-blind Placebo Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and

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Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) was the first randomized, placebo-controlled trial designed to evaluate the effect of ferric carboxymaltose in patients hospitalized for acute heart failure with concomitant iron deficiency. Patients randomized to ferric carboxymaltose initiated at hospital discharge had lower rates of the primary end point of hospitalizations for heart failure and cardiovascular death (rate ratio [RR], 0.79; 95% confidence interval [CI], 0.62 to 1.01;  $P = 0.06$ ) and experienced significantly fewer hospitalizations for heart failure (RR, 0.74; 95% CI, 0.58 to 0.94;  $P = 0.01$ ).<sup>23</sup>

It is unclear whether the benefits of ferric carboxymaltose extend to patients with heart failure and impaired kidney function and whether the magnitude of any such benefits is consistent across different levels of kidney function. This subgroup analysis aims to further characterize the effect of ferric carboxymaltose in patients with acute heart failure with iron deficiency and coexisting kidney impairment.

## Methods

### Study Design

The design of AFFIRM-AHF has been described previously.<sup>23,24</sup> In brief, this double-blind, placebo-controlled trial enrolled adults hospitalized between March 2017 and July 2019 with clinical signs, symptoms, and biomarkers consistent with acute heart failure. Patients were required to have a left ventricular ejection fraction of <50% and meet criteria for iron deficiency: serum ferritin <100 ng/ml or between 100 and 299 ng/ml with transferrin saturation (TSAT) <20%. Before discharge, eligible patients were randomly (1:1) assigned to receive either intravenous ferric carboxymaltose or placebo at discharge and week 6 (iron repletion phase). Randomization was performed using a validated centralized web-based response system using a minimization algorithm that included a random variable and was stratified by sex, age, heart failure etiology, duration of heart failure, country, and center. Maintenance doses were administered at weeks 12 and 24 if iron deficiency persisted. To ensure patient and clinician blinding, unblinded study personnel not involved in any study assessments prepared and administered study medication. The use of black syringes and a curtain/partition ensured participants remained blinded.

The trial was registered with [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02937454) (NCT02937454; October 18, 2016) and approved by the institutional review boards of all 121 study sites. All patients provided informed consent. AFFIRM-AHF was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines.

### End Points and Subgroups

The primary end point was a composite of total heart failure hospitalizations and cardiovascular death during a 52-week follow-up period.<sup>23,24</sup> Secondary end points were the composite of total cardiovascular hospitalizations and cardiovascular death, cardiovascular death, total heart failure hospitalizations, time to first heart failure hospitalization or cardiovascular death, and days lost because of heart failure hospitalizations or cardiovascular death. The number of days lost because of heart failure hospitalizations

within 30 days after randomization through 52 weeks after randomization was calculated for each patient as the total number of days of heart failure hospitalizations. For patients who died, an additional day was added to the total such that for a patient who died without any hospitalizations, the number of days lost was calculated as 1. Change in health-related quality of life was assessed using summary scores from the Kansas City Cardiomyopathy Questionnaire-12 (KCCQ-12).<sup>25</sup> All-cause mortality, not considered a primary or secondary end point, was analyzed as a prespecified end point.

Serum creatinine was assessed at the time of enrollment, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. For the present analysis, eGFR was categorized as <60 ml/min per 1.73 m<sup>2</sup> (the lower eGFR subgroup) or ≥60 ml/min per 1.73 m<sup>2</sup> (the higher eGFR subgroup). Such dichotomization, although not prespecified, is common in clinical practice and is the primary analysis presented. A prespecified subgroup analysis was performed using eGFR tertiles and is presented secondarily.

### Statistical Analysis

A sample size of 1100 patients was planned to detect a RR of 0.75 for the primary end point with a power of 80% and a two-sided  $\alpha$  of 0.05 based on assumptions of (1) 0.7 recurrent heart failure hospitalization or cardiovascular death events per year in the placebo arm and (2) 9% loss to follow-up. No interim analyses were planned or conducted before the trial ending in July 2020.

Demographic and baseline parameters were summarized by eGFR subgroup and treatment arm. The primary outcome was reported as the rate per 100 patient-years. The RR and associated 95% CI were analyzed using a negative binomial model adjusted for age (younger than 70 or 70 years or older), heart failure etiology (ischemic, nonischemic/unknown), heart failure duration (*de novo* or prior heart failure), and country using a *z*-score test to compare treatment groups. The same methodology was used for the secondary outcomes of total cardiovascular hospitalizations and cardiovascular death and total heart failure hospitalizations. An offset term for follow-up time (log follow-up) was included in the model; this had the effect of modifying each observation from a count into a rate over the follow-up period. Hazard ratios were analyzed for time-to-event analyses using Cox regression including the subgroup variable (eGFR category) and the interaction between treatment and subgroup effect as a covariate. *P* values by subgroup and the *P* value of the global effect of interaction between treatment and subgroup were calculated. Changes in KCCQ-12 scores were assessed with a mixed-effect model for repeated measures using an unstructured covariance matrix to model the within-participant variability. Analyses were performed with SAS version 9.4, and statistical significance was defined as  $P < 0.05$ .

*Post hoc* analyses examined the effect of treatment on the primary end point by eGFR group for patients classified by (1) heart failure etiology, (2) anemia status, and (3) history of heart failure. These analyses used the same modeling as the main model within each subgroup. The assumption of proportional hazards was tested for the time-to-event

analyses by eGFR subgroup to ensure the assumptions were valid. Laboratory data, including hemoglobin, serum ferritin levels, TSAT, and serum phosphate levels, were assessed at baseline and follow-up weeks 6, 12, 24, and 52. These data were summarized using descriptive statistics. In a *post hoc* analysis, the effects of treatment on these parameters were assessed with an analysis of covariance for repeated measures adjusted for baseline values. Adverse events (AEs) were collected throughout the study and coded according to the Medical Dictionary for Regulatory Activities (version 23.0). Treatment-emergent adverse events were defined as AEs that started, or worsened in severity or seriousness, after the first dose of medication. No formal analyses comparing AE rates across treatment groups were performed.

## Results

### Study Population, Baseline Characteristics, and Treatment Exposure

In AFFIRM-AHF, 1132 patients were randomly assigned to receive ferric carboxymaltose ( $n=567$ ) or placebo ( $n=565$ ).<sup>25</sup> Study treatment was started in 1110 patients (eight patients randomized to receive ferric carboxymaltose and 14 patients randomized to receive placebo never received therapy), and all but two patients (*i.e.*, 1108) had postrandomization data available.<sup>23</sup> Baseline creatinine data were missing for 141 patients, resulting in 967 participants in the present analysis cohort. At baseline, the mean (SD) eGFRs in the ferric carboxymaltose and placebo arms were 55.3 (21.3) and 55.7 (23.1) ml/min per 1.73 m<sup>2</sup>, respectively. Based on the distribution of eGFR values (Figure 1), eGFR tertiles were defined by cutoffs of 43.0 and 64.3 ml/min per 1.73 m<sup>2</sup>.

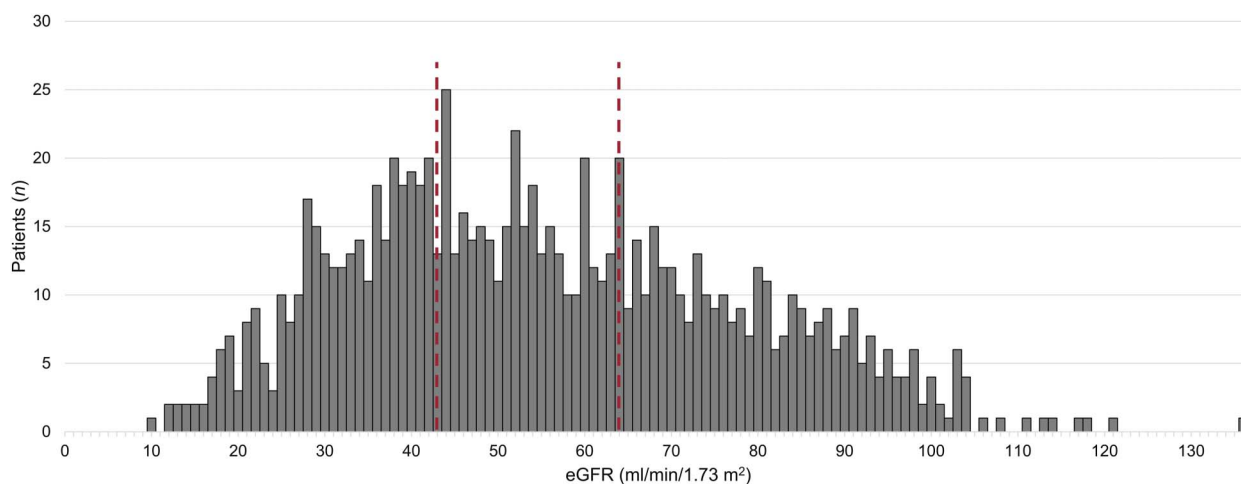
Across eGFR categories, baseline characteristics were generally similar between the treatment arms (Table 1). Compared with patients with a higher eGFR, those with a lower eGFR were older, were more likely to have diabetes, had higher proportions with nonischemic heart failure, and were less likely to have newly diagnosed heart

failure. Patients with an eGFR <60 ml/min per 1.73 m<sup>2</sup> were more likely to have anemia and less likely to be receiving guideline-directed triple therapy for heart failure. In the lower eGFR subgroup, baseline phosphate levels were lower in patients randomized to ferric carboxymaltose (versus placebo). Similar patterns were observed when eGFR was examined by tertile (Supplemental Table 1). Across eGFR categories, 80% of patients in the ferric carboxymaltose arm received one to two doses of ferric carboxymaltose, and patients received similar mean (SD) doses of ferric carboxymaltose (1377 [545] and 1318 [588] mg in the eGFR <60 ml/min per 1.73 m<sup>2</sup> and eGFR ≥60 ml/min per 1.73 m<sup>2</sup> groups, respectively).

### Efficacy Outcomes

Among patients with an eGFR ≥60 ml/min per 1.73 m<sup>2</sup>, the adjusted annualized event rates for the primary end point were 65.7 and 43.0 per 100 patient-years in the placebo and ferric carboxymaltose arms, respectively (RR, 0.65; 95% CI, 0.42 to 1.02;  $P = 0.06$ ). Event rates were higher among patients with an eGFR <60 ml/min per 1.73 m<sup>2</sup> (74.7 versus 56.7 per 100 patient-years), but the treatment effect associated with ferric carboxymaltose was similar (RR, 0.76; 95% CI, 0.54 to 1.06;  $P = 0.10$ ), interaction  $P$  value, 0.60 (Figure 2).

Similarly, for all end points examined, patients randomized to ferric carboxymaltose experienced fewer clinical events than those randomized to placebo (Figure 2). The interaction  $P$  values for all end points were nonsignificant ( $P$  for interaction, ≥0.2), indicating that the treatment effect was similar for patients with eGFR values above and below 60 ml/min per 1.73 m<sup>2</sup>. Similar results were observed when the analysis was repeated across prespecified eGFR tertiles (Supplemental Figure 1 and Supplemental Table 4). Overall, there were 76 deaths in the ferric carboxymaltose arm (16%) and 81 deaths in the placebo arm (17%). Although the mortality rate was highest among patients in the lowest eGFR tertile (26% versus <13% in other tertiles), no treatment effect was observed. An absence of heterogeneity in



**Figure 1. Distribution of kidney function by eGFR among randomized patients at baseline.** Dashed lines indicate cutoffs for eGFR tertiles (43.0 ml/min per 1.73 m<sup>2</sup> and 64.3 ml/min per 1.73 m<sup>2</sup>).

**Table 1. Baseline characteristics by dichotomized eGFR category**

Variable	eGFR <60 ml/min per 1.73 m <sup>2</sup> N=580		eGFR ≥60 ml/min per 1.73 m <sup>2</sup> N=387	
	Ferric Carboxymaltose n=292	Placebo n=288	Ferric Carboxymaltose n=195	Placebo n=192
Mean (SD) age, yr	75 (9)	74 (9)	67 (11)	67 (12)
Female, n (%)	134 (46)	140 (49)	78 (40)	76 (40)
Race, White, n (%)	275 (94)	274 (95)	188 (96)	182 (95)
Mean (SD) eGFR, ml/min per 1.73 m <sup>2</sup>	41 (11)	40 (12)	77 (12)	79 (14)
<b>Heart failure etiology, n (%)</b>				
Ischemic	145 (50)	154 (54)	81 (42)	68 (35)
Nonischemic	142 (49)	127 (44)	109 (56)	116 (60)
Unknown	5 (2)	7 (2)	5 (3)	8 (4)
<i>De novo</i> heart failure (not previously diagnosed), n (%)	72 (25)	68 (24)	71 (36)	81 (42)
Heart failure hospitalization in previous 1 yr, n (%)	82 (37)	87 (40)	44 (36)	43 (39)
Diabetes at baseline, n (%)	119 (41)	140 (49)	73 (37)	75 (39)
<b>Baseline LVEF</b>				
Mean (SD) LVEF, %	33 (9)	33 (10)	32 (10)	32 (11)
<40%, n (%)	201 (69)	187 (65)	138 (71)	134 (70)
≥40%, n (%)	91 (31)	101 (35)	57 (29)	57 (30)
<b>NYHA functional class, n (%)</b>				
I	6 (2)	3 (1)	6 (3)	3 (2)
II	129 (44)	116 (40)	94 (48)	88 (46)
III	149 (51)	159 (55)	91 (47)	95 (50)
IV	8 (3)	9 (3)	4 (2)	5 (3)
<b>Hemoglobin category, n (%)</b>				
<10 g/dl	31 (11)	42 (15)	11 (6)	14 (7)
10–14 g/dl	221 (76)	212 (74)	142 (73)	147 (77)
>14 g/dl	39 (13)	34 (12)	42 (22)	31 (16)
<b>Anemic, n (%)<sup>a</sup></b>				
Male	102 (35)	99 (34)	51 (26)	58 (30)
Female	67 (23)	85 (30)	25 (13)	28 (15)
<b>Ferritin category, n (%)</b>				
<100 ng/ml	226 (78)	209 (73)	132 (68)	125 (65)
100–300 ng/ml	65 (22)	78 (27)	63 (32)	67 (35)
≥300 ng/ml	0	1 (0.3)	0	0
TSAT <20%, %	231 (79)	244 (85)	167 (86)	160 (83)
Mean (SD) phosphate, mg/dl	3.7 (0.8)	4.0 (1.0)	3.6 (0.7)	3.6 (0.7)
Mean (SD) BNP, pg/ml	1361 (803)	1402 (880)	1209 (816)	1566 (994)
Mean (SD) NT-proBNP, pg/ml	7406 (6968)	7327 (6643)	5432 (4668)	5838 (4998)
<b>Treatment at baseline, n (%)</b>				
ACEi or ARB or ARNI	209 (72)	207 (72)	157 (81)	192 (79)
β-blocker	244 (84)	235 (82)	151 (77)	168 (88)
Mineralocorticoid receptor antagonists	177 (61)	162 (56)	148 (76)	147 (77)
Triple therapy (ACEi/ARB/ARNI+BB+MRA)	121 (41)	100 (35)	95 (49)	107 (56)

Percentages may not total 100% as a result of rounding. LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; TSAT, transferrin saturation; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro-brain-type natriuretic peptide; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BB, β-blocker; MRA, mineralocorticoid receptor antagonist.

<sup>a</sup>Defined as hemoglobin <13 g/dl in male patients and <12 g/dl in female patients.

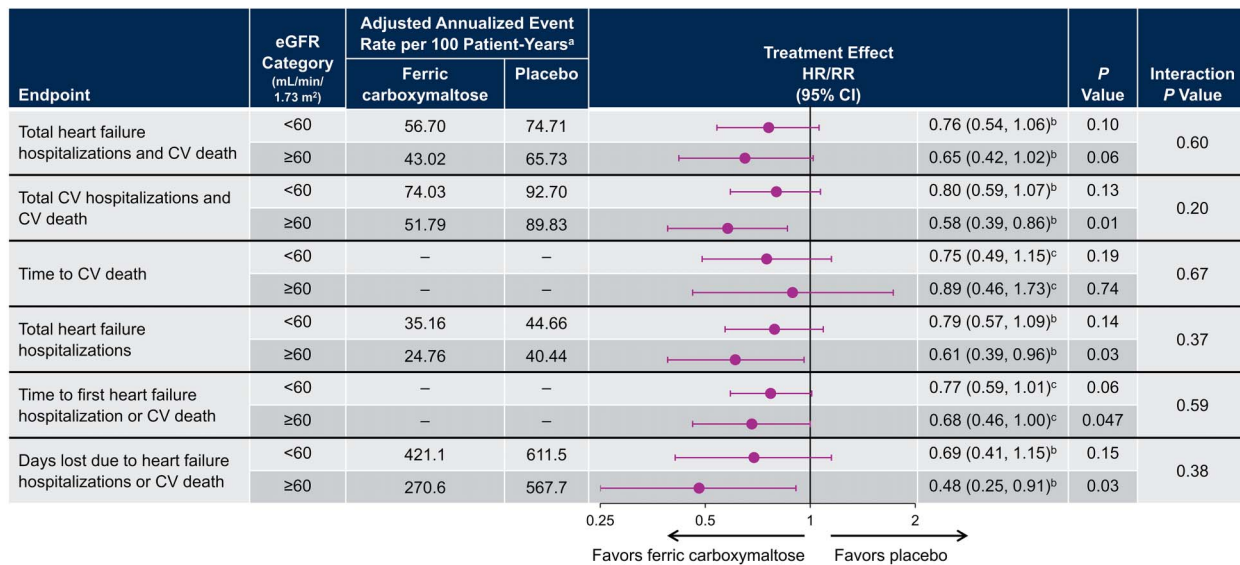
the treatment effect of ferric carboxymaltose was also evident when the primary end point was examined across subgroups of interest—heart failure etiology, baseline anemia status, and history of heart failure (Figure 3).

Across both treatment arms, KCCQ-12 summary scores improved from baseline during follow-up. The largest mean increases were observed between baseline and week 2 (Supplemental Figure 2). Across most time points, ferric carboxymaltose was associated with numerically greater improvements than placebo. Although the pattern of score changes was similar across both eGFR categories, the magnitude of improvements was somewhat diminished in the lower eGFR subgroup.

#### Laboratory Assessments and AEs

Among patients in both eGFR categories, ferric carboxymaltose administration resulted in sharp increases in mean serum ferritin levels (to approximately 340 ng/ml) by week 6. By contrast, patients in the placebo group exhibited only slight increases (mean levels, <130 ng/ml; Figure 4A). Mean TSAT increased in both treatment arms, but increases were of larger magnitude among ferric carboxymaltose-treated patients. Similar effects of ferric carboxymaltose treatment on TSAT were seen irrespective of baseline kidney function category (Figure 4B).

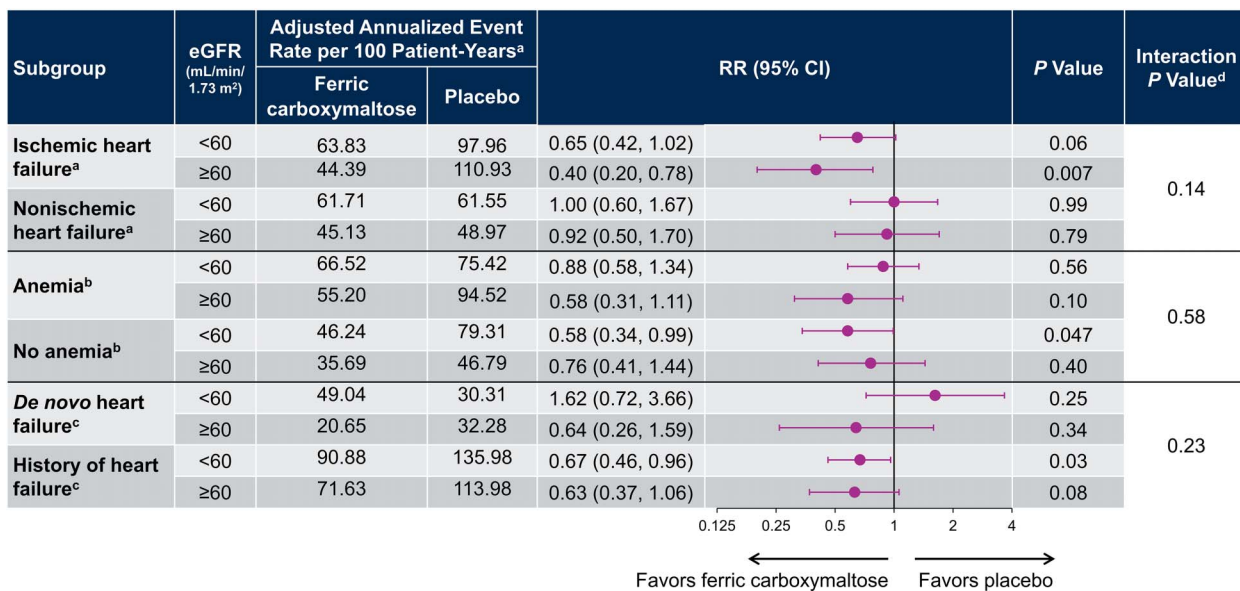
When examined by dichotomized eGFR, patients receiving ferric carboxymaltose demonstrated mean



**Figure 2. Study end points by eGFR category (dichotomized by eGFR ≥ or <60 ml/min per 1.73 m<sup>2</sup>).** <sup>a</sup>Negative binomial model adjusted for baseline covariates: sex, age, heart failure etiology, heart failure duration, country, baseline eGFR dichotomized, and baseline eGFR dichotomized×treatment. <sup>b</sup>Rate ratio. <sup>c</sup>Hazard ratio. The number of days lost because of heart failure hospitalizations or cardiovascular death was calculated for each patient, summed for each treatment group, and divided by the total patient-years of follow-up in each treatment group multiplied by 100. A negative binomial model was fitted on the number of days lost because of heart failure hospitalizations or cardiovascular death with the log-transformed time on study of each participant in years as an offset. Unadjusted data included in Supplemental Table 2. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; RR, rate ratio.

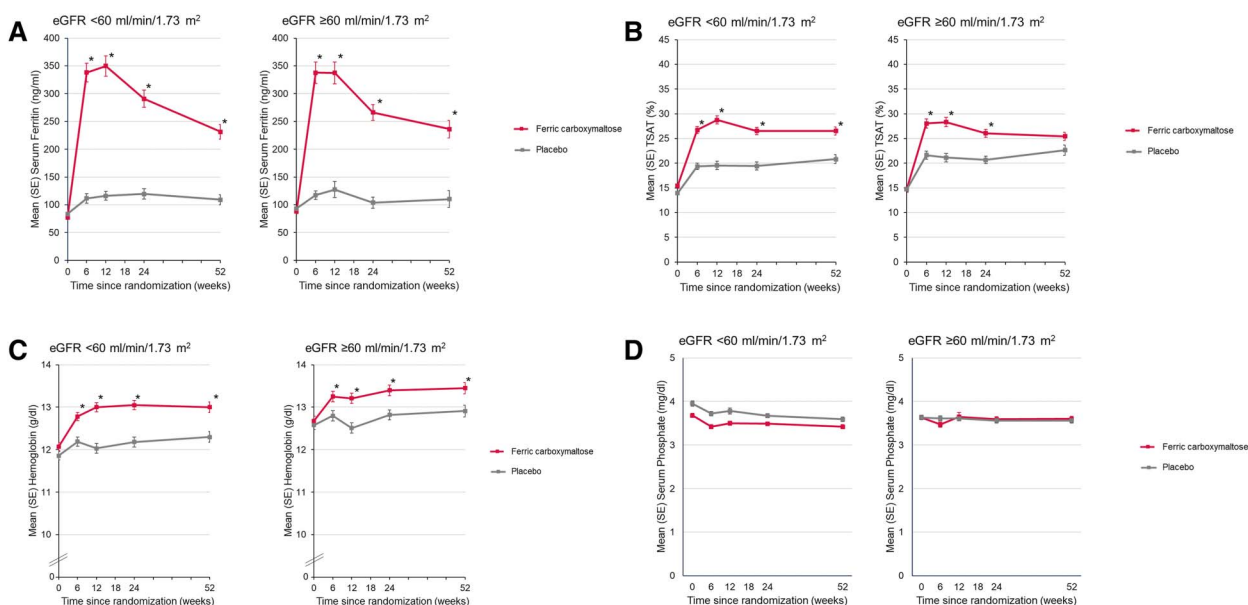
increases in hemoglobin of 0.59–0.86 g/dl during follow-up, with similar temporal relationships observed across both eGFR groups (Figure 4C). Among patients with a

baseline eGFR <60 ml/min per 1.73 m<sup>2</sup>, at week 6, the mean (SD) change from baseline in serum phosphate was –0.2 (0.9) and –0.2 (1.0) mg/dl in patients treated



**Figure 3. Primary end points by eGFR category (dichotomized by eGFR < or ≥60 ml/min per 1.73 m<sup>2</sup>) and subgroups of interest.** <sup>a</sup>Negative binomial model adjusted for baseline covariates: sex, age, history of heart failure, country, subgroup of eGFR category, and ischemic etiology of heart failure and subgroup×treatment. <sup>b</sup>Negative binomial model adjusted for baseline covariates: sex, age, history of heart failure, country, ischemic etiology of heart failure, subgroup of eGFR category, and anemic status and subgroup×treatment. <sup>c</sup>Negative binomial model adjusted for baseline covariates: sex, age, country, etiology of heart failure, subgroup of eGFR category, and history of heart failure and subgroup×treatment. <sup>d</sup>Term added to the model for derived variable interaction, where the derived variable represents the four combinations of the subgroup analyzed (e.g., ischemic heart failure [yes/no] and eGFR (<60, ≥60)). Unadjusted data included in Supplemental Table 3.

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**Figure 4. Laboratory measures over time for each treatment group by eGFR category.** Mean (A) serum ferritin, (B) TSAT, (C) hemoglobin, and (D) serum phosphate after administration of ferric carboxymaltose or placebo by eGFR subgroup. \* $P < 0.05$  for ferric carboxymaltose versus placebo. TSAT, transferrin saturation.

with ferric carboxymaltose and placebo, respectively (Figure 4D). In the subgroup of patients with a baseline eGFR  $\geq 60$  ml/min per  $1.73 \text{ m}^2$ , the mean (SD) change from baseline at week 6 was  $-0.2$  (0.8) and  $-0.02$  (0.8) mg/dl in the ferric carboxymaltose and placebo groups, respectively.

The rates of AEs and treatment-emergent adverse events (including severe events, serious events, and events leading to treatment discontinuation) were

similar in both treatment arms. AEs were consistently more common among patients with lower eGFR (Table 2 and Supplemental Table 5).

## Discussion

The present analyses extend the results of the AFFIRM-AHF trial and demonstrate that the benefits of intravenous ferric carboxymaltose are observed in patients with heart

**Table 2. Adverse events by dichotomized eGFR status at baseline**

Adverse Event Category	eGFR <60 ml/min per $1.73 \text{ m}^2$				eGFR $\geq 60$ ml/min per $1.73 \text{ m}^2$			
	Ferric Carboxymaltose N=293		Placebo N=289		Ferric Carboxymaltose N=195		Placebo N=192	
	n (%)	Incidence Rate per PY <sup>a</sup>	n (%)	Incidence Rate per PY <sup>a</sup>	n (%)	Incidence Rate per PY <sup>a</sup>	n (%)	Incidence Rate per PY <sup>a</sup>
All AEs	206 (70)	0.795	205 (71)	0.816	121 (62)	0.684	122 (64)	0.694
TEAEs	201 (69)	0.776	197 (68)	0.784	109 (56)	0.616	118 (62)	0.671
Severe TEAEs	90 (31)	0.347	106 (37)	0.422	45 (23)	0.254	54 (28)	0.307
Serious TEAEs	143 (49)	0.552	160 (55)	0.636	69 (35)	0.390	87 (45)	0.495
TEAEs leading to treatment discontinuation	31 (11)	0.120	49 (17)	0.195	14 (7)	0.079	22 (12)	0.125
TEAEs of clinical interest	95 (32)	0.367	105 (36)	0.418	41 (21)	0.232	50 (26)	0.284
Fatal TEAEs	53 (18)	0.205	57 (20)	0.227	24 (12)	0.136	24 (13)	0.137
Related fatal TEAEs	0	0	0	0	0	0	0	0

AEs of clinical interest include CV death and heart failure hospitalization; AEs of special interest include hypersensitivity reactions, hypophosphatemia, injection/infusion site reactions, and hemosiderosis. PY, patient-year; AE, adverse event; TEAE, treatment-emergent adverse event; CV, cardiovascular.

<sup>a</sup>Incidence rate is computed as the number of all participants with an AE in the treatment group divided by the total participant-years of follow-up in the treatment group. % represents the proportion of patients in the treatment arm experiencing events.

failure with and without moderate-to-severe kidney impairment at baseline. Patients included in AFFIRM-AHF had varying levels of kidney function at baseline, with eGFRs ranging from 10 to 136 ml/min per 1.73 m<sup>2</sup>. When the primary end point was examined by eGFR categories, the relative risk reductions associated with ferric carboxymaltose treatment were similar, with RRs between 0.65 and 0.76. The benefits of ferric carboxymaltose on the primary end point were driven by reductions in hospitalization for heart failure. Notably, ferric carboxymaltose treatment was associated with a numerically reduced risk of all primary and secondary end points examined, and this effect was consistent across eGFR subcategories (*P* for interaction, >0.05). In addition, among patients with a reduced eGFR, statistically significant improvements in quality of life (as assessed by KCCQ-12) were observed for 24 weeks after treatment. Treatment with ferric carboxymaltose did not affect all-cause mortality.

These findings suggest that the clinical efficacy of ferric carboxymaltose, initiated at hospital discharge after an episode of acute heart failure in patients with iron deficiency, is not affected by baseline kidney function based on eGFR. The observed clinical benefits of ferric carboxymaltose across a range of eGFR categories are consistent with previous evidence from the FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure) and CONFIRM-HF (Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure) studies that examined quality-of-life measures and functional status.<sup>18,20</sup> Our analysis builds on the limited available data assessing the effect of iron repletion on hard outcomes in patients with impaired kidney function and iron deficiency. In PIVOTAL (Proactive IV Iron Therapy in Haemodialysis Patients), a trial conducted in a hemodialysis population, proactive administration of intravenous iron decreased the occurrence of first and recurrent heart failure events in patients.<sup>26</sup>

Our results also emphasize the large proportion of patients with impaired kidney function among inpatients with heart failure. These data are consistent with recent data from the Get With The Guidelines–Heart Failure registry, in which approximately 63% of patients had an eGFR <60 ml/min per 1.73 m<sup>2</sup> at discharge.<sup>27</sup> The present results also demonstrate that impairments in kidney function are associated with higher risk of poor outcomes in patients with heart failure. The annualized rate of the primary end point was 72% (ferric carboxymaltose) and 52% (placebo) higher in the lower eGFR category relative to the higher eGFR category. These findings are consistent with published data demonstrating an association between reduced eGFR and adverse outcomes such as death, (re)hospitalization, and reduced quality of life.<sup>4,27–31</sup> Notably, the use of triple heart failure therapy at baseline was below 50% in the overall population, with lower rates observed among patients with reduced kidney function. Baseline use of sodium-glucose cotransporter-2 inhibitors was extremely low, likely a result of the evidence available on these therapies when the study was initiated.

The effects of ferric carboxymaltose were not affected by the presence or absence of baseline anemia. In contrast to most of the nephrology literature, heart failure guidelines make a clear distinction between iron deficiency and

anemia, and data have demonstrated that iron deficiency is an independent predictor of poor outcomes in the heart failure population.<sup>5</sup> Similarly, iron repletion, but not correction of anemia, has been associated with improved outcomes in the setting of heart failure. Such findings suggest a role for iron repletion that extends beyond erythropoiesis and correction of anemia.<sup>5,11,24</sup> Benefits seem to include increased cardiomyocyte iron concentrations, improved right and left ventricular ejection fractions, correction of mitochondrial dysfunction, and improved cardiomyocyte contractility and relaxation.<sup>32–35</sup> In an analysis of data from the FAIR-HF study, iron repletion was associated with modest, but significant, improvements in eGFR.<sup>5,36</sup> Researchers attributed the improvements to enhanced cellular energy production and/or adjustments in renal blood flow.

We found the safety profile of ferric carboxymaltose to be similar across eGFR categories. Given that ferric carboxymaltose was administered one to two times (over 52 weeks) to most patients, clinically significant hypophosphatemia would not be expected as a common AE.<sup>37</sup> In addition, patients with CKD may exhibit impaired phosphate excretion, further protecting them from the risk of hypophosphatemia.<sup>38–40</sup> In the present analysis, mean phosphate levels decreased slightly among ferric carboxymaltose-treated patients by week 6 and then returned toward baseline levels. The magnitude of changes was similar across eGFR categories. There was no evidence of an increased risk of serious infections among patients treated with ferric carboxymaltose.

The results of this analysis should be viewed in the context of several limitations. As the randomized population was predominantly White, generalizability to other populations is unknown. Because eGFR was assessed only at baseline, we are unable to discern differences between acute changes in eGFR—as might be associated with type 1 cardiorenal syndrome, medication-induced reductions in eGFR, or intercurrent illness—and long-term reductions in eGFR indicative of CKD. Finally, the study was not adequately powered to detect treatment effects in individual subgroups, and the observed treatment effects on the composite end point of heart failure hospitalization and cardiovascular death did not achieve significance.

The above limitations notwithstanding, we believe the results of AFFIRM-AHF have relevant implications for nephrologists. Despite improved recognition of cardiorenal syndrome, there are no guidelines related to management of iron deficiency among patients with both heart failure and kidney impairment. Current heart failure guidelines support the use of intravenous iron in patients with heart failure with reduced ejection fraction (HFrEF) and iron deficiency but do not make distinct recommendations for patients with impaired kidney function.<sup>41,42</sup> Conversely, nephrology guidelines on the management of iron deficiency do not make distinct recommendations for those patients with heart failure.<sup>43</sup> Our results support the concept that eGFR at baseline does not affect the clinical profile of ferric carboxymaltose when used to manage iron deficiency in patients with heart failure.

A management strategy that treats patients with iron deficiency, regardless of hemoglobin level and anemia status, is consistent with guidelines for the management of

heart failure.<sup>41,42</sup> It is worth noting that although evidence-based heart failure guidelines recommend assessment and management of iron deficiency in patients with heart failure, implementation of such guidelines remains poor.<sup>44</sup> The approach for managing iron deficiency in the nephrology setting differs from that recommended in cardiology. For patients with CKD, current guidelines only recommend consideration of iron therapy for adults with anemia (defined as hemoglobin <13.0 g/dl in men and <12.0 g/dl in women) and evidence of iron deficiency.<sup>43</sup> As such, the absence of anemia would seemingly preclude assessment and management of iron deficiency. By contrast, we believe the present results support the assessment and management of iron deficiency in those patients with CKD and heart failure, regardless of anemia. Such an approach requires validation in prospective randomized trials. The present results do not provide insight into the management of iron deficiency in patients without heart failure.

In conclusion, patients with iron deficiency who were stabilized after an episode of acute heart failure and treated with ferric carboxymaltose experienced numerically improved outcomes across all end points assessed, including total heart failure hospitalizations and cardiovascular death, total cardiovascular hospitalizations and cardiovascular death, days lost because of heart failure hospitalizations or cardiovascular death, and quality of life. In addition, no significant interaction between kidney function and ferric carboxymaltose efficacy was noted. These results support the prompt diagnosis and management of iron deficiency in patients with a left ventricular ejection fraction <50% regardless of kidney function.

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### Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/CJN/B786>.

**Supplemental Table 1.** Baseline characteristics by eGFR tertile.

**Supplemental Table 2.** Study end points by dichotomized eGFR category (data supporting [Figure 2](#)).

**Supplemental Table 3.** Primary end points by dichotomized eGFR category and subgroups of interest (data supporting [Figure 3](#)).

**Supplemental Table 4.** Study end points by eGFR tertiles (data supporting [Supplemental Figure 1](#)).

**Supplemental Table 5.** Adverse events by baseline eGFR tertile.

**Supplemental Figure 1.** Prespecified study end points by eGFR tertile.

**Supplemental Figure 2.** Mean change in KCCQ-12: (A) overall summary scores and (B) clinical summary scores by baseline eGFR category (dichotomized).

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