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CLINICAL RESEARCH
Clinical trials

The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: the results of the AFFIRM-AHF study

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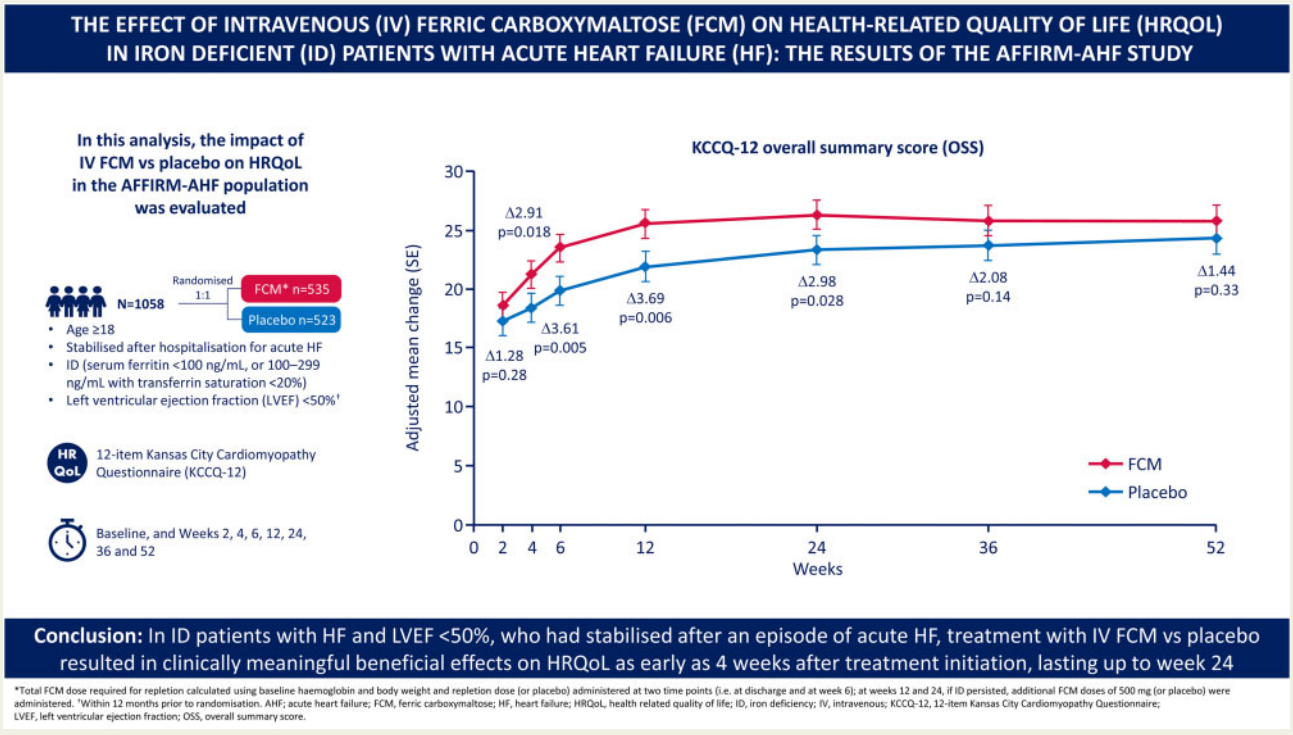
Aims Patients with heart failure (HF) and iron deficiency experience poor health-related quality of life (HRQoL). We evaluated the impact of intravenous (IV) ferric carboxymaltose (FCM) vs. placebo on HRQoL for the AFFIRM-AHF population.

Methods and results The baseline 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12), which was completed for 1058 (535 and 523) patients in the FCM and placebo groups, respectively, was administered prior to randomization and at Weeks 2, 4, 6, 12, 24, 36, and 52. The baseline KCCQ-12 overall summary score (OSS) mean ± standard error was 38.7 ± 0.9 (FCM group) and 37.1 ± 0.8 (placebo group); corresponding values for the clinical summary score (CSS) were 40.9 ± 0.9 and 40.1 ± 0.9. At Week 2, changes in OSS and CSS were similar for FCM and placebo. From Week 4 to Week 24, patients assigned to FCM had significantly greater improvements in OSS and CSS scores vs. placebo [adjusted mean difference (95% confidence interval, CI) at Week 4: 2.9 (0.5–5.3, P = 0.018) for OSS and 2.8 (0.3–5.3, P = 0.029) for CSS; adjusted mean difference (95% CI) at Week 24: 3.0 (0.3–5.6, P = 0.028) for OSS and 2.9 (0.2–5.6, P = 0.035) for CSS]. At Week 52, the treatment effect had attenuated but remained in favour of FCM.

Conclusion In iron-deficient patients with HF and left ventricular ejection fraction <50% who had stabilized after an episode of acute HF, treatment with IV FCM, compared with placebo, results in clinically meaningful beneficial effects on HRQoL as early as 4 weeks after treatment initiation, lasting up to Week 24.

Graphical Abstract



Keywords Heart failure • Acute heart failure • Iron deficiency • Intravenous ferric carboxymaltose therapy • Health-related quality of life • Randomized clinical trial

Introduction

Heart failure (HF) is a debilitating condition associated with considerable morbidity, premature mortality, and substantial use of healthcare resources.[1–4] In particular, HF patients experience a high burden of symptoms and physical and social limitations, all of which negatively impact upon their quality of life.[3,5,6] According to the European Society of Cardiology (ESC) guidelines on management of HF, an

improvement in health status (symptoms, function, and quality of life) is one of the major therapeutic goals in the management of these patients.[3] This view has also been acknowledged and endorsed by regulatory authorities and by the patients themselves.[7–9]

Iron deficiency (ID) negatively impacts upon symptom burden, exercise capacity, and quality of life in HF patients.[10–12] Randomized controlled trials have demonstrated that intravenous (IV) ferric carboxymaltose (FCM) alleviates symptoms, and improves exercise capacity and quality of life in ambulatory iron-deficient patients with chronic HF and left ventricular ejection fraction (LVEF) ≤45%.[13–15]

The AFFIRM-AHF trial, which was a randomized, double-blind, placebo-controlled trial, demonstrated that administration of IV FCM in iron-deficient patients who had stabilized after an acute HF episode reduced the risk of recurrent HF hospitalizations.[16] The effect of IV FCM on health-related quality of life (HRQoL) in this high-risk population has not been previously investigated—the latter was one of the predefined other secondary outcomes in the AFFIRM-AHF trial. In this analysis, we evaluated the effect of IV FCM, compared with placebo, administered just prior to discharge in patients with acute HF and ID on the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12) overall summary score (OSS) and clinical summary score (CSS) up to 52 weeks after randomization.

Methods

Study design and population

The rationale and design of the AFFIRM-AHF trial has been previously published.[17] Briefly, the AFFIRM-AHF trial was a double-blind, placebo-controlled trial in which eligible subjects were 18 years or older and hospitalized with clinical signs, symptoms, and biomarkers consistent with acute HF. During the index hospitalization, patients had to have received at least 40 mg of IV furosemide (or equivalent) and an LVEF <50% within 12 months prior to randomization. In addition, patients had to be iron-deficient, defined as serum ferritin <100 ng/mL, or between 100 and 299 ng/mL with transferrin saturation <20%.[16,17] Iron status was assessed on the basis of serum ferritin and transferrin saturation, with measurement allowed at any time during the index hospitalization.

Prior to discharge, eligible patients were randomly (1:1) assigned to receive either IV FCM or placebo. The total FCM dose required for repletion was calculated using baseline haemoglobin and body weight, and the repletion dose was administered at two time points (i.e. at discharge and Week 6). The first and subsequently administered doses were up to 1000 mg FCM (or placebo). At Weeks 12 and 24, if ID persisted, additional FCM doses of 500 mg (or placebo) were administered.[16,17]

The protocol was approved by the institutional review board at each participating centre. Written informed consent was obtained from all patients before any study-related procedures were performed. The first and the last authors (E.A.J. and P.P.) had full access to the data, and took responsibility for its integrity and analysis.

Assessment of HRQoL in the whole trial cohort using the KCCQ-12 was prospectively planned and was specified among other outcomes in the statistical analysis plan (SAP). The primary composite outcome of AFFIRM-AHF was recurrent HF hospitalizations and cardiovascular death, and there were five clinical secondary outcomes.

Health status outcome measures

The KCCQ-12 was used to evaluate the HF-specific health status.[18] The KCCQ-12 is a self-administered, disease-specific instrument for measuring HF-specific health status, regardless of HF aetiology. It is a 12-item questionnaire that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life.[6,18,19]

To simplify the clinical interpretation, all scores and subscores are represented on a scale from 0 to 100, in which lower scores represent comparatively more severe symptoms and/or limitations, and a score of 100 indicates no symptoms, no limitations, and excellent quality of life.[18,19] The KCCQ-12 tool is used to estimate the OSS, which includes pooled information on symptoms, physical and social functioning and perception of quality of life, whereas the CSS includes pooled information reflecting mainly symptoms and physical and social functioning of an examined patient. In addition to two summary scores, four domains can be derived in order to separately describe physical limitation, symptom frequency, quality of life, and social limitation.

The baseline KCCQ-12 was administered just prior to randomization during the index hospitalization. Patients completed the paper-based version of the questionnaire, and validated translations were used in countries where English was not the mother tongue. During follow-up, the KCCQ-12 was completed by patients at Weeks 2, 4, 6, 12, 24, 36, and 52. Participants were placed in a quiet environment and requested to complete the KCCQ-12 prior to any other assessment or procedure being performed at the visit concerned. For visits conducted by telephone (i.e. visits at Weeks 2, 4, and 36 post-randomization), participants were requested to complete the KCCQ-12 just prior to the call and to return the completed questionnaire at the next scheduled outpatient visit.

Statistical analyses

For each visit as described above, the KCCQ OSS and KCCQ CSS were calculated. The actual values and change from baseline in these two summary scores were descriptively summarized at each visit. The treatment difference in KCCQ-12 scores (one model for each summary score) at Weeks 2, 4, 6, 12, 24, 36, and 52 were analysed by comparing the model-adjusted means of the respective visits based on a repeated-measures model adjusted for corresponding baseline KCCQ-12 value, sex, age at randomization (<70 years/≥70 years), HF aetiology at randomization (ischaemic/non-ischaemic/unknown), HF duration (newly diagnosed at index hospitalization/known documented HF prior to index hospitalization), country, time, treatment, and treatment-by-time interaction using an unstructured covariance matrix to model the within-subject variability. Similar analyses were carried out using unadjusted models.

Taking into consideration the COVID-19 pandemic, which interfered with the progress of the trial and which could potentially have affected the subjective assessment of quality of life, COVID-19 sensitivity analyses were performed using adjusted and unadjusted models. In these analyses, all KCCQ-12 assessments occurring after the date when the first COVID-19 case was diagnosed in each country were deleted and were considered as missing values without any imputation.

In order to evaluate the consistency of the treatment effect, differences in adjusted mean changes in the KCCQ-12 OSS and CSS from baseline to Week 24 with IV FCM compared with placebo were assessed in 22 pre-specified subgroups.

The pre-specified analyses of the KCCQ-12 described in the SAP did not include any imputations for death. An additional sensitivity analysis with imputed values accounting for patient mortality was performed, in which KCCQ-12 values for patients who were dead at the time of the scheduled assessment were assigned 0 points (worst health status).

Responder analyses were performed, examining the proportion of patients with a deterioration or an improvement in KCCQ-12 during subsequent study visits. We used thresholds that had been established as clinically meaningful for KCCQ for patients with stable chronic HF.[19,20]

The number and percentage of subjects with respective improvements of ≥5, ≥8, ≥10, ≥20, and ≥30 points and deterioration of ≥5 points in KCCQ-12 OSS and CSS scores were assessed for the FCM and placebo groups. Odds ratios to estimate differences between the study groups (FCM vs. placebo) and their corresponding 95% confidence intervals (CIs) and two-sided *P*-values were estimated from logistic regression models.

Missing data were not imputed. The number of missing values were reported with the identification of missing values due to death. A *P*-value of <0.05 was considered statistically significant and no adjustments for multiple testing were carried out.

Results

Baseline characteristics

Among the 1108 patients included in the modified intention-to-treat AFFIRM-AHF analysis, a baseline KCCQ-12 was completed for 1058 (95%) patients (535 and 523 in the FCM and placebo groups, respectively). The baseline characteristics of the patients who completed the baseline KCCQ-12 were comparable between the two study groups (*Table 1*).

Overall, the KCCQ-12 completion rate decreased from 96% at Week 2 to 73% at Week 52 (*Figure 1*). The proportion of patients who did not complete the questionnaire during follow-up were similar in both the FCM and placebo groups.

The KCCQ-12 OSS and CSS scores were similar and markedly impaired at baseline for both study groups. The mean (± standard error) KCCQ-12 OSS scores in the FCM and placebo groups were 38.1 ± 0.9 points and 37.1 ± 0.8 points, respectively. The mean KCCQ-12 CSS scores in the FCM and placebo groups were 40.9 ± 0.9 points and 40.1 ± 0.9 points, respectively.

During the course of the trial, 5 patients in the FCM arm (0.9%) and 13 patients in the placebo arm (2.4%) received open-label IV iron preparations beyond the study treatment (see Supplementary material online, *Table S1* for details).

Changes in KCCQ scores

The mean adjusted changes from baseline in the KCCQ-12 OSS for both study groups are presented in *Figure 2A*. In both the FCM and placebo groups, the mean KCCQ-12 OSS score improved at 2 weeks post-discharge (by +18.5 ± 1.2 points and +17.2 ± 1.2 points in the FCM and placebo groups, respectively). The difference in OSS score change between FCM and placebo was not statistically significant ($P = 0.277$). As of Week 4 and up to Week 24 (i.e. end of the treatment period), the difference in OSS score was statistically significant in favour of FCM, with a mean change of +2.9 (95% CI 0.5–5.3, $P = 0.018$) and +3.0 (95% CI 0.3–5.6, $P = 0.028$) at Weeks 4 and 24, respectively. These results were also consistent across the KCCQ-12 CSS (*Figure 2B*). At Week 2 post-discharge, changes in CSS were similar between FCM and placebo (+20.94 ± 1.18 and +20.10 ± 1.21, respectively). The CSS mean change in favour of FCM at Week 4 and Week 24 was +2.8 (95% CI 0.3–5.3, $P = 0.029$) and +2.9 (95% CI 0.2–5.6, $P = 0.035$), respectively. At Week 52, the treatment effect was still present but in an attenuated manner [differences in adjusted mean changes for OSS and CSS at Week 52 were +1.44 (95% CI −1.45 to +4.33) and +0.63 (95% CI −2.21 to +3.47), respectively].

The COVID-19 sensitivity analyses (which excluded data on quality of life obtained after the outbreak of the COVID-19 pandemic) using the adjusted model confirmed that the pattern of changes in the KCCQ-12 OSS and CSS and differences between the two treatment groups were similar to the results obtained for the complete follow-up (Supplementary material online, *Figure S1A* and *B*).

The pattern of KCCQ-12 score changes and differences between the two treatment groups in analyses with unadjusted models were in agreement with those demonstrated with adjusted models, both for the overall study population (Supplementary material online, *Figure S2*) and for the COVID-19 sensitivity analysis population (Supplementary material online, *Figure S1C* and *D*).

The sensitivity analysis that incorporated imputed values to account for death of patients into the model (see Methods section for details) also showed a pattern of changes in the KCCQ-12 OSS and CSS and differences between study arms that were similar to that for the main results.

The effects of IV FCM, in comparison with placebo, on the KCCQ-12 OSS and CSS scores were assessed in 22 pre-specified subgroups (Supplementary material online, *Figure S3*).

Responder analyses

In the responder analyses, numerically fewer patients treated with FCM had a clinically meaningful deterioration (≥5-point decline in the KCCQ-12 OSS), and a greater proportion of patients had a clinically meaningful improvement in the KCCQ-12 OSS at Weeks 12 and 24, compared with the placebo group, although these results did not reach statistical significance (*Figure 3A and C*). An analogous pattern of responder analyses was seen for the KCCQ-12 CSS in the FCM group, compared with the placebo group (*Figure 3B and D*).

Discussion

In this pre-specified analysis of the AFFIRM-AHF trial, we observed that patients who had stabilized after an episode of acute HF and who had concomitant ID had severely impaired HRQoL at baseline, and after discharge experienced an improvement in health status during follow-up. Compared with placebo, patients treated with IV FCM had significantly greater improvements in health status starting at Week 4, and continuing up to Week 24, with a subsequent attenuation of treatment benefit by Week 52 (*Graphical abstract*).

Improving symptoms, function and quality of life is an important standalone target of therapy for patients with HF.[19] Previous analyses have identified IV iron as being one of a very limited number of HF treatments that is able to confer improvements in HRQoL.[5] Collectively, data on the impact of various treatments on health status have become an integral part of evaluating therapies and improving care for this high-risk patient population. Only a few interventions have demonstrated benefits in terms of health status in patients with chronic HF with reduced ejection fraction: these include dapagliflozin,[21] empagliflozin,[22] sacubitril/valsartan,[23] exercise training,[24] self-management interventions with or without remote monitoring,[25,26] and IV FCM.[13–15] Importantly, the modest effects of these therapies (a net effect of +1.5–3.0 points of the KCCQ, at maximum) have been demonstrated in three- to four-fold larger studies and under more stable clinical conditions, which cannot be extrapolated to

Table 1 Characteristics of patients at baseline[a]

	Ferric carboxymaltose (*N* = 535)	Placebo (*N* = 523)
Age (years)	71.0 ± 10.85	70.9 ± 11.3
Sex		
Male	298 (55.7)	283 (54.1)
Female	237 (44.3)	240 (45.9)
Race		
White	509 (95.1)	499 (95.4)
Other	26 (4.9)	24 (4.6)
Comorbidities		
Previous myocardial infarction	220 (41.1)	206 (39.4)
Previous stroke	51 (9.5)	63 (12.0)
Previous coronary revascularization	187 (35.0)	197 (37.7)
Hypertension	449 (83.9)	448 (85.7)
Atrial fibrillation	303 (56.6)	286 (54.7)
Diabetes mellitus	222 (41.5)	228 (43.6)
Dyslipidaemia	287 (53.6)	275 (52.6)
Chronic kidney disease	211 (39.4)	215 (41.1)
Smoking (current)	54 (10.1)	48 (9.2)
Smoking (former)	154 (28.8)	144 (27.5)
Body mass index (kg/m^2)	28.2 ± 5.7	28.1 ± 5.7
NYHA functional class		
I	14 (2.6)	8 (1.5)
II	242 (45.3)	229 (44.0)
III	263 (49.3)	263 (50.6)
IV	15 (2.8)	20 (3.8)
Left ventricular ejection fraction (%)[b]	32.8 ± 9.6	32.8 ± 9.9
Left ventricular ejection fraction[b]		
<25%	99 (18.5)	113 (21.6)
25–39%	272 (50.8)	234 (44.8)
40–49%	164 (30.7)	175 (33.5)
Ischaemic aetiology of HF	255 (47.7)	246 (47.0)
Device therapy		
Implantable cardioverter-defibrillator	64 (12.0)	60 (11.5)
Cardiac resynchronization therapy	31 (5.8)	30 (5.7)
Heart failure history		
Newly diagnosed at index hospitalization	144 (26.9)	153 (29.3)
Hospitalization for heart failure in previous 12 months	142 (36.3)	145 (39.2)
Pharmacotherapy		
Angiotensin-converting enzyme inhibitor	297 (55.5)	282 (53.9)
Angiotensin II receptor blocker	123 (23.0)	103 (19.7)
Angiotensin receptor-neprilysin inhibitor	27 (5.0)	27 (5.2)
Mineralocorticoid receptor antagonist	344 (64.3)	346 (66.2)
Beta-blocker	392 (73.3)	397 (75.9)
Digitalis glycosides	110 (20.6)	109 (20.8)
Loop diuretic	532 (99.4)	522 (99.8)
KCCQ-12		
Overall summary score, mean (±SE)	38.1 (±0.9)	37.1 (±0.8)
Clinical summary score, mean (±SE)	40.9 (±0.9)	40.1 (±0.9)
Laboratory test results		
Median NT-proBNP (Q1, Q3) (pg/mL)	4657 (2724, 8060)	4654 (2758, 8780)
Median BNP (Q1, Q3) (pg/mL)	1076 (820, 1715)	1170 (797, 1964)
Haemoglobin (g/dL)	12.2 ± 1.6	12.15 ± 1.6

Continued

Table I *Continued*

	Ferric carboxymaltose (*N* = 535)	Placebo (*N* = 523)
Anaemia		
Adult males (Hb <13 g/dL)	171 (32)	172 (32.9)
Adult females, non-pregnant (Hb <12 g/dL)	108 (20.2)	124 (23.7)
Ferritin (ng/mL)	84.3 ± 63.0	87.65 ± 67.5
Ferritin <100 ng/mL	390 (73.0)	362 (69.2)
Transferrin saturation (%)	15.2 ± 8.4	14.3 ± 7.6
Transferrin saturation <20%	439 (82.7)	444 (85.4)
eGFR (mL/min/1.73 m^2)	55.7 ± 21.3	56.0 ± 23.1
Phosphorus		
2.5–4.4 mg/dL	442 (87.0)	408 (81.6)
≥4.5 mg/dL	46 (9.1)	80 (16.0)

Data are mean ± standard deviation or *n* (%) unless otherwise indicated. Percentages might not add to 100% because of rounding.
BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; KCCQ-12, 12-item Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association.
[a]With a baseline KCCQ-12.
[b]Left ventricular ejection fraction was measured within a maximum of 12 months before randomization.

patients recovering from acute HF. Beyond pharmacotherapies with demonstrated benefits on quality of life in patients with HF, the beneficial effects of cardiac resynchronization therapy (CRT) merit attention. Although the heterogeneity in clinical response to CRT (including improvement in clinical status and quality of life) is commonly acknowledged, selected patients ('good responders') benefit from a clinically meaningful improvement in quality of life, as demonstrated by an increase in KCCQ score exceeding 10 points.[27,28]

In other recently reported trials (EVEREST[18] and SOLOIST-WHF[29]) patients with a recent episode of acute HF also demonstrated a markedly impaired HRQoL. These observations justify the particular need to consider this poor quality of life seen in patients directly after an episode of acute HF as an important therapeutic target.

The 23-item KCCQ is an instrument for measuring HRQoL in patients with HF and has excellent psychometric properties, but its major limitation for its broader use in clinical practice is its length, so it requires several minutes for patients to complete.[18,19] Therefore, we used a shorter and simpler measure (the KCCQ-12 derived and validated from the 23-item KCCQ), which allows the capture of symptom frequency, physical and social limitations, and quality of life impairment as a result of HF, as well as an OSS. The KCCQ-12 has been demonstrated to have high correlations with the original 23-item tool and high test–retest reliability, as well as comparable prognostic significance and interpretation of clinically important differences, compared with the 23-item KCCQ.[18,19]

In the AFFIRM-AHF study, we demonstrated the favourable effects of IV FCM treatment on KCCQ-12 OSS and CSS scores, which were statistically significant and clinically relevant between Weeks 4 and 24. It has been established that a two to three-point mean improvement in the KCCQ score translates into a relevant increase in subjective patient wellbeing.[19,20] In the AFFIRM-AHF trial, the beneficial effect of IV FCM treatment, compared to placebo, on the KCCQ-12 OSS and CSS scores was persistent up to Week 24, which was the end of the treatment phase. This suggests that treatment with FCM in these acutely ill patients positively impacts HRQoL, and the positive effect of FCM appears to correspond with the time points of IV FCM administration. Indeed, a diminishing proportion of patients with fully repleted iron status following treatment cessation may have contributed to the reduced quality of life benefit seen at Weeks 36 and 52. FCM was given at baseline and Week 6 in the vast majority of patients (i.e. 80% of patients in the FCM arm). In the FCM arm, only 20% required further administration of the drug at Weeks 12 and/or 24. In the placebo arm, approximately 50% of patients received the assigned therapy at either Week 12 and/or Week 24. The discontinuation of therapy (regardless of whether a placebo or an active drug was administered) could have had an impact on the subjective perception of quality of life by the patients.

We have demonstrated a significant increase in KCCQ-12 OSS and CSS scores as early as Week 2, which was evident in both FCM and placebo arms. The 'spontaneous improvement' in the placebo arm reached +17.2 ± 1.2 points and +20.1 ± 1.2 points for, respectively, the KCCQ-12 OSS and CSS, and was even more pronounced in the FCM group. Comparable patterns and magnitudes of changes in the KCCQ-12 OSS and CSS scores in patients having recently undergone hospitalization for acute HF have already been reported in the EVEREST trial (e.g. a change of +21.8 ± 21.3 points in KCCQ-12 OSS after 1 week in the placebo arm)[18] and in the SOLOIST-WHF trial (an increase of 13.6 points in KCCQ-12 OSS at Month 4 in the placebo arm).[29] Taking into consideration the important effect of 'spontaneous' improvement seen in the placebo group for the KCCQ-12 OSS and CSS scores, which is probably associated with the intensification of HF treatment during the index hospitalization, the traditional KCCQ-12 thresholds for responder analyses derived and validated for chronic settings are less meaningful and make the methodological approach much more challenging in the context of a recent episode of acute HF. Therefore, it is not surprising that the proportion of patients treated with FCM vs. placebo that experienced deterioration in health status was consistently numerically lower, and the proportion of patients with clinically meaningful

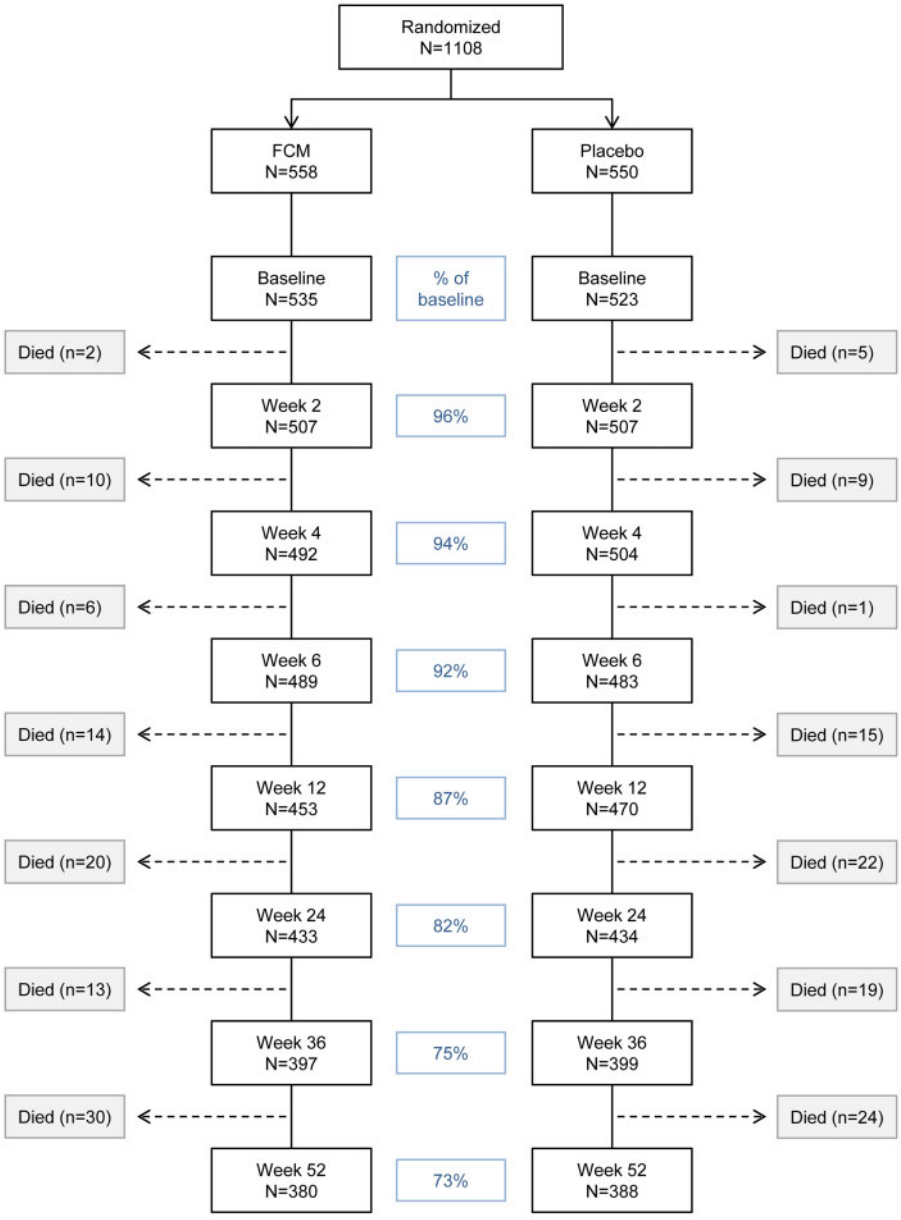


Figure 1 Proportion of patients with available HRQoL data through Week 52. Weeks shown are relative to randomization date. FCM, ferric carboxymaltose; HRQoL, health-related quality of life.

improvements established for chronic settings was numerically greater, although none of these differences reached statistical significance. The reported responder analyses for the KCCQ-12 OSS and CSS scores using the cut-off values validated for stable clinical settings are therefore not meaningful in a post-acute HF patient population, where the overwhelming majority of patients experience substantial improvements regardless of treatment. Additionally, it is important to distinguish between the clinically relevant difference in average KCCQ scores when compared between study groups (analysed collectively) and the clinically relevant change in KCCQ score for individual subjects. It should be emphasized that a difference of ≥2–3 points in average KCCQ scores compared between study groups has been shown as clinically relevant in several trials in patients with HF,[21–24] in contrast to greater increases in KCCQ scores considered to be clinically relevant for individuals with HF in stable clinical settings.

Study limitations

It is difficult to compare the changes we observed in the KCCQ-12 OSS and CSS scores with other data. Available evidence on the patterns of change in the KCCQ is limited mainly to assessments performed in stable ambulatory patients with HF. At the time when the trial was planned, there was no detailed information on changes in HRQoL after hospitalization due to circulatory decompensation reported regularly during the 12-month follow-up.

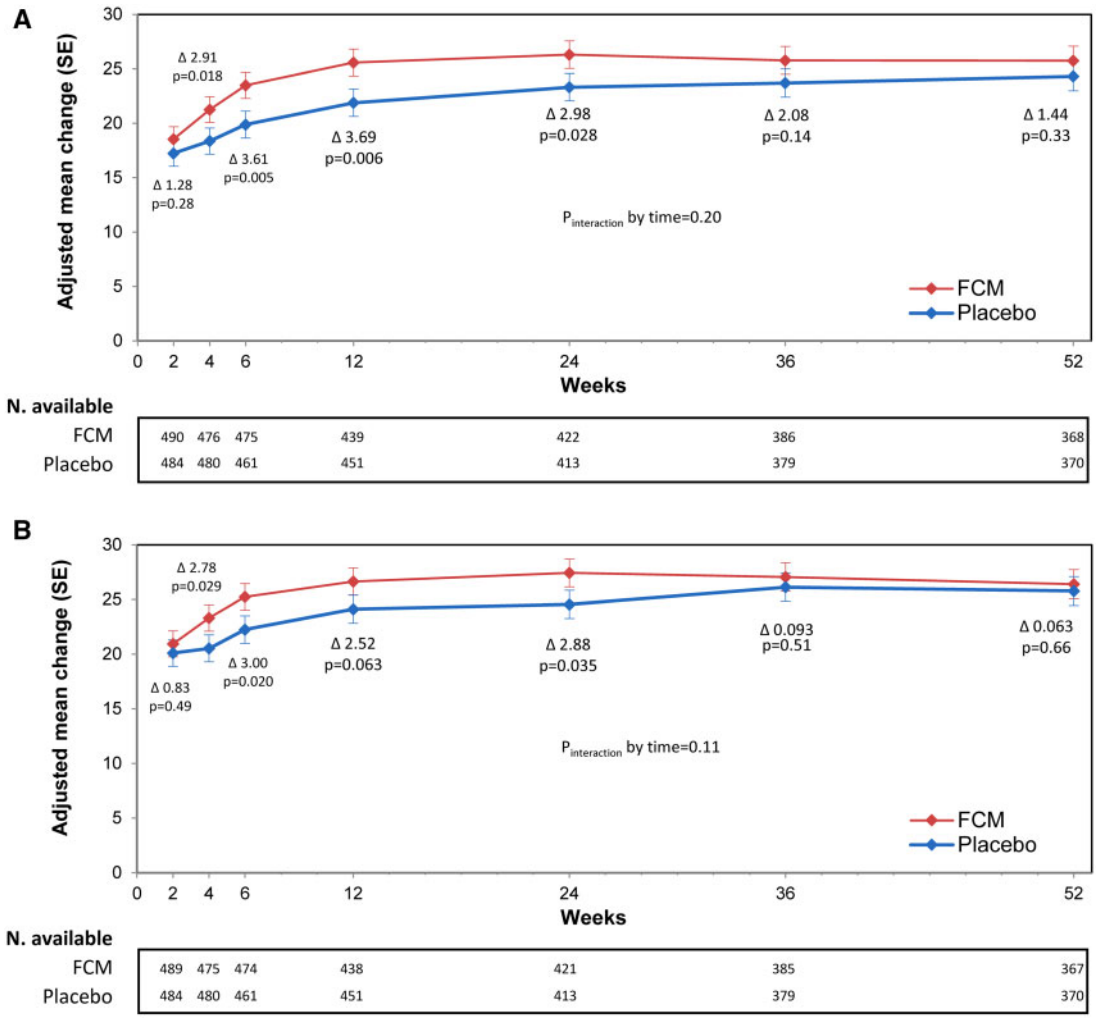


Figure 2 KCCQ-12—overall summary score and clinical summary score mean change—full analysis set (adjusted model). Effects of ferric carboxymaltose, compared with placebo, on mean overall summary score (*A*) and clinical summary score (*B*). FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy Questionnaire; SE, standard error.

Recently, the KCCQ-12 data were reported in the SOLOIST-WHF trial, but the follow-up assessment was limited to a single time point.[29] Taking into consideration the magnitude of dynamic changes seen in our trial after an episode of acute HF, being in contrast to patterns seen in stable cohorts, any conclusion about the clinical significance of reported changes in the KCCQ-12 in post-acute settings on the basis of standards developed in chronic settings needs to be considered with caution.

The primary analysis of AFFIRM-AHF showed a beneficial effect of IV FCM vs. placebo in the reduction in recurrent HF hospitalization in patients who were stabilized after an episode of acute HF. Our analysis provides evidence that these patients also benefit from an improvement in HRQoL. There is undoubtedly a relationship between HF hospitalizations and a subjective perception of quality of life in patients with HF, and the distinction between these two effects of any applied therapy is difficult. One may argue that the reported benefits in quality of life are just a reflection of fewer hospitalizations for HF. However, it needs to be emphasized that in the AFFIRM-AHF trial, all follow-up KCCQ-12 assessments were performed during ambulatory visits—hence the data for patients who were hospitalized at that time of scheduled assessments were missing and, as per the protocol, no data imputation was applied. Therefore, we could conclude that the changes in quality of life reported in this paper are independent of any direct influence of recent HF hospitalizations that patients could experience. There is no doubt that if the KCCQ assessments had been performed at the time of hospitalization and had been imputed in the model, the gradients in quality of life benefits would have been much more prominent.

In iron-deficient patients with HF and an LVEF <50% who had stabilized after an episode of acute HF, treatment with IV FCM, compared with placebo, results in clinically meaningful beneficial effects on quality of life as early as 4 weeks after treatment initiation that last up to Week 24.

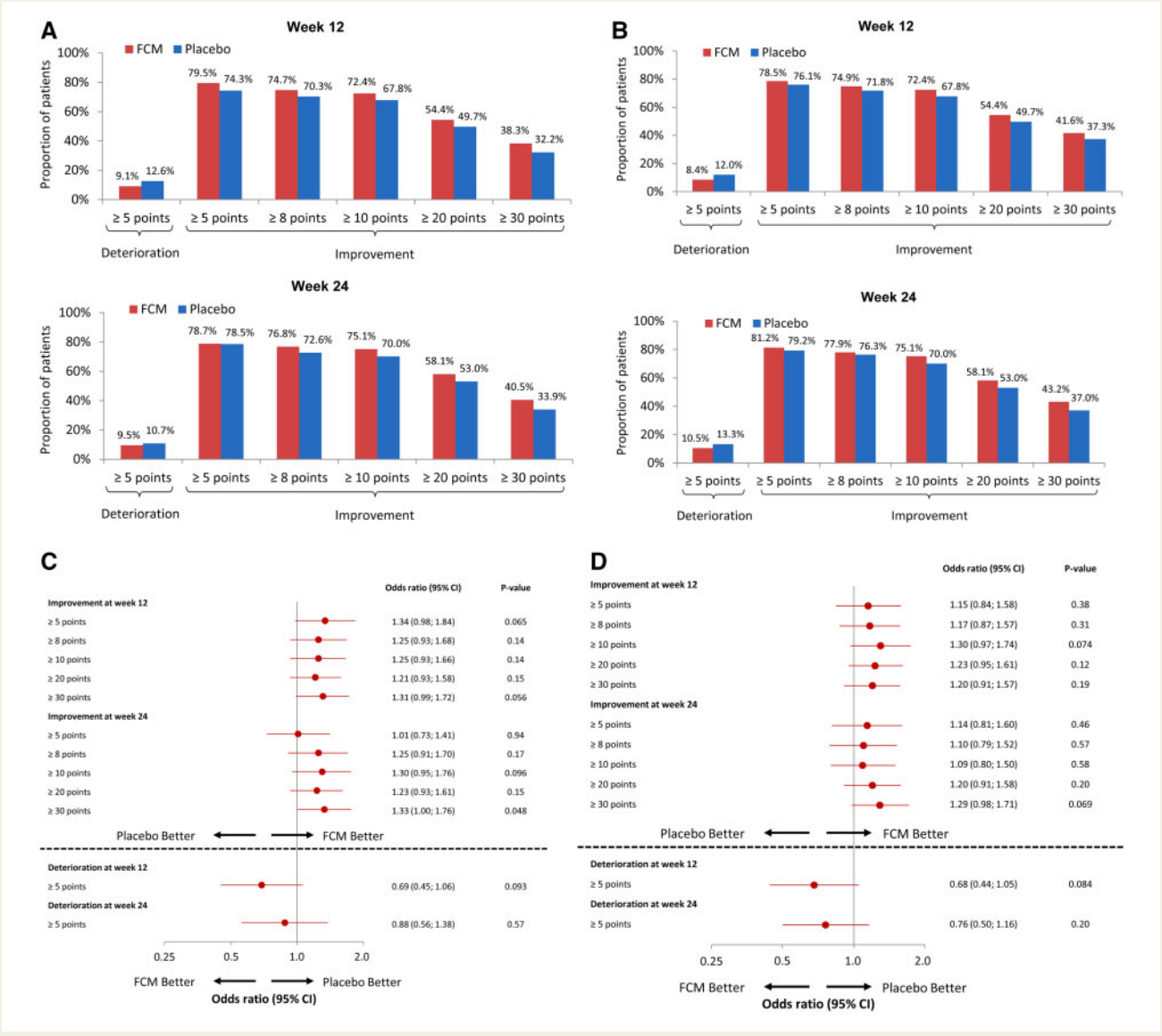


Figure 3 Responder analyses of clinically meaningful changes in the KCCQ-12 OSS and CSS at 12 and 24 months, comparing FCM with placebo. Responder analyses of clinically meaningful changes in KCCQ-12 OSS (*A* and *C*) and KCCQ-12 CSS (*B* and *D*) at Weeks 12 and 24 after randomization. %, proportion of patients; CSS, clinical summary score; FCM, ferric carboxymaltose; KCCQ, Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Data availability

The data that support the findings of this study are available from the corresponding author, E.A.J., upon reasonable request.

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