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RESEARCH ARTICLE

Responder analysis for improvement in 6-min walk test with ferric carboxymaltose in patients with heart failure with reduced ejection fraction and iron deficiency

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Aim Improving functional capacity is a key goal in heart failure (HF). This pooled analysis of FAIR-HF and CONFIRM-HF assessed the likelihood of improvement or deterioration in 6-min walk test (6MWT) among iron-deficient patients with chronic HF with reduced ejection fraction (HFrEF) receiving ferric carboxymaltose (FCM).

Methods and results Data for 760 patients (FCM: $n = 454$; placebo: $n = 306$) were analysed. The proportions of patients receiving FCM or placebo who had ≥20, ≥30, and ≥40 m improvements or ≥10 m deterioration in 6MWT at 12 and 24 weeks were assessed. Patients receiving FCM experienced a mean (standard deviation) 31.1 (62.3) m improvement in 6MWT versus 0.1 (77.1) m improvement for placebo at week 12 (difference in mean changes 26.8 [16.6–37.0]). At week 12, the odds [95% confidence interval] of 6MWT improvements of ≥20 m (odds ratio 2.16 [1.57–2.96]; $p < 0.0001$), ≥30 m (2.00 [1.44–2.78]; $p < 0.0001$), and ≥40 m (2.29 [1.60–3.27]; $p < 0.0001$) were greater with FCM versus placebo, while the odds of a deterioration ≥10 m were reduced with FCM versus placebo (0.55 [0.38–0.80]; $p = 0.0019$). Among patients who experienced 6MWT improvements of ≥20, ≥30, or ≥40 m with FCM at week 12, more than 80% sustained this improvement at week 24.

Conclusion Ferric carboxymaltose resulted in a significantly higher likelihood of improvement and a reduced likelihood of deterioration in 6MWT versus placebo among iron-deficient patients with HF. Of the patients experiencing clinically significant improvements at week 12, the majority sustained this improvement at week 24. These results are supportive of FCM to improve exercise capacity in HF.

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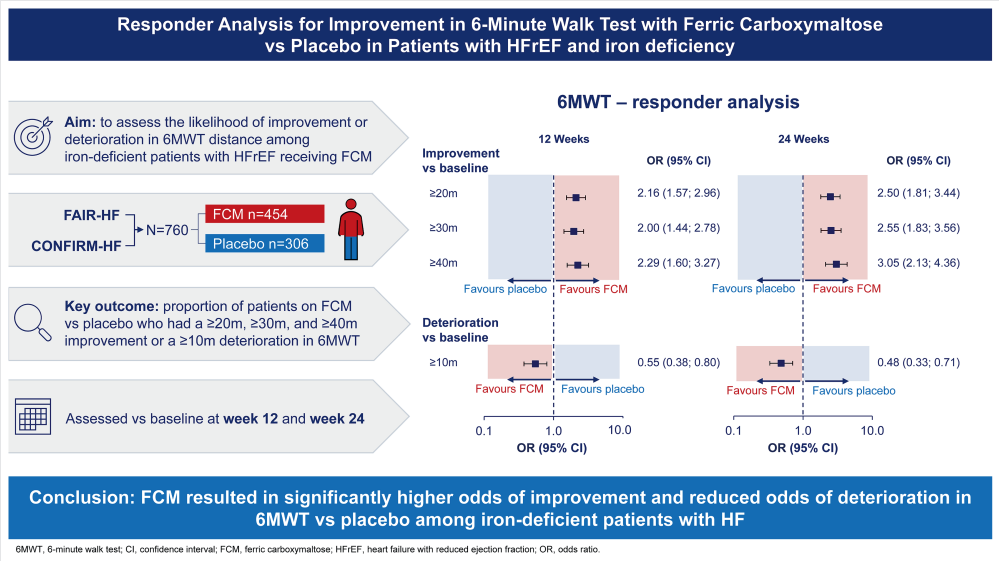
Graphical Abstract



Responder analysis for improvement in 6-minute walk test with ferric carboxymaltose vs placebo in patients with HFrEF and iron deficiency.

Keywords CONFIRM-HF • FAIR-HF • Ferric carboxymaltose • Heart Failure • Responder • 6-min walk test

Introduction

Iron deficiency is present in ~50% of patients with heart failure (HF)[1–3] and is associated with impaired functional capacity, reduced quality of life, and increased risk of mortality, regardless of anaemia.[3,4] Recent guidance statements from the US Food and Drug Administration have recognized change in functional capacity as a potentially relevant endpoint to assess the effectiveness of HF therapies.[5] In this respect, several randomized controlled trials (RCTs) have shown that intravenous administration of the nanoparticulate iron–carbohydrate complex, ferric carboxymaltose (FCM),[6,7] has favourable effects on a 6-min walk test (6MWT: a measure of exercise capacity) compared with placebo in patients with HF and iron deficiency.[8–11]

To aid the interpretation of these findings, it is fundamental to understand the magnitude of change in 6MWT distance that is meaningful to patients and to recognize clinically relevant thresholds for improvement and deterioration. Such thresholds can be used to perform 'responder analyses' to determine the proportion of patients who achieve clinically meaningful improvement or deterioration in 6MWT at various time points in clinical studies. In turn, this can facilitate clinical interpretation of RCT data and improve understanding among patients and clinicians regarding the clinical benefits of interventions. To the best of our knowledge at the time of writing, responder analyses for the 6MWT have not yet been performed for intravenous FCM versus placebo in an ambulatory, iron-deficient HF population.

This pooled analysis of FAIR-HF (Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure)[8] and CONFIRM-HF (ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure)[11] RCTs assessed the likelihood of improvement or deterioration in a 6MWT among iron-deficient patients with HF receiving FCM and examined the stability of the change over time.

Methods

Study design

Individual patient-level data from two double-blind RCTs (CONFIRM-HF and FAIR-HF) evaluating the effects of intravenous FCM versus placebo on outcomes in ambulatory patients with chronic HF with reduced ejection fraction and iron deficiency were included. The key trial characteristics of each RCT are available in online supplementary *Table S1*. The primary results of these studies have been previously reported, alongside safety outcomes and dosing information.[8,11] Both trials were approved by the appropriate regulatory authorities and ethics committees, and conformed with the principles outlined in the guidelines for International Council for Harmonization Good Clinical Practice[12] and the Declaration of Helsinki.[13] In each trial, all subjects provided their written informed consent to participate.

Exercise capacity assessment

The 6MWT is a submaximal exercise test that entails measuring distance (in metres) walked over a span of 6 min. It quantifies exercise

capacity, response to therapy, and prognosis across a broad range of chronic cardiopulmonary conditions, including HF.[14] Each participant is encouraged to walk on a straight, flat-surfaced, marked course for 6 min, pausing if necessary. The maximum distance walked is recorded at the end of the sixth minute.

Outcomes

The key outcomes assessed in this analysis were the mean change versus baseline in 6MWT with FCM versus placebo and the proportion of patients in each treatment group who achieved a clinically meaningful change in 6MWT versus baseline at 12 and 24 weeks. Clinically meaningful changes in 6MWT were defined using conventional thresholds (≥20, ≥30, or ≥40 m improvement or ≥10 m deterioration), as determined previously.[15,16] The 'stability' of the response was also investigated.

Statistical analysis

Baseline demographic and clinical data are reported as mean (standard deviation [SD]) for continuous variables, and *n* (%) for categorical variables.

Least-square (LS) mean (SD) changes from baseline in 6MWT at weeks 12 and 24 were reported per treatment group, and the corresponding LS mean treatment differences with 95% confidence intervals (CIs) and two-sided *p*-values were calculated using a mixed model for repeated measures (MMRM), adjusted for study and baseline 6MWT distance, age, estimated glomerular filtration rate (eGFR), diabetes status, sex, and left ventricular ejection fraction. To investigate between-study heterogeneity in the treatment effect, the MMRM was also expanded by including random treatment-by-study interactions. Missing values due to hospitalization or death were imputed. If a subject was hospitalized and unable to exercise at the planned time point when the 6MWT should have been performed, the worst non-null test across the study (i.e. for all time points and for all subjects) was used, which was 30 m. This worst non-value used for imputation of hospitalized patients was the same for patients from CONFIRM-HF and FAIR-HF, regardless of the treatment arm. If the subject died on or before the planned time point, the value was set to zero. Missing test values in subjects who were known to be alive and not hospitalized were not imputed.

For the responder analyses, the number and proportion of patients experiencing a clinically meaningful change in 6MWT versus baseline (responders) at weeks 12 and 24 was reported. Patients who had died or were hospitalized at the time of the assessment were recorded as 'not improved' in the analysis of improvement and 'deteriorated' in the deterioration analysis. The treatment effect was assessed using logistic regression models, with results reported as odds ratios (ORs) with 95% CIs and two-sided *p*-values. Because the pooled studies were similar in terms of design, patient populations, and endpoint assessments up to week 24, a fixed-effects model was considered appropriate for this exploratory analysis; however, a random-effects model including random treatment-by-study interactions was also used to account for the effect of between-trial heterogeneity. The logistic regression models were adjusted for treatment group, study, and the following baseline factors: 6MWT distance, age, eGFR, diabetes status, sex, and left ventricular ejection fraction. ORs were converted into number needed to treat (NNT) values using the formula described by Hutton[17] and the placebo control response/deterioration proportion. Treatment modification based on aetiology of HF was also evaluated.

To evaluate how many patients remained stable in their response, the proportions of patients that were categorized as having the same response (improved, not improved, deteriorated, not deteriorated) versus baseline in the 6MWT at both week 12 and week 24 were descriptively summarized. For this purpose, a flow chart detailing the proportion of patients for each permutation and combination at each time point was generated.

To evaluate for the changes in functional classification and quality of life measures according to 6MWT responder categories, LS mean treatment differences and changes in New York Heart Association (NYHA) functional classification scores, Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (KCCQ-OSS), and clinical summary score (KCCQ-CSS), EQ-5D index scores, and ED-5D Health State (VAS) scores from baseline to weeks 12 and 24 were calculated in both arms.

While the follow-up period was 24 weeks in FAIR-HF[8] and 1 year in CONFIRM-HF,[11] patient follow-up was restricted to 24 weeks for this pooled analysis (in which the data set was derived from both studies). SAS® Version 9.4 or later (SAS Institute, Inc, London, UK) or R version 3.6.3 or later (R Foundation for Statistical Computing, Vienna, Austria) were used for the analyses.

Results

Patient characteristics

Of the 760 patients included in the two studies, 454 (60%) were in the FCM group, while 306 (40%) were in the placebo group. The mean (SD) age of the patients was 68 (10) years, 51% were female, and 45% had haemoglobin <12 g/dL (*Table 1*). The mean (SD) 6MWT distance at baseline was similar in the FCM and placebo groups (278.6 [102.8] and 285.1 [104.2] m, respectively). 6MWT data were available for 685 patients (90%) at week 12 and 661 patients (87%) at week 24. In addition, values were imputed for the 11 patients who had died at week 12 and the 21 patients who had died at week 24. For hospitalizations, values were imputed for 12 patients at week 12 and 16 patients at week 24. Proportions of patients who had values imputed for death and hospitalization in each treatment arm at weeks 12 and 24 are shown in online supplementary *Table S2*.

Mean change in 6-min walk test by treatment group

The mean (SD) change versus baseline in 6MWT distance was 31.1 (62.3) m with FCM versus 0.2 (77.1) m with placebo at week 12 (fixed-effects model LS mean difference: 26.8 [95% CI: 16.6−37.0]) and 31.8 (79.2) m with FCM versus −4.8 (84.4) m with placebo at week 24 (fixed-effects model LS mean difference: 34.2 [95% CI 22.0−46.4]) (*Figure 1*). Mean differences based on the random-effects model showed similar effect sizes to those based on the fixed-effects model, with wider CIs (online supplementary *Figure S1*).

Responder analysis

At week 12, 56.8% of patients on FCM versus 37.4% of those on placebo experienced an improvement of ≥20 m (fixed-effects OR: 2.16 [95% CI 1.57−2.96]; $p < 0.0001$), 46.1% versus 29.1% experienced an improvement of ≥30 m (2.00 [1.44−2.78]; $p < 0.0001$), and 38.9% versus 21.1% experienced an improvement of ≥40 m

Table 1 Pooled baseline characteristics of patients in FAIR-HF and CONFIRM-HF trials

Variable	FCM pool (n = 454)	Placebo pool (n = 306)	Total (n = 760)
Age, years, mean (SD)	67.8 (10.1)	68.2 (10.4)	68.0 (10.2)
Female sex, *n* (%)	226 (49.8)	159 (52.0)	385 (50.7)
White European ethnicity, *n* (%)	452 (99.6)	305 (99.7)	757 (99.6)
NYHA class III, *n* (%)	321 (70.7)	186 (60.8)	507 (66.7)
LVEF, %, mean (SD)	33.6 (6.7)	34.7 (6.9)	34.1 (6.8)
BMI, kg/m^2, mean (SD)	28.1 (4.7)	28.6 (5.4)	28.3 (5.0)
6MWT distance, m, mean (SD)	278.6 (102.8)	285.1 (104.2)	281.2 (103.3)
Hypertension, *n* (%)	373 (82.2)	259 (84.6)	632 (83.2)
Diabetes mellitus, *n* (%)	131 (28.9)	82 (26.8)	213 (28.0)
Smoking, n (%)	133 (29.3)	82 (26.8)	215 (28.3)
Atrial fibrillation, *n* (%)	493 (53.9)	431 (57.7)	924 (55.6)
Myocardial infarction, *n* (%)	500 (54.7)	395 (52.9)	895 (53.9)
Stroke, *n* (%)	99 (10.8)	103 (13.8)	202 (12.2)
Coronary revascularization, *n* (%)	312 (34.1)	278 (37.2)	590 (35.5)
Ischaemic HF aetiology, *n* (%)	370 (81.5)	249 (81.4)	619 (81.4)
Laboratory test results			
Hb, g/dl, mean (SD)	12.1 (1.3)	12.2 (1.4)	12.1 (1.3)
Hb <10 g/dl, *n* (%)	26 (5.7)	12 (3.9)	38 (5.0)
Hb ≥10 and <12 g/dl, *n* (%)	181 (39.9)	120 (39.2)	301 (39.6)
Hb ≥12 g/dl, *n* (%)	247 (54.4)	174 (56.9)	421 (55.4)
Ferritin, ng/ml, mean (SD)	54.0 (52.6)	58.6 (55.6)	55.9 (53.8)
Ferritin <50 ng/ml, *n* (%)	266 (58.6)	172 (56.2)	438 (57.6)
Ferritin ≥50 and <100 ng/ml, *n* (%)	138 (30.4)	95 (31.1)	233 (30.7)
Ferritin ≥100 ng/ml, *n* (%)	50 (11.0)	39 (12.8)	89 (11.7)
TSAT, %, mean (SD)	18.5 (14.5)	17.4 (8.3)	18.1 (12.4)
TSAT ≥0% and ≤10%, *n* (%)	94 (20.7)	61 (19.9)	155 (20.4)
TSAT >10% and ≤20%, *n* (%)	213 (46.9)	140 (45.8)	353 (46.5)
TSAT >20%, *n* (%)	147 (32.4)	105 (34.3)	252 (33.2)
eGFR (CKD-EPI), ml/min/1.73 m^2, mean (SD)	64.4 (20.8)	64.2 (22.5)	64.3 (21.5)
eGFR <60 ml/min/1.73 m^2, *n* (%)	179 (39.4)	137 (44.8)	316 (41.6)
Concomitant medications, *n* (%)			
ARNI or SGLT2 inhibitor	0 (0.0)	0 (0.0)	0 (0.0)
ACEI, ARB or ARNI	423 (93.2)	283 (92.5)	706 (92.9)
Beta-blocker	393 (86.6)	267 (87.3)	660 (86.8)
Aldosterone antagonists	237 (52.2)	147 (48.0)	384 (50.5)
Triple therapy	194 (42.7)	122 (39.9)	316 (41.6)

6MWT, 6-min walk test; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CONFIRM-HF, ferric CarboxymaltOse evaluatioN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure; eGFR, estimated glomerular filtration rate; FAIR-HF, Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SGLT2, sodium–glucose cotransporter 2; SD, standard deviation; TSAT, transferrin saturation.

(2.29 [1.60–3.27]; $p < 0.0001$) in 6MWT compared with baseline (*Figure 2*). The proportions of patients in the FCM and placebo groups experiencing a ≥10 m deterioration compared with baseline at week 12 were 16.7% and 28.0%, respectively (fixed-effects OR: 0.55 [95% CI 0.38–0.80]; $p = 0.0019$). At week 24, 59.4% of patients on FCM versus 37.0% of those on placebo experienced an improvement of ≥20 m (fixed-effects OR: 2.50 [95% CI 1.81–3.44]; $p < 0.0001$), 51.1% versus 28.5% experienced an improvement of ≥30 m (2.55 [1.83–3.56]; $p < 0.0001$), and 44.8% versus 20.8% experienced an improvement of ≥40 m (3.05 [2.13–4.36]; $p < 0.0001$) in 6MWT compared with baseline (*Figure 2*). The proportions of patients in FCM and placebo groups experiencing a ≥10 m deterioration compared with baseline at week 24 were 16.6% and 30.6%, respectively (fixed-effects OR: 0.48 [95% CI 0.33–0.71]; $p = 0.0002$). ORs derived from the random-effects model were similar in terms of effect size, with slightly larger CIs (online supplementary *Figure S2*).

Responder analysis based on aetiology of heart failure

At week 12, the proportion of patients in the FCM arm versus placebo arm who achieved ≥20 m (ischaemic: fixed effects OR: 1.91 [1.35–2.72], $p = 0.0003$, non-ischaemic: 4.08 [1.90–8.75],

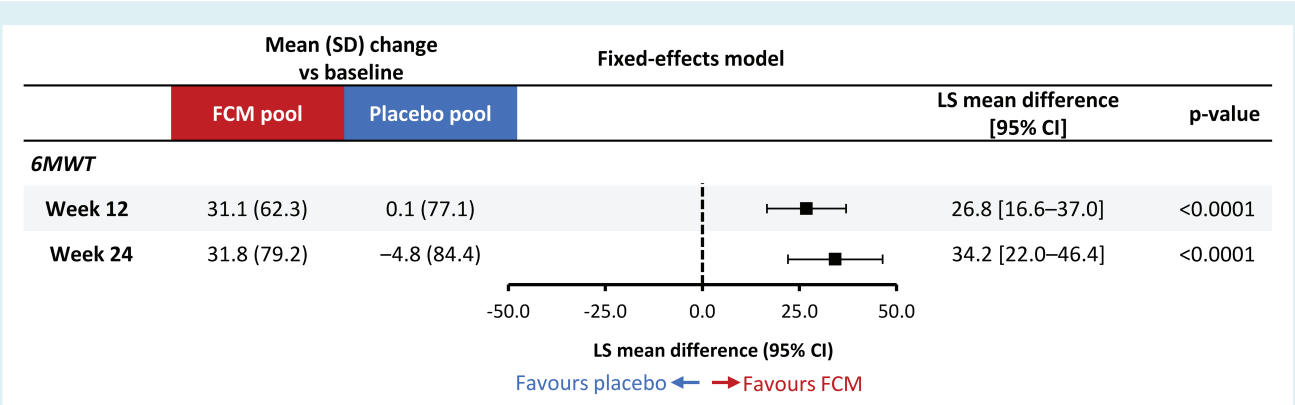


Figure 1 Mean change from baseline in 6-min walk test (6MWT) with ferric carboxymaltose (FCM) versus placebo at weeks 12 and 24 – fixed-effects model. Least-square (LS) mean difference based on a fixed-effects mixed model for repeated measures analysis adjusted for study, baseline 6MWT score, age, estimated glomerular filtration rate, diabetes status, sex, and left ventricular ejection fraction. Since only six patients are from Latin America and the remainder are from Europe, region was not included in the model. In FCM and placebo groups, patient numbers were 418 and 289, respectively, at week 12 and 415 and 283, respectively, at week 24. CI, confidence interval; SD, standard deviation.

$p = 0.0003$; p-interaction = 0.0765), ≥30 m (ischaemic: 1.77 [1.23–2.56], $p = 0.0022$, non-ischaemic: 3.60 [1.70–7.63]; $p = 0.0008$; p-interaction = 0.0960) and ≥40 m (ischaemic: 2.04 [1.37–3.04]; $p = 0.0005$, non-ischaemic: 3.91 [1.74–8.75]; $p = 0.0009$; p-interaction = 0.1559) improvement were similar in patients with ischaemic and non-ischaemic aetiology of HF. The proportion of patients who experienced deterioration ≥10 m (ischaemic: fixed-effects OR: 0.61 [95% CI 0.41–0.92]; $p = 0.0189$, non-ischaemic: 0.26 [95% CI 0.09–0.76]; $p = 0.0137$; p-interaction = 0.1432) at week 12 were also similar in ischaemic and non-ischaemic aetiology of HF. Results did not significantly change at week 24.

Number needed to treat

Based on the ORs derived from the fixed-effects model, the NNT for one patient to achieve an improvement versus baseline of ≥20, ≥30, and ≥40 m in 6MWT at week 12 was 6, 8, and 9, respectively (*Table 2*). Corresponding NNT values at week 24 were 6, 7, and 8, respectively. NNTs based on the random-effects model were similar (online supplementary *Table S3*).

Response stability analysis

Of 230 patients on FCM who experienced a ≥20 m improvement versus baseline in 6MWT at week 12, 199 (86.5%) also had a ≥20 m improvement versus baseline at week 24 (remained stable in their improvement) (*Figure 3*). The proportions of patients on FCM that remained stable in their improvement versus baseline between weeks 12 and 24 were 83.6% for both ≥30 m and ≥40 m thresholds. The proportions of patients on placebo that remained stable in their improvement versus baseline between weeks 12 and 24 were 75.0%, 72.5%, and 64.9% for ≥20 m, ≥30 m, and ≥40 m thresholds, respectively.

Of 175 patients on FCM who did not experience a ≥20 m improvement versus baseline in 6MWT at week 12, 49 patients (28%) experienced a ≥20 m improvement versus baseline at week 24 (reverted from non-improvement to improvement) (*Figure 3*). The corresponding proportions of patients on FCM that converted from non-improvement at week 12 to improvement at week 24 were 23.1% and 20.7% for ≥30 m and ≥40 m thresholds, respectively. In the placebo group, the proportions of patients that converted from non-improvement at week 12 to improvement at week 24 were 13.1%, 10.1%, and 9.9% for ≥20, ≥40, and ≥30 m thresholds, respectively.

Of 66 patients on FCM who experienced a ≥10 m deterioration versus baseline in 6MWT at week 12, 21 (31.8%) no longer had a ≥10 m deterioration versus baseline at week 24 (*Figure 3*). Of the 76 patients on placebo who experienced a ≥10 m deterioration versus baseline in 6MWT at week 12, 25 (32.9%) no longer had a ≥10 m deterioration versus baseline at week 24.

Changes in quality of life according to 6-min walk test responder categories

At week 12, the mean (SD) change in KCCQ-OSS was 10.6 (17.7) with FCM versus 4.8 (13.9) with placebo (fixed-effects model LS mean difference: 4.6 [95% CI 2.3–6.8]) while at week 24, the mean change was 11.4 (18.7) with FCM versus 5.7 (15.0) with placebo (fixed-effects model LS mean difference: 4.7 [95% CI 2.4–7.0]). The changes in KCCQ-OSS, KCCQ-CSS, EQ-5D VAS and EQ-5D index scores were in conjunction with changes in 6MWT at weeks 12 and 24 in both arms (online supplementary *Tables S4–S7*).

Change in functional classification according to 6-min walk test responder categories

At week 12, the mean (SD) change in NYHA functional classification was −0.2 (0.6) with FCM versus 0.0 (0.5) with placebo

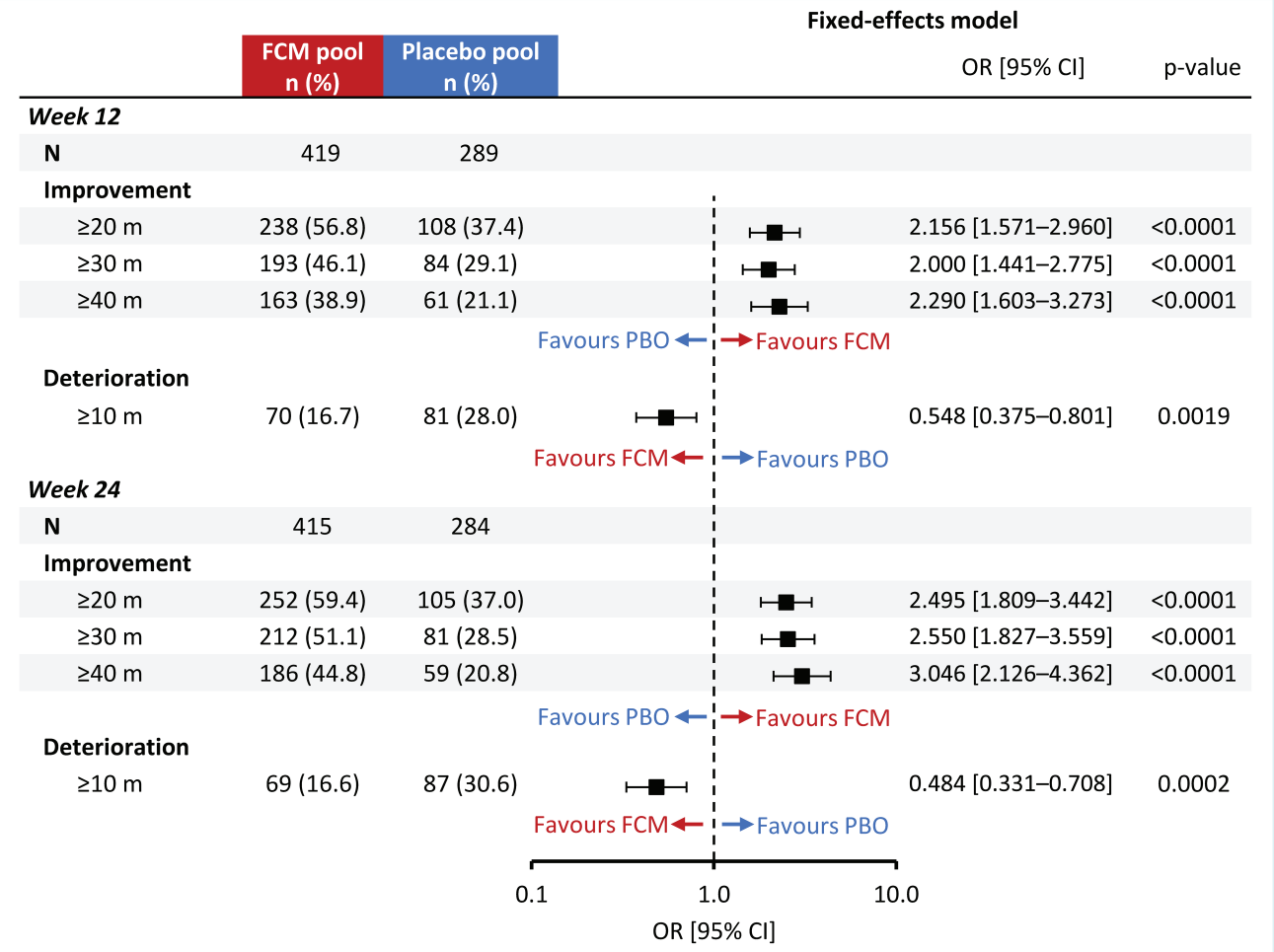


Figure 2 Responder analyses across minimal clinically important difference thresholds for 6-min walk test (6MWT). Odds ratios (ORs) with 95% confidence intervals (CIs) and *p*-values were obtained from logistic regression models, including treatment group, study, and the following baseline factors: 6MWT distance, age, estimated glomerular filtration rate, diabetes status, sex, and left ventricular ejection fraction. Patients were from Europe and Latin America, but since only six patients were from Latin America, region was not included in the model. Patients who had died or were hospitalized at weeks 12 and 24 were counted as deteriorated/non-responder at the respective time point. FCM, ferric carboxymaltose; PBO, placebo.

Table 2 Number needed to treat to achieve defined change versus baseline in 6-min walk test at weeks 12 and 24 (fixed-effects model)

	Week 12	Week 24
Improvement		
≥20 m	6	6
≥30 m	8	7
≥40 m	9	8
Deterioration		
≥10 m	7	6

Note: Odds ratios from the fixed-effects responder analysis logistic regressions were converted into number needed to treat using the formula described in Hutton[17] and the placebo control response/deterioration proportion.

(fixed-effects model LS mean difference: −0.19 [95% CI −0.27– −0.11]) while at week 24, the mean change was −0.2 (0.7) with FCM versus 0.1 (0.6) with placebo (fixed-effects model LS mean difference: −0.22 [95% CI −0.31– −0.12). The changes in NYHA functional classification corresponding to responder categories are shown in online supplementary *Table S8*.

Discussion

This pooled analysis of the CONFIRM-HF and FAIR-HF RCTs revealed several key findings. Firstly, as a group, patients receiving FCM experienced a significantly greater mean improvement in 6MWT distance than those receiving placebo at weeks 12 and 24. Secondly, a significantly higher proportion of individual patients experienced a ≥20, ≥30, and ≥40 m improvement in 6MWT with FCM versus placebo at weeks 12 and 24, corresponding with

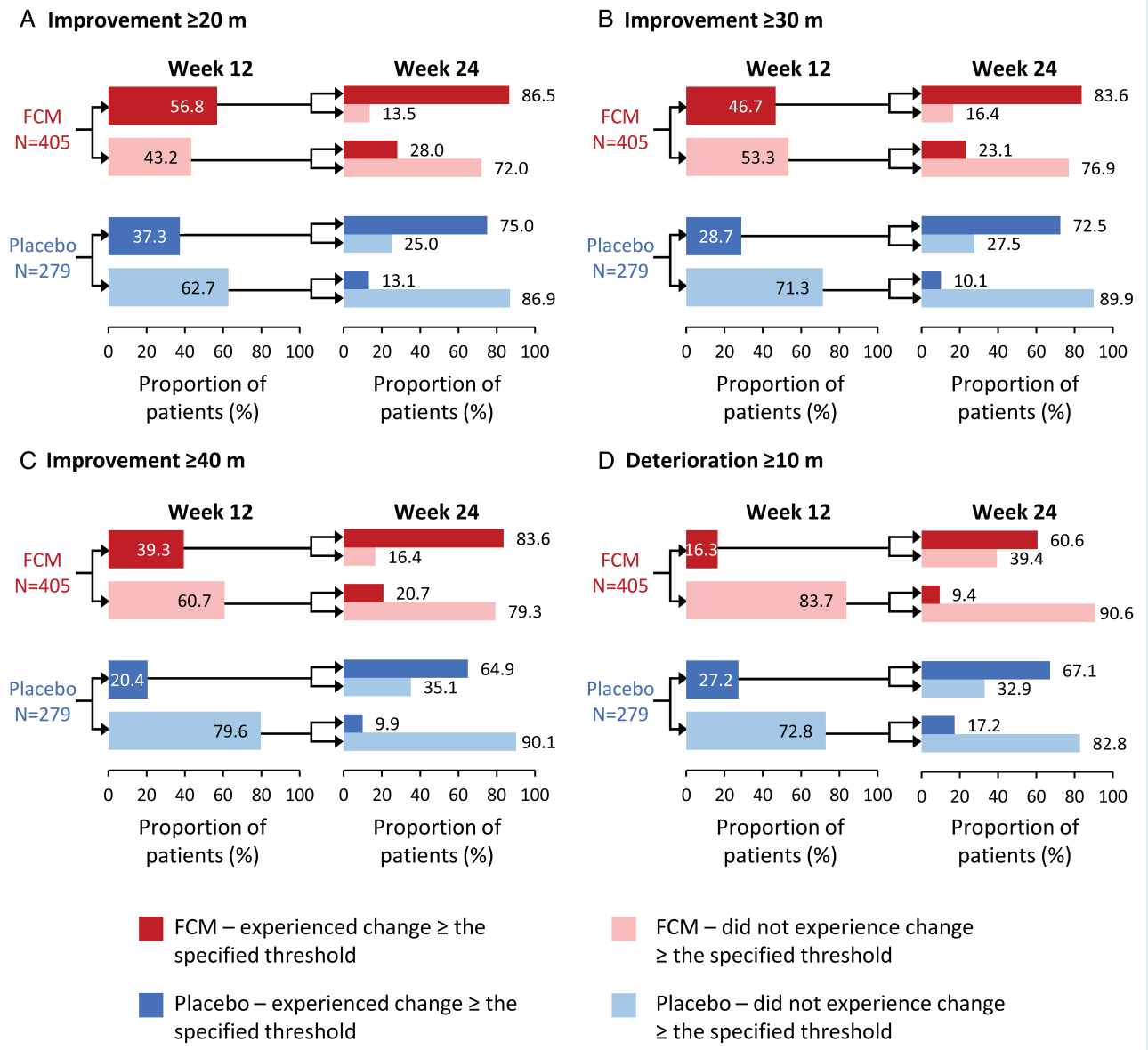


Figure 3 Response stability analysis – change in 6-min walk test (6MWT) response between week 12 and week 24. Patients who had died or were hospitalized at weeks 12 and 24 were counted as deteriorated/non-responder at the respective time point. N = the number of patients that had non-missing 6MWT information available at both week 12 and week 24. Changes in 6MWT at week 12 and week 24 are with respect to baseline. FCM, ferric carboxymaltose.

relatively low NNT values, and a ≥10 m deterioration in 6MWT was significantly less common with FCM versus placebo at weeks 12 and 24. Thirdly, among patients on FCM who had experienced a ≥20, ≥30, and ≥40 m improvement in 6MWT at week 12, more than 80% had a sustained improvement at week 24; this suggests that the improvement in exercise capacity with FCM remains stable over time in the majority of patients. Lastly, there was no treatment modification based on aetiology of HF. This suggests that favourable response of FCM is generalizable and not specific to aetiology of HF. These findings have important clinical implications as few interventions have been consistently demonstrated to improve functional capacity in patients with HF to the extent seen with FCM in the present analysis.

Addressing impaired functional capacity in patients with HF is among one of the main priorities in clinical management.[18] Treatment with FCM was shown to improve 6MWT distance by a mean of 31 m and 32 m at 12 and 24 weeks, respectively, in the overall pooled trial population. This number compares favourably with other interventions that have been shown to increase 6MWT in patients with HF. For instance, in the PRECISE (Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise) trial, carvedilol improved 6MWT distance by 17 m

at 6 months compared with baseline[19]; in HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training), exercise therapy resulted in a 20 m improvement in walking distance on the 6MWT at 3 months compared with baseline[20]; and in the RADIANCE (Randomized Assessment of [the effect of] Digoxin on Inhibitors of the Angiotensin-Converting Enzyme) study, digoxin improved 6MWT distance by approximately 14 m at week 10 compared with baseline.[21] Improvement in 6MWT distance with FCM is also comparable to device therapies. For example, in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, cardiac resynchronization therapy (CRT) improved 6MWT distance by 33 m at 3 months and by 40 m at 6 months,[22] in the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial, CRT resulted in a 39 m improvement in 6MWT distance at 6 months,[23] and in the PATH-CHF (Pacing Therapies in Congestive Heart Failure), CRT improved 6MWT distance by 44 m at week 4.[24]

These findings suggest that FCM may provide similar, if not greater, effects on exercise capacity compared with other therapies in patients with HF; however, comparing 6MWT results between studies is challenging for a number of reasons. Firstly, the 6MWT is heavily dependent on the effort of the operator and the patient at one point in time, which can result in significant variability due to lack of standardization. Secondly, 6MWT can be affected by other non-HF-related comorbidities such as orthopaedic limitations; consequently, it is possible that changes in HF-related physical limitations may not be accurately represented in 6MWT results. Thirdly, comparisons may be precluded by differences in patient populations and study design, including different assessment time points and variability in statistical methodology regarding deaths and missing data.

It is important to differentiate between clinically relevant changes in group mean 6MWT results and corresponding between-group mean differences and what constitutes a clinically relevant change in 6MWT for an individual subject. Our analysis showed that only 6, 8, and 9 iron-deficient patients with HF need to be treated with FCM for one patient to experience a ≥20, ≥30, and ≥40 m improvement in 6MWT at week 12, respectively, and the NNT changed only slightly when adjusted for between-study heterogeneity. Consistent with prior studies that have established associations of functional capacity with quality of life and NYHA functional classification,[25,26] our analysis showed that improvements in 6MWT were in conjunction with improvements in quality of life scores and NYHA functional classification. This suggests that changes in functional capacity may potentially be used as predictor of HF disease severity and overall patients' well-being.

This is the first study to report the proportion of patients with sustained 6MWT changes over time associated with a particular intervention. The concept of improvement 'stability' is clinically relevant because it controls for day-to-day intra-patient variability in 6MWT response. We observed that a high proportion of patients experienced a sustained level of improvement with FCM between weeks 12 and 24, which suggests that the benefits observed to date with FCM versus placebo on exercise capacity are robust. Moreover, the analysis showed that more than 20% of patients on FCM who did not reach the thresholds for ≥10, ≥30 or ≥40 m improvement at week 12 experienced respective improvements by week 24. Conversely, only about 10% of patients on placebo who failed to reach the respective thresholds at week 12 experienced improvements by week 24.

Although iron deficiency is common and becoming increasingly recognized as an important comorbidity among patients with HF, its screening and treatment are not often implemented in clinical practice. This is despite the European Society of Cardiology guideline recommendation for periodic screening of iron deficiency in all patients with HF and inclusion of FCM in the HF with reduced ejection fraction management algorithm to reduce HF hospitalization or mortality in patients with iron deficiency.[3] There is therefore a need to increase awareness among clinicians of the benefits of identifying iron deficiency among patients with HF and treating it with FCM as a standard of care.

Limitations in this study should be noted. Firstly, because of the pre-specified inclusion and exclusion criteria of the trials included, the generalizability of our results may be restricted in real-world clinical practice. Secondly, we could not determine the effect of dosing of FCM on exercise capacity. Thirdly, pooling of results from two different trials may have led to some heterogeneity; when accounting for this in the random-effects model responder analyses, the effect sizes changed only slightly, with wider CIs indicating a larger uncertainty of precision. Thus, while this *post hoc*, exploratory analysis suggests that FCM increases the likelihood of improving an individual's exercise capacity, a dedicated prospective study may be of benefit to determine the treatment effect more precisely.

In conclusion, treatment with FCM was associated with higher odds of improvement and lower odds of deterioration in exercise capacity (evaluated using 6MWT) versus placebo in patients with HF and iron deficiency (*Graphical Abstract*). Of the patients who experienced a clinically significant improvement in 6MWT with FCM at week 12, the majority sustained this improvement at week 24, suggesting the stability of the favourable response to FCM over time. These findings lend support to the role of FCM for improving exercise capacity in patients with HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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