SUPPLEMENTAL MATERIAL

Association between hemoglobin level and the efficacy of intravenous ferric carboxymaltose in patients with acute heart failure and iron deficiency: an AFFIRM-AHF subgroup analysis

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Supplemental Tables

Table S1. Baseline Demographics and Clinical Characteristics of Patients With Normal and Low Hb Levels According to the WHO Anemia Definition

Baseline characteristics	Low Hb level (n=604)	Normal Hb level (n=503)	*P*-value
Age, years	72.8 (10.0)	68.9 (11.7)	<0.0001
Sex, n (%)			
Male	361 (59.8)	252 (50.1)	0.001
Female	243 (40.2)	251 (49.9)	
Race, n (%)			
White	578 (95.7)	472 (93.8)	0.53
Asian	24 (3.9)	24 (4.8)	
Other	2 (0.3)	7 (1.4)	
BMI, kg/m^2	28.0 (5.7)	28.2 (5.6)	0.49
Comorbidities, n (%)			
Previous myocardial infarction	275 (45.5)	167 (33.2)	<0.0001
Previous stroke	64 (10.6)	54 (10.7)	0.94
Previous coronary revascularization	259 (42.9)	142 (28.2)	<0.0001
Hypertension	532 (88.1)	406 (80.7)	0.001
Atrial fibrillation	342 (56.6)	276 (54.9)	0.56
Diabetes	289 (47.8)	181 (36.0)	<0.0001
Dyslipidemia	343 (56.8)	248 (49.3)	0.013
Chronic kidney disease	282 (46.7)	166 (33.0)	<0.0001
Smoking	50 (8.3)	56 (11.1)	0.59
Systolic blood pressure, mmHg	119.8 (15.6)	119.6 (15.3)	0.85
Diastolic blood pressure, mmHg	71.2 (9.9)	73.4 (10.2)	0.0003
Heart rate, beats per minute	73.3 (12.6)	75.6 (13.3)	0.003
NYHA, n (%)			
Class ≤II	265 (43.9)	252 (50.4)	0.033
Class ≥III	338 (56.1)	248 (49.6)	
Left ventricular ejection fraction, %	33.4 (9.8)	31.8 (9.7)	0.006
Left ventricular ejection fraction, n (%)			
<25%	109 (18.0)	117 (23.3)	0.030
≥25% to <40%	287 (47.5)	243 (48.4)	
≥40% to <50%	208 (34.4)	142 (28.3)	
Ischemic HF	315 (52.2)	207 (41.2)	0.001
Device therapy, n (%)			
Implantable cardioverter-defibrillator	75 (12.4)	56 (11.1)	0.51

Cardiac resynchronization therapy	44 (7.3)	19 (3.8)	0.012
HF history, n (%)			
Documented history of HF	456 (75.5)	334 (66.4)	0.001
Newly diagnosed at index hospitalization	148 (24.5)	169 (33.6)	0.001
Hospitalization for HF in previous 12 months	170 (37.3)	135 (40.4)	0.37
Pharmacotherapy, n (%)			
ACEi	294 (48.7)	282 (56.1)	0.014
ARB	117 (19.4)	80 (15.9)	0.13
ARNI	37 (6.1)	33 (6.6)	0.77
Aldosterone antagonist	377 (62.4)	351 (69.8)	0.010
Beta blocker	498 (82.5)	415 (82.5)	0.98
Digitalis glycosides	92 (15.2)	92 (18.3)	0.17
Loop diuretic	512 (84.8)	435 (86.5)	0.42
Laboratory test results			
NT-pro-BNP, pg/mL (median [upper and lower quartiles])	5067 [2812;9000]	4585 [2749;7533]	0.61
BNP, pg/mL (median [upper and lower quartiles])	1197 [807;1852]	1053 [785;1637]	0.43
Hb, g/dL	11.1 (1.2)	13.6 (0.8)	<0.0001
Hb category, n (%)			<0.0001
<10 g/dL	114 (18.9)	0	
≥10 to <14 g/dL	490 (81.1)	342 (68)	
≥14 g/dL	0	161 (32)	
Serum ferritin, µg/L	79.4 (64.2)	94.2 (66.1)	0.0002
Serum ferritin <100 µg/L, n (%)	444 (73.5)	344 (68.4)	0.06
TSAT, %	13.7 (7.8)	15.9 (7.9)	<0.0001
TSAT <20%, n (%)	522 (87.1)	404 (80.5)	0.003
eGFR, $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$	50.5 (21.4)	61.3 (21.7)	<0.0001
Phosphorous, mg/dL	3.8 (1.0)	3.7 (0.7)	0.17

The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Data are mean (standard deviation) unless otherwise specified. Baseline medication was defined as any medication that was current on the initial dosing of study drug. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BMI, body mass index; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HF, heart failure; NT-pro-BNP, N-terminal-pro brain natriuretic peptide; NYHA, New York Heart Association; TSAT, transferrin saturation; and WHO, World Health Organization.

Table S2. Time-updated Hb* analysis of the effect of FCM versus placebo on time-to-first HF hospitalization or CV death at week 52 in Hb <12 g/dL and Hb ≥12 subgroups

Hb <12 g/dL (n=464)		Hb ≥12 g/dL (n=643)		Global effect of time-updated Hb value* on statistical model (*P*-value)	Global effect of interaction between treatment and time-updated Hb value* on statistical model (*P*-value)
Adjusted HR (95% CI) for effect of FCM vs placebo on time-to-first HF hospitalization or CV death at week 52	*P*-value	Adjusted HR (95% CI) for effect of FCM vs placebo on time-to-first HF hospitalization or CV death at week 52	*P*-value		
1.48 (0.28–7.85)	0.64	1.38 (0.20–9.27)	0.74	<0.001	0.60

*Last Hb value prior to event or censor day. Cox regression model adjusted for baseline sex, age, HF etiology, history of HF, country, baseline Hb subgroup (<12 vs ≥12 g/dL), treatment arm, interaction between treatment arm and baseline Hb subgroup (<12 vs ≥12 g/dL), time-updated Hb value, and interaction between treatment arm and time-updated Hb value. Respective n-numbers for patients with Hb <12 g/dL and ≥12 g/dL at baseline were 228 and 329 for FCM and 236 and 314 for placebo. Beyond those listed in the table, two other covariates had a significant global effect on the statistical model: history of HF (*P*<0.001) and country (*P*=0.017). CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; and HR, hazard ratio.

Table S3. Effect of FCM versus placebo on time-to-first HF hospitalization or CV death at week 52 in Hb <12 g/dL and Hb ≥12 g/dL subgroups, adjusting for intra-patient variations in Hb and iron parameters over time

Time-dependent factor included in statistical model	Adjusted HR (95% CI) for effect of FCM vs placebo on time-to-first HF hospitalization or CV death		Global effect of time-dependent iron parameter on statistical model (*P*-value)	Association between Hb subgroup and treatment effect ($P_{interaction}$)
	Hb <12 g/dL (n=464)	Hb ≥12 g/dL (n=643)		
Hb value	0.92 (0.68–1.24)	0.77 (0.58–1.01)	0.0018	0.38
Serum ferritin value	0.93 (0.68–1.26)	0.79 (0.59–1.06)	0.11	0.46
TSAT value	1.01 (0.74–1.37)	0.84 (0.63–1.11)	<0.0001	0.39

Cox regression model adjusting for time-dependent Hb, time-dependent serum ferritin, or time-dependent TSAT, in addition to baseline sex, age, HF etiology, history of HF, country, treatment arm, Hb subgroup (<12 g/dL and ≥12 g/dL), and interaction between treatment arm and Hb subgroup (<12 g/dL and ≥12 g/dL). All Hb, serum ferritin, or TSAT values recorded for each patient between baseline and the event or censor day were entered in the model. Respective n-numbers for patients with Hb <12 g/dL and ≥12 g/dL at baseline were 228 and 329 for FCM and 236 and 314 for placebo. History of HF and country also had a significant global effect on the statistical model including time-dependent Hb (*P*<0.0001 and *P*=0.0195, respectively), the statistical model including time-dependent serum ferritin (*P*<0.0001 and *P*=0.0144, respectively), and the statistical model including time-dependent TSAT (*P*<0.0001 and *P*=0.0263, respectively). CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; and TSAT, transferrin saturation.

Table S4. Summary of Adverse Events by Baseline Hb Level (SAS)

Events, n (%)	Hb <12 g/dL (n=466)				Hb ≥12 g/dL (n=643)			
	FCM (n=229)		Placebo (n=237)		FCM (n=265)		FCM (n=229)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
All adverse events	158 (69.0)	566	170 (71.7)	598	215 (65.3)	732	204 (65.0)	773
All TEAEs	151 (65.9)	544	161 (67.9)	572	205 (62.3)	701	199 (63.4)	742
Related to study drug	5 (2.2)	7	1 (0.4)	1	7 (2.1)	8	1 (0.3)	1
Leading to treatment discontinuation	35 (15.3)	41	34 (14.3)	38	25 (7.6)	29	45 (14.3)	50
Leading to hospitalization	96 (41.9)	220	113 (47.7)	258	130 (39.5)	263	144 (45.9)	303
Leading to study discontinuation	48 (21.0)	60	45 (19.0)	63	49 (14.9)	56	51 (16.2)	60
Serious TEAEs	105 (45.9)	254	127 (53.6)	301	144 (43.8)	292	155 (49.4)	331
Related to study drug	1 (0.4)	3	1 (0.4)	1	0	0	1 (0.3)	1
Fatal TEAEs	48 (21)	60	44 (18.6)	62	50 (15.2)	57	52 (16.6)	61
Related to study drug	0	0	0	0	0	0	0	0

FCM indicates ferric carboxymaltose; Hb, hemoglobin; SAS, safety analysis set; and TEAE, treatment-emergent adverse event.

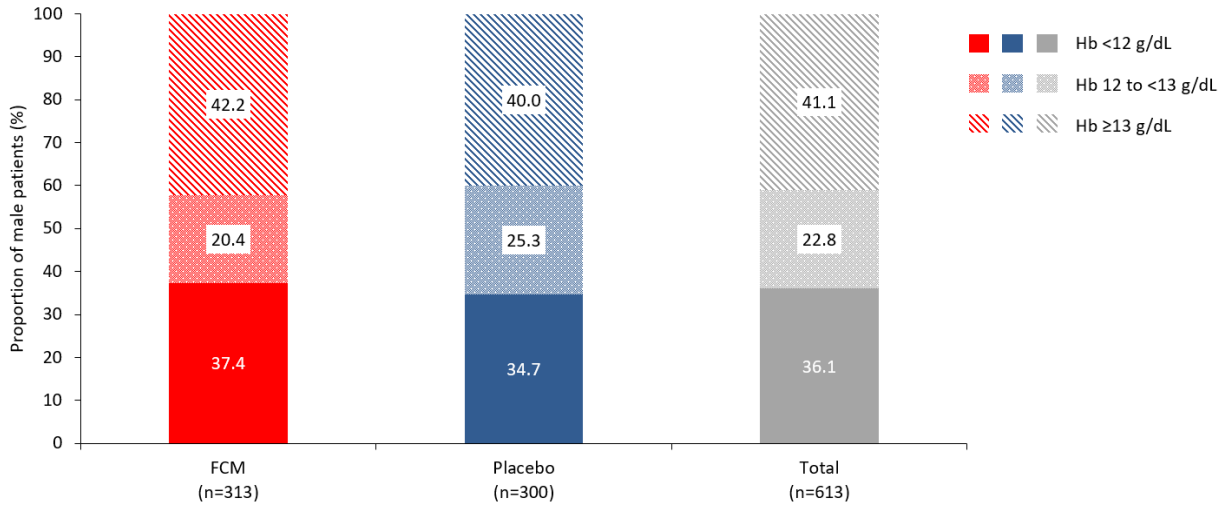
Table S5. Summary of Adverse Events Stratified by Normal and Low Hb Levels at Baseline According to the WHO Anemia Definition (SAS)

	Low Hb level* (n=606)				Normal Hb level† (n=503)			
	FCM (n=293)		Placebo (n=313)		FCM (n=265)		Placebo (n=238)	
Events, n (%)	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n	Patients, n (%)	Events, n
All adverse events	202 (68.9)	734	225 (71.9)	799	171 (64.5)	564	149 (62.6)	572
All TEAEs	195 (66.6)	711	215 (68.7)	769	161 (60.8)	534	145 (60.9)	545
Related to study drug	7 (2.4)	9	1 (0.3)	1	5 (1.9)	6	1 (0.4)	1
Leading to treatment discontinuation	41 (14.0)	49	48 (15.3)	52	19 (7.2)	21	31 (13.0)	36
Leading to hospitalization	123 (42.0)	285	151 (48.2)	342	103 (38.9)	198	106 (44.5)	219
Leading to study discontinuation	60 (20.5)	74	59 (18.8)	77	37 (14.0)	42	37 (15.5)	46
Serious TEAEs	134 (45.7)	325	168 (53.7)	390	115 (43.4)	221	114 (47.9)	242
Related to study drug	1 (0.3)	3	1 (0.3)	1	0	0	1 (0.4)	1
Fatal TEAEs	60 (20.5)	74	58 (18.5)	76	38 (14.3)	43	38 (16.0)	47
Related to study drug	0	0	0	0	0	0	0	0

The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into *the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and †the normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). FCM indicates ferric carboxymaltose; Hb, hemoglobin; SAS, safety analysis set; TEAE, treatment-emergent adverse event; and WHO, World Health Organization.

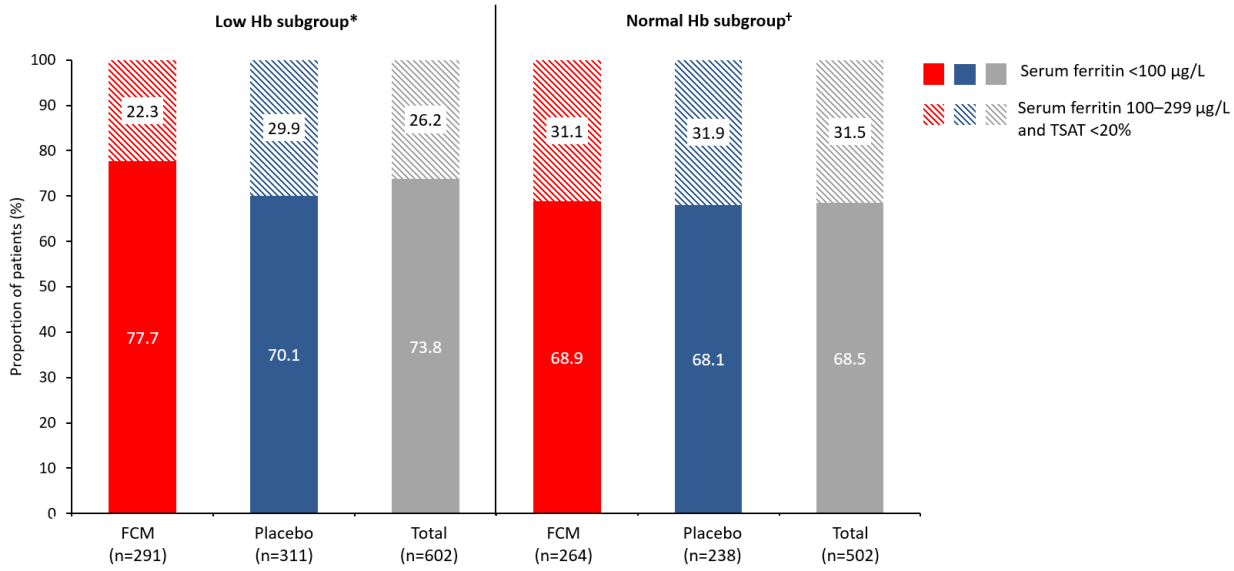
Supplemental Figures and Figure Legends

Figure S1. Proportion of male patients in Hb <12 g/dL, 12 to <13 g/dL, and ≥13 g/dL categories, at baseline



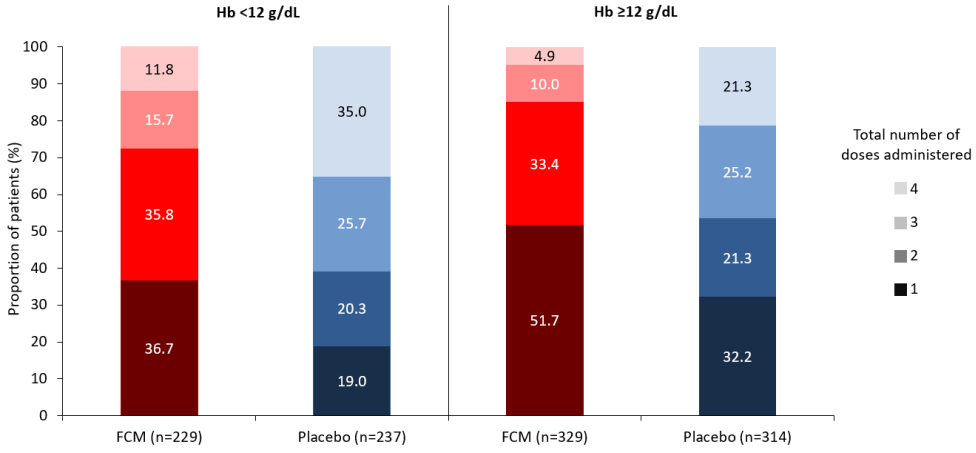
FCM indicates ferric carboxymaltose; and Hb, hemoglobin.

Figure S2. Proportion of patients with low and normal Hb levels at baseline according to the WHO definition of anemia who had iron deficiency defined as serum ferritin <100 µg/L and serum ferritin 100–299 µg/L with TSAT <20%



The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into *the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and †the normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Data were missing for one patient on FCM and one patient on placebo in the low Hb subgroup, and one patient on FCM in the normal Hb subgroup. Percentages are based on number of patients with data available. FCM indicates ferric carboxymaltose; Hb, hemoglobin; TSAT, transferrin saturation; and WHO, World Health Organization.

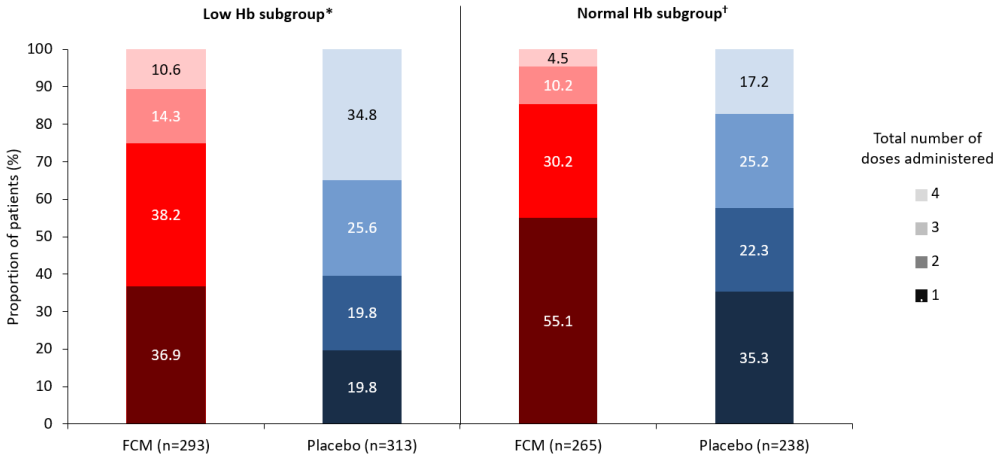
Figure S3. Treatment exposure stratified by baseline Hb level



Mean (SD) time on study drug, days	67.4 (69.6)	120.3 (72.0)	48.6 (63.7)	95.9 (77.3)
Mean (SD) cumulative dose administered, g	1.6 (0.6)	1.9 (0.6)	1.2 (0.5)	1.6 (0.7)

FCM indicates ferric carboxymaltose; Hb, hemoglobin; and SD, standard deviation.

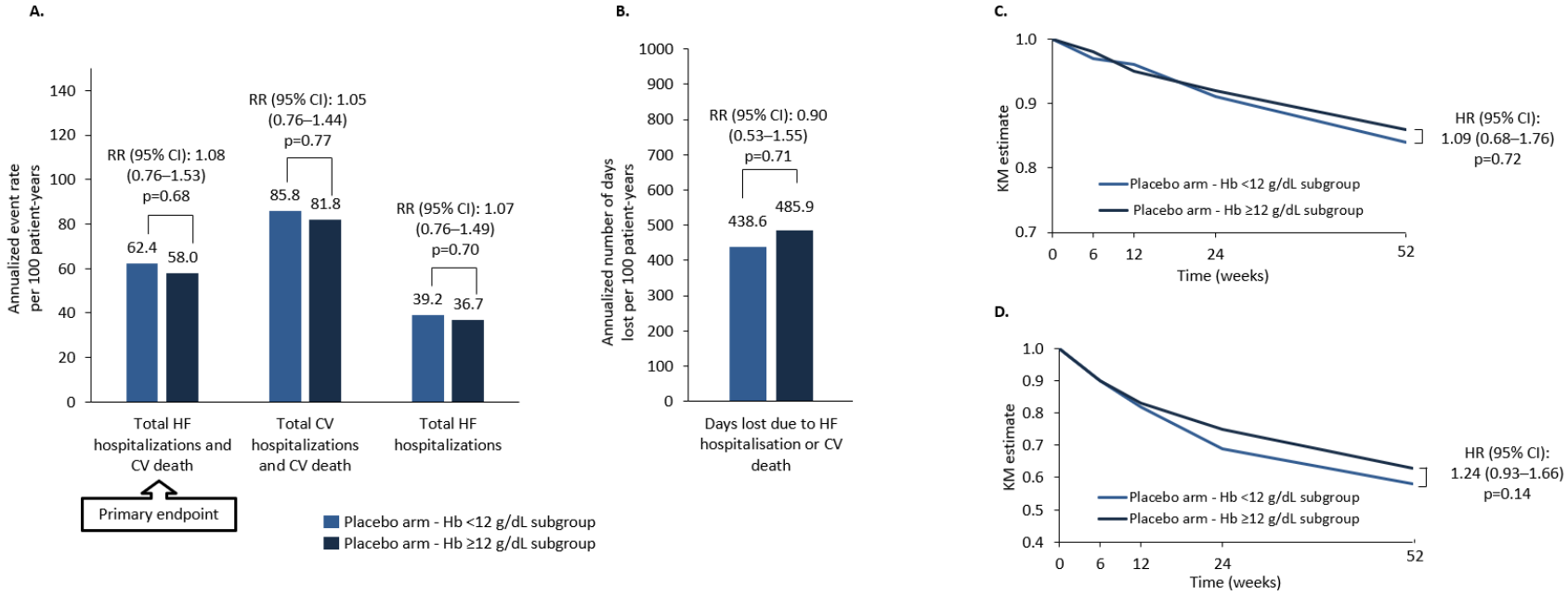
Figure S4. Treatment exposure by low and normal Hb levels according to the WHO definition of anemia



Mean (SD) time on study drug, days	64.98 (67.98)	117.34 (72.47)	46.69 (64.25)	91.99 (78.16)
Mean (SD) cumulative dose administered, g	1.537 (0.54)	1.919 (0.61)	1.149 (0.53)	1.467 (0.66)

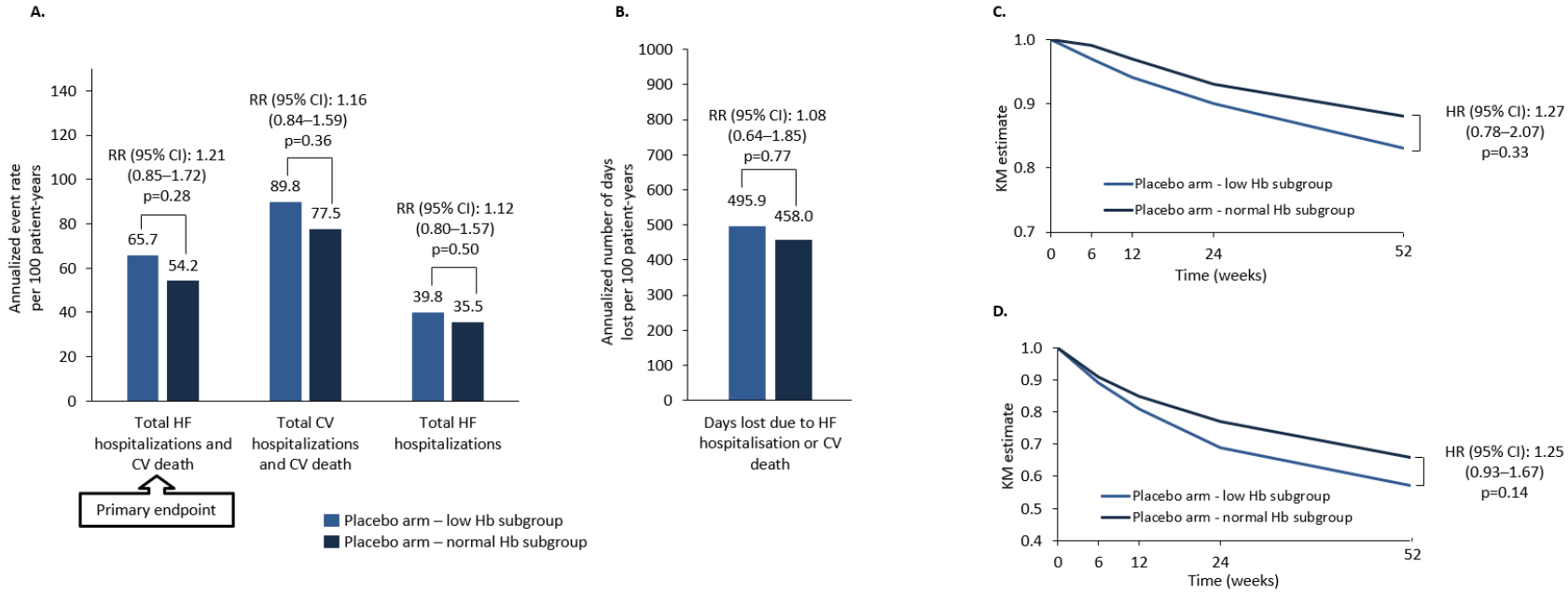
The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into *the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and †the normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). FCM indicates ferric carboxymaltose; Hb, hemoglobin; SD, standard deviation; and WHO, World Health Organization.

Figure S5. (A) Annualized event rates per 100 patient-years for primary and secondary outcomes; (B) annualized days lost to HF hospitalization or CV death per 100 patient-years; (C) Kaplan–Meier estimates for time to CV death; and (D) Kaplan–Meier estimates for time to first hospitalization or death, in the placebo arm of patients with Hb <12 g/dL and Hb ≥12 g/dL



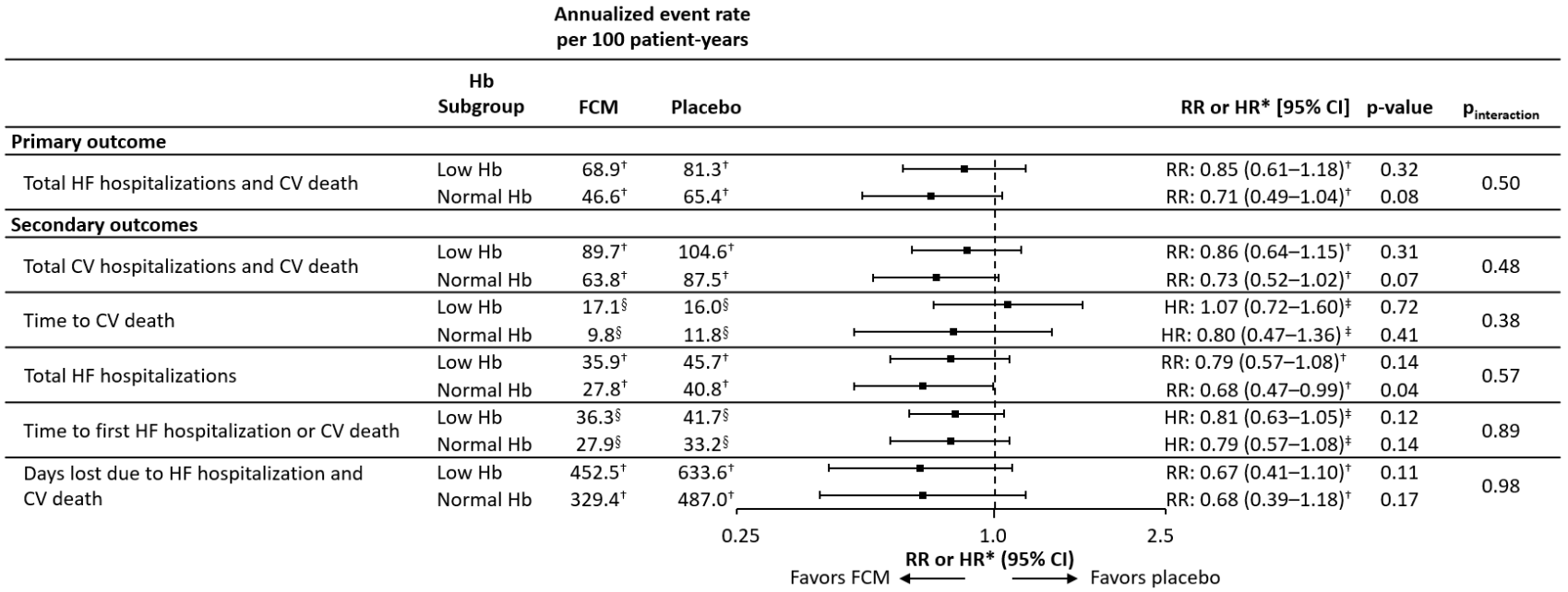
Annualized event RR for patients in the placebo group with Hb <12 g/dL vs Hb ≥12 g/dL were analyzed using a negative binomial model. HR for patients in the placebo group with Hb <12 g/dL vs Hb ≥12 g/dL were analyzed using a Cox regression model. Both models were adjusted for the following baseline covariates: sex, age, HF etiology, HF duration, country, and Hb <12 g/dL subgroup at baseline. Respective n-numbers for patients with Hb <12 g/dL vs Hb ≥12 g/dL at baseline assigned to the placebo arm were 236 and 314. CI indicates confidence interval; CV, cardiovascular; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; KM, Kaplan–Meier; and RR, rate ratio.

Figure S6. (A) Annualized event rates per 100 patient-years for primary and secondary outcomes; (B) annualized days lost to HF hospitalization or CV death per 100 patient-years; (C) Kaplan–Meier estimates for time to CV death; and (D) Kaplan–Meier estimates for time to first hospitalization or death, in the placebo arm of patients with low and normal Hb levels according to the WHO definition of anemia



The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Annualized event RRs for patients with low vs normal Hb levels were analyzed using a negative binomial model. HRs for patients with low vs normal Hb levels were analyzed using Cox regression model. Both models were adjusted for the following baseline covariates: sex, age, HF etiology, HF duration, country, and low Hb subgroup at baseline. Respective n-numbers for patients with low vs normal Hb level at baseline assigned to the placebo arm were 312 and 238. CI indicates confidence interval; CV, cardiovascular; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; KM, Kaplan–Meier; RR, rate ratio; and WHO, World Health Organization.

Figure S7. Primary and secondary outcomes stratified by patients with low and normal Hb levels according to the WHO definition of anemia

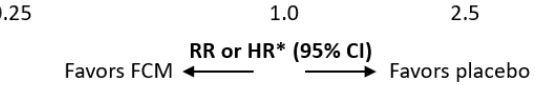


*RR or HR for FCM versus placebo in each subgroup. †Annualized event rate per 100 patient-years and RR analyzed using a negative binomial model. ‡HR for treatment difference analyzed using Cox regression model. §Percentage of patients with (at least one) event. The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Negative binomial model and Cox regression models both adjusted at baseline for: sex, age, HF etiology, HF duration, country, low Hb subgroup, and interaction between treatment group and low Hb subgroup. Respective n-numbers for patients with low and normal Hb levels according to the WHO definition were 292 and 265 for FCM and 312 and 238 for placebo. CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; RR, rate ratio; and WHO, World Health Organization.

Figure S8. Primary and secondary outcomes in the pre-COVID-19 sensitivity analysis set, with patients stratified according to (A) Hb level <12 g/dL versus ≥12 g/dL and (B) the WHO definition of anemia

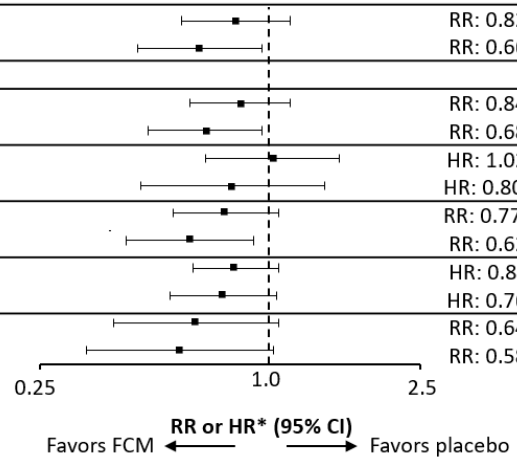
A.

	Hb Subgroup	Annualized event rate per 100 patient-years: FCM	Annualized event rate per 100 patient-years: Placebo	RR or HR* [95% CI]	p-value	$p_{interaction}$
Primary outcome						
Total HF hospitalizations and CV death	<12 g/dL	67.1†	71.2†	RR: 0.94 (0.64–1.38)†	0.76	0.10
	≥12 g/dL	43.7†	71.0†	RR: 0.62 (0.44–0.86)†	0.01	
Secondary outcomes						
Total CV hospitalizations and CV death	<12 g/dL	88.8†	92.6†	RR: 0.96 (0.68–1.36)†	0.82	0.09
	≥12 g/dL	61.6†	95.7†	RR: 0.64 (0.48–0.87)†	0.01	
Time to CV death	<12 g/dL	16.2§	15.3§	HR: 1.10 (0.69–1.75)‡	0.69	0.33
	≥12 g/dL	10.6§	12.7§	HR: 0.79 (0.50–1.25) ‡	0.32	
Total HF hospitalizations	<12 g/dL	35.1†	41.5†	RR: 0.85 (0.58–1.23)†	0.38	0.19
	≥12 g/dL	25.9†	42.8†	RR: 0.60 (0.43–0.84)†	0.003	
Time to first HF hospitalization or CV death	<12 g/dL	35.5§	40.3§	HR: 0.85 (0.63–1.15)‡	0.28	0.52
	≥12 g/dL	28.3§	35.0§	HR: 0.74 (0.56–0.98)‡	0.03	
Days lost due to HF hospitalization and CV death	<12 g/dL	403.6†	543.2†	RR: 0.74 (0.42–1.32)†	0.31	0.38
	≥12 g/dL	284.6†	543.9†	RR: 0.52 (0.32–0.87)†	0.01	



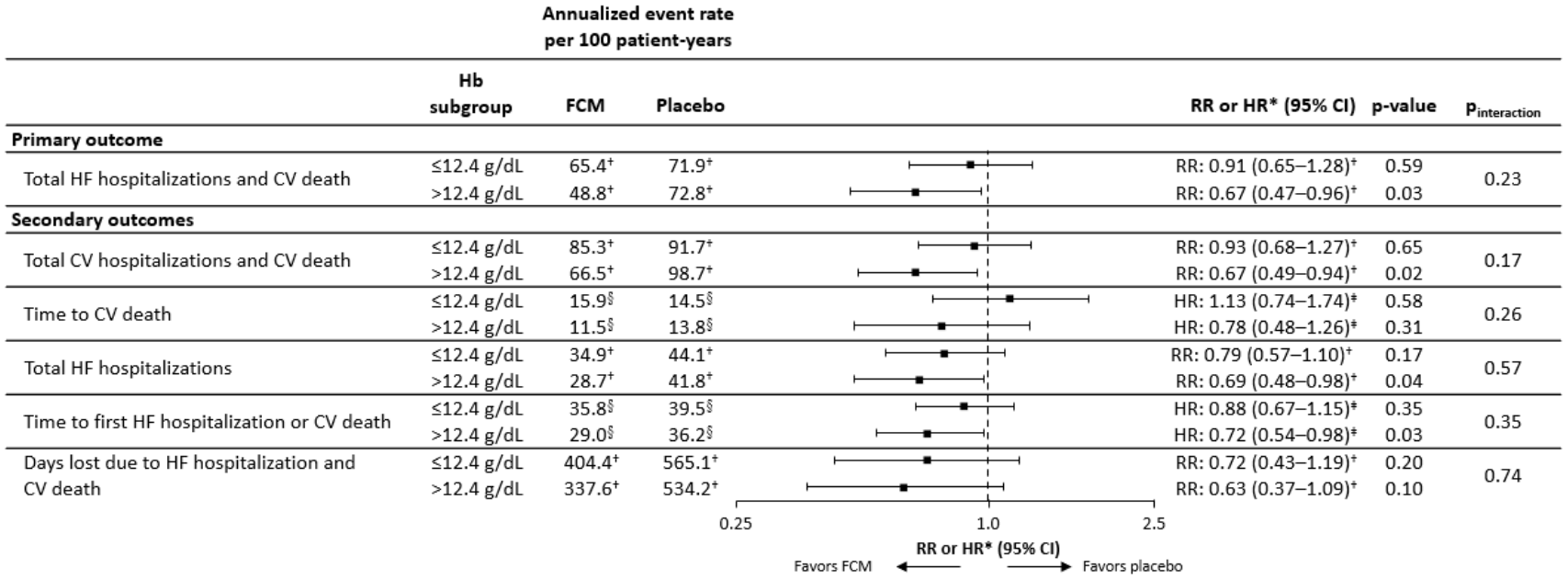
B.

	Hb Subgroup	Annualized event rate per 100 patient-years: FCM	Annualized event rate per 100 patient-years: Placebo	RR or HR*[95% CI]	p-value	$p_{interaction}$
Primary outcome						
Total HF hospitalizations and CV death	Low Hb	64.7†	78.9†	RR: 0.82 (0.59–1.14)†	0.24	0.39
	Normal Hb	41.8†	63.7†	RR: 0.66 (0.45–0.96)†	0.03	
Secondary outcomes						
Total CV hospitalizations and CV death	Low Hb	86.4†	102.5†	RR: 0.84 (0.62–1.14)†	0.27	0.36
	Normal Hb	58.7†	86.5†	RR: 0.68 (0.48–0.96)†	0.03	
Time to CV death	Low Hb	16.4§	16.0§	HR: 1.02 (0.68–1.53)‡	0.91	0.49
	Normal Hb	9.1§	10.9§	HR: 0.80 (0.46–1.40) ‡	0.44	
Total HF hospitalizations	Low Hb	33.8†	43.9†	RR: 0.77 (0.56–1.06)†	0.11	0.40
	Normal Hb	25.1†	40.4†	RR: 0.62 (0.42–0.91)†	0.01	
Time to first HF hospitalization or CV death	Low Hb	35.6§	40.7§	HR: 0.81 (0.63–1.06)‡	0.12	0.75
	Normal Hb	26.4§	32.8§	HR: 0.76 (0.55–1.05)‡	0.10	
Days lost due to HF hospitalization and CV death	Low Hb	393.2†	612.8†	RR: 0.64 (0.39–1.06)†	0.08	0.80
	Normal Hb	284.2†	489.7†	RR: 0.58 (0.33–1.03)†	0.06	



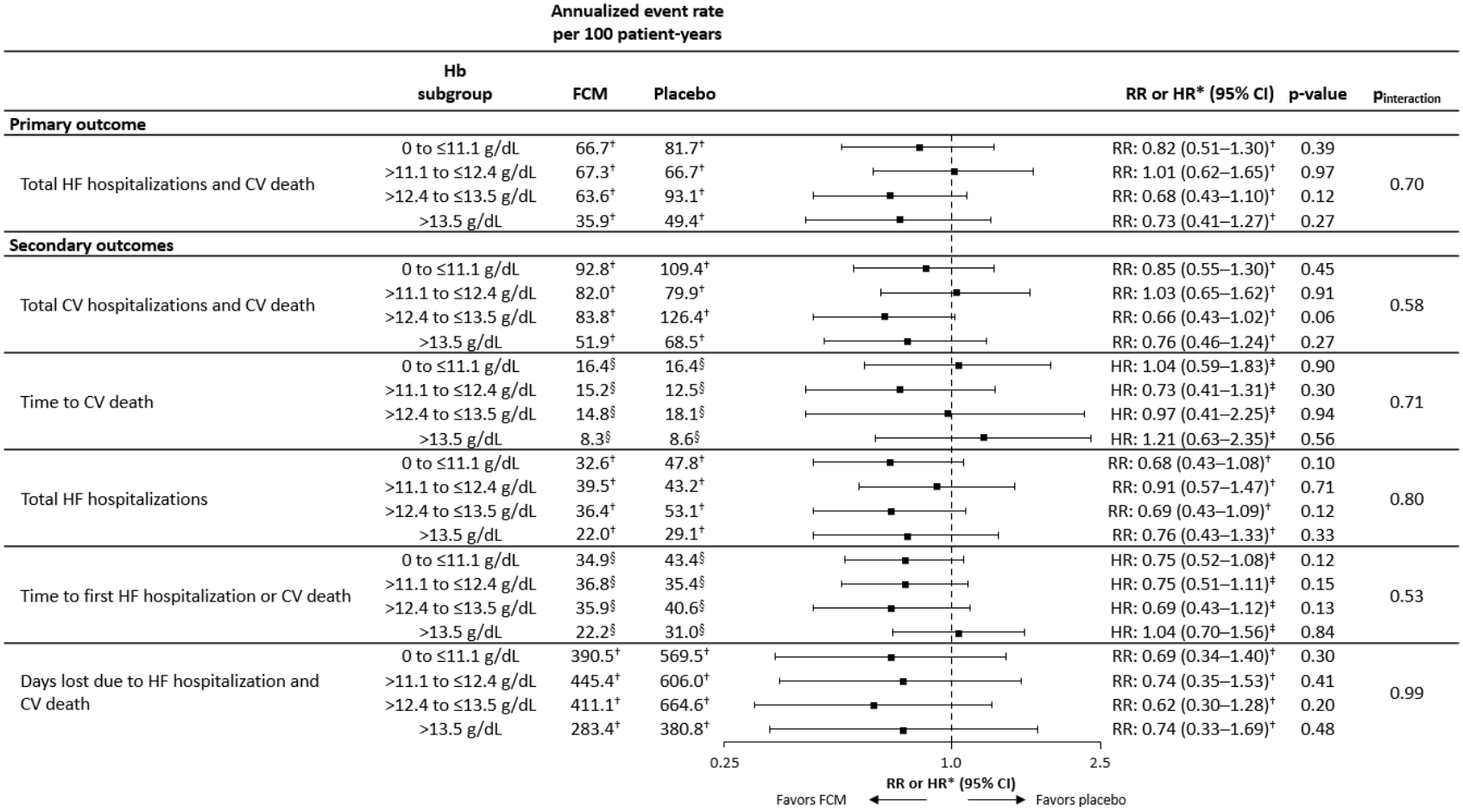
*RR or HR for FCM versus placebo in each subgroup. †Annualized event rate per 100 patient-years and RR analyzed using a negative binomial model. ‡HR for treatment difference analyzed using Cox regression model. §Percentage of patients with (at least one) event. The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Negative binomial model and Cox regression models both adjusted for baseline sex, age, HF etiology, HF duration, country, low Hb subgroup, and interaction between treatment group and low Hb subgroup. Respective n-numbers for patients with Hb <12 g/dL and ≥12 g/dL at baseline were 228 and 329 for FCM and 236 and 314 for placebo. Respective n-numbers for patients with low Hb and normal Hb at baseline according to the WHO definition of anemia were 292 and 265 for FCM and 312 and 238 for placebo. CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; pre-COVID-19, pre-coronavirus disease 2019; RR, rate ratio; and WHO, World Health Organization.

Figure S9. Primary and secondary outcomes at week 52 by baseline median Hb level



*RR or HR for FCM versus placebo in each subgroup. †Annualized event rate per 100 patient-years and RR analyzed using a negative binomial model. ‡HR for treatment difference analyzed using Cox regression model. §Percentage of patients with (at least one) event.
Patients were stratified into two subgroups according to median Hb level at baseline: Hb <12.4 g/dL and Hb ≥12.4 g/dL. Negative binomial model and Cox regression models both adjusted for baseline sex, age, HF etiology, country, Hb <12.4 g/dL versus ≥12.4 g/dL subgroup and interaction between treatment group and Hb <12.4 g/dL versus ≥12.4 g/dL subgroup. Respective n-numbers for patients with Hb ≤12.4 g/dL and >12.4 g/dL at baseline were 271 and 296 for FCM and 286 and 254 for placebo. CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; and RR, rate ratio.

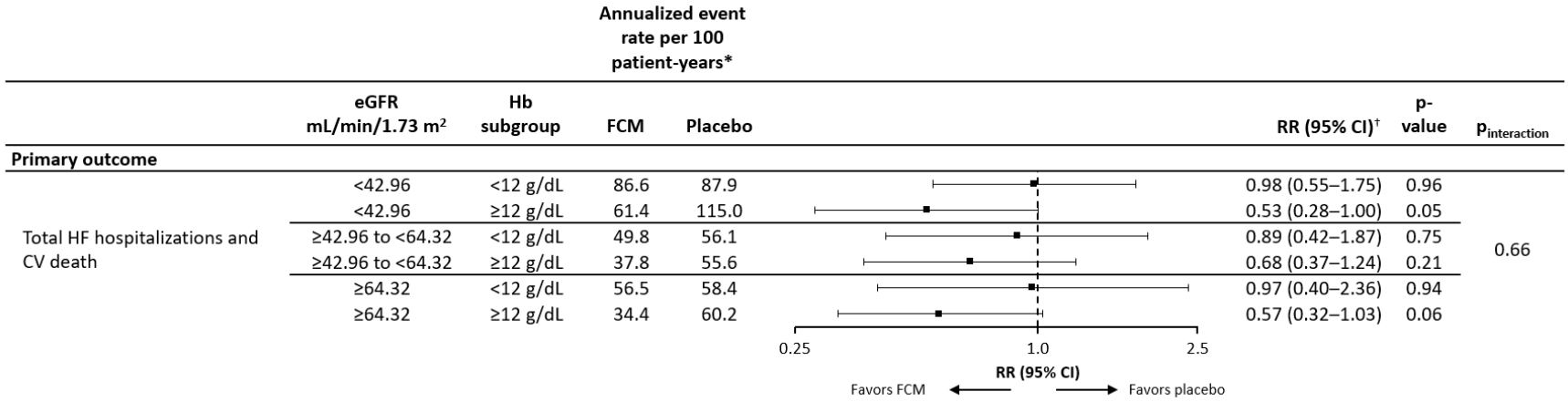
Figure S10. Primary and secondary outcomes at week 52 by baseline Hb quartiles



*RR or HR for FCM versus placebo in each subgroup. †Annualized event rate per 100 patient-years and RR analyzed using a negative binomial model. ‡HR for treatment difference analyzed using Cox regression model. §Percentage of patients with (at least one) event.
Patients were stratified into four subgroups according to Hb quartiles at baseline: Hb 0 to ≤11.1 g/dL, Hb >11.1 to ≤12.4 g/dL, Hb >12.4 to ≤13.5 g/dL, and Hb >13.5 g/dL. Negative binomial model and Cox regression models both adjusted for baseline sex, age, HF etiology, country, Hb quartile, and interaction between treatment group and Hb quartile. Respective n-numbers for patients with Hb 0 to ≤11.1 g/dL, >11.1 to

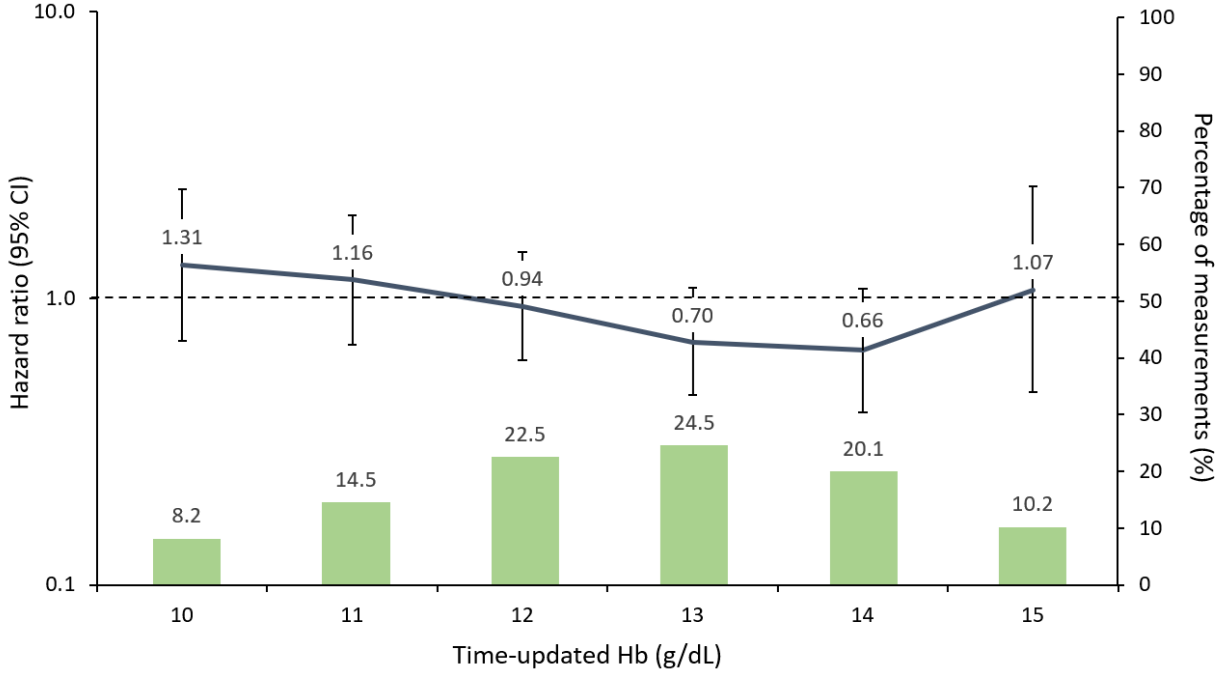
≤12.4 g/dL, >12.4 to ≤13.5 g/dL, and >13.5 g/dL at baseline were 146, 125, 142, and 144 for FCM and 152, 144, 138, and 116 for placebo.
CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; HR, hazard ratio; and RR, rate ratio.

Figure S11. Primary outcome at week 52 by baseline eGFR tertiles and Hb level



*Annualized event rate per 100 patient-years analyzed using a negative binomial model adjusted for baseline sex, age, HF etiology, country, Hb <12 g/dL subgroup, and interaction between treatment group and Hb <12 g/dL subgroup. †RR for FCM versus placebo in each subgroup. Respective n-numbers for patients with eGFR <42.96, ≥42.96 to <64.32, and ≥64.32 mL·min^{-1}·1.73 m^{-2} together with Hb <12 g/dL at baseline were 84, 61, and 48 for FCM and 98, 66, and 40 for placebo, and together with Hb ≥12 g/dL at baseline were 72, 105, and 116 for FCM and 67, 90, and 119 for placebo. CI indicates confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; Hb, hemoglobin; HF, heart failure; and RR, rate ratio.

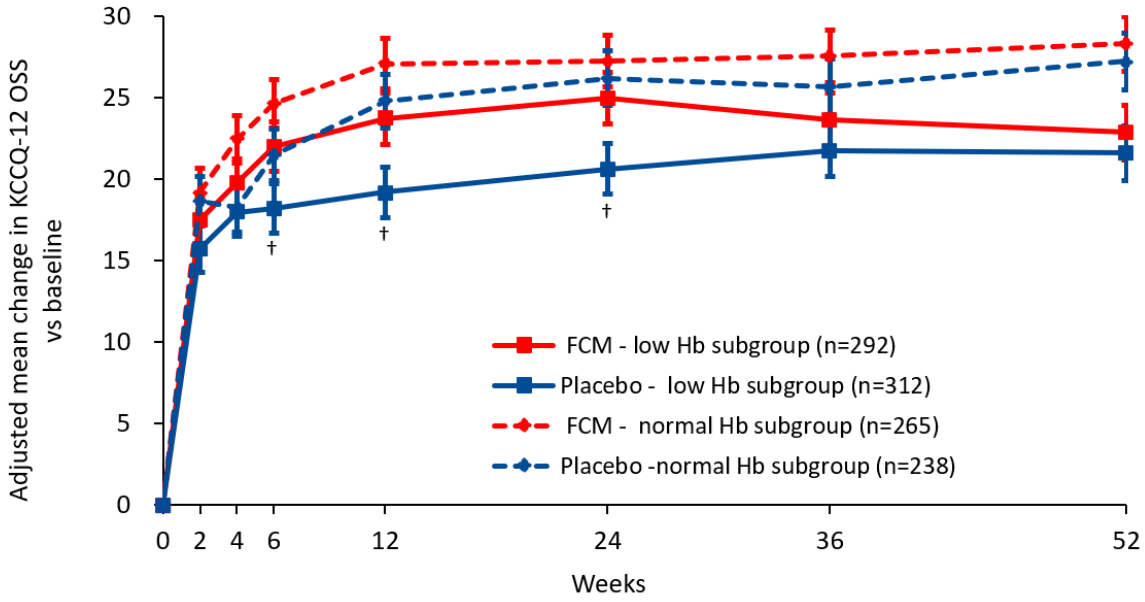
Figure S12. Relationship between time-updated Hb level and risk of HF hospitalizations or CV death up to week 52 with FCM vs placebo



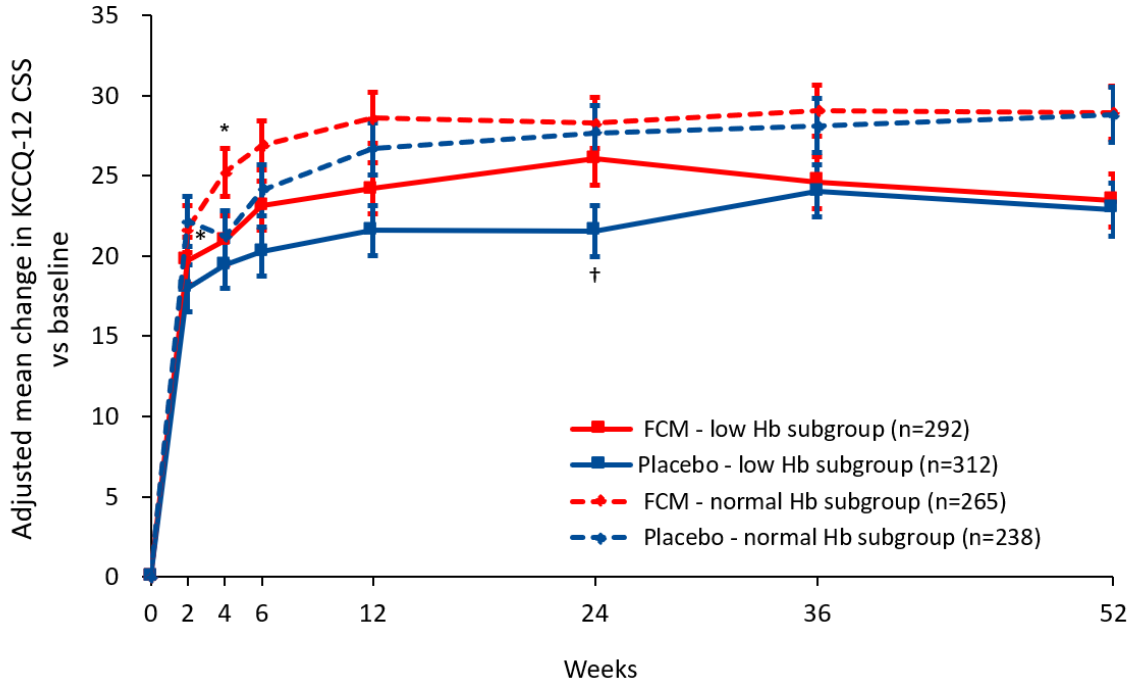
The blue line and error bars indicate the hazard ratio with 95% Wald CIs for the composite outcome of HF hospitalizations or CV death with FCM versus placebo up to week 52 (left y axis) in each time-updated Hb value (x-axis). The horizontal line represents a hazard ratio of 1; below the line indicates a lower risk of HF hospitalizations or CV death (composite outcome). The green bars indicate the frequency of an Hb value at any visit (right y-axis). For this analysis, Hb levels of 7, 8 ,9, 16, and 17 g/dL were excluded due to low patient numbers in at least one treatment group and where an event for 1 subject changed the figure; therefore, 80 patients (<10%) were excluded from the analysis. CI indicates confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; Hb, hemoglobin; and HF, heart failure.

Figure S13. Adjusted mean change in (A) KCCQ-12 OSS and (B) CSS in patients with low and normal Hb levels according to the WHO definition of anemia

A.



B.



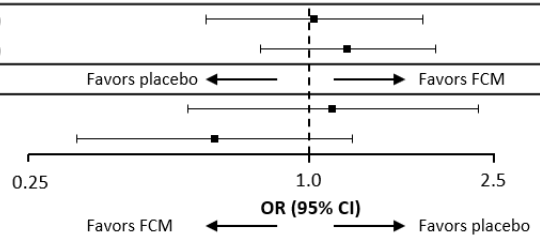
*p<0.05 for FCM vs placebo in normal Hb subgroup and †p<0.05 for FCM vs placebo in low Hb subgroup. The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Error bars are standard error of the mean. Estimates are based on a mixed-effect model of repeated measures using an

unstructured covariance matrix: change score = baseline score + treatment + visit + treatment × visit + subgroup + subgroup × visit + subgroup x treatment + subgroup x treatment × visit + baseline covariates. CSS indicates clinical summary score; FCM, ferric carboxymaltose; Hb, hemoglobin; KCCQ-12, 12-item Kansas City Cardiomyopathy Questionnaire; OSS, overall summary score; and WHO, World Health Organization.

Figure S14. Odds on an individual patient achieving a ≥5-point improvement or a ≥5-point deterioration in (A) KCCQ-OSS and (B) KCCQ-CSS at week 24, by Hb <12 g/dL versus ≥12 g/dL

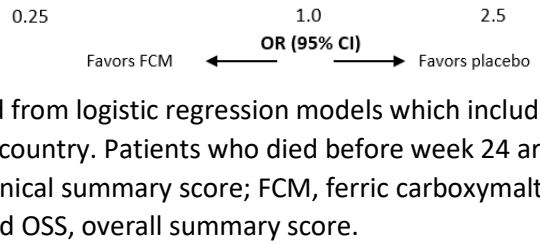
A.

KCCQ-OSS	Hb subgroup	FCM n/N (%)	Placebo n/N (%)	OR (95% CI)	p-value
Improvement at week 24					
≥5 points	<12 g/dL	130/173 (75.1)	137/183 (74.9)	1.027 (0.60–1.76)	0.92
	≥12 g/dL	202/260 (77.7)	187/251 (74.5)	1.213 (0.79–1.87)	0.38
Deterioration at week 24					
≥5 points	<12 g/dL	22/173 (12.7)	20/183 (10.9)	1.127 (0.55–2.31)	0.74
	≥12 g/dL	18/260 (6.9)	24/251 (9.6)	0.629 (0.32–1.24)	0.18



B.

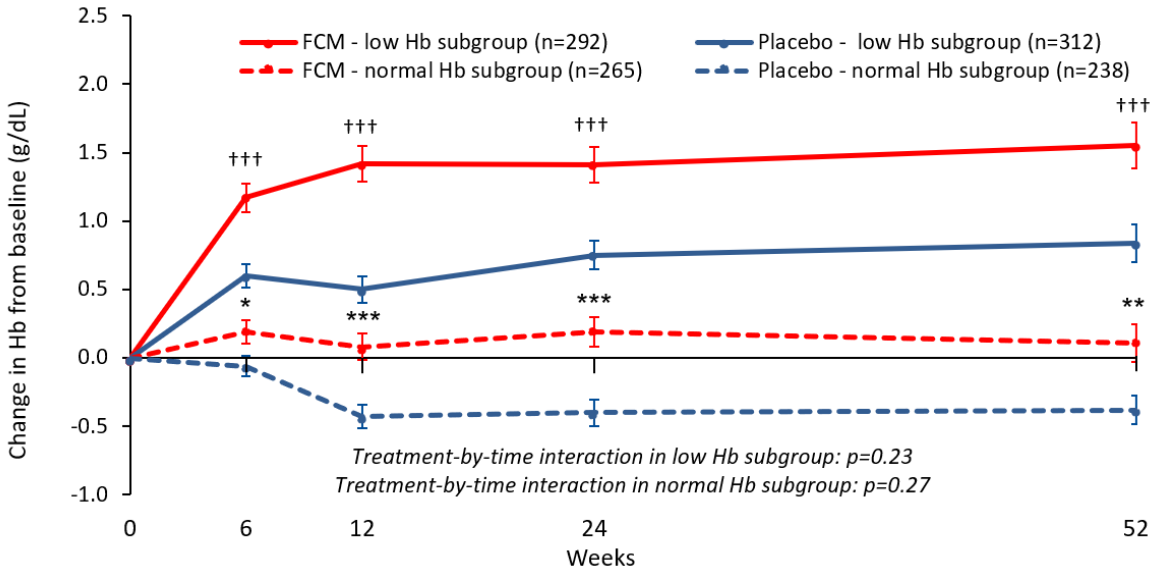
KCCQ-CSS	Hb subgroup	FCM n/N (%)	Placebo n/N (%)	OR (95% CI)	p-value
Improvement at week 24					
≥5 points	<12 g/dL	133/173 (76.9)	138/183 (75.4)	1.082 (0.63–1.86)	0.78
	≥12 g/dL	209/260 (80.4)	189/251 (75.3)	1.443 (0.92–2.26)	0.11
Deterioration at week 24					
≥5 points	<12 g/dL	22/173 (12.7)	26/183 (14.2)	0.776 (0.39–1.56)	0.48
	≥12 g/dL	22/260 (8.5)	29/251 (11.6)	0.605 (0.33–1.12)	0.11



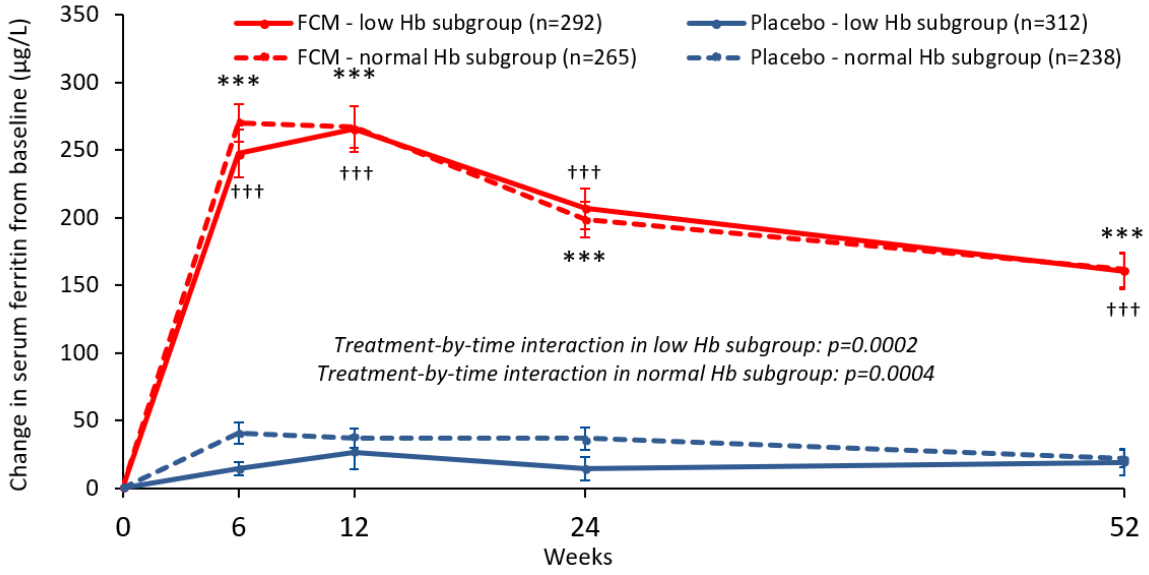
The odds ratios with confidence intervals and p-values were obtained from logistic regression models which included apart from the treatment group the baseline covariates sex, age, HF etiology, HF duration, and country. Patients who died before week 24 are counted as deteriorated/non-responder. CI indicates confidence interval; CSS, clinical summary score; FCM, ferric carboxymaltose; Hb, hemoglobin; KCCQ, Kansas City Cardiomyopathy Questionnaire; OR, odds ratio; and OSS, overall summary score.

Figure S15. Change versus baseline in (A) Hb, (B) serum ferritin, and (C) TSAT over time, and (D) details of FCM administration at each time point, stratified by low versus normal Hb levels according to the WHO definition of anemia

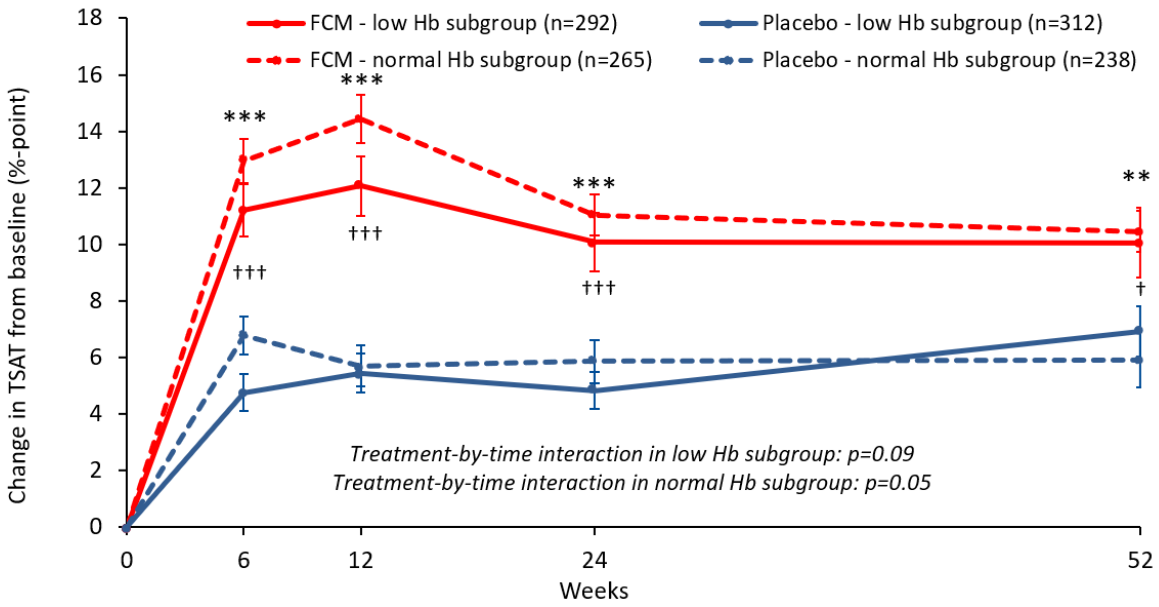
A.



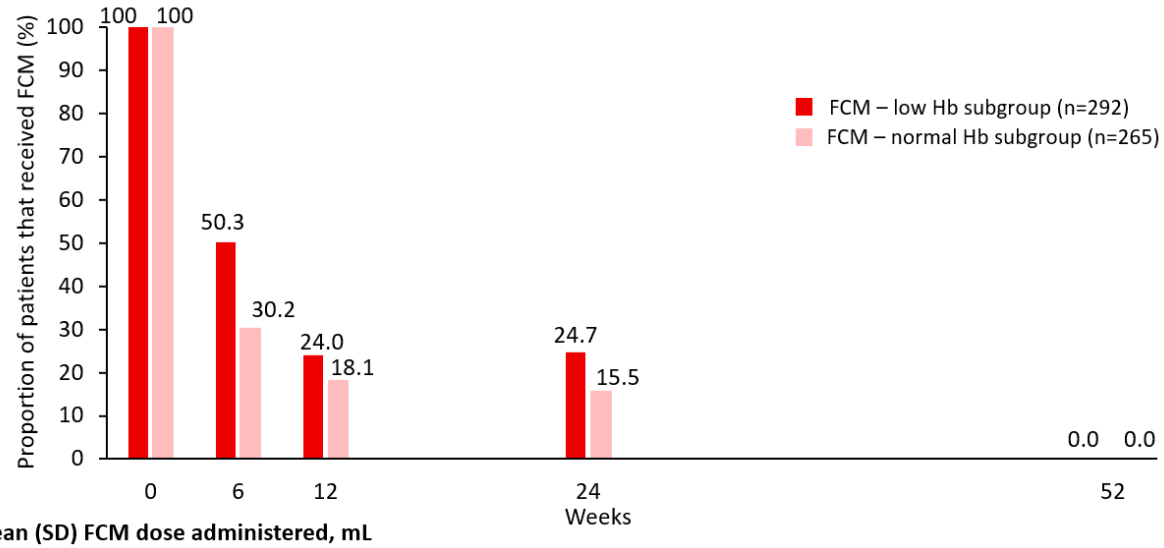
B.



C.



D.

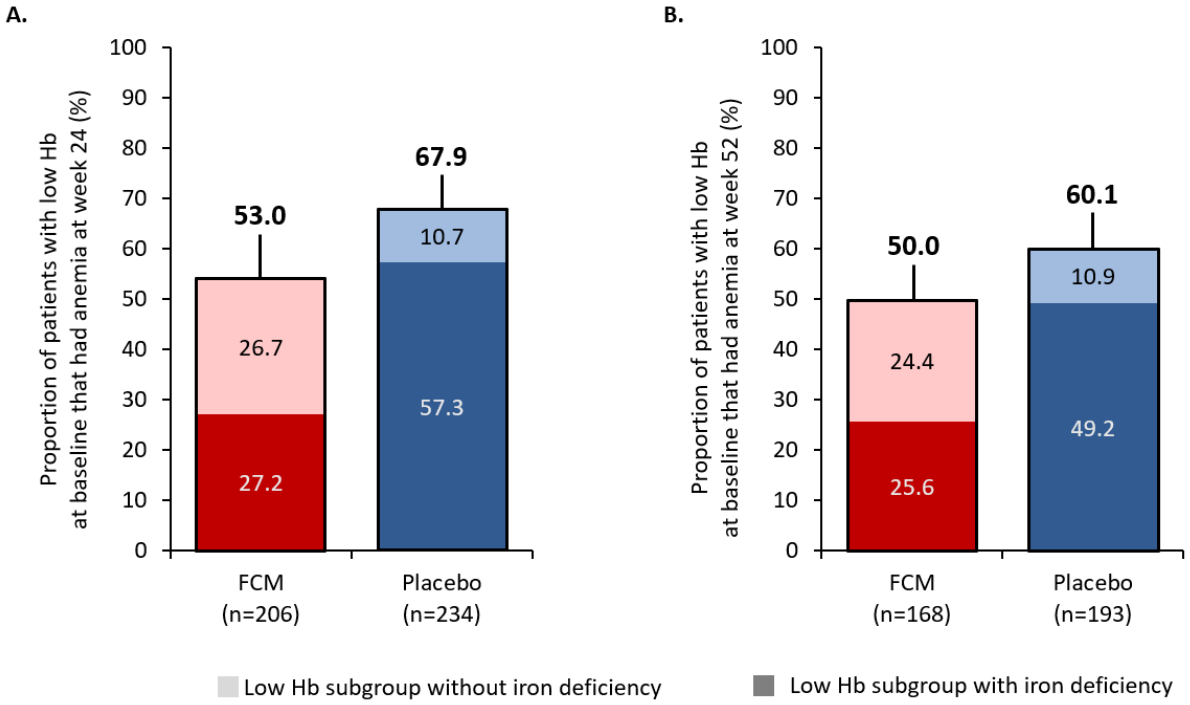


Mean (SD) FCM dose administered, mL

Week	0	6	12	24	52[§]
Low Hb subgroup	20.0 (0.0)	11.8 (3.9)	10.0 (0.0)	10.0 (0.0)	0
Normal Hb subgroup	16.6 (4.8)	10.0 (0.0)	10.0 (0.1)	10.2 (1.6)	0

*p<0.05, **p<0.01 and ***p<0.001 for FCM vs placebo in non-anemia subgroup and [†]p<0.05, [††]p<0.01 and [†††]p<0.001 for FCM vs placebo in anemia subgroup. [§]No study drug was administered after week 24, as per the protocol. The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). Error bars are standard error of the mean. FCM indicates ferric carboxymaltose; Hb, hemoglobin; SD, standard deviation; TSAT, transferrin saturation; and WHO, World Health Organization.

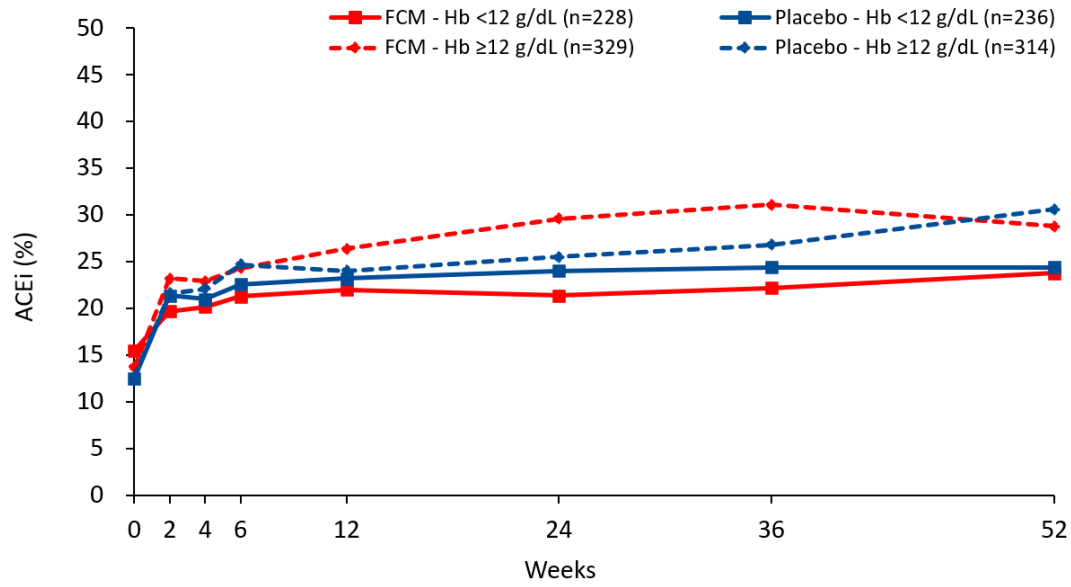
Figure S16. Proportion of patients within the low Hb subgroup, according to the WHO definition of anemia, at baseline who also had anemia at week 24 (A) and week 52 (B), and the proportion of these patients who had iron deficiency at the corresponding time point



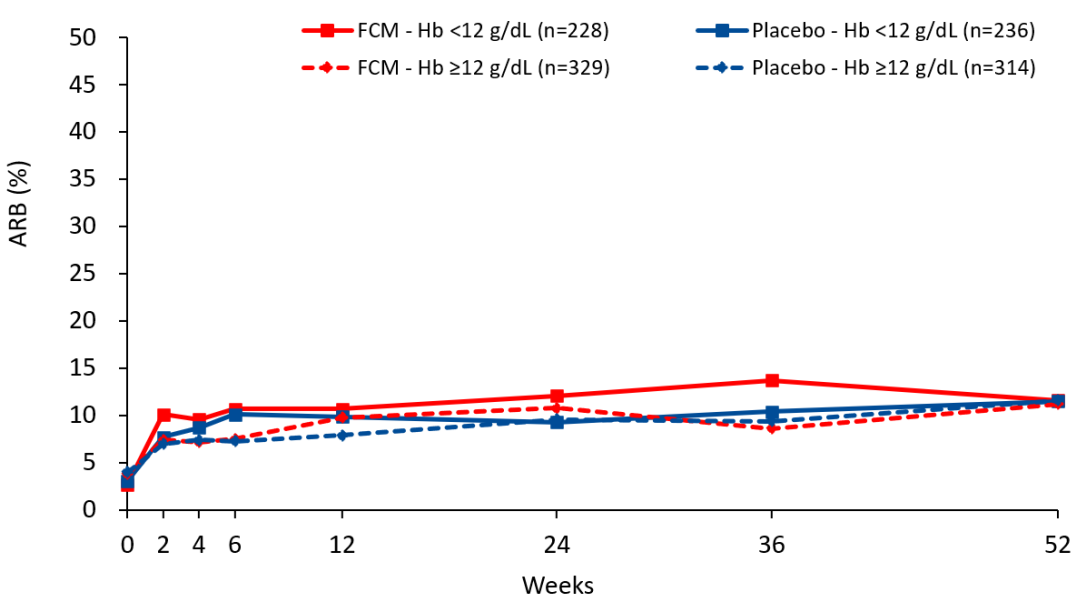
The WHO definition of anemia is Hb <12 g/dL in women and Hb <13 g/dL in men. Based on this definition, patients were stratified into the low Hb subgroup (Hb <12 g/dL in women and Hb <13 g/dL in men) and normal Hb subgroup (Hb ≥12 g/dL in women and Hb ≥13 g/dL in men). In A and B, 100% represents all patients who had anemia at baseline according to the WHO definition, who had non-missing data for anemia status and iron deficiency status at the respective time point. FCM indicates ferric carboxymaltose; Hb, hemoglobin; and WHO, World Health Organization.

Figure S17. Proportion of patients receiving (A) ACEi, (B) ARB, (C) ARNi, (D) MRA, and (E) beta blockers over 52 weeks treated with FCM and placebo, stratified by Hb level

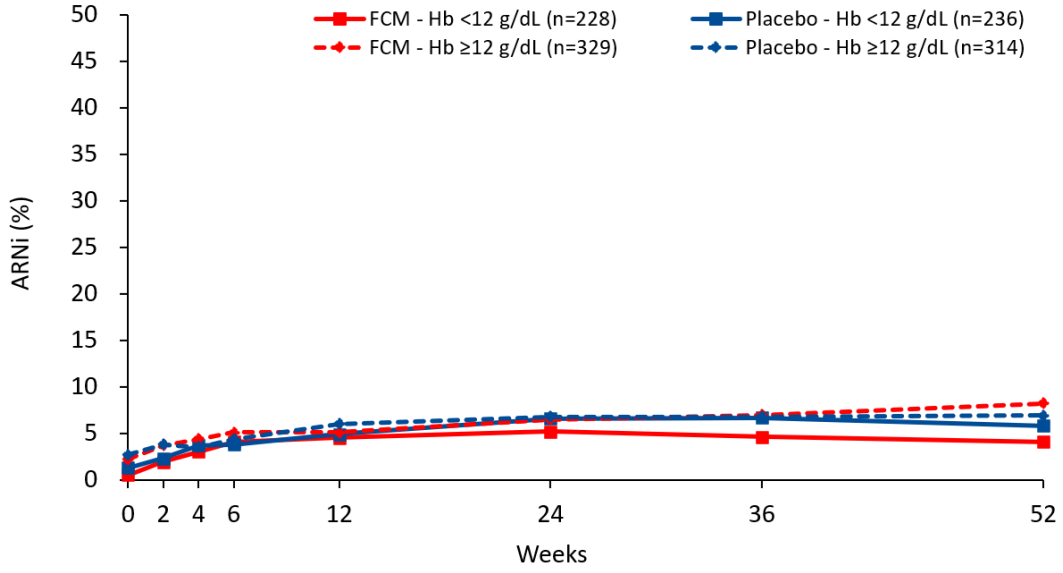
A.



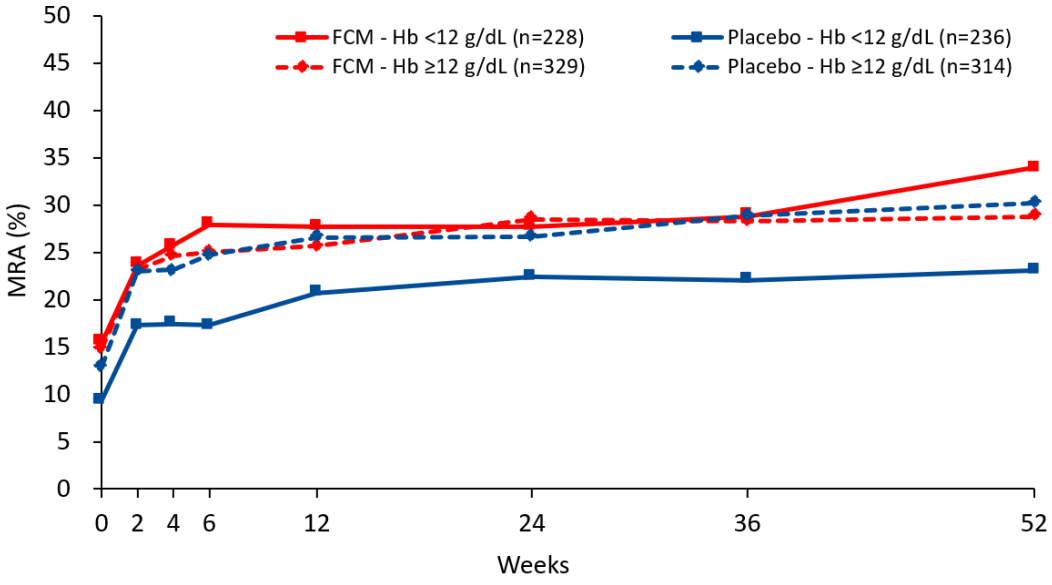
B.



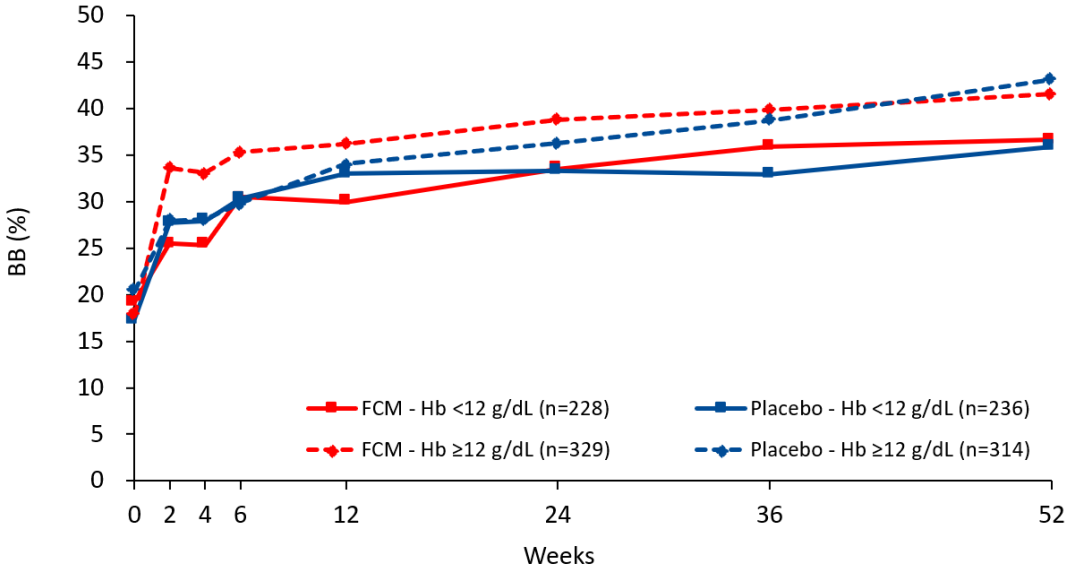
C.


FCM - Hb <12 g/dL (n=228)
FCM - Hb ≥12 g/dL (n=329)
Placebo - Hb <12 g/dL (n=236)
Placebo - Hb ≥12 g/dL (n=314)
ARNi (%)
50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 12 24 36 52
Weeks

D.


FCM - Hb <12 g/dL (n=228)
FCM - Hb ≥12 g/dL (n=329)
Placebo - Hb <12 g/dL (n=236)
Placebo - Hb ≥12 g/dL (n=314)
MRA (%)
50
45
40
35
30
25
20
15
10
5
0
0 2 4 6 12 24 36 52
Weeks

E.



Patients were stratified into two subgroups according to Hb level at baseline: Hb <12 g/dL (low Hb subgroup) and Hb ≥12 g/dL (normal Hb subgroup). Day of medication use at each week is based on the day the patient had a KCCQ assessment. Percentages are based on number of patients at each week and treatment group. ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; FCM, ferric carboxymaltose; Hb, hemoglobin; KCCQ, Kansas City Cardiomyopathy Questionnaire; and MRA, mineralocorticoid receptor antagonist.