2023 Focused Update of the 2021 ESC Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure

Recommendations for the management of iron deficiency in patients with heart failure

Recommendations	COR	LOE
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life.	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization.	IIa	A

HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

McDonagh TA, et al. *Eur Heart J*. Published online August 25, 2023. doi:10.1093/eurheartj/ehad195

IRONMAN Study Design

Inclusion criteria

Age ≥18 years

Left ventricular ejection fraction (LVEF) ≤45% within the last 2 years using any conventional imaging modality (most recent assessment)

NYHA class II-IV

Iron deficient – defined as transferrin saturation (TSAT) <20% and/or ferritin <100 ug/L

Evidence of being in a higher-risk heart failure group:

1. Current or recent (within 6 months) hospitalization for heart failure
2. Outpatients with NT-proBNP >250 ng/L in sinus rhythm or >1000 ng/L in atrial fibrillation (or BNP >75 pg/mL or 300 pg/mL, respectively)

Able and willing to provide informed consent

# of Patients	1,137
Diagnosis	Chronic HF (EF ≤ 45%)
Blinding	Open label
Study Arm	Ferric derisomaltose
Median Follow-Up	2.7 years (IQR 1.8-3.6)
Primary Endpoint	Hospitalizations for HF (first and recurrent) and CV death

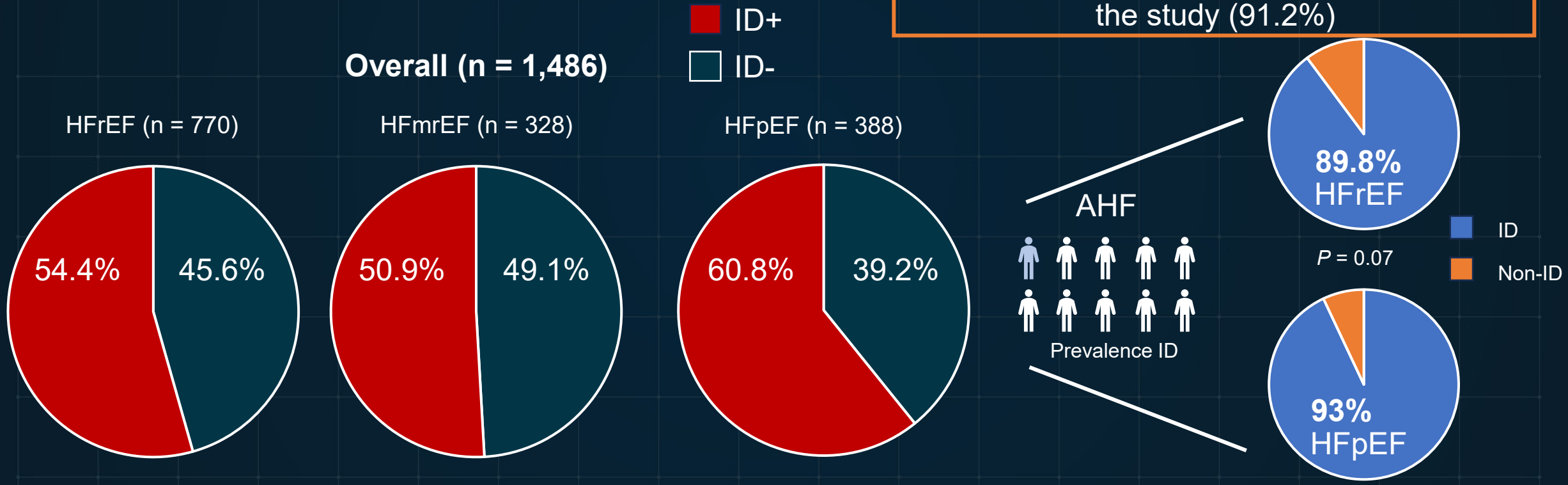
IRONMAN is a prospective, randomized, open-label, blinded-endpoint (PROBE) event-driven trial designed to assess the efficacy and safety of intravenous ferric derisomaltose in symptomatic patients with HFrEF and iron deficiency. The endpoints committee adjudicating events is kept blinded to assigned treatment.

Kalra PR, et al. *Lancet*. 2022;400(10369):2199-2209.

High Prevalence of Iron Deficiency in Patients with Chronic and Acute Heart Failure Across the EF Spectrum

ID prevalence 55% overall – Highest in HFpEF

ID was very common in the series of patients admitted for AHF who were included in the study (91.2%)



AHF, acute heart failure; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency.

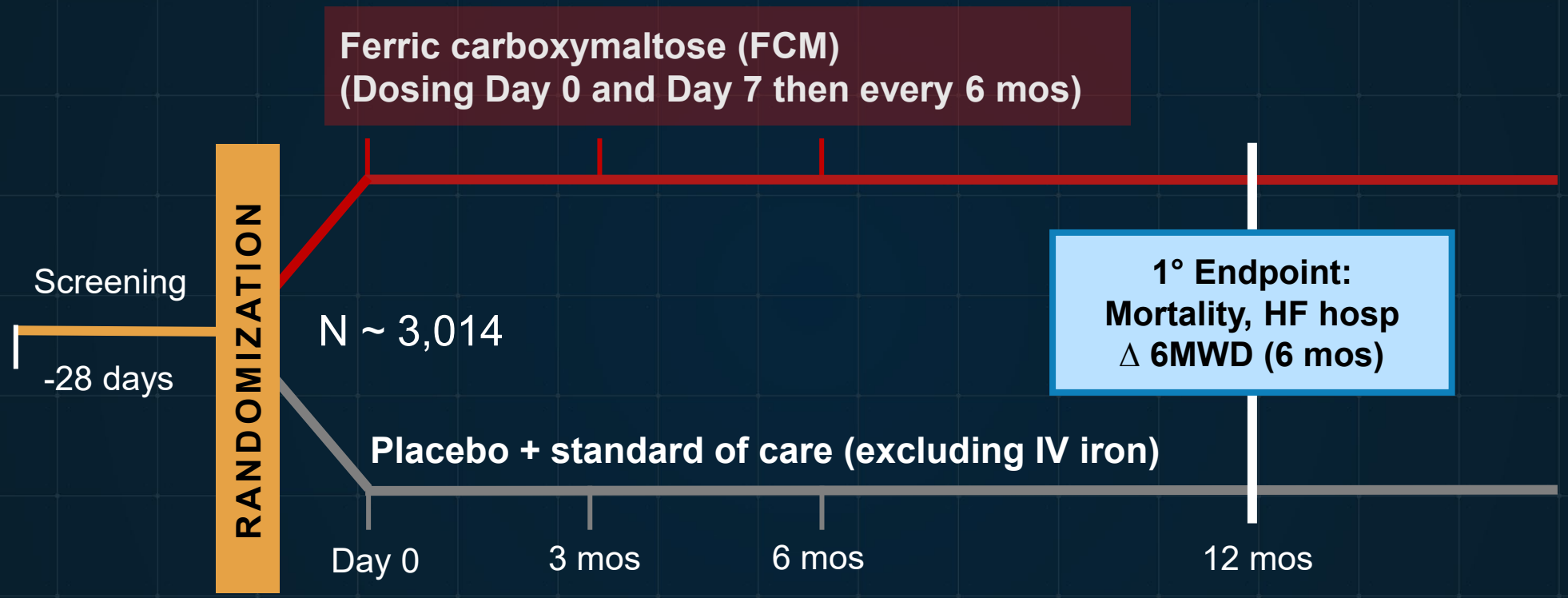
Lindberg F, et al. *Eur J Heart Fail*. Published online April 28, 2023. doi:10.1002/ejhf.2879

López-Vilella R, et al. *Life (Basel)*. 2022;12(11):1828.

HEART-FID

Largest randomized clinical trial to assess mortality and readmission in patients with HFrEF irrespective of anemia

Double-blind, placebo-controlled, event-driven trial (771 CVD + HF Hosp)



Chronic HF
EF ≤ 40%

750 mg FCM at day 0 & 7 = 1500 mg
(weight adjusted if <50 kg)

ClinicalTrials.gov Identifier:
NCT03037931

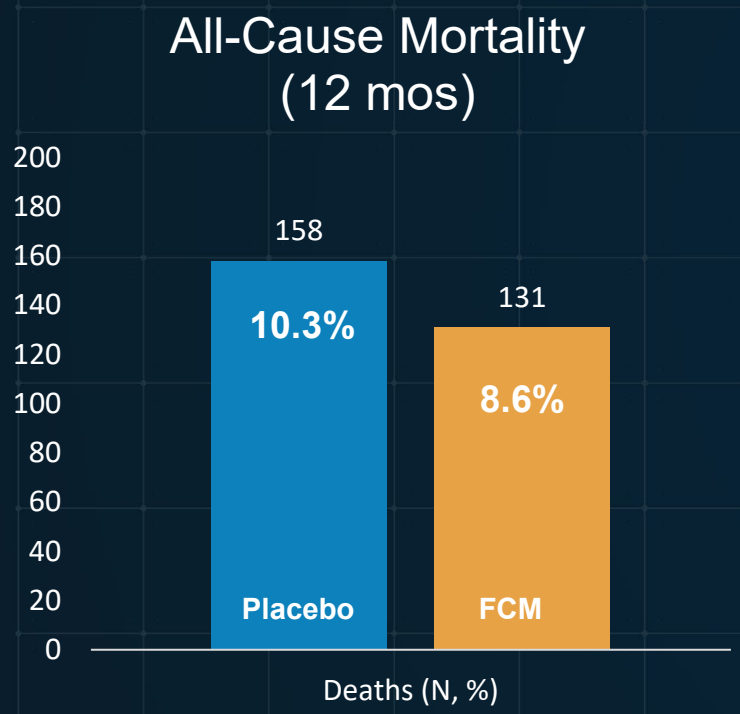
Mentz RJ, et al. *Circ Heart Fail*. 2021;14(5):e008100.

Study Characteristics

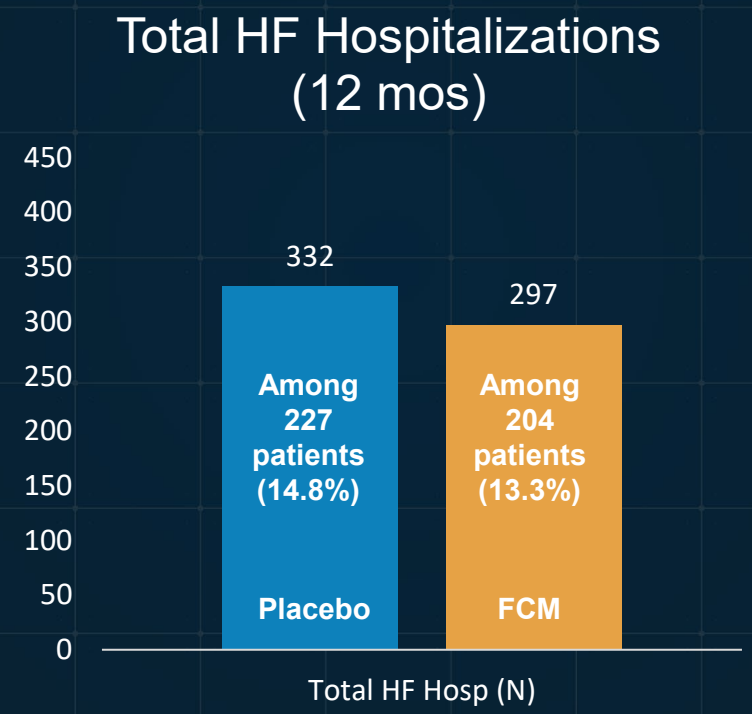
	HEART-FID
Randomization	1:1 (FCM:placebo)
Patients, n	1,532/1,533
Centers	Multicenter
Study duration, weeks	52
HF diagnosis and its severity	Ambulatory, optimally treated HF with ID, NYHA class II-IV, LVEF ≤40% within 24 months or ≤30% within 36 months of screening
Hemoglobin, g/dL	>9.0 and <13.5 (females) >9.0 and <15.0 (males)
Primary endpoint	Composite of (all cause) death and hospitalization for HF (12 months) and change in 6MWT distance (6 months)

6MWT, 6-minute walk test; FCM, ferric carboxymaltose; HF, heart failure; ID, iron deficiency; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Some endpoints not listed for each study because those data have not been published.
1. Ponikowski P, et al. *Eur Heart J*. 2015;36(11):657-668. 2. Ponikowski P, et al. *Lancet*. 2020;396(10266):1895-1904. 3. Kalra PR, et al. *Lancet*. 2022;400(10369):2199-2209. 4. Mentz RJ, et al. *N Engl J Med*. Published online August 26, 2023. doi:10.1056/NEJMoa2304968

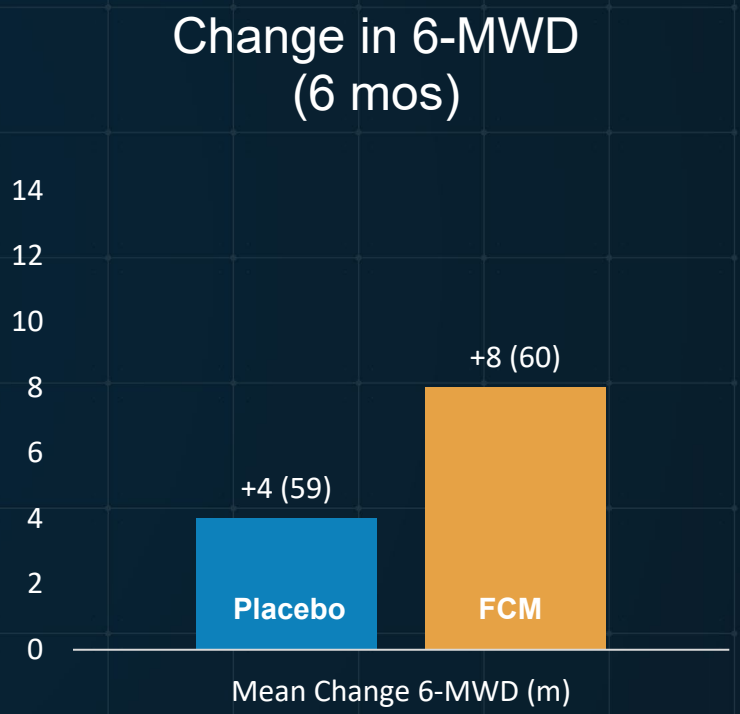
HEART-FID Primary Hierarchical Endpoint



1.7% ARR



270 fewer HF hospitalization days



6-MWD, 6-minute walk distance; ARR, absolute risk reduction; FCM, ferric carboxymaltose; HF, heart failure.

Mentz R, et al; HEART-FID Investigators. *N Engl J Med*. Published online August 26, 2023. doi:10.1056/NEJMoa2304968

Select Large and/or Ongoing HFrEF Trials

Study Name	AFFIRM-AHF	IRONMAN	HEART-FID	FAIR-HF-2
# of Patients	1,132	1,300	3,014	1,200
Diagnosis	Acute HF EF < 50%	Chronic HF EF < 45%	Chronic HF EF ≤ 40%	Chronic HF EF ≤ 45%
Blinding	Double blind	Open label	Double blind	Double blind
Study Arm	Ferric carboxymaltose	**Ferric derisomaltose**	Ferric carboxymaltose	Ferric carboxymaltose
Duration	52 weeks	120 weeks	Event driven + 12 mos last patient	Event driven + at least 12 mos f/u
Primary Endpoint	HF hospitalizations + CV death	CV death or HF hospitalizations	All-cause mortality + total HF hospitalizations through 12 mos and 6-month 6MWD	HF hospitalizations + CV death
Anticipated Completion Date	**Completed**	**Completed**	**Completed**	**May 2024**

von Haehling S, et al. *JACC Heart Fail.* 2019;7(1):36-46.

Study Characteristics

	Individual Patient Data			Study Level Data
	CONFIRM-HF	AFFIRM-AHF	HEART-FID	IRONMAN
Randomization	1:1 (FCM:placebo)	1:1 (FCM:placebo)	1:1 (FCM:placebo)	1:1 (FDI:usual care)
Patients, n	150/151	558/550	1,532/1,533	569/568
Centers	Multicenter	Multicenter	Multicenter	Multicenter
Study duration, weeks	52	52	52	140
HF diagnosis and its severity	Ambulatory, optimally treated, systolic CHF with ID, NYHA class II/III	Hospitalization for acute HF, treatment with IV furosemide at a dose of 40 mg, LVEF <50%	Ambulatory, optimally treated HF with ID, NYHA class II-IV, LVEF ≤40% within 24 months or ≤30% within 36 months of screening	Current or recent admission for HF (LVEF <45%) or elevated concentrations of natriuretic peptides
Hemoglobin, g/dL	<15	<15	>9.0 and <13.5 (females) >9.0 and <15.0 (males)	9-14
Primary endpoint	Change in 6MWT from baseline to week 24	Composite of recurrent events of HF hospitalization and CV death	Composite of (all cause) death and hospitalization for HF (12 months), and change in 6MWT distance (6 months)	Composite of recurrent events of HF hospitalization and CV death

6MWT, 6-minute walk test; CHF, congestive heart failure; CV, cardiovascular; FCM, ferric carboxymaltose; FDI, ferric derisomaltose; HF, heart failure; ID, iron deficiency; IV, intravenous; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.
Some endpoints not listed for each study because those data have not been published.

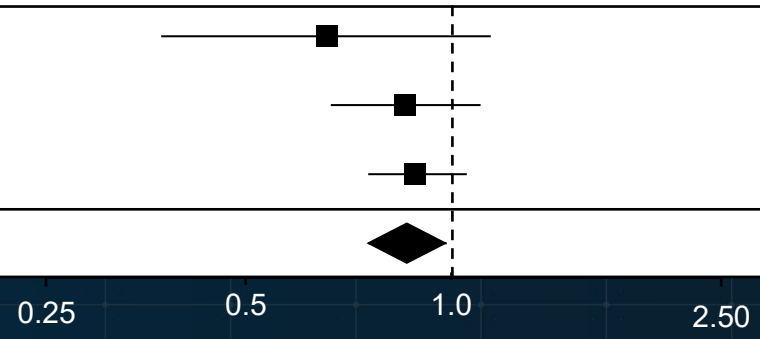
1. Ponikowski P, et al. *Eur Heart J*. 2015;36(11):657-668. 2. Ponikowski P, et al. *Lancet*. 2020;396(10266):1895-1904. 3. Kalra PR, et al. *Lancet*. 2022;400(10369):2199-2209. 4. Mentz RJ, et al. *N Engl J Med*. Published online August 26, 2023. doi:10.1056/NEJMoa2304968

Co-Primary Meta-Analysis Endpoints

Total CV Hospitalizations + CV Death

Study	FCM n/N (%)	PBO n/N (%)	Rate ratio (95% CI)	*P* value
CONFIRM-HF	28/150 (18.7)	38/151 (25.2)	0.65 (0.37–1.14)	0.131
AFFIRM-AHF	218/558 (39.1)	252/550 (45.8)	0.85 (0.66–1.10)	0.216
HEART-FID	371/1529 (24.3)	391/1532 (25.5)	0.88 (0.75–1.05)	0.150
Overall	**617/2237 (27.6)**	**681/2233 (30.5)**	**0.86 (0.75–0.98)**	**0.029**

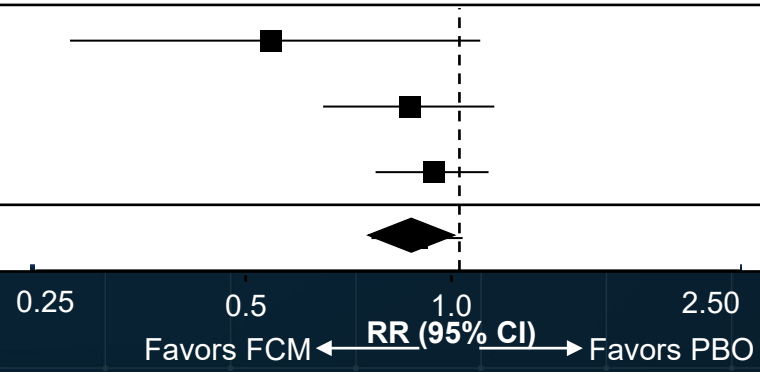
Cochran Q: 0.008; *P* = 0.996



Total HF Hospitalizations + CV Death

Study	FCM n/N (%)	PBO n/N (%)	Rate ratio (95% CI)	*P* value
CONFIRM-HF	18/150 (12.0)	31/151 (20.5)	0.54 (0.28–1.07)	0.079
AFFIRM-AHF	189/558 (33.9)	216/550 (39.3)	0.85 (0.64–1.12)	0.242
HEART-FID	296/1529 (19.4)	316/1532 (20.6)	0.92 (0.76–1.10)	0.356
Overall	**503/2237 (22.5)**	**563/2233 (25.2)**	**0.87 (0.75–1.01)**	**0.076**

Cochran Q: 0.024; *P* = 0.988



Ponikowski P, et al. *Eur Heart J*. Published online August 26, 2023. doi:10.1093/eurheartj/ehad586

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HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction.

McDonagh TA, et al. *Eur Heart J*. Published online August 25, 2023. doi:10.1093/eurheartj/ehad195

Quote by Ovidiu Chioncel, MD

“Iron deficiency treated with IV ferric carboxymaltose, totality of evidences are going in the same direction. I think that it's very encouraging for clinicians to start to identify, to assess, and to treat iron deficiency.”

Quote by Antoni Bayés-Genís, MD

“We need to look for iron deficiency of both in the chronic setting and in the hospital, because we will see that more often than we expect.”

Quote by Antoni Bayés-Genís, MD

“We need to pay more attention to the presence of iron deficiency in spite of normal hemoglobin levels.”

2021 ESC/HFA

Recommendations for the management of anemia and iron deficiency in patients with heart failure

Recommendations	Class	Level
It is recommended that all patients with HF be periodically screened for anemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100-299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100-299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization	IIa	B

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HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricle ejection fraction; QOL, quality of life; TSAT, transferrin saturation.

McDonagh TA, Metra M, et al. *Eur Heart J*. 2021;42(36):3599-3726.

McDonagh TA, et al. *Eur Heart J*. Published online August 25, 2023. doi:10.1093/eurheartj/ehad195