TERAPIA DELL'IRON DEFICIENCY PER IL RISCHIO EVITABILE DI EVENTI NELLO SCOMPENSO CARDIACO ACUTO

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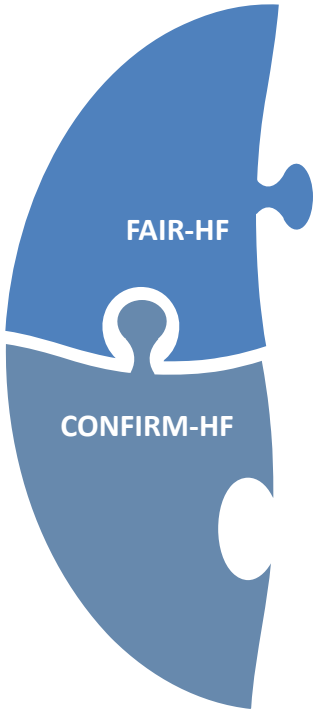
FCM* IMPROVES OUTCOMES FOR PATIENTS with STABLE HfrEF and iD

Randomized clinical trials such as FAIR-HF[1] and CONFIRM-HF[2] have shown that treatment with FCM improves functional capacity, exercise tolerance, symptoms, and quality of life in stable HF with reduced ejection fraction (HFrEF) patients with ID up to 52 weeks.



*** FCM = Ferrocarbossimaltosio**

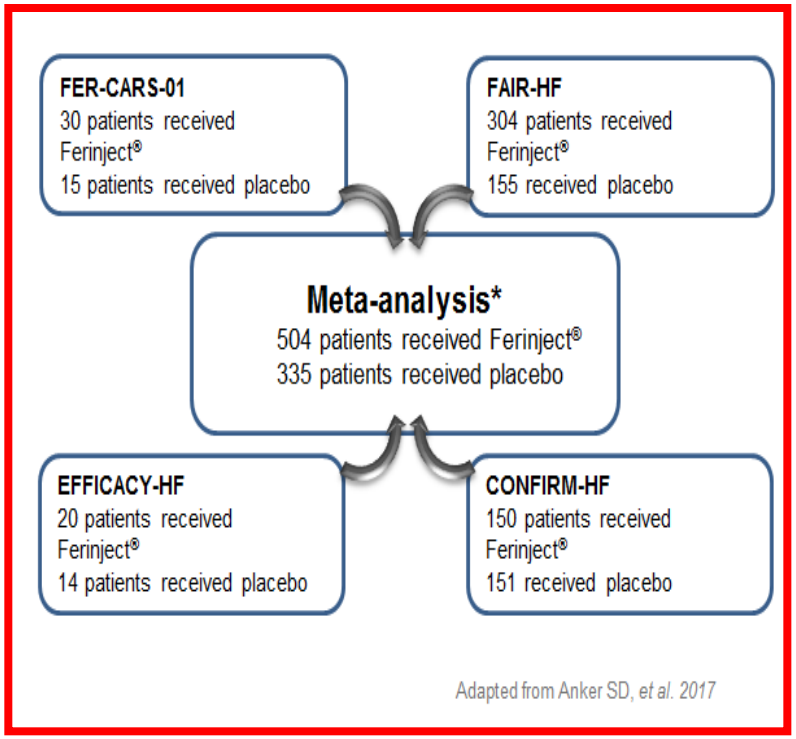
1. Anker SD et al. N Engl J Med. 2009; 2. Ponikowski P et al. Eur Heart J. 2015;

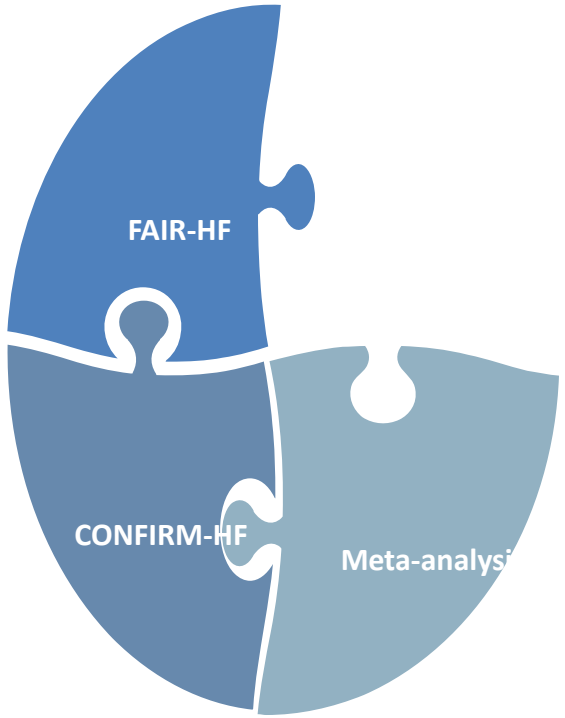
LINEE GUIDA ESC 2016

Recommendations	Class [a]	Level [b]
Iron deficiency		
Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.	IIa	A

HF PTS WITH ID HOSPITALIZED FOR AN ACUTE EPISODE

An individual patient data meta-analysis also suggested that treatment of ID with FCM in ambulatory HFrEF patients may decrease recurrent CV hospitalisations.[3]





Anker SD et al. Eur. J of Heart Failure 2017

Riduzione delle ospedalizzazioni

Table 3 Recurrent event outcomes

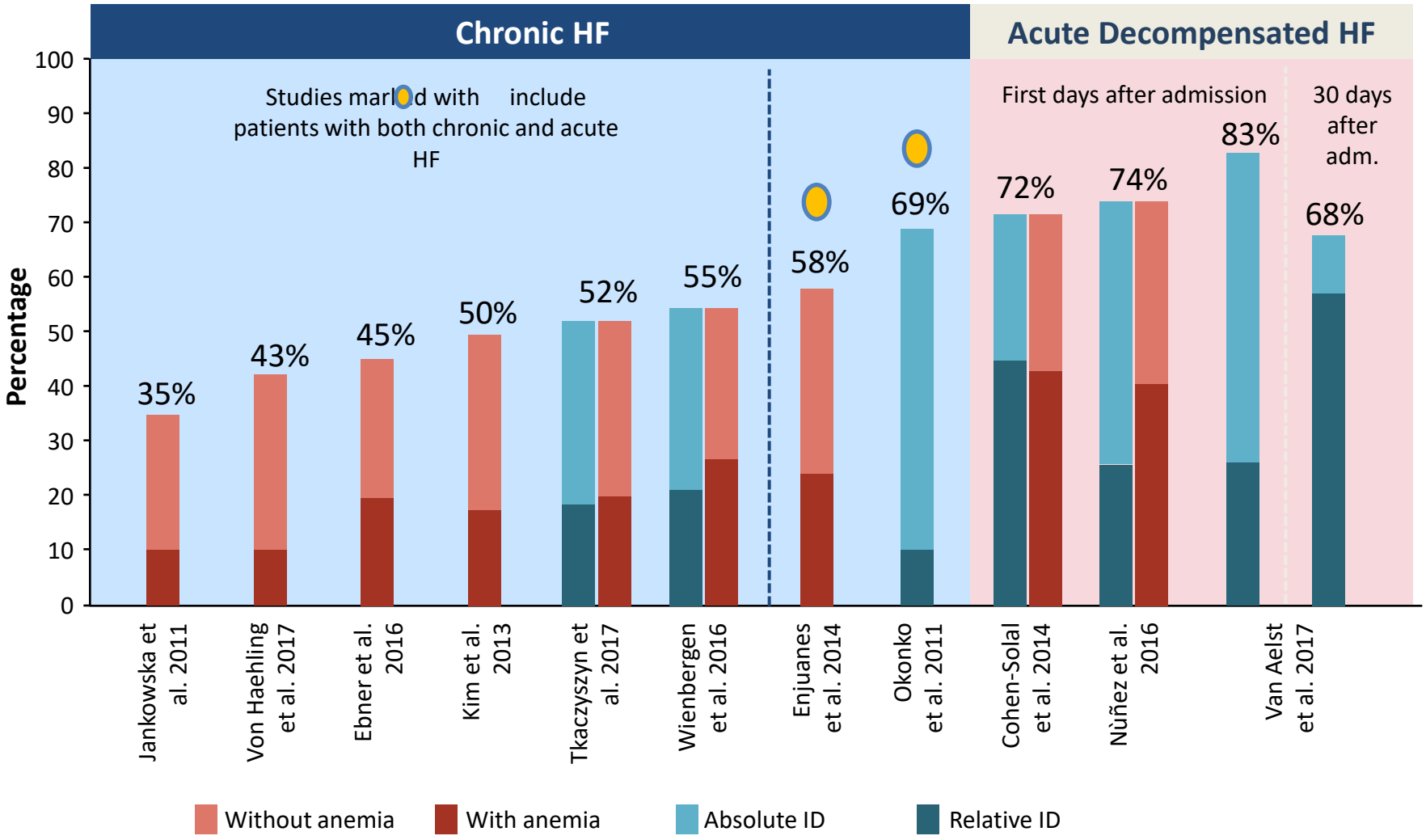
Outcomes	Total events, *n* (incidence per 100 patient-years of follow-up)		RR (95% CI)	*P*-value
	FCM pool (*n* = 504)	Placebo pool (*n* = 335)		
CV hospitalisations and CV mortality	69 (23.0)	92 (40.9)	0.59 (0.40–0.88)	0.009
HF hospitalisations and CV mortality	39 (13.0)	60 (26.7)	0.53 (0.33–0.86)	0.011
CV hospitalisations and all-cause mortality	71 (23.7)	94 (41.8)	0.60 (0.41–0.88)	0.009
HF hospitalisations and all-cause mortality	41 (13.7)	62 (27.6)	0.54 (0.34–0.87)	0.011
All-cause hospitalisations and all-cause mortality	108 (36.1)	118 (52.5)	0.73 (0.52–1.01)	0.060
HF hospitalisations	22 (7.3)	43 (19.1)	0.41 (0.23–0.73)	0.003
CV hospitalisations	52 (17.4)	75 (33.3)	0.54 (0.36–0.83)	0.004
All-cause hospitalisations	89 (29.7)	99 (44.0)	0.71 (0.50–1.01)	0.056

CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; RR, rate ratio.

Anker SD et al. Eur J Heart Fail 2017

ID IS COMMON IN HF

ESPECIALLY DURING ACUTE EXACERBATIONS



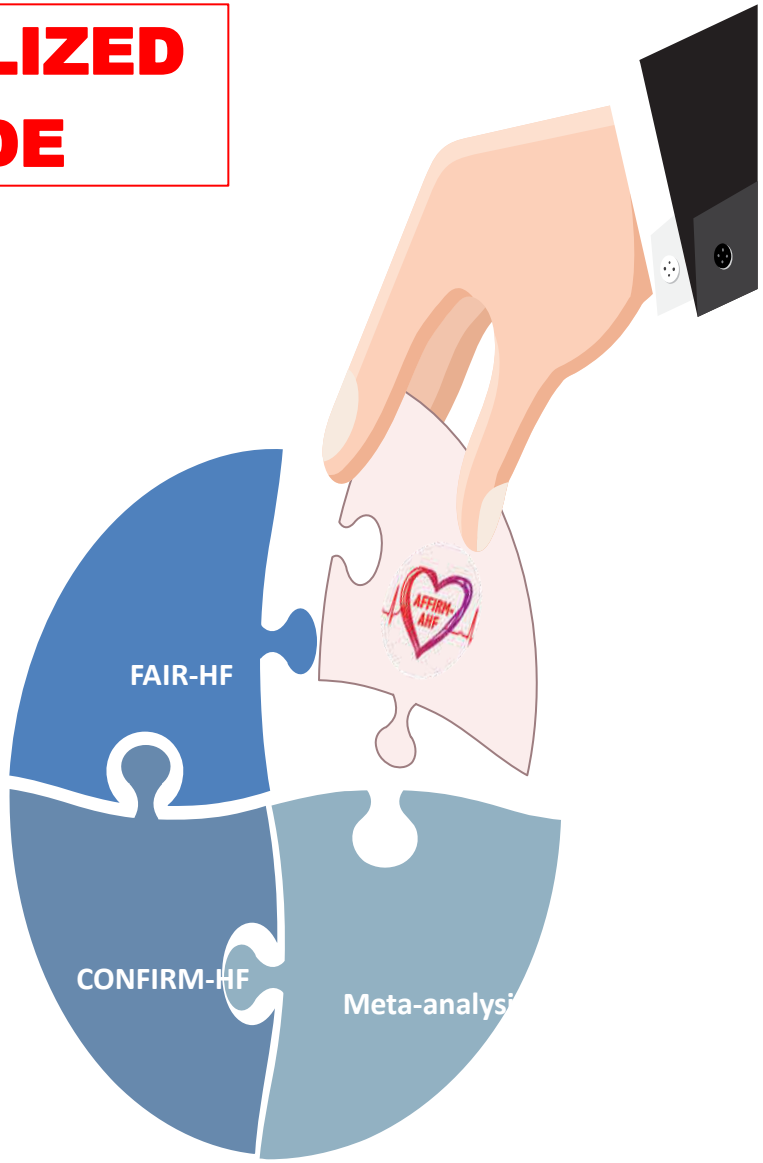
Adapted from Rocha BML et al. *J Am Coll Cardiol*. 2018;71(7):782-793.

HF PTS WITH ID HOSPITALIZED FOR AN ACUTE EPISODE

Randomized clinical trials such as FAIR-HF[1] and CONFIRM-HF[2] have shown that treatment with FCM improves functional capacity, exercise tolerance, symptoms, and quality of life in stable HF with reduced ejection fraction (HFrEF) patients with ID up to 52 weeks.

An individual patient data meta-analysis also suggested that treatment of ID with FCM in ambulatory HFrEF patients may decrease recurrent CV hospitalisations.[3]

AFFIRM-AHF is the first RCT designed to investigate, relative to placebo, the effects of IV FCM initiated at discharge on mortality and morbidity in HF patients with ID hospitalized for an acute episode[4]



1. Anker SD et al. N Engl J Med. 2009; 2. Ponikowski P et al. Eur Heart J. 2015;
3. Anker SD et al. Eur J Heart Fail. 2018 4. Ponikowski P et al. Eur J Heart Fail. 2019

KEY ELEGIBILITY CRITERIA

Inclusion criteria

Hospitalisation for acute HF
confirmed by signs/symptoms of acute HF and elevated natriuretic peptide (BNP or NT-proBNP) levels

Iron deficiency:
serum ferritin <100 ng/mL
OR
serum ferritin 100-299 ng/mL and TSAT <20%

Left ventricular ejection fraction <50%
not older than 12 months prior to randomization

Exclusion criteria

Clinical evidence of ACS, TIA, or stroke within 30 days

CABG, PTCA, cardiac device implantation (including CRT) within 30 days

Hb <8 g/dL[a] or >15 g/dL

Active infection requiring anti-microbial treatment during an index hospitalisation

ESA, i.v. iron or blood transfusion administered in last
3 months and oral iron (>100 mg/day) in previous 4 weeks

- [a]<10 g/dL for sites in The Netherlands, Spain and Singapore.
- ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; CABG, coronary artery bypass grafting; CRT, cardiac resynchronization therapy; ESA, erythropoiesis stimulating agent;
- Hb, haemoglobin; i.v., intravenous; NT-proBNP,
- N-terminal-pro hormone BNP; PTCA, Percutaneous transluminal coronary angioplasty; TIA, transient ischemic attack; TSAT, transferrin saturation.

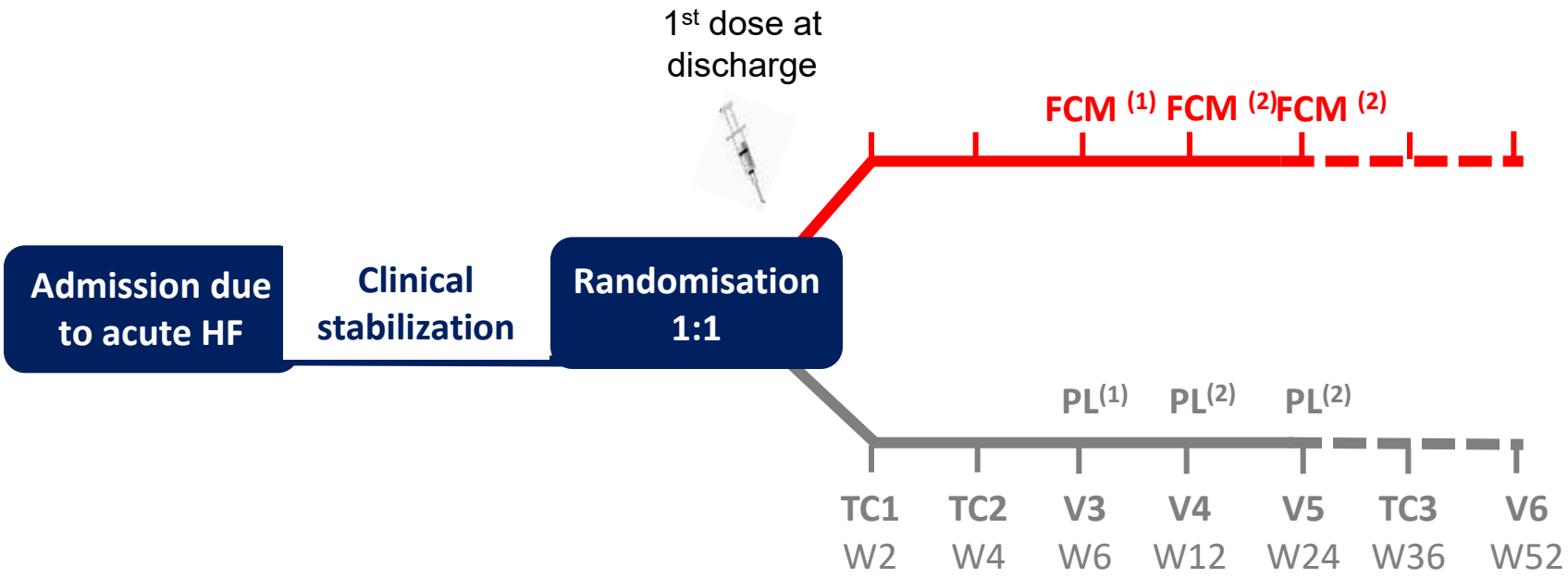
(Ponikowski P, et al. Eur J Heart Fail. 2019)

PRIMARY AND SECONDARY OUTCOMES

- **Primary**
  - **Composite of total HF hospitalizations and CV death up to 52 weeks**
- **Secondary**
  - Total HF hospitalizations
  - CV death
  - Time to first HF hospitalization or CV death
  - Composite of total CV hospitalizations and CV death
  - Days lost due to HF hospitalizations or CV death
- **Safety**
  - Adverse events

(Ponikowski P, et al. Eur J Heart Fail. 2019)

AFFIRM-AHF Study Design



Pre-screening (in-hospital)	Screening / Randomisation	Follow-up / Study treatment administration (1)(2)	Follow-up

•PL, placebo; TC, telephone contact; V, visit; W, week

•[1] The repletion dose of study treatment will be administered based on the iron need assessed at the baseline visit

•[2] Study treatment to be administered only if iron deficiency persisted

(Ponikowski P, et al. Eur J Heart Fail. 2019)

Study Treatment Dosing Regimen

Hb 8 to ≤14 g/dL	Hb >14 to ≤15 g/dL
1000 mg FCM / placebo	500 mg FCM / placebo

Hb 8 to ≤10 g/dL		Hb 10 to ≤14 g/dL		Hb >14 to ≤15 g/dL
<70 kg	≥70 kg	<70 kg	≥70 kg	
500 mg FCM/ placebo	1000 mg FCM/ placebo	No dose	500 mg FCM/ placebo	No dose

Only If Iron Deficiency Persisted
500 mg FCM / placebo

(Ponikowski P, et al. Eur J Heart Fail. 2019)

BASELINE CHARACTERISTICS

Characteristic	FCM (N=558)	Placebo (N=550)
Age, year	71.2 ± 10.8	70.9 ± 11.1
Female, %	44	45
Systolic BP, mm Hg	120 ± 15	120 ± 16
NYHA Class III-IV, %	52	54
LVEF, %	32.6 ± 9.6	32.7 ± 10.0
Ischaemic aetiology of HF, %	47	47
Newly diagnosed HF at index hospitalisation, %	27	30
Comorbidities, %		
Atrial fibrillation and/or flutter	56	55
Diabetes mellitus	41	44
Chronic kidney disease	40	41

- Results presented as mean ± SD unless otherwise noted.
- mITT population.
- BP, blood pressure; NYHA, New York Heart Association.

(Ponikowski P, et al. Eur J Heart Fail. 2019)

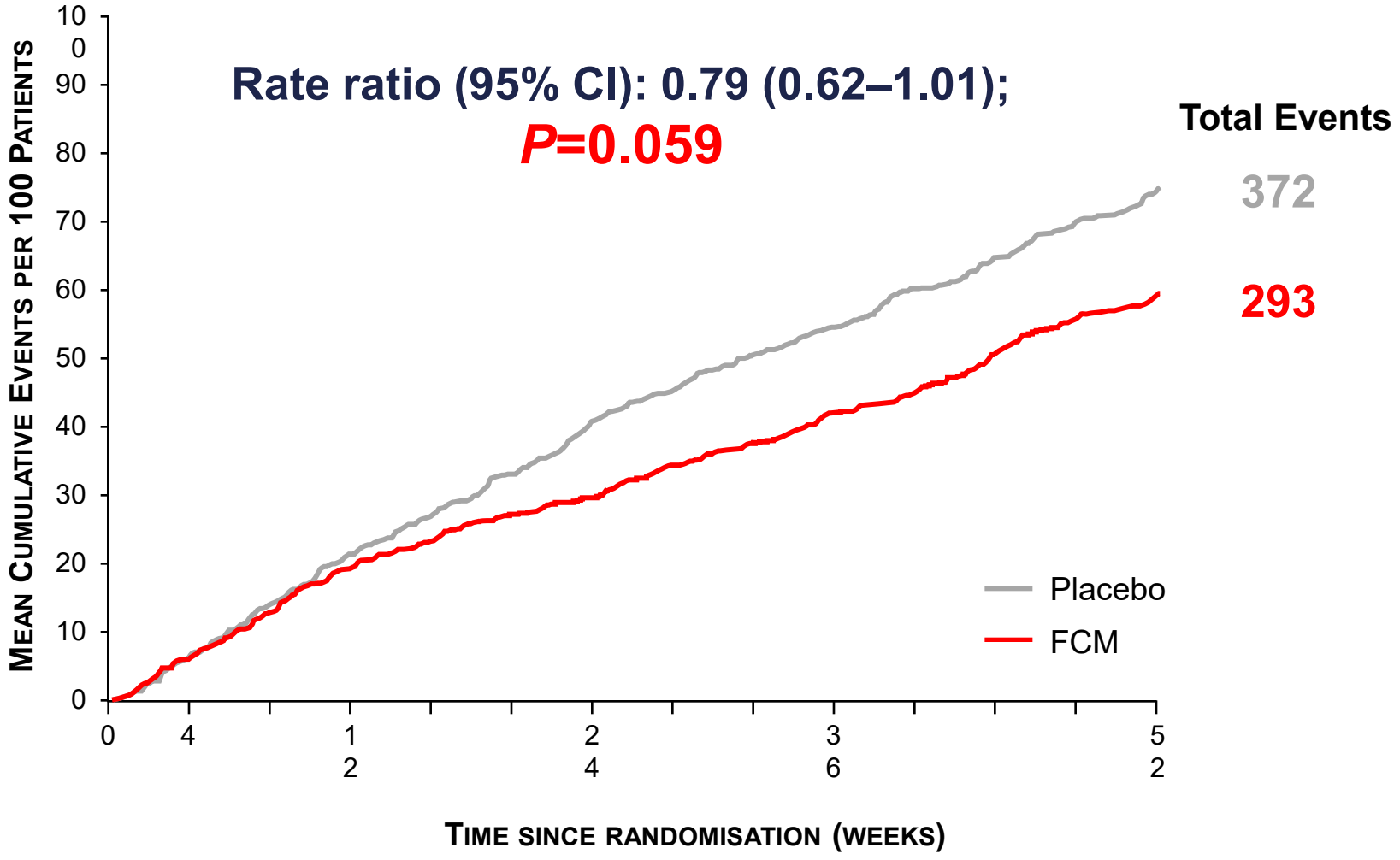
BASELINE PHARMACOTHERAPY

Pharmacotherapy, %	FCM (N=558)	Placebo (N=550)
Angiotensin converting enzyme inhibitor	53	51
Angiotensin receptor blocker	17	18
Angiotensin receptor neprilysin inhibitor	6	7
Mineralocorticoid receptor antagonist	67	64
Beta-blocker	81	84
Loop diuretic	87	85

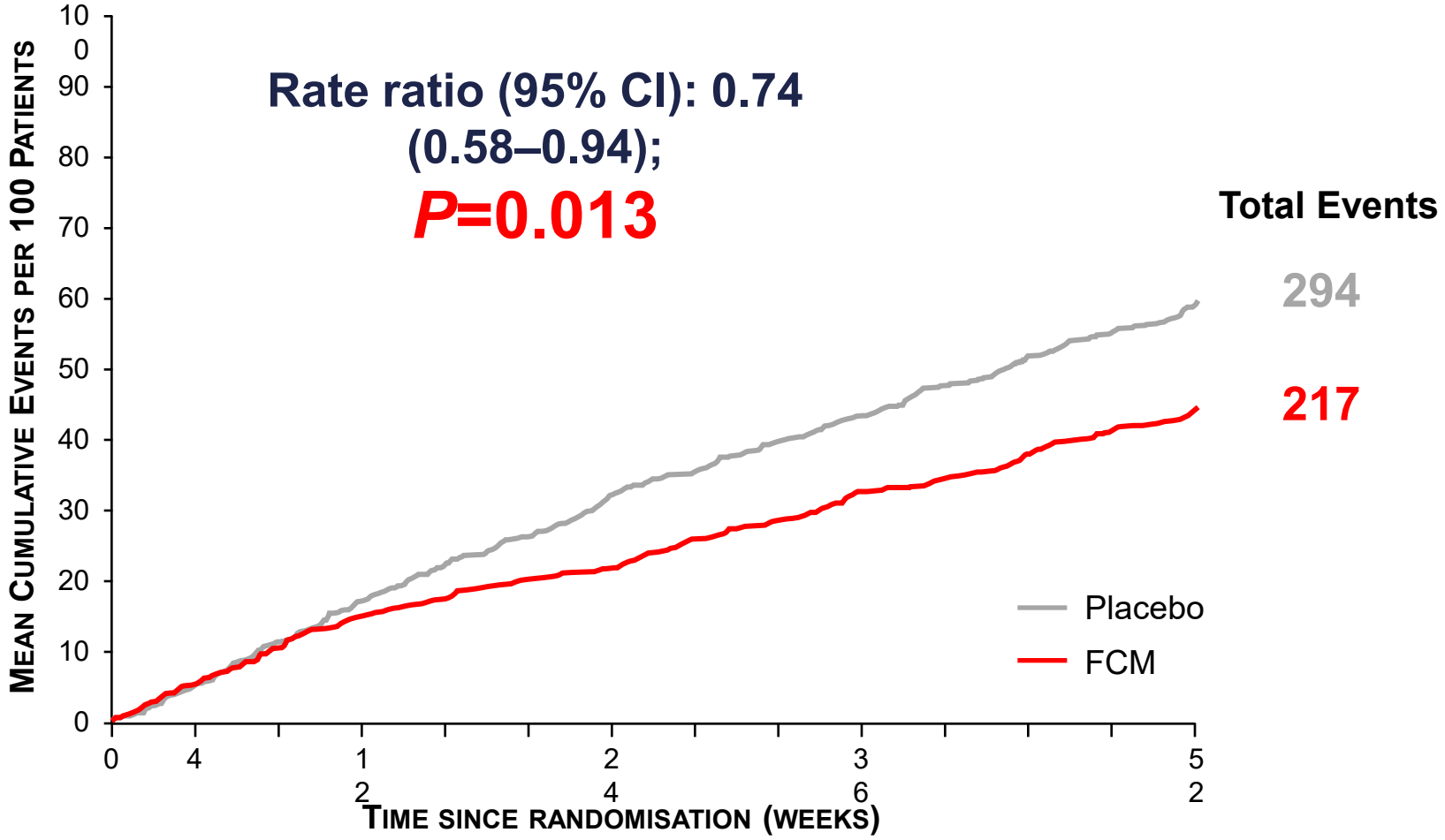
BASELINE LABORATORY DATA

Laboratory test results	FCM (N=558)	Placebo (N=550)
NT-proBNP, pg/mL, median (IQR)	4743 (2781, 8128)	4684 (2785, 8695)
BNP, pg/mL, median (IQR)	1068 (802, 1715)	1204 (803, 1955)
Haemoglobin, g/dL	12.3 ± 1.6	12.1 ± 1.6
Anaemia, %	52	57
Ferritin, ng/mL	83.9 ± 62.2	88.5 ± 68.6
Ferritin <100 ng/mL, %	73	69
TSAT (%)	15.2 ± 8.3	14.2 ± 7.5
TSAT <20%, %	82	85
eGFR, mL/min/1.73 m^2	55.3 ± 21.3	55.7 ± 23.1
eGFR <60 mL/min/1.73 m^2, %	52	52

TOTAL HF HOSPITALIZATION AND CV DEATH
PRIMARY ENDPOINT

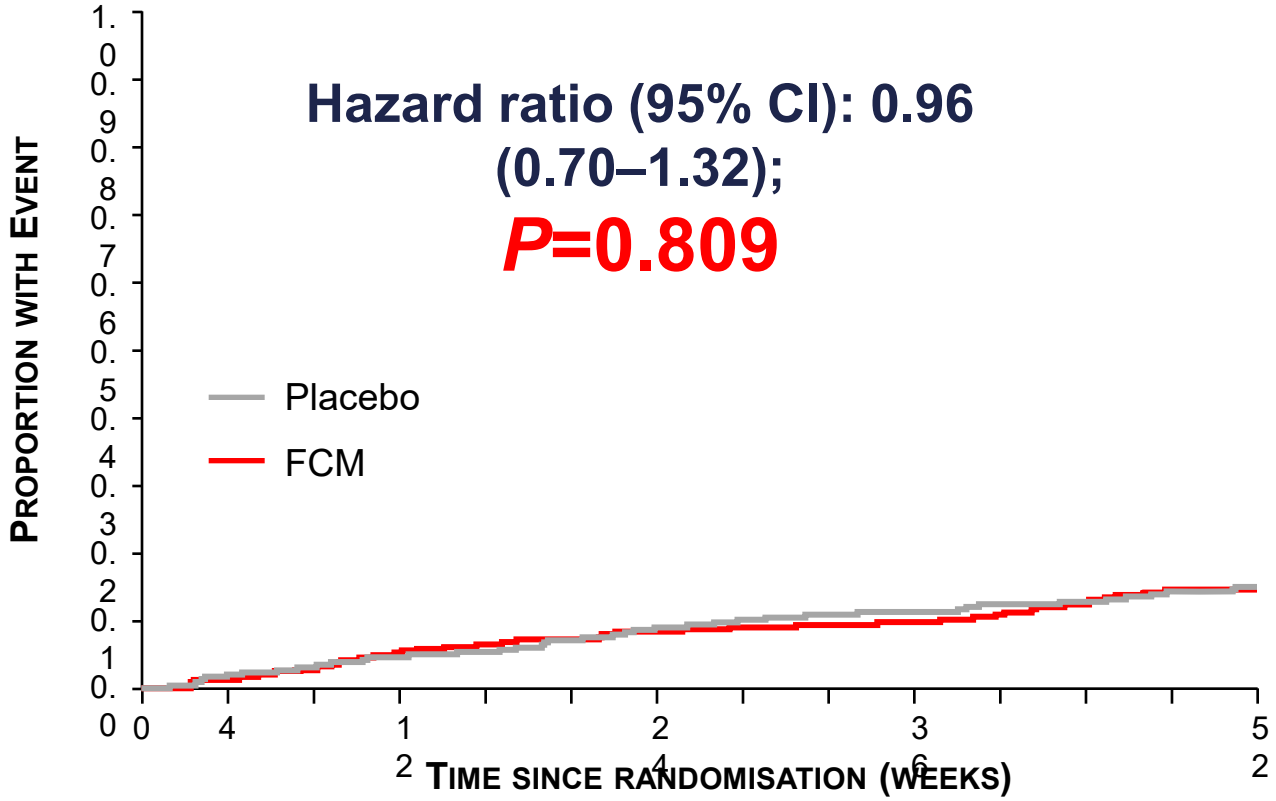


TOTAL HF HOSPITALIZATIONS COMPONENT OF PRIMARY ENDPOINT



(Ponikowski P, et al. Eur J Heart Fail. 2019)

CV DEATH
COMPONENT OF PRIMARY ENDPOINT

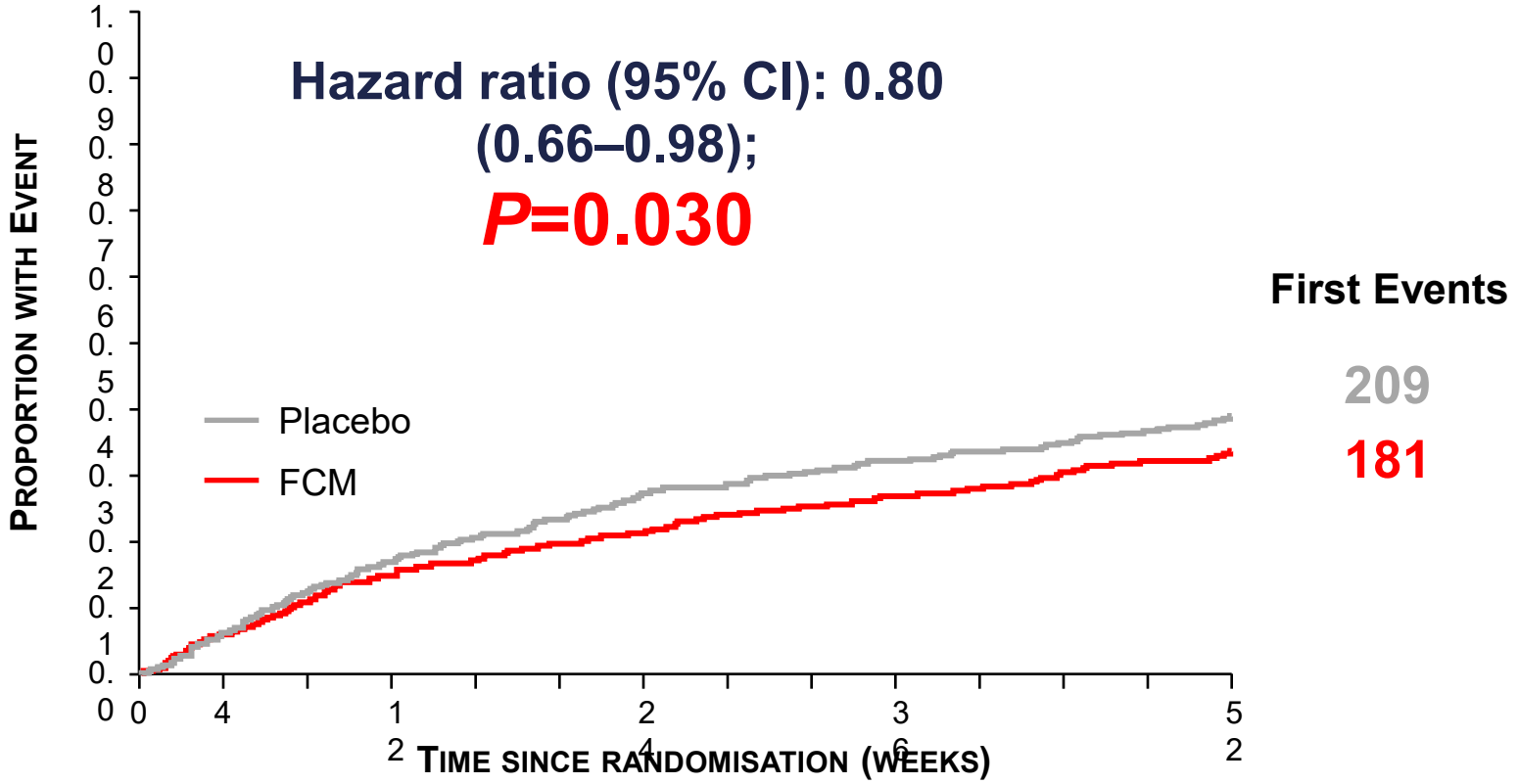


Number at risk

FCM	544	509	483	468	289
Control	537	511	486	465	285

(Ponikowski P, et al. Eur J Heart Fail. 2019)

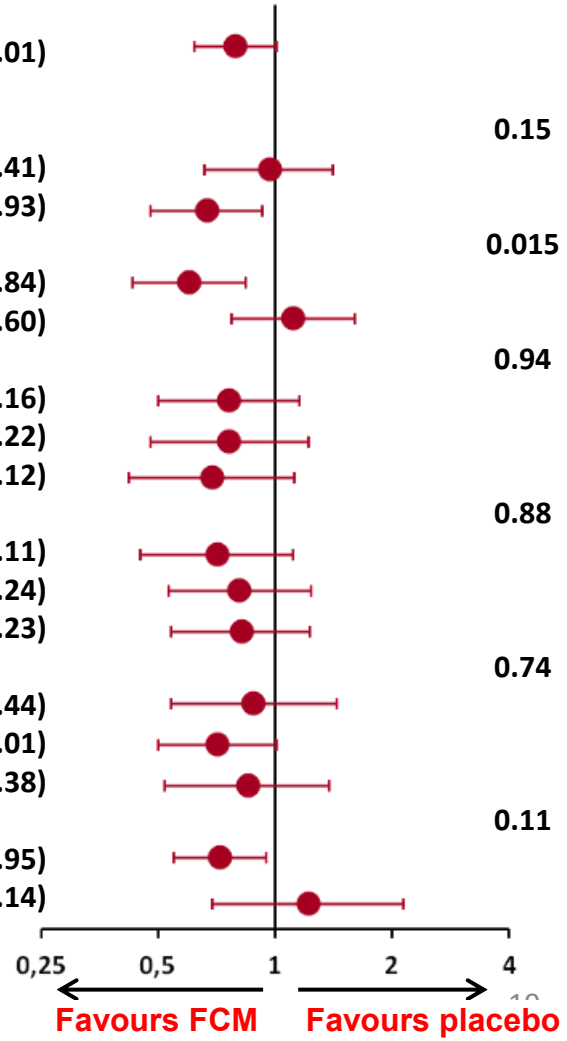
SECONDARY ENDPOINT
FIRST HF HOPITALIZATION OR CV DEATH



(Ponikowski P, et al. Eur J Heart Fail. 2019)

PRIMARY ENDPOINT FOR SELECTED PREDEFINED SUBGROUPS

	FCM Events / Patients	Placebo Events / Patients	Rate Ratio (95% CI)	P for interaction
Overall	293 / 558	372 / 550	**0.79 (0.62–1.01)**	
Hb level at baseline				**0.15**
<12 g/dL	136 / 228	171 / 236	**0.97 (0.66–1.41)**	
≥12 g/dL	156 / 329	201 / 314	**0.67 (0.48–0.93)**	
Heart Failure aetiology				**0.015**
Ischaemic	149 / 265	236 / 257	**0.60 (0.43–0.84)**	
Non-ischaemic	140 / 282	128 / 275	**1.11 (0.77–1.60)**	
eGFR tertiles at baseline				**0.94**
<42.96	115 /157	152 / 165	**0.76 (0.50–1.16)**	
≥42.96 to <64.32	76 /166	83 / 156	**0.76 (0.48–1.22)**	
≥64.32	56 /164	79 / 159	**0.69 (0.42–1.12)**	
NT-pro BNP or BNP at baseline				**0.88**
Lower tertile	69 / 187	105 / 177	**0.71 (0.45–1.11)**	
Middle tertile	99 / 191	115 / 183	**0.81 (0.53–1.24)**	
Upper tertile	125 / 179	152 / 189	**0.82 (0.54–1.23)**	
LV ejection fraction at baseline				**0.74**
<25%	84 / 104	113 / 122	**0.88 (0.54–1.44)**	
25% to <40%	144 / 288	178 / 243	**0.71 (0.50–1.01)**	
40% to <50%	65 / 166	80 / 184	**0.85 (0.52–1.38)**	
Diagnosis of HF				**0.11**
Documented HF prior to index hospital.	249 / 405	336 / 385	**0.72 (0.55–0.95)**	
Newly diagnosed at index hospital.	44 / 153	36 / 165	**1.22 (0.69–2.14)**	



(Ponikowski P, et al. Eur J Heart Fail. 2019)

ADVERSE EVENTS OF INTEREST

Adverse events (AE)	FCM (N=559)		Placebo (N=551)	
	Patients n (%)	Total Events (n)	Patients n (%)	Total Events (n)
Cardiac disorders	224 (40.1)	391	244 (44.3)	453
Infections	102 (18.2)	143	121 (22.0)	165
Diarrhea	17 (3.0)	19	14 (2.5)	16
Constipation	10 (1.8)	10	10 (1.8)	12
Hypophosphataemia	1(0.2)	1	1 (0.2)	1
Bone pain	0 (0)	0	1 (0.2)	1
Pruritis	3 (0.5)	3	3 (0.5)	3
Rash	2 (0.4)	2	2 (0.4)	2
Urticaria	1 (0.2)	1	1 (0.2)	1
Neoplasm	9 (1.6)	3	7 (1.3)	9
Drug hypersensitivity	2 (0.4)	2	0 (0)	0
Hypersensitivity	0 (0)	0	1 (0.2)	1

(Ponikowski P, et al. Eur J Heart Fail. 2019)

CONCLUSIONS

- **In patients with iron deficiency, stabilised after an episode of acute HF, treatment with FCM relative to placebo:**
  - **Reduced the risk for the combined endpoint of HF hospitalizations and CV death by 21%. The statistical significance was narrowly missed *(p=0.059)***
  - **The result of the primary endpoint, was mainly driven by a 26% reduction in HF re-hospitalisation *(p=0.013)***
  - **Statistically significant treatment benefits with FCM were seen on the time to first HF hospitalization or CV death**
- **80% of patients only required 1-2 injections of FCM during the dosing period**
- **Treatment with FCM was well tolerated**

Administration of FCM in patients with iron deficiency, LVEF <50%, stabilised after an episode of acute HF reduces the risk of subsequent HF hospitalisations

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

Recommendations	Class[a]	Level[b]
It is recommended that all patients with HF be periodically screened for anaemia 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.[710,722,724]	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.[512]	IIa	B

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HF = heart failure; LVEF = left ventricular ejection fraction; QOL = quality of life; TSAT = transferrin saturation.

[a]Class of recommendation.

[b]Level of evidence.