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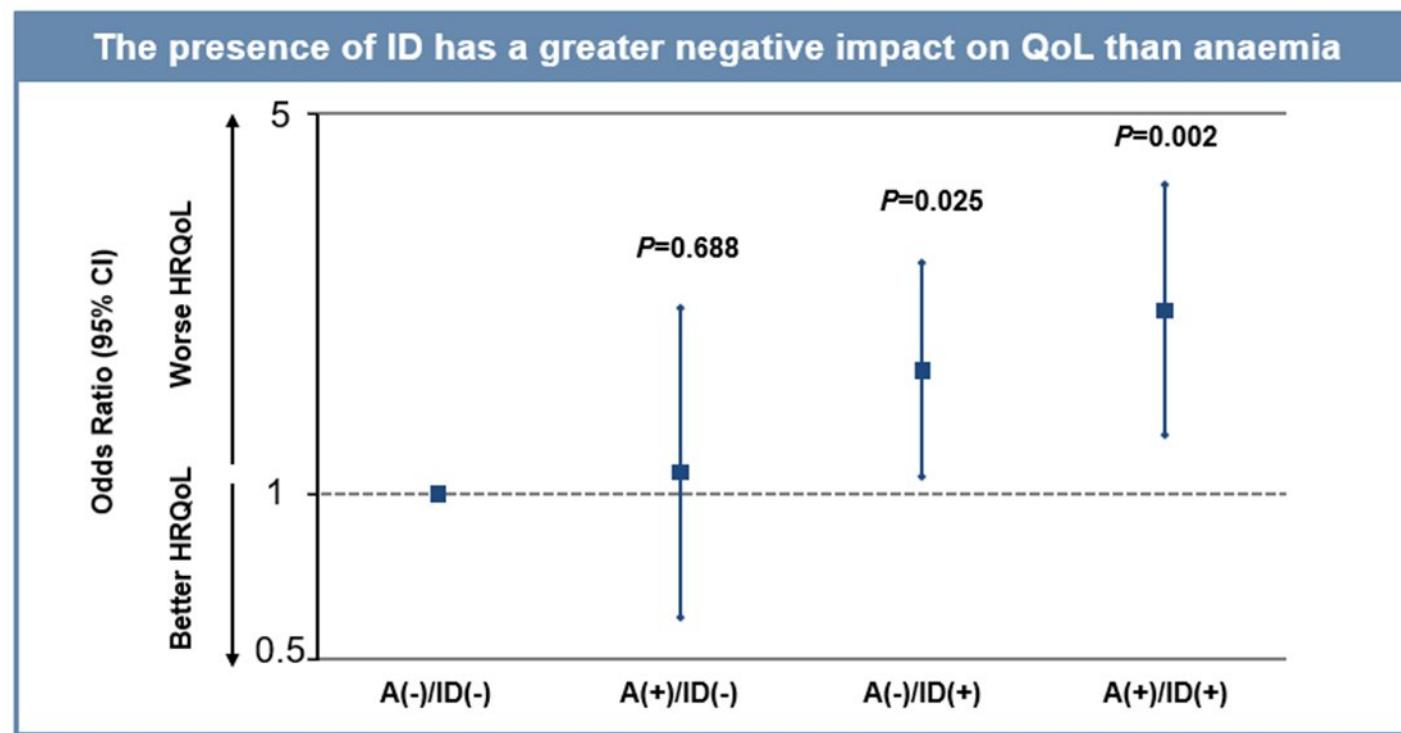
IL RUOLO DEL FERRO NELL'INSUFFICIENZA CARDIACA

Place, 1 Ottobre 2022

Declaration of potential conflict of interests

Type of job or financial support	Research Institution / Company
<u>Salary</u> <u>Ordinary funds</u> <u>Position in Public Committees</u>	<u>IRCCS San Raffaele Roma</u> <u>Univesrsità Telematica San Raffaele , uniroma5</u> <u>Italian Ministry of health</u>
<u>Support , Consultancy</u>	<u>Novartis, Bayer, Boheringher, Servier, MSD, Bruno , Amgen;</u> <u>Vifor ; Menarini; Astra</u>
<u>Conflict for this presentation</u>	<u>none</u>

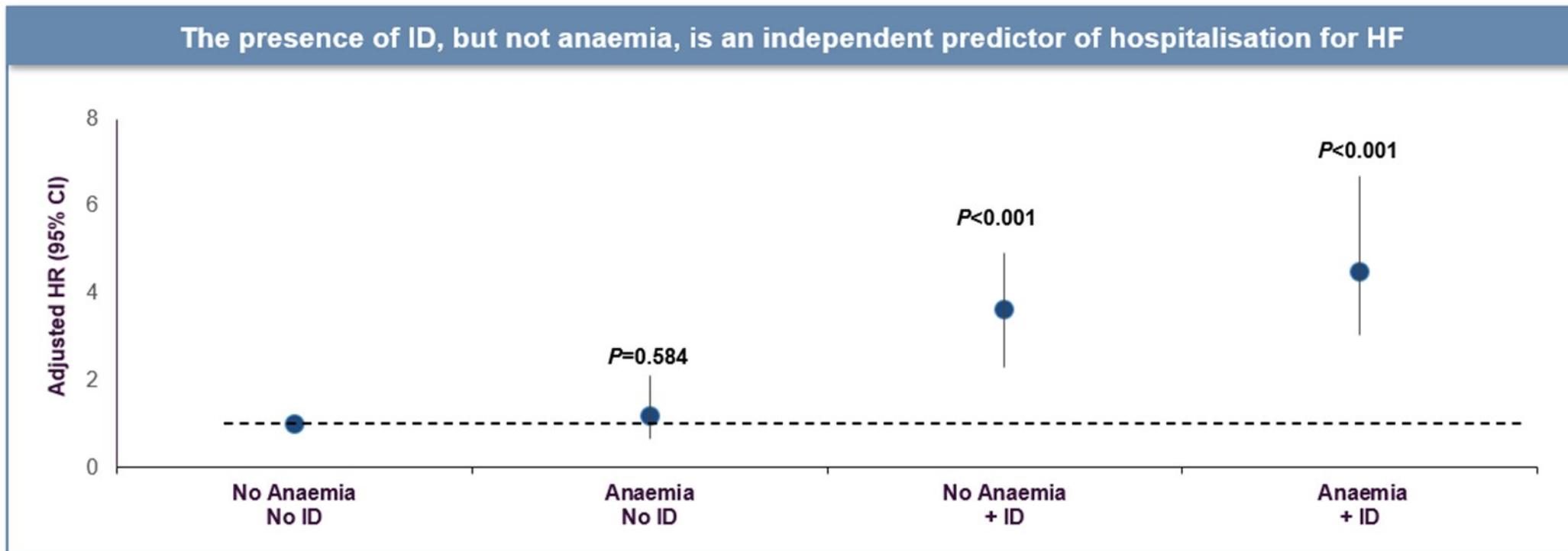
ID Reduces QoL Independently of Haemoglobin Concentrations in Patients with HF



International cohort of 1278 patients with chronic HF. HRQoL measured with the Minnesota Living with Heart Failure questionnaire (MLHFQ). Analyses adjusted for geographic location; age, BMI, SBP, HR, NYHA class, HFrEF vs HFpEF, LVEDP >55 mm, HF aetiology, HTN, DM, ACEi/ARB use, ARB use, statin use, loop diuretic use, antiplatelet use, Haemoglobin, RDW, MCH, NT-pro BNP, eGFR, and CRP.

A=anaemia; ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; BMI=body mass index; CI=confidence interval; CRP=C-reactive protein; DM=diabetes; eGFR=estimated glomerular filtration rate; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; HRQoL=health-related quality of life; HTN=hypertension; HR=heart rate; ID=iron deficiency; LVEDP=left ventricular diastolic pressure; MCH=mean corpuscular haemoglobin; NT-pro BNP=N-terminal pro B-type natriuretic peptide; NYHA=new York heart association; QoL=quality of life; RDW=red blood cell distribution width; SBP=systolic blood pressure.
Enjuanes C, et al. *Int J Cardiol*. 2014;174(2):268–275.

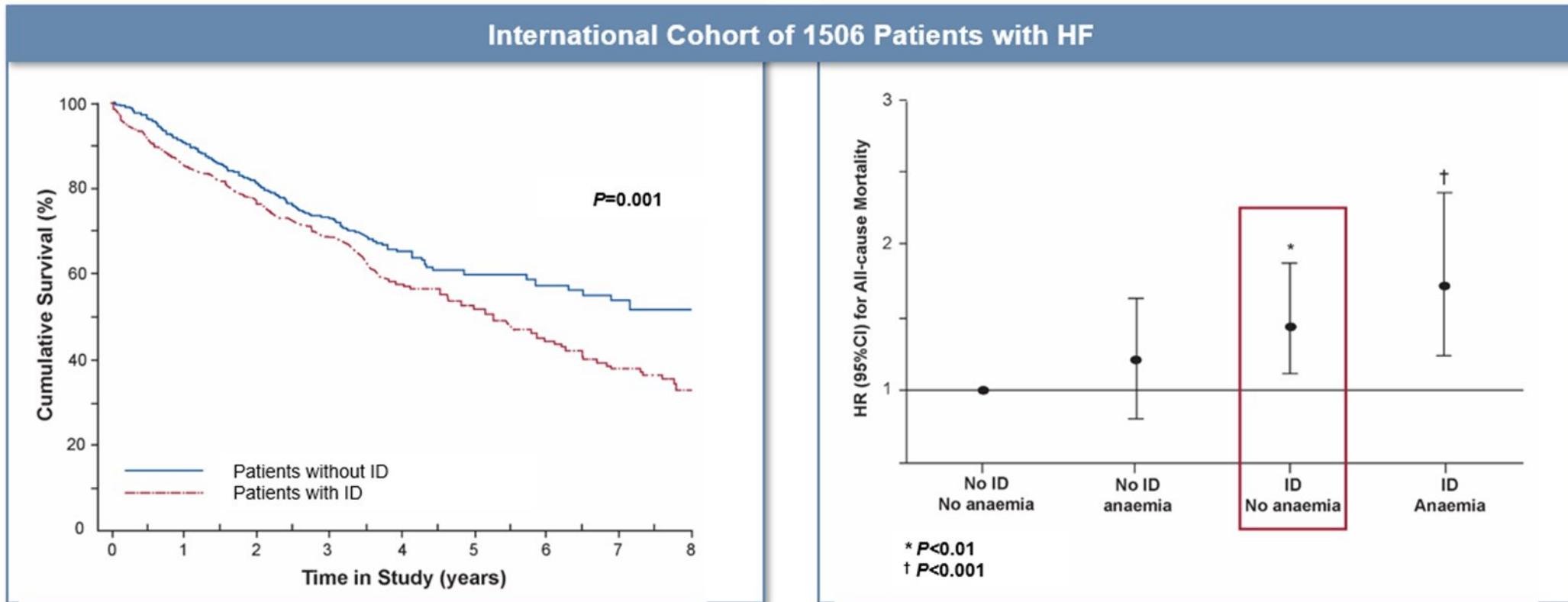
Among Patients with HF, ID Independently Increases the Risk of Hospitalisation for HF



Belgian study of 1197 patients with HF (HFrEF: n=897; HFmrEF: n=229; HFP EF: n=72) with a mean (SD) follow-up of 33 (21) months. Hazard ratios (HRs) were adjusted for following covariates: age, gender, implantable cardio-defibrillator use, CRT-use, ischaemic aetiology of HF, use of ACE-I, ARB, beta-blockers or MRAs, NYHA-functional class, loop diuretic use, and baseline LVEF. The prevalence of ID was higher in patients included in an acute HF versus a stable chronic HF setting (63% vs. 50%; $P<0.001$).

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval; CRT=cardiac resynchronisation therapy; HF=heart failure; HFmrEF=heart failure with mid-range ejection fraction; HFP EF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; ID=iron deficiency; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonists; NYHA>New York Heart Association; SD=standard deviation.
Martens P, et al. *Acta Cardiol.* 2018;73(2):115–123.

ID is a Stronger Prognostic Factor for Mortality than Anaemia in HF

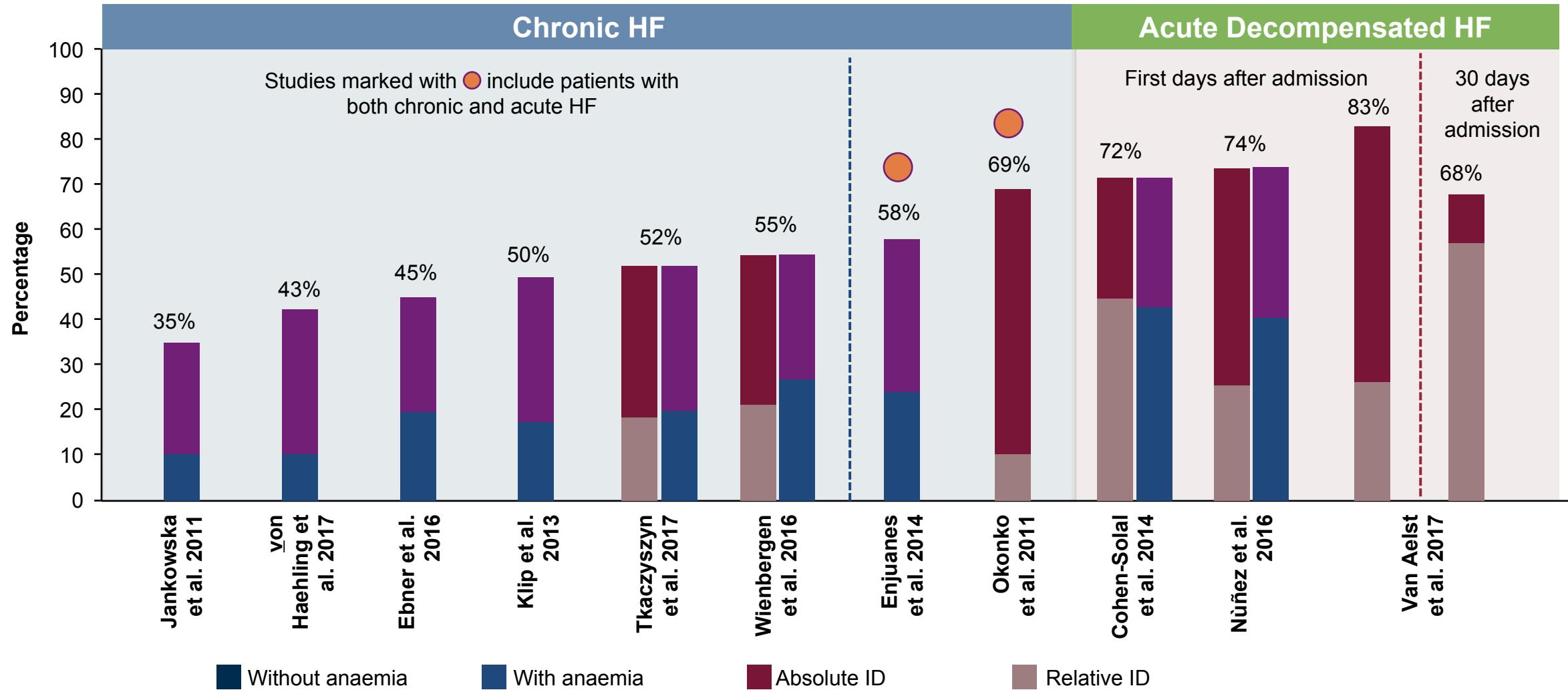


This study population consists of patients from 5 cohorts from Poland, Spain and The Netherlands, comprising 1506 chronic HF patients with reduced or preserved left ventricular ejection fraction.

CI=confidence interval; HF=heart failure; HR=hazard ratio; ID=iron deficiency.

Klip IT, et al. Am Heart J. 2013;165:575–82.e3.

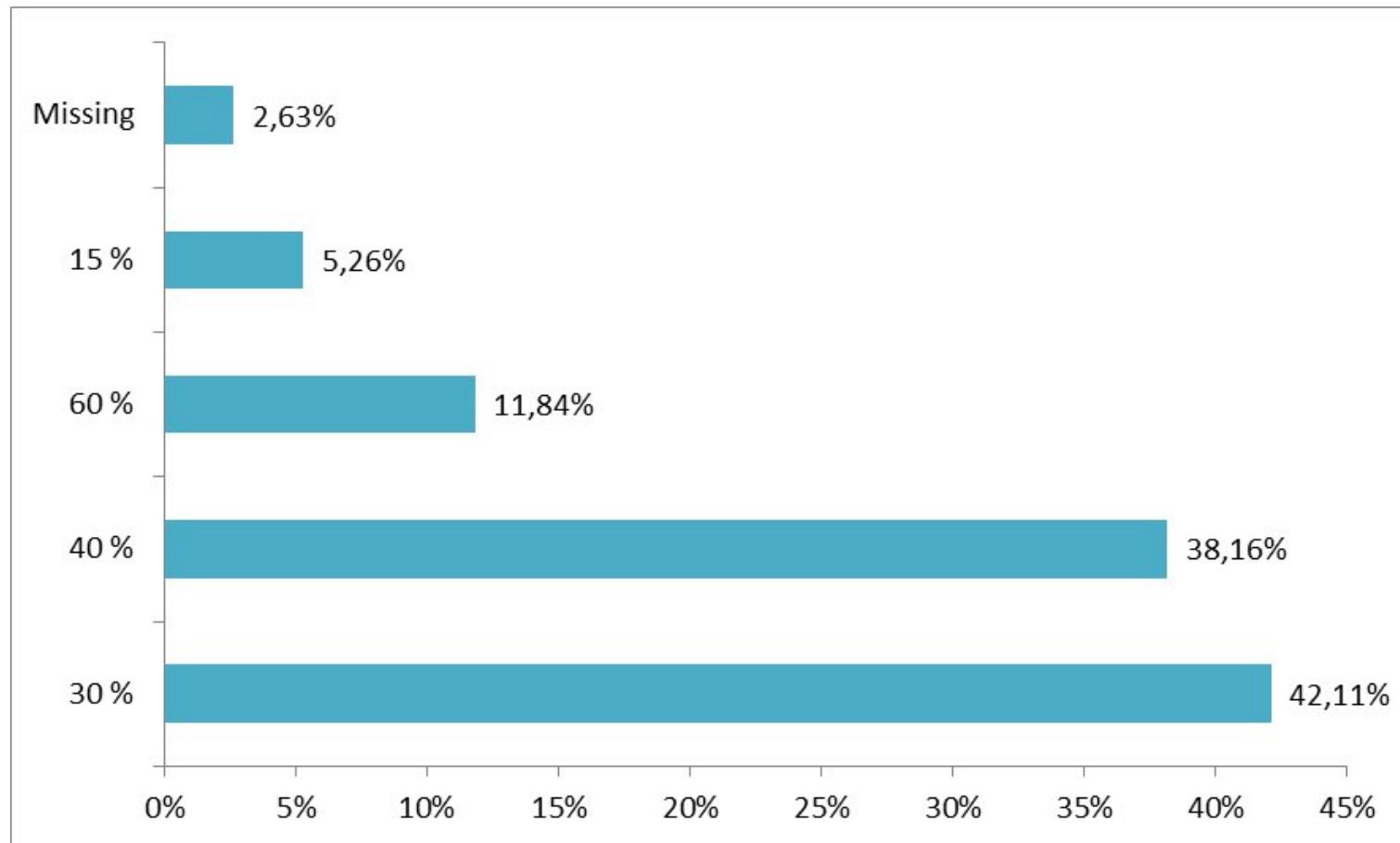
ID is Common in HF, Especially in Acute HF



• HF=heart failure; ID=iron deficiency.

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

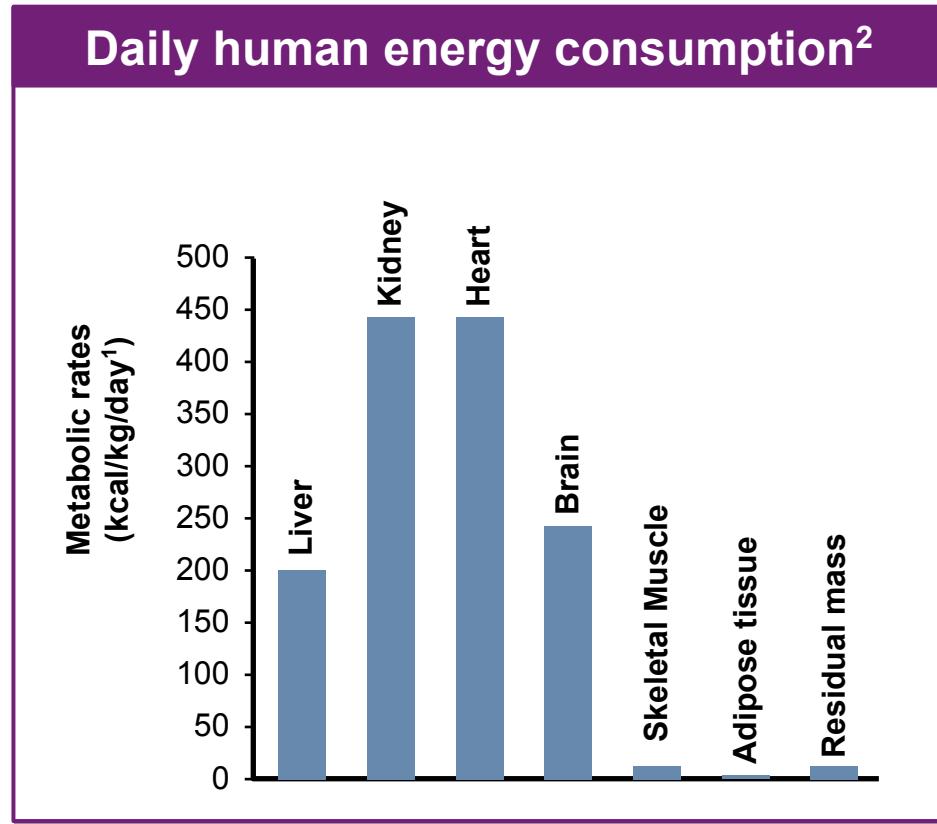
D3: Quale è la prevalenza della carenza marziale nei soggetti con scompenso cardiaco?



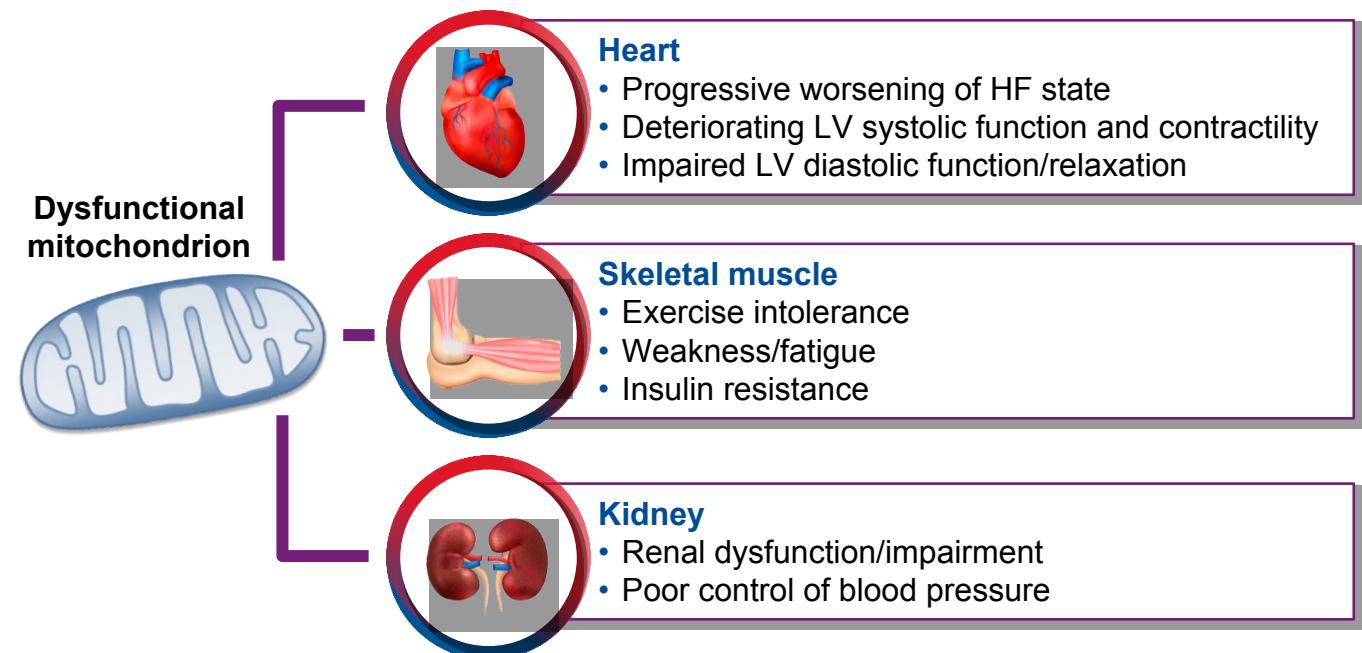
6400 Cardiologi intervistati via mail Ottobre 2022

ID-Induced Mitochondrial Dysfunction contributes to HF Symptoms

MITOCHONDRIA ARE MAJOR SITES OF IRON UTILISATION AND ACCUMULATION¹



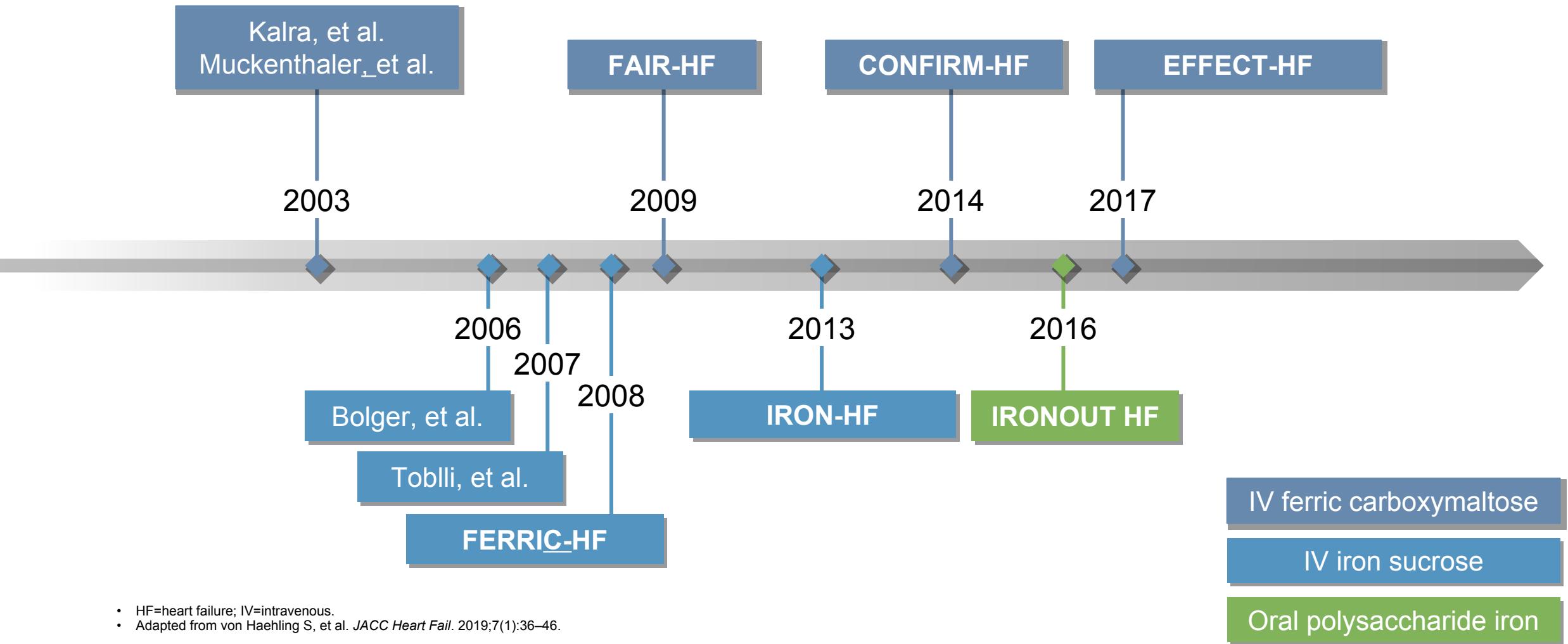
Dysfunctional mitochondrial energy production may account for many common HF symptoms³



• HF=heart failure; ID=iron deficiency; LV=left ventricle.

• 1. Paul BT, et al. *Expert Rev Hematol.* 2017;10(1): 65–79; 2. Boyman L, et al. *Trends Mol Med.* 2020;26(1):21–39; 3. Brown D, et al. *Nat Rev Cardiol.* 2017;14:238–250.

Selected Interventional Trials of Iron in HF



Hospitalizations – Results

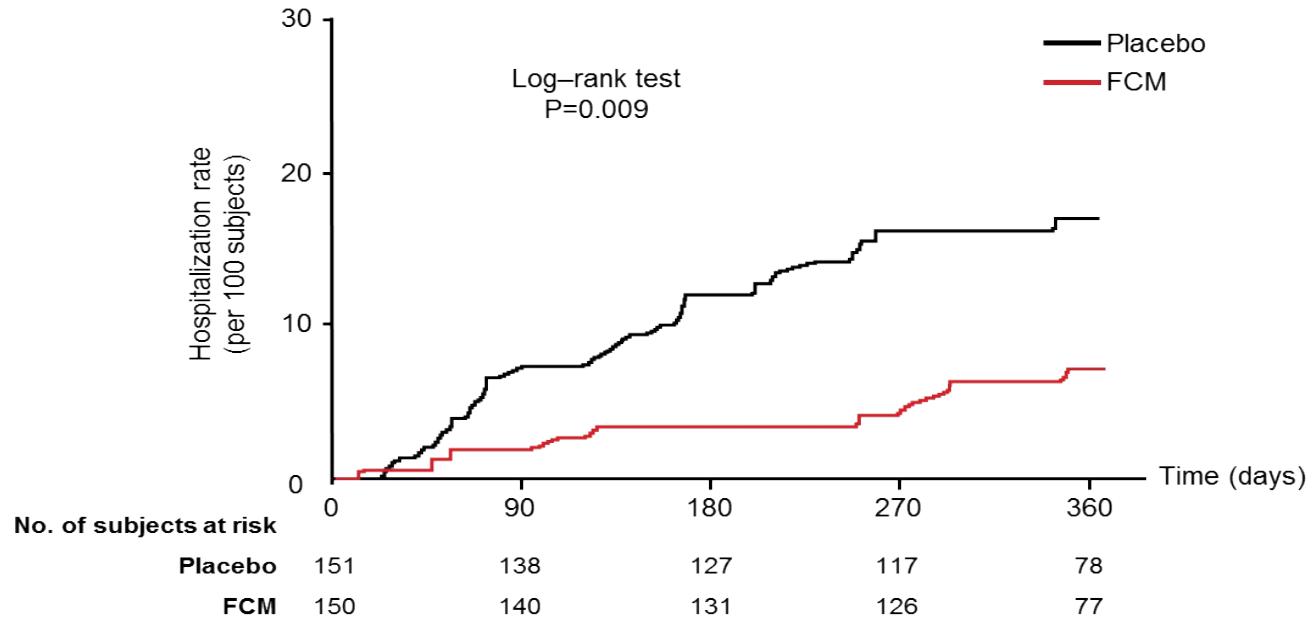


Table 3 Recurrent event outcomes

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)
HF hospitalisations and CV mortality	39 (13.0)	60 (26.7)	0.53 (0.33–0.86)
CV hospitalisations and all-cause mortality	71 (23.7)	94 (41.8)	0.60 (0.41–0.88)
HF hospitalisations and all-cause mortality	41 (13.7)	62 (27.6)	0.54 (0.34–0.87)
All-cause hospitalisations and all-cause mortality	108 (36.1)	118 (52.5)	0.73 (0.52–1.01)
HF hospitalisations	22 (7.3)	43 (19.1)	0.41 (0.23–0.73)
CV hospitalisations	52 (17.4)	75 (33.3)	0.54 (0.36–0.83)
All-cause hospitalisations	89 (29.7)	99 (44.0)	0.71 (0.50–1.01)

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

Anker SD et al. Eur J Heart Fail 2017

FCM significantly reduced the risk of hospitalisations for worsening CHF (by 61%)

- Ponikowski P et al. Eur Heart J. 2015;36:657-68.

Effect of IV FCM on symptoms and functional capacity in heart failure

	FAIR-HF ¹	CONFIRM-HF ²	EFFECT-HF ³
NYHA functional class	Improved from week 4	Improved from week 24	Improved from week 6
6MWT	Improved from week 4	Improved from week 24	—
PGA	Improved from week 4	Improved from week 12	Improved from week 12
EQ-5D	Improved from week 4	Improved from week 36	—
KCCQ	Improved from week 4	Improved from week 12	—
pVO ₂	—	—	Improved ^a
Safety	Similar nature, type, intensity, and frequency of AEs between treatment arms		

• ^aP<0.05; nonsignificant ($P=0.23$) after removing deaths from analysis.

- AEs=adverse events; CHF=chronic heart failure; EQ-5D=EuroQoL five-dimensional scale; FCM=ferric carboxymaltose; KCCQ=Kansas City Cardiomyopathy Questionnaire; NYHA>New York Heart Association; PGA=physician's global assessment; pVO₂=peak oxygen consumption; 6MWT=6-minute walk test.
- 1. Anker SD, et al. *Eur J Heart Fail*. 2009;11:1084–91; 2. Ponikowski P, et al. *ESC Heart Fail*. 2014;52–8; 3. van Veldhuisen DJ, et al. *Circulation*. 2017;136:1374–83.

Lack of Efficacy of Oral Iron Treatment in HF (IRONOUT HF)

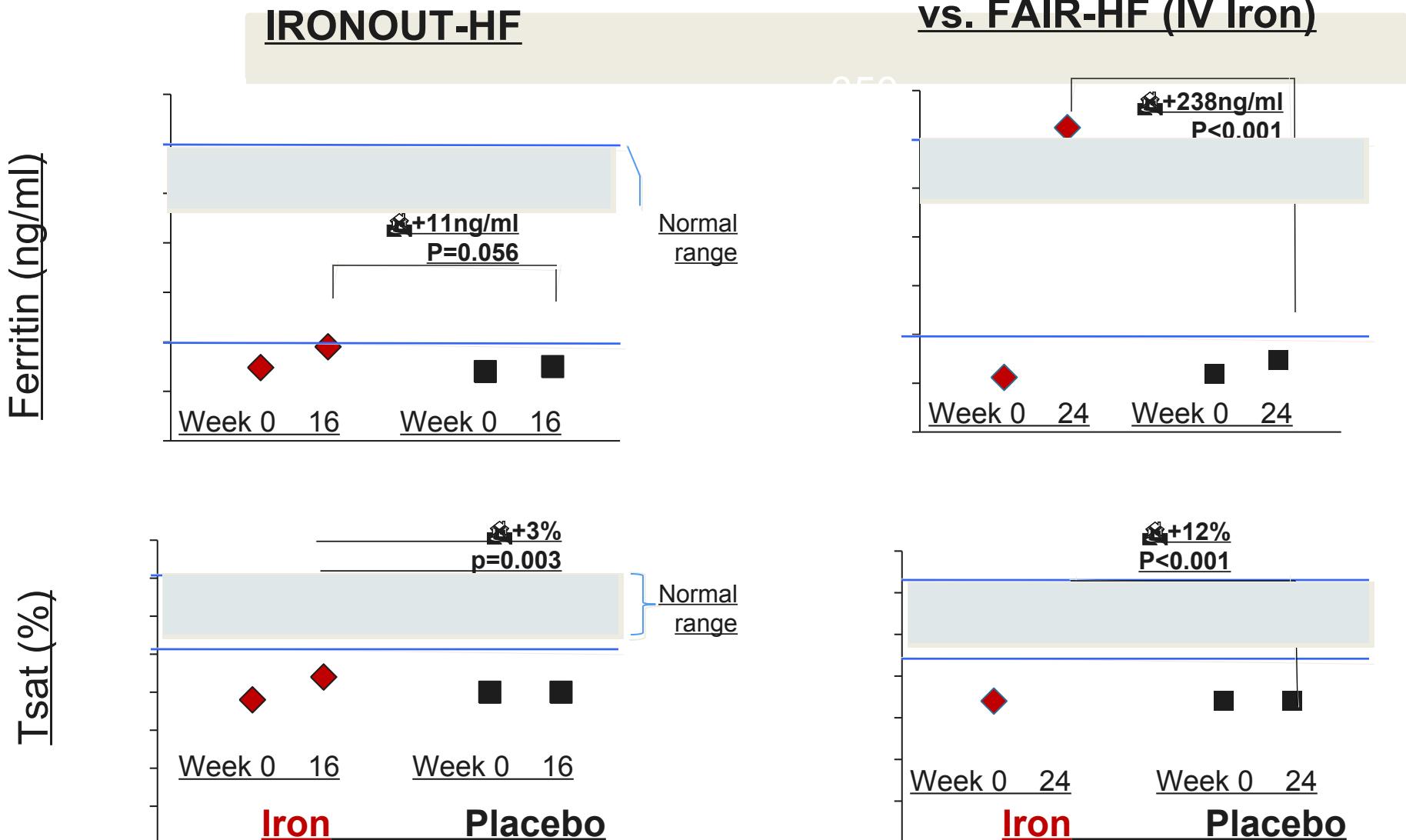
- N=225 patients with HFrEF, iron polysaccharide 150 mg twice daily for 16 weeks

	Median (IQR)		Change From Baseline to Week 16		Difference in Change From Baseline (95% CI)	P Value		
	Week-16 Values ^a		Oral Iron	Placebo				
	Oral Iron	Placebo						
Primary End Point								
Peak $\dot{V}\text{O}_2$ at 16 wk, mL/min	1218 (892 to 1500)	1187 (902 to 1425)	23 (-84 to 142)	-2 (-110 to 104)	21 (-34 to 76)	.46		
Ppeak $\dot{V}\text{O}_2$ at 16 wk, mL/kg/min	13.5 (11.7 to 16.3)	13.0 (10.2 to 15.9)	0.20 (-1.1 to 1.6)	0.01 (-1.1 to 0.9)	0.30 (-0.27 to 0.87)	.30		
Secondary End Points								
6-Min walk distance at 8 wk, m	380 (322 to 467)	376 (286 to 448)	15 (-17 to 55)	21 (-24 to 56)	-1 (-24 to 23)	.95		
6-Min walk distance at 16 wk, m	366 (315 to 456)	397 (299 to 472)	19 (-19 to 51)	32 (-12 to 66)	-13 (-32 to 6)	.19		
Mean response time (O_2 uptake kinetics), s	52 (46 to 61)	47 (40 to 58)	2.5 (-7 to 9)	1 (-10 to 6)	3 (-2 to 8)	.19		
Ventilatory efficiency ($\text{V}_\text{E}/\text{V}_{\text{CO}_2}$ slope)	34.8 (29.9 to 41.1)	33.5 (29.4 to 38.9)	-0.3 (-3.0 to 2.1)	-0.3 (-4.6 to 2.8)	0.8 (-0.3 to 2.6)	.35		
NT-proBNP, pg/mL	889 (376 to 2373)	1085 (447 to 2582)	4 (-342 to 288)	-37 (-412 to 363)	159 (-280 to 599)	.48		
KCCQ clinical summary score at 8 wk ^b	81.3 (70.8 to 91.7)	75.0 (58.9 to 87.5)	5.2 (-2.1 to 12.5)	1.0 (-7.3 to 8.3)	3.4 (-0.4 to 7.2)	.08		
KCCQ clinical summary score at 16 wk ^b	80.7 (67.7 to 91.6)	77.1 (65.1 to 89.6)	3.1 (-4.2 to 13.5)	3.0 (-4.2 to 10.4)	1.0 (-2.4 to 4.4)	.57		

Conclusions and relevance: Among participants with HFrEF with iron deficiency, high-dose oral iron did not improve exercise capacity over 16 weeks. These results do not support use of oral iron supplementation in patients with HFrEF.

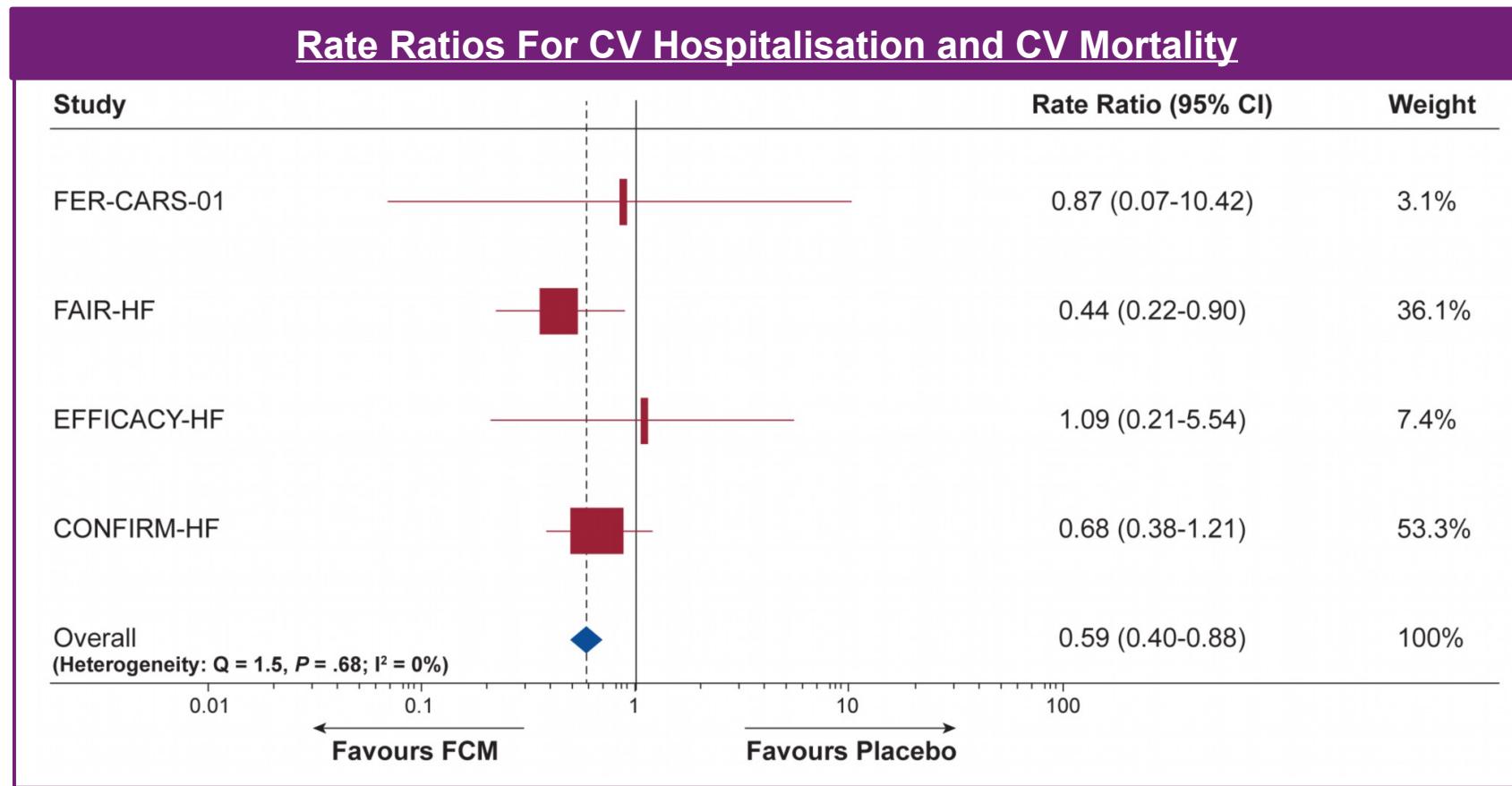
CI=confidence interval; HFrEF=heart failure with reduced ejection fraction; IQR=interquartile range; KCCQ=Kansas City Cardiomyopathy Questionnaire; Min=minute; NT-proBNP=N-terminal pro-B-type natriuretic peptide; NYHA>New York Heart Association; O₂=oxygen; pVO₂= peak oxygen consumption; V=volume; wk=week.
Lewis GD. JAMA 2017;317:1958–66.

Results: Iron Studies



Individual Patient Data Meta-Analysis

– FCM in Patients with HFrEF and ID



- CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; FCM=ferric carboxymaltose; HFrEF=heart failure with reduced ejection fraction; ID=iron deficiency.
- Adapted from Anker SD, et al. *Eur J Heart Fail*. 2018;20(1):125–133.

AFFIRM-AHF was Designed to Enroll a High-Risk HF Population

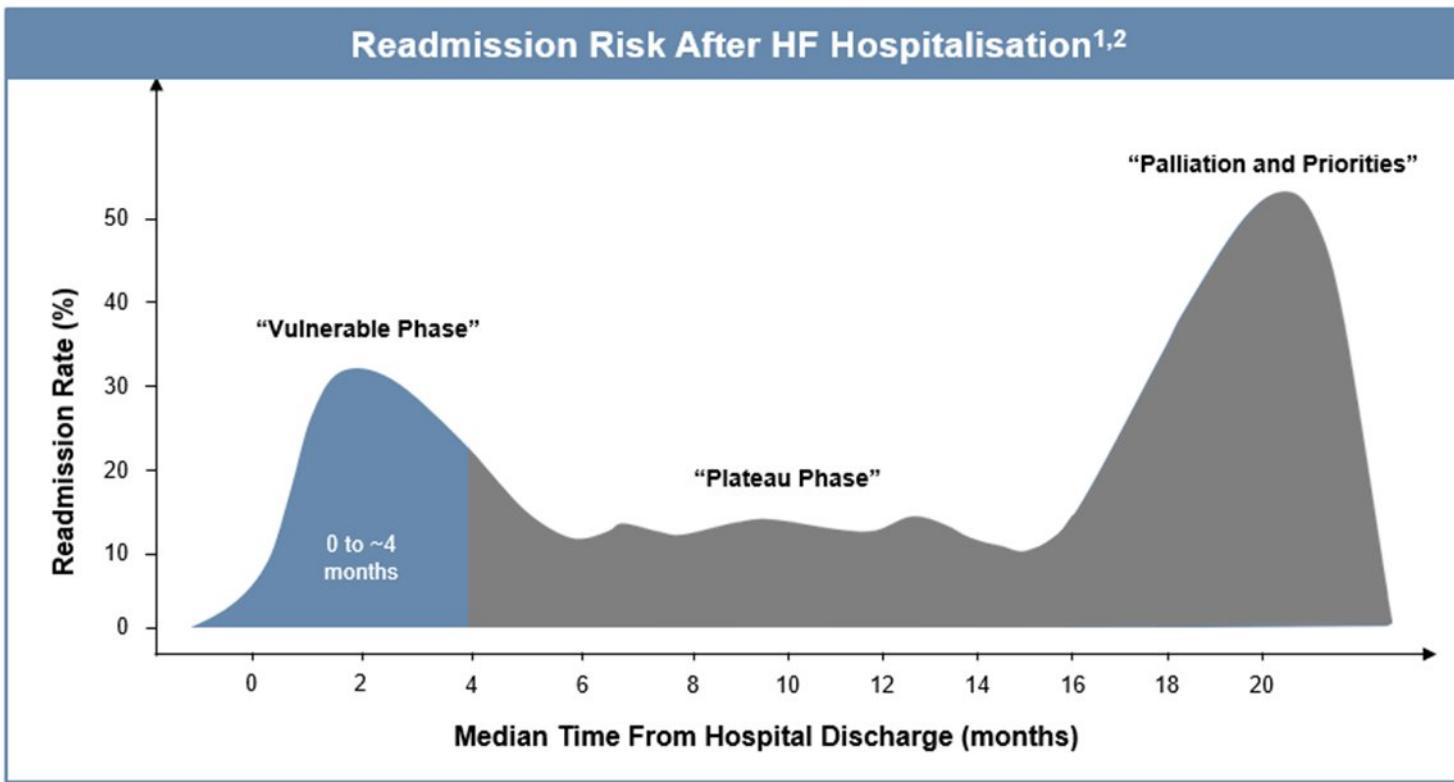


Figure adapted from Desai.¹

HF=heart failure.

1. Desai AS. Circ Heart Fail. 2012;5(4):398–400; 2. Gracia E, et al. Am J Ther. 2018;25(4):e456–e464; 3. Iacovoni Am, et al. Card Fail Rev. 2019;5(2):78–82.

Clinical Practice
Treating Patients Following Hospitalisation for Acute Decompensated Heart Failure: An insight into Reducing Early Rehospitalisation
Massimo Iacovoni, Ugo Gracia, Alessio Mazzucco, Antonio Ghezzi, Barbara Sestini
Abstracts from the 2019 European Congress of Cardiology (ECC) - Paris, France
Session: Clinical Practice
Topic: Clinical Practice
Category: Clinical Practice
Keywords: Acute heart failure, Hospital admission, Hospitalization, Heart failure, Hospitalization
Background: There is no consensus on the optimal approach to patients with acute decompensated heart failure (ADHF) after hospital discharge. The aim of this study was to evaluate the impact of a tailored pharmacotherapy on early rehospitalisation and readmission rates during the vulnerable phase after discharge.
Methods: A total of 100 consecutive patients with ADHF were included. All patients received standard medical therapy. In addition, patients were randomised to receive a tailored pharmacotherapy (n=50) or standard pharmacotherapy (n=50). The tailored pharmacotherapy included a combination of metformin, losartan, and spironolactone, while the standard pharmacotherapy included a combination of metformin, losartan, and furosemide. The primary endpoint was the rate of rehospitalisation and readmission during the first 3 months after discharge. Secondary endpoints included the rate of hospital admissions and readmissions during the first 6 months after discharge, and the rate of hospital admissions and readmissions during the first year after discharge.
Results: The rate of rehospitalisation and readmission during the first 3 months after discharge was significantly lower in the tailored pharmacotherapy group compared to the standard pharmacotherapy group (10% vs 22%, p=0.04). The rate of hospital admissions and readmissions during the first 6 months after discharge was also significantly lower in the tailored pharmacotherapy group compared to the standard pharmacotherapy group (15% vs 28%, p=0.03). The rate of hospital admissions and readmissions during the first year after discharge was also significantly lower in the tailored pharmacotherapy group compared to the standard pharmacotherapy group (25% vs 38%, p=0.02).
Conclusion: A tailored approach for HF pharmacotherapy while the patient is in hospital and immediately after discharge could be useful in reducing early adverse events that cause re-hospitalisation and, consequently, prevent worsening HF and readmission during the vulnerable phase after discharge.

—Iacovoni et al. 2019³

AFFIRM-AHF : Key Eligibility 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.

AFFIRM-AHF Primary and Secondary Outcomes

Primary

- Composite of total HF hospitalisations and CV death up to 52 weeks

Secondary

- Total HF hospitalisations
- CV death
- Time to first HF hospitalisation or CV death
- Composite of total CV hospitalisations and CV death
- Days lost due to HF hospitalisations or CV death

Safety

- Adverse events

Study Treatment Dosing Regimen



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



Hb 8 ^a 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 ID persisted
500 mg FCM / placebo

^a<10 g/dL for sites in The Netherlands, Spain and Singapore.

FCM=ferric carboxymaltose; Hb=haemoglobin; ID=iron deficiency.
Ponikowski P, et al. Eur J Heart Fail. 2019;21(12):1651–1658.

AFFIRM – AHF Baseline Characteristics (1500pts)

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

Results presented as mean \pm SD unless otherwise noted.

ITT population.

BP, blood pressure; NYHA, New York Heart Association.

Baseline Laboratory Data

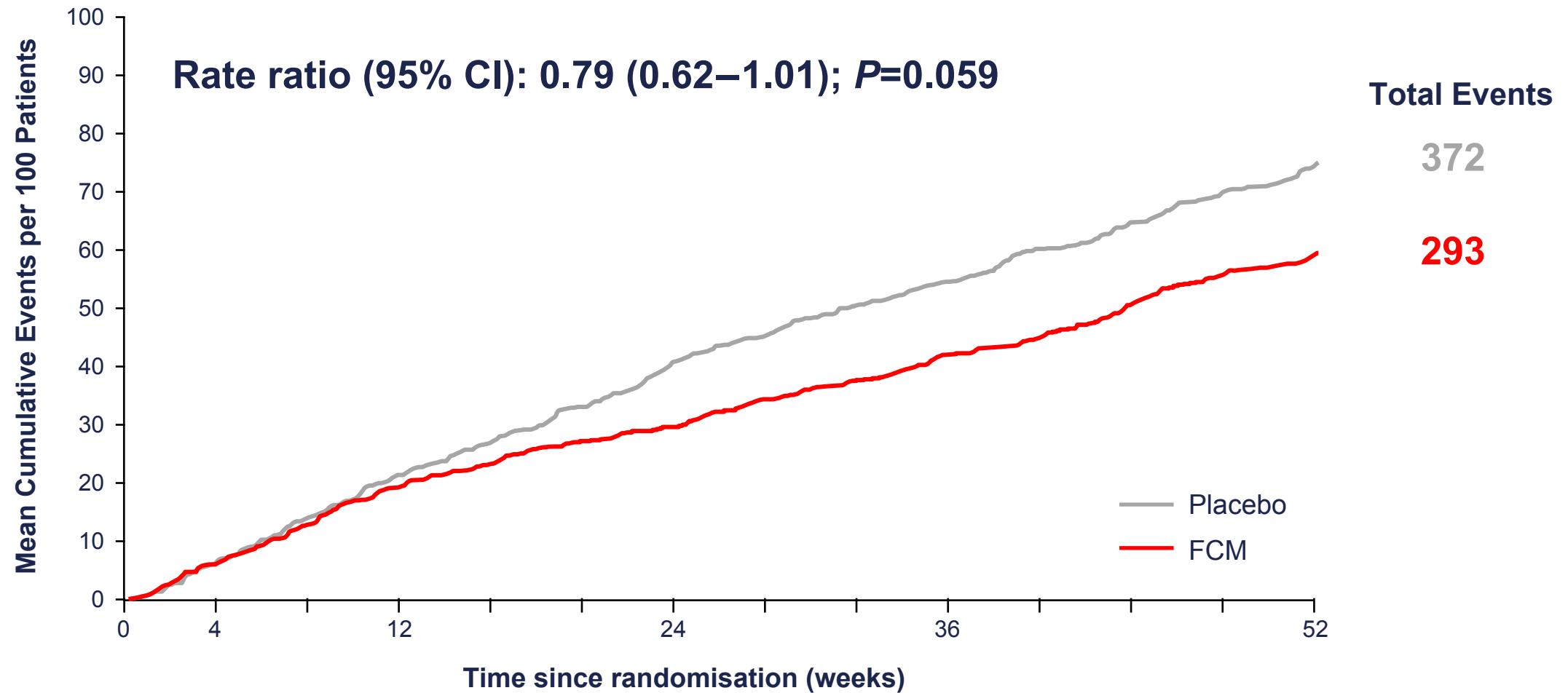
<u>Laboratory test results</u>	<u>FCM (N=558)</u>	<u>Placebo (N=550)</u>
<u>NT-proBNP, pg/mL, median (IQR)</u>	<u>4743 (2781, 8128)</u>	<u>4684 (2785, 8695)</u>
<u>BNP, pg/mL, median (IQR)</u>	<u>1068 (802, 1715)</u>	<u>1204 (803, 1955)</u>
<u>Haemoglobin, g/dL</u>	<u>12.3 ± 1.6</u>	<u>12.1 ± 1.6</u>
<u>Anaemia, %</u>	<u>52</u>	<u>57</u>
<u>Ferritin, ng/mL</u>	<u>83.9 ± 62.2</u>	<u>88.5 ± 68.6</u>
<u>Ferritin <100 ng/mL, %</u>	<u>73</u>	<u>69</u>
<u>TSAT (%)</u>	<u>15.2 ± 8.3</u>	<u>14.2 ± 7.5</u>
<u>TSAT <20%, %</u>	<u>82</u>	<u>85</u>
<u>eGFR, mL/min/1.73 m²</u>	<u>55.3 ± 21.3</u>	<u>55.7 ± 23.1</u>
<u>eGFR <60 mL/min/1.73 m², %</u>	<u>52</u>	<u>52</u>

Results presented as mean ± SD unless otherwise noted.

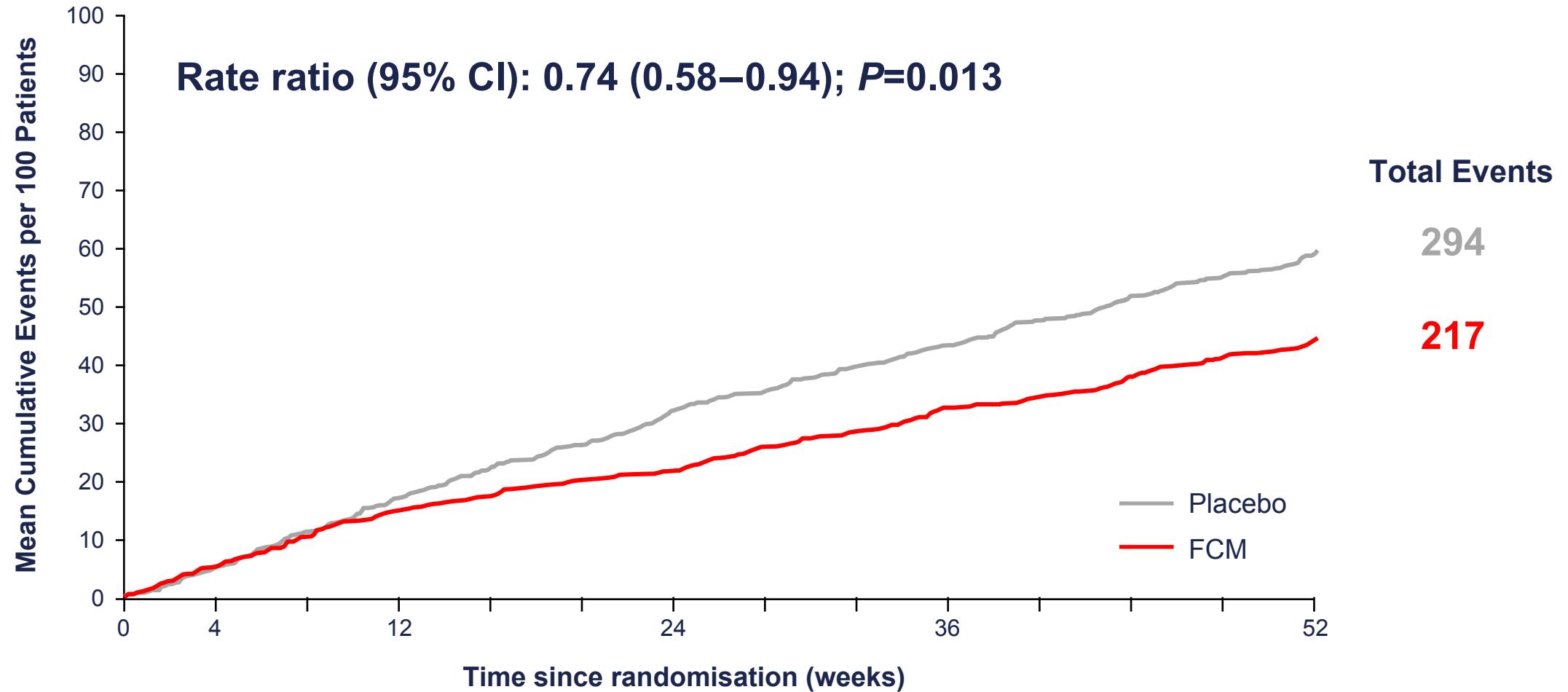
ITT population.

eGFR, estimated glomerular filtration rate.

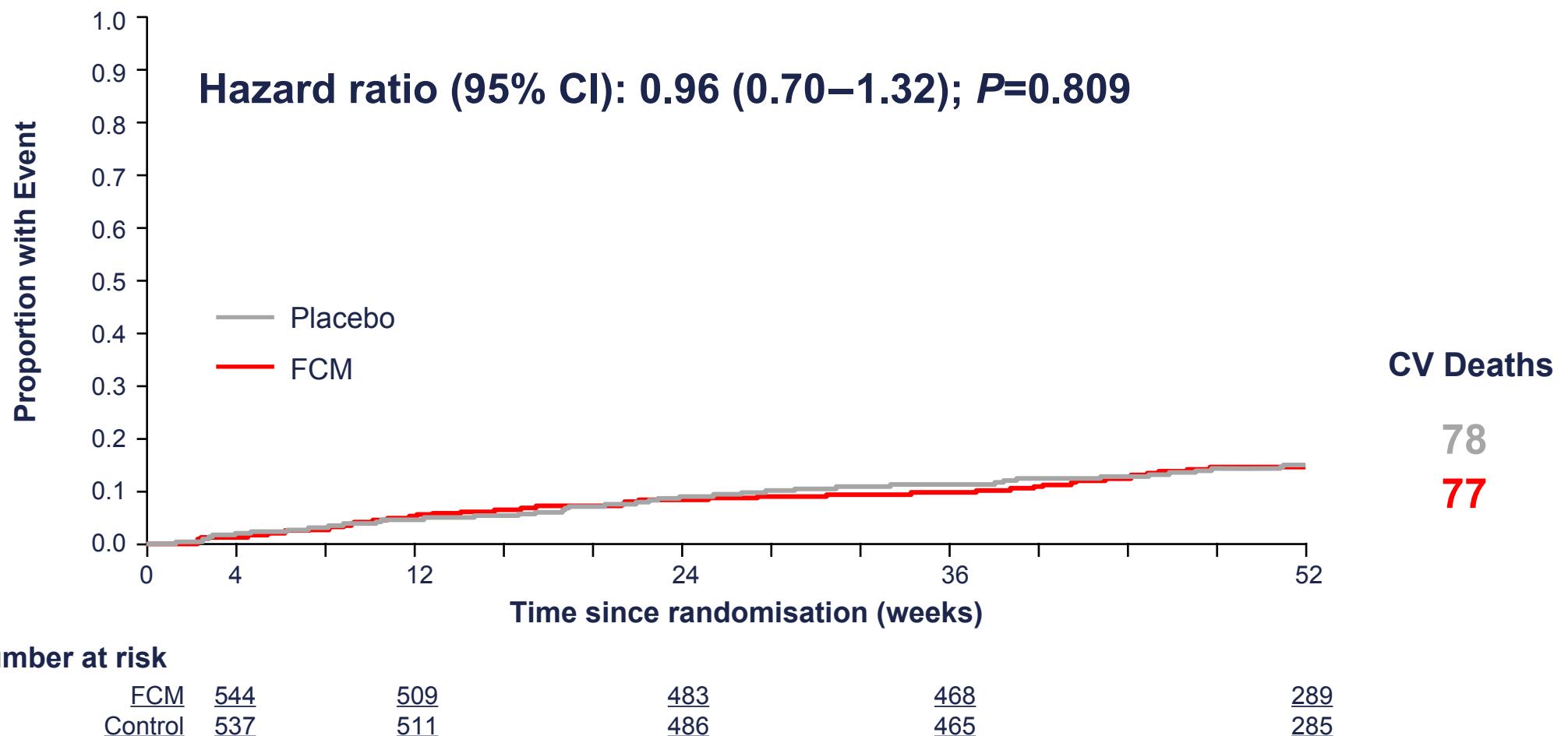
Primary Endpoint: Total HF Hospitalisations and CV Death



Component of Primary Endpoint: Total HF Hospitalisations



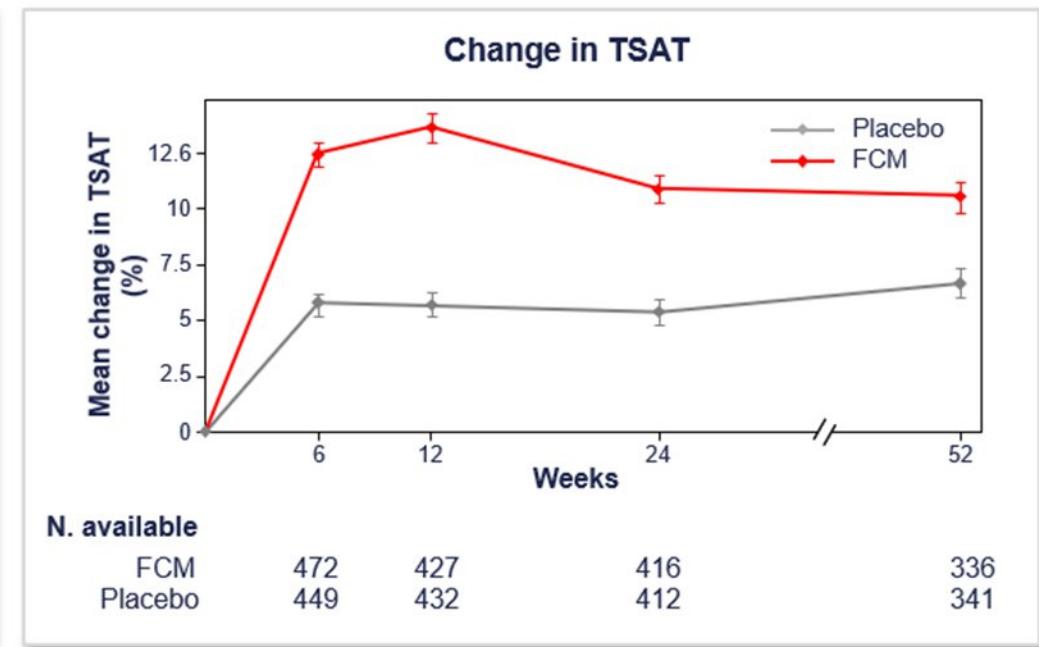
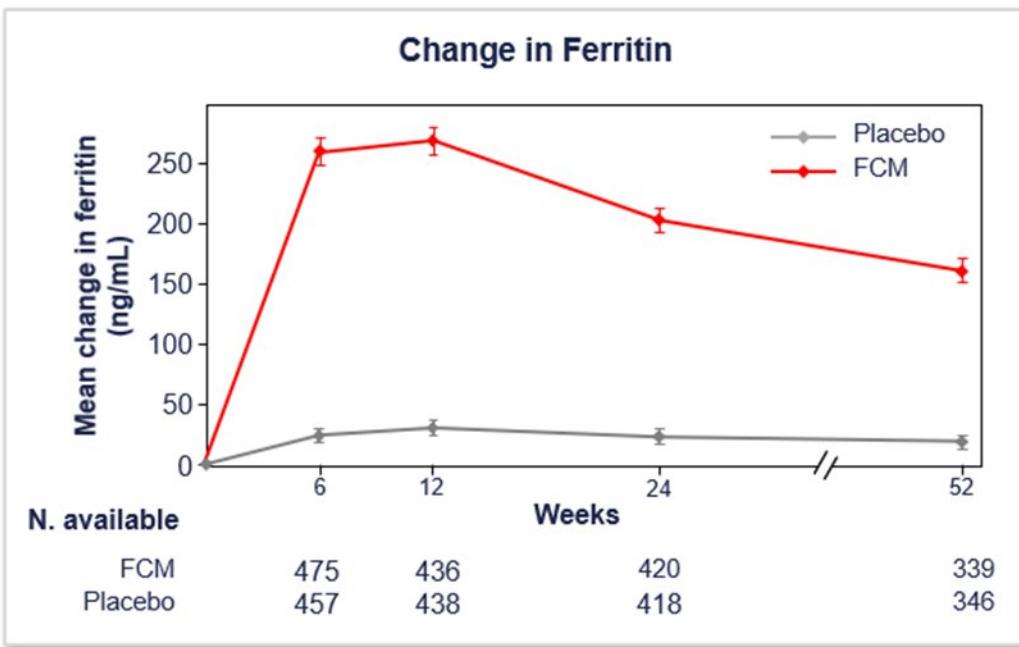
Component of Primary Endpoint: CV Death



COVID-19 Sensitivity Analysis

	mITT Population RR or HR (95% CI)	Pre-COVID sensitivity analysis RR or HR (95% CI)
Total HF Hospitalisations and CV Death	RR: 0.79 (0.62–1.01) <i>P</i>=0.059	RR: 0.75 (0.59–0.96) <i>P</i>=0.024
Total HF Hospitalisations	RR: 0.74 (0.58–0.94) <i>P</i>=0.013	RR: 0.70 (0.55–0.90) <i>P</i>=0.005
CV Death	HR: 0.96 (0.70–1.32) <i>P</i>=0.81	HR: 0.94 (0.68–1.29) <i>P</i>=0.69
First HF Hospitalisation or CV Death	HR: 0.80 (0.66–0.98) <i>P</i>=0.030	HR: 0.79 (0.65–0.97) <i>P</i>=0.023
Total CV Hospitalisations and CV Death	RR: 0.80 (0.64–1.00) <i>P</i>=0.050	RR: 0.77 (0.62–0.97) <i>P</i>=0.024

Change in Ferritin, TSAT, and Haemoglobin



Haemoglobin mean (SD) change from baseline to week 52

- FCM: 0.8 (1.8) g/dL
- Placebo: 0.3 (1.7) g/dL

FCM=ferric carboxymaltose; SD=standard deviation; TSAT=transferrin saturation.
Ponikowski P, et al. *Lancet*. 2020; [https://doi.org/10.1016/S0140-6736\(20\)32339](https://doi.org/10.1016/S0140-6736(20)32339).

Esc 2021 Heart Failure Guidelines

 ESC European Heart Journal (2021) 00, 1–128
European Society of Cardiology doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

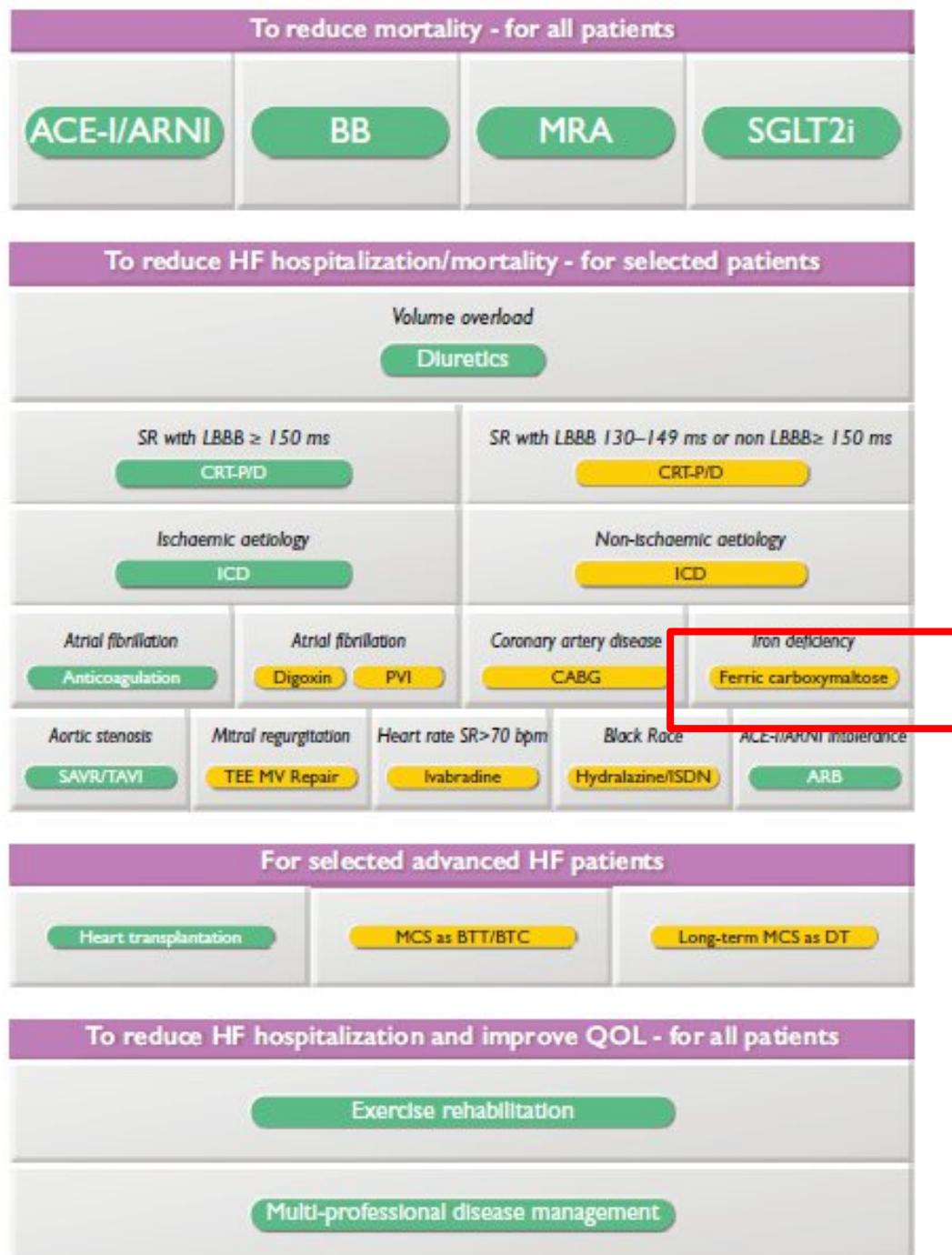
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

With the special contribution of the Heart Failure Association (HFA) of the ESC

Recommendations	Class ^a	Level ^b
<p>It is recommended that all patients with HF be periodically <u>screened for anaemia and iron deficiency</u> with a full blood count, <u>serum ferritin concentration</u>, and TSAT.</p>	I	C
<p>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%, <u>to alleviate HF symptoms, improve exercise capacity and QOL</u>.^{720,722,724}</p>	IIa	A
<p>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%, <u>to reduce the risk of HF hospitalization</u>.⁵¹²</p>	IIa	B

Esc 2021 Management of HFrEF



Esc 2021

Recommendations for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

Recommendations	Class ^a	Level ^b
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment. ^{427,472}	I	C
It is recommended that evidence-based oral medical treatment be administered before discharge. ^{103,513}	I	C
An early follow-up visit is recommended at 1–2 weeks after discharge to assess signs of congestion, drug tolerance and start and/or uptitrate evidence-based therapy. ^{517,518}	I	C
Ferric carboxymaltose should be considered for iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to improve symptoms and reduce rehospitalizations. ⁵¹²	IIa	B

RECOMMENDATIONS TO CONSIDER THE USE OF FCM

FCM should be considered for:

Symptomatic patients with LVEF <45% + ID

To alleviate HF symptoms, improve exercise capacity and QoL

Class

IIa

Level

A

Pre- and early-post discharge follow-up of patients hospitalised for AHF + ID

To improve symptoms and reduce rehospitalisations

Class

IIa

Level

B

Symptomatic patients recently hospitalised for HF with LVEF <50% + ID

To reduce the risk of HF hospitalisation

Class

IIa

Level

B