PERCHE' TRATTARE L'IRON DEFICIENCY NELLO SCOMPENSO CARDIACO

Congresso Patient Blood Management - PBM

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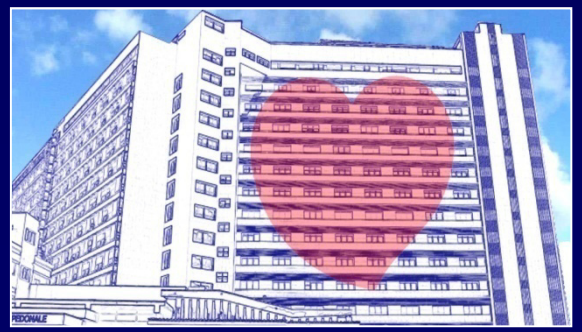

Iron Deficiency nello Scompenso Cardiaco

Agenda

- Burden della ID nello scompenso
- Diagnosi di ID
- Trattamento farmacologico della ID
- Considerazioni pratiche di gestione
- Take-home messages

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Iron Deficiency in Heart Failure

- Is common (25-40% dei pazienti)
- Is associated with more symptoms
- Is associated with poor outcome
- Treatment seems to be attractive

Detrimental Effects of Iron Deficiency

Mitochondria

- Decreased oxidative metabolism, iron-sulfur clusters synthesis, and density of mitochondrial cristae

Cell

- Deranged mitochondrial morphology
- ↓Number of mitochondria
- ↓Myoglobin pool; AMPK activation
- ↑Glycolytic activity

Tissue

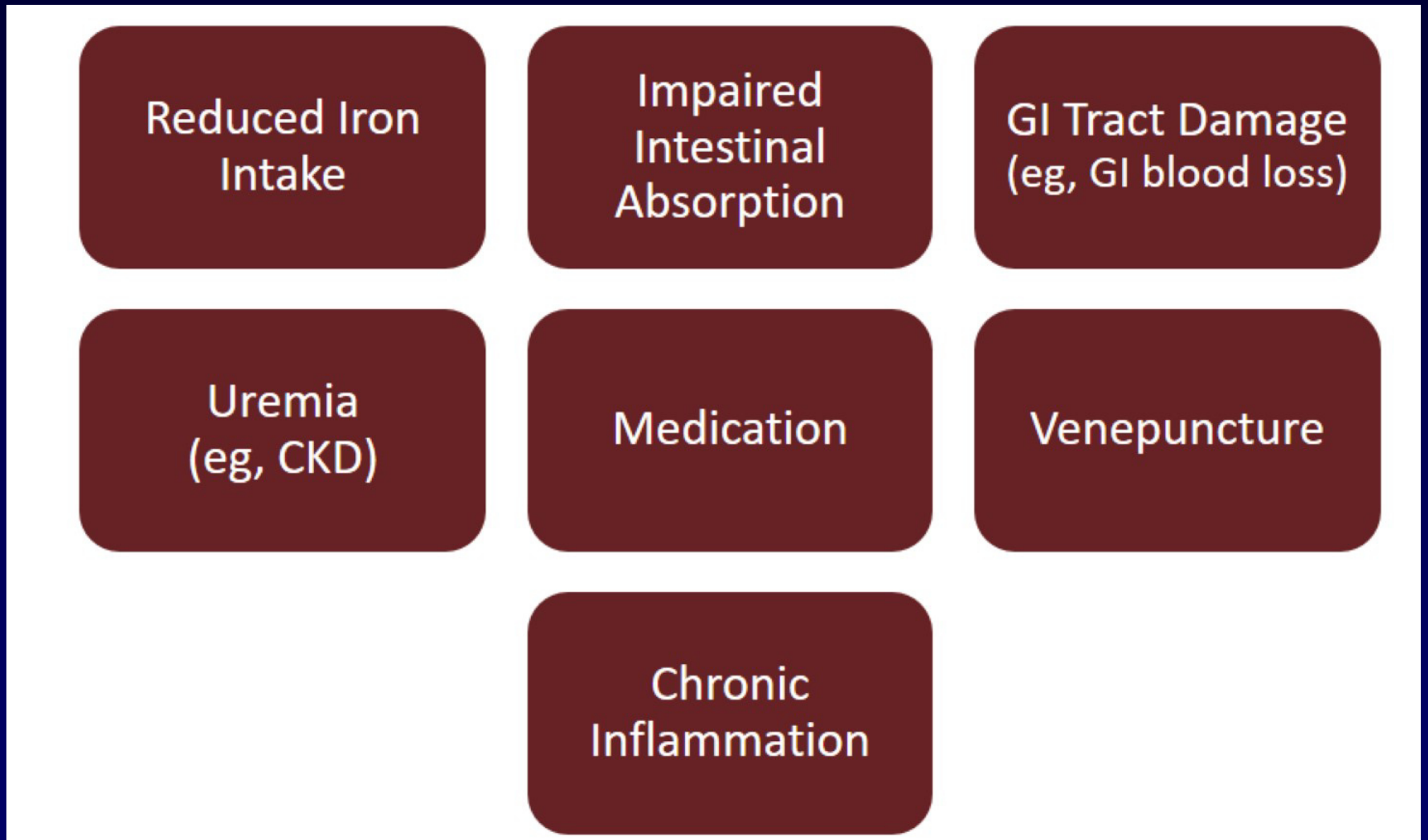
- Altered muscle fiber composition
- ↓Muscle mass

Organism

- Decreased overall physical work capacity, aerobic capacity, endurance capacity, and aerobic and endurance adaptation after training

Stugiewicz M, et al. *Eur J Heart Fail.* 2016;18:762-773.

Etiology of iron deficiency in HF



McDonagh T, Macdougall IC. *Eur J Heart Fail*. 2015;17:248-262.

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Definition of Iron Deficiency

Absolute Iron Deficiency

→Serum ferritin <100 mcg/L

Functional Iron Deficiency

→Ferritin between 100-299 mcg/L *AND*
→Transferrin saturation <20%

Symptoms of Iron Deficiency in HF patients

- Symptoms of ID are nonspecific and similar to symptoms of HF
  - Fatigue; exhaustion
- Patient often do not recognize that ID is present and, as a consequence, diagnosis is not pursued and the condition is left untreated

Cappellini MD et al. Am J Hematol 2017; 92:1068-1078

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Oral Iron Supplementation

Advantages

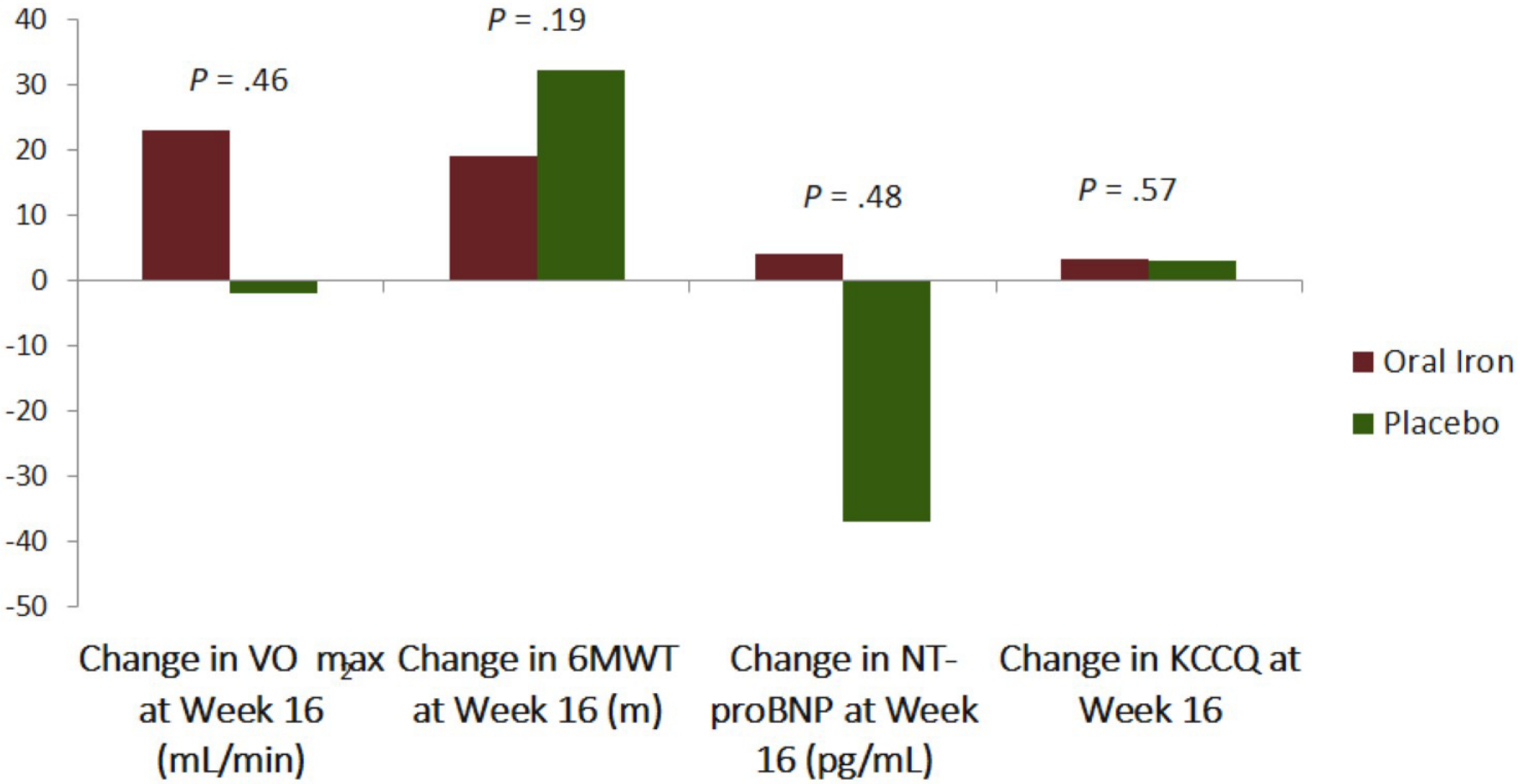
- Cheap
- Easy to administer

Disadvantages

- Poorly absorbed (max 5 to 10 mg/day)
- GI side effects common
- Compliance often poor
- Absorption limited if ferritin elevated
- Absorption reduced in inflammation

Drozd M, et al. *Am J Cardiovasc Drugs*. 2017;17:183-201.
McDonagh T, Macdougall IC. *Eur J Heart Fail*. 2015;17:248-262.

High-Dose Oral Iron in HFrEF: Results of the IRONOUT HF Trial



Lewis GD, et al. *JAMA*. 2017;317:1958-1966.

FCM: Summary of Clinical Evidence

Trial	FAIR-HF[a]	CONFIRM-HF[b]	EFFECT-HF[c]
N	459	304	172
Population	NYHA FC II-III; LVEF ≤ 40%; Hgb 9.5 g/dL to 13.5 g/dL	NYHA FC II-III; LVEF ≤ 45%; Hgb < 15 g/dL; NT-prop > 400 pg/mL or BNP > 100 pg/mL	NYHA FC II-III; LVEF ≤ 45%; VO_2 max 10 mL/kg/min to 20 mL/kg/min; Hgb < 15 g/dL; NT-proBNP > 400 pg/mL or BNP > 100 pg/mL
Therapy	FCM 200 mg until normalized iron status*	FCM 500 mg to 2000 mg at baseline and after 6 weeks; subsequently, 500 mg every 12 week if still with ID	FCM 500 mg to 2000 mg at baseline and after 6 and 12 weeks if still with ID
Study Period	24 weeks	52 weeks	24 weeks
Results	↓ NYHA FC; ↑ PGA; ↑ 6MWT; ↑ EQ-5D; ↑ KCCQ	↑ 6MWT; ↓ NYHA FC; ↑ PGA; ↑ EQ-5D; ↓ HHF†	Peak VO_2 maintained; ↓ NYHA FC; ↑ PGA

*After iron normalization, 200 mg once every 4 weeks; †Not a predefined endpoint.

a. Anker SD, et al. *N Engl J Med*. 2009;361: 2436-2348; b. Ponikowski P, et al. *Eur Heart J*. 2015;36:657-668.
c. van Veldhuisen DJ, et al. *Circulation*. 2017;136:1374-1383.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency

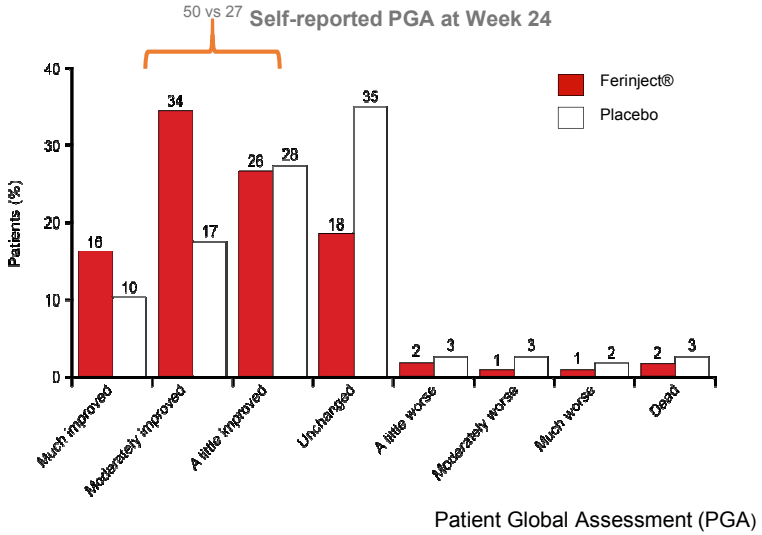
Stefan D. Anker, M.D., Ph.D., Josep Comin Colet, M.D.,
Gerasimos Filippatos, M.D., Ronnie Willenheimer, M.D.,
Kenneth Dickstein, M.D., Ph.D., Helmut Drexler, M.D.,*
Thomas F. Lüscher, M.D., Boris Bart, M.D., Waldemar Banasiak, M.D., Ph.D.,
Joanna Niegowska, M.D., Bridget-Anne Kirwan, Ph.D., Claudio Mori, M.D.,
Barbara von Eisenhart Rothe, M.D., Stuart J. Pocock, Ph.D.,
Philip A. Poole-Wilson, M.D.,* and Piotr Ponikowski, M.D., Ph.D.,
for the FAIR-HF Trial Investigators†

N Engl J Med 2009;361:2436-48

FAIR-HF: Efficacy Outcomes

– IV Iron Carboxymaltose improved self-reported PGA scores at week 24

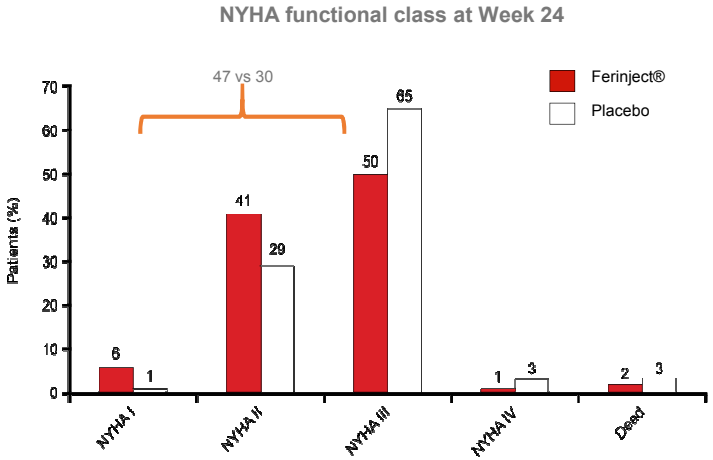
– Odds ratio for better rank: 2.51 (95% CI 1.75, 3.61), P<0.001



Patient Global Assessment (PGA)

– IV Iron Carboxymaltose improved NYHA functional class at week 24

– Odds ratio for improvement by 1 class: 2.40 (95% CI 1.55, 3.71), P<0.001



FAIR-HF

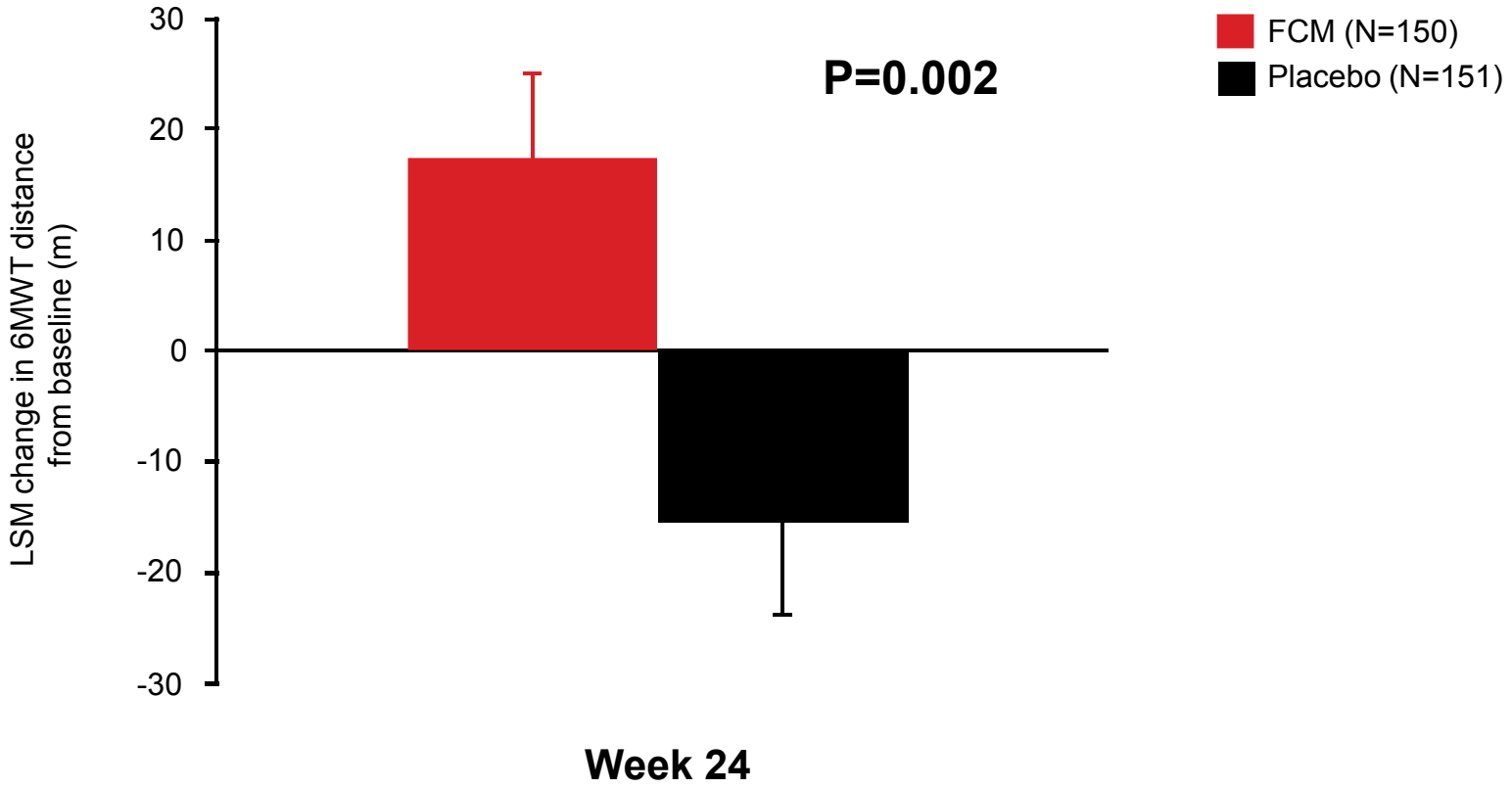
03/12/2018

Anker SD et al. N Eng J Med 2009;361:2436-48.

Primary endpoint: change in 6-minutes walking test distance at Week 24

FCM improved 6MWT at week 24

FCM vs placebo: 33 ± 11 m *(least squares mean ± SE)*



Ponikowski P et al. Eur Heart J 2015;36:657-668

European Heart Journal (2015) **36**, 657–668
doi:10.1093/eurheartj/ehu385

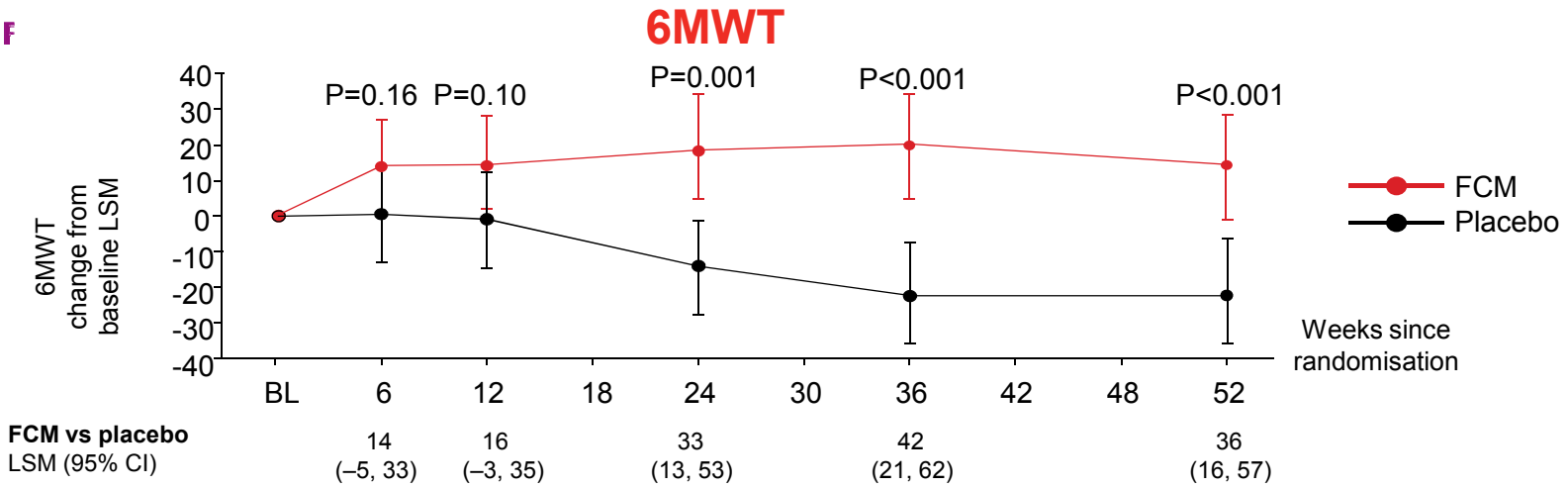
FASTTRACK ESC HOT LINE
Heart failure/cardiomyopathy

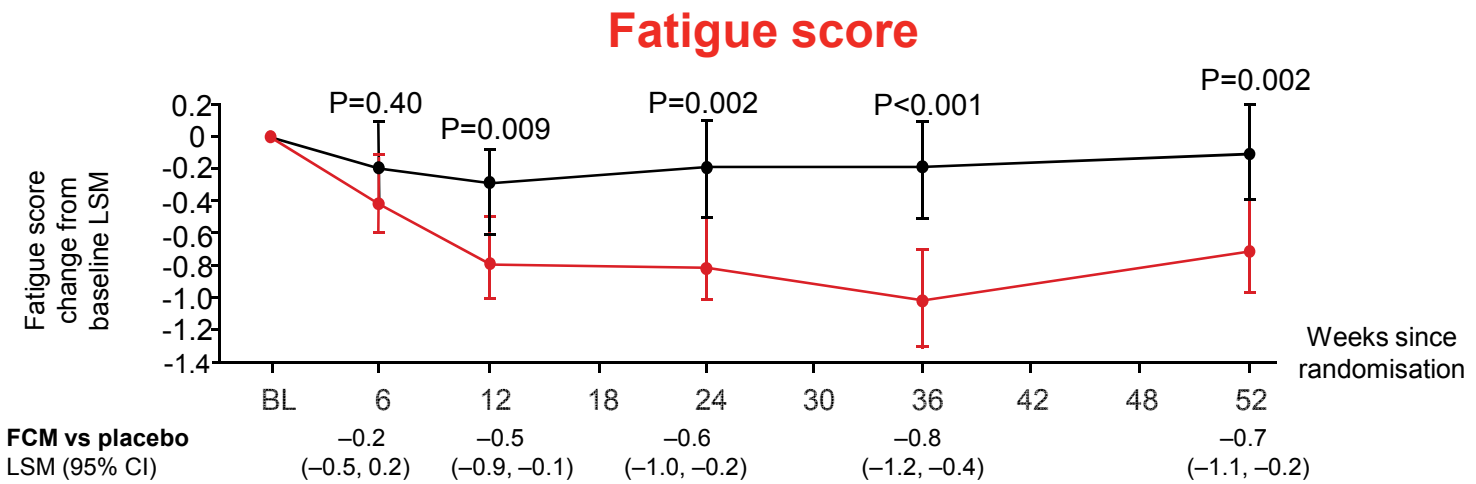
Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†

Piotr Ponikowski[1,2*], Dirk J. van Veldhuisen[3], Josep Comin-Colet[4], Georg Ertl[5,6], Michel Komajda[7], Viacheslav Mareev[8], Theresa McDonagh[9], Alexander Parkhomenko[10], Luigi Tavazzi[11], Victoria Levesque[12], Claudio Mori[12], Bernard Roubert[12], Gerasimos Filippatos[13], Frank Ruschitzka[14], and Stefan D. Anker[15], for the CONFIRM-HF Investigators

Secondary endpoints: Changes in 6MWT and Fatigue score over time

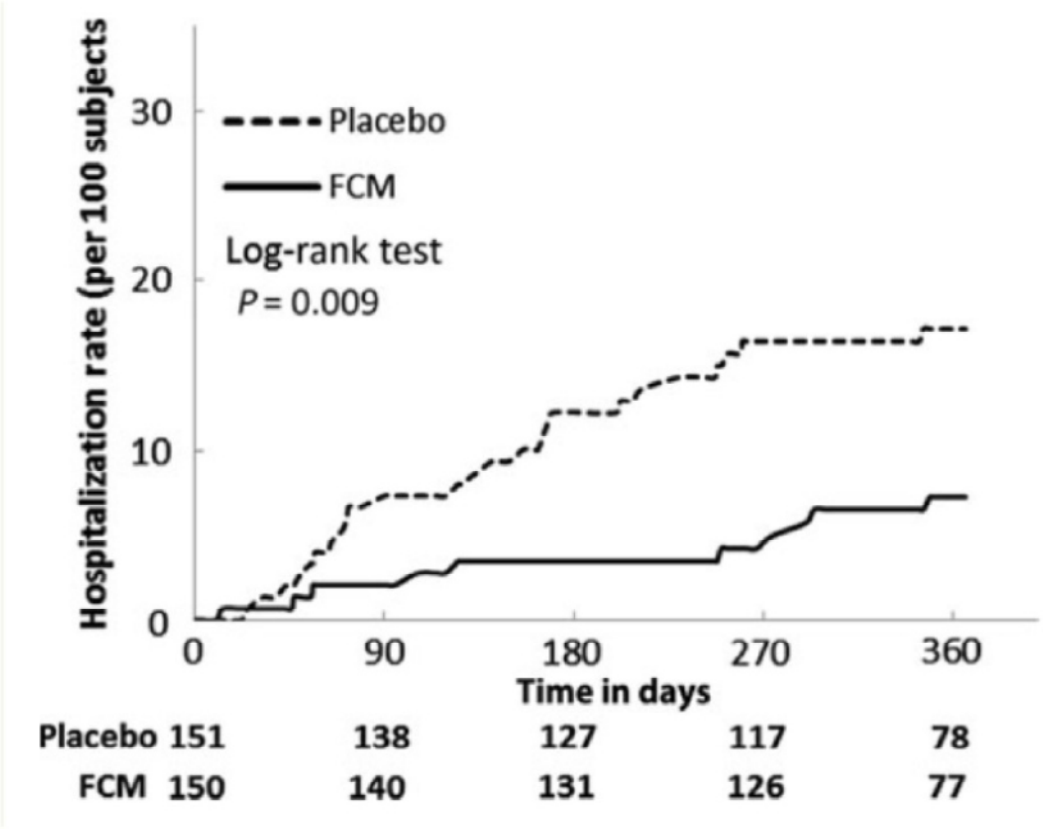
CONFIRM-HF





Ponikowski P et al. Eur Heart J 2015;36:657-668

CONFIRM-HF: Time to First Hospitalization Due to Worsening HF



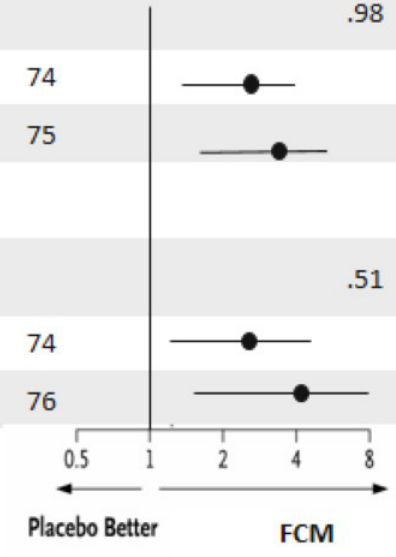
Ponikowski P, et al. *Eur Heart J*. 2015;36:657-668. *(Open access from Creative Commons)*

Ponikowski P et al, Eur Heart J 2015: 36, 657–668

Efficacy of FCM Stratified According to the Presence of Anemia

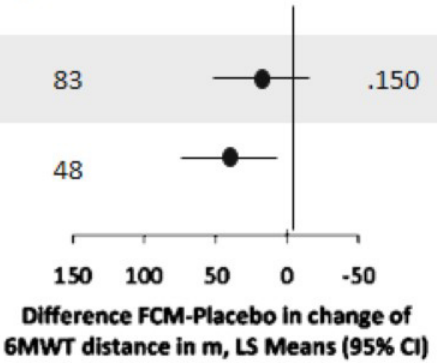
FAIR-HF[a]

Subgroups	FCM	Placebo	OR (95% CI)	*P* Value for Interaction
Self-reported PGA	*No. of patients*			
Hgb				.98
≤ 120 (g/L)	146	74		
> 120 (g/L)	146	75		
NYHA FC				
Hgb				.51
≤ 120 (g/L)	148	74		
> 120 (g/L)	146	76		



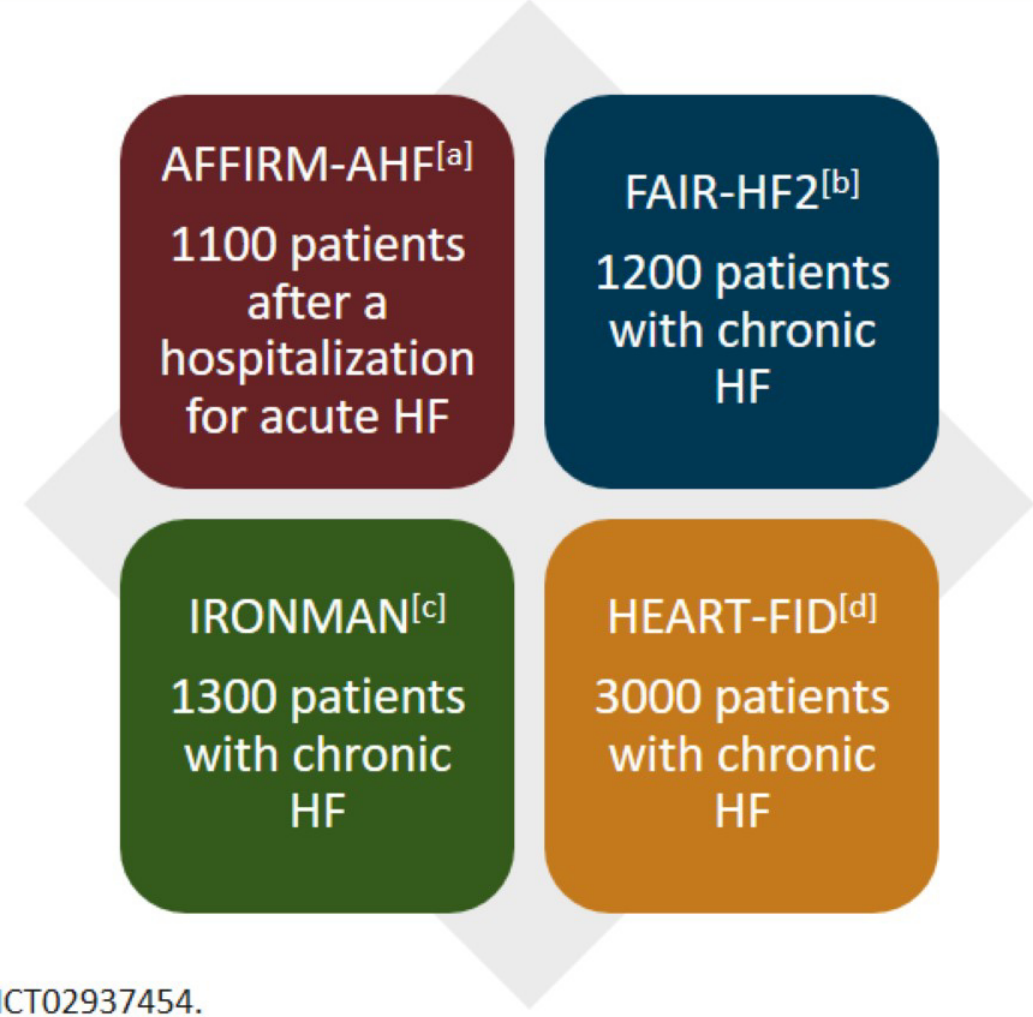
CONFIRM-HF[b]

Subgroups	FCM	Placebo	OR (95% CI)	*P* Value for Interaction
Hgb	*No. of patients*			
≥ 12 g/dL	86	83		.150
< 12 g/dL	44	48		



a. Anker SD, et al. *N Engl J Med*. 2009;361:2436-2348.
b. Ponikowski P, et al. *Eur Heart J*. 2015;36:657-668.

CVOTs in Patients Treated With FCM



a. ClinicalTrials.gov. NCT02937454.
b. ClinicalTrials.gov. NCT03036462.
c. ClinicalTrials.gov. NCT02642562.
d. ClinicalTrials.gov. NCT03037931.

Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality (FAIR-HF2)

Arms and Interventions

Go to ▾

Arm	Intervention/treatment
Experimental: Verum group (FCM) I.v. iron administration in the form of FCM will be carried out according to SmPC. I.v. iron bolus administration (1000 mg) will be followed by an optional administration of 500-1000 mg within the first 4 weeks, (up to a total of 2000 mg which is in-label), according to the approved dosing rules, followed by administration of 500 mg FCM at every 4 months, except when haemoglobin is > 16.0 g/dL or ferritin is > 800 µg/L .In the verum group, all patients will receive a saline administration, when no iron is indicated at the time of the visit and according to the values listed above.	Drug: Iron i.v. iron administration
Placebo Comparator: Placebo group (NaCL) Administration of i.v. NaCl at a volume according to the dosing rules for FCM, i.e. as described for the verum group.	Drug: Saline i.v. NaCl administration Other Name: salin

Outcome Measures

Go to ▾

Primary Outcome Measures:

1. Combined rate of recurrent hospitalisations for heart failure (HF) and of cardiovascular death (number of events) [Time Frame: at least after 12 month of follow-up]

   Combined rate of recurrent hospitalisations for heart failure and of cardiovascular death during follow-up.

Overall FCM Is Safe and Well Tolerated

Safety Reporting	FCM Pool (n = 507)		Placebo Pool (n = 335)	
	Patients with event, n (%)	Incidence/100 patient-years at risk	Patients with event, n (%)	Incidence/100 patient-years at risk
AEs	317 (62.5)	105.4	215 (64.2)	95.8
Serious AEs	86 (17.0)	28.6	79 (23.6)	35.2
AEs leading to study drug withdrawal	32 (6.3)	10.6	34 (10.1)	15.1
Study drug-related AEs	50 (9.9)	16.6	20 (6.0)	8.9
Serious drug-related AEs	0	0	1 (0.3)	0.4
Study drug-related AEs leading to study drug withdrawal	7 (1.4)	2.3	3 (0.9)	1.3

In a meta-analysis of patient data from 4 RCTs comparing FCM with placebo in patients with systolic HF and ID, FCM was not associated with an increase in AEs

Anker SD, et al. *Eur J Heart Fail*. 2018;20:125-133.

FCM: Safety and Tolerability

GI AEs

- Less frequent vs oral iron due to IV administration[a]
- Occurred in 2.9% of patients in clinical trials[b]

a. McDonagh T, Macdougall IC. *Eur J Heart Fail*. 2015;17:248-262.
b. Ferinject (ferric carboxymaltose) SMPC.

FCM: Safety and Tolerability (cont)

Hypersensitivity Reactions

- Risk of (very rare) anaphylaxis with dextran-containing formulations[a]
- Anaphylactoid reactions occurred very rarely in patients in clinical trials (≥ 1/10,000 to < 1/1000)[b]

a. McDonagh T, Macdougall IC. *Eur J Heart Fail*. 2015;17:248-262.
b. Ferinject (ferric carboxymaltose) SMPC.

FCM: Safety and Tolerability (cont)

Administration

- Administered by a healthcare professional; requires clinic visit
- Administration staff must be trained to evaluate and manage possible anaphylactic reaction
- Patient should be observed for at least 30 min following each injection

McDonagh T, Macdougall IC. *Eur J Heart Fail*. 2015;17:248-262.

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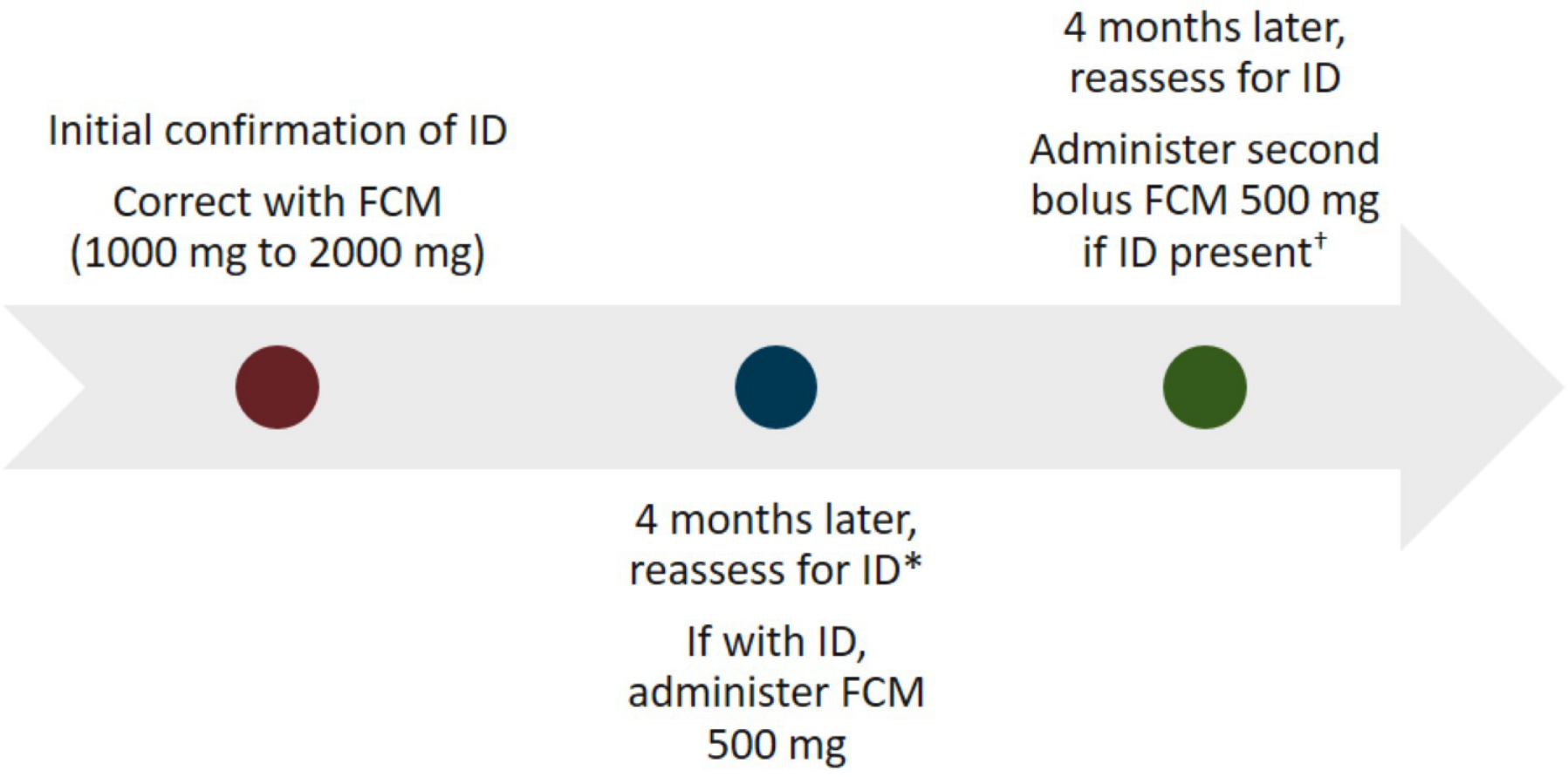
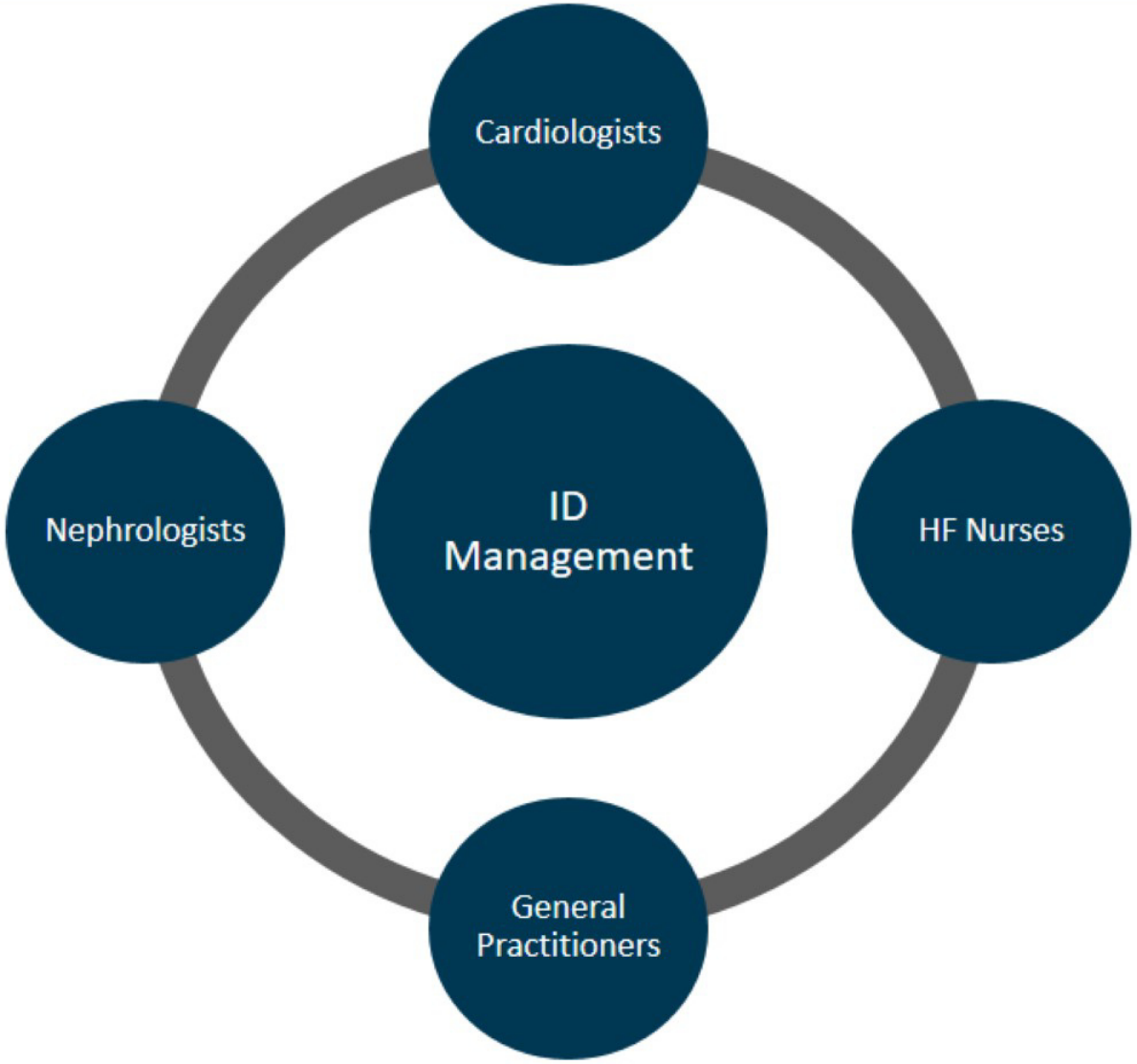
Replenishing Iron Stores: Monitoring and Follow-Up



*Experience based on dosing protocol from the CONFIRM-HF study.
†2000 mg to 3000 mg FCM generally administered over 1-year period.
Ponikowski P, et al. *ESC Heart Fail*. 2014;1:52-58.

Management of ID in Patients With HF: A Multidisciplinary Team Approach



Screening for iron deficiency is recommended for initial assessment of a patient with newly diagnosed HF

Recommendations for diagnostic tests in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:			
- haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin, AST, ALT, GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC	I	C	
- natriuretic peptides	IIa	C	

Ponikowski et al. Eur Heart J 2016; 37:2129-2200

Iron deficiency: 2016 Guidelines' recommendation

Recommendations	Class [a]	Level [b]	Ref [c]
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	469, 470

Ponikowski et al. Eur Heart J 2016; 37:2129-2200

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Take-home Messages

- La ID è frequente in pazienti con scompenso
  - può essere presente con o senza anemia
  - si associa a riduzione della tolleranza allo sforzo, riduzione della QOL e outcome sfavorevole
- Le linee guida ESC indicano in classe IC lo screening della ID

  in tutti i pazienti con scompenso cardiaco all'esordio
- L'utilizzo di FCM ev ha dimostrato sicurezza ed efficacia

  nel migliorare la classe funzionale e ridurre le ospedalizzazioni ed è raccomandato dalle linee guida.