Clinical Trials
Highlights in 2017

VII
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Novas Fronteiras
Em Cardiologia

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Ferro intravenoso na insuficiência cardíaca : FAIR-HF2

PMoraisSarmentoHospitaldaLuz**Fevereiro2017**

S2 Journal of Cardiac Failure Vol. 10 No. 1 Suppl. 2004

Table 1. Published Reports on Prevalence of Anemia in Patients with Chronic Heart Failure

Author, Year, Reference	Study	Number of Patients*	Definition of Anemia (Hb g/dL, Hct %)	Prevalence of Anemia (%)
Al-Ahmad, 2001[5]	SOLVD	6563	≤39% or <35%	22 or 4.3
Androne, 2003[14]		196	<41% (M), <38% (W)	61
Anker, 2002[17]	ELITE II	3044	<12.5 g/dL	16.9
Cleland, 2003[13]	EuroHeart	9971	<11.0 g/dL	18 (M), 23 (W)
Cronie, 2002[19]		269	≤11.0 g/dL	14.4
Ezekowitz, 2003[18]		12,065	ICD-9 codes 280, 285.9, 289†	17
Horwich, 2002[3]		1061	<13.0 g/dL (M), <12.0 g/dL (W)	30
Kosiborod, 2003[21]		2281	≤37%	48
Maggioni, 2002[11]	IN-CHF; Val-HeFT	2411; 5010	<12.0 g/dL (M), <11.0 g/dL (W)	15.5; 9.9
McClellan, 2002[23]		633	<30%, 30–35%, 36–39%, ≥40%	13.6, 33.2, 22.9, 30.3
Sarnack, 2002[22]	ARIC	14,410	<13.0 g/dL (M), <12.0 g/dL (W)	4.8 (M), 13 (W)
Silverberg, 2000[4]		142	<12.0 g/dL	55.6
Tanner, 2002[15]		193	<12.0 g/dL	15
Wisniacki, 2001[16]		201	<12.0 g/dL	49.8

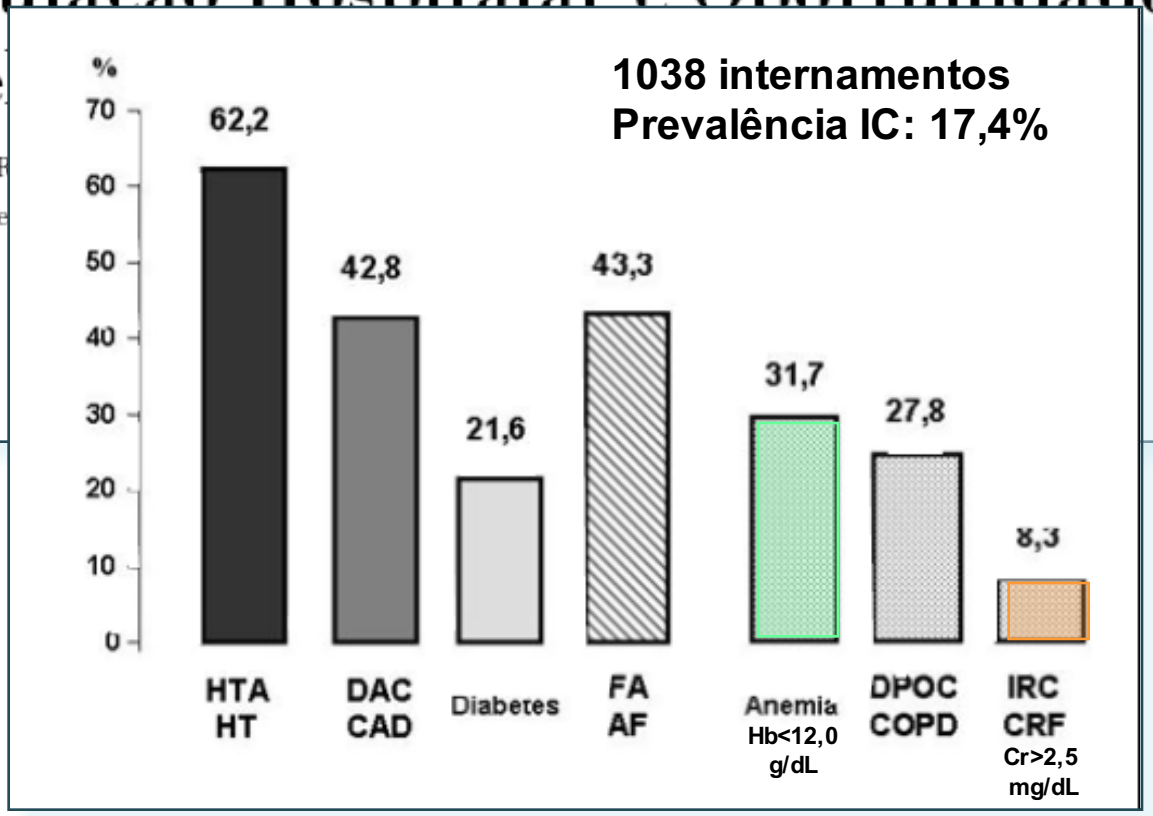
Hb, hemoglobin; Hct, hematocrit; M, men; W, women.
*Number of patients with reported Hb concentration.
†International Classification of Diseases, Ninth Revision, Clinical Modification Codes.

- **World Health Organization:**
  - Hb < 13 g/dl in men
  - Hb < 12 g/dl in women
- **National Kidney foundation:**
  - Hb < 12.5 g/dl in men and postmenopausal women

ARTIGOS ORIGINAIS

Insuficiência Cardíaca Aguda: Características de uma Popula[illegible] Hospitalar e Oportunidades para a Me[illegible]

PEDRO MORAES SA[illegible]
Se[illegible]



1038 internamentos
Prevalência IC: 17,4%

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Anemia Is Associated With Worse Symptoms, Greater Impairment in Functional Capacity and a Significant Increase in Mortality in Patients With Advanced Heart Failure

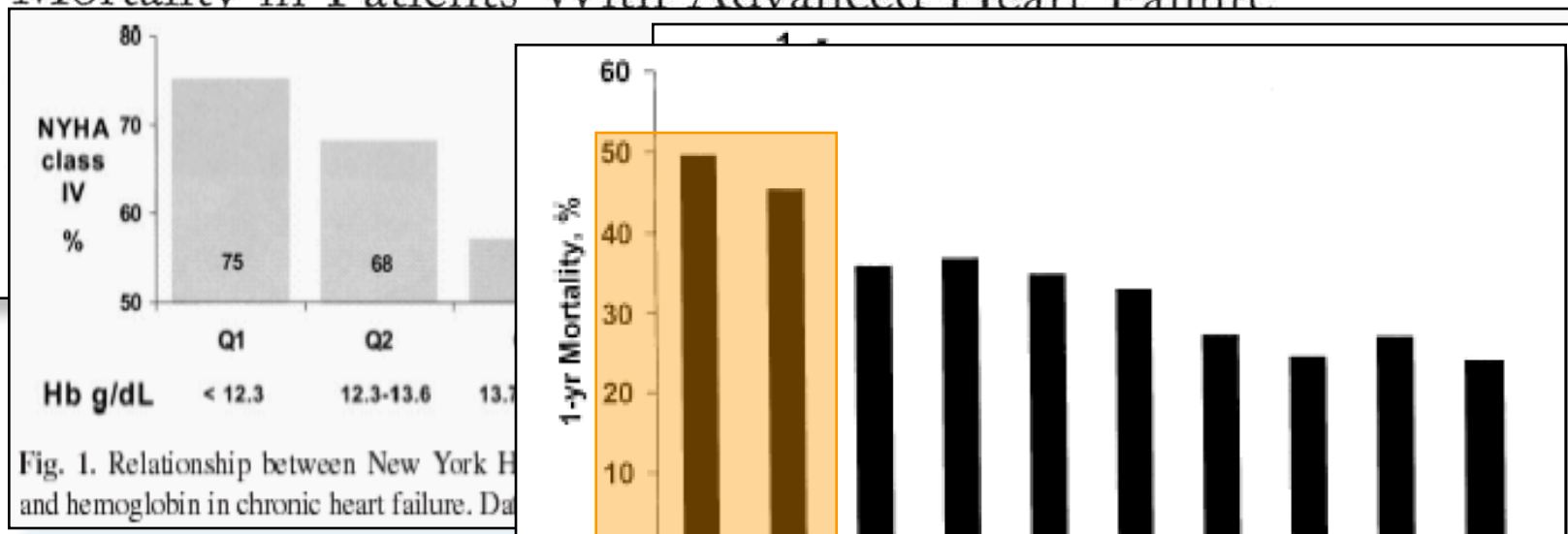

Fig. 1. Relationship between New York H
and hemoglobin in chronic heart failure. Da

Potenciais causas de anemia na IC

- Inibição da síntese da EPO pelos i-ECA/ARAII
- Deficiente produção de EPO por IRC
- Hemodiluição

~30%

- Ferropenia ou perdas GI pela ingesta de AAS profilática
- Deficiente aporte nutricional de ferro

- Alteração da absorção/metabolismo da Vit B12 e folato

- IC/Reacção inflamatória: citoquinas (TNFα, IL1, IL6)
  - ↓ eritropoiese
  - ↓ Sensibilidade medular EPO

- Baixo débito cardíaco – isquemia e disfunção medular renais
- Proteinuria: ↓ EPO, Fe, transferrina

Ferro intravenoso na insuficiência cardíaca : FAIR-HF2

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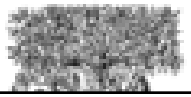
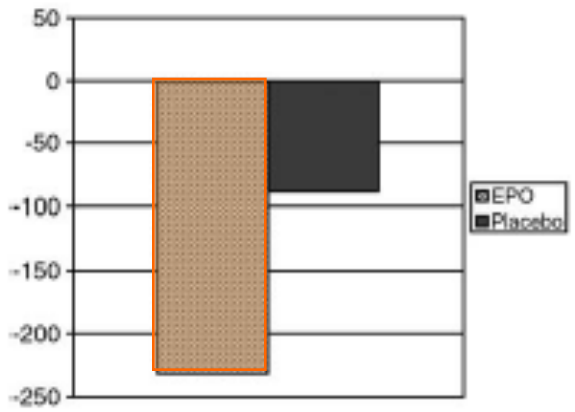


The European Journal

Table 1
Values before and after treatment in the 126 patients

	Before	
Hemoglobin (g%)	10.3±1.4	
Hematocrit (%)	30.6±4.1	
Serum ferritin	154.9±162	
Iron saturation (%)	20.0±7.6	
Serum iron	64.6±33.	
Serum creatinine (mg%)	2.4±1.1	
Δ GFR (ml min^{-1} month^{-1})	−0.95±1.1	
NYHA (0–4)	3.8±0.3	
Ejection fraction (%)	33.2±0.3	
Fatigue/SOB index (0–10)	8.9±1.4	
Hospitalizations (*n*)	3.7±3.5	
Systolic BP	132.0±22.2	131.6±27.9
Diastolic BP	75.2±11.7	76.2±11.8

Figure 3



Mean ΔBNP reduction values after three months in EPO and placebo groups.

European Heart Journal
doi:10.1093/eurheartj/ehs104

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11.2 Anaemia

Anaemia (defined as a haemoglobin concentration <13 g/dL in men and <12 g/dL in women) is common in HF, particularly in hospitalized patients. It is more frequent in women, the elderly, and in patients with renal impairment. Anaemia is associated with more symptoms, worse functional status, greater risk of HF hospitalization, and reduced survival. A standard diagnostic work-up should be undertaken in anaemic patients. Correctable causes should be treated in the usual way, although no definite aetiology is identified in many patients. Correction of iron deficiency using i.v. iron has been specifically studied in patients with HF (see Section 11.14). The value of erythropoietin-stimulating agents as a treatment for anaemia of unknown aetiology is unknown but is currently being tested in a large mortality–morbidity RCT.[187]

Table 3. Adverse Events of Interest.*

Adverse Event	Darbepoetin Alfa (N=1133)	Placebo (N=1140)	Risk Difference (95% CI)†	P Value‡
	no. of patients (%)		*percentage points*	
Any event of interest	660 (58.3)	662 (58.1)	0.2 (–3.9 to 4.2)	0.93
Cardiac failure	438 (38.7)	459 (40.3)	–1.6 (–5.6 to 2.4)	0.43
Ischemic heart disease	155 (13.7)	164 (14.4)	–0.7 (–3.6 to 2.2)	0.63
Cerebrovascular disorder				
Any	61 (5.4)	45 (3.9)	1.4 (–0.3 to 3.2)	0.10
Hemorrhagic	39 (3.4)	30 (2.6)	0.8 (–0.6 to 2.2)	0.26
Ischemic	51 (4.5)	32 (2.8)	1.7 (0.2 to 3.2)	0.03
Embolic and thrombotic events				
Any	153 (13.5)	114 (10.0)	3.5 (0.9 to 6.1)	0.009
Arterial§	87 (7.7)	73 (6.4)	1.3 (–0.8 to 3.4)	0.24
Venous¶	29 (2.6)	20 (1.8)	0.8 (–0.4 to 2.0)	0.19
Vessel type unspecified and mixed arterial and venous‖	51 (4.5)	27 (2.4)	2.1 (0.6 to 3.6)	0.005
Hemodialysis-related vascular access thrombosis	1 (0.1)	0	0.1 (–0.1 to 0.3)	0.50
Hypertension	81 (7.1)	69 (6.1)	1.1 (–0.9 to 3.1)	0.29
Cancer	69 (6.1)	68 (6.0)	0.1 (–1.8 to 2.1)	0.90
Convulsions	4 (0.4)	5 (0.4)	–0.1 (–0.6 to 0.4)	1.00
Hypersensitivity reactions	99 (8.7)	96 (8.4)	0.3 (–2.0 to 2.6)	0.79
Antibody-mediated pure red-cell aplasia	0	0	NA	NA

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European Jour
doi:10.1093/eu

VIEW

Beyond th
recognizi

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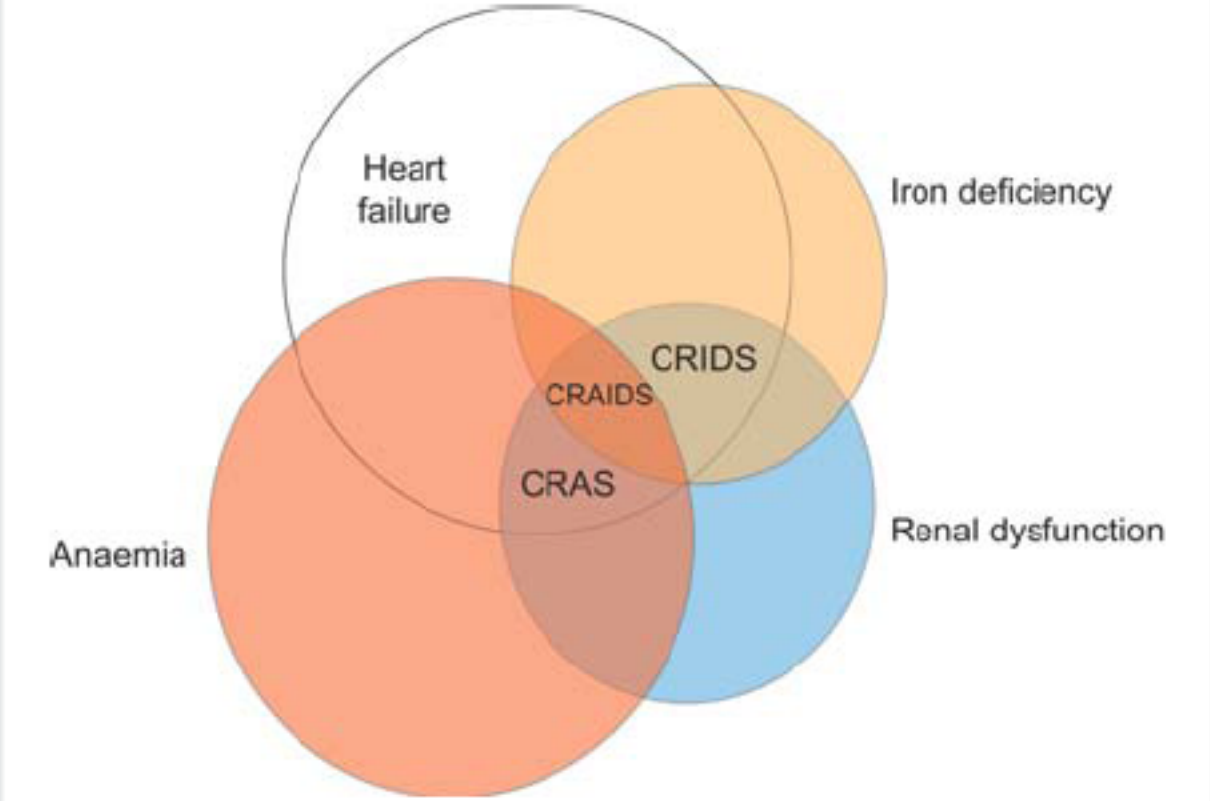

Figure 1 The interaction between heart failure, renal dysfunction, anaemia, and iron deficiency. CRAS, cardiorenal anaemia syndrome; CRIDS, cardiorenal–iron deficiency syndrome; CRAIDS, cardiorenal–anaemia–iron deficiency syndrome.

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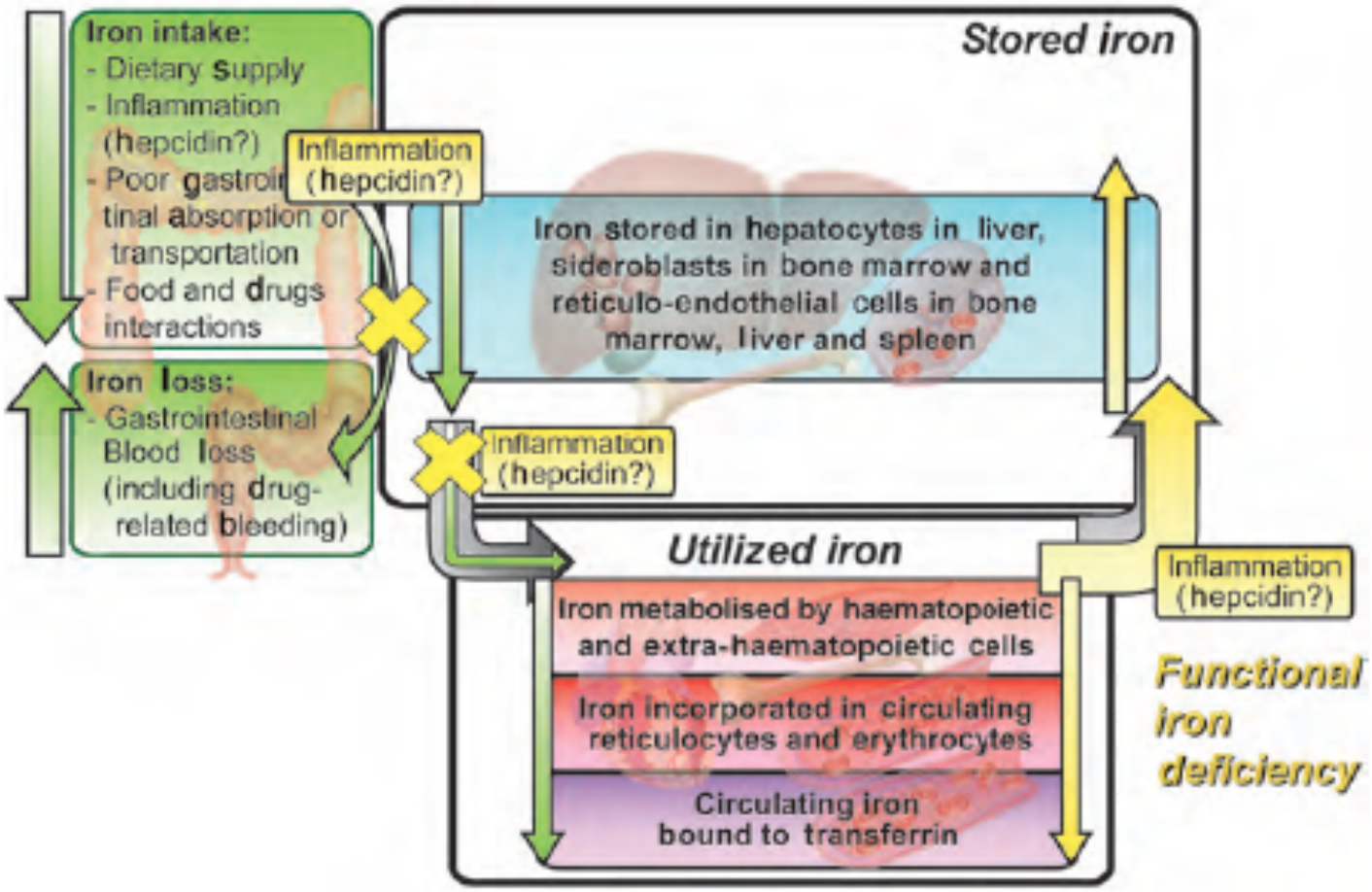
European Heart Journal (2013) **34**, 816–826

REVIEW

Absolute iron deficiency



Ferropénia e inflamação

Inflamação

↓

Aumento da IL6 (macrofagos)

↓

Libertação de ***hepcidina*** hepática

↓ absorção intestinal de ferro

e

↓ mobilização de ferro das reservas

↓

↓ ferro no sangue e ferropénia

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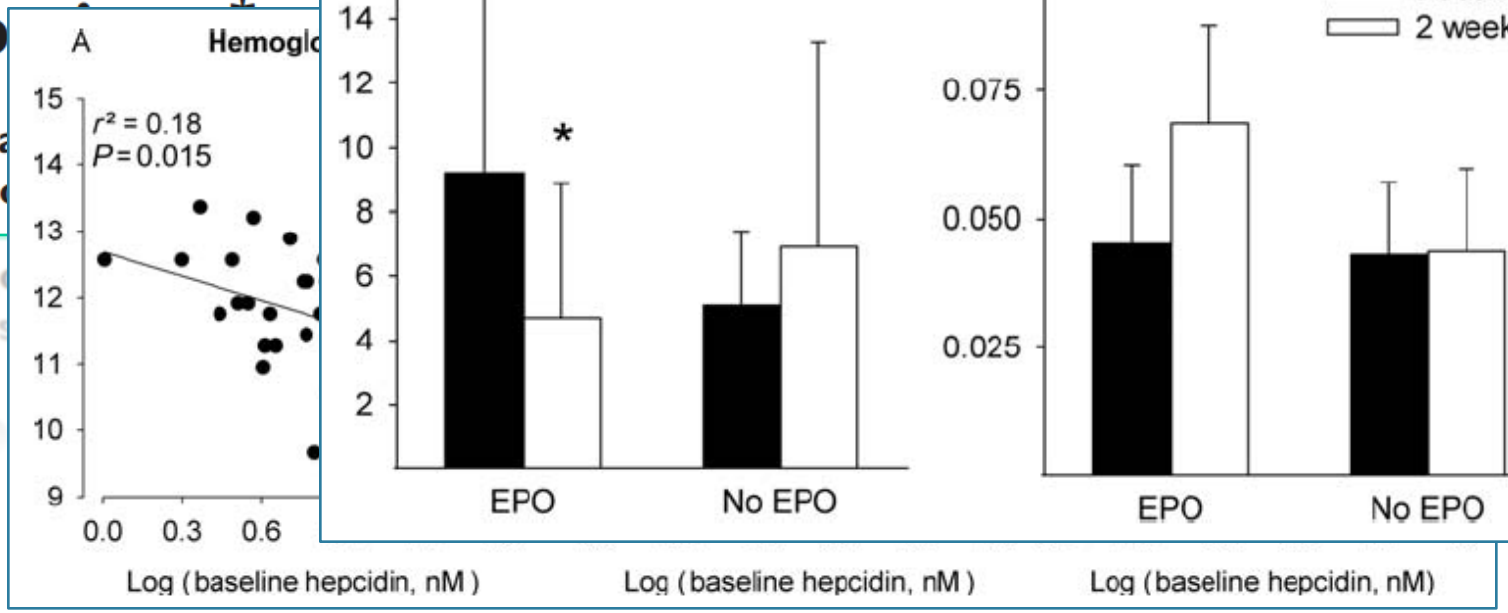
European Journal of Heart Failure (2010) **12**, 943–950
doi:10.1093/eurjhf/hfq099

Hepcidin-25 is a marker of the response rather than resistance to exogenous erythropoietin in chronic kid



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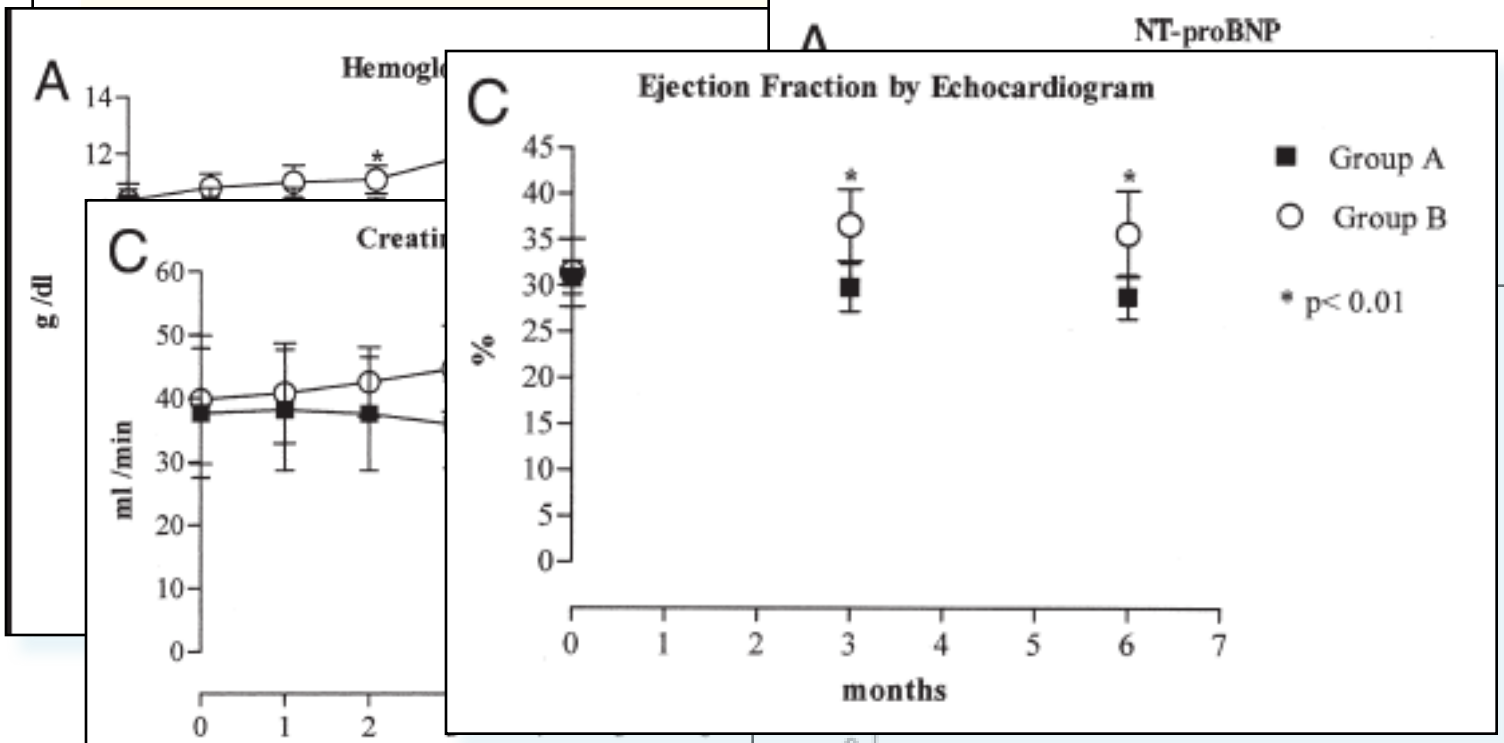
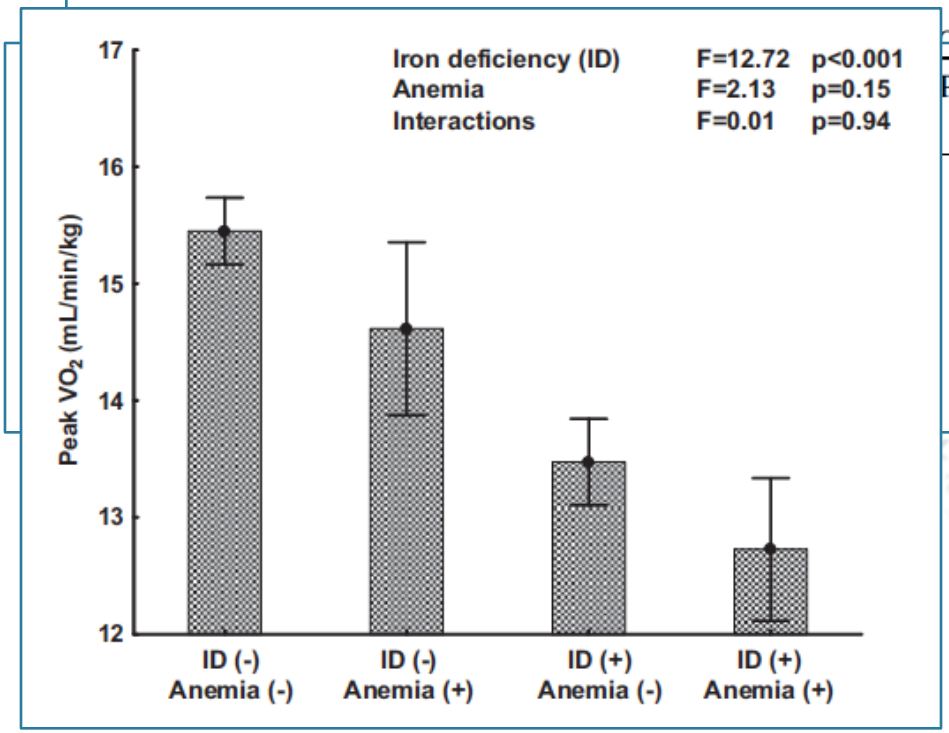
Heart Failure

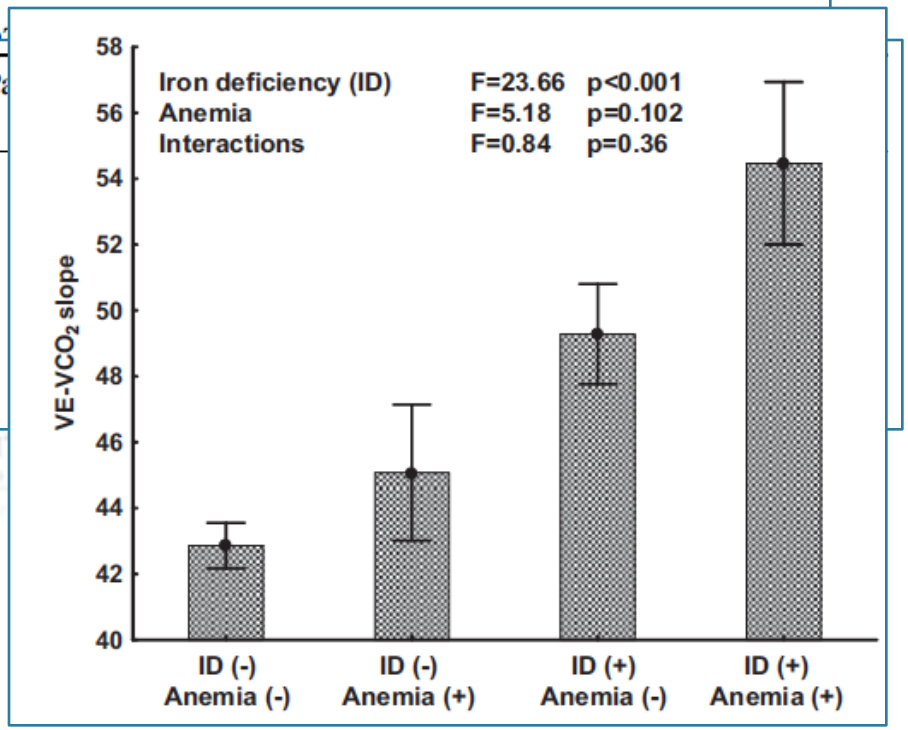
Intravenous Iron Reduces NT-Pro-Brain



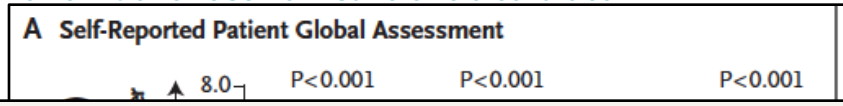
Journal of Cardiac Failure Vol. 17 No. 11 2011

Iron Deficiency Predicts Impaired Exercise Capacity in Patients With Systolic Chronic Heart Failure





Ferro intravenoso na insuficiência cardíaca : FAIR-HF2



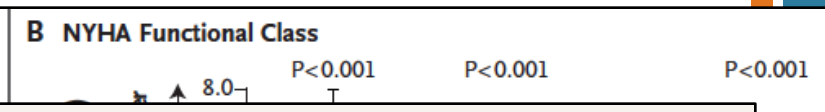


Table 3. Levels of Iron-Metabolism Markers and Hemoglobin at Week 24 According to Study Treatment.*

Variable	Ferric Carboxymaltose (N=305)	Placebo (N=154)	P Value
All patients			
Ferritin (μg/liter)	275±18	68±11	<0.001
Transferrin saturation (%)†	29±1	17±1	<0.001
Hemoglobin (g/liter)	127±1	118±2	<0.001
Mean corpuscular volume (μm³)	98±1	93±1	<0.001
Patients without anemia (hemoglobin >120 g/liter)			
Ferritin (μg/liter)	349±19	80±11	<0.001
Transferrin saturation (%)†	30±1	22±1	<0.001
Hemoglobin (g/liter)	133±1	132±1	0.21
Mean corpuscular volume (μm³)	96±1	95±1	0.91
Creatinine — mg/dl	1.2±0.6	1.2±0.6	
Estimated glomerular filtration rate — ml/min/1.73 m² of body-surface area¶	63.8±21.2	64.8±25.3	

Subgroup	Self-Reported Patient Global Assessment: Ferric Carboxymaltose (no. of patients)	Self-Reported Patient Global Assessment: Placebo (no. of patients)	Self-Reported Patient Global Assessment: Odds Ratio (95% CI)	Self-Reported Patient Global Assessment: P Value for Interaction	NYHA Functional Class: Ferric Carboxymaltose (no. of patients)	NYHA Functional Class: Placebo (no. of patients)	NYHA Functional Class: Odds Ratio (95% CI)	NYHA Functional Class: P Value for Interaction
Hemoglobin				0.98				0.51
≤120 (g/liter)	146	74			148	74		
>120 (g/liter)	146	75			146	76		

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European Heart Journal (2015) 36, 657–668
doi:10.1093/eurheartj/ehu38

FASTTRACK ESC HOT LINE

Beneficial effe
therapy with fe
symptomatic

Piotr Ponikowski[1,2*], Di
Michel Komajda[7], Viache
Luigi Tavazzi[11], Victoria
Gerasimos Filippatos[13],
CONFIRM-HF Investigat

Variable	FCM (N = 150) Mean (SD)	Placebo (N = 151) Mean (SD)
Laboratory Measurements		
Hb *g/dL*	12.37 (1.41)	12.42 (1.30)
Ferritin *ng/mL*	57.0 (48.4)	57.1 (41.6)
< 100 ng/ml *n (%)*	136 (91)	133 (88)
TSAT %	20.2 (17.6)	18.2 (8.1)
CRP *mg/L*	5.19 (9.00)	6.00 (11.60)
BNP *pg/mL*	772 (995)	770 (955)
NT Pro-BNP *pg/mL*	2511 (5006)	2600 (4555)
Sodium *mmol/L*	143 (3)	142 (5)
Potassium *mmol/L*	4.69 (0.54)	4.63 (0.55)
ALT *U/L*	21.1 (18.9)	18.7 (9.9)
AST *U/L*	26.2 (19.6)	23.5 (8.6)
eGFR *mL/min/1.73m²*	66.4 (21.7)	63.5 (20.9)

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

End-point or event	FCM (n = 150)		Placebo (n = 151)			
	Total number of events	Incidence/100 patient-years at risk	Total number of events	Incidence/100 patient- years at risk	Time to first event hazard ratio 95% CI	P-value
Death	12	12 (8.9)	14	14 (9.9)	0.89 (0.41– 1.93)	0.77
Death for any cardiovascular reason	11	11 (8.1)	12	12 (8.5)	0.96 (0.42– 2.16)	0.91
Death due to worsening HF	4	4 (3.0)	3	3 (2.1)	1.39 (0.31–6.21)	0.67
Death due to other cardiovascular reason	7	7 (5.2)	9	9 (6.4)	0.81 (0.30–2.17)	0.68
Hospitalizations	46	32 (26.3)	69	44 (37.0)	0.71 (0.45–1.12)	0.14
Hospitalizations for any cardiovascular reason	26	21 (16.6)	51	33 (26.3)	0.63 (0.37–1.09)	0.097
Hospitalizations due to worsening HF	10	10 (7.6)	32	25 (19.4)	0.39 (0.19–0.82)	0.009
Hospitalizations due to other cardiovascular reason	16	13 (10.0)	19	15 (11.0)	0.91 (0.43–1.92)	0.81

patients						
FCM	144	137				
placebo	147	148				

No. of patients	Weeks since randomization				
FCM	144	137	132	123	127
placebo	148	148	132	125	121

European Heart Journal
doi:10.1093/eurheartj/ehw128

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11.12 Iron deficiency and anaemia

Iron deficiency is common in HF, as it is with other chronic illnesses, and it can lead to anaemia and/or skeletal muscle dysfunc-

Recommendations	Class [a]	Level [b]	Ref [c]
Iron deficiency			
Intravenous FCM should be			

vival. A diagnostic workup to seek a cause for any finding of anaemia is indicated (e.g. occult blood loss, iron deficiency, B12/folate deficiency, blood dyscrasias), although in many patients no specific cause is found. The erythropoietin-stimulating agent darbepoetin alfa did not improve clinical outcomes in HFrEF patients with mild to moderate anaemia, but led to an excess of thromboembolic events and is therefore not recommended.[475]

Do we need a new study?

Primary EP

	FAIR-HF	CONFIRM-HF	Answered
FU	6 months	6 (to 12) months	≈
NYHA Class	↓	↓	✔
Self-reported PGA	↑	↑	✔
BNP/NTproBNP	↓	↓	✔
6MWT (m)	↑	↑	✔
CV death	n.a.	=	?
Rehospitalization for HF	n.a.	↓	?

Intravenous iron in patients with systolic heart failure and iron deficiency to improve morbidity & mortality

FAIR–HF2

Universitätsklinikum Hamburg-Eppendorf

Primary objective

- combined endpoint at 12 months of :
  - recurrent heart failure hospitalizations

  and

  - cardiovascular (CV) death

Secondary objectives

- the rate of recurrent CV hospitalizations
- the rate of recurrent hospitalizations of any kind
- all-cause mortality
- the cost effectiveness of the intervention.

Study design

- Phase IV study
- International, prospective, multi-centre, double-blind, parallel group, randomised, controlled, interventional trial.
- Comparing i.v. FCM vs i.v. placebo (0.9 % NaCl-solution) administration on top of usual care for HF with reduced EF.
- Eligible patients will be randomised (1:1)
  - (n = 1,200; 600 per group)
- Randomisation will be performed using the data capture tool of the DZHK centralised data management in Göttingen, Germany after the screening visit.

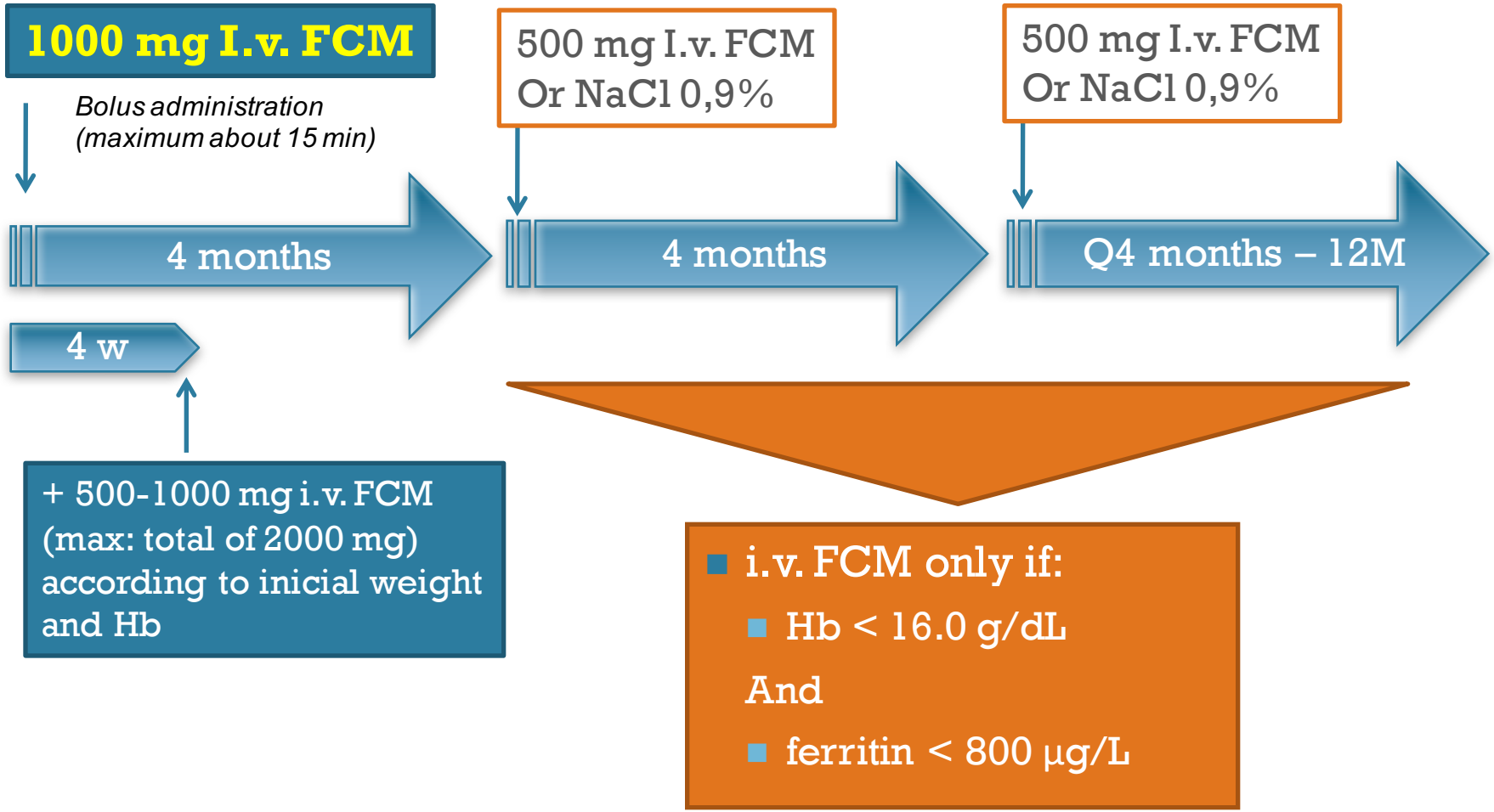
Inclusion criteria

- Patients with chronic HF (CHF) and LVEF ≤ 45 % present for at least 12 months in NYHA class II or III
- Confirmed presence of ID (ferritin < 100 ng/mL or ferritin 100 - 299 ng/mL with TSAT < 20 %)
- Serum haemoglobin of 9.5 - 14.0 g/dL
- At time of screening:
  - Hospitalized but considered re-stabilised and planned for discharge within next 24h

  or
  - stable in ambulatory
    - with a HF hospitalisation in the past 6 months,

    or
    - with BNP > 100 pg/mL or NT-proBNP > 300 pg/mL

Experimental intervention



Conclusões

- A anemia é uma comorbilidade prevalente na IC, com importante impacto na morbi-mortalidade da sindrome
- A correcção da anemia utilizando a EPO não demonstrou melhorar o prognostico da sindrome e associou-se a um aumento de eventos adversos tromboticos
- A ferropénia na IC correlaciona-se com o estado funcional do doente
- A correcção da ferropénia na IC, com ou sem anemia, demonstrou melhorar o a capacidade funcional e a qualidade de vida dos doentes com IC

Conclusões

- O estudo FAIR-HF2 é o primeiro estudo desenhado para estudar os efeitos da correcção da ferropenia com CMF na mortalidade CV e nos reinternamentos por IC em doentes com IC e FE reduzida, independentemente da presença de anemia.