Iron Deficiency:
New Therapeutic Target in Heart Failure

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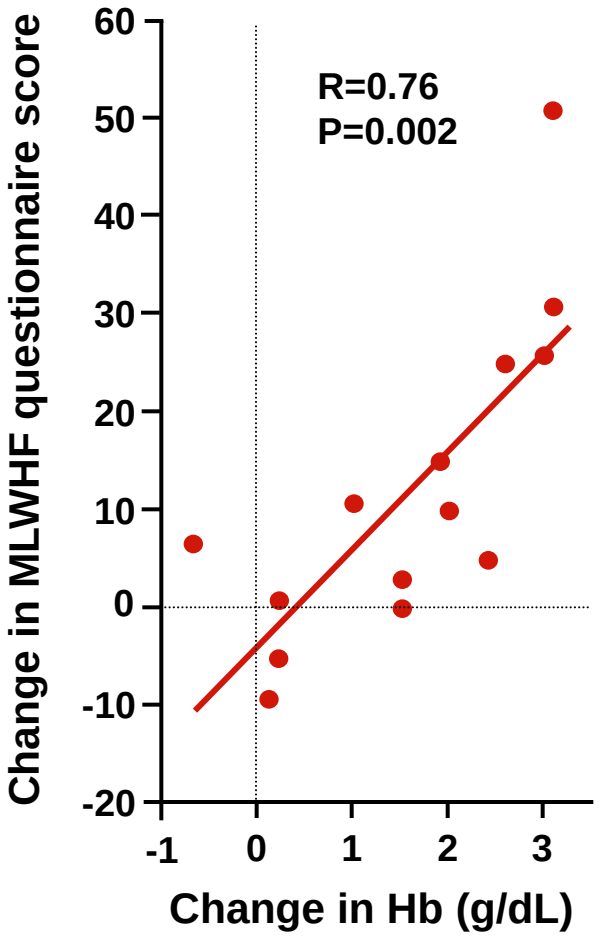
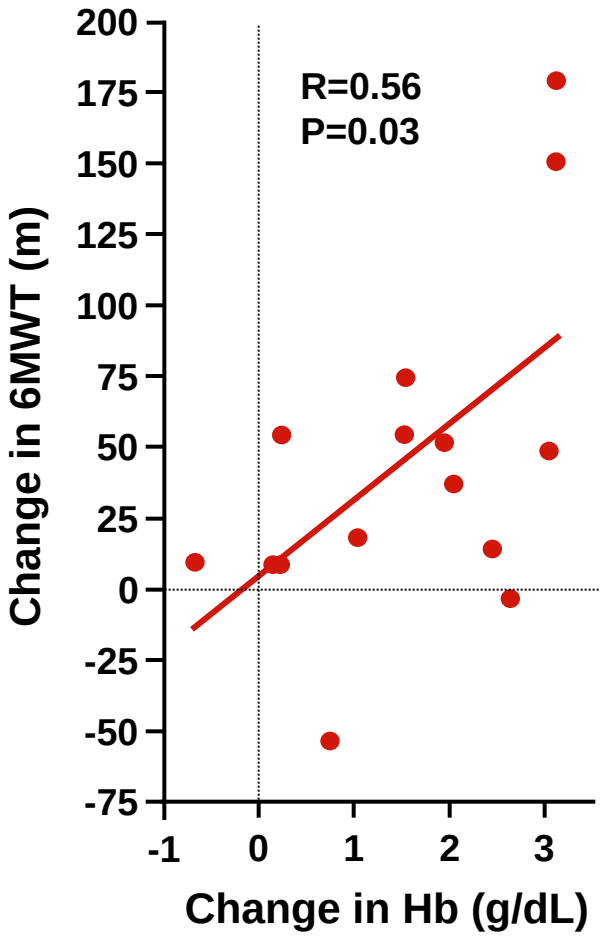
Intravenous Iron in CHF: Early Clinical Evidence

Authors	N	Design	Inclusion	Regimen and total iron dose	Follow-up (months)	Key results
Bolger[1] 2006	16	Open, no control	Hb ≤12 g/dL Serum ferritin ≤400 ng/mL	Iron sucrose, maximum 1000 mg iron i.v. (200 mg iron days 1, 3 and 5, plus days 15 and 17 if serum ferritin <400 ng/mL on day 12)	3	↑Hb ↑HRQoL ↑Exercise capacity (6MWT)
Toblli[2] 2007	40	Double-blind, randomized, placebo- controlled	Hb <12.5 g/dL for men; <11.5 g/dL for women Serum ferritin <100 ng/mL and/or TSAT ≤20%	Iron sucrose, 200 mg iron i.v. weekly for 5 weeks (total 1000 mg iron)	6	↑Hb ↑HRQoL ↑Exercise capacity (6MWT) ↑LVEF ↓NYHA ↑Renal function (↓NT-proBNP level)
Okonko[3] 2008	35	Single-blind, randomized, controlled	Hb <12.5 g/dL (anaemic group); 12.5–14.5 g/dL (non-anaemic group) Serum ferritin <100 ng/mL or 100–300 ng/mL with TSAT <20%	Iron sucrose, 200 mg iron i.v. weekly until serum ferritin ≥500 ng/mL, then 200 mg iron every 4 weeks to week 16. Required iron dose calculated using Ganzoni formula	4	↓HF symptoms (PGA) ↑Exercise tolerance (peak VO_2) ↓NYHA ↓Fatigue score
Usmanov[4]	32	Open, no control	Hb <11 g/dL Serum ferritin not specified	Iron sucrose, 100 mg iron i.v. three times weekly for 3 weeks, then once weekly for 23 weeks (total 3200 mg iron)	6	↓NYHA (in NYHA class III patients) ↑Echocardiographic indices

1. Bolger et al. *J Am Coll Cardiol* 2006;48:1225–7
2. Toblli et al. *J American Coll Cardiol* 2007;50:1657–65
3. Okonko et al. *J Am Coll Cardiol* 2008;51:103–12
4. Usmanov et al. *J Nephrol* 2008;21:236–42

i.v. Iron Sucrose Improves Functional Capacity and Quality of Life in Patients with CHF and Anemia





- Prospective, uncontrolled study with iron sucrose
- N=16
- Left ventricular ejection fraction (LVEF) 26±13%
- Hb ≤12 g/dL
- Ferritin ≤400 ng/mL

MLWHF Score

33 ± 19→19 ± 14 (p=0.02)

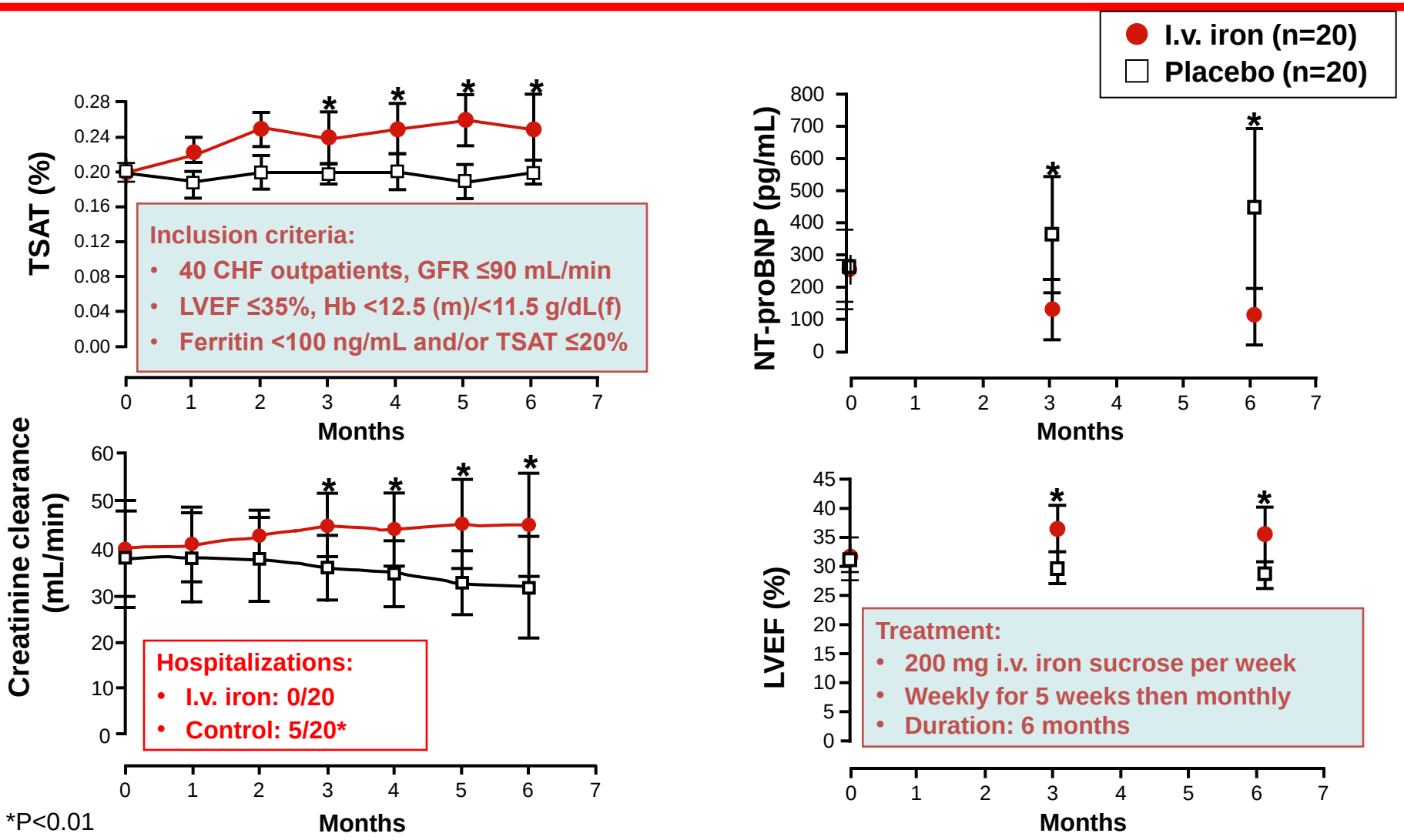
6MWT

242 ±78→ 286 ±72 m (p=0.01)

MLWHF, Minnesota Living With Heart Failure; 6MWT, 6-minute walk test

Bolger AP et al. *J Am Coll Cardiol* 2006;48:1225–1227

i.v. Iron Sucrose Improves Kidney Function in CHF Patients with ID and Anemia



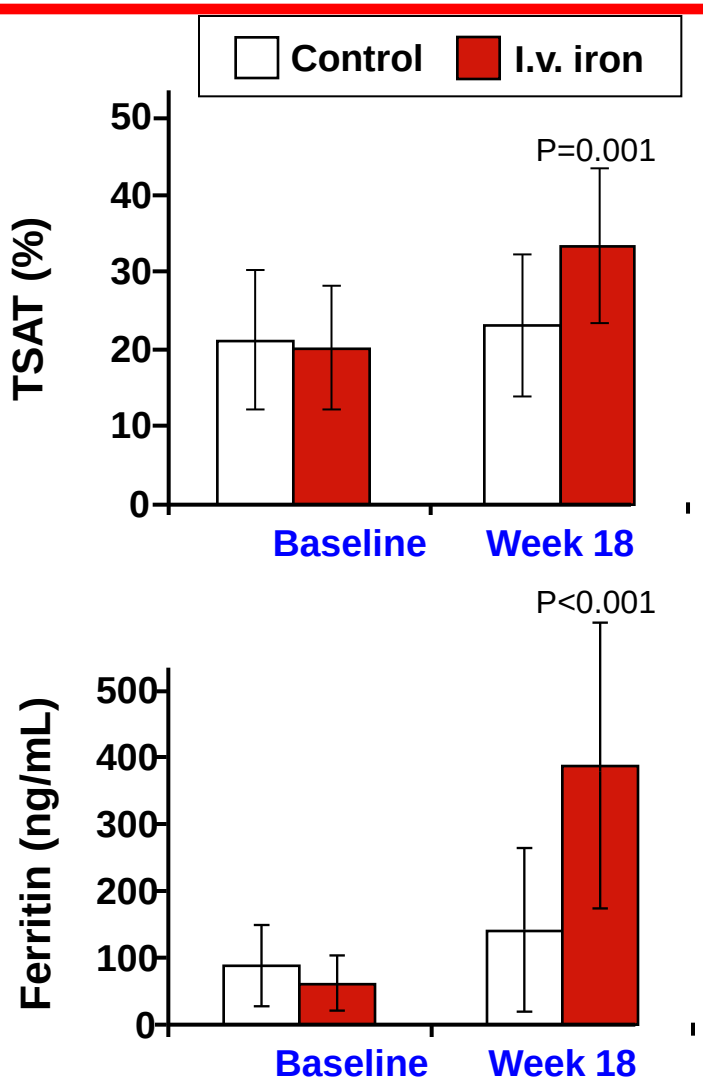
*P<0.01

Toblli JE et al. *J Am Coll Cardiol* 2007;50:1657–65

i.v. Iron Sucrose Improves Iron Status in Patients with and without Anemia

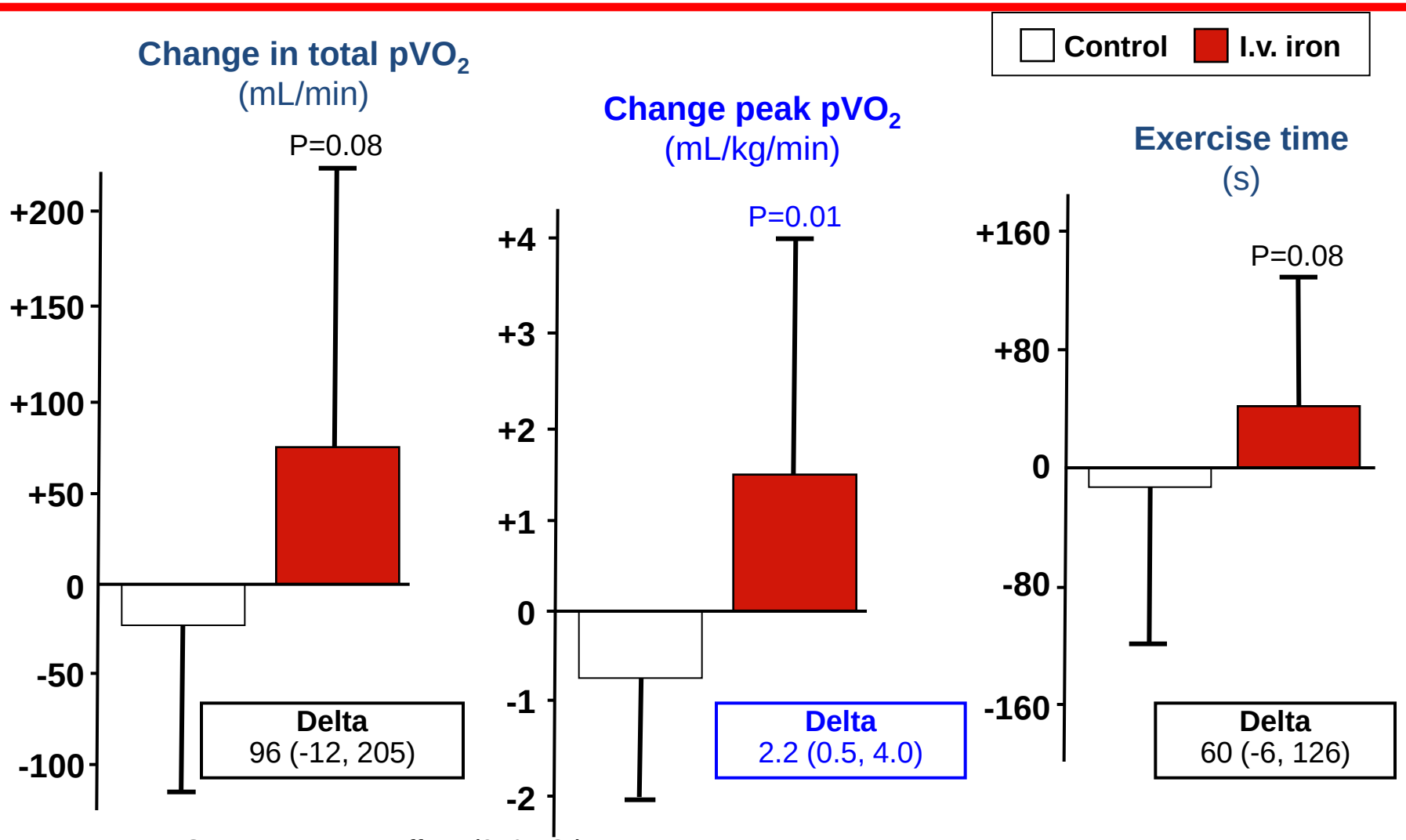
- Ferric Iron Sucrose in Heart Failure (FERRIC-HF)
  - Prospective randomized controlled trial (RCT) in CHF
  - n=35
  - Iron deficiency
    - Ferritin <100 µg/L or
    - Ferritin 100–300 µg/L and TSAT <20%
  - Anemia
    - Hb <12.5 g/dL
  - Non-Anemics
    - Hb 12.5 – 14.5 g/dL

i.v. iron administration improves iron status (increased TSAT and ferritin)



Okonko DO et al. *J Am Coll Cardiol* 2008;51:103–112

i.v. Iron Sucrose Improves Peak VO_2 and Exercise Time

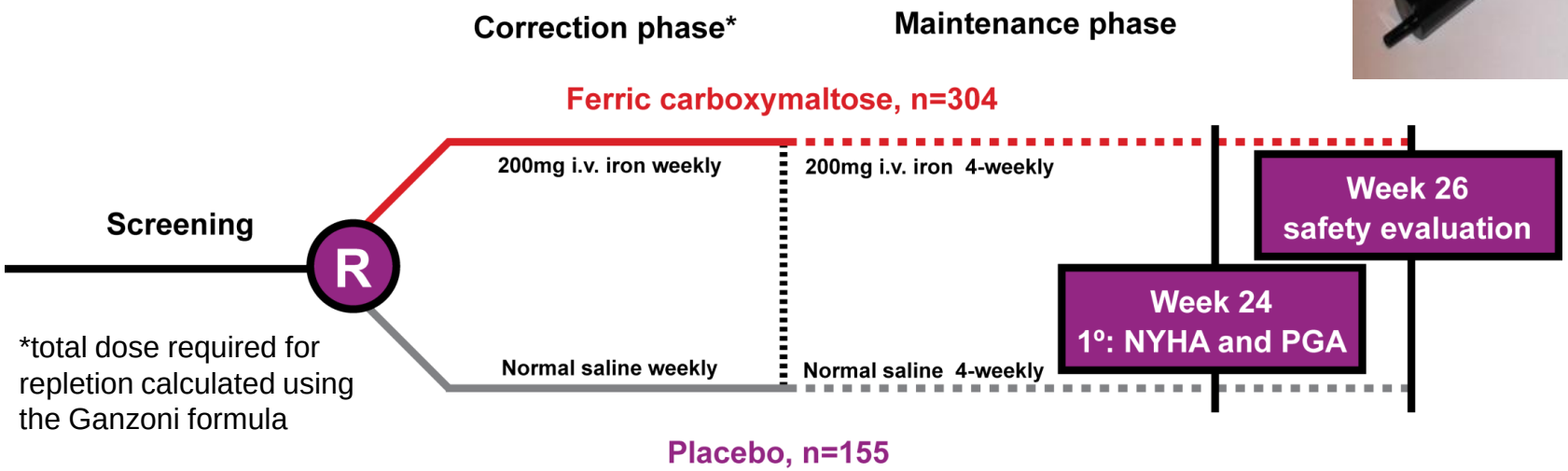


Data: mean±SD & treatment effect (95% CI)

Okonko DO et al. *J Am Coll Cardiol* 2008;51:103–112

FAIR-HF - Study Design

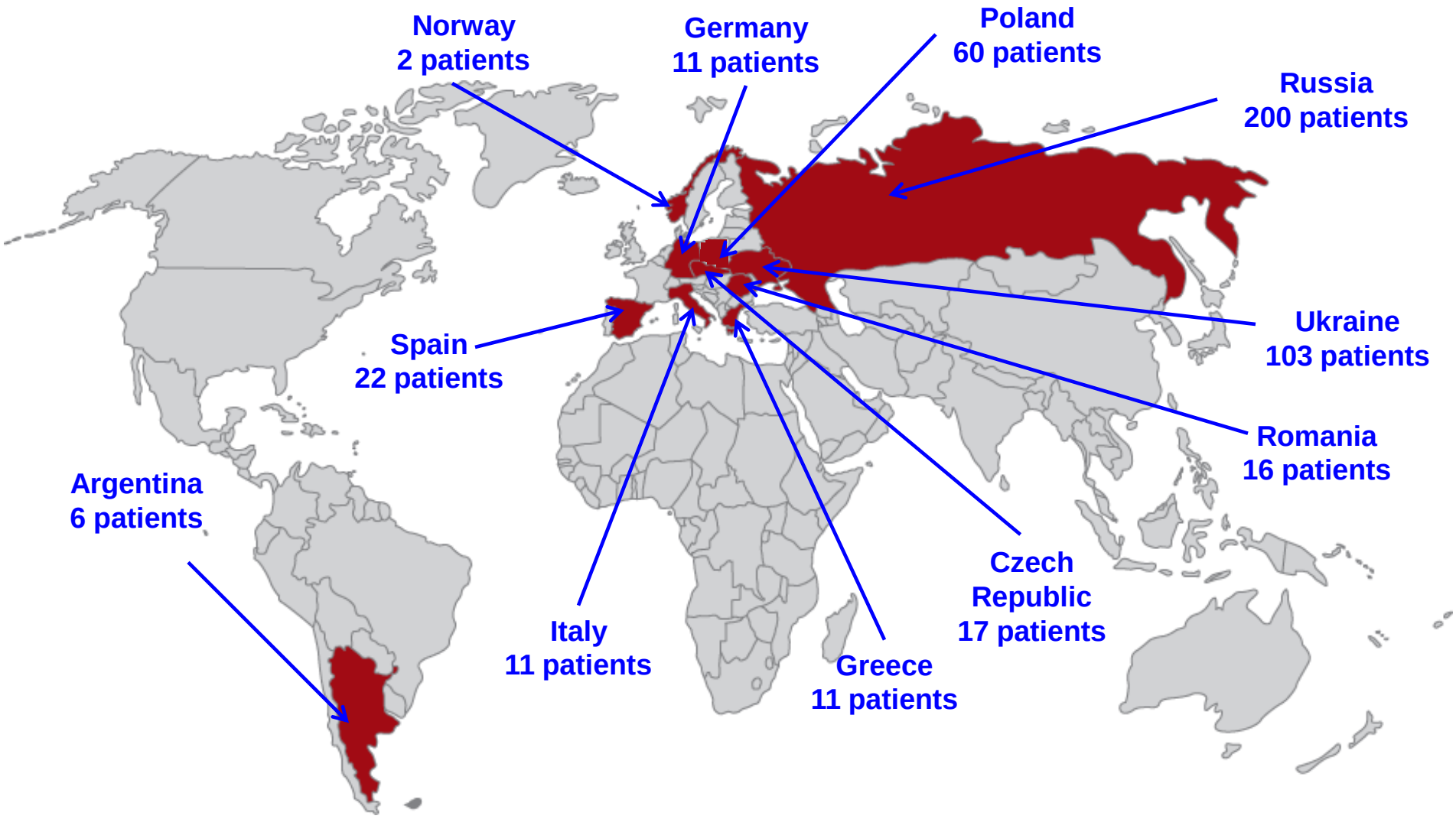
- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5g/dL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**
- **Treatment adjustment algorithm:**
  - Interruption: Hb>16.0g/dL or ferritin>800µg/L or ferritin>500µg/L, if TSAT>50%
  - Restart: Hb <16.0g/dL and serum ferritin <400µg/L and TSAT<45%
- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections



*total dose required for repletion calculated using the Ganzoni formula

Anker *et al, Eur J Heart Failure* 2009;11:1084-1091

75 centers from 11 countries



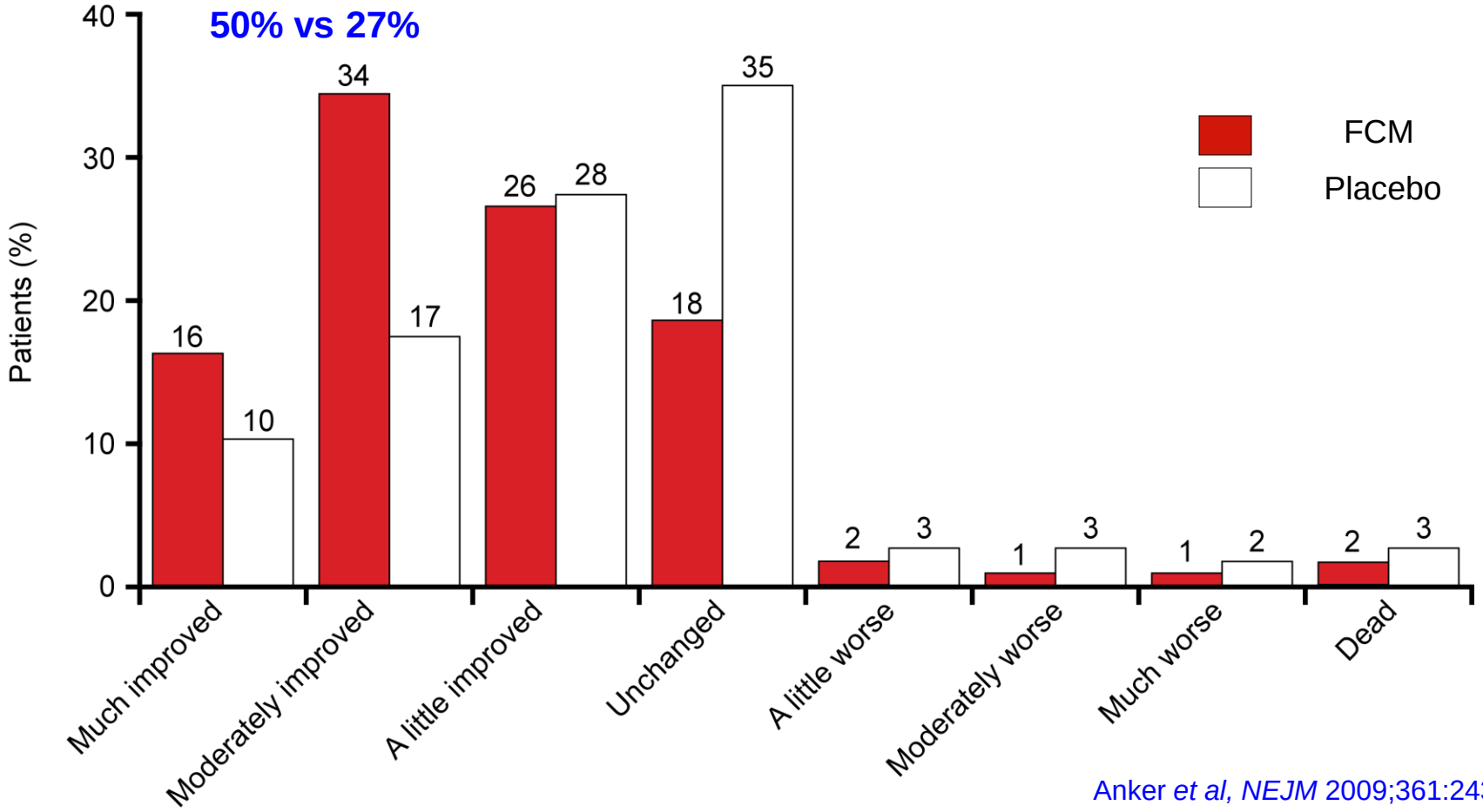
Anker *et al, NEJM* 2009;361:2436-2448

Patient Details

	FCM (N=304)	Placebo (N=155)
Age (years)	68	67
Gender (% female)	52	55
NYHA class III, n (%)	251 (82.6)	126 (81.3)
6-min walk test distance (m)*	274 ± 105	269 ± 109
Ischemic etiology (%)	81	79
Estimated GFR (mL/min/1.73m^2)*	64 ± 21	65 ± 25
LVEF (%)	32	33
Hb (g/L)*	119 ± 13	119 ± 14
Serum ferritin (μg/L)*	53 ± 55	60 ± 67
ACEi/ARB (%)	92	91
Beta-Blocker (%)	86	83
Diuretics (%)	92	90

i.v. Ferric Carboxymaltose Improves PGA

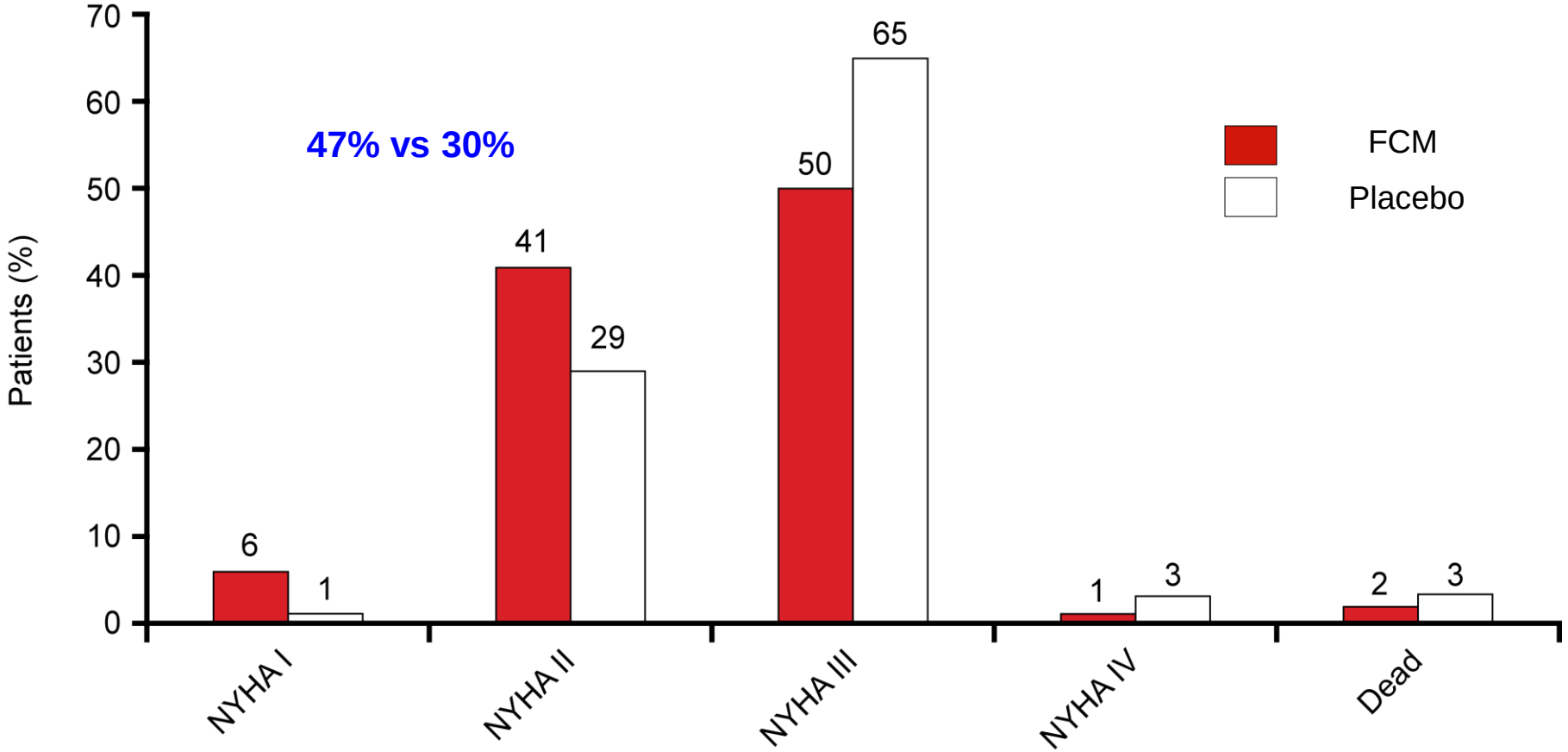
- Ferric carboxymaltose improved self-reported PGA scores at week 24
- Odds ratio for better rank: 2.51 (95% CI 1.75, 3.61), P<0.001



Anker *et al, NEJM* 2009;361:2436-2448

i.v. Ferric Carboxymaltose Improves NYHA

- Ferric 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*



*Adjusted for baseline

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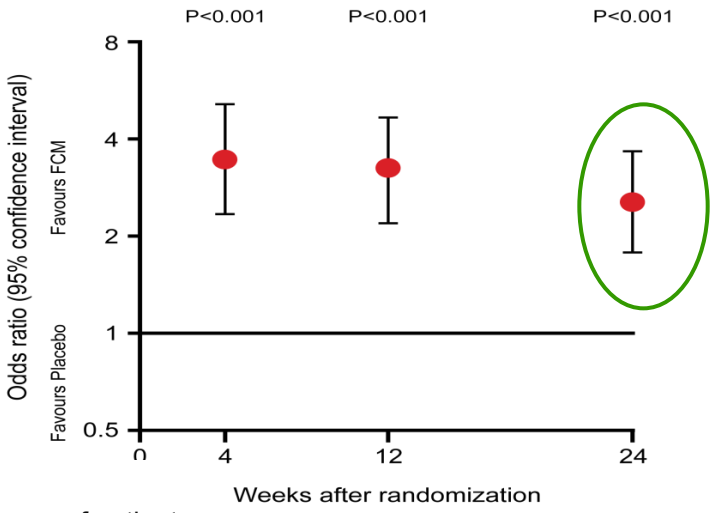
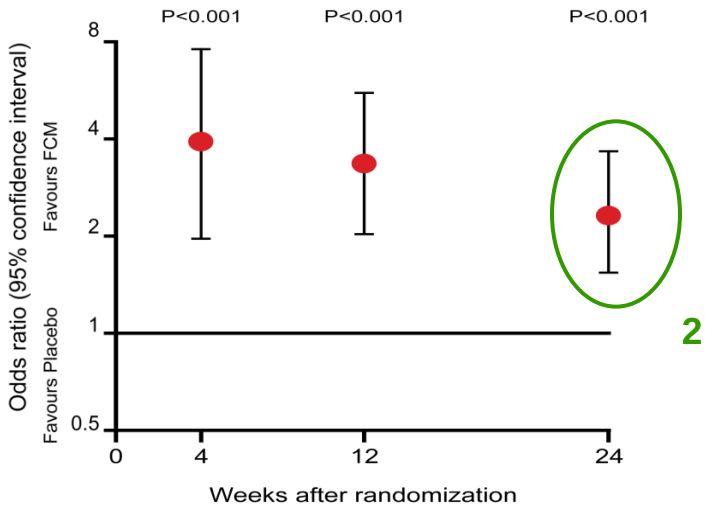
NYHA, PGA, QoL, 6min-Walking-Test
Week 4, 12 & 24

Patient Global Assessment

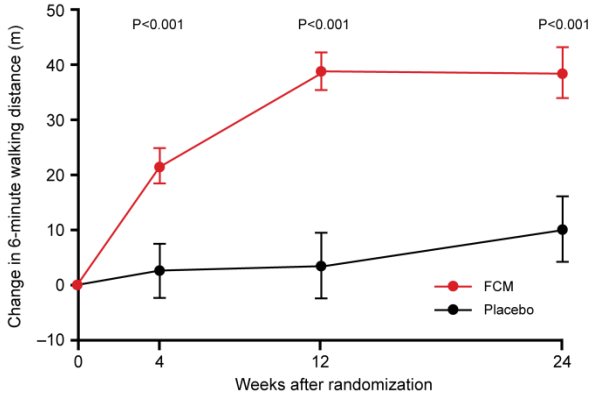


NYHA functional class

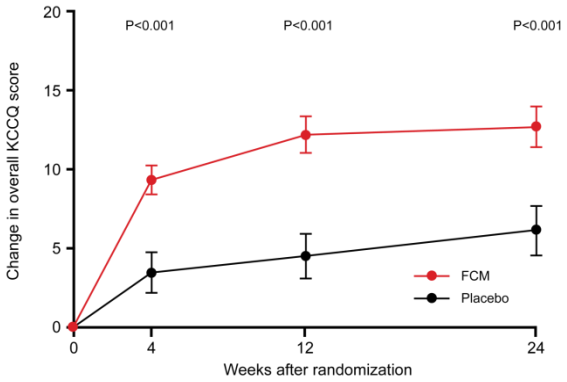


2 co-primary endpoints

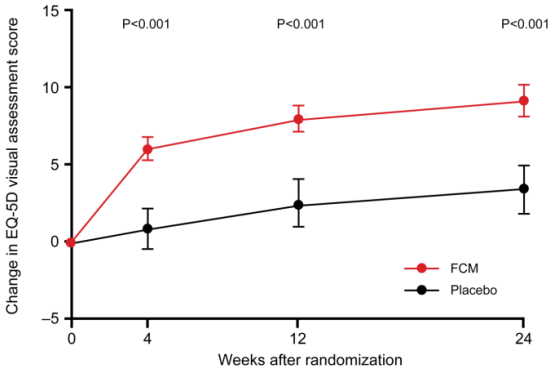
6-minute walk test



KCCQ overall score



EQ-5D VAS score



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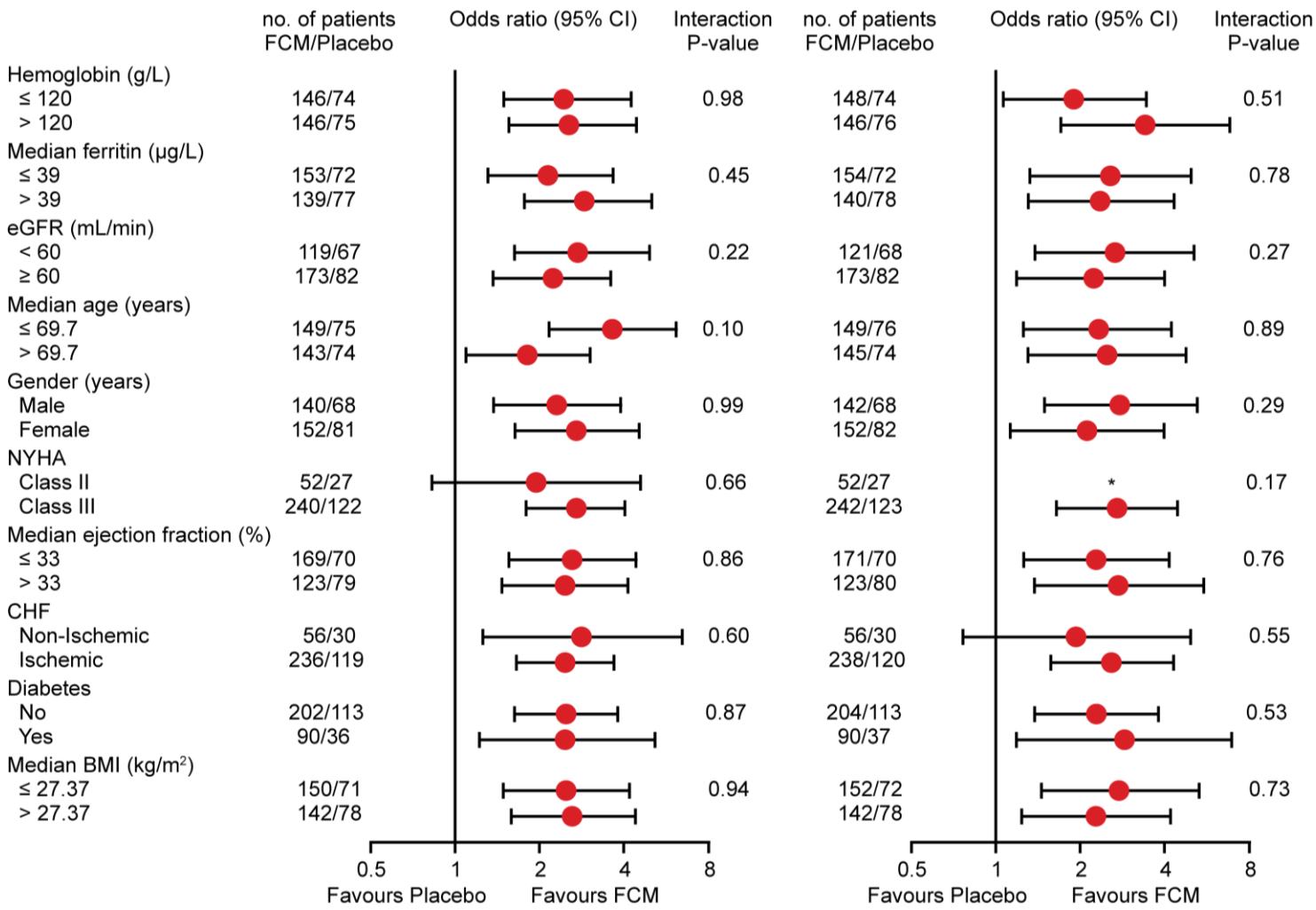
Secondary Endpoints: PGA & NYHA in pre-defined subgroups



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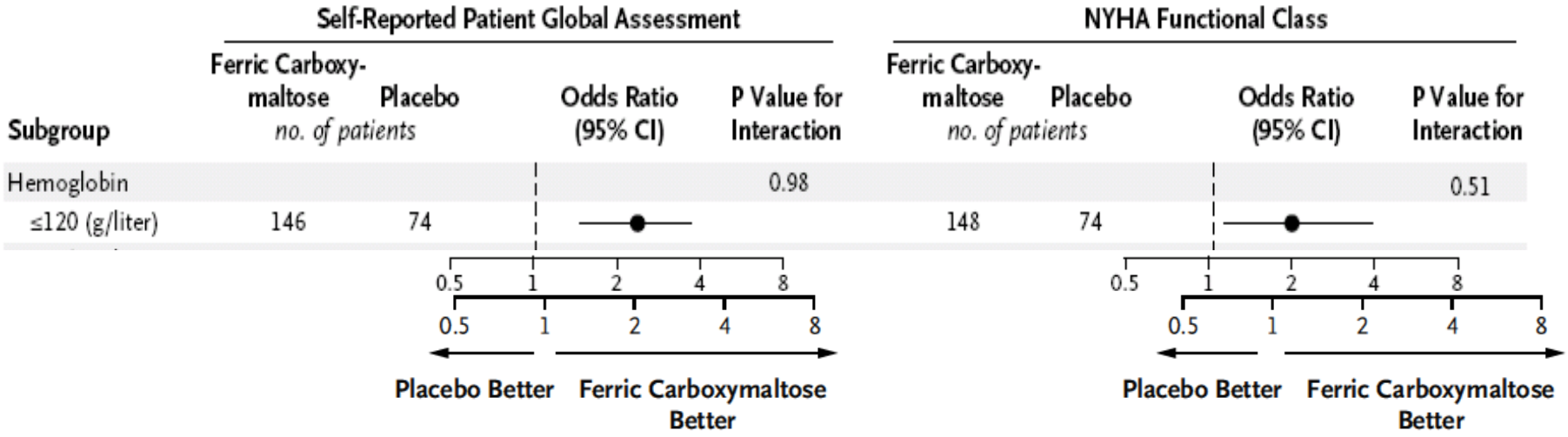
i.v. Ferric Carboxymaltose Improves PGA & NYHA in CHF Patients with and without Anemia

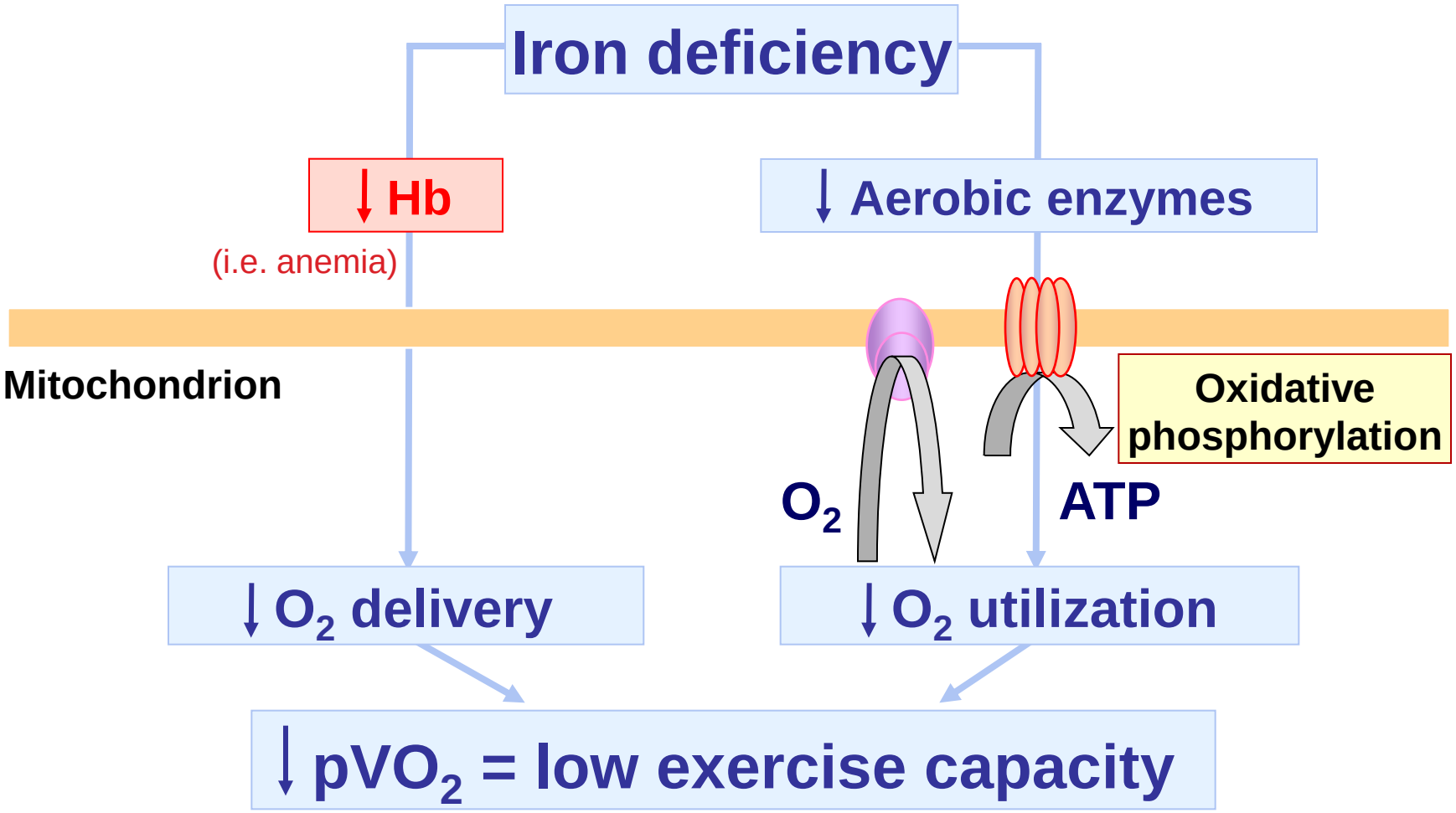


	FCM	Placebo	p value*
Patients with anaemia at Week 24			
Serum ferritin (µg/L)	275±18	68±11	<0.001
TSAT (%)	29±1	17±1	<0.001
Haemoglobin (g/L)	127±1	118±2	<0.001
Patients without anaemia at Week 24			
Serum ferritin (µg/L)	349±19	80±11	<0.001
TSAT (%)	30±1	22±1	<0.001
Haemoglobin (g/L)	133±1	132±1	0.21

*Mean treatment effect, adjusted for the baseline value

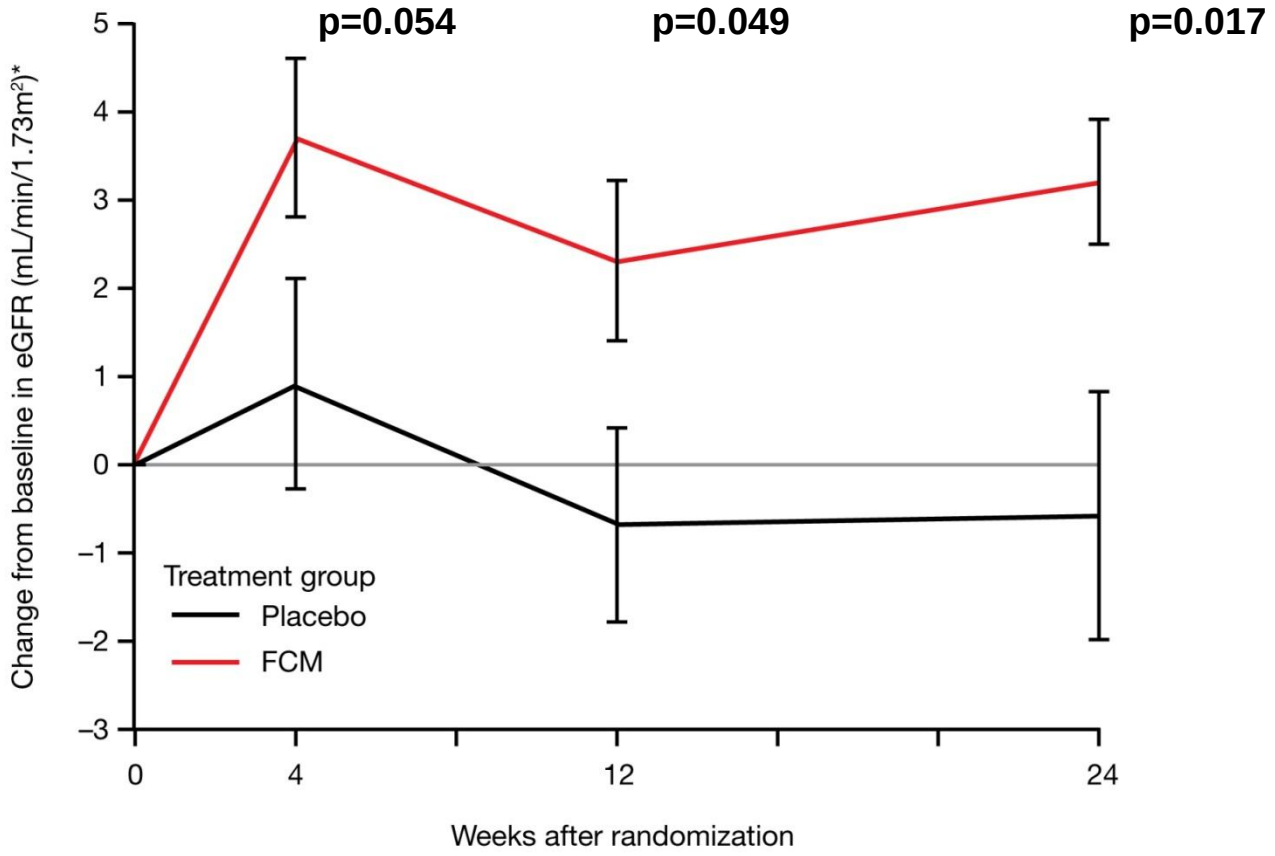
Anker *et al, NEJM* 2009;361:2436-2448

Anemia & Iron Deficiency & Exercise Capacity



Haas JD & Brownlie T. *J Nutr* 2001;131(2 suppl 2):676S–690S; Dallman PR. *J Intern Med* 1989;226:367–372; Willis WT & Dallman PR. *Am J Physiol* 1989;257:C1080–1085;
Figure adapted from: Anker et al. EJHF 2009

Effect of i.v. Ferric Carboxymaltose on Kidney Function (eGFR)



Treatment effect (mL/min/1.73m²)*:	**2.8 ± 1.5**	**3.0 ± 1.5**	**4.0 ± 1.7**

*LSM mean ± SE

Ponikowski P, et al. Heart Failure Association Congress 2010; abstract 114 and oral presentation

Safety Endpoints

	Overall	Patients with anaemia (Hb ≤120 g/L)		Patients without anaemia (Hb >120 g/L)	
		Correction phase	Maintenance phase	Correction phase	Maintenance phase
Number of patients	300	154	139	146	136
Mean ±SD dose (mg iron)	1850±433	1105±291	840±199	985±216	915±114
Median dose (mg iron)	2000	1100	800	1000	1000
Dose range (mg iron)	200–2400	200–1900	200–1000	200–1600	400–1000

Filippatos G, et al. AHA Scientific Sessions 2010; abstract 17546 & oral presentation

Safety Endpoints

	Patients with events (Incidence per 100-patient years at risk)		
	FCM (N=305)	Placebo (N=154)	P
Death	5 (3.4)	4 (5.5)	0.47
CV death	4 (2.7)	4 (5.5)	0.31
Death due to worsening HF	0 (0.0)	3 (4.1)	-
First hospitalization	25 (17.7)	17 (24.8)	0.30
Hospitalization for any CV reason	15 (10.4)	14 (20.0)	0.08
First hospitalization for worsening HF	6 (4.1)	7 (9.7)	0.11
Any hospitalization or death	30 (21.2)	19 (27.7)	0.38
Hospitalization for any CV reason or death	20 (13.9)	16 (22.9)	0.14
First hospitalization for worsening HF or death	11 (7.5)	10 (13.9)	0.15

Anker *et al, NEJM* 2009;361:2436-2448

Reported Adverse Events

	Patients with events (Incidence per 100-patient years at risk)		
	FCM (N=305)	Placebo (N=154)	P
Cardiac disorder	38 (27.6)	33 (50.2)	0.01
Gastrointestinal disorder	24 (16.9)	5 (6.9)	0.06
General disorder or administration site condition	23 (16.2)	6 (8.3)	0.14
Injection site pain or discoloration	6 (4.1)	0 (0.0)	-
Infection or infestation	50 (37.0)	24 (35.8)	0.97
Abnormal laboratory test, vital sign, physical finding	32 (23.0)	10 (14.0)	0.17
Nervous system disorder	22 (15.6)	14 (20.3)	0.44
Respiratory, thoracic or mediastinal disorder	9 (6.2)	10 (14.2)	0.06
Vascular disorder	20 (14.0)	11 (15.7)	0.80

No severe or serious hypersensitive reactions

Adverse events are classified by the Medical Dictionary for Regulatory Activities (MedDRA) and are reported by system organ class when they occurred for more than 4% of patients in total.

Anker *et al, NEJM* 2009;361:2436-2448

New ESC Guidelines HF 2012 (1)

Measurement of **iron parameters** are **newly recommended (1C)** as **standard** for the **diagnosis** in ambulatory patients suspected of having HF:

"*In addition to **standard biochemical** [sodium, potassium, creatinine/ estimated glomerular filtration rate (eGFR)] and haematological tests (haemoglobin, haematocrit, **ferritin**, leucocytes, and platelets), …"*

Measurement of blood chemistry (including sodium, potassium, calcium, urea/blood urea nitrogen, creatinine/estimated glomerular filtration rate, liver enzymes and bilirubin, ferritin/TIBC) and thyroid function is recommended to: (i) Evaluate patient suitability for diuretic, renin–angiotensin–aldosterone antagonist, and anticoagulant therapy (and monitor treatment) (ii) Detect reversible/treatable causes of HF (e.g. hypocalcaemia, thyroid dysfunction) and co-morbidities (e.g. iron deficiency) (iii) Obtain prognostic information.	I	C

TSAT= Serum iron/TIBCx100

TIBC = Total Iron-Binding Capacity

McMurray JJ, et *al. Eur Heart J* 2012;33:1787–1847
McMurray JJ, et *al. Eur J Heart Fail* 2012:14:803–869

New ESC Guidelines HF 2012 (2)

- Iron deficiency is for the first time mentioned as a co-morbidity in HF
- Iron parameter cut-off values are referenced as in FAIR-HF
  - Ferritin <100 µg/L or
  - Ferritin 100 and 299 µg/L when TSAT <20%
- Treatment with ferric carboxmaltose may be considered to improve symptoms, exercise capacity and QoL

11.14 Iron deficiency

Iron deficiency may contribute to muscle dysfunction in HF and causes anaemia. In a single RCT, 459 patients with NYHA class II or III systolic HF, a haemoglobin concentration between 9.5 and 13.5 g/dL, and iron deficiency (see below) were randomized 2:1 to i.v. ferric carboxymaltose or saline. In this trial, iron deficiency was diagnosed when serum ferritin was <100 µ/L or when the ferritin concentration was between 100 and 299 µg/L and transferrin saturation was <20%.[208] Over 6 months of treatment, iron therapy improved self-reported patient global assessment and NYHA class (as well as 6-min walk distance and health-related quality of life) and may be considered as a treatment for these patients. The effect of treating iron deficiency in HF-PEF and the long-term safety of iron therapy in HF is unknown.

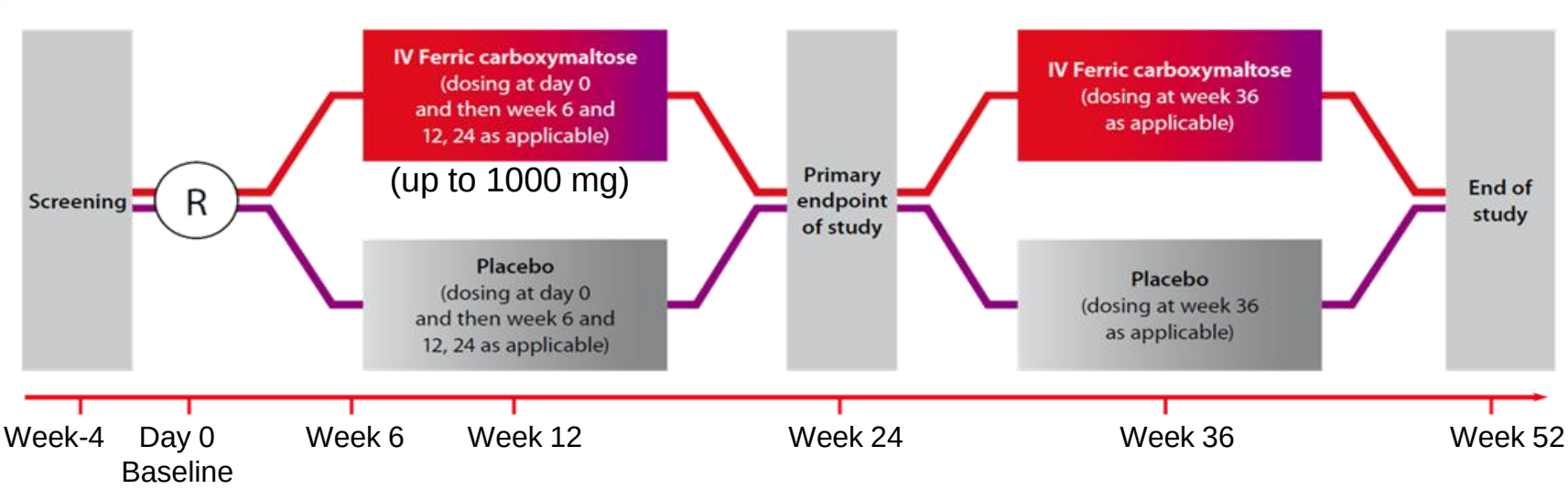
McMurray JJ, et *al. Eur Heart J* 2012;33:1787–1847
McMurray JJ, et *al. Eur J Heart Fail* 2012:14:803–869

Broadening the Evidence for Ferric Carboxymaltose in HF

- The FAIR-HF study:
  - Promising results, but the only double-blind, placebo-controlled clinical trial
    - Results need to be replicated
  - Primary endpoint: NYHA and PGA: optimal decision?
    - Studies need to evaluate different endpoints
  - Relatively short study duration (6 months)
    - Studies need longer follow-up (patients exposition), with more safety data
  - Repeated 200mg doses
    - Higher single doses (up to 1000 mg) to be evaluated

CONFIRM-HF

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤45%
  - BNP > 100 pg/mL or NT-proBNP > 400 pg/mL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**

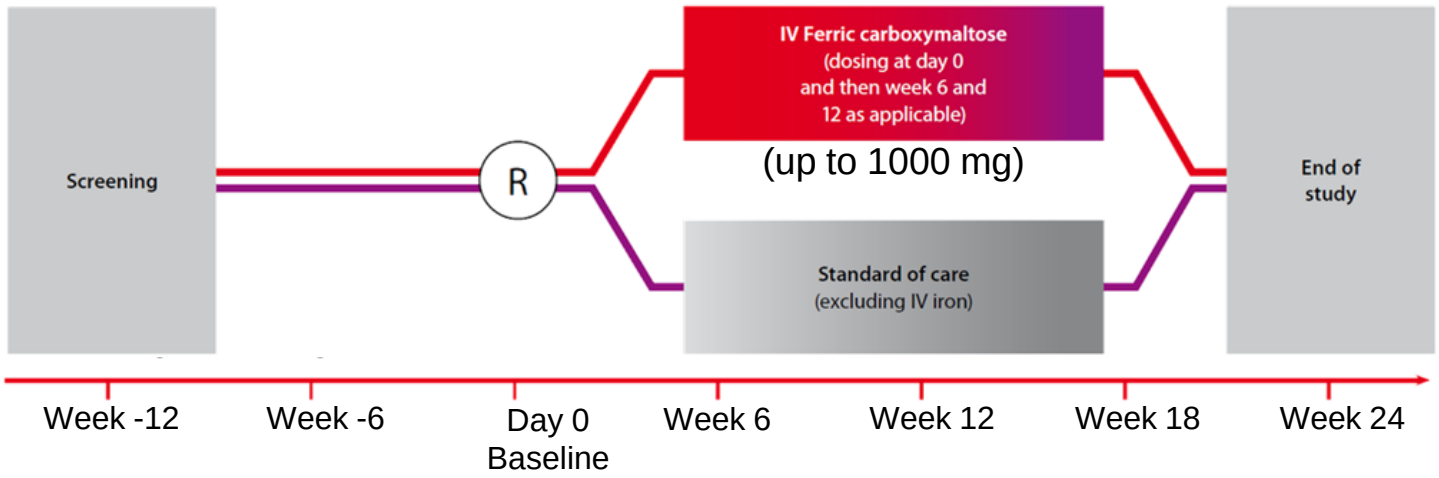


- **Primary endpoint**
  - Exercise capacity: change in 6MWT distance from baseline at week 24
- **Secondary objectives**
  - Change in biomarkers for iron deficiency, cardiac biomarkers, NYHA functional class, PGA and QoL
  - Overall safety over the treatment period

Clinicaltrials.gov identifier: NCT01453608

EFFECT-HF

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤45%
  - Peak VO_2 10-18 mL/Kg/min (reproducible)
  - BNP > 100 pg/mL
  - NT-proBNP > 400 pg/mL
  - **Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%**



- **Primary endpoint**
  - Exercise capacity: change in peak VO_2 from baseline at week 24
- **Secondary objectives**
  - Change in biomarkers for iron deficiency, renal function, cardiac function, NYHA functional class, PGA and QoL
  - Overall safety over the treatment period

Clinicaltrials.gov identifier: NCT01394562

Implications for Clinical Practice

Iron deficiency in CHF patients

- New therapeutic target (in patients ± anemia)
- FAIR-HF:

  Treatment with ferric carboxmaltose improve symptoms, exercise capacity and QoL
- New ESC Guidelines HF 2012:

  - Iron deficiency can easily be detected by measuring ferritin & TSAT

  - i.v. FCM “may be considered as a treatment for these patients”