

Innovazione terapeutica nella carenza di FE nello scompenso cardiaco : implicazioni cliniche nella gestione del pz fragile

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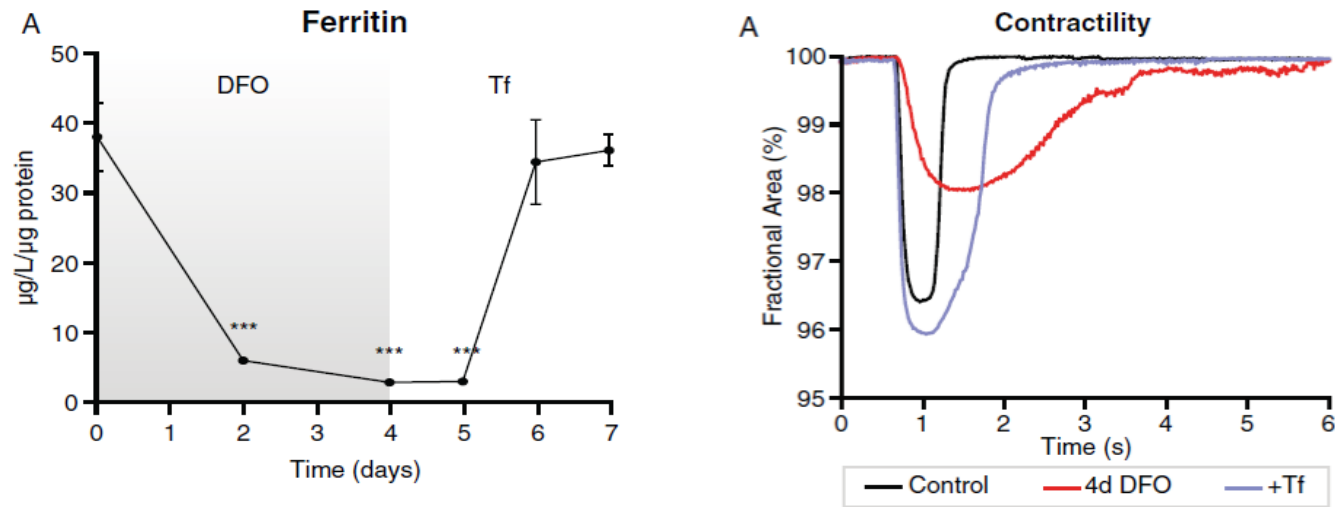
San Raffaele Open University- uniroma 5

Roma, 25 giugno 2026

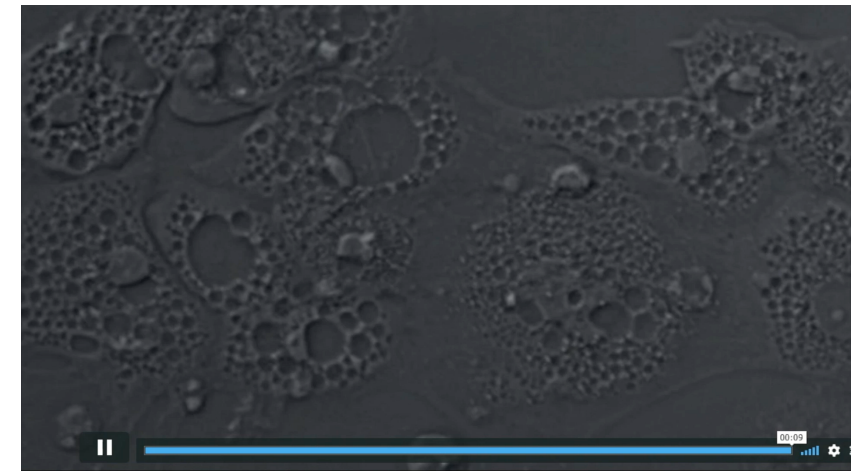
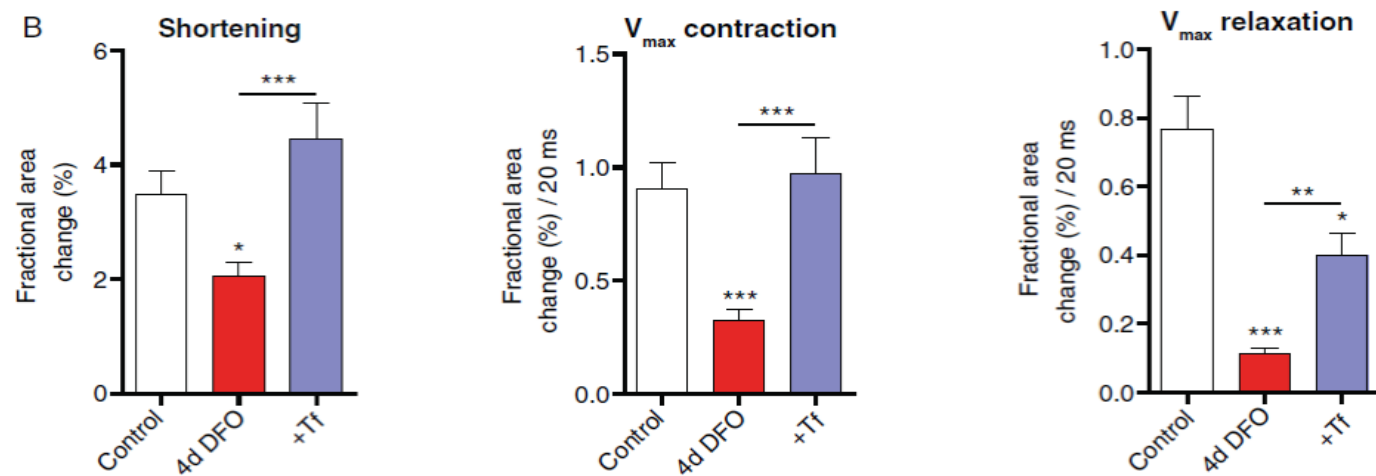
Declaration of potential conflict of interests

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

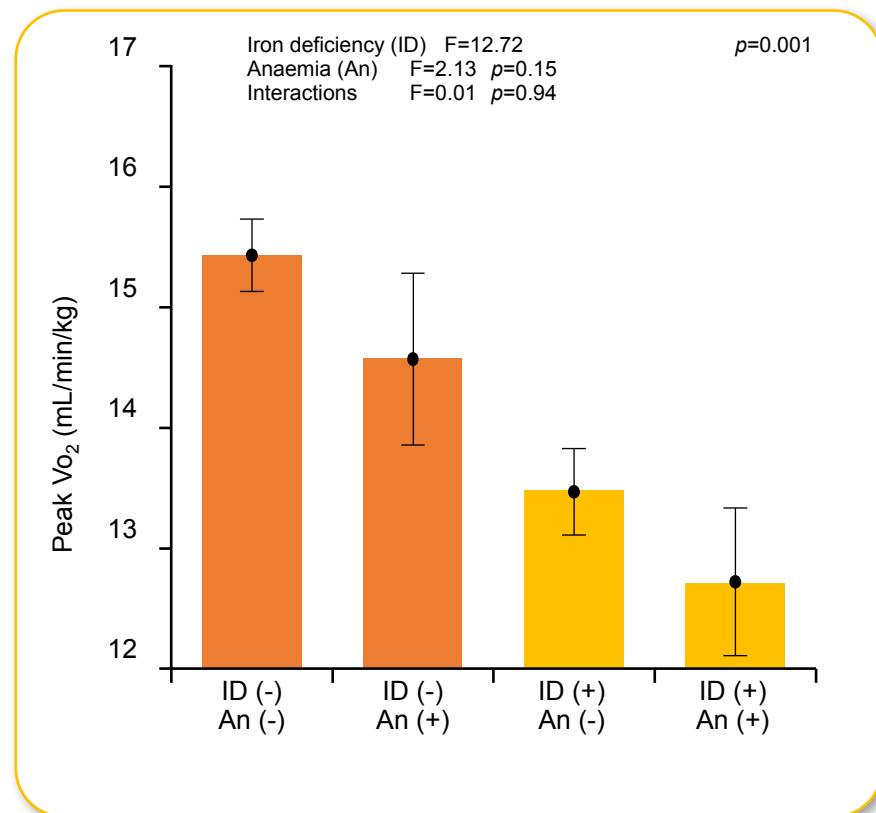
Baseline



4dDFO

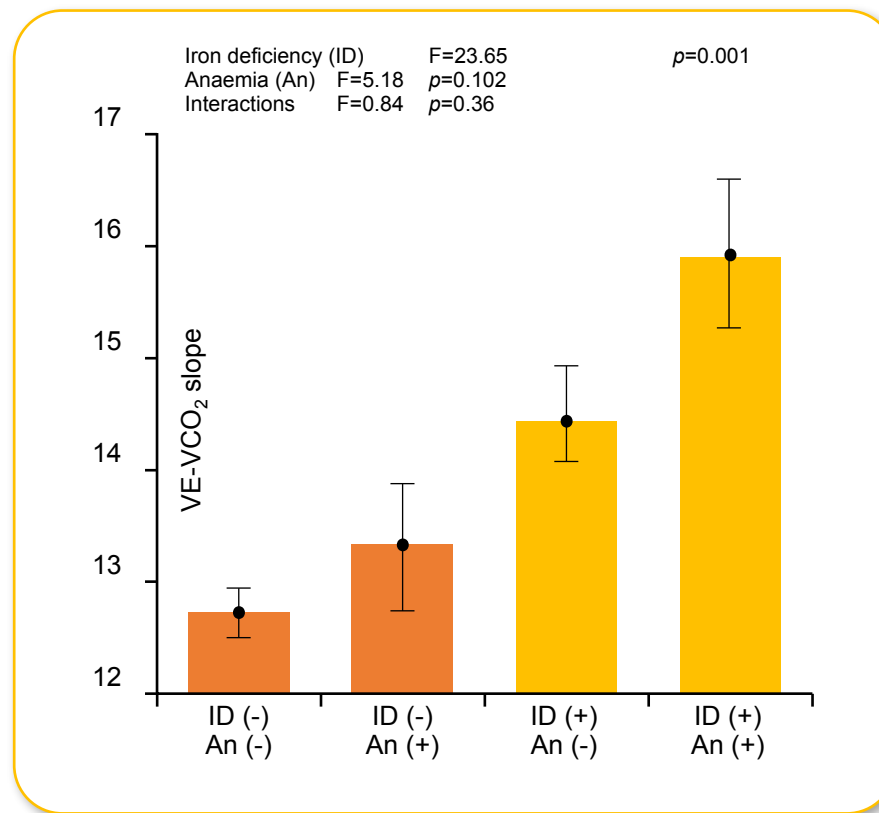


Consumo di ossigeno di picco (VO₂)



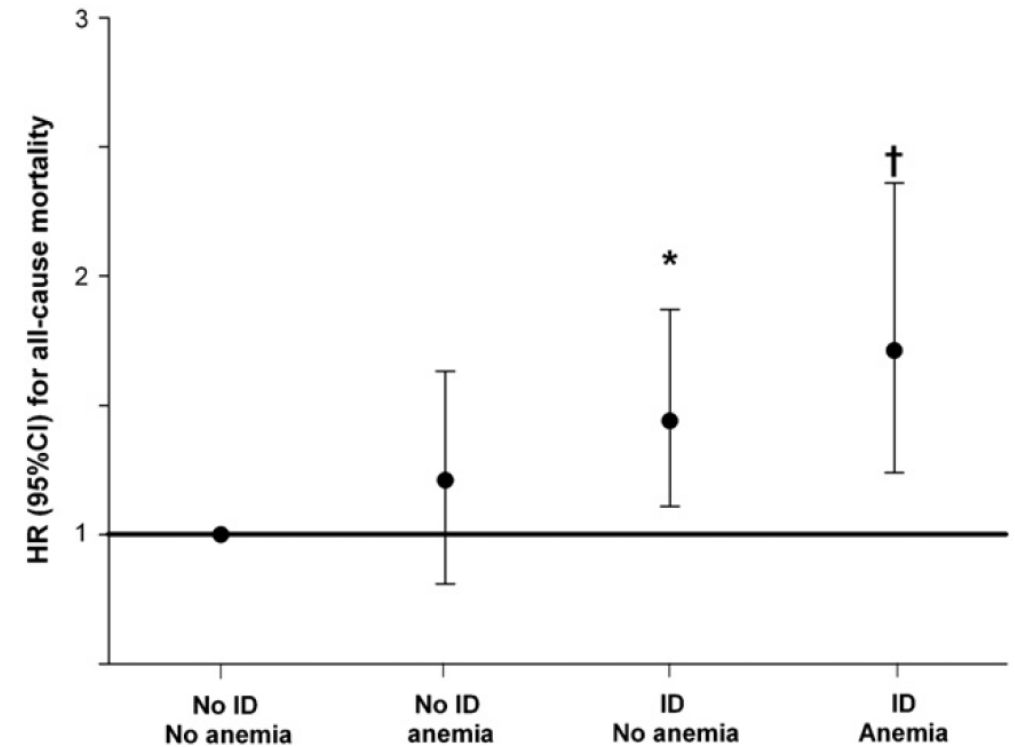
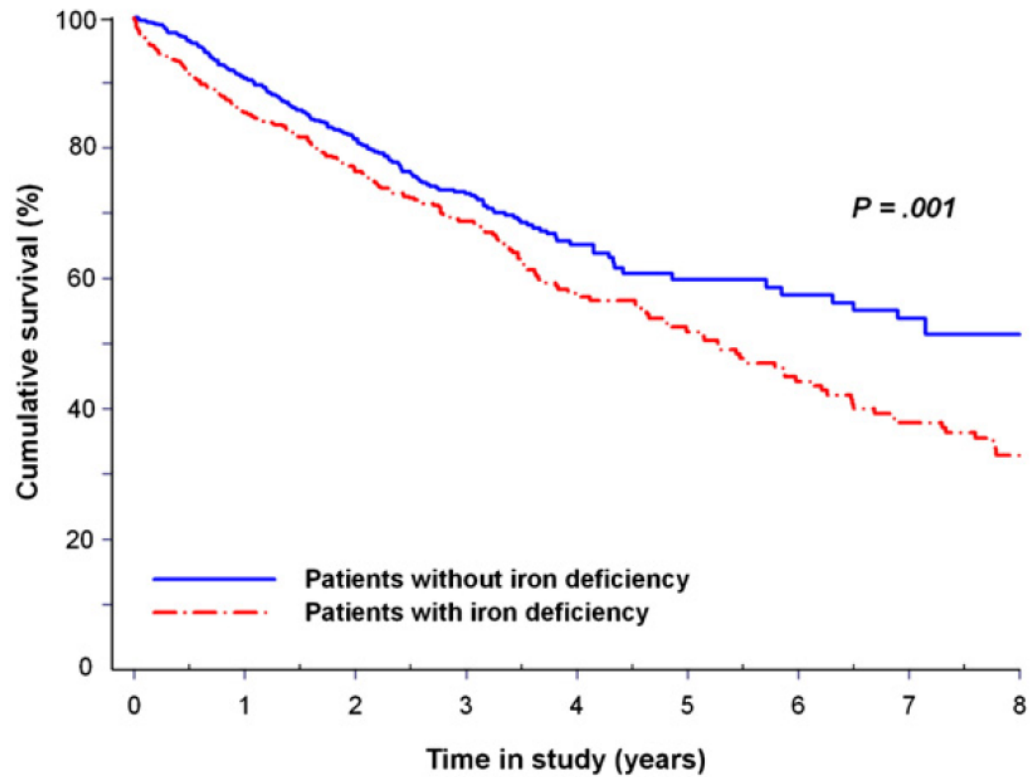
pendenza VE/VCO₂

(pendenza della retta di regressione che mette in relazione la ventilazione con la produzione di CO₂)



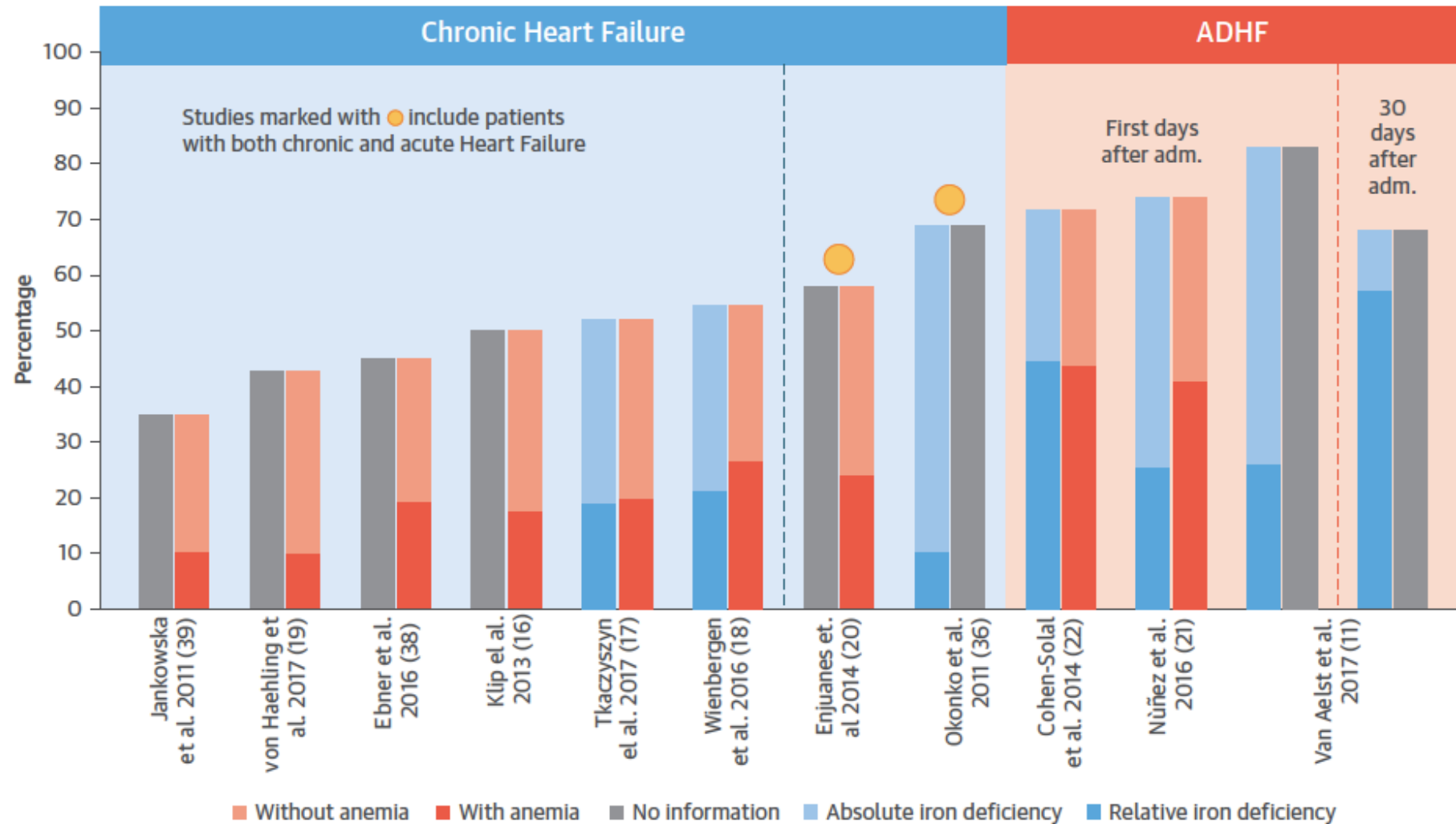
1. Jankowska EA et al. *J Card Fail.* 2011;17:899-906.
2. van Veldhuisen, DJ et al. *Nat. Rev. Cardiol.* 2011;8:485-493

Iron deficiency and outcome



1. Klip IT et al. *Am Heart J*. 2013;165:575–582.

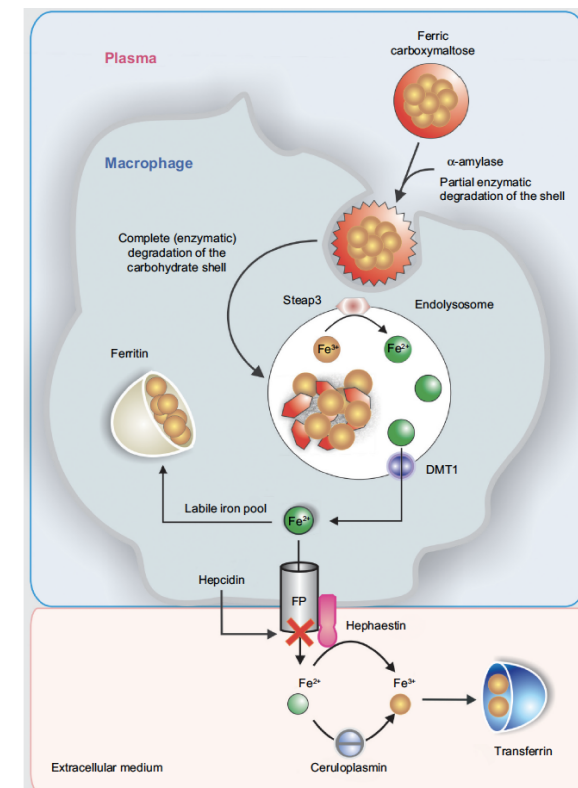
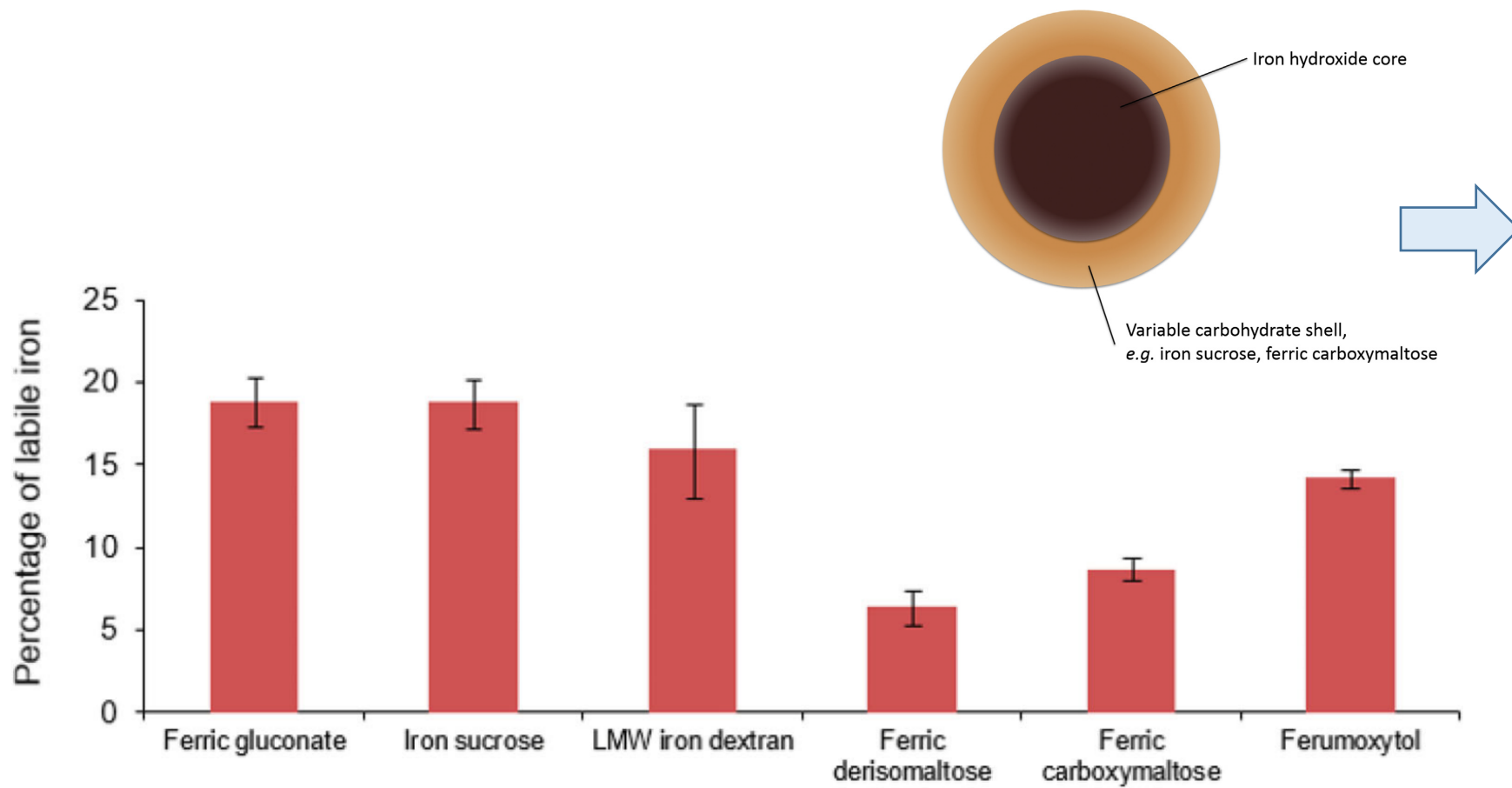
2. Jankowska EA et al. *European Heart Journal* 2010; 31, 1872–1880



Background HF medical therapy

	HFrEF	HFmrEF	HFpEF
<i>Background HF medical therapy</i>			
B-blockers	632 (91)	213 (87)	151 (75)
ACEi/ARB	125 (18)	82 (34)	100 (50)
ARNI	430 (61.8)	132 (54.5)	35 (17.6)
• <50%	45.2%	37.1%	37.1%
• 50 to <100%	30.4%	37.9%	34.3%
• ≥ 100%	24.4%	25%	28.6%
MRA	507 (72.7)	164 (67.5)	107 (53.5)
• <50%	55.9%	67.7%	57.1%
• 50 to <100%	35.8%	27.4%	38.1%
• ≥ 100%	8.3%	4.9%	4.8%
SGLT2i	455 (65.3)	139 (57.2)	67 (33.5)
• Dapagliflozin, %	72.2	82.0	65.7
• Empagliflozin, %	27.8	18.0	34.3
Diuretics	493 (71.1)	138 (57.5)	143 (71.5)
IV iron in the last 6 months	21 (3.1)	6 (2.5)	6 (3.1)
Potassium binders	20 (2.9)	7 (2.9)	1 (0.5)
Ivabradine	48 (7.0)	16 (6.7)	3 (1.5)

Data are presented as n (%)



Am J Hematol. 2021;96:727–734.

von Haehling, S. et al. J Am Coll Cardiol HF. 2019;7(1):36–46

Toblli and Angerosa. Drug Design, Development and Therapy 2014;8 2475–2491.

RCT with i.v. iron therapy in HFrEF trials

Chronic
Heart Failure

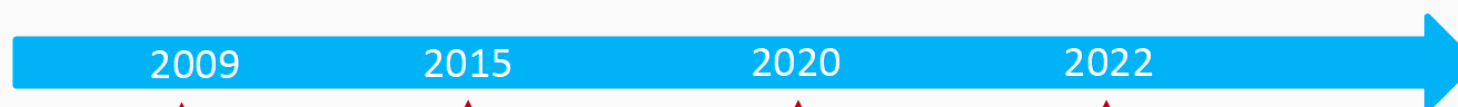


6MWT / QOL

Admitted
for Acute
Heart Failure

Recently Admitted
or Admitted for
Acute
Heart Failure

hHF – CV death



FAIR-HF ^a

459 pat.
24 weeks

CONFIRM-HF ^b

301 pat.
52 weeks

AFFIRM-HF ^c

1,108 pat.
52 weeks

IRONMAN ^d

1,137 pat.
140 weeks

^a NEJM. 2009;361:2436-48

^b EHJ. 2015;36:657-68

^c Lancet. 2020;396:1895-1904

^d Lancet. 2022;400:2199-2209

Ferric Carboxymaltose

Ferric Derisomaltose

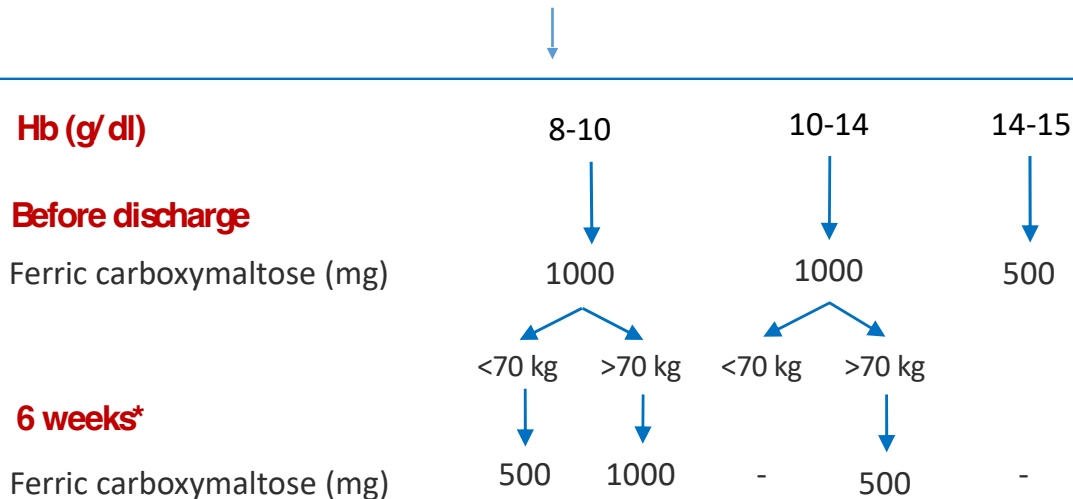
AFFIRM-AHF

- Hospitalised for acute heart failure

- LVEF $\leq 50\%$

- **Iron deficiency**

(Ferritin $< 100 \mu\text{g/L}$, or
 100–299 $\mu\text{g/L}$ with
 transferrin saturation $< 20\%$)

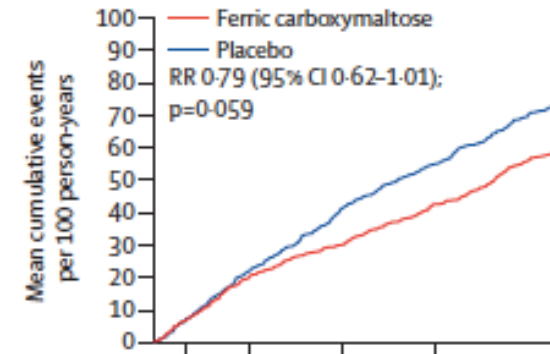


6 weeks*

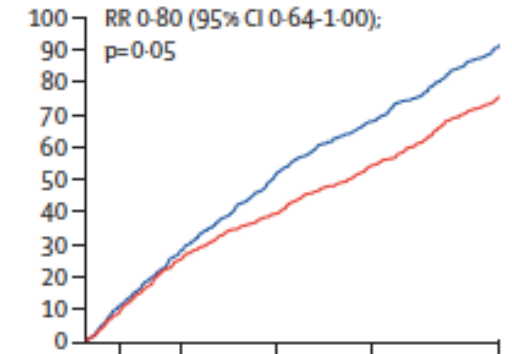
Ferric carboxymaltose (mg)

* 12 and 24 weeks in the case of persistence of iron deficiency

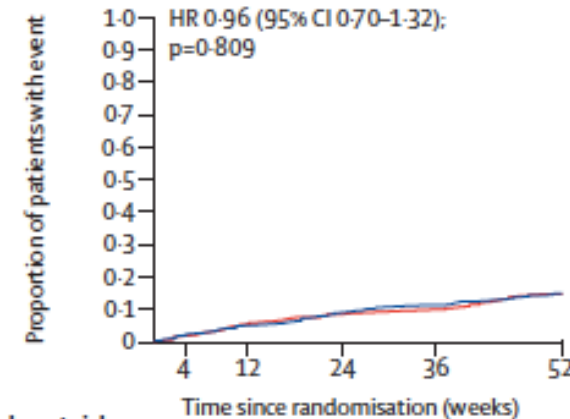
A Primary outcome: total heart failure hospitalisations and cardiovascular death



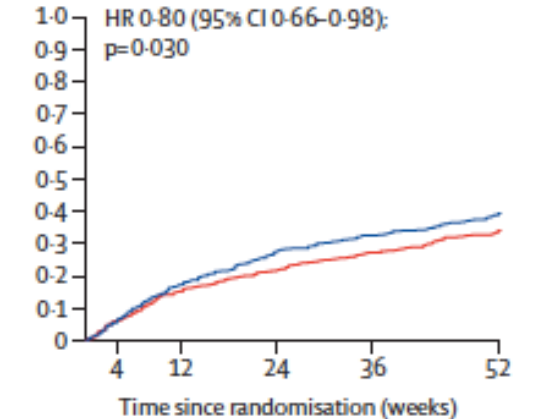
B Total cardiovascular hospitalisations and cardiovascular death



D Cardiovascular death



E First heart failure hospitalisation or cardiovascular death



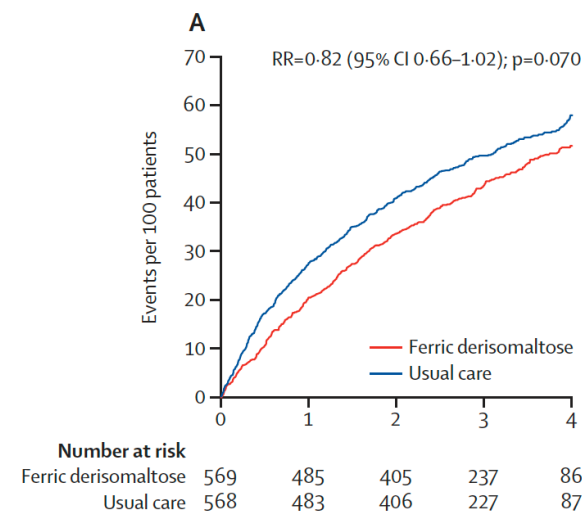
Number at risk	Time since randomisation (weeks)				
	4	12	24	36	52
Ferric carboxymaltose	544	509	483	468	289
Placebo	537	511	486	465	285

IRONMAN

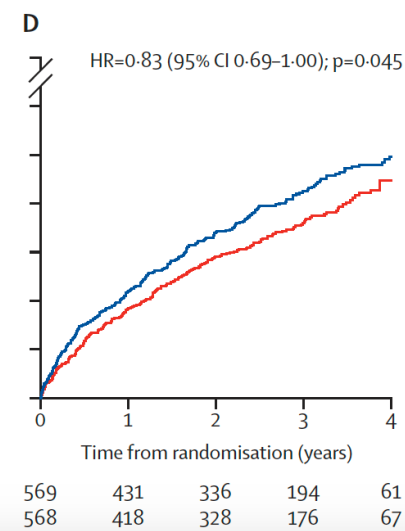
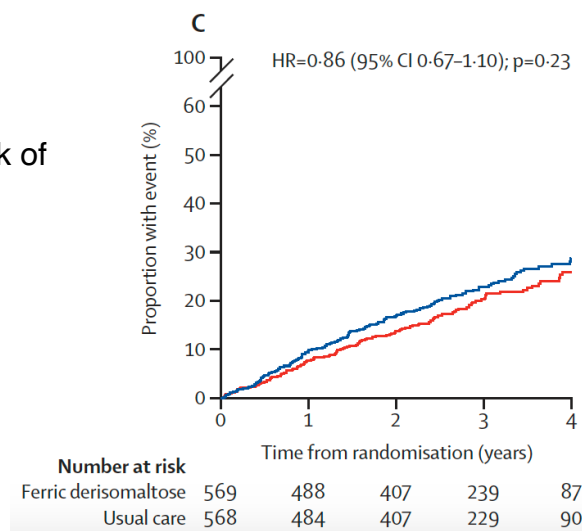
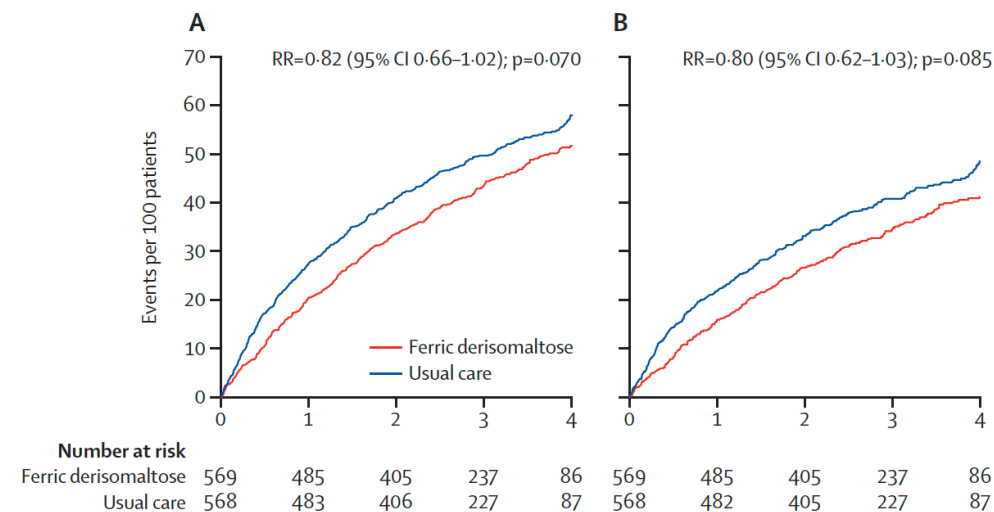
- New or established HF
- Serum ferritin <100 µg/L or transferrin saturation <20%
- LVEF<45%
- Current or recent (within 6 months) HF admission or high NT-proBNP

Both C and D show cumulative incidence functions, correcting for the competing risk of non-cardiovascular death.

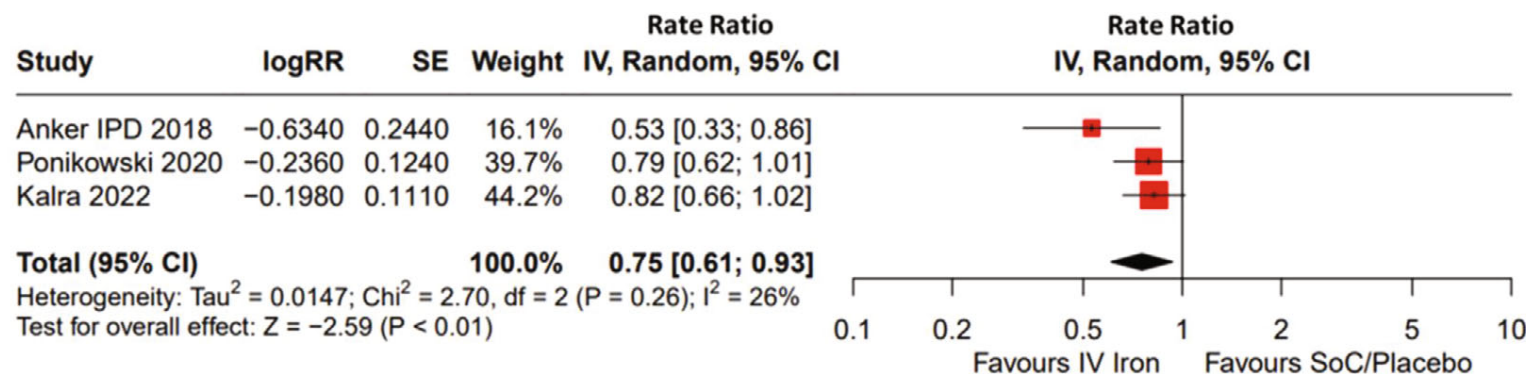
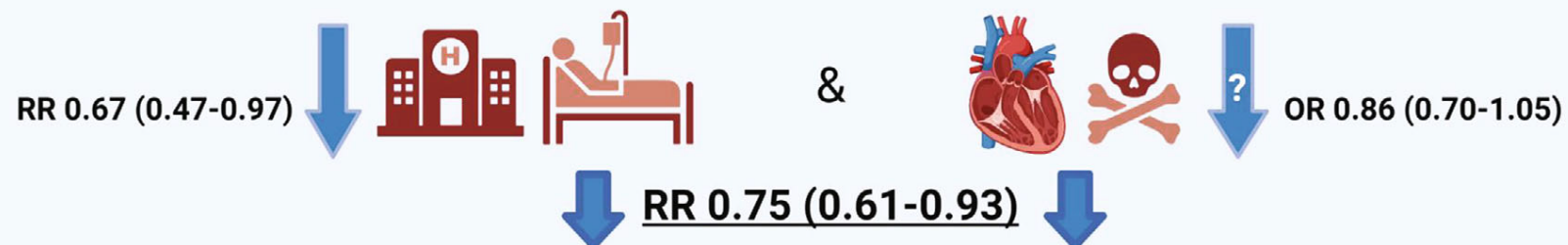
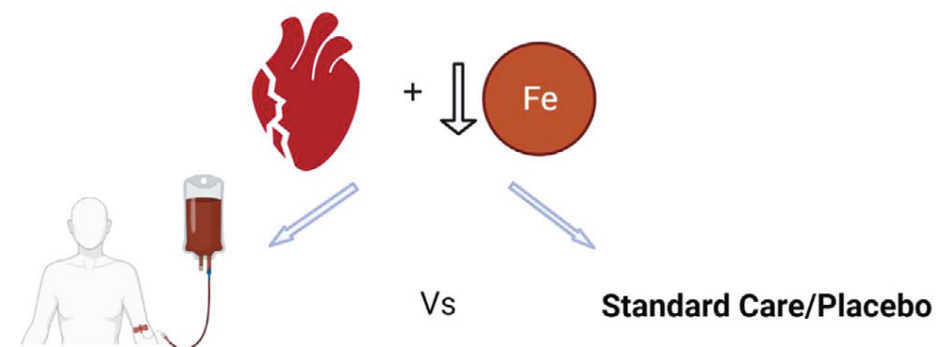
All hospital admissions for heart failure and cardiovascular death



All hospital admissions for heart failure



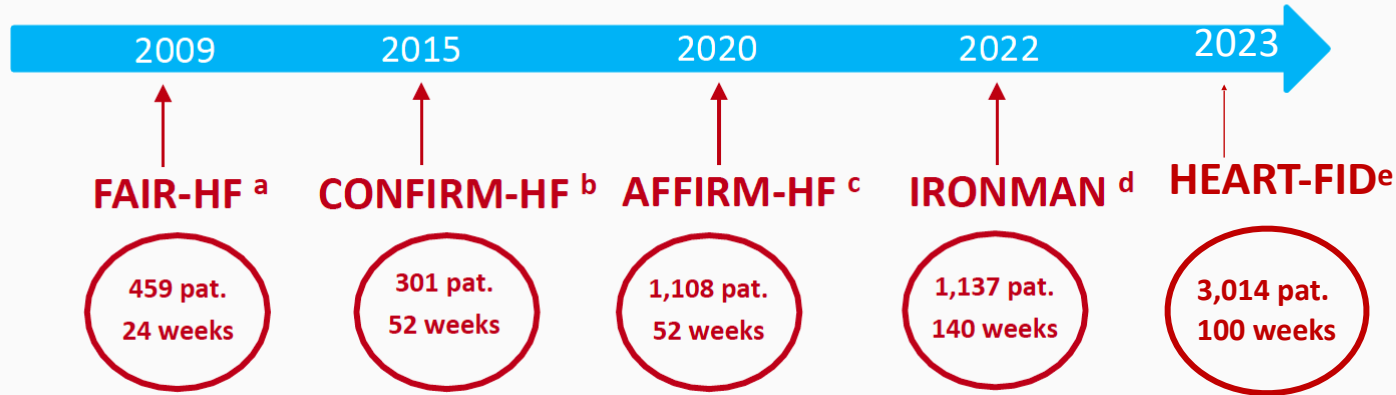
10 RCTs, including AFFIRM-AHF and IRONMAN
 >3000 patients with HF and ID
 IV iron: ↓ HHF and CVM by 25% vs standard care/placebo



2023 ESC Update on the 2021 Heart Failure Guidelines

Recommendations	Class ^a	Level ^b
Intravenous iron supplementation is recommended in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to alleviate HF symptoms and improve quality of life. ^{c 12,41,47–49}	I	A
Intravenous iron supplementation with ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic patients with HFrEF and HFmrEF, and iron deficiency, to reduce the risk of HF hospitalization. ^{c 12,41,43–46}	IIa	A

RCT with i.v. iron therapy in HFrEF trials



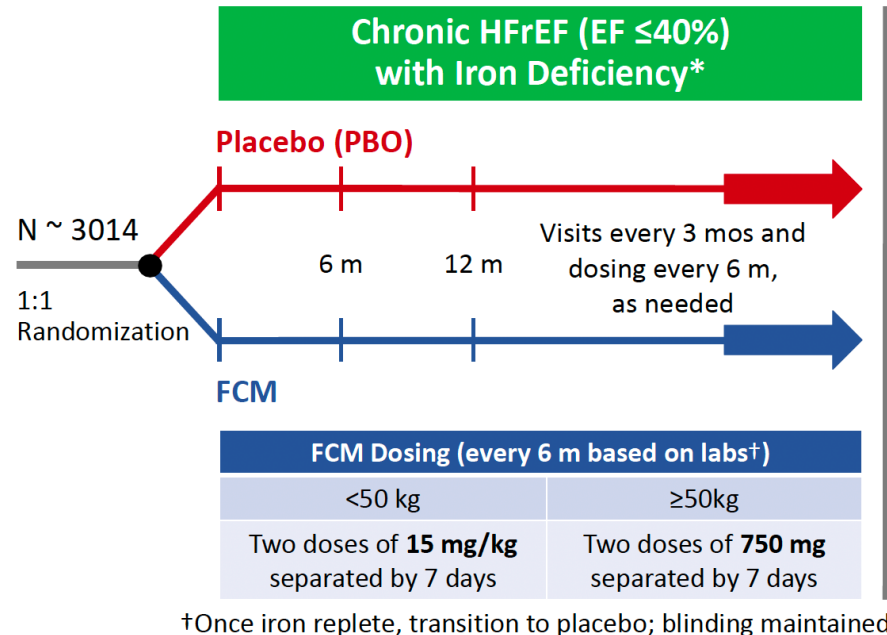
^a NEJM. 2009;361:2436-48

^b EHJ. 2015;36:657-68

^c Lancet. 2020;396:1895-1904

^d Lancet. 2022;400:2199-2209

^e N Engl J Med 2023;389:975-86.



Primary Endpoint:

Hierarchical Composite:

- All-cause mortality (12 m)
- HF hospitalizations (12 m)
- Change in 6-MWD (6 m)

Top Secondary Endpoint:

CV death or HF hospitalization

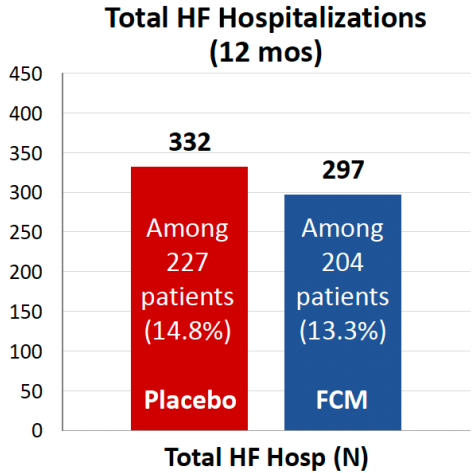
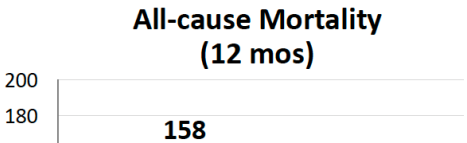
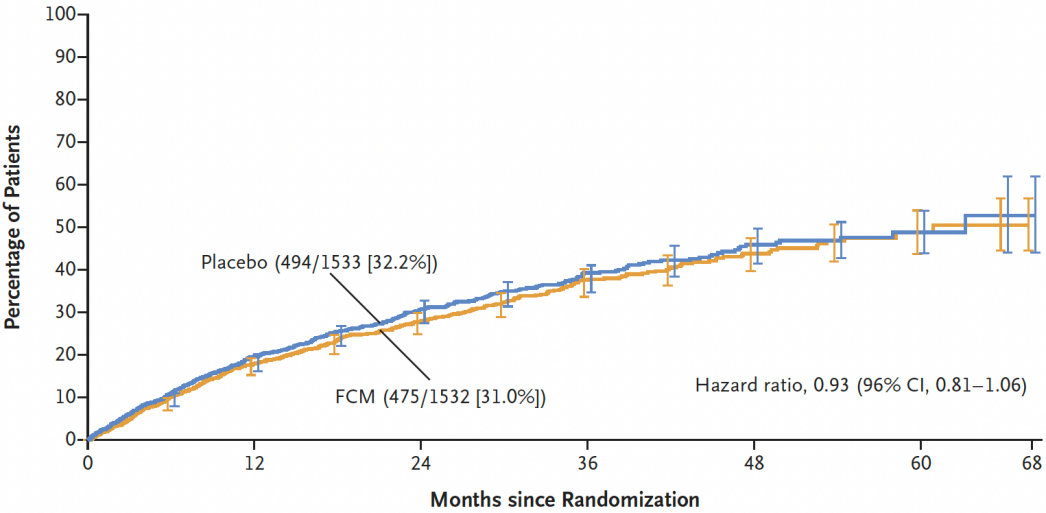
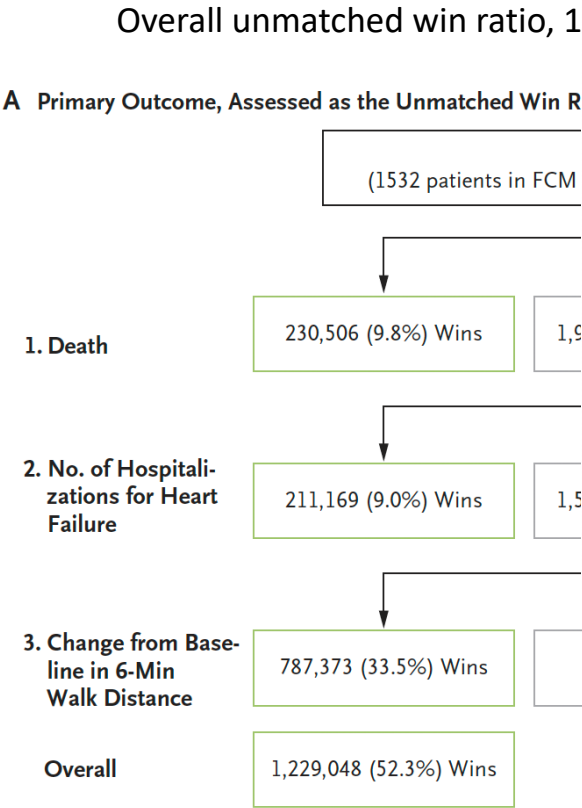
Key Inclusion Criteria:

- *Iron deficiency
 - Ferritin <100 ng/mL or
 - 100-300 ng/mL + TSAT <20%
- HF hosp (12 m) or ↑ NT-proBNP (90 d) [>600 pg/mL (NSR) or >1000 pg/mL (AF)]

HEART-FID

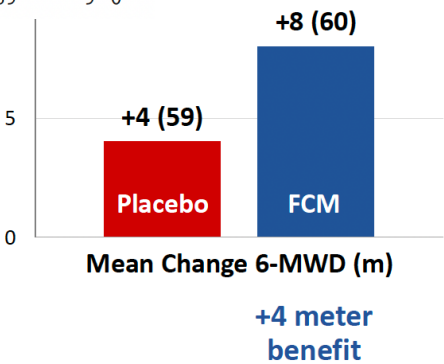
Unmatched win ratio (based on the first imputed data set)=
(total wins)/(total losses)=1,229,048/1,111,664=1.11 (99% CI, 0.99-1.23)

B Cardiovascular Death or First Hospitalization for Heart Failure



270 fewer HF hospitalization days

ange in 6-MWD (6 mos)

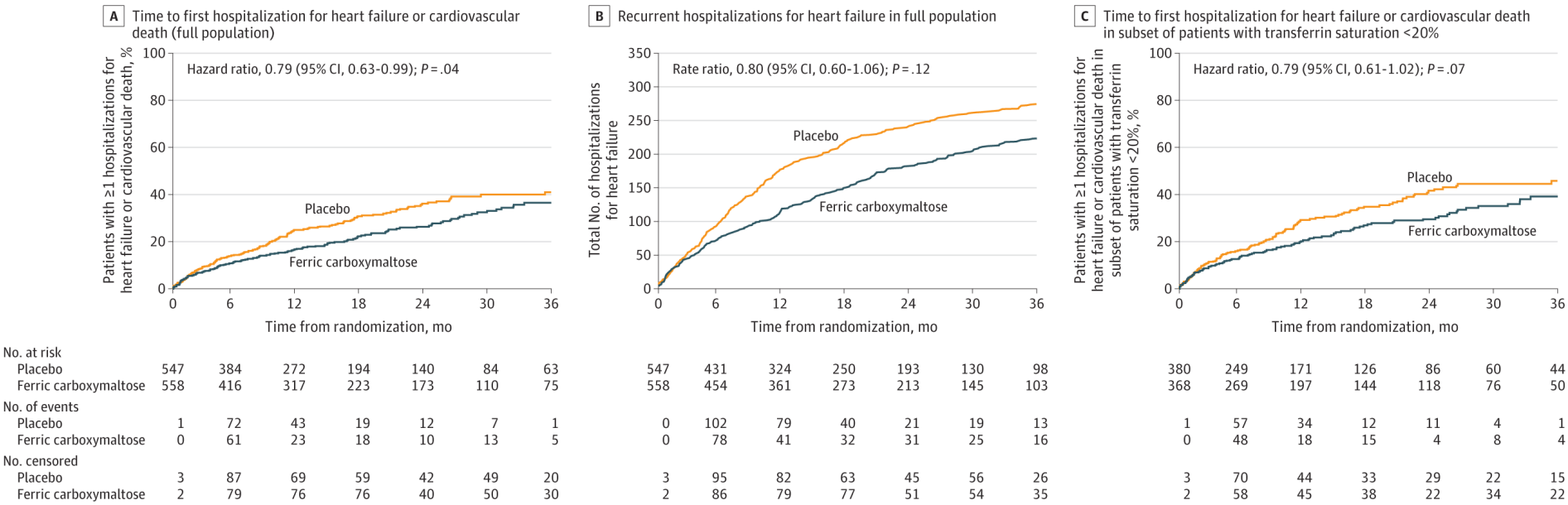


JAMA | Original Investigation

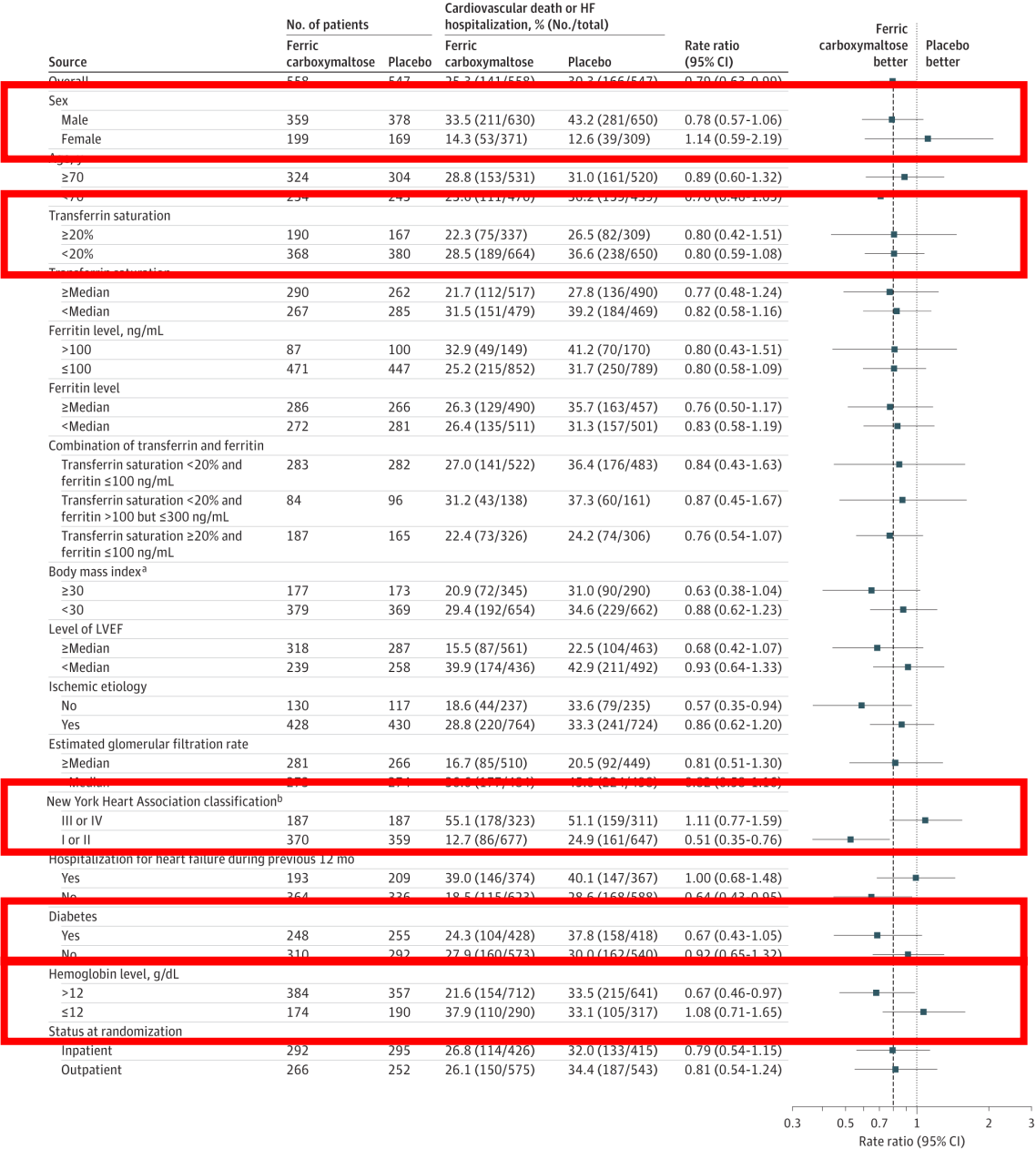
Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency

The FAIR-HF2 DZHK05 Randomized Clinical Trial

Stefan D. Anker, MD, PhD; Tim Friede, PhD; Javed Butler, MD, MPH; Khawaja M. Talha, MBBS; Marius Placzek, PhD; Monika Diek, MA; Anna Nosko, PhD; Adriane Stas, BA; Stefan Kluge, MD; Dominik Jarczak, MD; Geraldine deHeer, MD; Meike Rybczynski, MD; Antoni Bayés-Genís, MD, PhD; Michael Böhm, MD; Andrew J. S. Coats, MD; Frank Edelmann, MD; Gerasimos Filippatos, MD; Gerd Hasenfuß, MD; Wilhelm Haverkamp, MD; Mitja Lainscak, MD, PhD; Ulf Landmesser, MD; Iain C. Macdougall, MD; Bela Merkely, MD, PhD, DSc; Burkert M. Pieske, MD; Fausto J. Pinto, MD, PhD; Tienush Rassaf, MD; Jennifer K. Visser-Rogers, PhD; Giuseppe Rosano, PhD; Maurizio Volterrani, MD; Stephan von Haehling, MD, PhD; Markus S. Anker, MD; Wolfram Doehner, MD, PhD; Hüseyin Ince, MD; Friedrich Koehler, MD; Gianluigi Savarese, MD; Muhammad Shahzeb Khan, MD, MSc; Ursula Rauch-Kröhnert, MD; Tommaso Gori, MD; Teresa Trenkwalder, MD; Ibrahim Akin, MD; Christina Paitazoglou, MD; Iwona Kobielski-Gembala, MD; Luca Kuthi, MD; Norbert Frey, MD; Manuela Licka, MD; Stefan Käb, MD; Karl-Ludwig Laugwitz, MD; Piotr Ponikowski, MD, PhD; Mahir Karakas, MD, PhD, MBA



Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency





Systematic review and meta-analysis of intravenous iron therapy for patients with heart failure and iron deficiency

Received: 8 February 2025

Accepted: 20 March 2025

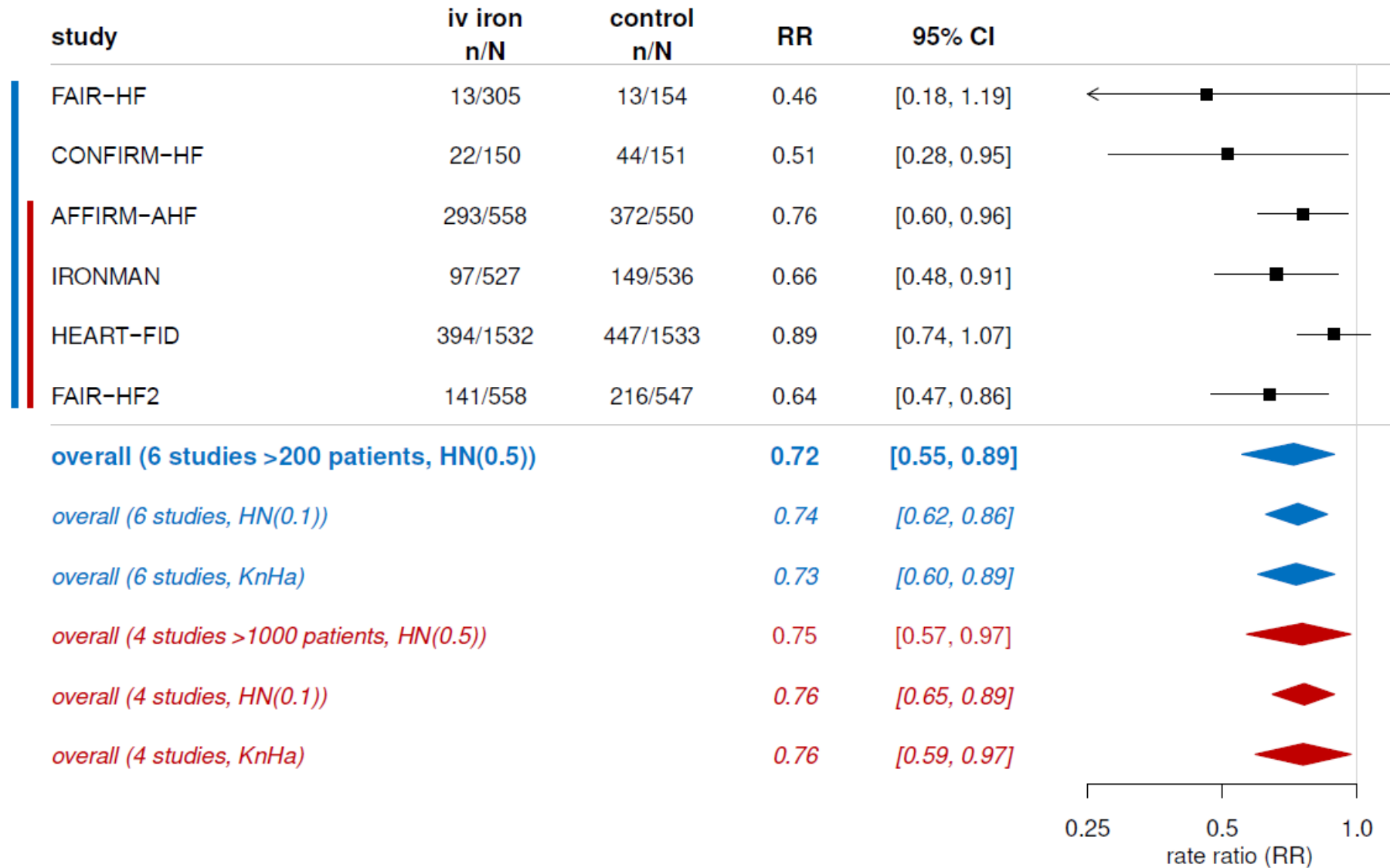
Published online: 30 March 2025

Check for updates

A list of authors and their affiliations appears at the end of the paper

Uncertainty remains about the effect of intravenous (i.v.) iron on outcomes for heart failure (HF) with iron deficiency. In the present study, we summarize the efficacy and safety of i.v. iron from six trials (FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN, HEART-FID and FAIR-HF2), including 7,175 patients. In comparison to prior analyses, this meta-analysis added new data from FAIR-HF2, used a harmonized and robust Bayesian approach and included individual participant data from five trials. Patients assigned

effect of i.v. iron on the composite endpoint of total (first and recurrent) HF hospitalizations and cardiovascular mortality for the first 12 months of follow-up



La correzione per os della carenza marziale

JAMA | Original Investigation

Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency The IRONOUT HF Randomized Clinical Trial

Gregory D. Lewis, MD; Rajeev Malhotra, MD; Adrian F. Hernandez, MD, MHS; Steven E. McNulty, MS; Andrew Smith, MD; G. Michael Felker, MD, MHS; W. H. Wilson Tang, MD; Shane J. LaRue, MD; Margaret M. Redfield, MD; Marc J. Semigran, MD; Michael M. Givertz, MD; Peter Van Buren, MD; David Whellan, MD; Kevin J. Anstrom, PhD; Monica R. Shah, MD, MHS; Patrice Desvigne-Nickens, MD; Javed Butler, MD; Eugene Braunwald, MD; for the NHLBI Heart Failure Clinical Research Network

Table 2. Primary, Secondary, and Safety End Points

	Median (IQR)				Difference in Change From Baseline (95% CI)	P Value
	Week-16 Values ^a		Change From Baseline to Week 16			
	Oral Iron	Placebo	Oral Iron	Placebo		
Primary End Point						
Peak $\dot{V}O_2$ 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 $\dot{V}O_2$ 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 (V_E/V_{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



Advantages

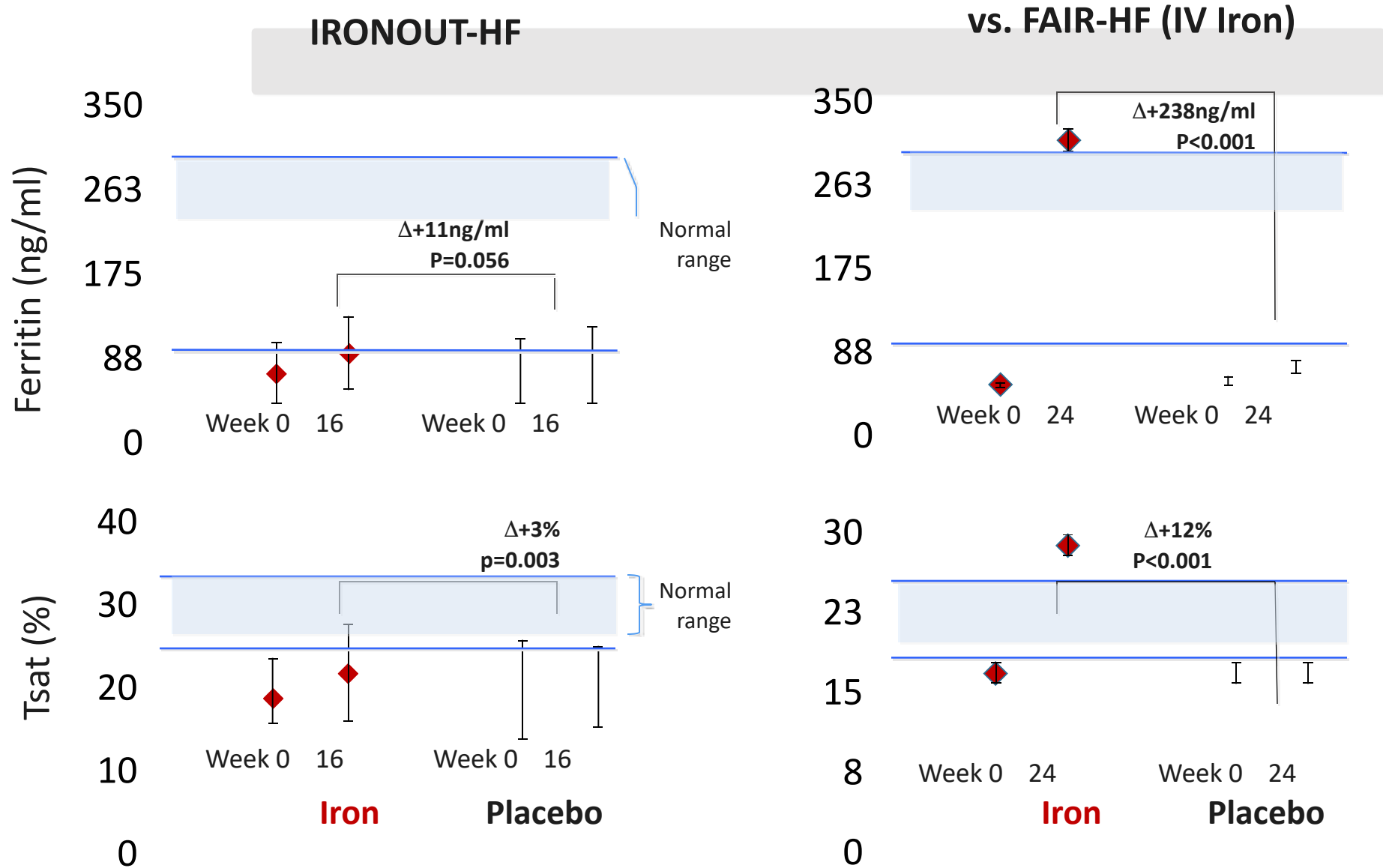
- cheap
- easy to administer



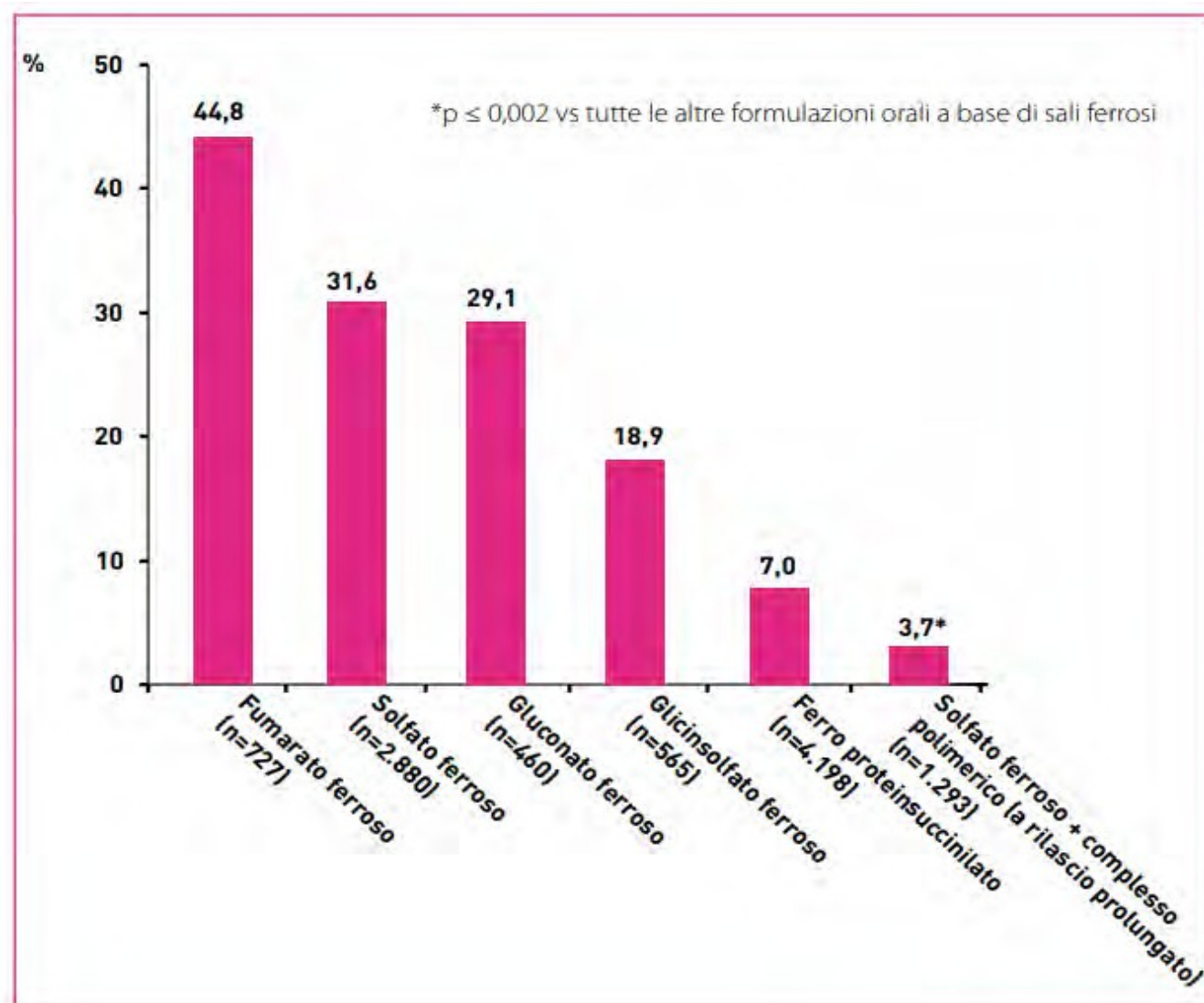
Disadvantages

- poorly absorbed (max 5 mg/day)
- GI side-effects common
- compliance often poor
- absorption limited by Ferritin elevated
- Absorption reduced in inflammation

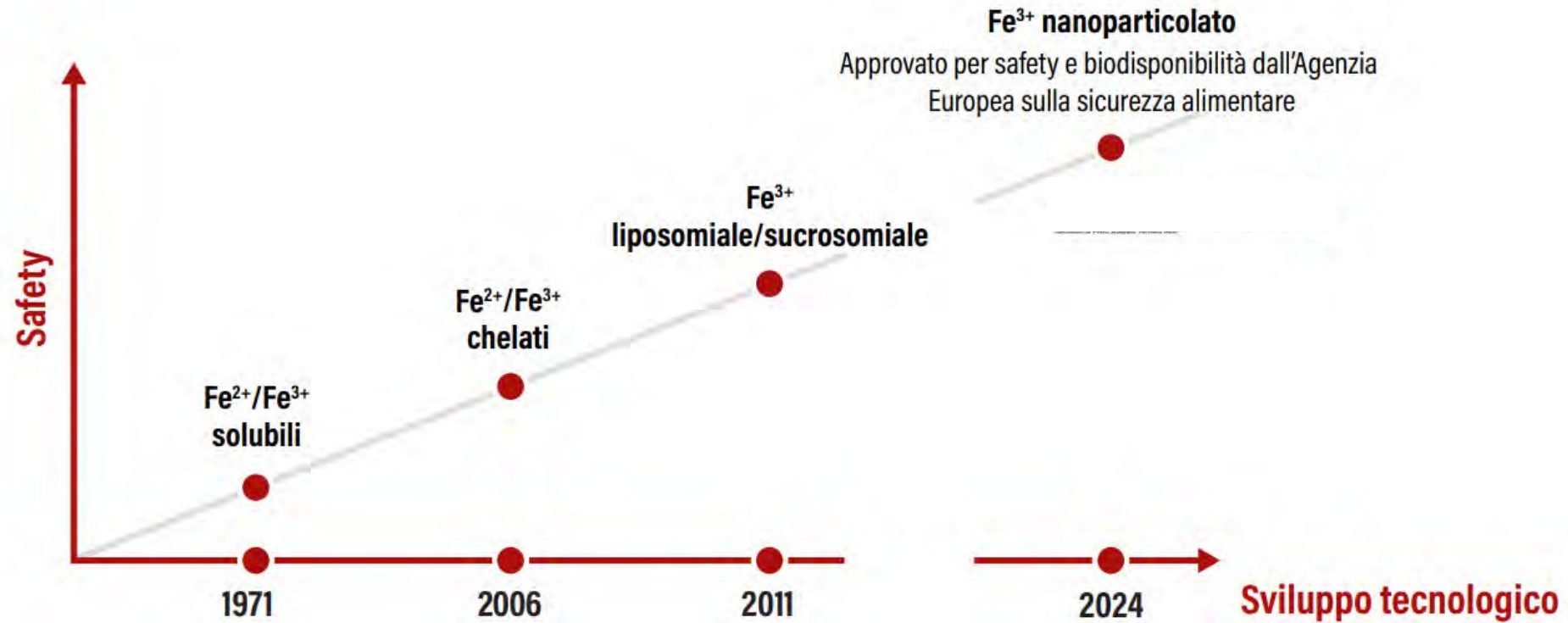
Results: Δ Iron Studies

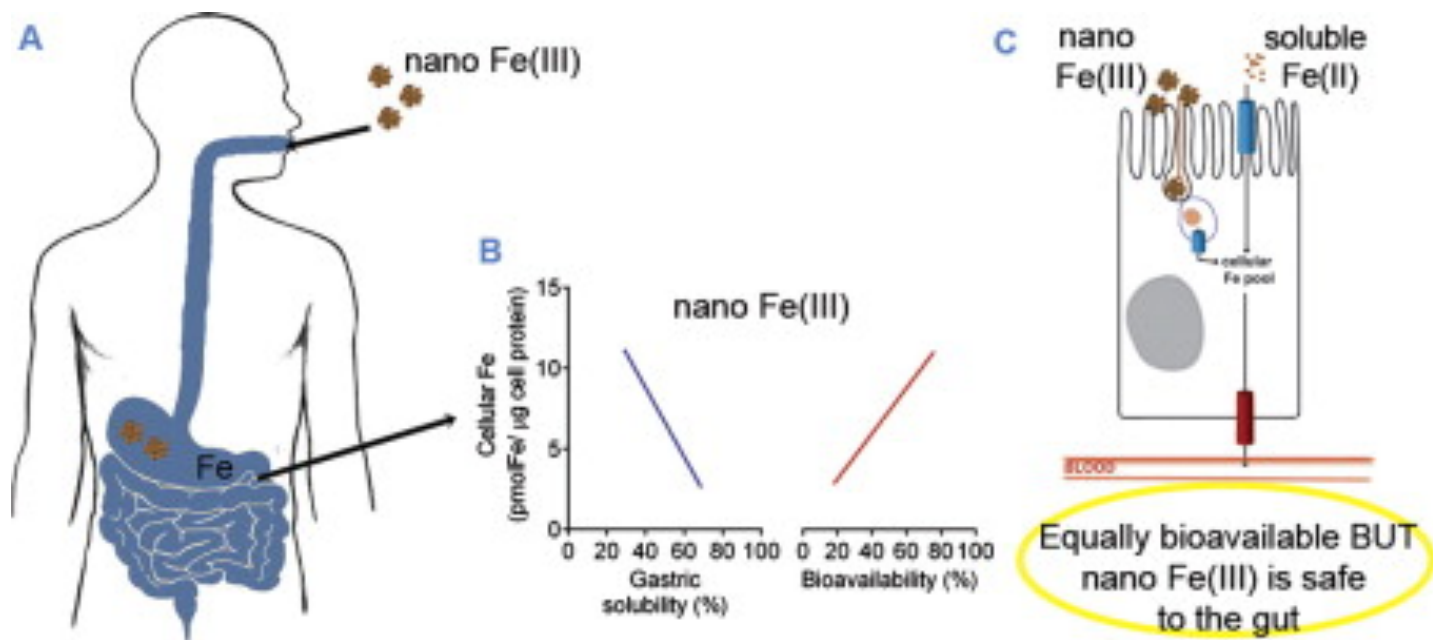


EVENTI AVVERSI GASTROINTESTINALI



L'EVOLUZIONE TECNOLOGICA DELLA SAFETY DEL FERRO

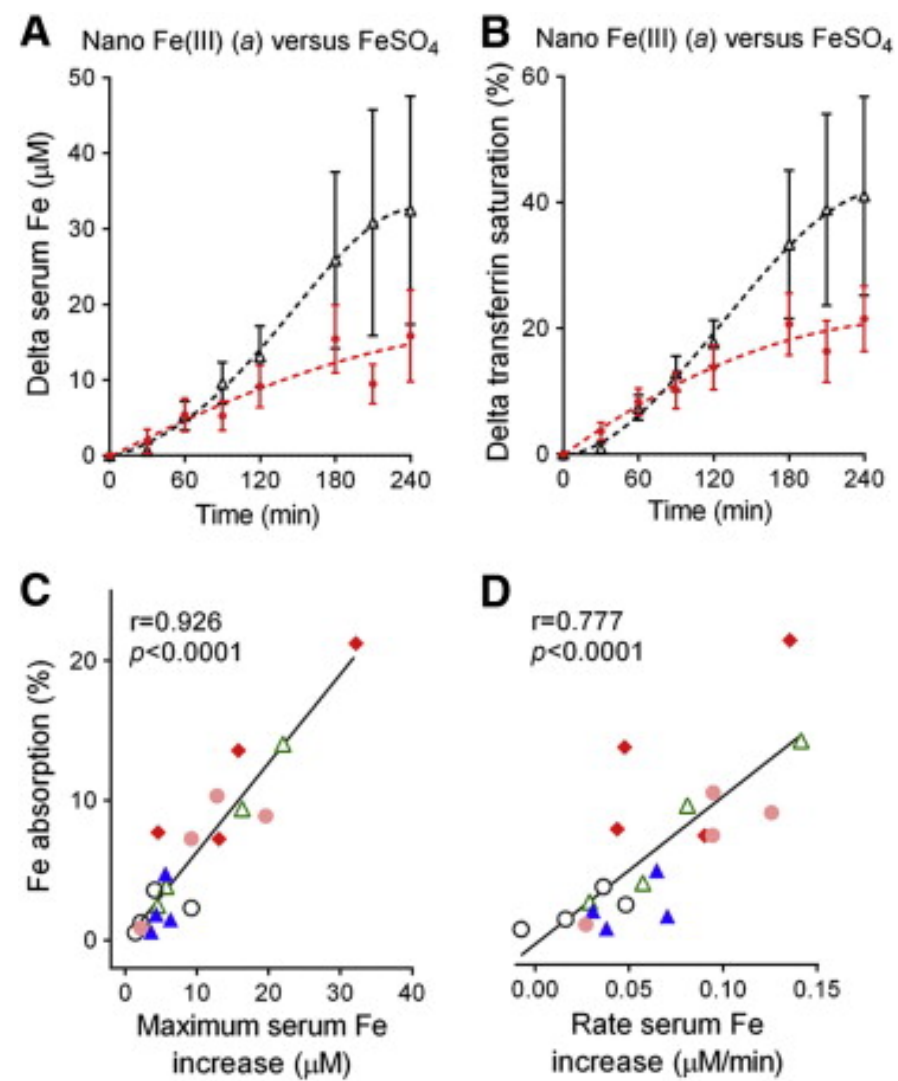




Idrossido di Ferro Adipato Tartrato

- nuova entità chimica di ferro,
 - simile per assorbimento e distribuzione alla ferritina naturale
- Sottoforma di nanoparticelle, con struttura destabilizzata amorfa
 - è altamente biodisponibile

Serum iron absorption following ingestion of a single-dose of the different Fe in iron-deficient women.

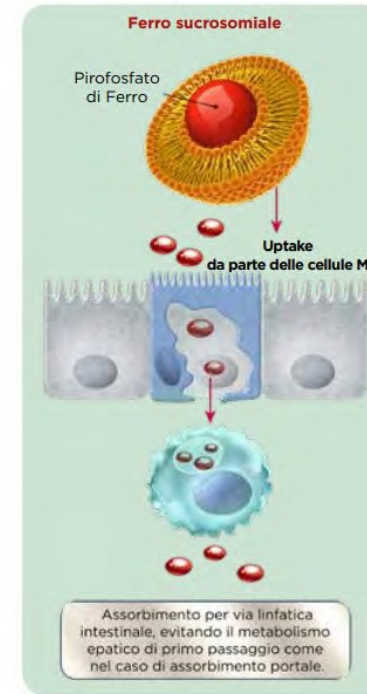
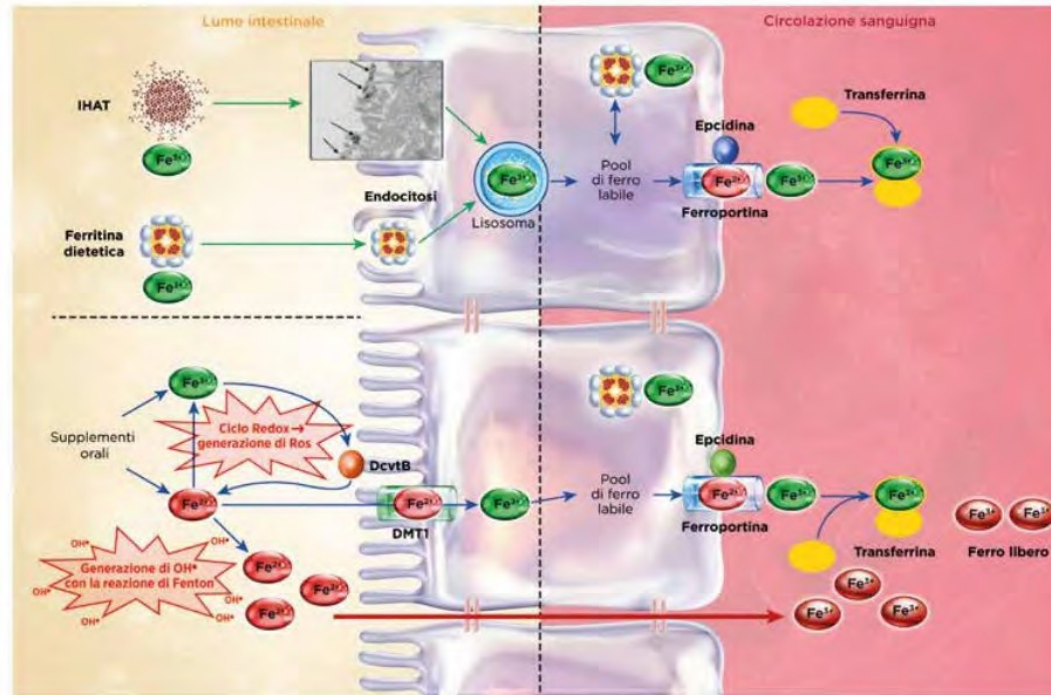


IHAT E ATTIVITA' OSSIDO-RIDUTTIVA

- Fe inorganico solubile [Fe(II) o Fe(III)] nell'ambiente intestinale alcalino perde parte della solubilità,
 - precipitando in situ a formare nanoparticelle di Fe(III) idrossido, contenute in un rivestimento mucinico (ferritina modificata)
- La continua conversione tra Fe(III) ferrico e Fe(II) ferroso nel lume intestinale, prima dell'assorbimento di Fe(II) nelle cellule intestinali, determina gastrolesività, oltre a modificare la flora intestinale
 - soppressione di *Lactobacillus*, *Bifidobacteria*, *Enterobacteriaceae*, con rischio potenziale di sviluppo di batteri patogeni
- IHAT viene assorbito esclusivamente con meccanismo endocitosico
 - senza determinare danni ossido-riduttivi alla mucosa intestinale

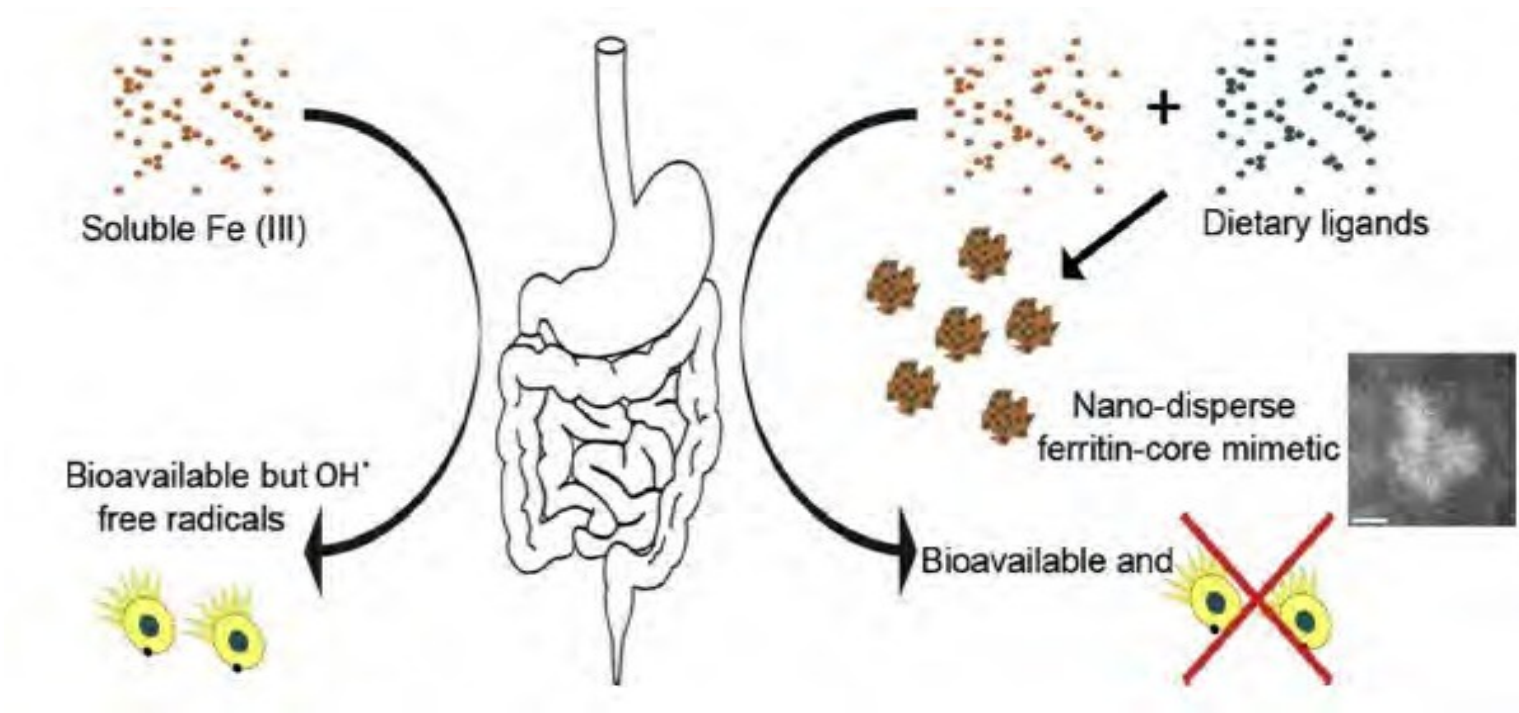
ASSORBIMENTO ENDOCITOSICO DI IHAT

Idrossido di Ferro Adipato Tartrato è assorbito lentamente per endocitosi⁶, mantenendo il livello di saturazione di ferritina <40% ed evitando la presenza in circolo di ferro in forma libera e quindi citotossico



IHAT NON OSSIDO-RIDUTTIVO E BIODISPONIBILE

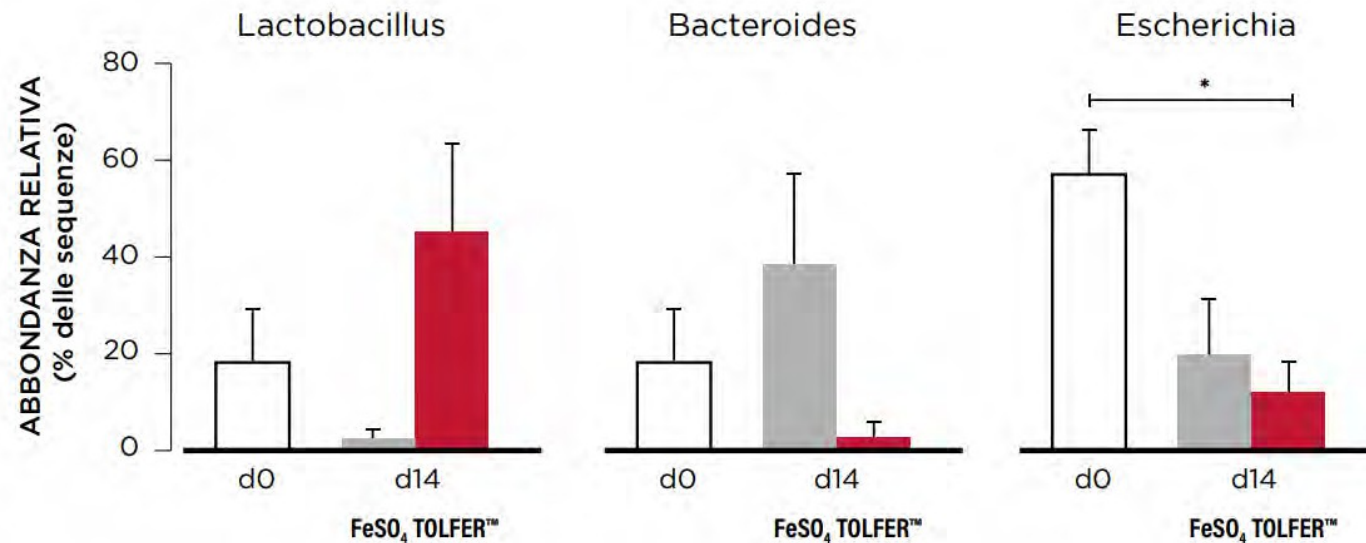
IHAT è Fe^{3+} nanoparticolato, con un core ferritina-mimetico, che lo rende biodisponibile, senza liberare radicali liberi



IHAT E MICROBIOMA

IHAT, vs ferro solfato, non determinando stress ossidativo, non altera il microbioma:

- aumenta la proporzione di *Lactobacillus spp.*
- riduce il rischio potenziale di sviluppo di *Bacteroides spp.* e di *Escherichia*



Conclusioni

- La carenza marziale è frequente e influenza prognosi e qualità di vita
- Terapia EV è efficace, ma poco diffusa : somministrazione intraospedaliera
- Considerare la supplementazione orale per mantenimento
- Innovatività nelle formulazioni per os

Nuova sinergia nel paziente con deficit di Fe

Paziente Acuto/Riacutizzato → Ferrocarbossalto

Paziente Cronico → terapia a lungo termine → IHAT