

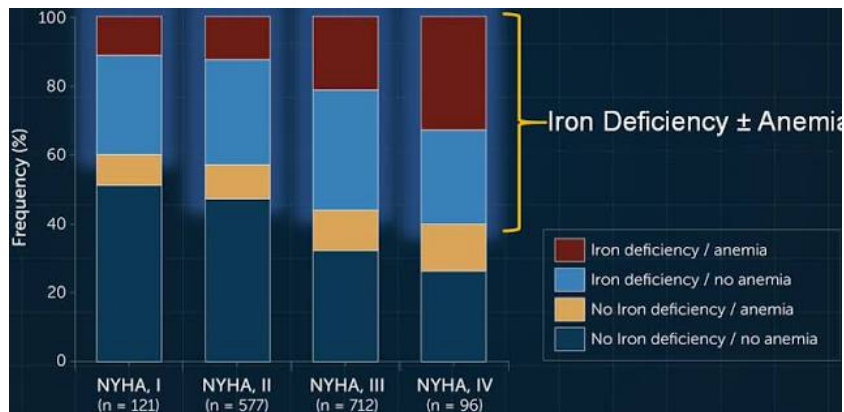
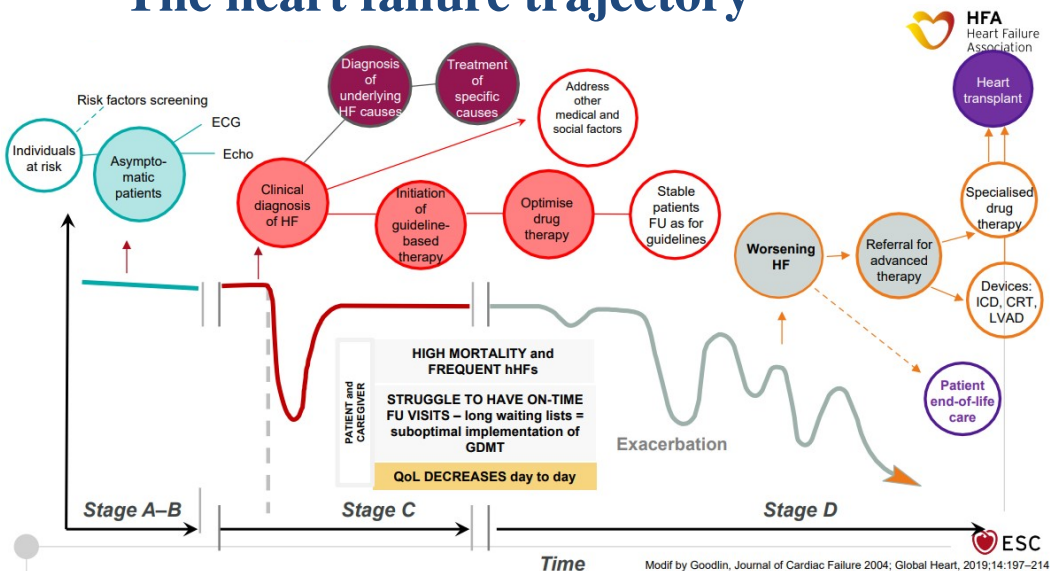
Insufficienza cardiaca cronica: le complessità

Carenza Marziale nell'insufficienza cardiaca

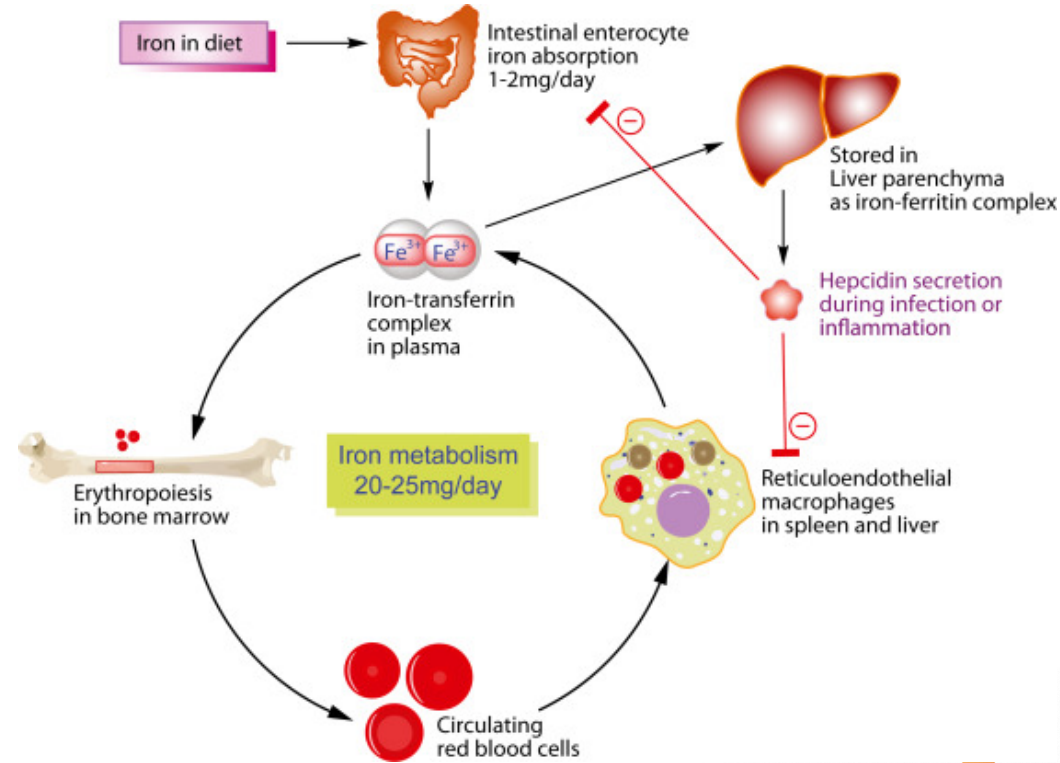
Dr. D'Amato Andrea

- Dipartimento di Scienze mediche e Cardiovascolari, Università degli studi di Roma La Sapienza
- UOC Cardiologia, F. Spaziani, Frosinone

The heart failure trajectory



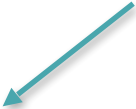
Metabolismo del ferro



JIRO J. KANEKO,
16 - Iron Metabolism, Editor(s): JIRO J. KANEKO, Clinical Biochemistry of Domestic Animals (Third Edition), Academic Press, 1980, Pages 649-669, ISBN 9780123963505,
<https://doi.org/10.1016/B978-0-12-396350-5.50021-8>



Meccanismi patogenetici della carenza marziale



Aumentato utilizzo



Aumentata perdita
(fisiologica o patologica)



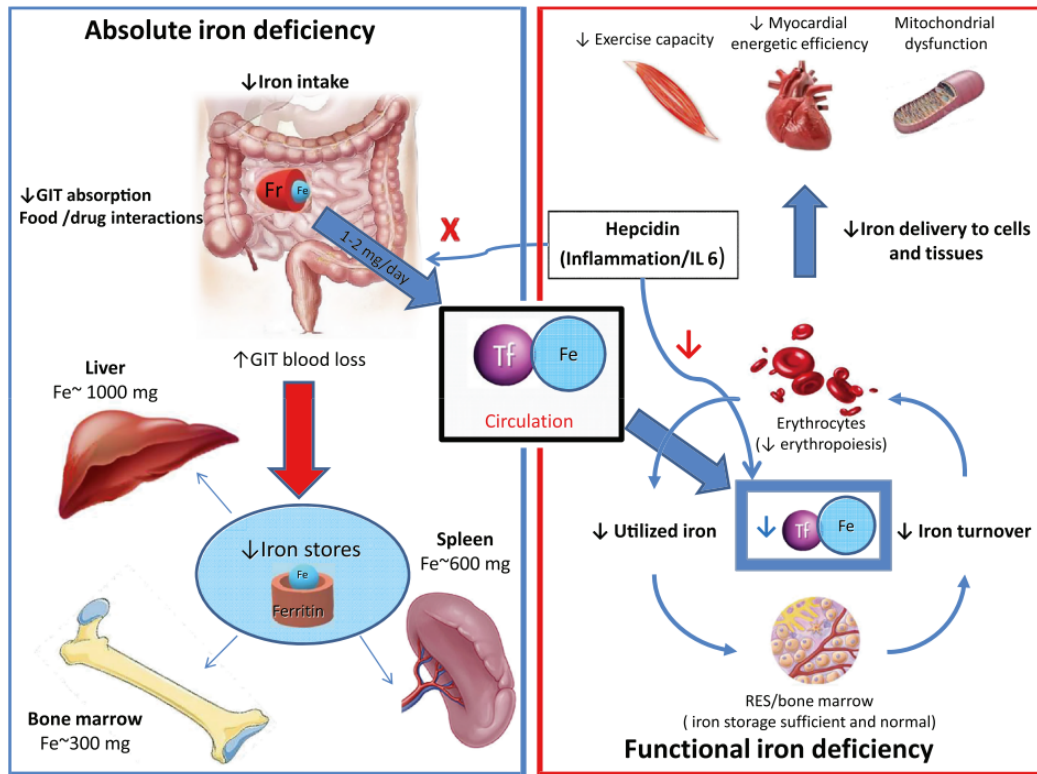
Diminuito apporto/ridotto
assorbimento



Infiammazione



Carenza Marziale nell'insufficienza cardiaca



Loncar G, Obradovic D, Thiele H, von Haehling S, Lainscak M. Iron deficiency in heart failure. ESC Heart Fail. 2021 Aug;8(4):2368-2379. doi: 10.1002/ehf2.13265. Epub 2021 May 1. PMID: 33932115; PMCID: PMC8318436.



Principali conseguenze della carenza marziale nell'insufficienza cardiaca



Ridotta eritropoiesi ed anemia



Alterazioni
metabolismo
dello stress
ossidativo



Alterazioni
energetiche e
funzionali del
miocardio



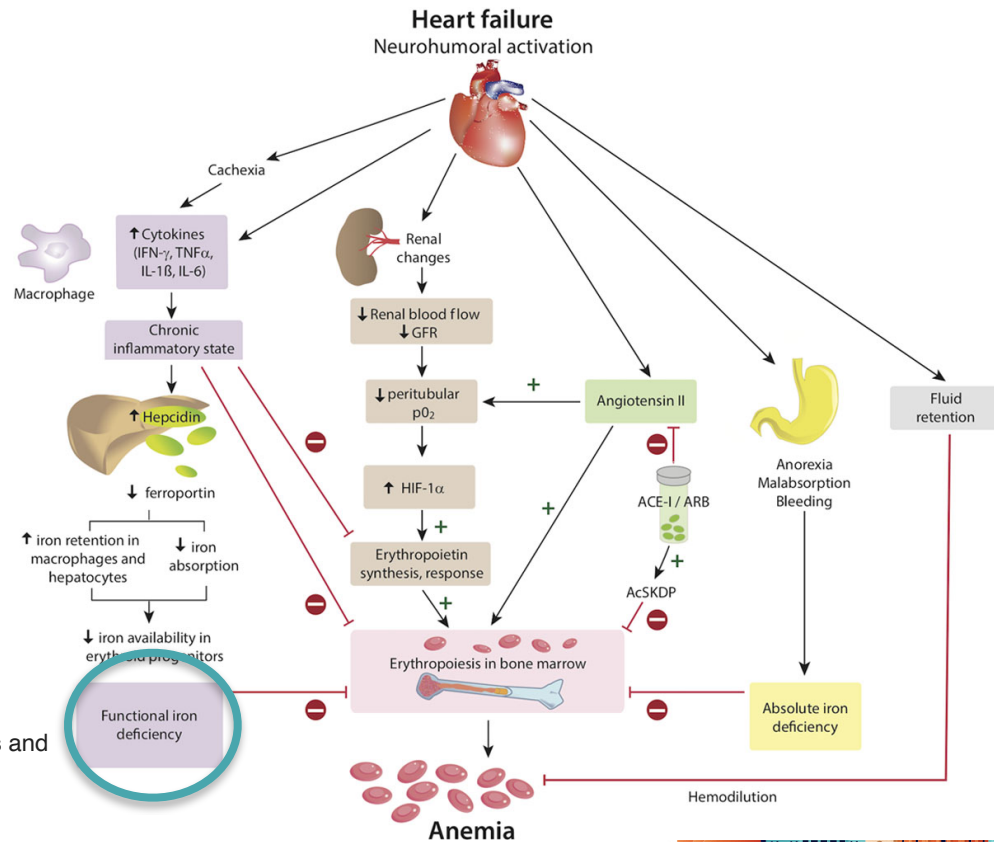
Ridotto
storage di
ossigeno
nella
mioglobina



Disfunzione mitocondriale



Principali meccanismi coinvolti nella patogenesi dell'anemia



Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. Circulation. 2018 Jul 3;138(1):80-98. doi: 10.1161/CIRCULATIONAHA.118.030099. PMID: 29967232.

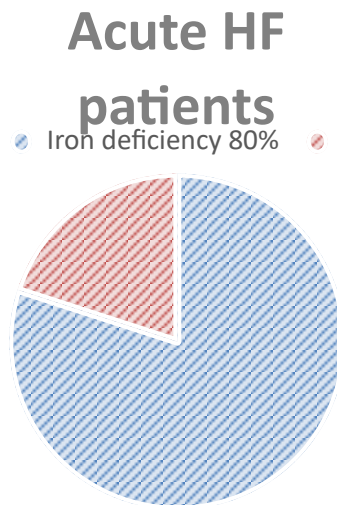
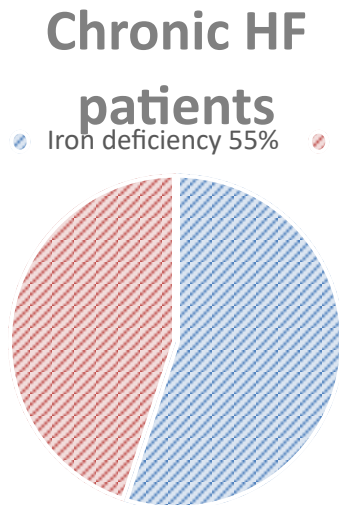
Definizione di carenza marziale nei pazienti con insufficienza cardiaca

- Concentrazione di ferritina sierica < 100 ng/mL
- Concentrazione di ferritina sierica tra 100 ng/mL e 299 ng/mL con saturazione della transferrina $< 20\%$

McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. <https://doi.org/10.1093/eurheartj/ehab368>



Epidemiologia



McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. <https://doi.org/10.1093/eurheartj/ehab368>



Conseguenze della carenza marziale nei pazienti con scompenso cardiaco

- Ridotta capacità di esercizio
- Peggioramento della qualità di vita
- Peggioramento della prognosi

Indipendentemente da anemia e LVEF

Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. Circulation. 2018 Jul 3;138(1):80-98. doi: 10.1161/CIRCULATIONAHA.118.030099. PMID: 29967232.



Raccomandazioni gestione dell'anemia

McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. <https://doi.org/10.1093/eurheartj/ehab368>

Recommendations for the management of anaemia and iron deficiency in patients with heart failure

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

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HF = heart failure; LVEF = left ventricular ejection fraction; QOL = quality of life; TSAT = transferrin saturation.

^aClass of recommendation.

^bLevel of evidence.



Trattare la carenza marziale nell'insufficienza cardiaca... Cosa ci dicono le linee guida ESC 2023

Recommendation Table 5 — Recommendations for the management of iron deficiency in patients with heart failure

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

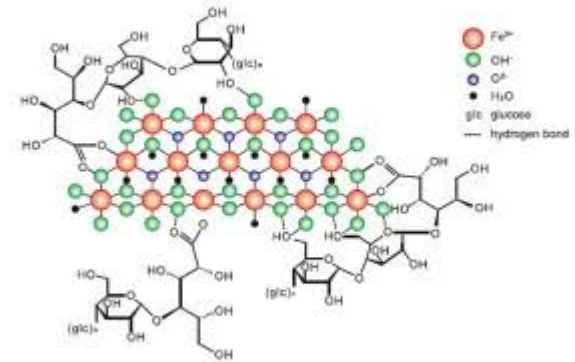
© ESC 2023

McDonagh TA, et al; ESC Scientific Document Group. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2023 Oct 1;44(37):3627-3639. doi: 10.1093/eurheartj/ehad195. Erratum in: Eur Heart J. 2024 Jan 1;45(1):53. doi: 10.1093/eurheartj/ehad613. PMID: 37622666.



Carbossimaltoso ferrico

- Complesso di ferro trivalente con polimero carbossimaltoso
- Determinazione fabbisogno in base a Hb e peso corporeo
- Infusione di massimo 1000 mg (20 mg/kg).
Seconda infusione non prima di 7 giorni
- Rivalutazione emoglobina a 4 settimane



Derisomaltosio ferrico

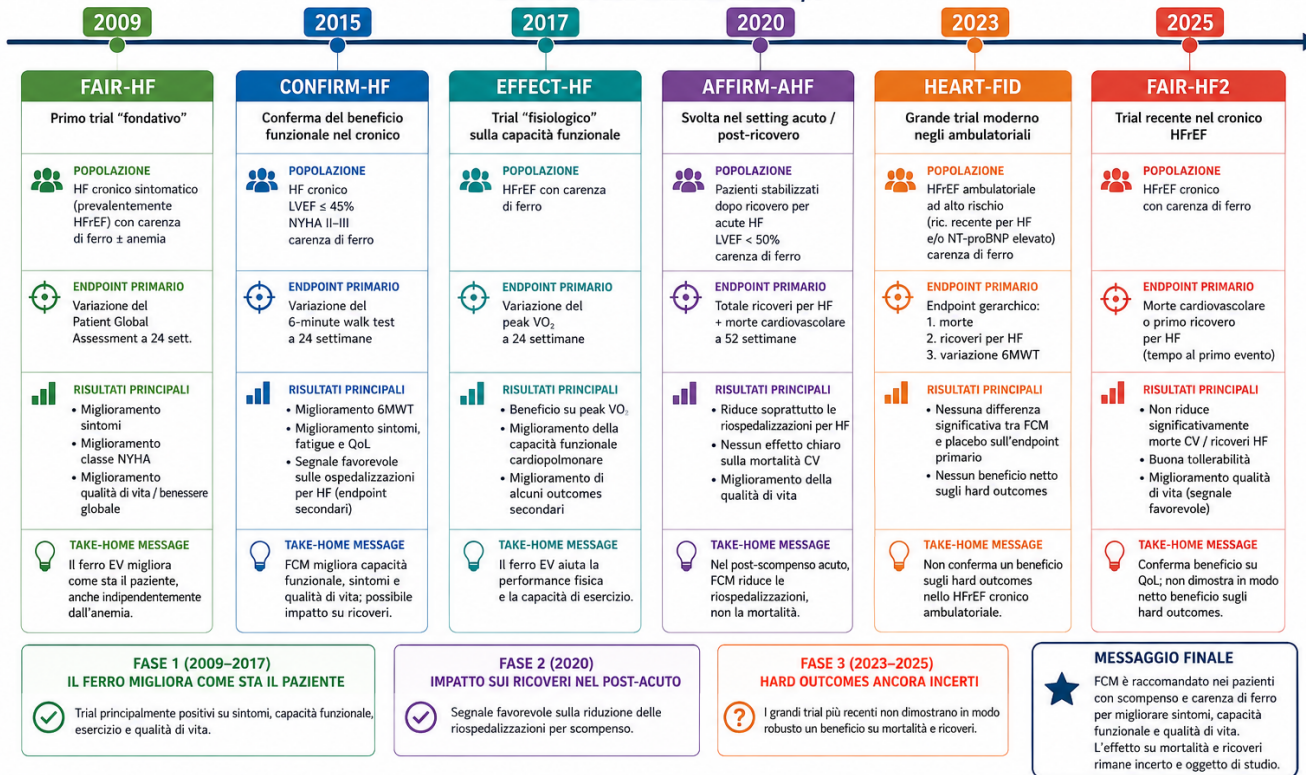
- Complesso di ferro trivalente con derisomaltosio
- Imitando la ferritina naturale, la matrice di carboidrati consente di rilasciare il ferro in modo sicuro e graduale all'interno dell'organismo
- Possibilità di somministrare dosi elevate (fino a 1000 mg) in un'unica infusione rapida, riducendo al minimo il rilascio di ferro libero



Carenza Marziale nell'insufficienza cardiaca

MAPPA CRONOLOGICA – TRIAL PRINCIPALI CON FERRO CARBOSSIMALTOSIO (FCM) NELLO SCOMPENSO CARDIACO

Evoluzione dell'evidenza nel tempo



POPOLAZIONE = principali caratteristiche dei pazienti

ENDPOINT PRIMARIO = obiettivo principale dello studio

RISULTATI PRINCIPALI = cosa ha mostrato il trial

TAKE-HOME MESSAGE = messaggio chiave per la pratica clinica

Nota: tutti i trial hanno utilizzato ferro carbossimaltoso per via endovenosa con dosaggi secondo protocollo specifico di ciascuno studio.



AFFIRM-AHF

- Studio randomizzato, multicentrico, in doppio-cieco
- Valutare l'effetto di infusione di carbossimaltoso ferrico ev vs placebo in pazienti ricoverati per insufficienza cardiaca acuta, trattati almeno con 40 mg di furosemide ev e LVEF < 50%
- 1132 pazienti randomizzati con differenza in caratteristiche e terapie non statisticamente significativa

Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396(10266):1895-1904. doi:10.1016/S0140-6736(20)32339-4



AFFIRM-AHF Risultati

Treatment with ferric carboxymaltose was safe and **reduced the risk of heart failure hospitalisations**, with no apparent effect on the risk of cardiovascular death.

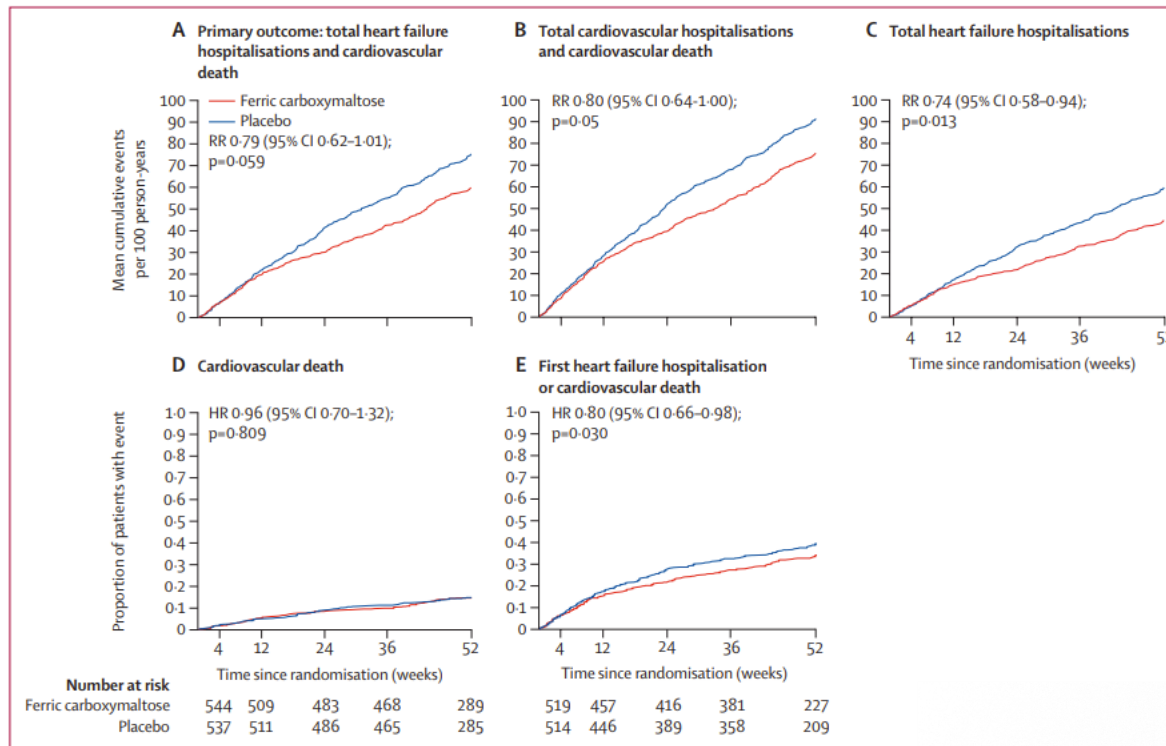


Figure 2: Primary and secondary outcomes
RR=rate ratio. HR=hazard ratio.

Ponikowski P, Kirwan BA, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet*. 2020;396(10266):1895-1904. doi:10.1016/S0140-6736(20)32339-4



IRONMAN

- Studio randomizzato, multicentrico, prospettico, blinded-endpoint
- Valutare l'effetto di infusione di derisomaltosio ferrico ev vs usual care in pazienti con LVEF < 45%, TSAT < 20% e Ferritina < 100
- 1137 pazienti randomizzati con differenza in caratteristiche e terapie non statisticamente significativa



Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199-2209. doi:10.1016/S0140-6736(22)02083-9



IRONMAN

Intravenous ferric derisomaltose administration was associated with a lower risk of hospital admissions for heart failure and cardiovascular death

Kalra PR, Cleland JGF, Petrie MC, et al. Intravenous ferric derisomaltose in patients with heart failure and iron deficiency in the UK (IRONMAN): an investigator-initiated, prospective, randomised, open-label, blinded-endpoint trial. *Lancet*. 2022;400(10369):2199-2209. doi:10.1016/S0140-6736(22)02083-9

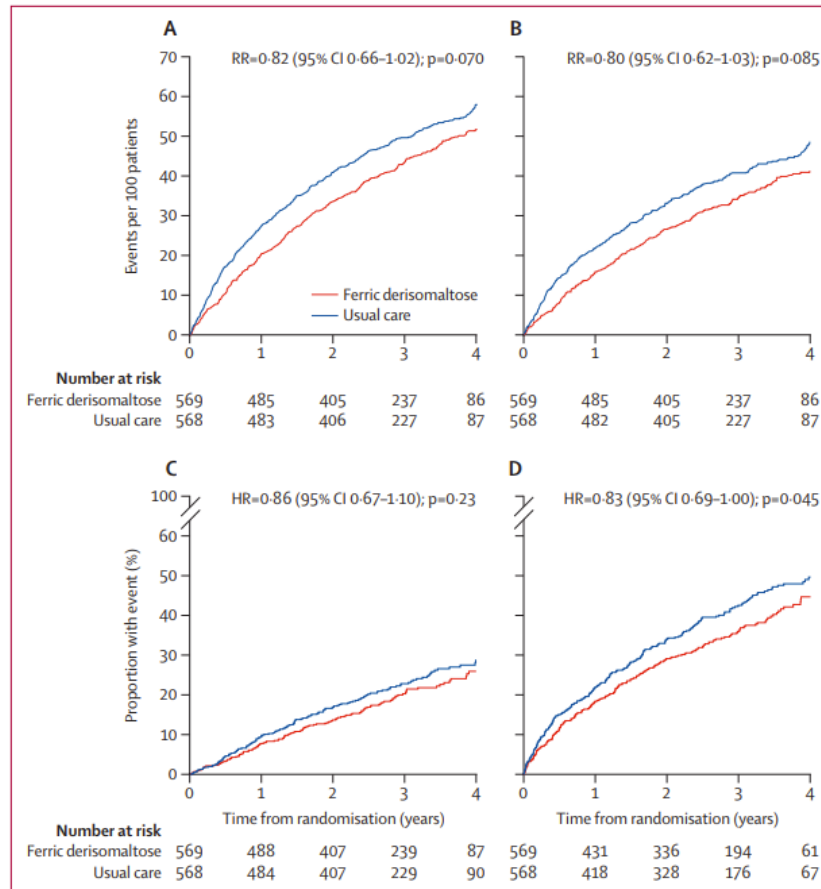
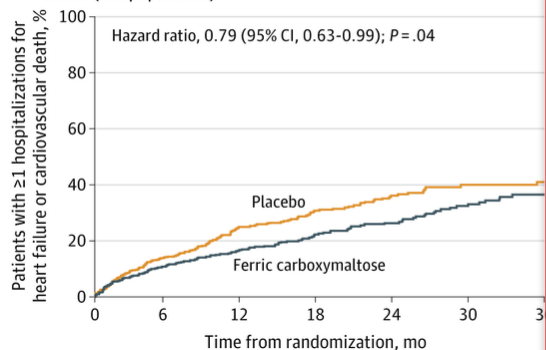


Figure 2: Estimated mean frequency functions and cumulative incidence curves for key cardiovascular outcomes

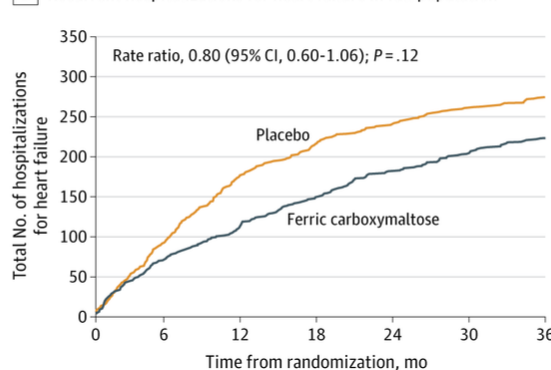


Carenza Marziale nell'insufficienza cardiaca

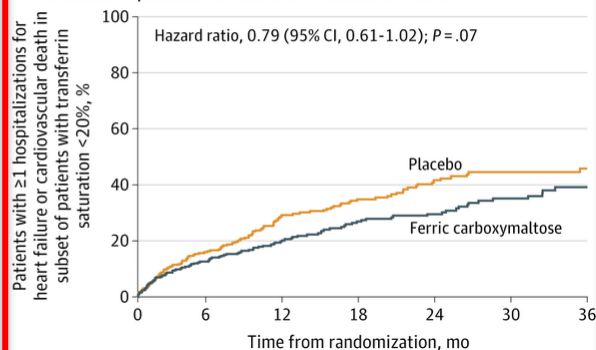
A Time to first hospitalization for heart failure or cardiovascular death (full population)



B Recurrent hospitalizations for heart failure in full population



C Time to first hospitalization for heart failure or cardiovascular death in subset of patients with transferrin saturation <20%



FAIR-HF2

In patients with heart failure and iron deficiency, ferric carboxymaltose did not significantly reduce the time to first heart failure hospitalization or cardiovascular death in the overall cohort or in patients with a **transferrin saturation less than 20%**, or reduce the total number of heart failure hospitalizations vs placebo.

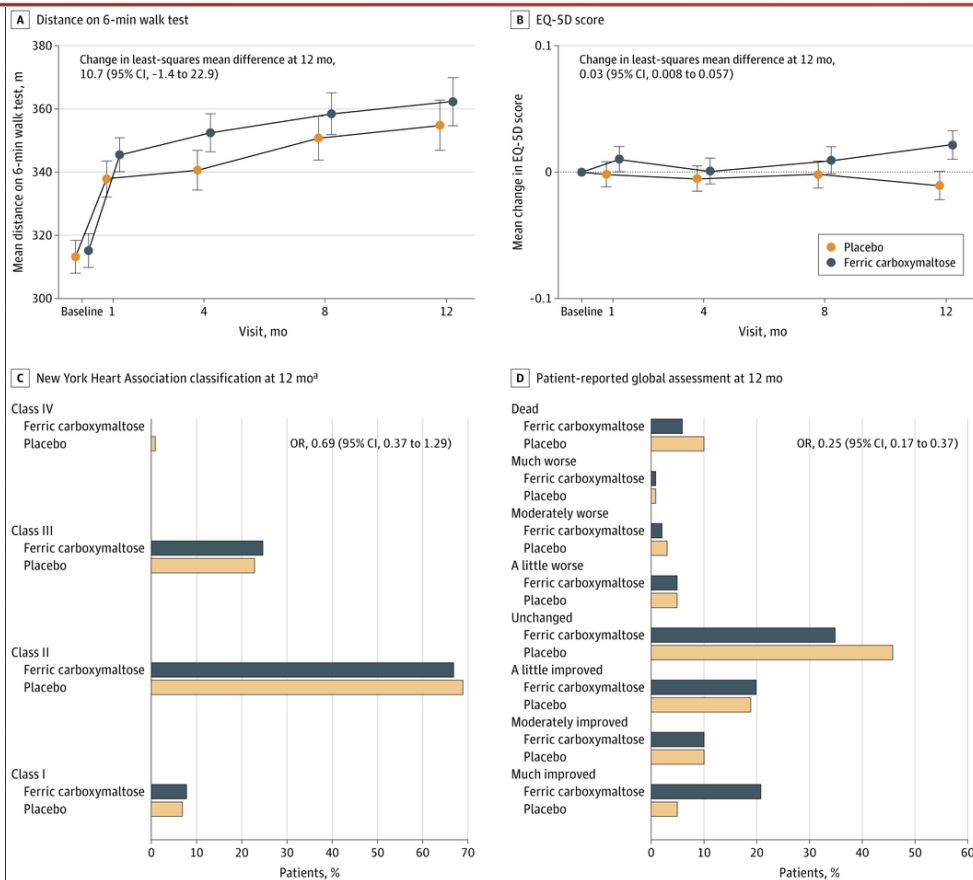
Anker SD, Friede T, Butler J, et al. Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency: The FAIR-HF2 DZHK05 Randomized Clinical Trial. *JAMA*. 2025;333(22):1965–1976. doi:10.1001/jama.2025.3833



The mean change in **distance from baseline** to 12 months was 27.2 m (SD, 91.1 m) in the ferric carboxymaltose group vs 19.7 m (SD, 84.7 m) in the placebo group (between-group mean difference, 10.7 [95% CI, -1.44 to 22.9]; For the **EQ-5D score**, the between-group mean difference in the change from baseline to 12 months was 0.03 (95% CI, 0.01 to 0.06) The change in **New York Heart Association functional class** was similar in both treatment groups (OR, 0.69 [95% CI, 0.37 to 1.29])

FAIR-HF2

Anker SD, Friede T, Butler J, et al. Intravenous Ferric Carboxymaltose in Heart Failure With Iron Deficiency: The FAIR-HF2 DZHK05 Randomized Clinical Trial. *JAMA*. 2025;333(22):1965–1976. doi:10.1001/jama.2025.3833



TAKE-HOME Messages

La carenza marziale:

- E' una problematica diffusa ma sottodiagnosticata nei pazienti con insufficienza cardiaca
- E' correlata all'anemia, ma è associata a peggioramento della prognosi e della qualità di vita indipendentemente da essa e dal tipo di scompenso cardiaco (LVEF)
- I principali trial randomizzati hanno dimostrato un miglioramento di prognosi e qualità di vita nei pazienti affetti da scompenso cardiaco e sottoposti ad infusione di carbossimaltosio ferrico e derisomaltosio ferrico
- Valutazione baseline dell'assetto marziale e FU del profilo marziale



GRAZIE PER L'ATTENZIONE!

