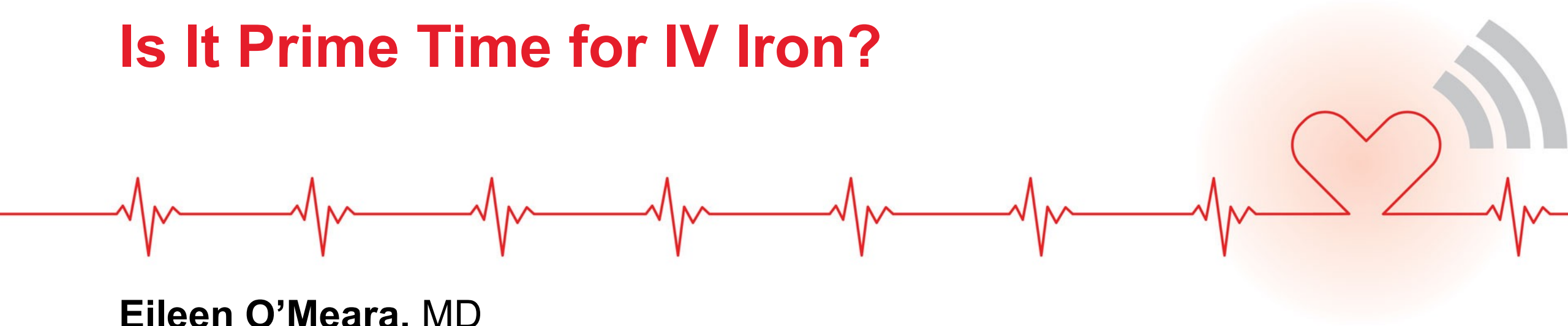
# Is It Prime Time for IV Iron?



**Eileen O'Meara,** MD
Cardiologist,
Associate Professor of Medicine,
Université de Montréal, Montreal Heart Institute
Montreal, QC

# Disclosures

- Consultation and speaker fees: Amgen, AstraZeneca,  Bayer, Boehringer Ingelheim, Merck and Novartis.
- Steering committee and National lead investigator for clinical studies - fees paid to the Montreal Heart Institute Research Center – HF group, from: American Regent, AstraZeneca, Cytokinetics and Novartis.
- Clinical trial participation: Amgen, Abbott, American Regent, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Eidos, Merck, Novartis, Pfizer, Sanofi.

# Objectives

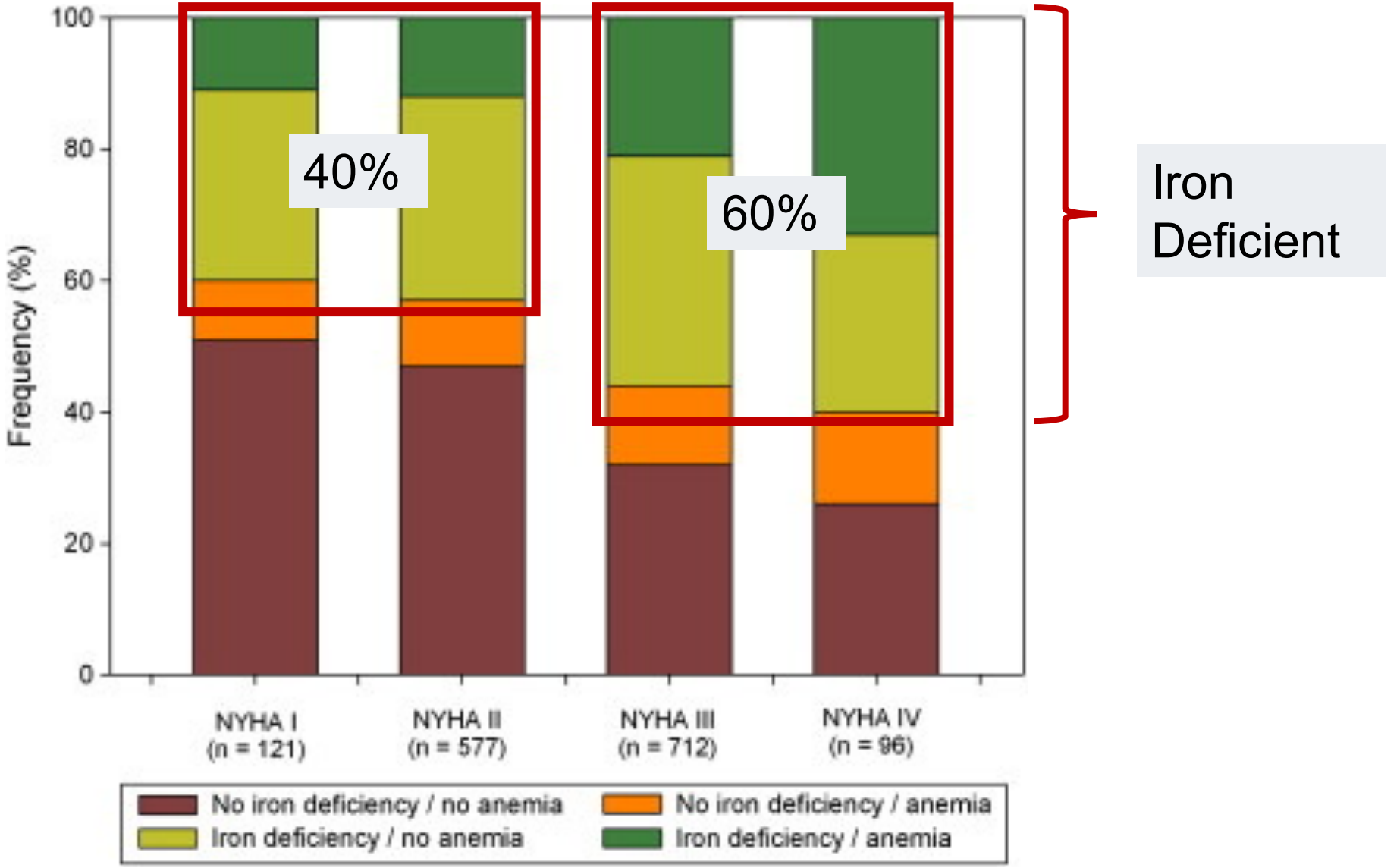
1. Understand key abnormalities of iron metabolism in patients with heart failure
2. Describe current status of treatment for iron deficiency in acute and chronic heart failure
3. Describe ongoing clinical trials examining the role of IV iron therapy for people with heart failure

# Iron Deficiency and HF

- The prevalence of iron deficiency in HF is >40-50%
  - Ferritin <100 ng/mL
  - Ferritin 100-300 ng/mL + transferrin saturation [TSAT] <20%
- In patients with and without anemia
- Associated with worse functional status, QOL and outcomes

Jankowska EA et al. *Eur Heart J*. 2013 Mar;34(11):816-29.

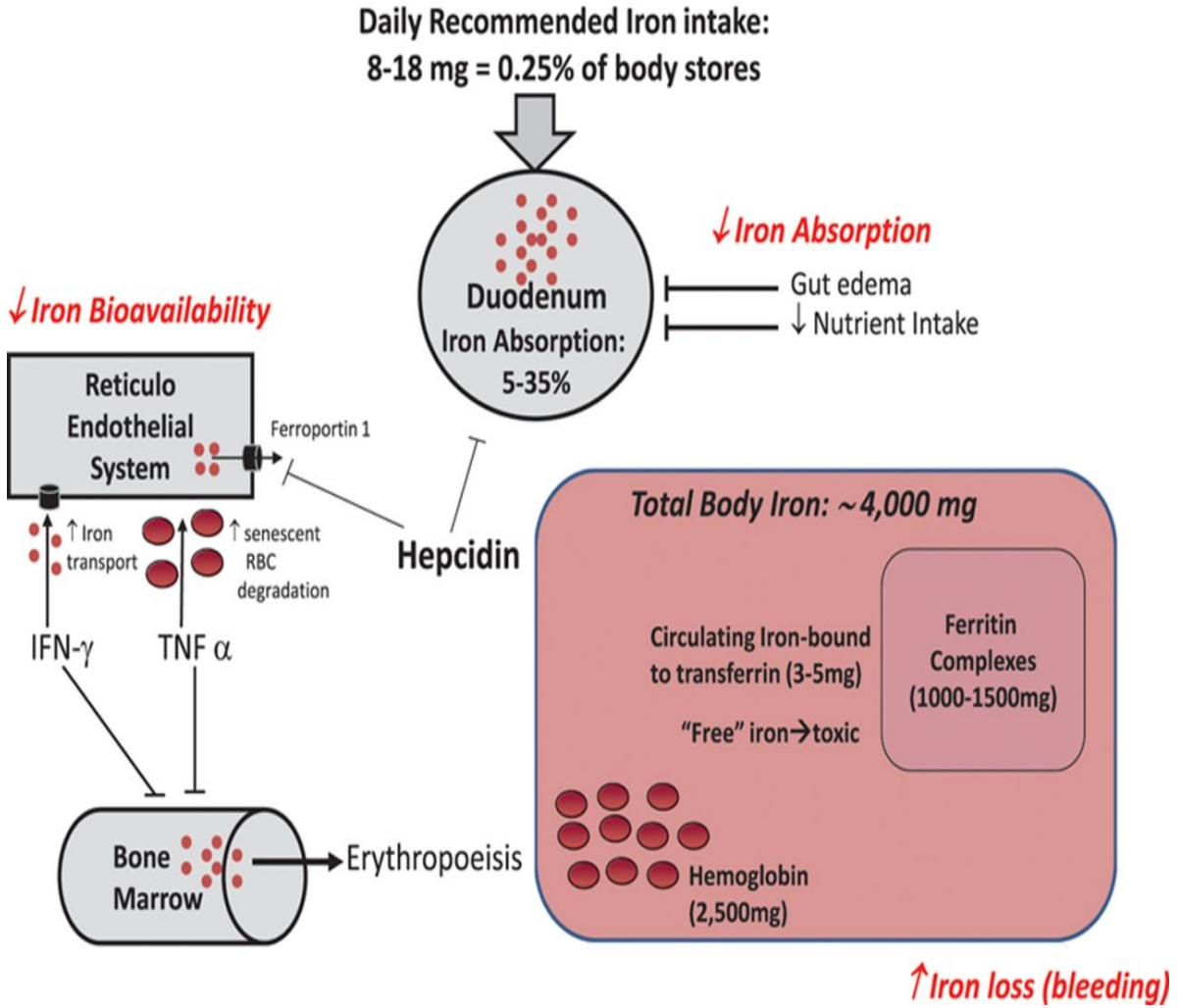
# Iron Deficiency is Common in Chronic HF




Klip IT. AHJ 2013

# Mechanisms of Iron Deficiency

- Functional iron deficiency is seen when there is a deficit in the mobilization of iron from tissues while iron stores are normal
- Frequent in chronic diseases with inflammation
- Hepcidin and soluble transferrin receptor (sTfR) have been proposed as more sensitive indices to evaluate ID in HF
- Hepcidin, synthesised by the liver, is a key regulator of iron homeostasis
- Hepcidin binds to ferroportin and induces its internalisation, thus blocking iron export from intestinal cells and iron recycling in macrophages of the reticuloendothelial system




Lewis GD. Circ HF 2016

ESC European Society of Cardiology
European Heart Journal (2019) **40**, 3616–3625
doi:10.1093/eurheartj/ehz680



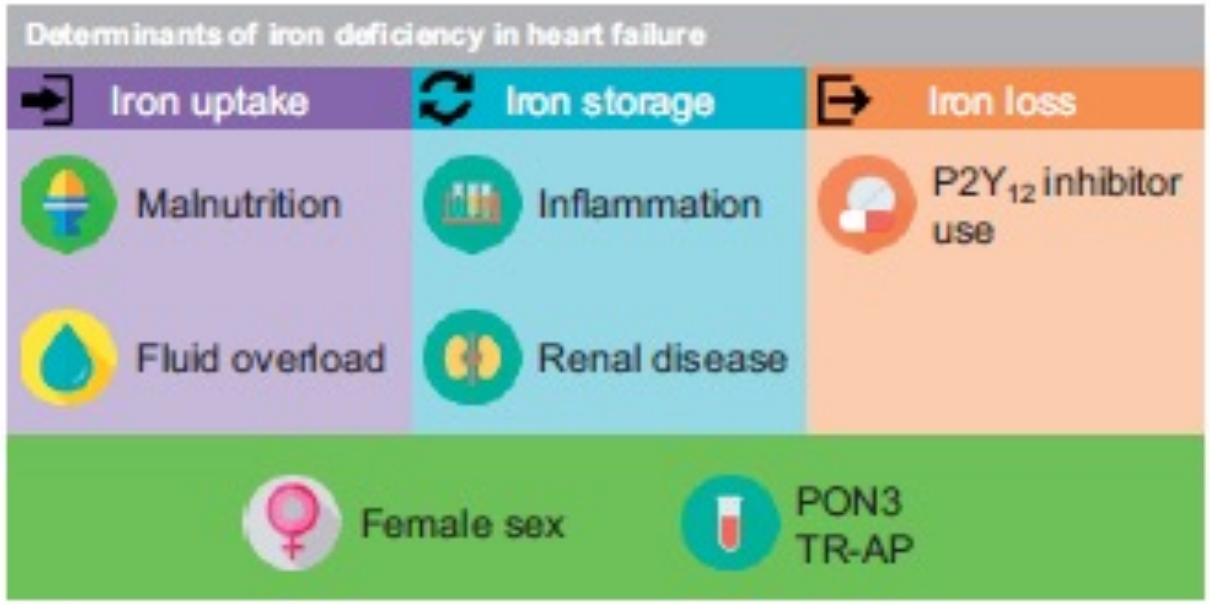
# Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use

**Haye H. van der Wal[1], Niels Grote Beverborg[1], Kenneth Dickstein[2,3], Stefan D. Anker[4], Chim C. Lang[5], Leong L. Ng[6,7], Dirk J. van Veldhuisen[1], Adriaan A. Voors[1], and Peter van der Meer[1]***

**Aims** Iron deficiency (ID) is common in heart failure (HF) patients and negatively i
aetiology of ID in HF is largely unknown. We studied determinants and the b
national HF cohort.

**Methods and results** We studied 2357 worsening HF patients from the BIOSTAT-CHF cohort. ID
<20%. Univariable and multivariable logistic regression models were constr
We measured 92 cardiovascular markers (Olink Cardiovascular III) to establ
mary endpoint was the composite of all-cause mortality and first HF rehosp
ation) of all patients was 69 ± 12.0 years, 26.1% were female and median N-t
levels (+interquartile range) were 4305 (2360–8329) ng/L. Iron deficiency
with highest prevalence in females (71.1% vs. 58.3%; $P < 0.001$). Independent determinants of ID were female sex, lower estimated protein intake, higher heart rate, presence of peripheral oedema and orthopnoea, chronic kidney disease, lower haemoglobin, higher C-reactive protein levels, lower serum albumin levels, and $P2Y_{12}$ inhibitor use (all $P < 0.05$). None of these determinants were sex-specific. The biomarker profile of ID largely consisted of pro-inflammatory markers, including paraoxonase 3 (PON3) and tartrate-resistant acid phosphatase type 5. In multivariable Cox proportional hazard regression analyses, ID was associated to worse outcome, independently of predictors of ID (hazard ratio 1.25, 95% confidence interval 1.06–1.46; $P = 0.007$).

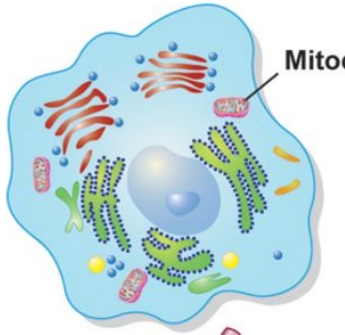
**Conclusion** Our data suggest that the aetiology of ID in worsening HF is complex, multifactorial and seems to consist of a combination of reduced iron uptake (malnutrition, fluid overload), impaired iron storage (inflammation, chronic kidney disease), and iron loss (antiplatelets).




**Take home figure** Determinants of iron deficiency in heart failure. Several graphical elements in this figure are provided by Freepik and DinosoftLabs from www.flaticon.com.

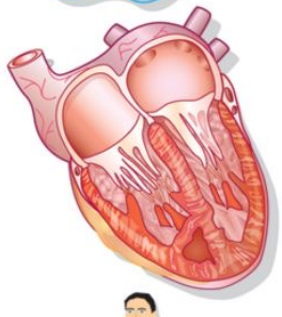
# Effects of Iron Deficiency

**Iron is critical for optimal functioning and survival of alive structures:**




**Iron deficiency results in:**

- **Mitochondrial dysfunction**
- **Deranged activity of enzymes**
- **Abnormal transport and structural proteins**
- **Apoptosis**



- **Tissue remodelling**
- **Impaired organ efficacy**

- **impaired exercise capacity**
- **Reduced work efficacy**
- **Impaired cognative performance and behaviour**
- **Increased morbidity and mortality**

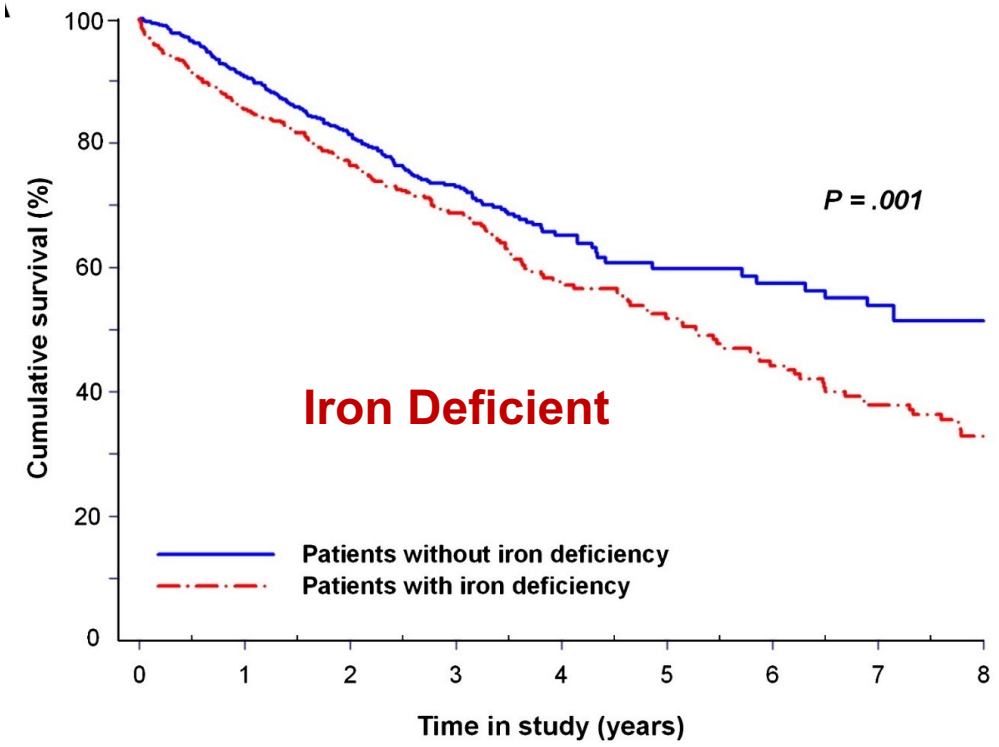
Jankowska EA et al. *Eur Heart J*. 2013 Mar;34(11):816-29.

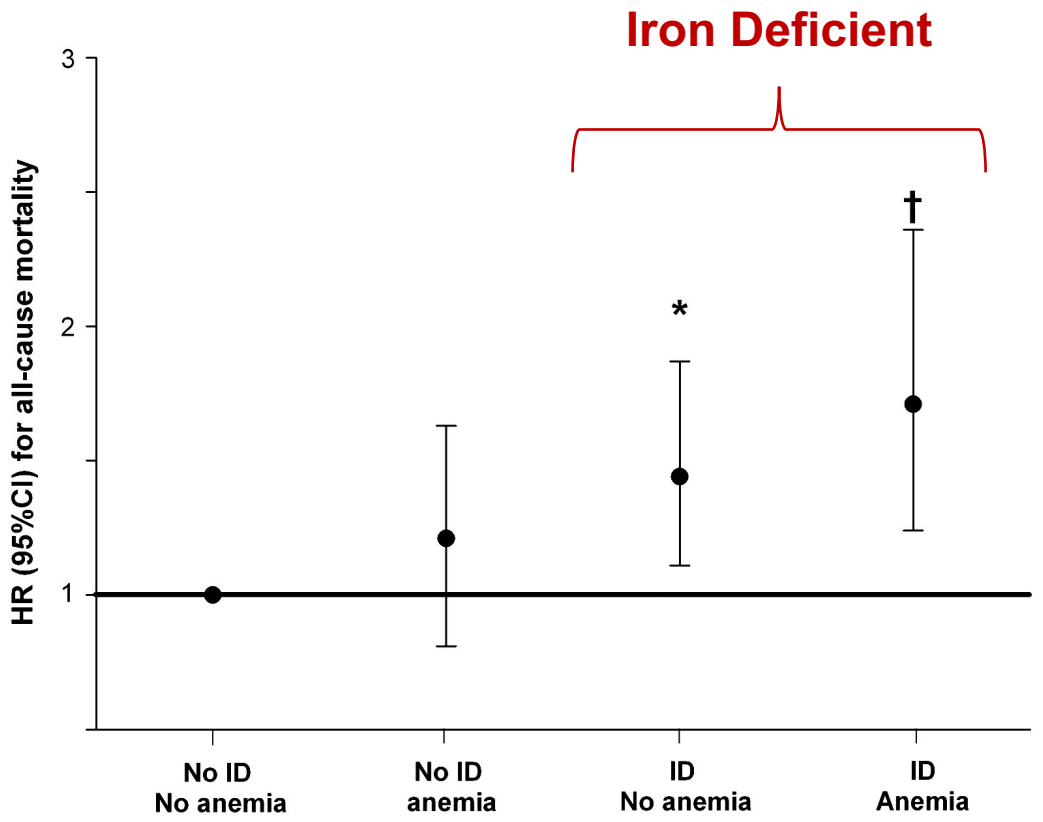
# Iron Deficiency and Poor Outcomes

- Impaired aerobic performance (peak VO2 and 6-MWD)
- Reduced health-related quality of life (HRQoL)
- Increased HF hospitalizations
- Increased mortality independent of anemia

Okonko DO. JACC 2011
Comin-Colet J. EJHF 2013
Núñez J. EJHF 2016
Klip IT. Am Heart J 2013
Jankowska EA. EHJ 2013

# Increased Mortality

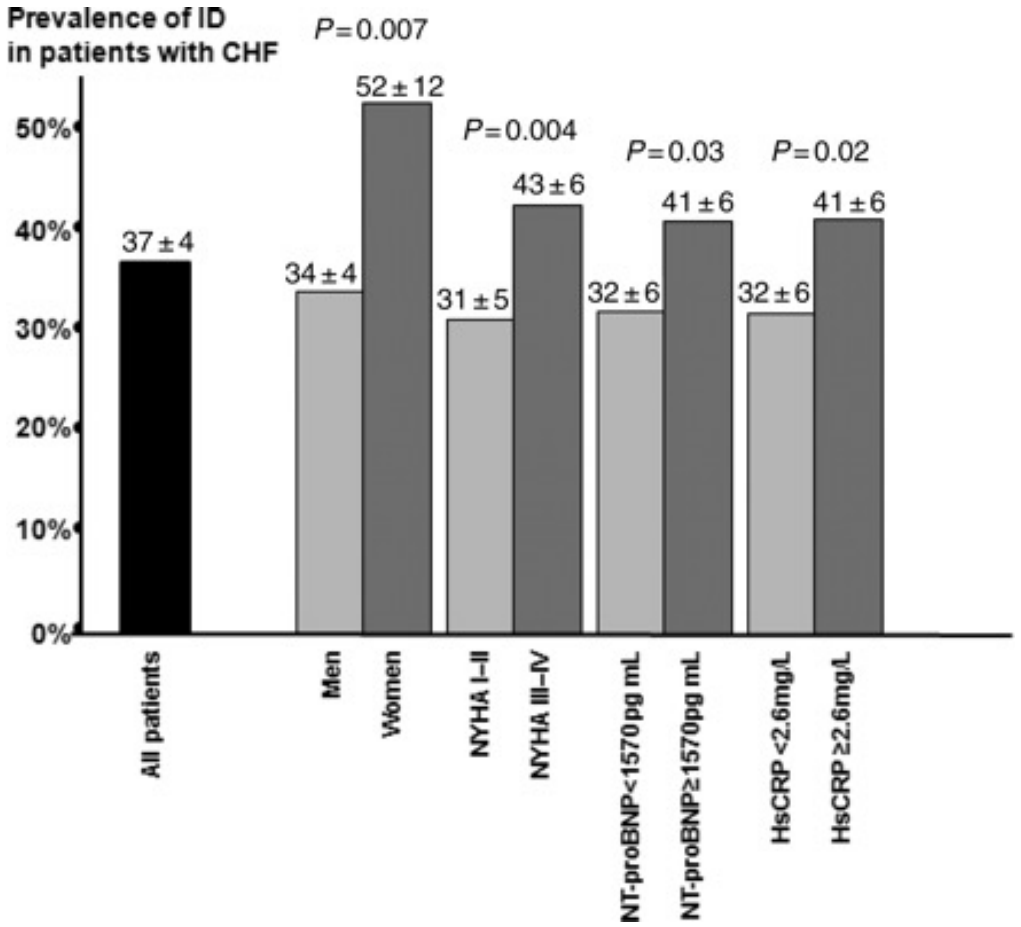



Klip IT. Am Heart J. 2013
Jankowska EA. Eur Heart J 2010

# Factors Associated with Iron Deficiency

- Women
- Worse NYHA class
- Higher NT-proBNP
- Higher hs-CRP




Jankowska EA. Eur Heart J 2010

# Work-up of Anemia and Iron Deficiency



**Table 22. Commonly available tests for the work-up of anemia and iron deficiency**

| Test | Suspected etiologies | Remarks |
|---|---|---|
| Transferrin saturation, ferritin, serum iron | Iron deficiency | Ferritin might be artificially elevated in chronic inflammatory states; transferrin saturation might be low in patients with cachexia |
| Fecal occult blood; upper and lower endoscopy | Gastrointestinal-related blood loss | Referral to gastroenterology |
| TSH | Thyroid-related disorders | |
| Peripheral smear, reticulocyte count/index, LDH, haptoglobin, bone marrow biopsy | Multiple | |
| B12 | Nutritional deficiency | Uncommon in Canada |
| Hemoglobin electrophoresis | Thalassemia; sickle cell disease | Target testing to those in high prevalence population |
| Serum and urine protein electrophoresis | Multiple myeloma, amyloidosis, and other protein disorders | |

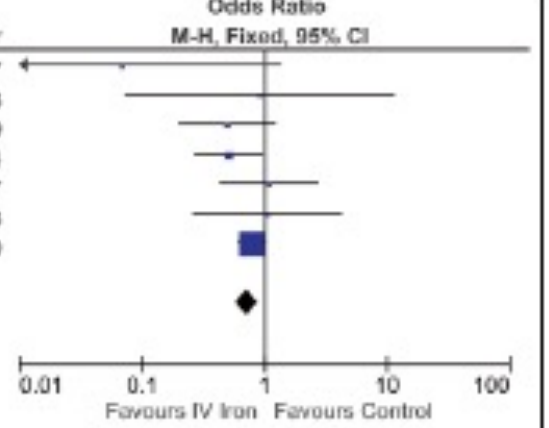
LDH, lactate dehydrogenase; TSH, thyroid-stimulating hormone.

# Iron Deficiency in HF – Trials

In a meta-analysis of 7 trials, administration of IV iron to patients with heart failure and iron deficiency reduces the risk of the composite outcome of first heart failure hospitalisation or cardiovascular mortality, but this outcome is driven predominantly by an effect on heart failure hospitalisations.

| Study or Subgroup | IV Iron Events | IV Iron Total | Control Events | Control Total | Weight | Odds Ratio M-H, Fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Tobli 2007 | 0 | 20 | 5 | 20 | 2.7% | 0.07 [0.00, 1.34] | 2007 |
| Okonko 2008 | 2 | 24 | 1 | 11 | 0.6% | 0.91 [0.07, 11.23] | 2008 |
| Anker 2009 | 10 | 304 | 10 | 155 | 6.3% | 0.49 [0.20, 1.21] | 2009 |
| Ponikowski 2014 | 18 | 150 | 32 | 151 | 13.9% | 0.51 [0.27, 0.95] | 2014 |
| van Veldhuisen 2017 | 11 | 88 | 10 | 86 | 4.4% | 1.09 [0.44, 2.71] | 2017 |
| Yeo 2018 | 5 | 24 | 5 | 25 | 1.9% | 1.05 [0.26, 4.22] | 2018 |
| Ponikowski 2020 | 181 | 558 | 209 | 550 | 70.2% | 0.78 [0.61, 1.00] | 2020 |
| **Total (95% CI)** | | **1168** | | **998** | **100.0%** | **0.73 [0.59, 0.90]** | |
| Total events | 227 | | 272 | | | | |

Heterogeneity: Chi² = 5.80, df = 6 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.96 (P = 0.003)





Heart failure & iron deficiency
n = 2,166

Intravenous iron
n = 1,168

Reduction in risk of hospitalisation for heart failure in subsequent 6-12 months by ~30%

Graham FJ, et al. Clin Res Cardiol 2021

# Why intravenous?

- Months of oral iron therapy would be required in order to replete ID in HF: typically requires ≥1000 mg.
- Oral iron is poorly absorbed, particularly in patients with chronic diseases such as HF, and adverse gastrointestinal effects limit its tolerability.
- With IV iron formulations such as FCM, a low risk of adverse events is observed and only few injections are needed (in CONFIRM-HF >75% of patients required a maximum of two injections).
- The cost-effectiveness of IV FCM therapy has been demonstrated in HF; related to improved quality of life and reduced HF hospitalizations.
- A replacement dose of IV iron sucrose (available in Canada) generally requires 3-5 clinical visits, while the benefits of IV iron therapy can be achieved in a shorter time with other formulations. These include FCM, iron isomaltoside, ferumoxytol and sodium ferric gluconate.
- Serious adverse events related to IV iron therapy are rare (≈1%) and life-threatening adverse events are extremely rare (<0.02%).
- However, allergic reactions have been reported with all IV iron preparations and patients should be observed during treatment and 30 minutes after the infusion.

# Oral Iron Supplementation

- Ferrous (Fe2+) form with absorption rate of 10-15%
- Doses range from 150-180 mg/day of elemental iron
- GI side effects
- Ferric polysaccharide iron complex (PIC) – 150 mg
- No clear benefit in HF
  - IRON-OUT Trial: Did not improve functional status or QOL

Lewis GD. Circ HF 2016
Lewis GD. AHA 2016

# Guidelines on HF and Iron Repletion

**RECOMMENDATION**

115. We recommend that I.V. iron therapy be considered for patients with HFrEF and ID, in view of improving exercise tolerance, quality of life, and reducing HF hospitalizations (Strong Recommendation; Moderate-Quality Evidence).

**Values and preferences.** The CONFIRM-HF trial, 3 meta-analyses, and the recent EFFECT-HF trial have improved the quality of evidence regarding benefits of I.V. iron therapy on the previously discussed outcome measures but there is yet no evidence regarding benefits on mortality. Because of the rapid rate of iron repletion using the I.V. route and the available evidence, this treatment should be considered rather than oral iron repletion. Ongoing hospitalization can provide a good opportunity to facilitate I.V. iron administration.

**TABLE 1 Guideline Recommendations for Diagnosis and Treatment of ID in HF**

| Iron Deficiency in HF | 2017 ACC/AHA/HFSA Focused Update of the U.S. Guideline for Management of HF | 2016 ESC Guidelines for Diagnosis and Treatment of Acute and Chronic HF |
|---|---|---|
| Diagnosis | Ferritin <100 ng/ml or ferritin 100-300 ng/ml if TSAT < 20% | Ferritin <100 ng/ml or ferritin 100-300 ng/ml if TSAT <20% |
| Target HF population | NYHA functional class II and III | Symptomatic HFrEF |
| Recommendations | IV iron replacement might be reasonable to improve functional status and QOL | IV FCM should be considered in order to alleviate HF symptoms and improve exercise capacity and QOL |
| Class of recommendation | IIb | IIa |
| Level of recommendation | B (randomized) | A |

ACC = American College of Cardiology; AHA = American Heart Association; ESC = European Society of Cardiology; FCM = ferric carboxymaltose; HF = heart failure; HFrEF = left ventricular ejection fraction < 40% in ESC; HFSA = Heart Failure Society of America; ID = iron deficiency; IV = intravenous; NYHA = New York Heart Association; QOL = quality of life; TSAT = transferrin saturation.

ESC European Society of Cardiology
European Journal of Preventive Cardiology
doi:10.1093/eurjpc/zwaa112

FULL RESEARCH PAPER
*Cardiovascular Disease*

# Prognostic role of transferrin saturation in heart failure patients

**Jeness Campodonico[1†], Flavia Nicoli[1†], Irene Motta[2,3], Margherita Migone De Amicis[2], Alice Bonomi[1], Maria Cappellini[2,3], and Piergiuseppe Agostoni[1,3*]**

[1]Centro Cardiologico Monzino, IRCCS, Via Parea 4, 20138 Milano, Italy; [2]Fondazione IRCCS Cà Granda Ospedale Policlinico, Via Franc
[3]Department of Clinical Science and Community Health, University of Milan, Via Festa del Perdono 7, 20122 Milan, Italy

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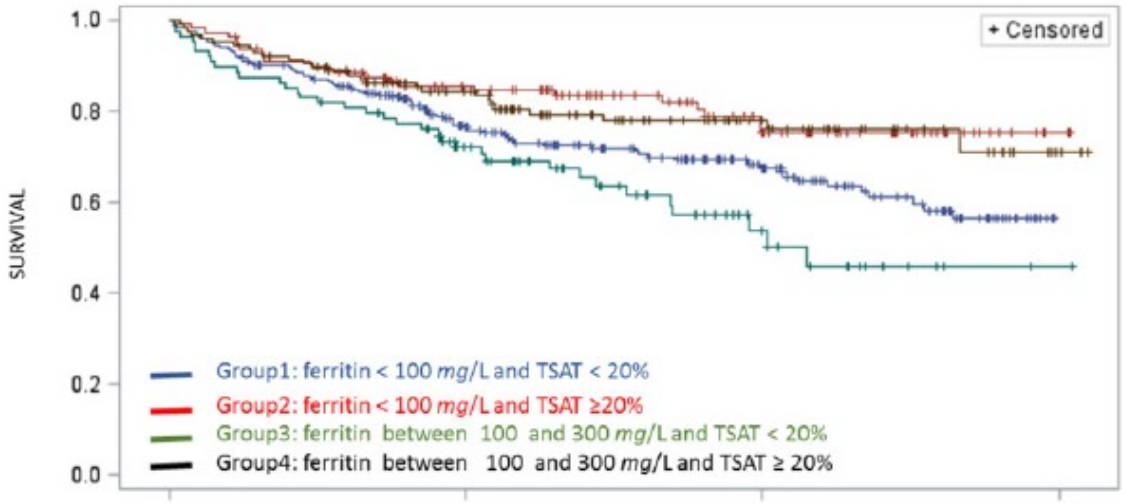
In conclusion, we demonstrated that TSAT <20%, in a cohort of HF patients, has a more relevant prognostic role than ferritin level in term of 5 years survival, but we also showed that among patients with low TSAT those with ferritin between 100 and 300 µg/L have the worst prognosis likely because of an high chronic inflammatory status.




| N at risk | | | | |
|---|---|---|---|---|
| Group 1 | 252 | 151 | 878 | 1 |
| Group 2 | 114 | 83 | 43 | 2 |
| Group 3 | 88 | 51 | 15 | 1 |
| Group 4 | 1260 | 88 | 39 | 3 |

**Figure 3** Five years Kaplan–Meier survival curves adjusted for age, sex, kidney function, chronic obstructive pulmonary disease, haemoglobin in patients with different degrees of ferritin and transferrin saturation. Group 1 (in red): ferritin <100 µg/L and TSAT <20%; Group 2 (in blue): ferritin <100 µg/L and TSAT ≥20%; Group 3 (in green): ferritin between 100 and 300 µg/L and TSAT <20%; and Group 4: (in black) ferritin between 100 and 300 µg/L and TSAT ≥20% subjects who are not considered as ID patients according to ESC and ACC/AHA/HFSA definitions.

# AFFIRM-AHF

| | Ferric carboxymaltose (n=558) | | Placebo (n=550) | | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|---|---|
| | Number of events (%) | Rate per 100 patient-years | Number of events (%) | Rate per 100 patient-years | | |
| **Modified intention-to-treat analysis** | | | | | | |
| First heart failure hospitalisation or cardiovascular death | 181 (32%) | 37·40 | 209 (38%) | 47·10 | 0·80 (0·66–0·98) | 0·030 |
| Cardiovascular death | 77 (14%) | 15·90 | 78 (14%) | 16·10 | 0·96 (0·70–1·32) | 0·81 |
| **COVID-19 sensitivity analysis*** | | | | | | |
| First heart failure hospitalisation or cardiovascular death | 175 (31%) | 44·59 | 205 (37%) | 52·20 | 0·79 (0·65–0·97) | 0·023 |
| Cardiovascular death | 73 (13%) | 16·13 | 76 (14%) | 16·78 | 0·94 (0·68–1·29) | 0·69 |

*Patients were censored in each country on the date when the first patient with COVID-19 was reported in the respective country.

*Table 3:* Time to first event outcomes

**Interpretation** In patients with iron deficiency, a left ventricular ejection fraction of less than 50%, and who were stabilised after an episode of acute heart failure, treatment with ferric carboxymaltose was safe and reduced the risk of heart failure hospitalisations, with no apparent effect on the risk of cardiovascular death.

*Ponikowski P, et al. The Lancet 2020; 396: 1895-904*

METHODS PAPER

# Randomized Placebo-Controlled Trial of Ferric Carboxymaltose in Heart Failure With Iron Deficiency

HEART-FID

## Rationale/Design

Robert J. Mentz, MD; Andrew P. Ambrosy, MD; Justin A. Ezekowitz, MBBCh, MSc; Gregory D. Lewis, MD; Javed Butler, MD, MPH, MBA; Yee Weng Wong, MBBS, MHS; Carmine G. De Pasquale, MBBS, PhD; Richard W. Troughton, MBChB, PhD; Eileen O'Meara, MD; Frank Rockhold, PhD; Jyostna Garg, MS; Marc D. Samsky, MD; Dianne Leloudis; Michael Dugan, MD; Linda M. Mundy, MD, PhD; Adrian F. Hernandez, MD, MHS; on behalf of the HEART-FID Trial Investigators

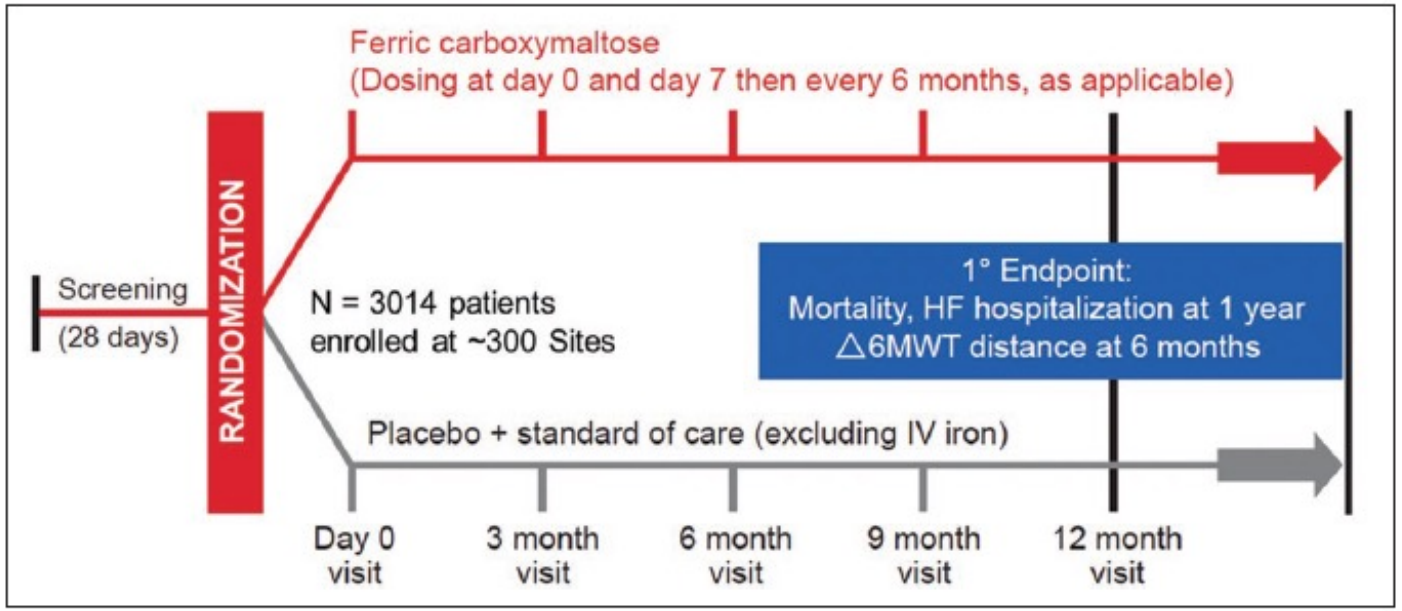



**Figure. HEART-FID study (Randomized Placebo-Controlled Trial of Ferric Carboxymaltose as Treatment for Heart Failure With Iron Deficiency) overview.**

After an initial screening period of up to 28 days, eligible participants are randomized in a 1:1 ratio to receive ferric carboxymaltose or placebo. Study drug administration occurs on days 0 and 7, with additional study visits at 3-month intervals and additional dosing every 6 mo, as applicable. Δ 6MWT distance indicates change in distance walked on the 6-minute walk test; and HF, heart failure.

HEART-FID

**Table. Study End Points**

| |
|---|
| Primary objective |
| Hierarchical composite |
| Death at 12 mo, and if not |
| Hospitalization for HF at 12 mo, and if not |
| Change from baseline in 6-MWT at 6 mo |
| Secondary objectives |
| Time to cardiovascular death or hospitalization for HF |
| Time to cardiovascular death or cardiovascular hospitalizations |
| Time to cardiovascular death |
| Time to cardiovascular death or intervention for worsening HF |
| Hospitalization for HF |
| Urgent HF visits |
| Change in 6-MWT distance at 12 mo |

Δ6MWT distance indicates change in distance walked on the 6-minute walk test; and HF, heart failure.

# Ongoing IV Iron Trials in HF

- FAIR-HF-2: target N 1200, chronic HFrEF, LVEF <= 45%, FCM, event-driven with primary endpoint of recurrent hospitalisations for HF and CV death.

- IRONMAN: target N 1300, UK, chronic HFrEF with LVEF < 45%, iron isomaltoside, 120 weeks with primary endpoints of CV death or hospitalisation for worsening HF –first and recurrent

- HEART-FID will be the largest, and the primary endpoint includes functional status as well as death and HF hospitalisations