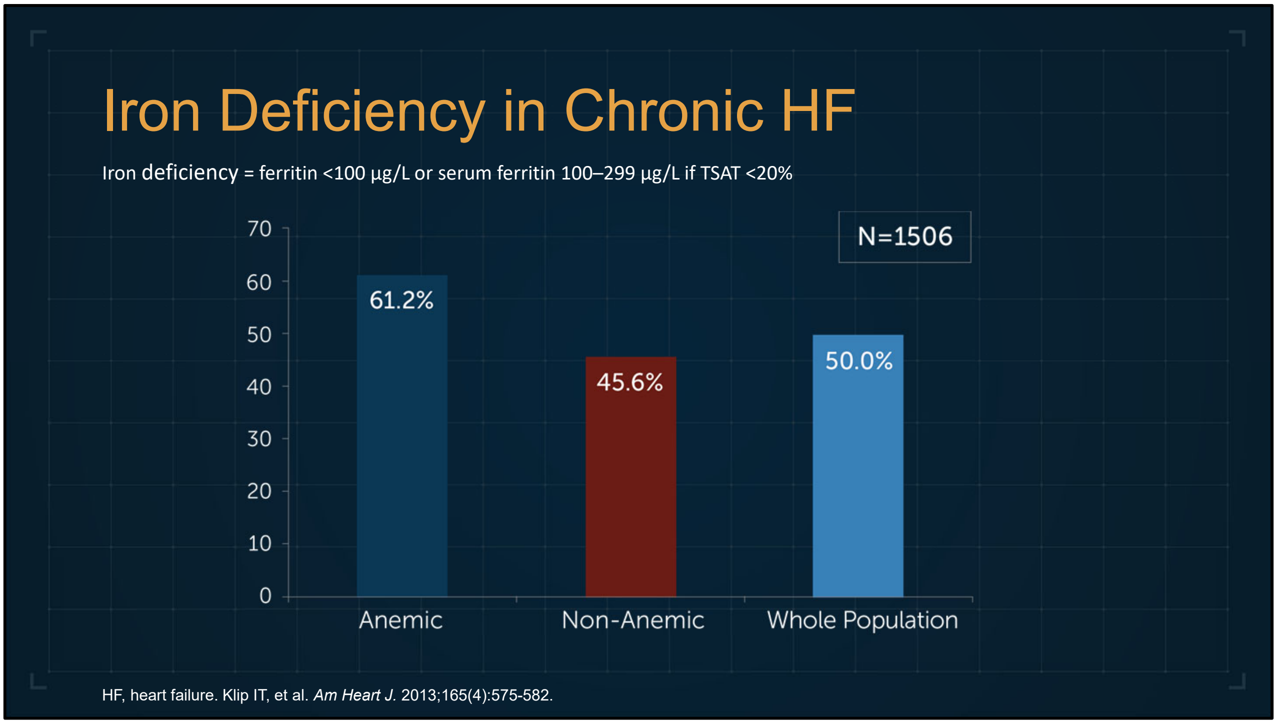
Iron Deficiency in Heart Failure

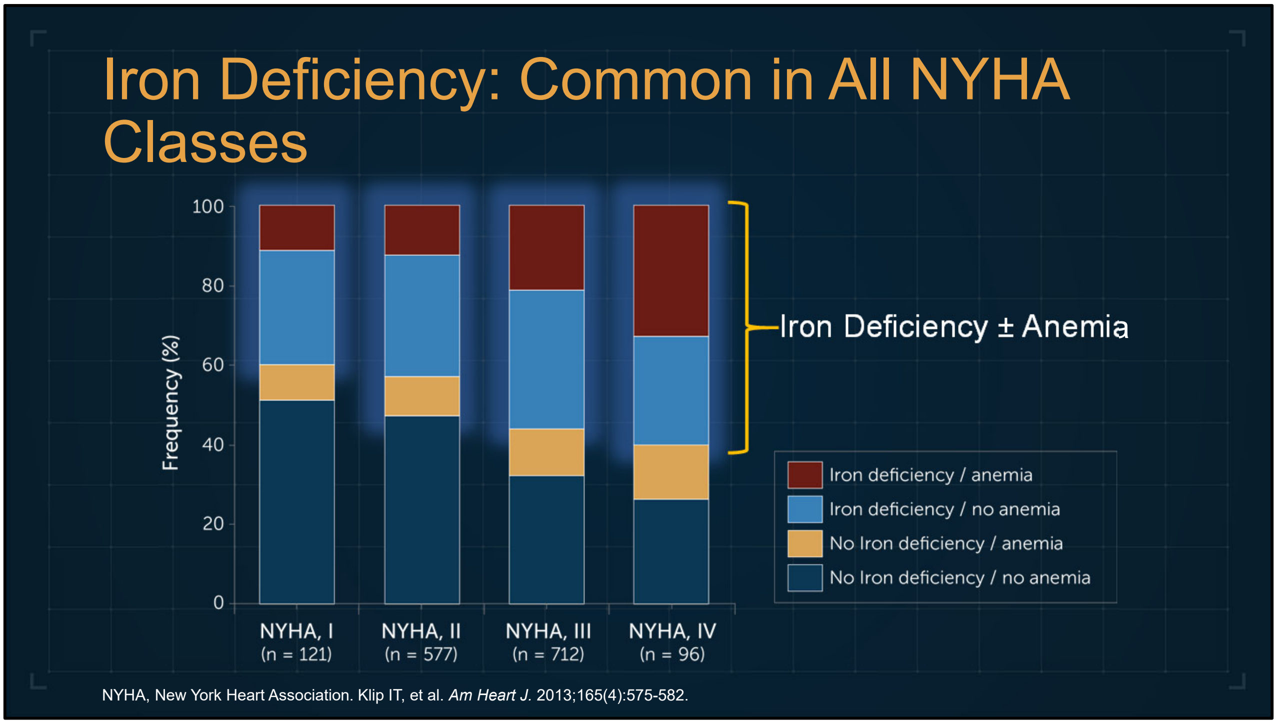
Agenda

- The Relationship Between Iron Deficiency and Heart Failure
- The Role of Iron in Cellular Metabolism
- Correcting Iron Deficiency in Heart Failure
- Treatment of Iron Deficiency
- Upcoming Clinical Trials

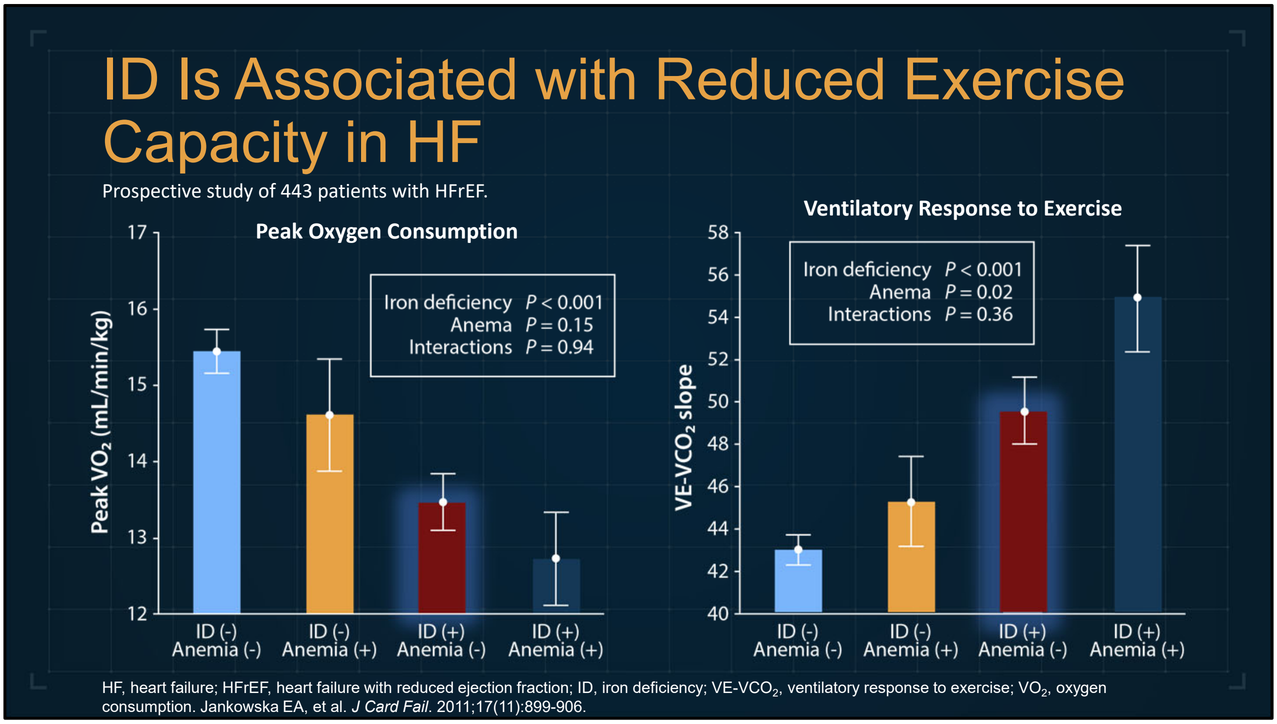
The Relationship Between Iron Deficiency and Heart Failure



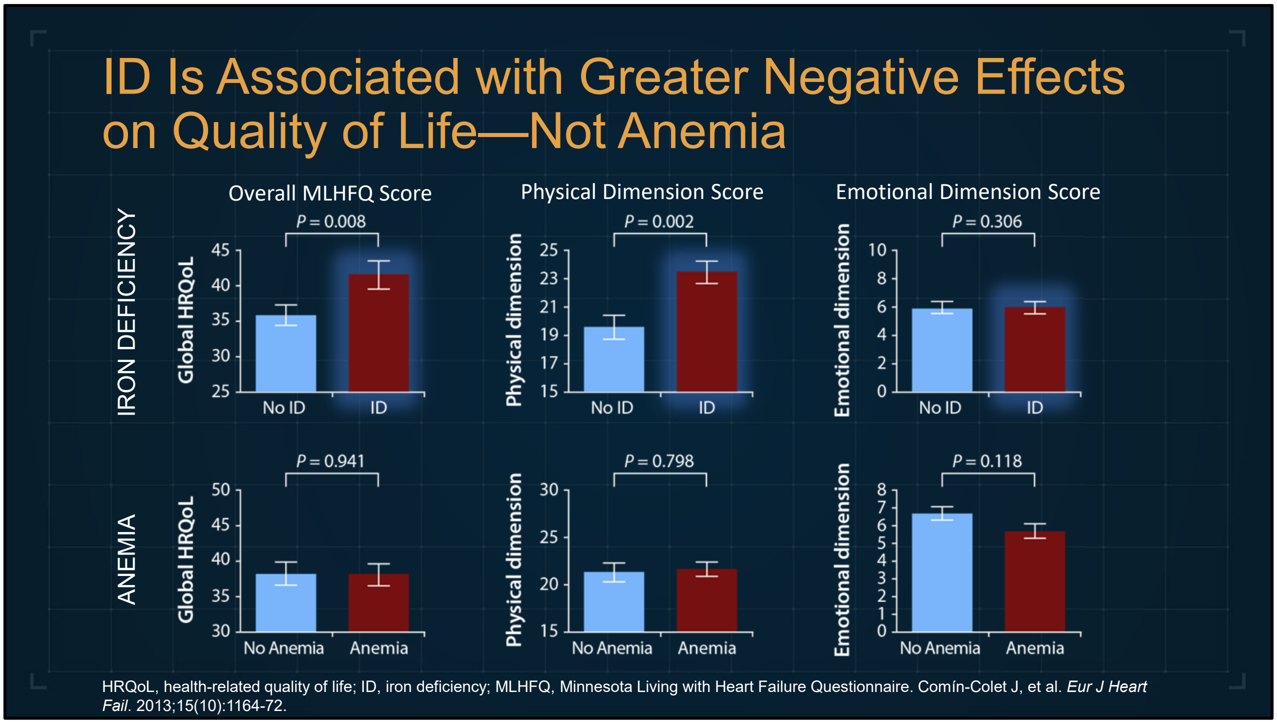
Iron deficiency is prevalent among patients with chronic heart failure. One study of an international pooled cohort of patients (N = 1,506) with chronic heart failure found that 50% of patients had iron deficiency. Although iron deficiency was present alongside anemia in 61.2% of patients, a substantial proportion of patients were diagnosed with iron deficiency in the absence of anemia (45.6%).



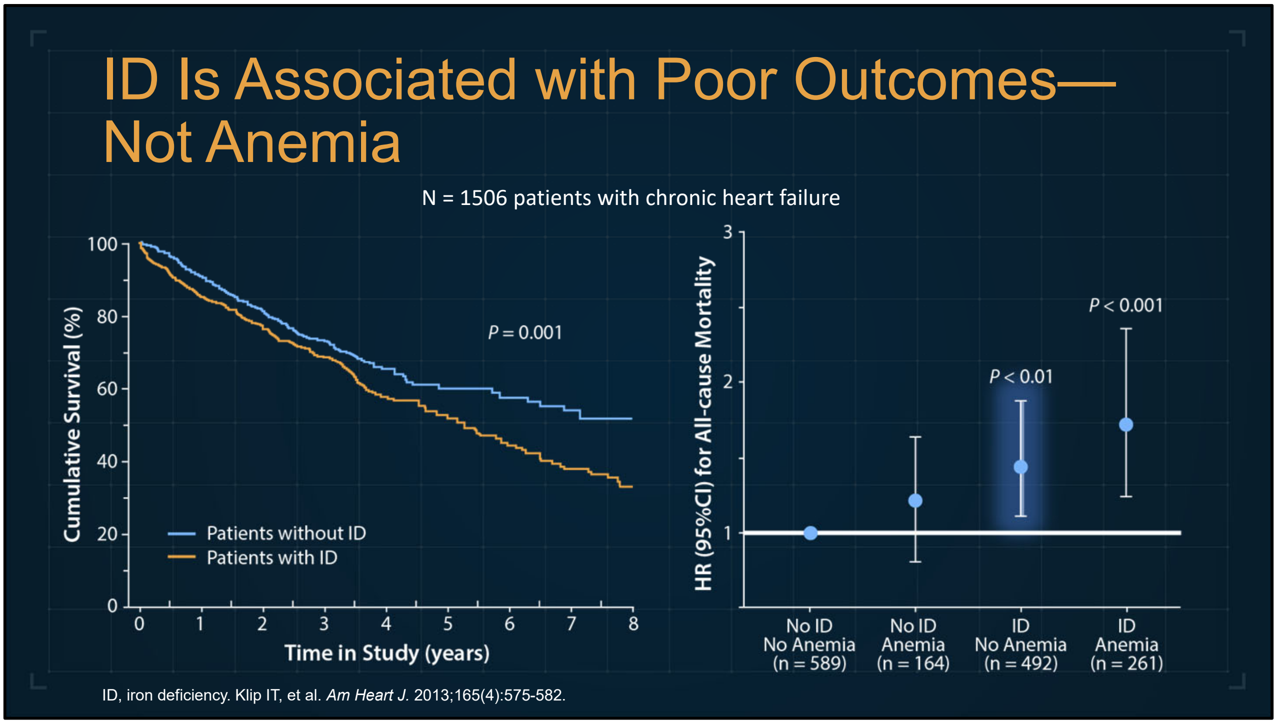
In the same study, iron deficiency was prevalent across all New York Heart Association (NYHA) functional classes. Iron deficiency in the absence of anemia was more common in lower NYHA classes (I and II). The prevalence of both iron deficiency and anemia increased with higher NYHA classes (III and IV).



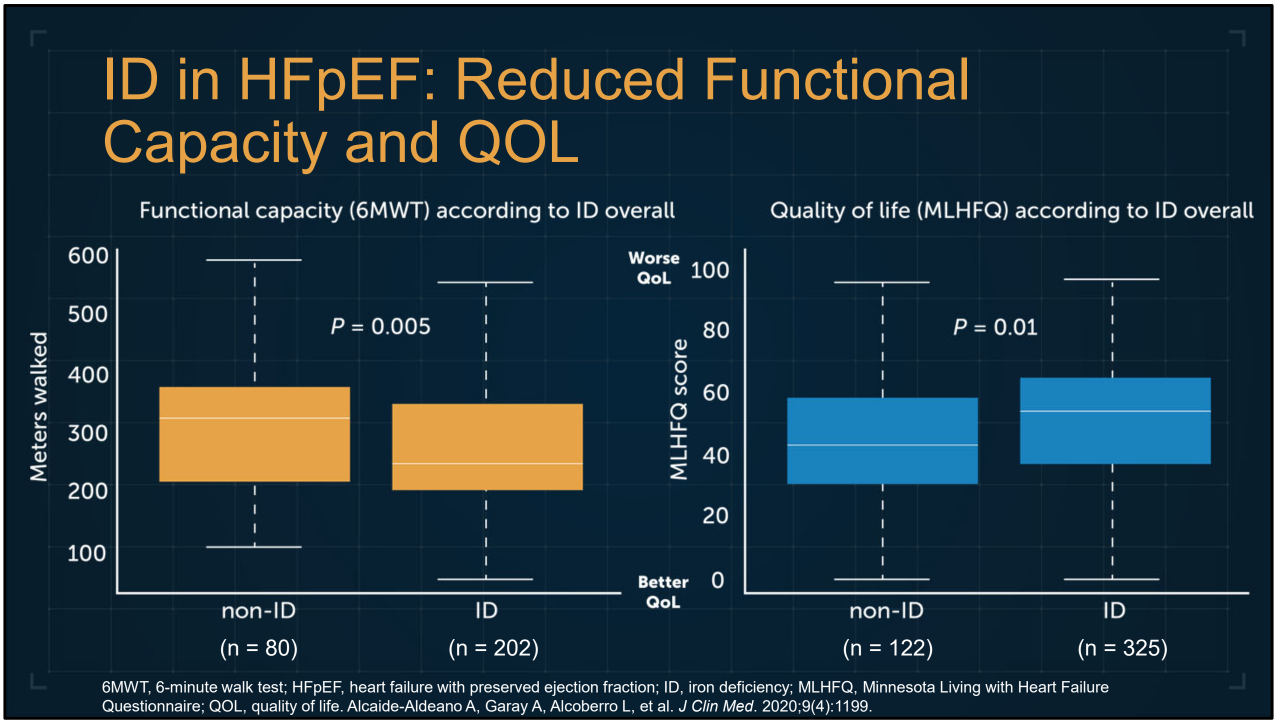
Exercise intolerance, which is a hallmark symptom of heart failure, is associated with iron deficiency. A prospective study of 443 patients with HFrEF (ejection fraction 26% ± 7%), iron deficiency was associated with significantly low rates of peak oxygen consumption and high rates of ventilatory response to exercise. These changes in exercise capacity were independent of the presence of anemia. In comparison, only significant changes in ventilatory response to exercise were associated with anemia independent of the presence of iron deficiency.



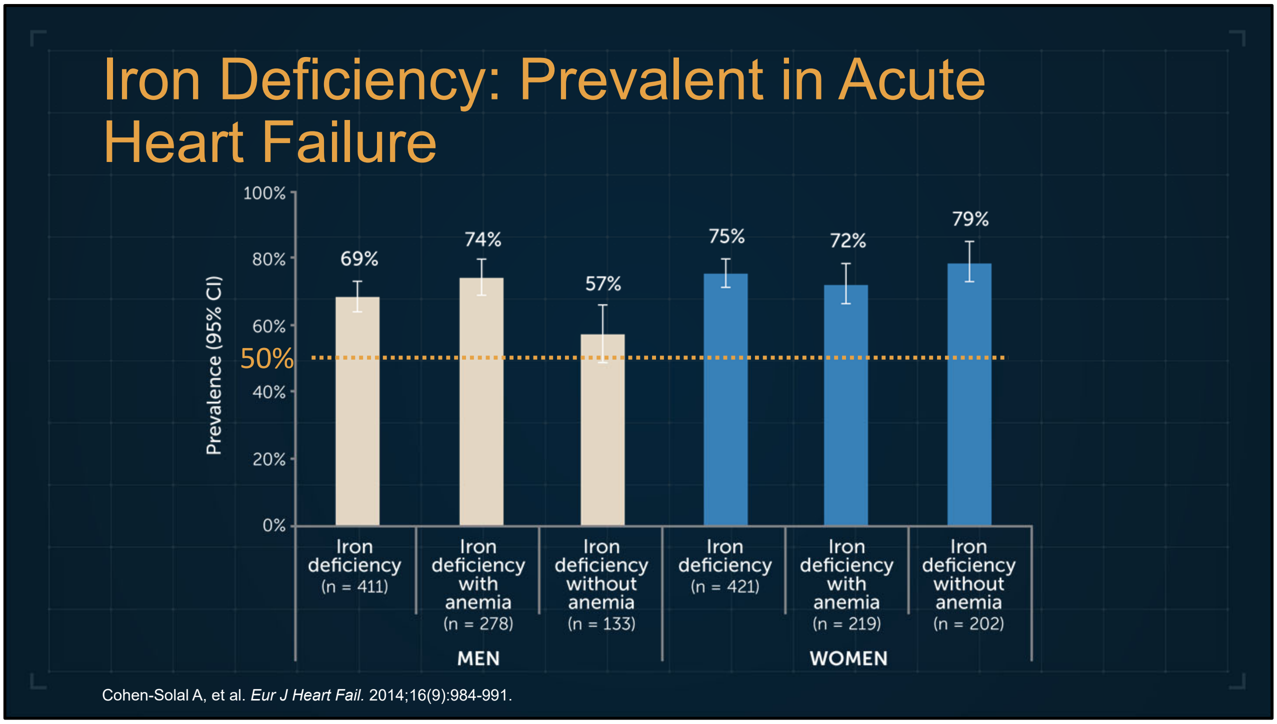
A post-hoc analysis of a cohort of 552 patients with chronic HF evaluated the influence of iron deficiency and anemia on quality of life. Iron deficiency was defined as ferritin <100 ng/mL or ferritin <800 ng/ml if TSAT <20%. Anemia was defined as hemoglobin ≤12 g/dL. The effect of iron deficiency or anemia status was measured based on responses to the Minnesota Living with Heart Failure questionnaire. The bars represent adjusted mean values of questionnaire responses for each of the overall, physical dimension, and emotional dimension scores. Results show that iron deficiency, not anemia, status is associated with greater negative effects on patient overall, physical, and emotional health-related quality of life.



Iron deficiency is a strong predictor of mortality and poor outcomes. In a pooled cohort of 1,506 patients with chronic heart failure, survival was significantly reduced in patients with iron deficiency and the presence of iron deficiency was an independent predictor of mortality.



Iron deficiency also affects functional capacity and quality of life in patients with heart failure with preserved ejection fraction (HFpEF). In an observational prospective cohort study of 447 with HFpEF (≥50%), 73% had iron deficiency. Among patients who were able to complete the 6-minute walk test, patients with iron deficiency walked a shorter distance than that walked by those with normal iron levels. Quality of life scores as measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) were higher among patients with iron deficiency indicating a worse quality of life.



Iron deficiency is highly prevalent in patients with acute heart failure. A prospective study of patients with a history of chronic heart failure who were hospitalized for acute decompensation found that overall iron deficiency was present in 69% of men (n = 411) and 75% of women (n = 421).

Iron Deficiency: Poor Outcomes in Acute Heart Failure

Hospital admissions of patients with acute heart failure = 78,805

	With ID/IDA (n = 26,530)	**Without ID/IDA (n = 52,275)**	***P* value**
Proportion with emergency admissions	94.8%	87.6%	<0.0001
Heart failure readmission rate ≤30 days	8.2%	5.2%	<0.0001
All-cause readmission rate ≤30 days	25.8%	17.7%	<0.05
Length of stay	15.8 days	12.2 days	<0.0001
Mortality			
In-hospital mortality rate	13.5% (n = 3,592)	12.9% (n = 6,730)	0.009

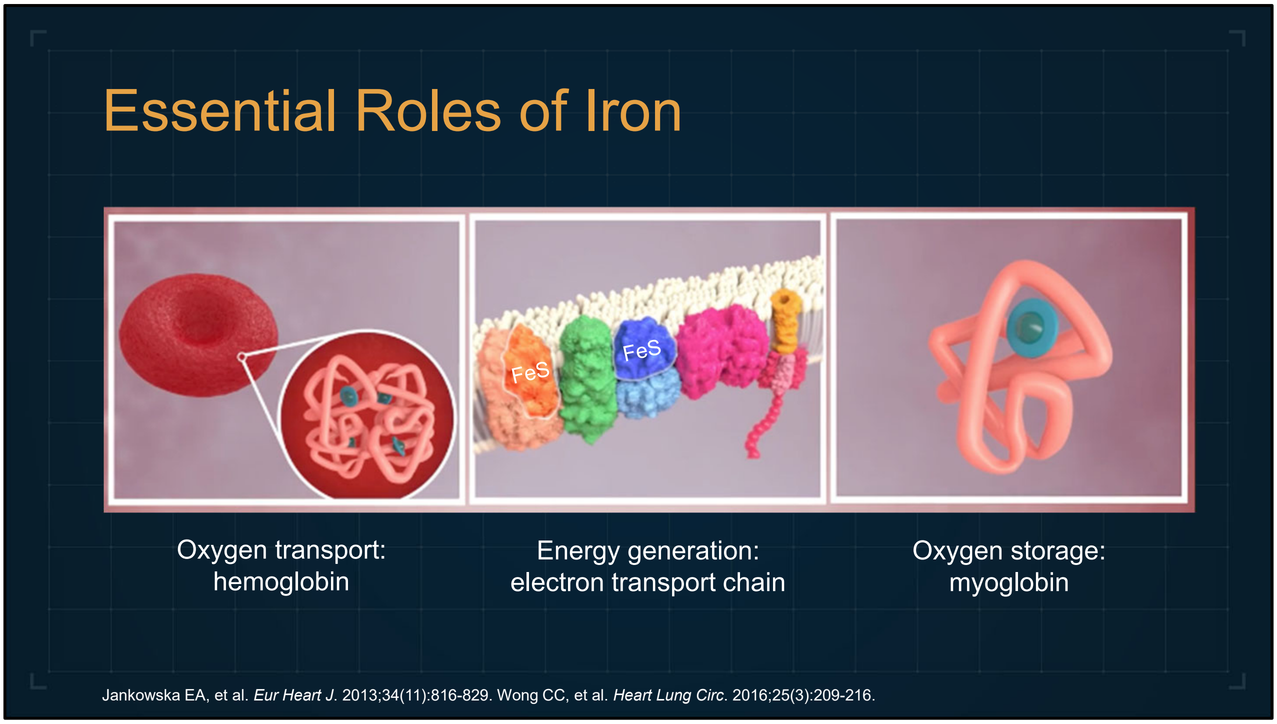
ID, iron deficiency; IDA, iron deficiency anemia. Beattie JM, et al. *Open Heart*. 2020;7(1):e001153.

A retrospective analysis of patients with heart failure admitted for acute decompensation (N = 78,805) showed that patients with a secondary diagnosis of iron deficiency (ID) or iron deficiency anemia (IDA) had higher emergency admission rates, higher rates of heart failure and all-cause readmission within 30 days, longer lengths of stay, and higher inhospital mortality rates.

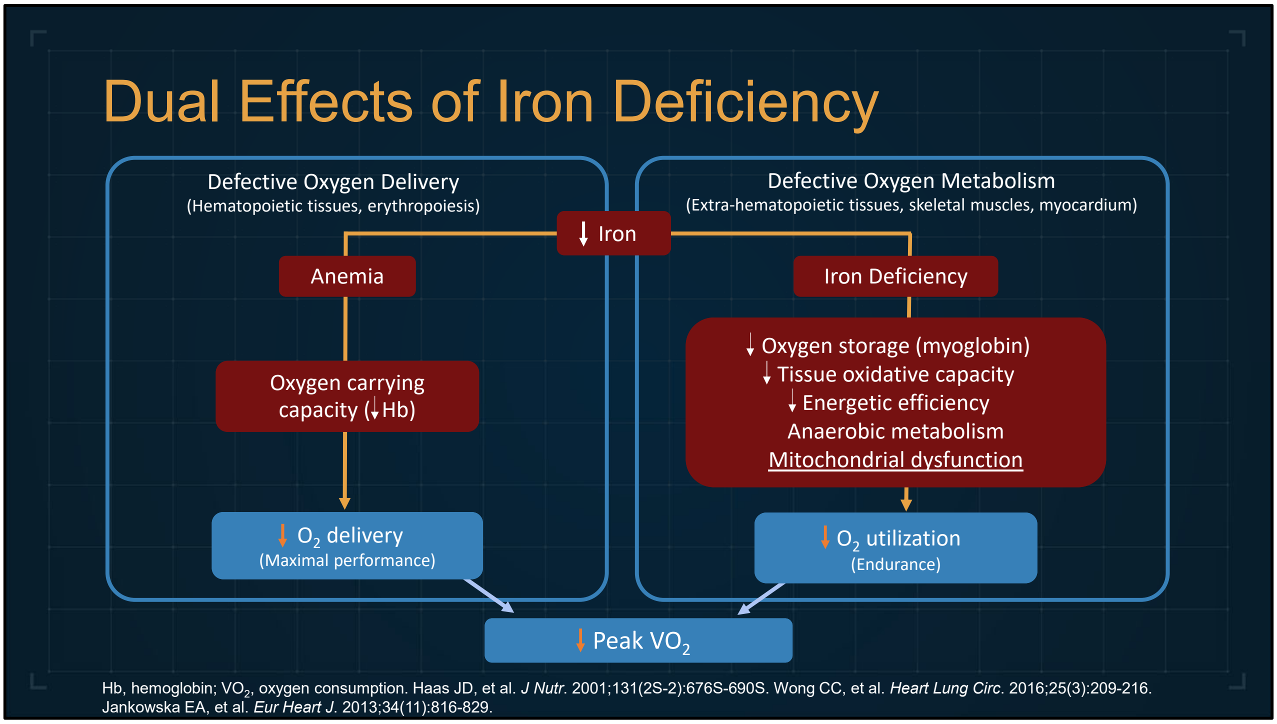
Iron Deficiency in Heart Failure

- Iron deficiency causes:
  - Reduced quality of life
  - Exercise intolerance
  - Increased morbidity and mortality
- Iron deficiency is independent of:
  - Severity of heart failure
  - Ejection fraction
  - Anemia status

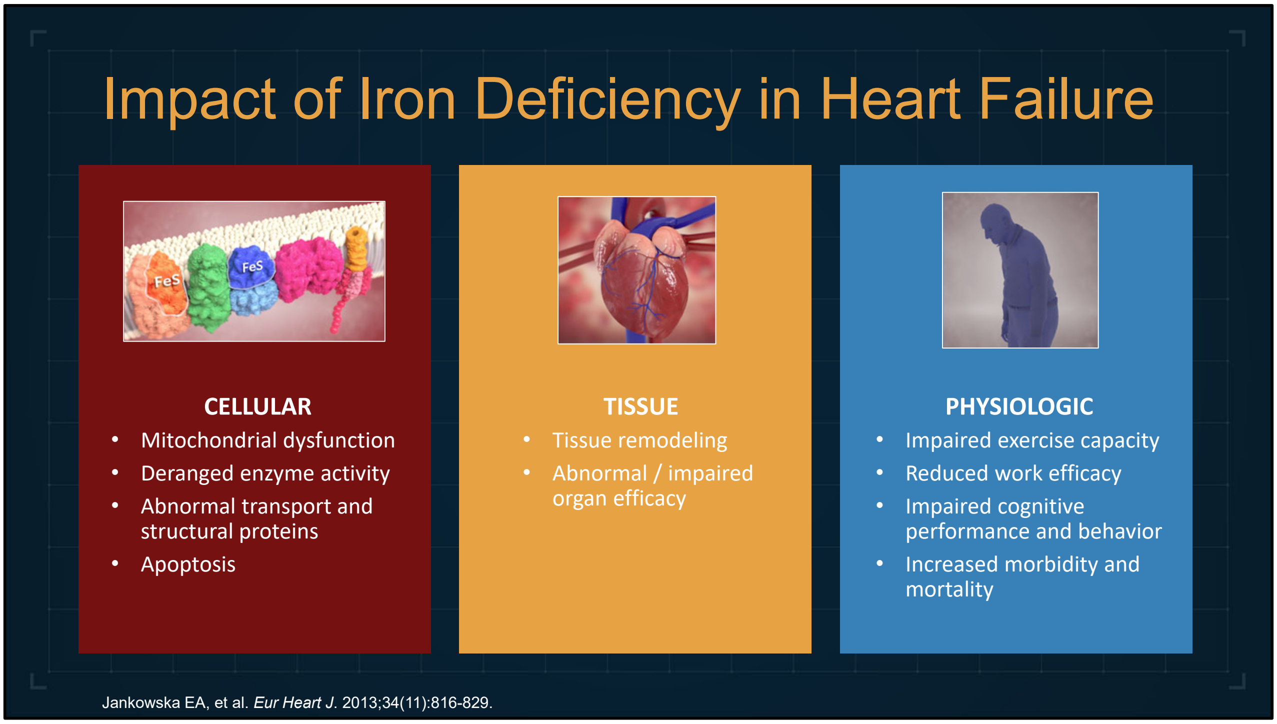
The Role of Iron in Cellular Metabolism



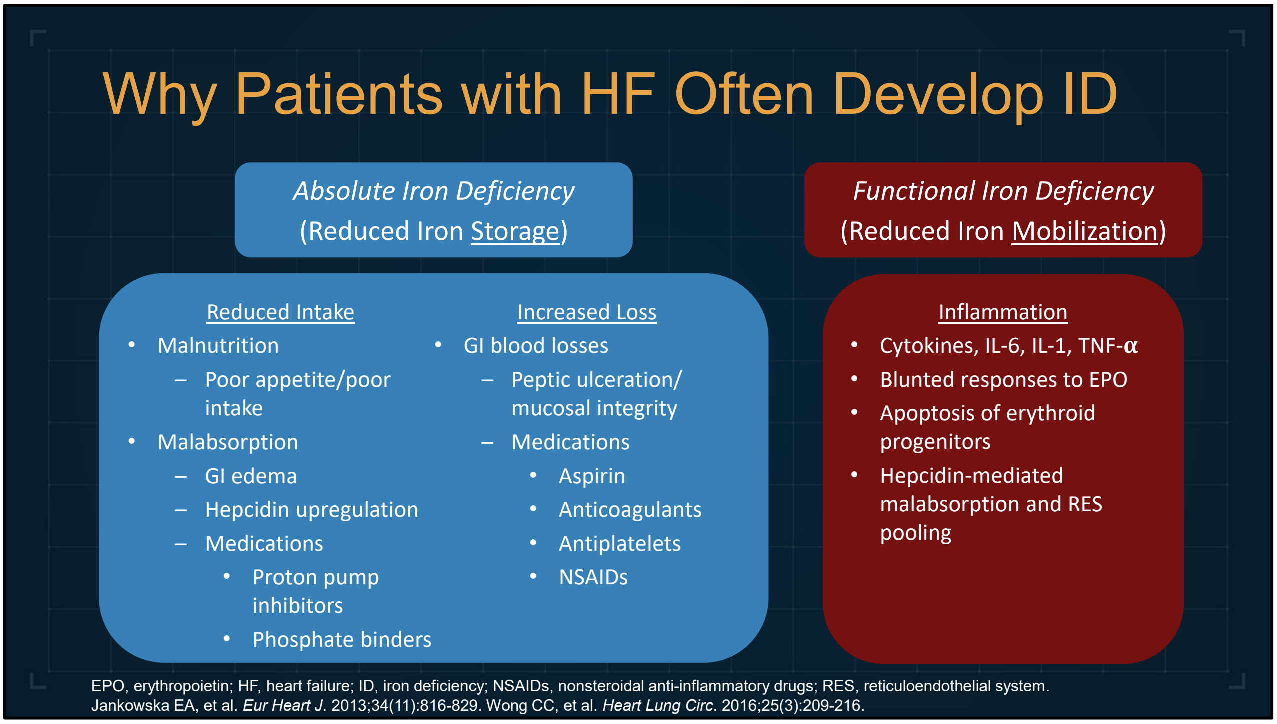
Iron is a vital element involved in numerous physiological processes such as oxygen transport, electron transport during oxidative phosphorylation within the mitochondria, oxygen storage, gene regulation, and cellular immunity. Most iron is used during hematopoiesis. However, iron is also indispensable for maintaining cellular energy and metabolism in extra-hematopoietic tissues.



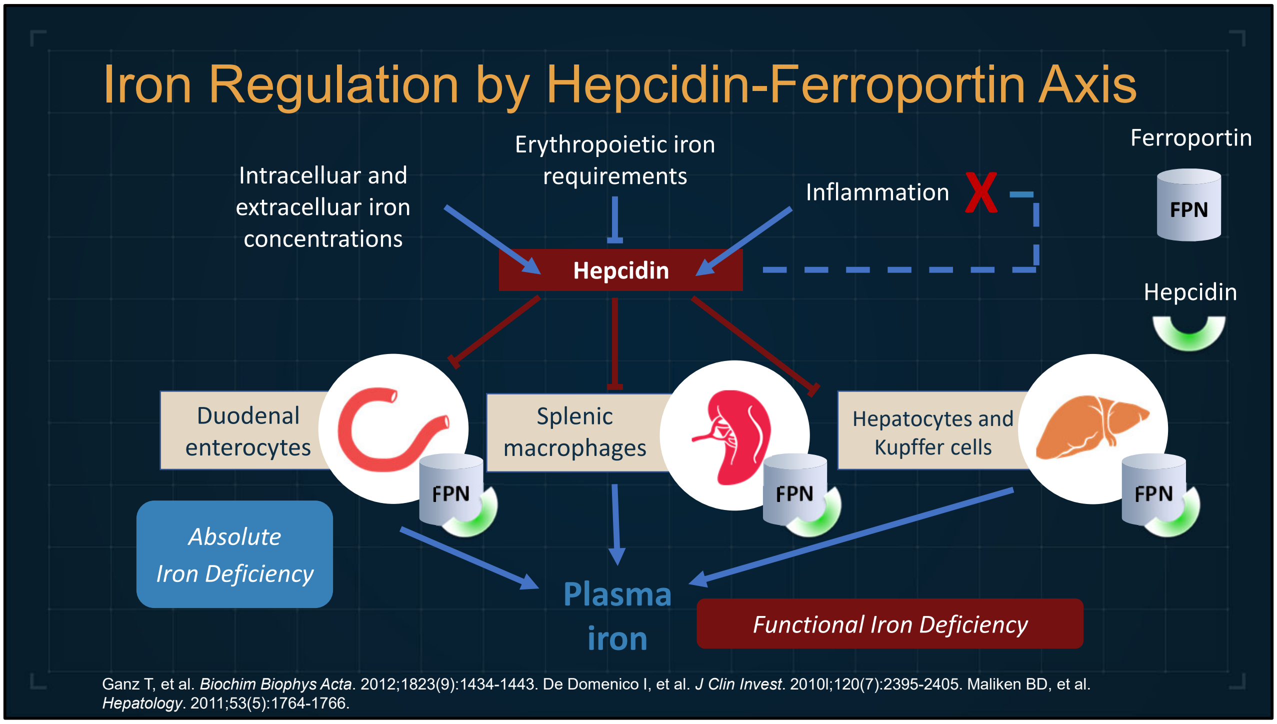
When the availability of iron is limited, two main effects are observed with respect to oxygen delivery and metabolism. The oxygen carrying capacity of hemoglobin declines resulting in lower rates of oxygen delivery and decreased exercise performance. Insufficient iron also results in declines in oxygen storage and mitochondrial dysfunction from decreasing oxidative capacity. Tissues with high energy demands, like skeletal and cardiac myocytes, are particularly sensitive to depleted iron stores and/or abnormal iron utilization. Defects in oxygen delivery and metabolism together contribute to exercise intolerance and heart failure pathophysiology.



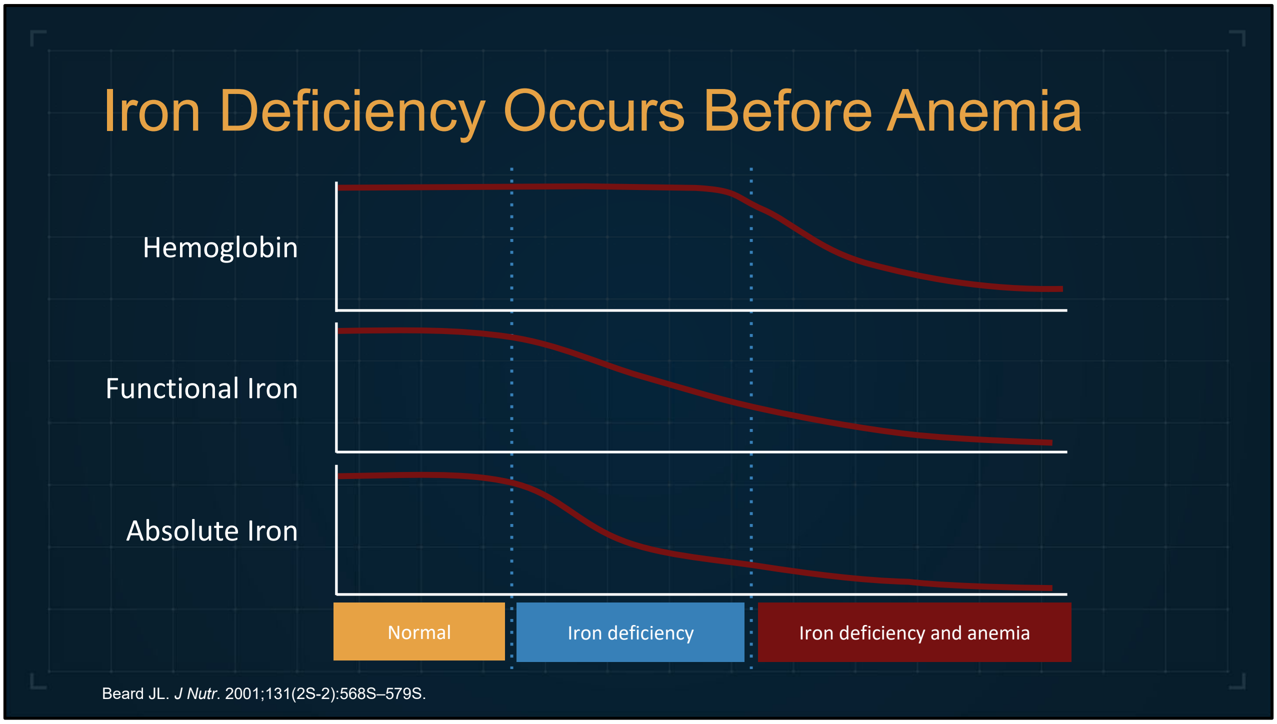
Throughout the body, iron deficiency adversely affects vital functions and reduces survival at the cellular, tissue, and physiologic levels.



Patients with heart failure frequently develop iron deficiency, which can be classified as absolute or functional. Depleted iron storage, or absolute iron deficiency, is mainly caused by reduced dietary intake, malabsorption, and chronic blood loss. Loss of iron mobilization, or functional iron deficiency, reflects an inadequate iron supply to meet body demands because iron is trapped the cells of the reticuloendothelial system (RES). Functional iron deficiency is believed to be primarily caused by pro-inflammatory activation, a state by which heart failure can be characterized, and increased hepcidin production. Hepcidin is a primary regulatory hormone of iron homeostasis and normally plays a role in sequestering iron within the cells of the RES. Additionally, hepcidin can also inhibit iron absorption within the gastrointestinal tract.

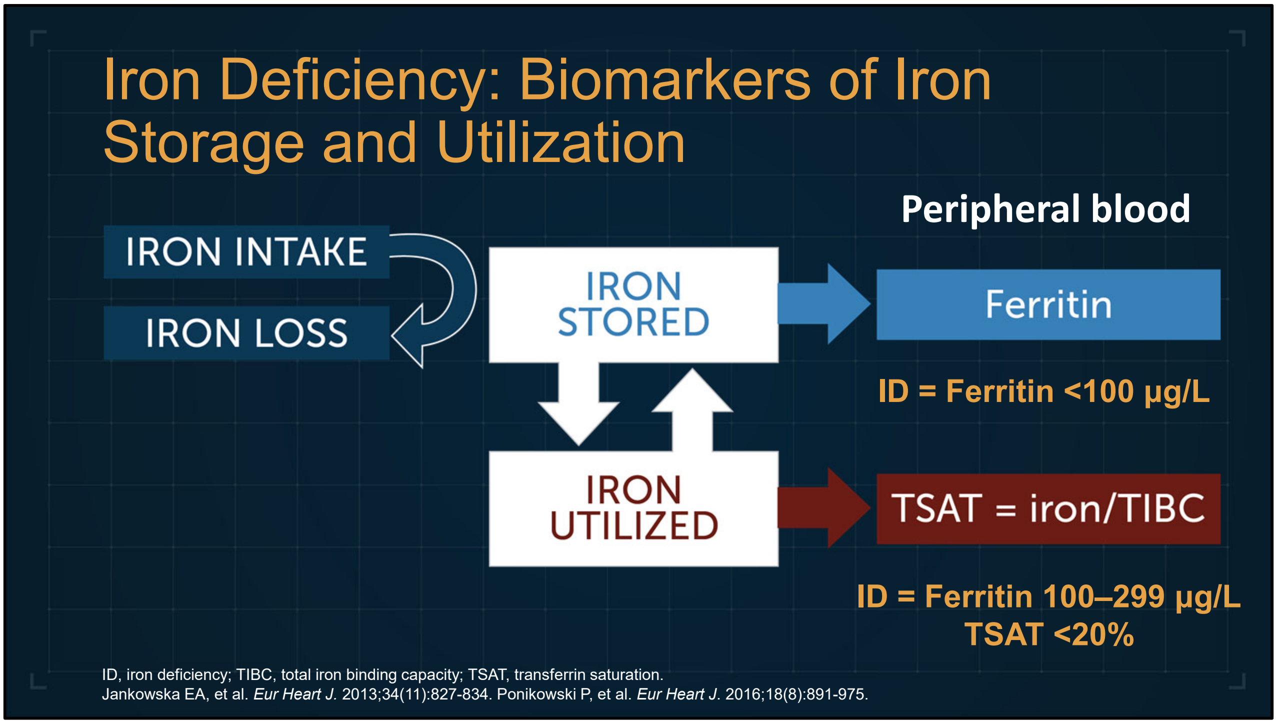


Hepcidin is a regulator of systemic iron metabolism and acts as an antimicrobial peptide to modulate inflammatory responses. Produced by the liver, hepcidin regulates intestinal iron absorption, plasma iron concentrations, and iron distribution from tissue via degradation of its receptor, ferroportin. Hepcidin-mediated loss of ferroportin decreases iron transfer to plasma resulting in functional iron deficiency. Hepcidin is also involved in a ferroportin/JAK2/STAT3-dependent anti-inflammatory negative feedback loop. The presence of inflammation increases hepcidin expression in the liver leading to downregulation of IL-6, TNF-α and other mediators to limit the inflammatory response.

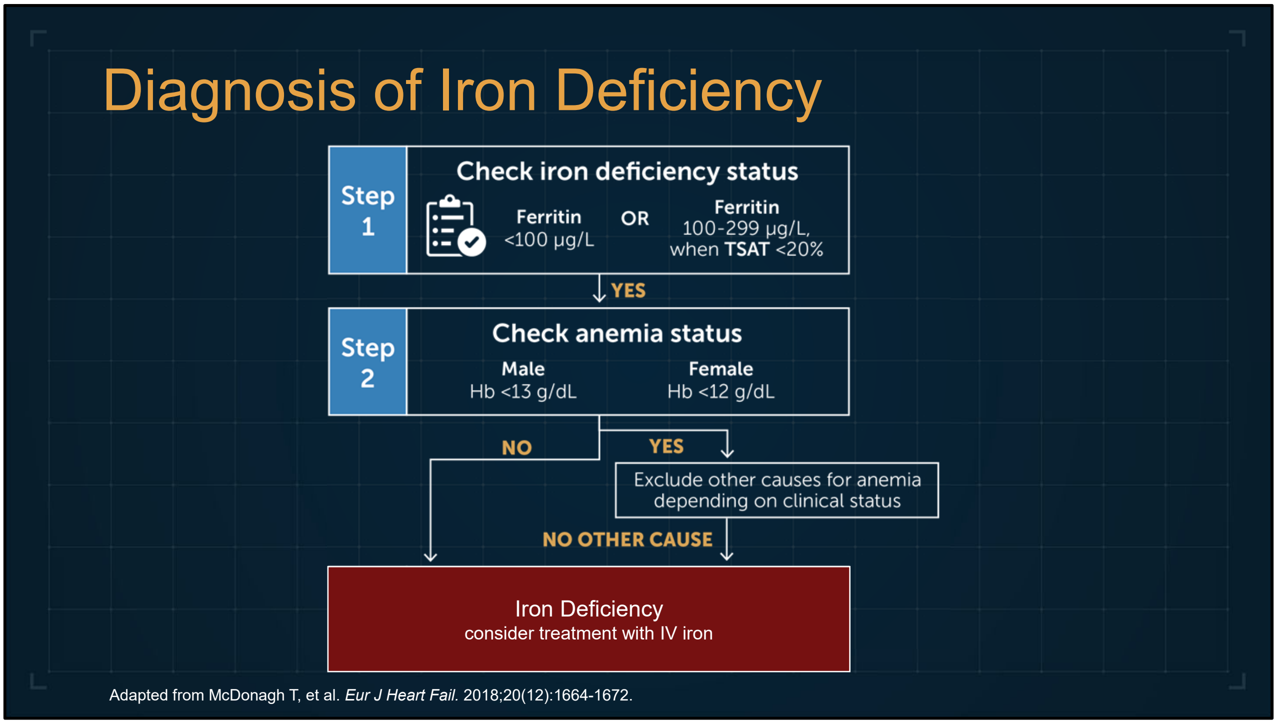


Iron store depletion and loss of iron mobilization typically precedes hemoglobin deficits. Although iron deficiency has been traditionally linked with anemia, iron deficiency often occurs in the absence of anemia. It is only with more advanced iron loss that iron deficiency anemia occurs.

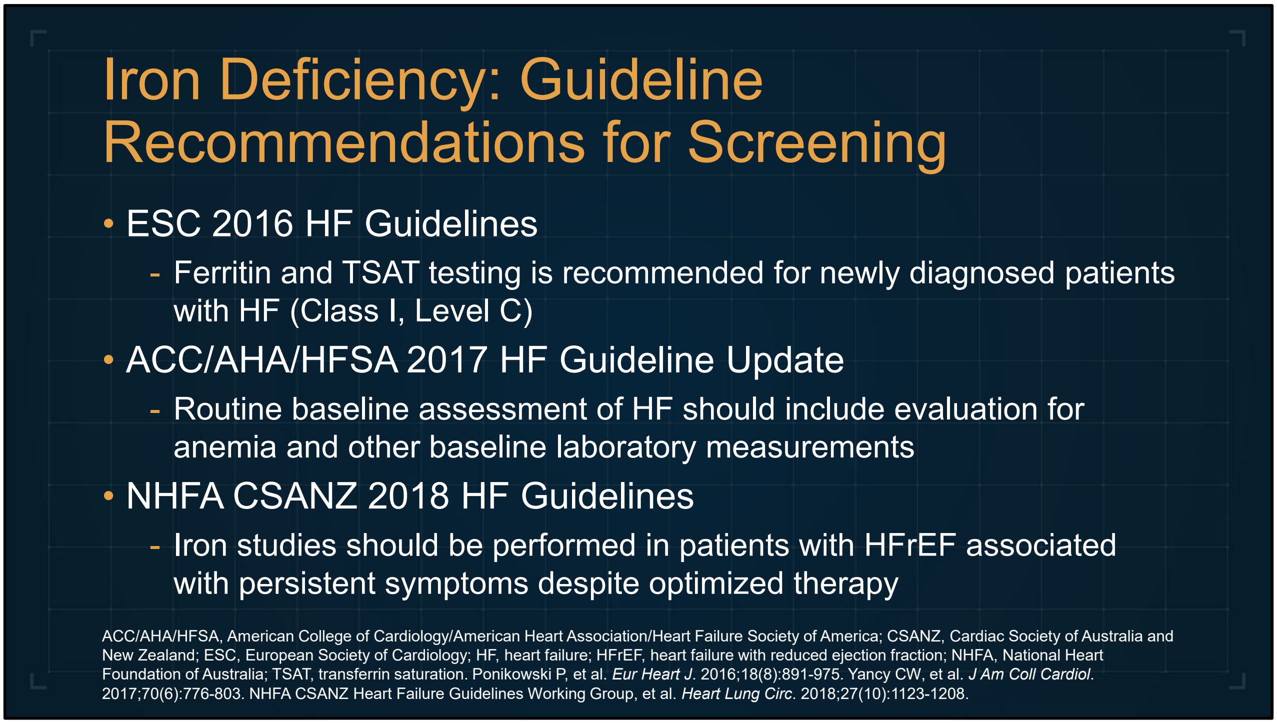
Beard JL. *J Nutr*. 2001;131(2S-2):568S–79S.
Jankowska EA, et al. *Eur Heart J*. 2013;34(11):816-29.
Chopra VK, et al. *ESC Heart Fail*. Published online June 30, 2020. doi: 10.1002/ehf2.12797



Both stored and mobilized forms of iron must be measured in order to appropriately assess iron status. Serum ferritin evaluates iron stores and levels greater than 100 µg/L (100 ng/mL) are considered normal unless transferrin saturation (TSAT) levels are below 20%. TSAT is calculated by dividing the serum iron concentration by total iron-binding capacity (TIBC) and multiplying by 100. A low TSAT value (<20%) indicates insufficient iron mobilization such that if ferritin levels are between 100 µg/L and 299 µg/L then iron deficiency is also present.



Diagnosis of iron deficiency can be thought of as a two-step process. First is evaluating stored and mobilized iron by measuring ferritin and TSAT. TSAT value is a percentage that is calculated by dividing serum iron concentration by the total iron-binding capacity (TIBC). Second, measurement of hemoglobin levels will identify the presence of anemia (men: Hb <13 g/dL and women: <12 g/dL).



Guidelines provide various recommendations around screening for iron deficiency given its prevalence in heart failure and the effects on quality of life, exercise tolerance, and outcomes. The European Society of Cardiology (ESC) directly states that all newly diagnosed patients with heart failure should undergo ferritin and TSAT testing. American guidelines recommend that anemia should be assessed at baseline along with other baseline measurements so it would be reasonable to include ferritin and TSAT testing as part of a comprehensive iron panel. Australian and New Zealand guidelines place more emphasis on evaluating patients with heart failure with reduced ejection fraction (HFrEF) who continue to experience symptoms despite optimal medical therapy.

Practical Recommendations for ID Screening

- Screen patients with existing chronic heart failure
  - If symptoms persist despite optimal medical therapy
- Reevaluate iron status as part of routine follow-up:
  - 1–2 times per year
  - After hospitalization for heart failure

McDonagh T, et al. *Eur J Heart Fail.* 2018;20(12):1664-1672.

Given the prevalence of iron deficiency in heart failure and its associated outcomes, experts recommend for routine clinical practice that patients with existing chronic heart failure be screened, particularly if patients are symptomatic despite receiving optimal guideline-recommended medical therapy. Additionally, re-evaluation for iron deficiency should be incorporated as a part of routine follow-up, as well as after any hospitalizations for heart failure.

Correcting Iron Deficiency in Heart Failure

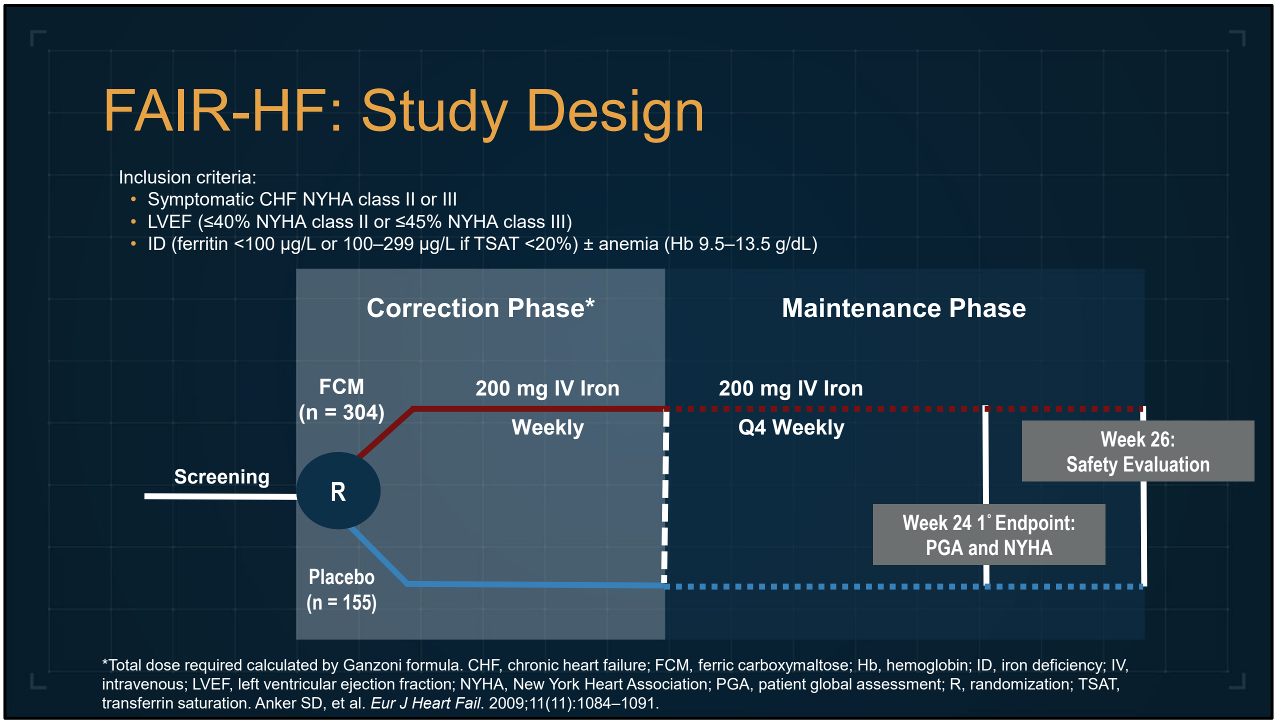
Oral Iron: No Clinical Benefit in HFrEF

IRONOUT HF: double-blind, randomized trial of 225 patients with HFrEF (<40%)

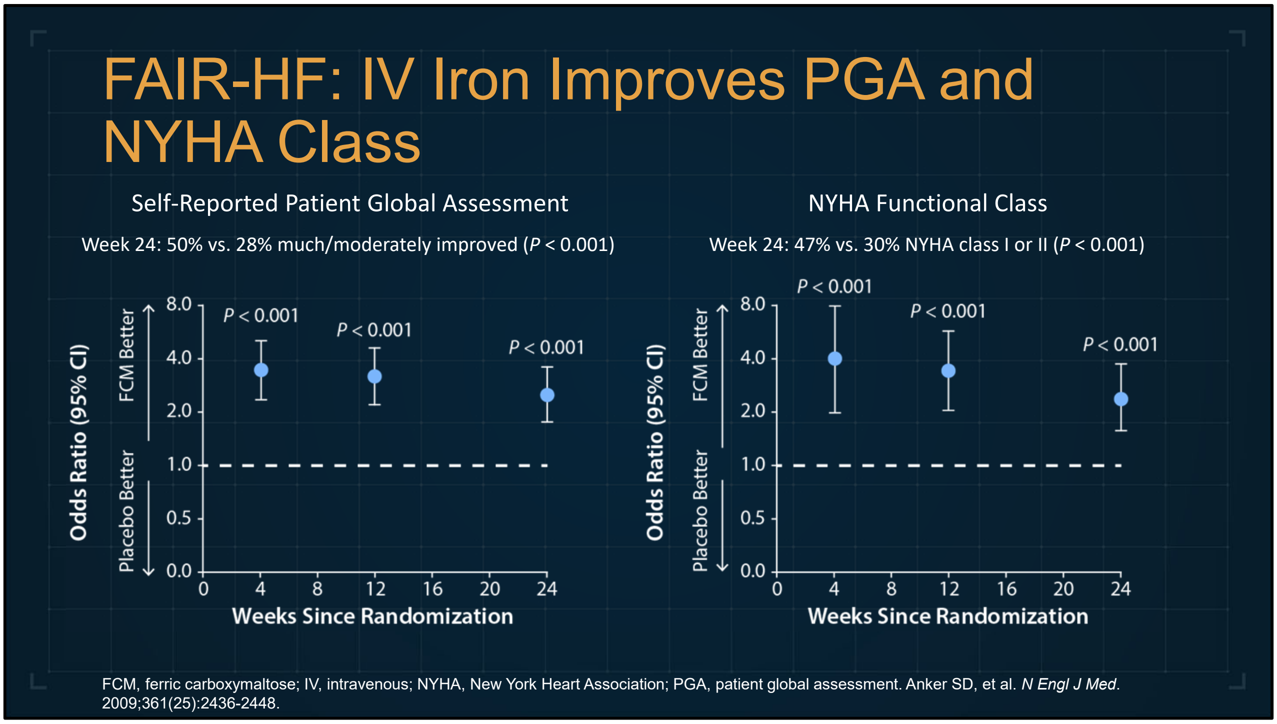
	Oral Iron (n = 111)	Placebo (n = 114)	Difference in Change from Baseline	*P* value
Primary Endpoint				
Δ Peak VO_2 at 16 wk (mL/kg/min)	0.20	0.01	+0.30	0.30
Secondary Endpoints				
Δ 6-min walk distance at 16 wk, m	19	32	-13	0.19
Δ NT-proBNP at 16 wk, pg/mL	4	-37	+159	0.48
Δ KCCQ clinical summary score at 16 wk	3.1	3.0	+1.0	0.57
Iron Metabolism Markers (median)				
Ferritin, ng/mL	95	75	-	0.06
TSAT, %	22	20	-	0.003

HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TSAT, transferrin saturation; VO_2, oxygen consumption. Lewis GD, et al. *JAMA*. 2017;317(19):1958-1966.

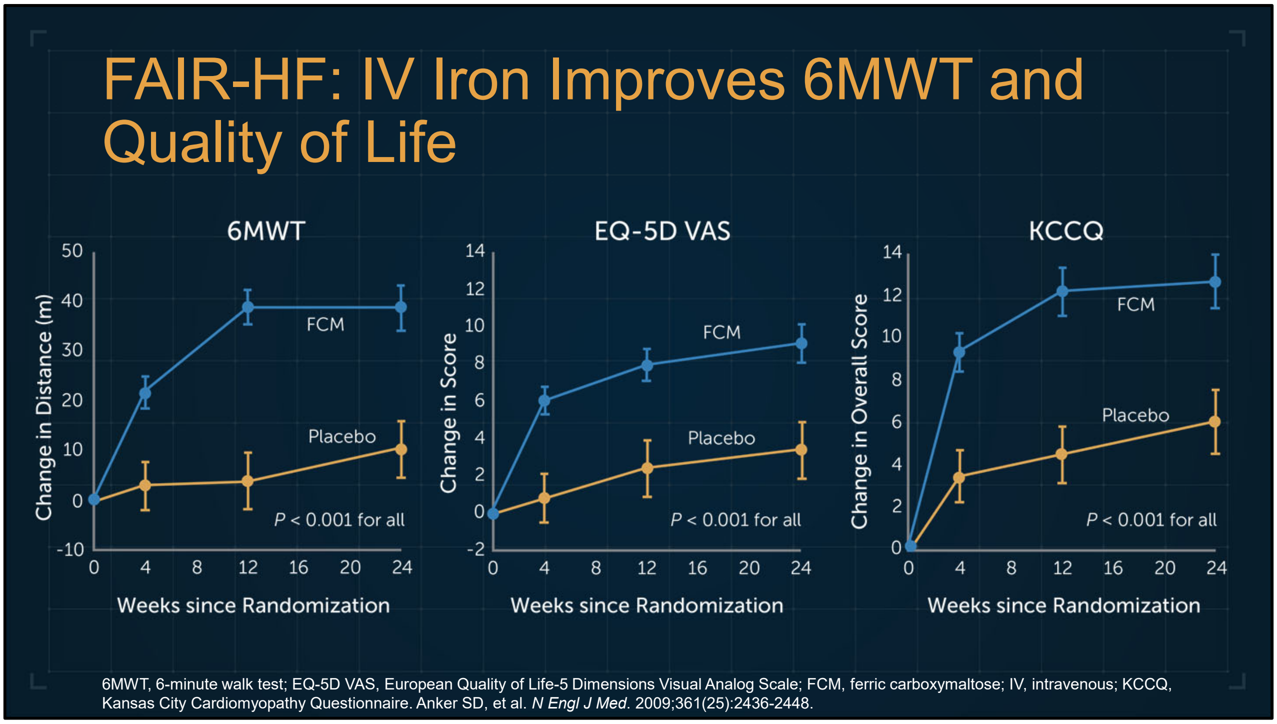
High-dose oral has been shown to be ineffective in improving clinical outcomes associated with iron deficiency. The IRONOUT-HF study showed that treatment with 150 mg oral iron polysaccharide twice daily failed to improve exercise capacity and endurance, inflammatory markers, and quality of life. The lack of improvement is likely due to impaired absorption and/or dose intolerance since the median ferritin levels remained below 100 ng/mL after 16 weeks indicating that iron deficiency was not reversed in more than half of subjects.



FAIR-HF was a multi-center, randomized, double-blind, placebo-controlled study designed to evaluate the effect of intravenous (IV) iron repletion using ferric carboxymaltose on iron deficiency, with or without anemia, in patients with symptomatic HFrEF. Primary endpoints were self-reported patient global assessment (PGA) and NYHA functional class.



Significant improvements in self-reported PGA and NYHA functional class were observed at weeks 4 and maintained throughout the 24-week study period in the FCM group compared with placebo (*P* < 0.001 for all) in patients independent of anemia status.



Similar and significant improvements were also seen with gains in 6-minute walk distances and quality of life scores evaluated by Kansas City Cardiomyopathy questionnaire (KCCQ) and the European Quality of Life-5 Dimensions Visual Analog Scale (EQ-5D VAS; *P* < 0.001 for all).

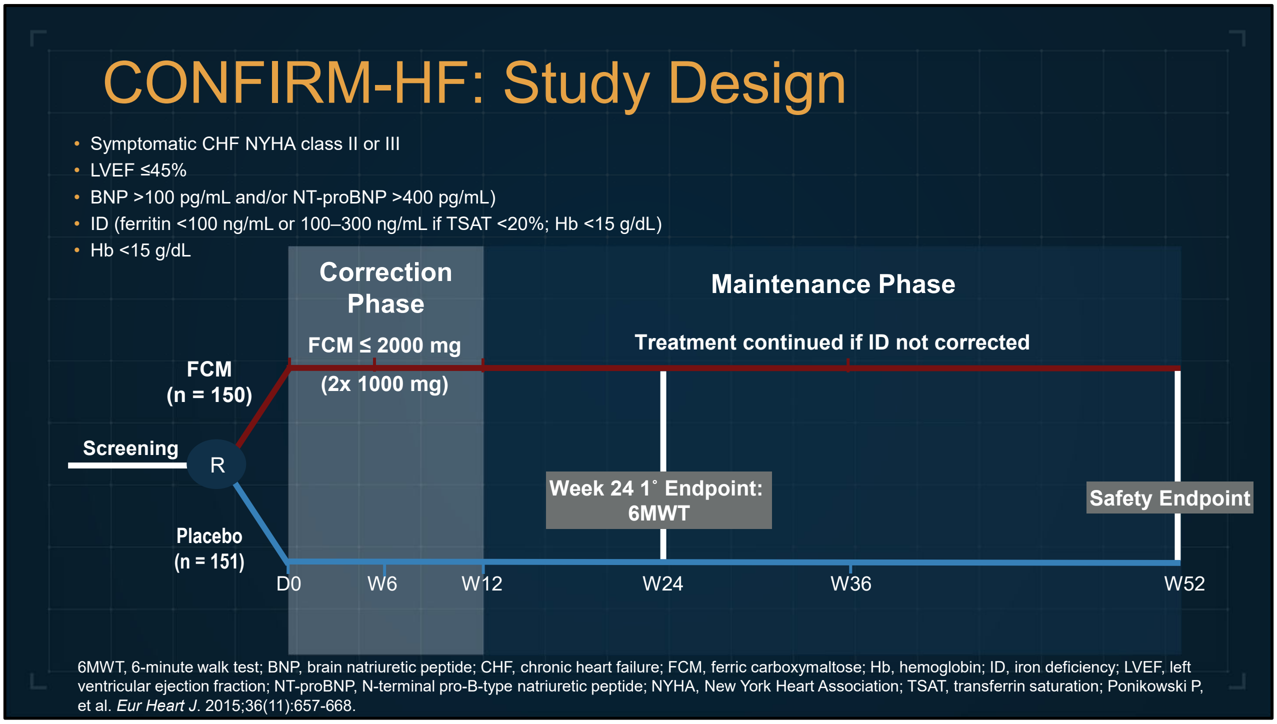
FAIR-HF: Safety Endpoints

	Patients with Events (Incidence per 100 patient-years at risk)		
	Oral Iron (n = 305)	Placebo (n = 154)	*P* value
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

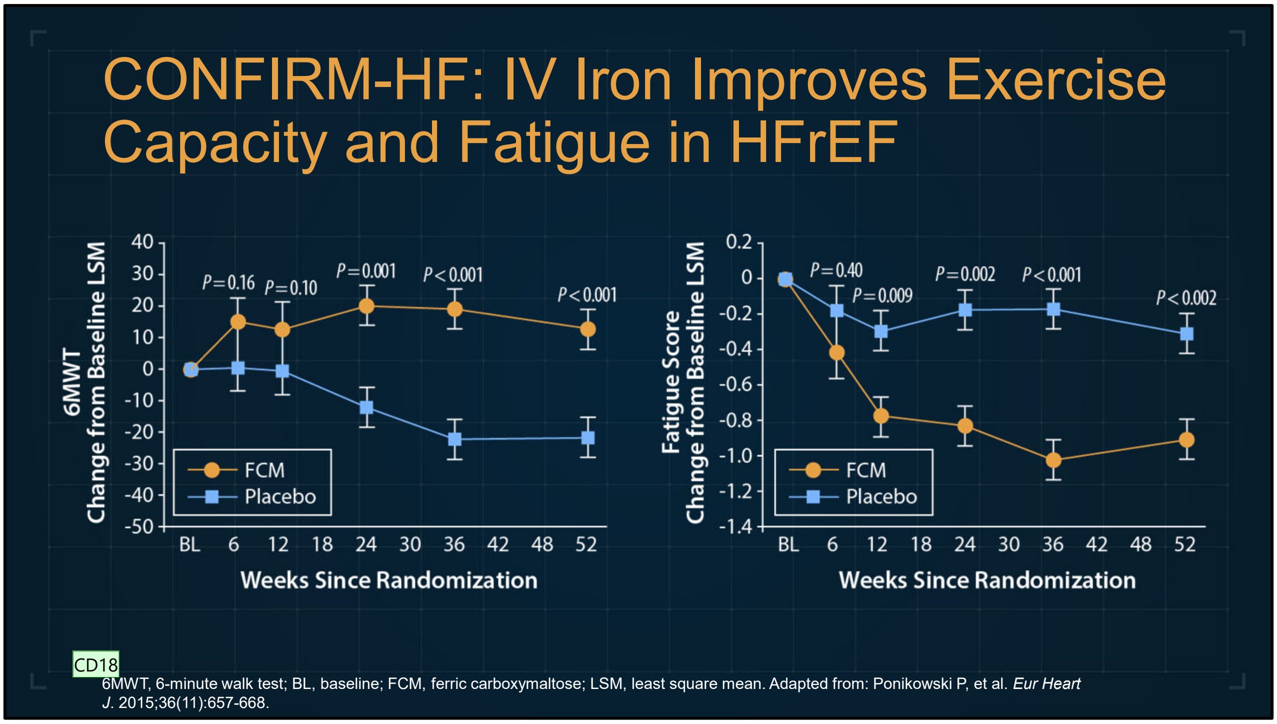
No severe or serious hypersensitivity reactions.

CV, cardiovascular; HF, heart failure. Anker SD, et al. *N Engl J Med*. 2009;361(25):2436-2448.

No severe or serious allergic reactions were observed with FCM. Both groups had similar rates of death and hospitalizations. A trend towards lower rates of first hospitalization for any CV reasons was observed among FCM-treated patients compared with placebo.



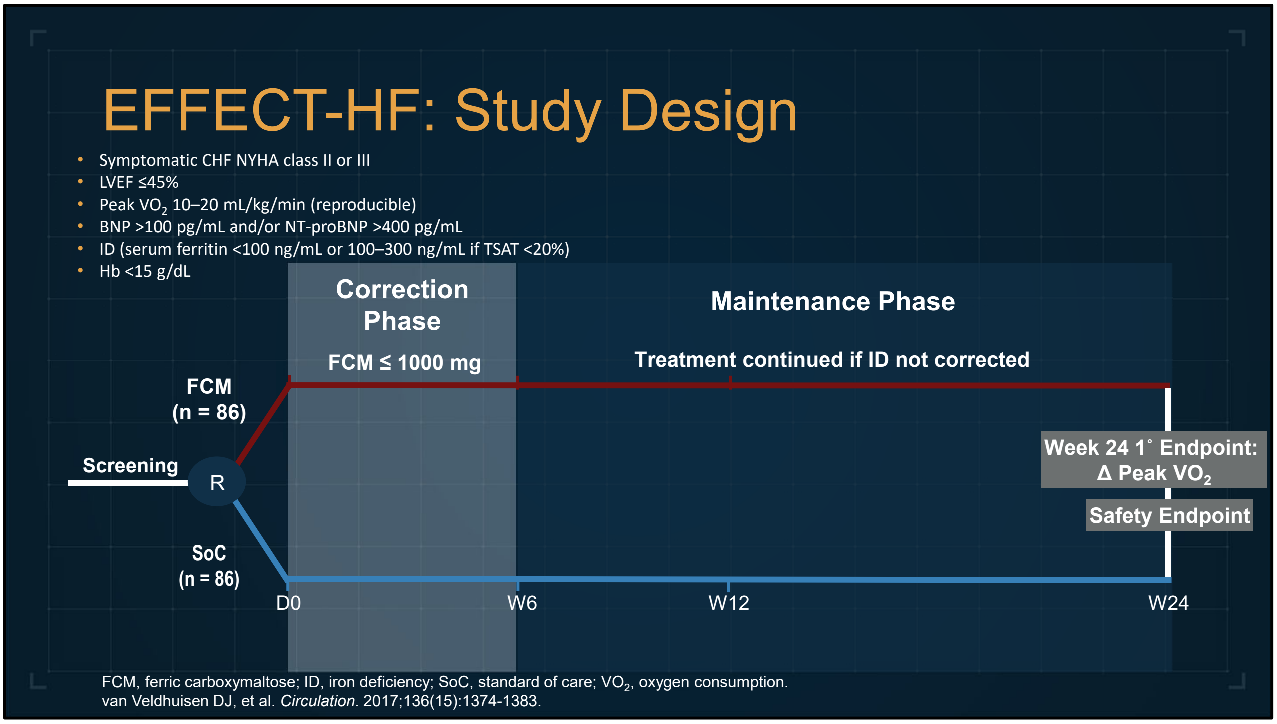
CONFIRM-HF was a randomized, double-blind, placebo-controlled study designed to examine longer-term outcomes associated with correction of iron deficiency in patients with symptomatic HFrEF.



The primary endpoint of 6MWT distance improved significantly from Week 24 onwards compared with placebo [difference 33 ± 11 m (least squares mean ± standard error), *P* = 0.002]. Benefits in 6MWT distance continued until the end of the 52-week study period. Fatigue scores also improved significantly beginning at Week 12 and onwards in the FCM group. Additionally, quality of life improvements were observed with FCM with increases in overall KCCQ scores at Weeks 12, 36, and 52 (*P* < 0.05 for all).

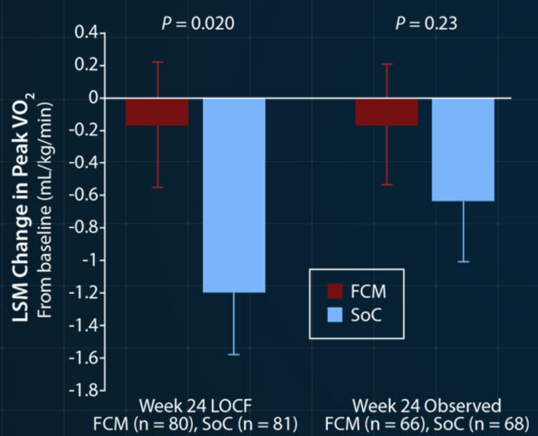
Slide 31

CD18 add BL?
Cindy Davidson, 11/23/2020



EFFECT-HF was a study of 172 patients with HFrEF (≤45%) with mild to moderate symptoms despite optimal guideline-directed medical therapy that was designed to evaluate the change in peak oxygen consumption after correction of iron deficiency. Of note, patients who were randomized to the standard of care (SoC) arm could receive oral iron at the discretion of the attending physician, and 34% received oral iron supplementation.

EFFECT-HF: Improvements in Peak Oxygen Consumption



Number of Deaths and Hospitalizations	Ferric carboxymaltose (n = 88)	Standard of care (n = 86)
# of deaths	0	4
Hospitalizations (total)	37	21
Reason for hospitalizations		
Worsening HF	13	13
Other CV reason	13	3
Non-CV reason	11	4
Unknown	0	1

CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; LSM, least square mean; LOCF, last observation carried forward (primary endpoint); SoC, standard of care; VO_2, oxygen consumption. van Veldhuisen DJ, et al. *Circulation*. 201710;136(15):1374-1383.

Analysis of the primary endpoint was conducted on the full analysis set, which included all subjects who received one or more administrations of FCM in the study arm and had one or more efficacy assessments after baseline. For subjects who died prior to Week 24, a peak VO_2 of 0 was imputed, and a last observation carried forward (LOCF) imputation was used for subjects without assessment data at Week 24. Of the 172 subjects, 161 subjects were assessed for the Week 24 primary endpoint. There was a significant difference in the change in peak VO_2, which substantially decreased in the SoC group compared with the minimal change in the FCM group ($P = 0.02$) when deaths were imputed. In the observed analysis when deaths were not imputed, the significant difference in change in peak VO_2 between study groups was not maintained suggesting a potential selection bias. The trial was underpowered to evaluate clinical events, such as deaths and hospitalization, but results suggest that exercise capacity is maintained with IV iron treatment.

Meta-Analysis: FCM in HFrEF

Data from FAIR-HF, FER-CARS-01, EFFICACY-HF, and CONFIRM-HF:
HFrEF and iron deficiency, N = 839

Recurrent Event Outcomes	HR (95% CI)	*P* value
CV hospitalizations and CV mortality	0.59 (0.40-0.88)	0.009
HF hospitalizations and CV mortality	0.53 (0.33-0.86)	0.011
CV hospitalizations and all-cause mortality	0.60 (0.41-0.88)	0.009
HF hospitalizations and all-cause mortality	0.54 (0.34-0.87)	0.011
All-cause hospitalizations and all-cause mortality	0.73 (0.52-1.01)	0.060
HF hospitalizations	0.41 (0.23-0.73)	0.003
CV hospitalizations	0.54 (0.36-0.83)	0.004
All-cause hospitalizations	0.71 (0.50-1.01	0.056

CI, confidence interval; CV, cardiovascular; FCM, ferric carboxymaltose; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio. Anker SD, et al. *Eur J Heart Fail.* 2018;20(1):125-133.

Data from four randomized clinical trials, including FAIR-HF and CONFIRM-HF, were evaluated for the main outcomes measures of recurrent CV hospitalizations and CV mortality in patients with HFrEF. Analyses showed that correction of iron deficiency with IV FCM was associated with lower rates of recurrent CV hospitalizations and CV mortality, heart failure (HF) hospitalizations and CV mortality, CV hospitalizations and all-cause mortality, and HF hospitalizations and all-cause mortality. These data suggest that iron deficiency is a modifiable risk factor with appropriate treatment.

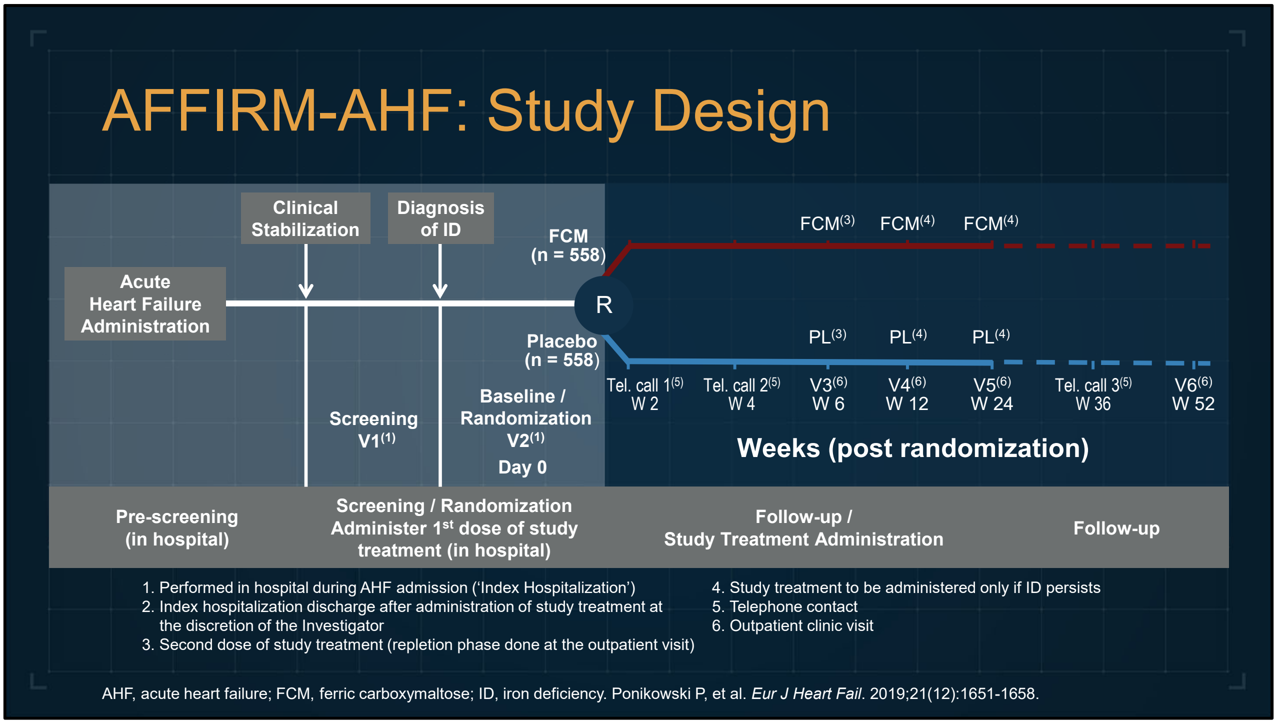
Meta-Analysis: Safety of FCM

Data from FAIR-HF, FER-CARS-01, EFFICACY-HF, and CONFIRM-HF:
HFrEF and iron deficiency, N = 839

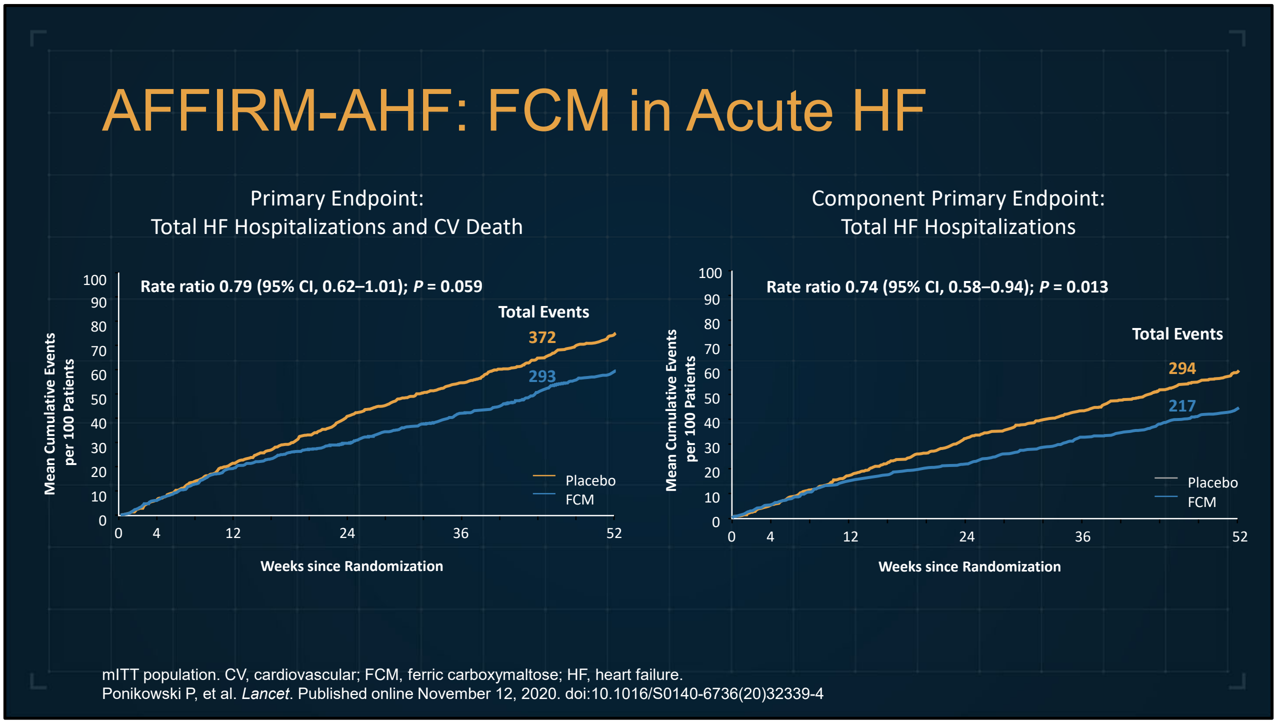
Investigator-reported Adverse Events (AEs)	Patients with Events	
	FCM (n = 507)	Placebo (n = 335)
AEs	317 (65.2%)	215 (64.2%)
Serious AEs	86 (17.0%)	79 (23.6%)
AEs leading to study drug withdrawal	32 (6.3%)	34 (10.1%)
Study drug-related AEs	50 (9.9%)	20 (6.0%)
Serious drug-related AEs	0	1 (0.3%)
Study drug-related AEs leading to study drug withdrawal	7 (1.4%)	3 (0.9%)

AE, adverse event; FCM, ferric carboxymaltose; HFrEF, heart failure with reduced ejection fraction. Anker SD, et al. *Eur J Heart Fail.* 2018;20(1):125-133.

Meta-analysis data showed a similar rate of adverse events occurred in both the treatment and placebo groups. Adverse events leading to study withdrawal were fewer in patients in the FCM group compared with placebo (6.3% vs. 10.1%). No serious or severe hypersensitivity reactions were observed by investigators.



AFFIRM-AHF was a randomized, double-blind, placebo-controlled trial evaluating treatment with IV FCM in 1108 patients with HFrEF (EF <50%) stabilized after an episode of acute heart failure and iron deficiency on the composite endpoint of recurrent heart failure hospitalizations and cardiovascular death up to 52 weeks after randomization.



Data show that the combined endpoint of total heart failure hospitalizations and cardiovascular death tended to be lower in patients treated with FCM compared with placebo. This observation was driven by the 26% reduction in total heart failure hospitalizations which was significantly lower among patients treated with FCM. During the treatment phase, 80% of received one or two administrations of FCM and the mean total dose of FCM administered during the trial was 1352 mg.

AFFIRM-AHF: Recurrent Event Outcomes with COVID-19 Sensitivity Analysis

	Hazard Ratio (95% CI)	*P* value
Modified intention-to-treat analysis		
Total heart failure hospitalizations[1] or cardiovascular death	0.79 (0.62-1.01)	0.059
Total cardiovascular hospitalizations[1] or cardiovascular death	0.80 (0.64-1.00)	0.050
Total heart failure hospitalizations[1]	0.74 (0.58-0.94)	0.013
COVID-19 sensitivity analysis[2]		
Total heart failure hospitalizations[1] or cardiovascular death	0.75 (0.59-0.96)	0.024
Total cardiovascular hospitalizations[1] or cardiovascular death	0.77 (0.62-0.97)	0.024
Total heart failure hospitalizations[1]	0.70 (0.55-0.90)	0.005

[1]Included first and recurrent events; [2]Patients were censored in each country on the date when the first patient with COVID-19 was reported in the respective country. Ponikowski P, et al. *Lancet*. Published online November 12, 2020. doi:10.1016/S0140-6736(20)32339-4

The AFFIRM-AHF trial was conducted during the COVID-19 pandemic which impacted management and follow-up of all patients and potentially affected data collection. The statistical analysis plan included a pre-specified COVID-19 sensitivity analysis as recommended by the Heart Failure Association of the European Society of Cardiology, the European Medicines Agency, and the US Food and Drug Administration where patients were censored in each country on the date when its first COVID-19 patient was reported. The COVID-19 analysis showed a significant benefit of FCM on the combined endpoint of total heart failure hospitalizations and cardiovascular death. This suggests that less complete follow-up, fewer hospitalizations, and other pandemic related factors may have prohibited full observation of treatment differences.

AFFIRM-AHF: Adverse Effects

Adverse Events (AE)	FCM (N = 558)		Placebo (N = 550)	
	Patients n (%)	Total Events (n)	Patients n (%)	Total Events (n)
Any AE	357 (64%)	1246	360 (65%)	1314
Serious AE	250 (45%)	547	282 (51%)	632
AE leading to withdrawal of study treatment	61 (11%)	71	79 (14%)	88
AE leading to study discontinuation	98 (18%)	117	96 (17%)	123

AE, adverse event; FCM, ferric carboxymaltose. Ponikowski P, et al. *Lancet*. Published online November 12, 2020. doi:10.1016/S0140-6736(20)32339-4

Treatment with FCM was safe and well-tolerated in patients stabilized after an episode of acute heart failure. Serious adverse events occurred in 45% of patients in the FCM arm compared with 51% of patients in the placebo arm. Additionally, the incidence of adverse events and adverse events leading to study discontinuation or drug withdrawal were similar in both groups.

Treatment of Iron Deficiency

Guideline Recommendations

2016 ESC Guidelines

Class	Level	Recommendation
IIa	A	Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin <100 µg/L or ferritin between 100–299 µg/L and transferrin saturation <20%) in order to alleviate HF symptoms and improve exercise capacity and quality of life.

2017 AHA/ACC/HFSA Guideline Update

COR	LOE	Recommendation
IIb	B-R	In patients with NYHA class II and III HF and iron deficiency (ferritin <100 ng/mL or 100–300 ng/mL if transferrin saturation is <20%), intravenous iron replacement might be reasonable to improve functional status and quality of life.

2018 NHFA CSANZ Guidelines

Grade	QOE	Recommendation
Strong FOR	Moderate	In patients with HFrEF associated with persistent symptoms despite optimized therapy, patients determined to be iron deficient (ie, ferritin <100 µg/L or ferritin between 100–300 µg/L and transferrin saturation <20%), intravenous iron should be considered to improve symptoms and and quality of life.

FCM, ferric carboxymaltose; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association. Ponikowski P, et al. *Eur J Heart Fail*. 2016;37(27):2129-2200. Yancy CW, et al. *J Am Coll Cardiol*. 2017;70(6):776-803. NHFA CSANZ Heart Failure Guidelines Working Group, et al. *Heart Lung Circ*. 2018;27(10):1123-1208.

Guidelines across Europe, the United States, and Australia concur that patients with heart failure should be treated with IV iron to improve symptoms and quality of life.

EU/AUS: Treatment of ID in HFrEF

- Ferric carboxymaltose dosage forms:
  - 100 mg, 500 mg, 1000 mg iron
- Dosing according to hemoglobin levels and body weight

Hemoglobin		**Patient body weight**		
g/dL	mmol/L	<35 kg	35 kg – <70 kg	≥70 kg
<10	<6.2	500 mg	1500 mg	2000 mg
10–14	6.2–8.7	500 mg	1000 mg	1500 mg
>14	>8.7	500 mg	500 mg	500 mg

AUS, Australia; EU, European Union, ID, iron deficiency; HFrEF, heart failure with reduced ejection fraction. Ferric carboxymaltose. Package leaflet. Vifor France; 2020. Ferric carboxymaltose. Australian Product information. Vifor Pharma Pty Ltd; 2020.

In Europe and Australia, dosing of FCM for the correction of iron deficiency in patients with HFrEF (NYHA class II-IV) should be based on hemoglobin levels and body weight.

US: Treatment of ID in HF (NYHA Class II and III)

- Ferric carboxymaltose dosage form:
  - 750 mg iron per 15 mL single-dose vial
- Patients weighing ≥50 kg (110 lbs)
  - 2x 750 mg (1500 mg total)
  - Separated by at least 7 days
- Patients weighing <50 kg (110 lbs)
  - 2x 15 mg/kg body weight
  - Separated by at least 7 days

HF, heart failure; ID, iron deficiency; NYHA, New York Heart Association; US, United States. Ferric carboxymaltose injection. Package insert. American Regent, Inc.; 2020.

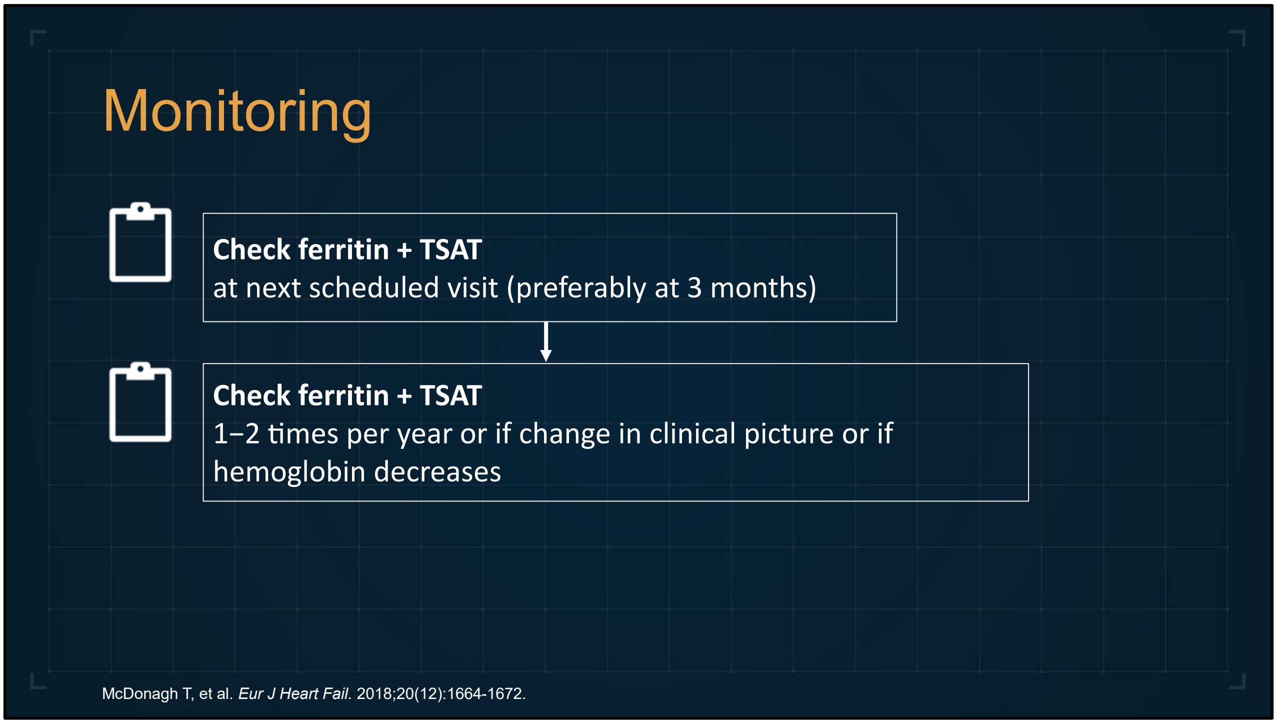
In the United States, dosing of FCM for the correction of iron deficiency in patients with heart failure (NYHA class II-IV) is based on patient weight. Two doses should be administered at least one week apart.

Safety Considerations

- Hypersensitivity reactions
  - Monitor patients for signs and symptoms of hypersensitivity during and at least 30 minutes after administration
- Symptomatic hypophosphatemia
  - Monitor serum phosphate levels in patients at risk for low serum phosphate who require a repeat course of treatment
- Hypertension
  - Monitor patients for signs and symptoms of hypertension following each administration

Ferric carboxymaltose injection. Package insert. American Regent, Inc.; 2020. Ferric carboxymaltose. Package leaflet. Vifor France; 2020.

Patients receiving FCM may experience hypersensitivity reaction and should be monitoring during and at least 30 minutes after administration. Symptomatic hypophosphatemia and hypertension may also occur, and patients should be monitored accordingly.



Following IV iron treatment, ferritin and TSAT levels should be measured at 3 months and 1–2 per year thereafter unless there is a change in status.

Upcoming Clinical Trials

Ongoing Trials in HF and ID

Study Name	FAIR-HF2	FAIR-HFpEF	HEART-FID	IRONMAN
# of Patients	1,200	200	3,014	1,300
Diagnosis	HFrEF EF ≤45%	HFpEF **EF ≥45%**	HFrEF EF ≤40%	HFrEF EF <45%
Blinding	Double blind	Double blind	Double blind	**Open label**
Study Arm	FCM	FCM	FCM	**Iron (III) isomaltoside**
Duration	Event driven + at least 12 mos f/u	52 weeks	Event driven + 12 mos last patient	120 weeks
Primary Endpoint	HF hospitalization + CV death	Δ 6MWT from baseline to Week 24	All-cause mortality + total HF hospitalization through 12 mos and Δ 6MWT after 6 mos	CV death or HF hospitalization
Anticipated Completion	December 2021	July 2021	June 2022	Suspended due to COVID-19 May 2020

6MWT, 6-minute walk test; CV, cardiovascular; EF, ejection fraction; FCM, ferric carboxymaltose; f/u, follow-up; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency.
von Haehling S, et al. *JACC Heart Fail.* 2019;7(1):36-46.

Multiple prospective trials are underway evaluating morbidity and mortality associated correction of comorbid iron deficiency with IV iron in patients with various forms of heart failure. The IRONMAN trial, which was examining patients with HFrEF, was suspended in May 2020 and it is unclear whether previously collected data will be released. FAIR-HFpEF is exploring whether exercise capacity is improved with IV iron in patients with HFpEF and iron deficiency.

Conclusions

- Iron deficiency is common in HF
- Proactively screen newly diagnosed and established patients with HF
- Correction of ID improves:
  - Exercise capacity
  - Quality of life
  - Cardiovascular and mortality outcomes
- Treat symptomatic patients regardless of anemia status
  - Oral iron is ineffective in correcting ID in HF
  - FCM is effective in treating comorbid ID in HF with demonstrated benefits
- Multiple ongoing studies are evaluating the effect of ID correction on HF morbidity and mortality