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Clinical Meeting & Exhibition

Ironing Out the Management of Anemia in Heart Failure

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

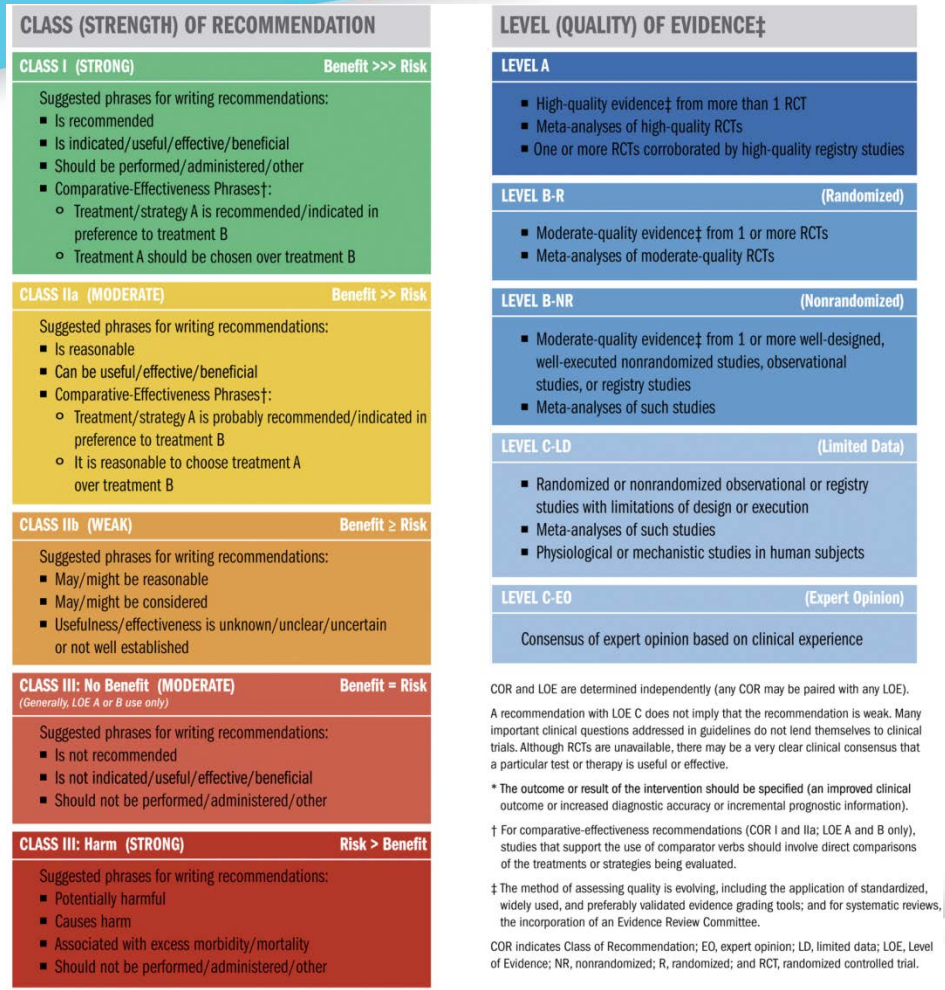
Learning Objectives

- Interpret the current guideline recommendations for the management of anemia in heart failure patients.
- Evaluate the underlying mechanism of iron deficiency in heart failure patients.
- Assess the effectiveness of oral versus intravenous iron replacement strategies on heart failure patients.
- Design a pharmacotherapy plan to manage iron deficiency in heart failure patients.

According to the 2017 ACC/AHA/HFSA Focused Update on the management of heart failure which of the following anemia treatments is no longer recommended for use in patients with heart failure?

A. Darbepoeitin alfa
B. Ferric carboxymaltose
C. Ferrous sulfate
D. Iron sucrose

ACC/AHA Clinical Practice Guideline Recommendation Classification System



CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

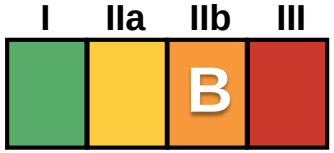
† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Halperin JL, et al. *J Am Coll Cardiol*. 2016;67(13):1572-1574.

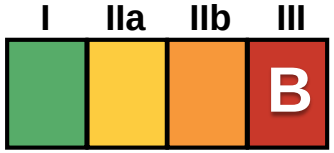
Anemia Recommendations in HF Patients



- IV iron replacement might be reasonable to improve functional status and quality of life in NYHA class II and III heart failure patients with iron deficiency
  - (ferritin < 100 ng/mL or 100 to 300 ng/mL if transferrin saturation is < 20%)

Yancy CW, et al. *J Am Coll Cardiol.* 2017;70:776-803.

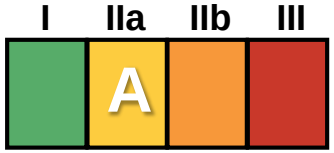
Anemia Recommendations in HF Patients



- Erythropoietin stimulating agents should not be used to improve morbidity and mortality in heart failure patients with anemia

Yancy CW, et al. *J Am Coll Cardiol.* 2017;70:776-803.

ESC Anemia Recommendations in HF Patients



- IV ferric carboxymaltose should be considered in symptomatic HFrEF and iron deficiency to alleviate HF symptoms, improve exercise capacity and quality of life
  - (ferritin < 100 µg/L, or 100 to 299 µg/L and transferrin saturation < 20%)

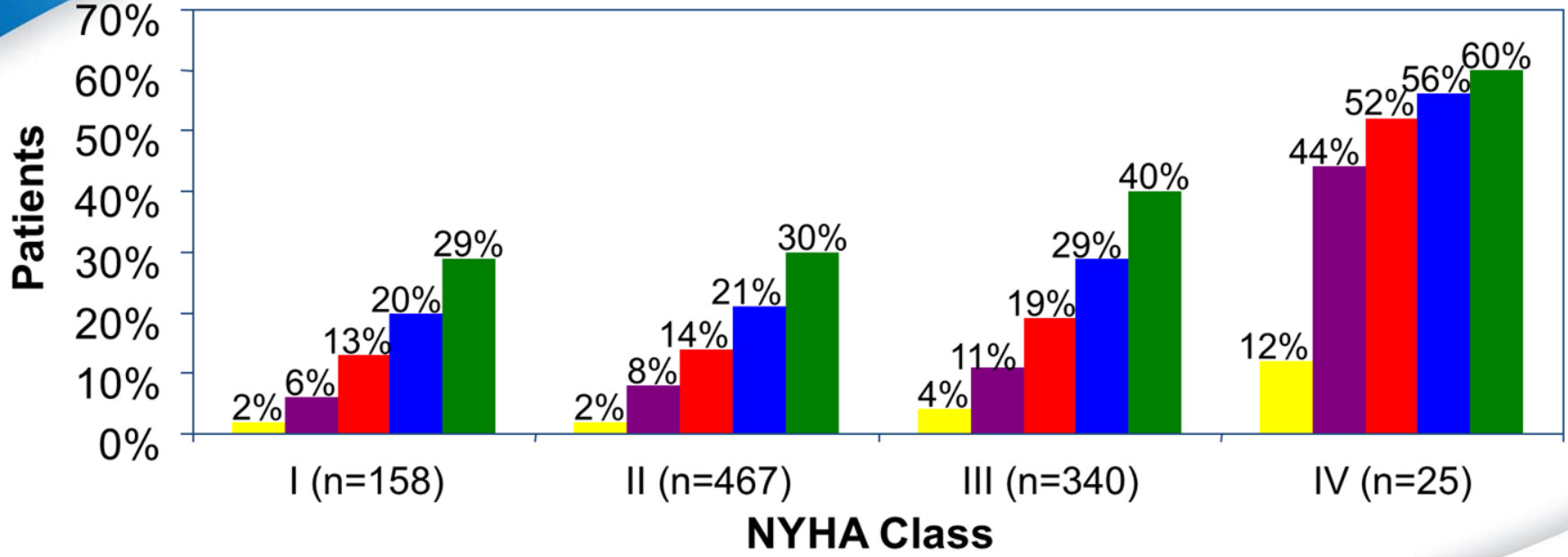
Ponikowski P, et al. *Eur Heart J.* 2016;37:2129-2200.

Iron deficiency in HF: Why does this matter?

- Reduced oxygen transportation to and utilization
  - Reduced exercise capacity
- Activation of the sympathetic nervous system
- Left ventricular hypertrophy and dilated cardiomyopathy
  - Diminished ejection fraction

Gstrein C, et al. *Swiss Med Wkly.* 2017;147:w14453.

The prevalence of anemia and the severity of heart failure



Source: STAMINA Registry – 45 General Cardiologist sites, n=673, 12 Academic sites (incl. HF Specialists), n=337

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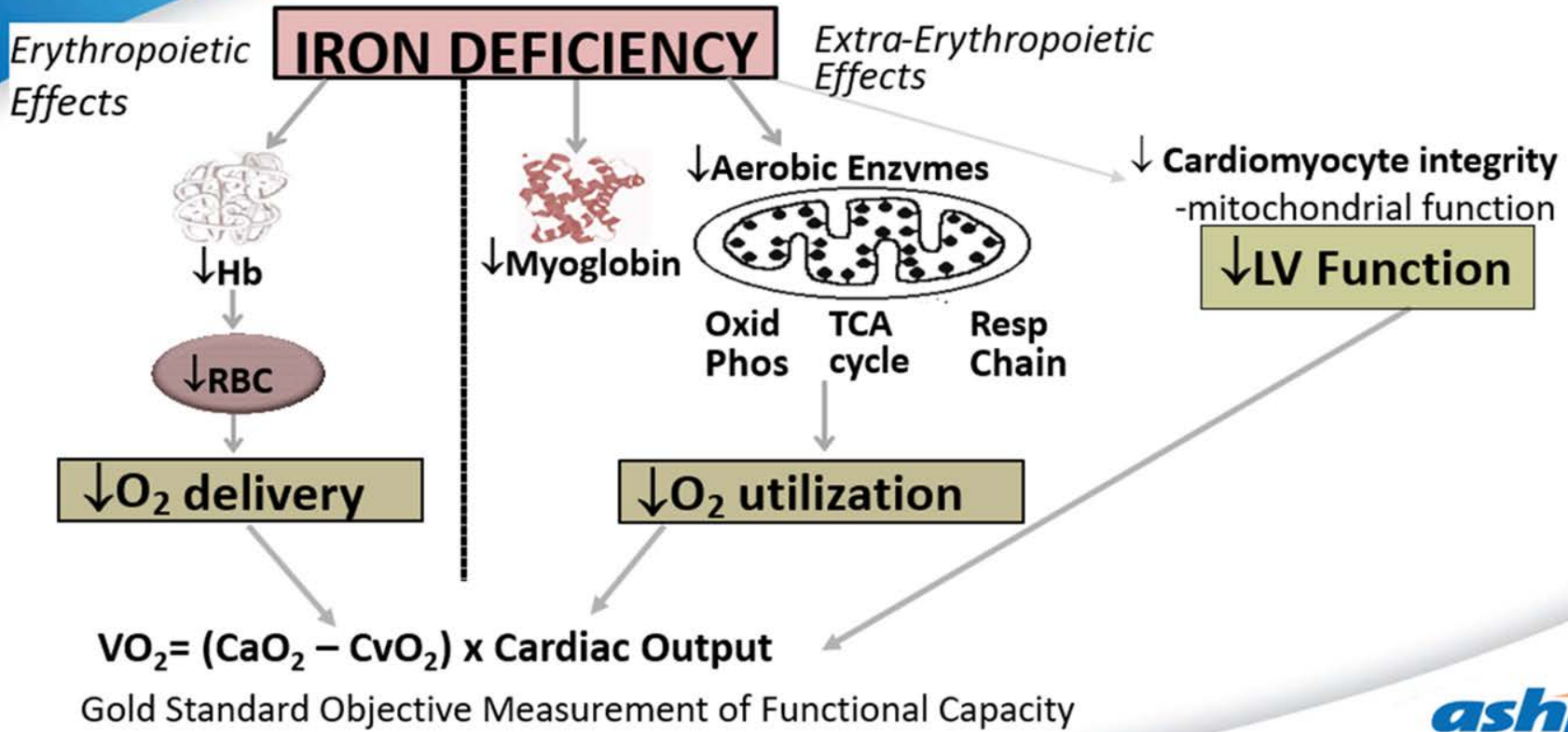
In patients with heart failure and anemia, elevated levels of which of the following could limit the patient's responsiveness to oral iron repletion?

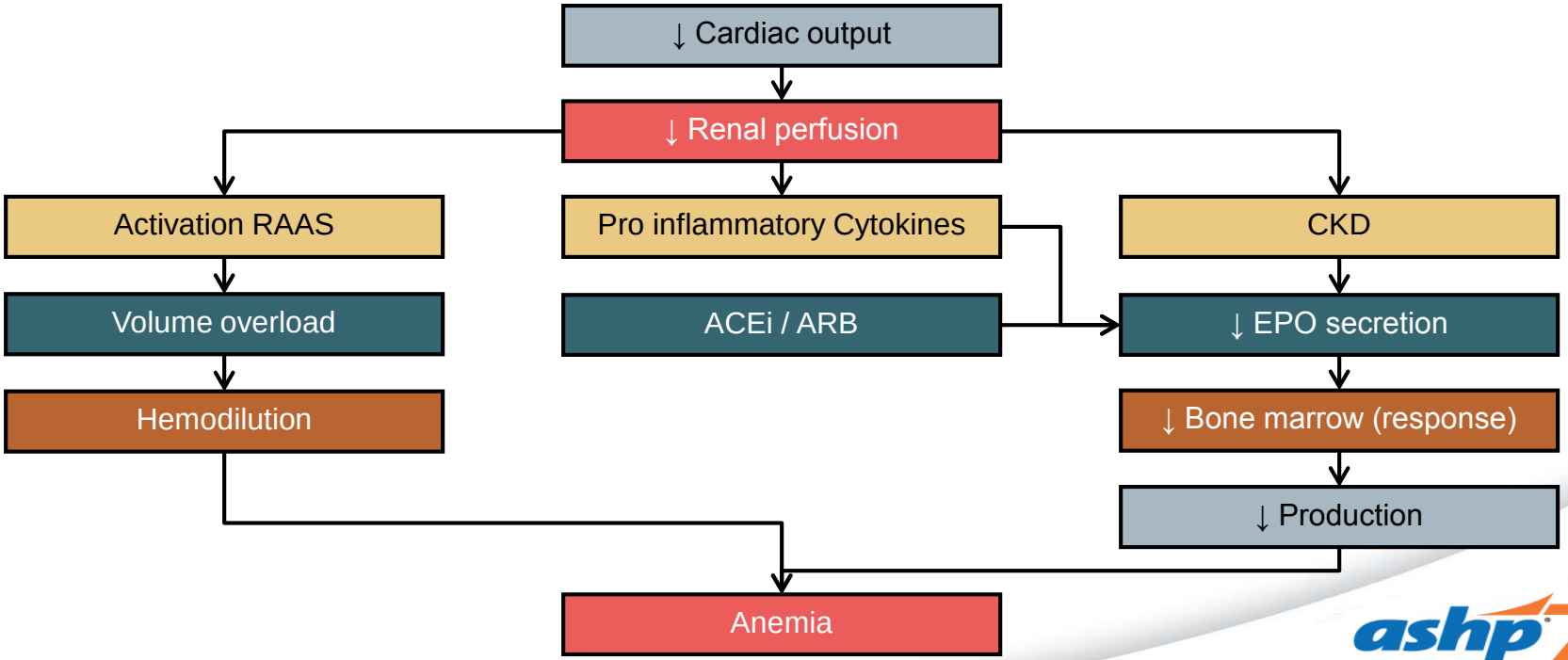
A. Ascorbic acid
B. Erythopeotin
C. Hepcidin
D. Homocysteine

Iron Deficiency Impacts Functional Capacity in Heart Failure



Anker S et al. EJHF 2009, Melanovsky et al. Circulation HF 2016

Mechanism of the development of anemia in HF



Anemia is associated with increased risk for hospitalization in heart failure patients

Study	Design	N	Anemia Risk Assessment	Limitations
Alexander[1]	Retrospective cohort study of a population based HF database	**90,316**	Anemia was an independent risk factor of 1-year re-hospitalization (RR 1.162; 95% CI: 1.134 to 1.191)	no confirmation of the HF diagnosis; undercounts of minorities and biased results.
Polanczyk[2]	Prospective, single center, observational study	**205**	Anemia was an independent predictor of 3-month re-hospitalization (p=0.002)	Too small of a population to resolve a small difference in readmission rates; role of confounding variables due to lack of control
OPTIME-CHF[3]	Retrospective chart review	**906**	Anemia was an independent predictor of 60-day death or rehospitalization (odds ratio of 0.89 per 1 g/dL increase in hemoglobin; 95% CI: 0.82 to 0.97)	Anemia may have been caused by hemodilution in hospitalized patients
Kosiborod[4]	Retrospective chart review	**2,281**	Patients had 2% higher risk of 1-year rehospitalization for every 1% lower hematocrit (95% CI: 1.01 to 1.03; p=0.0002)	Lack of data on transfusions or other treatments for anemia; study generalizability to non-study population
COPERNICUS[5]	Randomized, double blind, placebo controlled trial	**2,286**	Anemia was an independent risk factor for 1-year morbidity (HF hospitalization) and mortality outcomes	-

[1]Alexander M, et al. *Am Heart J.* 1999;137:919-927
[2]Polanczyk CA, et al. *J Card Failure.* 2001;7:289-298
[3]Felker GM, et al. *Am J Cardiol.* 2003;92:625-628
[4]Kosiborod M, et al. *Am J Med*. 2003;114:112-119
[5]Anker SD, et al. *J Am Coll Cardiol.* 2004;43(suppl A):Abstract 842-2

Iron Homeostasis in HF

Daily Recommended Iron intake:
8-18 mg = 0.25% of body stores

Heart Failure w/Iron Deficiency
Ferritin <100 ng/ml
Tsat < 20% w/Ferritin 100-300ng/ml
Hepcidin expected < 3 ng/ml

? Oral Iron

Iron Replete Status
Ferritin >100 ng/ml
Tsat >20%
↑ Hb

Gut edema
↓ Nutrient Intake

Duodenum
Iron Absorption
5-35%

↓Iron Absorption

Hepcidin

? ↑Hepcidin

Ferroportin 1

Reticulo Endothelial System

↑ Iron transport

IFN-γ

TNF α

↑ senescent RBC degradation

Total Body Iron: ~ 4,000 mg

Hemoglobin (2,500mg)

Ferritin Complexes (1000-1500mg)

Circulating Iron-bound to transferrin (3-5mg)

↑Iron loss (bleeding)

↓Iron Bioavailability

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Diagnosing iron deficiency in HF

	Absolute iron deficiency	Functional iron deficiency	Normal Values
Ferritin	< 100 µg/L	100 – 300 µg/L	40-300 µg/L (M) 20-200 µg/L (F)
Transferrin saturation	Typically ↓ (noncontributory)	< 20%	> 16% to < 45%

	Absolute iron deficiency	Functional iron deficiency
Possible causes	Diminished dietary intake Poor GI absorption	Inflammatory disorders Use of Erythropoietin stimulating agents
When does it occur?	Later stages of HF	Earlier stages of HF

Fitzsimons S, et al. *Eur Heart J.* 2015;1:58-64.
Gstrein C, et al. *Swiss Med Wkly.* 2017;147:w14453.
Camaschella C. *N Engl J Med.* 2015;372:1832-1843.

Clinical Trials

FERRIC-HF

- Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Non-anemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency

- To determine if iron replacement alone would improve exercise tolerance in anemic and non-anemic patients with iron deficiency and symptomatic heart failure

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

FERRIC-HF

- Study design
  - Prospective, randomized, open-label, observer-blinded, parallel, controlled trial
- Study population
  - 35 patients with symptomatic HF (NYHA Class II or III; EF ≤ 45%), exercise intolerance (pVO_2/kg ≤ 18 ml/kg/min), and iron deficiency (ferritin < 100 µg/L, or 100 to 300 µg/L and transferrin saturation < 20%) who were utilizing maximally tolerated dosages of HF medications for at least 4 weeks
    - Hb concentrations < 12.5 g/dl (anemic group) or 12.5 to 14.5 d/dl (non-anemic group)
- Treatment regimen
  - Iron sucrose via weekly IV infusion (therapeutic phase) until ferritin was ≥ 500 ng/ml and then weeks 4, 8, 12, 16 (maintenance phase) versus no treatment
- Primary endpoint
  - Change in absolute pVO_2 from baseline to week 18

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

FERRIC-HF: Results

Anemic Patients	No treatment	Iron Sucrose IV	Treatment effect (95% CI)	p Value
Absolute peak VO_2	-46 ± 116	158 ± 182	204 ml/min (31 to 378)	0.02
Peak VO_2/kg	-1.1 ± 0.9	2.8 ± 3.2	3.9 ml/kg/min (1.1 to 6.8)	0.009
Exercise duration	20 ± 114	63 ± 97	43 s (-66 to 153)	0.41
Transferrin saturation	2 ± 7	14 ± 9	12 % (3 to 22)	0.01
Ferritin	41 ± 79	299 ± 187	258 ng/ml (87 to 429)	0.006
Hemoglobin	0.6 ± 1.1	0.8 ± 1.5	0.2 g/dl (-1.3 to 1.7)	0.78
NYHA functional class	0.2 ± 0.4	-0.3 ± 0.5	-0.5 (-1.0 to 0)	0.048
Heart rate	9 ± 5	-4 ± 12	-13 beats/min (-24 to -2)	0.02

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

FERRIC-HF: Results

Non-anemic Patients	No treatment	Iron Sucrose IV	Treatment effect (95% CI)	p Value
Absolute peak VO_2	9 ± 132	-8 ± 54	-17 ml/min (-110 to 76)	0.71
Peak VO_2/kg	-0.3 ± 1.9	0.1 ± 0.8	0.4 ml/kg/min (-0.9 to 1.7)	0.53
Exercise duration	-55 ± 98	27 ± 66	83 s (-3 to 169)	0.06
Transferrin saturation	1 ± 8	10 ± 8	9 % (0 to 19)	0.046
Ferritin	62 ± 100	349 ± 197	287 ng/ml (87 to 487)	0.008
Hemoglobin	0.2 ± 0.8	0.2 ± 0.7	0 g/dl (-0.9 to 0.8)	0.96
NYHA functional class	0.2 ± 0.4	-0.4 ± 0.7	-0.6 (-1.3 to 0.1)	0.08
Heart rate	6 ± 9	6 ± 8	0 beats/min (-9 to 10)	0.97

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

FAIR-HF Trial

- **Ferric carboxymaltose Assessment in Patients with Iron Deficiency and Chronic Heart Failure**

- **Aim:** to determine whether treatment with intravenous iron (ferric carboxymaltose) would improve symptoms in patients who had heart failure, reduced left ventricular ejection fraction, and iron deficiency, either with or without anemia.

Anker SD et al. *N Engl J Med.* 2009;361:2436–2448.

FAIR-HF: Methods

- Study design
  - The FAIR-HF trial was a randomized, double-blind, multicenter study.
- Study population:
  - A total of 495 patients, who had chronic heart failure of NYHA class II or III, a LVEF of 40–45% or less, a hemoglobin level between 9.5 and 13.5 g/dL and iron deficiency.
- Treatment regimen:
  - Ferric carboxymaltose or saline was administered to the patients randomly as an intravenous bolus injection of 4 ml.
  - Dosing was done every week till repletion of iron was achieved, then:
  - Every 4 weeks as maintenance therapy after 8th or 12th week of initiation of therapy.
- Primary end point:
  - Self-reported Patient Global Assessment (PGA) form and NYHA functional class in the 24th week.
- Safety end points
  - Serious and non-serious adverse effects, hospitalization and death up to the 26th week of study.

Anker SD et al. *N Engl J Med.* 2009;361:2436–2448.

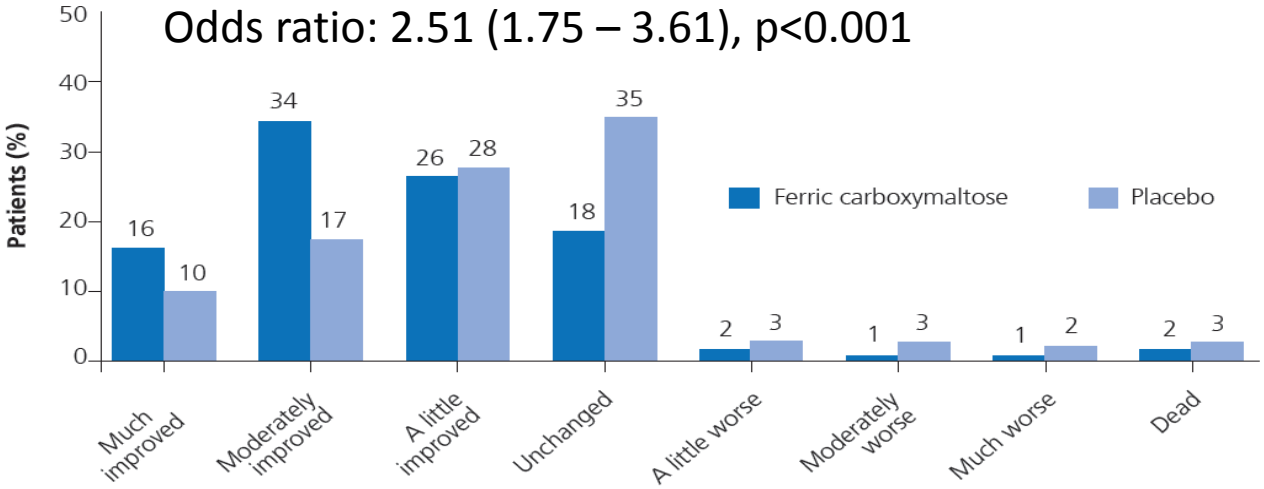
FAIR-HF: Levels of Iron Metabolism

Value	FCM	Placebo	p value
Ferritin (mcg/mL)	312	74	<0.001
Transferrin saturation (%)	29	19	<0.001
Hemoglobin (g/dL)	13	12.5	<0.001

FAIR-HF: Results

A: Self-reported Patient Global Assessment at Week 24

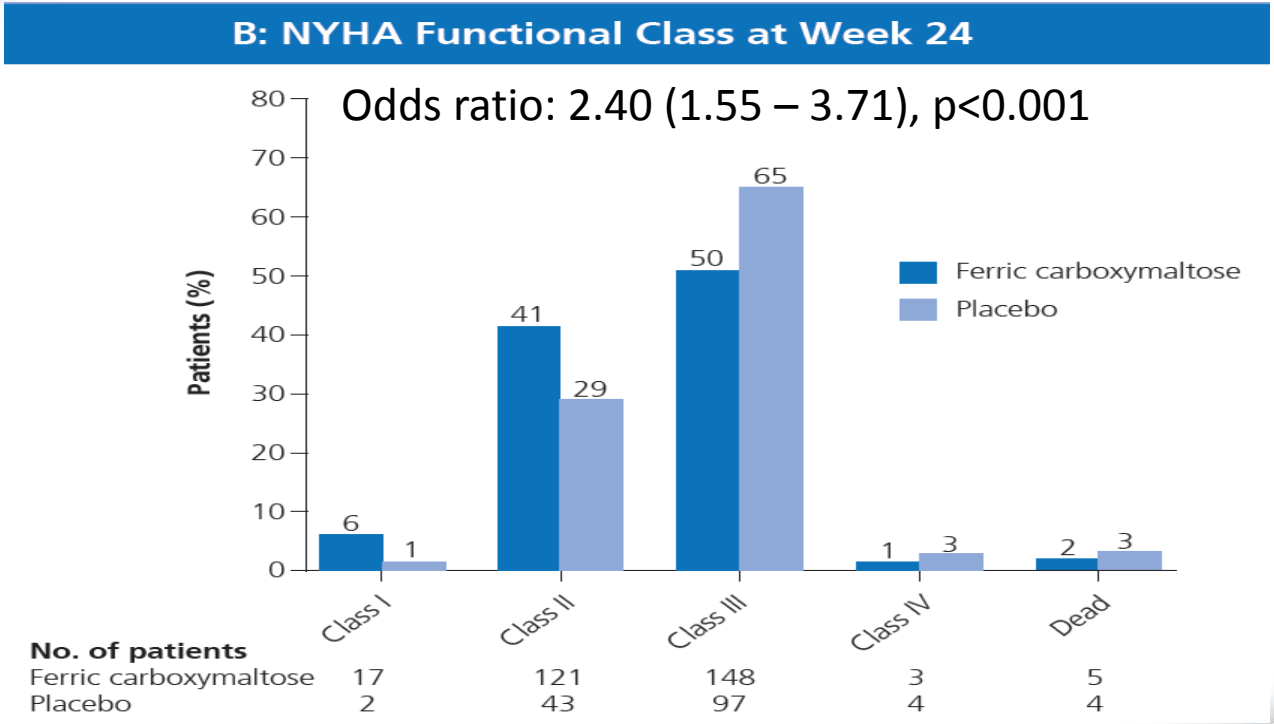
Odds ratio: 2.51 (1.75 – 3.61), p<0.001



No. of patients							
Ferric carboxymaltose	47	100	77	54	5	1	2	5
Placebo	15	26	41	52	4	4	3	2

Anker SD et al. *N Engl J Med.* 2009;361:2436–2448.

FAIR-HF: Results



Anker SD et al. *N Engl J Med.* 2009;361:2436–2448.

FAIR-HF: Safety Results

Endpoint	FCM (n=305)	Placebo (n=155)	p value
Death	3.4%	5.5%	0.47
Hospitalization for any cardiovascular causes	17.7%	24.8%	0.08
Hospitalization for worsening heart failure	4.1%	9.7%	0.11
Adverse event: Cardiac disorder	27.6%	50.2%	0.01

CONFIRM-HF

- Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency

- To assess the safety and efficacy of long-term intravenous iron therapy in iron-deficient patients with symptomatic heart failure

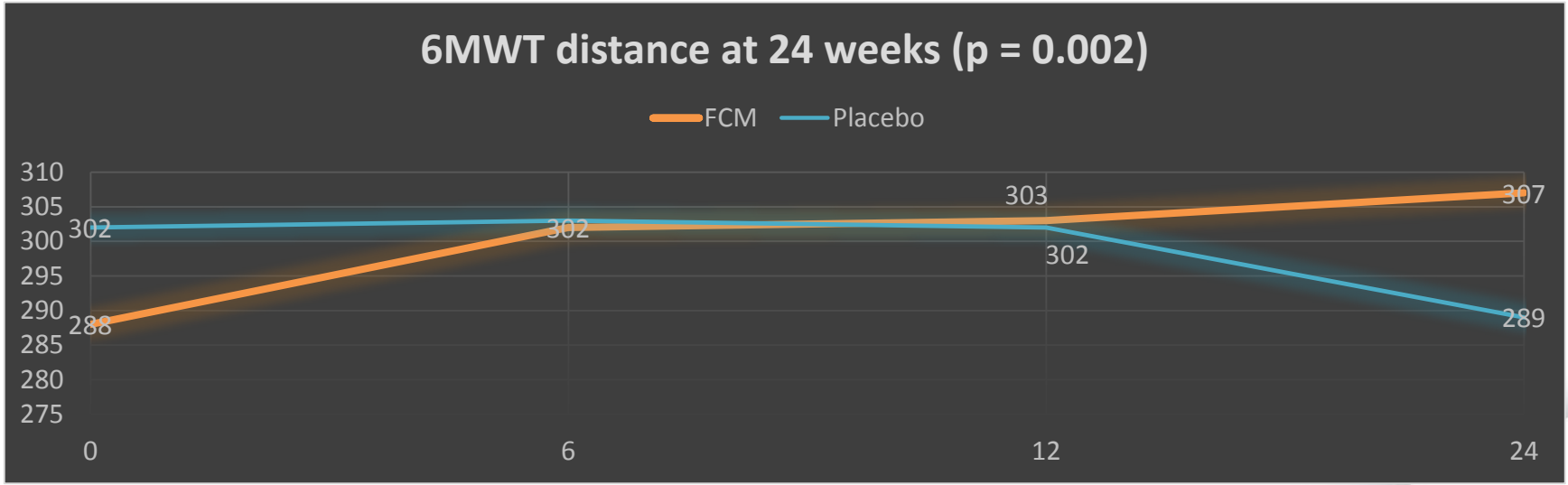
Ponikowski P, et al. *Eur Heart J.* 2015;36:657-668.

CONFIRM-HF

- Study design
  - Multicenter, double-blind, placebo-controlled trial
- Study population
  - 304 ambulatory symptomatic HF patients (NYHA Class II or III; EF ≤ 45%; elevated natriuretic peptides), with iron deficiency (ferritin < 100 ng/ml, or 100 to 300 ng/ml with a transferrin saturation < 20%) and a hemoglobin < 15 g/dL (excluding patients requiring transfusion)
    - Patients with uncontrolled hypertension, infection, malignancy, impaired liver or renal function, and who could not complete a 6 min walk test we're excluded
- Treatment regimen
  - Ferric carboxymaltose or saline was administered IV to patients on day 0 and week 6 based upon screening weight and hemoglobin (therapeutic phase) and then during weeks 12, 24, and 36 if ferritin < 100 ng/ml, or 100 to 300 ng/ml with a transferrin saturation < 20% (maintenance phase)
    - Dosages were 500 - 2000 mg of iron in the therapeutic phase and 500 mg of iron during maintenance
- Primary endpoint
  - Change in 6 min walk test (6MWT) distance from baseline to week 24

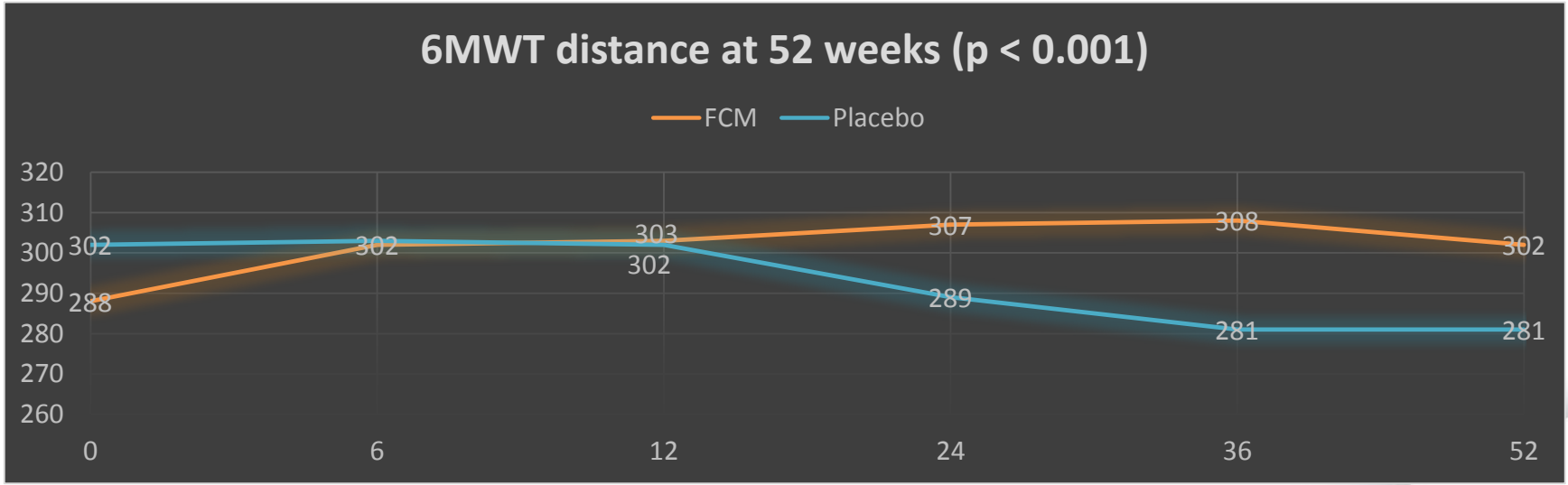
Ponikowski P, et al. *Eur Heart J.* 2015;36:657-668.

CONFIRM-HF: Results



Ponikowski P, et al. *Eur Heart J.* 2015;36:657-668.

CONFIRM-HF: Results



Ponikowski P, et al. *Eur Heart J.* 2015;36:657-668.

Oral Iron Repletion effects on Oxygen UpTake in Heart Failure (IRONOUT)

- Hypothesis: Oral iron polysaccharide is superior to oral placebo in improving exercise capacity (peak VO_2) in patients with HFrEF and iron deficiency at 16 weeks.

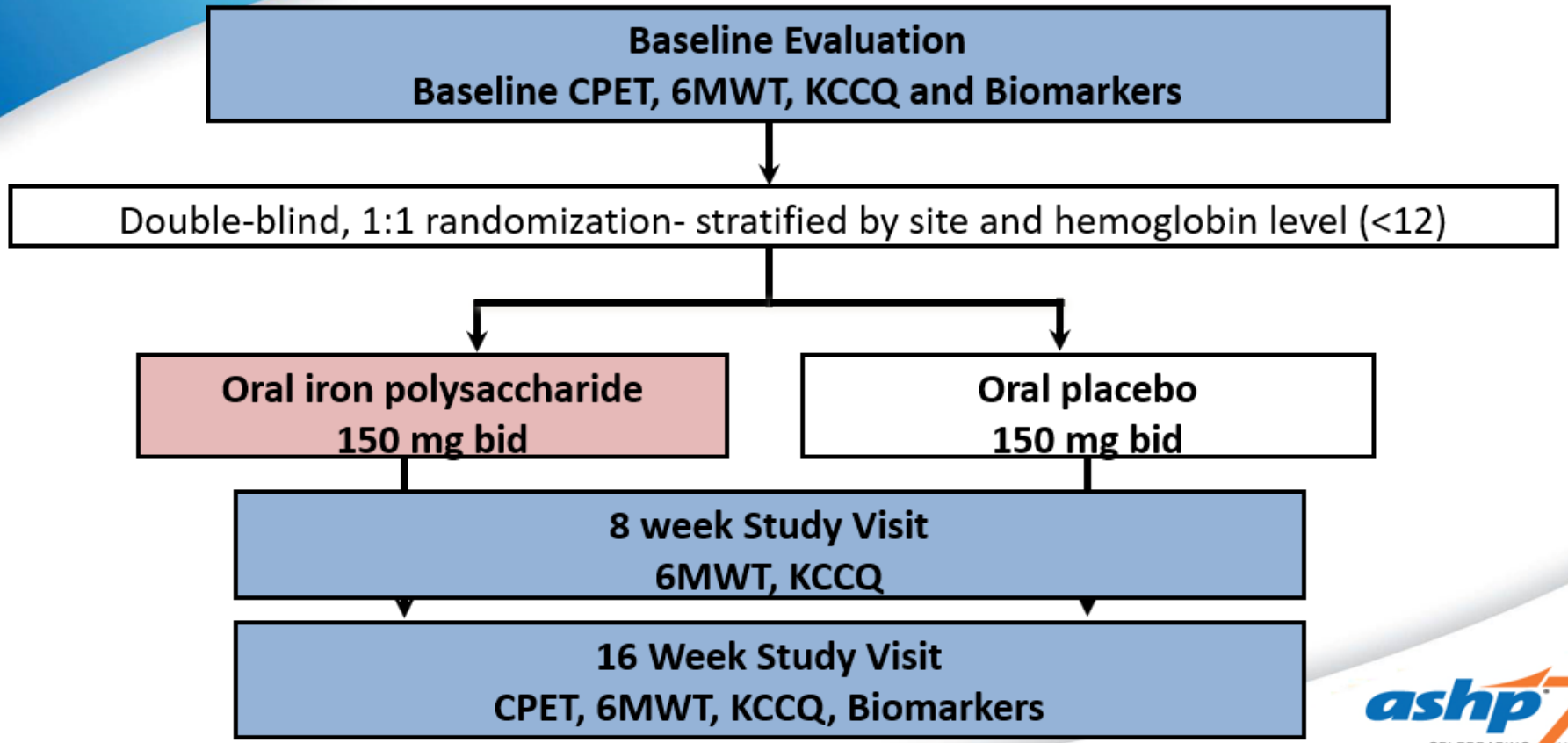
Lewis GD et al. JAMA 2017;317:1958-66.

IRONOUT: Study Population

- 225 patients with NYHA Class II-IV HF symptoms and LVEF≤0.40
- Serum ferritin between 15-100 ng/ml or serum ferritin between 100-299 ng/ml with transferrin saturation <20%
- Hemoglobin 9.0-13.5 g/dL in females, 9.0-15 g/dL in males
- Stable evidence-based medical therapy for HF
- Able to perform cycle/treadmill exercise testing with achievement of a respiratory exchange ratio of at least 1.0

Lewis GD et al. JAMA 2017;317:1958-66.

IRONOUT: Study Design



CPET: cardiopulmonary exercise testing, 6MWT: 6-minute walk test, KCCQ: Kansas City Cardiomyopathy Questionnaire

IRONOUT: Endpoints

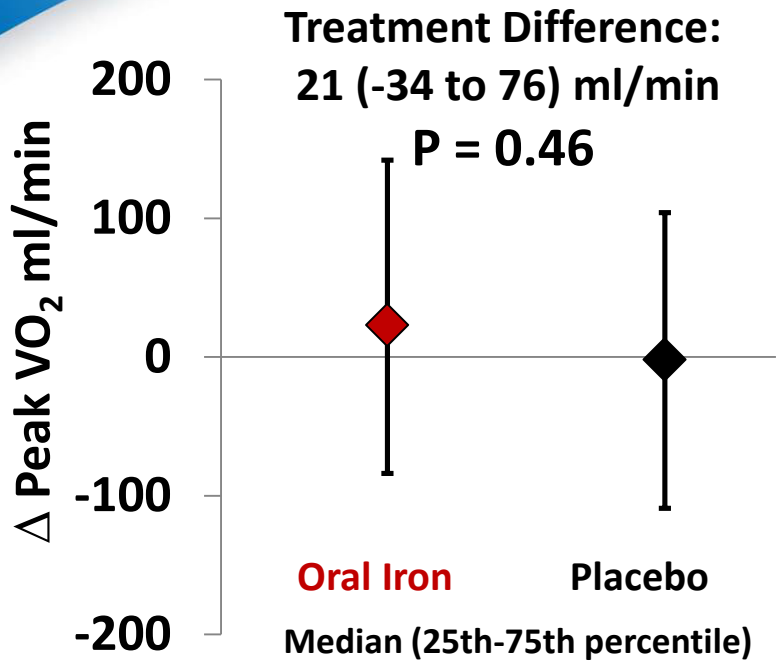
- **Primary Endpoint:** Δ peak VO_2 from baseline to week 16

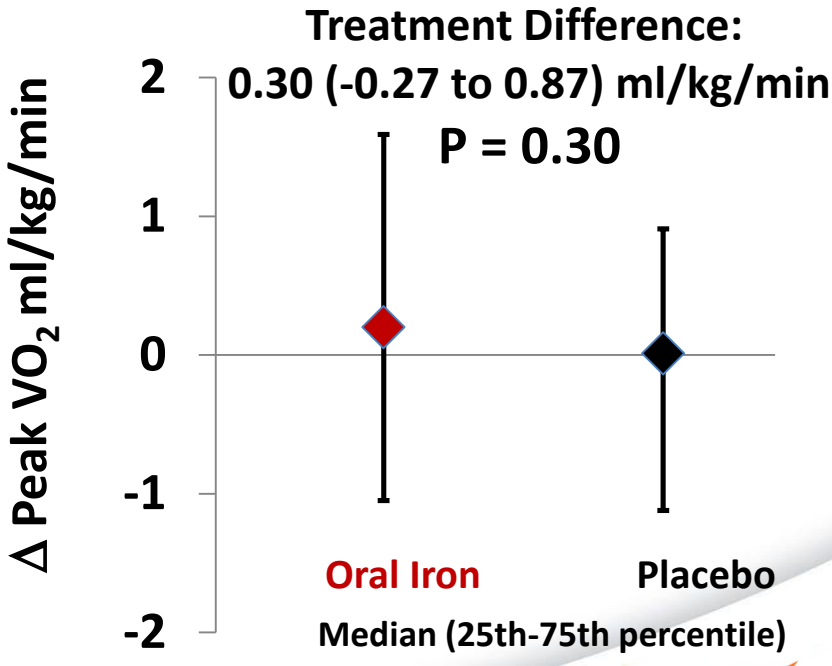
- **Secondary Endpoints:**
  - Δ 6MW distance, O_2 kinetics, ventilatory efficiency
  - Δ NT-proBNP and Δ KCCQ quality of life score

- **Exploratory Endpoints**
  - Differential impact of oral iron repletion based on
    - anemia status and venous congestion status
  - Δ iron studies, Δ renal function, Δ ventilatory threshold
  - Time to death or worsening HF

Lewis GD et al. JAMA 2017;317:1958-66.

Results: Primary Endpoint





Lewis GD et al. JAMA 2017;317:1958-66.

Results: Secondary and Exploratory Endpoints

Characteristic	Oral Iron N=111	Placebo N=114	p-Value
Secondary end points			
Δ 6 MW distance at 16 weeks, meters	19	32	0.19
Δ Mean response time, seconds	2.5	1	0.19
Δ Ventilatory efficiency (VE/VCO_2 slope)	-0.3	-0.3	0.35
Δ NT-BNP level, pg/ml	4	-37	0.48
Δ KCCQ score at 16 weeks	3.1	3.0	0.57
Exploratory Endpoints			
Δ Ventilatory threshold (ml/min)	22	-2	0.07
Δ Creatinine, mg/dL	0.03	0.00	0.65
Δ Cystatin C, mg/L	0.02	0.01	0.12

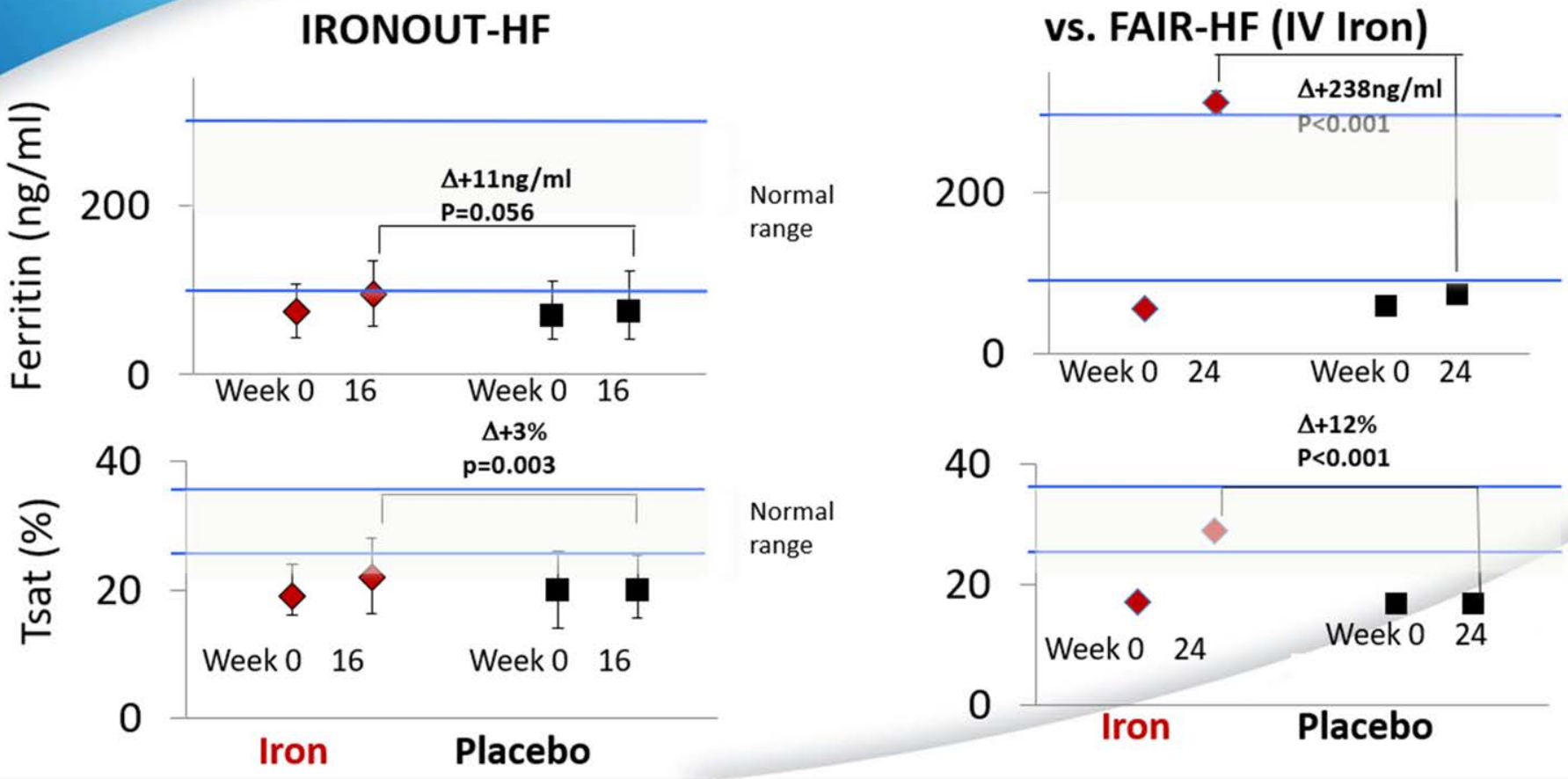
Lewis GD et al. JAMA 2017;317:1958-66.

Results: Safety Endpoints

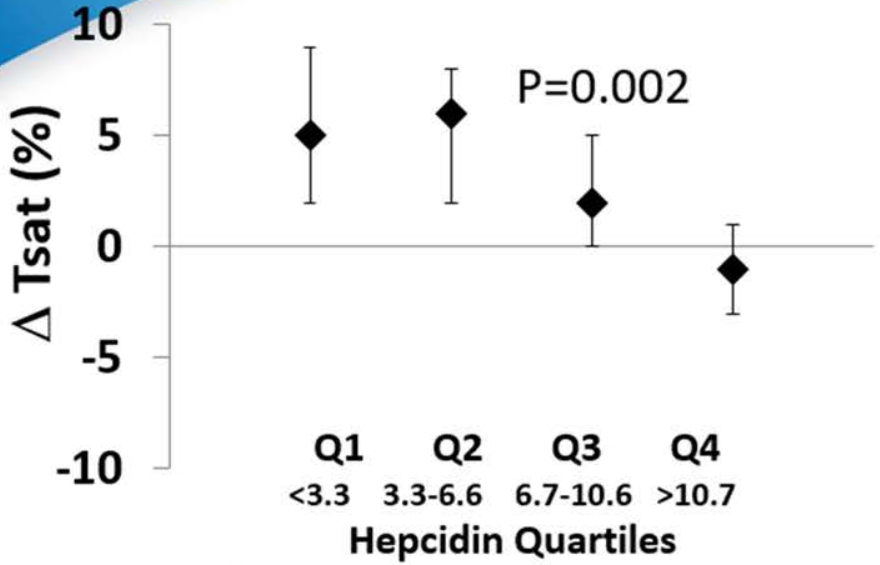
Characteristic	Oral Iron N=111	Placebo N=114	p-Value
Safety end points, No. (%)			
Adverse events	39 (35%)	45 (39%)	0.50
Serious adverse events	11 (10%)	10 (9%)	0.77
Permanent study drug discontinuation	15 (14%)	17 (15%)	0.76
Death or cardiovascular re-hospitalization	14 (13%)	12 (11%)	0.63

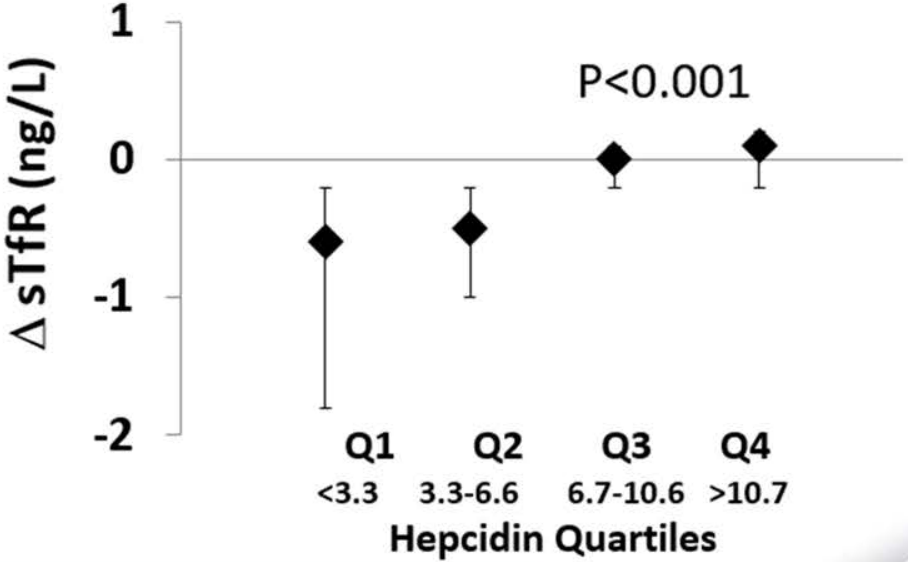
Lewis GD et al. JAMA 2017;317:1958-66.

Change in Iron Studies: FAIR-HR vs. IRONOUT



Results: Hepcidin Levels Predict Responsiveness to Oral Iron





Higher baseline hepcidin levels were related to:

↓ Δ iron bioavailability: Δ Tsat r=0.29, p=0.003

↓ Δ cellular iron levels: Δ sTr r=0.49, p<0.001

↓ Δ iron stores: Δ Ferritin r=0.30, p=0.003

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Summary and Conclusions

- High dose oral iron minimally repleted iron stores and did not improve peak VO_2 in patients with iron deficiency and HFrEF.
- Elevated hepcidin levels predicted refractoriness to oral iron repletion.
- These results do not support use of oral iron supplementation in patients with HFrEF.

Lewis GD et al. JAMA 2017;317:1958-66.

RED-HF Trial

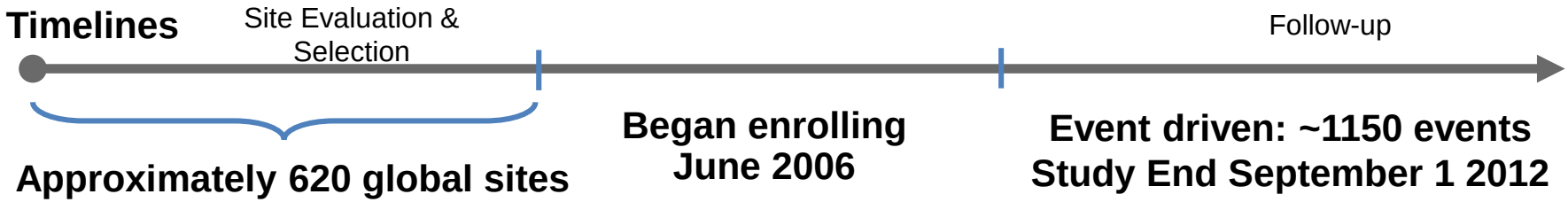
Study Population

- Hemoglobin 9 to 12 g/dL
- LVEF ≤ 35%
- NYHA Class II to IV

1:1 randomization

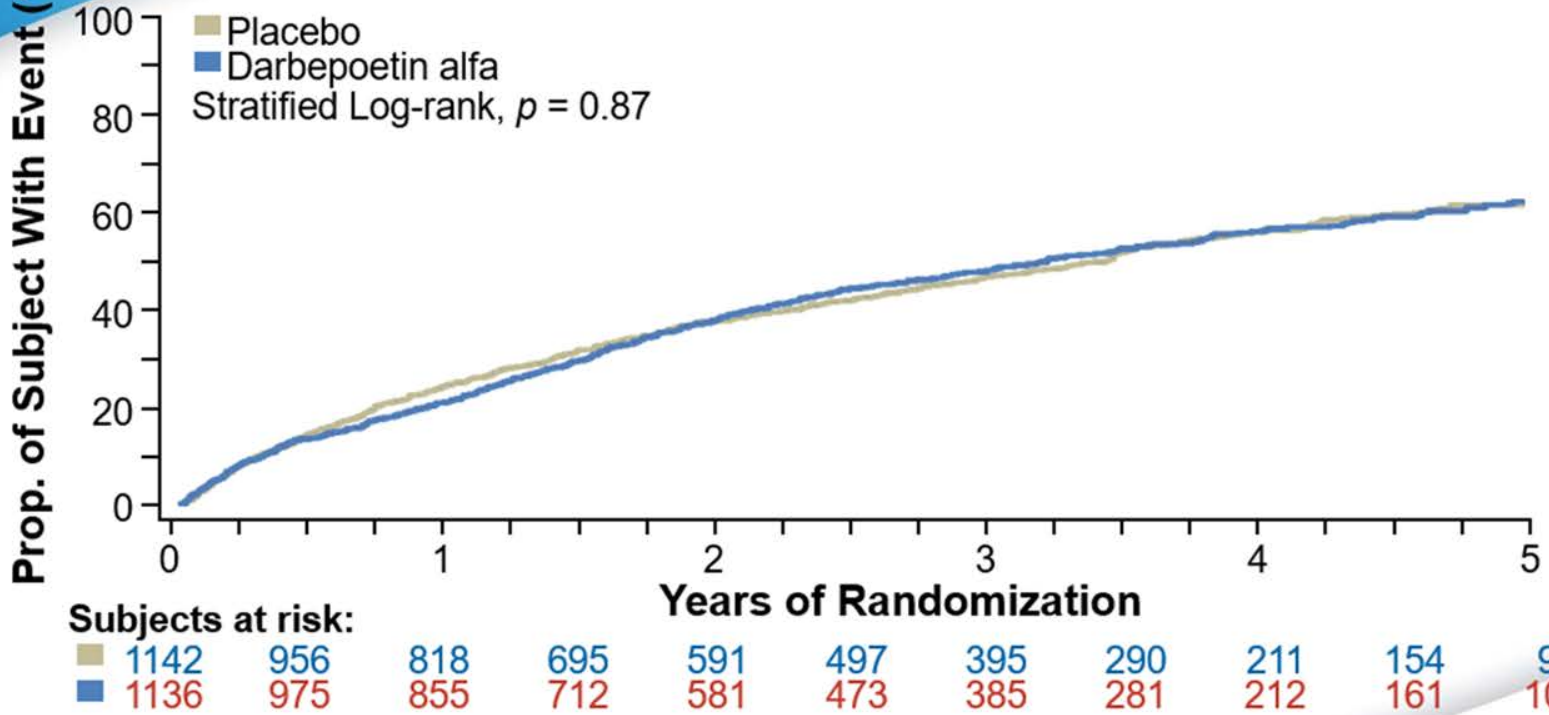
Darbepoetin alfa group (target hemoglobin 13.0 to 14.5 g/dL)
N = 1200

Placebo group
N = 1200



Swedberg K, et al. *N Engl J Med.* 2013;368:1210–1219.

Primary outcome: All cause death or first hospitalization for worsening heart failure



Swedberg K, et al. *N Engl J Med.* 2013;368:1210–1219.

Selected adverse events of interest

n (%)	Darbepoetin alfa (N = 1133)	Placebo (N = 1140)	Risk difference (95% CI)	p-value
Ischemic cerebrovascular conditions	51 (4.5)	32 (2.8)	1.7 (0.2, 3.2)	0.031
Embolic and thrombotic events	153 (13.5)	114 (10.0)	3.5 (0.9, 6.1)	0.009
Hypertension	81 (7.1)	69 (6.1)	1.1 (-0.9, 3.1)	0.292
Malignancies	69 (6.1)	68 (6.0)	0.1 (-1.8, 2.1)	0.900
Hypersensitivity reactions	99 (8.7)	96 (8.4)	0.3 (-2.0, 2.6)	0.787

Swedberg K, et al. *N Engl J Med.* 2013;368:1210–1219.

EFFECT-HF

- Effect of Ferric Carboxymaltose on Exercise Capacity in Patients with Chronic Heart Failure and Iron Deficiency

- To examine the effects of treatment with IV ferric carboxymaltose versus standard care on exercise capacity in patients with symptomatic heart failure and iron deficiency

van Veldhuisen DJ, et al. *Circulation.* 2017 Jul 12. [Epub ahead of print]

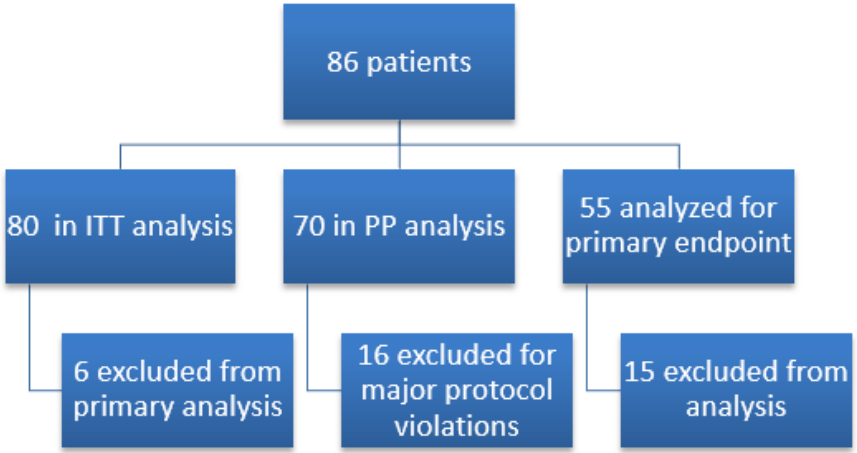
EFFECT-HF

- Study design
  - Prospective, multi-center, randomized, controlled, open-label trial with blinded end-point evaluation
- Study population
  - 172 patients with symptomatic HF (NYHA Class II or III; EF ≤ 45%; elevated natriuretic peptides), exercise intolerance (pVO_2/kg 10-20 ml/kg/min), and iron deficiency (ferritin < 100 ng/ml, or 100 to 300 µg/L and transferrin saturation < 20%) who were utilizing optimal HF medications for at least 4 weeks
- Treatment regimen
  - Ferric carboxymaltose (FCM) was administered IV to patients on day 0 and week 6 based upon screening weight and hemoglobin and then 500 mg FCM was given during week 12 only if ferritin < 100 ng/ml, or 100 to 300 ng/ml with a transferrin saturation < 20%
- Primary endpoint
  - Change in peak VO_2 from baseline to week 24

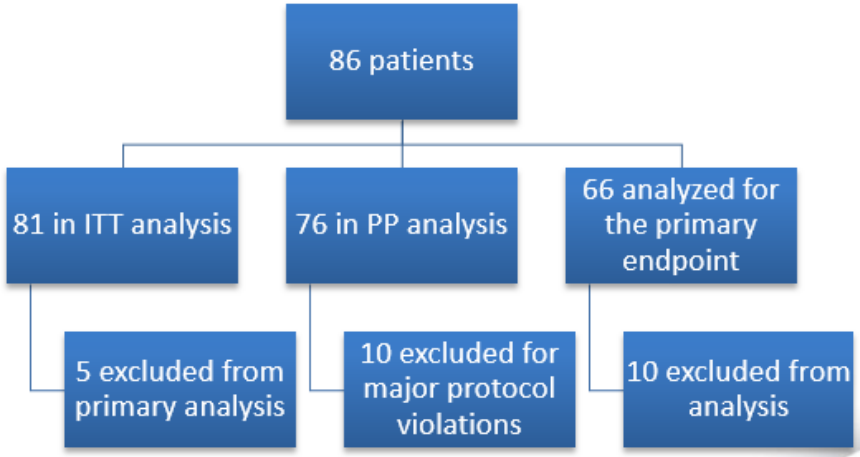
van Veldhuisen DJ, et al. *Circulation.* 2017 Jul 12. [Epub ahead of print]

EFFECT-HF: Analysis

Ferric Carboxymaltose



Control



ITT = Intention to treat analysis; PP = Per protocol analysis

van Veldhuisen DJ, et al. *Circulation.* 2017 Jul 12. [Epub ahead of print]

EFFECT-HF: Results

ITT: Peak VO_2 of 0 imputed for deaths LOCF imputation if no week 24 assessment	FCM (n=80)	Control (n=81)	p value
Peak VO_2 ml/min/kg (24 weeks)	-0.63	-1.19	0.020

PP: Peak VO_2 of 0 imputed for deaths LOCF imputation if no week 24 assessment	FCM (n=70)	Control (n=76)	p value
Peak VO_2 ml/min/kg (24 weeks)	+0.25	-1.10	0.011

van Veldhuisen DJ, et al. *Circulation.* 2017 Jul 12. [Epub ahead of print]

EFFECT-HF: Results

No imputation	FCM (n=55)	Control (n=66)	p value
Peak VO_2 ml/min/kg (24 weeks)	-0.16	-0.63	0.23

van Veldhuisen DJ, et al. *Circulation.* 2017 Jul 12. [Epub ahead of print]

Ongoing Clinical Trials

- **FAIR-HF2** (estimated completion 2020)
  - Evaluate the long-term effects IV ferric carboxymaltose versus placebo in symptomatic HFrEF patients with iron deficiency on a ***combined endpoint of recurrent HF hospitalizations and CV death over 12 months***

- **FAIR-HFpEF** (estimated completion 2018)
  - Examine the effects of IV ferric carboxymaltose versus placebo on exercise tolerance, symptoms, and quality of life in patients with HFpEF and iron deficiency with and without anemia.

- **AFFIRM-AHF** (estimated completion 2019)
  - Determine the effects IV ferric carboxymaltose versus placebo on ***hospitalizations and death*** in iron deficient patients admitted for a heart failure exacerbation

Intravenous Iron in Patients With Systolic Heart Failure and Iron Deficiency to Improve Morbidity & Mortality (FAIR-HF2). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03036462. Accessed September 2, 2017.
Effect of IV Iron in Patients With Heart Failure With Preserved Ejection Fraction (FAIR-HFpEF). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03074591. Accessed September 2, 2017.
Study to Compare Ferric Carboxymaltose With Placebo in Patients With Acute Heart Failure and Iron Deficiency (Affirm-AHF). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02937454. Accessed September 2, 2017.

What is the rationale for anemia correction?

Potential benefits and risks of treating anemia in HF:

Potential Benefits

- Improved oxygen delivery
- Improved exercise tolerance
- Attenuate adverse remodeling
- Improved Quality of Life
- Antiapoptotic?
- Decrease in hosp./death?

Potential Risks

- Increased thrombosis
- Platelet activation
- Hypertension
- Endothelial activation

Adapted from Felker and O' Connor *J Am Coll Cardiol*. 2004;44:959-966.

Think-Pair-Share: Case

- 79-year-old man with a chief complaint of shortness of breath

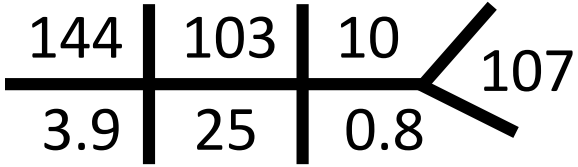
- JK has known HFrEF and notes increased dyspnea with exertion over the past 5 days. He complains that his weight is increased slightly to 240 pounds. Notes that he sleeps on a recliner at 45 degrees, however does not report orthopnea or PND. No SOB at rest. Patient denies any recent chest pain, palpitations. He reports that he was started on Lasix by his primary care physician, which was subsequently increased to 20mg daily, and then to 20 mg BID yesterday with some mild improvement in symptoms. Nonetheless, his leg swelling worsened and he developed DOE to the point where he required ED evaluation. Patient denies dietary indiscretion, saying he eats a low-salt diet. He states that he has continued to take his diuretics.

Patient Case: JK

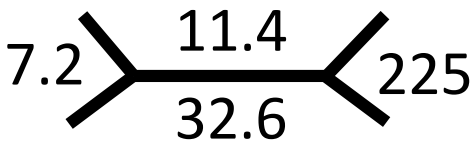
- In the ED initial vitals were: T 97.3, HR 139/67, BP 139/67, RR 18, SO2 98% RA
- Exam notable for: JVP 11cm, bibasilar crackles, Bilateral non-pitting edema
  - Weight: 109kg (dry weight: 98kg), height: 70 inches
- Labs notable for: NT-pro-BNP: 1197,
- Patient was given: 40mg IV Lasix x 1 dose; admitted for further care

Patient Case: JK

- Laboratory values the following morning:



Ca: 9.2	Iron: 23
PO4: 3.5	TIBC: 200
Mg: 2.1	Ferritin: 80
TSH: 2.7	TSAT: 15%



Please design a pharmacotherapy plan to manage iron deficiency for JK.

IV Iron Repletion Regimens

Trial	N	Follow-up	Regimen Studied
FERRIC - HF	35	18 weeks	Iron sucrose 200 mg IV weekly for 16 weeks (or until ferritin 500 ng/mL)
FAIR - HF	495	24 weeks	Ferric carboxymaltose 200 mg IV weekly until iron replaced then 200 mg 4 weekly
CONFIRM - HF	304	52 weeks	Ferric carboxymaltose 500 - 2000 mg IV at day 0 and week 6 then 500 mg at weeks 12, 24, 36 if iron deficient
EFFECT - HF	172	24 weeks	Ferric carboxymaltose 500-1000 mg IV on day 0 and week 6 based upon screening weight and hemoglobin and then 500 mg during week 12 if iron deficient

Okonko DO, et al. *J Am Coll Cardiol.* 2008;51:103-112.
Anker SD et al. *N Engl J Med.* 2009;361:2436–2448.
Ponikowski P, et al. *Eur Heart J.* 2015;36:657-668.
van Veldhuisen DJ, et al. *Circulation.* 2017 Jul 12. [Epub ahead of print]

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After Discussion

Key Takeaways

- Key Takeaway #1
  - Oral iron supplementation no longer appears to be a viable option in the treatment of iron deficiency in heart failure patients
- Key Takeaway #2
  - Erythropoietin stimulating agents should be avoided in heart failure patients due to lack of efficacy and risk of adverse effects
- Key Takeaway #3
  - IV iron repletion should be considered for use in symptomatic heart failure patients with iron deficiency incorporating a regimen established in clinic trials

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IRONING OUT THE MANAGEMENT OF ANEMIA IN HEART FAILURE