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

<table>
<thead>
<tr>
<th>CLASS (STRENGTH) OF RECOMMENDATION</th>
<th>LEVEL (QUALITY) OF EVIDENCE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong> Benefit &gt;&gt; Risk</td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td></td>
</tr>
<tr>
<td>- is recommended</td>
<td></td>
</tr>
<tr>
<td>- is indicated/useful/effective/beneficial</td>
<td></td>
</tr>
<tr>
<td>- Should be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td>Comparative-Effectiveness Phrases †:</td>
<td></td>
</tr>
<tr>
<td>- Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
</tr>
<tr>
<td>- Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL B-R</strong> (Randomized)</td>
<td></td>
</tr>
<tr>
<td>- Moderate-quality evidence‡ from 1 or more RCTs</td>
<td></td>
</tr>
<tr>
<td>- Meta-analyses of moderate-quality RCTs</td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL B-NR</strong> (Nonrandomized)</td>
<td></td>
</tr>
<tr>
<td>- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
<td></td>
</tr>
<tr>
<td>- Meta-analyses of such studies</td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL C-LD</strong> (Limited Data)</td>
<td></td>
</tr>
<tr>
<td>- Limited or nonrandomized observational or registry studies with limitations of design or execution</td>
<td></td>
</tr>
<tr>
<td>- Meta-analyses of such studies</td>
<td></td>
</tr>
<tr>
<td><strong>LEVEL C-EO</strong> (Expert Opinion)</td>
<td></td>
</tr>
<tr>
<td>Consensus of expert opinion based on clinical experience</td>
<td></td>
</tr>
</tbody>
</table>

**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

**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)
- Limited or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies

**LEVEL C-EO** (Expert Opinion)
- Consensus of expert opinion based on clinical experience

**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

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

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 vs. test should include 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.

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%)

Anemia Recommendations in HF Patients

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

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%)

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

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
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. Erythropoetin  
C. Hepcidin  
D. Homocysteine
Iron Deficiency Impacts Functional Capacity in Heart Failure

Iron Deficiency

Erythropoietic Effects
- ↓Hb
- ↓RBC
- ↓O₂ delivery

Extra-Erythropoietic Effects
- ↓Myoglobin
- ↓Aerobic Enzymes
- ↓Cardiomyocyte integrity
- ↓O₂ utilization
- ↓LV Function

\[ VO_2 = (CaO_2 - CvO_2) \times \text{Cardiac Output} \]

Gold Standard Objective Measurement of Functional Capacity

Mechanism of the development of anemia in HF

- ↓ Cardiac output
- ↓ Renal perfusion
- Activation RAAS
- Volume overload
- Hemodilution
- Pro inflammatory Cytokines
- ACEi / ARB
- CKD
- ↓ EPO secretion
- ↓ Bone marrow (response)
- ↓ Production
- Anemia
- ↓ EPO secretion
- ↓ Bone marrow (response)
- ↓ Production
- Anemia
### Anemia is associated with increased risk for hospitalization in heart failure patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Anemia Risk Assessment</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander¹</td>
<td>Retrospective cohort study of a population based HF database</td>
<td>90,316</td>
<td>Anemia was an independent risk factor of 1-year re-hospitalization (RR 1.162; 95% CI: 1.134 to 1.191)</td>
<td>no confirmation of the HF diagnosis; undercounts of minorities and biased results.</td>
</tr>
<tr>
<td>Polanczyk²</td>
<td>Prospective, single center, observational study</td>
<td>205</td>
<td>Anemia was an independent predictor of 3-month re-hospitalization (p=0.002)</td>
<td>Too small of a population to resolve a small difference in readmission rates; role of confounding variables due to lack of control</td>
</tr>
<tr>
<td>OPTIME-CHF³</td>
<td>Retrospective chart review</td>
<td>906</td>
<td>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)</td>
<td>Anemia may have been caused by hemodilution in hospitalized patients</td>
</tr>
<tr>
<td>Kosiborod⁴</td>
<td>Retrospective chart review</td>
<td>2,281</td>
<td>Patients had 2% higher risk of 1-year rehospitalization for every 1% lower hematocrit (95% CI: 1.01 to 1.03; p=0.0002)</td>
<td>Lack of data on transfusions or other treatments for anemia; study generalizability to non-study population</td>
</tr>
<tr>
<td>COPERNICUS⁵</td>
<td>Randomized, double blind, placebo controlled trial</td>
<td>2,286</td>
<td>Anemia was an independent risk factor for 1-year morbidity (HF hospitalization) and mortality outcomes</td>
<td>-</td>
</tr>
</tbody>
</table>

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

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

Total Body Iron: ∼ 4,000 mg
Hemoglobin (2,500mg)
Circulating Iron-bound to transferrin (3-5mg)
Ferritin Complexes (1000-1500mg)

↑ Iron loss (bleeding)
↓ Iron Bioavailability

Gut edema Nutrient Intake
↓ Iron Absorption

? Oral Iron

? Hepcidin

Iron Absorption

Duodenum
Iron Absorption
5-35%

Hepcidin

Reticulo Endothelial System

↑ Iron transport
↑ senescent RBC degradation

IFN-γ
TNF α

Ferroportin 1

↓ Iron Bioavailability
## Diagnosing iron deficiency in HF

<table>
<thead>
<tr>
<th></th>
<th>Absolute iron deficiency</th>
<th>Functional iron deficiency</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>&lt; 100 µg/L</td>
<td>100 – 300 µg/L</td>
<td>40-300 µg/L (M) 20-200 µg/L (F)</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Typically ↓ (noncontributory)</td>
<td>&lt; 20%</td>
<td>&gt; 16% to &lt; 45%</td>
</tr>
</tbody>
</table>

- **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

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

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

# FERRIC-HF: Results

<table>
<thead>
<tr>
<th>Anemic Patients</th>
<th>No treatment</th>
<th>Iron Sucrose IV</th>
<th>Treatment effect (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute peak VO$_2$</td>
<td>-46 ± 116</td>
<td>158 ± 182</td>
<td>204 ml/min (31 to 378)</td>
<td>0.02</td>
</tr>
<tr>
<td>Peak VO$_2$/kg</td>
<td>-1.1 ± 0.9</td>
<td>2.8 ± 3.2</td>
<td>3.9 ml/kg/min (1.1 to 6.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>20 ± 114</td>
<td>63 ± 97</td>
<td>43 s (-66 to 153)</td>
<td>0.41</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>2 ± 7</td>
<td>14 ± 9</td>
<td>12 % (3 to 22)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ferritin</td>
<td>41 ± 79</td>
<td>299 ± 187</td>
<td>258 ng/ml (87 to 429)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.6 ± 1.1</td>
<td>0.8 ± 1.5</td>
<td>0.2 g/dl (-1.3 to 1.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>0.2 ± 0.4</td>
<td>-0.3 ± 0.5</td>
<td>-0.5 (-1.0 to 0)</td>
<td>0.048</td>
</tr>
<tr>
<td>Heart rate</td>
<td>9 ± 5</td>
<td>-4 ± 12</td>
<td>-13 beats/min (-24 to -2)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

## FERRIC-HF: Results

<table>
<thead>
<tr>
<th>Non-anemic Patients</th>
<th>No treatment</th>
<th>Iron Sucrose IV</th>
<th>Treatment effect (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute peak VO$_2$</td>
<td>9 ± 132</td>
<td>-8 ± 54</td>
<td>-17 ml/min (-110 to 76)</td>
<td>0.71</td>
</tr>
<tr>
<td>Peak VO$_2$/kg</td>
<td>-0.3 ± 1.9</td>
<td>0.1 ± 0.8</td>
<td>0.4 ml/kg/min (-0.9 to 1.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Exercise duration</td>
<td>-55 ± 98</td>
<td>27 ± 66</td>
<td>83 s (-3 to 169)</td>
<td>0.06</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>1 ± 8</td>
<td>10 ± 8</td>
<td>9 % (0 to 19)</td>
<td>0.046</td>
</tr>
<tr>
<td>Ferritin</td>
<td>62 ± 100</td>
<td>349 ± 197</td>
<td>287 ng/ml (87 to 487)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.2 ± 0.8</td>
<td>0.2 ± 0.7</td>
<td>0 g/dl (-0.9 to 0.8)</td>
<td>0.96</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>0.2 ± 0.4</td>
<td>-0.4 ± 0.7</td>
<td>-0.6 (-1.3 to 0.1)</td>
<td>0.08</td>
</tr>
<tr>
<td>Heart rate</td>
<td>6 ± 9</td>
<td>6 ± 8</td>
<td>0 beats/min (-9 to 10)</td>
<td>0.97</td>
</tr>
</tbody>
</table>
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.

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.

<table>
<thead>
<tr>
<th>Value</th>
<th>FCM</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin (mcg/mL)</td>
<td>312</td>
<td>74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transferrin saturation (%)</td>
<td>29</td>
<td>19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13</td>
<td>12.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
FAIR-HF: Results

A: Self-reported Patient Global Assessment at Week 24

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

FAIR-HF: Results

### FAIR-HF: Safety Results

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

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 were 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

CONFIRM-HF: Results

6MWT distance at 24 weeks (p = 0.002)

CONFIRM-HF: Results

6MWT distance at 52 weeks (p < 0.001)

FCM  Placebo

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 VO₂) in patients with HFrEF and iron deficiency at 16 weeks.

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

Double-blind, 1:1 randomization- stratified by site and hemoglobin level (<12)

Baseline Evaluation
Baseline CPET, 6MWT, KCCQ and Biomarkers

Double-blind, 1:1 randomization- stratified by site and hemoglobin level (<12)

Oral iron polysaccharide
150 mg bid

Oral placebo
150 mg bid

8 week Study Visit
6MWT, KCCQ

16 Week Study Visit
CPET, 6MWT, KCCQ, Biomarkers

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

• **Primary Endpoint:** $\Delta$ peak VO$_2$ from baseline to week 16

• **Secondary Endpoints:**
  • $\Delta$ 6MW distance, O$_2$ kinetics, ventilatory efficiency
  • $\Delta$ NT-proBNP and $\Delta$ KCCQ quality of life score

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

Results: Primary Endpoint

Treatment Difference:
Oral Iron Placebo

21 (-34 to 76) ml/min
P = 0.46

Oral Iron Placebo

0.30 (-0.27 to 0.87) ml/kg/min
P = 0.30

Median (25th-75th percentile)

## Results: Secondary and Exploratory Endpoints

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral Iron N=111</th>
<th>Placebo N=114</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Delta) 6 MW distance at 16 weeks, meters</td>
<td>19</td>
<td>32</td>
<td>0.19</td>
</tr>
<tr>
<td>(\Delta) Mean response time, seconds</td>
<td>2.5</td>
<td>1</td>
<td>0.19</td>
</tr>
<tr>
<td>(\Delta) Ventilatory efficiency (VE/VCO(_2) slope)</td>
<td>-0.3</td>
<td>-0.3</td>
<td>0.35</td>
</tr>
<tr>
<td>(\Delta) NT-BNP level, pg/ml</td>
<td>4</td>
<td>-37</td>
<td>0.48</td>
</tr>
<tr>
<td>(\Delta) KCCQ score at 16 weeks</td>
<td>3.1</td>
<td>3.0</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Exploratory Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\Delta) Ventilatory threshold (ml/min)</td>
<td>22</td>
<td>-2</td>
<td>0.07</td>
</tr>
<tr>
<td>(\Delta) Creatinine, mg/dL</td>
<td>0.03</td>
<td>0.00</td>
<td>0.65</td>
</tr>
<tr>
<td>(\Delta) Cystatin C, mg/L</td>
<td>0.02</td>
<td>0.01</td>
<td>0.12</td>
</tr>
</tbody>
</table>

### Results: Safety Endpoints

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral Iron N=111</th>
<th>Placebo N=114</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety end points, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>39 (35%)</td>
<td>45 (39%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>11 (10%)</td>
<td>10 (9%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Permanent study drug discontinuation</td>
<td>15 (14%)</td>
<td>17 (15%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Death or cardiovascular re-hospitalization</td>
<td>14 (13%)</td>
<td>12 (11%)</td>
<td>0.63</td>
</tr>
</tbody>
</table>
Change in Iron Studies: FAIR-HR vs. IRONOUT

IRONOUT-HF

Ferritin (ng/ml)

Week 0 16

Week 0 16

Δ+11ng/ml

P=0.056

Tsat (%)

Week 0 16

Week 0 16

Δ+3%

p=0.003

Normal range

vs. FAIR-HF (IV Iron)

Normal range

Iron

Placebo

Iron

Placebo

Δ+238ng/ml

P<0.001

Δ+12%

P<0.001
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
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.

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

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

**Placebo group**
- N = 1200

**1:1 randomization**

**Timelines**
- Approximately 620 global sites
- Began enrolling: June 2006
- Event driven: ~1150 events
- Study End: September 1, 2012

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

Prop. of Subject With Event (%)

Placebo
Darbepoetin alfa
Stratified Log-rank, \( p = 0.87 \)

Subjects at risk:
- Placebo:
  - 1142, 956, 818, 695, 591, 497, 395, 290, 211, 154, 92
- Darbepoetin alfa:
  - 1136, 975, 855, 712, 581, 473, 385, 281, 212, 161, 101

## Selected adverse events of interest

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

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

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 (pVO₂/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 VO₂ from baseline to week 24

EFFECT-HF: Analysis

**Ferric Carboxymaltose**
- 86 patients
  - 80 in ITT analysis
  - 70 in PP analysis
  - 55 analyzed for primary endpoint
  - 6 excluded from primary analysis
  - 16 excluded for major protocol violations
  - 15 excluded from analysis

**Control**
- 86 patients
  - 81 in ITT analysis
  - 76 in PP analysis
  - 66 analyzed for the primary endpoint
  - 10 excluded for major protocol violations
  - 10 excluded from analysis

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

**EFFECT-HF: Results**

<table>
<thead>
<tr>
<th>ITT: Peak VO₂ of 0 imputed for deaths</th>
<th>FCM (n=80)</th>
<th>Control (n=81)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ ml/min/kg (24 weeks)</td>
<td>-0.63</td>
<td>-1.19</td>
<td>0.020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PP: Peak VO₂ of 0 imputed for deaths</th>
<th>FCM (n=70)</th>
<th>Control (n=76)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ ml/min/kg (24 weeks)</td>
<td>+0.25</td>
<td>-1.10</td>
<td>0.011</td>
</tr>
</tbody>
</table>

### EFFECT-HF: Results

<table>
<thead>
<tr>
<th>No imputation</th>
<th>FCM (n=55)</th>
<th>Control (n=66)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak VO₂ ml/min/kg (24 weeks)</td>
<td>-0.16</td>
<td>-0.63</td>
<td>0.23</td>
</tr>
</tbody>
</table>

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


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
  - PO4: 3.5
  - Mg: 2.1
  - TSH: 2.7
  - Iron: 23
  - TIBC: 200
  - Ferritin: 80
  - TSAT: 15%
Please design a pharmacotherapy plan to manage iron deficiency for JK.
## IV Iron Repletion Regimens

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<th>Follow-up</th>
<th>Regimen Studied</th>
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<td>FERRIC - HF</td>
<td>35</td>
<td>18 weeks</td>
<td>Iron sucrose 200 mg IV weekly for 16 weeks (or until ferritin 500 ng/mL)</td>
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<tr>
<td>FAIR - HF</td>
<td>495</td>
<td>24 weeks</td>
<td>Ferric carboxymaltose 200 mg IV weekly until iron replaced then 200 mg 4 weekly</td>
</tr>
<tr>
<td>CONFIRM - HF</td>
<td>304</td>
<td>52 weeks</td>
<td>Ferric carboxymaltose 500 - 2000 mg IV at day 0 and week 6 then 500 mg at weeks 12, 24, 36 if iron deficient</td>
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<tr>
<td>EFFECT - HF</td>
<td>172</td>
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<td>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</td>
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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
IRONING OUT THE MANAGEMENT OF ANEMIA IN HEART FAILURE