Iron-Deficiency Anemia and Heart Failure

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Objectives

1. Describe the impact of iron deficiency anemia on the heart failure patient

2. Identify treatment options for heart failure patients with iron deficiency anemia

Patient Case

- 75 y/o, 70-kg man with a 2 year history of HFpEF (EF 25%), NYHA class III, and a history of one hospitalization in the past 6 months presents for a regular f/u visit

- Current meds: carvedilol, furosemide, potassium chloride, losartan, aspirin, spironolactone, citalopram, acetaminophen, zolpidem, and vit D

- Routine labs are checked
  - SCr 1.4 mg/dL, calculated CrCl = 45 mL/min
  - K+ 4.5 mmol/L
  - Hb 10.5 g/dL
  - Low MCV
  - Ferritin 150 ng/mL
  - Tsat 14%

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Iron: an Important Micronutrient

Iron-Deficiency: Epidemiology in HF

- Iron deficiency occurs in > 1/3 of patients with HF
  - Common cause of anemia
  - More likely to occur in women vs men
  - Prevalence increases with HF disease severity

- 2 types of iron deficiency
  - Absolute: depleted iron stores, with intact iron homeostasis mechanisms
    - Common causes: low-dietary intake, impaired GI absorption, GI blood loss, menorrhagia
  - Functional: normal or high iron body stores, but iron is trapped inside cells of the reticuloendothelial system and is unavailable for cellular metabolism

Iron-Deficiency: Pathophysiology in HF

- Renal dysfunction, neurohormonal and proinflammatory cytokine activation
  - Inappropriate erythropoietin production and defective iron utilization, leading to intestinal iron absorption and accumulation within the reticuloendothelial stores
  - Hemodynamic responses to hypoxia: vasodilation-mediated high-output state with neurohormonal activation—to increase oxygen transport
Effects of Iron-Deficiency in HF: Adverse Outcomes

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

- Tissue remodeling
  - Impaired organ efficacy

- Impaired exercise capacity
- Reduced work efficacy
- Impaired cognitive performance and behavior
- Increased mortality and morbidity

Figure 1. Jankowska EA et al. Eur Heart J. 2013 Mar;34(11):816-29

Mortality with Iron-Deficiency (ID) in HF

![Graph showing mortality with and without iron deficiency over time](image)

- Patients without ID: Survival (98.7%)
- Patients with ID: Survival (95.4%)

P = 0.002

Iron-Deficiency Anemia: Symptoms

- Fatigue
- Exercise intolerance
- Exertional dyspnea
- Chest pain
  - Weakness
  - Headache
  - Irritability
  - Vertigo

Figure 5. Jankowska EA, et al. Eur Heart J. 2013 Mar;34(11):816-29
Iron-Deficiency Anemia: Diagnosis

- CBC
  - Low Hemoglobin (Hb) <13 g/dL (men) or <12 g/dL (women)
  - May have low mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH)

- Serum ferritin
  - May be low (<100 ng/mL = absolute iron deficiency)
  - May be normal (100-300 ng/mL = functional iron deficiency)
  - Iron binding panel = transferrin, % transferrin saturation (Tsat), total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC)
  - Tsat <20% accompanied by normal ferritin = functional iron deficiency
  - May also want to consider ordering serum vitamin B12

Iron Absorption

- Iron is absorbed in the upper GI tract
  - Duodenum is the site of maximal absorption

- Mucosal cells are responsible for iron absorption, and older adults with certain conditions may ↓ absorption
  - Celiac disease, atrophic gastritis, H. pylori infection, and previous bariatric surgery

Clinical Investigation of Iron Replacement

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>INCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>JACC² 2006</td>
<td>Hb ≤12 g/dL; NYHA II-III</td>
</tr>
<tr>
<td>FERRIC-HF² 2008</td>
<td>Ferritin &lt;100 ng/mL or 100-300ng/mL w/TSat &lt;20%; Hb ≤ 14.5 g/dL; NYHA II-III; EF ≤45%</td>
</tr>
<tr>
<td>NEPHROL² 2008</td>
<td>Hb &lt;11 g/dL; NYHA III-IV</td>
</tr>
<tr>
<td>FAM-HF² 2009</td>
<td>Ferritin &lt;100 ng/mL or 101-299ng/mL w/TSat &lt;20%; Hb 9.5-13.5g/dL; NYHA II-III; LVEF ≤40%</td>
</tr>
<tr>
<td>IRON-HF³ 2013</td>
<td>Ferritin &lt;500 ng/mL and Tsat &lt;20%; Hb 9-12 g/dL; Hb 9-15 g/dL; NYHA II-IV; LVEF ≤40%</td>
</tr>
<tr>
<td>CONFIRM-HF² 2015</td>
<td>Ferritin &lt;100 ng/mL or 100-300ng/mL w/TSat &lt;20%; Hb &lt;15 g/dL; Symptomatic HFrEF ≤45%, NYHA II-III, and high BNP</td>
</tr>
<tr>
<td>IRONOUT-HF² 2017</td>
<td>Ferritin &lt;100 ng/mL or 101-299ng/mL w/TSat &lt;20%; NYHA II-III, HFrEF ≤40%</td>
</tr>
<tr>
<td>EFFECT-HF² 2019</td>
<td>Ferritin &lt;100 ng/mL or 100-300ng/mL w/TSat &lt;20%; Hb &lt;15 g/dL; NYHA II-III; HFrEF ≤45%</td>
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Abstract

### Clinical Investigation of Iron Replacement

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<tr>
<th>TRIAL</th>
<th>N</th>
<th>DRUG REGIMEN</th>
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<tr>
<td>JACC(^1) 2006</td>
<td>16</td>
<td>IV IS 200mg x 3-5 doses over 17 days</td>
</tr>
<tr>
<td>FERRIC-HF 2008</td>
<td>35</td>
<td>IV IS 200 mg/wk until ferritin &gt;500, then Qmo; or no treatment</td>
</tr>
<tr>
<td>J NEPHROL(^2) 2006</td>
<td>32</td>
<td>IV IS 100mg TW x 3wks, then weekly x 23wks</td>
</tr>
<tr>
<td>FAIR-HF 2009</td>
<td>459</td>
<td>IV FCM 200mg weekly, then Qmo starting at wk 8 or 12; or placebo used Ganzoni formula(^9)</td>
</tr>
<tr>
<td>IRON-HF 2013</td>
<td>23</td>
<td>IV IS 200 mg/wk x 5 wks or FeSO(_4) 200mg TID x 8wks or placebo</td>
</tr>
<tr>
<td>CONFIRM-HF(^3) 2015</td>
<td>304</td>
<td>IV FCM 500-1000 mg based on weight; Hb at weeks 0, 6; 500mg at wks 12, 24, and 36 depending upon Tsat and ferritin or placebo</td>
</tr>
<tr>
<td>IRONOUT-HF(^4) 2017</td>
<td>225</td>
<td>Oral iron polysaccharide 150mg BID or placebo</td>
</tr>
<tr>
<td>EFFECT-HF Abstract</td>
<td>174</td>
<td>IV FCM at weeks 0, 6 and 12; or placebo ± oral iron</td>
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**IV IS = IV Iron sucrose = Venofer®; IV FCM = Ferric carboxymaltose = Injectafer®


### Clinical Investigation of Iron Replacement

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| JACC\(^1\) 2006 | • ↑ Hb (11.2 to 12.6), ↑ ferritin (87 to 217), ↑ Tsat (16 to 25%)
|               | • Improved functional class, improved 6MW distance, no effect on EF      |
| FERRIC-HF 2008 | • ↑ Hb by 0.1, ↑ ferritin by 273, ↑ Tsat by 11                           |
|               | • Improved exercise capacity, improved symptoms; effects if anemic         |
| J NEPHROL\(^2\) 2006 | • ↑ Hb (by 3), ↑ ferritin (by 40), ↑ Tsat (by 13-18)                      |
|               | • Improved functional class from III to II and improved cardiac defects   |
|               |   and LVEF in class III patients; less robust response in class IV patients |
| FAIR-HF 2009   | • Significant improvement in patient global assessment (50% much/moderately improved vs 28%, OR 2.51) |
|               | • Significant improvement in functional class (47% class I or II vs 30% at wk-24, OR 2.40) and significant improvement in 6MW test and QOL |
|               | • Results similar in patients with anemia/no anemia                        |
|               | • No difference in death or adverse events                                |

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<td>IRON-HF 2013</td>
<td>• No diff in Hb between oral/IV iron, ↑ ferritin in oral &amp; IV iron (only significant w/oral iron). Tsat ↑ significantly in IV compared to placebo</td>
</tr>
<tr>
<td></td>
<td>• VO(_2)max increased in IV iron group but not oral iron group</td>
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<tr>
<td>CONFIRM-HF(^5) 2015</td>
<td>• Significant improvement in 6MW, NYHA class, PFS, QOL &amp; fatigue starting at week 24–consistent amongst all subgroups through wk52</td>
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<tr>
<td></td>
<td>• Significant reduction in hospitalization for worsening HF (HR 0.39)</td>
</tr>
<tr>
<td></td>
<td>and trend for reduction in hosp due to any CV reason (HR 0.63)</td>
</tr>
<tr>
<td></td>
<td>• No difference in deaths or adverse event</td>
</tr>
<tr>
<td>IRONOUT-HF(^7) 2017</td>
<td>• ↑ Hb (by 0.74), ↑ ferritin (by 189), ↑ Tsat (by 5)</td>
</tr>
<tr>
<td></td>
<td>• Significant improvement in VO(_2)max with or without anemia</td>
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<td>• Significantly improved functional class &amp; patient global assessment</td>
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Meta-Analysis: IV Iron for Patients with HFrEF and Iron Deficiency

- **2016 European Society of Cardiology Guidelines**
  - Based upon FAIR-HF and CONFIRM-HF
  - Intravenous ferrous carboxymaltose (FCM)
  - Improve self-reported global assessment
  - Improve QOL
  - Improve NYHA class
  - Improve exercise capacity
  - Reduce HF hospitalizations
2017 AHA/ACC Guideline Recommendations

<table>
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<tr>
<th>Recommendations for Anemia</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
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<tbody>
<tr>
<td>SB</td>
<td>B-R</td>
<td>In patients with NYHA class II and III HF and iron deficiency (ferritin &lt;100 ng/mL or 100 to 300 ng/mL if transferrin saturation is &lt;20%), intravenous iron replacement might be reasonable to improve functional status and QoL (173, 174).</td>
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- Routine evaluation of HF patients should include evaluation for anemia
- In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity/mortality

Future Directions

- **FAIR-HF2**: Germany, Hungary and Spain
  - IV ferric carboxymaltose vs placebo in patients with HFrEF and iron deficiency
  - Major outcomes at 12 months: HF hosp, CV hosp and CV death
  - Funded by German University
- **AFFIRM-AHF**: Italy, Netherlands, Poland, UK
  - IV ferric carboxymaltose vs placebo in patients with acute HF and iron deficiency
  - Major outcomes at 12 months: HF hosp, CV death, CV hosp, all-cause mortality, functional outcomes
  - Funded by manufacturer, Vifor Inc.
- Long term safety with IV iron in patients with heart failure unknown
- Effects of IV iron in patients with HFpEF unknown

Patient Case

- 75 y/o, 70-kg man with a 2 year history of HFrEF (EF 25%), NYHA class III, and a history of one hospitalization in the past 6 months presents for a regular f/u visit
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- Should this patient be treated with oral iron?
- Should this patient be treated with IV iron?
Patient Case: IV Ferric Carboxymaltose

- FDA approved for iron-deficiency anemia in adults with NDD-CKD or those who have intolerance to oral iron or have had an unsatisfactory response to oral iron
- Dose: FDA approved 750mg weekly X 2 doses if >50 kg
- Re-dosing like in clinical studies to maintain ferritin/Tsat
- IV infusion over at least 15 min or slow IV push over at least 7.5 min
- Some clinical trials gave over 1 min
- Monitor for hypersensitivity and increases in BP for 30 min after administration
- Adverse effects: nausea (7%, all others <5%), HTN, HA, dizziness, vomiting
- Cost: ≈$1200 per 750 mg/15 mL single-use vial
- Insurance coverage: likely covered by Medicare Part B and commercial plans, possibly with PA, Medicaid may/may not cover

Example order for IV Iron—in EPIC

1. Select the ambulatory referral order set
2. Fill out the following referral order for Injectafer. Be sure to pick the dose that matches your patient’s body weight as there are two options for dosing.
3. Select how frequently you would like lab testing. The referral order will only allow you to select one time-frame per lab order. The CBC, ferritin, transferrin, and hemoglobin/hematocrit should be checked one month after receiving Injectafer. Once the 2 doses of Injectafer have been given, all lab tests associated with the order set will also be discontinued. Further or additional lab monitoring will need to be ordered separately.
4. Keep the auto-checked boxes as is (e.g. Yes is checked for nurse monitoring for infusion reactions, etc.).
5. Make sure to add the diagnosis code (D50.9 iron deficiency anemia) by clicking on the order-entry link. There also needs to be documentation in your clinical notes related to the order of why the patient needs IV versus oral iron therapy.
Example order for IV Iron—in EPIC

Dose based upon body weight

50 kg

Labs to order

Example order for IV Iron—in EPIC

If infusion reaction, give diphenhydramine IV

Monitoring of VS

Monitor s/s hypersensitivity

IV access/maintenance

Summary

- Iron-deficiency is common in adults with heart failure, increasing with HF severity
  - Independently leads to adverse outcomes
- Data and national guidelines support evaluating patients with NYHA class II-III HFrEF for iron deficiency
- IV iron replacement is recommended if patient is iron-deficient, regardless if anemic
  - Ferric carboxymaltose—recommended by guidelines, less frequent dosing, well tolerated
Questions?
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