History

- 73-year-old female
- History of heart failure with reduced ejection fraction (HFrEF)
- Diabetes
- Recently discharged from the hospital
  - NYHA class IV acute decompensation requiring inotropic support
  - Up-titration of ACE inhibitors and beta-blockers was limited due to symptomatic hypotension
- Readmitted when symptoms deteriorated from NYHA II to NYHA III

Labs

- Hb 13.5 g/dL
- Serum ferritin 150 ng/mL
- TSAT 11%
- Negative fecal occult blood test
Patient Case (cont’d)

73-year-old female HFrEF – NYHA III

Comorbidities

• Diabetes
• Iron deficiency
  • Non-anemic – Hb 13.5 g/dL
  • Serum ferritin 150 ng/mL
  • TSAT 11%

Diagnosis of Iron Deficiency

• In patients with HF, iron deficiency is defined as either a serum ferritin concentration <100 ng/mL or 100-299 ng/mL with transferrin saturation (TSAT) <20%

Iron Deficiency in Heart Failure

Risk Factors
- Female > Male
- Reduced iron intake
- Acute decompensated heart failure
- Reduced iron uptake

NYHA, New York Heart Association.
1. Martens P. Card Fail Rev. 2022;8:e06.
Prevalence of Iron Deficiency in HF: PrEP Registry

• The prevalence of iron deficiency in HF is ~40%-50%
  ▪ Absolute – Ferritin <100 ng/mL
  ▪ Relative – Ferritin 100-300 ng/mL and TSAT <20%

• Present in patients with and without anemia

• Higher rates of CV morbidity and mortality independent of baseline Hgb/Hct, higher rate of hospitalization, impaired functional status, and associated with worse QOL

CV, cardiovascular; Hct, hematocrit; HF, heart failure; Hgb, hemoglobin; ng/mL, nanograms per milliliter; QOL, quality of life, TSAT, transferrin saturation.

Prior IV Iron Studies (HFrEF + HFmEF)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Time (weeks)</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAIR-HF</td>
<td>459</td>
<td>24</td>
<td>Global assessment score</td>
</tr>
<tr>
<td>CONFIRM-HF</td>
<td>304</td>
<td>52</td>
<td>6-MWD</td>
</tr>
<tr>
<td>EFFECT-HF</td>
<td>172</td>
<td>24</td>
<td>Peak VO\textsubscript{2}</td>
</tr>
</tbody>
</table>

**Improvements in:**
- Patient global assessment
- Functional status (6-MWD, peak VO\textsubscript{2}, NYHA Class)
- Biomarkers (BNP)
- Reduction in HF hospitalizations

6-MWD, 6-minute walk distance; BNP, brain natriuretic peptide; HF, heart failure; HFmEF, heart failure with mid-range ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; NYHA, New York Heart Association; VO\textsubscript{2}, volume of oxygen.

Lack of Benefit with Oral Iron: IRONOUT-HF Study

- Double-blind, randomized, placebo-controlled trial
- Median ferritin levels remained below 100 ng/mL after 16 weeks
- In patients with HFrEF and ID, 150 mg oral iron polysaccharide twice daily failed to improve exercise capacity, inflammatory markers, and QOL compared to placebo

HFrEF, heart failure with reduced ejection fraction; ID, iron deficiency; QOL, quality of life; VO₂, volume of oxygen.

• IV ferric carboxymaltose (FCM)
• Composite of recurrent events of HF hospitalization and cardiovascular death
• 1,132 Patients
• Acute HF EF<50%

1 Administered dose of study treatment based on iron need as assessed at the baseline visit.
2 Study treatment administered only if iron deficiency persisted.

FCM, ferric carboxymaltose; HF, heart failure; LVEF, left ventricular ejection fraction; PL, placebo; R, randomization; TC, telephone contact; V, visit; W, week.

AFFIRM-AHF: Total Hospitalizations and QoL

Total HF Hospitalizations

Mean Cumulative Events per 100 Patients

Weeks since Randomization

Total Events

Rate ratio 0.74 (95% CI, 0.58–0.94); \( P = 0.013 \)

KCCQ-12 overall summary score (OSS)

Adjusted mean change (SE)

Weeks

mITT population. FCM, ferric carboxymaltose; HF, heart failure, mITT, modified intention to treat; QoL, quality of life.

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that all patients with HF be periodically screened for anemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF &lt;45% and iron deficiency, defined as serum ferritin &lt;100 ng/mL or serum ferritin 100-299 ng/mL with TSAT &lt;20%, to alleviate HF symptoms and improve exercise capacity and QOL.</td>
<td>IIa</td>
<td>B</td>
</tr>
</tbody>
</table>

### Recommendations

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>For patients who are diagnosed with HF, laboratory evaluation should include complete blood count, urinalysis, serum electrolytes, blood urea nitrogen, serum creatinine, glucose, lipid profile, liver function tests, iron studies, and thyroid-stimulating hormone to optimize management.</td>
<td>1</td>
<td>C-E0</td>
</tr>
<tr>
<td>In patients with HFrEF and iron deficiency with or without anemia, intravenous iron replacement is reasonable to improve functional status and QOL.</td>
<td>2a</td>
<td>B-R</td>
</tr>
</tbody>
</table>

HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; QOL, quality of life; TSAT, transferrin saturation.

Patient Case (cont’d)

Treatment and Management

• 4 Foundational Therapies for HFrEF
  • ACE inhibitor or sacubitril/valsartan
  • Beta-blocker
  • Mineralocorticoid receptor antagonist (MRA)
  • SGLT2 inhibitors
• Check for comorbidities
  • Address iron deficiency prior to release

Continuity of Care (IV iron)

• 1st dose IV iron prior to release
• 2nd dose 6 weeks after 1st dose irrespective of iron levels
• Follow up and recheck iron
• Rule out other etiologies

Important to Note:

• Avoid measuring ferritin and transferrin saturation too early after IV iron administration
• Levels will be high and lead to a high background signal

ACE, angiotensin-converting enzyme; HFrEF, heart failure with reduced ejection fraction; SGLT2, sodium-glucose cotransporter-2.
Key Takeaways

• “if you don’t look for comorbidities, you don’t find them”
• “don’t stop with the hemoglobin”