Iron deficiency: An Overlooked Aspect of Heart Failure Management

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Dealing with comorbidities in heart failure

Iron deficiency: a comorbidity that goes unnoticed in heart failure

Iron deficiency is an important comorbidity and is prevalent in patients with heart failure; however, it is often neglected.
Ten Principles for Successful Treatment of Heart Failure

I. Initiate & Switch
   Treatment algorithm for guideline-directed medical therapy including novel therapies (Figure 2 and 3)

II. Titration
   Target doses of select guideline-directed heart failure therapy (Tables 1, 2, 3, 4, 5)
   Considerations for monitoring

III. Referral
   Triggers for referral to HF specialist (Table 6)

IV. Care Coordination
   Essential skills for a HF team (Table 7)
   Infrastructure for team-based HF care (Table 8)

V. Adherence
   Causes of non-adherence (Table 9)
   Interventions for adherence (Table 10, 11)

VI. Specific Patient Cohorts
   Evidence based recommendations and assessment of risk for special cohorts:
   African Americans; older adults; frail (Table 12)

VII. Cost of Care
   Strategies to reduce cost (Table 13)
   Helpful information for completion of prior authorization forms (Table 14)

IX. Comorbidities
   Common cardiac and non-cardiac comorbidities with suggested actions (Table 16)

X. Palliative/Hospice Care
   Seven principles and actions to consider regarding palliative care
### Table 16: Common Cardiac and Noncardiac Comorbidities Encountered in Patients With HFpEF

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Association With Heart Failure Outcomes</th>
<th>Clinical Trial Evidence for Modulating Comorbidity</th>
<th>Suggested Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td>Strong</td>
<td>Strong</td>
<td>Evaluate and revascularize in appropriate patients</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>Strong</td>
<td>Intermediate</td>
<td>Treat according to current ACC/AHA/HRS Guideline for the Management of Patients with Atrial Fibrillation (94)</td>
</tr>
<tr>
<td>Atrial Fibrillation/Flutter</td>
<td>Strong</td>
<td>Intermediate</td>
<td>Refer to structural heart disease expert &amp; treat according to current AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease (95)</td>
</tr>
<tr>
<td>Mitral Regurgitation</td>
<td>Strong</td>
<td>Intermediate</td>
<td>Refer to structural heart disease expert &amp; treat according to current AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease (95)</td>
</tr>
<tr>
<td>Aortic Stenosis</td>
<td>Strong</td>
<td>Strong</td>
<td>Treat according to current ACC/AHA hypertension guidelines</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Strong</td>
<td>Strong for prevention</td>
<td>Treat according to current ACC/AHA hypertension guidelines</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Strong</td>
<td>Strong for prevention</td>
<td>Treat according to ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (96). Also see the nonstatin treatment of dyslipidemia clinical pathways (97)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>Moderate</td>
<td>None</td>
<td>Treat according to current AHA/ACC vascular guidelines (98)</td>
</tr>
<tr>
<td>Congenital Heart Disease</td>
<td>Moderate</td>
<td>Weak</td>
<td>Treat according to current AHA stroke guidelines (99)</td>
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<tr>
<th>Noncardiovascular</th>
<th></th>
<th>Further data needed</th>
<th></th>
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<tbody>
<tr>
<td>Obesity</td>
<td>Moderate (inverse association)</td>
<td>Weak</td>
<td></td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>Strong</td>
<td>Weak</td>
<td>Optimize therapy, consider pulmonary consultation</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Strong</td>
<td>Intermediate</td>
<td>Optimize therapy, consider SGLT2 inhibitors, consider endocrine consult and follow current American Diabetes Association Standards of Medical Care in Diabetes (100)</td>
</tr>
<tr>
<td>Chronic Renal Disease</td>
<td>Strong</td>
<td>Weak</td>
<td>Optimize RAS therapy, consider nephrology consult</td>
</tr>
<tr>
<td>Anemia</td>
<td>Moderate</td>
<td>Weak</td>
<td>Evaluate secondary causes, consider transfusion in severe cases</td>
</tr>
<tr>
<td>Iron Deficiency</td>
<td>Strong</td>
<td>Intermediate</td>
<td>Consider intravenous iron replacement for symptom improvement</td>
</tr>
<tr>
<td>Thyroid Disorder—hypothyroid</td>
<td>Strong</td>
<td>Weak</td>
<td>Consider referral to endocrinologist and/or treatment</td>
</tr>
<tr>
<td>Sleep Disordered Breathing</td>
<td>Strong</td>
<td>Intermediate</td>
<td>Consider sleep study and treat severe obstructive sleep apnea to improve sleep quality, consider referring to sleep specialist</td>
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### Types of iron deficiency

**A Absolute iron deficiency**
- **Reduced iron storage**

  - Ferritin (iron stores) < 100 µg/L
  - Transferrin saturation (bioavailable iron) < 20%

**B Functional iron deficiency**
- **Reduced iron mobilization**

  - Ferritin (iron stores) 100-299 µg/L
  - Transferrin saturation (bioavailable iron) < 20%
Causes of iron deficiency in heart failure

(Jankowska et al. Eur Heart J 2013)

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<th>Normal</th>
<th>Absolute ID</th>
<th>Functional ID</th>
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<tr>
<td>Serum Ferritin</td>
<td>&gt;300 µg/dL</td>
<td>&lt;100 µg/dL</td>
</tr>
<tr>
<td>Transferin saturation</td>
<td>&gt;20%</td>
<td>&lt;20%</td>
</tr>
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How should Iron deficiency be diagnosed?

2016 ESC guidelines for the diagnosis and treatment of HF

In these guidelines ID is defined as follows:

- Serum ferritin $<100 \mu g/L$ (absolute iron deficiency), or
- Serum ferritin $100–299 \mu g/L$ and transferrin saturation “TSAT” $<20\%$ (functional iron deficiency).

Prevalence of Iron Deficiency in Heart Failure

About 50% have some form of iron deficiency, with and without anaemia.
In heart failure patients iron deficiency adversely affects:

- Functional status, including exercise capacity
- Quality of life
- Outcome

If you suffer from both Heart Failure and Iron Deficiency, you will likely ...

- suffer from a 13% reduced exercise capacity...
- have your quality of life reduced by 19%...
- have an increased risk of 42% to die...

... compared to a patient without iron deficiency.
Consequences of iron deficiency in heart failure

Iron Deficiency + Heart Failure = BAD combination

- Iron deficiency is associated with HF disease severity, reflected in NYHA functional class and NT-proBNP levels.
- It has also been reported to be an independent predictor of all-cause and cardiovascular mortality.

ID is a negative prognostic factor, stronger than anemia

Mortality among groups of ID and/or anemia. Hazard ratios of mortality among groups with or without anemia, divided in patients with and without ID. Iron deficiency remained an independent predictor of mortality in both anemic and nonanemic patients. *P b< .01; † P b< .001, adjusted for all univariate associated variables (Klip et al. Am Heart J 2013.)
Survival analysis. Kaplan-Meier curves reflecting the difference in event-free survival rates in chronic HF patients with or without ID. Klip et al. Am Heart J 2013
As one in every two heart failure patients has iron deficiency,

*a key question is:*

“should iron be at the heart of our

Iron Deficiency in Heart Failure: A Therapeutic Target
Approach to the patient with heart failure with reduced ejection fraction.

Suggested algorithm for diagnosis of iron deficiency in patients with heart failure.
Iron therapy for the treatment of iron deficiency in chronic heart failure:

**Iron deficiency in heart failure**

**Clinical question**
Is intravenous iron more effective than oral iron for the treatment of iron deficiency in patients with heart failure?

**Evidence-Based Answer**
Randomized Clinical Trials

**Randomized Control Trials: Evidence Summary**

- **Symptom, QoL, Function**
  - FAIR-HF, CONFIRM-HF and EFFECT-HF trials

- **Morbidity, Mortality**
  - AFFIRM-AHF, FAIR-HF2 and HEART-FID trials

The three double-blind, placebo-controlled clinical trials, entitled **AFFIRM-AHF, FAIR-HF2 and HEART-FID**, will study the effects of **ferric carboxymaltose** versus placebo on morbidity and mortality outcomes. These trials follow the **FAIR-HF, CONFIRM-HF and EFFECT-HF** trials, which showed statistically significantly beneficial effects of **ferric carboxymaltose** versus placebo or standard of care, on symptoms, functional capacity and oxygen consumption, respectively.
Iron therapy for the treatment of iron deficiency in chronic heart failure: intravenous or oral?

Oral therapy is not so effective

- Poorly tolerated
- GI absorption impaired, standard doses often insufficient
- Drug interactions
- Hepcidin issues
  - Increased hepcidin levels, typical in inflammatory states such as HF, precludes resorption of iron from the gut
  - High levels of hepcidin can “TRAP” iron in storage cells

Effect of oral or i.v. iron therapy on ‘hepcidin block’ of iron release from macrophages.

(A) Under normal circumstances, ~25 mg of stored iron per day is transported out of macrophages to plasma transferrin by the iron transporter protein ferroportin.

(B) In chronic disease, elevated levels of hepcidin cause degradation of ferroportin, restricting ferroportin-mediated transport to ~15 mg iron/day
Effect of oral or i.v. iron therapy on ‘hepcidin block’ of iron release from macrophages.

(C) Oral iron: The rate of iron absorption from iron therapy is inadequate to influence this ‘hepcidin block’.

(D) I.V. iron therapy results in high intracellular iron levels which overcome the ‘hepcidin block’ by stimulating overexpression of ferroportin.

Conclusions and Relevance Among participants with HFrEF with iron deficiency, high-dose oral iron did not improve exercise capacity over 16 weeks. These results do not support use of oral iron supplementation in patients with HFrEF.
IV iron is the only valid treatment option for ID

Apart from replenishing iron stores, IV iron improves NYHA functional class, 6MWT distance, and quality of life.

Iron Deficiency, a Common Neglected Burden in Heart Failure

What do the guidelines say?
**Recommendations**

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<td>Intravenous FCM should be considered in symptomatic patients with HFrEF and iron deficiency (serum ferritin &lt;100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation &lt;20%) in order to alleviate HF symptoms, and improve exercise capacity and quality of life.</td>
</tr>
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FCM=ferric carboxymaltose
9. Important Comorbidities in HF

9.2. Anemia: Recommendations

<table>
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<tr>
<th>Recommendations for Anemia</th>
<th>Recommendations</th>
<th>Comment/Rationale</th>
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<tr>
<td><strong>IIb</strong> 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>
<td><strong>NEW</strong>: New evidence consistent with therapeutic benefit.</td>
</tr>
<tr>
<td>See Online Data Supplement D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>III: No Benefit</strong> B-R</td>
<td>In patients with HF and anemia, erythropoietin-stimulating agents should not be used to improve morbidity and mortality (176).</td>
<td><strong>NEW</strong>: Current recommendation reflects new evidence demonstrating absence of therapeutic benefit.</td>
</tr>
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ID Correction Algorithm Built on the premise: would my patient with HF and ID be enrolled in a main trial of FCM?
Conclusion
Key Points

Iron deficiency, regardless of haemoglobin level, is an indication for supplementation in symptomatic patients with heart failure with reduced ejection fraction.

Only intravenous carboxymaltose has been demonstrated to be safe and effective for iron repletion in these patients. Oral iron supplementation is not effective in iron deficient patients with heart failure.

Morbidity-mortality trials have been launched to verify whether iron repletion improves outcomes in patients with heart failure.

Thank you for your attention!