Iron Substitution in Heart Failure: Current Evidence and New Concepts

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Iron = Source of energy
Iron is essential for mitochondrial ATP generation.

Definition of iron deficiency

Healthy (no apparent disease)
Absolute iron deficiency:
Ferritin < 20 ug/L (female)
Ferritin < 30 ug/L (male)

Chronic disease
Absolute iron deficiency:
Ferritin < 100 ug/L (male and female)

Functional iron deficiency:
Ferritin < 300 ug/L + TSAT < 20% (male and female)

Adapted from Anker S.
Pathophysiology of iron deficiency in HF

Chronic heart failure

\[ \downarrow \]

Inflammatory cytokines (TNFα, IL-6)

\[ \downarrow \]

Hepcidin↑

Liver congestion

Gastro-intestinal congestion

Iron absorption↓

Iron release↓

Iron deficiency

Chronic blood loss

- Antiplatelet therapy
- Anticoagulation
Prevalence of iron deficiency in a Swiss HF Cohort

n = 223

- No iron deficiency: 48%
- Functional iron deficiency (ferritin 100 – 300 ng/ml; Tsat < 20%): 36%
- Absolut iron deficiency (ferritin < 100 ng/ml; Tsat < 20%): 18%
- 54%

Pfister O, EVITA-RAID Registry (Swiss Cohort) preliminary data
## Prevalence of iron deficiency in HF patients

<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>LVEF %</td>
<td>27</td>
<td>33</td>
<td>26</td>
</tr>
<tr>
<td>NYHA ≥ III %</td>
<td>60</td>
<td>54</td>
<td>49</td>
</tr>
<tr>
<td>Women %</td>
<td>24</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>69</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>Anemia %</td>
<td>30</td>
<td>28</td>
<td>ND</td>
</tr>
<tr>
<td>ID %</td>
<td>54</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>ID in anemic %</td>
<td>68</td>
<td>61</td>
<td>57</td>
</tr>
<tr>
<td>ID in non-anemic %</td>
<td>42</td>
<td>46</td>
<td>32</td>
</tr>
</tbody>
</table>
Factors associated with iron deficiency

- women
- higher NYHA class
- higher BNP
- higher CRP

Jankowska E A et al. Eur Heart J 2010
Iron deficiency: Impact on morbidity

<table>
<thead>
<tr>
<th>Condition</th>
<th>No iron deficiency</th>
<th>Iron deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stable Dx</td>
<td>67%</td>
<td>49%</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>Worsening Heart Failure</td>
<td>31%</td>
<td>47%</td>
</tr>
<tr>
<td>Reduction in Activities of Daily Living</td>
<td>47%</td>
<td>65%</td>
</tr>
</tbody>
</table>

*O. Pfister, unpublished data*
Iron deficiency: Impact on mortality

A

Cumulative survival (%) vs. Time in study (years)

- Patients without iron deficiency
- Patients with iron deficiency

Numbers at risk:
- ID absent: 753, 386, 104, 63, 40
- ID present: 753, 343, 100, 49, 33

P = .001
Iron replacement in HF: Clinical evidence

- Bolger AP et al, J Am Col Cardiol, 2006; \( n=16 \); single arm
- Toblli JE et al, J Am Col Cardiol, 2007; \( n=40 \); randomized, placebo-controlled
- Okonko DO et al, J Am Col Cardiol, 2008 (FERRIC-HF); \( n=35 \); randomized, placebo-controlled
- Usmanov RI et al, J Nephrol, 2008; \( n=32 \); single arm

**Multicenter, placebo-controlled, double blind Trials**

- Anker SD et al, N Engl J Med, 2009 (= FAIR-HF study); \( n=459 \); randomized, placebo-controlled, double blind
- Ponikowski P et al, Eur Heart J, 2014 (CONFIRM-HF study); \( n=304 \); randomized, placebo-controlled, double blind
Effects of iron replacement in HF patients

- Increase in hemoglobin in anemic patients
- Improvement of NYHA class in anemic and non-anemic patients
- Improvement of peak VO2
- Improvement of NT-proBNP
- Improvement of left ventricular ejection fraction (LVEF)
- Improvement of creatinine clearance

Toblli JE, J Am Coll Cardiol 2007
Usmanov RI, J Nephrol 2008
Okonko DO et al. J Am Coll Cardiol 2008
FAIR-HF Trial Design

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤40% (NYHA II) or ≤45% (NYHA III)
  - Hb: 9.5–13.5 g/dL
  - Iron deficiency: serum ferritin <100 ng/mL or <300 ng/mL, if TSAT <20%

- **Treatment adjustment algorithm:**
  - Interruption: Hb>16.0 g/dL or ferritin>800 ng/mL or ferritin>500 ng/mL, if TSAT>50%
  - Restart: Hb <16.0 ng/mL and serum ferritin <400 ng/mL and TSAT<45%

- **Blinding:**
  - Clinical staff: unblinded and blinded personnel
  - Patients: usage of curtains and black syringes for injections

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**Diagram:**
- **Correction phase:** Ferric carboxymaltose, n=304
  - 200mg i.v. iron weekly
- **Maintenance phase:**
  - 200mg i.v. iron 4-weekly
- **Placebo:** Normal saline weekly
  - Normal saline 4-weekly
- **Screening:**
- **Week 26 safety evaluation:**
- **Week 24 1°: NYHA and PGA**

*Anker et al. Eur J Heart Failure 2009*
Results FAIR-HF Trial

Patient Global Assessment

NYHA functional class

6-minute walk test

KCCQ overall score

EQ-5D VAS score

Clinical improvement is independent of Hb

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>FCM no. of patients</th>
<th>Placebo no. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>p value for interaction</th>
<th>FCM no. of patients</th>
<th>Placebo no. of patients</th>
<th>Odds ratio (95% CI)</th>
<th>p value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤12 g/dL</td>
<td>146</td>
<td>74</td>
<td></td>
<td>0.98</td>
<td>148</td>
<td>74</td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>&gt;12 g/dL</td>
<td>146</td>
<td>75</td>
<td></td>
<td></td>
<td>146</td>
<td>76</td>
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Results CONFIRM-HF Trial

A 6MWT

Primary endpoint

<table>
<thead>
<tr>
<th>FCM</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>No of patients</td>
<td>143</td>
</tr>
<tr>
<td>LS mean (95% CI)</td>
<td>14 (0, 28)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FCM vs Placebo</th>
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<tr>
<td>14 (-5, 33)</td>
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</table>

<table>
<thead>
<tr>
<th>FCM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>137</td>
</tr>
<tr>
<td>LS mean (95% CI)</td>
<td>15 (1, 29)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>FCM vs Placebo</th>
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<tbody>
<tr>
<td>16 (-3, 35)</td>
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Secondary endpoint

B Fatigue

<table>
<thead>
<tr>
<th>FCM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>139</td>
</tr>
<tr>
<td>LS mean (95% CI)</td>
<td>-0.4 (-0.6, -0.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FCM vs Placebo</th>
</tr>
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<tbody>
<tr>
<td>-0.2 (-0.5, 0.2)</td>
</tr>
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</table>

Results CONFIRM-HF Trial

Secondary endpoint: Heart failure hospitalisation

- HF Hosp: 10/32 p=0.009
- HF Hosp or death: 22/46 p=0.03
- Death: 12/14 p=0.77

How to substitute, oral or i.v.? 

No evidence for clinical meaningful outcome for oral iron

Limitations of oral iron:

• Poor gastro-intestinal absorption in heart failure
• Long treatment period (150 – 200 days)
• Gastro-intestinal side effects in 20%
• Poor treatment adherence

i.v. iron = 100% adherence and absorption
Effects of i.v. iron on ferroportin

McDonagh T, Eur J Heart Fail 2015
Chronic HF (NYHA II-IV)

ID
Ferritin <100ng/mL or Ferritin 100-300ng/ml when TSAT <20%

yes

Anaemia
Male Hb < 13 g/dL
Female Hb < 12 g/dL

no

ID treatment

yes

Exclude other causes for anaemia depending on clinical status:
- Occult bleeding (e.g. GI, malignancies)
- Renal (erythropoietin)
- Other deficiencies (e.g. Vit B12, folic acid)
- Other haemoglobinopathies (e.g. thalassaemia, sick cell)

no

No treatment
Treatment algorithm

Iron deficiency treatment

Evidence based (FAIR-HF)

- Ferric carboxymaltose as weekly 200 mg single doses to correct iron deficiency calculated by Ganzoni formula
  - Check ferritin/TSAT at next scheduled visit (preferable 1–3 months)
- Ferric carboxymaltose as 4-weekly 200 mg single doses for maintenance

Evidence-based in CONFIRM-HF Being assessed in EFFECT-HF

- Ferric carboxymaltose as 500–1000 mg single doses to correct iron deficiency*
  - Check ferritin/TSAT at next scheduled visit (preferable 1–3 months)
- Ferric carboxymaltose as 500 mg to maintain ferritin/TSAT on target
  - Check ferritin/TSAT if change in clinical picture or Hb decrease or 1–2 times per year

McDonagh T, Eur J Heart Fail 2015
Ongoing clinical trials

Mortality trials

- FAIR-HF2
- IRON-MAN
Conclusion

- Iron deficiency is an emerging problem in CHF, affecting half of the patients.
- Iron deficiency = mitochondrial dysfunction.
- Iron deficiency represents a strong and independent predictor of mortality.
- Screening for iron deficiency should be part of the work up and management in patients with heart failure.
- i.v. iron substitution should be considered in symptomatic patients with iron deficiency to improve HF symptoms, quality of life and to reduce HF hospitalizations.
Vielen Dank

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Iron in the Guidelines

ESC Guidelines 2012

11. Importance and management of other co-morbidity in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction

11.1 Heart failure and co-morbidities
11.2 Anaemia
11.3 Angina
11.4 Asthma: see chronic obstructive pulmonary disease
11.5 Cachexia
11.6 Cancer
11.7 Chronic obstructive pulmonary disease
11.8 Depression
11.9 Diabetes
11.10 Erectile dysfunction
11.12 Gout
11.13 Hyperlipidaemia
11.14 Hypertension
11.14 Iron deficiency
11.15 Kidney dysfunction and cardiorenal syndrome
Iron in the Guidelines 2012

therapy improved self-reported patient global assessment and NYHA class (as well as 6-min walk distance and health-related quality of life) and may be considered as a treatment for these patients. The effect of treating iron deficiency in HF-PEF and the long-term safety of iron therapy in HF is unknown.