Oral Iron Repletion effects on Oxygen UpTake in Heart Failure (IRONOUT)

Gregory D. Lewis, M.D.
on behalf of
The NHLBI Clinical Heart Failure Network
Iron deficiency is present in ~50% of patients with chronic heart failure with reduced ejection fraction (HFrEF).

Iron deficiency is an independent predictor of mortality in patients with HFrEF.
Background: Iron Deficiency Impacts Functional Capacity in Heart Failure

**IRON DEFICIENCY**

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

- Extra-Erythropoietic Effects
  - ↓Aerobic Enzymes
  - ↓Myoglobin
  - ↓O₂ utilization

- Cardiomyocyte integrity - mitochondrial function
  - ↓LV Function

**VO₂ = (CaO₂ − CvO₂) x Cardiac Output**

Gold Standard Objective Measurement of Functional Capacity

- Anker S et al. EJHF 2009
- Petering LH, Ann Nutr Metab 1990
- Melanovsky et al, Circulation HF 2016
Two multicenter intravenous iron repletion trials in HFrEF:
- FAIR-HF and CONFIRM-HF\textsuperscript{1,2}
  - $\uparrow$6 min walk distance, $\uparrow$quality of life, $\downarrow$HF hospitalizations

Promising results from IV iron studies have served as an impetus for clinicians to prescribe iron supplementation. However:

- Regular administration of IV iron poses logistical challenges and is expensive
- Oral iron is safe and readily available, but its efficacy in HF is unknown
- Patient characteristics that influence responsiveness to oral iron in HF remain undefined

Background: Iron Homeostasis in HF

**Daily Recommended Iron intake:**
8-18 mg = 0.25% of body stores

**Duodenum Iron Absorption:**
5-35%

**Iron Absorption**
↓

**Gut edema**
↓
**Nutrient Intake**

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

**Iron loss (bleeding)**

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

**Iron Deficiency**
- Ferritin <100 ng/ml
- Tsat < 20% w/Ferritin 100-300 ng/ml
- Hepcidin expected < 3 ng/ml

**Heart Failure w/Iron Deficiency**

**Hepcidin**

**↓ Iron Bioavailability**

**↑Iron Absorption**

**↑Hepcidin**

**Ferroportin 1**

**Reticulo Endothelial System**
- ↑ Iron transport
- ↑ senescent RBC degradation

**IFN-γ**

**TNF α**
Hypothesis

Oral iron polysaccharide is superior to oral placebo in improving exercise capacity (peak VO$_2$) in patients with HFrEF and iron deficiency at 16 weeks.
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
Study Design

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

8 week Study Visit
6MWT, KCCQ

Oral placebo 150 mg bid

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

CPET: cardiopulmonary exercise testing
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**
  - $\Delta$ iron studies, $\Delta$ renal function
  - $\Delta$ VO$_2$ at the ventilatory threshold
  - Time to death or worsening HF
Baseline Features (n=225)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral Iron, N=111</th>
<th>Placebo, N=114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), y</td>
<td>63 (54-71)</td>
<td>63 (55-70)</td>
</tr>
<tr>
<td>Female sex</td>
<td>40%</td>
<td>32%</td>
</tr>
<tr>
<td>Racial Minority</td>
<td>29%</td>
<td>25%</td>
</tr>
<tr>
<td>NYHA II/III</td>
<td>73%/27%</td>
<td>60%/40%</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25 (20-34)</td>
<td>25 (20-33)</td>
</tr>
<tr>
<td>Peak VO₂, median (IQR), ml/kg/min</td>
<td>13.3 (11.4-15.8)</td>
<td>12.9 (10.5-15.6)</td>
</tr>
<tr>
<td>HF Duration, median (IQR), y</td>
<td>5.3 (1.4-10.3)</td>
<td>6.2 (2.0-9.8)</td>
</tr>
<tr>
<td>Ischemic etiology of HF</td>
<td>77%</td>
<td>78%</td>
</tr>
<tr>
<td>History of Hypertension</td>
<td>72%</td>
<td>73%</td>
</tr>
<tr>
<td>History of Atrial fibrillation</td>
<td>39%</td>
<td>38%</td>
</tr>
<tr>
<td>History of Diabetes mellitus</td>
<td>34%</td>
<td>44%</td>
</tr>
</tbody>
</table>

There were no significant baseline differences between groups
Baseline Features (n=225)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Oral Iron, N=111</th>
<th>Placebo, N=114</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Concomitant medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>88%</td>
<td>80%</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP, pg/ml</td>
<td>1072 (413-2286)</td>
<td>1170 (527-2530)</td>
</tr>
<tr>
<td>Estimated GFR, ml/min/1.73m²</td>
<td>56 (43-71)</td>
<td>61 (46-73)</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.6 (11.7-13.3)</td>
<td>12.7 (11.8-13.4)</td>
</tr>
<tr>
<td>Ferritin, ng/mL</td>
<td>69 (42-98)</td>
<td>69 (37-98)</td>
</tr>
<tr>
<td>Transferrin Saturation, %</td>
<td>18 (14-24)</td>
<td>17 (15-21)</td>
</tr>
<tr>
<td>Sol. transferrin receptor, mg/L</td>
<td>3.8 (3.3-4.8)</td>
<td>3.8 (2.9-4.8)</td>
</tr>
<tr>
<td>Hepcidin, ng/ml</td>
<td>6.6 (3.3-10.8)</td>
<td>6.5 (3.3-11.1)</td>
</tr>
</tbody>
</table>

There were no significant baseline differences between groups
Results: Primary Endpoint

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

Oral
Iron

Placebo

Median (25th-75th percentile)

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

Oral
Iron

Placebo

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>Δ 6 MW distance at 16 weeks, meters</td>
<td>19</td>
<td>32</td>
<td>0.19</td>
</tr>
<tr>
<td>Δ Mean response time, seconds</td>
<td>2.5</td>
<td>1</td>
<td>0.19</td>
</tr>
<tr>
<td>Δ Ventilatory efficiency (VE/VCO₂ slope)</td>
<td>-0.3</td>
<td>-0.3</td>
<td>0.35</td>
</tr>
<tr>
<td>Δ NT-BNP level, pg/ml</td>
<td>4</td>
<td>-37</td>
<td>0.48</td>
</tr>
<tr>
<td>Δ 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>Δ Ventilatory threshold (ml/min)</td>
<td>22</td>
<td>-2</td>
<td>0.07</td>
</tr>
<tr>
<td>Δ Creatinine, mg/dL</td>
<td>0.03</td>
<td>0.00</td>
<td>0.65</td>
</tr>
<tr>
<td>Δ 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>
Results: Δ Iron Studies

IRONOUT-HF

Ferritin (ng/ml)

Week 0 16
Week 0 16

Δ+11ng/ml
P=0.056

Normal range

Tsat (%)

Week 0 16
Week 0 16

Δ+3%
P=0.003

Normal range

Iron
Placebo

vs. FAIR-HF (IV Iron)

Δ+238ng/ml
P<0.001

Week 0 24
Week 0 24

Iron
Placebo

Δ+12%
P<0.001

Week 0 24
Week 0 24
Results: Hepcidin Levels Predict Responsiveness to Oral Iron

Higher baseline hepcidin levels were related to:

- ▼ △ iron bioavailability: △ Tsat r=-0.29, p=0.003
- ▼ △ cellular iron levels: △ sTfR r=0.49, p<0.001
- ▼ △ iron stores: △ Ferritin r=-0.30, p=0.003
Results: Potential Alternative Explanations for Lack of Iron Repletion with Oral Iron

Rates of venous congestion were low:
- 12% of patients had ↑ JVP
- 10% of patients had >mild edema

There was no major bleeding episodes in patients receiving oral iron
Results: Relationship between iron biomarkers and endpoints

Higher baseline Tsat levels were related to:

- ↑ Peak VO$_2$: $r=0.17$, $p=0.01$
- ↑ 6 min walk distance: $r=0.28$, $p<0.001$
- ↓ NT-proBNP: $r=0.16$, $p=0.015$
- ↑ KCCQ score: $r=0.28$, $p<0.001$

$\Delta$ Tsat was modestly correlated with $\Delta$ peak VO$_2$ ($r=0.17$, $p=0.03$)

Patients in the highest quartile of $\Delta$Tsat (>7%) demonstrated improvement in KCCQ scores ($p=0.046$) and a trend toward higher VO$_2$ at the ventilatory threshold ($p=0.07$)
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, whereas rates of venous congestion and bleeding were low during the study.

- These results do not support use of oral iron supplementation in patients with HFrEF.