Anemia In Heart Failure

When & How to Treat
BY

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Agenda

- Causes
- When to treat
- How to treat
“Ceiling Benefit” of Neurohumoral blocking

Neurohormonal blocking appears to have reached a benefit plateau.

Presumed limit for CHF drug treatment

- ACE-inhibitors
- Beta-blockers
- Aldosterone B
- ARBs

Reduction of CHF

Anemia: has recently been recognized as a potentially novel therapeutic target in patients with heart failure.
Scope of the problem

- In recent years, the occurrence of anemia in patients with chronic heart failure (CHF) has received increasing attention.
- The prevalence of anemia reported in HF varies considerably, from 4% to 55%.
- *This wide variation is due to*
  - Different recruitment profiles
  - Different threshold HB or hematocrit levels
  - No consensus on the definition of anemia in cardiology
Anemia In Patients With Heart Failure

The prevalence of anemia in heart failure patients is approximately:

- 30% for Inpatients
- 20% for Outpatients
Definition of anemia

- WHO criteria
  - Men: <13.0 g/dL
  - Women: <12.0 g/dL

- National Kidney Foundation criteria
  - Hb <12 g/dL in men and postmenopausal women
  - Hb <11 g/dL in premenopausal women
Increased Risk of Anemia

1. Increasing age
2. Female gender
3. Chronic kidney disease  
   (increased serum Cr or decreased GFR)
4. Decreased body mass index
5. Use of ACE inhibitors
6. Increased jugular venous pressure
7. Lower-extremity edema
Potential Cause of Anemia in CHF

LV dysfunction
- Decreased CO
- Renal Hypoperfusion

RAS Activation
- Sympathetic activation
  - Plasma volume expansion
    - Hemodilution
  - RAS Inhibition
    - Decreased EPO secretion
      - Decreased BM response
    - Pro-inflammatory cytokine
      - Decreased RBC production
    - CKD

Anemia
## Causes of Anemia in HF

| ↓ Cardiac Output | • Impaired renal perfusion, leading to impaired renal function, decreased EPO production and anemia\(^1\)  
<table>
<thead>
<tr>
<th></th>
<th>• Impaired bone marrow perfusion leading to impaired function and anemia(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines</td>
<td>• TNF and other inflammatory cytokines may cause bone marrow suppression, interfere with the action of EPO and the cellular release and utilization of iron(^2)</td>
</tr>
</tbody>
</table>
| Iron Deficiency | • Edematous GI may diminish absorption of iron  
|                 | • Chronic aspirin therapy may lead to blood loss |
| ACE inhibitors  | • Down-regulation of EPO by angiotensin-converting enzyme (ACE) inhibitors\(^3\) |
| Dilutional      | • Plasma volume expansion\(^4\) |

Mechanisms of anemia

3. Use ACE inhibitor

- Decrease angiotensin II level; decreased stimulation of the proliferation of erythroid progenitor cells
- Increasing N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP); hematopoiesis inhibitor
  - almost exclusively hydrolyzed by ACE,
  - partially eliminated in the kidney
- SOLVED trial; more anemia by 56% in enalapril
Mechanisms of anemia

1. Cytokines – TNF, IL-1, IFN
   - Reducing EPO production in kidney
   - EPO insensitivity at bone marrow level
   - Inhibiting iron release from RES
   - Bone marrow depression

2. Renal dysfunction
   - Cardio-renal-anemia syndrome
Causes of anemia

Total n = 12,065 (anemia : 17%)

- Iron deficiency (21% = 1,190)
- Other (13% = 226)
- Other deficiency (8% = 166)
- Anemia of chronic disease (58% = 1,190)

The etiology of iron deficiency in HF patients is likely multifactorial; some of the postulated causes are:

1. Poor nutrition,
2. Malabsorption due to edematous bowel wall,
3. Increased gastrointestinal blood loss due to antiplatelet and/or oral anticoagulation.
4. Altered iron homeostasis due to proinflammatory cytokine activation.
When To Treat?
**When To Treat?**

- Hemoglobin level $\leq 12.0\text{g/dl}$
- With repeated episode of ADHF
- Already receiving maximally therapy
HOW TO TREAT ?
- **Use of maximally tolerated doses of optimal CHF treatment.**

- **Normal red cell folate and vitamin B12**
### Potential benefits and risks of treating anemia in heart failure

<table>
<thead>
<tr>
<th>Potential benefits</th>
<th>Potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved oxygen delivery</td>
<td>Increased thrombosis</td>
</tr>
<tr>
<td>Improved exercise tolerance</td>
<td>Platelet activation</td>
</tr>
<tr>
<td>Attenuate adverse remodeling</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Antiapoptotic</td>
<td>Endothelial activation</td>
</tr>
<tr>
<td>Improved QOL</td>
<td></td>
</tr>
<tr>
<td>Decrease in hospitalization</td>
<td></td>
</tr>
<tr>
<td>Improved survival</td>
<td></td>
</tr>
</tbody>
</table>

*(Felker et al., JACC, 2004)*
Management of Anemia

- Anemia; consistent association with adverse clinical outcome
  - Potential therapeutic target

- Potential treatment
  1. RBC transfusion
  2. Fe supplementation
  3. Erythropoietin
“Transfusion threshold”

- Hematocrit < 30% in CV disease
  - Based on expert opinion
- The clinical utility in CV disease is controversial.
- Transfusion may be considered as an acute treatment for severe anemia.
- Not appear to be strategy for the long-term management in CHF.
- provide only temporary benefit
Transfusion

- Potential Risk
  - Infection
  - Immunosuppressive effect
  - Hemolytic reaction
  - Iron overload
  - Volume overload
Erythropoietin
Three available Erythropoietin

1. Epoetin-α and
2. Epoetin-β:
   - rHuEpo, $T_{1/2}$ 6-8h
   - Since 1985
3. Dabepoetin-α:
   - N-linked supersialylated analog, $T_{1/2}$ 48h
   - Since 2001
Effect of EPO in Heart Failure

1. Severe, resistant CHF with mild anemia with EPO & Iron → ↑LVEF, ↓hospitalization
   (Silverberg et al. JACC 2001)

2. DM & severe, resistant CHF with mild anemia with EPO → ↑LVEF, ↓hospitalization
   (Silverberg et al. Nephrol Dial Transplant 2003)

3. Moderate to severe CHF treated with EPO → ↑exercise duration
   (Mancini et al. Circulation 2003)
<table>
<thead>
<tr>
<th>Author, Year (Ref. #)</th>
<th>Study Design</th>
<th>Inclusion Criteria</th>
<th>Patients (n)</th>
<th>Follow-Up Duration (months)</th>
<th>Baseline Hgb (g/dl)</th>
<th>Target Hgb (g/dl)</th>
<th>Achieved Hgb (g/dl)</th>
<th>Agents and Dose Used</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silverberg et al., 2000 (65)</td>
<td>Single-center, uncontrolled, open-label</td>
<td>EF &lt;35, Hgb &lt;12 g/dl</td>
<td>26</td>
<td>7.2 ± 5.5</td>
<td>10.2</td>
<td>12.0</td>
<td>12.1</td>
<td>Subcutaneous epoetin alfa (mean 5,277 IU/week) + IV ferrous sulfate (mean 185 mg/month)</td>
<td>↓ NYHA functional class (3.7 ± 0.5 to 2.7 ± 0.7, p &lt; 0.05); ↑ LVEF (28 ± 5% to 35 ± 8%, p &lt; 0.001); Decrease in diuretic dose; Decrease in hospitalizations</td>
</tr>
<tr>
<td>Silverberg et al., 2001 (66)</td>
<td>Single-center, randomized, no placebo, open-label</td>
<td>NYHA functional class III/IV, EF &lt;40%, Hgb 10–11.5 g/dl</td>
<td>16 usual care, 16 EPO</td>
<td>8.2 ± 2.8</td>
<td>10.3</td>
<td>12.5</td>
<td>12.9</td>
<td>Subcutaneous epoetin alfa (4,000 IU 1–3x/week) + IV iron sucrose (200 mg/2x weeks)</td>
<td>↓ NYHA functional class, ↑ LVEF +5.5%; Decrease in diuretic dose; Decrease in hospitalizations</td>
</tr>
<tr>
<td>Mandini et al., 2003 (67)</td>
<td>Single-center, single-blind, randomized, placebo-controlled</td>
<td>NYHA functional class II/IV, Hct &lt;35%</td>
<td>9 control, 17 EPO</td>
<td>3.0</td>
<td>11.0 ± 0.6</td>
<td>Hct &gt;45%</td>
<td>14.3 ± 1.2</td>
<td>Subcutaneous epoetin alfa, 15,000 to 30,000 IU/week + oral iron 325 mg and folic acid 1 mg OD</td>
<td>↑ Peak VO2 11 ± 0.8 to 12.7 ± 2.8 ml/kg/min (p &lt; 0.05); ↑ 6MWD; Improvement in MLHFQ</td>
</tr>
<tr>
<td>Palazzuoli et al., 2007 (68)</td>
<td>Single-center, randomized, double-blind, placebo-controlled</td>
<td>NYHA functional class II/IV, EF &lt;40%, Hgb 9.0–12.0 g/dl, serum creatinine 1.6–3.0 mg/dl</td>
<td>25 control, 28 beta EPO</td>
<td>12</td>
<td>10.4 ± 0.6</td>
<td>NA</td>
<td>12.4 ± 0.8</td>
<td>Subcutaneous epoetin alfa, 6,000 IU/2x/week + oral iron 300 mg for 1 year</td>
<td>↑ LVEF, ↓ LV volumes, mass ↓ PAP and BNP; No change in serum creatinine</td>
</tr>
<tr>
<td>Pontkowski et al., 2007 (69)</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Hgb 9.0–12.0 g/dl, peak VO2 &lt;16 ml/kg/min</td>
<td>22 placebo, 19 darbepoeitin</td>
<td>27 weeks</td>
<td>11.8 ± 0.2</td>
<td>13.0–15.0</td>
<td>13.9 ± 0.4</td>
<td>Darbepoeitin alfa, 0.75 μg/kg Q2W + 200–300 oral iron if serum ferritin &lt;800 ng/ml</td>
<td>Mean change in peak VO2 (45 ml/min, p = 0.27) or (0.5 ml/kg/min, p = 0.40); Ex duration 108 s (p = 0.08); ↑ PCA (70% vs. 41%, p = 0.01); No change in KCQ/MHF; No change in BNP or Cr</td>
</tr>
<tr>
<td>van Veldhuisen et al., 2007 (70)</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Hgb &gt;9.0 and &lt;12.5 g/dl, NYHA functional class II/III CHF, LVEF &lt;40%</td>
<td>55 placebo, 56 darbepoeitin (weight based), and 54 darbepoeitin (fixed dose)</td>
<td>27 weeks</td>
<td>11.5</td>
<td>14 ± 1.0</td>
<td>13.3</td>
<td>Darbepoeitin weight adjusted 0.75 μg/kg vs. fixed dose 50 μg vs. placebo Q2W + oral iron (200 mg OD if serum ferritin &lt;800 ng/ml)</td>
<td>Rate of rise Hgb 1.87 ± 1.64 g/dl in weight-based vs. fixed dose (p = 0.07); improvement in KCQ (p &lt; 0.03), no significant improvement in 6MWG (p = 0.074), patients global assessment (p = 0.067); NYHA functional class, LVEF, or MLHFQ score</td>
</tr>
<tr>
<td>Chali et al., 2008 (STAMINA-Heart Failure) (71)</td>
<td>Multicenter, randomized, double-blind, placebo-controlled</td>
<td>Hgb &gt;9.0 and &lt;12.5 g/dl, NYHA functional class II/IV CHF, LVEF &lt;40%,</td>
<td>157 placebo, 162 darbepoeitin</td>
<td>27 weeks for efficacy SS weeks for safety</td>
<td>11.4</td>
<td>14 ± 1.0</td>
<td>13.4 at 27 weeks, 13.4 at 53 weeks</td>
<td>Darbepoeitin dose 0.75 μg/kg Q2W vs. placebo + oral iron (200 mg OD if serum ferritin &lt;800 ng/ml)</td>
<td>No significant difference in exercise duration, NYHA functional class or quality of life scores at 27 weeks but trend to a decrease in the combined and point of death and hospitalization for HF</td>
</tr>
<tr>
<td>van Veldhuisen and McMurray 2007 (72)</td>
<td>Combined safety analysis</td>
<td>Hgb &gt;9.0 and &lt;12.5 g/dl, NYHA functional class II/IV CHF, LVEF &lt;40%,</td>
<td>200 placebo, 266 darbepoeitin</td>
<td>55 weeks</td>
<td>11.4 ± 0.8</td>
<td>14 ± 1.0</td>
<td>13.4</td>
<td>Darbepoeitin dose 0.75 μg/kg or 50 μg vs. placebo Q2W + oral iron (200 mg OD if serum ferritin &lt;800 ng/ml)</td>
<td>Trend to a decrease in the combined endpoint of death and hospitalization for HF (hazard ratio and 95% confidence interval) for darbepoeitin vs. placebo 0.67 (0.44 to 1.03), p = 0.06</td>
</tr>
</tbody>
</table>
Comparison of trials with erythropoietin

<table>
<thead>
<tr>
<th>Study population</th>
<th>CREATE n = 603</th>
<th>CHOIR n = 1432</th>
<th>TREAT n = 4000*</th>
<th>RED-HF n = 3400</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m²)</td>
<td>15-35</td>
<td>15-50</td>
<td>20-60</td>
<td>“Normal”</td>
</tr>
<tr>
<td>Hb eligibility (g/dL)</td>
<td>11-12.5</td>
<td>≤ 11</td>
<td>≤ 11</td>
<td>9-12</td>
</tr>
<tr>
<td>Target Hb (g/dL) in treatment arm</td>
<td>13-15</td>
<td>13.5</td>
<td>13.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Study drug</td>
<td>Epoetin beta</td>
<td>Epoetin alfa</td>
<td>Darbepoetin alfa</td>
<td>Darbepoetin alfa</td>
</tr>
<tr>
<td>Control arm</td>
<td>Active</td>
<td>Active</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Presence of diabetes</td>
<td>26%</td>
<td>49%</td>
<td>100%</td>
<td>(30?)**</td>
</tr>
<tr>
<td>Presence of heart failure</td>
<td>32%</td>
<td>23%</td>
<td>(30%)?**</td>
<td>100%</td>
</tr>
<tr>
<td>Presence of hypertension</td>
<td>90%</td>
<td>94%</td>
<td>(70%)?**</td>
<td>(40%)?**</td>
</tr>
<tr>
<td>Baseline systolic BP (mm Hg)</td>
<td>139</td>
<td>136</td>
<td>(135-140)?**</td>
<td>(110?)**</td>
</tr>
<tr>
<td>Baseline GFR (ml/min/1.73 m²)</td>
<td>24.5</td>
<td>27.2</td>
<td>(25?)**</td>
<td>(53?)**</td>
</tr>
<tr>
<td>No. of patients experiencing a primary cardiovasc. endpoint</td>
<td>105</td>
<td>222</td>
<td>-900</td>
<td>-1450*</td>
</tr>
</tbody>
</table>

* Projected; study still ongoing; **assumptions; based on similar/earlier studies.
BP = blood pressure; CKD = chronic kidney disease; CHF = chronic heart failure,
GFR = glomerular filtration rate

Advantages of EPO Therapy

1. Increase hemoglobin level
2. Increases peak O2 consumption
3. Improve functional class
4. Decreases ventricular remodeling
5. Improve cardiac and renal functions
6. Reduce diuretic dose
7. Reduce hospitalizations
8. Reduce mortality rate (small study)
Pleiotropic Effect of EPO

1. Reduce oxidative stress
2. Promote neuronal survival after ischemia
3. Protect against ischemic vascular injury
4. Increasing Circulating EPC & BM stem cell
5. Angiogenesis
6. Mitogenic effect on cardiac myocytes
Disadvantages of EPO Therapy

1. Increase hypertension
2. Increase thrombosis
3. Increase endothelin activation
4. Expensive
Mechanisms of the Adverse Effects of EPO therapy

1. Increased viscosity
2. Reduced nitric oxide availability
3. Increase in vascular cytosolic calcium.
4. Increase in endothelin-1
5. Increase in (TS) renin-angiotensin activity
Eleven studies (794 participants) were revised. Nine studies being placebo-controlled but only five double-blinded. Compared to control, **ESA treatment significantly improved**:

- Exercise duration by 96.8 seconds (p=0.04)
- 6-minute walk distance by 69.3 metres (p=0.009).
- Benefit peak VO2 (+2.29 mL/kg/min, p=0.007),
- NYHA class (-0.73, p<0.001),
- Ejection fraction (+5.8%, p<0.001),

---

Erythropoiesis-stimulating agents for anaemia in chronic heart failure

- B-type natriuretic peptide (-226.99 pg/mL, p<0.001)
- Quality-of-life indicators,
- A mean increase in haemoglobin of 1.98 g/dL (p<0.0001).
- A significantly lower rate of HF related hospitalisations
- Lower all-cause mortality

No increase in adverse events with ESA therapy was observed, however studies were of small sample sizes and limited duration.

Ngo K Cochrane Syst Rev 2010, Jan 20;(1).
<table>
<thead>
<tr>
<th></th>
<th>EPO-alpha</th>
<th>Darbepoetin-alpha</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (s.c.)</strong></td>
<td>80-120 U/kg/week</td>
<td>0.45mg/kg/week</td>
</tr>
<tr>
<td><strong>Interval (recommended)</strong></td>
<td>Divided 2x/week</td>
<td>Weekly</td>
</tr>
<tr>
<td><strong>Interval range</strong></td>
<td>Up to once every 2-3 weeks</td>
<td>Up to monthly</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Every 2 weeks until stable; then monthly</td>
<td>Every 2 weeks until stable; then monthly</td>
</tr>
<tr>
<td><strong>Dose adjustment (25%-50%)</strong></td>
<td>Every 2 weeks</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

Locatelli et al., *American Journal of Kidney Disease* 2002
Intravenous Iron
Distinguishing ACD From IDA

<table>
<thead>
<tr>
<th>Blood test</th>
<th>ACD</th>
<th>IDA</th>
<th>ACD + IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Iron-binding capacity (IBC)</td>
<td>↓</td>
<td>↑</td>
<td>LN or ↓</td>
</tr>
<tr>
<td>% saturation of IBC</td>
<td>↓ or N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Ferritin</td>
<td>↑</td>
<td>↓</td>
<td>↓ or N</td>
</tr>
<tr>
<td>Soluble transferrin receptor</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

LN = low normal, N = normal

intravenous iron can rapidly replenish iron stores in patients having iron-deficiency anemia, with resultant increased hemoglobin levels and improved functional capacity.

Intravenous iron therapy can improve functional capacity even in those subjects without anemia.

The mechanisms responsible for this may be related to beneficial effects of iron supplementation on mitochondrial respiration in skeletal muscle.

Potential Risks of Intravenous Iron

- Iron is a known pro-oxidant factor that can inhibit nitric oxide signaling irreversibly injury cells.
- Increased iron stores are associated with vascular endothelial dysfunction and increased risk of CAD events.
- Additional clinical trials are needed to more fully characterize the therapeutic potential and safety of intravenous iron in HF patients.

Stuart D. Katz, Cardiology in Review 2010;18: 240–50
Numerous mechanisms unrelated to hemodynamic dysfunction may underlie impaired exercise tolerance in patients with CHF.

Among them, inadequate oxygen supply and impaired oxygen use by skeletal muscle during exercise,

In addition, anemia may aggravate symptoms in patients with HF.

Targeting these abnormalities may confer functional benefits to such patients.

Ferinject Assessment in Patients with Iron Deficiency and Chronic Heart Failure (FAIR-HF)

METHODS

- 459 patients with chronic heart failure of (NYHA) functional class II or III, a left ventricular ejection fraction of 40% or less

- Iron deficiency (ferritin level <100 μg per liter or between 100 and 299 μg per liter, if the transferrin saturation was <20%), and a hemoglobin level of 95 to 135 g per liter.

- Patients were randomly assigned, in a 2:1 ratio, to receive 200 mg of intravenous iron \textit{(ferric carboxymaltose)} or (placebo).

- The primary end points were the self-reported Patient Global Assessment and NYHA functional class, at week 24.

- Secondary end points included the distance walked in 6 minutes and the health-related quality of life.

A  Self-Reported Patient Global Assessment at Wk 24

No. of Patients

<table>
<thead>
<tr>
<th></th>
<th>Ferric carboxymaltose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much improved</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Moderately improved</td>
<td>34</td>
<td>17</td>
</tr>
<tr>
<td>A little improved</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Unchanged</td>
<td>18</td>
<td>35</td>
</tr>
<tr>
<td>A little worse</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Moderately worse</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Much worse</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dead</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

B  NYHA Functional Class at Wk 24

No. of Patients

<table>
<thead>
<tr>
<th></th>
<th>Ferric carboxymaltose</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Class II</td>
<td>121</td>
<td>43</td>
</tr>
<tr>
<td>Class III</td>
<td>148</td>
<td>97</td>
</tr>
<tr>
<td>Class IV</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Dead</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>
Conclusion; in stable, symptomatic, ambulatory patients with chronic HF, with impaired LVEF, and iron deficiency, treatment with ferric arboxymaltose over a 24-week period improves symptoms, physical performance, and the quality of life and has acceptable side-effect and adverse-event profiles.
Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency

FERRIC-HF: A Randomized, Controlled, Observer-Blinded Trial

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London and Slough, United Kingdom; Wroclaw, Poland; and Würzburg and Berlin, Germany
Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency

FERRIC-HF

Objectives

We tested the hypothesis that Intravenous Iron Improves exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure (CHF) and Iron deficiency.

Background

Anemia is common in heart failure. Iron metabolism is disturbed, and administration of Iron might improve both symptoms and exercise tolerance.

Methods

We randomized 35 patients with CHF (age 64 ± 13 years, peak oxygen consumption [pVO₂] 14.0 ± 2.7 ml/kg/min) to 16 weeks of Intravenous Iron (200 mg weekly until ferritin >500 ng/ml, 200 mg monthly thereafter) or no treatment in a 2:1 ratio. Ferritin was required to be <100 ng/ml or ferritin 100 to 300 ng/ml with transferrin saturation <20%. Patients were stratified according to hemoglobin levels (<12.5 g/dl [anemic group] vs. 12.5 to 14.5 g/dl [nonanemic group]). The observer-blinded primary end point was the change in absolute pVO₂.
Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients With Symptomatic Chronic Heart Failure and Iron Deficiency

Results
The difference (95% confidence interval [CI]) in the mean changes from baseline to end of study between the iron and control groups was 273 (151 to 396) ng/ml for ferritin (p < 0.0001), 0.1 (−0.8 to 0.9) g/dl for hemoglobin (p = 0.9), 96 (−12 to 205) ml/min for absolute $p$-Vo$_2$ (p = 0.08), 2.2 (0.5 to 4.0) ml/kg/min for $p$-Vo$_2$/kg (p = 0.01), 60 (−6 to 126) s for treadmill exercise duration (p = 0.08), −0.6 (−0.9 to −0.2) for New York Heart Association (NYHA) functional class (p = 0.007), and 1.7 (0.7 to 2.6) for patient global assessment (p = 0.002). In anemic patients (n = 18), the difference (95% CI) was 204 (31 to 378) ml/min for absolute $p$-Vo$_2$ (p = 0.02), and 3.9 (1.1 to 6.8) ml/kg/min for $p$-Vo$_2$/kg (p = 0.01). In nonanemic patients, NYHA functional class improved (p = 0.06). Adverse events were similar.

Conclusions
Intravenous iron loading improved exercise capacity and symptoms in patients with CHF and evidence of abnormal iron metabolism. Benefits were more evident in anemic patients. (Effect of Intravenous Ferrous Sucrose on Exercise Capacity in Chronic Heart Failure;

J. Am. Coll. Cardiol. 2008;51;103-112
IV iron available in Egypt

- Iron saccharate (one ampoule 5 ml = 100 mg trivalent iron)
- **Iron** dextran complex (2 ml = 100 mg iron)
- **Iron** dextran complex (5 ml = 250 mg iron)
Silverberg et al. were the first to report the effect of epoetin alfa and intravenous (IV) iron in 26 patients with anemia and HF.

An increase in Hgb was associated with improvements in NYHA functional class and LV ejection fraction and decreases in diuretic dose and hospitalizations.
The hematological and clinical data of the 26 CHF patients at onset and at the end of the intervention period

<table>
<thead>
<tr>
<th>Test</th>
<th>Initial</th>
<th>Final</th>
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</thead>
<tbody>
<tr>
<td>Hematocrit, vol%</td>
<td>30.14 +/-3.12</td>
<td>35.9 +/-4.22</td>
</tr>
<tr>
<td>Hemoglobin, g%</td>
<td>10.16 +/-0.95</td>
<td>12.1 +/-1.21</td>
</tr>
<tr>
<td>Serum ferritin, mg/liter</td>
<td>177.07 +/-113.80</td>
<td>346.73 +/-207.4</td>
</tr>
<tr>
<td>Serum iron, mg%</td>
<td>60.4 +/-16.0</td>
<td>74.8 +/-20.7</td>
</tr>
<tr>
<td>%iron saturation</td>
<td>20.5 +/-6.04</td>
<td>26.14 +/-5.23</td>
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<tr>
<td>Serum creatinine, mg%</td>
<td>2.59 +/-0.77</td>
<td>2.73 +/-1.55</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>27.7 +/-4.8</td>
<td>35.4 +/-7.6</td>
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<tr>
<td>No. hospitalization/patient</td>
<td>2.72 +/-1.21</td>
<td>0.22 +/-0.65</td>
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<tr>
<td>Systolic BP, mm Hg</td>
<td>127.1 +/-19.4</td>
<td>128.9 +/-26.4</td>
</tr>
<tr>
<td>Diastolic BP mm Hg</td>
<td>73.9 +/-9.9</td>
<td>74.0 +/-12.7</td>
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<tr>
<td>NYHA (0-4)</td>
<td>3.66 +/-0.47</td>
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(AFTER SILVERBERG et al., JACC, 2000)
The Use of Subcutaneous Erythropoietin and Intravenous Iron for the Treatment of the Anemia of Severe, Resistant Congestive Heart Failure Improves Cardiac and Renal Function and Functional Cardiac Class, and Markedly Reduces Hospitalizations

Donald S. Silverberg, MD, Dav Wechsler, MD, Marian Riem, MD, Carl Korcz, MD, David Slep, MD, Brian Liebman, MD, David Eskin, MD, Sibine Leckoko, MD, Lewis Schwartz, MD, Tatsuyuki Yuda, MD, Rajk Supekar, MD, Dov Garash, MD, Ron Sasson, MD, Shulie Kolodka, MD, Ciel Kaplan, MD, Shoshana Steinbach, RN, Adriel Izu, MD
Tel Aviv, Israel

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>15 months F/U</th>
<th>Final</th>
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</thead>
<tbody>
<tr>
<td>Hematocrit, vol%</td>
<td>30.14 ± 3.12</td>
<td>35.90 ± 4.22*</td>
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<td>Hemoglobin, g/dl</td>
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*Significantly different from baseline.
Palazzuoli et al. reported the effects of **epoetin beta and oral iron on**:

- LV structure and function
- Pulmonary artery pressure
- BNP

In 51 anemic HF patients with CKD.

After 12 months,

Hgb increased, LV dimensions, volume, and mass decreased, the pulmonary artery pressure and BNP also decreased.

*Palazzuoli A,. Am Heart J 2007;154:645e9 –15.*
Take Home Massage!

- Anemia has emerged as a possible treatment target in HF.
- But, larger controlled clinical trials are needed for further information and therapy guidelines.

- Recommendation based on the available data
  1. Hemoglobin level $\leq 12.0$g/dl
  2. with repeated episode of ADHF
  3. and already receiving maximally therapy
Thank You