Heart failure and anaemia – investigation and management

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Conflict of interest:
Speaker fees and advisory boards for Vifor International and Vitaline Pharmaceuticals
### Prevalence of anaemia in large CHF studies

-- sorted by CHF severity --

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Definition (g/dL)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx assessment</td>
<td>F</td>
<td>&lt;12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>&lt;13</td>
<td>30.0</td>
</tr>
<tr>
<td>Horwich H et al. JACC 2002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>M+F</td>
<td>&lt;12.5</td>
<td>19</td>
</tr>
<tr>
<td>IN CHF</td>
<td>F</td>
<td>&lt;11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>&lt;12</td>
<td>15.6</td>
</tr>
<tr>
<td>ELITE II</td>
<td>F</td>
<td>&lt;12</td>
<td>16.6</td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>&lt;12</td>
<td>7.2</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>F</td>
<td>&lt;11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>&lt;12</td>
<td>9.0</td>
</tr>
</tbody>
</table>
Prevalence of anaemia

• Systematic review and meta-analysis

• 34 studies

• n=153,180

• Majority WHO definition (18/34)

• Using study definition, anaemia present in:

  37.2%

Groenveld et al. J Am Coll Cardiol 2008;52:818-827
Acute heart failure in the elderly

- Italian Survey on AHF – 206 departments enrolled 2,807 in 3 months
- Octogenarians (mean age 84) - 28% of cohort
- Females 50% (36% in those <80 yrs)
- Anaemia (64% vs 53%, p< 0.0001) and CKD (56% vs 43%, p<0.0001) more common in those >80 yrs
- In-hospital mortality twice as high in octogenarians (11.8% vs 5.6%, p<0.001).

Prevalence of anaemia increases with NYHA class in elderly CHF patients

Prospective study: 201 patients (aged >65 years)

Results: 49.8% had haemoglobin (Hb) <12 g/dL

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>36.4</td>
</tr>
<tr>
<td>3</td>
<td>52.0</td>
</tr>
<tr>
<td>4</td>
<td>65.9</td>
</tr>
</tbody>
</table>

$P = 0.01$

Wisniacki N et al. Heart 2001
Independent relation between peak VO₂ and Hb in males with CHF

All patients (n=93)
\[ r = 0.36, \ p = 0.0004 \]

Hb ≥ 13 g/dL (n=57)
\[ r = -0.05, \ p = 0.7 \]

Hb < 13 g/dL (n=36)
\[ r = 0.41, \ p=0.01 \]

Kalra et al. Am J Cardiol 2003;91:888-91
CHF: Hb level vs Mortality (n=1,061)

Hb independent predictor of mortality with relative risk 1.131 per 1 g/dL decrease (95% CI 1.045 to 1.224)

Horwich et al. J Am Coll Cardiol 2002;39:1780-6
Hb and survival in ELITE II (n=3044)

Risk ratio for death during follow-up

- RR 0.986 p<0.0001
- RR 1.033 p<0.0001

### Possible mechanisms of anaemia in CHF

<table>
<thead>
<tr>
<th>Haemodilution</th>
<th>Chronic immune activation (TNF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Volume ↑</td>
<td>- production of Epo ↓</td>
</tr>
<tr>
<td></td>
<td>- Epo activity in BM ↓</td>
</tr>
<tr>
<td></td>
<td>- Impaired release and utilization of Fe</td>
</tr>
<tr>
<td>Decreased CO</td>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td>Bone Marrow (BM)</td>
<td>ACE-I: Epo synthesis ↓</td>
</tr>
<tr>
<td>dysfunction</td>
<td>Epo activity in BM ↓</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td><strong>Chronic kidney failure</strong></td>
</tr>
<tr>
<td>Fe^{++} uptake ↓</td>
<td>Production of Epo ↓</td>
</tr>
<tr>
<td>malabsorption</td>
<td>Loss in urine ↑</td>
</tr>
<tr>
<td>chronic bleeding</td>
<td></td>
</tr>
<tr>
<td>(aspirin)</td>
<td></td>
</tr>
</tbody>
</table>

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Aetiology of anaemia in CHF

- n=173 LVSD, n=123 preserved LV
- anaemia <12.5 g/dL: 35% LVSD, 33% preserved LV
- 6% Vit B12 and 8% folate deficient

Witte et al. Am Heart J 2004;147:924-930

- Advanced HF n=37, extensive Ix including bone marrow biopsy: 73% iron deficient

Nanas et al. J Am Coll Cardiol 2006

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92% of patients with anaemia of chronic disease exhibited iron deficiency for erthropoiesis and/or defective endogenous EPO production
Impact of anaemia on cardiac function

Anaemia

Remodeling
LVH ... cell death

↑ LV diameter

↑ Plasma volume ... Oedema

Fluid retention

↑ Renin Angiotensin Aldosterone ADH

↑ Blood pressure

↓ Renal blood flow

Peripheral vasodilatation

CHF

Tissue Hypoxia

↓ Blood pressure

Activation of SNS

Oedema

Remodeling
LVH ... cell death
Placebo controlled study confirms benefit of anaemia Rx in CHF patients

32 patients (NYHA Class III/IV) on maximal medical therapy randomized to placebo or EPO + iv iron (goal Hb 12.5) with mean follow-up of 8.2 months.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EPO + iv Fe (n=16)</th>
<th>Placebo (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>0 deaths</td>
<td>4 deaths</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>+ 18%</td>
<td>– 19%</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>– 78%</td>
<td>+ 57%</td>
</tr>
<tr>
<td>Oral Furosemide (mg/d)</td>
<td>– 51%</td>
<td>+ 28%</td>
</tr>
<tr>
<td>iv. Furosemide (mg/wk)</td>
<td>– 91%</td>
<td>+ 27%</td>
</tr>
</tbody>
</table>

Change in peak VO₂ vs change in Hb

Change in Hb (g/dL)

Change in VO₂ (ml/kg/min)

N=22
R = 0.53
P < 0.02

Intravenous iron alone for the treatment of anaemia in patients with chronic heart failure

Open label study n=16, Hb<12

<table>
<thead>
<tr>
<th></th>
<th>Baseline (Hb 11.2)</th>
<th>Completion (Hb 12.6)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA functional class (II/III)</td>
<td>9/7</td>
<td>16/0</td>
<td>0.02</td>
</tr>
<tr>
<td>MLHF Questionnaire (0-105)</td>
<td>32.9 (19.0)</td>
<td>19.4 (14.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>6-minute walk test (m)</td>
<td>242 (78)</td>
<td>286 (72)</td>
<td>0.01</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>26 (13)</td>
<td>27 (12)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Bolger et al. J Am Coll Cardiol 2006;48:1225-7
Relationship between changes in quality of life and exercise capacity and change in Hb

Change in MLHF questionnaire score

Change in 6MW (m)

R = 0.76
p = 0.002

R = 0.56
p = 0.03
FERRIC-HF (n=35)
(mean age 63, peak VO$_2$ 14.0, LVEF 30%, Ferritin 75, Hb 12.4)

Randomization – 2 : 1
active vs control

Iron sucrose i.v.

correction phase  →  maintenance phase
weekly (200mg i.v.)  →  every 4 weeks

Open-label, observer blinded

Primary endpoint:
Change from baseline in exercise tolerance
(total peak VO$_2$)

Screening

W-2
W-1
W0  W1  W4  W8  W12  W16  W18

Control

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Okonko D et al. J Am Coll Cardiol 2008;51:103-12
FERRIC-HF: Results
change in exercise capacity

Total peak VO₂ (mL/min)  Peak VO₂ (mL/kg/min)  Exercise time (s)

- Controls
- Iron sucrose

**Total peak VO₂ (mL/min)**
- Iron sucrose: 96 (range: -12, 205)
- Control: 0

**Peak VO₂ (mL/kg/min)**
- Iron sucrose: 2.2 (range: 0.5, 3.9)
- Control: 0

**Exercise time (s)**
- Iron sucrose: 60 (range: -6, 126)
- Control: 0

*Data: mean±SD and treatment effect (95%CI)*

*P = 0.08*  
*P = 0.01*  
*P = 0.08*
Darbepoetin in CHF: n=41
exercise time – treadmill

Difference in adjusted* mean (95% CI) change of exercise duration from baseline to week 27 between darbepoetin alfa and placebo groups:

109 sec (-11 to 228); *P* = 0.07

*Adjusted for baseline value and study centre.

Data shown are means (± SE)

**Improved PGA with Darbe:**  *p*=0.03

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Pre-specified Pooled Analysis, Darbepoetin Alfa and Morbidity and Mortality Events

as reported by Abraham et al, ESC 2006

K-M Plot of All-cause Mortality or First Hospitalization for Worsening Heart Failure*
Integrated Analysis from Two Studies

- Age 70±11 yrs
- LVEF 33±10%
- Hb 11.4±0.8 g/dL

All Mortality / HF hospitalization: HR 0.67 (0.44–1.03), P=0.064

Subjects at risk:
Placebo 209 205 199 197 190 189 186 187 179 175 174 170 167 166 158 124 120 119 117 113 110 108 107 104 100 88 41
Darbepoetin alfa 266 262 260 255 253 248 243 241 237 236 231 228 224 222 201 133 127 126 126 125 124 121 120 119 112 36

Study Week

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**ESA and po iron vs po iron alone (n=40)**

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Final</th>
<th>Initial</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beat/min)</td>
<td>84 ± 8</td>
<td>80 ± 8</td>
<td>82 ± 8</td>
<td>84 ± 10</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>134 ± 10</td>
<td>136 ± 10</td>
<td>130 ± 10</td>
<td>128 ± 12</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>82 ± 6</td>
<td>85 ± 8</td>
<td>82 ± 5</td>
<td>80 ± 8</td>
</tr>
<tr>
<td>Distance walked (m)</td>
<td>278 ± 55</td>
<td>356 ± 88*</td>
<td>285 ± 68</td>
<td>266 ± 45</td>
</tr>
<tr>
<td>Exercise duration (min)</td>
<td>5.8 ± 2.2</td>
<td>7.8 ± 2.5</td>
<td>5.8 ± 2.4</td>
<td>6.0 ± 2.4</td>
</tr>
<tr>
<td>V·O₂ (mL/kg per min)</td>
<td>12.8 ± 2.8</td>
<td>15.1 ± 2.8†</td>
<td>12.5 ± 3.1</td>
<td>12.0 ± 2.5</td>
</tr>
<tr>
<td>V·O₂ AT (mL/kg per min)</td>
<td>9.2 ± 2.0</td>
<td>13.2 ± 3.6*</td>
<td>9.0 ± 2.5</td>
<td>8.7 ± 2.7</td>
</tr>
<tr>
<td>Respiratory rate (breath/min)</td>
<td>21.2 ± 4.8</td>
<td>31.1 ± 6.3†</td>
<td>20.8 ± 4.5</td>
<td>21.5 ± 5.2</td>
</tr>
<tr>
<td>RER (V·CO₂/V·O₂)</td>
<td>0.96 ± 0.20</td>
<td>1.15 ± 0.18</td>
<td>0.99 ± 0.18</td>
<td>1.0 ± 0.21</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.5 ± 0.6</td>
<td>2.8 ± 0.5†</td>
<td>3.4 ± 0.6</td>
<td>3.6 ± 0.4</td>
</tr>
<tr>
<td>BNP pg/mL</td>
<td>568 ± 320</td>
<td>271 ± 120*</td>
<td>585 ± 342</td>
<td>496 ± 320</td>
</tr>
</tbody>
</table>

*V·O₂, Oxygen consumption during maximal exercise; V·O₂ AT, is oxygen consumption at anaerobic threshold; BP, blood pressure; RER, respiratory exchange rate.

*P < .01 (intergroup and intragroup).
†P < .05 (intragroup and intergroup).

**ESA and po iron Hb 10.4 → 12.4, NO change with po iron**

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Outstanding questions

• Need large-scale efficacy and safety data (RED-HF and FAIR-HF ongoing)

• What level of haemoglobin to initiate treatment

• Target haemoglobin

• What constitutes ‘best practice’ for investigation

• Iron or ESA or both
Investigation of CHF and anaemia

- History (including drugs) and examination – fundamental
- FBC, U&Es, LFTs, TFTs, CRP
- B12, folate, ferritin
- Simple markers of changes in RBCs that accompany iron deficiency:
  - decrease in mean cell Hb (MCH)
  - hypochromia (% hypochromics)
  - reduced mean cell volume (MCV)
• Serum markers of iron deficiency:
  - low ferritin (<12-15µmg/L) – very good if no co-existent disease
  - with co-existent disease ferritin <50 – suggestive of iron deficiency (<200 in severe CKD)
  - low iron
  - increase in total iron binding capacity (TIBC)
  - reduction in transferrin saturation (TSAT, <16%, <20%)
  - soluble transferrin binding receptor

• Erythropoietin level

• Some GI and/or haematological revue
Case

- 77 year old female
- CHF secondary to IHD, previously stable NYHA II
- Rx: loop diuretic, ACE inhibitor, beta-blocker, aspirin
- Presents to GP with fatigue and exertional dyspnoea (NYHA III)
- Clinically euvolaemic
- Sinus rhythm 60  BP 100/60

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Case

- ECG SR QRSd 118 ms
- Ix: eGFR 45 CRP 7
  - Hb 10.8 g.dL MVC 80
  - B12 & folate normal Ferritin 50
  - TSAT 15%

- Who would treat with:
  (i) po iron  (ii) iv iron  (iii) ESA +/- iron
  (iv) Transfusion  (v) no further options