Iron Deficiency Anemia: from the Cardiologist Perspective.

-- Washington / DC, 5th November 2019 --

Stefan D. Anker, MD PhD

Division of Cardiology & Metabolism: Heart Failure, Cachexia and Sarcopenia
Dept of Cardiology & BCRT, Charité (CVK), Berlin, Germany

s.anker@cachexia.de
The management of iron deficiency (± anemia) in chronic heart failure & CKD: the most common, undertreated co-morbidity

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Relevant co-morbidities in CHF
– the key to (realistic) personalised / precision medicine –

• CAD / ischemia & Hypertension
• Diabetes mellitus & Metabolic syndrome
• Sleep apnoea
• COPD
• Iron deficiency & Anemia
• Liver & bowel dysfunction
• Renal dysfunction & kidney injury
• Cachexia & muscle wasting
• Depression / other neurological disease
Relevant co-morbidities in CHF
– some information on what not to do –

- CAD / ischemia & Hypertension
- Diabetes mellitus & Metabolic syndrome
- Sleep apnoea
- COPD
- Iron deficiency & Anemia
- Liver & bowel dysfunction
- Renal dysfunction & kidney injury
- Cachexia & muscle wasting
- Depression / other neurological disease

consider SERVE-HF
consider RED-HF
Inclusion criteria:

- NYHA II-IV (in NYHA II also CV hosp in last 12 months)
- LVEF \( \leq 40\% \); CHF for \( \geq 3 \) months
- Hb 9-12 g/dL
- TSAT \( \geq 15\% \)

**RED-HF**

**Main results**

- ESA leads to correction of anaemia
- ESA does not lead to improvements in survival or QoL or exercise capacity !
- ESA shows somewhat increased risk for thromboembolic adverse events
- Cancer-related adverse events similar in both groups

---

**Primary endpoint**

Death from any cause or first hospitalization for worsening HF

---

**Haemoglobin**

![Graph showing median haemoglobin levels over months for Placebo and Darbepoetin alfa](image)

**Patients with Event (%)**

![Graph showing patients with event over years since randomization](image)

- **(HR = 1.04; 95%CI)**
- **P=0.87 by stratified log-rank test**

ESA = Erythropoiesis stimulating agent

RED-HF
Main results

Haemoglobin

Primary endpoint
Death from any cause or first HF hospitalization

Treating a co-morbidity per se, does not provide proof of efficacy!

→ we need randomized controlled trials!

• Cancer-related adverse events similar in both groups

ESA = Erythropoiesis stimulating agent

RED-HF and the iron status

- Exclusion criterion: TSAT <15%, no ferritin assessed
- Baseline: median TSAT: 24% (19-31) median ferritin: 102 µg/L (53-194)
- When TSAT <20%, iron supplementation was considered (a ferritin cut-off value was not used):
  - i.v. iron: 4.9% (D) vs 5.6% (P), p=0.47
  - p.o. iron: 72.3% (D) vs 73.5% (P), p=0.52

→ ~50% were iron deficient at time of randomization according to the current definition (ESC HF GLs 2012)
→ Predominant treatment with oral iron

Relevant co-morbidities in CHF
– in some areas many trials take place –

- CAD / ischemia & Hypertension
- Diabetes mellitus & Metabolic syndrome
- Sleep apnoea
- COPD
- Iron deficiency & Anemia
- Liver & bowel dysfunction
- Renal dysfunction & kidney injury
- Cachexia & muscle wasting
- Depression / other neurological disease

M&M trials with SGLT2-inhibitors
- EMPEROR-HFpEF N=5500 (to 6000)
- EMPEROR-HFrEF N=3500 (to 4000)
- DAPA-HF (HFrEF) N=4774
- DELIVER (HFpEF) N=4700
- SOLOIST-WHF N=4000-4900
Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

HR 0.74 (0.65, 0.85)
p=0.00001
NNT=21

Cumulative Percentage (%)

Months since Randomization

Number at Risk
Dapagliflozin 2373 2305 2221 2147 2002 1560 1146 612 210
Placebo 2371 2258 2163 2075 1917 1478 1096 593 210

McMurray et al., NEJM 2019
No diabetes/diabetes subgroup: Primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
</tbody>
</table>

*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.
Relevant co-morbidities in CHF – T2DM will now be targeted in several trials –

- CAD / ischemia & Hypertension
- Diabetes mellitus & Metabolic syndrome
- Sleep apnoea
- COPD
- Depression / other neurological disease
- Liver & bowel dysfunction
- Renal dysfunction and kidney injury
- Anemia and iron deficiency
- Cachexia & muscle wasting

**KDIGO**

- EMPEROR-HFrEF
- EMPEROR-HFpEF
- DAPA-HF
- DELIVER
- SOLOIST-WHF
  (all M&M studies)

- EMPERIAL-HFrEF
- EMPERIAL-HFpEF
  2 x N=300
- Determine-Reduced
- Determine-Preserved
  2 x N=300-400
  (=9 clinical trials for regulatory purposes)
Co-morbidities in CHF
Challenges that require new solutions

- COPD
- CAD / ischemia & Hypertension
- Atrial Fibrilation
- Valve Disease → Functional MR & TR
- Diabetes mellitus & Metabolic Syndrome
- Sleep Apnoea
- Depression & Stroke
- Anemia & Iron Deficiency
- Renal Dysfunction and Kidney Injury
- Cachexia & Muscle Wasting
Co-morbidities in CHF
Challenges that require new solutions

- COPD
- CAD / ischemia & Hypertension
- Atrial Fibrilation
- Valve Disease → Functional MR & TR
- Diabetes mellitus & Metabolic Syndrome
- Sleep Apnoea
- Depression & Stroke
- Anemia & Iron Deficiency ± anemia
- Renal Dysfunction and Kidney Injury
- Cachexia & Muscle Wasting

FAIR-HF2
AFFIRM-HF
IRONMAN
HEART-FID
1. Absolute iron deficiency
   (Reduction in iron stores)
   - Causes: chronic blood loss (aspirin), malnutrition, malabsorption
   - Diagnosis: low serum ferritin level <30 µg/L

2. Functional iron deficiency
   (Disturbed iron metabolism in bone marrow; iron stores /=/↓)
   - Causes: chronic inflammation & kidney dysfunction
   - Diagnosis: serum ferritin 30–99 µg/L or serum ferritin 100–299 µg/L and TSAT<20%

Functional Iron Deficiency = poor Prognosis
definition: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%

Prevalence of ID in CHF patients

% of CHF pts

Non-anaemics
79 / 182 (43%)

Anaemics
22 / 36 (61%)

Follow-up (days)

ID (n=64)

Non-ID (n=103)

HR 2.9 (95%CI: 1.6-5.1)
P<0.001

Endpoint:
Death & HF hospitalisation

Jankowska et al., EHJ 2010
Grzeslo A et al. (abstract at HFA 2006)
Iron deficiency is a bigger problem than anemia

- 157 consecutively eligible patients with CHF
- 2-fold greater risk for mortality in iron-deficient non-anemic patients vs. iron-replete anemic subjects
- 3-fold escalated risk for death irrespective of anaemic status

Okonko et al. JACC 2011
Iron metabolism in humans

uptake heme-iron vs non-heme iron 3:1

Inflammation, Hepcidin, Ferroportin &
the regulation of iron metabolism


Macrophages (including in liver)

Intestine cells (Enterocytes)

Iron status ↑
Inflammation

↓O₂ saturation
↑ Iron need

Liver

Bone Marrow

Hepcidin

Transferrin

Erythrocytes

Macrophages

Chyme

Fe²⁺

Hepcidin

Ferroportin
Treatment of CRS, anemia & iron deficiency
– Options –

• Blood transfusion (in severe anemia, very costly & with infection risks !)

• EPO in combination with iv iron or with Vitamin B12 / folic acid
  – Mancini DM et al., Circulation 2003

• ESAs alone  (in some cases also with [mostly oral] iron)
  – Amgen Study Programme (Phase 3: RED-HF – neutral results)

• Iron (oral or iv)
  – 3 PoC / Phase 2 studies have been reported
  – Phase 3: FAIR-HF, CONFIRM-HF
  – Phase 3: FIND-CKD (FCM reduces required EPO dose)
The structure of intravenous iron

- Dextran can cause anaphylactic reactions
- Larger/heavier iron–carbohydrate complexes are more stable than smaller/lighter complexes

FAIR-HF Trial -- Study Design

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

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

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

## Dosing

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Patients with anaemia (Hb ≤120 g/L)</th>
<th>Patients without anaemia (Hb &gt;120 g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correction phase</td>
<td>Maintenance phase</td>
<td>Correction phase</td>
</tr>
<tr>
<td>Number of patients</td>
<td>300</td>
<td>154</td>
<td>139</td>
</tr>
<tr>
<td>Mean ±SD dose (mg iron)</td>
<td>1850±433</td>
<td>1105±291</td>
<td>840±199</td>
</tr>
<tr>
<td>Median dose (mg iron)</td>
<td><strong>2000</strong></td>
<td><strong>1100</strong></td>
<td><strong>800</strong></td>
</tr>
<tr>
<td>Dose range (mg iron)</td>
<td>200–2400</td>
<td>200–1900</td>
<td>200–1000</td>
</tr>
</tbody>
</table>

NYHA, PGA, QoL, 6min-Walking-Test
-- Week 4, 12 & 24 --

Patient Global Assessment

NYHA functional class

6-minute walk test

KCCQ overall score

EQ-5D VAS score

Anker et al, NEJM 2009;361:2436-2448
NYHA, PGA, QoL, 6min-Walking-Test
-- Week 4, 12 & 24 --

Patient Global Assessment

NYHA functional class

6-minute walk test

KCCQ overall score

EQ-5D VAS score

Anker et al, NEJM 2009;361:2436-2448
### Secondary Endpoints:
**PGA & NYHA in pre-defined subgroups**

<table>
<thead>
<tr>
<th></th>
<th>Self-reported PGA score</th>
<th>NYHA functional class</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients FCM/Placebo</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Hemoglobin (g/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 120</td>
<td>146/74</td>
<td>0.98</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>146/75</td>
<td></td>
</tr>
<tr>
<td><strong>Median ferritin (μg/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 39</td>
<td>153/72</td>
<td>0.45</td>
</tr>
<tr>
<td>&gt; 39</td>
<td>139/77</td>
<td></td>
</tr>
<tr>
<td><strong>eGFR (mL/min)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>119/67</td>
<td>0.22</td>
</tr>
<tr>
<td>≥ 60</td>
<td>173/82</td>
<td></td>
</tr>
<tr>
<td><strong>Median age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 69.7</td>
<td>149/75</td>
<td>0.10</td>
</tr>
<tr>
<td>&gt; 69.7</td>
<td>143/74</td>
<td></td>
</tr>
<tr>
<td><strong>Gender (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>140/68</td>
<td>0.99</td>
</tr>
<tr>
<td>Female</td>
<td>152/81</td>
<td></td>
</tr>
<tr>
<td><strong>NYHA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>52/27</td>
<td>0.66</td>
</tr>
<tr>
<td>Class III</td>
<td>240/122</td>
<td></td>
</tr>
<tr>
<td><strong>Median ejection fraction (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 33</td>
<td>169/70</td>
<td>0.86</td>
</tr>
<tr>
<td>&gt; 33</td>
<td>123/79</td>
<td></td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Ischemic</td>
<td>56/30</td>
<td>0.60</td>
</tr>
<tr>
<td>Ischemic</td>
<td>236/119</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>202/113</td>
<td>0.87</td>
</tr>
<tr>
<td>Yes</td>
<td>90/36</td>
<td></td>
</tr>
<tr>
<td><strong>Median BMI (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 27.37</td>
<td>150/71</td>
<td>0.94</td>
</tr>
<tr>
<td>&gt; 27.37</td>
<td>142/78</td>
<td></td>
</tr>
</tbody>
</table>
iv-FCM improves PGA & NYHA class in CHF patients with and without anemia

**Self-Reported Patient Global Assessment**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ferric Carboxy-maltose</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤120 (g/liter)</td>
<td>146</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120 (g/liter)</td>
<td>146</td>
<td>75</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**NYHA Functional Class**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ferric Carboxy-maltose</th>
<th>Placebo</th>
<th>Odds Ratio (95% CI)</th>
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<td>≤120 (g/liter)</td>
<td>148</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;120 (g/liter)</td>
<td>146</td>
<td>76</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Week 24 Results**

**Patients with anemia (at BL)**

<table>
<thead>
<tr>
<th></th>
<th>FCM</th>
<th>Placebo</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>275±18</td>
<td>68±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>29±1</td>
<td>17±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>127±1</td>
<td>118±2</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Patients without anemia (at BL)**

<table>
<thead>
<tr>
<th></th>
<th>FCM</th>
<th>Placebo</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>349±19</td>
<td>80±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TSAT (%)</td>
<td>30±1</td>
<td>22±1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>133±1</td>
<td>132±1</td>
<td>0.21</td>
</tr>
</tbody>
</table>

*Mean treatment effect, adjusted for the baseline value

Anker et al, NEJM 2009;361:2436-2448
Anemia & iron deficiency & tissue energy / performance

Iron deficiency

↓ Hb
(i.e. anemia)

Mitochondrion

↓ O₂ delivery

↓ O₂ utilization

↓ tissue energy / performance status

Figure adapted from: Anker et al. EJHF 2009
IV iron improves skeletal muscle performance in HF patients

shorter PCr recovery half-time → better muscle energetics & better mitochondrial function

Method:
dynamic phosphorus magnetic resonance spectroscopy

Effect of iv-iron on kidney function

Change in eGFR from baseline (mL/min.1.73m²)

Treatment effect (mL/min/1.73m²):*

- Placebo: 2.8 ± 1.5
- FCM: 3.0 ± 1.5
- 4.0 ± 1.7

* LSM mean ± SE

Ponikowski P et al. 2015
Effect of iv-iron on plasma volume status

FCM causes lower plasma volume and weight = decongestion → one mechanism how iron repletion aids HF patients

Okonko DO et al. ESC-HF 2019
CONFIRM-HF
Design

- **Design:** Multicentre, randomized (1:1), double-blind, placebo-controlled

- **Main inclusion criteria:**
  - NYHA class II / III, LVEF ≤45%
  - BNP > 100 pg/mL or NT-proBNP > 400 pg/mL
  - Iron deficiency: serum ferritin <100 µg/L or <300 µg/L, if TSAT <20%
  - Hb≤ 15 g/dL

- **Primary endpoint**
  - Exercise capacity: change in 6MWT distance from baseline at week 24

- **Secondary endpoints**
  - Change in biomarkers for iron deficiency, cardiac biomarkers, NYHA functional class, PGA and QoL
  - Overall safety over the treatment period

Clinicaltrials.gov identifier: NCT01453608.
Primary endpoint: change in 6-minutes walking distance at Week 24

FCM improved 6MWT at week 24

FCM vs placebo: $33 \pm 11$ m (least squares mean ± SE)

![Bar chart showing LSM change in 6MWT distance from baseline (m) at Week 24]

- FCM: $33 \pm 11$ m
- Placebo: $0 \pm 11$ m

P-value: 0.002
Secondary endpoints: Changes in 6MWT and Fatigue score over time

**6min-walking-test distance**

- FCM vs placebo
  - LSM (95% CI): 14 (−5, 33) 16 (−3, 35) 33 (13, 53) 42 (21, 62) 36 (16, 57)
  - P-values:
    - 6 months: P=0.16
    - 12 months: P=0.10
    - 24 months: P=0.001
    - 36 months: P<0.001
    - 48 months: P<0.001

**Fatigue score**

- FCM vs placebo
  - LSM (95% CI): −0.2 (−0.5, 0.2) −0.5 (−0.9, −0.1) −0.6 (−1.0, −0.2) −0.8 (−1.2, −0.4) 0.7 (−1.1, −0.2)
  - P-values:
    - 6 months: P=0.40
    - 12 months: P=0.009
    - 24 months: P=0.002
    - 36 months: P<0.001
    - 48 months: P=0.002
Secondary endpoints: Changes in PGA & NYHA class over time

Self-reported Patient Global Assessment (PGA) score

New York Heart Association Functional (NYHA) class

No. of patients

<table>
<thead>
<tr>
<th>Weeks since randomisation</th>
<th>FCM</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>144</td>
<td>147</td>
</tr>
<tr>
<td>12</td>
<td>137</td>
<td>148</td>
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<td>18</td>
<td>131</td>
<td>130</td>
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<td>24</td>
<td>123</td>
<td>124</td>
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<tr>
<td>30</td>
<td>127</td>
<td>119</td>
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<td>42</td>
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<tr>
<td>52</td>
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No. of patients

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<td>52</td>
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</table>
### Iron deficiency

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>IIa</td>
<td>A</td>
</tr>
</tbody>
</table>

Recommendation based on: **FAIR-HF & CONFIRM-HF**

Secondary endpoints: Outcome events

<table>
<thead>
<tr>
<th>End-point or event</th>
<th>FCM (N=150)</th>
<th>Placebo (N=151)</th>
<th>Time to first event</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>12 (8.9)</td>
<td>14 (9.9)</td>
<td>0.89</td>
<td>(0.41 – 1.93)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Death for any CV reason</td>
<td>11 (8.1)</td>
<td>12 (8.5)</td>
<td>0.96</td>
<td>(0.42 – 2.16)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>46 (26.3)</td>
<td>69 (37.0)</td>
<td>0.71</td>
<td>(0.45 – 1.12)</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for any CV reason</td>
<td>26 (16.6)</td>
<td>51 (26.3)</td>
<td>0.63</td>
<td>(0.37 – 1.09)</td>
<td>0.097</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation due to worsening HF</td>
<td>10 (7.6)</td>
<td>32 (19.4)</td>
<td>0.39</td>
<td>(0.19 – 0.82)</td>
<td>0.009</td>
<td></td>
</tr>
</tbody>
</table>

FCM reduced the risk of recurrent hospitalisations due to worsening HF (post hoc): Incidence Rate Ratio (95% CI) – 0.30 (0.14-0.64), p=0.0019
Secondary endpoint: First hospitalization due to worsening HF

Cumulative Hospitalization Rate (in %)

Log–rank test $P=0.009$

No. of subjects at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>FCM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>151</td>
<td>150</td>
</tr>
<tr>
<td>90 days</td>
<td>138</td>
<td>140</td>
</tr>
<tr>
<td>180 days</td>
<td>127</td>
<td>131</td>
</tr>
<tr>
<td>270 days</td>
<td>117</td>
<td>126</td>
</tr>
<tr>
<td>360 days</td>
<td>78</td>
<td>77</td>
</tr>
</tbody>
</table>
**Rate ratio analysis (recurrent event analyses)**

<table>
<thead>
<tr>
<th>Recurrent event outcomes</th>
<th>FCM (N=504)</th>
<th>Placebo (N=335)</th>
<th>Rate Ratio (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV hospitalization and CV death</td>
<td>69 (23.0)</td>
<td>92 (40.9)</td>
<td>0.59 (0.40-0.88)</td>
<td>0.009</td>
</tr>
<tr>
<td>HF hospitalization and CV death</td>
<td>39 (13.0)</td>
<td>60 (26.7)</td>
<td>0.53 (0.33-0.86)</td>
<td>0.011</td>
</tr>
<tr>
<td>CV hospitalization and all-cause death</td>
<td>71 (23.7)</td>
<td>94 (41.8)</td>
<td>0.60 (0.41-0.88)</td>
<td>0.009</td>
</tr>
<tr>
<td>HF hospitalization and all-cause death</td>
<td>41 (13.7)</td>
<td>62 (27.6)</td>
<td>0.54 (0.34-0.87)</td>
<td>0.011</td>
</tr>
<tr>
<td>All-cause hospitalization and all-cause death</td>
<td>108 (36.1)</td>
<td>118 (52.5)</td>
<td>0.73 (0.52-1.01)</td>
<td>0.060</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>22 (7.3)</td>
<td>43 (19.1)</td>
<td>0.41 (0.23-0.73)</td>
<td>0.003</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>52 (17.4)</td>
<td>75 (33.3)</td>
<td>0.54 (0.36-0.83)</td>
<td>0.004</td>
</tr>
<tr>
<td>All-cause hospitalization</td>
<td>89 (29.7)</td>
<td>99 (44.0)</td>
<td>0.71 (0.50-1.01)</td>
<td>0.056</td>
</tr>
</tbody>
</table>

Meta-analysis on individual patient data with FCM
4 double-blind FCM trials – 839 patients

Anker SD, et al. Eur J Heart Fail 2017
More M&M trials in HF – The Iron Consortium

• **IRONMAN:**
  - UK, randomised, controlled, PROBE design
  - test substance: at least 1000-2000 mg iron isomaltoside (Monofer®)
  - n=1300 – LVEF<45% – TSAT<20% and/or ferritin ≤100 µg/L
  - 1. EP: recurrent event of CV mortality & HF hospitalisation

• **HEART-FID**
  - USA, randomised, double-blind, placebo-controlled
  - test substance: FCM, full dose as per US label (up to 2x750 at BL)
  - n=3000
  - 1. EP: CV mortality & HF hospitalisation (time to 1st event)

• **AFFIRM-HF**
  - international, randomised, double-blind, placebo-controlled
  - test substance: FCM, full dose as per label
  - n=1200 – recruited during or immediately after HHF
  - 1. EP: recurrent event of CV mortality & HF hospitalisation
Primary endpoint
– Rate of recurrent hospitalisations for heart failure or CV death during follow-up.

Secondary endpoints
– CV / HF hospitalisation, CV death (recurrent events, time-to-first event)
– Change in NYHA functional class, EQ-5D, and PGA

Design: Multi-centre, international, randomised (1:1), double-blind, placebo-controlled

Main inclusion criteria:
– CHF with LVEF ≤ 45% and NYHA class II / III
– HF hospitalisation within 6 mo or BNP/NT-proBNP >100/>300 pg/mL or MRproANP>120 mmol/L
– Iron deficiency: serum ferritin <100 µg/L or ferritin 100-299ng/mL with TSAT <20%
– Hb: ≤ 14.0 g/dL

FAIR-HF-2
DZHK TRIAL 05
Primary Endpoint (IIT)

- CPET: 10W / min incremental ramp protocol & core lab
- 96 (iron) and 95 (plac) complete study per protocol

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

$P = 0.46$

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

$P = 0.30$

Baseline peak VO$_2$ (IQR) 13.3 (11.4–15.8) 12.9 (10.5–15.6)
# 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>

Lewis GD et al., IRONOUT-HF – JAMA 2017
Results: Δ Iron Studies

IRONOUT-HF

- Ferritin (ng/ml)
  - Week 0: 150
  - Week 16: 160
  - Δ: +3 ng/ml (P = 0.003)
  - Normal range: 20-400 ng/ml

- Tsat (%)
  - Week 0: 32%
  - Week 16: 35%
  - Δ: +3% (P = 0.003)
  - Normal range: 20-40%

Iron vs. Placebo

- Δ: +11 ng/ml (P = 0.056)

vs. FAIR-HF (IV Iron)

- Ferritin (ng/ml)
  - Week 0: 300
  - Week 24: 538
  - Δ: +238 ng/ml (P < 0.001)
  - Normal range: 20-400 ng/ml

- Tsat (%)
  - Week 0: 30%
  - Week 24: 42%
  - Δ: +12% (P < 0.001)
  - Normal range: 20-40%

Iron vs. Placebo

- Δ: +238 ng/ml (P < 0.001)

Lewis GD et al., IRONOUT-HF – JAMA 2017
Hazard ratio, 0.85 (95% CI, 0.73–1.00)
P<0.001 for noninferiority
P=0.04 for superiority

No. at Risk
Reactive, low-dose iron regimen 1048 732 496 183
Proactive, high-dose iron regimen 1093 799 548 194

Macdougall IC et al. New Engl J Med 2019
PIVOTAL – 2. EPs

| Secondary efficacy and points                                                                 | 429 (19.4) | 507 (24.6) | 0.77 (0.66 to 0.92) |
| Death from any cause and a composite of myocardial infarction, stroke, or hospitalization for heart failure as recurrent events — no. of events (rate per 100 patient-yr) | 246 (22.5) | 269 (25.7) | 0.84 (0.71 to 1.00) |
| Death from any cause — no. (%)                                                              | 149 (13.6) | 168 (16.0) | 0.80 (0.64 to 1.00) |
| Fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, or hospitalization for heart failure — no. (%) | 78 (7.1)   | 102 (9.7)  | 0.69 (0.52 to 0.93) |
| Fatal or nonfatal myocardial infarction — no. (%)                                          | 34 (3.1)   | 35 (3.3)   | 0.90 (0.56 to 1.44) |
| Fatal or nonfatal stroke — no. (%)                                                          | 51 (4.7)   | 70 (6.7)   | 0.66 (0.46 to 0.94) |
| Hospitalization for heart failure — no. (%)                                                 | 29,757 (18,673 to 48,833) | 38,805 (24,377 to 60,620) | -7539 (-9485 to -5582) |
| Median monthly dose of erythropoiesis-stimulating agent (IQR) — IU                          |            |            |                  |
| Blood transfusion                                                                           |            |            |                  |
| Any transfusion — no. (%)                                                                   | 198 (18.1) | 226 (21.6) | 0.79 (0.65 to 0.95) |
| Total no. of units transfused                                                                | 967        | 1122       | NA              |

- MACE recurrent: -23%
- All-cause mortality: -16%
- Fatal or non-fatal MI: -31%
- Hospitalization for HF: -34%

- Safety:
  - no difference in infection
  - no other safety issue for high dose therapy

Macdougall IC et al. New Engl J Med 2019
### ESC Guidelines on HF 2016

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron deficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous FCM should be</td>
<td>IIA</td>
<td>A</td>
</tr>
<tr>
<td>considered in symptomatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>patients with HFrEF and iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>deficiency (serum ferritin &lt; 100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>µg/L, or ferritin between 100–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>299 µg/L and transferrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>saturation &lt; 20%) in order to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alleviate HF symptoms, and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>improve exercise capacity and</td>
<td></td>
<td></td>
</tr>
<tr>
<td>quality of life.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Relevant co-morbidities in CHF
– the key to (realistic) personalised / precision medicine –

- Diabetes mellitus & Metabolic syndrome
- CAD / ischemia & Hypertension
- Sleep apnoea
- Depression & Stroke
- **Iron deficiency** ± anaemia
- COPD
- Renal dysfunction and kidney injury
- Liver & bowel dysfunction
- Cachexia & muscle wasting
New Trends in Drugs & Devices for HF
The Future is Now!

**DEVICES**
- Valves
- Ventricular Reshaping
- Neurostimulation et al.
- Assist Devices
- Telemedicine

**DRUGS**
- Sacubitril / Valsartan
- SGLT2 inhibitors
- iv-iron (FCM)
- Potassium binders
- Omecamtiv Mecarbil

RESHAPE-HF-2 (MitraClip)
CARILLON Trial – FDA pivotal trial
Corvia, V-Wave & Occlutech
Bioventrix (REVIVE-HF)

FAIR-HF-2 et al (iv-iron)
SGLT2i phase III trials
GALACTIC-HF (OM)
DIAMOND-HF (K-binder)

Many New Clinical Trials in HF