Industry Symposia
Summary Reports
The value of anaemia management in a Cardio Renal clinic

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Introduction and objectives
Anaemia is a common condition in cardio-renal disease and is associated with worsening of heart failure symptoms, increased morbidity, and mortality. The management of anaemia in cardio-renal clinics can play a crucial role in improving patient outcomes. This presentation aims to highlight the importance of anaemia management in a cardio-renal clinic and discuss the value that nephrologists can bring to optimize therapies and improve patient care.

Key Results
Haemoglobin (Hb) and Survival in ELITE II
The ELITE II study demonstrated that lower Hb levels were associated with a higher risk of death in patients with heart failure with reduced ejection fraction (HFrEF). The risk ratio for death increased as Hb levels decreased, emphasizing the significance of anaemia management in heart failure patients. The increased risk with higher haemoglobin may have been related to haemoconcentration in patients with worse heart failure (figure 1).

Impact of Iron Deficiency on patients with chronic heart failure (CHF)
Iron deficiency is a major reason for the development of anaemia. Iron is essential for oxygen metabolism and energy production. Understanding the distribution of iron in the body helps to highlight the importance of maintaining adequate iron levels for optimal physiological functionings. Iron deficiency and anaemia are common in heart failure patients and are associated with worsening symptoms, increased morbidity, risk of hospitalization and mortality (Figure 2).

Figure 1. Hb and survival in ELITE II (HFrEF; n=3044), RR risk ratio.
(Adapted from Sharma et al. Eur Heart J 2004; 25: 1021-8 fig 3a)

Figure 2. Iron deficiency predicts prognosis in patients with CHF (n=546; 57% with anaemia); ID, iron deficiency; HR, hazard ration; CI, confidence interval (adapted from Jankowska E et al. Eur Heart J 2010;31(15):1872-80).
The FAIR-HF study evaluated the use of intravenous ferric carboxymaltose in heart failure patients with iron deficiency. Treatment with intravenous ferric carboxymaltose resulted in improved patient functional outcomes (six-minute walking test and quality of life) compared to placebo, highlighting the potential benefits of iron therapy in this patient population.

Salford Renal Centre Population Requiring Anaemia Management

The Salford Renal Centre plays a crucial role in managing anaemia therapy within its catchment population of 1.55 million. Notably, 12% of non-dialysis chronic kidney disease (CKD) patients in the centre also have heart failure (HF). In the Salford cardio-renal clinic key aspects of care of the cardio-renal patients are considered including screening for underlying renal disease (e.g., RAS or causes of proteinuric renal disease) where appropriate, hyperkalaemia management to enhance optimal RAASI use, and anaemia management. Specific targets and treatments have been established for effective anaemia management. One of the primary interventions in the clinic is intravenous (IV) iron therapy. Patients with ferritin levels below 100 μg/L and/or transferrin saturation below 20% receive IV iron to replenish iron stores. Additionally, when patients are iron replete but still experience low Hb levels (<110 g/L) and symptomatic anaemia, erythropoiesis-stimulating agent (ESA) therapy is used. A combined approach using both IV iron and ESA is used in cases where both iron parameters and Hb levels are low. This strategy may address the unique needs of CKD patients with concomitant heart failure.

To streamline the treatment process, the clinic has implemented a single visit IV iron protocol using ferric derisomaltose (FDI). This approach allows for the treatment of 8-12 CKD or cardio-renal patients per day in just two chairs. By reducing the number of hospital visits required for IV iron therapy, this protocol improves patient convenience and resource utilization in the CKD and cardio-renal clinics.

Regarding the safety profile of FDI in the CKD and cardio-renal clinics, from >4,000 total dose infusions there has been one reported serious hypersensitivity reaction (requiring adrenaline) but more frequent mild reactions were observed in approximately 1-2% of cases. These findings highlight the suitability of FDI as a well-tolerated IV iron option for anaemia management in CKD patients with heart failure.

**Conclusion**

Anaemia management plays a crucial role in improving outcomes for patients with cardio-renal disease. Nephrologists in cardio-renal clinics can contribute to optimizing therapies, identifying and managing important renal conditions, and ensuring appropriate iron and erythropoiesis-stimulating agent (ESA) therapy. The use of intravenous iron, such as FDI, in a total dose infusion protocol has shown promising results in terms of patient convenience and safety. Collaborative efforts between nephrologists, Heart failure specialist nurses and cardiologists in cardio-renal clinics can enhance patient care and improve outcomes in this complex patient population.

**Further reading**

The emerging role of intravenous ferric derisomaltose* to reduce cardiovascular risk (HFH) in patients with heart failure and iron deficiency: the UK IRONMAN trial

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Introduction and objectives
Heart failure (HF) and chronic kidney disease (CKD) are significant health conditions with high morbidity and mortality rates. The presence of CKD increases the risk of HF, leading to worse patient outcomes. Iron deficiency is common in both HF and CKD and has been linked to adverse cardiovascular (CV) effects. Iron is vital for various physiological processes, including oxygen transport and CV function. Its deficiency can contribute to reduced exercise capacity, impaired contractility, and increased oxidative stress, all of which are detrimental to the progression of HF.

In recent years, intravenous iron has been shown to improve quality of life and exercise capacity and reduce the risk of re-hospitalisation for heart failure. HF patients with iron deficiency. However, the long-term effectiveness, specifically regarding hospitalization and mortality over a period exceeding 12 months, as well as the safety profile of repeated intravenous (IV) iron dosing in patients with heart failure, remains uncertain. The IRONMAN study, which evaluated the use of the intravenous iron formulation ferric derisomaltose (FDI) compared to usual care, was designed to address these uncertainties.

UK IRONMAN Trial Design and Results
The UK Intravenous Iron Treatment in Patients with Heart Failure and Iron Deficiency (IRONMAN) trial is a prospective, randomised, open-label, blinded-endpoint trial undertaken in 70 hospitals across the UK. It aimed to evaluate the longer-term efficacy and safety of IV FDI in reducing CV risk in HF patients with iron deficiency (figure 1).

<table>
<thead>
<tr>
<th>Hb</th>
<th>BW&lt;50 kg</th>
<th>BW 50 to &lt;70 kg</th>
<th>BW≥70 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 g/dl</td>
<td>20 mg/kg</td>
<td>1000 mg</td>
<td>20 mg/kg up to a maximum of 1500 mg</td>
</tr>
<tr>
<td>&lt;10 g/dl</td>
<td>20 mg/kg</td>
<td>20 mg/kg</td>
<td>20 mg/kg up to a maximum of 2000 mg</td>
</tr>
</tbody>
</table>

Review at week 4, month 4, and 4 monthly thereafter
Re-dose if either ferritin <100 µg/L or TSAT <25% (provided ferritin was ≤400 µg/L)

Figure 1. IRONMAN trial design (Kalra PR, et al. Lancet 2022)
Key Results

Primary Endpoint:

The primary endpoint of recurrent heart failure hospitalizations and CV death approached statistical significance in favour of FDI but did not reach a predetermined level of significance (p=0.07) (figure 2). However, in a prespecified COVID-19 sensitivity analysis, the primary endpoint was nominally statistically significant (p=0.047). Figure 2. Primary endpoint: recurrent HF hospitalizations and CV death (FDI vs usual care) in full analysis and pre-specified COVID-19 sensitivity analysis (Kalra PR, et al. Lancet 2022)

![Figure 2](image_url)

Secondary Endpoints

CV death: the FDI group had a nominally significant lower instance of first event (CV death, or hospitalisation for HF, myocardial infarction (MI) or cerebral vascular accident (CVA)) vs usual care (37% vs 43%; p=0.045, respectively) with a trend compared with usual care in terms of all-cause mortality, although the difference did not reach statistical significance. Moreover, there was an improvement in patient quality of life (Minnesota Living with Heart Failure Questionnaire, MLHFQ) (figure 3) at four months.

Key secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FDI (95% CI)</th>
<th>Usual Care (95% CI)</th>
<th>RRR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF hospitalizations*</td>
<td>250 (16.7*)</td>
<td>313 (20.9*)</td>
<td>0.80 (0.62 - 1.03)</td>
<td>0.085</td>
</tr>
<tr>
<td>CV death, n (%)</td>
<td>119 (21%)</td>
<td>138 (24%)</td>
<td>0.86 (0.67 - 1.10)</td>
<td>0.23</td>
</tr>
<tr>
<td>First event: CV death or hosp. for HF, MI or CVA</td>
<td>209 (37%)</td>
<td>246 (43%)</td>
<td>0.83 (0.69 - 1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>184 (32%)</td>
<td>193 (34%)</td>
<td>0.95 (0.78 - 1.17)</td>
<td>0.64</td>
</tr>
<tr>
<td>MLHFQ 4 months</td>
<td>36.9</td>
<td>40.2</td>
<td>-3.33 (-6.67 to 0.00)</td>
<td>0.050</td>
</tr>
<tr>
<td>MLHFQ 20 months</td>
<td>40.1</td>
<td>42.7</td>
<td>-2.57 (-6.72 to 1.59)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Figure 3. Key Secondary outcomes; * no. of events (rate per 100 patient-year) † estimated mean difference (Kalra PR, et al. Lancet 2022).
Hospitalization for heart failure: the FDI group demonstrated a reduction in hospitalizations for heart failure compared versus usual care, indicating a potential benefit of FDI in reducing the risk of HF exacerbations and hospital admissions.

Other CV events: FDI treatment was associated with a decreased incidence of MI, stroke and CV death. These results suggest a potential protective effect of FDI against various CV complications.

Safety Profile
FDI demonstrated a generally-well tolerated safety profile. The incidence of serious adverse cardiac events was lower in the FDI group vs the usual care group (36% vs 43%, respectively). Additionally, there was no significant increase in serious adverse events related to infection. Only one infusion reaction associated with FDI was reported.

Conclusion
The UK IRONMAN trial supports the use of IV FDI in HF patients with iron deficiency. Although the primary endpoint did not reach statistical significance, a prespecified COVID-19 sensitivity analysis revealed a significant reduction in recurrent heart failure hospitalizations and CV death with FDI. Furthermore, FDI demonstrated a favourable safety profile and was associated with a decreased risk of hospitalization for heart failure and other CV events. These findings suggest that FDI has the potential to reduce CV risk and improve outcomes in HF patients with iron deficiency.

Further research is needed to better understand the underlying mechanisms and long-term effects of FDI treatment in this patient population.

Further reading