Iron Replacement Therapy in Patients with Heart Failure with Reduced Ejection Fraction and Iron Deficiency: A Scoping Review

Amanda Sambrielaz, BSc(H), PharmD; Shaylee Peterson, BSc(Pharm), ACPR, PharmD

Background

- Iron deficiency has been shown to be present in up to 30-50% of heart failure patients and these patients have been shown to have higher hospitalization rates, increased mortality, less functional or exercise capacity and impaired quality of life regardless of ejection fraction or if the patient is anemic or not
- Many heart failure guidelines address the use of iron in HFrEF and iron deficiency but fail to give specific recommendations regarding the most effective and safest way of doing so.

Objectives

- **Primary:** Systematically identify, describe, and critically appraise literature on current therapeutic options for iron replacement, including clinical efficacy and safety, in patients with HFrEF and iron deficiency.
- **Secondary**: To identify any knowledge gaps in current therapeutic options for the treatment of iron deficiency in patients with HFrEF and iron deficiency in regards to clinical efficacy and/or safety.

Methods

- **Design**: Scoping review per PRISMA-ScR, Arksey & O'Malley, and JBI.
- **Databases searched**: Embase, Medline, Cochrane, TRIP, Google Scholar, clinicaltrialresults.org, clinicaltrials.gov, last searched Jan 6/22
- **Search strategy**: In consultation with UBC librarian; [(heart failure or systolic heart failure or HFrEF or HF or cardiomyopathy) AND (iron deficiency anemia OR iron deficiency OR iron decifien*) AND ((iron adj5 (replace* or replenish* or therap* or intravenous* or IV or parenter* or oral) OR (sodium ferric gluconate OR ferrlecit OR ferrous fumarate OR palafer OR ferrous gluconate OR fergon OR ferrous sulfate OR fer in sol OR iron isomaltoside OR monoferric etc.))]
- **Inclusion criteria:** Papers that included adult human patients with HFrEF (LVEF <40%) and iron deficiency in a prospective, quantitative study design (eg. RCTs, prospective observational trials) with an iron intervention and a pre-reported outcome of interest.
- **Selection of studies**: Covidence was used to compile search results and all titles and abstracts were screened by AS (100%) and SP (10%) using Cohen's kappa index to assess intra-rater agreeability. Full text screening, extraction of data, and risk of bias assessment was completed in the same manner. (k=0.95)

Figure 1. PRISMA-ScR Flow Diagram

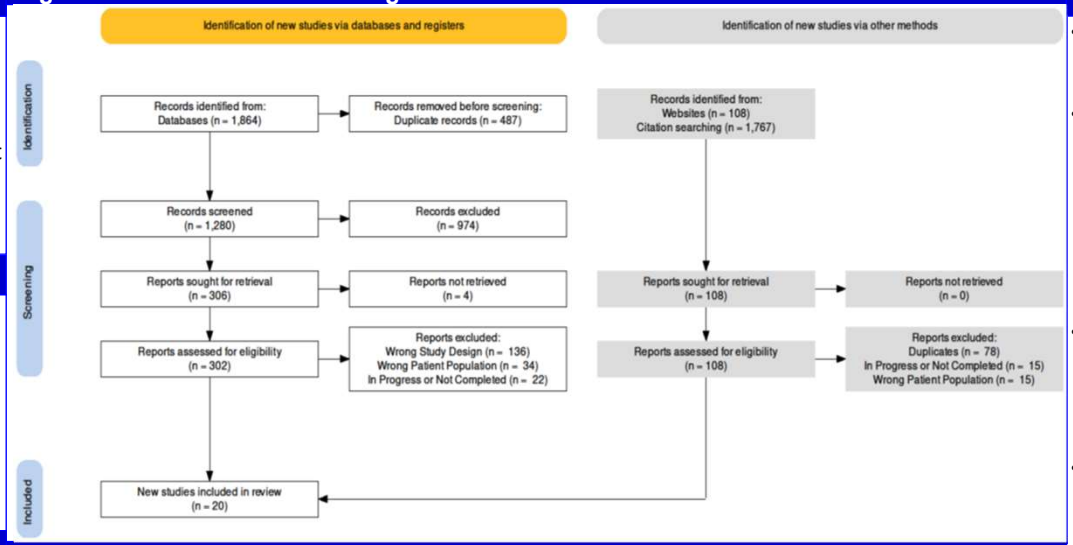

Table 1. Characteristics of Studies on Iron Therapy in Patients with HFrEF and Iron Deficiency

Intervention	Studies	# Patients	Duration	Overall Results*	Risk Of Bias
Iron Isomaltoside IV	1 RCT	40 outpatients	2 weeks	Improvement in ferritin, TSAT, NYHA class, skeletal muscle energetics, post-exercise Borg dyspnea score, and decrease in respiratory rate. No difference in LVEF, VO2, SCr, CRP, KCCQ, or 6MWT.	Low Risk
Sodium Ferric Gluconate IV	1 Cohort	13 inpatients	1-4 weeks	Increase in Hgb, ferritin, and TSAT. No difference in BP or HR.	Moderate Risk
Ferric Carboxymaltose IV	6 RCTs 1 Cohort	2188 RCT 61 Cohort All outpatients	12-52 weeks	Reduction in HF hospitalizations alone, days lost to HF hospitalizations or CV death, fatigue scores, hospitalizations for any CV reason, and hospitalizations due to worsening HF Improvement in Hgb, ferritin, TSAT, NYHA class, patient global assessment, 6MWT, health-related quality of life (MLHFQ/KCCQ), LVEF, cardiac performance, VO2.	Low to Moderate Risk
Iron Polysaccharide PO	1 RCT 1 Case Series	225 outpatients 30 outpatients	12-16 weeks	Increase in ferritin. No difference in VO2, NT-pro-BNP, 6MWT, or KCCQ.	Low to Moderate Risk
Iron Sucrose IV	5 RCTs 3 Cohorts	138 outpatients 86 outpatients	6 weeks – 5 years	Statistically significant improvement in 5 year survival, Hgb, ferritin, TSAT, NYHA class, CrCl, CRP, NT-pro-BNP, and MLHFQ. Decrease in hospitalizations, LVEF, LVSd, LVDd, BNP, and CRP.	Low to Serious Risk
IV Iron (salt not specified)	1 Cohort	25 outpatients	6 months	Reduction in rate of hospitalization and NYHA class. Increase in LVEF 6MWT, and short form health survey scores.	Low Risk

*Statistically Significant Efficacy Results

Results

- Majority of available trials studied various IV iron regimens in the outpatient HFrEF population.
- IV iron regimens including iron isomaltoside, sodium ferric gluconate, ferric carboxymaltose, and iron sucrose appear to improve exercise surrogates such as 6MWT, NYHA class, skeletal muscle energetics, and max VO2 compared to placebo or when uncontrolled.
- IV iron regimens also appear to improve biochemical surrogate markers such as ferritin, TSAT, Hgb, BNP, and NT-pro-BNP compared to placebo or when uncontrolled.
- Select IV iron trials saw reduction in mortality, and heart failure or CV related hospitalizations.
- Oral iron polysaccharide appeared to improve only ferritin with no benefit in exercise surrogates , but there appears to be a lack of evidence looking at PO iron.
- Only one head to head trial compared PO iron ferrous sulfate to IV iron sucrose with an increase in exercise surrogates in the IV arm, and both arms seeing increases in biochemical surrogates.
- There was a lack of further comparisons between regimens.
- The risk of bias assessment show some concerns in quality of literature available, mostly in the included observational trials.

Limitations

- Variability as review methodology was not done in full duplication, but Cohen's kappa demonstrated high intra-rater agreeability throughout
- Some unpublished data missing as unpublished manuscripts were not retrievable despite attempt contacting authors
- Unable to assess possible superiority of individual iron therapy regimens due to heterogeneity of interventions and lack of head to head trials
- Lack of trials longer than several months available to assess long term benefits or safety concerns with iron administration in this HF population
- Ferric carboxymaltose is not on the market in Canada

Conclusions

- There is high quality evidence supporting the use of IV iron in patients with HFrEF to improve exercise and biochemical surrogate outcomes. One high quality trial saw reductions in hospitalizations with IV iron, trials assessing mortality were low quality or underpowered.
- Variety of interventions in trials make it difficult to interpret optimal regimen.
- Future research needs include: administration for inpatient HF population, longer term comparisons of IV vs. PO regimens, comparisons of different iron salts and regimens head to head, and iron isomaltoside trials addressing mortality and hospitalizations as outcomes due to availability of this formulation in Canada.

UBC

Interior Health