Advances in Clinical Trials

Oral Iron Therapy for Heart Failure With Reduced Ejection Fraction

Design and Rationale for Oral Iron Repletion Effects on Oxygen Uptake in Heart Failure

Gregory D. Lewis, MD; Marc J. Semigran, MD; Michael M. Givertz, MD; Rajeev Malhotra, MD; Kevin J. Anstrom, PhD; Adrian F. Hernandez, MD, MHS; Monica R. Shah, MD; Eugene Braunwald, MD

Abstract—Iron deficiency is present in ≈50% of patients with heart failure and is an independent predictor of mortality. Despite growing recognition of the functional and prognostic significance of iron deficiency, randomized multicenter trials exploring the use of oral iron supplementation in heart failure, a therapy that is inexpensive, readily available, and safe, have not been performed. Moreover, patient characteristics that influence responsiveness to oral iron in patients with heart failure have not been defined. Although results of intravenous iron repletion trials have been promising, regularly treating patients with intravenous iron products is both expensive and poses logistical challenges for outpatients. Herein, we describe the rationale for the Oral Iron Repletion effects on Oxygen Uptake in Heart Failure (IRONOUT HF) trial. This National Institute of Health-sponsored trial will investigate oral iron polysaccharide compared with matching placebo with the primary end point of change in exercise capacity as measured by peak oxygen consumption at baseline and at 16 weeks.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT02188784. (Circ Heart Fail. 2016;9:e000345. DOI: 10.1161/CIRCHEARTFAILURE.115.000345.)

Key Words: clinical trial ■ exercise ■ heart failure ■ iron ■ oxygen consumption

Impaired exercise capacity is a cardinal manifestation of heart failure (HF) that is closely related to reduced quality of life and poor outcomes.1–3 Therapeutic options beyond neurohormonal blockade to improve functional capacity and symptoms in HF are currently limited and must be pursued. Iron deficiency is associated with reduced functional capacity and poorer quality of life in HF. Here, a rationale for oral iron repletion in patients with HF and iron deficiency is provided with an overview of the study design for the Iron Repletion effects on Oxygen Uptake in Heart Failure (IRONOUT HF) trial, which aims to study the effect of oral iron repletion on functional capacity in patients with HF and reduced ejection fraction (HFrEF).

Contributing Factors to Exercise Intolerance in Heart Failure

In patients with HF, multiple mechanisms contribute to exercise intolerance.4–8 Abnormal central hemodynamic responses and the degree of left ventricular systolic dysfunction do not adequately explain the early onset of anaerobic metabolism and impaired peak oxygen uptake ($V_{O_2}$) observed in HF.9–11 Prevalent anemia in HF compromises convective delivery of $O_2$ to exercising skeletal muscle. On delivery of $O_2$ to the periphery, diffusive $O_2$ conductance and utilization is limited by impaired skeletal muscle oxidative metabolism.12 Morphological and histochemical changes in skeletal muscle include a shift to type II fibers13 and a reduction in oxidative enzymes.13 As a result, patients with HF experience an early transition from oxidative to glycolytic metabolism and glycolytic end products, in turn, stimulate exaggerated ventilatory responses to exercise through intramuscle afferents sensitive to products of skeletal muscle work (ie, ergoreflex signaling).14 These findings have led to the concept of a central role of the periphery as a dominant mechanism to explain breathlessness and exertional intolerance in HF.9,15 Strategies to target impaired peripheral utilization of oxygen during exercise, therefore, offer promise for improving functional capacity in HF.

Central Role of Fe in $O_2$ Delivery and Utilization

Iron plays a critical role in systemic $O_2$ delivery and utilization (Figure 1).16–23 The contribution of iron to erythropoiesis and the...
role of iron deficiency in decreasing O₂-carrying capacity of the blood through reduced hemoglobin are widely recognized. A less well-appreciated consequence of iron deficiency is impairment in O₂ storage capacity in skeletal muscle through reduced myoglobin. In addition, iron is an obligate component of enzymes involved in cellular respiration, oxidative phosphorylation, vascular homeostasis, and the citric acid cycle (Table 1).

Animal studies have suggested that during iron repletion, improvements in hemoglobin levels and peak V̇O₂ evolve in parallel, whereas enhancements in endurance track with the increase in aerobic enzyme activity. Studies in animals and humans without HF have demonstrated that iron deficiency anemia reduces indices of work capacity by 10% to 50%. The correction of iron deficiency in both anemic and nonanemic patients without HF improves symptoms, quality of life, and exercise performance.

Iron Homeostasis in Heart Failure

There are multiple factors that predispose patients with HF to iron deficiency (Figure 2). Reduced nutrient intake is common in HF, which may result in failure to meet the recommended 8 to 18 mg of daily oral intake of elemental iron. Impairment in iron homeostasis in HF is partially attributable to proinflammatory processes. Hecidin, a heptically derived peptide that is increased by proinflammatory cytokines, blocks intestinal absorption of iron and impairs iron delivery by diverting iron into the reticuloendothelial system. Gut edema may also impair the absorption of oral iron and contribute to iron deficiency in HF. Finally, frequent use of anticoagulants and antiplatelet agents predisposes patients with HF to blood loss and associated depletion in iron stores.

Definition, Prevalence, and Significance of Iron Deficiency in HF

Historically, assessment of iron levels in patients with HF has been performed as part of the evaluation of anemia, which is often multifactorial in HF. However, recent studies have focused on the importance of iron deficiency independent from anemia in HF pathophysiology.

Definition

The gold standard for measurement of iron stores is a bone marrow biopsy. However, because of the invasiveness of this procedure, blood biomarkers, including ferritin and transferrin saturation, can be used instead to reflect iron bioavailability in patients. A ferritin value <30 ng/mL has historically been used as a cutoff for defining iron deficiency. However, the inflammatory processes in HF and their tendency to increase serum ferritin concentration cause iron deficiency in patients with HF to be widely under recognized using this definition. Therefore, for patients with HF, iron deficiency has been defined as either ferritin <100 ng/mL, indicating a deficiency in iron stores, or ferritin between 100 and 300 ng/mL with transferrin saturation <20%, suggesting a disruption in iron delivery.

Circulating levels of hepcidin and soluble transferrin receptor levels complement measurements of ferritin, iron, and total iron-binding capacity. Hecidin inhibits iron absorption and bioavailability and is downregulated in primary iron deficiency, whereas soluble transferrin receptor levels are upregulated and...
reduced myocardial iron content (as defined by magnetic resonance imaging–based T2 star values in excess of 25) was associated with increased left ventricular end diastolic volume, decreased left ventricular ejection fraction, and poorer outcomes. Based on the multiple deleterious effects of iron deficiency on cardiac and peripheral performance, iron deficiency represents an attractive target to improve functional capacity in patients with HF.

**Efficacy and Safety of Treatment of Iron Deficiency in HF**

Clinical studies of intravenous iron repletion in HF are summarized in Table 2. Initial single-center trials focused on patients with HFrEF and iron-deficiency anemia, and consistently observed improvements in peak $V_{O_2}$, patient global assessment scores, and N-terminal B-type natriuretic peptide levels. Correction of iron deficiency has also been shown to have direct effects on myocardial contractility. Two meta-analyses reported significant improvement in echocardiography–derived left ventricular ejection fraction with iron therapy (mean improvement +5%). In another single-center study, an improvement in LV strain rate was reported after 3 months of intravenous iron therapy in 40 patients with iron deficiency and HFrEF. Based on the multiple deleterious effects of iron deficiency on cardiac and peripheral performance, iron deficiency represents an attractive target to improve functional capacity in patients with HF.

![Diagram of Iron Homeostasis in Heart Failure](http://circheartfailure.ahajournals.org/)

**Figure 2.** Iron homeostasis in heart failure. IFN-$\gamma$ indicates interferon gamma; IRONOUT HF, Oral Iron Repletion effects on Oxygen Uptake in Heart Failure; RBC, red blood cell; and TNF-$\alpha$, tumor necrosis factor alpha.

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Iron deficiency has also been associated with ultrastructural changes in cardiomyocytes, including mitochondrial swelling and abnormal sarcomere structure. Patients with HF have lower myocardial iron content and transferrin receptor concentrations than controls, and severe iron deficiency leads to LV systolic dysfunction. In a recent study of patients with nonischemic cardiomyopathy, reduced myocardial iron content (as defined by magnetic resonance imaging–based T2 star values in excess of 25) was associated with increased left ventricular end diastolic volume, decreased left ventricular ejection fraction, and poorer outcomes. Based on the multiple deleterious effects of iron deficiency on cardiac and peripheral performance, iron deficiency represents an attractive target to improve functional capacity in patients with HF.
Table 2. Trials Evaluating Intravenous Iron Supplementation for Treatment of Heart Failure

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<tr>
<th>Drug</th>
<th>Authors/Journal</th>
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<th>Subjects Studied</th>
<th>Iron Deficiency Definition</th>
<th>Time</th>
<th>Primary End point</th>
<th>Findings</th>
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<tr>
<td>Intravenous iron sucrose</td>
<td>Bolger et al37 J Am Coll Cardiol 2006</td>
<td>16</td>
<td>NYHA 2–3</td>
<td>Ferritin&lt;400 ng/mL</td>
<td>12 wk</td>
<td>Δ 6MWT</td>
<td>↑6MWD, ↓NYHA, ↓MLHF scores</td>
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<tr>
<td>Intravenous iron sucrose</td>
<td>Tobilli et al38 J Am Coll Cardiol 2007</td>
<td>40</td>
<td>NYHA 3–4</td>
<td>Ferritin&lt;100 ng/mL and Tsat&lt;20%</td>
<td>5 wk</td>
<td>Δ global assessment score</td>
<td>↑PGAS, ↑6MWD, ↓NT-BNP, ↓LVEF</td>
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<tr>
<td>Intravenous iron sucrose</td>
<td>Usmanov et al41 J Nephrol 2008</td>
<td>32</td>
<td>NYHA 3–4</td>
<td>Hb&lt;11 g/dL; Iron indices not specified</td>
<td>26 wk</td>
<td>Δ NYHA</td>
<td>↓NYHA, ↓LVEF</td>
</tr>
<tr>
<td>Intravenous iron sucrose</td>
<td>Okonko et al42 J Am Coll Cardiol 2008</td>
<td>35</td>
<td>NYHA 2–3</td>
<td>Ferritin&lt;100 ng/mL or 100–300 with Tsat&lt;20%</td>
<td>16 wk</td>
<td>Δ peak VO2</td>
<td>↓PGAS, ↓NYHA, ↑peak VO2 α/α Tsat</td>
</tr>
<tr>
<td>Intravenous iron carboxymaltose</td>
<td>Anker et al43 N Engl J Med 2009</td>
<td>459</td>
<td>NYHA 2–3</td>
<td>Ferritin&lt;0.4 Hb, 9.5–13.5</td>
<td>24 wk</td>
<td>Δ global assessment score</td>
<td>↑PGAS, ↑NYHA, ↑LVEF Similar benefit Hb&lt;&gt;12</td>
</tr>
<tr>
<td>Intravenous iron carboxymaltose</td>
<td>Bonkowski et al44 Eur Heart J 2014</td>
<td>304</td>
<td>NYHA 2–3</td>
<td>Ferritin&lt;0.45 Hb&lt;15</td>
<td>52 wk</td>
<td>Δ 6MWD</td>
<td>↑6MWD, ↓PGAS, ↓NYHA Similar benefit Hb&lt;&gt; or &gt;12 ↓HF hospitalization</td>
</tr>
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</table>

6MWD indicates 6-minute walk distance; 6MWT, 6-minute walk test; Hb, hemoglobin; HF, heart failure; LVEF, left ventricular ejection fraction; MLHF, Minnesota Living with Heart Failure; NT-BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association functional class; PGAS, patient global assessment score; Tsat, transferrin saturation; and VO2, oxygen consumption.

Controlled Phase 4 study to compare the efficacy and safety of intravenous ferric carboxymaltose with placebo in patients with chronic heart failure and iron deficiency (CONFIRM-HF) trial, which assessed long-term therapy with intravenous ferric carboxymaltose in HFrEF, extended findings from Ferinject Assessment in Patients with Iron Deficiency-HF by demonstrating improvement in 6-minute walk distance and quality of life in patients with hemoglobin values ≤15 g/dL, while also demonstrating reduction in HF hospitalizations.41 The fact that iron repletion demonstrates similar efficacy in anemic and nonanemic patients clearly distinguishes this strategy from that of treatment of anemia alone with erythropoiesis-stimulating agents, which has been shown to not improve HF outcomes.42

**Oral Iron**

With the exception of a truncated study that included one individual randomized to oral iron,39 trials exploring the use of oral iron supplementation in patients with HF and iron deficiency have not been performed. A recent retrospective observational study of 105 patients with HFrEF and iron deficiency who showed that oral iron supplementation improved ferritin (median 39 to 75 ng/mL), Tsat (10% to 21%), iron (34 to 69 µg/dL), and hemoglobin (10.4 to 11.6 g/dL) values (all P<0.0001) during a median follow-up period of 164 days. In non-HF populations, intravenous and oral Fe repletion have resulted in similar sustained increases in circulating ferritin levels, transferrin saturations, and hemoglobin concentrations.31 A study in iron-deficient patients with congenital heart disease demonstrated functional improvements with oral iron supplementation after 3 months of iron fumarate (600 mg total daily dose).52 However, further investigation is clearly needed to determine the use of oral therapies in iron-deficient HF populations.

**Rationale for IRONOUT**

Despite growing recognition of the functional and prognostic significance of iron deficiency, current HF guidelines in the United States do not specify when, or whether, to assess for and treat iron deficiency. European guidelines have recently recommended evaluation of iron studies without specifically addressing whether to implement treatment strategies.

Although results of intravenous iron repletion trials have been promising, regularly treating patients with intravenous iron products is both expensive and poses logistical challenges for outpatients. In Ferinject Assessment in Patients with Iron Deficiency-HF, 8 to 12 weekly injections of intravenous iron sucrose (200 mg) were required to achieve iron repletion, followed by monthly injections during the maintenance phase. Intravenous iron infusions are expensive ($=4000/injection for the least expensive preparation, iron sucrose 200 mg) and pose logistical challenges for outpatients based on the frequency of required visits and need for the infrastructure within HF clinics to administer infusions. Although a higher-dose intravenous iron preparation is now available (ferumoxytol [Feraheme], 510 mg elemental iron), this preparation has been associated with hypersensitivity reactions in 3.7% of patients, including anaphylaxis, cardiac arrest, and hypotension.53 Randomized multicenter trials exploring the use of oral iron supplementation in HF, a therapy that is inexpensive, readily available, and safe, have not been performed. There is also a need to understand patient characteristics that influence responsiveness to oral iron. A recent retrospective study showed lack of relationship between dose of elemental iron and change in iron stores, suggesting host factors play an important role.54 There may be subsets of patients with HFrEF (ie, lack of right HF and intestinal edema, low hepcidin levels) that benefit from oral iron supplementation even if the strategy is not effective in all.

**Study Design**

Oral Iron Repletion effects on Oxygen Uptake in Heart Failure (IRONOUT HF) is an National Institute of Health-sponsored multicenter, randomized, double-blinded, placebo-controlled trial of oral iron polysaccharide compared with matching placebo with the primary end point of change in peak VO2 measured by cardiopulmonary exercise testing (CPET) at baseline.
Lewis et al  Oral Iron for Heart Failure

Figure 3. Flow diagram of Oral Iron Repletion effects on Oxygen Uptake in Heart Failure (IRONOUT HF) trial. 6MWT indicates 6-minute walk test; CPET, cardiopulmonary exercise test; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; and NT-BNP, N-terminal pro B-type natriuretic peptide.

and at 16 weeks (clinicaltrials.gov, NCT02188784, Figure 3). A total of 220 patients with HFrEF meeting the eligibility criteria (Table 3) are being enrolled and randomized in the study. Screening is being conducted in outpatients with chronic symptomatic HFrEF. Willing participants who are found to have iron deficiency and meet other entry criteria are being consented for the trial.

Randomization and Stratification
After providing written informed consent, research participants complete all baseline procedures, including clinical evaluation, blood samples, and CPET. Eligible participants are randomized with a 1:1 allocation ratio to either oral iron polysaccharide 150 mg twice daily or matching placebo. Randomization is stratified by anemia status (anemia is defined as hemoglobin <12 g/dL). A permuted block randomization method stratified by site is used to ensure relatively equal distribution of subjects to each arm within each clinical site.

Polysaccharide iron complex is being studied as the oral iron preparation of choice for this study because it is relatively nontoxic, thus permitting a higher therapeutic dosage (150–300 mg elemental iron daily) than other iron preparations.55 Polysaccharide iron complex capsules are a highly water-soluble complex of iron and a low-molecular weight polysaccharide. Iron polysaccharide is considered to be a dietary supplement, and although it has a human over-the-counter drug label, it is not an food drug administration-approved drug. From previous studies using inclusion criteria based on the same iron study results, we estimated an average iron deficit of \( \approx 1 \) g using the Ganzoni formula. 56 Assuming 5% absorption of iron polysaccharide, a period of 10 weeks of 300 mg daily dosing is required to completely make up this deficit.

Participants are started on polysaccharide iron complex 150 mg or placebo administered twice daily in a double-blinded fashion. Instructions are provided to take pills separately from meals and to avoid taking antacids, dairy products, tea, or coffee within 2 hours before or after this medication because they will decrease effectiveness. Drug administration with orange juice or other products rich in Vitamin C may enhance absorption and, therefore, is encouraged.

Primary End Point
Impaired exercise capacity is a cardinal manifestation of HF and it can be objectively and reproducibly measured by quantifying peak oxygen uptake (peak \( \text{VO}_2 \)) through CPET. The multiple mechanisms by which iron repletion is expected to improve systemic \( \text{O}_2 \) delivery and utilization (Figure 1) are captured with assessment of peak \( \text{VO}_2 \), making this measure ideally suited to be the primary end point. Unlike changes in alternative trial end points, such as circulating biomarkers or echocardiographic parameters, there is significant intrinsic value to patients associated with improving exercise capacity.

For assessment of changes in exercise capacity in response to iron repletion, there are several advantages of CPET in comparison to 6-minute walk tests used in previous multicenter trials of intravenous iron repletion.42,43 First, CPET permits precise assessment of volitional effort based on whether the respiratory exchange ratio (\( \text{VCO}_2/\text{VO}_2 \)) exceeds 1.0 during exercise; second, CPET provides insights into the organ system limiting gas exchange; third, CPET-derived peak \( \text{VO}_2 \) has been shown to outperform 6-minute walk distance in predicting HF outcomes57; and finally, CPET permits measurement of an array of variables that reflect metabolic responses to low level, intermediate, and maximum exercise and thereby permits comprehensive assessment of the impact of a therapy that is expected to affect oxygen utilization via multiple mechanisms.

Secondary End Points and Exploratory Studies
Secondary end points of IRONOUT HF include assessments of the impact of oral Fe repletion on (1) submaximal exercise capacity, as measured by \( \text{O}_2 \) uptake kinetics on initiation of exercise56; (2) ventilatory efficiency, as measured by minute ventilation relative to \( \text{CO}_2 \) production throughout exercise; (3) 6-minute walk distance; (4) plasma N-terminal pro B-type
Table 3. IRONOUT HF Inclusion and Exclusion Criteria

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<th>Inclusion criteria</th>
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<tr>
<td>Age ≥ 18 y</td>
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<tr>
<td>Previous clinical diagnosis of heart failure with current NYHA class II–IV symptoms, LVEF ≤ 0.40 within 2 y before consent, and ≥ 3 mo after a major change in cardiac status (ie, CABG or CRT)</td>
</tr>
<tr>
<td>Serum ferritin between 15 and 100 ng/mL or serum ferritin between 100 and 299 ng/mL with transferrin saturation &lt; 20%</td>
</tr>
<tr>
<td>Hemoglobin 9.0–15.0 g/dL (males), 9.0–13.5 (females) at time of enrollment</td>
</tr>
<tr>
<td>Evidence-based medical therapy for HF (including β-blocker and ACE inhibitor/ARB unless previously deemed intolerant and diuretics as necessary) with ≤ 100% change in dose for 30 days before randomization. Changes in diuretic dose guided by a patient-directed flexible dosing program are considered stable medical therapy</td>
</tr>
<tr>
<td>Willingness to provide informed consent</td>
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</table>

Exclusion criteria

| Presence of a neuromuscular, orthopedic, or other noncardiac condition that prevents the patient from exercise testing on a cycle/treadmill ergometer and inability to achieve an RER ≥ 1.0 on screening/baseline CPET |
| Severe renal dysfunction (eGFR < 20 mL/min per 1.73 m²)                              |
| Severe liver disease (ALT or AST > 3 × normal, alkaline phosphatase, or bilirubin > 2 × normal) |
| Gastrointestinal conditions known to impair Fe absorption (ie, inflammatory bowel disease) |
| Known active infection as defined by current use of oral or intravenous antimicrobial agents |
| Documented active gastrointestinal bleeding                                           |
| Active malignancy other than nonmelanoma skin cancers                               |
| Anemia with known cause other than iron deficiency or chronic disease               |
| Fe overload disorders (ie, hemochromatosis or hemosiderosis)                        |
| History of erythropoietin, intravenous or oral Fe therapy, or blood transfusion in previous 3 mo |
| Current ventricular assist device                                                    |
| Anticipated cardiac transplantation within the next 4 mo                             |
| Primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis, or tamponade |
| Previous adverse reaction to study drug or other oral Fe preparation                 |
| Known or anticipated pregnancy in the next 4 mo                                     |

ACE indicates angiotensin converting enzyme; ALT, alanine transaminase; ARB, angiotensin receptor blocker; AST, aspartate transaminase; CABG, coronary artery bypass surgery; CPET, cardiopulmonary exercise testing; CRT, cardiac resynchronization therapy; eGFR, epidermal growth factor receptor; HF, heart failure; IRONOUT HF, Oral Iron Repletion effects on Oxygen Uptake in Heart Failure; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association functional class.

Iron deficiency is present in ≤ 50% of patients with HFrEF and predicts poor prognosis independently of anemia. Despite these recent observations and trials suggesting benefits from intravenous iron repletion, current HF guidelines do not specify when or if to assess for and treat iron deficiency. The IRONOUT HF trial design has several strengths, including entry criteria that permit assessment of effects of oral iron repletion on patients with and without anemia. Objective measurements of submaximum and maximum exercise capacity, novel secondary end points (ie, assessment of oxygen uptake kinetics) that directly reflect mechanisms of action of iron repletion, and careful patient phenotyping to aid in identification of subgroups that may benefit most from oral iron repletion.

Although the sample size and short duration of this trial precludes definitive assessment of patient outcomes, the results of IRONOUT HF could lead to guideline recommendations for use of oral iron to improve functional capacity in HF. Based on the low cost and widespread availability of this therapy, the trial is anticipated to affect the clinical practice of administering oral iron to patients with HF whether the
results are positive. If patients with HFrEF derive no benefit from oral iron repletion, it would mitigate polypharmacy effects on erythropoiesis, it will profoundly affect the treatment of HF.

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quirements identifies patients at the highest risk of death after an episode
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