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.2-4 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 (VO2) observed in HF.5-11 Prevalent anemia in HF compromises convective delivery of O2 to exercising skeletal muscle. On delivery of O2 to the periphery, diffusive O2 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 O2 Delivery and Utilization
Iron plays a critical role in systemic O2 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 VO₂ 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. Hepcidin, a hepatically 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. Hepcidin inhibits iron absorption and bioavailability and is downregulated in primary iron deficiency, whereas soluble transferrin receptor levels are upregulated and

Table 1. Fe-Containing Proteins That Are Altered in Heart Failure

<table>
<thead>
<tr>
<th>Name of Protein</th>
<th>Functional Site</th>
<th>Status in HF</th>
<th>Biological Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>Red blood cell</td>
<td>↓</td>
<td>O₂ transport</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>Cytoplasm of muscle cells</td>
<td>↓</td>
<td>Facilitation of O₂ transport</td>
</tr>
<tr>
<td>Oxidative enzymes (ie, cytochrome oxidase)</td>
<td>Mitochondrial inner membrane</td>
<td>↓</td>
<td>Substrate oxidation→NADH, FADH₂</td>
</tr>
<tr>
<td>Respiratory chain proteins</td>
<td>Mitochondrial inner membrane</td>
<td>↓</td>
<td>Electron transfer from O₂→NADH, FADH₃</td>
</tr>
<tr>
<td>Soluble guanylate cyclase</td>
<td>Vascular smooth muscle cells, cardiomyocytes</td>
<td>↓</td>
<td>Nitric oxide stimulation of cGMP synthesis</td>
</tr>
</tbody>
</table>

cGMP indicates cyclic guanosine monophosphate; FADH₂, reduced form of flavin adenine dinucleotide; HF, heart failure; and NADH, reduced form of nicotinamide adenine dinucleotide. Adapted with permission from Haas and Brownlie. Copyright © 2001, Wiley Brothers.
released into the bloodstream by cells avid for iron during states of iron deficiency. Jankowska et al recently reported that hepcidin levels <14.5 ng/mL coupled with soluble transferrin receptor >1.6 mg/L are indicators of iron deficiency that independently predict poor prognosis in HF.

Prevalence
Approximately 70% of patients with HFrEF have reduced bone marrow iron stores, and 37% to 67% meet criteria to have iron deficiency. Although circulating ferritin levels can increase as an acute phase reactant, and thereby potentially mask iron deficiency in patients admitted with acute HF, a recent study found that 72% of hospitalized patients met diagnostic criteria for iron deficiency. Notably, 25% to 42% of patients with HF and iron deficiency are not anemic, which highlights the importance of considering iron deficiency even when hemoglobin levels are normal.

Functional and Prognostic Significance
Iron deficiency reduces indices of functional and endurance capacity in patients with HF which likely reflects its broad impact on oxygen transport and cellular oxidative capacity. Patients with HF and iron deficiency had a worse health-related quality of life (as assessed by Minnesota Living with Heart Failure questionnaire scores) than those without iron deficiency. In addition, iron deficiency was associated with poorer outcomes in patients with systolic HF, independent of other well-established prognostic factors, including anemia, New York Heart Association class, left ventricular ejection fraction, 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. These findings reinforce the hypothesis that iron repletion may directly improve cardiac function in addition to promoting improved peripheral oxygen delivery and utilization.

The landmark randomized trial of iron repletion in patients with HFrEF and iron deficiency, Ferinject Assessment in Patients with Iron Deficiency-HF, demonstrated significant improvements in patient global assessment scores and decreases in New York Heart Association class with the administration of 200 mg intravenous ferric carboxymaltose weekly until repletion. Improvements in patient global assessment score and 6-minute walk distance were similar in patients with and without anemia. The Randomised, Double-blind
saturations, and hemoglobin concentrations.51 A study in iron-deficient patients with congenital heart disease demonstrated intestinal edema, low hepcidin levels) that benefit from oral iron. A recent retrospective study showed lack of relation between dose of elemental iron and change in iron stores, oral iron. 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 visits and need for the infrastructure within HF clinics 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 HFrefEF (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.
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. 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 FDA-approved drug. From previous studies using inclusion criteria based on the same iron study results, we estimated an average iron deficit of ≈1 g using the Ganzoni formula. 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 VO₂) through CPET. The multiple mechanisms by which iron repletion is expected to improve systemic O₂ delivery and utilization (Figure 1) are captured with assessment of peak VO₂, 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. First, CPET permits precise assessment of volitional effort based on whether the respiratory exchange ratio (VCO₂/VO₂) exceeds 1.0 during exercise; second, CPET provides insights into the organ system limiting gas exchange; third, CPET-derived peak VO₂ has been shown to outperform 6-minute walk distance in predicting HF outcomes; 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 IRONOT HF include assessments of the impact of oral Fe repletion on (1) submaximal exercise capacity, as measured by O₂ uptake kinetics on initiation of exercise; (2) ventilatory efficiency, as measured by minute ventilation relative to CO₂ production throughout exercise; (3) 6-minute walk distance; (4) plasma N-terminal pro B-type
Table 3. IRONOUT HF Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 18 y</td>
<td>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</td>
</tr>
<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>
<td>Severe renal dysfunction (eGFR &lt; 20 mL/min per 1.73 m²)</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>
<td>Severe liver disease (ALT or AST &gt; 3 × normal, alkaline phosphatase, or bilirubin &gt; 2 × normal)</td>
</tr>
<tr>
<td>Hemoglobin 9.0–15.0 g/dL (males), 9.0–13.5 (females) at time of enrollment</td>
<td>Gastrointestinal conditions known to impair Fe absorption (ie, inflammatory bowel disease)</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>
<td>Known active infection as defined by current use of oral or intravenous antimicrobial agents</td>
</tr>
<tr>
<td>Willingness to provide informed consent</td>
<td>Documented active gastrointestinal bleeding</td>
</tr>
<tr>
<td></td>
<td>Active malignancy other than nonmelanoma skin cancers</td>
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<td></td>
<td>Anemia with known cause other than iron deficiency or chronic disease</td>
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<tr>
<td></td>
<td>Fe overload disorders (ie, hemochromatosis or hemosiderosis)</td>
</tr>
<tr>
<td></td>
<td>History of erythropoietin, intravenous or oral Fe therapy, or blood transfusion in previous 3 mo</td>
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<tr>
<td></td>
<td>Current ventricular assist device</td>
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<tr>
<td></td>
<td>Anticipated cardiac transplantation within the next 4 mo</td>
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<tr>
<td></td>
<td>Primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy, acute myocarditis, constrictive pericarditis, or tamponade</td>
</tr>
<tr>
<td></td>
<td>Previous adverse reaction to study drug or other oral Fe preparation</td>
</tr>
<tr>
<td></td>
<td>Known or anticipated pregnancy in the next 4 mo</td>
</tr>
</tbody>
</table>

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.

Conclusions

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

dema; and (3) patients with and without an RER > 1.1 during maximum incremental exercise. Other exploratory objectives include whether iron repletion influences clinical outcomes: time to death and HF hospitalization or renal function (creatinine, cystatin C). The primary iron studies (iron, total iron-binding capacity, ferritin) will be measured at baseline and after 16 weeks of study medication to determine the extent to which oral iron leads to iron repletion in patients with HF.

Statistical Considerations

All primary analyses are based on the intention-to-treat principle. A general linear model with the change in peak VO₂, measured at 16 weeks as the response variable and predictor variables including a treatment indicator and the baseline measure of peak VO₂ are used in the primary analysis. Using a minimally important difference for peak VO₂ of 1.0 mL/ (kg-min), and an estimate of 2.0 mL/kg-min) for the SD for peak VO₂, a sample size of 172 subjects (86 per group) provides 90% power to detect the minimally important difference with a 2-sided type I error of 0.05. Allowing for 20% missing data results in a sample size of 108 per group, or a total sample size of 220 subjects.

A secondary analysis of the peak VO₂ outcome uses a repeated measures analysis. For this analysis, all measurements of peak VO₂ (including baseline) are treated as response variables. The following covariates are included in the regression model: treatment group, time period, treatment group*time period interaction, baseline VO₂, and baseline Fe level. An unstructured correlation matrix is assumed for the repeated measures within subjects.

General linear models and nonparametric approaches are used to analyze the continuous outcomes. For binary outcomes, χ² tests and Fisher exact test are used for unadjusted comparisons. For adjusted comparisons, logistic regression analysis is used to compare oral iron versus placebo with the estimated odds ratio and associated 95% confidence interval.


diplopia in 6% of patients, suggesting that the use of oral iron in HF may be associated with an increased risk of diplopia.
results are positive. If patients with HFpEF derive no benefit from oral iron repletion, it would mitigate polypharmacy that is nearly ubiquitous in patients with HF. However, if iron repletion is shown to improve exercise capacity beyond its effects on erythropoiesis, it will profoundly affect the treatment of HF.

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Disclosures

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