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Effect of Oral Iron Repletion on Exercise Capacity in Patients With Heart Failure With Reduced Ejection Fraction and Iron Deficiency
The IRONOUT HF Randomized Clinical Trial

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IMPORTANCE Iron deficiency is present in approximately 50% of patients with heart failure with reduced left ventricular ejection fraction (HFrEF) and is an independent predictor of reduced functional capacity and mortality. However, the efficacy of inexpensive readily available oral iron supplementation in heart failure is unknown.

OBJECTIVE To test whether therapy with oral iron improves peak exercise capacity in patients with HFrEF and iron deficiency.

DESIGN, SETTING, AND PARTICIPANTS Phase 2, double-blind, placebo-controlled randomized clinical trial of patients with HFrEF (<40%) and iron deficiency, defined as a serum ferritin level of 15 to 100 ng/mL or a serum ferritin level of 101 to 299 ng/mL with transferrin saturation of less than 20%. Participants were enrolled between September 2014 and November 2015 at 23 US sites.

INTERVENTIONS Oral iron polysaccharide (n = 111) or placebo (n = 114), 150 mg twice daily for 16 weeks.

MAIN OUTCOMES AND MEASURES The primary end point was a change in peak oxygen uptake ($\dot{V}O_2$) from baseline to 16 weeks. Secondary end points were change in 6-minute walk distance, plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, and health status as assessed by Kansas City Cardiomyopathy Questionnaire (KCCQ, range 0-100, higher scores reflect better quality of life).

RESULTS Among 225 randomized participants (median age, 63 years; 36% women) 203 completed the study. The median baseline peak $\dot{V}O_2$ was 1196 mL/min (interquartile range [IQR], 887-1448 mL/min) in the oral iron group and 1167 mL/min (IQR, 887-1449 mL/min) in the placebo group. The primary end point, change in peak $\dot{V}O_2$ at 16 weeks, did not significantly differ between the oral iron and placebo groups (+23 mL/min vs −2 mL/min; difference, 21 mL/min [95% CI, −34 to +76 mL/min]; $P = .46$). Similarly, at 16 weeks, there were no significant differences between treatment groups in changes in 6-minute walk distance (−13 m; 95% CI, −32 to 6 m), NT-proBNP levels (159; 95% CI, −280 to 599 pg/mL), or KCCQ score (1; 95% CI, −2.4 to 4.4), all $P > .05$.

CONCLUSIONS AND RELEVANCE Among participants with HFrEF with iron deficiency, high-dose oral iron did not improve exercise capacity over 16 weeks. These results do not support use of oral iron supplementation in patients with HFrEF.

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Supplemental content

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Iron deficiency is the most common nutritional deficiency worldwide, affecting more than 15% of the global population as of 2010[1] and approximately one-half of patients with symptomatic heart failure.[2] The presence of iron deficiency in patients with heart failure, regardless of hemoglobin status, is associated with reduced functional capacity, poorer quality of life, and increased mortality.[2,3]

Iron plays a critical role in systemic oxygen (O_2) delivery and utilization.[3-6] Iron contributes to erythropoiesis and therefore iron deficiency decreases O_2-carrying capacity of the blood through reduced hemoglobin levels. Iron is also an obligate component of enzymes involved in cellular respiration, oxidative phosphorylation, vascular homeostasis, nitric oxide generation, and the citric acid cycle.[7,8] Hence, cells with high-energy demands, including skeletal and cardiac myocytes, are particularly sensitive to depleted iron stores.[9] Cardiac iron deficiency is present in patients with heart failure and associated with impaired mitochondrial function,[10] abnormal sarcomere structure,[5] and left ventricular systolic dysfunction.[11,12]

Despite growing recognition of the functional and prognostic significance of iron deficiency, randomized multicenter trials exploring the utility of oral iron supplementation, a therapy that is inexpensive, readily available, and safe, have not been performed in patients with heart failure. Moreover, patient characteristics and biochemical profiles that may influence responsiveness to oral iron in patients with heart failure have not been defined. Although results of intravenous iron repletion trials have been favorable,[13,14] regularly treating patients with intravenous iron products is expensive and poses logistical challenges for outpatients. The Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT HF) trial was designed to test the hypothesis that, compared with placebo, oral iron repletion in heart failure patients with iron deficiency improves exercise capacity after 16 weeks of therapy.

Key Points

Question Does therapy with oral iron improve exercise capacity in patients with heart failure and iron deficiency?

Findings In this randomized clinical trial of 225 adults with heart failure and reduced ejection fraction, oral iron polysaccharide minimally repleted iron stores and had no significant effect on exercise capacity at 16 weeks compared with placebo (+23 mL/min for oral iron polysaccharide vs −2 mL/min for placebo).

Meaning These findings do not support the use of oral iron supplementation in patients with heart failure and reduced left ventricular ejection fraction and iron deficiency.

Methods

Study Oversight

All study participants provided written informed consent prior to enrollment. The National Heart, Lung, and Blood Institute-sponsored Heart Failure Clinical Research Network investigators conceived, designed, and conducted this study. The trial protocol was approved by a National Heart, Lung, and Blood Institute-appointed protocol review committee and data and safety monitoring board and by the institutional review board at each participating site. The Duke Clinical Research Institute served as the coordinating center.

Study Design

The rationale and design of this study have been previously described[15] and are reported in the full protocol (see Supplement 1). Patients with reduced left ventricular ejection fraction (≤40%) and heart failure (with New York Heart Association functional class II through IV symptoms) (HFrEF) who were stable while receiving medical therapy were eligible to participate if they had objective evidence of iron deficiency (ferritin 15-100 ng/mL or between 100-299 ng/mL with a transferrin saturation [Tsat] level <20%) and hemoglobin levels between 9 and 15 g/dL (men) or 9 and 13.5 g/dL (women).[15] Individuals were excluded if a neuromuscular, orthopedic, or other noncardiac condition prevented cardiopulmonary exercise testing (CPET). Inability to achieve a respiratory exchange ratio greater than or equal to 1.0 on baseline screening CPET was also an exclusion criterion. A complete list of the trial inclusion and exclusion criteria is provided in eTable 1 in Supplement 2.

Race, ethnicity, and sex were included as data elements to satisfy the National Heart, Lung, and Blood Institute Policy for Inclusion of Women and Minorities in Clinical Research. Race, ethnicity, and sex determinations were provided by the participants and collected as fixed categories. CPETs were performed by CPET Core Laboratory-certified sites using equipment and calibration approaches that met American Thoracic Society standards. CPETs were performed using a 10-W/min incremental ramp protocol, and breath-by-breath measures of oxygen uptake were uniformly analyzed by the CPET Core Laboratory. Quality control measures included repeated physiologic calibration testing individuals who tested within the normal range to ensure proper equipment calibration and performance. Participants who met screening criteria underwent baseline studies, including obtainment of medical history and physical examination, CPET, Kansas City Cardiomyopathy Questionnaire (KCCQ),[16] 6-minute walk test, and phlebotomy for biomarkers, and were then randomly assigned in a 1:1 ratio to receive either oral iron polysaccharide or placebo with the use of an automated web-based system. A permuted block-randomization method (4 participants/block) was stratified by enrolling site and anemia status (defined as hemoglobin <12 g/dL).

Study drug was administered orally at 150 mg, twice daily for 16 weeks. At the end of 8 weeks, medical history was again recorded and participants underwent a physical examination, a 6-minute walk test, and completed a KCCQ quality of life questionnaire. At the end of 16 weeks, each participant's medical history, physical examination, KCCQ, CPET, and 6-minute walk test were repeated in the same order. If adverse effects developed, study personnel could recommend a discontinuation of the study drug or a dose frequency reduction to once daily. Blinded central core laboratories assessed biomarkers (University of Vermont) and CPET end points (Massachusetts General Hospital, Harvard University).

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Study End Points

The primary end point was the change in peak oxygen uptake (peak $\dot{V}O_2$) after 16 weeks of therapy. Change in peak $\dot{V}O_2$ reflects the multiple mechanisms by which iron repletion is expected to improve systemic oxygen delivery and utilization (previously described).[15] There is also significant intrinsic value to patients in improving impaired exercise capacity, a cardinal manifestation of heart failure.

Secondary end points included assessments of (1) submaximal exercise capacity, as measured by O_2 uptake kinetics at initiation of exercise[17]; (2) ventilatory efficiency, as measured by minute ventilation relative to CO_2 production throughout exercise; (3) 6-minute walk distance; (4) plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels; and (5) KCCQ. Exploratory objectives sought to determine if the following prespecified subgroups of patients would derive differential benefit from oral iron: (1) patients with or without anemia; (2) patients with or without venous congestion based on jugular venous pressure (>10 cm) or lower extremity edema; and (3) patients with and without a respiratory exchange ratio greater than 1.1 during both maximum incremental exercise tests. Other exploratory objectives were used to examine whether oral iron repletion influenced clinical outcomes: time to death, time to heart failure hospitalization, O_2 uptake at the ventilatory threshold, and renal function (creatinine, cystatin C). Iron studies (iron, total iron binding capacity, and ferritin) were measured at baseline and after 16 weeks of study medication to determine the extent to which oral iron led to iron repletion in HFrEF patients.

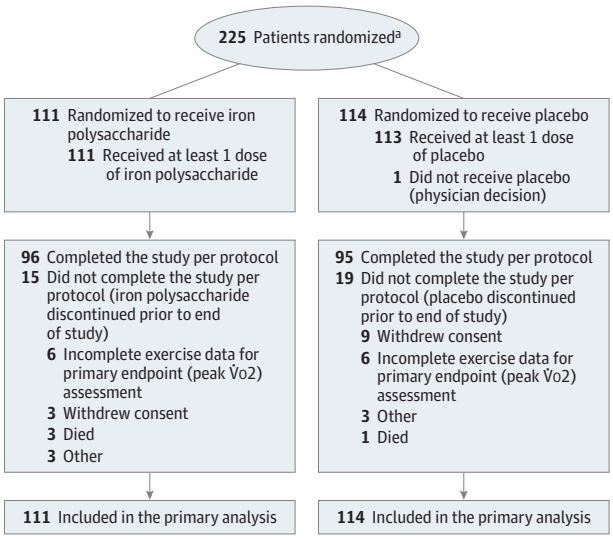
Hepcidin is a hepatically derived peptide that inhibits intestinal iron absorption by interacting with its specific transmembrane receptor (ferroportin) on target cells. Hepcidin causes reduced expression of ferroportin, which is responsible for importing systemic iron from enterocytes and also iron release from the reticuloendothelial system.[18-21] An iron-replete state stimulates hepcidin expression and reduces iron absorption. Iron depletion suppresses hepcidin levels and enhances iron absorption. Inflammation can also induce hepcidin expression independent of iron stores and thus, inappropriately limit iron absorption.[22] Because heart failure is associated with increased inflammation, predisposing to hepcidin dysregulation, this study sought to determine if baseline hepcidin levels predicted oral iron responsiveness. In addition, we measured soluble transferrin receptor levels because elevated levels are observed in states of high cellular avidity for iron, but whether levels normalize with oral iron repletion is unknown.[18] Therefore plasma hepcidin levels and soluble transferrin receptor levels were measured at baseline and after 16 weeks to gain mechanistic insight into oral iron responsiveness in heart failure.

Statistical Analysis

The full statistical analysis plan appears in Supplement 3. All primary analyses were based on the intention-to-treat principle, meaning that study participants were analyzed as members of the treatment group to which they were randomized regardless of their adherence to or receipt of the intended treatment. A minimally important difference for peak $\dot{V}O_2$ of 1.0 mL/kg/min was used based on a previously determined significant relationship between that change in peak $\dot{V}O_2$ and heart failure outcomes.[23] Using an estimate of 2.0 mL/kg/min for the standard deviation for peak $\dot{V}O_2$, a sample size of 172 participants (86 per group) provided 90% power to detect the minimally important difference with a 2-sided type I error of .05. Allowing for 20% missing data (to account for death, study withdrawal, or missing data) resulted in a sample size of at least 108 per group.

Baseline data are presented as medians with interquartile ranges (IQRs). A general linear model with the change in peak $\dot{V}O_2$ measured at 16 weeks as the response variable and predictor variables including a treatment indicator and the baseline measure of peak $\dot{V}O_2$ were used in the primary analysis. The primary analysis for peak $\dot{V}O_2$ used multiple imputation techniques to address incomplete data (statistical analysis plan in Supplement 3). A sensitivity analysis of the peak $\dot{V}O_2$ outcome used values from participants with complete data at baseline and 16 weeks. A mixed-effects model was used to analyze site effects for the primary end point. For primary and secondary end points, *P* values less than .05 were considered statistically significant with 2-sided significance testing. All analyses were conducted using SAS statistical software, version 9.4.

Figure 1. Flow of Participants for the IRONOUT HF Study



Secondary end points were analyzed with multiple imputation techniques when data were unavailable for the end point.

[a] Data on patients screened for eligibility were not available.

Results

A total of 225 participants were enrolled (**Figure 1**) in the trial from September 3, 2014, through November 18, 2015, at 23 sites in the United States. Baseline characteristics are presented in **Table 1.** The median age was 63 years and 36% of the participants were women. Median duration of heart failure was 5.7 years. Ischemic heart disease was the primary etiology of HFrEF in 78% of participants. Despite high rates of guideline-directed medical therapies for HFrEF, the median NT-proBNP

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Table 1. Baseline Characteristics of Participants in the IRONOUT HF Study[a]

	Oral Iron (n = 111)	Placebo (n = 114)	All (N = 225)
Age, median (IQR), y	63.0 (54-71)	63 (55-70)	63 (55-70)
Women	44 (40)	36 (32)	80 (36)
Race/ethnicity[b]			
White	79 (71)	85 (75)	164 (73)
Black	31 (28)	26 (23)	57 (25)
Asian	1 (1)	2 (2)	3 (1)
More than 1 race	0	1 (1)	1 (1)
Body mass index, median (IQR)[c]	28.9 (25.3-33.7)	29.6 (25.9-33.8)	29.2 (25.7-33.8)
Left ventricular ejection fraction, median (IQR), %	25 (20-34)	25 (20-33)	25 (20-34)
Functional Measures			
New York Heart Association classification			
II	81 (73)	69 (61)	150 (67)
III	30 (27)	45 (39)	75 (33)
Summary score, median (IQR)[d]			
KCCQ clinical score	77.1 (63.5-89.6)	74.2 (58.3-87.5)	75.5 (61.5-88.5)
KCCQ overall score	75.0 (59.6-87.3)	70.1 (50.8-85.4)	71.9 (56.0-85.9)
6-min walk distance, median (IQR), m	365 (304-433)	360 (273-428)	363 (292-428)
Physical examination			
Weight, median (IQR), kg	86 (71-100)	90 (76-105)	90 (75-103)
Systolic blood pressure, median (IQR), mm Hg	112 (100-125)	112 (98-125)	112 (98-125)
Heart rate, median (IQR), beats/min	70 (64-77)	73 (64-80)	71 (64-79)
Elevated jugular venous pressure	13 (12)	13 (11)	26 (12)
Peripheral edema	14 (13)	9 (8)	23 (10)
Medical history			
Time since diagnosis of heart failure, median (IQR), y	5.3 (1.4-10.3)	6.2 (2.0-9.8)	5.7 (1.9-10.0)
Prior hospitalization for heart failure within past year	46 (41)	51 (45)	97 (43)
Ischemic heart disease	86 (77)	89 (78)	175 (78)
Hypertension	80 (72)	82 (73)	162 (72)
Atrial fibrillation	43 (39)	43 (38)	86 (39)
Diabetes mellitus	38 (34)	50 (44)	88 (39)
Stage ≥3 chronic kidney disease[e]	21 (19)	31 (27)	52 (23)
Heart failure medications at enrollment			
β-Blocker	106 (95)	110 (96)	216 (96)
ACE inhibitor or ARB	98 (88)	91 (80)	189 (84)
Loop diuretic	96 (86)	89 (79)	185 (83)
Antiplatelet agent	74 (67)	79 (69)	153 (68)
Aldosterone antagonist	68 (61)	68 (60)	136 (60)
Anticoagulant agent	55 (50)	49 (43)	104 (46)
Digoxin	23 (21)	27 (24)	50 (22)
Long-acting nitrates	21 (19)	25 (22)	46 (20)
Hydralazine	15 (14)	18 (16)	33 (15)
Laboratory measurements, median (IQR)			
Creatinine, mg/dL	1.3 (1.0-1.6)	1.2 (0.9-1.5)	1.2 (1.0-1.5)
Cystatin C, mg/L	1.1 (0.9-1.3)	1.1 (0.8-1.3)	1.1 (0.8-1.3)
NT-proBNP, pg/mL[f]	1072 (413-2286)	1170 (527-2530)	1111 (453-2412)
Hemoglobin, g/dL	12.6 (11.7-13.3)	12.7 (11.8-13.4)	12.6 (11.8-13.3)
Iron, μg/dL[f]	71 (59-89)	72 (53-94)	62 (51-78)
Total iron-binding capacity, μg/dL[f]	383 (350-434)	370 (336-415)	349 (305-392)
Ferritin, ng/mL[f]	75 (43-108)	70 (42-111)	69 (40-98)
Transferrin saturation, %[f]	19 (16-24)	20 (14-26)	18 (15-22)
Soluble transferrin receptor, mg/L[f]	3.9 (3.2-4.8)	3.8 (2.9-4.8)	3.8 (3.1-4.8)
Hepcidin, ng/mL[f]	6.7 (3.4-11.3)	7.4 (3.6-11.6)	7.0 (3.5-11.4)

(continued)

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Table 1. Baseline Characteristics of Participants in the IRONOUT HF Study[a] (continued)

	Oral Iron (n = 111)	Placebo (n = 114)	All (N = 225)
CPET Measurements, Median (IQR)			
Peak oxygen uptake, $\dot{V}O_2$, mL/min	1196 (887-1448)	1167 (887-1449)	1172 (887-1449)
Peak oxygen uptake, $\dot{V}O_2$, mL/kg/min	13.3 (11.4-15.8)	12.9 (10.5-15.6)	13.2 (11.1-15.7)
Peak respiratory exchange ratio	1.1 (1.1-1.2)	1.1 (1.1-1.2)	1.1 (1.1-1.2)
Ventilatory efficiency, V_E/VCO_2 slope	35 (29-40)	33 (30-39)	34 (30-40)
Mean response time, O_2 uptake kinetics, s	50 (43-58)	47 (40-58)	48 (43-58)
Ventilatory threshold, mL/min	675 (509-841)	703 (580-853)	695 (540-852)

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; CPET, cardiopulmonary exercise test; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-B-type natriuretic peptide; VE/VCO2, minute ventilation/carbon dioxide elimination; $\dot{V}O_2$, oxygen uptake.

SI conversion factors: To calculate creatinine to μmol/L, multiply by 88.4; ferritin to pmol/L, multiply by 2.247; iron and iron-binding capacity to μmol/L, multiply by 0.179; hepcidin to nM, multiply by 0.358.

[a] Data are reported as No. (%) unless otherwise indicated.

[b] Race and ethnicity were self-reported.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Higher scores indicate better function (range, 1-100).

[e] Determined by enrollment site.

[f] Determined by a central core laboratory. Normal reference ranges: iron, 60-170 μg/dL; total iron binding capacity, 240-450 μg/dL; ferritin, 100-300 ng/mL; transferrin saturation, 20%-50%; soluble transferrin receptor, 0.9-2.3 mg/L; and hepcidin, <6 ng/mL when iron deficient.

level at the time of enrollment was 1111 (IQR, 453-2412) pg/mL and the median left ventricular ejection fraction was 25% (IQR, 20%-34%). Exercise capacity was reduced as evidenced by median peak $\dot{V}O_2$ of 13.2 (IQR, 11.1-15.7) mL/kg/min. Venous congestion was uncommon as only 12% of participants had jugular venous pressure elevation on examination, and 10% of participants had at least mild peripheral edema. In the setting of low ferritin levels (median, 69 ng/mL [IQR, 40-98]) and low Tsat levels (median, 18% [IQR, 15%-22%]), median hemoglobin levels were reduced at 12.6 (IQR, 11.8-13.3) g/dL. Levels of soluble transferrin receptors, which increase during states of iron deficiency and high cellular avidity for iron, were elevated with a median value of 3.8 (IQR, 3.1-4.8) mg/L. Plasma levels of the iron regulatory peptide hepcidin were also elevated with a median value of 7.0 (IQR, 3.5-11.4) ng/mL. Use of antiplatelet drugs (68%) and anticoagulants (46%) was common. There was no important differences in any of the baseline clinical, laboratory, or CPET characteristics between participants in the 2 treatment groups.

At least 1 dose of study medication was received by all participants randomized to receive oral iron and 113 of the 114 participants randomized to receive placebo (Figure 1). Frequency of permanent study drug discontinuation prior to study termination were similar in the oral iron group (14%; 15 participants) and the placebo group (15%; 17 participants) (Figure 1), and the hazard ratio for time to permanent study drug discontinuation (0.90 favoring oral iron [95% CI, 0.45 to 1.79]; $P = .76$) did not significantly differ between groups.

Primary End Point

The median baseline peak $\dot{V}O_2$ was 1196 mL/min (IQR, 887 to 1448 mL/min) in the oral iron group and 1167 mL/min (IQR, 887 to 1449 mL/min) in the placebo group (Table 1). The primary end point, change in peak $\dot{V}O_2$, did not differ between groups (oral iron, +23 mL/min [95% CI, −84 to 142 mL/min] vs placebo, −2 mL/min [−110 to 104 mL/min]), with a between-group difference of 21 mL/min (95% CI, [−34 to 76 mL/min]; $P = .46$; **Table 2**). The mean treatment difference in peak $\dot{V}O_2$ between oral iron and placebo was 0.3 mL/kg/min (95% CI, −0.27 to 0.87 mL/kg/min; $P = .30$) when peak $\dot{V}O_2$ was normalized to body weight. Between-group differences in change in peak $\dot{V}O_2$ remained nonsignificant after adjustment for site effects using mixed-effects modeling (oral iron, + 23 mL/min [95% CI, −28 to 75]; $P = .37$) and with sensitivity analyses using complete cases (oral iron, +23 mL/min [95% CI, −33 to 80]; $P = .42$) and worst-rank analyses (oral iron, 108 vs placebo, 95, with higher values indicating greater positive change in peak $\dot{V}O_2$ [$P = .46$]). In prespecified subgroup analyses, the change in peak $\dot{V}O_2$ was not significantly different between treatment groups in men vs women, participants with or without hemoglobin level of less than 12 g/dL in women and of less than 13.5 g/dL in men, participants with or without baseline venous congestion, or participants with and without peak respiratory exchange ratios greater than 1.1 (a threshold indicative of maximum volitional effort)[24] on baseline and 16-week CPETs (eFigure 1 in Supplement 2).

Secondary End Points and Safety

At 16 weeks, there were no significant differences between treatment groups in change in 6-minute walk distance (difference, −13 m [95% CI, −32 to 6 m]; $P = .19$), NT-proBNP levels (159 pg/mL [−280 to 599 pg/mL]; $P = .48$), KCCQ score (1.0 [−2.4 to 4.4]; $P = .57$), O_2 uptake kinetics (3 s [−2 to 8 s]; $P = .19$), or ventilatory efficiency, as indicated by the slope of minute ventilation relative to carbon dioxide elimination (V_E/VCO_2 slope, 0.8 [−0.3 to 2.6]; $P = .35$). The rates of serious adverse events observed with oral iron and placebo were similar, as reported in Table 2 and in eFigure 2 and eTable 2 in Supplement 2. Time to first adverse event did not differ between groups (hazard ratio, 0.85 favoring oral iron [95% CI, 0.56-1.31]; $P=.47$).

Exploratory End Points

At 16 weeks, when compared with placebo, oral iron was associated with an increment in $\dot{V}O_2$ at the ventilatory threshold that was not statistically significant (+36.4 mL/min [−3.4 to 76.2 mL/min]; $P = .07$). There were no differences in change

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Table 2. Primary, Secondary, and Safety End Points

	Median (IQR)					
	Week-16 Values[a]		Change From Baseline to Week 16		Difference in Change From Baseline (95% CI)	*P* Value
	Oral Iron	Placebo	Oral Iron	Placebo		
Primary End Point						
Peak $\dot{V}O_2$ at 16 wk, mL/min	1218 (892 to 1500)	1187 (902 to 1425)	23 (−84 to 142)	−2 (−110 to 104)	21 (−34 to 76)	.46
Ppeak $\dot{V}O_2$ at 16 wk, mL/kg/min	13.5 (11.7 to 16.3)	13.0 (10.2 to 15.9)	0.20 (−1.1 to 1.6)	0.01 (−1.1 to 0.9)	0.30 (−0.27 to 0.87)	.30
Secondary End Points						
6-Min walk distance at 8 wk, m	380 (322 to 467)	376 (286 to 448)	15 (−17 to 55)	21 (−24 to 56)	−1 (−24 to 23)	.95
6-Min walk distance at 16 wk, m	366 (315 to 456)	397 (299 to 472)	19 (−19 to 51)	32 (−12 to 66)	−13 (−32 to 6)	.19
Mean response time (O_2 uptake kinetics), s	52 (46 to 61)	47 (40 to 58)	2.5 (−7 to 9)	1 (−10 to 6)	3 (−2 to 8)	.19
Ventilatory efficiency (V_E/V_{CO2} slope)	34.8 (29.9 to 41.1)	33.5 (29.4 to 38.9)	−0.3 (−3.0 to 2.1)	−0.3 (−4.6 to 2.8)	0.8 (−0.3 to 2.6)	.35
NT-proBNP, pg/mL	889 (376 to 2373)	1085 (447 to 2582)	4 (−342 to 288)	−37 (−412 to 363)	159 (−280 to 599)	.48
KCCQ clinical summary score at 8 wk[b]	81.3 (70.8 to 91.7)	75.0 (58.9 to 87.5)	5.2 (−2.1 to 12.5)	1.0 (−7.3 to 8.3)	3.4 (−0.4 to 7.2)	.08
KCCQ clinical summary score at 16 wk[b]	80.7 (67.7 to 91.6)	77.1 (65.1 to 89.6)	3.1 (−4.2 to 13.5)	3.0 (−4.2 to 10.4)	1.0 (−2.4 to 4.4)	.57
Exploratory End Points						
Ventilatory threshold at 16 wk, mL/min	685 (546 to 884)	714 (558 to 873)	22 (−49 to 127)	−2 (−86 to 75)	36 (−3 to 76)	.07
Creatinine at 16 wk, mg/dL	1.31 (1.01 to 1.56)	1.21 (0.90 to 1.49)	0.03 (−0.10 to 0.13)	0.00 (−0.10 to 0.11)	−0.02 (−0.09 to 0.05)	.65
Cystatin C at 16 wk, mg/L	1.06 (0.86 to 1.38)	1.02 (0.78 to 1.31)	0.02 (−0.04 to 0.09)	0.01 (−0.08 to 0.07)	0.03 (−0.01 to 0.08)	.12
Safety End Points, No. (%)	**Oral Iron**	**Placebo**			**OR (95% CI)**	
Adverse events	39 (35)	45 (39)			0.83 (0.48 to 1.43)	.50
Serious adverse events	11 (10)	10 (9)			1.14 (0.47 to 2.81)	.77
Permanent study drug discontinuation	15 (14)	17 (15)			0.90 (0.45 to 1.79)	.76
Death or cardiovascular rehospitalization	14 (13)	12 (11)			1.19 (0.55 to 2.59)	.64

Abbreviations: IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OR, odds ratio; $\dot{V}O_2$, volume of oxygen uptake.

[a] Values are for measurements made at week 16 unless otherwise specified for 8 week measurements.

[b] Higher scores indicate improved clinical status (range, 1-100).

Table 3. Levels of Iron Metabolism Markers According to Treatment Group

	Median (95% CI)					
	Week-16 Values		Change From Baseline to Week 16		Difference in Change From Baseline (95% CI)	*P* Value
Iron Indexes	Oral Iron	Placebo	Oral Iron	Placebo		
Iron, µg/dL	80 (59 to 99)	72 (58 to 90)	6 (−12 to 29)	1 (−23 to 18)	11.0 (2.8 to 19.1)	.009
TIBC, µg/dL	371 (336 to 405)	374 (339 to 428)	−12 (−43 to 5)	−0.5 (−22 to 17)	−13.4 (−22.2 to −4.6)	.003
Tsat, %	22 (16 to 28)	20 (15 to 25)	2 (−3 to 7)	0 (−5 to 5)	3.3 (1.1 to 5.4)	.003
Ferritin, ng/ml	95 (58 to 134)	75 (42 to 123)	18 (−8 to 38)	1 (−15 to 17)	11.3 (−0.3 to 22.9)	.06
Hepcidin, ng/ml	8.9 (5.0 to 14.3)	7.8 (4.2 to 12.7)	1.7 (−1.0 to 5.6)	−0.3 (−3.2 to 3.1)	1.5 (−0.6 to 3.7)	.17
sTfR, mg/L	3.7 (2.9 to 4.4)	3.9 (3.1 to 4.8)	−0.3 (−0.8 to 0.1)	0.0 (−0.5 to 0.4)	−0.3 (−0.6 to −0.1)	.01

Abbreviations: sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; Tsat, transferrin saturation.

in renal function between groups: creatinine (−0.02 mg/dL [−0.09 to 0.05 mg/dL]; *P* = .65) and cystatin C (0.03 mg/L [−0.01 to 0.08 mg/L]; *P* = .12).

Iron Bioavailability

Measures of exercise capacity (peak $\dot{V}O_2$ [*r* = 0.17; *P* = .01]; 6-minute walk distance [*r* = 0.28; *P* < .001]), NT-proBNP (*r* = −0.16; *P* = .02), and KCCQ Clinical Summary score (*r* = 0.28; *P* < .001) were all correlated with baseline Tsat levels (18% [IQR, 15% to 22%]).

Compared with placebo, oral iron increased Tsat levels (+3.3% [95% CI, 1.1% to 5.4%]; *P* = .003) and ferritin levels (+11.3 ng/mL [−0.3 to 22.9 ng/mL]; *P* = .06) (**Table 3** and eTable 2 in Supplement 2). Levels of soluble transferrin receptors decreased in participants treated with oral iron when compared with placebo (−0.3 mg/L [95% CI, −0.6 to −0.1 mg/L]; *P* = .01, Table 3). Participants in the highest quartile of response in Tsat, in response to oral iron, demonstrated improvement in KCCQ clinical summary scores (5.2 [95% CI, 0.1 to 10.4]; *P* = .047), and an increase in $\dot{V}O_2$ at the ventilatory threshold (58 mL/min [95% CI, −7 to 123 mL/min]; *P* = .08) that was not statistically significant. Changes in peak $\dot{V}O_2$ (*r* = 0.16; *P* = .03) and in NT-proBNP (*r* = −0.18; *P* = .02) correlated directly with change in Tsat.

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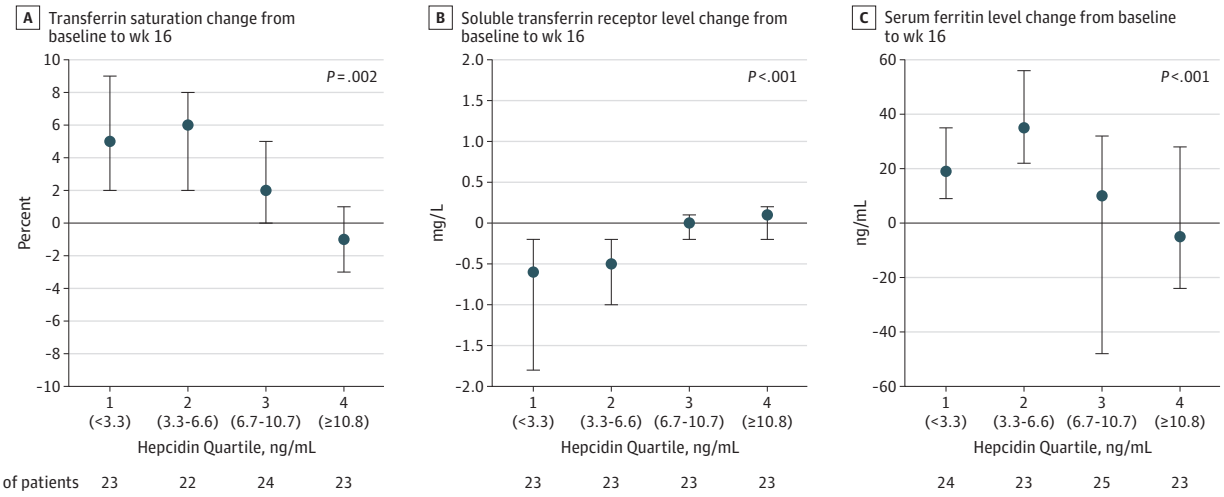
Figure 2. Relationships Between Quartiles of Baseline Plasma Hepcidin Levels and Response in Participants Treated With Iron Polysaccharide



P values indicate differences across all 4 quartiles using the Wilcoxon rank-sum test.

Responders to Oral Iron Therapy

Median hepcidin levels increased from 6.7 to 8.9 ng/mL (+1.7 ng/mL [95% CI, −1.0 to 5.6 ng/mL]; *P* = .007) in the oral iron group, consistent with the anticipated response to increased iron exposure, and remained unchanged in the placebo group (7.4 to 7.8 ng/mL; −0.3 ng/mL [95% CI, −3.2 to 3.1 ng/mL]; *P* = .91). The between-group comparison of change in hepcidin levels was not statistically significant (+1.5 ng/mL [95% CI, −0.6 to 3.7 ng/mL]; *P* = .17 [Table 3]).

In response to 16 weeks of oral iron across quartiles of increasing baseline hepcidin levels, there were reduced increments in Tsat and ferritin and a blunted fall in soluble transferrin receptor levels (**Figure 2**). Changes in Tsat (r = −0.29; *P* = .004), ferritin (r = −0.30; *P* = .004), and soluble transferrin receptor levels (r = 0.48; *P* < .001) at 16 weeks were correlated with baseline hepcidin levels.

Discussion

High-dose oral iron did not improve exercise capacity in patients with iron deficiency and HFrEF. The lack of effect of oral iron on exercise capacity, including peak $\dot{V}O_2$ and 6-minute walk distance, and quality of life scores (KCCQ) stands in contrast to results from trials of intravenous iron repletion in similar patient populations.[13,14,25] Also in contrast to previous studies with intravenous iron repletion, in this study, oral iron therapy produced minimal improvement in iron stores, implicating the route of administration rather than the strategy of iron repletion in the lack of clinical benefit. The significant relationship between higher baseline hepcidin levels and lack of iron repletion provides mechanistic insight into this study's observed findings.

With the exception of one study that included 7 individuals randomized to receive oral iron,[26] this is the first multicenter randomized clinical trial exploring the utility of oral iron supplementation in HFrEF patients with iron deficiency. In light of the failure of oral iron to improve measures of functional capacity in this study, a comparison of the patient populations and relative changes in iron stores to trials of intravenous iron repletion is warranted.

The patient population in this study was similar to that investigated in trials of intravenous iron repletion (FAIR-HF [Ferinject Assessment in Patients With Iron Deficiency and Chronic Heart Failure] and CONFIRM-HF [Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency in Combination with Chronic Heart Failure])[13,14] in patient age and body mass index, as well as underlying heart failure etiology and baseline pharmacotherapy. In addition, baseline laboratory indices of iron stores were similar across the 3 studies. However, iron indices following oral repletion, as compared with intravenous iron repletion, differed markedly (eTable 3 in Supplement 2). Despite administering approximately 15-fold more iron orally in this study than that administered intravenously in FAIR-HF (ie, 33.6 g vs ≈ 2 g), there was only a modest 3%-median increment in Tsat and 11-ng/mL increment in ferritin in participants randomized to receive oral iron vs placebo in this study, compared with a 70%-median increment in Tsat and a 550%-increment in ferritin with intravenous iron administration in the FAIR-HF Trial.[13]

There are several potential explanations for failure of oral iron to improve iron stores and exercise capacity in this trial. Hepcidin plays a critical role in inhibiting iron absorption.[18-21] In this study, participants with higher baseline hepcidin levels demonstrated reduced Tsat and ferritin augmentation and an attenuated decline in soluble transferrin receptor levels in response to 16 weeks of oral iron supplementation (Figure 2). Taken together, these findings indicate that higher hepcidin levels may limit responsiveness to oral iron. Expected hepcidin levels in individuals with iron deficiency and anemia are lower than the values measured in this study.[27,28]

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Other potential mediators of refractoriness to oral iron in heart failure seem less likely to have affected our findings. Use of anticoagulants and antiplatelet agents was prevalent, but the rate of expected loss of iron (1-1.5 mg/d) is markedly less than the repletion dose (300 mg/d) administered. Therefore, in the absence of overt gastrointenstinal bleeding, which did not occur in any of the participants treated with oral iron during the trial, blood loss would not be expected to account for the observed minimal increases in iron stores with oral iron treatment.

The choice of iron polysaccharide formulation for this study was based on its offering the highest dose of elemental iron among available oral supplements, coupled with its tolerance profile to aid in adherence and minimize risk of unblinding participants. Polysaccharide iron preparations have been shown to provide comparable iron repletion to iron salts.[29-31] Recommended daily oral iron intake is 8 to 18 mg. Hence, even after accounting for limited gastrointestinal iron absorption, the 20-fold increase in oral iron exposure, compared with the recommended daily intake, served to adequately test the hypothesis that oral iron supplementation would improve iron stores and functional capacity in HFrEF. The low incidence of oral iron discontinuation, which was 14% among participants receiving iron and 15% in the placebo group, argues against the observed findings being related to lack of adherence with oral iron.

The selection of change in peak $\dot{V}O_2$ for the primary end point, as previously described,[15] was based on the fact that peak $\dot{V}O_2$ is the gold standard indicator of functional capacity in heart failure and has been shown to improve with iron repletion in non–heart failure populations. The lack of treatment effect on quality of life, NT-proBNP, and other physiological end points is consistent with the observed lack of treatment effect on maximal exercise capacity. The exploratory end point, change in $\dot{V}O_2$ at the ventilatory threshold, showed a 5% increment in the iron group and no change in placebo, although the study may have been underpowered for this modest between-group difference to reach significance (P = .08). Submaximum exercise capacity, indicative of endurance and independent of volitional effort, may be more sensitive to subtle changes in iron bioavailability as opposed to peak $\dot{V}O_2$.[8]

Recognition of the high prevalence of iron deficiency (≈ 50%) in patients with HFrEF and the consistent clinical benefit demonstrated in studies with intravenous iron repletion is motivating clinicians to prescribe iron supplementation. This trial complements recent studies about intravenous iron treatment in informing the appropriate approach to iron repletion in HFrEF. This study's findings of minimal changes in iron stores and lack of effect on peak exercise capacity suggests that prescription of oral iron in patients with HFrEF offers no benefit. However, the correlates observed between baseline iron indices and exercise capacity, as well as changes in Tsat being related to improvement in peak $\dot{V}O_2$ are consistent with results of recent trials suggesting beneficial effects of intravenous iron on functional capacity in HFrEF.

This study has some important limitations. This study was not powered to detect differences in clinical events or safety end points. There was also no direct comparison between intravenous vs oral iron repletion. Given the relatively short duration of the trial, it is possible that longer duration or higher dose of exposure may have led to more significant improvement in iron stores and increased exercise capacity, particularly among those participants with appropriately low hepcidin levels. In addition, this study was confined to patients with HFrEF and findings may differ in heart failure with preserved ejection fraction.

Conclusions

Among participants with iron deficiency and HFrEF, high-dose oral iron minimally augmented iron stores and did not improve exercise capacity over 16 weeks. These findings do not support the use of oral iron supplementation to treat iron deficiency in patients with HFrEF.

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