HEART FAILURE NETWORK

Oral Iron Repletion effects on Oxygen UpTake in Heart Failure (IRONOUT)

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on behalf of
The NHLBI Clinical Heart Failure Network

U.S. Department of Health and Human Services
National Institutes of Health

National Heart Lung and Blood Institute
People Science Health

Background: Iron Deficiency in Heart Failure

- Iron deficiency is present in ~50% of patients with chronic heart failure with reduced ejection fraction (HFrEF).

- Iron deficiency in an independent predictor of mortality in patients with HFrEF.

Klip I et al, AHJ 2013

Background : Iron Deficiency Impacts Functional Capacity in Heart Failure

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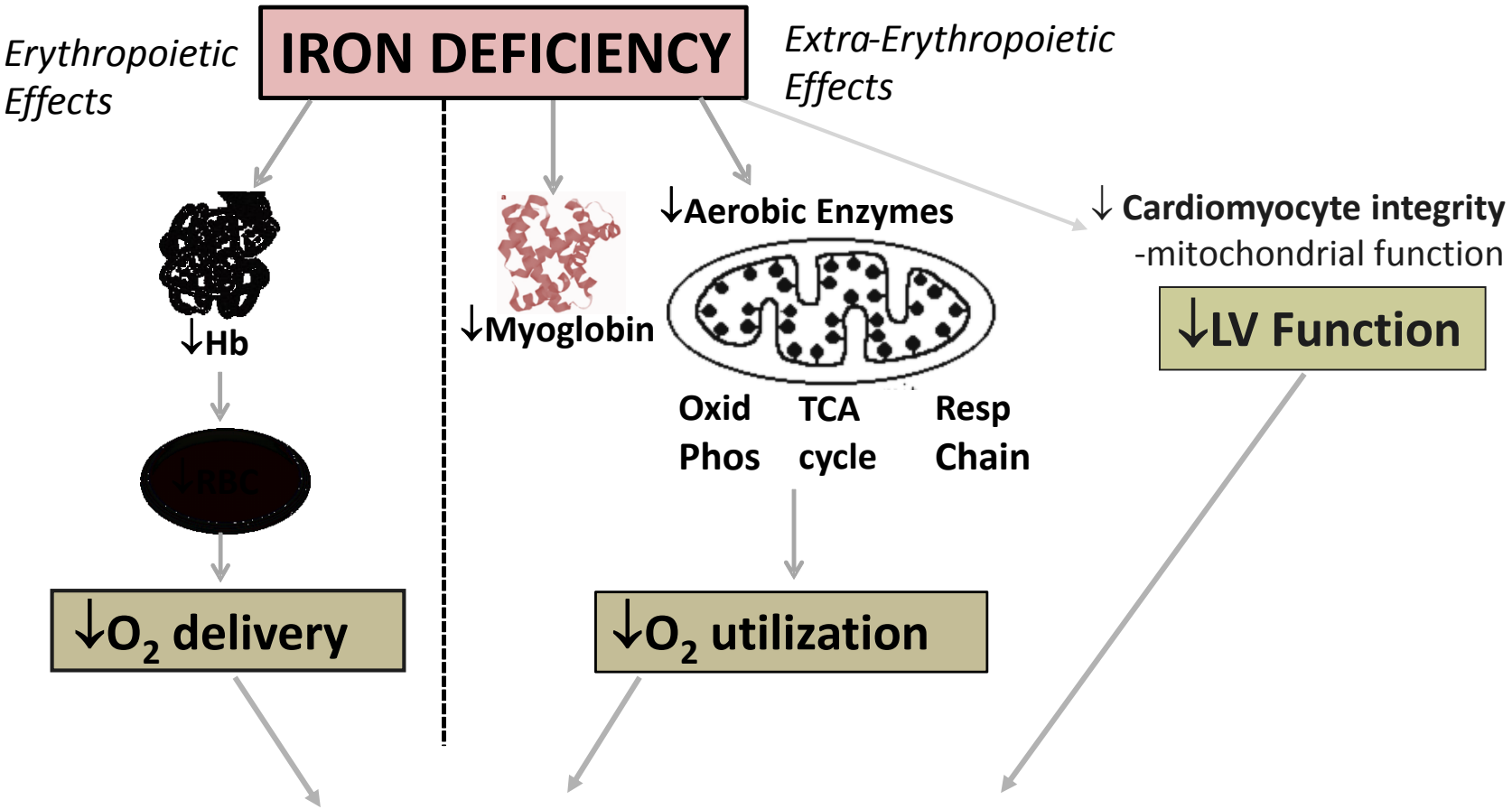

$$VO_2 = (CaO_2 - CvO_2) \times \text{Cardiac Output}$$

Gold Standard Objective Measurement of Functional Capacity

Anker S et al. EJHF 2009
Dong Clin Sci, 2005, Tobolli JACC 2008
Petering LH, Ann Nutr Metab 1990
Melanovsky et al, Circulation HF 2016

Background

Two multicenter intravenous iron repletion trials in HFrEF:

- FAIR-HF and CONFIRM-HF[1,2]

- ↑6 min walk distance, ↑quality of life, ↓ HF hospitalizations

Promising results from IV iron studies have served as an impetus for clinicians to prescribe iron supplementation. However:

-Regular administration of IV iron poses logistical challenges and is expensive

-Oral iron is safe and readily available, but its efficacy in HF is unknown

-Patient characteristics that influence responsiveness to oral iron in HF remain undefined

1. FAIR-HF Anker S et al. NEJM 2009, 2. CONFIRM-HF Ponikowski P EHJ 2014

Background: Iron Homeostasis in HF

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Daily Recommended Iron intake:
8-18 mg = 0.25% of body stores

Heart Failure w/Iron Deficiency
Ferritin <100 ng/ml
Tsat < 20% w/Ferritin 100-300ng/ml
Hepcidin expected < 3 ng/ml

? Oral Iron

Iron Replete Status
Ferritin >100 ng/ml
Tsat >20%
↑ Hb

Gut edema
↓ Nutrient Intake

Duodenum
Iron Absorption
5-35%

↓Iron Absorption

Hepcidin

? ↑Hepcidin

Ferroportin 1

Reticulo Endothelial System

↑ Iron transport

↑ senescent RBC degradation

IFN-γ

TNF α

↓Iron Bioavailability

Total Body Iron: ~4,000 mg

Hemoglobin (2,500mg)

Ferritin Complexes (1000-1500mg)

Circulating Iron-bound to transferrin (3-5mg)

↑Iron loss (bleeding)

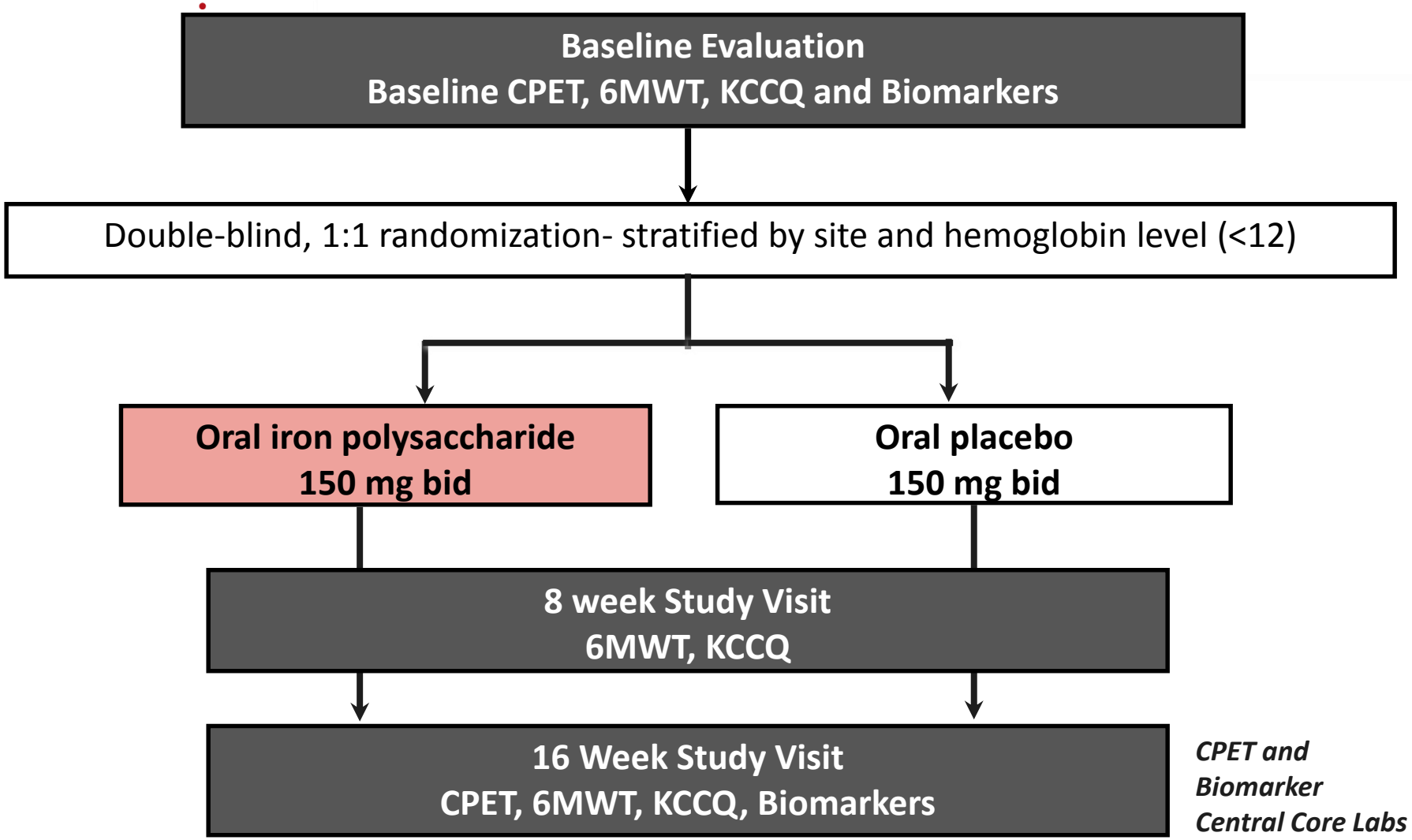
Hypothesis

Oral iron polysaccharide is superior to oral placebo in improving exercise capacity (peak VO_2) in patients with HFrEF and iron deficiency at 16 weeks.

Study Population

- 225 patients with NYHA Class II-IV HF symptoms and LVEF≤0.40
- Serum ferritin between 15-100 ng/ml or serum ferritin between 100-299 ng/ml with transferrin saturation <20%
- Hemoglobin 9.0-13.5 g/dL in females, 9.0-15 g/dL in males
- Stable evidence-based medical therapy for HF
- Able to perform cycle/treadmill exercise testing with achievement of a respiratory exchange ratio of at least 1.0

Study Design



CPET: cardiopulmonary exercise testing

IRONOUT Endpoints

- **Primary Endpoint:** Δ peak VO_2 from baseline to week 16

- **Secondary Endpoints:**
  - Δ 6MW distance, O_2 kinetics, ventilatory efficiency
  - Δ NT-proBNP and Δ KCCQ quality of life score

- **Exploratory Endpoints**
  - Δ iron studies, Δ renal function
  - Δ VO_2 at the ventilatory threshold
  - Time to death or worsening HF

Baseline Features (n=225)

Characteristic	Oral Iron, N=111	Placebo, N=114
Age, median (IQR), y	63 (54-71)	63 (55-70)
Female sex	40%	32%
Racial Minority	29%	25%
NYHA II/III	73%/27%	60%/40%
LVEF (%)	25 (20-34)	25 (20-33)
Peak VO_2, median (IQR), ml/kg/min	13.3 (11.4-15.8)	12.9 (10.5-15.6)
HF Duration, median (IQR), y	5.3 (1.4-10.3)	6.2 (2.0-9.8)
Ischemic etiology of HF	77%	78%
History of Hypertension	72%	73%
History of Atrial fibrillation	39%	38%
History of Diabetes mellitus	34%	44%

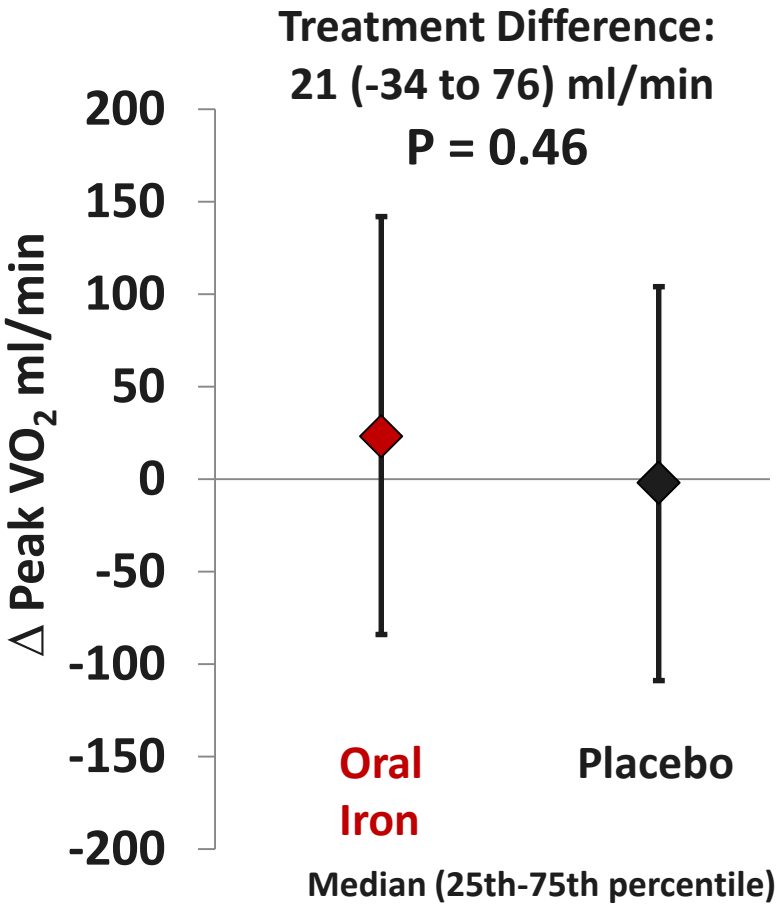
There were no significant baseline differences between groups

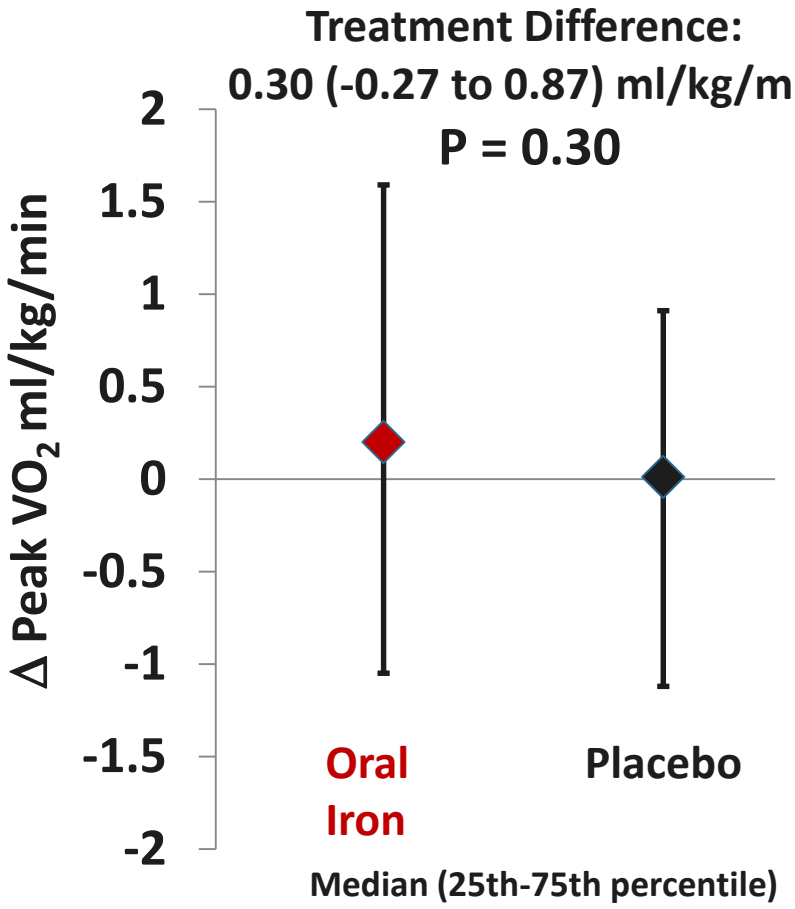
Baseline Features (n=225)

Characteristic	Oral Iron, N=111	Placebo, N=114
Concomitant medications		
β-Blocker	95%	96%
ACE inhibitor or ARB	88%	80%
Aldosterone antagonist	61%	60%
Laboratory values		
NT-proBNP, pg/ml	1072 (413-2286)	1170 (527-2530)
Estimated GFR, ml/min/1.73m^2	56 (43-71)	61 (46-73)
Hemoglobin, g/dL	12.6 (11.7-13.3)	12.7 (11.8-13.4)
Ferritin, ng/mL	69 (42-98)	69 (37-98)
Transferrin Saturation, %	18 (14-24)	17 (15-21)
Sol. transferrin receptor, mg/L	3.8 (3.3-4.8)	3.8 (2.9-4.8)
Hepcidin, ng/ml	6.6 (3.3-10.8)	6.5 (3.3-11.1)

There were no significant baseline differences between groups

Results: Primary Endpoint





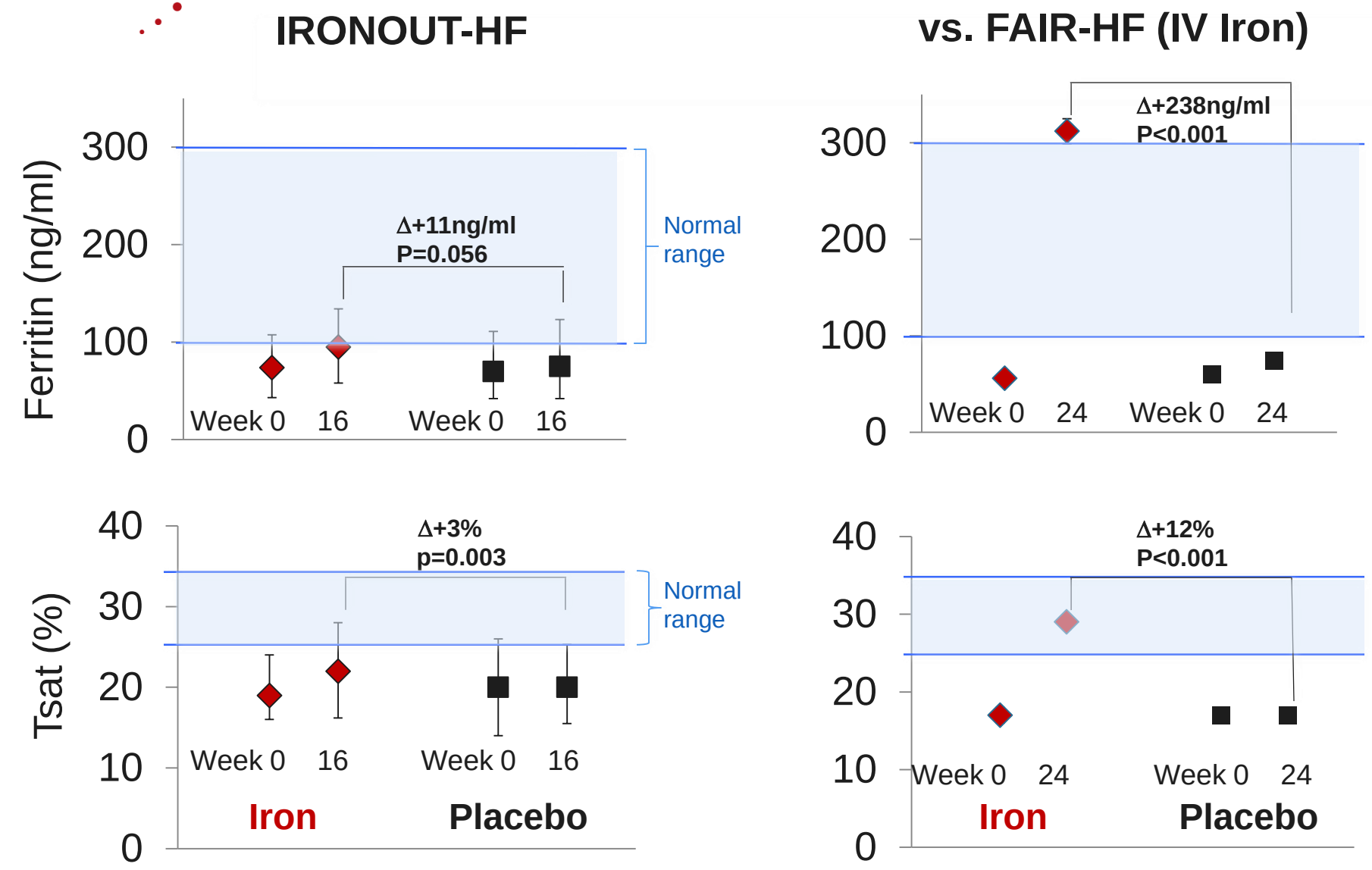
Results: Secondary and Exploratory Endpoints

Characteristic	Oral Iron N=111	Placebo N=114	p-Value
Secondary end points			
Δ 6 MW distance at 16 weeks, meters	19	32	0.19
Δ Mean response time, seconds	2.5	1	0.19
Δ Ventilatory efficiency (VE/VCO_2 slope)	-0.3	-0.3	0.35
Δ NT-BNP level, pg/ml	4	-37	0.48
Δ KCCQ score at 16 weeks	3.1	3.0	0.57
Exploratory Endpoints			
Δ Ventilatory threshold (ml/min)	22	-2	0.07
Δ Creatinine, mg/dL	0.03	0.00	0.65
Δ Cystatin C, mg/L	0.02	0.01	0.12

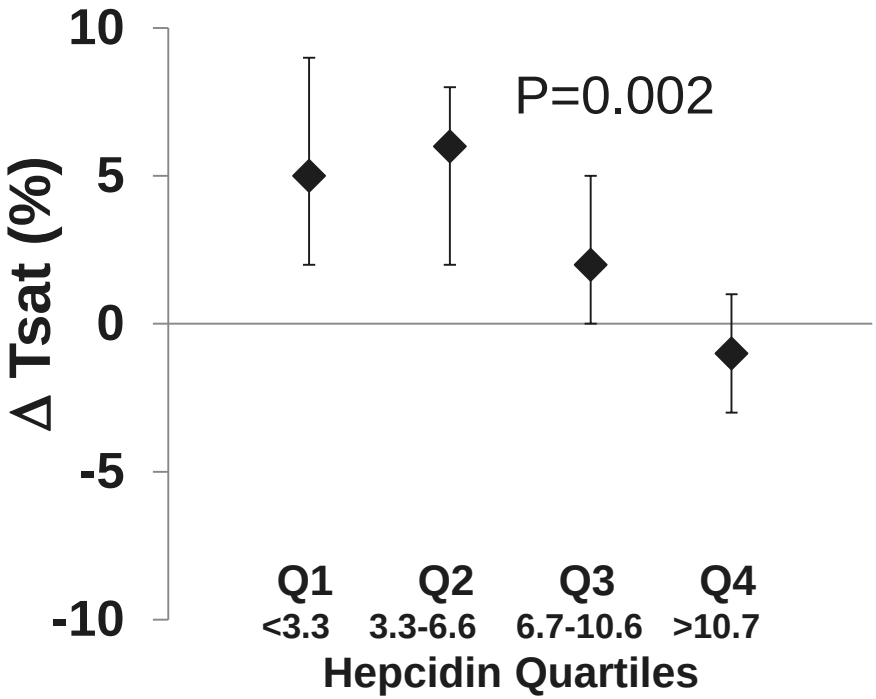
Results: Safety Endpoints

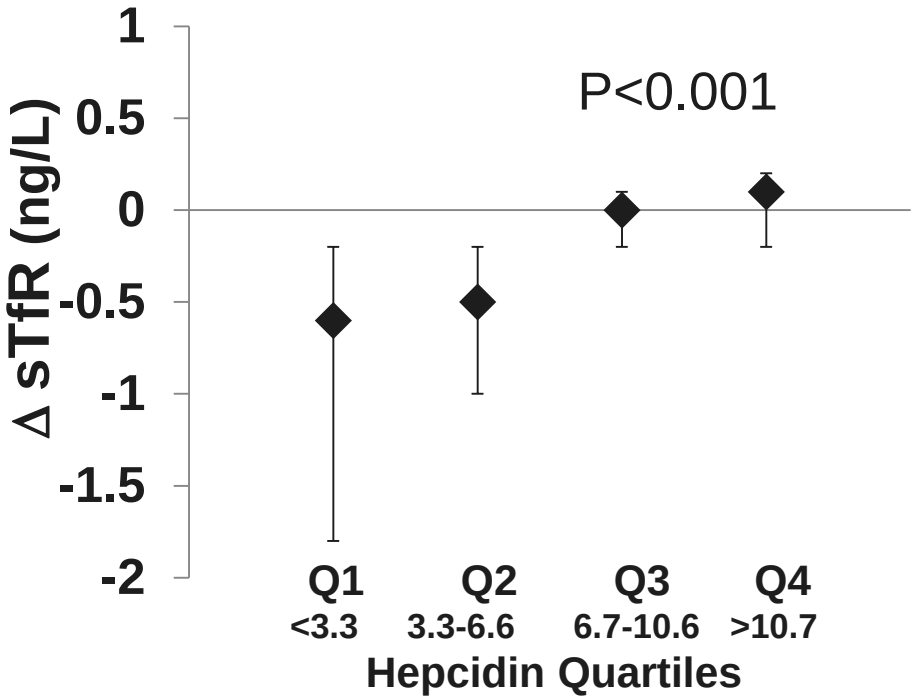
Characteristic	Oral Iron N=111	Placebo N=114	p-Value
Safety end points, No. (%)			
Adverse events	39 (35%)	45 (39%)	0.50
Serious adverse events	11 (10%)	10 (9%)	0.77
Permanent study drug discontinuation	15 (14%)	17 (15%)	0.76
Death or cardiovascular re-hospitalization	14 (13%)	12 (11%)	0.63

Results: Δ Iron Studies



Results: Hepcidin Levels Predict Responsiveness to Oral Iron





Higher baseline hepcidin levels were related to:

- ↓ Δ iron bioavailability: Δ Tsat r=-0.29, p=0.003
- ↓ Δ cellular iron levels: Δ sTr r=0.49, p<0.001
- ↓ Δ iron stores: Δ Ferritin r=-0.30, p=0.003

Results: Potential Alternative Explanations for Lack of Iron Repletion with Oral Iron

Rates of venous congestion were low:

- **12% of patients had ↑ JVP**
- **10% of patients had >mild edema**

There was no major bleeding episodes in patients receiving oral iron

Results: Relationship between iron biomarkers and endpoints

Higher baseline Tsat levels were related to:

↑ Peak VO_2:	r=0.17, p=0.01
↑ 6 min walk distance:	r=0.28, p<0.001
↓ NT-proBNP:	r=0.16, p=0.015
↑ KCCQ score:	r=0.28, p<0.001

Δ Tsat was modestly correlated with Δ peak VO_2 (r=0.17, p=0.03)

Patients in the highest quartile of ΔTsat (>7%) demonstrated improvement in KCCQ scores (p=0.046) and a trend toward higher VO_2 at the ventilatory threshold (p=0.07)

Summary and Conclusions

- High dose oral iron minimally repleted iron stores and did not improve peak VO_2 in patients with iron deficiency and HFrEF.
- Elevated hepcidin levels predicted refractoriness to oral iron repletion, whereas rates of venous congestion and bleeding were low during the study.
- These results do not support use of oral iron supplementation in patients with HFrEF.

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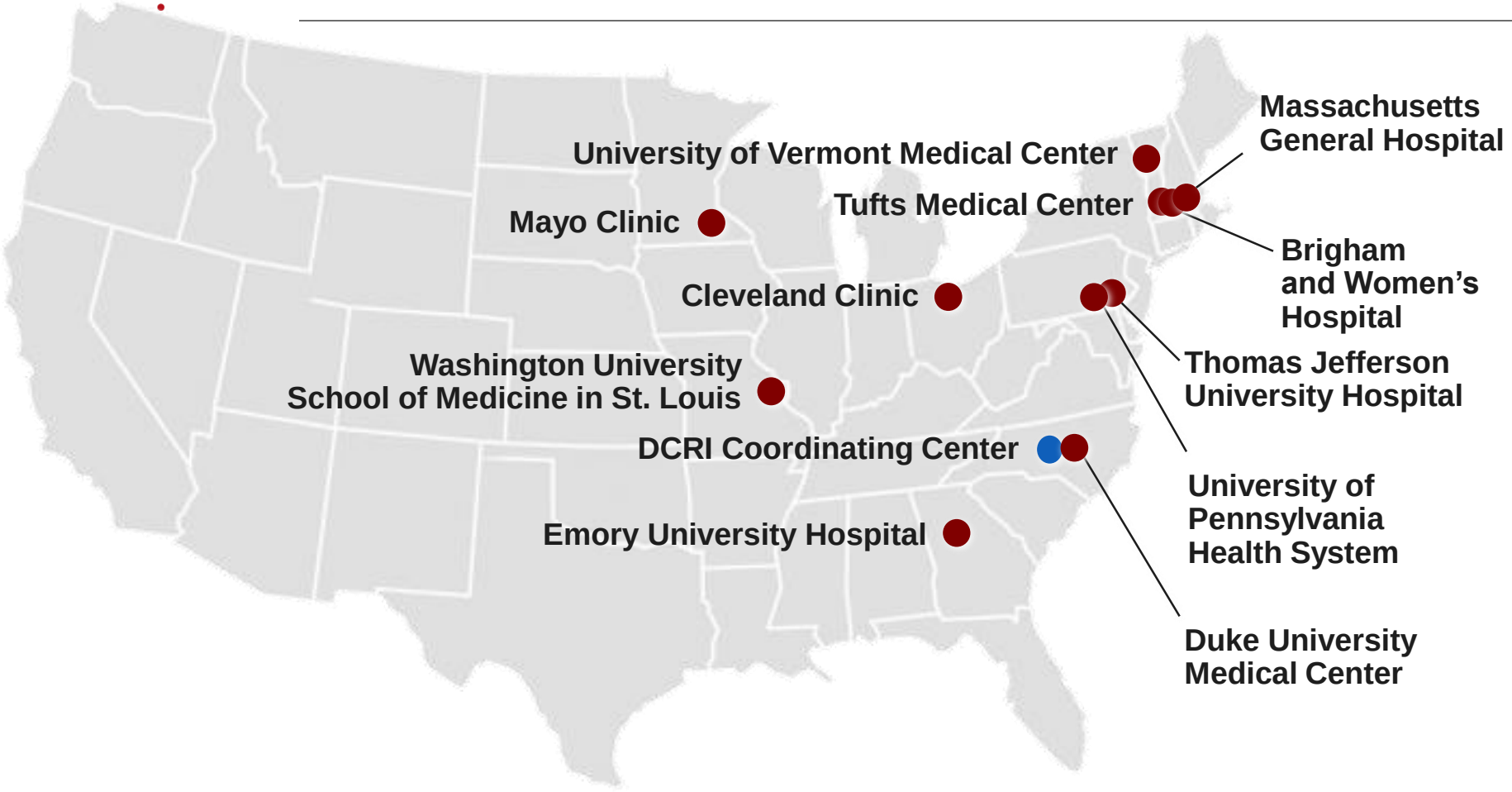
Heart Failure Clinical Research Network



- Regional Clinical Centers
- Coordinating Center

www.hfnetwork.org

NIH National Heart, Lung, and Blood Institute