

## Clinical Trials: Methods and Design

## Rationale and Design of the IRON-HF Study: A Randomized Trial to Assess the Effects of Iron Supplementation in Heart Failure Patients With Anemia

LUÍS BECK-DA-SILVA, MD, ScD,<sup>1</sup> LUÍS EDUARDO ROHDE, MD, ScD,<sup>1</sup>  
ANTÔNIO CARLOS PEREIRA-BARRETTO, MD, PhD,<sup>2</sup> DENÍLSON DE ALBUQUERQUE, MD,<sup>3</sup>  
EDIMAR BOCCHI, MD,<sup>4</sup> FÁBIO VILAS-BOAS, MD,<sup>5</sup> LÍDIA ZYTNYZKI MOURA, MD,<sup>6</sup>  
MARCELO W. MONTERA, MD,<sup>7</sup> SALVADOR RASSI, MD,<sup>8</sup> AND NADINE CLAUSELL, MD, PhD<sup>1</sup>

Porto Alegre, Brazil; São Paulo, Brazil; Rio de Janeiro, Brazil; Salvador, Brazil; Curitiba, Brazil; Goiânia, Brazil

### ABSTRACT

**Background:** Anemia is a common finding in heart failure (HF) patients and has been associated with increased morbidity and mortality. It is generally denominated as anemia of chronic disease (ACD), but the association with true ferropenic anemia is common. Many studies have investigated the effects of treating anemia in HF patients with either erythropoietin alone or combination of erythropoietin and intravenous iron. However, the effect of iron supplementation alone in HF patients with ACD, ferropenic anemia, or both is unknown.

**Methods and Results:** IRON-HF study is a multicenter, investigator initiated, randomized, double-blind, placebo controlled trial that will enroll anemic HF patients with relatively preserved renal function, low transferrin saturation, low iron levels, and low to moderately elevated ferritin levels. Interventions are iron sucrose intravenously 200 mg once per week for 5 weeks, ferrous sulfate 200 mg by mouth 3 times per day for 8 weeks, or placebo. The primary objective is to assess the impact of iron supplementation (intravenously or by mouth) compared with placebo in HF patients with anemia from deficient iron availability. The primary end point is variation of peak oxygen consumption assessed by ergospirometry over 3-month follow-up. Secondary end points include functional class, brain natriuretic peptide levels, quality of life scores, left ventricular ejection fraction, adverse events, HF hospitalization, and death.

**Conclusions:** The results of IRON-HF should help to clarify the potential clinical impact of mild to moderate anemia correction in HF patients. (*J Cardiac Fail* 2007;13:14–17)

**Key Words:** Congestive heart failure, Treatment, Ferrous sulfate, Iron sucrose.

From the <sup>1</sup>Hospital de Clínicas de Porto Alegre, Porto Alegre; <sup>2</sup>InCor Unidade Hospital Cotoxó, São Paulo; <sup>3</sup>Hospital Pedro Ernesto, UERJ, Rio de Janeiro; <sup>4</sup>InCor, São Paulo; <sup>5</sup>Hospital Santa Isabel, Salvador; <sup>6</sup>Hospital da PUC, Curitiba; <sup>7</sup>Santa Casa do Rio de Janeiro and Hospital Pró-Cardíaco, Rio de Janeiro and <sup>8</sup>Hospital das Clínicas da Universidade Federal de Goiás, Goiânia, Brazil.

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Reprint requests: Nadine Clausell, MD, PhD, Cardiology Division, Hospital de Clínicas de Porto Alegre (HCPA), Rua Ramiro Barcelos, 2350, CEP: 90035-003, Porto Alegre-RS, Brazil.

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Anemia has been demonstrated to be a common finding in patients with heart failure (HF). More importantly, anemic patients with HF have definite increased morbidity and mortality.<sup>1</sup>

The mechanisms underlying anemia in HF patients are multifactorial. The most frequent cause of HF-associated anemia is related to mild to moderate form of chronic disease anemia.<sup>2</sup> HF patients who develop this form of anemia have less exercise tolerance, accelerated progression of the disease, and increased mortality.<sup>1</sup> It appears that HF patients develop anemia from both blunted endogenous erythropoietin (EPO) production and iron-deficient erythropoiesis. Inflammatory cytokines, particularly

hepcidin, are responsible for blocking the iron utilization from the reticuloendothelial system, resulting in iron unavailability.<sup>3</sup> In addition, the association with true ferropenic anemia is not uncommon. Ferropenic anemia is by far the most common cause of anemia in Brazilian population,<sup>4</sup> and is the most common cause of anemia throughout the world.<sup>5</sup> Among anemic HF patients, regardless of renal function, the most common form of hematinic deficiencies is iron deficiency, thus it is reasonable to correct deficiencies first before other therapies are started.<sup>6</sup>

Many studies have investigated the effects of treating anemia in HF patients, with positive results in most of them. However, all such studies have used either EPO and oral iron<sup>7</sup> or a combination of EPO and intravenous iron.<sup>8,9</sup>

It is well known that patients with HF actually have increased levels of EPO<sup>10</sup> and therefore may not need EPO supplementation. Increased plasma EPO levels have been found to be associated with an impaired prognosis, independent of hemoglobin levels, in patients with HF.<sup>11</sup> Therefore, it is not clear if the benefit of the combination is provided by EPO or by intravenous (IV) iron.

The effect of iron supplementation in patients with HF who have preserved renal function and either a chronic disease anemia, or ferropenic anemia, or both is not known. It

is also unsolved which route of administration would be most clinically effective. Because oral administration of iron could not overcome the reticuloendothelial iron block,<sup>12</sup> IV iron may be more effective for treating anemic HF patients.

The aim of this study is to assess the impact of iron supplementation alone (IV or by mouth [PO]) in patients with HF and anemia with decreased availability of iron in a Brazilian multicenter, prospectively designed, randomized, double-blind, placebo-controlled clinical trial: the IRON-HF study.

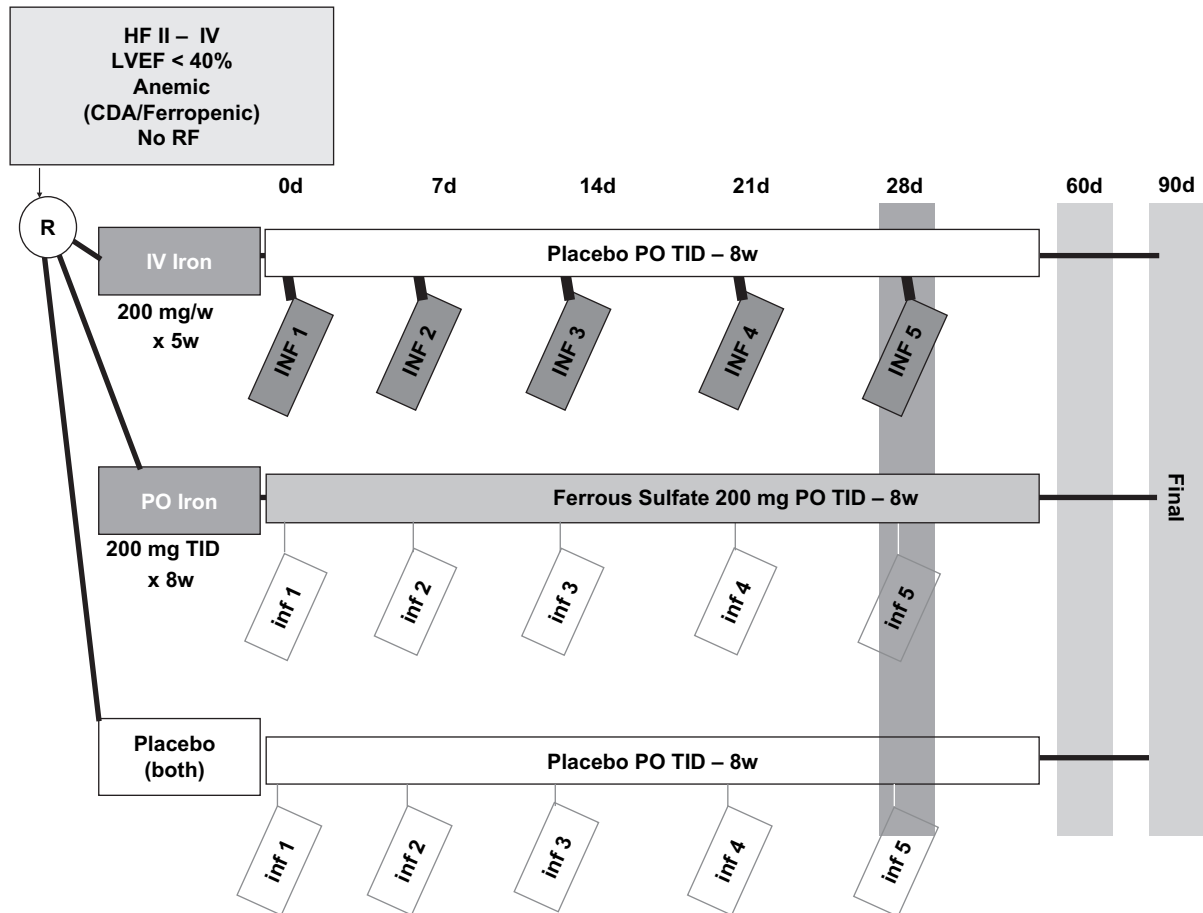
## Methods

### Hypothesis

Iron supplementation (IV or PO) has a clinically relevant impact on changes in oxygen maximal consumption (VO<sub>2</sub> max) assessed by ergospirometry over a 3-month follow-up period in patients with HF and anemia with decreased availability of iron.

### Primary and Secondary End Point

The primary end point of the IRON-HF study is to assess the impact of iron supplementation alone (IV or PO) on changes in oxygen maximal consumption (VO<sub>2</sub> max) assessed by



**Fig. 1.** IRON-HF study design. HF, heart failure; LVEF, left ventricular ejection fraction; CDA, chronic disease anemia; RF, renal failure; IV, intravenous; PO, oral; TID, three times a day; INF, iron sucrose infusion; inf, placebo infusion.

ergospirometry over a 3-month follow-up period. The ergospirometry evaluation will follow the Naughton modified protocol.

The IRON-HF trial has a number of a priori defined secondary end points (comparing changes from baseline with final assessment):

1. New York Heart Association functional class;
2. B-type natriuretic peptide levels;
3. Quality of life using the Living with Heart Failure Minnesota Questionnaire;
4. Left ventricular ejection fraction as assessed by the biplanar modified Simpson method in 2-dimensional echocardiography;
5. Renal function as assessed by the serum levels of creatinine;
6. Incidence of hospitalizations from HF;
7. Mortality;
8. Incidence of adverse events (drug tolerance).

### Subgroup Analysis

The IRON-HF trial has a number of a priori-defined subgroup analyses:

1. Gender;
2. Age;
3. Correction of anemia, defined as hemoglobin higher than 12 g/dL for women and higher than 13 g/dL for men;
4. Hemoglobin variation of more than 1.5 g/dL;
5. Ischemic versus nonischemic etiology;
6. Left ventricular ejection fraction > or less or equal than 30%;
7. Patients who have been admitted during the trial versus those not admitted;
8. High-sensitivity C-reactive protein levels;
9. Transferrin saturation > or < 20%.

### Ethical Issues

This study will be conducted in accordance with the principles stated in the Declaration of Helsinki, 1964. The Ethics Committee of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, approved this study on April 4, 2006 (protocol number 06-115). The revised version of the protocol was approved on May 18, 2006. The study protocol is also being submitted to each Ethics Committee of the 8 additional participating Brazilian sites. Written informed consent will be given by all patients before enrollment into the study.

### Study Design

The IRON-HF study is an investigator initiated, multicenter, prospectively designed, randomized, double-blind, placebo controlled clinical trial (Fig. 1).

### Eligibility

The IRON-HF inclusion and exclusion criteria are listed in Table 1.

### Randomization

Each of the 8 participating centers will randomize patients by telephone contact with the randomization center at Hospital de Clínicas de Porto Alegre. The randomization system will be based on a computerized table of random numbers and performed in blocks of 3 per participating center.

### Interventions

Group 1: Iron sucrose IV 200 mg once per week in 30-minute infusions for 5 weeks, and placebo of oral presentation 3 times per day for 8 weeks.

**Table 1.** Inclusion and Exclusion Criteria

Inclusion criteria
18 years of age or older
Outpatients followed at a HF clinic in a tertiary care hospital with clinical diagnosis of HF for at least 3 months before study entry
NYHA functional Class II-IV, who are able to perform ergospirometry
Documentation of LVEF <40% within the last 6 months
Adequate baseline therapy for HF based on patient's functional class ( $\beta$ -blockers, ACE inhibitors irrespective of functional class except if contraindications, digoxin, spironolactone if NYHA Class III or IV)
Stable baseline HF therapy with same doses of medications and no intent to increase doses for the following 3 months
Hemoglobin $\leq$ 12 g/dL and $\geq$ 9 g/dL
Transferrin saturation <20% and ferritin <500 $\mu$ g/L
Ability to provide written informed consent
Exclusion criteria
Any clinically overt bleeding: gastrointestinal bleeding, hypermenorrhea, history of peptic ulcer without evidence of healing or inflammatory intestinal diseases
Uncorrected hypothyroidism
Other inflammatory, neoplastic or infectious disease
Serum creatinine > 1.5 mg/dL
Previous intolerance to oral elemental iron compounds
HF from alcoholic cardiomyopathy, current regular drinker of alcoholic beverages, or HF from peripartum cardiomyopathy
Recent admission for decompensated HF (last month)
Recent myocardial revascularization procedures (last 3 months)
Recent ACS, stroke, or TIA (last 3 months)
Active or metastatic neoplastic disease with life expectancy of less than 1 year
Patients on heart transplantation list
Patients that had participated in any other clinical trial or study within the last month
Pregnant or lactating women
Pre-menopausal women who are not using any effective method of contraception
Patients using prohibited medications or that have not yet accomplished the washout period
Patients participating in cardiovascular rehabilitation programs

HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ACS, acute coronary syndrome; TIA, transient ischemic attack.

Group 2: Ferrous sulfate 200 mg PO 3 times per day for 8 weeks, and placebo of IV presentation once per week for 5 weeks.

Group 3: Placebo of oral presentation 3 times per day for 8 weeks and placebo of IV presentation once a week for 5 weeks.

### Blinding

Each participating center will elect a third-party blind individual (usually a registered nurse) who will open the allocated medication box, prepare iron sucrose infusions or saline, and administer the preparations to patients using opaque devices. Both patient and attending physicians or nurses will be blind to allocated therapy.

Oral medications and oral placebo will be identical in all aspects.

### Statistical Considerations

**Sample Size.** Based on previous studies in which ergospirometry had been used as a clinical end point for therapeutic interventions in HF,<sup>7</sup> we accepted a 20% increment in maximal oxygen consumption ( $\text{VO}_2\text{max}$ ) as clinically relevant. For an improvement of 20% on  $\text{VO}_2\text{max}$ , considering a mean  $\text{VO}_2\text{max}$  of 16 mL·kg·min (standard deviation of 5.0 mL·kg·min), a study power of 80% and a 5% chance of  $\alpha$  error, we calculated a sample size of 39 patients per group.

**Statistical Analysis.** All the analyses will be performed according to intention-to-treat principle. All study data will be presented stratified by treatment group. All baseline data will be presented using appropriate descriptive summary tables. Continuous variables with normal distribution will be expressed as means and standard deviations, while continuous variables with non-normal distribution will be expressed as medians and quartiles. Categorical variables will be expressed as absolute numbers and percentages. Comparisons between groups will be performed by Student *t*-test, analysis of variance for repeated measures, chi-square test, or Fischer exact test, as appropriate. Between-groups comparisons will be performed in a priori-defined priority basis: Primary comparison is between Group 1 and Group 3; secondary comparison is between Group 2 and Group 3. Bonferroni correction for multiple comparisons may be applied, if needed. Event-free survival analysis will be presented by Kaplan-Meier curves for treatment groups, and analyzed by the log-rank test. A two-sided *P* value < .05 will be considered statistically significant. Statistical analysis will be performed using SAS statistical package (version 8.02; SAS Institute Inc., Cary, NC).

### End Point and Safety Monitoring

A blinded end point committee will validate primary and secondary end points. No interim efficacy analysis is planned during enrollment or follow-up. An independent safety monitoring committee will review data by the time 50% of the patients

have been enrolled. The safety monitoring committee will be responsible for reviewing safety aspects of the study development and make recommendations to the Executive and Steering Committee members during the course of the trial.

### Status of the Study

The study has been approved by all participating centers' ethics committees; the first patient is planned to be enrolled in August 2006. The last patient is expected to finish the study in July 2007.

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