

How I Treat Anemia in Heart Failure

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Randomized Studies that Tested the Effects of Intravenous Iron in Patients with Anemia and Heart Failure.

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Author	Study Design	Inclusion Criteria	Patient (n)	Follow-up Duration	Baseline Hb (g/dL)	Achieved Hb (g/dL)	Agents and dose used	Outcomes
Toblli 2007 ¹	Randomized Double-blind Placebo-controlled	Hb <12.5 g/dL, TSAT <20%, Ferritin <100 µg/L, CrCl <90 ml/min, LVEF ≤35%	20 Saline 20 IV iron sucrose	6 months	Placebo 10.2 ± 0.5 IV iron sucrose 10.3 ± 0.6	Placebo 9.8 ± 0.7 IV iron sucrose 11.8 ± 0.7	200 mg iron sucrose weekly for 5 weeks	↑ in Hb 1.4 g/dL ↑ LVEF 36 ± 4.7 vs. 29 ± 2.4 (P <0.01) ↓ NT-proBNP 118±87 vs. 451±249 pg/mL, P <0.01) ↓ CRP (2.3±0.8 vs. 6.5±3.7 mg/L, P <0.01) ↑ 6MWD (P <0.01) ↓ MLHFQ scores (P <0.01)
Okonko 2008 ² FERRIC-HF	Randomized Observer-blinded Placebo-controlled	NYHA class II-III, anemic (Hb <12.5 g/dL) or non-anemic (Hb >12.5 g/dL) Ferritin <100 µg/L or ferritin 100-300 µg/L with TSAT <20% Peak VO ₂ <18 ml/kg/min	11 Control 24 IV iron sucrose	18 weeks	Placebo 12.2 ± 1.0 IV iron sucrose 12.6 ± 1.2	Placebo 12.6 ± 1.2 IV iron sucrose 13.2 ± 1.1	200 mg weekly until ferritin >500 µg/L, 200 mg monthly thereafter	↑ in Peak VO ₂ (P = 0.009) ↓ in NYHA class (P <0.007)
Beck-da-Silva 2013 ³ IRON-HF	Randomized Double-blind Placebo-controlled	NYHA class II, LVEF <40% Anemia (Hb 9.0-12.0 g/dL) Ferritin <500 µg/L and TSAT <20%	6 Placebo 10 IV iron sucrose 7 Oral iron	5 weeks to 3 months	Placebo 10.9 ± 0.7 Iron 11.2 ± 10.6	Δ Hb 1.04 in IV iron group; Δ Hb 1.69 in oral iron group; Δ Hb 1.1 in placebo group	Iron sucrose 200 mg/week x 5; Oral ferrous sulfate 200 mg tid for 8 weeks versus placebo	↑ Peak VO ₂ by 3.5 ml/kg/min in IV group ↓ Peak VO ₂ by 0.86 in oral iron ↑ Peak VO ₂ by 1.86 in placebo
Anker 2009 ⁴ FAIR-HF	Randomized Double-blind Placebo-controlled	NYHA class II, LVEF <40% NYHA class III, LVEF <45% Hb 9.5-13.5 g/dL Ferritin <100 µg/L or ferritin 100-300 µg/L with TSAT <20%	155 Placebo 304 FCM	24 weeks	Placebo 11.9 ± 1.4 FCM 11.9 ± 1.3	Placebo 12.5 ± 1.0 FCM 13.0 ± 1.0	200 mg weekly until ferritin >500 µg/L, 200 mg monthly thereafter	PGA improved (P <0.001) ↑ KCCQ QoL (P <0.001) ↑ EQ-5D Score NYHA class improved ↑ 6MWD
Ponikowski 2015 ⁵ CONFIRM-HF	Randomized Double-blind Placebo-controlled	NYHA class II, LVEF <45% BNP >100 pg/mL, NT-proBNP >400 pg/mL, Hb <15 g/dL Ferritin <100 µg/L or 100-300 µg/L if TSAT <20%	152 Saline 152 FCM	52 weeks	Placebo 12.4 ± 1.3 FCM 12.37 ± 1.4	Δ Hb at 52 wks. 1.0 (FCM vs placebo; P <0.001)	FCM 500-2000 mg at baseline and week 6 then 500 mg at weeks 12, 24, & 36 if ID still present	PGA improved (P <0.001) ↑ KCCQ QoL (P <0.001) ↑ EQ-5D Score NYHA class improved ↑ 6MWD

Supplemental Table 1 (continued): Randomized Studies that Tested the Effects of Intravenous Iron in Patients with Anemia and Heart Failure.

Author	Study Design	Inclusion Criteria	Patient (n)	Follow-up Duration	Baseline Hb (g/dL)	Achieved Hb (g/dL)	Agents and dose used	Outcomes
van Veldhuisen 2017 ⁶ EFFECT-HF	Randomized controlled	NYHA class II-III, LVEF<45% BNP >100 pg/mL, NT-proBNP >400 pg/mL, Hb <15 g/dL Ferritin <100 µg/L or 100-300 µg/L if TSAT <20%, Peak VO ₂ 10 to 20 ml/kg/min	86 Control 86 FCM	24 weeks	Control 13 ± 1.5 FCM 12.9 ± 1.3	Control 13.2 ± 1.4 FCM 13.9 ± 1.3	FCM 500-1000 mg at baseline and week 6 based on weight and Hb then at week 12 if ID still present	Δ in Peak VO ₂ by -0.16 ml/kg/min in FCM and -0.63 ml/kg/min in control (P = 0.23) not imputed PGA improved (P <0.05) NYHA class improved (P <0.05)

Table adapted from Anand and Gupta⁷ with permission from Circulation.

6MWD, 6-minute walk distance; CrCl, creatinine clearance; CRP, C-reactive protein; Hb, hemoglobin; IV, intravenous; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, N-terminal brain natriuretic peptide; NYHA, New York Heart Association; PGA, Patient's Global Assessment; TSAT, Transferrin saturation; VO₂, peak oxygen consumption.

Data from two smaller randomized trials are not included in the above table. Summary data from FER-CARS-01 (N=30 FCM, 27 iron sucrose and 15 placebo) have been reported in abstract form.⁸ The EFFICACY-HF trial (NCT00821717; n=20 FCM and 14 placebo) was terminated early due to low recruitment.

References for Supplemental Table 1

1. Toblli JE, Lombrana A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol.* 2007;50(17):1657-1665.
2. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol.* 2008;51(2):103-112.
3. Beck-da-Silva L, Piardi D, Soder S, et al. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. *Int J Cardiol.* 2013;168(4):3439-3442.
4. Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med.* 2009;361(25):2436-2448.
5. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J.* 2015;36(11):657-668.
6. van Veldhuisen DJ, Ponikowski P, van der Meer P, et al. Effect of Ferric Carboxymaltose on Exercise Capacity in Patients With Chronic Heart Failure and Iron Deficiency. *Circulation.* 2017;136(15):1374-1383.

7. Anand IS, Gupta P. Anemia and Iron Deficiency in Heart Failure: Current Concepts and Emerging Therapies. *Circulation*. 2018;138(1):80-98.
8. Arutyunov GP, Bylova NA, Ivleva AY, Kobalava ZD. The safety of intravenous (IV) ferric carboxymaltose versus IV iron sucrose in patients with chronic heart failure (CHF) and chronic kidney disease (CKD) with iron deficiency (ID). *Eur J Heart Fail*. 2009;8(Suppl 2):ii71.

