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A Meta-analysis of Intravenous Iron Therapy for Patients With Iron Deficiency and Heart Failure

Iron deficiency is highly prevalent among heart failure patients and is associated with worse quality of life and a higher risk of hospitalizations and mortality. Early randomized clinical trials (RCTs)[1–4] evaluating the efficacy of intravenous iron replacement in heart failure patients with iron deficiency showed promising results in improving objective clinical outcomes, including heart failure hospitalizations and cardiovascular mortality. However, they were not explicitly powered for these outcomes. The 2017 ACC/AHA/HFSA focused guideline update provides a IIb recommendation for intravenous iron repletion in NYHA class II and III heart failure patients and iron deficiency to improve functional status and quality of life.[5] Most recently, the results of the AFFIRM-AHF (A Randomized, Double-blind Placebo-Controlled Trial Comparing the Effect of Intravenous Ferric Carboxymaltose on Hospitalisations and Mortality in Iron Deficient Subjects Admitted for Acute Heart Failure) was presented in the American Heart Association Scientific Sessions and has refueled the interest regarding the utility of intravenous iron therapy in patients with heart failure.[4] We aimed to pool results from all randomized controlled trials evaluating the efficacy of intravenous iron in improving cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF).

We performed a comprehensive electronic database search for RCTs comparing the outcomes of intravenous iron therapy to standard of care in patients HFrEF who were diagnosed with iron

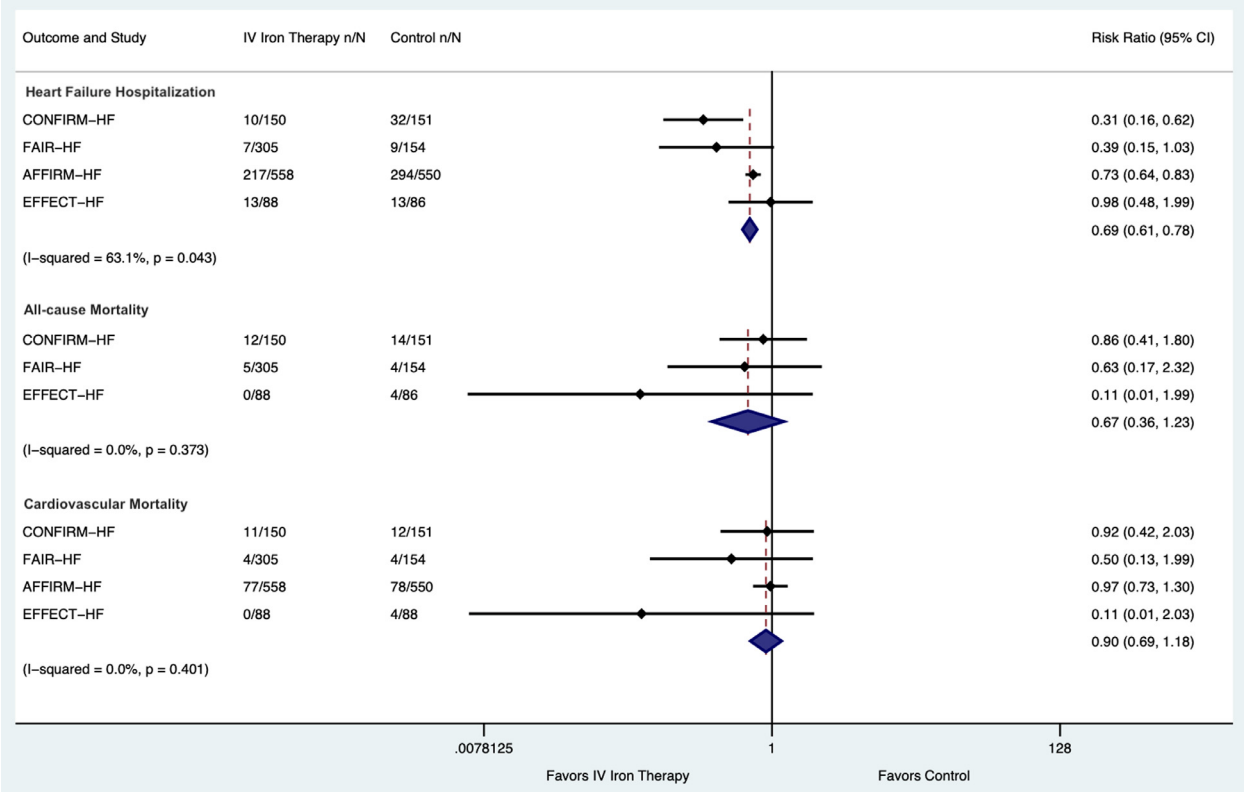

Figure 1. Forest plot summarizing the main findings from the meta-analysis.

deficiency. Iron deficiency was defined as (serum ferritin level,100 ng/ ml, or between 100 and 300 ng/ml if transferrin saturation <20%). We only included RCTs, which enrolled more than 100 patients to avoid the small studies effect. Two authors extracted and analyzed the data using STATA v15.1 software. The outcomes of interest were all-cause mortality, cardiovascular mortality, and heart failure hospitalization. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model.

We identified 4 RCTs with 2,042 patients, mean duration of follow up (31± 14 weeks) (age 69 ± 3 years; females 51%). Compared with the standard of care, intravenous iron therapy was associated with a significant reduction of heart failure hospitalization (RR 0.69, 95% CI 0.61 to 0.78, p = 0.043; Figure 1). There was no difference between intravenous iron therapy and standard of care in all-cause mortality (RR 0.67, 95% CI 0.36 to 1.23, p = 0.37) and cardiovascular mortality (RR 0.90, 95% CI 0.19 to 1.18, p = 0.40; Figure 1).

The exact mechanism by which intravenous iron supplementation improves functional status and clinical outcomes in heart failure patients is unclear. Several mechanisms have been proposed, including improving oxygen transport and metabolism through increased hemoglobin, especially in cells with high oxygen requirements, like cardiac and skeletal myocytes. Randomized trials examining the role of oral iron on improving clinical endpoints in heart failure patients have failed to show benefit likely due to poor absorption of oral iron in the setting of chronic inflammatory state associated with heart failure.[1–4]

In conclusion, in patients with HFrEF and iron deficiency, treatment with intravenous iron therapy has reduced the risk of heart failure hospitalization by almost 30% with no difference in all-cause mortality and cardiovascular mortality compared to standard of care.

Disclosures

The authors have no conflicts of interest to report.

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Systemic Fibrinolytic Therapy Versus Ultrasound-Assisted Catheter-Directed Thrombolysis for Acute İntermediate-High Risk Pulmonary Embolism

We have recently read the article by Stępniewski et al entitled ''Hemodynamic Effects of Ultrasound-Assisted, Catheter-Directed, Very Low-Dose, Short-Time Duration Thrombolysis in Acute Intermediate-High Risk Pulmonary Embolism (From the EKOS-PL Study).''[1] We appreciate the authors for their research describing the efficacy and safety of ultrasound-assisted catheter-directed thrombolysis (USAT) in patients with acute intermediate-high risk pulmonary embolism (PE). In contrast, we would like to emphesis some points in the light of the current evidence.

Acute PE is a life-threatening disorder which usually presents as a severe complication of venous thromboembolism.[2] Noninvasive "low-dose" systemic thrombolytic therapy (50 mg t-PA) has been advocated, based on the hypothesis that all venous return and right heart output washes the pulmonary circulation, with lower dosage and avoidance of "invasive" vascular access can maintain increased thrombolytic efficacy with less bleeding. This approach has previously been reported with a limited number of data which dramatically eliminated major bleeding complications while achieving excellent clinical results.[3] Current literature included multiple case reports regarding the use of low-dose t-PA for the treatment of PE. The doses and administration times are inconsistent, and many of these case reports use low-dose t-PA in patients with massive PE when full-dose t-PA was contraindicated or relatively contraindicated.[4] Previously, Sharifi et al[3] reported that low-dose thrombolytic therapy (a 10-mg bolus by an intravenous push within 1 minute followed by infusion of the remaining 40 mg within 2 hours) achieved excellent clinical results with a striking absence of bleeding in patients with submassive PE. Based on these promising results, we adopted this low-dose systemic thrombolytic therapy with a 6-hour infusion strategy as an option for "escalation of care" in PE cases that had intermediate-high risk.[2] Recently, we indicated that this regimen was associated with an overall excellent clinical outcome, in contrast to these prior reports which eliminated bleeding complications.[2] The incidence of the total bleeding (n = 2, epistaxis and hemoptysis) in this was 12.5% with this thrombolytic therapy regimen.

There are some remarkable points about pulmonary circulation. Unlike

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