Editorial

Heart Failure, Iron Deficiency, and Supplementation: Where Do We Stand?

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See article by Qian et al., pages 151-159 of this issue.

In patients with chronic heart failure (HF), anemia and chronic kidney disease are independent predictors of mortality and hospitalizations for HF.1 Iron deficiency (ID), either absolute or functional, has recently emerged as another independent predictor of outcomes and a major contributor to exercise intolerance, even in the absence of anemia.2 ID might be detected before anemia appears, and provide an earlier opportunity to improve outcomes. In a cohort of 1506 patients with chronic HF, ID, defined as a ferritin level < 100 μg/L or ferritin 100-299 μg/L if the transferrin saturation was < 20%, had a prevalence of 50%.3 It is estimated that 60% of HF patients with anemia and 40% of those without anemia have ID.4

How to diagnose ID? Use of the definition provided herein probably leads to underestimation of the prevalence of ID. Nanas and colleagues showed that despite apparently adequate iron stores assessed according to levels of serum iron and ferritin, up to 73% of patients with anemia, normal kidney function, and advanced HF had ID on the basis of the results of bone marrow aspiration.5 Functional ID is seen when there is a deficit in the mobilization of iron from tissues while iron stores are normal, which is frequent in chronic diseases with inflammation.6,7 Hepcidin and soluble transferrin receptor (sTfR) have been proposed as more sensitive indices to evaluate ID in HF. The peptide hepcidin, synthesized by the liver, is a key regulator of iron homeostasis. It binds to ferroportin and induces its internalization, thus blocking iron export from intestinal cells and iron recycling in macrophages of the reticuloendothelial system.6 Circulating levels of hepcidin are regulated by iron stores. sTfR originates from all cells that metabolize iron and reflects tissue iron demand. When iron delivery to the tissues is insufficient for metabolic requirements, the expression of the sTfR increases to facilitate intracellular influx of iron. Circulating sTfR then quantitatively reflects the tissue iron demand and the erythroid proliferation rate.8 Although sTfR is not yet clinically available, the combination of ferritin and sTfR might eventually be the most accurate method to evaluate ID noninvasively,9 using the transferrin receptor-ferritin index (ratio of serum transferrin receptor level to log ferritin level). Other proposed indices to assess ID are the percentage of hypochromic red cells and reticulocyte hemoglobin concentrations.9

Why is iron so important in HF? Iron is necessary for optimal hematopoiesis but also plays a central role in oxygen transport (hemoglobin), storage (myoglobin), cardiac and skeletal muscle metabolism, synthesis, and degradation of proteins, lipids, ribonucleic acids, and for mitochondrial function.5 Cardiac iron uptake and intracellular iron handling are essential for cardiac function. Iron in circulation is carried by transferrin, which acts as a transport protein and maintains iron in a nonreactive state. Maeder and colleagues10 observed reduced transferrin receptor-1 (TfR1) mRNA expression in the failing heart, which provided an explanation for the reduced levels of iron in such hearts. They also found that aldosterone and norepinephrine (increased in HF) reduced the expression of TfR1 in cardiomyocytes. The decrease in TfR1 gene expression mediated by norepinephrine appears to be predominantly mediated via the β-receptor. In addition to the putative role of neurohormones as regulators of TfR1, previous studies in nonmyocardial cells showed that cytokines (abundant in HF) can down-regulate TfR1.11 These findings suggest that optimization of HF therapy for patients with ID is important, but can also be seen as a further argument to consider iron therapy in HF.

In this issue of the Canadian Journal of Cardiology, Qian and colleagues1 report on the benefits of intravenous (IV) iron therapy on clinical outcomes in HF, by way of a meta-analysis, including a total of 907 patients from 5 clinical...
trials. As shown in Table 1 by Qian et al., most patients came from the 2 larger trials, Conventional Ablation of AF With or Ferric Carboxymaltose Evaluation on Performance in Patients With Iron Deficiency In Combination With Chronic Heart Failure (CONFIRM-HF) (n = 301) and Ferricinjection Assessment in Patients With Iron Deficiency and Chronic Heart Failure (FAIR-HF) (n = 459). This table also highlights that the definition of ID was the same for both larger trials but the degree of anemia varied (proportion of anemic patients not shown), and hemoglobin levels required for inclusion in the studies were progressively higher over the course of time. The third study included in Table 1 was only published in abstract form, and did not include any details on the patient population, concomitant treatments, or the ID definition used.

This meta-analysis is, in fact, somewhat of an update of a previous meta-analysis by Avni et al., who had reported improvements in quality of life, 6-minute walk distance, and all-cause hospitalization rates with iron replacement therapy. It adds to this previous meta-analysis by including the more recently published CONFIRM-HF trial. The CONFIRM-HF trial included 301 patients (251 completed the trial) with moderate HF symptoms (New York Heart Association class II-III), left ventricular ejection fraction < 45%, increased levels of brain natriuretic peptide > 100 pg/mL and/or N-terminal-pro-brain natriuretic peptide > 400 pg/mL, and ID. IV iron was given as a ferric carboxymaltose (FCM) solution equivalent to 500 or 1000 mg of iron. At week 24, the primary end point of change in the 6-minute walk test distance improved significantly more in the FCM group (a difference of 33 ± 11 m; P = 0.002). The benefit was maintained up to 52 weeks. Fatigue and quality of life scores also significantly improved on through week 52, as did New York Heart Association class and Patient Global Assessment scores. Furthermore, FCM was associated with a significant reduction in the risk of hospitalization due to worsening HF (hazard ratio, 0.39; 95% confidence interval [CI], 0.19-0.82; P = 0.009).

Thus, by including these positive results in their meta-analysis, the data from Qian et al. suggest that IV iron therapy significantly reduces the rate of hospitalizations for HF to an impressive degree (odds ratio [OR], 0.28; 95% CI, 0.16-0.49; P < 0.001). An effect of that magnitude, if confirmed, could have a major effect in HF, from a patient and from a health economics perspective. Nevertheless, all-cause mortality was not significantly different (OR, 0.81; 95% CI, 0.42-1.57); and because of the sample size, the power to detect a difference in mortality was limited. However, 4 studies reported the combined end point of hospitalization for HF and death, which was significantly lower in the iron supplementation groups compared with the placebo groups (OR, 0.47; 95% CI, 0.29-0.76; P = 0.002). The analyses by Qian et al. provide further evidence on the potential benefits of treating ID in HF patients. In addition, there were no increases in adverse events with IV iron therapy, using iron sucrose or FCM. It should be noted that the figures in the meta-analysis by Qian et al. clearly show that the weight of evidence is derived from the 2 larger clinical trials.

Nevertheless, more data are required before the routine use of IV iron for all HF patients with ID can be recommended. A recent example in related research might be used to demonstrate that there is no substitute for a large, placebo-controlled clinical trial to assess the benefits of a treatment on cardiovascular events: despite meta-analyses that showed very promising results with erythropoietin stimulating agents, we know now that these do not provide benefits for anemic HF patients, and can increase thromboembolic events. Moreover, any new treatment investigated should be in addition to the standard of care. Of note, the treatments recommended for HF also evolved since the publication of many of the studies included in the meta-analysis by Qian and colleagues, and there is no mention of the use of mineralocorticoid receptor antagonists or devices, even in the CONFIRM-HF trial. Mineralocorticoid receptor antagonists might be of particular interest because of their potential interaction with cellular iron metabolism, based on the previously cited fundamental research observations. The use of devices was not reported in any of those studies, which is rather intriguing, because of the effect of resynchronization therapy on exercise capacity and HF hospitalizations.

Why intravenous administration? Oral iron is poorly absorbed, particularly in patients with chronic diseases such as HF, and adverse gastrointestinal effects limit its tolerability. Several months of oral iron therapy would be required to replete ID in HF, which typically requires ≥ 1000 mg. In contrast, with FCM as studied in HF, a low risk of adverse events was observed and only few injections are needed (in CONFIRM-HF > 75% of patients required a maximum of 2 injections). In a recently reported retrospective study of 105 patients, significant increases in markers of iron stores were observed with oral iron supplementation. The merits of oral vs IV iron repletion are thus still debated, but the cost-effectiveness of IV FCM therapy has been demonstrated in HF; most likely related to improved quality of life and reduced HF hospitalizations. A replacement dose of IV iron sucrose (available in Canada) generally requires 5 clinical visits (approximately 200 mg per dose), and the benefits of IV iron therapy (in various patient populations) can be achieved in a shorter time with other formulations. These include FCM (approved as 1000 mg in 15 minutes in Europe and 750 mg in the United States, but not yet approved in Canada), iron isomaltoside (Europe), ferumoxytol (2 doses of 510 mg, available in Canada), and sodium ferric gluconate (available in Canada). Serious adverse events related to IV iron therapy are rare (approximately 1%) and life-threatening adverse events are extremely rare (<0.02%). However, allergic reactions have been reported with all IV iron preparations and patients should be observed during treatment and 30 minutes after the infusion. Anaphylactic reactions might be more frequent with the high molecular-weight iron dextran (which is now rarely used) and a test dose is required with this type of iron preparation, before considering the infusion.

What to do now for ID in HF patients? In HF patients with anemia and ID in whom iron repletion is being contemplated, oral or IV iron supplementation should be considered to improve functional capacity. Because of the potential effect of IV iron on HF hospitalizations, this therapy should definitely be considered for symptomatic anemic systolic HF patients with ID, making sure that the causes of absolute ID (such as iron loss) have also been investigated and treated by other means when possible (eg, gastric ulcer, colon cancer). In such cases, concomitant IV iron therapy can...
reduce the time needed to correct anemia, and the need for transfusions. National recommendations should be followed for guidance on the treatment of anemia with concomitant severe chronic kidney disease. Pharmacological and device therapies known to improve outcomes in HF should be optimized in all cases. Further evidence is warranted regarding the effect of iron repletion on major cardiovascular events (namely death), especially for nonanemic HF patients and those with HF and preserved ejection fraction. Cost-effectiveness also requires further validation with various iron formulations.

In conclusion, the analysis by Qian and colleagues reminds us of the clinical importance of ID in patients with HF; a serious comorbid condition, often overlooked, and potentially easily reversible. The best means to treat this condition and the effect on hard clinical outcomes are still up for debate. More studies will hopefully provide the answers. Although medium-size studies are ongoing, we found no large event-driven clinical trial registered on clinicaltrials.gov at this time.

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**References**