Ferric Carboxymaltose in Heart Failure with Iron Deficiency

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Ferric Carboxymaltose in Heart Failure with Iron Deficiency

TO THE EDITOR: The definition of iron deficiency that has been widely adopted in the care of patients with heart failure and in the HEART-FID trial by Mentz et al. (Sept. 14 issue)[1] blurs the difference between absolute and functional iron deficiency, a distinction that is evident in the bone marrow of patients with heart failure.[2] Functional iron deficiency is characterized by a transferrin saturation (TSAT) of less than 20%, with normal or elevated ferritin levels. In the accompanying editorial, Martens and Mullens[3] discuss why patients with a ferritin level of less than 100 ng per milliliter may be eligible for intravenous iron treatment only if the TSAT is less than 20%. In patients who have heart failure with a TSAT of less than 20%, intravenous iron appears to confer benefits even if the ferritin level is more than 300 ng per milliliter.[4] Patients with a ferritin level of less than 100 ng per milliliter have the lowest mortality.[5] Therefore, the treatment benefit seems to be determined by a functional rather than an absolute iron deficiency. Thus, we think that the dose of iron should be reconsidered accordingly in future studies. Among patients with heart failure, doses of 200 to 400 mg periodically may be sufficient to maintain a TSAT above 20%. There is no physiologic mechanism for active iron excretion, and the long-term harmful effects of its excess are challenging to assess.

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TO THE EDITOR: The HEART-FID trial showed that among ambulatory patients who had heart failure with a reduced ejection fraction and iron deficiency, there was no apparent difference between ferric carboxymaltose and placebo with respect to the composite primary outcome of death, hospitalization for heart failure, or change in the 6-minute walk distance. The neutral results made clear that it is time to abandon the current definition of iron deficiency in heart failure, which is based on a ferritin level of less than 100 μg per liter or a level of 100 to 300 μg per liter with a TSAT of less than 20%. In contrast to previous studies[1,2] (but using the same definition of iron deficiency), the HEART-FID investigators included more than half of its population with a TSAT level above 20%, which leads to questions as to whether these patients truly had iron deficiency. In patients with heart failure with a reduced ejection fraction, a TSAT of less than 20% is associated with an increased risk of death and corresponds to iron deficiency as identified by the standard iron staining of bone marrow.[3,4] Although debate exists on how to define iron deficiency, a TSAT of less than 20% should be required at least, similar to the definition used for patients with chronic kidney disease.[5]

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Pharma, Pharmacosmos, and Astellas (in all instances paid to his institution). No other potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In the HEART-FID trial, there was no apparent difference between ferric carboxymaltose and placebo with respect to the hierarchical composite end point that was assessed. We suggest that the main controversial issue of the trial is the use of a very tight approach to withholding ferric carboxymaltose therapy during follow-up. The criteria that the investigators used to guide iron repletion were the same as those used at baseline to diagnose iron deficiency (ferritin level, <100 μg per liter or 100 to 300 μg per liter with a TSAT of <20%). Other trials have used much more liberal cutoffs for withholding iron, including a hemoglobin level of more than 15 g per deciliter,[1] a TSAT of 25% or more, a ferritin level of more than 400 μg per liter,[2] or a ferritin level of more than 800 μg per liter or a hemoglobin level of more than 16 g per deciliter.[3] Clinical guidelines have not addressed this topic.[4]

The HEART-FID approach to withholding iron resulted in the lack of treatment in more than 80% of the patients during months 6 to 36 (Table S3 in the Supplementary Appendix to the article). But when a therapy is not given, it cannot exert effects. We would be interested to learn about the on-treatment effects of ferric carboxymaltose in the trial patients, with "on treatment" defined as any period of time covered by the administration of intravenous iron plus an additional 6 to 12 months.

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THE AUTHORS REPLY: We appreciate the opportunity to provide further context regarding how iron deficiency was defined and how the associated iron repletion strategy was used in the HEART-FID trial. Although the definitions that are used for iron deficiency may differ, the key issue is that with a definition that is commonly used in clinical care, practice guidelines, and previous research studies, we observed the results as reported in our trial. Payán-Pernía and

colleagues and Eisenga note that evolving data may suggest the potential utility of a definition of iron deficiency that relies on transferrin saturation alone, but that definition has not been incorporated into clinical guidelines or clinical trials.[1] Alternative definitions that are based on the soluble transferrin receptor may actually better reflect depleted iron stores in bone marrow,[2,3] but questions remain on whether that is the best indicator for cardiovascular health or heart failure. Thus, given that earlier studies of ferric carboxymaltose used the cited standard criteria (ferritin level, <100 ng per milliliter or 100 to 300 ng per milliliter with a TSAT of <20%), as incorporated into guideline recommendations,[4] we selected this definition for consistency to evaluate the most common, agreed-upon standard definition. Ongoing work in HEART-FID is further evaluating these criteria as well as whether the baseline transferrin saturation was associated with any differential effect on outcomes or how any differences in our trial as compared with previous trials may have influenced the results despite the use of the same definition.[5] In future studies, investigators will no doubt evaluate the requirement of a TSAT of less than 20% for eligibility.

Payán-Pernía et al. and Anker et al. also note that the iron dose and timing may have had an effect on the trial results. We tested a strategy of iron repletion, whereas the correspondents note the need to evaluate an intravenous iron intervention with ongoing supplementation over time. In our trial, up to 1500 mg of ferric carboxymaltose was given every 6 months for repletion as compared with the AFFIRM-AHF trial, in which up to 1000 mg was given at baseline followed by repletion at 6 weeks, with additional iron administered at 12 and 24 weeks if needed for maintenance on the basis of iron levels and hemoglobin levels.[5] The ongoing FAIR-HF2 trial (ClinicalTrials.gov number, NCT03036462) is assessing ongoing iron supplementation (i.e., not merely repletion) with 500 mg every 4 months as long as the ferritin level is less than 800 ng per milliliter. Thus, further analyses from HEART-FID (including an on-treatment analysis, as suggested by Anker et al.) along with additional randomized data from ongoing trials will inform both the definition of iron deficiency and the most effective strategy for iron therapy.

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Since publication of the article, the authors report no further potential conflict of interest.

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Asthma in Adults

TO THE EDITOR: To bring focus to discrepancies in asthma-related incidence, morbidity, and mortality falling along socioeconomic lines, the inequity in the availability of guideline-concordant care should be noted in the Clinical Practice article by Mosnaim (Sept. 14 issue).[1] The inhaled glucocorticoid–formoterol combination, as recommended in the Global Initiative for Asthma (GINA) 2023 track 1 guidelines for first-line therapy, is often unattainable,[2] especially for underinsured and uninsured persons. In a sad juxtaposition, the most available (and sole) over-the-counter medication for asthma that has been approved by the Food and Drug Administration