Iron deficiency is common among patients with heart failure, occurring in 40 to 50% of patients with chronic heart failure and in up to 80% of patients with acute heart failure. Features intrinsically related to heart failure, such as inflammation, neurohormonal activation, use of antiplatelet medication, congestion, and chronic kidney disease, are associated with the development of iron deficiency. Observational studies have shown a negative association between iron deficiency and functional status and exercise capacity, as well as an increased degree of cardiac remodeling and a higher risk of readmission for heart failure and cardiovascular death with iron deficiency. Iron deficiency worsens the heart-failure syndrome by affecting energy metabolism in myocardial and skeletal muscle, the oxidation–reduction balance, and contractile function. Previous randomized, controlled trials showed that supplementation with intravenous ferric carboxymaltose improved functional status and exercise capacity and induced cardiac reverse remodeling in patients with heart failure and a reduced ejection fraction. The AFFIRM-AHF trial and the IRONMAN trial assessed whether intravenous iron (ferric carboxymaltose and ferric derisomaltose, respectively) reduced the risk of hospital readmissions for heart failure and cardiovascular death (primary end point) in symptomatic patients with heart failure and a reduced or midlevel ejection fraction, with all patients in the AFFIRM-AHF trial and some in the IRONMAN trial being enrolled during a hospitalization for heart failure. Both trials were affected by the coronavirus disease 2019 pandemic and showed that intravenous iron did not differ from placebo with respect to the risk of a primary end-point event, but prespecified sensitivity analyses showed that intravenous iron reduced the risk of readmission for heart failure. Mentz et al. now report in the Journal the results of the Ferric Carboxymaltose in Heart Failure with Iron Deficiency (HEART-FID) trial. In this double-blind, randomized, controlled trial, 3065 symptomatic ambulatory patients who had heart failure with a reduced ejection fraction (defined as ≤40%) and iron deficiency were assigned, in a 1:1 ratio, to receive ferric carboxymaltose or placebo, in addition to standard therapy for heart failure. Among the inclusion criteria were hospitalization for heart failure within the previous 12 months or an elevated natriuretic peptide level. The primary efficacy end point was a hierarchical composite of death at 12 months, hospitalizations for heart failure at 12 months, and the change in the 6-minute walk distance from baseline to 6 months, assessed as the unmatched win ratio. The trial was designed and analyzed in accordance with a Food and Drug Administration protocol to document substantial evidence for a new drug application that is based on data from a single randomized, controlled trial. This substantial evidence is reflected by the use of a more stringent 99% confidence interval. Intravenous iron was safe, but the unmatched win ratio (ferric carboxymaltose vs. placebo) with respect to the hierarchical primary end point was 1.10 (99% confidence interval, 0.99 to 1.23), and the difference was not significant (P=0.02). The P value does suggest some treatment effect if it would be considered in the context of a usual 95% confidence interval. The treatment effect of ferric carboxymaltose on the 6-minute walk distance was surprisingly small in the HEART-FID trial, and the
lack of a long-term reduction in hospitalizations for heart failure was unexpected, given the results of the AFFIRM-AHF and IRONMAN trials.\textsuperscript{5,7}

Mentz et al. suggest that the lower-risk population in their trial might be one of the explanations for the lower treatment effects in the HEART-FID trial than in the AFFIRM-AHF and IRONMAN trials. Although more patients were enrolled in the HEART-FID trial than in the AFFIRM-AHF and IRONMAN trials, the numbers of deaths and hospital admissions for heart failure were lower in the HEART-FID trial than in the other two trials combined. Characteristics of a trial population at baseline will clearly influence the absolute treatment effects (absolute risk reductions) but will typically have less influence on the relative treatment effects (win ratios or rate ratios), making the lower event rate a less likely explanation of the lower observed relative treatment effect in this event-driven trial. However, the number of patients with true iron deficiency in the HEART-FID trial is unclear, and whether the absence of true iron deficiency could have influenced the observed lower relative treatment effect is unknown.

The classic definition of iron deficiency is a ferritin level of less than 100 ng per milliliter, or less than 300 ng per milliliter with a transferrin saturation of less than 20%. Previous studies have shown that patients with heart failure who meet that definition with a low serum ferritin level but with a transferrin saturation of more than 20% do not exhibit iron deficiency on bone marrow staining and have a lower risk of hospitalization for heart failure.\textsuperscript{9} Furthermore, analyses from previous trials suggested that intravenous iron did not have a treatment effect in patients with a transferrin saturation of more than 20%.\textsuperscript{6} In the ferric carboxymaltose group in the HEART-FID trial, the mean (±SD) transferrin saturation was 23.9%±11.2 at baseline, which clearly differs from the mean transferrin saturation of 15.2%±8.3 at baseline in the AFFIRM-AHF trial, the median of 15% (interquartile range, 11 to 20) at baseline in the IRONMAN trial, and the transferrin saturation at baseline in other intravenous iron trials.\textsuperscript{3,5}

Therefore, the transferrin saturation at baseline was relatively high in the HEART-FID trial, and in both trial groups the transferrin saturation at year 1 of follow-up was nearly identical to the value at baseline. The subgroup analysis of patients with a ferritin level of less than 100 ng per milliliter (Fig. 3 in the article by Mentz et al.) is insufficient to explore this interaction because the subgroup consisted of both patients with a transferrin saturation of at least 20% and those with a transferrin saturation below 20%. Future analyses — preferably a meta-analysis of individual-patient data from all intravenous iron trials — should assess the importance of the transferrin saturation value at baseline. This could help redefine the definition of iron deficiency in patients with heart failure and, we hope, help clinicians determine which patients might benefit from intravenous iron supplementation.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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