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Combating Therapeutic Inertia: Optimizing Iron Deficiency Treatment in Heart Failure

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Iron deficiency (ID) is a common condition in patients with heart failure (HF) and has been associated with poor prognosis and impaired quality of life, regardless of the presence of anemia (1, 2). Intravenous iron replacement therapy with ferric carboxymaltose (FCM) has shown improvements in symptoms, functional capacity and overall health status in patients with reduced and mildly reduced ejection fraction HF (2-4). However, the implementation of guideline recommendations for testing and treating ID in HF patients remains challenging in real-world clinical practice.

The study published by Lindberg et al.(5) in this issue of the European Journal of Heart Failure utilized data from the Swedish HF registry and the Stockholm CREATinine Measurements project to assess the testing and prevalence of ID in HF patients. The results revealed that testing for ID, defined by ferritin and transferrin saturation measurements, increased over time but remained markedly suboptimal. In 2018, only 24% of HF patients underwent ID testing, with higher rates observed in HF with reduced ejection fraction (HFrEF) (31%) compared to patients with preserved EF (HFpEF) (15%) (5). These findings highlight the insufficient adherence to guideline recommendations for systematic screening of ID in HF patients, as outlined in the Heart Failure Association (HFA) / European Society of Cardiology (ESC) guidelines (2).

Probably even more surprisingly, despite the high prevalence of ID, the utilization of intravenous iron treatment was remarkably low, with only a small fraction of patients receiving iron supplementation consistent with guideline recommendations. Actually the utilization of IV iron was marginally higher in patients with ID (13%) than in patients without (5%) (when considering a period later than 2017). However, as ID was screened in a minority of patients (about 30% of HFrEF), it is probable that 5-10% of patients with ID (either diagnosed or undiagnosed) were actually treated with IV iron. Of note, according to 2021 guidelines (2), IV iron supplementation should be considered in symptomatic patients with LVEF <45% or recently hospitalized for HF with LVEF <50%. Yet, as early as in the 2016 guidelines, FCM was recommended in symptomatic patients with HFrEF (Class IIa, level A recommendation) (6). Considering that around 50% of the patients included in Lindberg et al.'s study had HFrEF, we can estimate that roughly 10% to 20% of individuals with ID, who met the criteria outlined in the guidelines, received IV iron treatment (assuming IV iron was administered to patients in accordance with the guidelines).

These findings are consistent with previous research, including the analysis conducted in the OFICSel cohort (7), which demonstrated that out of 2,822 patients, 1,075 (38%) underwent testing for iron deficiency (ID). Among the tested individuals, 364 were diagnosed with ID, and subsequently, 128 patients (35% of ID patients) received intravenous (IV) iron treatment (7). However, as only 38% of patients were screened, we can estimate that overall, approximately 13% of truly eligible patients (i.e. diagnosed or undiagnosed) were treated with IV iron (35% of 38%). This number is surprisingly similar to the number obtained in the study of Lindberg et al. (i.e. 10% to 20%).

The reasons behind this underutilization remain unclear. Possible factors contributing to this underutilization include the identification of ID by non-cardiologists, who may follow practice guidelines recommending oral iron supplementation instead of IV administration (28% of oral iron in ID patients in this study). The absence of dedicated ambulatory facilities to perform the IV iron infusion could also be a limiting factor. However, it is important to explore other potential factors, as these explanations alone is unlikely to account for the underutilization observed.

The underutilization of intravenous iron treatment in HF patients with ID most probably reflects a pattern of therapeutic inertia, which is not unique to iron therapy but extends to other GDMTs for HF. Studies have consistently shown suboptimal adherence to guidelines-directed medical therapies for HF across different healthcare systems. This therapeutic inertia contributes to the suboptimal management of HF and leads to worse outcomes for patients (8).

Specifically, the CHAMP-HF registry (9) showed that, on the data of 3,518 outpatients with HFrEF, among eligible patients, 27% were not prescribed angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin II receptor blockers (ARBs)/angiotensin receptor neprilysin inhibitors (ARNIs), 33% were not prescribed beta-blockers, and 67% were not prescribed mineralocorticoid receptor antagonists (MRAs). When these medications were prescribed, only a small percentage of patients achieved target doses: ACEI/ARB (17%), ARNI (14%), and beta-blockers (28%), whereas a higher proportion attained target doses of MRA therapy (77%). Based on these data, target doses are obtained overall in about 12% of patients for ACEIs/ARBs/ARNIs (i.e. 14 to 17% of the 73% of treated patients), 19% for beta-blockers (28% of the 66% treated patients) and 25% for MRA (77% of the 33% treated patients).

Similarly, the EVOLUTION HF study (10) recently showed that, in an international setting gathering data from Japan, Sweden, and the United States, attempted GDMT initiation peaked at 100 days after an hospitalization for HF at approximately 70% for SGLT2i, 75% for ARNi, 90% for ACEi and BB and 85% for MRA. However, even if initiated, discontinuation was frequent. The discontinuation rates within 12 months of initiation were lower for dapagliflozin (23.5%) compared to sacubitril/valsartan (26%), ACE inhibitors (38%), ARBs (33%), beta-blockers (25%), and MRAs (42%). In addition, the study found that target dose achievements were low for most GDMTs, ranging from 5.1% (for MRA) to 75.7% (for SGLT2i). The combination of inadequate initiation, frequent discontinuation, and suboptimal overall dosage leads to a low percentage of patients receiving the recommended doses: approximately 20% for ACEi/ARNi (20 of 75% for ARNi and 28% of 90% for ACEi), 6% for BB (7% of 90%), 4% for MRAs (5% of 85%), and 50% for SGLT2i (75.7% of 70%).

Taking all of these data into consideration, a clear and consistent pattern emerges (as depicted in the figure): In the case of HFrEF, with the notable exception of SGLT2i, treatment utilization, whether GDMT or IV iron, reaches its maximum potential in approximately 10 to 20% of patients. Remarkably, these numbers demonstrate a remarkable alignment and suggest that the limitations lie more within the systemic healthcare systems rather than individual/patient constraints. It is plausible that the 10 to 20% of patients receiving optimal care are the ones fortunate enough to be managed within optimal healthcare systems, rather than the 10 to 20% for whom treatment initiation/optimization is comparatively simpler. It is truly surprising how little we understand the sociological barriers that physicians face and the organizational obstacles that hinder the optimization of GDMT.

These concerning findings underscore the pressing urgency to address therapeutic inertia in HF as a comprehensive issue. As we recently discussed (8), tackling therapeutic inertia is not a straightforward task. However, there are several tools that can potentially aid in treatment optimization, including IV iron. Some of these tools worth mentioning are:

- Implementing multidisciplinary HF team management, such as mobile HF units and HF clinics, involving HF cardiologists and specialist HF nurses.
- Emphasizing the importance of transition of care, including early follow-up visits after discharge, participation in disease management programs (DMPs), and inclusion in home-visiting programs and multidisciplinary HF clinic interventions.
- Utilizing telemedicine and e-health approaches, including telemonitoring and possibly remote monitoring of pulmonary artery pressure.
- Leveraging the expertise of specialist HF nurses in DMPs and HF clinics to take on tasks such as initiation and up-titration of HF drugs.
- Empowering patients and involving their close circle of friends, family, and caregivers in the physician-patient-caregiver within a patient-care partner approach.

In conclusion, the study by Lindberg et al. (5) sheds light on the insufficient testing for ID and the low utilization of IV iron treatment in HF. Despite the recognized importance of diagnosing and correcting ID, the implementation of guideline recommendations remains challenging in real-world clinical practice. This study emphasizes the imperative for heightened awareness and adherence to guideline recommendations for the testing and treatment of ID in HF, with the ultimate goal of enhancing patient outcomes. However, considering the consistent evidence regarding the utilization of HF treatments (as depicted in the Figure), irrespective of the specific treatment modality, it becomes evident that therapeutic inertia in HF needs to be addressed comprehensively. Implementing systemic solutions to combat therapeutic inertia holds the potential to improve treatment outcomes, not only for GDMT initiation but also for the utilization of IV iron. By tackling therapeutic inertia in HF management as a whole, we can effectively optimize the delivery of evidence-based therapies and elevate the quality of patient care. It emerges as the next crucial battle to conquer in order to achieve these goals.

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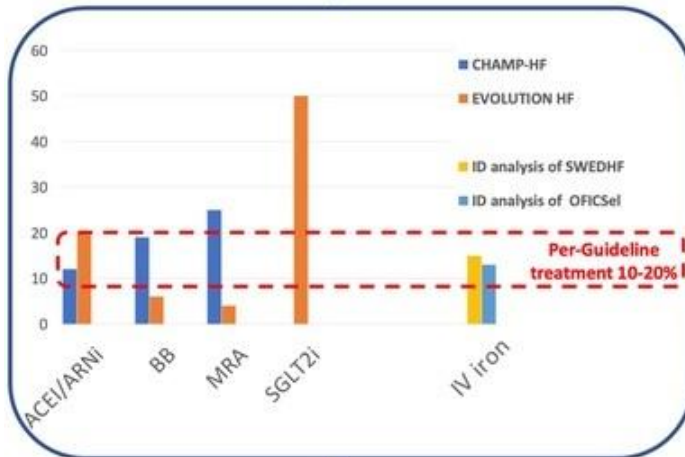
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Figure

HFrEF guidelines

Use evidence-based dose
of **ARNi/ACEi, BB, MRA**
and **SGLT2i**

Use of **IV iron** in patients with iron
deficient (ID) and symptoms
and/or following hospitalization



Urgent need to have a systemic approach to **Therapeutic Inertia** in HFrEF

- Establish HF units/teams with cardiologists and specialist nurses (p.e. mobile HF units and HF clinics)
- Emphasize transitional care: post-discharge follow-up, disease management programs (DMPs), and home-visiting interventions
- Utilize telemedicine and e-health solutions, including telemonitoring
- Leverage specialized HF nurses for medication management
- Empower patients and engage support networks