REVIEW ARTICLE

VIA MEDICA

Iron deficiency as an emerging therapeutic target in patients stabilized after an episode of acute heart failure

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Abstract
Acute heart failure (AHF) syndromes are among the most frequent causes of hospitalization in the elderly and put a heavy financial burden on healthcare systems, mainly due to high early readmission rates. The understanding of AHF has evolved over the years from a significant hemodynamic failure to a multi-organ disease in the course of which peripheral mechanisms such as dysregulated cardiorenal axis or inflammation also play essential roles. A few available observational studies investigating iron deficiency (ID) in patients hospitalized for AHF indicate that this comorbidity is more prevalent than in chronic heart failure, and iron status presents some dynamics in these subjects. ID in AHF predicts increased mortality, greater risk for early readmission and is related to prolonged hospitalization. This paper reviews the results of the first multicenter, double-blind, randomized clinical trial on ferric carboxymaltose in patients who were stabilized after an episode of AHF who had concomitant ID (AFFIRM-AHF), and potential pathophysiological links between dysregulated iron status and AHF syndromes are discussed. (Cardiol J 2021; 28, 6: 962–969)

Key words: acute heart failure, cardiac decompensation, iron deficiency, ferric carboxymaltose

Introduction

Acute heart failure (AHF) syndromes constitute one of the most frequent causes of hospitalization in the elderly and, analyzed in total, put a heavy financial burden on healthcare systems in developed countries [1–4]. Importantly, 30-day readmission rates exceed 25% in this patient population and it has been demonstrated that among these frequent early re-hospitalizations, a significant proportion will also be due to heart failure (HF) (recurrent episodes) [5]. From a clinical perspective, hospitalization due to AHF should always be considered a highly important adverse health event because such an episode represents the "inflection point" [6] in the natural history of the disease. The perception of AHF (in both observational and interventional trials overrepresented by the form of decompensation of pre-existing or de novo heart failure — ADHF) has evolved over the years from a hemodynamic failure (most frequently with fluid overload/congestion) to a multi-organ disease during which peripheral mechanisms such as dysregulated cardiorenal axis (acute "cardiorenal syndrome") or systemic (pro-)inflammation also play important pathophysiological roles [7, 8]. It needs to be acknowledged that the unsatisfactory results of randomized clinical trials (RCTs) investigating short- to mid-term effects of different intravenous (i.v.) vasodilators or cardiac calcitropes adminis-

Table 1. Major large clinical trials investigating the impact of early pharmacological interventions in acute on "hard" clinical outcomes (morbidity and mortality).

Trial acronym, year of publication [reference number]	Population	Intervention and comparator	Outcomes analyzed and results
SURVIVE, 2007 [9]	1327 patients hospitalized with ADHF requiring inotrope agents	Levosimendan (inodilator/ /cardiac calcitrope) vs. dobutamine	All-cause mortality at 180 days; NS
ASCEND-HF, 2011 [10]	7141 patients with AHF	Nesiritide (vasodilator) or placebo for 24 to 168 h	Rate of re-hospitalization for HF or death from any cause within 30 days; NS
TRUE-AHF, 2017 [11]	2157 patients with AHF	Ularitide (vasodilator) or placebo for 48 h	CV death during a median follow-up of 15 months; NS
RELAX-AHF-2, 2019 [12]	6545 patients with AHF	48 h infusion of serelaxin (vasodilator) or placebo within 16 h after presentation	Death from CV causes at 180 days; NS, and worsening HF at 5 days; NS

AHF — acute heart failure; ADHF — acute decompensated heart failure; CV — cardiovascular; HF — heart failure; NS — not significant

tered in hospital to impact 'hard' clinical outcomes in AHF (Table 1) [9–12] have highlighted the need to search for other interventions than modulating cardiac inotropy, fluid (re-)distribution or vascular tone during the acute phase of the disease.

Indeed, available evidence from well-designed clinical trials in AHF implies that the concept of short but intensive support for cardiovascular hemodynamics presumably does not impact mid--to-long-term morbidity and mortality significantly in such patients. The only positive clinical trial in the broadly understood setting of AHF refers to subjects with acute decompensated heart failure (ADHF) and diabetes who were assigned early (before or shortly after discharge) to a chronic HF (CHF) drug sodium-glucose co-transporter 2 inhibitor (sotagliflozin) vs. placebo [13]. Therefore, there is still a need to test substances administered as a specific intervention for this acute state to improve outcomes. Moreover, it seems reasonable that a potential pharmaceutical should first act longer than in a hospital (ideally for weeks/ /months following one or a few easy administrations during the acute phase). Secondly, it is essential to target mechanisms involved in a complex AHF pathophysiology other than hemodynamics [14].

Iron deficiency in the setting of acute heart failure: Data from observational studies and evidence from clinical trials

Iron deficiency (ID), defined as reduced serum ferritin and/or transferrin saturation index (TSAT, serum iron divided by total iron-binding capacity), is highly prevalent in HF (in CHF it affects up to 50% patients) and worsens both symptoms and outcomes in these subjects independently of anemia [15–17]. There is evidence from multicenter, double-blind, RCTs (also aggregated in a few meta-analyses) that in patients with CHF with reduced to mid-range ejection fraction and concomitant ID (defined as serum ferritin < 100 μg/L or 100–299 μg/L if TSAT < 0.2) the administration of i.v. ferric carboxymaltose (FCM) improves exercise capacity, symptoms and the quality of life [18–21]. A few available observational studies investigating ID in patients hospitalized for AHF (Table 2) indicate that this comorbidity not only may even be more frequent in this clinical setting, but also iron status presents somewhat dynamics in AHF (Table 2) [16, 22–27].

Not surprisingly, ID in patients with AHF predicted increased mortality, greater risk for early unplanned readmission, and prolonged in-hospital stay. Although there were attempts to define ID more precisely and pathophysiology-oriented in AHF [16], most observational studies on the prevalence of ID in AHF used classical iron biomarkers implemented from CHF — serum ferritin and TSAT. Regarding i.v. iron therapy in patients hospitalized for AHF, data was limited until recently. In one small RCT PRACTICE-ASIA-HF conducted in two centers in Singapore yielding a total number of 50 patients hospitalized due to ADHF, there was a trend towards greater distance in 6-minute walking test distance over the 12-week study period in subjects given a single-dose FCM pre-discharge compared to placebo, and the drug was well-tolerated [28].

AFFIRM-AHF trial (NCT02937454) was designed to investigate the effects of i.v. FCM on

Table 2. Summary of observational studies investigating the prevalence, clinical correlates and consequences of iron deficiency in patients with acute heart failure.

Number of study (chronologically)	Authors	Number of patients	Females	LVEF (%, mean ± SD unless otherwise stated)	Natriuretic peptides (median and interquartile range for NT-proBNP unless otherwise stated)	Definition of ID	Prevalence of ID	Prevalence of anemia	Clinical correlates of ID	Impact ID on outcomes
1	Jankowska et al., 2014 [16]	165	19%	33 ± 13	4800 (2471–8056) pg/mL	Serum ferritin < 100 µg/L or serum ferritin 100–299 µg/L with TSAT < 20% (standard definition)*	65%	37%	Peripheral edema, higher NT-proBNP, higher uric acid, anemia	↑ 12-month mortality
2	Cohen-Solal et al., 2014 [22]	832	51%	Preserved LVEF: 16% men, 36% women	Mean values for ID+: men 8933 pg/mL, women 8047 pg/mL	Standard definition	Men: 69% Women: 75%	60%	Men: anemia and antiplatelets Women: diabetes and low CRP	Not analyzed
3	Núñez et al., 2016 [23]	626	48%	Preserved LVEF: 52% of patients	3756 (1634–7566) pg/mL	Standard definition	74%	54%	Dyslipidemia and diabetes, anemia, higher troponin T	↑ early readmissions (absolute ID)
4	Van Aelst et al., 2017 [24]	47	32%	39 ± 16	BNP: 1004 (652–1676) pg/mL	Standard definition	83% (on admission)	N/A	Soluble suppression of tumorigenicity 2, IL-6, galectin-3	Not analyzed
5	Beale et al., 2019 [25]	430	43%	48 ± 16	Mean ± SD: 3926 ± 6763 pg/mL	Serum ferritin < 100 µg/L or 100–200 µg/L with TSAT < 20%	HFrEF: 54% HFpEF: 56%	N/A	HFpEF: female, gender, COPD, CRP	↑ LOS (HFpEF)
6	Beattie et al., 2020 [26]	78 805 HF admissions were analyzed of which 91% were classified as emergency	ID/IDA: 34%	–	–	ICD-10 codes: D50.0, D50.8, D50.9, D64.9 (ID/IDA)	66%	N/A	–	↑ readmissions ↑ mortality ↑ LOS and costs
7	Jacob et al., 2020 [27]	221	61%	–	Mean ± SD: 5092 ± 6125 pg/mL	Standard definition	86%	30%	Female gender, anemia	No differences; 83% of patients with ID were treated with ferric carboxymaltose

*Additional definition of ID based on low serum hepcidin and high serum soluble transferrin receptor was applied in this study. BNP — B-type natriuretic peptide; CHF — chronic heart failure; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein CV — cardiovascular; HF — heart failure; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; ID — iron deficiency; IDA — iron deficiency anemia; IL — interleukin; LOS — length of stay; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal prohormone of B-type natriuretic peptide; SD — standard deviation; TSAT — transferrin saturation; N/A — not available
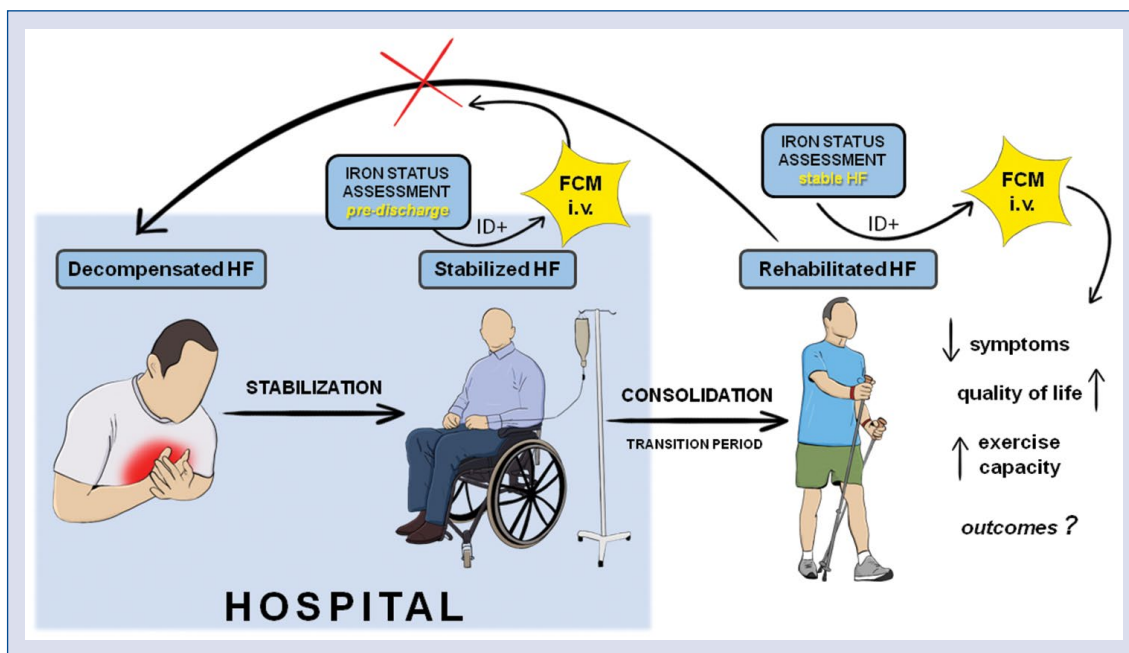
Central illustration. Positioning and beneficial effects of intravenous (i.v.) ferric carboxymaltose (FCM) therapy in patients with heart failure (HF) and iron deficiency (ID) based on published randomized clinical trials.

morbidity and mortality in iron-deficient patients hospitalized for AHF [29]. In this multicenter, multinational, double-blind RCT, more than 1100 patients aged > 18 years who were hospitalized for AHF (with reduced or mildly reduced in-hospital left ventricular ejection fraction [LVEF], i.e. < 50%) and had ID detected during index hospitalization (standard definition implemented from nephrology through RCTs in stable HF based on serum ferritin and TSAT) were randomized before hospital discharge (after achieving clinical stabilization) in a 1:1 proportion to receive i.v. FCM or placebo for up to 24 weeks (dosing based on ID severity) [30]. The primary outcome in the trial was a composite of total hospitalizations for HF and cardiovascular death up to 52 weeks. Although the primary endpoint did not reach the statistical significance (293 primary events in FCM arm vs. 372 in the placebo group with a rate ratio [RR] of 0.79, 95% confidence interval [CI] 0.62–1.01, p = 0.059), there were fewer HF hospitalizations in an active treatment arm (217 total hospitalizations in FCM group vs. 294 in subjects assigned for placebo [RR 0.74; 95% CI 0.58–0.94, p = 0.013]) [30]. Notably, such therapy resulted in clinically meaningful beneficial effects on health-related quality of life (assessed using Kansas City Cardiomyopathy Questionnaire) as early as 4 weeks after the first dose of iron, lasting up to week 24 [31]. Additionally, based on a modeling methodology,

it has been estimated that FCM is homogeneously cost-effective in patients with AHF in different countries characterized by variant healthcare system design [32]. Based on the results of the AFFIRM-AHF trial in the recently published 2021 European Society of Cardiology Guidelines for the diagnosis and treatment of AHF and CHF [33], the indications for i.v. iron supplementation with FCM have been extended beyond stable, CHF. Namely, such therapy should be considered in symptomatic HF patients with LVEF ≤ 50% and ID (guidelines recommend the definition based on serum ferritin and TSAT — see above) and recently hospitalized for HF to improve symptoms and reduce the risk of HF hospitalization — as an element of peri-discharge management (class or recommendation IIa, level of evidence B) [33]. The guidelines also emphasize the need to actively screen for ID and anemia in all subjects with HF by clearly recommending the assessment of iron parameters (ferritin and TSAT as well as hemoglobin concentration/complete blood count) regularly (class of recommendation I, level of evidence C) [33].

Acute heart failure and iron deficiency: Pathophysiological links

The concept of modulating adverse clinical trajectories after an episode of acute HF (Cen-

tral illustration) in terms of improving indices of morbidity and mortality by administering i.v. iron already in-hospital after clinical stabilization is based on a few (patho)physiological assumptions. There have also been discussions regarding, e.g., the appropriateness of the definition of ID in AHF borrowed from stable HF or the safety of such intense iron load in an acute setting.

Analogously to CHF, the exact mechanisms of clinical benefits of i.v. iron (FCM) after an episode of AHF are not fully elucidated. The one hypothesized mechanism is linked with the energetic hypothesis of AHF. It emphasizes the critical involvement of iron in energy generation within all types of cells/tissues. Indeed, the chemical properties of iron warrant its crucial role in comprehensive cellular energetics through effective mitochondrial respiration [34]. Apart from oxygen transportation and storage as the constituent of hemoglobin and myoglobin, iron is an element of two key groups of proteins involved in cellular energy production — hemoproteins (e.g., cytochromes), and non-heme iron-containing proteins such as citric acid cycle enzyme aconitase [35, 36]. Just as stable HF is associated with a chronic cardiac energetic dysfunction and/ /or deficit, AHF is characterized by a rapid energetic imbalance within the myocardial muscle. Chronic (stable) HF has long been associated with energetic disturbances within the heart as a muscle that is undeniably energetically demanding [37, 38]. The so-called "metabolic remodeling" of a chronically failing heart is visible functionally in terms of abnormal substrate utilization and impaired metabolism of high-energy phosphates and structurally through abnormal mitochondria that present with decreased biogenesis [39, 40]. For AHF, which is an acute and particularly dynamic process, less data is available, even experimental data. In one of the few available animal models of a pacing-induced decompensated HF, in dogs developing severe HF in this (patho)mechanism rapidly (within a few weeks), metabolic derangements were already observed in terms of substrate utilization shift in favor of glucose at the expense of free fatty acids [41]. Some information can also be obtained from hearts explanted during the orthotopic transplantation to treat refractory HF from life indications. The morpho-functional and energetic end-stage state of these organs reflects the acute phase of cardiac dysfunction in AHF/ADHF. For example, Leszek et al. [42] have demonstrated a notable reduction in left and right ventricular myocardial iron content in 33 explanted failing hearts compared to 11 non-failing organs.

Historically, depleted iron has been associated with anemia. However, experimental and clinical evidence shows that i.v. iron therapy in HF is about more than just elevating hemoglobin concentration. Moreover, this intervention exerts therapeutic effects longer than hours/days following its administration. It is worth noting that parenteral iron supplementation is simpler compared to infusion of vasoactive drugs/inotropes (requiring supervised and blood pressure-guided control of infusion in the setting of an acute cardiac care unit). Characteristics mentioned above of i.v. iron is known from clinical trials on FCM in stable HF with reduced ejection fraction (HFrEF) with concomitant ID. For example, in the CONFIRM-HF trial demonstrating sustained beneficial effects of FCM on functional capacity in subjects with HFrEF and ID during the 1-year study period, as much as over 75% of patients assigned for FCM required only 1–2 administrations of the study drug at week 0 and optionally at week 6 [19]. Importantly, FCM brings clinical benefits in HF patients with concomitant ID regardless of anemia [21]. How i.v. iron improves functional capacity in HF has not been fully elucidated (oral does not work due to poly-etiological low absorption). We have proposed an explanation that i.v. iron could improve the functioning of skeletal muscles [43–45]. Charles-Edwards et al. [46] have demonstrated in an interventional study that in iron-deficient CHF patients, iron repletion indeed can improve skeletal muscle energetics (assessed in vivo using phosphorus magnetic resonance spectroscopy). Still, it is unknown whether such a mechanism may play a role in the myocardial muscle.

Until recently, it was not unequivocally clear if the CHF definition of ID would be appropriate for AHF patients (whose iron status is dynamic to some extent, as mentioned previously) in terms of differentiating potential beneficiaries of i.v. iron therapy group vs. subjects not requiring i.v. iron. There were also some doubts whether the definition of ID in AHF could be firmly based on serum ferritin, an acute phase reactant protein, and whether ferritin-guided referral for i.v. iron (the threshold for ID: < 100 μg per litre or 100–299 with TSAT < 20%) will be appropriate in AHF analogously to stable disease. The latter for cutoffs above were introduced based on nephrology expertise. Although not fully understood, hyperferritinemia in the course of inflammation (e.g. progressive bacterial infection leading to septic shock) is considered a protective mechanism through diverse immunomodulatory and anti-microbial effects [47].

There is no doubt that AHF is related to increased inflammatory processes within the organism. The roles of diverse circulating inflammatory biomarkers are still discussed for direct pathogenesis of acute myocardial dysfunction and the subsequent injury of other organs such as kidneys and lungs or liver [48]. The magnitude of systemic inflammation in the course of AHF is less expressed than, e.g., in sepsis. For example, in the sub-analysis of the ASCEND-HF trial investigating the effects of vasodilator nesiritide vs. placebo in more than 7 thousand patients hospitalized for AHF, it was demonstrated that high sensitivity C-reactive protein is significantly increased within the first days of index hospitalization, followed by the general decline through the first month after admission (median concentrations for baseline, 48–72 h, and 30-day follow-up: 12.6, 11.0, and 4.7 mg/L, respectively) [49]. Regardless of some doubts if CHF definition of ID will be valid for AHF subjects, another question arose if such therapy will be safe as in chronic, stable conditions. Cellular iron status is tightly controlled as cellular viability represents a U-shaped relationship with amounts of iron. Some authors express their doubts whether an intensive iron load is unequivocally safe in terms of potential overproduction of reactive oxygen species in particular tissues [50]. The results of the AFFIRM--AHF trial confirm the safety of FCM in patients hospitalized for AHF and add to our knowledge regarding clinical benefits of i.v. iron at different stages of the natural history of HF.

Conclusions

In the AFFIRM-AHF trial recruiting subjects with AHF and ID, there have been demonstrated treatment benefits of i.v. iron beyond what is known about the chronic stage of HF, namely the administration of FCM vs. placebo initiated pre-discharge has been shown to reduce the risk of HF hospitalizations. The exact mechanisms of how intravenous iron improves outcomes in this clinical setting are not fully understood. Further translational research is needed to elucidate the acute and long-term myocardial vs. peripheral effects of such therapy. The results of sufficiently powered (to assess the impact on morbidity and mortality) RCTs on i.v. iron in chronic HF with ID is awaited.

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