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Review Article

Iron Deficiency in Heart Failure: A Korea-Oriented Review

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ABSTRACT

Iron deficiency (ID) occurs at high frequency across the spectrum of heart failure (HF), with HF severity and race being potentially important predictors for its development. ID, irrespective of anaemia status, leads to poor outcomes in patients with HF, including exacerbated reduction in exercise capacity, poor quality of life (QoL) and increased risk of HF hospitalisation. As ID has a large public health and economic burden in Asia, and patients hospitalised with acute HF in the Asia Pacific vs. other regions commonly present with more severe clinical symptoms, there is a clear need to identify and treat ID promptly in Asian patients with HF. The biomarkers serum ferritin and transferrin saturation are used for ID diagnosis, and periodic screening is recommended in all patients with HF. The intravenous iron treatments, ferric carboxymaltose (FCM) and ferric derisomaltose, have demonstrated efficacy and tolerability in patients with acute or chronic HF and ID, with FCM shown to be cost-effective (and in some cases cost-saving). Meta-analyses support the likely benefits of intravenous FCM for improving QoL and reducing HF hospitalisation, without reducing mortality risk in patients with HF and ID. Accordingly, European Society of Cardiology guidelines recommend considering intravenous FCM for patients with symptomatic HF with left ventricular ejection fraction ≤50% who were recently hospitalised for HF and have ID. Although analyses of Asian patients with HF and ID are limited, the effects of intravenous iron would be expected to be similar to that in White populations; further clarifying studies may be of interest.

Keywords: Asia; Heart failure; Iron deficiency; Iron; Supplies; Korea

EPIDEMIOLOGY OF IRON DEFICIENCY (ID)

ID is the most prevalent micronutrient deficiency, affecting greater than one-third of the world's population.[1] It can result in microcytic anaemia, causing symptoms such as fatigue, weakness and shortness of breath.[1] ID is particularly common in countries with a low and low–middle sociodemographic index.[1] In 2019, the age-standardised prevalence rate of ID per 100,000 persons was greater than 14,000 globally, with rates in Asia varying from 4,724 in East Asia to 27,404 in South Asia.[1]

EPIDEMIOLOGY OF ID IN HEART FAILURE (HF)

HF is a considerable health burden, affecting approximately 64.3 million people globally.[2] In the Western Pacific region, HF has been found to occur at a slightly younger mean age of 67 years compared with 70 years in the USA, with an even younger mean age of 54 years observed for HF diagnosis in Southeast Asia.[3] In Korea specifically, the prevalence of HF has been increasing in the last 2 decades, from 0.77% of the population reported as having HF in 2002 to 2.24% reported in 2018.[4]

ID is a non-cardiovascular co-morbidity that occurs at high frequency across the whole spectrum of HF, affecting as many as 37–83% of patients with HF overall and 65–83% of patients following an acute HF episode.[5-9] In a multi-ethnic Southeast Asian population, the odds of having ID was 3.5-fold higher in patients with HF than control patients who did not have HF.[10] In this study, the prevalence of ID in the Southeast Asian population with HF (61%) exceeded that reported for European counterparts with HF (37–50%).[10] In Korea, 53.8% of patients hospitalised with acute HF were reported to have ID.[11]

HF severity and race have been highlighted as important predictors of ID in patients with HF. In global studies, significant, independent associations were seen between ID and New York Heart Association Functional Classification (NYHA) > II, high serum high-sensitivity C-reactive protein, and high plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP).[7,12] In a Southeast Asian population, a lower left ventricular ejection fraction (LVEF), and being an inpatient (vs. an outpatient), with a higher body-mass index, and Indian (vs. Chinese) race were all associated with significantly increased odds of having ID.[10] In Korea, a higher heart rate, anaemia, and use of clopidogrel were independent predictors of ID in patients hospitalised with acute HF, as was female sex.[11] Although these factors can help predict patients at the highest risk of ID, periodic ID screening is recommended for all patients with HF.[13]

ID is associated with poorer outcomes in patients with HF, irrespective of whether the patient has anaemia or not.[7,8,14] In a prospective, multicentre cohort study in Korea, 53.8% of patients hospitalised with acute HF had ID, while only 34.9% had ID anaemia.[11]

PATHOPHYSIOLOGY OF ID IN HF

Iron is essential for the functioning of haematopoietic and non-haematopoietic cells. Iron is required for erythropoiesis and immune responses, is present in every cell and is essential for various metabolic processes(**Figure 1**).[15-17] Therefore, ID has critical consequences for organs in which the tissue has high energy requirements, such as the kidneys, skeletal muscle and myocardium(**Figure 2**).[17,18]

The mechanism behind the high prevalence of ID in HF has not been fully elucidated. One hypothesis is that the mechanism underpinning ID in chronic kidney disease (inflammation leading to a cascade of hepcidin production, which triggers the migration of iron into reticuloendothelial cells where it is unavailable for metabolic processes) may also apply to the pathogenesis of ID in HF.[17,19-21] However, the inflammation-catalysed iron redistribution hypothesis remains disputed because of the limited

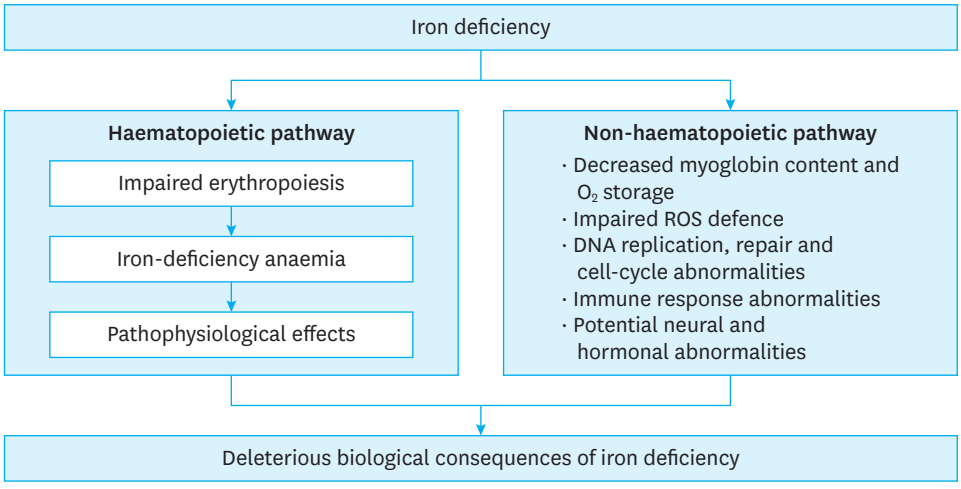

Figure 1. Involvement of iron in haematopoietic and non-haematopoietic metabolic pathways.[15-17]
ROS = reactive oxygen species.

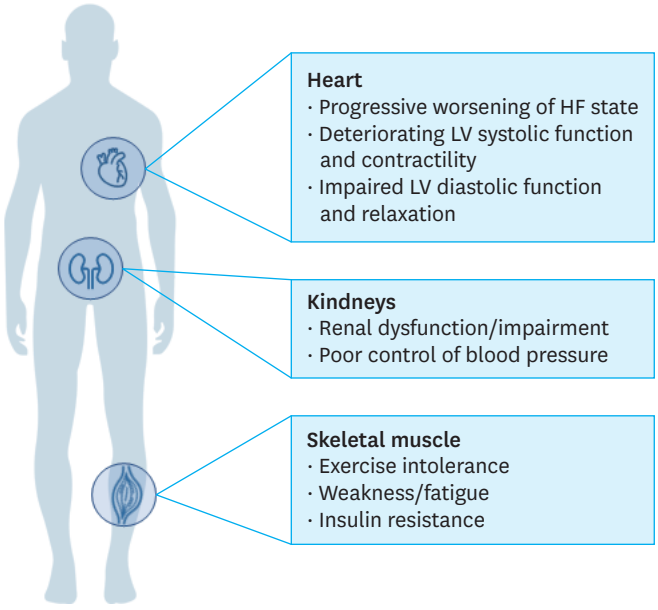

Figure 2. Iron deficiency impairs functioning of organs characterised by high daily energy consumption.[17,18]
HF = heart failure; LV = left ventricular.

supporting evidence for inflammation as a catalyst in ID and the contrasting finding that patients with chronic[22,23] or acute[8] HF have very low levels of circulating hepcidin as opposed to high levels of hepcidin. This suggests that ID in patients with HF may instead be associated with iron store depletion.[23] The reliability of hepcidin as a sole marker for ID in HF may be limited because the level of hepcidin can be influenced by various factors.[24]

Iron store depletion may result from a reduction in iron consumption or iron absorption, abnormal iron loss (i.e., from gastrointestinal disorders such as peptic ulcers and colitis, or blood loss from the urinary tract) or iron deposition to stores that are inaccessible for metabolic processes.[24] However, while these mechanisms are logical, their contribution to ID in HF remains unclear. More research is required to investigate the mechanisms underlying ID in HF.

DEFINING ID IN HF

Haematological assessment of iron stores within bone marrow is considered the gold standard approach to diagnosing ID.[16,24] However, the invasiveness and lack of availability of the bone aspiration procedure renders it impractical outside specialist haematology settings.[24] Additionally, results from bone marrow predominantly provide insight into iron status for erythropoietic processes. Thus, biomarker identification is considered a more suitable method to diagnose ID in patients with HF.[24] Serum ferritin and transferrin saturation (TSAT) are the standard biomarkers recommended in European Society of Cardiology (ESC) guidelines for diagnosing ID in patients with HF.[13] Ferritin is a blood protein that stores iron and is predominantly found in reticuloendothelial cells and hepatocytes.[25] Transferrin is a protein that transports iron in the blood serum; thus, the measure of TSAT is given as a percentage of transferrin binding and transporting iron. This percentage is calculated as the serum iron divided by the total iron binding capacity of transferrin, which is then multiplied by 100.[17,26,27]

One proposed definition of ID in HF is low levels of serum ferritin (<100 ng/mL).[13] However, ferritin production is increased during periods of inflammation (as seen in HF), meaning that serum ferritin alone cannot be used to definitively diagnose ID in HF.[17,27] Therefore, a secondary biomarker, TSAT, is used to provide further indication of iron depletion.[17,27] In the presence of ID, transferrin is upregulated, leading to a higher volume of circulating non-iron bound transferrin, which results in a relative TSAT decrease. Thus, a decrease in TSAT indicates ID. Therefore, the second definition of ID in HF is defined as TSAT <20% with serum ferritin 100–299 ng/mL.[13] To account for the inflammation seen in HF, researchers and treating clinicians apply a high cut-off level for serum ferritin in combination with a low TSAT to diagnose ID in HF more accurately.[17,27] ESC 2021 HF guidelines and the 2022 Korean Society of Heart Failure (KSHF) Guideline for the Management of HF recommend diagnosis of ID in patients with HF if serum ferritin values are <100 ng/mL, or 100–299 ng/mL accompanied by TSAT <20%.[13,28] This definition has been used as an inclusion criterion in several clinical studies investigating the effect of intravenous (IV) iron in patients with ID and HF, which have demonstrated improved clinical outcomes.[29-31] This suggests that the definition can help to identify patients with ID who are likely to benefit from iron-repletion therapy.

An alternative definition of ID has been explored using the novel iron biomarkers: hepcidin and soluble transferrin receptors.[8,22] Low serum hepcidin reflects depleted iron stores more accurately than ferritin, while high soluble transferrin receptors reflect depleted intracellular iron that is insufficient for metabolic processes.[8,22] Future studies assessing the specificity and selectivity of different combinations and cut-offs of the aforementioned ID biomarkers would be informative for their potential diagnostic application and to help guide therapy.

CLINICAL CONSEQUENCES OF ID IN HF

HF is a condition in which there is high morbidity and mortali-

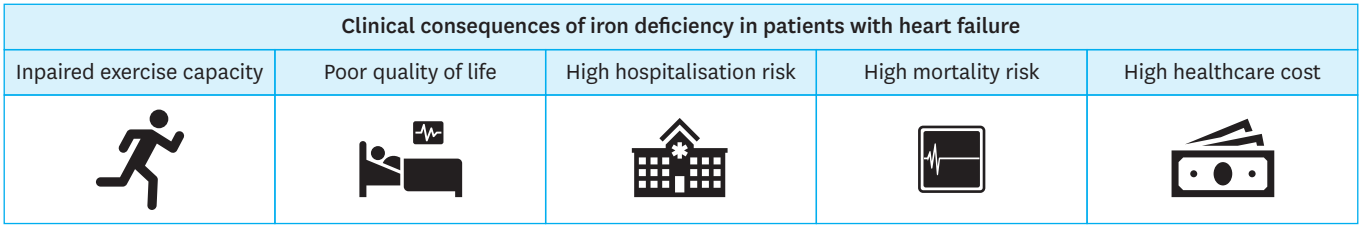

Figure 3. Clinical consequences of iron deficiency in patients with heart failure.[7,14,33-36]

ty.[32] ID (irrespective of anaemia status) exacerbates the clinical symptoms of HF[33] and has been associated with reduced exercise capacity,[34] poor health-related quality of life (QoL),[35] increased risk of non-fatal cardiovascular events (HF hospitalisation, acute coronary syndrome, severe arrythmia and stroke),[14] and increased risk of all-cause death,[7] as well as high healthcare costs (**Figure 3**).[36]

Patients hospitalised with acute HF in the Asia Pacific region commonly present with more severe clinical symptoms and at an earlier age than patients from other regions,[37] suggesting an 'Asian phenotype' of aggressive disease progression.[38] This highlights the large public health and economic burden of HF in Asia.[10] As such, the need to identify and treat ID promptly in patients with HF in Asia may be even more important.

EXISTING DATA ON IRON REPLETION THERAPY IN PATIENTS WITH HF

While inexpensive and widely available, oral formulations of iron sulphate, gluconate, or fumarate[39] are not recommended to treat iron deficiency in patients with HF[13] because there is a lack of evidence for their clinical benefit.[40,41] However, there is growing evidence supporting the use of IV iron treatment for patients with HF, which is recognised in the ESC[13] and the 2022 KSHF Guideline for the Management of HF.[28] IV ferric carboxymaltose (FCM) and ferric derisomaltose (FDI) are iron (III) hydroxides in complex with carboxymaltose[42] and derisomaltose,[43] respectively. While the exact mechanism of action of iron (III) hydroxide complexes—such as FCM—is not known, studies have reported that iron released from these complexes binds to transferrin and is delivered to reticuloendothelial cells.[42,44] In clinical trials, FCM and FDI have demonstrated efficacy and tolerability in patients with ID in acute and chronic HF (results are summarised in **Table 1**).[29-31,45] Initial adverse effects such as nausea, hypotension and peripheral oedema were originally observed with IV iron due to the oxyhydroxide complex formulation; however, in the more recently-developed formulations, FCM and FDI, the iron is encased in a carbohydrate shell, largely averting these adverse effects.[29-31,45,46]

Iron sucrose is another type of IV iron complex, and while it is a different complex to that of FCM and FDI, it has also showcased desirable effects in patients with HF.[47,48] In the FERRIC-HF[48] and IRON-HF[47] trials, iron sucrose use resulted in an improvement in exercise capacity in patients with HF. However, patients can be administered a much higher iron dosage in a single administration with FCM compared with iron sucrose, which requires multiple administrations to reach the optimal dose.[39]

Key trials investigating IV iron in patients with ID and HF

The FAIR-HF and CONFIRM-HF trials investigated the effects of IV FCM vs. placebo on clinical and QoL outcomes in patients with ID (with or without anaemia) and chronic HF with reduced ejection fraction (LVEF <45%).[29,30,49] In both trials, improvements in 6-minute walk test (6MWT) distance, QoL, NYHA class, and self-reported disease activity and overall health (based on patient global assessment score), were seen with FCM vs. placebo. In CONFIRM-HF, IV FCM was also found to reduce the secondary endpoint of risk of hospitalisation for worsening HF at week 52.[30] Results were found to be independent of anaemia status.[29,49]

Two pooled analyses of the FAIR-HF and CONFIRM-HF trials with increased statistical power reinforced the findings of the individual trials. In the first pooled analysis, significantly higher proportions of patients in the FCM arm experienced a clinically meaningful (≥20 m) improvement in 6MWT compared with placebo at week 12 (56.8% vs. 37.4%; odds ratio [OR], 2.156; 95% confidence interval [CI], 1.571–2.960; p<0.0001).[50] Among the patients who had a significant improvement in 6MWT at week 12, >80% sustained this improvement at week 24.[50] In the second pooled analysis, a significantly higher proportion of patients experienced a clinically meaningful (≥4.3-point) improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS; representing QoL) with IV FCM than placebo at week 12 (60.5% vs. 46.6%; OR, 1.75; 95% CI, 1.26–2.44; p=0.0008).[51] Thus, pooled data from FAIR-HF and CONFIRM-HF showed that FCM can improve HF clinical status, exercise capacity and QoL in patients with ID and chronic HF with reduced ejection fraction compared with placebo.[50,51]

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Table 1. Intravenous iron in heart failure clinical trials

Characteristics	FAIR-HF[29]	CONFIRM-HF[30]	IRONMAN[45,53]	AFFIRM-AHF[29]	PRACTICE-ASIA-HF[55]
Patient population					
Number of patients	459	304	1,137	1,132	50
Mean age in IV iron vs. comparator arm (years)	67.8 vs. 67.4	68.8 vs. 69.5	73.2 vs. 73.5	71.2 vs. 70.9	61.1 vs. 64.0
Region	Europe	Europe	UK	Europe, South America, Singapore	Southeast Asia*
HF type	Chronic	Chronic	Chronic and acute	Acute	Acute
NYHA class	II/III	II/III	II/III/IV	I/II/III/IV	Not specified
LVEF	≤45%	≤45%	≤45%	≤50%	Regardless of LVEF
Definition of ID	Serum ferritin <100 μg/L or 100–299 μg/L if TSAT <20%	Serum ferritin 100 μg/L or 100–300 μg/L if TSAT <20%	Serum ferritin <100 μg/L and/or TSAT <20%	Serum ferritin <100 μg/L or 100–299 μg/L if TSAT <20%	Serum ferritin <300 μg/L if TSAT <20%
Type of IV iron	FCM	FCM	FDI	FCM	FCM
Endpoints					
Primary	PGA at week 24 (OR, 2.51; 95% CI, 1.75–3.61; p<0.001) Improvement by one NYHA class at week 24 (OR, 2.40; 95% CI, 1.55–3.71; p<0.001)	6MWT at week 24 (LS mean difference ± SE 33±11 m; p=0.002)	Composite of recurrent HF hospitalisations and CV death at 12 months (RR, 0.82; 95% CI, 0.66–1.02; p=0.070)	Composite of total HF hospitalisations and CV death up to 52 weeks (RR, 0.79; 95% CI, 0.62–1.01; p=0.059)	Difference in 6MWT distance over 12 weeks (adjusted mean distance 0.9 m [95% CI, −30.2 to 32.0; p=0.956)
Key secondary	· 6MWT distance · KCCQ · EQ-5D · VAS	· NYHA class · PGA · 6MWT distance · Fatigue score and HRQoL (KCCQ, EQ-5D) · HF hospitalisation	· CV death or first HF hospitalisation · MLHFQ · EQ-5D · 6MWT distance	· CV hospitalisations and CV death · HF hospitalisations · Time to first HF hospitalisation or CV death · Days lost owing to HF hospitalisations or CV death	· QoL (KCCQ and VAS) · HF readmissions

6MWT = 6-minute walk test; CI = confidence interval; CV = cardiovascular; EQ-5D = European Quality of Life–5 Dimensions; FCM = ferric carboxymaltose; FDI = ferric derisomaltose; HF = heart failure; ID = iron deficiency; IV = intravenous administration; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association Functional Classification; OR = odds ratio; PGA = patient global assessment score; QoL = quality of life; RR = rate ratio; VAS = visual analogue scale; TSAT = transferrin saturation; SE = standard error; HRQoL = health related quality of life; MLHFQ = Minnesota Living with Heart Failure Questionnaire.
*Two centres in Singapore.

Following on from the success of FCM in patients with ID and chronic HF, the AFFIRM-AHF clinical trial investigated the effect of IV FCM compared with placebo in patients with ID after stabilisation following an acute HF episode (when risk of rehospitalisation and mortality is high) with LVEF <50%.[31] Given the lack of data on the safety of IV iron supplementation in this high-risk population, repeat dosing was only performed up to week 24 in AFFIRM-AHF, with clinical efficacy endpoints assessed at week 52. The trial narrowly missed its composite primary endpoint of total HF hospitalisations and cardiovascular death at week 52 (rate ratio [RR], 0.79; 95% CI, 0.62–1.01; p=0.059). This was potentially in part due to the impact of the coronavirus disease 2019 (COVID-19) pandemic on data collection and follow-up. A sensitivity analysis that censored patients at the first date of COVID-19 detection in their region revealed a significant effect of FCM vs. placebo on the primary endpoint (RR, 0.75; 95% CI, 0.59–0.96; p=0.024).

In terms of secondary endpoints in AFFIRM-AHF, IV FCM was associated with a significant reduction in total HF hospitalisations vs. placebo at week 52 (RR, 0.74; 95% CI, 0.58–0.94; p=0.013),[31] as well as a significantly greater improvement in QoL score (evaluated using KCCQ-12 OSS and clinical summary score) as early as week 4 after the start of treatment (adjusted mean difference for OSS: 2.9, 95% CI, 0.5–5.3; p=0.018), lasting up to week 24 (adjusted mean difference for OSS: 3.0, 95% CI, 0.3–5.6; p=0.028).[52] These latter findings were drivers of dominance (cost saving with additional health improvement; Switzerland, UK and USA) and high cost-effectiveness (Italy) in a pharmacoeconomic analysis of IV FCM in acute HF based on AFFIRM-AHF data,[36] with no effect of FCM vs. placebo on cardiovascular death observed in the AFFIRM-AHF trial (hazard ratio [HR], 0.96; 95% CI, 0.70–1.32; p=0.81).[31] Other secondary clinical endpoints, including time to first HF hospitalisation or cardiovascular death (HR, 0.80; 95% CI, 0.66–0.98; p=0.030) and days lost due to HF hospitalisations and cardiovascular death (RR, 0.67; 95% CI, 0.47–0.97; p=0.035) also significantly favoured FCM vs. placebo[31]; however, secondary endpoints were considered hypothesis-generating only, given the non-significant primary endpoint.

The investigator-initiated, open-label, randomised IRONMAN trial investigating another IV iron preparation, FDI, in patients with ID and new or established symptomatic HF with LVEF ≤45%, was reported in November 2022.[45] This trial assessed similar outcomes to the AFFIRM-AHF trial, but in a lower-risk pop-

ulation and over a longer follow-up period (median of 2.7 years), with repeat dosing permitted throughout the trial.

While AFFIRM-AHF only enrolled patients during hospitalisation for an acute HF episode, IRONMAN also enrolled non-hospitalised patients with elevated plasma NT-proBNP, elevated plasma B-type natriuretic peptide or prior hospitalisation for HF within the last 6 months. Furthermore, the iron parameters indicating a patient for redosing in IRONMAN (serum ferritin <100 μg/L or <400 μg/L if TSAT <25%) were more lenient compared with prior trials.[53] Despite these differences, IRONMAN data were largely in agreement with findings from the AFFIRM-AHF trial.

While the composite primary endpoint of recurrent hospitalisations for HF and cardiovascular death with IV FDI vs. usual care (excluding IV iron) was missed in IRONMAN, a numeric reduction in this endpoint was observed (RR, 0.82; 95% CI, 0.66–1.02; p=0.070). Similar to AFFIRM-AHF, the COVID-19 pandemic had a considerable impact on the IRONMAN trial, influencing the ability of patients to attend in-person visits for assessment of iron levels and repeat IV FDI dosing, as well as recruitment and retention. As in AFFIRM-AHF, when a sensitivity analysis accounting for the effects of COVID-19 in IRONMAN was performed, a significant reduction in the primary endpoint was observed with IV FDI compared with usual care (RR, 0.76; 95% CI, 0.58–1.00; p=0.047). This suggests that COVID-19 was a key, unanticipated interferent in both AFFIRM-AHF and IRONMAN statistical analysis plans, with potentially greater influence in IRONMAN due to COVID-19 restricting FDI dosing from March 2020.

The impact of COVID-19 is also reflected in many of the secondary clinical endpoints in IRONMAN, including hospitalisation for HF (RR, 0.80; 95% CI, 0.62–1.03; p=0.085) and change in 6MWT at 20 months (estimated mean difference: −35.9, 95% CI, −74.4 to 2.64; p=0.068). Only the secondary endpoint of time to first cardiovascular death or hospital admission for stroke, myocardial infarction or HF was significantly reduced in the FDI vs. usual care arm (HR, 0.83; 95% CI, 0.69–1.00; p= 0.045). Additionally, although patients treated with IV FDI had a significantly better overall Minnesota Living with HF Questionnaire (MLHFQ) score at 4 months (adjusted mean difference −3.33, 95% CI, −6.67 to 0.00; p=0.050) when compared with the usual care group, no significant difference in overall MLHFQ score was observed between the 2 groups at 20 months (adjusted mean difference −2.57, 95% CI, −6.72 to 1.59; p=0.23).The role of COVID-19 in limiting FDI redosing may potentially have affected this outcome, similar to the attenuation of the treatment effect after cessation of FCM dosing in AFFIRM-AHF.[52]

Taken together, results from individual trials support the likely benefit of IV iron supplementation for reducing hospitalisation for HF and improving QoL across a spectrum of patients with acute or chronic HF and ID, with the cost-effectiveness (and in some cases cost-savings) of FCM predicted from a number of healthcare system perspectives.

IV iron in Asian populations with ID and HF

Of the 1,108 patients included in AFFIRM-AHF analyses and the 1,137 patients included in IRONMAN analyses, 4.3% and 5.8%, respectively, were of Asian race,[29,45] with analyses by race currently unavailable. No patients from Asia were included in the FAIR-HF and CONFIRM-HF analyses; however, FAIR-HF data have been used to perform cost-effectiveness and cost-utility analyses of FCM in patients with chronic HF and ID anaemia from a Korean healthcare payer perspective, based on the ratio of healthcare resource utilisation in Korea using NYHA class and NYHA improvement rates in FAIR-HF.[54] In the base-case scenario, IV FCM was cost-effective vs. placebo for ID, with an incremental cost-effectiveness ratio of ₩25,010,451 ($22,192) per quality-adjusted life year.

One small pilot study, PRACTICE-ASIA-HF, of IV iron in Southeast Asian patients with ID and HF has been conducted.[55] A single 1,000 mg dose of IV FCM or placebo was administered to 50 Southeast Asian patients with ID (defined as serum ferritin <300 ng/mL with TSAT <20%), who had stabilised following acute decompensated HF (regardless of LVEF) (results are summarised in **Table 1**).[55] This study differed from other trials of IV FCM (FAIR-HF, CONFIRM-HF and AFFIRM-AHF) in several ways. To account for the average lower weight of a Southeast Asian patient with HF compared with a Caucasian patient with HF and assuming an Hb of ≥10 g/dL, a fixed dose of 1,000 mg was administered in PRACTICE-ASIA-HF, with no repeat dosing for persistent ID. This resulted in incomplete iron repletion in some patients. As PRACTICE-ASIA-HF was a pilot study, it was small (25 patients per treatment arm) and relatively short (12 weeks), which greatly limited the statistical power available to detect significant treatment effects.

PRACTICE-ASIA-HF found an increase in mean 6MWT distance from 252 m at baseline to 334 m at week 12 in the FCM arm, with continued incremental improvement throughout the 12 weeks, and from 243 m at baseline to 301 m at week 12 in the placebo arm, with a plateau after 4 weeks. However, no significant effect of FCM vs. placebo on change from baseline in 6MWT distance at 12 weeks (primary endpoint) was observed following covariate adjustment (mean difference: 0.88 m, 95% CI, −30.2 to 32.0; p=0.956). Given that significant treatment effects for the 6MWT

became apparent at 24 weeks in CONFIRM-HF,[30] the shorter study duration of PRACTICE-ASIA-HF may have been insufficient to capture significant improvements in exercise capacity with IV FCM.

Similarly, changes in QoL measures (secondary endpoints) did not differ significantly between treatment arms in PRACTICE-ASIA-HF. Respective mean KCCQ OSS scores at baseline and week 12 increased from 50.0 to 82.4 in the FCM arm and from 51.2 to 87.1 in the placebo arm (adjusted mean difference: −1.48, 95% CI, −8.27 to 5.31; p=0.67). Mean visual analogue scale scores increased from 6.4 at baseline to 7.7 at week 4 in the FCM arm, before decreasing slightly to 6.8 at week 12 (potentially highlighting initial benefits of iron repletion followed by fall-off of the effect due to lack of repeat dosing); in the placebo arm, scores increased from 5.7 at baseline to 6.9 at week 4, remaining stable thereafter (adjusted mean difference in change from baseline to week 12 with FCM vs. placebo: 0.26, 95% CI, −0.33 to 0.86; p=0.39). IV FCM was well tolerated in PRACTICE-ASIA-HF with no serious treatment-associated adverse events reported. Given the aforementioned limitations of PRACTICE-ASIA-HF, data from this pilot study are encouraging but insufficient to draw firm conclusions regarding the efficacy of IV FCM in Southeast Asian patients with ID following an acute HF episode; further clarifying studies in this population may be informative.

Totality of evidence

A meta-analysis investigated the effect of IV iron in 5 trials of patients with systolic HF (LVEF ≤45%) and ID.[56] The FAIR-HF[30] and CONFIRM-HF[30] trials included in the meta-analysis investigated IV FCM vs. placebo, whereas the Toblli et al.,[57] FERRIC-HF,[48] and IRON-HF[47] trials investigated IV iron sucrose vs. placebo. Patients in IRON-HF were also treated with oral ferrous sulphate. This meta-analysis revealed that IV iron reduced the composite endpoint of hospitalisation for cardiovascular causes or all-cause death by 66% vs. placebo (OR, 0.44; 95% CI, 0.30–0.64; p<0.0001), as well as the composite endpoint of hospitalisation for worsening HF or cardiovascular death (OR, 0.39; 95% CI, 0.24–0.63; p=0.0001). Outcomes for which individual endpoints were given as mean net effects showed a reduction in NYHA class of −0.54 classes (95% CI, −0.87 to −0.21; p=0.001), an increase in 6MWT distance of 31 m (95% CI, 18–43; p<0.0001) and an overall improvement in QoL scores with FCM vs. placebo. These findings support those from individual trials.

A second meta-analysis that extracted individual patient data from 4 double-blind, randomised controlled trials (FER-CARS-01, FAIR-HF, EFFICACY-HF and CONFIRM-HF) found that IV FCM significantly reduced the rates of recurrent cardiovascular hospitalisations and cardiovascular mortality vs. placebo in patients with systolic HF and ID (RR, 0.59; 95% CI, 0.40–0.88; p=0.009).[58] However, a more recent meta-analysis that included 7 trials in patients with HF and ID suggested that a reduction in cardiovascular, rather than mortality, events with IV iron, may be the key driver of composite endpoint results including such events.[59] In this meta-analysis, IV iron reduced the rate of HF hospitalisations or cardiovascular death (OR, 0.73; 95% CI, 0.59–0.90; p=0.003); however when the individual components of this composite endpoint were analysed, the rate of first HF hospitalisation remained significantly reduced (OR, 0.67; 95% CI, 0.54–0.85; p=0.0007), but the rate of cardiovascular death did not (OR, 0.89; 95% CI, 0.66–1.21; p=0.47). This finding is in agreement with the results of the AFFIRM-AHF analysis, which showed a reduction in HF hospitalisations but not cardiovascular death with FCM vs. placebo.[31]

Thus, the totality of evidence suggests that IV iron should be considered in patients with ID and HF to reduce hospitalisation rates, and improve functional outcomes and QoL, without an expectation for reduced mortality risk. Indeed, recommendations surrounding the use of IV iron in patients with HF are now included in a number of regional cardiology society guidance documents: the ESC guidelines include a class IIa recommendation to consider the use of IV FCM to reduce the risk of HF hospitalisation in patients with symptomatic HF, LVEF ≤50% and ID who have been recently hospitalised for HF[13]; and the Asian Pacific Society of Cardiology consensus statements include a recommendation to consider IV FCM in patients with symptomatic chronic HF with reduced (moderate level of evidence; 100% consensus) or mildly reduced (low level of evidence; 100% consensus) ejection fraction who have concomitant ID (defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%).[60] Practical advice on treatment and diagnosis of ID in patients with HF has previously been given[61]; further considerations are outlined in **Figure 4**.

CONCLUSIONS AND FUTURE DIRECTIONS

ID is common in patients with acute or chronic HF, where it is associated with undesirable effects, such as exacerbating reductions in exercise capacity and QoL, and increased risk of HF hospitalisation. Data suggest a severe clinical phenotype in Asian patients with HF and ID, highlighting a need for early identification and treatment of ID in these patients. While the pathophysiology underlying ID in HF is unclear, evidence suggests that IV iron supplementation is beneficial for reducing hospitalisation

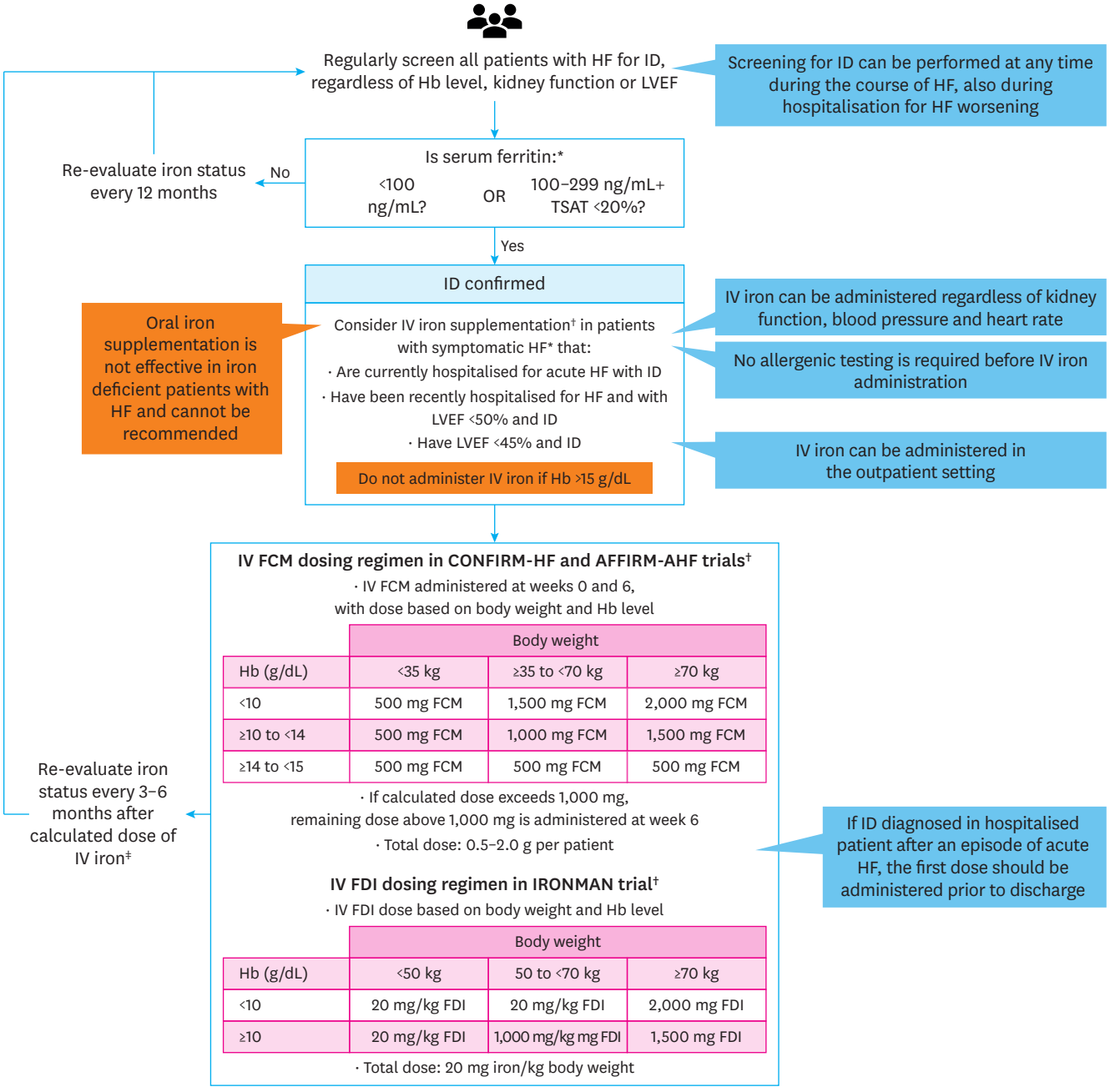

Figure 4. Practical considerations for the diagnosis and treatment of iron deficiency in patients with heart failure.[13,31,45,61]
BNP = B-type natriuretic peptide; FCM = ferric carboxymaltose; FDI = ferric derisomaltose; Hb = haemoglobin; HF = heart failure; ID = iron deficiency; IV = intravenous; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSAT = transferrin saturation.
*AFFIRM-AHF only enrolled patients during hospitalisation for an acute HF episode[31]; in addition to enrolling those patients, IRONMAN also enrolled non-hospitalised patients with elevated plasma NT-proBNP, elevated plasma BNP or with prior hospitalisation for HF within the last 6 months.[45]
†Note the 2021 European Society of Cardiology guidelines were updated prior to the availability of IRONMAN data, and so include a class IIa recommendation for use of IV FCM in patients with symptomatic HF, LVEF ≤50% and ID that have been recently hospitalised for HF based on the results of the AFFIRM-HF trial, but do not include FDI[13]; please refer to latest FCM and FDI Summary of Product Characteristics/Prescribing Information for approved indications and correct dosing.
‡In IRONMAN following initial treatment of ID (defined as serum ferritin <100 ng/mL and/or TSAT <20%), FDI was readministered if serum ferritin was <100 ng/mL, or ≤400 ng/mL when TSAT was <25% after 4 weeks and every 4 months with the aim of maintaining iron repletion between treatment visits[45,53]; please note that IRONMAN uses a different definition of ID to the European Society of Cardiology and the Korean Society of Heart Failure Guidelines (serum ferritin values <100 ng/mL, or 100–299 ng/mL accompanied by TSAT <20%).

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rates and improving functional disease state, exercise capacity and QoL in patients with ID and HF. The upcoming FAIR-HF2 (NCT03036462) and HEART-FID (NCT03037931) clinical trials will provide further evidence regarding the effect of IV iron supplementation on the long-term CV mortality, exercise capacity and QoL in patients with HF and ID. Although analyses investigating the effect of IV iron in patients from Korea (or even from Asia in general) are limited, the effects of IV iron would not be expected to differ substantially in this population; nevertheless, clarifying studies may be of interest.

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Conflict of Interest
Jankowska EA has received research grants and personal fees from Vifor Pharma (co-PI of the AFFIRM trial); and personal fees from Bayer, Novartis, Abbott, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cardiac Dimensions, Fresenius, Respicardia, Zoll, Sanofi, Takeda, and Gedeon Richter. Ponikowski P has received research grants and personal fees from Vifor Pharma (PI of AFFIRM-AHF; participation in clinical trials); and personal fees from Amgen, Bayer, Novartis, Abbott Vascular, Boehringer Ingelheim, Pfizer, Servier, AstraZeneca, Berlin Chemie, Cibiem, BMS, Impulse Dynamics (participation in clinical trials).

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