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RESEARCH ARTICLE

Phenotyping heart failure patients for iron deficiency and use of intravenous iron therapy: data from the Swedish Heart Failure Registry

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Aims Iron deficiency (ID) is associated with poor prognosis regardless of anaemia. Intravenous iron improves quality of life and outcomes in patients with ID and heart failure (HF) with reduced ejection fraction (HFrEF). In the Swedish HF registry, we assessed (i) frequency and predictors of ID testing; (ii) prevalence and outcomes of ID with/without anaemia; (iii) use of ferric carboxymaltose (FCM) and its predictors in patients with ID.

Methods and results We used multivariable logistic regressions to assess patient characteristics independently associated with ID testing/FCM use, and Cox regressions to assess risk of outcomes associated with ID. Of 21 496 patients with HF and any ejection fraction enrolled in 2017–2018, ID testing was performed in 27%. Of these, 49% had ID and more specifically 36% had ID−/anaemia−, 15% ID−/anaemia+, 29% ID+/anaemia−, and 20% ID+/anaemia+ (48%, 39%, 13%, 30% and 18% in HFrEF, respectively). Risk of recurrent all-cause hospitalizations was higher in patients with ID regardless of anaemia. Of 1959 patients with ID, 19% received FCM (24% in HFrEF). Important independent predictors of ID testing and FCM use were anaemia, higher New York Heart Association class, having HFrEF, and referral to HF specialty care.

Conclusion In this nationwide HF registry, ID testing occurred in only about a quarter of the patients. Among tested patients, ID was present in one half, but only one in five patients received FCM indicating low adherence to current guidelines on screening and treatment.

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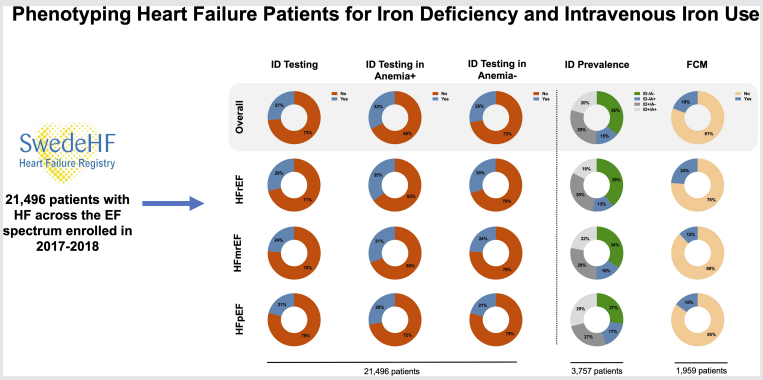
Graphical Abstract



Iron deficiency (ID) testing use, prevalence of ID/anaemia (A), and use of ferric carboxymaltose (FCM) in the unmatched cohort across the ejection fraction spectrum. HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction.

Keywords Iron deficiency • Anaemia • Heart failure • Registry • Outcome

Introduction

Iron deficiency (ID) is highly prevalent in patients with chronic heart failure (HF) and independently associated with high risk of hospitalizations and mortality.[1] ID is the main cause of anaemia and is documented in almost 50% of HF patients in Europe.[2] In addition, it has been shown to impact prognosis *per se*, i.e. independently of anaemia and chronic kidney disease, in patients with HF.[1,3] Based on these prognostic implications, the 2016 European Society of Cardiology (ESC) guidelines on HF recommend testing for ID in all newly diagnosed patients with HF regardless of haemoglobin levels.[4]

Treatment with oral iron has not been successful in improving outcomes in HF patients and might be limited by low absorption and high occurrence of gastrointestinal side effects.[5] Several randomized controlled trials (RCTs) demonstrated intravenous (IV) iron treatment with ferric carboxymaltose (FCM) improving symptoms, quality of life, functional capacity and reducing risk of HF hospitalizations in patients with symptomatic HF with ejection fraction (EF) <50% and ID regardless of concomitant anaemia.[6–9] Therefore, based on the available data, the 2016 ESC guidelines on HF had class IIa, level of evidence A recommendation for FCM in patients with symptomatic HF with reduced EF (HFrEF) and ID in order to improve quality of life, exercise capacity and lessen HF symptoms.[4]

Despite proven efficacy for optimal guideline-directed medical therapy from RCTs, patients with HFrEF are often undertreated or receive suboptimal doses of HF medications.[10] Additionally, limited routine laboratory screening for ID might lead to its underdiagnosis and undertreatment.

Thus, we aimed to (i) assess the likelihood of being tested for ID and identify patient characteristics independently associated with it; (ii) phenotype patients with HF and ID; and (iii) assess the use of FCM and the independent predictors of its use in a real-world cohort of patients with HF across the EF spectrum.

Methods

Study protocol and setting

The Swedish Heart Failure Registry (SwedeHF, www.swedeHF.se) has been described previously.[11] For the current analysis, SwedeHF was linked with the National Patient Registry, Statistics Sweden and the Cause of Death Registry. More details on the data sources are reported in the online supplementary *Methods S1*.

Study population

Patient selection is illustrated in online supplementary *Figure S1*. For the analyses focusing on ID testing, the study population consisted of all patients enrolled in SwedeHF between 1 January 2017 and 31 December 2018 (as ID biomarkers were collected in SwedeHF during this period but not earlier). For the analyses aiming to characterize ID and to investigate FCM use, registrations with missing data for ferritin/transferrin saturation levels, haemoglobin, and use of FCM were excluded. If the same patient had multiple registrations in SwedeHF, the first one reporting data on the biomarkers of interest was selected. The index date was defined as either the day of the outpatient visit or of hospital discharge linked with the registration in SwedeHF.

Statistical analyses

Missing data

Of 28 919 registrations in SwedeHF between 1 January 2017 and 31 December 2018, 22 602 (78%) missing values were reported for ferritin, 24 037 (83%) for transferrin saturation, 4979 (17%) for haemoglobin, and 1190 (4%) for FCM use. Missing data for variables considered for adjustments in the multivariable models were handled by chained-equations multiple imputation (R package *mice*). Analyses were performed in 10 imputed datasets and then the estimates were combined by Rubin's rules. Variables used for the multiple imputation are marked in *Table 1* and online supplementary *Table S1*. The composite outcome of first HF hospitalization/all-cause death was included as the Nelson–Aalen estimator.

Definitions

Patients were considered as tested for ID whether they had a ferritin or transferrin saturation measurement, i.e. missing values were interpreted as lack of testing.

Overall, ID was defined as ferritin <100 µg/L, or ferritin between 100–299 µg/L and transferrin saturation <20%.[4] However, in the analyses aiming to explore the use of FCM, we assumed that patients who were reported as treated with FCM but who did not fulfil the criteria for a diagnosis of ID had normalized ferritin/transferrin saturation levels following a previous treatment with FCM ($n = 55$). Therefore, these patients were assumed as with ID. Anaemia was defined as haemoglobin <12.0 g/dL in women and <13.0 g/dL in men.[4]

Patient characteristics

Baseline characteristics were compared across patients with vs. without ID, also stratifying by anaemia status, i.e. ID−/anaemia−, ID−/anaemia+, ID+/anaemia−, ID+/anaemia+, by Kruskal–Wallis (if continuous) and by chi-squared test (if categorical). Similarly, patient characteristics were compared in patients receiving vs. not receiving ID testing and FCM (online supplementary *Table S2*).

To evaluate patient characteristics which were independently associated with ID testing and use of FCM, logistic regression models were fitted, with use of ID testing and use of FCM, respectively, as dependent variables and the patient characteristics reported in *Figure 1* as covariates. Odds ratio (OR) and 95% confidence interval (CI) were calculated for each potential predictor. In patients receiving FCM, the used doses were visualized by a Kernel density plot.

Outcome analysis

We assessed the associations between ID/anaemia and ferritin/transferrin saturation levels with the following outcomes: a composite of time to first HF hospitalization or all-cause death, time to first HF hospitalization, time to all-cause death, time to first all-cause hospitalization, time to first HF outpatient visit as well as the total number of HF hospitalizations, all-cause hospitalizations and HF outpatient visits. Data were censored on 31 December 2018 or at death (if not defined as an event)/emigration from Sweden.

To investigate the association between ID/anaemia, ferritin/transferrin saturation levels and outcomes, cumulative incidence curves were fitted. Multivariable Cox regression models for time to event analyses and negative binomial regressions (including the log of time as an offset in the model) for repeated event analyses were performed to provide adjusted estimates (variables used for the adjustment are marked in *Table 1* and online supplementary *Table S1*). The proportional hazard assumption was verified by Schoenfeld residuals and met.

All statistical analyses were performed by R 4.0.2 and the R code for data handling and statistical analyses can be found at https://github.com/KIHeartFailure/iron. A two-sided *P*-value <0.05 was considered as statistically significant.

Results

Iron deficiency testing and predictors of iron deficiency testing use

Between 1 January 2017 and 31 December 2018, there were 21 496 patients registered in SwedeHF and 5708 (27%) were tested for ID [i.e. measurement of only ferritin (1472, 7%), of only transferrin saturation (221, 1%), or of both ferritin and transferrin saturation (4015, 19%)] (*Graphical Abstract*, *Table 1*, online supplementary *Table S3*). Of these, 2691 (57%) had HFrEF, 1113 (24%) HF with mildly reduced EF (HFmrEF), and 907 (19%) HF with preserved EF (HFpEF). ID testing was performed in 32% of patients with anaemia and 28% of those without anaemia, with similar differences in testing according to anaemia status across the EF spectrum (*Graphical Abstract*).

Of all tested variables, key patient characteristics independently associated with higher likelihood of ID testing were enrolment in SwedeHF registry as an outpatient, having HFrEF vs. HFmrEF vs. HFpEF, more severe/symptomatic HF [i.e. higher New York Heart Association (NYHA) class, use of diuretics and mineralocorticoid receptor antagonists (MRAs)], use of beta-blockers, anaemia, male sex, longer HF duration, follow-up referral to HF nurse-led clinic, referral to follow-up in primary care, and being registered in SwedeHF in 2018 vs. 2017 (*Figure 1*). Geographical distribution of ID testing in Sweden is shown in online supplementary *Figure S2* and *Table S4*.

Characterization of iron deficiency

Prevalence

Of 3757 patients with available data on ferritin, transferrin saturation, haemoglobin and FCM, 36% had neither ID nor anaemia (ID−/anaemia−), 29% had only ID (ID+/anaemia−), 15% had only anaemia (ID−/anaemia+), and 20% had both ID and anaemia (ID+/anaemia+) (*Graphical Abstract*, *Table 2*, online supplementary *Table S5*). In patients with HFpEF, 27% had ID−/anaemia−, 27% had ID+/anaemia−, 17% had ID−/anaemia+, and 29% had ID+/anaemia+. Corresponding estimates in patients with HFmrEF were 34% for ID−/anaemia−, 28% for ID+/anaemia−, 16% for ID−/anaemia+, and 22% for ID+/anaemia+. In HFrEF, 39% had ID−/anaemia−, 30% ID+/anaemia−, 13% ID−/anaemia+, and 18% ID+/anaemia+ (*Graphical Abstract*, *Table 2*, online supplementary *Tables S6–S8*). Prevalence of ID regardless of anaemia was 49% in the overall population, 56% in HFpEF, 50% in HFmrEF, and 48% in HFrEF.

Table 1 Baseline characteristics in patients with vs. without iron deficiency testing (i.e. measurement of ferritin or transferrin saturation)

Variable	Missing	ID testing No	ID testing Yes	*P*-value
n (%)		15 788 (73)	5708 (27)	
Male sex[a], *n* (%)	0.0	10 025 (63.5)	3810 (66.7)	<0.001
Age (years)[a], *n* (%)	0.0	75.0 [67.0–82.0]	75.0 [66.0–81.0]	<0.001
Outpatient location[a], *n* (%)	0.0	11 497 (72.8)	5120 (89.7)	<0.001
LVEF, *n* (%)[a]	14.4			<0.001
HFrEF		6713 (49.0)	2691 (57.1)	
HFmrEF		3543 (25.9)	1113 (23.6)	
HFpEF		3433 (25.1)	907 (19.3)	
NYHA class[a], *n* (%)	27.9			<0.001
I		1366 (12.7)	452 (9.5)	
II		5462 (50.9)	2255 (47.4)	
III		3707 (34.5)	1992 (41.8)	
IV		202 (1.9)	61 (1.3)	
Systolic blood pressure (mmHg), median [IQR]	3.4	130.0 [115.0–140.0]	125.0 [110.0–140.0]	<0.001
Diastolic blood pressure (mmHg), median [IQR]	3.2	75.0 [67.0–80.0]	70.0 [65.0–80.0]	<0.001
Heart rate (bpm), median [IQR]	4.6	72.0 [64.0–84.0]	70.0 [62.0–80.0]	<0.001
BMI (kg/m^2), median [IQR]	44.2	27.0 [23.8–30.9]	26.6 [23.7–30.5]	0.019
eGFR (CKD-EPI) (mL/min/1.73 m^2), median [IQR]	4.8	61.8 [45.6–79.6]	62.1 [45.1–79.8]	0.865
NT-proBNP (pg/mL), median [IQR]	25.5	1975.0 [781.0–4338.0]	1864.0 [766.5–4000.0]	0.038
Smoking, former/current[a], *n* (%)	33.4	5547 (54.7)	2434 (58.1)	<0.001
Diabetes[a], *n* (%)	0.0	4340 (27.5)	1561 (27.3)	0.851
Atrial fibrillation/flutter[a], *n* (%)	0.0	9144 (57.9)	3193 (55.9)	0.010
Ischaemic heart disease[a], *n* (%)	0.0	7992 (50.6)	2940 (51.5)	0.258
Hypertension[a], *n* (%)	0.0	11 170 (70.7)	3968 (69.5)	0.083
Valvular heart disease[a], *n* (%)	0.0	3017 (19.1)	1022 (17.9)	0.048
COPD[a], *n* (%)	0.0	2102 (13.3)	730 (12.8)	0.326
ACEi/ARB/ARNi[a], *n* (%)	0.6	13 306 (85.0)	5051 (88.7)	<0.001
Beta-blocker[a], *n* (%)	0.3	13 986 (88.9)	5201 (91.2)	<0.001
MRA[a], *n* (%)	0.5	6385 (40.7)	2657 (46.6)	<0.001
Device therapy (CRT/ICD)[a], *n* (%)	1.6	1837 (11.9)	764 (13.5)	0.002
Diuretic[a], *n* (%)	0.5	11 367 (72.5)	4298 (75.5)	<0.001
Statin[a], *n* (%)	0.4	7873 (50.1)	2995 (52.5)	0.002
Nitrate[a], *n* (%)	0.5	1545 (9.8)	534 (9.4)	0.327
Follow-up referral HF nurse-led clinic[a], *n* (%)	6.7	11 219 (77.2)	4810 (87.3)	<0.001
Follow-up referral specialty[a], *n* (%)	3.9			<0.001
Hospital		10 099 (67.1)	3933 (70.2)	
Primary care		4707 (31.3)	1618 (28.9)	
Other		251 (1.7)	54 (1.0)	
Education[a], *n* (%)	1.6			0.022
Compulsory school		6041 (38.9)	2071 (36.9)	
Secondary school		6534 (42.1)	2464 (43.9)	
University		2954 (19.0)	1081 (19.2)	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ID, iron deficiency; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.
[a]Included in the multiple imputation models and logistic/Cox regressions.

Baseline characteristics according to iron deficiency and anaemia status

Regardless of the EF phenotype, patients with ID−/anaemia+ and ID+/anaemia+ were more likely older, more symptomatic for HF [i.e. higher NYHA class and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, use of diuretics], and more likely to have ischaemic heart disease (*Table 2*, online supplementary *Table S5*).

Patients with ID+/anaemia+ were more likely to have HFpEF, more symptomatic/severe HF (i.e. higher NYHA class, higher NT-proBNP, use of diuretics and nitrates) and higher comorbidity burden (ischaemic heart disease, diabetes, hypertension, prior

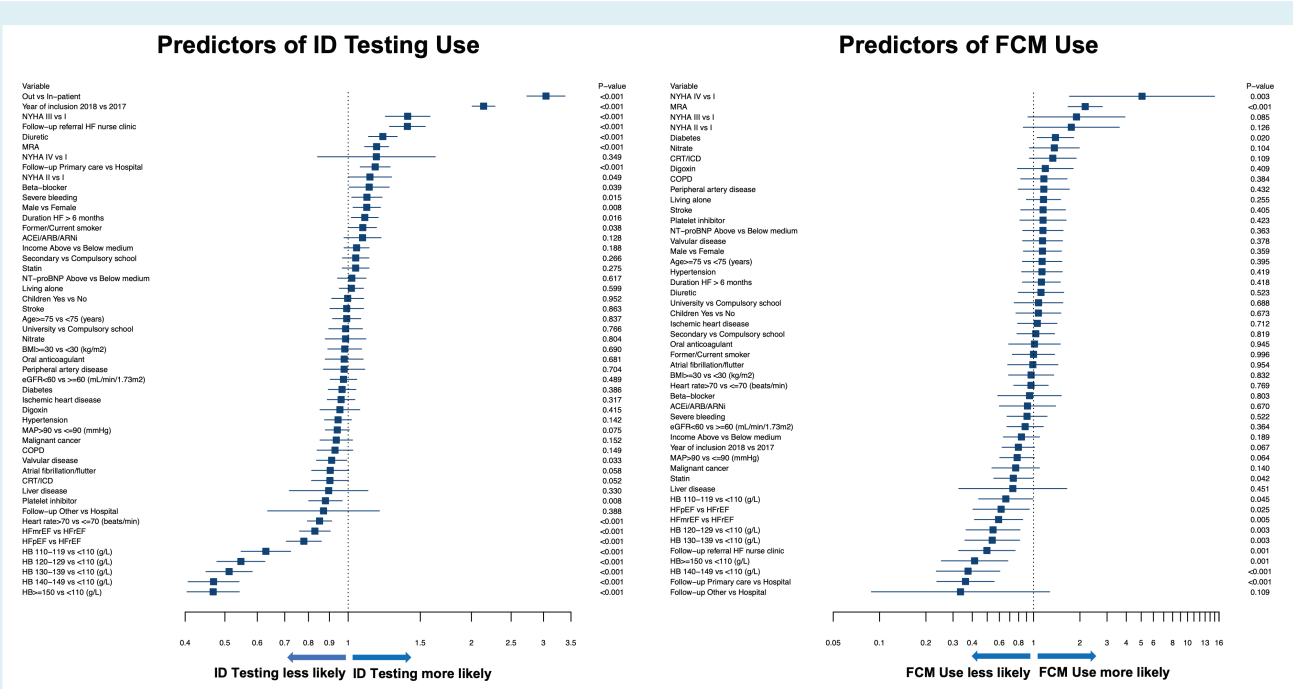


Figure 1 Predictors of iron deficiency (ID) testing use (*A*) and predictors of ferric carboxymaltose (FCM) use (*B*). ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HB, haemoglobin; HF, heart failure; ICD, implantable cardioverter-defibrillator; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; MRA, mineralocorticoid receptor antagonist.

stroke, chronic obstructive pulmonary disease, valvular disease) and to be followed up in primary care compared with those with ID−/anaemia− (*Table 2*, online supplementary *Tables S5* and *S6*). Patients with ID−/anaemia+ showed a profile which resembled more ID+/anaemia+, whereas ID+/anaemia− resembled more ID−/anaemia−. Use of HF treatments (i.e. MRA and device therapy) was highest in patients with ID+/anaemia− and ID−/anaemia−, who also were more likely to have preserved renal function and HFrEF (online supplementary *Table S8*). Overall, patient characteristics according to ID/anaemia were consistent across the EF spectrum (online supplementary *Tables S6–S8*).

Outcome analysis according to iron deficiency and anaemia status

Over a median (interquartile range) follow-up of 19.4 (0.1–35.9) months, in time to event analyses and compared with ID−/anaemia−, ID+/anaemia+ was associated with the higher risk of all the outcomes [all-cause death/first HF hospitalization: adjusted hazard ratio (HR) 1.48 (95% CI 1.25–1.74), $P < 0.001$; all-cause death: adjusted HR 1.55 (95% CI 1.23–1.95), $P < 0.001$; first HF hospitalization: adjusted HR 1.38 (95% CI 1.14–1.67), $P = 0.001$; and first all-cause hospitalization: adjusted HR 1.39 (95% CI 1.23–1.58), $P < 0.001$] except for first HF visit (whose risk was similar across the study groups); ID−/anaemia+ was associated with higher risk of all-cause death/first HF hospitalization [adjusted HR 1.23 (95% CI 1.03–1.48), $P = 0.024$] and all-cause death [adjusted HR 1.41 (95% CI 1.10–1.82), $P = 0.008$]; there were no statistically significant differences in risk of outcomes with ID+/anaemia− (*Figure 2*, *Table 3*, online supplementary *Figure S3*).

In the recurrent event analyses, ID+/anaemia+ was associated with statistically significant higher risk of all-cause and HF hospitalizations [adjusted incident rate ratio [IRR] 1.43 (95% CI 1.25–1.63), $P < 0.001$; and adjusted IRR 1.37 (95% CI 1.10–1.72), $P = 0.005$], whereas ID+/anaemia− [adjusted IRR 1.17 (95% CI 1.04–1.31), $P = 0.008$] and ID−/anaemia+ [adjusted IRR 1.30 (95% CI 1.12–1.50), $P < 0.001$] with higher risk of all-cause hospitalizations compared with ID−/anaemia− (*Table 3*).

Of note, when included in the same Cox regression (including also the covariates reported in *Table 1*), transferrin saturation <20% vs. ≥20% was significantly associated with higher risk of all the investigated outcomes (i.e. all-cause death/first HF hospitalization, all-cause death, first and recurrent HF hospitalizations, first and recurrent all-cause hospitalizations, first and recurrent HF visits), whereas ferritin <100 vs. ≥100 μg/L was only associated with higher risk of recurrent HF hospitalizations and recurrent all-cause hospitalizations (online supplementary *Table S9*).

Characterizing ferric carboxymaltose use

Ferric carboxymaltose use

In the overall HF cohort with ID, 19% of patients received FCM treatment and of these 52% had anaemia (*Graphical Abstract*, online

Table 2 Baseline characteristics in the study population stratified according to iron deficiency/anaemia status

Variable	Missing	ID−/A−	ID−/A+	ID+/A−	ID+/A+	*P*-value
n (%)		1351 (36)	541 (15)	1100 (29)	765 (20)	
Male sex[a], *n* (%)	0.0	985 (72.9)	444 (82.1)	654 (59.5)	496 (64.8)	<0.001
Age (years), median [IQR]	0.0	72.0 [64.0–78.5]	77.0 [71.0–83.0]	73.0 [63.0–79.2]	77.0 [71.0–84.0]	<0.001
Outpatient location[a], *n* (%)	0.0	1299 (96.2)	471 (87.1)	1047 (95.2)	611 (79.9)	<0.001
HF subtype[a], *n* (%)	15.0					<0.001
HFrEF		749 (65.0)	249 (54.0)	571 (61.8)	334 (50.8)	
HFmrEF		249 (21.6)	117 (25.4)	202 (21.9)	159 (24.2)	
HFpEF		155 (13.4)	95 (20.6)	151 (16.3)	164 (25.0)	
NYHA class[a], *n* (%)	16.2					<0.001
I		153 (13.1)	36 (8.4)	86 (9.1)	31 (5.2)	
II		599 (51.2)	191 (44.3)	468 (49.3)	225 (37.8)	
III		406 (34.7)	200 (46.4)	390 (41.1)	327 (54.9)	
IV		12 (1.0)	4 (0.9)	6 (0.6)	13 (2.2)	
Systolic blood pressure (mmHg), median [IQR]	2.0	125.0 [110.0–140.0]	121.0 [110.0–135.0]	125.0 [111.0–140.0]	126.0 [110.0–140.0]	0.005
Diastolic blood pressure (mmHg), median [IQR]	1.8	73.0 [65.0–80.0]	70.0 [60.0–79.5]	73.0 [65.0–80.0]	70.0 [60.0–80.0]	<0.001
Heart rate (bpm), median [IQR]	2.4	69.0 [60.0–79.0]	70.0 [61.0–80.0]	70.0 [62.0–80.0]	72.0 [64.0–82.0]	<0.001
BMI (kg/m^2)	50.9	27.2 [24.6–30.8]	25.0 [22.5–27.7]	27.3 [24.1–31.1]	26.4 [23.2–30.6]	<0.001
eGFR (CKD-EPI) (mL/min/1.73 m^2), median [IQR]	0.5	68.0 [52.1–82.6]	52.7 [37.9–72.3]	65.5 [48.8–83.2]	52.6 [39.0–70.1]	<0.001
NT-proBNP (pg/mL), median [IQR]	10.0	1293.5 [527.2–2668.0]	2890.0 [1332.0–6008.0]	1590.0 [596.0–3471.0]	3196.5 [1420.0–6921.2]	<0.001
Smoking, former/current[a], *n* (%)	27.1	574 (58.0)	213 (56.6)	489 (60.1)	341 (61.2)	0.423
Diabetes[a], *n* (%)	0.0	294 (21.8)	159 (29.4)	307 (27.9)	267 (34.9)	<0.001
Atrial fibrillation/flutter[a], *n* (%)	0.0	744 (55.1)	322 (59.5)	560 (50.9)	457 (59.7)	<0.001
Ischaemic heart disease[a], n (%)	0.0	632 (46.8)	328 (60.6)	572 (52.0)	469 (61.3)	<0.001
Hypertension[a], *n* (%)	0.0	855 (63.3)	391 (72.3)	739 (67.2)	607 (79.3)	<0.001
Valvular heart disease[a], *n* (%)	0.0	211 (15.6)	130 (24.0)	176 (16.0)	204 (26.7)	<0.001
COPD[a], *n* (%)	0.0	126 (9.3)	71 (13.1)	151 (13.7)	131 (17.1)	<0.001
RASi/ARNi[a], *n* (%)	0.2	1268 (94.0)	474 (87.6)	995 (90.8)	638 (83.5)	<0.001
Beta-blocker[a], *n* (%)	0.1	1261 (93.3)	487 (90.0)	1030 (93.9)	678 (88.6)	<0.001
MRA[a], *n* (%)	0.1	743 (55.0)	242 (44.7)	517 (47.1)	358 (46.8)	<0.001
Device therapy (CRT/ICD)[a], *n* (%)	0.4	249 (18.5)	79 (14.7)	180 (16.5)	65 (8.6)	<0.001
Diuretic[a], *n* (%)	0.2	946 (70.0)	444 (82.1)	787 (71.8)	639 (83.7)	<0.001
Statin[a], *n* (%)	0.1	691 (51.2)	303 (56.0)	583 (53.1)	449 (58.8)	0.006
Nitrate, *n* (%)[a]	0.2	63 (4.7)	69 (12.8)	112 (10.2)	102 (13.4)	<0.001
Follow-up referral HF nurse-led clinic[a], *n* (%)	2.8	1188 (89.3)	428 (82.9)	971 (89.7)	605 (83.8)	<0.001
Follow-up referral specialty[a], *n* (%)	1.4					<0.001
Hospital		1106 (82.7)	406 (76.3)	865 (79.4)	539 (72.3)	
Primary care		225 (16.8)	117 (22.0)	215 (19.7)	192 (25.8)	
Other		7 (0.5)	9 (1.7)	10 (0.9)	14 (1.9)	
Education[a], *n* (%)	1.7					0.006
Compulsory school		415 (31.3)	213 (39.7)	377 (34.9)	290 (38.5)	
Secondary school		619 (46.7)	223 (41.6)	493 (45.6)	320 (42.5)	
University		292 (22.0)	100 (18.7)	210 (19.4)	143 (19.0)	

A, anaemia; ARNi, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; ID, iron deficiency; IQR, interquartile range; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RASi, renin–angiotensin system inhibitor.
[a]Included in the multiple imputation models and logistic/Cox regressions.

supplementary *Table S2*). Most patients received 1000 mg of FCM (online supplementary *Figure S4*). In particular, of 963 HFrEF patients with ID, 24% received FCM and 47% of them had anaemia, while corresponding proportions were 12% and 71% in HFmrEF, and 15% and 80% in HFpEF (*Graphical Abstract*, online supplementary *Tables S2* and *S10–S12*). Detailed information on geographical distribution of FCM use in Sweden is shown in online supplementary *Figure S2* and *Table S13*.

Baseline characteristics and independent predictors of ferric carboxymaltose use

Patients receiving FCM vs. non receiving FCM were less likely encountered in outpatient care and more likely to have anaemia, diabetes, ischaemic heart disease, HFrEF, and more severe HF (i.e. higher NYHA class, higher NT-proBNP levels and lower blood pressure) (online supplementary *Table S2*). They were also more likely to receive MRAs, diuretics and device therapies.

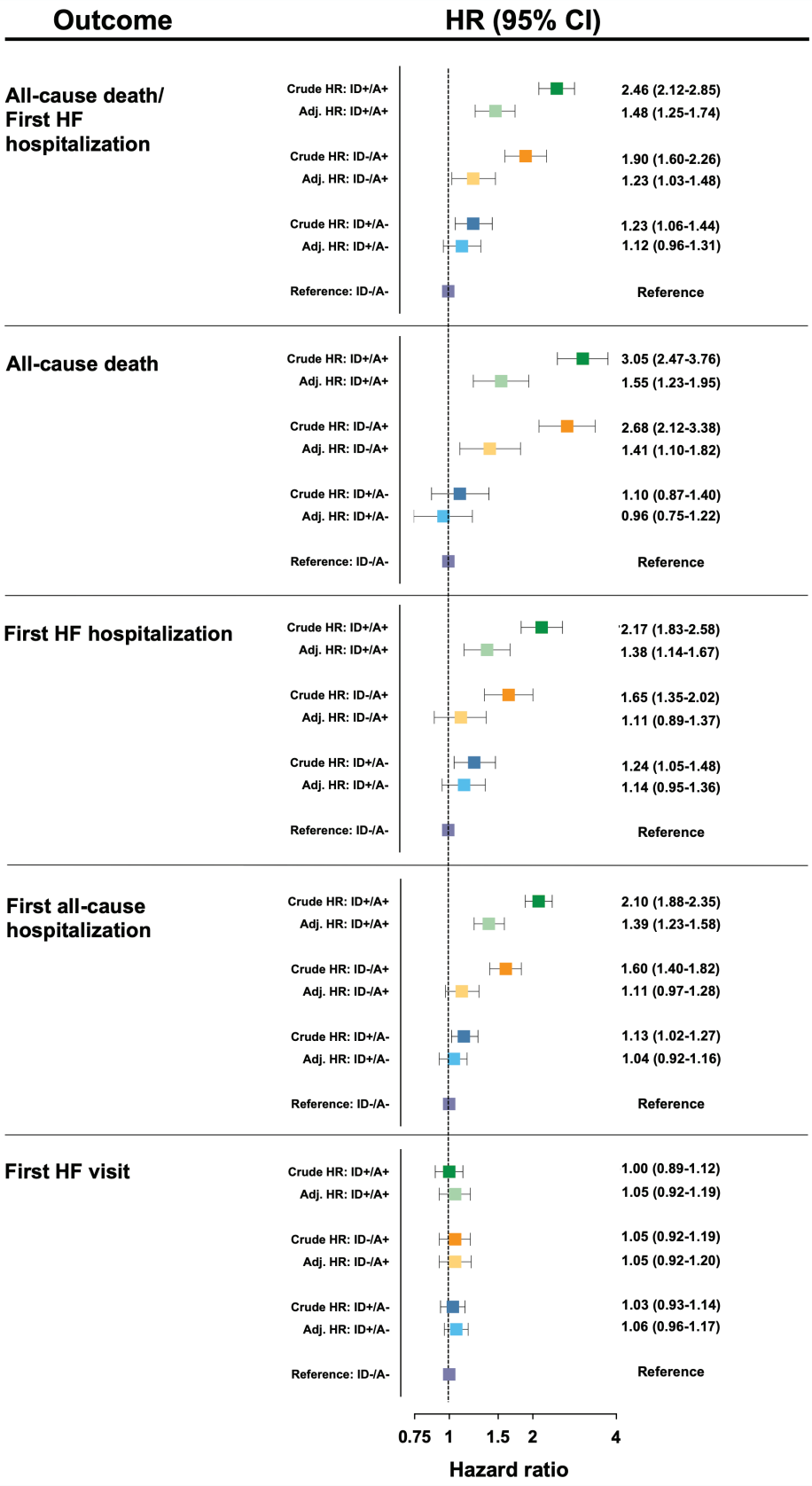


Figure 2 Outcome analysis according to iron deficiency/anaemia (ID/A) status. CI, confidence interval; HF, heart failure; HR, hazard ratio.

Table 3 Outcome analyses according to iron deficiency/anaemia status

Outcome	ID−/A−	ID−/A+	ID+/A−	ID+/A+
All-cause death/first HF hospitalization				
Event rates (*1000 pt-years)	160 (143–178)	312 (272–356)	198 (176–221)	405 (365–448)
Crude HR (95% CI), *P*-value	Reference	1.90 (1.60–2.26), <0.001	1.23 (1.06–1.44), 0.008	2.46 (2.12–2.85), <0.001
Adjusted HR (95% CI), *P*-value	Reference	1.23 (1.03–1.48), 0.024	1.12 (0.96–1.31), 0.160	1.48 (1.25–1.74), <0.001
All-cause death				
Event rates (*1000 pt-years)	62 (53–74)	166 (140–197)	69 (57–82)	190 (166–217)
Crude HR (95% CI), *P*-value	Reference	2.68 (2.12–3.38), <0.001	1.10 (0.87–1.40), 0.433	3.05 (2.47–3.76), <0.001
Adjusted HR (95% CI), *P*-value	Reference	1.41 (1.10–1.82), 0.008	0.96 (0.75–1.22), 0.727	1.55 (1.23–1.95), <0.001
First HF hospitalization				
Event rates (*1000 pt-years)	125 (110–141)	214 (181–251)	156 (137–176)	283 (250–319)
Crude HR (95% CI), *P*-value	Reference	1.65 (1.35–2.02), <0.001	1.24 (1.05–1.48), 0.014	2.17 (1.83–2.58), <0.001
Adjusted HR (95% CI), *P*-value	Reference	1.11 (0.89–1.37), 0.350	1.14 (0.95–1.36), 0.163	1.38 (1.14–1.67), 0.001
HF hospitalizations				
Event rates (*1000 pt-years)	224 (205–244)	339 (300–381)	292 (268–317)	423 (386–461)
Crude IRR (95% CI), *P*-value	Reference	1.72 (1.34–2.22), <0.001	1.30 (1.06–1.60), 0.012	2.12 (1.70–2.65), <0.001
Adjusted IRR (95% CI), *P*-value	Reference	0.98 (0.76–1.25), 0.850	1.16 (0.95–1.42), 0.141	1.37 (1.10–1.72), 0.005
First all-cause hospitalization				
Event rates (*1000 pt-years)	419 (388–452)	701 (629–778)	477 (439–517)	943 (867–1023)
Crude HR (95% CI), *P*-value	Reference	1.60 (1.40–1.82), <0.001	1.13 (1.02–1.27), 0.026	2.10 (1.88–2.35), <0.001
Adjusted HR (95% CI), *P*-value	Reference	1.11 (0.97–1.28), 0.128	1.04 (0.92–1.16), 0.551	1.39 (1.23–1.58), <0.001
All-cause hospitalizations				
Event rates (*1000 pt-years)	677 (644–712)	1228 (1153–1306)	871 (829–915)	1438 (1370–1508)
Crude IRR (95% CI), *P*-value	Reference	1.98 (1.71–2.29), <0.001	1.30 (1.15–1.46), <0.001	2.34 (2.06–2.66), <0.001
Adjusted IRR (95% CI), *P*-value	Reference	1.30 (1.12–1.50), <0.001	1.17 (1.04–1.31), 0.008	1.43 (1.25–1.63), <0.001
First HF visit				
Event rates (*1000 pt-years)	710 (664–759)	753 (674–839)	721 (669–777)	698 (635–766)
Crude HR (95% CI), *P*-value	Reference	1.05 (0.92–1.19), 0.463	1.03 (0.93–1.14), 0.525	1.00 (0.89–1.12), 0.992
Adjusted HR (95% CI), *P*-value	Reference	1.05 (0.92–1.20), 0.473	1.06 (0.96–1.17), 0.278	1.05 (0.92–1.19), 0.480
HF visits				
Event rates (*1000 pt-years)	993 (952–1034)	1050 (982–1123)	1034 (989–1081)	1062 (1004–1122)
Crude IRR (95% CI), *P*-value	Reference	1.09 (0.96–1.25), 0.183	1.06 (0.95–1.17), 0.298	1.10 (0.98–1.24), 0.098
Adjusted IRR (95% CI), *P*-value	Reference	1.04 (0.91–1.18), 0.567	1.08 (0.98–1.19), 0.110	1.04 (0.93–1.17), 0.495

A, anaemia; CI, confidence interval; HF, heart failure; HR, hazard ratio; ID, iron deficiency; IRR, incident rate ratio; pt, patient.

Of all the variables which were tested in our multivariable model, patient characteristics independently associated with FCM use were more severe HF (i.e. higher NYHA class and MRA use), HFrEF vs. HFmrEF vs. HFpEF, lower haemoglobin levels, diabetes, and follow-up to specialty care (*Figure 1*). FCM use did not significantly differ in 2017 vs. 2018 ($P = 0.067$) (*Figure 1*).

Discussion

This analysis from SwedeHF demonstrated six major findings: (i) testing for diagnosing ID was performed only in approximately a quarter of our HF population; (ii) key patient characteristics associated with ID testing were anaemia, HFrEF, more severe HF, and more specialized follow-up; (iii) ID was highly prevalent, i.e. observed in half of the population; (iv) comorbid ID and anaemia were associated with the highest risk of morbidity and mortality, with ID alone associated with higher risk of all-cause hospitalizations; (v) only one out of five patients with an indication received FCM treatment; and (vi) patients receiving FCM had more severe HF and higher burden of comorbidities including anaemia.

Iron deficiency testing and burden of iron deficiency in real-world heart failure

Previous studies report the prevalence of ID in HF ranging between 35% and 43%.[12,13] Consistently, routine evaluation of iron status in HF is recommended by international guidelines.[4]

We observed that ID testing was performed in only about a quarter of the population. Anaemia was among the strongest predictors of ID testing, with the likelihood of being tested increasing with lower haemoglobin levels, which might suggest a diagnostic work-up for anaemia rather than screening for ID in HF, which is both prognostic and treatable regardless of anaemia.[14]

Consistent with other studies, half of our HF population had ID.[15] We found that HF patients who were tested for ID had more symptomatic HF, which might highlight physicians' efforts to identify non-cardiac causes of dyspnoea and, potentially, to consider treatment of ID when diagnosed. Patients who were tested for ID were more likely to receive HF treatments, which might suggest that those receiving optimal care in terms of HF treatments are also more likely tested for ID as part of the HF management. Consistently, ID testing was associated with referral to HF nurse-led clinic, which might be explained by an enhanced multidisciplinary care in these patients and by HF nurse teams administering IV iron treatment as part of the optimization of HF therapy.[16] ID testing was more frequent in an outpatient setting, which is counterintuitive since ID might be more easily treated during a hospitalization for HF when IV iron treatment might further help in the amelioration of HF symptoms. The likelihood of being tested for ID was higher in HFrEF although recommended by guidelines in HF regardless of EF. This might indicate that physicians might be more likely to search for ID in a setting where there is good evidence and clear recommendation for treatment, i.e. FCM use in HFrEF.[4] However, undertesting is not only observed for ID in HF, with natriuretic peptide assessment still limitedly implemented although there is clear evidence for its diagnostic and prognostic role.[17]

In our study, we explored the different profiles of patients with vs. without ID, also stratifying by anaemia status. Importantly, a significant proportion of our population had ID without anaemia (29%), which is consistent with findings from previous studies (32%).[12] Patients with ID+/anaemia− had a profile overall resembling more ID−/anaemia− than ID+/anaemia+ in terms of comorbidity burden and HF severity. In accordance with previous studies, we found that patients with ID+/anaemia− were more likely female, had higher NT-proBNP levels, higher NYHA class, and slightly impaired renal function compared with patients with ID−/anaemia−,[12,18] whereas highest NT-proBNP levels and NYHA class were observed in patients with anaemia regardless of ID, who also reported the highest comorbidity burden.[1,13,19] Consistently with previous studies, we observed the most impaired renal function in patients with anaemia with and without ID,[20–22] with anaemia having been shown in other analyses as an additional marker of severity rather than a causal factor of chronic kidney disease.[23]

Consistent with these differences in patient profiles and in agreement with previous reports, we could show that patients with concomitant anaemia and ID were at highest risk of mortality.[1,24] However, those analyses highlighted higher risk of all-cause death in patients with ID without anaemia and no prognostic role of anaemia in absence of ID, whereas we observed higher mortality with anaemia without ID and no significantly increased risk of all-cause death in those with ID without anaemia.[1,24] These discrepancies might be at least partially explained by selection bias and residual confounding, with patients with anaemia and more advanced HF being more likely to be tested and thus included in the current study compared with those with severe HF but without anaemia. Even if there was a bias in our analysis, we could provide an overall picture of ID/anaemia as appears according to the current practice in ID testing in real-world HF. We also showed that the risk of recurrent all-cause hospitalizations was higher in patients with ID regardless of concomitant anaemia, with similar HRs for recurrent HF hospitalizations although in absence of statistically significance likely due to sample size issues. The finding of increased risk of hospitalizations with ID appears consistent with RCTs showing reductions in cardiovascular/HF hospitalizations without an effect on mortality alone with FCM.[8,9]

Finally, we observed that transferrin saturation <20% vs. ≥20% was associated with higher risk of all investigated outcomes after adjustments for ferritin levels and other patient characteristics, whereas ferritin <100 μg/L vs. ≥100 μg/L was only associated with higher risk of recurrent all-cause hospitalizations and recurrent HF hospitalizations after adjustment for transferrin saturation and other potential confounders. These findings are consistent with previous studies suggesting a worse prognostic role for transferrin saturation <20% regardless of ferritin levels, anaemia, and other comorbidities.[24,25] Consistently, it has been previously shown that an impaired iron transport (transferrin saturation <20%) but not impaired iron storage (ferritin <100 μg/L) is independently associated with increased sympathetic activation, i.e. elevated norepinephrine levels, in patients with chronic HF.[26]

Use of ferric carboxymaltose in real-world care

Pooled data from several RCTs have highlighted a role for IV iron in reducing the combined risk of all-cause death or cardiovascular hospitalization, alleviating HF symptoms, and improving exercise capacity and quality of life.[8] Accordingly,[4,6,8] the European and US guidelines recommend that IV iron treatment should be offered to symptomatic patients with HFrEF and ID, but the class of recommendation varies between IIa and IIb.[4,27] Additionally, beyond impacting outcomes, quality of life and improving symptoms, data from the AFFIRM-AHF trial have shown that treatment with FCM is also highly cost-effective in patients with ID stabilized after a hospitalization for acute HF,[28] which was mainly explained by the reduction in HF hospitalizations.

There are currently scarce data on the use of IV iron treatment in real-world HF, with few studies suggesting limited implementation, i.e. ranging between 3% and 24%.[15] We observed that 19% of our HF population with ID received FCM treatment, more than half of them with concomitant anaemia, and, as expected, use was highest in HFrEF. These data highlight that despite current guideline recommendation, FCM is still underutilized in HF patients in clinical practice. This is also in line with the observed underutilization of several guideline-recommended medications, device therapies and multidisciplinary strategies in HF.[16,29–31] In our analysis, key patient characteristics independently associated with FCM use were more severe HF and a higher burden of comorbidities including anaemia, which might highlight the attempt to reduce symptoms by treating ID. While ID testing use was more common in an outpatient setting, FCM was more likely used in inpatients, which might indicate that although patients are diagnosed with ID, treatment might not occur after ID testing but might be delayed in some cases until an urgent hospitalization due to clinical inertia or

prioritization or logistical issues. Anaemia was not only a major determinant for ID screening, but was also associated with FCM administration. This finding underlines the commonly held belief that treating ID is only needed in the presence or on the basis of the degree of anaemia.

Limitations

Our study has several limitations that should be acknowledged. First, we defined missing values for ID biomarkers as lack of testing. However, some patients might have been tested for ferritin/transferrin saturation levels, but the values could not have been entered in the registry. Second, our data suggest that testing was performed for suspect of anaemia rather than of ID, which might have led to overestimate the prevalence of anaemia and underestimate that of ID. Third, repeated assessment of ferritin/transferrin saturation levels and of FCM use was not available, which prevented to capture later use of FCM during follow-up and to investigate the longitudinal relationship between ferritin/transferrin saturation levels, ID status and treatment with FCM. Forth, in SwedeHF there is no information regarding the indications underlying the prescription of specific medications. Therefore, we could only assume that patients receiving FCM but with normal ferritin/transferrin saturation levels had ID which had been successfully treated with FCM. Finally, SwedeHF is a nationwide continuous registry, but it does not have complete coverage and enrols primarily patients in secondary care. Therefore, selection bias may still represent a limitation, with better treated patients enrolled in our registry, which could have led to overestimate FCM use.[32]

Conclusion

In this nationwide HF registry, ID testing was performed in only about a quarter of the population. ID was highly prevalent, i.e. half of the study cohort, but only one in five patients with ID received FCM treatment. A major determinant for limited testing and treatment of ID was the lack of concomitant anaemia. Consistently, ID testing rates were higher in patients with vs. without anaemia. This highlights the misconception that ID is a treatment target only in the presence of anaemia. Our data indicate low adherence to current guidelines in terms of screening for and treatment of ID in HF patients. Appropriate diagnostic and interventional strategies are needed to improve ID management and overall HF care.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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