CHAPTER 2

IRON DEFICIENCY IN CHRONIC HEART FAILURE
AN INTERNATIONAL POOLED ANALYSIS

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ABSTRACT

Background

Iron deficiency (ID) is an emerging problem in patients with chronic heart failure (HF) and can be a potential therapeutic target. However, not much is known about the prevalence, predictors, and prognosis of ID in patients with chronic HF.

Methods

In an international pooled cohort comprising 1506 patients with chronic HF, we studied the clinical associates of ID and its prognostic consequences.

Results

Iron deficiency (defined as a ferritin level < 100 μg/L or ferritin 100–299 μg/L with a transferrin saturation < 20%) was present in 753 patients (50%). Anemic patients were more often iron deficient than non-anemic patients (61.2% vs 45.6%, P < 0.001). Other independent predictors of ID were higher New York Heart Association class, higher N-terminal pro-brain-type natriuretic peptide levels, lower mean corpuscular volume levels, and female sex (all P < 0.05). During follow-up (median 1.92 years, interquartile range 1.18–3.26 years), 440 patients died (29.2%). Kaplan-Meier survival analysis revealed ID as a strong predictor for mortality (log rank $\chi(2)$ 10.2, P = 0.001). In multivariable hazard models, ID (but not anemia) remained a strong and independent predictor of mortality (hazard ratio 1.42, 95% confidence interval 1.14–1.77, P = 0.002). Finally, the presence of ID significantly enhanced risk classification and integrated discrimination improvement when added to a prediction model with established risk factors.

Conclusions

Iron deficiency is common in patients with chronic HF, relates to disease severity, and is a strong and independent predictor of outcome. In this study, ID appears to have greater predictive power than anemia.

ABBREVIATIONS

HF	=	Heart failure
hs-CRP	=	high-sensitive C-reactive protein
ID	=	Iron deficiency
LVEF	=	Left ventricular ejection fraction
NT-proBNP	=	N-terminal pro-brain-type natriuretic peptide
NYHA	=	New York Heart Association
TSAT	=	Transferrin saturation

INTRODUCTION

Despite improvements in chronic heart failure (HF) treatment over the years, normal daily activities of many patients remain restricted.1 Anemia, a common comorbidity in HF, is associated with increased disease severity and may contribute to a worse outcome.2-5 Thee mechanism through which anemia contributes to adverse outcome in chronic HF patients is complex and multifactorial.6 Important factors include renal failure, bone marrow resistance to erythropoietin, chronic inflammation, medication use and hematinic deficiencies, in particular iron deficiency (ID).7-9

Traditionally, the presence of ID is only considered clinically relevant in the presence of anemia. However, a reduced hemoglobin levels can be viewed as the end result of a process beginning with gradual depletion of iron stores.10,11 Even if patients are not anemic, ID may already be common in chronic HF.12,13 Iron deficiency, with or without anemia, is associated with decreased aerobic performance and exercise intolerance,14 recently also shown in chronic HF.15

In recent years, a number of studies have shown that correction of ID through intravenous iron supplementation in patients with chronic HF may improve functional status and quality of life.16-21 This was observed in both anemic and nonanemic patients with chronic HF, shifting the focus for anemia in HF away from hemoglobin and toward iron.20 The prevalence and potential importance of ID per se, irrespective of hemoglobin, are currently a subject of interest in HF. However, data on this topic are scarce and only a few studies have reported on ID as a predictor of outcome in chronic HF.13,22,23 These studies show conflicting data regarding the prognostic value of ID with or without anemia. Therefore, the current study was initiated by a European iron consortium to investigate the prevalence, clinical determinants, and prognostic significance of ID in a large international pooled cohort of 1506 chronic HF patients.

METHODS

Component studies

This study population consists of patients from 5 cohorts from Poland, Spain and The Netherlands, comprising 1506 chronic HF patients with reduced or preserved left ventricular ejection fraction (LVEF). Preserved left ventricular systolic function was defined as LVEF ≥ 45%, as proposed in previous studies.24,25 For inclusion and exclusion criteria per participating study cohort,

see *Supplementary Table 1*. Four hundred seventy-four chronic stable HF patients with reduced or preserved ejection fraction, referred to the outpatient HF unit, were included from the Spanish cohort.26 Two cohorts from Poland comprised 735 stable patients with chronic HF and reduced LVEF, attending outpatient clinics or admitted electively to 2 tertiary referral cardiology centers.13,15 Finally, 2 Dutch patient cohorts comprising 297 stable chronic HF patients with reduced or preserved LVEF were included in the present analysis.27,28 All study protocols were approved by local ethics committees, and all patients gave separate written informed consent, for the present study. The study was conducted in accordance with the Declaration of Helsinki.

Pooled methodology

The pooled data in the present study were assessed at a patient level. The 5 cohorts selected for analysis all had comparable clinical information available, including demographics, New York Heart Association (NYHA) classification, current medical therapy, physical examination, plasma and serum biochemistry results, and LVEF (assessed via echocardiography or radionuclide ventriculography). No patient received blood transfusions, erythropoietin therapy, or intravenous iron therapy at the time of inclusion. Vital status was determined via direct contact with patients or relatives or review of chronic HF clinical databases or hospital records. No patient was lost to follow-up, and none received left ventricular assist device therapy during follow-up. The end point for the present study was all-cause mortality. Follow-up for survivors with events was censored when < 5% of the cohort was at risk (after 8 years).

Iron status and other laboratory measurements

Peripheral venous blood samples were collected from all patients. Hematologic indices were assessed from fresh venous blood using EDTA. After centrifugation, the remainder was frozen and stored before analysis. Anemia was defined as a hemoglobin level < 12 g/dL in women and < 13 g/dL in men.29 The following blood biomarkers reflecting iron status were measured: ferritin (ug/L), serum iron (umol/L), total iron binding capacity (ug/L), and transferrin (g/L). Transferrin measurements were available for most patients (n = 1202). Transferrin saturation (TSAT) was reported as serum iron/(25.2 x transferrin), multiplied by 100. When transferrin was not available (n = 304), TSAT was reported as a ratio of serum iron (ug/L) and total iron- binding capacity (ug/L) multiplied by 100.30 There was a strong correlation between both TSAT measurements (R2 = 0.89, P <

0.001). Iron deficiency was defined as a ferritin level < 100 µg/L or serum ferritin 100 to 299 µg/L in combination with a TSAT < 20%. Similar definitions of ID have been used in recent observational and intervention trials in chronic HF.[13,15–20,25,30] Concentrations of N-terminal pro-brain-type natriuretic peptide (NT-proBNP) (pg/mL) were measured using an immunoassay based on electrochemiluminescence on the Elecsys System (Roche Diagnostics, Basel, Switzerland). Renal function was assessed estimating glomerular filtration rate (eGFR) (mL/ min/1.73 m2) using the abbreviated Modification of Diet in Renal Disease equation. Serum concentrations of high-sensitive C-reactive protein (hs-CRP) (mg/L) were assessed at each institution using standard methods. High-sensitive C-reactive protein was not measured in the Spanish cohort.

Statistical analyses

Data are expressed as means ± SD when normally distributed, as medians with lower and upper quartiles when non-normally distributed or as numbers and percentages when categorical. Intergroup differences were tested using the Student t-test, one-way analysis of variance test, Kruskal-Wallis test, Mann-Whitney U test, or Pearson $\chi 2$ test when appropriate. For further analyses, logarithmic transformation was performed to achieve a normal distribution for skewed variables (NT-proBNP and hs-CRP).

To establish clinical determinants of ID, multiple logistic regression models were constructed. Variables with a significant univariable association with ID ($P < 0.10$) were entered in a stepwise backward multivariate model based on the strength of their univariable association. Additional bootstrap analysis (1000 cycles) of the multivariate model was performed to measure accuracy of the estimated model. Variables selected > 700 times were assumed to be accurate. Kaplan-Meier curves were constructed to demonstrate the effect of ID on cumulative survival. Differences in event-free survival rates were tested using the Cox-Mantel log-rank test. Univariable and multivariate Cox proportional hazard regression models were used to calculate the predictive value of ID and anemia for all-cause mortality. The proportionality assumption for the Cox regression analysis was evaluated using Schoenfeld residuals and was proven to hold ($\chi 2$ 18.04, $P = 0.261$). In 2 consecutive multivariable models, both ID and anemia were adjusted for age, sex, eGFR, NT-proBNP levels, and finally for all significant univariable variables. Furthermore, we analysed the relationship between ID and mortality in patients with and without anemia.

Finally, risk stratification improvement of ID on top of established clinical risk factors was tested using net reclassification improvement and inte-

grated discrimination improvement.31 Clinical risk factors included age, sex, diabetes, NYHA functional class, eGFR, levels of NT-proBNP and hs-CRP, and the presence of anemia. We used risk categories of < 5%, 5 – 10%, 10 – 20%, and > 20%. All tests were 2 sided, and a *P* value < 0.05 was considered statistically significant. All statistical analyses were performed using STATA version 11.0 (StataCorp LP, College Station, TX).

RESULTS

Baseline characteristics

Baseline patient characteristics for all 1506 patients are shown in *Table 1.* Iron deficiency was present in 753 patients (50%). Anemia was present in 426 patients (28.3%). Patients with anemia were more often iron deficient compared to nonanemic patients (61.2% vs. 45.6%, respectively, *P* < 0.001). Patients with both ID and anemia were older and had a higher NYHA class, more comorbidities, and higher biomarker levels compared with patients with ID and no anemia (*Supplementary Table 2*). Stratification by NYHA functional class revealed that both anemia and ID increased with higher NYHA class (*Figure 1*). Characteristics stratified per participating cohort were also described (*Supplementary Table 3*).

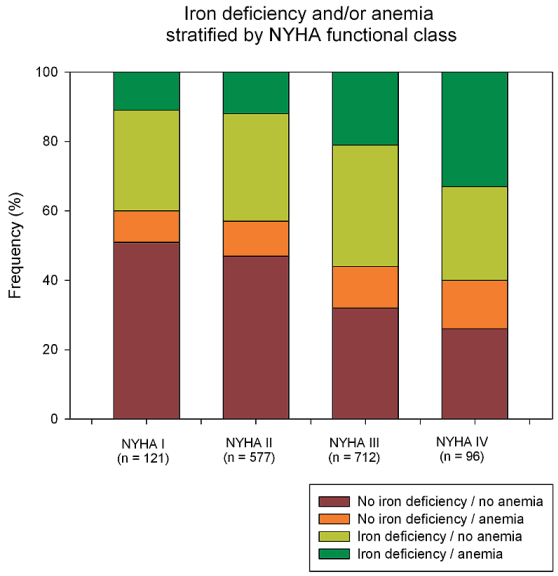


Figure 1. Prevalence of iron deficiency and and/or stratified by NYHA functional class.

Table 1. Baseline characteristics.

Variables	All patients n = 1506	Chronic HF and no ID n = 753	Chronic HF and ID* n = 753	P - value
Age (y)	64 ± 13	62 ± 13	67 ± 13	< 0.001
Women (%)	26	20	32	< 0.001
BMI (kg/m2)	27.5 ± 4.8	27.6 ± 4.7	27.4 ± 4.9	0.531
Ischemic cause	60	60	61	0.712
LVEF (%)	33 ± 14	32 ± 13	34 ± 14	0.008
HFrEF	87	89	84	0.003
NYHA functional class (%)				< 0.001
I/II	46	53	39	
III	47	42	53	
IV	7	5	8	
Comorbidities (%)				
Anemia†	28	22	35	< 0.001
Diabetes mellitus	35	32	37	0.040
AF	20	18	21	0.052
Hypertension	20	19	21	0.124
Laboratory				
Hb (g/dL)	13.6 ± 1.8	13.9 ± 1.8	13.2 ± 1.8	< 0.001
MCV (fL)‡	90.9 ± 5.9	91.8 ± 5.8	89.8 ± 5.8	< 0.001
Iron (µg/L)	73 (49–105)	96 (74–127)	54 (38–72)	NA
Ferritin (µg/L)	154 (82–280)	272 (165–415)	82 (53–137)	NA
TSAT (%)	22 (15–32)	30 (23–40)	15 (11–19)	NA
NT-proBNP (pg/mL)	1395 (550–3572)	1226 (525–3084)	1553 (595–4083)	< 0.001
hs-CRP (mg/L)§	2.9 (1.3–6.9)	2.4 (1.2–5.8)	3.2 (1.4–8.0)	< 0.001
eGFR (mL/min/1.73m2)	79.9 ± 33.8	80.6 ± 31.9	79.1 ± 35.6	0.484
Treatment (%)				
ACE inhibitor and/or ARB	91	93	89	0.005
β-Blocker	90	92	88	0.010
Loop diuretic	79	75	83	< 0.001
Statin	64	66	62	0.068
Aldosterone antagonist	48	51	44	0.002
Antiplatelet and/or anticoagulant	84	84	84	0.833

Values are means ± standard deviation, medians (interquartile range) or proportions (%).
*ID was defined as ferritin < 100 µg/L or 100–299 µg/L with a TSAT < 20%.
† Anemia was defined as hemoglobin < 12 g/dL in women and < 13 g/dL in men.
‡ MCV was measured in 596 non-iron deficient and 527 iron deficient patients.
§ hs-CRP was measured in 549 non-iron deficient and 451 iron deficient patients.
ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HFrEF = heart failure with reduced ejection fraction; hs-CRP = high-sensitive C-reactive protein; ID = Iron deficiency; LVEF = left ventricular ejection fraction; MCV = mean corpuscular volume; NA = not applicable; NT-proBNP = N-terminal pro-brain-type natriuretic peptide; NYHA = New York Heart Association; RDW = red blood cell distribution width; TSAT = transferrin saturation.

Clinical predictors of iron deficiency

The univariable logistic regression model is shown in *Table 2.* When combined in a stepwise backward multivariable logistic regression model, only female sex, higher NYHA class, lower mean corpuscular volume, higher NT-proBNP levels and anemia remained independent predictors of ID in chronic HF patients. In additional bootstrap analysis, these 5 parameters remained highly selected. Moreover, there was no significant association between ID and treatment with antiplatelet drugs, anticoagulants, or other medication.

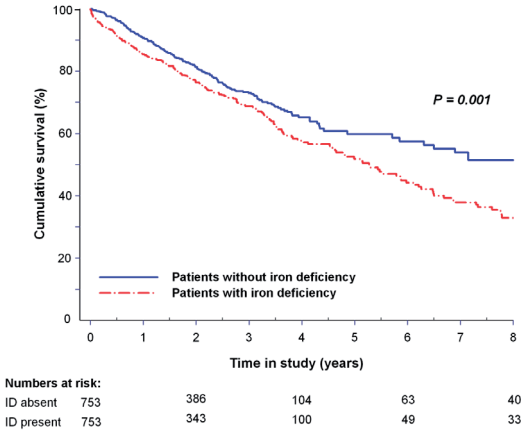
Table 2. Clinical variables associated with iron deficiency in chronic heart failure.

Variables	Univariable OR (95% CI)	P-value	Multivariable OR (95% CI)	P-value
Age, per 5 year	1.16 (1.12–1.21)	< 0.001		
Female vs. male	1.85 (1.45–2.35)	< 0.001	1.67 (1.17–2.31)	0.005
Ischemic cause, yes vs. no	0.96 (0.78–1.19)	0.723		
BMI, per 1 kg/m2	1.00 (0.98–1.02)	0.831		
LVEF, per 1%	1.01 (1.00–1.02)	0.005		
NYHA functional class				
III vs I/II	1.73 (1.41–2.14)	< 0.001	1.61 (1.25–2.11)	< 0.001
IV vs I/II	2.07 (1.34–3.20)	< 0.001	1.80 (1.02–3.20)	0.022
Comorbidities				
Anemia, yes vs. no	2.06 (1.63–2.61)	< 0.001	1.68 (1.20–2.38)	0.033
Diabetes, yes vs. no	1.27 (1.02–1.58)	0.030		
AF, yes vs. no	1.36 (1.06–1.77)	0.017		
Hypertension, yes vs. no	1.12 (0.91–1.38)	0.290		
Laboratory				
MCV, per 1 fL	0.99 (0.98–0.99)	0.001	0.99 (0.98–0.99)	< 0.001
NT-proBNP, per 1 log pg/mL	1.21 (1.12–1.32)	< 0.001	1.15 (1.05–1.34)	0.010
hs-CRP, per 1 log mg/L	1.24 (1.12–1.39)	0.001		
eGFR, per 5 mL/min/1.73 m2	1.00 (0.99–1.01)	0.422		
Treatment				
ACE inhibitor and/or ARB, yes vs. no	0.57 (0.40–0.83)	0.003		
Beta blocker, yes vs. no	0.60 (0.42–0.85)	0.004		
Loop diuretic, yes vs. no	1.94 (1.47–2.55)	< 0.001		
Statins, yes vs. no	0.82 (0.67–1.02)	0.068		
Aldosterone antagonist, yes vs. no	0.73 (0.59–0.89)	0.002		
Antiplatelet and/or anticoagulant, yes vs. no	0.97 (0.73–1.29)	0.837		

Values are odds ratios ± 95% confidence intervals. Iron deficiency was defined as a ferritin level < 100 µg/L or 100–299 µg/L with a TSAT < 20%. *Anemia was defined as hemoglobin < 12 g/dL in women and < 13 g/dL in men. †MCV was measured in 596 non-iron deficient and 527 iron deficiency patients. ‡ hs-CRP was measured in 549 non-iron deficient and 451 iron deficient patients.

Iron deficiency and prognosis in chronic heart failure

During a mean follow-up of 2.52 ± 2.05 years (median 1.92 years, interquartile range 1.18 – 3.26 years), 440 patients (29.2%) died. No significant association was observed between participating study cohort and outcome (P = 0.784). Similarly, no significant interaction was seen between ID or anemia and study cohort (P = 0.616 and 0.184, respectively). After 6 months of follow-up, mortality rates between people with and without ID already



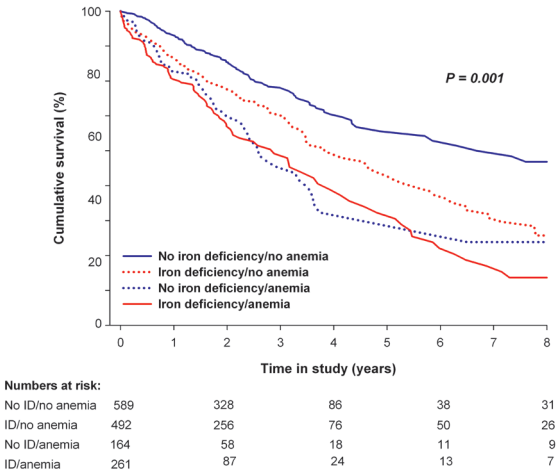


Figure 2. Kaplan-Meier curves reflecting the difference in event-free survival rates in chronic heart failure patients with or without iron deficiency (ID) (A) and between iron deficient and non-iron deficient patients with or without anemia (B).

differed significantly (8.7% vs. 3.6% respectively, *P* < 0.001). Differences remained statistically significant for the duration of follow-up. Differences in event-free 8-year survival between different patient groups are shown in *Figure 2.* Increased mortality was observed in patients with ID versus without ID (P = 0.001). Similarly, increased mortality was observed in patients with both ID and anemia versus iron-deficient patients without anemia (*P* < 0.001).

In consecutive multivariable Cox regression models, ID - but not anemia - remained an independent predictor for mortality (hazard ratio [HR] 1.42, 95% CI 1.14 – 1.77,P = 0.002), even after adjustment for all univariable associated variables (*Table 3*). Multivariable hazard analyses of ID among specific clinical and comorbid subgroups of chronic HF patients are described in *Figure 3*. Iron deficiency had more prognostic power in patients with

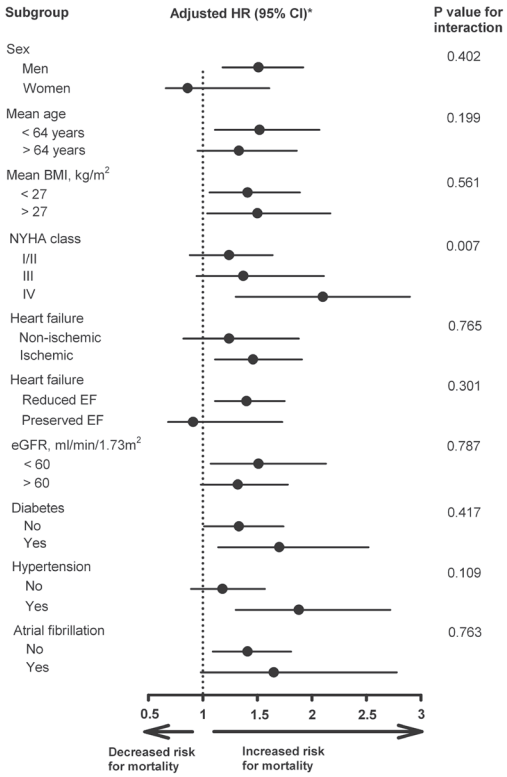


Figure 3. Prognosis of iron deficiency among specific subgroups in heart failure.
*Adjusted for all univariable associated variables.
Abbreviations: BMI = Body mass index; EF = Ejection fraction; eGFR = estimated glomerular filtration rate; HR = Hazard ratio; NYHA = New York Heart Association.

more advanced HF (based on NYHA class) and had a trend toward worse outcome in men, younger patients, ischemic HF, HF with reduced ejection fraction, and patients with a decreased eGFR (b60 mL/min/1.73 m2). Finally, we investigated the predictive value of ID for mortality in patients with or without anemia (*Figure 4*). No significant interaction was observed between ID and anemia (P = 0.841). Iron deficiency remained an independent predictor of mortality in anemic (HR 1.71, 95% CI1.24 – 2.36, P = 0.001) and nonanemic patients (HR 1.44, 95% CI 1.11 – 1.87, P = 0.006).

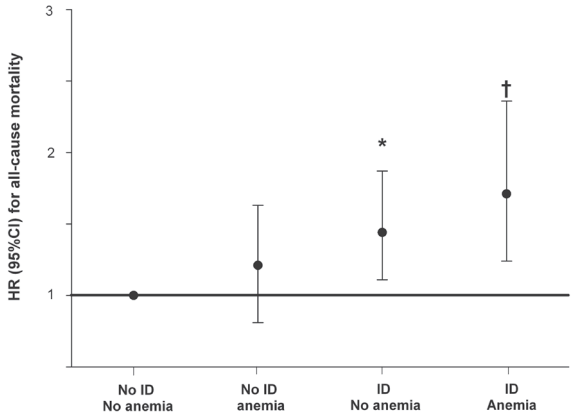


Figure 4. Mortality among groups of iron deficiency (ID) with or without anemia.
* *P* < 0.01. † *P* < 0.001

Additive prognostic value of iron deficiency

Deceased and alive patients were classified separately into low (< 5%), intermediate (5 – 10%, 10 – 20%), or high risk (> 20%) categories for mortality. The net improvement in reclassification was estimated at 0.071 (*P* < 0.001) after the presence of ID was added to the prediction model. The integrated discrimination improvement was estimated at 0.008 (P = 0.003).

DISCUSSION

In a large international pooled cohort of diverse chronic HF patients, we demonstrated that ID is common, affecting half the study population. Secondly, ID was closely related to disease severity, assessed using NYHA functional class and NT-proBNP levels. Thirdly, our findings demonstrate that ID identifies those with an enhanced risk for death, independently of other well- established predictors of outcome, including anemia. The pres-

Table 3. Cox proportional hazard analysis for the presence of iron deficiency in predicting mortality.

Variable	HR (95% CI)	Harrell's C-statistic	P-value
Iron deficiency			
Univariable	1.39 (1.13–1.64)	0.563	0.001
Model 1	1.30 (1.08–1.58)	0.603	0.008
Model 2	1.32 (1.09–1.61)	0.714	0.005
Model 3	1.42 (1.14–1.77)	0.722	0.002
Anemia			
Univariable	1.86 (1.56–2.28)	0.568	< 0.001
Model 1	1.76 (1.43–2.16)	0.602	0.001
Model 2	1.31 (1.07–1.62)	0.708	0.011
Model 3	1.21 (0.94–1.55)	0.722	0.131

Model 1 is adjusted for age, sex and study cohort.
Model 2 is adjusted for model 1 + eGFR and NT-proBNP.
Model 3 is adjusted for model 2 + all univariate significant variables (age, sex, BMI, diabetes, NYHA functional class, LVEF, renal function, levels of hs-CRP and NT-proBNP, treatment with ACE inhibitor and/or ARB, statins, loop diuretics and the presence of anemia or ID)

ent study also shows that the presence of ID adds significant prognostic information on top of established clinical risk factors.

Pathophysiology of ID in chronic HF

It was recently shown that patients with chronic HF are more susceptible to become iron deficient. This could be explained by gradual depletion of iron stores,(absolute ID) due to low iron intake, gastrointestinal blood loss, or iron malabsorption.32 Chronic inflammation, commonly observed in chronic HF, may also play a role. Inflammation causes reduced iron absorption and availability of iron recycled in the reticuloendothelial system (functional ID).33–35 Therefore, functional ID may occur despite adequate iron stores, whereas iron stores are depleted in absolute ID.

Prevalence and definition of ID

In recent years, the prevalence and prognosis of ID in chronic HF have received greater attention. Despite this, there is no standard definition of ID in chronic HF, leading to a wide variation in reported prevalence. Opasich *et al* reported that among 148 patients with chronic HF and anemia, impaired iron supply was the cause in nearly all patients with anemia of chronic disease.36 In an observational trial by Jankowska *et al,* ID was present in 37% of all systolic chronic HF patients.13 In another recent study, Parikh *et al* reported a prevalence of 61% among community-dwelling HF patients.23 Serum iron markers, however, may be inadequate to detect decreased iron status. Only

1 study conducted by Nanas et al, used the criterion standard of bone marrow iron staining to determine the prevalence of ID in patients with chronic HF.37 They found that 73% of patients with advanced HF and anemia had depleted iron stores. Nonetheless, the criteria most commonly used for detecting ID in chronic HF are a ferritin level < 100 µg/L or ferritin 100 to 299 µg/L in combination with a TSAT < 20%.[13,15 - 20,25,30] Using this definition, we demonstrated that the prevalence of ID in this large cohort was 50%. There was also a significant difference in the prevalence of ID between anemic and nonanemic patients (61.2% vs. 45.6%, *P* < 0.001).

Predictors of iron deficiency

In the present study, several clinical characteristics were associated with ID. Disease severity, assessed by NYHA functional class and NT-proBNP levels, proved to be powerful and independent predictors of a disordered iron status. Recent studies by Okonko *et al* and Jankowska *et al* also found NYHA class and NT-proBNP levels to be independent and inverse predictors of impaired iron status.[13,21] Besides NYHA functional class, other variables that were associated with ID were female sex, lower mean corpuscular volume, and anemia. The association between ID and female sex has been reported in other studies.[38,39] Another important and similar observation from both this study and the study by Okonko *et al* was lack of a significant relationship between ID and the use of antiplatelet and/or anticoagulant drugs or other medication.22 In contrast with the presence of anemia, which has been associated with angiotensin-converting enzyme inhibitors in chronic HF,7 such an association was not observed for ID in this study.

Iron deficiency and survival

Only a few studies have reported on ID as an outcome predictor in chronic HF, and available data are conflicting. Jankowska *et al* examined 546 patients with mild to severe systolic chronic HF.13 In both univariable and multivariable analyses, ID - but not anemia - was an independent predictor of all-cause mortality or heart transplantation. Okonko *et al* identified ID as a predictor of elevated mortality in 157 chronic HF patients, independent of hemoglobin level.22 In contrast, Parikh *et al* found that ID was not associated with all-cause or cardiovascular mortality in 574 patients with self-reported HF.23 However, Parikh *et al* did not assess disease severity using NYHA functional class or NT-proBNP levels.

In this study, ID is a strong predictor for mortality, independently of other well-established outcome predictors including anemia. Even in non-anemic patients, ID still predicts outcome, whereas the presence of anemia

in patients without ID does not. Over the years, anemia has been associated with an adverse outcome in patients with chronic HF. The mechanism by which anemia contributes to an adverse outcome in these patients is complex and multifactorial.6 It is unknown whether it is anemia that contributes to adverse prognosis or whether one of the factors contributing factors to anemia, such as inflammation, also contributes to adverse outcome.40

Study limitations

First, only data from a single measurement in time were available, so the present study cannot comment on the effects of changes in iron status or hemoglobin levels over time. More studies with serial measurements of iron indices over time are warranted. Second, patient volume status was not assessed. Therefore, this study cannot comment on hemodilution as a possible cause of anemia in patients without ID. Westenbrink *et al* reported that anemic patients without ID had higher extracellular volumes compared with nonanemic patients.9 In addition, higher extracellular volume was an independent predictor of lower hemoglobin levels. Third, this study had no follow- up information regarding treatment of deficiencies or device therapy (except for left ventricular assist device therapy). In addition, no information on hospitalizations (cardiovascular/HF), heart transplantation, or cause of death was available for the present analysis. Parikh *et al* found that TSAT was associated with cardiovascular mortality and all-cause mortality in age- and sex-adjusted hazard analysis.23 However, this association was not significant in multivariate analysis. Nonetheless, more studies on ID and cardiovascular or HF outcome are warranted.

Finally, there is no clear-cut definition of ID in chronic HF, and using the criterion standard of bone marrow iron staining in all patients with suspected ID is unfeasible. As a result, most studies rely on serum markers reflecting a disordered iron status. In this study, we defined ID as a serum ferritin level < 100 µg/L or serum ferritin 100 to 299 µg/L in combination with a TSAT < 20%. This definition is based on nephrological studies and Kidney Disease Outcomes Quality Initiative guidelines.41,42 Like chronic kidney disease, patients with chronic HF present with a generalized inflammatory status and the activation and production of inflammatory cytokines and acute phase proteins, such as ferritin. Therefore, it may be better to use a higher cut-off to define absolute ID (serum ferritin < 100 µg/L) in chronic HF and distinguish it from functional ID (an increased ferritin level, usually between 100 and 299 µg/L, with a TSAT < 20%; a reduced TSAT better reflects depleted iron stores in this situation).41-43 More studies are needed to identify potential new or additional serum markers reflecting iron status with comparison with the criterion standard of bone marrow iron staining.

CONCLUSIONS

Iron deficiency is an emerging problem in chronic HF, affecting half of the patients. A decreased iron status is associated with disease severity (assessed by NYHA functional class and NT-proBNP levels), the presence of anemia and female sex. In this large international pooled cohort, ID is a strong and independent predictor of outcome. Finally, inclusion of ID provides additive prognostic value when added to a prediction model with established risk factors.

REFERENCES

1. Jessup M, Brozena S. Heart failure. *N Engl J Med* 2003;348:2007–2018.
2. Ghali JK. Anemia and heart failure. *Curr Opin Cardiol* 2009;24:172–178.
3. Groenveld HF, Januzzi JL, Damman K, van Wijngaarden J, Hillege HL, van Veldhuisen DJ, van der Meer P. Anemia and mortality in heart failure patients a systematic review and meta-analysis. *J Am Coll Cardiol* 2008;52:818–827.
4. Silverberg DS, Wexler D, Iaina A, Schwartz D. The role of correction of anaemia in patients with congestive heart failure: a short review. *Eur J Heart Fail* 2008;10:819–823.
5. von Haehling S, van Veldhuisen DJ, Roughton M, Babalis D, de Boer RA, Coats AJ, Manzano L, Flather M, Anker SD. Anaemia among patients with heart failure and preserved or reduced ejection fraction: results from the SENIORS study. *Eur J Heart Fail* 2011;13:656–663.
6. van der Meer P, van Veldhuisen DJ. Anaemia and renal dysfunction in chronic heart failure. *Heart* 2009;95:1808–1812.
7. van der Meer P, Lipsic E, Westenbrink BD, van de Wal RM, Schoemaker RG, Vellenga E, van Veldhuisen DJ, Voors AA, van Gilst WH. Levels of hematopoiesis inhibitor N-acetyl-seryl-aspartyl-lysyl-proline partially explain the occurrence of anemia in heart failure. *Circulation* 2005;112:1743–1747.
8. van Veldhuisen DJ, Anker SD, Ponikowski P, Macdougall IC. Anemia and iron deficiency in heart failure: mechanisms and therapeutic approaches. *Nat Rev Cardiol* 2011;
9. Westenbrink BD, Visser FW, Voors AA, Smilde TD, Lipsic E, Navis G, Hillege HL, van Gilst WH, van Veldhuisen DJ. Anaemia in chronic heart failure is not only related to impaired renal perfusion and blunted erythropoietin production, but to fluid retention as well. *Eur Heart J* 2007;28:166–171.
10. Beard JL. Iron biology in immune function, muscle metabolism and neuronal functioning. *J Nutr* 2001;131:568S-579S; discussion 580S.
11. Fairbanks V BE. Iron deficiency. In: Beutler E, ed. *Williams hematology.* 6th ed. New York: McGraw-Hill; 2001. p. 1941.
12. Besarab A, Horl WH, Silverberg D. Iron metabolism, iron deficiency, thrombocytosis, and the cardiorenal anemia syndrome. *Oncologist* 2009;14 Suppl 1:22–33.
13. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, Banasiak W, Polonski L, Filippatos G, McMurray JJ, Anker SD, Ponikowski P. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010;31:1872–1880.
14. Haas JD, Brownlie T,4th. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr* 2001;131:676S-688S; discussion 688S-690S.
15. Jankowska EA, Rozentryt P, Witkowska A, Nowak J, Hartmann O, Ponikowska B, Borodulin-Nadzieja L, von Haehling S, Doehner W, Banasiak W, Polonski L, Filippatos G, Anker SD, Ponikowski P. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. *J Card Fail* 2011;17:899–906.
16. Bolger AP, Bartlett FR, Penston HS, O'Leary J, Pollock N, Kaprielian R, Chapman CM. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol* 2006;48:1225–1227.
17. Toblli JE, Lombrana A, Duarte P, Di Gennaro F. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic

patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol* 2007;50:1657–1665.

18. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, Missouris CG, Poole-Wilson PA, Anker SD, Ponikowski P. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol* 2008;51:103–112.
19. Usmanov RI, Zueva EB, Silverberg DS, Shaked M. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. *J Nephrol* 2008;21:236–242.
20. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, Luscher TF, Bart B, Banasiak W, Niegowska J, Kirwan BA, Mori C, von Eisenhart Rothe B, Pocock SJ, Poole-Wilson PA, Ponikowski P, FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;361:2436–2448.
21. Comin-Colet J, Lainscak M, Dickstein K, Filippatos GS, Johnson P, Luscher TF, Mori C, Willenheimer R, Ponikowski P, Anker SD. The effect of intravenous ferric carboxymaltose on health-related quality of life in patients with chronic heart failure and iron deficiency: a subanalysis of the FAIR-HF study. *Eur Heart J* 2013;34:30–38.
22. Okonko DO, Mandal AK, Missouris CG, Poole-Wilson PA. Disordered iron homeostasis in chronic heart failure: prevalence, predictors, and relation to anemia, exercise capacity, and survival. *J Am Coll Cardiol* 2011;58:1241–1251.
23. Parikh A, Natarajan S, Lipsitz SR, Katz SD. Iron deficiency in community-dwelling US adults with self-reported heart failure in the National Health and Nutrition Examination Survey III: prevalence and associations with anemia and inflammation. *Circ Heart Fail* 2011;4:599–606.
24. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;14:803–869.
25. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J, CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet* 2003;362:777–781.
26. Comin-Colet J, Enjuanes C, Gonzalez G, Torrens A, Cladellas M, Merono O, Ribas

N, Ruiz S, Gomez M, Verdu JM, Bruguera J. Iron deficiency is a key determinant of health-related quality of life in patients with chronic heart failure regardless of anaemia status. *Eur J Heart Fail* 2013;

27. Hartog JW, Willemsen S, van Veldhuisen DJ, Posma JL, van Wijk LM, Hummel YM, Hillege HL, Voors AA, BENEFICIAL investigators. Effects of alagebrium, an advanced glycation endproduct breaker, on exercise tolerance and cardiac function in patients with chronic heart failure. *Eur J Heart Fail* 2011;13:899–908.
28. Bruggink-Andre de la Porte PW, Lok DJ, van Wijngaarden J, Cornel JH, Pruijsers-Lamers D, van Veldhuisen DJ, Hoes AW. Heart failure programmes in countries with a primary care-based health care system. Are additional trials necessary? Design of the DEAL-HF study. *Eur J Heart Fail* 2005;7:910–920.
29. Nutritional anaemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser* 1968;405:5–37.
30. Beilby J, Olynyk J, Ching S, Prins A, Swanson N, Reed W, Harley H, Garcia-Webb P. Transferrin index: an alternative method for calculating the iron saturation of transferrin. *Clin Chem* 1992;38:2078–2081.
31. Pencina MJ, D'Agostino RB S, Steyerberg EW. Extensions of net reclassification improvement calculations to measure usefulness of new biomarkers. *Stat Med* 2011;30:11–21.
32. Alexandrakis MG, Tsirakis G. Anemia in heart failure patients. *ISRN Hematol* 2012;2012:246915.
33. Weiss G. Iron metabolism in the anemia of chronic disease. *Biochim Biophys Acta* 2009;1790:682–693.
34. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011–1023.
35. Balla J, Jeney V, Varga Z, Komodi E, Nagy E, Balla G. Iron homeostasis in chronic inflammation. *Acta Physiol Hung* 2007;94:95–106.
36. Opasich C, Cazzola M, Scelsi L, De Feo S, Bosimini E, Lagioia R, Febo O, Ferrari R, Fucili A, Moratti R, Tramarin R, Tavazzi L. Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. *Eur Heart J* 2005;26:2232–2237.
37. Nanas JN, Matsouka C, Karageorgopoulos D, Leonti A, Tsolakis E, Drakos SG, Tsagalou EP, Maroulidis GD, Alexopoulos GP, Kanakakis JE, Anastasiou-Nana MI. Etiology of anemia in patients with advanced heart failure. *J Am Coll Cardiol* 2006;48:2485–2489.
38. Cook JD, Finch CA, Smith NJ. Evaluation of the iron status of a population. *Blood* 1976;48:449–455.
39. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL. Prevalence of iron deficiency in the United States. *JAMA* 1997;277:973–976.
40. Kleijn L, Belonje AM, Voors AA, De Boer RA, Jaarsma T, Ghosh S, Kim J, Hillege HL, Van Gilst WH, van Veldhuisen DJ, van der Meer P. Inflammation and anaemia in a broad spectrum of patients with heart failure. *Heart* 2012;98:1237–1241.
41. Kalantar-Zadeh K, Kalantar-Zadeh K, Lee GH. The fascinating but deceptive ferritin: to measure it or not to measure it in chronic kidney disease? *Clin J Am Soc Nephrol* 2006;1 Suppl 1:S9–18.
42. Wish JB. Assessing iron status: beyond serum ferritin and transferrin saturation. *Clin J Am Soc Nephrol* 2006;1 Suppl 1:S4–8.
43. Kim JM, Ihm CH, Kim HJ. Evaluation of reticulocyte haemoglobin content as marker of iron deficiency and predictor of response to intravenous iron in haemodialysis patients. *Int J Lab Hematol* 2008;30:46–52.

SUPPLEMENTAL FILES

Table S1. Inclusion and exclusion criteria within study cohorts.

All cohorts N = 1506	**Inclusion criteria**	**Exclusion criteria**
Dutch cohort 1 N = 20227	1. NYHA class III-IV.	1. Dementia or psychiatric illness
	2. Stable HF in conjunction with echocardiographic findings of a reduced left ventricular systolic function (LVEF ≤ 45%) or preserved left ventricular systolic function.	2. Staying in a nursing home
	3. Able to understand the study procedures and willing to provide informed consent.	3. Other disease with expected survival < 1 year.
		4. Participation in other trial(s)
		5. Ongoing or planned hospitalization
		6. Undergoing kidney replacement therapy
Dutch cohort 2 N = 9526	1. NYHA class II-IV	1. History of myocardial infarction or stroke in previous 6 months.
	2. Echocardiographic LVEF ≤ 45%.	2. Severe valvular dysfunction.
	3. HF duration of at least 3 month.	3. Severe pulmonary disease or uncontrolled diabetes.
	4. Stable HF medical therapy for at least 1 month.	4. History of systemic inflammatory or collagen vascular disease.
	5. Able to understand the study procedures and willing to provide informed consent.	5. Active and/or treated malignancies within 12 months before inclusion.
		6. Clinically significant renal dysfunction or liver function abnormalities.
		7. Severe anemia at baseline (hemoglobin < 10 g/dL).
		8. Pregnancy or active breast-feeding (pregnancy tests will be performed on all female subjects of child-bearing potential)
		9. Use of any investigational drugs (within 30 d before screening).

Table S1. Inclusion and exclusion criteria within study cohorts. (continued)

All cohorts N = 1506	**Inclusion criteria**	**Exclusion criteria**
Polish cohorts N = 7351315	1. NYHA class I-IV.	1. Acute coronary syndrome, coronary revascularization or any major surgery within 3 months preceding the study
	2. A documented history of HF of ≥ 6 months.	2. Unplanned hospitalization due to heart failure deterioration or any other cardiovascular reason within 1 month preceding the study
	3. Left ventricular ejection fraction ≤ 45% as assessed by echocardiography.	3. Any acute or chronic illness that might influence iron metabolism.
	4. Clinical stability and unchanged medications for ≥ 1 month preceding the study.	4. Any anemia or/and iron deficiency treatment either at the time of the study or within the past 12 months.
	5. Able to understand the study procedures and willing to provide informed consent.	
Spanish cohort N = 47425	1. NYHA class I-IV.	1. Significant primary valvular disease or significant pericardial disease.
	2. Clinically stable condition ≥ 1 month preceding the study.	2. Severe anemia (hemoglobin < 8.5 g/dL).
	3. A reduced left ventricular systolic function (LVEF ≤ 45%) or preserved left ventricular systolic function.	3. Restrictive and hypertrophic cardiomyopathy.
	4. Patients able to understand the study procedures and willing to provide informed consent.	4. Active malignancy, presence of an active infection or clinically significant liver function abnormalities.

Abbreviations: NYHA = New York Heart Association, LVEF = Left ventricular ejection fraction.

Table S2. Baseline characteristics divided in 4 groups regarding iron status and/or anemia.

Variables	All patients	No ID*/No anemia†	ID*/No anemia†	No ID*/Anemia†	ID*/Anemia†	P-value
	n = 1506	n = 589	n = 492	n = 164	n = 261	
Age, years	64 ± 13	60 ± 12	65 ± 13	68 ± 13	70 ± 11	< 0.001
Women	26	18	31	27	33	< 0.001
BMI (kg/m2)	27.5 ± 4.8	27.9 ± 4.8	27.3 ± 4.7	26.3 ± 4.0	27.6 ± 5.3	0.079
Ischemic cause	60	59	60	61	60	0.882
LVEF (%)	33 ± 14	31 ± 12	32 ± 12	35 ± 16	38 ± 16	< 0.001
HFrEF	87	92	90	79	74	< 0.001
NYHA functional class						< 0.001
I/II	46	57	43	41	32	
III	47	39	51	51	56	
IV	7	4	6	8	12	
Comorbidities						
Diabetes mellitus	35	30	31	41	49	< 0.001
AF	20	18	21	16	22	0.240
Hypertension	20	19	22	20	21	0.476
Laboratory						
Hb (g/dL)	13.6 ± 1.8	14.6 ± 1.3	14.2 ± 1.1	11.5 ± 1.3	11.3 ± 1.1	< 0.001
MCV (fL)‡	90.9 ± 5.9	92.1 ± 5.1	90.7 ± 5.5	91.0 ± 7.6	88.4 ± 6.0	< 0.001
Serum iron (ug/L)	73 (49 – 105)	100 (82 – 131)	59 (42 – 84)	74 (54 – 103)	45 (32 – 61)	< 0.001
Ferritin (ug/L)	154 (82 – 280)	250 (160 – 399)	83 (54 – 128)	291 (218 – 371)	79 (49–151)	< 0.001
TSAT (%)	22.3 (14.5 – 32.7)	31.2 (24.6 – 41.3)	17.2 (12.5 – 23.3)	24.0 (19.8 – 32.2)	12.8 (9.1 – 14.5)	< 0.001
NT-proBNP (pg/mL)	1395 (550 – 3572)	1092 (459 – 2358)	1284 (499 – 3492)	2139 (868 – 5070)	2179 (812 – 5733)	< 0.001
hs-CRP (mg/L)§	2.9 (1.3 – 6.9)	2.3 (1.2 – 5.1)	3 (1.3 – 7.2)	3.8 (1.2 – 10)	5.0 (2.0 – 12.8)	< 0.001
eGFR (ml/min/1.73m2)	79.9 ± 33.8	81.1 ± 29.6	81.8 ± 33.9	78.7 ± 39.4	73.8 ± 38.2	0.035

Table S2. Baseline characteristics divided in 4 groups regarding iron status and/or anemia. (continued)

Variables	All patients	No ID*/No anemia†	ID*/No anemia†	No ID*/Anemia†	ID*/Anemia†	P-value
	n = 1506	n = 589	n = 492	n = 164	n = 261	
Treatment						
ACE inhibitor and/or ARB	91	95	92	85	83	< 0.001
Beta blocker	90	92	89	91	85	0.025
Loop diuretic	79	73	80	83	89	< 0.001
Statin	64	67	63	64	59	0.190
Aldosterone antagonist	48	51	43	52	45	0.041
Antiplatelet and/or anticoagulant	84	84	84	85	84	0.954

Values are means ± SD, medians (interquartile range), or proportions *Iron deficiency was defined as ferritin < 100 µg/L or 100 to 299 µg/L with a TSAT < 20%. †Anemia was defined as hemoglobin < 12 g/dL in women and < 13 g/dL in men. ‡Mean corpuscular volume was measured in 596 non–iron-deficient and 527 iron-deficient patients. §High-sensitive C-reactive protein was not measured in 549 non–iron-deficient and 451 iron-deficient patients. For abbreviations, see Table 1.

Table S3. Baseline characteristics stratified per study cohort.

Variables	All patients n = 1506	Holland 1 n = 2027	Holland 2 n = 9526	Poland 1 n = 3641 3	Poland 2 n = 3711 5	Spain n = 4742 5	p - value
Age (years)	64 ± 13	71 ± 12	60 ± 12	61 ± 11	54 ± 10	72 ± 11	< 0.001
Men (%)	74.2	73.3	78.9	82.7	86.8	57.2	< 0.001
BMI (kg/m2)	27.5 ± 4.8	26.3 ± 5.6	27.9 ± 4.2	27.8 ± 4.2	26.5 ± 4.2	27.0 ± 6.7	0.072
Ischemic cause (%)	60.2	61.9	69.5	70.3	70.9	41.6	< 0.001
LVEF (%)	33 ± 14	31 ± 9	32 ± 9	31 ± 9	24 ± 6	42 ± 17	< 0.001
HFrEF (%)	87.3	96.5	100	100	100	61.0	< 0.001
NYHA functional class (%)							< 0.001
I/II	46.3	0.0	64.2	66.2	47.2	46.6	
III	47.3	96.5	32.6	31.0	43.6	44.5	
IV	6.4	3.5	3.2	2.8	9.2	8.9	
Comorbidities (%)							
ID*	23.5	15.8	56.8	19.5	20.8	25.3	< 0.001
Diabetes mellitus	34.9	29.2	16.8	34.3	26.4	48.1	< 0.001
AF	19.7	28.7	0.0	25.3	0	30.8	< 0.001
Hypertension	20.3	26.2	11.6	25.6	8.4	24.9	< 0.001
Laboratory							
Hb (g/dL)	13.6 ± 1.8	13.6 ± 1.6	14.4 ± 1.2	14.0 ± 151	14.2 ± 1.6	11.3 ± 1.1	< 0.001
MCV (fL)†	90.9 ± 5.9	NA	NA	90.7 ± 1.5	91.0 ± 7.6	88.4 ± 6.0	NA
Serum iron (ug/L)	73 (49 – 105)	100 (82 – 131)	100 (82 – 131)	59 (42 – 84)	74 (54 – 103)	45 (32 – 61)	< 0.001
Ferritin (ug/L)	154 (82 – 280)	140 (74 – 272)	127 (71 – 203)	164 (87 – 278)	179 (102 – 310)	145 (75 – 274)	< 0.001
TSAT (%)	22.3 (14.5 – 32.7)	14.3 (6.5 – 22.0)	17.6 (14.0 – 22.0)	31.1 (21.4 – 42.2)	29.3 (20.2 – 39.6)	17.7 (12.0 – 24.9)	< 0.001
NT-proBNP (pg/mL)	1395 (550 – 3572)	2135 (989 – 4473)	388 (143 – 807)	1467 (488 – 3951)	1364 (652 – 3109)	1395 (652 – 3109)	< 0.001

Table S3. Baseline characteristics stratified per study cohort. (continued)

Variables	All patients n = 1506	Holland 1 n = 20227	Holland 2 n = 9526	Poland 1 n = 36413	Poland 2 n = 37115	Spain n = 47425	p - value
Serum sodium (mmol/L)	139 ± 5	138 ± 3	140 ± 2	141 ± 3	136 ± 4	140 ± 7	< 0.001
hs-CRP (mg/L)‖	2.9 (1.3 – 6.9)	5.0 (2.0 – 14.0)	1.6 (0.8 – 3.7)	3.1 (1.4 – 6.8)	2.4 (1.2 – 5.6)	NA	NA
eGFR (ml/min/1.73m2)	79.9 ± 33.8	51.1 ± 14.1	79.9 ± 20.3	71.0 ± 20.4	84.0 ± 25.8	97.8 ± 45.6	< 0.001
Treatment (%)							
ACE inhibitor and/or ARB	90.9	95.1	94.7	94.2	94.6	82.9	< 0.001
Beta blocker	89.9	62.4	93.7	96.2	98.9	89.0	< 0.001
Loop diuretic	79.2	97.0	55.8	54.4	86.0	90.1	< 0.001
Statin	64.0	39.6	81.1	78.3	71.4	54.2	< 0.001
MRA	47.5	0.0	29.5	33.8	91.6	47.5	< 0.001
Antiplatelet and/or anticoagulant	84.0	89.6	75.8	84.9	83.0	83.3	0.078

Values are means ± SD, medians (interquartile range), or proportions (%). *Iron deficiency was defined as ferritin < 100 µg/L or 100 to 299 µg/L with a TSAT < 20%. † Mean corpuscular volume was measured in 596 non–iron-deficient and 527 iron-deficient patients. ‡High-sensitive C-reactive protein was not measured in 549 non–iron-deficient and 451 iron-deficient patients. For abbreviations, see Table 1.