Iron deficiency in chronic heart failure: An international pooled analysis

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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 1,506 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 nonanemic patients (61.2% vs 45.6%, $P < .001$). 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 $P < .05$). 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 χ^2 10.2, $P = .001$). 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, $P = .002$). 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. (Am Heart J 2013;165:575-582.e3.)

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] The 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.[12,22,23] These studies

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Table I. 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	<.001
Women (%)	26	20	32	<.001
BMI (kg/m²)	27.5 ± 4.8	27.6 ± 4.7	27.4 ± 4.9	.531
Ischemic cause	60	60	61	.712
LVEF (%)	33 ± 14	32 ± 13	34 ± 14	.008
HFrEF	87	89	84	.003
NYHA functional class (%)				<.001
I/II	46	53	39	
III	47	42	53	
IV	7	5	8	
Comorbidities (%)				
Anemia†	28	22	35	<.001
Diabetes mellitus	35	32	37	.040
AF	20	18	21	.052
Hypertension	20	19	21	.124
Laboratory				
Hb (g/dL)	13.6 ± 1.8	13.9 ± 1.8	13.2 ± 1.8	<.001
MCV (fL)‡	90.9 ± 5.9	91.8 ± 5.8	89.8 ± 5.8	<.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)	<.001
hs-CRP (mg/L)§	2.9 (1.3-6.9)	2.4 (1.2-5.8)	3.2 (1.4-8.0)	<.001
eGFR (mL/min/1.73m²)	79.9 ± 33.8	80.6 ± 31.9	79.1 ± 35.6	.484
Treatment (%)				
ACE inhibitor and/or ARB	91	93	89	.005
β-Blocker	90	92	88	.010
Loop diuretic	79	75	83	<.001
Statin	64	66	62	.068
Aldosterone antagonist	48	51	44	.002
Antiplatelet and/or anticoagulant	84	84	84	.833

Values are means ± SD, medians (interquartile range), or proportions (%). Abbreviations: *ACE*, Angiotensin-converting enzyme; *AF*, atrial fibrillation; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *Hb*, hemoglobin; *HFrEF*, HF with reduced ejection fraction; *MCV*, mean corpuscular volume; *NA*, not applicable.
* Iron deficiency was defined as ferritin <100 μg/L or 100 to 299 μg/L with a TSAT <20%.
† Anemia was defined as hemoglobin level <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 measured in 549 non–iron-deficient and 451 iron-deficient patients.

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 1,506 chronic HF patients.

Methods

Component studies

This study population consists of patients from 5 cohorts from Poland, Spain and The Netherlands, comprising 1,506 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 the online Appendix Supplementary Table I. 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.[12,15] 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