

Anemia at hospital admission and its relation to outcomes in patients with heart failure (from the polish cohort of 2 European Society of Cardiology Heart Failure Registries)

Agata Tymińska MD^a, Agnieszka Kapłon-Cieślicka MD, PhD^a, Krzysztof Ozierański MD^a, Michał Peller MD^a, Paweł Balsam MD, PhD^a, Michał Marchel MD, PhD^a, Maria G. Crespo-Leiro MD, PhD^b, Aldo P. Maggioni MD, PhD^c, Ewa A. Jankowska MD, PhD^d, Jarosław Drożdż MD, PhD^e, Krzysztof J. Filipiak MD, PhD^a, Grzegorz Opolski MD, PhD^a

^a Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

^b Unidad de Insuficiencia Cardíaca Avanzada y Trasplante Cardíaco, Hospital Universitario, A Coruña, La Coruña, Spain

^c Associazione Nazionale Medici Cardiologi Ospedalieri Research Center, Florence, Italy

^d Cardiology Department, Centre for Heart Diseases, Military Hospital, Wrocław, Poland

^e Department of Cardiology, Medical University of Łódź, Łódź, Poland

Anemia is a commonly observed co-morbidity in heart failure (HF). The aim of the study was to assess prevalence, risk factors for, and effect of anemia on short- and long-term outcomes in HF. The study included 1,394 Caucasian patients hospitalized for HF, with known hemoglobin concentration on hospital admission, participating in 2 HF registries of the European Society of Cardiology (Pilot and Long-Term). Anemia was defined as hemoglobin concentration of <13 g/dl for men and <12 g/dl for women. Primary end points were (1) all-cause death at 1 year and (2) a composite of all-cause death and rehospitalization for HF at 1 year. Secondary end points included inter alia death during index hospitalization. In addition, we investigated the effect of changes in hemoglobin concentration during hospitalization on prognosis. Anemia occurred in 33% of patients. Predictors of anemia included older age, diabetes, greater New York Heart Association class at hospital admission and kidney disease. During 1-year follow-up, 21% of anemic and 13% of nonanemic patients died ($p < 0.0001$). Combined primary end point occurred in 45% of anemic and in 33% of nonanemic patients ($p < 0.0001$). Anemia was strongly predictive of all the prespecified clinical end points in univariate analyses but not in multivariate analyses. Changes in hemoglobin concentration during hospitalization had no effect on 1-year outcomes. In conclusion, anemia was present in 1/3 of patients with HF. Mild-to-moderate anemia seems more a marker of older age, worse clinical condition, and a higher co-morbidity burden, rather than an independent risk factor in HF.

Identification and prevention of risk factors for heart failure (HF) decompensation constitute the fundamentals of comprehensive care in HF.^{1, 2, 3} Although anemia is a commonly observed comorbidity in HF, associated with significantly worse prognosis, there is no certain explanation on how it affects mortality, provokes HF exacerbations, and influences the course of hospitalization.^{4, 5, 6, 7, 8, 9} There are encouraging reports on the effectiveness of iron therapy in reducing HF symptoms; however, there are no favorable results in terms of mortality in HF.^{10, 11, 12, 13} Thus, clinical implications of anemia in HF remain to be established. The aim of this study was to evaluate the prevalence of anemia in patients hospitalized for HF, compare baseline characteristics and course of index hospitalization of anemic and nonanemic HF patients, and determine the impact of anemia on short- and long-term outcomes in HF. Additional objectives of the analysis were to assess risk factors for anemia in HF patients and to evaluate changes in hemoglobin concentration during hospitalization and their prognostic significance in HF.

Methods

The study is based on 2 prospective, multicenter, observational surveys of patients with HF, conducted by the European Society of Cardiology (ESC). The first, ESC-HF Pilot Survey, which has already been completed, was conducted from October 2009 to May 2010 in 136 European cardiology centers, including 29 centers from Poland.¹⁴ The second, ESC-HF Long-Term Registry, is a 3-phase study, conducted in 211 European cardiology centers, including 35 centers from Poland.¹⁵ In the ESC-HF Pilot Survey and during phase I of the ESC-HF Long-Term Registry (lasting from May 2011 to April 2013), patients were enrolled on 1 specific day of the week for 12 consecutive months in each of the participating centers. In phase II and phase III (still on-going) of the ESC-HF Long-Term Registry, patients are enrolled during 5 days per trimester. The current analysis included Polish participants of the ESC-HF Pilot Survey and of phase I of the ESC-HF Long-Term Registry.

The surveys included both ambulatory and hospitalized HF patients, who were aged over 18 years. There were no specific exclusion criteria. Local ethics committees approved the surveys in accordance with the regulations of each participating country. All patients were provided with detailed information on the registries and signed informed written consent.

The current analysis included only patients admitted to hospital for new-onset or worsening HF, in whom data on hemoglobin concentration on hospital admission were available.

Patients were divided into 2 groups (anemic and nonanemic) according to hemoglobin concentration on admission. Following the World Health Organization criteria, anemia was defined as hemoglobin concentration of <13 g/dl for men and <12 g/dl for women. Severe anemia was defined as hemoglobin level <9 g/dl. Anemic and nonanemic patients were compared with regard to baseline characteristics, course of index hospitalization, diagnostic tests results, implemented treatment, in-hospital outcomes (death during hospitalization, length of hospital stay, time in intensive cardiac care unit [ICCU]) and 1-year outcomes (all-cause death and death or rehospitalization for decompensated HF).

The primary end points were (1) all-cause death at 1 year and (2) a composite of all-cause death and hospital readmissions for decompensated HF at 1 year. Secondary end points included (1) death during index hospitalization, (2) hospital stay >7 days, (3) time in ICCU >3 days, and (4) a worse clinical status (New York Heart Association [NYHA] class III or IV) at hospital discharge.

The main goal of the study was to determine whether anemia at hospital admission was predictive of the primary and the secondary end points in patients with HF. In addition, we assessed, whether changes in hemoglobin concentration during index hospitalization were related to 1-year outcomes (all-cause death and death or rehospitalization for decompensated HF). Increase and decrease in hemoglobin concentration were defined as changes of ≥ 1 g/dl during index hospitalization. Finally, we sought to identify risk factors for anemia at admission in hospitalized HF patients.

Statistical analyses were performed using SPSS 22 (SPSS Statistics, Inc., Chicago, Illinois) and SAS 9.2 (SAS Institute Inc., Cary, North Carolina) software. Normally distributed continuous variables were presented as mean value and SD, whereas for ordinal variables and nonnormally distributed continuous variables, median value and interquartile range were given. Significance of differences between the 2 groups was determined by Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous and ordinal variables. Cox proportional hazards regression model was used to identify predictors of the primary end points, as well as to assess association of hemoglobin changes during index hospitalization and 1-year outcomes. To determine the predictors of the remaining secondary end points, univariate and multivariate logistic regressions were performed. Multivariate analyses included all variables found to be statistically significant in univariate analyses, maintaining adequate events per predictor variable values.¹⁶ The list of all variables included in univariate analyses (both in Cox proportional hazards analyses and in logistic regression analyses) is provided in Supplementary Table S1. Kaplan-Meier curves were developed for both primary end points. For all tests, *p* value below 0.05 was considered significant. All tests were 2 tailed.

Results

Figure 1 shows the flow chart of patient selection for the present study. Finally, the study group included 1,394 Caucasian patients. Median hemoglobin concentration at hospital admission was 13.4 g/dl (interquartile range: 12.0 to 14.5 g/dl). Anemia at hospital admission was present in 466 of the 1,394 patients (33%). Severe anemia was reported in 28 patients (2%). Comparison of clinical characteristics and course of index hospitalization of anemic and nonanemic patients is presented in Tables 1 and 2.

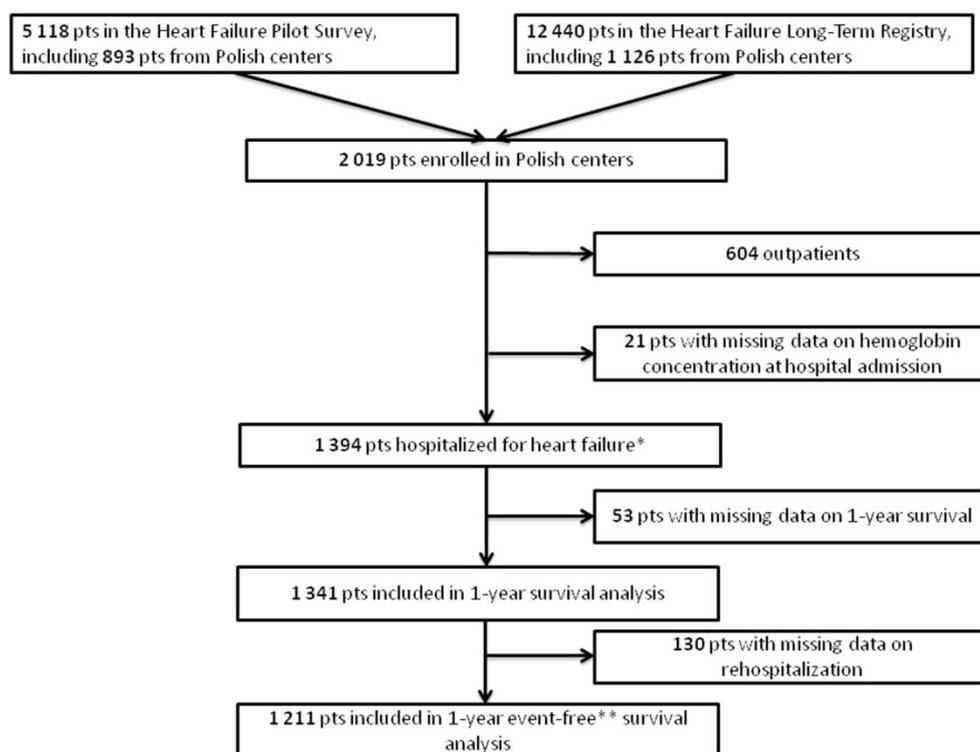


Figure 1. Flow chart of patient enrollment in the current analysis. *included in the comparative analysis of anemic and nonanemic patients and in the analyses of in-hospital outcomes. **death or rehospitalization for heart failure. pts = patients.

Table 1. Baseline characteristics, clinical, and laboratory status at hospital admission of anemic and nonanemic patients

Variable	Non-anemic (n=928)	Anemic (n=466)	P-value
Baseline characteristics			
Age (years)	67.6 (58.0-77.0)	73.0 (64.2-81.0)	< 0.0001
Men	599 (65%)	319 (69%)	0.15
Body mass index (kg/m ²)	28.0 (25.0-31.3); n=885	26.8 (24.4-30.8); n=432	0.003
Current left ventricular ejection fraction (%)	36 (25-50); n=814	37 (25-50); n=398	0.45
Previous heart failure hospitalization	473/927 (51%)	288/464 (62%)	< 0.0001
Idiopathic dilated cardiomyopathy	133 (15%)	41 (9%)	0.003
Ischemic etiology of heart failure	513 (55%)	293 (63%)	0.01
Prior percutaneous coronary intervention or coronary artery bypass grafting	296 (32%)	177/465 (38%)	0.02
Valve disease etiology of heart failure	109 (12%)	67 (14%)	0.17
Moderate or severe aortic stenosis	61/830 (7%)	39/403 (10%)	0.18
Moderate or severe aortic regurgitation	53/830 (6%)	46/403 (11%)	0.003
Moderate or severe mitral regurgitation	412/828 (50%)	210/404 (52%)	0.47
Moderate or severe tricuspid regurgitation	274/827 (33%)	181/404 (45%)	< 0.0001
Hypertension	629/926 (68%)	330 (71%)	0.30
History of atrial fibrillation	376/926 (41%)	232 (50%)	0.001
Peripheral artery disease	101/927 (11%)	77/465 (17%)	0.004
Diabetes	296 (32%)	198 (43%)	< 0.0001
Chronic kidney disease	161 (17%)	132/464 (28%)	< 0.0001
Chronic obstructive pulmonary disease	142 (15%)	119/464 (26%)	< 0.0001
Prior stroke or transient ischemic attack	95 (10%)	51/464 (11%)	0.71
3 or more non-cardiac comorbidities*	60 (7%)	54/464 (12%)	0.001
Current or former smoking	519/915 (57%)	251/455 (55%)	0.60
Alcohol usage	515/899 (57%)	236/448 (53%)	0.12
Previous pharmacotherapy			
Diuretic	598/912 (66%)	316/449 (70%)	0.09
Aldosterone antagonist	409/907 (45%)	197/450 (44%)	0.69
Angiotensin converting enzyme inhibitor	574/908 (63%)	275/449 (61%)	0.51
Angiotensin receptor blocker	87/906 (10%)	28/448 (6%)	0.04
β-blocker	677/908 (75%)	334/449 (74%)	0.95
Statin	490/910 (54%)	252/447 (56%)	0.39
Anticoagulant	270/911 (30%)	156/448 (35%)	0.054
Antiplatelet	476/909 (52%)	248/448 (55%)	0.33
Clinical status at admission			
Cardiogenic shock	22/890 (3%)	12/448 (3%)	0.86
Heart rate (b.p.m.)	80 (70-100); n=927	80 (70-100); n=464	0.75
Systolic blood pressure (mmHg)	130 (112-147); n=926	130 (110-140); n=465	0.17
NYHA class I	6/924 (1%)	4/463 (1%)	0.74
NYHA class II	249/924 (27%)	76/463 (16%)	< 0.0001
NYHA class III	425/924 (46%)	221/463 (48%)	0.57
NYHA class IV	244/924 (26%)	162/463 (35%)	0.001
Ventricular fibrillation or ventricular tachycardia as a cause of admission	87/925 (9%)	21 (5%)	0.001
Acute coronary syndrome as a cause of heart failure decompensation	184/926 (20%)	88/465 (19%)	0.72
Atrial fibrillation as a cause of heart failure decompensation	235/927 (25%)	115 (25%)	0.79
Infection as a cause of heart failure decompensation	85/924 (9%)	85 (18%)	< 0.0001

Table 1. Baseline characteristics, clinical, and laboratory status at hospital admission of anemic and nonanemic patients

Variable	Non-anemic (n=928)	Anemic (n=466)	P-value
Laboratory findings at admission			
Hemoglobin (g/dl)	14.1 (13.4-15.0)	11.5 (10.5-12.1)	<0.0001
Serum creatinine (mg/dl)	1.04 (0.89-1.29); n=908	1.21 (0.99-1.64); n=462	<0.0001
Estimated glomerular filtration rate (ml/min/1.73m ²)	66.8 (52.3-86.3); n=908	56.2 (40.3-75.8); n=462	<0.0001
Serum sodium (mmol/l)	139 (137-141); n=925	138 (135-141); n=463	0.03

Categorical data are presented as number of patients and percentages. Continuous variables are shown as a median and interquartile range. p Values are given for differences between the groups. Bolded text indicates p values <0.05.

* Included diabetes, stroke or transient ischemic attack, peripheral artery disease, chronic obstructive pulmonary disease, and chronic kidney disease.

Table 2. Clinical course of index hospitalization, in-hospital, and long-term outcomes of anemic and nonanemic patients

Variable	Non-anemic (n=928)	Anemic (n=466)	P-value
Management during index hospitalization			
Inotropic support	97/925 (11%)	73/464 (16%)	0.01
Intravenous diuretics	580/925 (63%)	357/464 (77%)	<0.0001
Intravenous nitrates	116/925 (13%)	78/463 (17%)	0.03
Percutaneous coronary intervention / coronary artery bypass grafting during hospitalization	127/925 (14%)	51/465 (11%)	0.15
Status at discharge*			
Heart rate (b.p.m.)	70 (65-80); n=900	70 (66-80); n=436	0.14
Systolic blood pressure (mmHg)	120 (110-130); n=906	120 (105-130); n=441	0.10
NYHA class I	60/909 (7%)	31/442 (7%)	0.82
NYHA class II	597/909 (66%)	242/442 (55%)	<0.0001
NYHA class III	238/909 (26%)	162/442 (37%)	<0.0001
NYHA class IV	14/909 (2%)	7/442 (2%)	1.00
Hemoglobin (g/dl)	13.8 (12.9-14.9); n=534	11.4 (10.5-12.4); n=305	<0.0001
Serum creatinine (mg/dl)	1.05 (0.90-1.30); n=639	1.20 (0.97-1.67); n=334	<0.0001
Serum sodium (mmol/l)	139 (136-141); n=683	138 (136-141); n=357	0.04
Pharmacotherapy at discharge*			
Diuretic	762/907 (84%)	391/443 (88%)	0.04
Aldosterone antagonist	618/906 (68%)	268/443 (61%)	0.01
Angiotensin converting enzyme inhibitor	700/908 (77%)	313/443 (71%)	0.01
Angiotensin receptor blocker	96/906 (11%)	34/442 (8%)	0.10
β-blocker	824/908 (91%)	390/443 (88%)	0.13
Statin	627/908 (69%)	301/443 (68%)	0.71

Table 2. Clinical course of index hospitalization, in-hospital, and long-term outcomes of anemic and nonanemic patients

Variable	Non-anemic (n=928)	Anemic (n=466)	P-value
Anticoagulant	371/907 (41%)	205/443 (46%)	0.07
Antiplatelet	590/908 (65%)	292/443 (66%)	0.76
In-hospital outcome			
Hospitalization length (days)	7 (4-10)	8 (5-13)	<0.0001
Time in Intensive Cardiac Care Unit (days)	0 (0-3); n=895	1 (0-6); n=447	<0.0001
Death during hospitalization	19 (2%)	23 (5%)	0.004
1-year outcome [†]			
Death	118/898 (13%)	95/443 (21%)	<0.0001
Death or rehospitalization	266/803 (33%)	183/408 (45%)	<0.0001

Categorical data are presented as number of patients and percentages. Continuous variables are shown as a median and interquartile range. p Values are given for differences between the groups. Bolded text indicates p values <0.05.

* In patients who survived to hospital discharge.

† Including patients who died during index hospitalization.

In the study group, independent predictors of anemia at hospital admission included older age, diabetes, greater NYHA class at admission, and kidney disease.

Data on 1-year survival were available for 1,341 patients. A total of 213 patients (16%) died during 1-year follow-up: 21% of the anemic and 13% of the nonanemic groups (Table 2). Kaplan-Meier curves for death at 1 year are presented in Figure 2. Predictors of death at 1 year are listed in Table 3.

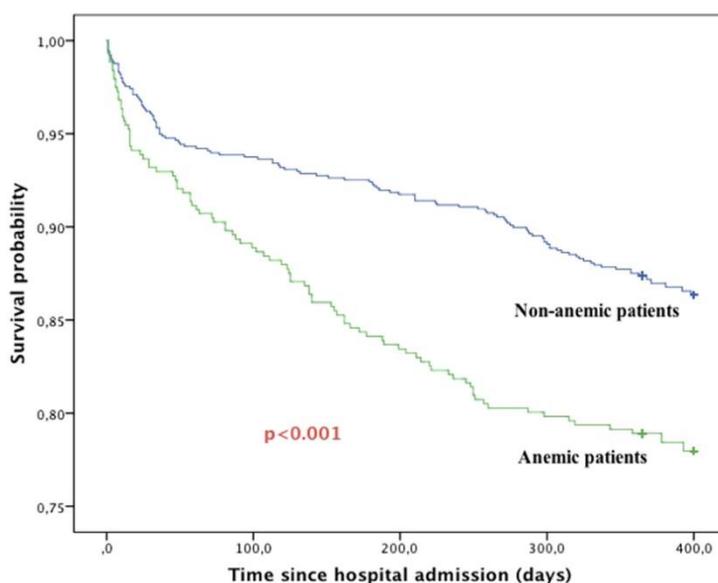


Figure 2. Kaplan-Meier curves for all-cause death at 1 year.

Table 3. Univariate and multivariate analyses of predictors of death at 1 year

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Anemia at admission	1.74 (1.33-2.28)	<0.0001	0.91 (0.72-1.44)	0.91
Age (per 10 years)	1.04 (1.03-1.05)	<0.0001	1.03 (1.02-1.05)	<0.0001
Current left ventricular ejection fraction (per 5%)	0.98 (0.97-0.99)	0.001	0.97 (0.96-0.98)	<0.0001
Peripheral artery disease	1.50 (1.05-2.15)	0.03	1.48 (0.98-2.25)	0.064
Chronic kidney disease	1.87 (1.40-2.49)	<0.0001	1.40 (0.98-2.00)	0.063
NYHA class at admission (per 1 class)	2.33 (1.90-2.86)	<0.0001	1.74 (1.32-2.29)	<0.0001
Serum sodium at admission (per 1 mmol/l)	0.91 (0.89-0.93)	<0.0001	0.93 (0.90-0.96)	<0.0001
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker at discharge	0.32 (0.24-0.43)	<0.0001	0.57 (0.38-0.83)	0.004
β-blocker at discharge	0.30 (0.22-0.40)	<0.0001	0.55 (0.36-0.84)	0.01

Besides anemia, this table depicts only variables found to be predictive (or with a trend to be predictive) of the primary end point in the multivariate model. Other variables predictive of the primary end point in univariate analyses included body mass index, heart rate and systolic blood pressure at admission, history of atrial fibrillation, chronic obstructive pulmonary disease, diabetes and alcohol usage, infection as a cause of heart failure decompensation, moderate or severe mitral regurgitation, moderate or severe tricuspid regurgitation, serum creatinine at admission, statin, and antiplatelet treatment at discharge, all of them were also included in the multivariate model but did not prove independent predictors of death at 1 year.

Bolded text indicates p values <0.05.

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.

Data on hospital readmissions for decompensated HF at 1 year were available for 1,211 patients. A total of 449 patients (37%) died or were readmitted for HF during 1-year follow-up: 45% of the anemic and 33% of the nonanemic groups (Table 2). Kaplan-Meier curves for death or rehospitalization for HF at 1 year are presented in Figure 3. Predictors of death or rehospitalization for HF at 1 year are presented in Table 4.

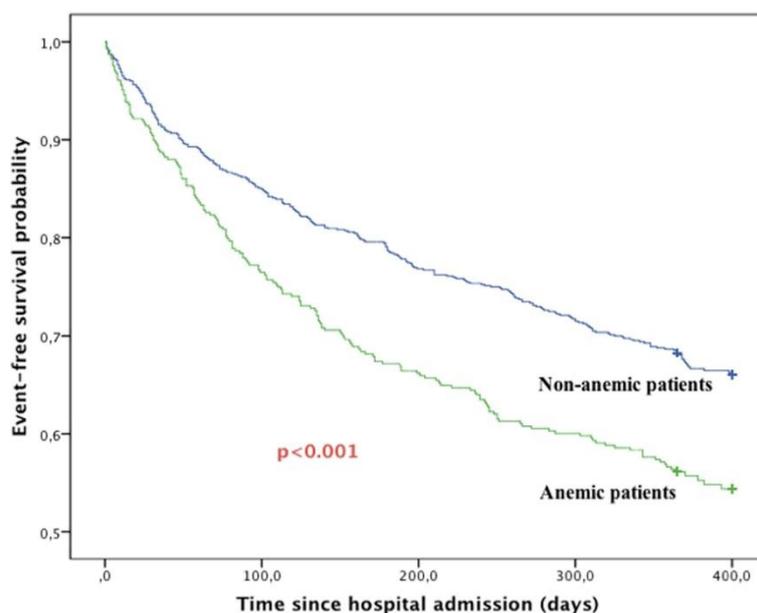


Figure 3. Kaplan-Meier curves for all-cause death or rehospitalization for heart failure at 1 year.

Table 4. Univariate and multivariate analyses of predictors of death or rehospitalization for heart failure at 1 year

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
Anemia at admission	1.50 (1.25-1.81)	<0.0001	1.11 (0.89-1.40)	0.35
Age (per 10 years)	1.01 (1.01-1.02)	0.001	1.01 (1.003-1.02)	0.04
Current left ventricular ejection fraction (per 5%)	0.98 (0.98-0.99)	<0.0001	0.98 (0.98-0.99)	<0.0001
History of heart failure hospitalization	1.40 (1.16-1.69)	0.001	1.25 (0.996-1.58)	0.053
Diabetes	1.32 (1.10-1.60)	0.004	1.27 (1.02-1.58)	0.03
Chronic kidney disease	1.60 (1.31-1.96)	<0.0001	1.24 (0.97-1.59)	0.085
Alcohol usage	0.73 (0.60-0.88)	0.001	0.78 (0.63-0.98)	0.03
NYHA class at admission (per 1 class)	1.82 (1.59-2.08)	<0.0001	1.40 (1.18-1.66)	<0.0001
Serum sodium at admission (per 1 mmol/l)	0.95 (0.93-0.96)	<0.0001	0.97 (0.95-0.99)	0.002
Angiotensin-converting-enzyme inhibitor or angiotensin receptor blocker at discharge	0.48 (0.39-0.59)	<0.0001	0.69 (0.53-0.90)	0.01
β -blocker at discharge	0.52 (0.41-0.66)	<0.0001	0.72 (0.52-0.98)	0.04

Besides anemia, this table depicts only variables found to be predictive (or with a trend to be predictive) of the primary end point in the multivariate model. Other variables predictive of the primary end point in univariate analyses included heart rate and systolic blood pressure at admission, history of coronary artery disease, atrial fibrillation and chronic obstructive pulmonary disease, infection as a cause of heart failure decompensation, moderate or severe tricuspid regurgitation, serum creatinine at admission, statin, and antiplatelet treatment at discharge, all of them were also included in the multivariate model but did not prove independent predictors of death or rehospitalization for heart failure at 1 year.

Bolded text indicates p values <math>< 0.05</math>.

CI = confidence interval; HR = hazard ratio; NYHA = New York Heart Association.

Anemia was found to be strongly predictive of both primary end points only in univariate analyses, without statistical significance in multivariate analyses (Tables 3 and 4).

With regard to the analysis of the secondary end points, in the study group of 1,394 patients, 42 patients (3%) died during index hospitalization: 5% of the anemic and 2% of the nonanemic groups (Table 2). Predictors of death during hospitalization are listed in Table 5.

Table 5. Univariate and multivariate analyses of predictors of death during hospitalization

Variable	Univariate analysis		Multivariate analysis	
	OR (95%CI)	P-value	OR (95%CI)	P-value
Anemia at admission	2.48 (1.34-4.61)	0.004	1.93 (0.86-4.35)	0.11
Age (per 10 years)	1.04 (1.01-1.07)	0.01	1.04 (1.01-1.08)	0.02
Current left ventricular ejection fraction (per 5%)	0.95 (0.92-0.98)	0.001	0.95 (0.92-0.99)	0.004
Systolic blood pressure at admission (per 10 mmHg)	0.97 (0.96-0.98)	<0.0001	0.99 (0.97-0.999)	0.04
Heart rate at admission (per 10 b.p.m.)	1.02 (1.01-1.03)	0.003	1.02 (1.01-1.03)	0.01
NYHA class at admission (per 1 class)	5.80 (3.07-10.94)	<0.0001	3.41 (1.60-7.25)	0.001
Serum sodium at admission (per 1 mmol/l)	0.88 (0.83-0.92)	<0.0001	0.88 (0.83-0.94)	<0.0001
Serum creatinine at admission (per 1 mg/dl)	1.44 (1.13-1.85)	0.004	1.41 (1.04-1.91)	0.03

Besides anemia, this table depicts only variables found to be predictive (or with a trend to be predictive) of the secondary end point in the multivariate model. Other variables predictive of the secondary end point in univariate analyses included acute coronary syndrome as a cause of heart failure decompensation, moderate or severe mitral regurgitation, and moderate or severe tricuspid regurgitation, all of them were also included in the multivariate model but did not prove independent predictors of death during hospitalization.

Bolded text indicates p values <0.05.

CI = confidence interval; NYHA = New York Heart Association; OR = odds ratio.

Hospital stay >7 days was reported in 603 patients (43% of the study group), including 221 of the 466 anemic patients (47%) and 382 of the 928 nonanemic patients (41%; p = 0.007). Time in ICCU >3 days was reported in 343 patients (26% of the 1,342 patients with data on ICCU stay), including 135 of 447 anemic patients (30%) and 208 of 895 nonanemic patients (23%; p = 0.003). At hospital discharge, anemic patients more often were in NYHA class III or IV compared with nonanemic patients (p <0.0001; Table 2).

Anemia was found to be predictive of all the aforementioned secondary end points only in univariate analyses, without statistical significance in multivariate analyses.

Data on hemoglobin concentration at both hospital admission and hospital discharge were available for 871 patients. During index hospitalization, hemoglobin concentration increased (by ≥ 1 g/dl) in 132 patients (15%), decreased (by ≥ 1 g/dl) in 183 patients (21%) and remained unchanged in 556 patients (64%). Changes in hemoglobin concentration during hospitalization had no effect on 1-year outcomes.

Discussion

Prevalence of anemia in patients with HF ranges from 5% to 70% in different studies, depending on anemia definition and patient characteristics.^{5,9} In our study, prevalence of anemia (33%) was similar to the frequencies observed in a meta-analysis by Groenveld et al and in the Swedish HF Registry.^{6,17} Lower prevalence of anemia (approximately 23% to 25%) was reported in 2 randomized clinical trials; however, recruited HF participants were significantly younger.^{18,19} In most randomized clinical trials, severe anemia is an exclusion criterion, which makes it difficult to precisely assess this group of patients.^{18,20}

There is a variety of pathogenetic pathways of anemia development in HF.^{7,18,21,22,23,24} In our analysis, independent risk factors for anemia included older age, diabetes, higher NYHA functional class at hospital admission, and kidney disease. In addition, anemic patients had significantly lower body mass index and were characterized by a higher cardiac and noncardiac co-morbidity burden, which might be partly explained by their older age. Due to decreased erythropoiesis, advanced chronic kidney disease leads to anemia.²² In advanced HF, anemia may also result from iron deficiency due to malabsorption, nutritional deficiencies, and impaired metabolism and from subclinical inflammation associated with bone marrow depression (anemia of chronic disorders).^{7,8,18} Furthermore, in hospitalized patients with severe HF, increased plasma volume and hemodilution may explain a higher prevalence of anemia.^{7,18}

The EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) study and the IN-CHF Registry have demonstrated that anemic patients are less likely to receive guideline-recommended HF therapy, including β blockers and angiotensin-converting enzyme inhibitors.^{21,25} In our study, at hospital discharge, angiotensin-converting enzyme inhibitors and aldosterone antagonists were significantly less often prescribed to anemic patients. This might have been due to worse renal function in anemic patients and might also add to worse 1-year outcomes observed in anemic patients.

A meta-analysis of randomized clinical trials has shown that there is a strong association between anemia and adverse outcomes in HF.⁶ However, it is unclear that how anemia affects mortality and morbidity and whether it is indeed an independent risk factor or only a marker of worse clinical condition and a mediator of increased risk.^{18,20,21}

The results of our study suggest that although anemia is a strong marker of unfavorable prognosis in HF, it is not an independent risk factor for adverse outcomes. This may be dictated by the fact that most predictors of anemia, such as older age, higher NYHA class at hospital admission, kidney disease, and diabetes overlapped with predictors of clinical endpoints. Likewise, the same risk factors for anemia were identified in the Swedish HF Registry, IN-CHF Registry (Italian Registry of Congestive Heart Failure), and Val-HeFT (Valsartan in Heart Failure Trial) trial.^{17,18,25}

In our study, mean age of the entire population (68 years) and the anemic cohort (73 years) was consistent with those of patients studied in the Swedish HF Registry and the EVEREST trial.^{17,21} In contrast, in the randomized Val-HeFT trial and in the IN-CHF Registry, anemic HF patients were younger (66 and 67 years, respectively); in those patients, anemia was associated with increased morbidity and mortality.^{17,25} In the Swedish HF Registry, the influence of anemia on mortality was significantly greater in younger patients and in those with more stable HF.¹⁷ In the ATTEND (Acute Decompensated Heart Failure Syndromes) registry, there was no association between anemia on hospital admission and all-cause mortality in elderly patients.⁹

Similarly, to the relation between anemia and 1-year outcomes in our study, in-hospital mortality rate was not influenced by anemia in multivariate analysis, despite a significant association in univariate analysis (with an odds ratio of almost 2.5). This indicates that although anemia itself may not be a direct cause of unfavorable in-hospital outcome, HF patients with concomitant anemia constitute a high-risk group and might therefore require more intensive monitoring.

The results of our study imply that the previously observed relation between anemia and worse prognosis in HF is secondary to its association with older age, higher prevalence of cardiac and noncardiac comorbidities, and less frequent implementation of HF-modifying treatment. Reliability of our results is supported by the fact that other proved risk factors for in-hospital and long-term mortalities maintained statistical significance in multivariate analyses of the primary and the secondary end points.^{1, 2, 3, 26, 27, 28}

Recently, studies on the impact of anemia correction in HF have been undertaken. In the IRON-HF (Randomized Trial to Assess the Effects of Iron Supplementation in Heart Failure Patients With Anemia) and FAIR-HF (Ferric carboxymaltose Assessment in patients with IRon deficiency and chronic Heart Failure) trials, HF patients with iron deficiency treated with intravenous iron experienced an improvement in quality of life, exercise tolerance, and NYHA functional class.^{10, 11} Moreover, in the CONFIRM-HF (Ferric CarboxymaltOse evaluationN on perFormance in patients with IRon deficiency in coMbination with chronic Heart Failure) trial, intravenous iron therapy was associated with a significant reduction in rehospitalizations for worsening HF and with an insignificant reduction of mortality.¹² However, it needs to be emphasized that inclusion criterion in these trials was iron deficiency, and not anemia itself, as the studies included both anemic and nonanemic patients. Iron deficiency may lead to anemia but also to muscle dysfunction without anemia.¹ Thus, the beneficial effects of iron therapy in HF probably result from mechanisms other than merely correction of anemia. Furthermore, in a meta-analysis on erythropoiesis stimulating therapy (with darbepoetin or erythropoietin) for mild and moderate anemia in chronic HF, this treatment did not reduce all-cause mortality and rehospitalizations.²⁰ This could also be a confirmation that anemia is merely a marker of a worse clinical status, including the presence of iron deficiency. Thus, it seems that alignment of hemoglobin level itself should not be a goal of HF treatment.

The limitations of our study derive mainly from general drawbacks of registries, including incompleteness of data (e.g., data on 1-year survival and hospital readmissions). The scope of data collected in the registries was preestablished by their coordinators. Data on the underlying causes of anemia, parameters of iron deficiency, and information on possible iron supplementation were not available.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary Data

Supplementary data related with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.amjcard.2017.03.035>.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37:2129-2200.

2. Kaplon-Cieslicka A, Tyminska A, Peller M, Balsam P, Ozieranski K, Galas M, Marchel M, Crespo-Leiro MG, Maggioni AP, Drozd J, Filipiak KJ, Opolski G. Diagnosis, Clinical Course, and 1-Year Outcome in Patients Hospitalized for Heart Failure With Preserved Ejection Fraction (from the Polish Cohort of the European Society of Cardiology Heart Failure Long-Term Registry). *Am J Cardiol* 2016;118:535-542.
3. Gaçsior M, Pyka L, Gorol J, Hawranek M, Tajstra M, Slonka G, Kurek A, Krajewski A, Rozentryt P, Gierlotka M, Lekston A, Zembala M, Polonski L. Contemporary Modalities In Treatment of Heart Failure: a report from the COMMIT-HF registry. *Kardiol Pol* 2016;74:523-528.
4. Tomaszuk-Kazberuk A, Bolinska S, Mlodawska E, Lopatowska P, Sobkowicz B, Musial W. Does admission anaemia still predict mortality six years after myocardial infarction? *Kardiol Pol* 2014;72:488-493.
5. Young JB, Abraham WT, Albert NM, Gattis Stough W, Gheorghide M, Greenberg BH, O'Connor CM, She L, Sun JL, Yancy CW, Fonarow GC; OPTIMIZE-HF Investigators and Coordinators. Relation of low hemoglobin and anemia to morbidity and mortality in patients hospitalized with heart failure (insight from the OPTIMIZE-HF registry). *Am J Cardiol* 2008;101:223-230.
6. 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.
7. 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.
8. Jankowska EA, von Haehling S, Anker SD, Macdougall IC, Ponikowski P. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2010;31:1872-1880.
9. Kajimoto K, Sato N, Takano T; Investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry. Association between anemia, clinical features and outcome in patients hospitalized for acute heart failure syndromes. *Eur Heart J Acute Cardiovasc Care* 2015;4:568-576.
10. Beck-da-Silva L, Piardi D, Soder S, Rohde LE, Pereira-Barretto AC, de Albuquerque D, Bocchi E, Vilas-Boas F, Moura LZ, Montera MW, Rassi S, Clausell N. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. *Int J Cardiol* 2013;168:3439-3442.
11. Gutzwiller FS, Pfeil AM, Comin-Colet J, Ponikowski P, Filippatos G, Mori C, Braunhofer PG, Szucs TD, Schwenkglens M, Anker SD. Determinants of quality of life of patients with heart failure and iron deficiency treated with ferric carboxymaltose: FAIR-HF sub-analysis. *Int J Cardiol* 2013;168:3878 e3883.
12. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, McDonagh T, Parkhomenko A, Tavazzi L, Levesque V, Mori C, Roubert B, Filippatos G, Ruschitzka F, Anker SD; CONFIRM-HF Investigators. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015;36:657 e668.
13. Jankowska EA, Tkaczyszyn M, Suchocki T, Drozd M, von Haehling S, Doehner W, Banasiak W, Filippatos G, Anker SD, Ponikowski P. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016;18:786 e795.
14. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Leiro MC, Drozd J, Fruhwald F, Gullestad L, Logeart D, Metra M, Parissis J, Persson H, Ponikowski P, Rauchhaus M, Voors A, Nielsen OW, Zannad F, Tavazzi L; Heart Failure Association of ESC (HFA). EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2010;12:1076 e 1084.
15. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozd J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavaliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A; Heart Failure Association (HFA) of the European Society of Cardiology (ESC). European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *Eur J Heart Fail* 2016;18:613 e625.
16. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol* 2007;165: 710 e718.
17. Jonsson A, Hallberg AC, Edner M, Lund LH, Dahlstrom U. A comprehensive assessment of the association between anemia, clinical covariates and outcomes in a population-wide heart failure registry. *Int J Cardiol* 2016;211:124 e131.
18. Anand IS, Kuskowski MA, Rector TS, Florea VG, Glazer RD, Hester A, Chiang YT, Aknay N, Maggioni AP, Opasich C, Latini R, Cohn JN. Anemia and change in hemoglobin over time related to mortality and morbidity in patients with chronic heart failure: results from Val-HeFT. *Circulation* 2005;112:1121 e1127.

19. O'Meara E, Clayton T, McEntegart MB, McMurray JJ, Lang CC, Roger SD, Young JB, Solomon SD, Granger CB, Ostergren J, Olofsson B, Michelson EL, Pocock S, Yusuf S, Swedberg K, Pfeffer MA; CHARM Committees and Investigators. Clinical correlates and consequences of anemia in a broad spectrum of patients with heart failure: results of the Candesartan in Heart Failure: assessment of Reduction in Mortality and Morbidity (CHARM) Program. *Circulation* 2006;113:986 e994.
20. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJ, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van Veldhuisen DJ; RED-HF Committees; RED-HF Investigators. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013;368:1210 e1219.
21. Mentz RJ, Greene SJ, Ambrosy AP, Vaduganathan M, Subacius HP, Swedberg K, Maggioni AP, Nodari S, Ponikowski P, Anker SD, Butler J, Gheorghide M. Clinical profile and prognostic value of anemia at the time of admission and discharge among patients hospitalized for heart failure with reduced ejection fraction: findings from the EVEREST trial. *Circ Heart Fail* 2014;7:401 e408.
22. Pulignano G, Del Sindaco D, Di Lenarda A, Tinti MD, Tarantini L, Cioffi G, Tolone S, Pero G, Minardi G. Chronic renal dysfunction and anaemia are associated with cognitive impairment in older patients with heart failure. *J Cardiovasc Med (Hagerstown)* 2014;15:481 e490.
23. Larina VN, Bart BI. Clinical manifestations of anemia syndrome and its significance in the course of chronic heart failure in elderly patients. *Ter Arkh* 2014;86:53 e58.
24. van der Meer P, Postmus D, Ponikowski P, Cleland JG, O'Connor CM, Cotter G, Metra M, Davison BA, Givertz MM, Mansoor GA, Teerlink JR, Massie BM, Hillege HL, Voors AA. The predictive value of short-term changes in hemoglobin concentration in patients presenting with acute decompensated heart failure. *J Am Coll Cardiol* 2013;61:1973 e1981.
25. Maggioni AP, Opasich C, Anand I, Barlera S, Carbonieri E, Gonzini L, Tavazzi L, Latini R, Cohn J. Anemia in patients with heart failure: prevalence and prognostic role in a controlled trial and in clinical practice. *J Card Fail* 2005;11:91 e98.
26. Balsam P, Tyminska A, Kaplon-Cieslicka A, Ozieranski K, Peller M, Galas M, Marchel M, Drozd J, Filipiak KJ, Opolski G. Predictors of one-year outcome in patients hospitalised for heart failure: results from the Polish part of the Heart Failure Pilot Survey of the European Society of Cardiology. *Kardiol Pol* 2016;74:9 e17.
27. Kaplon-Cieslicka A, Ozieranski K, Balsam P, Tyminska A, Peller M, Galas M, Wyzgal M, Marchel M, Drozd J, Opolski G. Clinical characteristics and 1-year outcome of hyponatremic patients hospitalized for heart failure. *Pol Arch Med Wewn* 2015;125:120 e131.
28. Ozieranski K, Kaplon-Cieslicka A, Peller M, Tyminska A, Balsam P, Galas M, Marchel M, Crespo-Leiro M, Maggioni AP, Drozd J, Opolski G. Clinical characteristics and predictors of one-year outcome of heart failure patients with atrial fibrillation compared to heart failure patients in sinus rhythm. *Kardiol Pol* 2016;74:251 e261.