









Heart rate control and its predictors in patients with heart failure and sinus rhythm. Data from the European Society of Cardiology Long-Term Registry

Agata Tymińska¹, Krzysztof Ozierański¹, Marek Wawrzacz¹, Paweł Balsam¹,
 Cezary Maciejewski¹, Magdalena Kleszczewska¹, Magdalena Zawadzka¹,
 Michał Marchel¹, Maria G. Crespo-Leiro², Aldo P. Maggioni³, Jarosław Drożdż⁴,
 Grzegorz Opolski¹, Marcin Grabowski¹, Agnieszka Kapłon-Cieślicka¹

¹1st Department of Cardiology, Medical University of Warsaw, Poland

²Complexo Hospitalario Universitario A Coruña (CHUAC)-CIBERCV, La Coruña, Spain

³Centro Studi ANMCO (Associazione Nazionale Medici Cardiologi Ospedalieri), Florence, Italy

⁴Department of Cardiology, 1st Chair of Cardiology and Cardiac Surgery, Medical University of Lodz, Poland

Abstract

Background: Higher resting heart rate (HR) in patients with heart failure (HF) and sinus rhythm (SR) is associated with increased mortality. In patients hospitalized for HF, the aim herein, was to assess the use and dosage of guideline-recommended HR lowering medications, HR control at discharge and predictors of HR control.

Methods: In the present study, were Polish participants of the European Society of Cardiology HF Long-Term (ESC-HF-LT) Registry. Those selected were hospitalized for HF, with reduced ejection fraction (HFrEF) and SR at discharge ($n = 236$). The patients were divided in two groups (< 70 bpm and ≥ 70 bpm). Logistic regression was used to identify the predictors of HR ≥ 70 bpm.

Results: Of patients with HFrEF and SR, 59% had HR ≥ 70 bpm at hospital discharge. At discharge, 96% and only 0.5% of the patients with HFrEF and SR received beta-blocker and ivabradine, respectively. In the HF groups < 70 bpm and ≥ 70 bpm, only 11% and 4% of patients received beta-blocker target doses, respectively. There was no difference in the use of other guideline-recommended medications. Age, New York Heart Association class, HR on admission and lack of HR lowering medications were predictors of discharge HR ≥ 70 bpm.

Conclusions: Heart rate control after hospitalization for HFrEF is unsatisfactory, which may be attributed to suboptimal doses of beta-blockers, and negligence in use other HR lowering drugs (including ivabradine). (Cardiol J 2023; 30, 6: 964–973)

Key words: acute heart failure, hospitalization, sinus rhythm, target heart rate, beta-blocker, ivabradine

Introduction

Large studies have shown that a higher resting heart rate (HR) in patients with heart failure (HF) is associated with an increased risk of major

adverse cardiovascular events, including patient death [1–7]. Consequently, HR reduction has been shown to improve clinical outcomes in patients with chronic HF [8–13]. However, data regarding the targeted HR control are inconclusive for these

Address for correspondence: Krzysztof Ozierański, MD, PhD, First Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 5992958, fax: +48 22 5991957, e-mail: krzysztof.ozieranski@gmail.com

Received: 24.01.2022

Accepted: 17.07.2022

Early publication date: 11.08.2022

This article is available in open access under Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

patients and the new HF guidelines do not indicate the exact recommended resting HR value [14]. The lack of clear recommendations may be due to the heterogeneity of the HF group consisting of patients with atrial fibrillation/in sinus rhythm (SR), different values of left ventricular ejection fraction (LVEF), varying severity of symptoms and comorbidities, and therefore inconsistent effectiveness of HF medications. It can be hypothesized that the optimal target resting HR may differ in different HF subgroups. The available data refer mostly to patients with HF with reduced ejection fraction (HFrEF), suggesting a HR recommended value of ≤ 70 beats per minute (bpm) (based mainly on the findings from the SHIFT trial on ivabradine in SR) [15].

There is a lack of data on whether therapeutic goals in patients with HF are achieved in everyday clinical practice [16]. More valuable data can be obtained from registries that represent real-world patients and are of particular importance to the analysis of the HR distribution and its control in patients with HF.

The aim of this study was to assess HR control at discharge in real-life Polish patients with HFrEF and SR. The secondary goal was to analyze the association between HR control at discharge and clinical characteristics, use and dosage of guideline-recommended HR lowering medications. HR was also assessed at discharge in patients with HF with mildly reduced LVEF (HFmrEF), and HF with preserved LVEF (HFpEF).

Methods

Study design

The European Society of Cardiology (ESC) Heart Failure Pilot (ESC-HF-Pilot) survey and the ESC Heart Failure Long-Term (ESC-HF-LT) Registry were multicenter, prospective, observational surveys conducted in European countries, including a significant number of Polish centers. Patient recruitment in the ESC-HF-Pilot survey lasted from October 2009 to May 2010 and in the ESC-HF-LT Registry from April 2011 to April 2013. Both registries included all outpatients with HF and patients admitted for new-onset or worsening HF. More data on the design of the registries have been published previously [17, 18]. Briefly, records collected in both registries refer to clinical characteristics, laboratory parameters, HF management, and 1-year follow-up. Both HF registries collected the same type of clinical data. Adult patients with

HF were enrolled, without specific exclusion criteria. The study protocol was approved by the local ethics committees. All participating patients gave written informed consent for the study.

The current analysis included Polish patients hospitalized for HF included in the ESC-HF-LT Registry (the data from ESC-HF-Pilot survey was used for the comparison of HR control at discharge and concomitant pharmacotherapy over time). Only patients with a known heart rhythm and HR at discharge were included in the analysis. A case report form enabled the investigators to choose only one leading heart rhythm for each patient (SR, atrial fibrillation, paced rhythm, or other) based on a 12-lead electrocardiogram (ECG). The exclusion criteria were as follows: death during index hospitalization, rhythm other than SR or lack of ECG documentation on the leading heart rhythm, and lack of information on HR at discharge.

Bar graphs were plotted to present HR distribution at discharge in HF patients in SR in both registries.

The patients were further divided into three groups based on LVEF: HFrEF (LVEF of $\leq 40\%$), HFmrEF (LVEF of 41–49%), and HFpEF (LVEF of $\geq 50\%$) [14]. As the current ESC recommendations on HR control mainly account for patients with HFrEF in SR, we focused on this group in further analyzes. Patients with HFrEF in SR included in the ESC-HF-LT Registry were divided into two groups with an HR at discharge of < 70 bpm or ≥ 70 bpm and were compared in terms of baseline characteristics. The use and dosage of guideline-recommended HR lowering medications in these groups were also assessed. In order to analyze the predictors of poor HR control (HR ≥ 70 bpm) at discharge in the HFrEF group, common risk factors for increased HR in HF patients in SR were collected from the literature.

Statistical analysis

The Fisher exact test for the comparison of categorical variables and the Mann–Whitney test for continuous and ordinal variables were used, respectively. The results were presented as median and quartiles for continuous variables and as frequencies and percentages for ordinal variables. Logistic regression analysis was used for the analysis of the predictors of poor HR control (≥ 70 bpm). P value below 0.05 was considered significant for all tests. All tests were two-tailed. Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics 22, USA, New York).

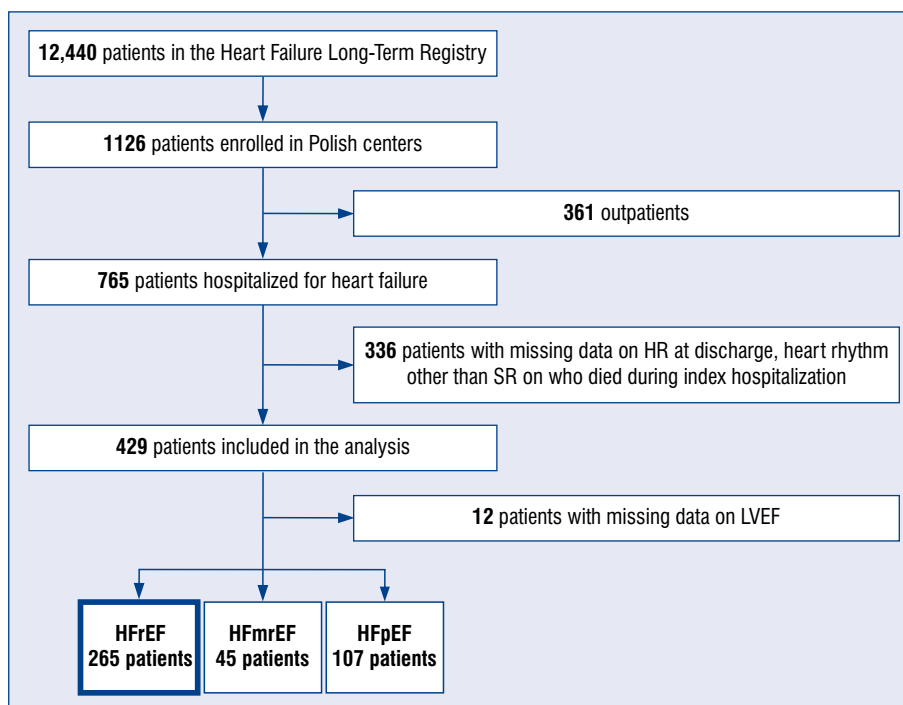


Figure 1. Flow chart of patient enrollment in the current analysis; LVEF — left ventricular ejection fraction; HFrEF — heart failure with reduced LVEF; HFmrEF — heart failure with mildly reduced LVEF; HFpEF — heart failure with preserved LVEF; HR — heart rate; SR — sinus rhythm.

Results

Baseline characteristics and HR distribution

Figure 1 shows the flow chart of patient selection for the present study. The final analysis included 429 hospitalized Polish patients from the ESC-HF-LT Registry in SR and with a known HR at discharge. The median patient age was 76 years; men constituted 67.9% of the population. By comparison, the ESC-HF-Pilot survey included 399 hospitalized patients in SR (the median age was 73 years; men constituted 64.4%). In both registries, the majority of the patients had resting HR ≥ 70 bpm at hospital discharge (65.7% and 56.6%; $p = 0.01$ in the ESC-HF-Pilot and ESC-HF-LT registries, respectively). The same was also observed in a subgroup of patients in SR with HFrEF (66.3% and 56.8%; $p = 0.048$, respectively) (Table 1). Based on these results, it seems that the HR management only slightly improved over time in patients participating in the ESC-HF registries.

Heart rate distribution at discharge among patients in SR participating in the ESC-HF-LT Registry and the ESC-HF-Pilot survey are presented in Figures 2A and 2B, respectively.

HFrEF patients ($n = 265$) in SR included in the ESC-HF-LT Registry were divided into two groups with an HR at discharge of < 70 or ≥ 70 bpm (112 patients, 41.5% and 153 patients, 58.5%, respectively). There were no relevant differences between the groups in most baseline clinical characteristics (Table 2). Median HR on admission was 73 (60–80) bpm and 85 (75–100) bpm ($p < 0.001$), respectively. While on discharge, the median HR was 60.0 (60–65) and 76.0 (70–80) bpm ($p < 0.001$), respectively. There was no significant change in HR from admission to discharge between both groups. Similar analyzes for patients with HFmrEF and HFpEF are presented in **Supplementary Tables S1 and S2**, respectively.

Almost all HFrEF patients in SR in the ESC-HF-LT Registry received beta-blockers (approx. 96%) irrespective of the resting HR group. However, patients with lower HR (< 70 bpm) were treated with amiodarone more frequently (21.4%) compared to patients with HR ≥ 70 bpm (9.8%; $p = 0.01$). The doses of beta-blockers in both groups were suboptimal (10.9% and 4.4% patients received 100% of the beta-blocker target dose, respectively) (Table 3). Ivabradine was used in

Table 1. Comparison of heart rate (HR) control at discharge and concomitant pharmacotherapy between patients with heart rate with reduced ejection fraction (HFrEF) in sinus rhythm (SR) participating in the ESC-HF-Pilot and ESC-HF-LT registries (patient recruitment 2009–2010 and 2011–2013, respectively).

	Total (n = 464)	HFrEF-Pilot Registry (n = 199; 42.9%)	HFrEF-LT Registry (n = 265; 57.1%)	P
HR at admission [bpm]	78 (70–90)	80 (70–100)	80 (70–95)	0.05
HR at discharge [bpm]	70 (64–78)	70 (65–80)	70 (63–76)	0.08
Change in HR [bpm]*	8 (0–20)	10 (0–25)	10 (0–20)	0.20
Patients with HR < 70 bpm at hospital discharge	169 (38.9%)	67 (33.7%)	102 (43.2%)	0.048
Pharmacotherapy at hospital discharge				
Beta-blocker	412/434 (94.9%)	185/198 (93.4%)	227 (96.2%)	0.27
Dose of beta-blocker	5.0 (2.5–5.0); <i>401</i>	5.0 (5.0–5.0); <i>185</i>	5.0 (2.5–5.0); <i>216</i>	< 0.001
Ivabradine	2/434 (0.5%)	0/198 (0%)	2 (0.8%)	–
Digoxin	79/434 (18.2%)	40/198 (20.2%)	39 (16.5%)	0.38
Amiodaron	56/434 (12.9%)	20/198 (10.1%)	31 (13.0%)	0.12
Other antiarrhythmics	36/434 (8.3%)	28/198 (14.1%)	8 (3.4%)	< 0.001
Diuretics	379/434 (87.3%)	167/198 (84.3%)	212 (89.8%)	0.11
Aldosterone antagonist	333/434 (76.7%)	149/198 (75.3%)	184 (78.0%)	0.57
ACEI	349/434 (80.4%)	157/198 (79.3%)	192 (81.4%)	0.63
ARB	41/434 (9.4%)	18/198 (9.1%)	23 (9.7%)	0.87
CCB	44/434 (10.1%)	25/198 (12.6%)	19 (8.1%)	0.15
Statins	331/434 (76.3%)	157/198 (79.3%)	174 (73.7%)	0.21
Anticoagulants	117/433 (27.0%)	51/197 (25.9%)	66 (28.0%)	0.67
Antiplatelets	341/434 (78.6%)	161/198 (81.3%)	180 (76.3%)	0.24

*From admission to discharge. Bolded text indicates p-values < 0.05. Numbers in italics indicate available cases for the analyzed continuous variable. ACEI — angiotensin-converting-enzyme inhibitor; ARB — angiotensin receptor blocker; bpm — beats per minute; CCB — calcium channel blocker; ESC-HF-LT — European Society of Cardiology Heart Failure Long-Term Registry; ESC-HF-Pilot — European Society of Cardiology Heart Failure Pilot Registry

a marginal percentage (0.01%) of patients in both groups. There was no difference in terms of the use of other guideline-recommended medications (Table 2).

Predictors of poor HR control

Age, New York Heart Association (NYHA) class, HR on admission and lack of HR lowering medications were the predictors of poor HR control (≥ 70 bpm) at discharge in patients with HFrEF in SR (Table 4).

Discussion

The results of this analysis provided important epidemiological data on HR control and associated clinical characteristics in real-life patients with HF. The study showed that HR over 70 bpm was present in the majority of HF patients in SR and that the patients were treated sub-optimally with HR

lowering drugs. What is more, the study revealed the predictors of poor HR control.

Despite strict guidelines on the treatment of HFrEF, the readmission rate within 6 months of hospitalization for HF is as high as 50% [14, 19]. It is known that increased resting HR in patients with HF is associated with higher mortality [4, 20], particularly when above 110 bpm and with concomitant atrial fibrillation [21, 22]. HR can also contribute to tachyarrhythmic cardiomyopathy and HF decompensation. In the previous analysis from the ESC-HF registries, among all tested major electrocardiography (ECG) abnormalities in patients with HF (regardless of the type of HF), only tachycardia (> 100 bpm) remained an independent predictor of all-cause death in multivariable analysis [23].

In patients hospitalized for HF decompensation doses of guideline-recommended medications should be initially uptitrated before discharge

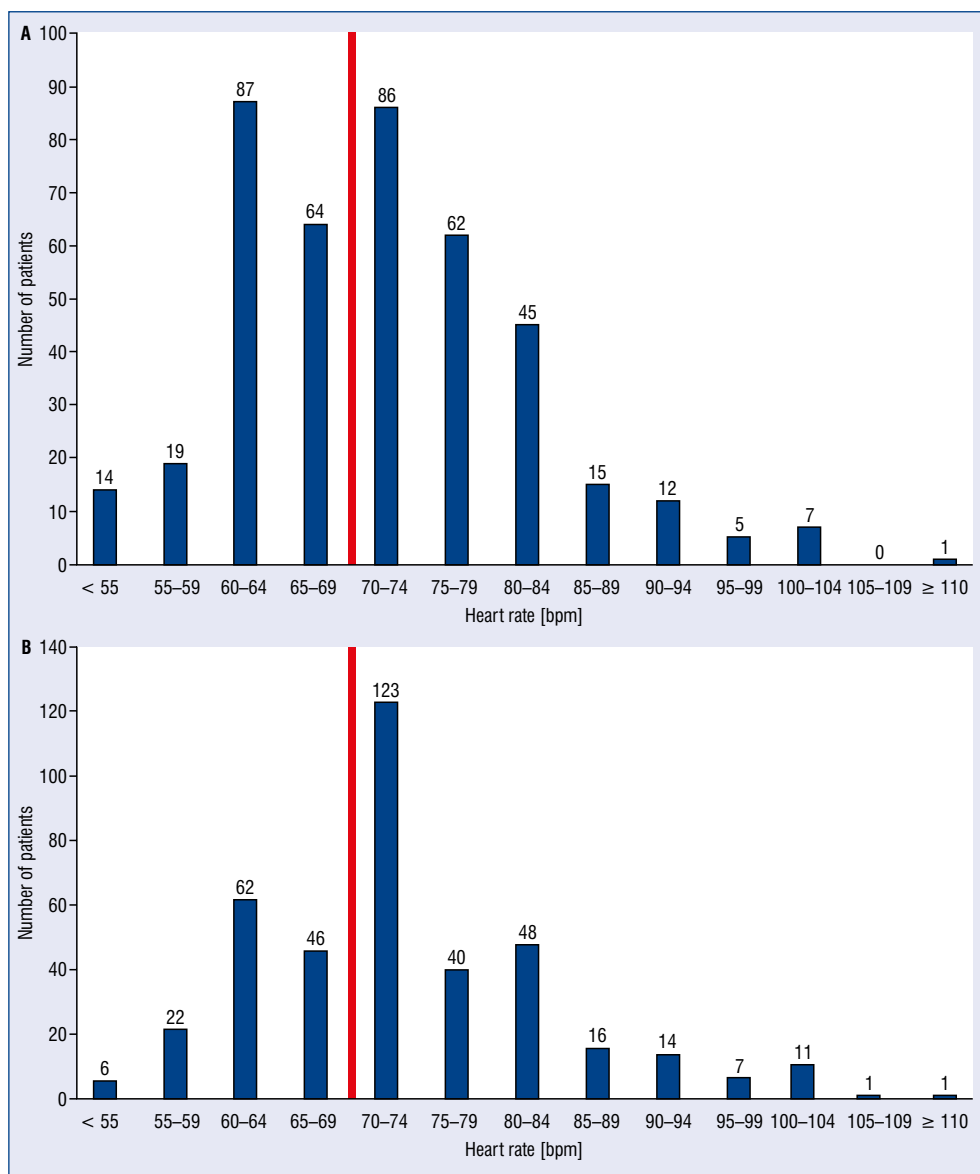


Figure 2. Distribution of heart rate at discharge in heart failure patients in sinus rhythm participating in the European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) (A) and European Society of Cardiology Heart Failure Pilot Registry (ESC-HF Pilot survey) (B). Red line separates the graph into two heart rate groups: < 70 bpm and ≥ 70 bpm.

and/or in the early post-discharge period. HR control should be assessed during every follow-up appointment to further adjust the medications [14]. In patients with HF, HR reduction is achieved mostly by beta-blocker therapy through their negative chronotropic effect and direct antagonization of toxic effects of catecholamines. Ivabradine acts by selectively and specifically inhibiting the channel responsible for the cardiac pacemaker current (If), and thus it regulates the HR in patients in SR. Other guideline-recommended medications commonly used in chronic HF also have the ability to reduce

the HR by reducing sympathetic and renine-angiotensine system activity [24]. The international QUALIFY survey (QUALITY of adherence to guideline recommendations for Life-saving treatment in heart failure) has demonstrated that the adherence to guidelines is associated with an improved prognosis in patients with HF [25]. In the Polish population of the QUALIFY registry nearly 97.0% of the patients received beta-blockers, with only 17.7% of the patients reaching the target dose [25]. The general adherence score (calculated based on the use of five main guideline-recommended

Table 2. Baseline characteristics, clinical course of index hospitalization and pharmacotherapy in hospitalized heart rate with reduced ejection fraction (HFrEF) patients in sinus rhythm (SR) stratified by heart rate at discharge < 70 and ≥ 70 bpm (from the Polish cohort of the ESC-HF-LT Registry).

	HFrEF, SR < 70/min (n = 112; 41.5%)	HFrEF, SR ≥ 70/min (n = 153; 58.5%)	P
Demographics			
Age [years]	66.5 (57.6–75.3)	63.9 (57.2–72.3)	0.09
Male	90 (80.4%)	118 (77.1%)	0.55
Body mass index [kg/m ²]	27.7 (24.6–29.5)	27.8 (24.7–31.0)	0.58
Medical history			
Previous HF hospitalization	63 (56.2%)	79 (51.6%)	0.53
Ischemic etiology	82 (73.2%)	105 (68.6%)	0.50
Valve disease	6 (5.4%)	4 (2.6%)	0.33
Dilated cardiomyopathy	17 (15.2%)	32 (20.9%)	0.27
Hypertension	82/111 (73.2%)	102/152 (66.7%)	0.28
Atrial fibrillation	25 (22.3%)	34 (22.2%)	1.00
Coronary artery disease	80 (71.4%)	101 (66.0%)	0.42
Prior PCI or CABG	55 (49.1%)	72 (47.1%)	0.80
Peripheral artery disease	16 (14.3%)	22/152 (14.5%)	1.00
Diabetes	43 (38.4%)	50 (32.7%)	0.36
Chronic kidney disease	25 (22.3%)	46 (30.1%)	0.20
COPD	14 (12.5%)	22 (14.4%)	0.71
Stroke	10 (8.9%)	15 (9.8%)	0.83
Current smoking	82 (73.2%)	105 (68.6%)	0.49
Alcohol ¹	79/108 (73.1%)	108/146 (74%)	0.88
Clinical status at admission			
NYHA class:			0.16
I	0 (0%)	0 (0%)	–
II	32 (28.6%)	35 (22.9%)	–
III	52 (46.4%)	66 (43.1%)	–
IV	26 (23.2%)	52 (34.0%)	–
Heart rate [bpm]	73.0 (60.0–80.0)	85.0 (75.0–100.0)	< 0.001
SBP [mmHg]	130.0 (110.0–140.0)	120.0 (110.0–140.0)	0.04
DBP [mmHg]	80.0 (70.0–86.2)	80.0 (70.0–84.0)	0.88
Laboratory findings at admission			
Hemoglobin [g/dL]	13.4 (12.6–14.6); 111	13.2 (11.3–14.4); 152	0.11
Serum creatinine [mg/dL]	1.1 (0.9–1.3); 111	1.1 (0.9–1.4); 152	0.45
Serum sodium [mmol/L]	139.0 (137.0–141.0); 111	139.0 (136.9–141.0); 152	0.76
Serum potassium [mmol/L]	4.4 (4.1–4.7); 111	4.5 (4.1–4.9); 152	0.37
BNP [pg/mL]	901.5 (199.8–1449.0); 14	766.5 (319.4–1058.2); 16	0.67
NT-proBNP [pg/mL]	4263.5 (1505.0–8783.8); 48	4819.5 (2565.8–10108.5); 74	0.27
Clinical status at discharge			
NYHA class:			0.22
I	2 (1.8%)	9 (5.9%)	–
II	61 (54.5%)	90 (58.8%)	–
III	46 (41.1%)	52 (34.0%)	–
IV	3 (2.7%)	2 (1.3%)	–
Heart rate [bpm]	60.0 (60.0–65.0)	76.0 (70.0–80.0)	< 0.001
Change in heart rate [bpm] ²	–10.0 (–21.2–0.0)	–7.0 (–20.0–1.0)	0.15

→

Table 2 (cont.). Baseline characteristics, clinical course of index hospitalization and pharmacotherapy in hospitalized heart rate with reduced ejection fraction (HFrEF) patients in sinus rhythm (SR) stratified by heart rate at discharge < 70 and ≥ 70 bpm (from the Polish cohort of the ESC-HF-LT Registry).

	HFrEF, SR < 70/min (n = 112; 41.5%)	HFrEF, SR ≥ 70/min (n = 153; 58.5%)	P
SBP [mmHg]	120.0 (105.0–130.0)	118.0 (105.0–126.0)	0.66
DBP [mmHg]	70.0 (64.5–79.5); <i>111</i>	70.0 (65.0–80.0); <i>153</i>	0.59
Laboratory findings at discharge			
Hemoglobin [g/dL]	13.2 (12.0–14.7); <i>62</i>	12.4 (10.4–13.4); <i>88</i>	0.002
Serum creatinine [mg/dL]	1.1 (0.9–1.3); <i>81</i>	1.1 (0.9–1.4); <i>106</i>	0.88
Serum sodium [mmol/L]	138.9 (137.0–141.4); <i>82</i>	139.0 (137.0–141.1); <i>114</i>	0.65
Serum potassium [mmol/L]	4.4 (4.1–4.7); <i>85</i>	4.4 (4.1–4.7); <i>115</i>	0.34
Pharmacotherapy at hospital discharge			
Beta-blocker	108 (96.4%)	147 (96.1%)	1.00
Dose of beta-blocker ³	5.0 (2.5–5.0); <i>99</i>	5.0 (2.5–5.0); <i>143</i>	0.96
Digoxin	16 (14.3%)	24 (15.7%)	0.86
Ivabradine	0 (0.0%)	2 (1.3%)	0.51
Amiodaron	24 (21.4%)	15 (9.8%)	0.01
Other antiarrhythmics	3 (2.7%)	6 (3.9%)	0.73
Diuretics	95 (84.8%)	135 (88.2%)	0.46
ACEI	91 (81.2%)	130 (85.0%)	0.50
Dose of ACEI ⁴	5.0 (2.5–5.0); <i>89</i>	5.0 (2.5–5.6); <i>128</i>	0.22
ARB	12 (10.7%)	11 (7.2%)	0.37
Aldosterone antagonist	86 (76.8%)	113 (73.9%)	0.66
Dose of aldosterone antagonist ⁵	25.0 (25.0–25.0); <i>85</i>	25.0 (25.0–50.0); <i>113</i>	0.50
CCB	10 (8.9%)	13 (8.5%)	1.00
Statins	89 (79.5%)	109 (71.2%)	0.15
Anticoagulants	33 (29.5%)	33 (29.5%)	0.66
Antiplatelets	87 (77.7%)	116 (75.8%)	0.77

Bolded text indicates p-values < 0.05. Numbers in italics indicate available cases for the analyzed continuous variable. ¹Former or sometimes; ²Change was calculated as the heart rate on admission minus the heart rate at discharge; ³Total daily doses of commonly used beta-blockers converted to the corresponding dose of bisoprolol; ⁴Total daily doses of commonly used ACE-Is converted to the corresponding dose of ramipril; ⁵Total daily doses of commonly used aldosterone antagonists converted to the corresponding dose of eplerenone. ACEI — angiotensin-converting-enzyme inhibitor; ARB — angiotensin receptor blocker; BNP — B-type natriuretic peptide; bpm — beats per minute; CABG — coronary artery bypass grafting; CCB — calcium channel blocker; COPD — chronic obstructive pulmonary disease; DBP — diastolic blood pressure; ESC-HF-LT — European Society of Cardiology Heart Failure Long-Term Registry; HF — heart failure; NT-proBNP — N-terminal-pro-B-type natriuretic peptide; NYHA — New York Heart Association; PCI — percutaneous coronary intervention; SBP — systolic blood pressure

medications) in the study population was good in 72.2% of the patients [25]. In another analysis performed among the Spanish population included in the same registry (ESC-HF-LT Registry) showed that only 13% of patients with low ejection fraction received a beta-blocker in the recommended dosage [26]. In the current study, beta-blockers were administered in the majority of the patients (approx. 96%). However, only 10.9% of the patients with HR < 70 bpm and 4.4% ≥ 70 bpm reached the target dose of the beta-blocker. Ivabradine was administered only to 0.5% of patients with LVEF ≤ 35%. To compare, in the QUALIFY registry,

ivabradine was prescribed to 13.9% of patients, but the target dose was attained only in 13.8% of patients [25]. It should be highlighted that ivabradine reduces the risk of cardiovascular mortality and HF hospitalization and should be considered in symptomatic patients with reduced ejection fraction (≤ 35%) in SR and a resting HR ≥ 70 bpm despite optimal medical therapy with other HF recommended-medications (or in patients who are unable to tolerate or have contraindications to beta-blockers) [14, 27].

Observational studies have demonstrated that in every third patient with chronic HF, despite the

Table 3. Use of guideline-recommended heart rate lowering drugs among hospitalized heart rate with reduced ejection fraction patients in sinus rhythm (SR) stratified by heart rate at discharge < 70 and ≥ 70 bpm (from the Polish cohort of the ESC-HF-LT Registry). Use of ivabradine was not presented, as only 2 patients were administered this drug.

Beta-blockers, target dose [mg/d]	Patients, n (%)	Dose [mg/d], mean (SD)	Target dose, %	
			≥ 50% of target dose	100% of target dose
SR < 70 bpm				
Any beta-blocker	108/112 (96.4%)	–	41.1%*	10.9%*
Bisoprolol, 10 mg/d	29/108 (26.9%)	3.88 (2.66)	37.9%	6.9%
Carvedilol, 50 mg/d	58/108 (53.7%)	19.1 (12.5)	37.9%	10.3%
Metoprolol succinate, 200 mg/d	13/108 (12%)	78.8 (60.2)	38.5%	15.4%
Nebivololol, 10 mg/d	8/108 (7.4%)	3.75 (1.34)	50%	0%
Other	0/108 (0%)	–	–	–
SR ≥ 70 bpm				
Any beta-blocker	147/153 (96.1%)	–	46.1%*	4.4%*
Bisoprolol, 10 mg/d	43/147 (29.3%)	3.95 (2.08)	53.5%	4.7%
Carvedilol, 50 mg/d	71/147 (48.3%)	17.5 (11.2)	35.2%	5.6%
Metoprolol succinate, 200 mg/d	16/147 (10.9%)	71.9 (37.5)	31.3%	0%
Nebivololol, 10 mg/d	14/147 (9.5%)	4.55 (2.28)	64.2%	7.1%
Other	3/147 (2%)	–	–	–

*Patients on other beta-blockers (not recommended in the HFrEF) were not included in the analysis; bpm — beats per minute; ESC-HF-LT — European Society of Cardiology Heart Failure Long-Term Registry; SD — standard deviation

Table 4. Multivariable analysis of predictors of poor heart rate control (≥ 70 bpm) at discharge in hospitalized heart rate with reduced ejection fraction patients in sinus rhythm (SR) (from the Polish cohort of the ESC-HF-LT Registry).

Covariates	OR	95% CI	P
Age	0.96	0.93–0.99	0.02
Male	0.62	0.29–1.29	0.20
Coronary artery disease	1.54	0.77–3.12	0.22
Chronic obstructive pulmonary disease	1.00	0.42–2.43	0.99
Chronic kidney disease	2.06	0.93–4.63	0.08
SBP at discharge	1.00	0.98–1.01	0.65
NYHA class III/IV (NYHA I/II as reference) at discharge	0.39	0.20–0.75	0.01
Heart rate at admission	1.05	1.03–1.07	< 0.001
Hemoglobin concentration at admission	0.89	0.75–1.04	0.16
Left ventricular ejection fraction	1.00	0.96–1.04	0.90
Beta-blocker dosage at discharge	1.05	0.96–1.17	0.28
Drugs lowering heart rate*	0.43	0.21–0.86	0.02

Bolded text indicates p-values < 0.05. *Other than beta-blockers; bpm — beats per minute; CI — confidence interval; ESC-HF-LT — European Society of Cardiology Heart Failure Long-Term Registry; NYHA — New York Heart Association; OR — odds ratio; SBP — systolic blood pressure

use of the recommended treatment, the control of resting HR was insufficient [28]. In the QUALIFY registry less than 40% of the patients reached the

target HR < 70 bpm [25]. In the present study, 66.3% and 56.8% of patients (ESC-HF-Pilot and ESC-HF-LT; p = 0.048) had HR over 70 bpm.

There was a difference in terms of adequate HR control between the ESC-HF-Pilot and ESC-HF-LT groups in favor of the latter. Unfortunately, still more than half of the patients were not optimally treated (HR was ≥ 70 bpm). This was despite the fact that the percentage of the patients receiving HF guideline-recommended drugs was higher in the ESC-HF-LT registry in comparison with the ESC-HF-Pilot group [29].

On the other hand, it may be emphasized that the therapeutic benefit correlates with the degree of HR reduction, and not with the dose of the beta-blocker, and the optimal HR should be the goal of HF therapy. A meta-analysis by McAlister et al. [30] showed that a 5-bpm reduction in HR reduces mortality by 18%. While, every 1 bpm increase in HR the increases the risk by 3% [2]. In the current study the group with HR < 70 bpm patients had a more than twice the rate of amiodarone use than the group with HR > 70 bpm, which could result in better HR control.

In the present study, in the multivariable analysis it was observed that younger age, lower NYHA class at discharge, higher HR on admission and no use of HR lowering medications were independent predictors of poor HR control (HR ≥ 70 bpm). A study assessing, i.e., the extent of HR reduction achieved in clinical practice, showed that patients with increased HRs were younger, more often male, with a higher NYHA class and lower LVEF [31].

The suboptimal use of chronotropic negative therapy is observed especially in patients with co-existing lung diseases [32]. It should be noted that the use of beta-blockers in patients with chronic obstructive pulmonary disease is not only safe but it also reduces their all-cause and in-hospital mortality [32, 33]. Therefore, apart from typical HF medications, adequate HR control and treatment of comorbidities should constitute a cornerstone element of HF therapy.

Limitations of the study

The inclusion of real-life patients followed-up by cardiologists is an important advantage of the ESC-HF registries; however, there are limitations that have to be acknowledged. First, it is the partial incompleteness of the data and its observational character. Second, the registries did not primarily focus on heart rhythm analysis. Thirdly, taking into account the fact that the mean HR is slightly higher in females than in males of the same age, it should be noted that females were underrepresented in the current study. Fourthly, in the analysis there

was a marked difference in hemoglobin levels between the HF groups with HR < 70 and ≥ 70 bpm [34]. Anemia is a known risk factor that can cause a hyperdynamic circulatory state and affect resting HR and could have altered the HR control [35].

Conclusions

The results of this study suggest that HR control in real-life patients with HF only slightly improved over time (between the ESC-HF-Pilot and ESC-HF-LT groups), and it remains unsatisfactory. This might be due to the suboptimal use and dosage of HF guideline-recommended medications, particularly of beta-blockers and ivabradine.

Conflict of interest: None declared

References

- Greene S, Vaduganathan M, Wilcox J, et al. The prognostic significance of heart rate in patients hospitalized for heart failure with reduced ejection fraction in sinus rhythm. *JACC: Heart Failure*. 2013; 1(6): 488–496, doi: [10.1016/j.jchf.2013.08.005](https://doi.org/10.1016/j.jchf.2013.08.005).
- Böhm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. *Lancet*. 2010; 376(9744): 886–894, doi: [10.1016/s0140-6736\(10\)61259-7](https://doi.org/10.1016/s0140-6736(10)61259-7).
- DeVore AD, Schulte PJ, Mentz RJ, et al. Relation of elevated heart rate in patients with heart failure with reduced ejection fraction to one-year outcomes and costs. *Am J Cardiol*. 2016; 117(6): 946–951, doi: [10.1016/j.amjcard.2015.12.031](https://doi.org/10.1016/j.amjcard.2015.12.031), indexed in Pubmed: [26805662](https://pubmed.ncbi.nlm.nih.gov/26805662/).
- Laskey WK, Alomari I, Cox M, et al. Heart rate at hospital discharge in patients with heart failure is associated with mortality and rehospitalization. *J Am Heart Assoc*. 2015; 4(4), doi: [10.1161/JAHA.114.001626](https://doi.org/10.1161/JAHA.114.001626), indexed in Pubmed: [25904590](https://pubmed.ncbi.nlm.nih.gov/25904590/).
- Vollmert T, Hellmich M, Gassanov N, et al. Heart rate at discharge in patients with acute decompensated heart failure is a predictor of mortality. *Eur J Med Res*. 2020; 25(1): 47, doi: [10.1186/s40001-020-00448-9](https://doi.org/10.1186/s40001-020-00448-9), indexed in Pubmed: [33032633](https://pubmed.ncbi.nlm.nih.gov/33032633/).
- Cierpka-Kmieć K, Hering D. Tachycardia: The hidden cardiovascular risk factor in uncomplicated arterial hypertension. *Cardiol J*. 2020; 27(6): 857–867, doi: [10.5603/CJ.a2019.0021](https://doi.org/10.5603/CJ.a2019.0021), indexed in Pubmed: [30799548](https://pubmed.ncbi.nlm.nih.gov/30799548/).
- Yetkin E, Ozturk S, Cuglan B, et al. Golden ratio in congestive heart failure: A promising proportion for prognosis and decompensation. *Cardiol J*. 2020; 27(6): 904–905, doi: [10.5603/CJ.2020.0177](https://doi.org/10.5603/CJ.2020.0177), indexed in Pubmed: [33432572](https://pubmed.ncbi.nlm.nih.gov/33432572/).
- Hess PL, Sheng S, Matsouaka R, et al. Strict versus lenient versus poor rate control among patients with atrial fibrillation and heart failure (from the Get With The Guidelines — Heart Failure Program). *Am J Cardiol*. 2020; 125(6): 894–900, doi: [10.1016/j.amjcard.2019.12.025](https://doi.org/10.1016/j.amjcard.2019.12.025), indexed in Pubmed: [31980141](https://pubmed.ncbi.nlm.nih.gov/31980141/).
- Sartipy U, Savarese G, Dahlström U, et al. Association of heart rate with mortality in sinus rhythm and atrial fibrillation in heart failure with preserved ejection fraction. *Eur J Heart Fail*. 2019;

- 21(4): 471–479, doi: [10.1002/ejhf.1389](https://doi.org/10.1002/ejhf.1389), indexed in Pubmed: [30698317](https://pubmed.ncbi.nlm.nih.gov/30698317/).
10. Swedberg K, Komajda M, Böhm M, et al. SHIFT Investigators. Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study. *J Am Coll Cardiol*. 2012; 59(22): 1938–1945, doi: [10.1016/j.jacc.2012.01.020](https://doi.org/10.1016/j.jacc.2012.01.020), indexed in Pubmed: [22617188](https://pubmed.ncbi.nlm.nih.gov/22617188/).
 11. Packer M, Coats A, Fowler MB. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001; 344(22): 1651–1658, doi: [10.1056/NEJM200105313442201](https://doi.org/10.1056/NEJM200105313442201), indexed in Pubmed: [11386263](https://pubmed.ncbi.nlm.nih.gov/11386263/).
 12. Fowler MB, Vera-Llonch M, Oster G. Influence of carvedilol on hospitalizations in heart failure: incidence, resource utilization and costs. *J Am Coll Cardiol*. 2001; 37(6): 1692–1699, doi: [10.1016/s0735-1097\(01\)01190-1](https://doi.org/10.1016/s0735-1097(01)01190-1), indexed in Pubmed: [11345386](https://pubmed.ncbi.nlm.nih.gov/11345386/).
 13. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996; 334(21): 1349–1355, doi: [10.1056/NEJM199605233342101](https://doi.org/10.1056/NEJM199605233342101), indexed in Pubmed: [8614419](https://pubmed.ncbi.nlm.nih.gov/8614419/).
 14. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021; 3599–3726, doi: [10.1093/eurheartj/ehab368](https://doi.org/10.1093/eurheartj/ehab368), indexed in Pubmed: [34447992](https://pubmed.ncbi.nlm.nih.gov/34447992/).
 15. Borer JS, Böhm M, Ford I, et al. Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study. *Eur Heart J*. 2012; 33(22): 2813–2820, doi: [10.1093/eurheartj/ehs259](https://doi.org/10.1093/eurheartj/ehs259), indexed in Pubmed: [22927555](https://pubmed.ncbi.nlm.nih.gov/22927555/).
 16. Ramgobin D, Vo M, Golamari R, et al. Congestive heart failure clinics and telemedicine: The key to reducing hospital readmissions in the United States. *Cardiol J*. 2021 [Epub ahead of print], doi: [10.5603/CJ.a2021.0073](https://doi.org/10.5603/CJ.a2021.0073), indexed in Pubmed: [34308538](https://pubmed.ncbi.nlm.nih.gov/34308538/).
 17. Maggioni AP, Dahlström U, Filippatos G, et al. EURObservational Research Programme: the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail*. 2010; 12(10): 1076–1084, doi: [10.1093/eurjhf/hfq154](https://doi.org/10.1093/eurjhf/hfq154), indexed in Pubmed: [20805094](https://pubmed.ncbi.nlm.nih.gov/20805094/).
 18. Crespo-Leiro MG, Anker SD, Maggioni AP, et al. 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(6): 613–625, doi: [10.1002/ejhf.566](https://doi.org/10.1002/ejhf.566).
 19. Desai AS, Stevenson LW. Rehospitalization for heart failure: predict or prevent? *Circulation*. 2012; 126(4): 501–506, doi: [10.1161/CIRCULATIONAHA.112.125435](https://doi.org/10.1161/CIRCULATIONAHA.112.125435), indexed in Pubmed: [22825412](https://pubmed.ncbi.nlm.nih.gov/22825412/).
 20. Kapłon-Cieślicka A, Balsam P, Ozierański K, et al. Resting heart rate at hospital admission and its relation to hospital outcome in patients with heart failure. *Cardiol J*. 2014; 21(4): 425–433, doi: [10.5603/CJ.a2013.0147](https://doi.org/10.5603/CJ.a2013.0147), indexed in Pubmed: [24142684](https://pubmed.ncbi.nlm.nih.gov/24142684/).
 21. Ozierański K, Kapłon-Cieślicka A, Balsam P, et al. Effect of beta-blockers on 1-year survival and hospitalizations in patients with heart failure and atrial fibrillation: results from ESC-HF Pilot and ESC-HF Long-Term Registry. *Pol Arch Intern Med*. 2018; 128(11): 649–657, doi: [10.20452/pamw.4346](https://doi.org/10.20452/pamw.4346), indexed in Pubmed: [30303491](https://pubmed.ncbi.nlm.nih.gov/30303491/).
 22. Simpson J, Castagno D, Doughty RN, et al. Is heart rate a risk marker in patients with chronic heart failure and concomitant atrial fibrillation? Results from the MAGGIC meta-analysis. *Eur J Heart Fail*. 2015; 17(11): 1182–1191, doi: [10.1002/ejhf.346](https://doi.org/10.1002/ejhf.346), indexed in Pubmed: [26358762](https://pubmed.ncbi.nlm.nih.gov/26358762/).
 23. Tymińska A, Ozierański K, Balsam P, et al. The prevalence and association of major ECG abnormalities with clinical characteristics and the outcomes of real-life heart failure patients - Heart Failure Registries of the European Society of Cardiology. *Kardiol Pol*. 2021; 79(9): 980–987, doi: [10.33963/KPa2021.0053](https://doi.org/10.33963/KPa2021.0053), indexed in Pubmed: [34227675](https://pubmed.ncbi.nlm.nih.gov/34227675/).
 24. Hori M, Okamoto H. Heart rate as a target of treatment of chronic heart failure. *J Cardiol*. 2012; 60(2): 86–90, doi: [10.1016/j.jjcc.2012.06.013](https://doi.org/10.1016/j.jjcc.2012.06.013), indexed in Pubmed: [22920717](https://pubmed.ncbi.nlm.nih.gov/22920717/).
 25. Opolski G, Ozierański K, Lelonek M, et al. Adherence to the guidelines on the management of systolic heart failure in ambulatory care in Poland. Data from the international QUALIFY survey. *Pol Arch Intern Med*. 2017; 127(10): 657–665, doi: [10.20452/pamw.4083](https://doi.org/10.20452/pamw.4083), indexed in Pubmed: [28786405](https://pubmed.ncbi.nlm.nih.gov/28786405/).
 26. Crespo-Leiro M, Segovia-Cubero J, González-Costello J, et al. Adherence to the ESC Heart Failure Treatment Guidelines in Spain: ESC Heart Failure Long-term Registry. *Rev Esp Cardiol (Engl Ed)*. 2015; 68(9): 785–793, doi: [10.1016/j.rec.2015.03.008](https://doi.org/10.1016/j.rec.2015.03.008).
 27. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010; 376(9744): 875–885, doi: [10.1016/s0140-6736\(10\)61198-1](https://doi.org/10.1016/s0140-6736(10)61198-1).
 28. Moran D, Buckley A, Daly K, et al. Heart rate awareness in patients with chronic stable heart failure. A multi-center observational study. *Int J Cardiol*. 2014; 177(2): 380–384, doi: [10.1016/j.ijcard.2014.08.119](https://doi.org/10.1016/j.ijcard.2014.08.119).
 29. Balsam P, Ozierański K, Kapłon-Cieślicka A, et al. Differences in clinical characteristics and one-year outcomes of hospitalized heart failure patients in succeeding European Society of Cardiology-Heart Failure Registries – Pilot and Long-Term. *Pol Arch Intern Med*. 2019; 129(2): 106–116, doi: [10.20452/pamw.4418](https://doi.org/10.20452/pamw.4418).
 30. McAlister FA, Wiebe N, Ezekowitz JA, et al. Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure. *Ann Intern Med*. 2009; 150(11): 784–794, doi: [10.7326/0003-4819-150-11-200906020-00006](https://doi.org/10.7326/0003-4819-150-11-200906020-00006), indexed in Pubmed: [19487713](https://pubmed.ncbi.nlm.nih.gov/19487713/).
 31. Franke J, Wolter JS, Meme L, et al. Optimization of pharmacotherapy in chronic heart failure: is heart rate adequately addressed? *Clin Res Cardiol*. 2013; 102(1): 23–31, doi: [10.1007/s00392-012-0489-2](https://doi.org/10.1007/s00392-012-0489-2), indexed in Pubmed: [22760479](https://pubmed.ncbi.nlm.nih.gov/22760479/).
 32. Villalobos RE, Tan IR, Divinagracia RM. Safety and benefits of beta-blockers in chronic obstructive pulmonary disease: a review of current evidence and meta-analysis. *Eur Resp J*. 2018; 52 (suppl 62): PA742.
 33. Yang YL, Xiang ZJ, Yang JH, et al. Association of β -blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J*. 2020; 41(46): 4415–4422, doi: [10.1093/eurheartj/ehaa793](https://doi.org/10.1093/eurheartj/ehaa793), indexed in Pubmed: [33211823](https://pubmed.ncbi.nlm.nih.gov/33211823/).
 34. Prabhavathi K, Selvi KT, Poornima KN, et al. Role of biological sex in normal cardiac function and in its disease outcome — a review. *J Clin Diagn Res*. 2014; 8(8): BE01–BE04, doi: [10.7860/JCDR/2014/9635.4771](https://doi.org/10.7860/JCDR/2014/9635.4771), indexed in Pubmed: [25302188](https://pubmed.ncbi.nlm.nih.gov/25302188/).
 35. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: current concepts and emerging therapies. *Circulation*. 2018; 138(1): 80–98, doi: [10.1161/CIRCULATIONAHA.118.030099](https://doi.org/10.1161/CIRCULATIONAHA.118.030099), indexed in Pubmed: [29967232](https://pubmed.ncbi.nlm.nih.gov/29967232/).