Resting heart rate and real-life treatment modalities in outpatients with left ventricular systolic dysfunction study: A multicenter, prospective, observational, and national registry

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On behalf of the REALITY HF investigators

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Abstract

Objective: Heart rate (HR) reduction is associated with improved outcomes in heart failure (HF). This multicenter, prospective, observational, and national registry aimed to evaluate resting HR and the impacts of HR-related medications in real-life clinical practice in patients with HF.
Methods: The Resting HR and Real-Life Treatment Modalities in Outpatients with Left Ventricular Systolic Dysfunction (REALITY HF) study enrolled 1054 patients with HF and left ventricular ejection fraction (LVEF) of <40% from 16 centers. Clinical characteristics, HR, and medications were noted (enrollment phase). A total of 487 patients with sinus rhythm and HR of ≥70 bpm were included in a further 4-month follow-up (FU) program (V0). Changes in HR and medications were reevaluated at 1-month (V1) and 4-month (V2) FU visits. The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess the quality of life (QoL) of 320 patients in a 4-month FU program.
Results: During enrollment, 794 patients (75.3%) were in sinus rhythm, in whom resting HR was 76.7±14 bpm, 69.1% had a resting HR of ≥70 bpm, 79.1% were receiving beta blocker (BB), and 6.1% were receiving ivabradine. Resting HR was lower in patients receiving BB (75.8±13 vs. 80.4±16 bpm; p=0.001); however, 65.8% of those still had a resting HR of ≥70 bpm. A significant association was found between elevated HR and worse New York Heart Association (NYHA) class, worse QoL, or lower LVEF. During the 4-month FU, adjustment of HR-lowering therapy was left to the physician's discretion. Resting HR significantly reduced from 83.6±12 (80) bpm at V0 to 78.6±13 (77) bpm at V1 (p=0.001) and further decreased to 73.0±11 (73) bpm at V2 (p=0.001). Patients achieving a resting HR of <70 bpm were 21.7% at V1 (p=0.001) and 39.9% at V2 (p=0.001). KCCQ significantly increased from 59.7±23 (62.7) at V0 to 73.1±18 (78.5) at V2 (p=0.001). In addition, patients with NYHA I increased from 22.2% at V0 to 29.2% at V1 and 39.4% at V2 (p=0.01).
Conclusion: In real-life clinical practice, elevated HR is highly prevalent in HF despite widely used BB therapy and is associated with worse clinical picture. Therapeutic interventions targeting HR significantly reduce HR, and HR lowering is associated with improved clinical outcomes.
Keywords: heart failure, heart rate, treatment modalities, clinical outcomes

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Introduction

Elevated resting heart rate (HR) is known to be a strong marker of mortality and morbidity in patients with chronic heart failure (HF) with reduced left ventricular ejection fraction (LVEF), particularly in those with sinus rhythm (1, 2). Regardless of clinically overt HF, an association has been found between elevated HR and worse clinical outcomes even in patients with LV systolic dysfunction with coronary artery disease (CAD) (2). Elevated HR is a strong predictor of mortality not only for HF patients with reduced EF (HFrEF) but also for HF patients with preserved EF (3). Although the underlying mechanism of the deleterious effect of elevated HR is not fully understood, shortening diastole, impairing ventricular loading and ventricular efficiency, reduc-

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HIGHLIGHTS

- Elevated heart rate (HR) in heart failure (HF) is known to be a strong predictor for poor clinical outcomes and HR-lowering therapy has been shown to provide significant improvements in cardiovascular death or HF hospitalization.
- This study showed that in real-life clinical practice, almost two-third of patients with HF and sinus rhythm have elevated resting HR (≥70 bpm) despite widely used beta blocker therapy.
- In addition, our findings showed a clear association between elevated HR and worse NYHA class, worse health-related QoL, or lower LVEF.
- Furthermore, this study suggested that treatment modalities targeting HR reduction are associated with improved NYHA functional class and health-related QoL.

ing myocardial blood supply, and increasing myocardial oxygen consumption are believed to be the mechanisms of unfavorable effects of elevated HR in HF (4).

Resting HR is also referred as a target of therapy because HR reduction has been consistently reported to be associated with improved clinical outcomes in randomized clinical trials. In patients with chronic HFrEF, HR reduction with the use of beta blocker (BB) therapy has been shown to be associated with marked improvements in clinical outcomes, and these improvements in clinical outcomes have also been reported to be associated with the magnitude of HR reduction (5, 6). Furthermore, recently published data suggested that a pure HR reduction obtained by a novel HR-lowering agent ivabradine provides a significant improvement in cardiovascular death or HF hospitalization in chronic HFrEF patients with sinus rhythm and a resting HR of >70 bpm (7). However, less is known about resting HR in relation to current treatment modalities implemented in real-life clinical practice. Resting HR and Real-Life Treatment Modalities in Outpatients with Left Ventricular Systolic Dysfunction (REALITY HF) study was a multicenter, prospective registry aimed to (1) describe clinical characteristics of HFrEF population, (2) examine resting HR in relation to patients' clinical characteristics, and (3) evaluate the effect of current HR-lowering treatment modalities on clinical outcomes in real-life clinical practice in patients with chronic HFrEF.

Methods

Study population

This multicenter study involved patients who were 18 years of age or older and admitted to the outpatient clinic with the diagnosis of chronic HF and left ventricular EF of <40% as measured by transthoracic echocardiography and New York Heart Association (NYHA) functional class I–IV. Patients with recent acute coronary syndromes within the previous 1 month, uncontrolled thyroid disease, uncontrolled hypertension, hypertrophic cardiomyopathy, and acute myocarditis, who were receiving chemotherapeutic agents, being currently enrolled in another HF study, and who were pregnant were excluded from this study.

Trial design and protocol

The REALITY HF study was a prospective, multicenter, observational, and national registry designed to evaluate resting HR, patients' clinical characteristics, and current treatment modalities in real-life clinical practice in outpatients with chronic HFrEF admitted to 16 participating centers including academic centers and community hospitals in various geographical areas in Turkey (8). Patients were recruited between March 2013 and April 2014. The study protocol was approved by the Ethics Committee and was performed according to the guidelines of the Declaration of Helsinki. A written informed consent was obtained from all patients before enrollment.

The REALITY HF has had 2 phases: enrollment phase and follow-up (FU) phase (Fig. 1). During the enrollment phase, 1054 patients compatible with the inclusion and exclusion criteria were enrolled in this study. Clinical characteristics and laboratory variables including age, sex, HR, blood pressure, waist circumference, body mass index, comorbid conditions, etiology of HF, NYHA functional class, electrocardiogram (ECG), EF, N-terminal pro brain natriuretic peptide (NT-proBNP) levels, biochemical parameters, complete blood count, and HF medications including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), BB, mineralocorticoid receptor antagonists (MRAs), diuretics, ivabradine, and digoxin were noted. In 794 patients with sinus rhythm, 487 patients with a HR of ≥70 bpm were included in a further

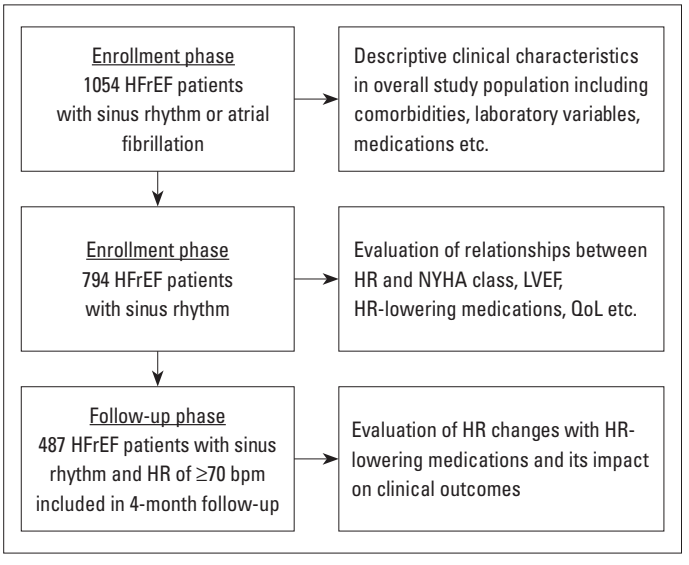

Figure 1. Flow chart of study design and targeted outcome measures

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4-month FU program (V0). Patients with permanent, persistent, or paroxysmal atrial fibrillation or flutter, second or third degree atrioventricular block, sick sinus syndrome, cardiac pacemaker, systolic blood pressure of <90 mm Hg, severe hepatic or renal dysfunction, severe chronic obstructive pulmonary disease (COPD), and severe anemia and those in the list of ventricular assist device or cardiac transplantation and who refused to sign an additional informed consent permitting participation in the 4-month FU program were excluded from the FU cohort. During the 4-month FU, adjustment of HF medication was left to the physician's discretion because of the observational nature of the study design. Changes in HR, NYHA functional class, and HF medications were reevaluated at 1-month (V1) and 4-month (V2) FU visits. Health-related quality of life (QoL) was assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) during enrollment (V0) and at 4 months (V2) in 320 patients who were able to comply with questionnaire.

Resting heart rate measurement

Resting HR was obtained from the 12-lead ECG after at least 5-minute rest. In addition, resting HR was measured by arterial pulse palpation during physical examination at sitting position after at least 5-minute rest. Although resting HR from ECG was used in all analysis, study data were analyzed to evaluate whether there is a correlation or any difference between the resting HR measured on ECG and the resting HR obtained from arterial pulse palpation.

Kansas City Cardiomyopathy Questionnaire

The KCCQ is a health-related QoL questionnaire that was developed to measure self-reported health status in patients with HF and has been shown to be a reliable and feasible method (9). The Turkish version has been used for this study in 320 patients with sinus rhythm. The KCCQ summary scores range from 0 to 100. The higher score shows better patient's self-reported health status. Changes in the KCCQ summary scores were analyzed from V0 to V2.

Outcomes measures

The targeted outcomes include the effect of current treatment modalities and clinical characteristics on resting HR in patients with sinus rhythm at enrollment and also whether changes in resting HR with the HR modulation therapy during FU period have an impact on clinical status of these patients. Prevalence of resting HR of >70 bpm, the effect of BB treatment on resting HR, any correlation between ECG-based HR and pulse palpation-measured HR, any relationships between resting HR and NYHA class, LVEF, or KCCQ summary scores were also analyzed. Patients were divided into 4 subgroups based on the quartiles of resting HR for the evaluation of relationship between resting HR and KCCQ scores and into 3 subgroups based on the tertiles of baseline LVEF for the evaluation of relationship between resting HR and LVEF.

Statistical analysis

The Statistical Package for Social Sciences software 20.0 (IBM SPSS 20, SPSS Inc., Chicago, USA) for the statistical analysis. The variables were expressed as mean±standard deviation (median and interquartile range). Data analysis was performed according to the intention-to-treat principle by the assigned study group. Continuous data were analyzed the Wilcoxon signed-rank test. Categorical data were presented as frequencies and percentages and were analyzed by Pearson chi-square, continuity correction chi-square, and Fisher's exact tests. Kruskal–Wallis test with Bonferroni correction was used to evaluate the relationship between resting HR and NYHA class, LVEF, or KCCQ scores. Spearman correlation test was used for correlation analysis. $P<0.05$ was considered statistically significant.

Results

Clinical characteristics and laboratory measures

Baseline demographic characteristics of the study population (n=1054) including laboratory measures, assessments of cardiac function, NYHA functional capacity, health-related QoL, and HF medication are presented in Table 1. The mean age of study population was 61±12 (63.0) years and 75.5% (n=795) were male. The most frequently reported etiological reasons for HF were CAD, idiopathic dilated cardiomyopathy (without known systemic, immune, toxic, metabolic diseases or CAD) and valvular heart disease. CAD, previous myocardial infarction, hypertension, diabetes mellitus, and COPD were the more prevalent comorbid conditions. Approximately 75.3% of the patients were in sinus rhythm and 24.7% had AF. The mean EF was 30±7% (median, 30), NT-proBNP was 2300±3451 (3165) pg/mL, creatinine level was 1.19±0.78 (1.01), and hemoglobin level was 13.4±2 (13.7) gr/dL. Almost 70% of patients were in NYHA functional class II or III. The KCCQ clinical summary scores with sinus rhythm were >75 in 43.2% of 320 patients.

At the time of enrollment, 93% of patients were receiving evidence-based HF medication and 82% were on ≥2 drug therapy. The use of ACEI/ARB, MRA, and diuretic was 68.7%, 34.8%, and 67.2%, respectively. In terms of HR modulation therapy, 79.1% of patients were receiving BBs and 6.1% were receiving ivabradine. The target doses of BB treatment, as defined by HF guidelines, had only been reached in 13.9% of patients.

Resting HR in patients with sinus rhythm

In patients with sinus rhythm (n=794), the mean resting HR was 76.7±14 bpm (median 75.0), and 69.1% of the patients had a resting HR of ≥70 bpm. The mean HR was significantly lower in patients who were already receiving BB therapy than those who were not (75.8±13 bpm vs. 80.4±15 bpm, respectively; p=0.001). Although patients receiving BB therapy had lower resting HR, 65.8% of patients receiving BB therapy and 75% of patients not receiving BB had a resting HR of ≥70 bpm (p=0.026). Further-

Table 1. Clinical characteristics and laboratory parameters in study population

	Overall study population (n=1054)	Patients in sinus rhythm (n=794)	Patients with sinus rhythm and HR of ≥70 bpm included in 4-month FU (n=487)
Age*, years	61±12 (63.0)	60±12 (60.0)	60±11 (60.0)
Gender, male n (%)	795 (75.5)	626 (78.9)	376 (77.4)
Waist circumference*, cm	97.9±14 (98.0)	98.0±15 (98.0)	98.6±12 (98.0)
BMI*	28.1±4.9 (27.6)	28.2±4.9 (27.8)	28.9±5.2 (27.9)
HR by ECG*, bpm	78±16 (75.0)	76±13 (75.0)	83±12 (81.0)
HR by radial pulse palpation*, bpm	77±14 (76.0)	76±12 (75.0)	82±11 (80.0)
Systolic blood pressure*, mm Hg	122±21 (120.0)	125±21 (120.0)	125±20 (120.0)
Diastolic blood pressure*, mm Hg	74±13 (71.0)	75.2±13 (73.0)	75.2±12 (75.0)
CAD, n (%)	758 (72)	600 (75.6)	376 (77.4)
Previous MI, n (%)	723 (68.6)	569 (71.7)	339 (69.8)
Hypertension, n (%)	345 (32.8)	282 (35.6)	162 (33.3)
Diabetes, n (%)	373 (35.4)	286 (36.1)	188 (38.7)
COPD, n (%)	209 (19.9)	139 (17.5)	92 (18.9)
CKD, n (%)	63 (6)	28 (3.6)	20 (4.1)
Previous stroke, n (%)	63 (6)	42 (5.3)	26 (5.5)
Etiology of HF			
CAD, n (%)	758 (72)	600 (75.6)	376 (77.4)
DCM, n (%)	193 (18.4)	137 (17.3)	82 (16.9)
VHD, n (%)	61 (5.8)	21 (2.7)	15 (3.1)
HT, n (%)	28 (2.7)	23 (2.9)	12 (2.6)
NYHA Classification			
NYHA I, n (%)	235 (22.3)	190 (23.9)	108 (22.2)
NYHA II, n (%)	422 (40.1)	317 (39.9)	206 (42.3)
NYHA III, n (%)	311 (29.5)	222 (27.9)	149 (30.6)
NYHA IV, n (%)	86 (8.2)	47 (5.9)	24 (4.9)
LVEF*, %	30±7 (30.0)	30±6.6 (30.0)	29.7 (30.0)
NT-proBNP*, pg/mL	2300±3451 (3165)	1683±2654 (2452)	1812±2945 (1640)
Creatinine*, mg/dL	1.19±0.78 (1.01)	1.20±0.8 (1.00)	1.20±1.1 (1.02)
Hemoglobin*, gr/dL	13.4±2 (13.7)	13.6±1.9 (13.9)	13.2±2.2 (13.6)
HF Medications			
Beta blocker use, n (%)	833 (79.1)	643 (81.0)	381 (78.5)
ACEI/ARB use, n (%)	724 (68.7)	593 (74.7)	371 (76.2)
MRA use, n (%)	366 (34.8)	281 (35.4)	179 (36.9)
Diuretic use, n (%)	708 (67.2)	535 (67.4)	331 (68.1)
Ivabradine use, n (%)	64 (6.1)	53 (6.8)	31 (6.5)
Digoxin use, n (%)	202 (19.2)	100 (12.6)	57 (11.8)
KCCQ OSS (n=320 in sinus rhythm)			60, 91±22 (63.5)
≤25, n (%)	-	-	22 (6.9)
26–49, n (%)	-	-	61 (19.1)
50–74, n (%)	-	-	99 (30.8)
≥75, n (%)	-	-	138 (43.2)

*Mean±standard deviation (median and interquartile range)
ACEI - angiotensin-converting enzyme inhibitor; ARB - angiotensin receptor blocker; BMI - body mass index; FU - follow-up; MRA - mineralocorticoid receptor antagonist; KCCQ - Kansas City Cardiomyopathy Questionnaire; OSS - overall summary score; NYHA - New York Heart Association; LVEF - left ventricular ejection fraction; ECG - electrocardiogram; COPD - chronic obstructive pulmonary disease; HR - heart rate; HF - heart failure; CAD - coronary artery diseases; DCM - dilated cardiomyopathy; VHD - valvular heart disease; HT- hypertension

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more, no significant difference was found in mean HR between patients on target doses of BB therapy and those who were not (75.1±12 bpm and 75.7±13 bpm, respectively; p=0.999).

In 665 patients in sinus rhythm with both ECG-based HR and radial pulse palpation-measured HR, the mean resting HR obtained from ECG was 76.4±14 bpm and the mean resting HR measured by arterial pulse palpation during physical examination was 76.6±12 bpm. A statistically significant correlation was found between ECG-based HR and pulse palpation-measured HR (r=0.758; p<0.001), suggesting that one of these methods can be used in determining resting HR in everyday clinical practice.

The mean (median) resting HR in patients with sinus rhythm was 72.8±12 (70.0) bpm in those with NYHA class I (n=190), 76.1±13 (75.0) bpm in those with NYHA class II (n=317), 80.2±15 (78.0) bpm in those with NYHA class III (n=222), and 78.9±16 (74.5) bpm in those with NYHA class IV (n=47) (Fig. 2). Overall, the mean resting HR level was found to gradually and significantly increase across NYHA functional class categories (Kruskal–Wallis test, p<0.001). In addition, the mean resting HR was significantly higher in those with NYHA II than those NYHA I (p=0.005) and significantly higher in those with NYHA III than those with NYHA II (p=0.003) or NYHA I (p=0.001), whereas no significant difference was found in resting HR levels between NYHA III and NYHA IV patients.

The KCCQ was completed by 320 patients with sinus rhythm. Patients were classified into 4 groups according to the quartiles of resting HR: Q1, <68 bpm (n=27); Q2, 69–75 bpm (n=99); Q3, 76–87 bpm (n=125); and Q4, >87 bpm (n=69). The KCCQ overall summary score (OSS) was 75.7±13.2 (69.5) in those in Q1, 65.5±20.8 (66.6) in those in Q2, 64.4±20.6 (63.8) in those in Q3, and 58.3±21.2 (59.9) in those in Q4 (p=0.004), and the KCCQ clinical summary score (CSS) was 80.4±15.7 (80.2) in those in Q1, 70.0±22.4 (68.2) in Q2, 69.9±21.9 (69.2) in Q3, and 63.8±23.3 (61.7) in Q4 (p=0.016) (Fig. 3). In addition, a significant negative correlation was found between resting HR and OSS (p=0.008) or CSS (p=0.031).

Patients with sinus rhythm (n=794) were classified into 3 groups according to the tertiles of LVEF: lowest tertile, LVEF of <27.6% (n=255); second tertile, LVEF of 27.7% to 34.6% (n=233); and highest tertile, LVEF of >34.7% (n=306). Resting HR was 78.9±13.6 (77.0) bpm in those in the lowest tertile, 76.8±13.5 (72.5) bpm in those in the second tertile, and 74.9±14.3 (72.0) bpm in those in the highest tertile (Kruskal–Wallis, p<0.001) (Fig. 4). The mean HR was significantly higher in the lowest LVEF tertile than the highest LVEF tertile (Mann–Whitney, p=0.001) and also significantly higher in the second LVEF tertile than the highest LVEF tertile (Mann–Whitney, p=0.043). Moreover, a significant negative correlation was found between resting HR and LVEF (p=0.001).

Resting HR during the 4-month follow-up program in patients with sinus rhythm

In patients who participated the 4-month FU program (n=487), BB therapy was initiated or up-titrated in 43.7% of patients at V0 and 12.9% at V1, ivabradine in 7.6% of patients at V0 and 11.5% at V1, digoxin in 3.9% of patients at V0 and 1.8% of patients at

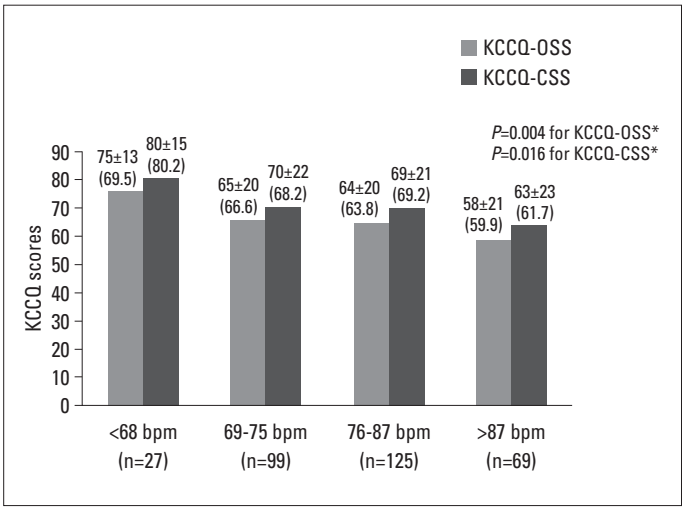

Figure 3. KCCQ scores† according to HR quartiles (n=320)
*Kruskal–Wallis
†Mean±standard deviation (median and interquartile range)

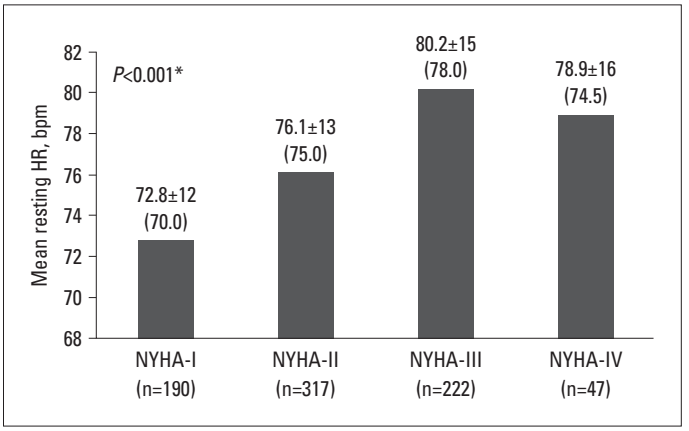

Figure 2. Mean resting HR† in relation to NYHA class (n=776)
*Kruskal–Wallis
†Mean±standard deviation (median and interquartile range)

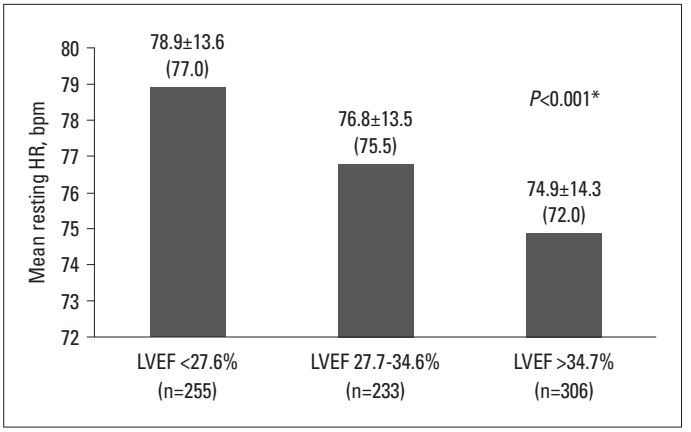

Figure 4. Mean resting HR† according to LVEF tertiles (n=794)
*Kruskal–Wallis
†Mean±standard deviation (median and interquartile range)

V1, ACEI/ARB in 13.7% of patients at V0 and 6.4% of patients at V1, MRA in 4.2% of patients at V0 and 2.3% of patients at V1, and loop diuretics in 5.9% of patients at V0 and 2.3% of patients at V1 by the clinicians. Overall, the mean resting HR significantly reduced from 83.6±12 (80.0) bpm at V0 to 78.6±13 (77.0) bpm at V1 (p=0.001) and further decreased to 73.0±11 (73.0) bpm at V2 (p=0.001) (Fig. 5). The proportion of patients who achieved a resting HR of <70 bpm was 21.7% at V1 (p=0.001) and 39.9% at V2 (p=0.001). The KCCQ OSS significantly increased from 59.7±23 (62.7) at V0 to 73.1±18 (78.5) at V2 (p=0.001). In addition, the proportion of patients with NYHA I increased from 22.2% at V0 to 29.2% at V1 and 39.4% at V2 (p=0.001). Improvements in NYHA class during 4-month FU are presented in Table 2.

In patients receiving ivabradine added to BB therapy, the mean resting HR significantly reduced from 80.9±15 (80.0) bpm at V0 to 74.0±10 (73.0) bpm at V1 (p=0.005) and further decreased to 66.9±9 (65.5) bpm at V2 (p=0.001). Initially, resting HR slightly increased from 74.4±13 (74.0) bpm at V0 to 74.5±12 (76.5) bpm at V1 (p=0.001) and then slightly but significantly decreased to 73.8±12 (73.0) bpm at V2 (p=0.001) in patients receiving BB alone. In patients receiving ivabradine and BB combination therapy, the proportion of patients with a resting HR of <70 bpm increased from 21.7% at V0 to 27% at V1 and further increased to 65% at V2. In patients receiving BB therapy alone, the proportion of patients achieving a resting HR of <70 bpm was 38.2% at V0, 30.9% at V1, and 39 % at V2.

Table 2. Changes of NYHA functional class during 4-month follow-up

	V0	V1	V2	*P**
NYHA-I, % (n)	22.2 (108)	29.2 (112)	39.4 (121)	<0.001
NYHA-II, % (n)	42.3 (206)	42.6 (163)	39.1 (120)	
NYHA-III, % (n)	30.6 (149)	21.7 (83)	16.9 (52)	
NYHA-IV, % (n)	4.9 (24)	6.5 (25)	4.6 (14)	
Total, % (n)	100 (487)	100 (383)	100 (307)	

*Chi-Square tests
NYHA - New York Heart Association

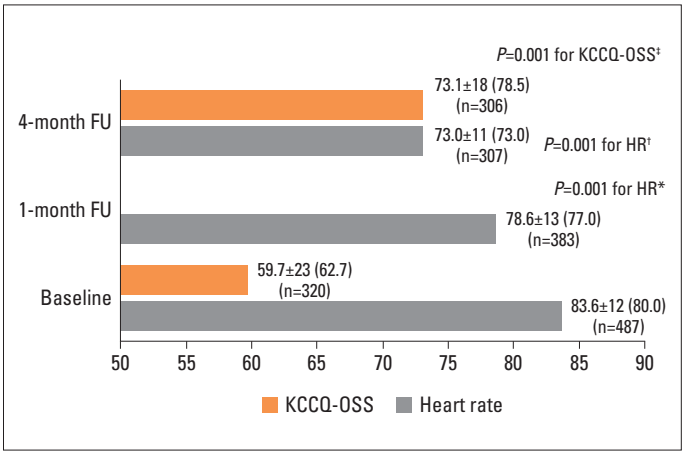

Figure 5. Changes in resting HR and KCCQ during 4-month follow up
*Wilcoxon signed-rank test for comparison baseline and 1-month FU
†Wilcoxon signed-rank test for comparison 1-month FU and 4-month FU
‡Wilcoxon signed-rank test for comparison baseline and 4-month FU
-Mean±standard deviation (median and interquartile range)

Discussion

This study showed that in real-life clinical practice, almost two-third of patients with chronic HFrEF and sinus rhythm have elevated resting HR despite the highly prevalent use of evidence-based guidelines recommended therapy including BB treatment. In addition, our findings showed a clear association between elevated HR and worse NYHA class, worse health-related QoL, or lower LVEF. Furthermore, the results of this study suggested that treatment modalities targeting HR reduction are associated with improved NYHA functional class and health-related QoL.

High resting HR has long been known to be associated with poor cardiovascular outcomes in all stages of the cardiovascular continuum, starting from cardiovascular risk factors (hypertension, diabetes, obesity, etc.) to CAD and HF (10-12). In patients with LV systolic dysfunction in sinus rhythm, the BEAUTIFUL trial demonstrated a 53% increased risk of hospitalization and a 34% increased risk of cardiovascular death in those with a HR of >70 bpm (2). In patients with symptomatic HF, the SHIFT trial showed that cardiovascular death is increased from >75 bpm, whereas HF hospitalization risk is elevated from >70 bpm (13). Furthermore, HR reduction with BB and/or ivabradine treatment has been shown to be associated with marked improvements in clinical outcomes in HFrEF patients (5-7). Therefore, resting HR is not only referred as a risk marker but also considered as a target of therapy.

The evidence-based treatment modalities targeting HR reduction in HFrEF are mainly BBs and ivabradine. The beneficial effects of BBs in HFrEF are believed to be related to their negative chronotropic effects through sympathetic inhibition that reduces HR and myocardial oxygen consumption and their antiarrhythmic effects. BB trials with metoprolol (MERIT-HF) (14), bisoprolol (CIBIS II) (15), and carvedilol (COPERNICUS) (16) including almost 10,000 HFrEF patients with NYHA class II–IV and EF of <40% demonstrated a significant reduction in mortality and HF hospitalization. A meta-analysis with BB trials including 19,537 patients with a mean FU duration of 9.6 months showed a strong correlation between all-cause mortality and HR (adjusted R2=0.60; p=0.0004), and a close correlation was also found between the magnitude of HR reduction and an increase in EF (adjusted R2=0.48; p=0.001) (6). Another meta-analysis including 17 BB trials with 17,831 HF patients demonstrated that every HR rate reduction of 5 bpm with BB treatment leads to a 18% reduction in the risk of death (p=0.006), and interestingly, no significant relationship was found between all-cause mortality and BB dosing (p=0.69) (5). The SHIFT trial in symptomatic

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HFrEF patients in sinus rhythm and HR of ≥70 bpm showed that HR reduction by ivabradine treatment in addition to evidence-based HF therapy including BBs significantly improves the primary endpoint of cardiovascular death or HF hospitalization, death from HF, symptoms, and QoL (7). Furthermore, a close relationship between HR reduction and reverse remodeling (improvements in EF and LV end-systolic and end-diastolic volumes) has been shown with BB (17) and ivabradine treatment (18). These data with treatment modalities targeting HR reduction suggested clear clinical benefits with HR reduction in HFrEF patients.

The best clinical results have been reported to be obtained when BBs or ivabradine was initiated in patients with a HR of ≥70 bpm, and a target of resting HR between 55 and 65 bpm was achieved during HR-lowering therapy (7, 19). Large-scale HF registries showed that more than 70% of HF patients receiving evidence-based therapy had a resting HR of >70 bpm despite the highly prevalent use of BB with >85% (20, 21). The target dose of BB was reported to be reached in 13% to 37% of patients in these registries (20, 21). In our study population, 69.1% of the patients had a resting HR of ≥70 bpm despite the use of BBs. Although patients receiving BB therapy had a lower resting HR than the patients not receiving BB (75.8±13 vs. 80.4±15 bpm; p=0.001), 65.8% of patients using BB still had a resting HR of ≥70 bpm. Furthermore, no significant difference was found in resting HR between patients on target doses of BB therapy and those who were not (75.1±12 vs. 75.7±13 bpm; p=0.999). It can be speculated that in clinical practice, clinicians tend to easily up-titrate the dose of BBs and reach the target doses in patients with a much higher HR, whereas less effort for up-titration is made in patients with less high HR. However, all these findings suggest that almost two-thirds of patients showed an elevated resting HR even in the presence of BB therapy and need further effort to achieve the targets of resting HR.

The results of our study suggested a close relationship between resting HR and NYHA functional class, LVEF, or QoL. The mean resting HR was found to gradually and significantly increase across NYHA functional class categories (p=0.001), although no significant difference was found in HR between NYHA 3 and NYHA 4 that are both considered as worse clinical picture of HF. In addition, there was a significant negative correlation between resting HR and KCCQ OSS (p=0.008) or LVEF (p=0.001). These findings indicated that patients with worse functional capacity, lower LVEF, and poor QoL have a higher resting HR. Insights from the EVEREST trial (22) suggested that hospitalized HF patients in sinus rhythm with a higher HR tended to have lower LVEF and worse NYHA class, and results from the SHIFT trial (23) indicated an inverse association between resting HR and KCCQ score, which all are consistent with our findings.

HR lowering with evidence-based HF therapy has not only been shown to reduce clinical hard endpoints of all-cause death, cardiovascular death, HF death, or HF hospitalization, but also demonstrated to be associated with the improvement in symptoms, exercise capacity, LVEF, and QoL. Although the improvements in symptoms, exercise capacity, and QoL have not been the primary outcomes in most trials, they are also of the utmost importance from the patient's perspective. HR reduction with ivabradine on top of HF therapy including BB has been shown to improve KCCQ scores, and the magnitude of HR reduction was found to be related to the extent of improvement in QoL (23). The SHIFT trial also found significant improvements in the NYHA class and patient-reported global assessment (7). Both BB (6) and ivabradine (18) have been proven to increase LVEF over 6–8 months, and this increase in LVEF was reported to be associated with the magnitude of HR reduction. Increasing evidence suggests that better HR control with a strategy of adding ivabradine to BB therapy provides better improvements in exercise capacity, NYHA class, LVEF, and QoL than BB therapy alone (24-27). In a retrospective study, the optimization of HR-lowering therapy with BB and ivabradine in hospitalized patients before discharge has been reported to reveal better HR control and improvements in NYHA class and QoL at 12-month FU (25). In RELIf-CHF study in 767 chronic HFrEF patients, which was a prospective cohort study, of whom 497 were on BB, HR lowering with ivabradine significantly improved NYHA class, LVEF, and QoL (26). The randomized ETHIC-AHF study on hospitalized patients with an HR of >70 bpm and LVEF of <40% indicated that adding ivabradine in those patients after reaching the optimal dose or the maximum-tolerated dose of BBs was associated with a significant improvement of LVEF and a trend to a better clinical status of patients at 1-year FU (27). Although the findings from our 4-month FU program showed a submaximal effort made by clinicians for up-titration and optimization of HR-lowering medications in real-life clinical practice, overall, the resting HR significantly reduced from 83.6±12 (80.0) bpm at baseline to 78.6±13 (77.0) bpm at 1-month (p=0.001) and further decreased to 73.0±11 (73.0) bpm at 4-month (p=0.001) and almost 40% of patients achieved a resting HR of <70 bpm. Nevertheless, significant improvements were found in KCCQ scores (p=0.001) and NYHA class (p=0.01) despite the submaximal effort of modification of HR-lowering therapy. Furthermore, in patients with added ivabradine to BB therapy, patients with a resting HR of <70 bpm increased from 21.7% at baseline to 27% at 1 month and further increased 65% at 4 months. Hence, more effort for the optimization of HR-lowering medications might be expected to provide more clinical benefits for more patients.

In general, most of the abovementioned large-scale randomized studies and retrospective or prospective real-life registries focused on improvements on clinical hard endpoints (HF hospitalization, CV death, HF death, etc.) or improvements on NYHA class, reverse remodeling variables (LVEF, LV systolic/end-diastolic volumes), or QoL in some. Different from these studies, our study demonstrated a significant relationship between resting HR and NYHA functional class categories, LVEF, and KCCQ scores, indicating a higher resting HR with worse

functional capacity, lower LVEF, and poor QoL. Furthermore, the abovementioned studies generally examined the improvements in NYHA class and QoL at 6- or 12-month FU. The results of our study indicated that improvements in NYHA and QoL with HR lowering could be achieved at the end of 4 months. Moreover, to the best of our knowledge, for the first time, our study indicated a significant correlation between ECG-based HR and pulse palpation-measured HR, suggesting that one of these methods can be used in the assessment of resting HR in everyday clinical practice.

Study limitations

This was a prospective, multicenter, observational registry. There was no intervention on the HR-lowering therapy. The optimization of HF medication was left to the physician's discretion because of the observational nature of the study design. Changes in other medications including ACEI/ARB or MRA may have had an impact on the results. Therefore, the results of clinical improvements are not conclusive. Furthermore, the lack of a control group with patients who have a resting HR of <70 bpm in 4-month FU program is one of the other limitations. A control group would further improve quality and reliability of the investigation. However, in clinical practice, the optimization of HR-lowering therapy seems to provide clinical benefits. Furthermore, we could show that elevated HR is highly prevalent in HF patients despite widely used BB therapy and is associated with worse clinical picture.

Conclusion

Despite the use of evidence-based BB treatment, most patients with chronic HFrEF in sinus rhythm have elevated resting HR in real-life clinical practice. HR is even much higher in HFrEF patients with worse functional capacity, lower LVEF, and poor QoL. Treatment modalities targeting HR reduction are associated with improved clinical outcomes, and therefore, most patients need further optimization of HR-lowering therapy.

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