VIA MEDICA
ORIGINAL ARTICLE
2015, Vol. 22, No. 2, 227–232
DOI: 10.5603/CJ.a2014.0057

ISSN 1897–5593

I_f current inhibitor ivabradine in patients with idiopathic dilated cardiomyopathy: Impact on the exercise tolerance and quality of life

Zainab Abdel-Salam, Mona Rayan, Ayman Saleh, Mohamed G. Abdel-Barr, Mohamed Hussain, Wail Nammas

Cardiology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

Abstract

Background: *Evidence supported a beneficial effect of ivabradine on clinical outcome of patients with systolic heart failure, and a sinus heart rate (HR) ≥ 70 bpm. We explored the effect of ivabradine, vs. placebo, added to evidence-based treatment on exercise tolerance and quality of life in patients with idiopathic dilated cardiomyopathy.*

Methods: *We enrolled 43 consecutive patients with dilated cardiomyopathy of no apparent cause, a left ventricular ejection fraction (LVEF) < 40%, New York Heart Association class ≥ II, sinus HR ≥ 70 bpm, and background evidence-based anti-failure medications. Ischemic heart disease was ruled out. Patients were randomized (1:1) to receive ivabradine or placebo. Ivabradine was titrated up gradually till 7.5 mg twice daily, or a HR < 60 bpm, and continued for 3 months. Symptom-limited exercise tolerance test was performed, and quality of life was assessed by the Minnesota Living With Heart Failure Questionnaire at 0, and 3 months.*

Results: *Forty-three patients were randomized to ivabradine (n = 20), or placebo (n = 23). Mean age was 50.8 ± 14.5 years (53.5% males). Mean HR was 85 ± 12 bpm, and mean LVEF was 32 ± 6%. Mean dose of carvedilol was 31.2% of the target dose. Baseline HR, blood pressure, exercise tolerance, Minnesota questionnaire score, and left ventricular systolic function were comparable between the two groups (p > 0.05 for all). At 3 months, mean dose of ivabradine was 6.8 mg bid. Ivabradine-treated patients had a lower HR, and improved left ventricular dimensions and systolic function, versus placebo-treated ones (p < 0.05 for all). HR dropped by a mean of 14 bpm in the ivabradine group, corrected for placebo. Both exercise tolerance, and Minnesota questionnaire score were better in the ivabradine group (p < 0.05 both). Ivabradine was well-tolerated.*

Conclusions: *In symptomatic patients with idiopathic dilated cardiomyopathy, the addition of ivabradine, vs. placebo, to evidence-based treatment, reduced HR, and improved functional capacity, at short-term follow-up.* (Cardiol J 2015; 22, 2: 227–232)

Key words: ivabradine, idiopathic dilated cardiomyopathy, exercise tolerance, quality of life

Address for correspondence: Wail Nammas, PhD, Cardiology Department, Faculty of Medicine, Ain Shams University. Abbassia, Cairo, Egypt, P.O. 11381, tel: +2 0122 4063718, fax: +2 02 24820416, e-mail: wnammas@hotmail.com

Received: 02.06.2014 Accepted: 13.07.2014

Introduction

Heart rate (HR) reduction improves left ventricular (LV) diastolic filling, reduces myocardial oxygen consumption, and increases coronary perfusion time. Ivabradine reduces HR by selectively inhibiting I_f current in the sinoatrial node pacemaker cells, in a dose-dependent manner [1]. In patients with chronic stable angina, ivabradine improved exercise tolerance, vs. placebo [2], was non-inferior to atenolol and amlodipine for improving total exercise duration and decreasing the frequency of anginal attacks at 3-month follow-up [3, 4].

In an animal model of ischemia-induced heart failure (HF), HR reduction with ivabradine improved LV systolic function, an effect that persisted after drug withdrawal, possibly mediated by modification of LV structure and myocyte function resulting from chronic HR reduction [5]. Moreover, in patients with idiopathic dilated cardiomyopathy, ivabradine proved safe and effective for HR reduction at short-term follow-up [6]. Yet, evidence is limited on the effect of ivabradine on the functional capacity of these patients. In a prospective randomized study design, we tested the hypothesis that the administration of ivabradine, vs. placebo, as add-on therapy to evidence-based medical treatment would improve the exercise tolerance and quality of life at short-term follow-up, in patients with idiopathic dilated cardiomyopathy.

Methods

Patient selection

We conducted a randomized, double-blinded, placebo-controlled, parallel-arm trial to explore the effect of ivabradine, vs. placebo, as add-on therapy to optimal medical treatment on the exercise tolerance and quality of life, in patients with idiopathic dilated cardiomyopathy. Patients were recruited from the outpatient clinic during the period from July 2011 to March 2012. Eligible patients were above 18 years, confirmed to have dilated cardiomyopathy with no apparent cause, with a left ventricular ejection fraction (LVEF) < 40%, New York Heart Association (NYHA) class ≥ II, in sinus rhythm with a resting HR ≥ 70 bpm, who were symptomatic for at least 4 weeks. Patients needed to be on stable, background evidence-based medications of HF (maximally tolerated doses of carvedilol, angiotensin converting enzyme inhibitors [ACEI], and spironolactone) for at least 4 weeks. Ischemic heart disease was ruled out based on previous history of myocardial infarction, prior coronary revascularization, coronary angiogram showing at least 50% stenosis in at least one sizable coronary artery, or negative myocardial perfusion imaging for exercise-induced myocardial ischemia. Exclusion criteria included atrial fibrillation/flutter, pacemaker or cardiac resynchronization therapy, second or third degree atrioventricular block, serum transaminases > 3 times the upper reference limit, serum creatinine > 2 mg/dL, hemoglobin < 10 mg/dL, uncontrolled thyroid disease, recent treatment with amiodarone, significant valvular or congenital heart disease, pregnancy, and inability to perform exercise tolerance test.

Study design

Before inclusion, informed written consent was obtained from each patient, and the study protocol was reviewed and approved by our Institutional Human Research Committee as it conforms to the ethical guidelines of the 1975 Declaration of Helsinki, as revised in 2002. Qualifying patients were randomly assigned (1:1 ratio) to receive either ivabradine (Procoralan®, Servier, France) as add-on therapy or placebo. Randomization was performed by computer-generated allocation schedule drawn by an independent statistician. Ivabradine was initiated at a dose of 2.5 mg once daily for the first week, 2.5 mg twice daily for the second week, and then titrated up by 2.5 mg increments every week till a maximal dose of 7.5 mg twice daily, or a drop of HR < 60 bpm. Study drugs were identical in appearance. Patients remained in the same allocation, and standard medications of HF remained unchanged throughout the study period. Treatment was continued for 3 months. Both the patients and the investigators performing the baseline and follow-up assessment were blinded to the treatment allocation.

Echocardiographic assessment

Assessment of LV systolic function was performed by trans-thoracic echocardiography at day 0, and at the end of 3 months. Doppler echocardiography was performed using a General Electric Vivid 7 Pro cardiac ultrasound machine (GE Medical Systems, Horten, Norway). A 3.5 MHz phased-array transducer was used to obtain standard 2 dimensional (2-D), M-mode, and Doppler flow. Patients were examined in the left lateral recumbent position using standard parasternal and apical views. LV systolic function was assessed by M-mode in parasternal long-axis view using the Teichholz method, and by 2-D in apical 2- and 4-chamber views using the biplane modified Simpson's method. Cardiac chamber quantification was performed as recommended by the American Society of Echocardiography [7].

Exercise tolerance test

Symptom-limited exercise tolerance test was performed according to the modified Bruce protocol [8] at day 0, and at the end of 3 months. Patients were examined after 4 h fast, and abstinence from smoking, alcohol, and caffeine for at least 2 h. Reasons for termination were limiting dyspnea or extreme fatigue. The total exercise duration was calculated.

Quality of life assessment

The quality of life was assessed by the Minnesota Living With Heart Failure Questionnaire, based on 21 questions that refer to symptoms of HF, physical and sexual activity, work, social relationships, and emotions. The answer for each question was chosen from a scale of 0 (none) to 5 (very much); the greater the score, the worse the quality of life [9]. Assessment was performed at day 0 and at the end of 3 months.

Statistical analysis

Continuous variables were presented as mean ± standard deviation, if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with absolute and relative (percentage) frequencies. Comparisons between the two groups were performed using the unpaired t-test or Mann-Whitney test for continuous variables, and Pearson's χ^2 or Fisher's Exact test for categorical variables, as appropriate. Pearson's correlation coefficient test was performed to study the correlation between HR at 3 months on one hand; and exercise tolerance and quality of life, on the other hand. All tests were 2-sided and a probability value of $p < 0.05$ was considered statistically significant. Analyses were performed with SPSS version 16.0 statistical package (SPSS Inc., Chicago, IL, USA).

Results

Baseline clinical characteristics

A total of 43 consecutive symptomatic patients with idiopathic dilated cardiomyopathy were randomized to receive ivabradine as add-on therapy (n= 20), or placebo (n= 23), and completed follow-up for 3 months. Mean age of the study cohort was 50.8 ± 14.5 years; 23 (53.5%) patients were males. Mean HR was 85 ± 12 bpm, and mean LVEF was 32% ± 6 by both M-mode and 2-D measurements. At baseline, 9 (20.9%) patients were in NYHA class II, 26 (60.5%) patients in class III, and 8 (18.6%) patients in class IV. All patients received carvedilol as a beta-blocker. The median (range) dose of carvedilol was 9.375 mg daily (6.25–12.5 mg daily). Forty (93%) patients received captopril as an ACEI; 3 (7%) patients received enalapril. The median (range) dose of captopril was 37.5 mg daily in three divided doses (18.75–100 mg daily). All patients received spironolactone as an aldosterone antagonist at a dose of 25 mg daily. The mean dose of carvedilol was 31.2 ± 26.8% of the target dose and mean dose of ACEI was 70.5 ± 24.8% of the target dose, as defined by the European Society of Cardiology guidelines [10]. The main reasons for patients not receiving target doses of carvedilol were hypotension, asthma, chronic obstructive airway disease, and fatigue; and the main reasons for not receiving target doses of ACEI were hypotension and severe dizziness. Table 1 shows the baseline clinical characteristics of the two groups. Baseline HR, blood pressure, exercise tolerance, Minnesota questionnaire score, and LV systolic function were all comparable between the two groups ($p > 0.05$ for all) (Table 2).

Table 1. Baseline characteristics of the two study groups.

	Ivabradine group (n = 20)	Placebo group (n = 23)
Age [years]	49.1 ± 15.7	52.3 ± 13.5
Male gender	10 (50%)	13 (56.5%)
Smoking	2 (10%)	3 (13%)
Hypertension	5 (25%)	4 (17.4%)
Diabetes mellitus	4 (20%)	5 (21.7%)
ACEI of target dose [%]	66.7 ± 24.1	73.9 ± 25.5
Carvedilol dose [mg]	18.9 ± 16.2	12.8 ± 10

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as frequency (percentage); ACEI — angiotensin converting enzyme inhibitors

Clinical outcome at 3-month follow-up

At the end of a 3-month follow-up, 16 (80%) patients of the ivabradine group were on 7.5 mg twice daily, 3 (15%) on 5 mg twice daily, and 1 (5%) on 2.5 mg once daily (severe visual symptoms). The mean dose of ivabradine received was 6.8 mg twice daily. The main reasons for patients not reaching the target dose of ivabradine were symptomatic bradycardia, and visual symptoms (phosphenes).

Table 2. Functional capacity and echocardiographic data of the two study groups at baseline and 3-month follow-up.

	Baseline			3-month follow-up		
	Ivabradine group (n = 20)	Placebo group (n = 23)	P	Ivabradine group (n = 20)	Placebo group (n = 23)	P
NYHA class:			> 0.05			> 0.05
I	0 (0%)	0 (0%)		2 (10%)	0 (0%)	
II	6 (30%)	5 (21.7%)		12 (60%)	12 (52.2%)	
III	12 (60%)	14 (60.9%)		5 (25%)	8 (34.8%)	
IV	2 (10%)	4 (17.4%)		1 (5%)	3 (13%)	
Resting heart rate [bpm]	85 ± 12	84 ± 10	> 0.05	68 ± 11	81 ± 13	< 0.05
Systolic BP [mm Hg]	101 ± 17	91 ± 5	> 0.05	100 ± 17	89 ± 6	> 0.05
Diastolic BP [mm Hg]	69 ± 12	61 ± 4	> 0.05	63 ± 10	61 ± 4	> 0.05
LV EDD [mm]	66 ± 6	70 ± 5	> 0.05	61 ± 7	70 ± 7	< 0.05
LV ESD [mm]	56 ± 6	59 ± 6	> 0.05	49 ± 7	58 ± 7	< 0.05
M-mode EF [%]	32 ± 7	32 ± 5	> 0.05	38 ± 10	34 ± 7	> 0.05
LV EDV [mL]	171 ± 35	184 ± 44	> 0.05	150 ± 32	190 ± 62	< 0.05
LV ESV [mL]	113 ± 26	126 ± 31	> 0.05	92 ± 27	130 ± 41	< 0.05
Two-dimensional EF [%]	34 ± 4	30 ± 8	> 0.05	39 ± 7	33 ± 10	< 0.05
Left atrial diameter [mm]	42 ± 6	47 ± 5	> 0.05	41 ± 5	47 ± 5	< 0.05
Total exercise duration ≥ 6 min	5 (25%)	6 (26.1%)	> 0.05	12 (60%)	7 (30.4%)	< 0.05
Minnesota questionnaire score	58.8 ± 7.2	60.3 ± 5.5	> 0.05	46.4 ± 7.3	51.7 ± 6.6	< 0.05

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are presented as frequency (percentage); NYHA — New York Heart Association; BP — blood pressure; LV — left ventricular; EDD — end-diastolic dimension; ESD — end-systolic dimension; EF — ejection fraction; EDV — end-diastolic volume; ESV — end-systolic volume

At 3 months, ivabradine-treated patients had a lower HR, and improved LV dimensions and systolic function compared with placebo-treated ones ($p < 0.05$ for all). At follow-up, HR was reduced by a mean of 17 bpm in the ivabradine group compared with baseline; when corrected for such reduction in the placebo group, the net HR reduction in the ivabradine group was 14 bpm. Both exercise tolerance, and Minnesota questionnaire score were better in the ivabradine group ($p < 0.05$ for both). Yet, NYHA class and blood pressure were comparable in the two groups (Table 2). At the end of follow-up, resting HR correlated negatively with the total exercise duration ($r = –0.377$, $p = 0.024$) (Fig. 1), and positively with Minnesota questionnaire score ($r = 0.316$, $p = 0.047$) (Fig. 2).

One (5%) patient in the ivabradine group was hospitalized for worsening HF (defined as new or increasing symptoms and signs of HF, with evidence of fluid retention), vs. 2 (8.7%) in the placebo group. One patient in either group died of decompensated HF. Symptomatic bradycardia occurred in 3 (15%) patients in the ivabradine group, and visual symptoms (phosphenes) in 1 (5%). No one in the placebo group developed such adverse effects.

Discussion

Major findings

The current pilot study demonstrated that in symptomatic patients with idiopathic dilated cardiomyopathy who are already receiving the maximally tolerated doses of beta-blockers and ACEI, the administration of ivabradine as add-on therapy reduced HR, improved LV systolic function, exercise tolerance, and quality of life, compared with placebo, at short-term follow-up. Yet, no effect on blood pressure or NYHA class was observed. To the best of the authors' knowledge, this is the first piece of evidence for a beneficial effect of ivabradine on exercise tolerance and quality of life in patients with non-ischemic cardiomyopathy.

Heart rate reduction as a therapeutic target

Increased resting HR is a known risk factor for worse clinical outcome in patients with HF, and chronic stable angina [11, 12]. Evidence suggests that HR reduction is associated with improved clinical outcome in patients with HF and LV systolic dysfunction [13]; the magnitude of benefit is related to the extent of HR reduction

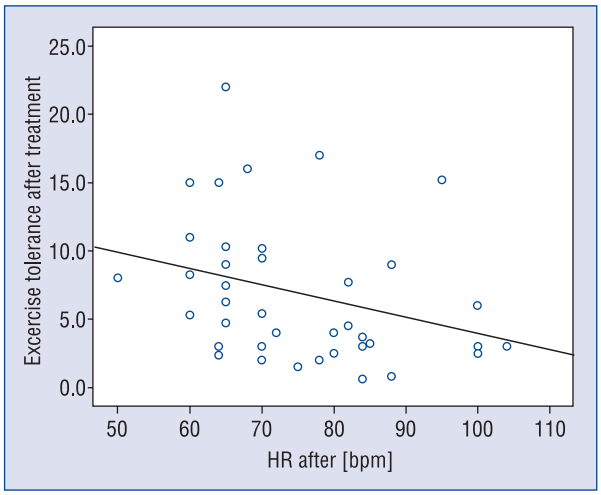

Figure 1. Correlation between resting heart rate (HR) and the total exercise duration at 3-month follow-up.

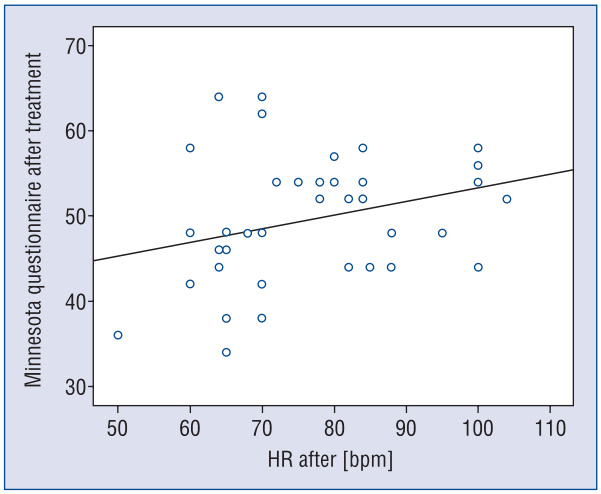

Figure 2. Correlation between resting heart rate (HR) and Minnesota questionnaire score at 3-month follow-up.

[11, 14]. Unfortunately, in most patients with HF receiving beta-blockers, HR remains substantially elevated [15]. In this context, selective I_f current inhibition with ivabradine has emerged as a promising therapeutic approach in these patients. In the multicenter randomized placebo-controlled SHIFT trial, ivabradine reduced the composite endpoint of cardiovascular death or hospitalization for HF, at long-term, in patients with systolic HF (67.5% ischemic, 56% prior myocardial infarction) and a sinus HR ≥ 70 bpm, a benefit largely driven by reduction of HF hospitalization [16]. This was the main drive for the 2012 updated guidelines of the European Society of Cardiology to consider ivabradine for reduction of HF hospitalization in patients with symptomatic HF, LVEF ≤ 35%, and a sinus HR ≥ 70 bpm, despite the maximally tolerated doses of evidence-based therapy (class IIa, level of evidence B), and in patients unable to tolerate a beta-blocker (class IIb, level of evidence C) [10]. Improvement of clinical outcome in the SHIFT trial was associated with improvement of the NYHA class, and both patient- and physician-reported assessment of quality of life [16]. Similarly, in the CARVIVA HF trial, ivabradine — alone or in combination with carvedilol — improved exercise tolerance and quality of life, vs. carvedilol alone, in patients with HF (81% ischemic) [17]. The current study serves to support and extend these results to patients with idiopathic dilated cardiomyopathy whose HF is non-ischemic in origin.

Heart rate reduction with ivabradine

In the current study, the mean dose of beta-blockers received by patients was far from the target dose recommended by the guidelines of the European Society of Cardiology (31.2%). This was mainly due to intolerance to beta-blockers. Not surprisingly, the mean baseline HR was 85 bpm. Likewise, in the SHIFT trial, only 26% of patients received the target dose of beta-blockers (56% received ≥ 50% of target dose), and the mean HR was 80 bpm [16]. The mean HR reduction — corrected for placebo — in the current study was 14 bpm at 3 months (mean ivabradine dose 6.8 mg), compared with 11 bpm at 28 days (mean ivabradine dose 6.5 mg) in the SHIFT trial [16]. In the current study, the magnitude of benefit in terms of exercise tolerance and quality of life correlated with the final HR at follow-up. The extent of HR reduction, rather than background beta-blocker dose, accounted for the effect of ivabradine on clinical outcome in the SHIFT trial [11, 14]. Yet, lack of statistically significant improvement of the NYHA class in the current study might be due to the small sample size.

Heart rate reduction with ivabradine was associated with maintenance of systolic blood pressure, possibly due to improved stroke volume. This is supported by the improvement of LV dimensions and LVEF. In a rat model of ischemia-induced HF, ivabradine improved LV systolic function and stroke volume, and preserved cardiac output at 90-day follow-up, despite HR reduction [5]. In that study, improvement was related not only to HR reduction, but also to modification of extracellular matrix, and cardiac myocyte function, as result of sustained HR reduction [5].

Clinical implications

Evidence supported a beneficial effect of ivabradine on the long-term clinical outcome of patients with systolic HF (predominantly ischemic) in whom sinus HR remains ≥ 70 bpm [16], and on the ischemia-related outcome of patients with stable angina, LV systolic dysfunction, and a sinus HR ≥ 70 bpm [18]. The ongoing SIGNIFY trial examines the effect of ivabradine, vs. placebo, on the clinical outcome in patients with stable angina, normal ejection fraction, and no HF [19]. The current study suggested that ivabradine may be considered to improve functional capacity and LV systolic function in patients with non-ischemic HF due to idiopathic dilated cardiomyopathy. Further large-scale randomized trials are needed to explore the effect of ivabradine vs. placebo on the long-term clinical outcome in such patients.

Limitations of the study

Our findings are based on a single-center study with a rather small sample size, and relatively short follow-up. Therefore, our results should be taken with caution. Moreover, most patients were not receiving the target doses of evidence-based therapy. Hence, our results cannot be generalized to patients on the target doses of background therapy. Additionally, we excluded patients with device therapy. The effect of ivabradine in such subset needs further exploration. Finally, we enrolled patients with a sinus HR ≥ 70 bpm, therefore, our findings do not apply to patients with atrial fibrillation/flutter.

Conclusions

In symptomatic patients with idiopathic dilated cardiomyopathy who are already receiving the maximally tolerated doses of evidence-based treatment, the addition of ivabradine, vs. placebo, reduced HR and improved functional capacity at short-term follow-up.

Disclosures: The current study was sponsored by a research grant from Ain Shams University.

Conflict of interest: None declared

References

1. Bois P, Bescond J, Renaudon B, Lenfant J. Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. Br J Pharmacol, 1996; 118: 1051–1057.
2. Borer JS, Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: A randomized, double-blind, multicentered, placebo-controlled trial. Circulation, 2003; 107: 817–823.
3. Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J, 2005; 26: 2529–2536.
4. Ruzyllo W, Tendera M, Ford I, Fox KM. Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: A 3-month randomised, double--blind, multicentre, noninferiority trial. Drugs, 2007; 67: 393–405.
5. Mulder P, Barbier S, Chagraoui A et al. Long-term heart rate reduction induced by the selective I(f) current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. Circulation, 2004; 109: 1674–1679.
6. Rayan M, Tawfik M, Alabd A, Gamal A. Ivabradine, a novel heart rate slower: Is it a sword of double blades in patients with idiopathic dilated cardiomyopathy? Anadolu Kardiyol Derg, 2011; 11: 402–406.
7. Lang RM, Bierig M, Devereux RB et al. Recommendations for chamber quantification: A report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr, 2005; 18: 1440–1463.
8. McInnis KJ, Balady GJ, Weiner DA, Ryan TJ. Comparison of ischemic and physiologic responses during exercise tests in men using the standard and modified Bruce protocols. Am J Cardiol, 1992; 69: 84–89.
9. Quittan M, Wiesinger GF, Crevenna R et al. Cross-cultural adaptation of the Minnesota Living with Heart Failure Questionnaire for German-speaking patients. J Rehabil Med, 2001; 33: 182–186.
10. McMurray JJ, Adamopoulos S, Anker SD et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J, 2012; 33: 1787–1847.
11. 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: 886–894.
12. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A subgroup analysis of a randomised controlled trial. Lancet, 2008; 372: 817–821.
13. Flannery G, Gehrig-Mills R, Billah B, Krum H. Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol, 2008; 101: 865–869.
14. Swedberg K, Komajda M, Böhm M et al. 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: 1938–1945.
15. Komajda M, Follath F, Swedberg K et al. The EuroHeart Failure Survey programme: A survey on the quality of care among patients with heart failure in Europe. Part 2: Treatment. Eur Heart J, 2003; 24: 464–474.
16. Swedberg K, Komajda M, Böhm M et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. Lancet, 2010; 376: 875–885.
17. Volterrani M, Cice G, Caminiti G et al. Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with Heart Failure (the CARVIVA HF trial). Int J Cardiol, 2011; 151: 218–224.
18. Fox K, Ford I, Steg PG, Tendera M, Ferrari R. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): A randomised, double-blind, placebo-controlled trial. Lancet, 2008; 372: 807–816.
19. Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Rationale, design, and baseline characteristics of the Study assessInG the morbidity-mortality beNefits of the If inhibitor ivabradine in patients with coronarY artery disease (SIGNIFY trial): A randomized, double-blind, placebo-controlled trial of ivabradine in patients with stable coronary artery disease without clinical heart failure. Am Heart J, 2013; 166: 654–661.e6.