ORIGINAL ARTICLE

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Effect of ivabradine on ventricular arrhythmias in heart failure patients with reduced ejection fraction

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SUMMARY

BACKGROUND/INTRODUCTION: Heart failure patients with reduced ejection fraction are at high risk for ventricular arrhythmias and sudden cardiac death. Ivabradine, a specific inhibitor of the I_f current in the sinoatrial node, provides heart rate reduction in sinus rhythm and angina control in chronic coronary syndromes.

OBJECTIVE: The effect of ivabradine on ventricular arrhythmias in heart failure patients with reduced ejection fraction patients has not been fully elucidated. The aim of this study was to investigate the effect of ivabradine use on life-threatening arrhythmias and long-term mortality in heart failure patients with reduced ejection fraction patients.

METHODS: In this retrospective study, 1,639 patients with heart failure patients with reduced ejection fraction were included. Patients were divided into two groups: ivabradine users and nonusers. Patients presenting with ventricular tachycardia, the presence of ventricular extrasystole, and ventricular tachycardia in 24-h rhythm monitoring, appropriate implantable cardioverter-defibrillator shocks, and long-term mortality outcomes were evaluated according to ivabradine use.

RESULTS: After adjustment for all possible variables, admission with ventricular tachycardia was three times higher in ivabradine nonusers (95% confidence interval 1.5–10.2). The presence of premature ventricular contractions and ventricular tachycardias in 24-h rhythm Holter monitoring was notably higher in ivabradine nonusers. According to the adjusted model for all variables, 4.1 times more appropriate implantable cardioverter-defibrillator shocks were observed in the ivabradine nonusers than the users (95%CI 1.8–9.6). Long-term mortality did not differ between these groups after adjustment for all covariates.

CONCLUSION: The use of ivabradine reduced the appropriate implantable cardioverter-defibrillator discharge in heart failure patients with reduced ejection fraction patients. Ivabradine has potential in the treatment of ventricular arrhythmias in heart failure patients with reduced ejection fraction patients.

KEYWORDS: Ivabradine. Mortality. Implantable cardioverter defibrillator. Cardiac arrhythmia. Heart failure.

INTRODUCTION

Heart failure (HF) patients, especially those with HF with reduced ejection fraction (HFrEF), are at high risk for ventricular arrhythmias and sudden cardiac death. Both implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with an ICD (CRT-D) have been shown to successfully treat life-threatening ventricular arrhythmias and to reduce cardiac mortality in patients with HFrEF[1,2]. Traditionally, patients with HFrEF who survive from life-threatening ventricular arrhythmias are at increased risk for recurrent lethal arrhythmias in the long-term follow-up. In addition, detection of ventricular arrhythmia in such patients has been reported to be a poor prognostic predictor[3].

Ivabradine, a specific inhibitor of the I_f current in the sinoatrial node, provides a pure heart rate reduction in patients with sinus rhythm[4]. Ivabradine is currently recommended to treat patients with stable angina, HF, as well as inappropriate sinus tachycardia[5-7]. Outcomes of randomized trial on chronic heart failure demonstrated that ivabradine improved the long-term survival and reduced the rate of hospitalization in patients with HFrEF[6]. However, in this study, ventricular arrhythmias were not monitored, and patients with high ventricular arrhythmia burdens were excluded from the trial. Therefore, the effects of ivabradine on ventricular arrhythmias in HFrEF patients have not been fully elucidated. Thus, in this study, we aimed to investigate the effect of ivabradine on life-threatening arrhythmias and long-term mortality in HFrEF patients.

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METHODS

Data collection

In this retrospective study, we reviewed all patients with HFrEF who were admitted to our center between January 2010 and April 2021. The diagnosis of HFrEF was made based on the ICD codes in the hospital electronic database system and a previous transthoracic echocardiographic report demonstrating a left ventricle ejection fraction (LVEF) of ≤40%. In all, 1,639 HFrEF patients were evaluated in this investigation. The electronic database at our institution was employed to gather baseline information, laboratory results, and echocardiographic data. All patients received guideline-directed medical therapy for HFrEF. Transthoracic echocardiography was performed on all patients by a cardiovascular imaging specialist using the Vivid 7 (GE Vingmed Ultrasound AS, Horten, Norway) system. The LVEF was measured using the modified Simpson's method, and left ventricular end-diastolic and end-systolic volumes were evaluated on apical two- and four-chamber views. In addition, patients whose echocardiographic data could not be evaluated accurately and under the age of 18 years were excluded from the study. A 24-h rhythm Holter monitoring was performed in patients with palpitations, presyncope, and unexplained syncope complaints. For the presence of premature ventricular contractions (PVCs), the arrhythmia burden limit was determined to be >10% in 24-h rhythm Holter monitoring[8]. In HFrEF patients who were implanted with ICD or CRT-D, device therapy, such as anti-tachycardia pacing or shock, delivered in response to ventricular tachycardia (VT) or ventricular fibrillation (VF), was considered an appropriate therapy. Inappropriate device therapy was defined as any therapy given in reaction to atrial fibrillation, supraventricular tachycardia, sinus tachycardia, or device malfunction. Data on device therapy were acquired from patients' records and, where applicable, verified with device interrogation records. The regular use of ivabradine was confirmed by the data of the Ministry of Health since ivabradine is required to be used based on the medical reports according to the rules of the current insurance system.

Study outcomes

The primary endpoints of this investigation were long-term all-cause mortality and the occurrence of ventricular tachycardia, the presence of PVC burden >10% on 24-h Holter monitoring, the presence of ventricular tachycardia on 24-h Holter monitoring, and proper ICD shock. The long-term survival status of each patient was determined using the National Death Notification System.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences 20.0 software (IBM SPSS 20, SPSS Inc., Chicago, Illinois, USA). The study population was divided into two groups according to patients' ivabradine use: patients not using ivabradine (n=1363), and patients using ivabradine (n=276). The demographic features and clinical characteristics of the study groups were compared. Kolmogorov-Smirnov test was used for the evaluation of normality. Continuous variables were presented as median and interquartile range or mean and standard deviation compared using the t-test or the Mann-Whitney U test, as appropriate. A $p<0.05$ was considered statistically significant. Categorical variables were presented as numbers and percentages. Analyses of categorical variables were performed by Pearson's chi-square test or the Fisher's exact test. Cox regression models were formed in order to elucidate the effect of ivabradine use on the outcomes. The results of regression analysis were presented as a hazard ratio (HR) with a 95% confidence interval (CI). Two models were used in the Cox regression analysis: model I, unadjusted, and model II, adjusted. Model II was adjusted to baseline demographics and risk factors for admissions, serving as a reference group. The variables co-variated in the model II were age, gender, hypertension, diabetes mellitus, smoking, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, chronic renal failure, HF etiology, LVEF, beta-blockers, angiotensinogen-converting enzyme inhibitors or angiotensinogen receptor blockers, spironolactone, and furosemide.

RESULTS

A total of 1,639 patients with HFrEF [median age: 71 (63–79) years and 946 (57.7%) were males] were included in the study. In total, 276 patients were in the ivabradine group. In terms of baseline features, 1086 (66.3%) patients had ischemic HFrEF, while 553 patients (33.7%) had nonischemic HFrEF. In regard to device therapy, 281 patients had ICD implantation and 105 patients had CRT-D implantation. The mean LVEF was 30% (25.0–35.0). The study population included 91 patients using ivabradine and implanted ICDs, compared to 295 patients with ICDs not using ivabradine. Baseline clinical features are summarized in Table 1.

In terms of arrhythmias, 44 patients who presented with VT on admission were not treated with ivabradine, while 4 patients who developed VT on admission were treated with ivabradine (Table 2). PVCs were observed in 24-h rhythm Holter monitoring in 169 (36.2%) non-ivabradine users, while they were observed in 64 (21.7%) ivabradine users. While VT was detected in 12 (2.6%) patients not using ivabradine in 24-h rhythm Holter monitoring applied to patients, it was detected in 2 (0.7%) patients using ivabradine. The frequency of ICD discharge was significantly higher in patients who were not treated with ivabradine compared with

Table 1. Comparison of demographic, clinical characteristics, laboratory, and echocardiography parameters of patients according to ivabradine usage in patients with heart failure with reduced ejection fraction.

	Overall (n=1639)	Patients not using ivabradine (n=1363)	Patients using ivabradine (n=276)	p-value
Age, years	71 (63–79)	71 (62–79)	74 (65–82)	<0.001
Male gender	946 (57.7%)	797 (58.5%)	149 (54.0%)	0.169
Hypertension	969 (59.1%)	809 (59.4%)	160 (58.0%)	0.670
Diabetes mellitus	596 (36.4%)	486 (35.7%)	110 (39.9%)	0.186
Hyperlipidemia	469 (28.8%)	393 (29.1%)	76 (27.7%)	0.657
Smoking	156 (9.6%)	130 (9.6%)	26 (9.5%)	0.937
Chronic renal failure	408 (25.0%)	345 (25.4%)	63 (22.8%)	0.370
COPD	186 (11.5%)	152 (11.3%)	34 (12.4%)	0.592
Cerebrovascular accident	26 (1.6%)	21 (1.6%)	5 (1.8%)	0.791
Hypothyroidism	63 (3.9%)	51 (3.8%)	12 (4.4%)	0.645
Hyperthyroidism	37 (2.3%)	28 (2.1%)	9 (3.3%)	0.249
Coronary artery disease	1142 (69.7%)	942 (69.1%)	200 (72.5%)	0.269
Heart failure etiology				
Ischemic	1086 (66.3%)	913 (67.0%)	173 (62.7%)	0.168
Nonischemic	553 (33.7%)	450 (33.0%)	103 (37.3%)	0.168
Device types				
ICD	281 (17.2%)	212 (15.6%)	69 (25.1%)	<0.001
CRT-D	105 (6.4%)	83 (6.1%)	22 (8.0%)	0.259
All defibrillators	386 (23.7%)	295 (21.8%)	91 (33.2%)	<0.001
Laboratory values				
Creatinine, mg/dL	1.0 (0.8–1.3)	1.0 (0.8–1.3)	1.0 (0.8–1.3)	0.350
Potassium, mEq/L	4.5 (4.2–4.8)	4.5 (4.2–4.8)	4.4 (4.1–4.7)	0.108
Magnesium, mEq/L	2.1 (1.9–2.3)	2.1 (1.9–2.3)	2.1 (1.9–2.3)	0.330
Calcium, mEq/L	9.3 (8.9–9.6)	9.3 (8.9–9.6)	9.3 (9.0–9.6)	0.252
Echocardiography data				
LVEF, %	30 (25–35)	30 (25–35)	30 (25–35)	0.475
LVEDD, mm	60 (54–68)	60 (54–68)	61 (56–67)	0.114
LVESD, mm	48 (41–56)	48 (41–56)	50 (42–57)	0.154
LAAP, mm	44 (40–49)	44.0 (40–50)	45 (40–48)	0.949
Out-hospital medication				
Beta-blockers	1624 (99.1%)	1350 (99.0%)	274 (99.3%)	0.715
ACEIs or ARBs	1105 (67.4%)	921 (67.6%)	184 (66.7%)	0.770
Spironolactone	1026 (62.6%)	845 (62.0%)	181 (65.6%)	0.262
Furosemide	1516 (92.5%)	1256 (92.1%)	260 (94.2%)	0.238
Follow-up, months				

Continuous variables are presented as median (interquartile range). Nominal variables are presented as frequency (%). COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter defibrillator; CRT-D: cardiac resynchronization therapy with a pacemaker and an ICD; LVEF: left ventricle ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LAAP: left atrium anteroposterior diameter; ACEIs: angiotensinogen-converting enzyme inhibitors; ARBs: angiotensinogen receptor blockers.

those who were treated (n=64 vs. n=7), respectively. Finally, long-term mortality was observed in 143 (10.5%) non-ivabradine users, while it was observed in 22 (8%) ivabradine users.

According to the model adjusted for all covariates, the risk of VT on admission was observed three times more in non-ivabradine users than in users (Table 3). There was no significant difference between the two groups in terms of long-term mortality. According to the adjusted model for all variables, the presence of PVCs in 24-h rhythm Holter monitoring was 2.4 times higher in patients not using ivabradine than in those using it. All variable-adjusted analyses showed 4.2 times more VT on 24-h rhythm Holter monitoring in non-ivabradine users than in ivabradine users. According to the model adjusted for all variables, approximately 4.1 times more ICD discharges were observed in the group that did not use ivabradine than in the group that used it.

DISCUSSION

The current study has shown that ivabradine reduces appropriate ICD therapy in HFrEF patients. Additionally, the use of ivabradine significantly reduced VT on admission, the presence of PVCs, and VT detection in 24-h rhythm Holter monitoring in HFrEF patients.

Table 2. Distribution of patients' ventricular arrhythmias, appropriate implantable cardioverter defibrillator treatments, and long-term mortality according to ivabradine use.

	Patients not using ivabradine (n=1363)	Patients using ivabradine (n=276)
Admission with ventricular tachycardia	44 (3.2%)	4 (1.4%)
Presence of premature ventricular contractions >5% in 24-h rhythm Holter monitoring	169 (36.2%)	60 (21.7%)
Ventricular tachycardia in 24-h rhythm Holter monitoring	12 (2.6%)	2 (0.7%)
Appropriate ICD shock in follow-up	64 (21.7%)	7 (7.7%)
Long-term mortality	143 (10.5%)	22 (8%)

ICD: implantable cardioverter defibrillator.

Table 3. Multivariate analysis for admission with ventricular tachycardia, presence of premature ventricular contractions >5% in 24-h rhythm Holter monitoring, ventricular tachycardia in 24-h rhythm Holter monitoring, appropriate implantable cardioverter defibrillator shock in follow-up, and long-term mortality by ivabradine usage.

	Patients not using ivabradine	Patients using ivabradine
Admission with ventricular tachycardia, HR (95%CI)		
Model 1: unadjusted	3.6 (1.3–10.2)	1 [Reference]
Model 2: adjusted for all covariates[a]	3.0 (1.5–7.4)	1 [Reference]
Long-term mortality, HR (95%CI)		
Model 1: unadjusted	1.9 (1.2–3.0)	1 [Reference]
Model 2: adjusted for all covariates[a]	1.4 (0.8–2.8)	1 [Reference]
Presence of premature ventricular contractions in 24-h rhythm Holter monitoring, HR (95%CI)		
Model 1: unadjusted	2.9 (2.1–3.9)	1 [Reference]
Model 2: adjusted for all covariates[a]	2.4 (1.1–3.1)	1 [Reference]
Ventricular tachycardia in 24-h rhythm Holter monitoring, HR (95%CI)		
Model 1: unadjusted	6.7 (1.4–30.4)	1 [Reference]
Model 2: adjusted for all covariates[a]	4.2 (1.9–12.1)	1 [Reference]
Appropriate ICD shock in follow-up, HR (95%CI)		
Model 1: unadjusted	4.3 (2.0–9.5)	1 [Reference]
Model 2: adjusted for all covariates[a]	4.1 (1.8–9.6)	1 [Reference]

CI: confidence interval; HR: odds ratio. [a]Adjusted for: age, gender, hypertension, diabetes mellitus, smoking, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, chronic renal failure, heart failure etiology, ejection fraction, beta-blockers, angiotensinogen-converting enzyme inhibitors or angiotensinogen receptor blockers, spironolactone, and furosemide.

The I_f channel, which is one of the most important ionic currents regulating the pacemaker activity in the sinoatrial (SA) node, is a mixed Na–K inward current activated by hyperpolarization. Ivabradine exerts this effect without prolonging QTc or altering conductance, refractoriness, or repolarization time of the atria, atria-ventricle (AV) node, His-Purkinje system, and ventricles[9]. It prolongs diastole by decreasing the diastolic depolarization slope in SA node cells[10]. As a result, by prolonging diastole time, it reduces myocardial oxygen demand and increases myocardial perfusion. Heart rate plays an important role in the pathophysiology of HF, and ivabradine-induced heart rate reduction improves clinical outcomes in selected patient groups[6]. With the use of ivabradine in our patients, heart rate reduction may have improved myocardial perfusion by prolonging diastole and may have prevented ventricular arrhythmias by reducing Ischemia.

The cyclic nucleotide-gated channel 4 current (HCN4), the primary site of action of ivabradine, is highly expressed in the SA node. It is expressed at a low level in normal ventricular myocytes, whereas the expression of HCN channels is increased in ventricular myocytes in HF. I_f currents may be responsible for the abnormal automaticity in the ventricles in HF, and ivabradine may prevent ventricular arrhythmias by blocking the HCN channel[11]. This increased HCN channel expression observed in the ventricles of HF patients may underlie the possible anti-arrhythmic effect of ivabradine observed in our patients.

Ivabradine has also been shown to inhibit $I_f$channels, which are normally found only in the SA node but pathologically expressed in the ventricular myocardium with HF[12]. Heart rate during Ischemia is associated with reperfusion arrhythmias, and a lower heart rate during Ischemia delays Ischemia-induced electrophysiological changes[13]. It has been shown that $I_f$current activity increases the pro-arrhythmogenic potential as a result of prolongation of the ventricular repolarization phase[14]. In conclusion, I_f channel blockers suggest a potential approach to prevent sudden death in HFrEF patients. There is a case report where ivabradine was used in addition to antiarrhythmic drugs and catheter ablation in patients with resistant ventricular arrhythmia[15].

The exact mechanisms of ivabradine's efficacy in the treatment of tachycardias originating from outside the sinus node and due to enhanced automaticity are not yet known. The first possible mechanism is that it inhibits increased automaticity as a result of increased expression of HCN channels in ventricular myocytes. There are case reports suggesting that ivabradine may have potential in the pediatric population for the treatment of a variety of atrial tachycardias in which increased automaticity is considered the primary underlying mechanism[16,17]. The possible anti-arrhythmic effect of ivabradine can be considered as a result of suppressing automaticity, reducing PVC burden, and preventing VT trigger. The second possible explanation is that ivabradine prevents triggered activity-mediated arrhythmias induced by prolonging ventricular repolarization by its inhibiting effect on hERG channels[18].

There are various case reports in the literature regarding the suppression of ventricular arrhythmias. In a study of mice with cardiomyopathy, ivabradine was shown to suppress early PVCs, sustain ventricular arrhythmias, and improve survival[19]. Experimental studies suggest that the antiarrhythmic effects of ivabradine are due to the following mechanisms: [1] it conserves energy by reducing heart rate and prevents electrophysiological effects of Ischemia and [2] it blocks HCN channels that are overexpressed in the ventricles in HF[11].

All these studies show that ivabradine reduces ventricular arrhythmias in HF patients and support our current study results. In our HFrEF patient group, ivabradine may have reduced the ventricular arrhythmias by the abovementioned possible mechanisms. The presence of PVC, appropriate ICD shocks, and ventricular arrhythmias in HFrEF patients is associated with high mortality[20-22]. In the present study, we showed that ivabradine reduces ventricular arrhythmias in HFrEF patients. However, no statistically significant reduction in total mortality was demonstrated. The reason for the statistical insignificance may be that HFrEF patients in our population died because of pump failure. Prospective studies with larger patient populations are needed to demonstrate the effects of ivabradine more clearly on ventricular arrhythmias.

Our study has several limitations. First, our study had a single-center, retrospective design. Second, the optimization of medical treatment for all patients in the follow-up period is unknown. Third, all patients could not be evaluated with 24-h rhythm Holter monitoring. Unfortunately, 24-h rhythm Holter monitoring was applied only to patients with symptoms. Fourth, the optimal medical treatment of patients did not include SGLT-2 inhibitors, which might have affected the results. Finally, the brain natriuretic peptide levels of all patients were not routinely checked during hospitalizations.

CONCLUSION

The use of ivabradine has been shown to reduce appropriate ICD therapy in patients with HFrEF. The use of ivabradine in HFrEF patients may have potential for preventing ventricular arrhythmias.

COMPLIANCE WITH ETHICAL STANDARDS

This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHORS' CONTRIBUTIONS

LP: Conceptualization, Investigation, Writing – original draft. **AÇY**: Data curation, Validation. **OT**: Writing – review & editing. **TÇe**: Methodology. **KK**: Data curation, Software. **SE**: Data curation. **GÇ**: Formal Analysis, Supervision, Visualization. **MİH**: Supervision, Writing – review & editing. **TÇı**: Investigation, Formal Analysis. **AİT**: Project administration, Supervision.

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