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Original Article

Ivabradine effects in hospitalized acute heart failure patients: a single center retrospective study

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Abstract: Background: An increased heart rate (HR) is deleterious in patients with decompensated heart failure. Ivabradine, an HR lowering agent which acts by inhibiting the I_f current in the sinoatrial node, is indicated for chronic heart failure with reduced ejection fraction. However, data regarding the safety and efficacy of ivabradine in acute decompensated heart failure is limited. This retrospective observational study aimed to investigate the effects of ivabradine on morbidity and short-term mortality of hospitalized patients with acute decompensated heart failure. Methods: A total of 998 patients with acute decompensated heart failure on top of a chronic status from 1/5/2014 to 1/5/2019 who were already on guideline-directed treatment including a beta-blocker were included. Patients were divided into two groups, the first group (No-ivabradine) where patients continued the same dose of beta-blocker alone while the second group (ivabradine group) ivabradine 5 mg BID was added in addition to the same dose of beta-blocker. Patients with hemodynamic instabilities were excluded from the study. Propensity matching was performed to exclude confounding factors. Results: There was no significant difference between groups regarding baseline patient characteristics, laboratory, and echocardiographic data. There were significant differences between groups regarding average HR (87 ± 15 and 90 ± 12 bpm in ivabradine and control groups, consecutively, P = 0.0006*) and length of hospital stay (5.3 ± 2.3 and 7.7 ± 5.6 days in ivabradine and control groups, consecutively, P < 0.0001*). However, there were no differences in rehospitalization and mortality rates at 1 month and 6 months. Conclusion: In a retrospective cohort study aimed to investigate the effects of ivabradine on morbidity and short-term mortality of hospitalized patients with acute decompensated heart failure. Ivabradine was associated with significantly lower average HR and length of hospital stay. However, there was no benefit in the reduction of rehospitalization and mortality rates at 1- and 6-month follow-ups.

Keywords: Ivabradine, beta blockers, heart rate control, acute heart failure, chronic heart failure, decompensated heart failure

Introduction

Studies have suggested that increased heart rate (HR) is deleterious in decompensated heart failure due to a blunted or reverse Bowditch-Treppe response, which refers to the idea that an increase in heart rate increases the force of contraction generated by the myocardial cells with each heartbeat despite accounting for all other affecting factors, thus in decompensated patients there is no augmentation in the inotropic response to increased HR [1]. Paradoxically, increased heart rate is an independent predictor of cardiovascular mortality in patients with heart failure regardless of ejection fraction [2]. Heart rate control may be beneficial in critically ill patients, but heart rate-reducing drugs like beta-blockers or antiarrhythmic drugs can alter inotropy and hemodynamics. Ivabradine is an HR-lowering agent which acts by inhibiting the I_f current in the sinoatrial node, and by reducing the heart rate it can hinder the tachycardia induced left ventricular remodeling in heart failure. Ivabradine is char-

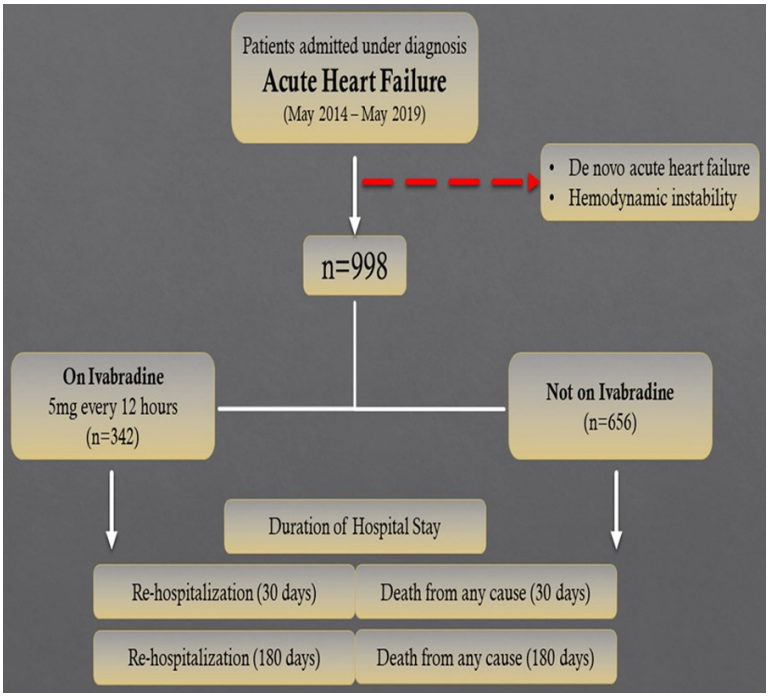

Figure 1. Central illustration demonstrating the study design.

acterized by having no effect on inotropy and no actual effect on corrected QT-interval, and it is currently indicated for patients with chronic heart failure with reduced ejection fraction (HFrEF) as class (IIa) in both European Society of Cardiology (ESC) and American College of Cardiology (ACC) guidelines depending on the data derived from the two major trials in heart failure, Systolic Heart Failure Treatment With the If Inhibitor Ivabradine Trial, SHIFT trial and Morbidity-Mortality Evaluation of the *If* Inhibitor Ivabradine in Patients With Coronary Artery Disease and Left Ventricular Dysfunction, BEAUTIFUL trial [3, 4]. However, data regarding the safety and efficacy of ivabradine in acute decompensated heart failure is scarce and only limited to case series and trials on animal models [5]. This retrospective observational cohort study aimed to investigate the effects of ivabradine on morbidity and short-term mortality of hospitalized patients with acute decompensated heart failure.

Patients and methods

Study population

This study was a retrospective cohort observational study that included patients admitted to our facility with acute decompensated on top of chronic heart failure from 1/5/2014 to 1/5/2019 (Study design illustrated in **Figure 1**).

Inclusion criteria

A total of 998 patients presented with acute decompensated heart failure on top of a chronic status were included.

- All included patients were adults (age more than 18 years) who are already on optimal heart failure treatment according to the latest ESC guidelines at the time of study enrollment including a beta-blocker medication.

- Patients were divided into two groups:

1. Patients who continued the same dose of beta-blocker alone (No-ivabradine). 2. Patients for whom ivabradine 5 mg BID was added in addition to the same dose of beta-blocker (Ivabradine group).

Exclusion criteria

- Patients with hemodynamic instabilities such as cardiogenic shock and pulmonary edema.

Baseline clinical evaluation

Full history, clinical examination including vital signs and oxygen saturation, routine laboratory investigations including (complete blood count (CBC), comprehensive metabolic panel (CMP), troponin, and Brain natriuretic peptide (BNP), a standard 12 lead electrocardiogram (ECG), and transthoracic echocardiography (TTE)) were acquired from all patients.

Follow-up

All included patients were assessed with emphasis on days of hospital stay, 30-day, and 6-month rehospitalization, and mortality rates.

Statistical analysis of the data

Statistical analyses were performed using IBM SPSS software version 22 (SPSS Inc., Chicago,

Table 1. Comparison between both groups regarding demographic and clinical characteristics

	No Ivabradine (n = 656)	Ivabradine (n = 342)	*P*-value
Age (years)	61.2 ± 14.4	61.6 ± 13.9	0.67
Male Sex	490 (74.7)	255 (74.6)	0.97
Ischemic etiology	509 (77.6)	265 (77.5)	0.97
Hypertension	492 (75)	247 (72.2)	0.34
Diabetes Mellitus	321 (48.9)	177 (51.8)	0.38
Smoking	433 (66)	209 (61.1)	0.13
Dyslipidemia	118 (18)	55 (16.1)	0.45
Ejection fraction (%)	46 ± 12	47 ± 13	0.23
Hemoglobin (g/dl)	12.8 ± 1.4	12.7 ± 1.5	0.3
Serum creatinine (mg/dl)	0.71 ± 1.1	0.82 ± 0.9	0.11
Platelet count (10^3/ml^{-3})	259 ± 113	265 ± 99	0.41
ACEIs/ARBs	429 (65.4)	225 (65.8)	0.9
ARNI	190 (29)	93 (27.2)	0.55
MRA	499 (76.1)	253 (74)	0.47
Baseline Heart rate (BPM)	90 ± 12	87 ± 15	0.0006*

Data are number (%) or mean ± S.D. ACEIs: Angiotensin Converting Enzymes Inhibitors, ARBs: Angiotensin Receptor Blockers, ARNI: Angiotensin Receptor Neprilysin Inhibitor, MRA: Mineralocorticoid Receptor Antagonist, BPM: beats per minute. *Significant *P*-value < 0.05.

Table 2. Comparison between both groups regarding short-term morbidity and mortality

	No Ivabradine (n = 656)	Ivabradine (n = 342)	*P*-value
Hospital stay (days)	7.7 ± 5.6	5.3 ± 2.3	< 0.0001*
Re-hospitalization (30 days)	8 (1.2)	2 (0.6)	0.36
Death (30 days)	2 (0.3)	0 (0)	0.31
Re-hospitalization (180 days)	24 (3.7)	10 (2.9)	0.51
Death (180 days)	6 (0.9)	1 (0.3)	0.28

Data are represented in number (%) or mean ± S.D. *Significant *P*-value < 0.05.

IL, USA) and its related materials. Categorical data are presented as frequency and percentages while continuous data are presented as a mean and standard deviation for normally distributed variables or as a median and interquartile range for non-normally distributed variables. A *p*-value of less than 0.05 was considered significant. Propensity matching for age, sex, and cardiovascular risk factors was done to exclude the effect of any confounding factors.

Statistical tests used: 1. Chi-square test for categorical variables comparing different groups. 2. Fisher's exact correction for chi-square if > 20% of the cells have expected count < 5. 3. Mann Whitney test for abnormally distributed quantitative variables comparing two groups. 4. Wilcoxon signed ranks test for abnormally distributed quantitative variables, to comparing two periods.

The study protocol was approved by the ethics committee and the study is compatible with the Declaration of Helsinki. Informed consent was acquired from all patients before participation.

Results

Demographic and clinical data

The study included 998 patients divided into two groups, no ivabradine and ivabradine groups which included 656, and 342 patients respectively. Comparing baseline clinical characteristics between both groups, no statistically significant difference was noted. There was a significant difference between both groups regarding average HR (87 ± 15 and 90 ± 12 bpm in ivabradine and control groups consecutively, *p*-value = 0.0006*). Patient demographic and clinical characteristics of both groups were illustrated in **Table 1**.

Follow-up

There was a significant difference between both groups regarding days of hospital stay (5.3 ± 2.3 and 7.7 ± 5.6 days in ivabradine and control groups consecutively, *p*-value < 0.0001*). However, there were no differences in 1-month, 6-month hospitalization rates or mortality rates at 1-month, and 6-month (Illustrated in **Table 2**; **Figures 2**, **3**).

Propensity matching

After propensity matching of both groups, the difference between both groups regarding days

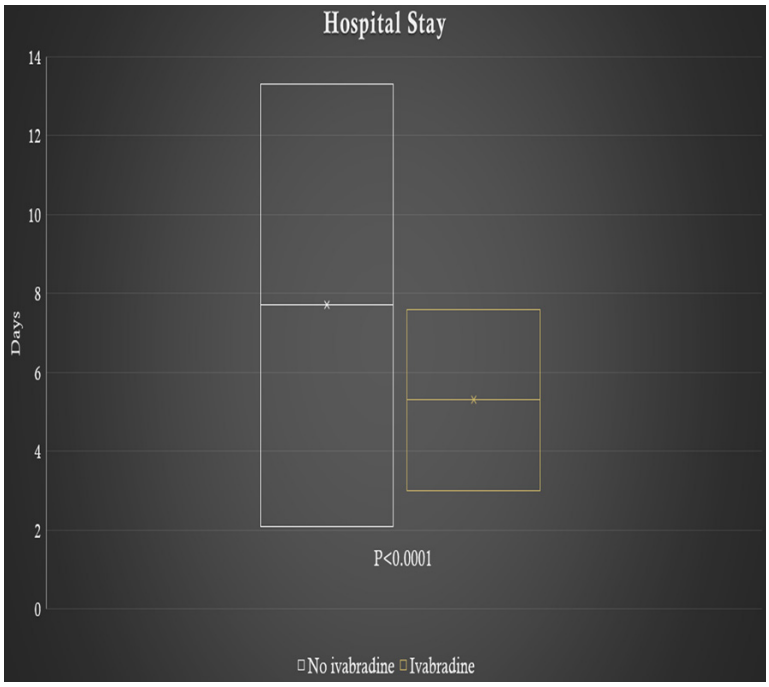

Figure 2. Comparison between both groups in relation to hospital stay (Days).

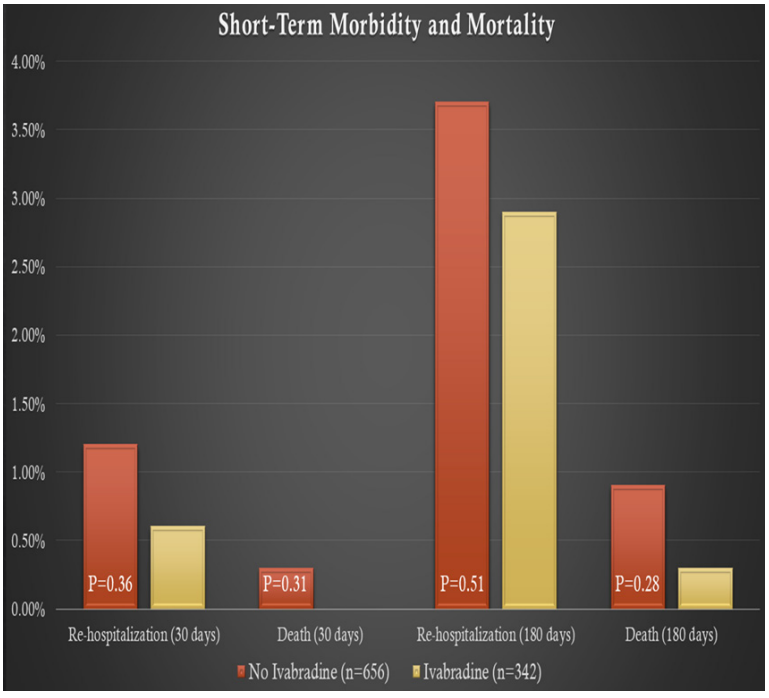

Figure 3. Comparison between both groups in relation to short-term morbidity and mortality.

of hospital stay was still statistically significant (5.3 ± 2.3 and 6.5 ± 5.3 days in ivabradine and control groups consecutively, *p*-value < 0.014*) (Illustrated in **Table 3**).

Discussion

Our study showed that (1) ivabradine was associated with decreased heart rate and length of hospital stay in patients with acute decompensated heart failure on top of chronic heart failure who were already on optimal anti-failure medical therapy including beta blockers, (2) ivabradine exerted no mortality benefit, and (3) in contrast to the studies done on chronic heart failure patients, ivabradine did not mitigate rehospitalization rate. Ivabradine was approved for patients with stable chronic heart failure with LVEF ≤ 35% who are in sinus rhythm with a resting HR above 70 bpm despite a maximally tolerated dose of beta-blocker to reduce hospitalization rate [6]. Its HR-lowering effect is achieved by blocking the cardiac pacemaker current (I_f), thus prolonging the diastolic depolarization phase, without interfering with inotropic or dromotropic effects [6]. Despite the significant reduction in heart failure hospitalization, the effects on all-cause or cardiovascular mortality were reportedly neutral [7, 8]. It was postulated that sympathetic overactivity, which was mitigated by certain beta-blockers but not ivabradine, was responsible for mortality in chronic heart failure patients [8]. Thus, according to this study and the data available in literature, the role of ivabradine in the setting of acute decompensated heart failure remains mostly unknown. As it is well-established that inotropic agents used in acute cardiogenic shock are associated with increasing HR and subsequent higher myocardial oxygen consumption and risk of arrhythmias [5]. Izco et al, demonstrated that

Table 3. Comparison between both groups regarding short-term morbidity and mortality after propensity matching

	No Ivabradine (n = 342)	Ivabradine (n = 342)	*P*-value
Hospital stay (days)	6.5 ± 5.3	5.3 ± 2.3	0.014*
Re-hospitalization (30 days)	2 (0.6)	2 (0.6)	1
Death (30 days)	0 (0)	0 (0)	1
Re-hospitalization (180 days)	9 (2.6)	10 (2.9)	0.81
Death (180 days)	2 (0.6)	1 (0.3)	0.56

Data are represented in number (%) or mean ± S.D. *Significant *P*-value < 0.05.

ivabradine led to temporary increased stroke volume followed by a paradoxical reduction in cardiac output and elevated central venous pressure in a swine model with acute cardiogenic shock induced by left anterior descending (LAD) coronary artery ligation [5]. According to a case series of 68 patients with acute HF or cardiogenic shock treated with ivabradine conducted by Treptau et al, there was a significant reduction in HR without an alteration in blood pressure [9]. Yang et al, in a retrospective study showed that early administration of ivabradine, compared to the non-ivabradine group was associated with lower HR with no changes in HF hospitalization, all-cause mortality, or 1-year mortality [10].

All these results were consistent with our study despite the difference in patient population as only patients without a previous diagnosis of heart failure were included in that study.

Study limitations

The study had some limitations, this was a single-center retrospective observational study with a relatively small sample size and specific patient population therefore, the generalizability of the results might be affected.

Study recommendations

Large-scale randomized placebo-controlled trials are required to determine whether ivabradine initiation in acute decompensated heart failure can be associated with improved morbidity or mortality apart from heart rate control.

Conclusion

In this retrospective study that evaluated the effects of ivabradine in hospitalized patients with acute decompensated heart failure. Ivabradine was associated with a significantly lower average heart rate and lower duration of hospital stay. However, it didn't show any significant benefit in the reduction of rehospitalization and mortality rates at 1- and 6-month follow-ups. Early addition of ivabradine might be rational in acutely decompensated heart failure patients to control heart rate and reduce the duration of hospital stay unless contraindicated.

Disclosure of conflict of interest

None.

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