

Ivabradine and Bisoprolol Prescribed in Combination versus Maximum Dose Titration of Bisoprolol in Patients with Systolic Heart Failure and Left Ventricular Systolic Dysfunction

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Abstract

Original Research Article

Background: Heart failure is a clinical syndrome which occurs due to structural or functional abnormalities characterized by inability of heart to fill or eject blood. Mostly all types of cardiac diseases may lead to heart failure with reduced ejection fraction (HFREF). Despite high volume prescribers of beta blockers patients does not achieve recommended target heart rate. **Objective:** To assess the efficacy of ivabradine as adjunct therapy with beta blockers in systolic heart failure and left ventricular systolic dysfunction. **Methodology:** This single center, open labelled, randomized study included 113 patients in sinus rhythm with HFREF and left ventricular systolic dysfunction from outpatient department of Cardiology, 250 Bed Sadar General Hospital, Kishoreganj, Bangladesh from January to December-2020. Ivabradine was initiated in 45% patients with SR. Patients with LVEF < 35% by Teichholz method, NYHA class II-III, sinus rhythm and resting HR >70 bpm, already on bisoprolol 5 mg were divided into 2 groups; Group 1 (n= 56) patients were uptitrated to bisoprolol 10 mg and Group 2 (n= 57) patients received ivabradine 5 mg b.i.d in addition to bisoprolol 5 mg. Blood samples for NTproBNP level, an ECG, echocardiogram, NYHA functional class, systolic and diastolic BP were taken at baseline and at the end of 6 months follow-up in both groups. **Results:** After 6 months HR decreased significantly from 94.82±7.03 to 68.75±5.35 bpm (p < 0.0001), with more patients in NYHA functional Class I than Class II and III and decrease in BNP level from 969.8.3±348.9 to 348.6±230.2 pg/ml (p < 0.0001) in group 2 patients. A significant increase in LVEF was observed with the addition of ivabradine from 31.40±5.37 to 41.68±5.33 % (p < 0.0001). However, mean systolic and diastolic blood pressure was not affected by the addition of ivabradine. **Conclusion:** This study concludes that patients with HFREF demonstrated good tolerability, efficacy and NYHA functional class with the combination of ivabradine and bisoprolol therapy.

Keywords: Ivabradine, Bisoprolol, Heart failure with Reduced Ejection Fraction, Left ventricular systolic dysfunction.

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INTRODUCTION

Mostly all types of cardiac diseases may lead to heart failure with reduced ejection fraction (HFREF). However, when these responses become persistent, they lead to the structural and molecular changes which characterize ventricular remodelling [1]. It is estimated that heart failure affects more than 23 million people worldwide, with the prevalence of symptomatic heart failure ranging from 0.4-2%. In the Framingham Heart Study, at 40 years of age, the lifetime risk for the development of heart failure for both men and women is 1 in 5 [2]. Heart failure is a clinical syndrome which occurs due to structural or functional abnormalities characterized by inability of heart to fill or eject blood.

Cardiac diseases which cause myocardial pressure/volume overload, or decreased contractility triggers adaptive responses to improve cardiac output and maintain blood flow to vital organs. The annual incidence rates per 1,000 population in the age groups for those 65-74 years of age is 15.2 for males and 8.2 for females, for those 75-84 years of age is 31.7 for males and 19.8 for females and for those ≥ 85 years of age is 65.2 for males and 45.6 for females [3]. Elevated heart rate is a modifiable risk factor for cardiovascular morbidity and mortality as it causes the activation of sympathetic nervous system and withdrawal of parasympathetic activity which are components of neurohumoral response to heart failure. It produces

detrimental effects as it decreases the myocardial perfusion and increases myocardial oxygen consumption. Beta blockers and ivabradine both are effective in treatment of chronic heart failure of ischemic etiology. They have shown to be efficacious in reducing LV remodeling by prolonging the diastolic time & improving left ventricle filling, thus increasing the stroke volume by heart rate reduction [4]. Beta blocker therapy has been a cornerstone in the treatment of patients with HFREF based on strong data from multiple randomized trials including CIBIS II. Besides suppression of ventricular arrhythmias, they improve the diastolic filling time in CHF patients. It is for this reason ACC/ AHA focused update 2005 (management of CHF in adults) recommended beta blocker for symptomatic and asymptomatic patients with heart failure who have LVEF < 45% [5]. Ivabradine may be a novel selective inhibitor of the pacemaker “If” channels which induces a selective pulse reduction in humans and animals. It had been mainly used as antianginal drug and was given together with the beta blockers. It's also utilized in the management of patients with sinus rhythm (SR) that suffer from moderate to severe coronary failure with impaired left ventricular systolic function to scale back morbidity and deathrate supported SHIFT data. Ivabradine is taken into account a big drug within the management of angina and HFREF with beneficial effects on cardiac remodelling and capillary density [6]. Despite the safe use of beta blockers as a primary line therapy for pulse reduction in patients with systolic coronary failure, patients might not tolerate the target dose well due to side effects like hypotension, light headedness, lethargy, dyspnea, depression, gastrointestinal disturbances, bronchospasm and excessive bradycardia and AV blocks. In contrast, Ivabradine together is safe with lesser adverse effects like headache, dizziness, vertigo, diarrhea [7, 8]. This study compares the efficacy and effects of ivabradine utilized in combination with beta-adrenergic blocker versus up titration of beta-adrenergic blocker on HR, LVEF, LV systolic and diastolic dimensions, BNP, and vital sign in Bangladeshi population with systolic coronary failure and left ventricular systolic dysfunction.

MATERIALS AND METHODS

This single center, open labelled, randomized study included 113 patients in sinus rhythm with HFREF and left ventricular systolic dysfunction from outpatient

department of Cardiology, 250 Bed Sadar General Hospital, Kishoreganj, Bangladesh from January to December-2020. Ivabradine was initiated in 45% patients with SR. Patients with LVEF < 35% by Teichholz method, NYHA class II-III, sinus rhythm and resting HR > 70 bpm, already on bisoprolol 5 mg were divided into 2 groups; Group 1 (n= 56) patients were uptitrated to bisoprolol 10 mg and Group 2 (n= 57) patients received ivabradine 5 mg b.i.d in addition to bisoprolol 5 mg. Blood samples for NTpro BNP level, an ECG, echocardiogram, NYHA functional class, systolic and diastolic BP were taken at baseline and at the end of one year follow-up in both groups.

Inclusion Criteria

Male or female out patients with stable symptomatic chronic heart failure alongside functional capacity of NYHA Class I-III for ≥ 4 weeks with ischemic or non- ischemic etiology and a prior history of hospitalization with worsening heart failure in past 12 months. Left ventricular systolic dysfunction is defined by reduction in left ventricular ejection fraction due to reduced myocardial contractility documented within past 3 months. It is graded as mild (LVEF 41-45%), moderate (LVEF 36-40%) and severe (LVEF \leq 35%). Patients were in sinus rhythm with resting heart rate ≥ 70 b.p.m selected on two consecutive visits (duration between two visits was 14 days) before randomization measured by a 12-lead electrocardiogram performed after at least 5 minutes rest.

Exclusion Criteria:

Exclusion criteria includes mainly male or female patients with left ventricular diastolic dysfunction or preserved left ventricular systolic function with heart failure preserved ejection fraction (HFpEF) and recent MI within 2 months of presentation. Patients with paroxysmal or permanent atrial fibrillation, sick sinus syndrome, history of symptomatic sustained or non-sustained ventricular arrhythmias, sinoatrial block, brad yarrhythmias, second and third degree AV block, and pacemaker with atrial or ventricular pacing are excluded. Patients with family history of QT prolongation or congenital prolong QT syndrome or treated with certain QT- prolonging products are also excluded. Patients who are eligible candidates for cardiac transplantation or have started CRT within previous 6 months are excluded as well.

Table-1: Design of Study

	Patients with stable chronic heart failure, NYHA Class I-III, treated by Bisoprolol 5mg	
Visit 0	Assessment of patients by eligibility criteria Allocation of patients to control groups (1 & 2)	
Visit 1 (randomization, Day 14th)	Standard therapy: up titration of Bisoprolol 5mg od to Bisoprolol 10mg od (Treatment group 1)	Addition of Ivabradine 5mg/day b.i.d (Treatment group 2)
Visit 2 (Week 4)	Check for possible signs of bradycardia and other adverse effects	
Visit 3 (Week 12)	Assessment of treatment efficacy and tolerability	
Visit 4 (Week 24)	Assessment of treatment efficacy and tolerability End of Study	

Statistical Analysis

The analysis was performed using intention to treat method. The mean values of variables in both groups were compared with their respective baseline control groups. Data of qualitative parameters were expressed in frequencies and percentages and quantitative parameters were expressed as mean arithmetic value \pm 1 standard deviation (SD). Changes in the quantitative variables between groups at the end of 6 months treatment were analyzed by applying column statistics and using paired Student's t test at 95% confidence interval. A p value of < 0.05 was considered statistically significant. This analysis was done using SPSS windows version 20.0.

RESULTS

This study included 113 ambulatory, clinically stable symptomatic patients selected. Patients already on bisoprolol 5 mg od/p.o (control group) were randomly divided into 2 groups. Patients in control group 1 (n= 56) on bisoprolol 5 mg od/p.o were up

titrated to bisoprolol 10 mg od/p.o (treatment group 1) while patients in control group 2 (n= 57) received ivabradine 5 mg b.i.d/p.o in addition to bisoprolol 5 mg od/p.o (treatment group 2). Patients were evaluated for full clinical workup at selection (visit 0), after 2 weeks (visit 1), at 4 weeks (visit 2), at 12 weeks (visit 3), and finally at 24 weeks after completion of treatment follow up of study (visit 4). Following data was collected at all the visits I) medical history with physical examination and duration of illness II) NYHA class of heart failure III) concomitant medications IV) physical examination of patient V) reported adverse effects VI) systolic and diastolic blood pressure VII) laboratory analysis for BNP level VIII) 12- lead electrocardiogram and IX) echocardiography. After the initiation of treatment at day 14th, patients were seen on 4th week to check for possible signs of bradycardia, if there were any signs reported the patient was to be withdrawn from the study. Patients were informed to visit immediately if any symptoms that led to withdrawal side effects reported with the medication.

Table-2: Main characteristics of Group 1 (SMT) & Group 2 (SMT + Ivab) (N=113)

	Group 1 (SMT)	Group 2 (SMT + Ivab)
Age (Mean \pm SD)	68.4 \pm 5.7	67.8 \pm 6.2
Gender (Males/ Females) (%)	71.4/28.5	73.6/26.3
Smokers (%)	33.9	36.8
Diabetes (%)	78.5	80.7
Hypertension (%)	82.1	84.2
Previous MI (%)	87.5	89.4
Previous Revascularization (PCI/CABG) (%)	80.3	82.4
NYHA Functional Class (II/III) (%)	26.7/73.2	24.5/75.4
Aspirin/Antiplatelet drugs (%)	87.5	89.4
ACEI/ARB (%)	82.1	84.2
Diuretics (%)	98.2	100
Statins (%)	89.2	91.2

Echocardiography

Standard 2D and M-mode imaging were obtained for the measurements of left ventricle prior to the initiation of therapy and post therapy. Using M mode method from the leading edge of one interface to the leading edge of other interface the diameters of left ventricle both systolic and diastolic were measured. With the help of ultrasound software, LVEF was measured by Teichholz formula [9]. LVEF increased from 33.68 \pm 4.52% baseline to 39.79 \pm 5.77%, with a significant p value < 0.0001 with the up titration of bisoprolol fumarate 5 mg od/p.o to bisoprolol fumarate 10 mg od/p.o od after 6 months of therapy. While combination of ivabradine 5 mg b.i.d/p.o with bisoprolol fumarate 5 mg od/p.o improved LVEF to 41.68 \pm 5.33 from 31.40 \pm 5.37% baseline, with a significant p value < 0.0001 after 6 months of therapy.

Electrocardiogram

Standard 12- lead ECGs were obtained. Heart rate was determined by counting the small boxes

between two consecutive R waves (R-R interval) and divided this number into 1500. The rhythm was determined by an upright P wave in lead II that is followed by QRS complex then it is said to be a normal sinus rhythm (NSR). ECGs were also evaluated for any intra cardiac block and intraventricular conduction delay, rhythm abnormalities i.e. atrial fibrillation specifically in ivabradine group as it has been reported [10]. The heart rate decreased from 96.33 \pm 8.03 to 81.58 \pm 8.87 b.p.m baseline, with a significant p value < 0.0001 with the up titration of bisoprolol fumarate 5 mg od/p.o to bisoprolol fumarate 10 mg od/p.o after 6 months of therapy. While combination of ivabradine 5 mg b.i.d/p.o with bisoprolol fumarate 5 mg od/p.o decreased heart rate to 68.75 \pm 5.35 from 94.82 \pm 7.03 b.p.m baseline, with a significant p value < 0.0001 after 6 months of therapy.

BNP

Standard BNP test was performed to measure the level of brain natriuretic peptide hormone in the

blood at the start and endpoint of treatment. BNP test was performed by drawing a blood sample from patient. The values were evaluated in picograms per milliliter (pg/ml) [11]. The level of BNP decreased in bisoprolol fumarate 10 mg od/p.o group from baseline 927.3±350.3 to 460.4±311.9 pg/mL, with a significant p

value < 0.0001 after 6 months of therapy. While with the addition of ivabradine 5 mg b.i.d/p.o to bisoprolol fumarate 5 mg od/p.o BNP level was reduced from 969.8±348.9 at baseline to 348.6±230.2 pg/mL, with a significant p value < 0.0001 after 6 months of therapy.

Table-3: Mean values of changes in different clinical parameters observed in Group 1 patients with bisoprolol 5 mg od/p.o (control group 1) vs. bisoprolol 10 mg od/p.o (treatment group 1) in patients with systolic heart failure and left ventricular systolic dysfunction (N=113)

Groups	Heart Rate (bpm)	LVEF (%)	LVEDD (mm)	LVESD (mm)	BNP (pg/ml)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Control 1 (Bisoprolol 5 mg)	96.33 ± 8.03	33.68 ± 4.52	62.18 ± 5.65	51.96 ± 6.06	927.3 ± 350.3	133.5 ± 9.95	92.37 ± 8.71
Treatment 1 (Bisoprolol 10 mg)	81.58 ± 8.87 ****	39.79 ± 5.77 ****	57.23 ± 5.32 ****	45.93 ± 6.35 ****	460.4 ± 311.9 ****	119.6 ± 7.75 ****	80.61 ± 6.88 ****

**** = P < 0.0001

Blood Pressure

Standard mercurial sphygmomanometer was used for measurement of blood pressure. Patient was allowed to rest for 5 to 10 minutes to stabilize the heart rate and blood pressure. The values are evaluated in mmHg [12, 13]. Pretreatment systolic and diastolic blood pressure was 133.5 ± 9.95 mmHg and 92.37 ± 8.71 mmHg which reduced to 119.6 ± 7.75 mmHg and 80.61 ± 6.88 mmHg respectively, with a significant p

value < 0.0001 with the up titration of bisoprolol fumarate 5 mg od/p.o to bisoprolol fumarate 10 mg od/p.o od after 6 months of therapy. While combination of ivabradine 5 mg b.i.d/p.o with bisoprolol fumarate 5 mg od/p.o decreased systolic blood pressure from 127.1± 7.55 mmHg to 124.8 ± 5.97 mmHg, with a significant p value 0.0144 and diastolic blood pressure from 85.53 ± 7.17 mmHg to 83.77 ± 6.14 mmHg, with a significant p value 0.0011.

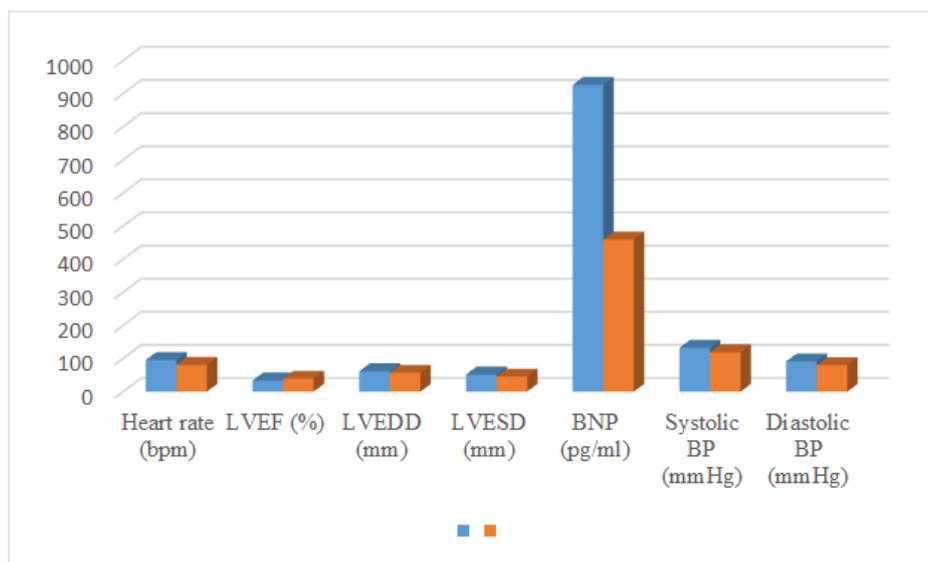


Fig-1: Mean values of changes in different clinical parameters observed in Group 1 patients.

Table-4: Mean values of changes in different clinical parameters observed in Group 2 patients with bisoprolol 5 mg od/p.o (control group) vs. bisoprolol 5 mg od/p.o+ ivabradine 5 mg b.i.d/p.o (treated group) in patients with systolic heart failure and left ventricular systolic dysfunction (N=113)

Groups	Heart Rate (bpm)	LVEF (%)	LVEDD (mm)	LVESD (mm)	BNP (pg/ml)	Systolic BP (mmHg)	Diastolic BP (mmHg)
Control 2 (Bisoprolol 5 mg)	94.82 ± 7.03	31.40 ± 5.37	61.11 ± 6.25	51.44 ± 6.22	969.8 ± 348.9	127.1 ± 7.55	85.53 ± 7.17
Treatment 2 (Bisoprolol 5 mg + Ivabradine 5 mg)	68.75 ± 5.35 ****	41.68 ± 5.33 ****	54.40 ± 4.86 ****	42.56 ± 5.65 ****	348.6 ± 230.2 ****	124.8 ± 5.97 *	83.77 ± 6.14 **

**** = P < 0.0001, ** = P = 0.0011, * = P = 0.0144

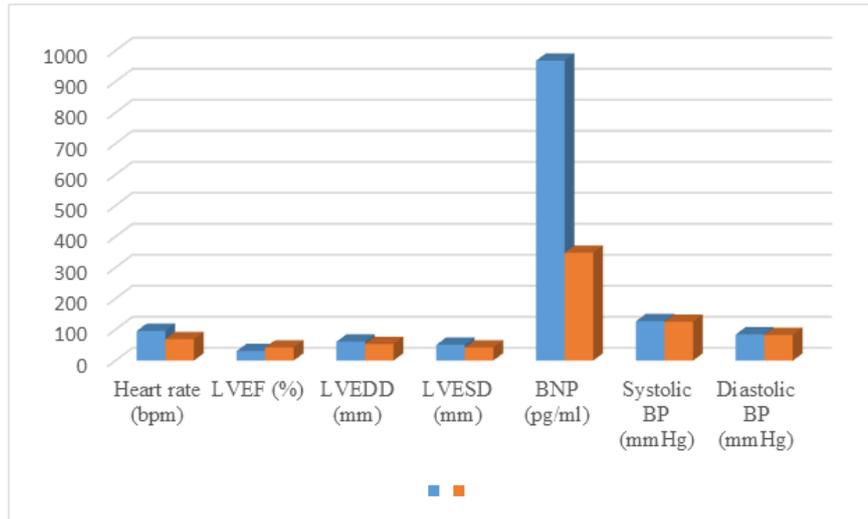


Fig-2: Mean values of changes in different clinical parameters observed in Group 2 patients.

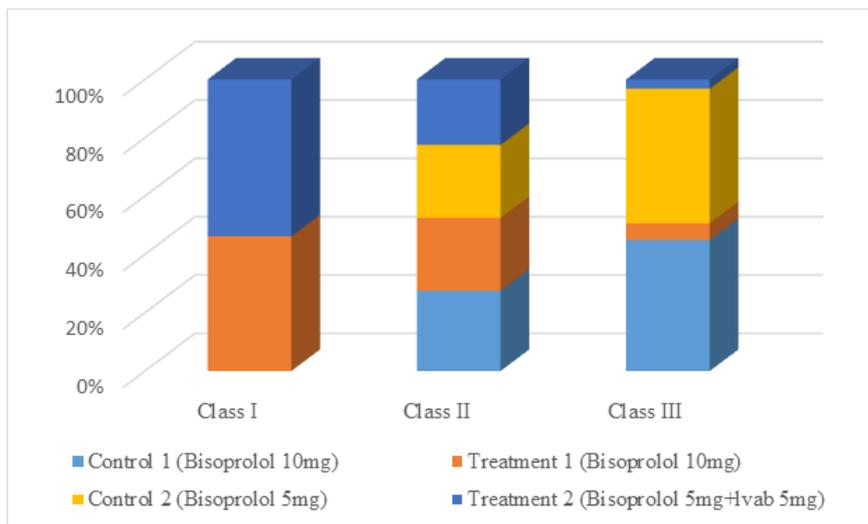


Fig-3: Percentage change in NYHA Functional class observed in Control and Treatment groups.

DISCUSSION

This study six patients (10%) reported paroxysmal atrial fibrillation in the first four weeks of initiation of therapy with ivabradine, which required discontinuation of therapy [14]. Five patients reported lethargy (8.7%), six patients reported dizziness (10%) and four patients reported sexual dysfunction (7%) with bisoprolol 10mg od/p.o [15, 16]. It has been noticed in a clinical practice that only few patients receive target dose of beta blocker that is recommended for systolic heart failure according to ACC/ AHA guidelines and up titration of beta blocker has been a focal point in the treatment of heart failure patients as it requires time and effort [17]. Ivabradine is a novel selective inhibitor of the sinoatrial node “If” channels which induces a selective heart rate reduction in humans and animals. It is given in combination with the beta blockers in the management of patients with NSR who suffer from moderate to severe heart failure and impaired left

ventricular systolic function to reduce morbidity and mortality rate based on SHIFT data [7]. Heart rate reduction with ivabradine could be helpful in a group of patients with systolic heart failure, (I) who may not tolerate the target dose well because of side effects such as hypotension, lethargy, light headedness, dyspnea, depression, sexual dysfunction, (II) who have contraindications to beta blockers such as bronchospasm and AV blocks, (III) whose heart rate remains high ≥ 70 b.p.m despite maximum tolerated dose of beta-blockers [18]. This shows that patients who cannot tolerate maximum dose of beta blocker and in whom sufficient heart rate reduction is not achieved despite beta blocker, combination of ivabradine with beta blockers appears to be an appropriate therapeutic regimen. The dose of ivabradine given in this study was clinically well tolerated without any evidence of adverse effects. Besides clinical parameters pathologic BNP findings, electrocardiogram monitoring and echocardiographic changes confirm the severity of

disease in patients with HFrEF. Heart rate reduction is a modifiable prognostic risk factor and potential therapeutic target in general population as well as in those with coronary artery disease and heart failure with reduced ejection fraction (HFrEF). Increased resting heart rate is inversely correlated with cardiovascular outcomes and all-cause mortality [19]. An elevated heart rate is caused by the activation of sympathetic nervous system and withdrawal of parasympathetic activity which are components of neurohumoral response to heart failure. It produces detrimental effects as it decreases the myocardial perfusion and increases myocardial oxygen consumption [20]. According to the findings of study by Paul Dubach et al. with magnetic resonance myocardial imaging, at baseline mean heart rate was 81 ± 12 (b.p.m) and LVEF was 25.0 ± 7 (%). After 6 months of therapy with bisoprolol fumarate, mean heart rate decreased to 64 ± 13 (bpm) and LVEF increased to 29.2 ± 8 (%), respectively [21]. Left ventricular ejection fraction (LVEF) is a most important prognostic indicator of cardiovascular outcomes and death in patients with systolic heart failure. It is inversely related to mortality, as lower the LVEF, the higher is the mortality rate in heart failure patients with systolic dysfunction [22]. It has been shown that in patients with $< 45\%$ ejection fraction, every 10% decrease in LVEF is associated with 39% increase risk of all-cause mortality and with every 5% increase in LVEF there is 19% lower relative risk of mortality [23]. Increase in cardiac dimensions such as left ventricular end systolic (LVESD) and left ventricular end diastolic diameters (LVEDD) are important determinant of clinical outcomes in heart failure patients. Patients with heart failure and left ventricular systolic dysfunction show marked improvement in symptoms and reduction in risk of congestive heart failure with relatively reduced size of cardiac chambers [24, 25]. Similar findings were observed in a study conducted by Luis Beck da Silva et al. where the baseline heart rate was 84 ± 14 (b.p.m) and left ventricular ejection fraction was 21.7 ± 9.4 (%). The heart rate decreased significantly to 70 ± 10 (b.p.m) and LVEF increased significantly by 7.9% ($p = 0.0003$) after 4 months of treatment with bisoprolol fumarate [26]. According to the findings of BEAUTIFUL (trial) there is 16% reduction in new onset or worsening of heart failure with the use of ivabradine [27]. The findings of systolic heart failure treatment with the If inhibitor ivabradine trial (SHIFT) shows 18% reduction in risk of cardiovascular death and worsening of heart failure. According to the echocardiographic findings of SHIFT trial, left ventricular ejection fraction was increased by $2.4 \pm 7.7\%$ in ivabradine group with 36% patients having $\geq 5\%$ increase in left ventricular ejection fraction [28]. It has also shown that heart rate and left ventricular ejection fraction are inversely related, as decrease in heart rate is associated with improvement in LVEF [29]. Similarly another echocardiographic study in rats' model also shows improved LVEF and marked reduction in LV diameters with the use of ivabradine. BNP is a

natriuretic peptide, which is released as a result of increased myocardial wall stress/remodeling. Its activation helps in natriuresis, vasodilation and diuresis [30]. It is an independent predictor of cardiovascular mortality and is used as a diagnostic tool for the management and treatment of heart failure. The rise in the level of BNP is directly proportional to the worsening of heart failure symptoms and myocardial failure [31]. Serkan Ordu *et al.*, demonstrated a study that revealed in ivabradine group vs. non-ivabradine group, the heart rate decreases from baseline 84.10 ± 8.76 to 68.36 ± 8.32 b.p.m after 6 months of therapy, with a significant value ($p = 0.001$). The NT-proBNP level in ivabradine group was significantly reduced from baseline 1353.02 ± 1453.77 to 717 ± 834.76 pg/mL after 6 months of therapy, with a significant value $p < 0.001$ [32]. Hypertension is a major independent risk factor for the cardiovascular diseases. Increased vascular tone is directly related to increase in blood pressure and cardiovascular outcomes in hypertensive patients [33]. The risk of heart failure increases by two to three folds affecting 50- 60% population in hypertensive patients. According to Framingham study, about one quarter of heart failure cases is associated with hypertension [34].

CONCLUSION

This study concludes that patients with HFrEF demonstrated good tolerability, efficacy and NYHA functional class with the combination of ivabradine and bisoprolol therapy. Ivabradine is effective in the treatment of patients with systolic heart failure and left ventricular systolic dysfunction. These results indicate that ivabradine can reverse the cardiac remodelling in patients with systolic heart failure and severe LV systolic dysfunction. Thus the combination of ivabradine 5 mg b.i.d/p.o and bisoprolol 5 mg od/p.o used in patients with systolic heart failure has proven to be more efficacious as compared to beta blocker uptitration with tolerated safety profile in a group of population.

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