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RESEARCH ARTICLE

Ivabradine alone and in combination with metoprolol reduces the incidence of major adverse cardiac events in patients with heart failure: A prospective study

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ABSTRACT

Background: Altered hemodynamics of heart failure patients is associated with an increased heart rate (HR). The effect of β-blockers on prognosis has been linked to their HR lowering effect. Ivabradine is an I_f current inhibitor and it decreases the heart rate. **Aims and Objectives:** The aim of this study was to compare the efficacy of ivabradine, a combination of ivabradine and metoprolol, with that of metoprolol alone in patients with heart failure. **Materials and Methods:** This prospective observational study was done in patients with New York Heart Association (NYHA) Class III/IV heart failure over 18 months. Patients were categorized into Group A: Ivabradine (5 mg BD), Group B: metoprolol (12.5 mg BD), and Group C: Combination of both (5 mg BD and 12.5 mg BD). At the end of 6 months follow-up, the outcomes of therapy were assessed based on the occurrence of major adverse cardiac events (MACE) such as acute coronary syndrome, rehospitalization, or death. Effectiveness was also measured in terms of a decrease in HR, improvement in left ventricular ejection fraction (LVEF), and NYHA functional class. **Results:** One hundred and fifty-two patients were included in this study in three groups – 51 patients in Group A, 50 patients in Group B, and 51 patients in Group C. At the end of follow-up period, it was found that the highest number of MACE occurred in Group B followed by A and C. Group C showed significant improvement with therapy in terms of decrease in HR, increase in LVEF, and improvement in NYHA class. **Conclusion:** Administration of ivabradine alone or a combination of ivabradine and metoprolol is more effective than metoprolol in reducing the incidence of MACE in heart failure.

KEY WORDS: Heart Failure; Heart Rate; Ivabradine; Metoprolol; Major Adverse Cardiac Events; New York Heart Association class

INTRODUCTION

Heart failure constitutes a major public health problem with a current prevalence of over 23 million worldwide.[1] The estimated prevalence of heart failure in India is 1.3–4.6 million, with an annual incidence of 0.5–1.8 million.[2] It has a substantial clinical, social, and economic burden, notably due to significant functional limitations and the reduced quality of life of patients.[3] Digitalis was considered as a sole drug therapy for the treatment of heart failure centuries back, but now considerable progress has been made in the field of heart failure from the delineation of the pathophysiology to the investigation of neurohumoral, the molecular basis of the illness and drugs were developed based on these mechanisms. At present, the most commonly used and effective drugs for

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the treatment of heart failure are angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists.[4]

It is well known that altered hemodynamics of heart failure patients is associated with an increased heart rate (HR). Therefore, the risk of adverse events in heart failure is closely related to HR.[5] Cardiovascular risk of increased HR was first reported in the Framingham study which showed that cardiovascular death is increased by 14% with an increase of 10 bpm in HR.[6] HR is considered to be an independent prognostic factor in all cardiovascular syndromes.[7-9]

In this context, the effect of beta-blockers on prognosis has been linked to their HR lowering effect. However, the use of beta-blockers is associated with various adverse effects. Ivabradine, an I_f current inhibitor, was introduced recently which can lower the HR without blocking the beta-adrenergic receptors.[10] Studies done to assess the efficacy of ivabradine in heart failure yielded mixed results. Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT)[11] showed that it improved the survival rate, whereas the BEAUTIFUL study[12] says that ivabradine had no added benefit when it was given along with standard therapy in patients with heart failure. A subgroup analysis of the BEAUTIFUL trial[13] showed that ivabradine may be helpful to reduce major cardiovascular events in patients with stable coronary artery disease (CAD) and left ventricular systolic dysfunction (LVSD) who present with limiting angina. This study was conducted to find whether the rehospitalization/death/development of acute coronary syndrome (ACS) is reduced by ivabradine alone (without background treatment with beta-blocker) or by the addition of ivabradine to beta-blocker in patients with heart failure compared to the standard treatment guidelines.

MATERIALS AND METHODS

Study Design

A prospective observational study was conducted at a tertiary care teaching hospital for a duration of 18 months. The data were collected from the patients admitted in the cardiology ward and intensive care unit (ICU). Patients of either sex aged between 20 and 70 years with newly diagnosed cases of advanced cardiac failure – New York Heart Association (NYHA) functional Class III, IV or cardiac failure due to ACS or cardiomyopathy or valvular heart disease were included in the study. Patients with baseline HR <60/min, patients with atrioventricular block, sick sinus syndrome, atrial fibrillation, patients with pacemaker, pregnant and lactating women, or patients with history of liver or renal disease were excluded from the study. Informed consent was obtained from eligible patients after explaining the details of the study process to them in their own language. Institutional Ethics Committee approval was obtained before the commencement of the study.

Study Procedure

Potential patients for the study were identified from the cardiology ward, ICU, and were recruited for the study after satisfying the inclusion, exclusion criteria. Data were collected from patients using a predesigned and pretested proforma, by referring to their case records as well as by taking history. This included demographic data, clinical data, and treatment data. At the beginning of the study, data on previous medical history were collected to know the risk factors such as the history of hypertension, diabetes mellitus, dyslipidemia, and ischemic heart disease (IHD). Data regarding the baseline parameters of patients such as HR, blood pressure (BP), and NYHA functional class were also collected. Echocardiographic findings of the patient at admission were also noted. The details of treatment received by the patient indicating the drugs received by patient for heart failure were taken by analyzing the prescriptions at discharge.

Based on the treatment data, the patients were assigned into three groups – Group A patients receiving ivabradine (5 mg BD), Group B metoprolol (12.5 mg BD), and Group C (both ivabradine 5 mg BD and metoprolol 12.5 mg BD). Patients were followed up monthly for a period of 6 months to assess the outcome. At the end of 6 months follow-up, data were collected from the patients. Assessment of outcome was based on the patient's HR, left ventricular ejection fraction (LVEF), and NYHA functional class at follow-up and comparing it with baseline data. Followed up data also included any history of major adverse cardiac events (MACE) such as rehospitalization or development of ACS or death within 6 months.

Statistical Analysis

Statistical analysis was done using SPSS v20 and Microsoft Word Excel was used to generate graphs and tables. Mostly descriptive statistics were used to summarize the baseline data, namely, mean and standard deviation for quantitative variables. The baseline data of the three groups were compared using a Chi-square test to compare the categorical variables. Kruskal–Wallis test was used to compare the outcome variables and data in three groups. Mann–Whitney U test was used to compare the outcomes of treatment between any two groups (A vs. B, B vs. C). For all the parameters assessed, a $P < 0.05$ was considered to be statistically significant.

RESULTS

The present study was conducted at a tertiary care teaching hospital for a period of 18 months. A total of 156 patients admitted with heart failure in the cardiology ward and ICU, fulfilling the inclusion and exclusion criteria were recruited for the study. Of 156 patients, 2 patients receiving metoprolol, 1 patient receiving ivabradine, and 1 patient on combination

therapy did not turn up for follow-up and were excluded from the study. Hence, the total sample size turned to 152 with 51 patients each in ivabradine, ivabradine + metoprolol therapy group and 50 patients in the metoprolol group.

The mean age of patients recruited in the study was 58.8 ± 9.2 years. The mean age of patients in Group A was 57.4 ± 10.9 years, in Group B was 60.8 ± 7.8 years, in Group C was 58.3 ± 9.1 years. Majority of the study population was in the age group >60 years of age (48.7%) followed by 51–60 years (30.3%), <50 years (21.0%). The difference in age distribution between the three groups is not statistically significant. Among 152 patients recruited for the study, 105 (69.1%) patients were males and 47 (30.9%) were females. The difference in gender distribution between the three groups is not statistically significant ($P > 0.05$).

Etiology and Risk Factors

Ischemic cardiomyopathy was the most common cause of heart failure (almost 94% of cases). Of these, 107 (70.3%) patients had a history of ST-segment elevation myocardial infarction and 37 (24.3%) patients had history of non-ST segment elevation myocardial infarction. Only 6 (3.9%) patients had history of valvular heart disease. Dilated cardiomyopathy was reported in 55 (36.2%) patients.

Hypertension was the most common risk factor seen in 147 (96.7%) patients, followed by dyslipidemia in 145 (95.4%) patients, history of smoking in 70 (46.0%) patients, and diabetes mellitus in 67 (44.1%) patients. Other comorbidities were reported in 19 (12.5%) patients which included anemia in 12 patients, hyperthyroidism in 3 patients, CVA in 3 patients, and 1 patient had a history of peripheral vascular disease. The risk factors for development of heart failure were almost equally distributed in the three groups as shown in Table 1. There was no statistically significant difference between the groups in the distribution of risk factors.

Clinical Characteristics

In this study, majority of the patients (97 [63.8%]) were found to be in NYHA Class IV and 55 (36.2%) were in NYHA Class III heart failure. Patients with NYHA Class III and Class IV were equally distributed in the three study groups.

The mean HR of patients at the time of admission was 106 ± 12.9 bpm. Mean systolic BP at the time of admission was 146.4 ± 22.8 mm of Hg and the mean diastolic BP was 91.6 ± 11.8 mm of Hg. The mean LVEF was 26.8 ± 1.7 %. The mean HR, systolic blood pressure, diastolic blood pressure, and LVEF of patients in Groups A, B, and C are mentioned in Table 2. Of the 152 patients, 28 (18.4%) patients presented with ACS, 29 (19.1%) with pulmonary edema, 64 (42.1%) patients with congestive cardiac failure (CCF), and 31 (20.4%) patients with both ACS and CCF at the time of admission.

Diuretics were most commonly prescribed in 146 (96.1%) patients followed by aldosterone antagonists in 136 (89.5%) patients. ACE inhibitors were administered in 104 (68.4%) patients and angiotensin II receptor antagonists

Table 1: Risk factors and etiology of heart failure

Concomitant diseases and history	Group A (ivabradine) *n* (%)	Group B (metoprolol) *n* (%)	Group C (both ivabradine and metoprolol) *n* (%)	*P* value
Hypertension	49 (96.1)	48 (96.0)	50 (98.0)	0.99
Diabetes mellitus	24 (47.1)	21 (42.0)	22 (43.1)	0.86
Dyslipidemia	48 (94.1)	49 (98.0)	48 (94.1)	0.56
Chronic smoking	28 (54.9)	22 (44.0)	20 (39.2)	0.27
STEMI	38 (74.5)	34 (68.0)	35 (68.6)	0.73
NSTEMI	13 (25.5)	11 (22.0)	13 (25.5)	0.89
Dilated cardiomyopathy	13 (25.5)	19 (38.0)	23 (45.1)	0.11
Valvular heart disease	0 (0)	2 (4.0)	4 (7.8)	0.13
Other comorbidities	7 (13.7)	7 (14.0)	5 (9.8)	0.77

*$P<0.05$ considered statistically significant. STEMI: ST elevation myocardial infarction, NSTEMI:Non ST elevation myocardial infarction

Table 2: Baseline parameters at admission

Baseline parameter	Group A (ivabradine)	Group B (metoprolol)	Group C (both ivabradine and metoprolol)
Heart rate (bpm)	101.9±11.5	101.3±12.8	104.2±12.7
Mean SBP (mm of Hg)	136.7±21.9	139.0±21.2	136.5±22.1
Mean DBP (mm of Hg)	89.9±11.2	92.6±11.3	96.4±11.6
LVEF (%)	26.8±1.6	27.2±1.8	26.4±1.7

Values are mean±SD. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, LVEF: Left ventricular ejection fraction

(ARBs) in 48 (31.6%) patients. Twenty-seven (17.8%) patients received Digoxin. The other drugs received by the patients include statins in 78% of patients, antiplatelet drugs such as aspirin and clopidogrel in 84% of the patients.

Occurrence of MACE in the 3 Treatment Groups

Of 152 patients, the occurrence of MACE such as ACS, rehospitalization, or death due to worsening heart failure during the follow-up period was reported in 21 patients, i.e., 13.8% of the total study population. The highest number of events was reported in Group B (26%) when compared to Group A (9.8%) and Group C (5.9%) [Table 3].

Occurrence of ACS during Follow-up Period

The occurrence of ACS during the follow-up period after initiation of therapy was highest in the group receiving metoprolol which was seen in 8 (16%) patients. Two patients in Group A and 1 patient in Group C also developed ACS during the follow-up period [Figure 1].

Rehospitalization

Of the three groups, Group B reported the highest number of rehospitalization for worsening heart failure. In Group B, 13 (26%) patients had a history of rehospitalization whereas it was seen in 5 (9.8%) patients of Group A and 3 (5.9%) patients of Group C. There was a statistically significant difference between the groups with a $P = 0.008$ [Figure 2].

Death Due to Worsening Heart Failure

The number of deaths due to worsening heart failure during the 6 months follow-up period was found to be higher in the group receiving metoprolol or Group B. Of 152 patients, Group B reported 6 (12%) deaths, whereas Group A reported 1 (2%) death. No deaths were reported in Group C within 6 months. On analysis, there was a statistically significant difference between the groups [Figure 3].

Decrease in HR

The extent of decrease in HR after treatment for 6 months was significant in Group C (ivabradine + metoprolol) followed by Group A (ivabradine) when compared to Group B (metoprolol). Group C showed a mean decrease in

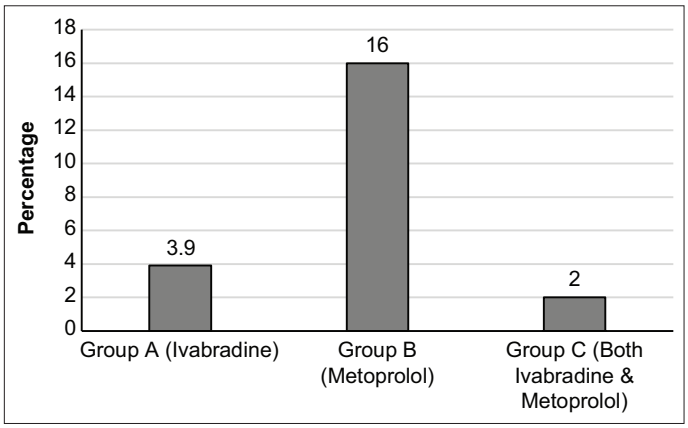

Figure 1: Comparison of groups based on the occurrence of acute coronary syndrome

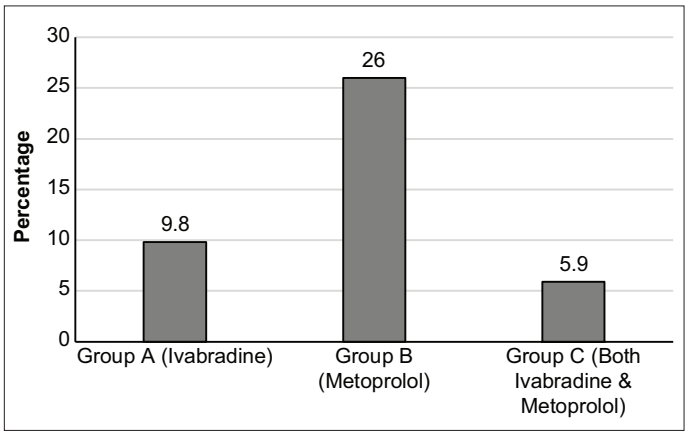

Figure 2: Comparison of three groups based on rehospitalization

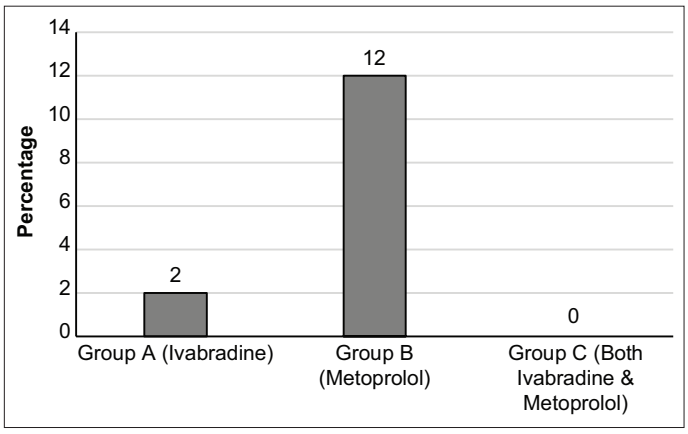

Figure 3: Comparison of groups based on number of deaths

Table 3: Comparison of occurrence of major adverse cardiac events in the three treatment groups

MACE	Group A (ivabradine) *n* (%)	Group B (metoprolol) *n* (%)	Group C (both ivabradine and metoprolol) *n* (%)	Kruskal–Wallis test	Mann–Whitney U test	
				P value	A vs. B	B vs. C
Absent	46 (90.2)	37 (74)	48 (94.1)	0.008	0.034	0.006
Present	5 (9.8)	13 (26)	3 (5.9)			

MACE: Major adverse cardiac events

HR of 43.6 ± 12.8 bpm when compared to Group B which was 21.5 ± 10.4 bpm. Group A showed a mean decrease in HR of 25.5 ± 9.6 bpm. There was significant difference between the groups when compared in terms of decrease in HR with a $P = 0.000$ [Table 4].

Increase in Ejection Fraction

Increase in ejection fraction was highest in Group C followed by Group A when compared to Group B. The mean increase in ejection fraction in Group C was 6.2 ± 2.8%, in Group A was 4.6 ± 2.2%, whereas Group B showed a mean increase of only 1.4 ± 1.9%. There was significant difference between the groups when compared in terms of increase in the LVEF with a significant ($P < 0.05$) [Table 5].

Improvement in NYHA Functional Class

There was no improvement in NYHA functional class in 2 patients belonging to Group B. Twenty-five patients in Group A, 32 patients in Group B, 17 patients in Group C showed improvement of 1 NYHA class. Twenty-five patients in Group A, 10 patients in Group B, and 34 patients in Group C showed improvement of more than one NYHA class. This improvement in NYHA class is more obvious in Group C when compared to Group B. There is statistically significant difference with respect to change in NYHA functional class between the groups with a $P < 0.05$ [Table 6].

DISCUSSION

Heart failure is a major public health problem with an impact on the quality of life of the patients. It is one of the leading causes for cardiovascular mortality. There are very limited numbers of studies on the use of ivabradine in heart failure. The present study was done to assess the efficacy of ivabradine in patients with heart failure and to compare its efficacy with that of metoprolol.

This study was conducted in 152 patients with heart failure satisfying the inclusion and exclusion criteria. The mean age of patients included in our study was 58.8 ± 9.2 years, with male patients constituting about 69.1% of the study population. In our study, IHD was the most common etiology in about 94% of the cases. Dilated cardiomyopathy was reported in 36.2% of patients. Hypertension was the most common risk factor for heart failure according to our study which was seen in 96.7% of cases. Other risk factors were dyslipidemia (95.4%), chronic smoking (46%), and diabetes mellitus (44.1%). In this study, the majority of the patients were found to be in NYHA Class IV (63.8%) and the rest were in Class III (36.2%). The mean HR of patients in our study was found to be 106 ± 12.9 bpm. The mean LVEF of patients in our study was 26.8 ± 1.7%. The treatment of heart failure patients in hospital was in accordance with the standard guidelines (American College

Table 4: Comparison of groups based on decrease in heart rate

Treatment group	Mean±SD	Median	Kruskal–Wallis test	Mann–Whitney U test	
			P value	A versus B	B versus C
Patients receiving ivabradine (A)	25.5±9.6	24	0.000	0.028	0.000
Metoprolol (B)	21.5±10.4	18			
Both ivabradine and metoprolol (C)	43.6±12.8	43			

Values are mean±SD

Table 5: Comparison of groups based on increase in LVEF

Treatment group	Mean±SD	Median	Kruskal–Wallis test	Mann–Whitney U test	
			P value	A versus B	B versus C
Patients receiving ivabradine (A)	4.6±2.2	5	0.000	0.000	0.000
Metoprolol (B)	1.4±1.9	1			
Both ivabradine and metoprolol (C)	6.2±2.8	6			

Values are mean±SD, LVEF: Left ventricular ejection fraction

Table 6: Comparison of groups based on improvement of NYHA functional class

Treatment group	Group A (ivabradine) *n* (%)	Group B (metoprolol) *n* (%)	Group C (both ivabradine and metoprolol) *n* (%)	Kruskal–Wallis test	Mann–Whitney U test	
				P value	A versus B	B versus C
No improvement	0 (0)	2 (4.5)	0 (0)	0.000	0.002	0.000
Improvement by 1 class	25(50)	32 (72.7)	17 (33.3)			
Improvement by more than 1 class	25 (50)	10 (22.8)	34 (66.7)			

Values are mean±SD. NYHA: New York Heart Association

of Cardiology Foundation/American Heart Association guidelines). Diuretics were the most commonly prescribed in 96.1% of the patients as most of the patients presented with congestive symptoms. About 89.5% of patients received aldosterone antagonists, 68.4% received ACE inhibitors, 31.6% received ARBs, and 17.8% were on Digoxin. Other drugs prescribed included statins in 78% of patients, antiplatelet drugs such as aspirin and clopidogrel in 84% of the patients. This study evaluated the efficacy of ivabradine in heart failure and compared its efficacy with that of metoprolol. In this study, ivabradine was prescribed at a dose of 5 mg BD and dose of metoprolol was 12.5mg BD. The results of our study showed that of 152 patients, the occurrence of MACE such as ACS, rehospitalization, or death was reported in 21 patients, i.e., 13.8% of the total study population. The highest number of events was reported in Group B (26% of patients) when compared to Group A (9.8%) and Group C (5.9%). The incidence of ACS during the follow-up period was high in Group B (16%) when compared to Group A (3.9%) and Group C (2%). History of rehospitalization for worsening heart failure was reported to greater extent in Group B (26%) when compared to Group A (9.8%) and Group C (5.9%). The number of deaths for worsening heart failure was less in Group A (2%) when compared to Group B (12%). No deaths were reported in Group C. The secondary outcome measures of our study were extent of the decrease in HR, an increase in LVEF and improvement in NYHA functional class. Group C showed significant improvement with therapy in terms of decrease in HR, increase in LVEF, improvement in NYHA class when compared to Group B and Group A was found to be better than Group B. No adverse effects were reported during the course of the study.

Only a few studies have assessed the role of ivabradine in heart failure. In a multicentric study conducted by Borrer *et al*.,[11] the mean age of patients was 60.4 ± 11.4 years and males constituted 70% of the study population, which is almost similar with the presentation in our study. In the SHIFT study,[11] heart failure due to IHD was seen in 68% of cases. The previous studies suggest that rheumatic valvular heart disease was the major cause of heart failure in patients getting admitted to the hospital.[14,15] However, the finding of this study suggests that IHD is the underlying cause for heart failure. A study conducted by Jafary *et al*.[16] on 196 patients with systolic heart failure showed that 67% of patients had hypertension and 60% of the patients were diabetic. A study by Karadag *et al*.[17] on patients with heart failure showed that 67% patients had dyslipidemia and 69% had hypertension making these two the most common risk factors for heart failure. The risk factors reported in our study are similar to previous studies. In the SHIFT study, 49% of patients were in NYHA Class II, 50% of patients were in NYHA Class III, and only 2% of the patients were in NYHA Class IV.[11] The subgroup analysis of BEAUTIFUL trial included patients with limiting symptoms of angina who were in NYHA Class II or III and excluded patients with NYHA Class IV.[13] In contrast to this, the majority of patients in our study belonged to NYHA Class IV. The mean HR during recruitment in our study population is higher than that reported in the SHIFT trial (79.9 ± 9.6 bpm), in the BEAUTIFUL study[12] (71.6 ± 9.9 bpm) and in a study conducted by Zugck *et al*.[18] (85 ± 11.8 bpm). The mean LVEF of patients in SHIFT trial was 29.0 ± 5.1% and in the carvedilol, ivabradine, or their combination on exercise capacity in patients with heart failure (CARVIVA – HF) trial[19] was 26% which is similar to our study. Treatment data of patients in SHIFT trial showed that 90% were on beta-blockers, 84% on diuretics, 78% on ACE inhibitors, 60% received aldosterone antagonists, 22% on Digoxin, and 14% on ARBs. This is similar to the treatment data obtained in our study. The duration of follow-up in our study was short when compared to SHIFT trial in which the median follow-up period was 22.9 months, and in the BEAUTIFUL trial, it was 19 months.

Based on primary endpoints, the results of our study are similar to that of the SHIFT trial which showed that ivabradine reduced the risk of heart failure by 26% and risk of hospitalization for heart failure by 26%. Bagriy *et al*.[20] studied early addition of ivabradine to carvedilol therapy in patients with chronic heart failure showed a greater reduction of HR in combination group (12.9 ± 3.5bpm) when compared to carvedilol alone (7.2 ± 2.4bpm). The CARVIVA-HF trial[19] showed that the HR is reduced to similar extent by ivabradine, carvedilol and significantly more by combination therapy. It showed a non-significant improvement in LVEF in both ivabradine and combination group whereas there was no change in carvedilol group. It also showed that the NYHA class improved significantly in patients receiving ivabradine and combination therapy compared to the carvedilol group. Echocardiographic substudy of SHIFT[21] showed that reducing the HR with ivabradine led to significant increase in LVEF by 2.4%. A study by Sarullo *et al*.[22] showed that ivabradine was associated with improvement of NYHA functional class of heart failure and thereby improved the quality of life of the patients.

The results of this study support the evidence from the SHIFT trial and substudy of BEAUTIFUL trial,[13] which showed that administration of ivabradine had favorable outcomes in patients with IHD as IHD was the most common etiology for heart failure in our study population. The mean HR of patients included in our study was higher than the mean HR of patients in other studies. This higher baseline HR could be one of the reasons for better results in ivabradine and combination group as the magnitude of HR reduction with ivabradine depends on the baseline HR. Majority of patients in our study were in NYHA Class IV when compared to previous studies which had a considerably lower number of patients in Class IV. The

better results observed in the groups receiving ivabradine or combination therapy indicate that ivabradine might be more beneficial in patients with higher grades of heart failure. In this study, the dose of metoprolol was 12.5 mg BD. The dose of metoprolol could not be uptitrated in many patients to the target dose (200 mg/day) due to intolerance to the beta-blocker. Hypotension and dizziness were the reasons for intake of lower than recommended dose of metoprolol. This inability to administer the target dose of the beta-blocker could be one of the reasons for higher incidence of ACS and rehospitalization in the Group B.

The results of this study established that the addition of ivabradine to standard guideline-based treatment for heart failure with the background therapy with beta-blockers significantly reduced the primary endpoints and improved the clinical status of patients with a decrease in HR, increase in LVEF and improvement of NYHA class. The study also shows that ivabradine can be considered as an alternative to beta-blocker when it is contraindicated or in case of intolerance. In situations where up-titration of beta-blocker dose is not possible due to intolerance, the addition of ivabradine can be considered to reduce the risk of future cardiovascular events. Limitation of the study is that it is an open-label, observational, and non-interventional design with no placebo group which can lead to an overestimation of the treatment effects. Another limitation is the relatively short duration of follow-up of 6 months which is nevertheless sufficient to evaluate the outcomes of treatment in patients with heart failure (i.e., survival analysis).

CONCLUSION

Administration of ivabradine alone or a combination of ivabradine and metoprolol is more effective than metoprolol in reducing the incidence of MACE in heart failure.

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