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Original Research Article

CARVEDILOL AND BISOPROLOL RELATIVE EFFECT IN HEART FAILURE WITH REDUCED EJECTION FRACTION

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Abstract

Background: Carvedilol and bisoprolol are two common beta-blocker drugs recommended for treating patients with heart failure with reduced ejection fraction (HFrEF); however their relative efficacy in reducing mortality cause are contradictory. The present study evaluated the relative effect of carvedilol and bisoprolol on left ventricle ejection fraction (LVEF), heart rate and blood pressure in patients with HFrEF. **Materials and Methods:** This was a prospective study including 60 patients who consulted hospital for HFrEF. The study population was divided into two groups, each with 30 patients. To one group carvedilol and to other bisoprolol was prescribed. The clinical conditions were compared with the report after 3-months. **Result:** Male dominance of 63.33% and 56.67% was observed in carvedilol and bisoprolol groups. Most of the patients were identified as New York Heart Association class III in both groups. Statistically significant improvement ($p \leq 0.05$) was found after 3-months treatment in carvedilol and bisoprolol group. In carvedilol group, the LVEF% was increased from an average 33.46% to 46.4%, heart rate and blood pressure was decreased from an average value 102.23 to 87.13beats/minute (bpm) and 125.6/83.3 to 106.3/78.5mmHg respectively. In bisoprolol group, LVEF%, heart rate and blood pressure was improved from 31.7% to 44.8%, 103.8 to 84.9bpm and 126.1/84.4 to 108.4/77.1mmHg respectively. However, the improvement was insignificant between the groups ($p > 0.05$). **Conclusion:** The study revealed that reduction in mortality cause of carvedilol and bisoprolol were equally effective for treating HFrEF patients.

INTRODUCTION

Heart failure (HF) is considered as one of the most expensive, debilitating, and often fatal cardiac disorder, affecting approximately 26 million global populations.[1] It is a structural and functional cardiovascular abnormality characterized by a rapid heartbeat due to the pumping inefficiency of heart.[2] The cardiac functional abnormality in terms of left ventricle ejection fraction (LVEF) ≤40% develops heart failure with reduced EF (HFrEF) and is most prevalent in developing as well as developed countries. Several disease-modifying medicines have been developed in past years; however their efficacy results are still under contradictions.

Beta-blockers are the most recommended primary drugs as per international guidelines for the treatment of HFrEF.[3] It has been found to improve symptoms and survival rate in HFrEF patients. Randomized clinical experiments and HF registries have convinced that the controlled or extended release of beta blockers carvedilol, bisoprolol, and metoprolol lowers the risk of re-hospitalization and the mortality rate in HFrEF patients.[3]

Carvedilol is a relatively non-selective type of beta blocker that has three blocking effects on β1-, β2-, and α1 receptor whereas bisoprolol has selective blocking effects against β1-receptor only. Several evidences have been published regarding efficacy of carvedilol followed by sustained use of bisoprolol and metoprolol.[1,4-6] However, based on the registries and meta-analysis reviews it has been observed that usage of different classes of beta blockers has different pharmacological effects due to bioavailability, receptor selectivity and vasodilator action resulting in varied clinical outcomes.[7] There is dearth of data related to effectiveness of carvedilol vs bisoprolol. The conflicting results regarding the survival rates of patients with HF managed by beta blockers led the base of present investigation. Therefore, the present

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study was conducted to compare the efficacy of carvedilol and bisoprolol in patients with HFrEF.

MATERIALS AND METHODS

Study Area and Design: This was a prospective cohort clinical study which was conducted over the period of 12 months at the Department of General Medicine, Darbhanga Medical College and Hospital (DMCH), Bihar, India.

Study Population: The study was conducted on patients of heart failure attending Medicine outpatient department (MOPD) or admitted in DMCH. The study protocol was approved by the institutional ethical committee. All the patients were informed about the study and an informed written consent was obtained from each patient before the initiation of the study. The data and the investigational reports of every patient were maintained confidential during the study. Patients >14 years of any gender with HFrEF were included in the study. The exclusion criteria included patients <14 years, pregnant females, patients with HFpEF and acute HF and patients underwent any cardiac surgery.

Methodology: The study comprised of demographic and clinical information which included medical history, signs and symptoms, laboratory testing, electrocardiography, echocardiography, medications applied, hospital course and outcomes will be obtained prospectively at the time of admission and during follow up period.

Primary investigation started with enquiring medical history and thorough physical examining of patients suspected of HF. Entire symptoms and signs were diagnosed. All etiological factors and risk factors were assessed. Patients were looked for symptoms such as dyspnea, edema, hepatic congestion, abdominal distress, orthopnea, fatigue, lethargy, anorexia, wheezing, bendopnea, palpitations and dizziness. The signs and symptoms were analyzed at every patient's visit to ensure therapeutic response and stability of health condition. Demographic parameters were assessed using questionnaire asked by trained medical practitioner.

Parameters to be used: Clinical parameters: Patients with breathlessness and generalized body swelling having ejection fraction <40%

Biochemical Parameters: Laboratory testings were performed to check biochemical parameters. For instance, blood test was done to analyze for iron deficiency, renal impairment and liver dysfunctioning.

Radiological Parameters: This included 2-dimensional echocardiography and electrocardiography.

Management of patients: Patients were prescribed for beta-blocker medicines carvedilol and bisoprolol and therapeutic responses were analyzed.

Statistical analysis: The statistical analysis was performed to validate the results using Graphpad Prism software and Microsoft Excel. The results were described as frequencies, percentages and mean± standard deviation, where p-value ≤0.05 was considered statistically significant.

RESULTS

The study comprised 60 individuals who satisfied the inclusion-exclusion criteria and were suspected of having HFrEF. After gaining formal consent from them, the study was initiated with standard demographic investigation. The patients were split into two groups. The first group (n=30) was prescribed carvedilol whereas the second group (n=30) was given bisoprolol as the primary therapeutic drug. Clinical and echographical assessment of every patient was done at the beginning of treatment and followed after 3rd month.

Demograhic and clinical characterization of patients

The patients with HFrEF in each group were enquired for their demographic details and were looked for clinical characteristics [Table 1]. The patients under carvedilol treatment had age group ranged 30-90 years with mean age 55.2±14.38 years whereas bisoprolol patient's age group varied between 24 and 80 years with mean age of 55.4±14.31 years.

In the present study, most of the patients in groups taking carvedilol and bisoprolol drugs belonged to adults 41-60 years age groups (53.33% vs. 40%) followed by old patients 61-90 years (26.67% vs. 40%) and least number of patients belonged to 20-40 years (20% in each group). Total 19 male and 11 female were prescribed for carvedilol, however 17 male and 13 female were put on bisoprolol medications. (Figure 1) describes distribution of patients on the basis of gender and age.

Clinical characteristics: NYHA class is used to determine the severity of patients on the basis of their symptoms and functional incapability. In the present study, maximum patients were detected of NYHA grade III in both groups. Total 80% (15 male and 9 female) and 20% (4 male and 2 female) patients under carvedilol medication were detected with NYHA grade III and IV symptoms respectively. Grade III and IV was detected in 60% (9 male and 9 female) and 40% (8 male and 4 female) patients under bisoprolol (Table 1).

Medical testing of patients with HFrEF: The patients were tested for clinical abnormalities using physical and laboratory tests at the time of investigation (Table 2). There was statistically no difference between the carvedilol and bisoprolol group patient's initial clinical reports in terms of LVEF percentage, heart rate, blood pressure, creatinine concentration and saturated oxygen level and blood urea nitrogen level. The echocardiography report revealed 33.46±4.89 and 31.76±4.95 percent mean ejection fraction in

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patients prescribed with carvedilol and bisoprolol respectively. Total 2 patients each in carvedilol and bisoprolol groups died within a week of hospital consultancy due to severity of syndrome.

In the present investigation, the mean heart rate of HFrEF patients in carvedilol and bisoprolol groups was increased to 102.23± 10.25 and 103.86±9.87 bpm at the time of hospital assistance respectively.

In present study, the admission systolic pressure was 125.6±11.07 mm Hg and 126.13±8.67 mm Hg in carvedilol vs bisoprolol groups.

The mean haemoglobin level in carvedilol and bisoprolol was determined as 12.1±1.67 g/dl and 11.6±1.93 g/dl respectively. In the present analysis 13 male and 6 female in carvedilol group as well as 14 male and 7 female in bisoprolol group had reduced haemoglobin level and were considered in anaemic condition. The clinical differences between the two groups were statistically insignificant (Table 2).

Drug dosage prescribed to patients with HFrEF

Carvedilol daily optimal dosage ranged from 3.12 to 6.25 mg and bisoprolol daily dosage ranged 2.5 to 5 mg was given to patients with HFrEF. However, the dosage difference was statistically non-significant (p= 0.35). The average dosage of carvedilol and bisoprolol prescribed to patients was 4.79±1.58 and 4.6±0.86 mg per day respectively. Along with carvedilol and basiprolol, patients were also prescribed for one or more medications including long-acting muscarinic antagonists (LAMA) bronchodilators as ramipril, furosmide and spironolactone.

Differences in ejection fraction, heart rate and blood pressure value post 3 month follow-up

The LVEF%, heart beat rate and systolic as well as diastolic blood pressure was also analyzed after 3 months in patients with HFrEF. The follow up results were compared with the values at the time of hospital consultancy in both the groups. There was statistically significant improvement ($p<0.05$) in the health condition of patients treated with carvedilol and bisoprolol. It was observed that there was 12.94% improvement in LVEF % from 33.47% to 46.5% within 3 months treatment with carvedilol and 13% improvement in case of bisoprolol. Similarly heart rate and blood pressure also decreased significantly towards normal value and reduced causes of mortality in both treated groups from carvedilol and bisoprolol (Table 3).

Treatment response of patients with HFrEF

Post 3 months of medication, patients were followed up and improvement in ejection fraction, heart beat rate and blood pressure was diagnosed. However, the outcome of the drugs carvediolol and bisoprolol showed no statistical significant differences in treatment ($p>0.05$; Table 4). Although, the overall outcome of the treatment was improved in both the groups after 3 months, but the changes between the groups treated with carvedilol and bisoprolol were statistically insignificant. The results signified that both beta blockers carvedilol and bisoprolol does not have much difference towards result outcome. There was no statistically significant difference in the reducing mortality cause among individuals who received carvedilol and bisoprolol.

Table 1: Demographic and clinical details of patients with HFrEF

Variables	Carvedilol (n=30)		Bisoprolol (n=30)		p-value
Age (Years)	**No. of patients**	**Percentage (%)**	**No. of patients**	**Percentage (%)**	
20-40	6	20	6	20	0.4
41-60	16	53.33	12	40	
61-90	8	26.67	12	40	
Sex					
Male	19	63.33	17	56.67	0.3
Female	11	36.67	13	43.33	
NYHA grade					
Grade III	24	80	18	60	0.01
Grade IV	6	20	12	40	

NYHA: New York Heart Association

Table 2: Baseline report of patients with HFrEF

Variables	Carvedilol	Bisoprolol	p-value
LVEF (%)	33.46±4.89	31.76±4.95	0.06
Heart rate (bpm)	102.23± 10.25	103.86±9.87	0.21
Blood Pressure (mm/Hg)			
Systolic	125.6±11.07	126.13±8.67	0.40
Diastolic	83.3±7.76	84.4±6.77	0.29
Haemoglobin (Hb; g/dl)	12.1±1.67	11.6±1.93	0.14
Anaemic			
Male (Hb <13 g/dl)	13 (43.33%)	14 (46.67%)	
Female (Hb <12 g/dl)	6 (20%)	7 (23.33%)	
Serum Creatinine (mg/dl)	0.81±0.09	0.80±0.09	0.35
Blood urea nitrogen (mg/dl)	59.3±11.3	53.4±12.52	0.06
SPO_2RA (%)	93.7±3.9	93.1±4.42	0.23
Mortality	2	2	NA

Data are represented as mean and standard deviation. LVEF: Left ventricle ejection fraction; bpm: beats per minute; SPO_2: Saturation of peripheral oxygen; RA: Radial artery; $p<0.05$ was considered significant.

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Table 3: Changes in ejection fraction, heart rate and blood pressure post 3 month follow-up

Variables	Carvedilol			Bisoprolol		
	At admission	Post 3 months	p-value	At admission	Post 3 months	p-value
LVEF (%)	33.46±4.89	46.4±5.41	0.0001	31.76±4.95	44.8±6.68	0.0003
Heart rate (bpm)	102.23±10.25	87.13±6.00	0.0001	103.86±9.87	84.93±6.19	0.0001
Blood Pressure (mm/Hg)						
Systolic	125.6±11.07	106.36±9.14	0.0006	126.13±8.67	108.47±7.91	0.0001
Diastolic	83.3±7.76	78.5±5.29	0.0009	84.4±6.77	77.16±6.45	0.0003

Data are represented as mean and standard deviation and p<0.05 was considered significant. LVEF: Left ventricle ejection fraction; bpm: beats per minute

Table 4: Medication outcome after 3 months follow up

Variables	Carvedilol	Bisoprolol	p-value
LVEF (%)	46.4±5.41	44.8±6.68	0.21
Heart rate (bpm)	87.13±6.00	84.93±6.19	0.12
Blood Pressure (mm/Hg)			
Systolic	106.36±9.14	108.47±7.91	0.16
Diastolic	78.5±5.29	77.16±6.45	0.18

Data are represented as mean and standard deviation and p<0.05 was considered significant. LVEF: Left ventricle ejection fraction; bpm: beats per minute

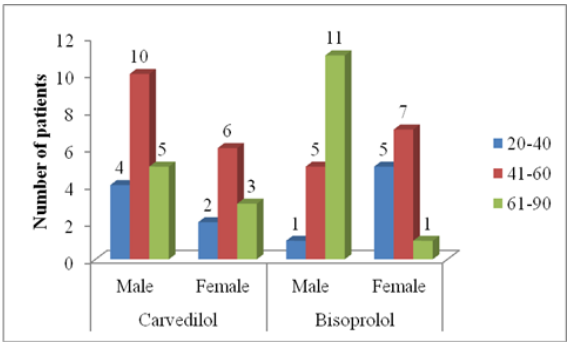

Figure 1: Distribution of patients on the basis of age and gender

DISCUSSION

HF syndrome is one of the biggest threats among cardiovascular diseases contributing to approximately 26 million mortality rate all over the planet.[1] Universally, it is defined as a syndrome characterized by cardiac malfunction structurally and functionally along with elevated natriuretic peptide levels and pulmonary/systemic blockage. The LVEF less than or equal to 40% is referred as HFrEF or systolic HF and is most prevalent type of HF globally. Beta blockers are the drugs consensually recommended as first-line therapy for the treatment of HFrEF.[3]

Carvedilol and bisoprolol are the most widely accepted beta blockers. Carvedilol is non-selective alpha- beta receptor blocking anti hyperselective drug where as bisoprolol is cardio selective beta-1 receptor blocker. The therapeutic efficacy of drugs depends on vasodilating activity, selectivity of cardiac receptors and severity of cases. Several studies have speculated that both carvedilol and bisoprolol have led to the improved medical condition of HFrEF patients, but the available findings are conflicting and urge further studies for better understanding. In the current study, the major mortality cause like changes in LVEF, heart rate and blood pressure was retrospectively examined along with demographic observation and biochemical diagnosis. The study compared the mortality benefit of carvedilol and bisoprolol in patients with HFrEF which would assist in undertaking appropriate tailored approach towards selection of therapy.

Demograhic characterization of patients

In present study, total 60 individuals with HFrEF were included and were divided equally. Half of the selected individuals were prescribed for carvedilol (n=30) and other half were given bisoprolol. The demographic details showed male dominance in both carvedilol (63.3%) and bisoprolol (56.67%) group. Most of the patients in groups taking carvedilol and bisoprolol drugs belonged to adults 20-60 years age groups (73.33% vs. 60%) as compared to old patients 61-90 years (26.67% vs. 40%). Danielsen et al. also mentioned male dominance in HF patients as compared to women with 19.3% prevalence in patience above 69 years.[8] The present study also corroborated with the findings by Magnussen et al. which reported the prevalence of HF patients ranged from 24 to 99 years and predominance in male than female.[9] Ho et al. and Cesaroni et al. also mentioned higher risk of HF in men than women for HFrEF as compared to HFpEF.[10,11] In contrast to the present study, Postigo and Martinez-Selles had dissimilar findings and stated prevalence increases in women than men which may be attributed to biological differences.[12] The recognition of symptoms as per NYHA grade has long been used to identify the risk and severity of HF as well as to evaluate clinical medications to be followed. In the current study, maximum patients were detected of NYHA grade III in carvedilol (80%) and bisoprolol (60%) as compared to NYHA grade IV (20% vs 40%). Most of the patients categorized under NYHA class IV were elder individuals than younger individuals. Although there is contradictory data regarding NYHA classification and HF outcome,[13] but several studies have revealed NYHA criteria an important prognostic toll in HF syndrome. Siegersma et al,

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2020 stated that NYHA grade III and IV is associated with higher risk in HF patients.[14] Ahmed et al. reported 20.9% and 1.2% patients under NYHA grade III and IV respectively. The NYHA grade III and grade IV were patients with systolic HF particularly in old generation patients.[15] Green et al. classified 28% in class III and 1.6% in class IV group.[16]

Medical testing of patients with HFrEF

The baseline investigation depicted no significant differences (P>0.05) between the patients' clinical reports suggested for carvedilol and bisoprolol medication. The clinical conditions of the patients at same pace assisted in evaluating the efficacy of the two drugs carvedilol and bisoprolol notably. HF with LVEF <40% is referred as HFrEF. In the present study, baseline investigations revealed LVEF% to be 33.46±4.89 and 31.76±4.95 percent in carvedilol and bisoprolol groups of patients.

The elevated average heart rate of 102.23± 10.25 and 103.86±9.87 beats per minute was evident in carvedilol vs. bisoprolol prescribed patients in present study. The resting heart rate of 60-90 beats per minute (bpm) has been accepted as normal heart rate worldwide,[17] however, elevation in hear beat rate autonomously predicts the probability of HF rate.[9]

The systolic blood pressure of 120 mm Hg and diastolic blood pressure of 80 mm Hg has been considered as normal blood pressure.[18] The blood pressure in HFrEF patients was also found to be increased than their normal threshold limit. The mean (SD) systolic and diastolic blood pressure in carvedilol and bisoprolol groups was measured as 125.6±11.07/83.3±7.76 and 126.13±8.67/84.4±6.77 mm Hg.

Haemoglobin is an important test to check anaemic condition of the patients. The haemoglobin level of <13 g/dl in male, <12 g/dl in female is considered as low haemoglobin level than normal limit signifying anaemic condition.[19] In the present study patients under carvedilol prescription had an average of 12.1±1.67 g/dl and bisoprolol group patients had 11.6±1.93 g/dl haemoglobin level. On the basis of current statistics 43% men, 20% women and 47% men, 23% women in carvedilol and bisoprolol respectively, were found to be anaemic during their first consultancy in hospital.

Creatinine is the waste product of muscle protein creatine catabolism to produce energy for muscular contractions. Normal creatinine range in male and female is 0.6 to 1.2 mg/dl and 0.5 to 1.1 mg/dl respectively. BUN is the amount of urea, a waste product produced in turn of biological processes (especially protein metabolism) in liver and ranges from 5-20 mg/dl normally.[20] The ratio of BUN and creatinine is an important parameter in risk assessment of HF. BUN/creatinine values within 5-20 mg/dl is normal which is directly proportional to age but inversely proportional to muscular mass.[21] In carvedilol and bisoprolol groups serum creatinine level was 0.81±0.09 vs. 0.80±0.09 mg/dl, which was within normal range whereas increased BUN value of 59.3±11.3 vs. 53.4±12.52 mg/dl was diagnosed via biochemical enzymatic assay. BUN/createnine ratio was also much higher than the normal limit in both group patients. Similar report was published by Parrinello et al. who stated increased BUN/createnine ratio was associated with severity of HF risk.[22]

The findings of Hossain et al,[6] were similar to the present findings. Their findings also stated insignificance in baseline investigation reports in between carvedilol and bisoprolol groups. Carvediolol and bisoprolol group patients had average (SD) LVEF percentage of 34.7±2.9 and 34.1±3.6 respectively with elevated heart beat rate (88.8±9.1 vs. 87.7±9 bpm) and increased blood pressure (115±13.3/73.7±9.3 vs. 116.3±14.8/75.5±10.1).[6] Choi et al,[4] also compared the efficacy of carvedilol and bisoprolol and showed corroboration with the present study. The reduced LVEF % of 82.4±18.7 and 27.1±7.1, elevated heart rate (96.6 ± 25.2 and 94.5 ± 23.5 bpm) and increased systolic/diastolic blood pressure (133.0 ± 31.1/82.3 ± 19.4 and 130.3 ± 26.8/82.4 ± 18.7 mm Hg) was analyzed in carvedilol and bisoprolol groups at the time of first consultancy. Createnine level was 1.54 ± 1.4 and 1.41 ± 1.5 mg/dl and haemoglobin was 13.0 ± 2.2 and 12.9 ± 2.3 g/dl in carvedilol and bisoprolol groups respectively.[4]

Improvement in survival factors post 3 months follow-ups

Beta blockers carvedilol, bisoprolol and metoprolol enhance survival rate in HFrEF patients,[23] however there are contradictive findings available regarding their efficacy.[24,25] The evaluation and optimization of drug usage in HF syndrome is critical for optimizing drug dosage for future intervention. In the present study the clinical parameters evaluated at the time of hospital consultancy was compared with the reports after 3 months after treatment with beta blockers carvediolol and bisoprolol in two separate groups.

In present study, there was insignificant dosage difference between carvedilol and bisoprolol. Carvedilol average daily optimal dosage of 4.79±1.58 mg/day ranging from daily dose of 3.12 to 6.25 mg and bisoprolol average daily dosage was 4.6±0.86 mg ranging from 2.5 to 5 mg per day was prescribed to HF patients. The prescribed dosage of carvedilol was below recommended limit and bisoprolol was within the recommended limit as per international accepted guidelines. As per Bhatt et al,[23] the recommended dosage of carvedilol and bisoprolol is within 6.25-25 mg/day and 1.25 to maximum 10 mg/ day respectively.[23] Choi et al,[4] compared survival rate in HFrEF patients after treating with carvedilol and bisoprolol at dosage ranged 6.25-12.5 vs. 1.25-2.50 mg per day.[4] Toyodo et al. also divided patients in two groups. To group 1, bisoprolol ranged from minimum 0.625 mg/day to maximum 5 mg/day and to other group

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carvedilol was given ranging from 1.25 mg/day to 20 mg/day and significantly improved survival rate was observed.[26]

After 3 months, the all-cause mortality factors (LVEF%, heart rate and blood pressure) were diagnosed again and the improvement was found to be statistically significant in both the groups ($p<0.05$). The current study revealed both carvedilol and bisoprolol improved ejection fraction percentage significantly within 3 months of treatment of patients with HFrEF. The average heart beat rate and blood pressure also improved significantly in turn improved survival rate of patients with HFrEF in both the groups. There was almost equivalent improvement rate (28%) in LVEF% of carvedilol and bisoprolol group patients with HFrEF. Heart rate was reduced to normal level by 14% in carvedilol and 22% by bisoprolol. This showed heart rate was better improved during bisoprolol activity. However, blood pressure was significantly improved by carvedilol administration as compared to bisoprolol. Similar observations were made by Hossain et al,[6] who stated better improvement result in heart rate and LVEF via bisoprolol treatment and improved blood pressure after treatment with carvedilol however the improvement between the groups were insignificant.[6]

Treatment response of patients with HFrEF

The overall outcome revealed that both the drugs showed comparable results. The present study demonstrated no superiority between carvedilol and bisoprolol over drug dosage and efficacy. The data obtained signify that the tolerability capacity of both the drugs carvedilol and bisoprolol among stable HFrEF patients was satisfactorily equal. Konishi et al,[27] also performed comparative study between carvedilol and bisoprolol. Total 217 HF patients were included in the study and divided in two groups. Carvedilol group included 110 patients and bisoprolol group included 107 patients. The study reported that both the drugs were having same efficacy rate in improving health status of HF patients.[27] Similar findings were observed by Dungen et al,[28] The study reported that carvedilol at 50 mg and bisoprolol at 10 mg everyday had common effect.[28]

Hori et al,[29] also performed comparative study between carvedilol and bisoprolol. The study included 28 patients in carvedilol and 30 patients in bisoprolol. The study reported that bisoprolol was equally effective as that of carvedilol but at lower dosage in patients with HF.[29] However, Bolling et al,[5] reported contradictory result with carvedilol showing higher survival rate as compared to other beta blockers metaprolol. This difference may be attributed to difference in dosage amount prescribed to patients.[5]

Jun et al,[30] enrolled 1,806 patients in bisoprolol and 3,612 in carvedilol group. Their findings were in corroboration with present study and stated that both the drugs were equally effective in primary and secondary endpoints (fatal and non-fatal consequences) in HF patients after 7 years of study.[30] Choi et al,[4] studied the mortality benefit between carvedilol and bisoprolol and had similar findings as that of present investigations. The study revealed that both the medications showed equivalent mortality benefit in HF patients post stabilization.[4]

CONCLUSION

In conclusion, the present findings suggested that a beta blockers carvedilol and bisoprolol are good choice for initiating treatment of HF syndrome which was in accordance with the present available guidelines.

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