

# Effects of Carvedilol as an Adjunct Therapy in the Treatment of Chronic Heart Failure

MUHAMMAD ALI YASEEN\*, KHURRUM SALEEM, ANSER ASRAR\*.

## ABSTRACT

Heart failure is an imbalance in pump function in which heart fails to maintain the circulation of blood adequately. Progressive and debilitating heart failure affects almost 5 million, mostly elderly, individuals in United States. As the elderly population is growing in coming decades, the prevalence of heart failure is expected to increase substantially. Moreover, despite modern management, heart failure has dismissal prognosis, with only 50% of the patients surviving five years after diagnosis. The objective of this study was to determine the effect of carvedilol as an adjunct therapy in the treatment of chronic heart failure in patients admitted in West medical and cardiology wards of Mayo Hospital Lahore. A Quasi experimental study was conducted including 100 patients of chronic heart failure for 6 months and it concluded that In patients of chronic heart failure, the addition of carvedilol to standard therapy ameliorates the severity of heart failure and reduces the risk of clinical deterioration, and other serious adverse clinical events.

**Key words:** Heart failure, Carvedilol, adjunct therapy

---

## INTRODUCTION

Heart failure is an imbalance in pump function in which heart fails to maintain the circulation of blood adequately<sup>1</sup>.

Progressive and debilitating heart failure affects almost 5 million, mostly elderly, individuals in United States. As the elderly population is growing in coming decades, the prevalence of heart failure is expected to increase substantially<sup>2</sup>. Moreover, despite modern management, heart failure has dismissal prognosis, with only 50% of the patients surviving five years after diagnosis<sup>3</sup>.

In the past, pharmacological treatment of heart failure was aimed only at relieving edema and improving hemodynamics. Today, however, a major aim of treatment is to antagonize the sympathetic nervous system and renin-angiotensin-aldosterone system, and to avert harmful effects of neurohormonal activation on the myocardium and peripheral vessels<sup>4</sup>.

The modern management of chronic heart failure has led to improved life expectancy, functioning and health related quality of life.<sup>5</sup> Despite clinical trials demonstrating that inhibitors of renin-angiotensin and sympathetic nervous system can reduce the mortality and morbidity associated with heart failure, these drugs have remained underutilized in general practice. In particular many patients with heart failure due to left ventricular

dysfunction fail to receive beta blockers, although this class of drugs, as well as other antihypertensive agents such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, are recommended as part of routine heart failure therapy by consensus guidelines<sup>6</sup>.

Beta blocker administration in patients with chronic heart failure decreases circulating levels of N-terminal portion of brain natriuretic peptide and thus improves left ventricular function but there is no significant effect on plasma levels of plasma renin activity, angiotensin-II and aldosterone.<sup>7</sup> Beta blockers are effective in preventing left ventricular remodelling and cardiac contractile dysfunction in failing heart.<sup>8</sup> Compared with metoprolol, long term treatment with carvedilol exerts a substantially greater reduction in mortality and led to improvement in well-being in patients with chronic heart failure<sup>9</sup>.

Carvedilol treatment improves diastolic function in chronic heart failure with severe diastolic impairment. These changes remain also after one year of therapy and appear to precede an increase of systolic function and improvement of hemodynamic status<sup>10</sup>.

Carvedilol is a third-generation beta-1 and beta-2-blocker that also possesses alpha-1-adrenergic-blocking properties. This compound has: i) shown superior efficacy to certain other beta-blockers in heart failure, ii) can improve myocardial function (e.g., in myocardial infarction) and iii) is the only beta-blocker shown to significantly reduce mortality and morbidity (such as reinfarction and development of

---

Department of Medicine & Cardiology\*, Mayo Hospital, Lahore

\*Department of Physiology, Lahore Medical & Dental College, Lahore

Correspondence to Dr. Khurram Saleem, Senior Registrar  
Email: khurramsaleem@hotmail.com

heart failure) in postmyocardial infarction patients with left ventricular dysfunction (LVD)<sup>11</sup>.

Carvedilol is effective in reduction of hypertension, and of mortality and morbidity as a supplement to conventional drugs of heart failure therapies (diuretics, ACE inhibitors), based on randomized controlled trials and retrospective analysis<sup>12</sup>.

Of all beta-blockers, only bisoprolol, carvedilol, nebivolol and metoprolol CR are proven effective in stable chronic heart failure with impaired left ventricular systolic function and can be recommended in elderly patients on standard treatment with diuretics and ACE inhibition<sup>13</sup>.

## MATERIAL AND METHODS

A Quasi experimental study was conducted in patients of Medical and cardiology wards of Mayo Hospital Lahore for Six months from 15<sup>th</sup> Feb 2008 to 15<sup>th</sup> July 2008. Total 100 patients with purposive sampling were included with the following criterions. All patients presenting with chronic heart failure with NYHA class II, III and IV due to ischemic heart disease, hypertensive heart disease and dilated cardiomyopathy, in whom echocardiogram shows ejection fraction of less than 40%, all those receiving standard management of heart failure like ACE inhibitors or angiotensin receptor blockers, diuretics and digitalis (as needed) for the last 3 months were included in the study. All those patients with valvular heart disease, bronchial asthma or other bronchospastic diseases, with second or third degree AV blocks, cardiogenic shock, chronic liver disease, with chronic heart failure with ejection fraction of more than 40% were excluded from the study.

A total of 100 patients of chronic heart failure were included in this study and they were divided into two groups, group A 50 patients and group B 50 patients. The patients were collected from out patients and in patients departments of west medical and Cardiology wards of Mayo Hospital Lahore. All the patients were explained about the study and an informed consent was taken from every patient. A brief history of the disease and family history was taken from the patient. After initial assessment and baseline echocardiogram, patients fulfilling the inclusion criteria were randomly allocated into two groups, Group A and Group B, using random number table. Group A was continued on standard therapy for heart failure including ACE inhibitors or angiotensin receptor antagonists, diuretics and digitalis (as needed). Group B patients were given carvedilol, starting dose 3.125mg BD in addition to above mentioned standard therapy. If the patient tolerated then the dose was titrated upto 25mg BD over a

period of one month and then continued for the rest of the study. At the start and at the end of 6 months therapy, patients of both groups were assessed in terms of echocardiographic parameters like ejection fraction. Findings were recorded on the pre-designed proforma.

**Group A** Left ventricular ejection fraction of less than 40% and on standard treatment alone for 3 months.

**Group B** Left ventricular ejection fraction of less than 40% and on standard treatment for 3 months plus carvedilol.

**Data analysis:** Data analysis was computer based by using its statistical package for social sciences (SPSS-10). The sex was presented by male to female ratio and age was presented by mean and standard deviation. Independent student 't' test was applied to find the difference between mean and standard deviation in ejection fraction in the patients of group A and of group B. P value  $\leq 0.05$  was taken as significant.

## RESULTS

Out of 100 patients 66 (66%) patients were males and 34 (34%) patients were females. Individual group male-female ratio given in table 1. Mean age of the patients in group A was 56.3±12.9 years while the mean age in group B was 53.5±12.2 years. Individual age group detail given in Table 2.

Two patients in each group expired during the study period while three patients in group A and four patients in group B lost the follow up (Table 4).

The mean baseline Ejection fraction of the patients on presentation was 31.36±4.3 in group A and 32.36±3.8 in group B as measured by echocardiography. P value was 0.2, which was statistically not significant between the two groups. After the six months follow up the mean ejection fraction of the patients was 35.95±4.7 in group A and 38.93±4.8 in group B. P value was 0.01 which was statistically significant between the two groups.

The patients of both the groups were re-assessed after six months by way of echocardiography. It was noticed that after six months of treatment, the group receiving only standard therapy showed mean increase of 4.59% in ejection fraction whereas in the other group receiving carvedilol in addition to standard therapy showed increase of 6.57%.

Table 1: Sex distribution of patients (n=100)

Gender	Group A (n=50)	Group B (n=50)
Male	32 (64.0%)	34 (68.0%)
Female	18 (36.0%)	16 (32.0%)
Total	50 (100.0%)	50 (100.0%)
M:F ratio	2:1.12	2.12:1

**Key:** M:F ratio Male to female ratio

Table 2: Age distribution of patients (n=100)

Age in years	Group A (n=50)	Group B (n=50)
30-40	5 (10.0%)	9 (18.0%)
41-50	11 (22.0%)	13 (26.0%)
51-60	13 (26.0%)	15 (30.0%)
61-70	13 (26.0%)	9 (18.0%)
>70	8 (16.0%)	4 (8.0%)
Mean±SD	56.3±12.9	53.48±12.2

Key: SD Standard deviation

Table 3: Ejection fraction of patients on presentation (n=100) P value 0.2

Age in years	Group A (n=50)	Group B (n=50)
21-25	6 (10.0%)	3 (6.0%)
26-30	18 (36.0%)	15 (30.0%)
31-35	13 (26.0%)	17 (34.0%)
36-40	13 (26.0%)	15 (30.0%)
Mean±SD	31.36±4.3	32.36±3.8

Key: SD Standard deviation

Table 4: Ejection fraction of patients after 6 months(n=100)

Age in years	Group A (n=50)	Group B (n=50)
24-30	8 (16.0)	3 (6.0)
31-35	11 (22.0)	9 (18.0)
36-40	15 (30.0)	13 (26.0)
41-45	11 (22.0)	12 (24.0)
46-50	0	7 (14.0)
Expired patients	2 (4.0)	2 (4.0)
Patients lost from follow up	3 (6.0)	4 (8.0)
Mean±SD	35.95±4.7	38.93±4.8

Key: SD Standard deviation

Table 5: Improvement in mean ejection fraction (n=100)

	Group A (n=50) Mean±SD)	Group B (n=50) Mean±SD)
On presentation	31.36±4.3	32.36±3.8
After 6 months	35.95±4.7	38.93±4.8
Improvement	4.59	6.57
P vale	0.01	0.002

Key: SD Standard deviation

## DISCUSSION

Chronic heart failure is a common cardiovascular condition, whose prevalence is increasing, particularly in elderly patients.<sup>14</sup> This condition is associated with high morbidity and mortality. Approximately 2 million persons in the United States have chronic heart failure; every year there are 400,000 new cases<sup>15</sup> and 274000 deaths.<sup>16</sup> Furthermore, as the US population becomes older, the prevalence of chronic heart failure may continue to increase<sup>17</sup>.

The present study demonstrates that  $\beta$ -blockade with carvedilol produces clinical and hemodynamic benefits in patients with severe chronic heart failure.

These beneficial clinical effects were accompanied by a significant enhancement of left ventricular performance, as evidenced by an increase in left ventricular ejection fraction. Moreover, in the study it was observed that, carvedilol was well tolerated and produced few serious adverse reactions. The major side effect of the drug was dizziness, which could generally be controlled by alterations in the doses of diuretics and ACE inhibitors. The results of this clinical trial indicated that combined  $\alpha$  and  $\beta$ -blockade with carvedilol may be useful in the management of advanced heart failure.

Mean age in our study was 56.3±12.9 years in group A and 53.48±12.2 years in group B. While in the study of Doughty et al<sup>16</sup> the mean age was 61±12 years. The difference in age is because cardiomyopathy patients (relatively young) were also included in our study and Doughty et al<sup>18</sup> included only patients of acute myocardial infarction.

In our study the ejection fraction was measured only at the start and at 6 months interval. The mean ejection fraction at the start in our study was 31.36±4.3 in group A and 32.36±3.8 in group B (p=0.2). The mean ejection fraction after 6 months interval in our study was 35.95±4.7 in group A and 39.93±4.8 in group B (p=0.01). While comparing our study with other internationally done studies previously the CAPRICORN Echo Substudy, which was conducted on 127 patients of acute myocardial infarction and having ejection fraction of less than 40%, with or without heart failure, whereas we included 100 patients of chronic heart failure with ejection fraction of less than 40%. Ninety three percent (93%) of the patients were already receiving ACE therapy and 47% patients were randomized to carvedilol and 53% patients to placebo and ejection fraction was measured at 1, 3 and 6 months intervals by echocardiogram.<sup>18</sup> While we checked ejection fraction in the start and at the end of 6 months only. In Doughty et al<sup>18</sup> study the mean ejection fraction was 39.3±8 and in our study it was 31.36±4.3 in group A and 32.38±3.8 in group B. Ejection fraction improvement after 6 months therapy with carvedilol was 5.0 and in our study it was 6.57 with p=0.002. Regarding placebo the improvement was negligible whereas in our study the ejection fraction improvement in standard group was 4.59 with p=0.01. The difference in improvement in ejection fraction is probably because we used standard therapy (ACEI/ARBS, diuretics and digitalis) in the standard group (Group A).

While comparing with the study by Lombardo et al<sup>19</sup> they assessed the effects of nebivolol compared with carvedilol on left ventricular function in patients with chronic heart failure and reduced left ventricular systolic function. Seventy patients with a left

ventricular ejection fraction  $\leq 40\%$  and in New York Heart Association functional class II or III were randomly assigned to receive carvedilol or nebivolol therapy for 6 months. The mean improvement in ejection fraction in carvedilol group increased from  $33 \pm 6$  to  $37 \pm 11$  whereas in my study it increased from  $32.36 \pm 3.8$  to  $38.93 \pm 4.8$  with  $p=0.002$ . Therefore our results are comparable with the study of Lombardo et al<sup>17</sup> and similar improvement was observed in both studies.

In the study of Figulla et al<sup>20</sup> the carvedilol was compared with betaxol. NYHA II or III heart failure patients were uptitrated to either carvedilol 25mg BD and betaxolol 20mg OD. While in our study the comparison was between carvedilol in addition of standard therapy and standard therapy alone. The dose of carvedilol was the same as used in the above study. The duration of this study was 8 months whereas our study duration was 6 months. Left ventricular ejection fraction (LVEF) increased from 30% to 43% in carvedilol group, whereas in our study ejection fraction improvement was 6.57. The difference is probably because the above study was conducted for 8 months and my study was conducted for 6 months.

## CONCLUSION

In conclusion, the findings of the present study indicated that long-term treatment with the  $\beta$ -blocker, carvedilol in addition to ACE-I / ARBs, diuretics and digoxin provides additional hemodynamic and clinical benefits in patients of moderate to severe chronic heart failure.

## REFERENCES

1. Vim S, Ahmadi H. Factors influencing the length of hospital stay of patients with heart failure. *Pak J Cardiol* 2005; 6:29-34.
2. Berkowitz R, Blank LJ, Powel SK. Strategies to reduce hospitalization in management of heart failure. *Lippincotts Case Manag* 2005; 10:S1-15.
3. Chagani H, Memon F, Mahmood A. Epidemiology of heart failure. *Pak J Cardiol* 1999; 10:74-7.
4. Czuriga I. Chronic heart failure the epidemic of the 21st century. *Orv Hetil* 2005; 146:1075-87.
5. Dunderdale K, Thompson DR, Miles JN, Beer SF, Furze G. Quality-of-life measurement in chronic heart failure: do we take account of the patient's perspective? *Eur J Heart Fail* 2005; 7:572-82.
6. Williams RE. Early initiation of beta blockade in heart failure: issues and evidence. *J Clin Hypertens (Greenwich)* 2005; 7:520-8.
7. Wang F, Xu ZM, Wang L, Bian WY, Jia X, Duan B, et al. Beneficial neurohormonal profiles of beta blockades in chronic heart failure. *Zhonghua Nei Ke Za Zhi* 2005; 44: 490-4.
8. Sun YL, Hu SJ, Wang LH, Hu Y, Zhou JY. Effects of beta-blockers on cardiac function and calcium handling protein in post infarction heart failure rats. *Chest* 2005; 128:1812-21.
9. Cleland JG. Comprehensive adrenergic receptor blockade with carvedilol is superior to beta-1-selective blockade with metoprolol in patients with heart failure: COMET. *Curr Heart Fail Rep* 2004; 1: 82-8.
10. Palazzuoli A, Quatrini I, Vecchiato L, Scali C, De paola V, Lovine F, et al. Effects of carvedilol on left ventricular diastolic function and chamber volumes in advanced heart failure. *Minerva Cardioangi* 2005;53:321-8.
11. Fonarow GC. Profile of carvedilol controlled-release: a new once-daily formulation of carvedilol. *Expert Opin Pharmacother* 2006; 7:2533-46.
12. Karpati K, Brodszky V, Farsang C, Jermendy G, Vandorfi G, Zamolyi K, et al. The effectiveness of carvedilol in heart failure. *Orv Hetil* 2006; 147:1931-7.
13. Middeljans-Tijssen CW, Jansen RW. Elderly heart failure patients and the role of beta-blocker therapy. *Tijdschr Gerontol Geriatr* 2006; 37: 67-77.
14. National Heart, Lung, and Blood Institute. Morbidity and Mortality: Chartbook on Cardiovascular, Lung, and Blood Disease 1992. Bethesda, Md: US Department of Health and Human Service; 1992.
15. Smith WM. Epidemiology of congestive heart failure. *Am J Cardiol* 1985; 55:3A-8A.
16. Yusuf S, Thom T, Abbott RD. Changes in hypertension treatment and in congestive heart failure mortality in the United States. *Hypertension* 1989;13:1-74.
17. Kannel WB, Belanger AJ. Epidemiology of heart failure. *Am Heart J* 1991;121:951-7.
18. Doughty RN, Whalley GA, Walsh HA, Gamble GC, Lopez-Sendon J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction. The CAPRICORN Echo Substudy. *Circulation* 2004; 109:201-06.
19. Lombardo RM, Reina C, Abrignani MG, Rizzo PA, Braschi A, De-Castro S. Effects of nebivolol versus carvedilol on left ventricular function in patients with chronic heart failure and reduced left ventricular systolic function. *Am J Cardiovasc Drugs* 2006; 6:259-63.
20. Figulla HR, Krzeminska-Pakula M, Wrabec K, Chochola J, Kalmbach C, Fridl P. Betaxolol is equivalent to carvedilol in patients with heart failure NYHA II or III: Result of a randomized multicenter trial (BETACAR Trial). *Int J Cardiol* 2006; 113:153-60.