Importance of non-selective beta blockers in congestive heart failure - experiences with carvedilol treatment in Bosnia and Herzegovina

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Abstract

Objectives: The aim of this study was to investigate the effects of carvedilol treatment through improvement of New York Heart Association (NYHA) class, ejection fraction (EF) and blood pressure (BP) values in patients with chronic heart failure (CHF).

Methods: This multicenter, observational, non-interventional was conducted in 25 medical centers in Bosnia and Herzegovina, from April 2015 until December 2015 (nine months). It included 167 patients of both genders, older than 50 years, who were diagnosed with CHF according to the NYHA classification and had EF <50%. The patients were administered carvedilol tablets and were followed during six visits: baseline and five follow-ups, over the period of 24 weeks.

Results: At the beginning of the study, CHF NYHA class I was present in 5 (3.0%) patients, NYHA class II in 76 (45.5%) and NYHA class III in 66 (39.5%) patients. After 24 weeks, CHF NYHA class I was present in 43 (25.7%) patients, NYHA class II in 75 (44.9%) and NYHA class III in 21 (12.6%) patients. There is a statistically significant change of NYHA class before and after 24 weeks of treatment with carvedilol (rho=0.272; p=0.002). At the baseline observation, mean value of EF was 43.06±9.6%. after 24 weeks of treatment, the mean value of EF increased to 48.15±10.51% (p=0.0001). Average increase of EF after the treatment was 5%, or ranging from 1.5-7.5%. Systolic and diastolic blood pressure significantly decreased from baseline to final observation (-15.4 mmHg and -9.18 mmHg; p=0.0001).

Conclusion: Carvedilol is effective in improvement of NYHA class and ejection fraction as well as in reduction of high blood pressure in patients with congestive heart failure.

Keywords: chronic heart failure, NYHA classification, carvedilol, treatment efficacy

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Introduction

Congestive heart failure (CHF) is classically a progressive disease initiated by injury to the myocardium that produces changes in the structure and function of the left ventricle. With time, elevated adrenergic tone and neurohormonal activity mediate progressive left ventricular dysfunction (LVD) and structural remodeling marked by dilatation, hypertrophy, and declining LV ejection fraction (1).

The prevalence of CHF increases in the ageing European population. Estimates of symptomatic heart failure range from 0.4% to 2% in the present European population, with an increase from 6 to 10% after the age of 65 (2,3). In Bosnia and Herzegovina there is a high death rate from diseases that are associated with CHF: cardiomyopathy (63.6/100.000 inhabitants), acute myocardial infarction (69.4/100.000 inhabitants) and hypertension (48.6/100.000 inhabitants) (4). CHF is the major cause of hospitalizations (5%), especially in persons aged above 65, resulting in high hospital treatment and health insurance costs (3–6).

The severity of CHF is usually assessed on the basis of New York Heart Association (NYHA) functional classification (7).

Modern therapeutic approach to CHF implies not only working on improvement of symptoms but also on prevention of asymptomatic cardiac dysfunction to
become CHF, stopping progress of CHF and reducing the mortality (8). Treatment of CHF consists of general measures, pharmacological therapy, usage of versatile apparatuses and surgical interventions (9). Randomized controlled trials have allowed the selection of therapies able to improve quality of life and outcomes in patients with chronic CHF. Hence guidelines now recommend the administration of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and, in NYHA class III to IV patients, aldosterone antagonists, to improve prognosis of the patients with CHF. Beta-blockers are therefore the mainstay of current medical treatment of HF (10). At present, the clinical use of β-blockers in patients with heart failure remains limited, reflecting uncertainty about the tolerability, safety, and efficacy of β-blockade in this large patient population (11).

The aim of this study was to investigate the effects of carvedilol treatment through improvement of NYHA class, ejection fraction and blood pressure values in patients with chronic heart failure.

**Materials and Methods**

**Patients**

This study was designed as multicenter, observational, non-interventional study that was conducted in 25 medical centers in Bosnia and Herzegovina, from April 2015 until December 2015. The study included 167 patients of both genders, older than 50 years, who were diagnosed with congestive heart failure according to the NYHA classification and had ejection fraction (EF) <50%.

The patients with chronic heart failure (current NYHA class IV) that would require intravenous inotropes, 2nd or 3rd degree atrioventricular block, asthma and chronic obstructive pulmonary disease were not included in the study. Patients who showed deterioration of the underlying disease, developed serious adverse reactions that required discontinuation of therapy or developed diseases that affected the course of research were further excluded from the study.

**Study design and patient monitoring**

The patients were followed during six visits: baseline and five follow-ups, over the period of 24 weeks. The degree of CHF was determined using NYHA classification based on symptoms of fatigue, dyspnea and palpitations. The EF was determined using a standard echocardiogram, performed by two cardiologists before the beginning of the study. Blood pressure (BP) was recorded during each observation, using a standard ambulatory sphygmomanometer. A common cuff was centered to the left upper arm for BP measurement and the cuff size was chosen according to the circumference of the mid upper arm. Therapy tolerance, possible adverse effects and patient’s compliance were assessed using previously designed Likert-type scale.

During the baseline observation, general patients’ characteristics (gender, age, body mass index, smoking status), comorbidities and carvedilol dosage were recorded, as well as NYHA class and EF values. The second observation was performed in the 4th week from the baseline observation, the third observation was performed in the 12th week of the study, the fourth observation was performed in the 16th week of the study and the fifth observation was performed in the 20th week of the study and they all included an assessment of the efficacy and safety of treatment with the drug dose adjustments. The final, sixth observation was performed in the 24th week of research and it included reevaluation of the EF values and NYHA class, along with a final overall evaluation of the efficacy and safety of therapy.

All patients were treated with carvedilol tablets in addition to their standard therapy. The recommended initial dosage of carvedilol in the study was 3.125 mg, twice a day, during two weeks. If the patients tolerated the treatment well, the dosage was increased every two weeks to 6.25 mg twice a day, then to 12.5 mg twice a day and finally to 25 mg twice a day. In certain cases, the dosage of carvedilol was not increased until heart failure aggravation or vasodilation symptoms stabilized. The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Agency for medical products and medical devices of Bosnia and Herzegovina, according to the Law on medicines of Bosnia and Herzegovina.

**Assessment of the drug effectiveness and safety**

The drug effectiveness was assessed on the basis of physician’s examination of the patients and symptoms relief. The safety of the study was provided by the monitoring the incidence of adverse reactions of the drug with the assessment of the link between drug application and reporting adverse reactions (certain, probable, possible, not probable, unclassified relation and non-classifiable).

**Statistical Analysis**

Statistical analysis was performed by SPSS (Statistical Package for Social Sciences), version 16.0. To measure the significance of differences in variables measured at time intervals, a Student-t test for dependent samples or Wilcoxon signed-rank test for repeated measurements was used. For rank correlation we used Spearman’s rho correlation test and Chi-square test for comparison of frequencies. The level of significance was set to p<0.05.
RESULTS

General characteristics of the patients are shown in the Table 1. Out of the total number of patients, 85 (50.9%) were men and 82 (42.1%) were women. There was no statistical significance in gender distribution (p=0.094). There was no significant difference in age, anthropometric parameters, smoking or duration of heart failure between men and women (Table 1).

At the beginning of the study, CHF NYHA class I was present in 5 (3.0%) patients, NYHA class II in 76 (45.5%) and NYHA class III in 66 (39.5%) patients. Classification hasn't been done in 20 (12%) patients. After 24 weeks, CHF NYHA class I was present in 43 (25.7%) patients, NYHA class II in 75 (44.9%) and NYHA class III in 21 (12.6%) patients. Classification hasn't been done in 28 (16.8%) patients. CHF before and after 24 weeks of therapy was classified in 133/167 (79%) subjects according to NYHA classification.

At the beginning of the study, 61 patient had CHF class III. Out of that number only 15 (24.6%) had the same level of CHF after 24 weeks of the therapy. A total of 46 (75.6%) patients had improvement of their cardiac function, and they were classified into II or I NYHA class. Prior to the therapy, 70 patients had CHF class II and, out of that number, 40 (57.1%) remained in the same class. In 26 (37.4%) patients, heart failure has decreased by one level (class) and in 4 (5.7%) patients CHF class has increased by one level. Two subjects had CHF class II and they remained in the same class after the treatment. There is a statistically significant change of NYHA class before and after 24 weeks of treatment with carvedilol (rho=0.272; p=0.002).

At the baseline observation, mean value of EF was 43.06±9.6%. after 24 weeks of treatment, the mean value of EF increased to 48.15±10.51% (Figure 1). The increase in EF before and after treatment was statistically significant (p=0.0001). Average increase of EF after the treatment was 5%, or ranging from 1.5-7.5%. In 10% of patients there was no improvement in EF, while in 20% of patients EF improved from 7.5 to 12.8%.

Table 1. General patient’s characteristics between men and women

<table>
<thead>
<tr>
<th>General patient’s characteristics</th>
<th>Men (N=85)</th>
<th>Women (N=82)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>22</td>
<td>25.9</td>
<td>11</td>
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<tr>
<td>Overweight</td>
<td>42</td>
<td>49.4</td>
<td>38</td>
</tr>
<tr>
<td>Obesity</td>
<td>21</td>
<td>24.7</td>
<td>33</td>
</tr>
<tr>
<td>Smokers</td>
<td>39</td>
<td>45.9</td>
<td>20</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>68.86±6.29</td>
<td>68.77±7.08</td>
<td>0.932</td>
</tr>
<tr>
<td>Mean duration of cardiac insufficiency (months)</td>
<td>24 (6-60)</td>
<td>24 (12-60)</td>
<td>0.904</td>
</tr>
</tbody>
</table>
Table 2. Systolic and diastolic blood pressure during carvedilol treatment

<table>
<thead>
<tr>
<th>BP</th>
<th>Follow-ups</th>
<th>Mean ± SD</th>
<th>Δ BP</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic Blood Pressure (mm Hg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>146.13 ±18.45</td>
<td>-5.53</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>140.60 ±16.74</td>
<td>-4.97</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>140.60 ±16.74</td>
<td>-4.97</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td>135.63 ±16.74</td>
<td>-2.18</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>3rd</td>
<td>133.45 ±15.59</td>
<td>-2.38</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>4th</td>
<td>131.07 ±15.28</td>
<td>-0.34</td>
<td>0.856</td>
<td></td>
</tr>
<tr>
<td>5th</td>
<td>130.73 ±14.02</td>
<td>-0.27</td>
<td>0.150</td>
<td></td>
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<tr>
<td><strong>Diastolic Blood Pressure (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>89.08 ±10.09</td>
<td>-2.92</td>
<td>0.0001</td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>86.16 ±8.81</td>
<td>-3.28</td>
<td>0.0001</td>
<td></td>
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<tr>
<td>2nd</td>
<td>82.88 ±8.9</td>
<td>-1.31</td>
<td>0.013</td>
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<tr>
<td>3rd</td>
<td>81.57 ±8.1</td>
<td>-0.59</td>
<td>0.261</td>
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<tr>
<td>4th</td>
<td>80.98 ±7.6</td>
<td>-1.08</td>
<td>0.120</td>
<td></td>
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<tr>
<td>5th</td>
<td>79.90 ±7.28</td>
<td>-1.00</td>
<td>0.120</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Percentage of patients and their daily carvedilol dosage in each follow-up
At the end of the study, 76/152 (83.6%) of patients reported improvement in symptoms and clinical presentation, while 25/152 (16.4%) reported no change. None of the patients reported deterioration in clinical presentation. Out of 151 patients reported, 137 (88.7%) felt complicit with the therapy used. No adverse reactions to carvedilol were reported during the study. From the total number of 156 patients, 92 (59%) evaluated the treatment as very good, 57 (36.5%) evaluated it as good and 7 (4.5%) patients evaluated the treatment as bad.

**DISCUSSION**

With this study, we aimed to investigate the effects of carvedilol treatment through improvement of NYHA class, EF and BP values in patients with CHF.

The results of our study demonstrated that there was a significant improvement of CHF shown through change in NYHA class. At the beginning of the study, 61 patients were classified as NYHA III class and out of that number 46 (75.6%) patients changed to NYHA class I or II at the end of the study.

The results also show that there was an improvement in EF of an average 5% (ranging between 1.5 and 7.5%) 24 weeks after the initiation of the treatment, which suggest that carvedilol has a positive effect on improvement of EF.

SBP and DBP values significantly decreased from baseline to final observation. SBP reduction was -15.4 mmHg and DBP reduction was -9.18 mmHg.

The initial dose of carvedilol used was 3.125 mg twice a day and it was gradually increased every two weeks to a maximum of 25 mg twice a day for patients weighing below 85 kg and 50 mg twice a day for patients weighing over 85 kg. By using the upward titration for treatment of CHF, i.e. with gradual increase of the dosage every two weeks we were able to avoid potential adverse effects of carvedilol. No adverse reactions to carvedilol were reported during the study.

Carvedilol is a novel multiple-action neurohormonal antagonist. Its primary activities are nonselective β-adrenoceptor blockade, vasodilatation and antioxidant activity (12). In patients with heart failure, carvedilol improves the left ventricle's function, it reduces symptoms, dramatically reduces mortality, reduces number of hospitalizations and improves the quality of life (12,13). Clinical benefits of carvedilol in the treatment of heart failure are preserved even in patients in whom comorbidity is present, such as diabetes, renal failure and in elderly patients (13). In addition, carvedilol helps retain endogenous antioxidative systems, and its antioxidative potential as well as potential of its metabolites is 10 -1000 times greater than antioxidative potential of vitamin E (14).

Several randomized clinical trials have been performed with beta-blockers for treatment of patients with heart failure. Three major clinical studies were: CIBIS II (Heart failure Bisoprolol Study II), COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival) and MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure). They involved almost 9000 patients with moderate to severe form of heart failure of whom more than 90% were previously administered only ACE inhibitors or ARBs (15). In COPERNICUS and MERIT-HF studies, symptom improvement has been reported in patients who administered therapy with beta-blockers as compared to those who used only ACEI or angiotensin II blockers. Owing to high significant influence on mortality, the Ethics Committee reached Decision on 14 March 2000 for this randomized study to be interrupted earlier and that carvedilol be administered to all the patients (15). This study has demonstrated that carvedilol is effective even in low doses unlike other beta-blockers.

CAPRICORN (Carvedilol Post-infarct survival Control in LV dysfunction) trial investigated the efficacy of carvedilol in patients with systolic dysfunction of the left ventricle after the acute myocardial infarction treated according to the valid standards of medical practice based on scientific evidence. Long-lasting usage of carvedilol in these patients has led to: decrease in total mortality by 23%, reduced risk of cardiovascular hospitalizations by 8%, decreased risk of sudden death by 26%, lowered cardiovascular mortality by 26%, and decreased risk of non-fatal myocardial infarction by 41% (16).

The results of our study may be limited by a relatively small number of patients involved and possibly a short follow up period, which is why a large-scale study can provide a better insight into long-term efficacy of carvedilol.

In conclusion, the results of our study further confirm that carvedilol is effective in improvement of NYHA class and ejection fraction as well as in reduction of high blood pressure in patients with congestive heart failure.

**DECLARATION OF INTEREST**

The authors declare no conflict of interest.
References