

# Beta Blockers for Congestive Heart Failure

*Daulat Manurung, Hanafi B. Trisnohadi*

## ABSTRACT

*The prognosis remains poor for many patients with congestive heart failure, despite maximal medical treatment with ACE inhibitor, diuretics and digitalis. In heart failure, activation of sympathetic nervous system has been described as one of the most important pathophysiologic abnormalities in patients with congestive heart failure and as one of the most important mechanisms that may be responsible for progression of heart failure. The use of beta blockers which may inhibit sympathetic activity, might reduce the risk of disease progression in heart failure, improve symptoms and increase survival.*

*Several large clinical trials with metoprolol, carvedilol and bisoprolol have shown that long term use of these agents can improve left ventricular function and symptoms of CHF, it may also reduce hospital readmission and decrease mortality.*

*Current guidelines recommend the use of beta blocker in mild, moderate and severe CHF, in the absence of contraindications or tolerance in combination with ACE inhibitor and diuretics. Beta blocker should be initiated in patients after maximal medical therapy with diuretics, ACE inhibitor and digitalis and patients already stabilized and in compensated conditions. Beta blocker should be started in low doses and require slow titration over weeks or months before patients can attain maintenance doses.*

**Key words:** *beta blockers, congestive heart failure.*

## INTRODUCTION

The role of beta blockers has changed dramatically in the management of heart failure.<sup>1</sup> In the past, beta blockers were contraindicated in patients with heart failure, because the negative inotropic effects of beta blocker will decrease further the left ventricular function and will worsen the course of this disease. However, pathophysiology of heart failure has changed. In heart failure there was an increase of neurohormonal activity

which will damage the myocardium. Beta blockers may block sympathetic nervous system activity and slow the progression of disease, improve symptoms and increase survival.

Several large clinical trials have demonstrated that beta blockers decrease mortality in patients who have already received standard heart failure therapy such as diuretics, ACE inhibitors with or without digoxin.<sup>2,3</sup> Current guidelines recommend that beta blockers should be used in mild to moderate heart failure, class II or III NYHA (New York Heart Association).<sup>4</sup> Recent trial COPERNICUS demonstrated that beta blocker is also beneficial in severe heart failure (Class IV NYHA) and another trial CAPRICORN showed the beneficial effects of beta blockers in mild heart failure (Class I NYHA).<sup>5,6</sup>

## RATIONALE FOR BETA BLOCKER THERAPY IN HEART FAILURE

Left ventricular systolic dysfunction in heart failure will be compensated by activating the sympathetic nervous system and increasing adrenergic activity to improve cardiac performance.<sup>2,3,6</sup> This compensatory mechanism may improve contractility and provide hemodynamic support in short term. However, chronic adrenergic stimulation can be deleterious because it may cause myocardial damage due to changes in left ventricular remodeling, loss of myocardial cells and abnormal gene expression.<sup>7</sup> Sympathetic activation is also associated with positive chronotropic effects, which will deplete the energy stores of the myocardium and have direct effects on myocardial cells, thereby adversely affecting outcome and accelerating progression to advanced heart failure.<sup>8</sup> Attenuation of these mechanisms is associated with improvement in survival.

Adrenergic stimulation will affect the heart via three adrenergic receptors: beta1, beta2 and alpha1, which present in human cardiac myocytes. Beta blockers function by reversibly binding with beta-adrenergic receptors to block the response to sympathetic nerve impulses or catecholamines (norepinephrine or epinephrine).<sup>9</sup>

*Division of Cardiology, Department of Internal Medicine, Faculty of Medicine, Indonesia University/Dr.Cipto Mangunkusumo Hospital, Jakarta.*

Treatment is aimed at halting this increased sympathetic drive and stopping the adverse effects of chronic adrenergic stimulation in chronic congestive heart failure is being the fundamental basis for the rationale use of beta-adrenergic antagonists.

## CLINICAL TRIALS OF BETA BLOCKADE

Various studies have been shown beneficial effects of beta blocking agents in patients with heart failure.

### Ventricular Performance

Waagstein reported that administration of metoprolol to 7 patients with congestive cardiomyopathy resulted in improvement in left ventricular ejection fraction (LVEF) and overall clinical status, while withdrawal of the drug resulted in deterioration of clinical conditions.<sup>11</sup>

Subsequent reports consistently confirmed these findings, demonstrating that beta blocker administration could improve LVEF and hemodynamic condition over a 3 to 6 month period.<sup>12-14</sup> One study performed double blind, placebo controlled comparing bucindolol with placebo plus standard therapy for heart failure due to dilated cardiomyopathy. Bucindolol is a nonselective beta blocker with direct vasodilatory activity. Long term therapy resulted in improvements in LVEF, cardiac index and LV stroke work, while mean pulmonary capillary wedge pressure and heart rate decreased, NYHA functional class also improved in bucindolol group ( $p < 0.01$ ).<sup>14</sup> Similar improvements have been demonstrated with metoprolol and bisoprolol and carvedilol.<sup>15-17</sup>

### Improvement in Patients Survival

During the last few years many studies have shown that beta-adrenergic blockade dramatically reduced the morbidity and mortality in heart failure, a number of trials confirmed this benefit with several beta blockers (metoprolol, carvedilol and bisoprolol).<sup>18</sup> A meta analysis that included 22 trials involving more than 10,000 patients almost all of whom had NYHA class II or III heart failure and were also treated with standard therapy including ACE inhibitors. The results showed beta blockers significantly reduced mortality in one year (odds ratio 0.65, 95% CI 0.53 to 0.80) and two years (odds ratio 0.72, 95% CI 0.61 to 0.84). Assuming a mortality rate in the placebo group was 12% in one year. Beta blocker saved 3.8 lives in the first year per 100 patients treated. Beta blocker also reduced hospitalization for heart failure (odds ratio 0.64, 95% CI 0.53 to 0.79) with an absolute benefit of 4 fewer hospitalization in the first year per 100 patients treated.<sup>19</sup> Three large mortality trials

investigated the outcomes in congestive heart failure patients randomly assigned to receive either beta blockers or placebo therapy.<sup>20</sup>

### MERIT-HF Trial

In MERIT-HF trial metoprolol, a beta1 selective adrenoreceptor blocker was compared with placebo for the treatment of heart failure.<sup>21,22</sup> In this trial, 3991 patients with class II to IV heart failure and an ejection fraction of less than 40 percent who were receiving digoxin, an ACE inhibitor and a diuretics were randomly assigned to therapy with extended release metoprolol, beginning with 12.5 or 25 mg daily and titrated up to 200 mg daily or placebo. The mean dose was 159 mg daily, with 64 percent of patients receiving target dose; the discontinuation of patients taking active drug was 14 percent in one year. The study was terminated early because significant benefits had already been noted in the metoprolol group.

The results showed that in the metoprolol group there was 34 percent decrease in all cause mortality at 12 months (7.2 versus 11 percent for placebo,  $p = 0.006$ ), there was also reduction in the combined end point of death and need for transplant (7.5 versus 10.3 percent,  $p < 0.001$ ). There was also reduction in the hospitalization for cardiovascular causes (20 versus 25 percent,  $p < 0.001$ ) or for heart failure (10 versus 15 percent,  $p < 0.001$ ). The NYHA class and quality of life was improved. When analyzed by mode of deaths, there were significantly fewer sudden cardiac death (3.9 vs 6.6%) and fewer deaths from worsening of heart failure (1.5 vs 2.9 percent) in the metoprolol group.<sup>21,22</sup>

### Carvedilol Trials

Carvedilol a third generation beta blocker, is a nonselective beta-receptor antagonist that also blocks alpha receptors and has unique antioxidant properties.<sup>23</sup> The benefits of carvedilol for the treatment of heart failure have been shown in the 1996 US Carvedilol Heart Failure Study.<sup>24</sup> This study was a compilation of results from four smaller trials that evaluated the effect of carvedilol on morbidity and mortality in patients with congestive heart failure.<sup>17,25-27</sup>

A total of 1094 patients with left ventricular systolic dysfunction (ejection fraction less than 35%) and NYHA class II and IV symptoms were enrolled in this carvedilol study. Patients continued to receive the standard therapy for heart failure consisting of the use of digoxin, diuretics and ACE inhibitors and were randomly assigned to receive carvedilol in a target dose of 25 to 50 mg twice daily or placebo.

The trial was terminated early when an analysis

showed that overall mortality was significantly lower among patients taking carvedilol than among those taking placebo. (3.2 vs 7.8%). The reduction of death was 65% (96% CI, 39-80%;  $P < 0.001$ ) in patients treated with carvedilol over a period of 6.5 months. There was a 27% risk reduction for hospitalization for cardiovascular causes among the carvedilol group (14.1%) compared with 19.6% in the placebo group (95%CI, 3%-45%;  $p=0.036$ ).

The investigators concluded that carvedilol reduced the risk of death and the risk of hospitalization for cardiovascular causes in patients with congestive heart failure, who had already received the standard heart failure therapy.

### **CIBIS-II**

In this study bisoprolol, a second generation B1 selective adrenoreceptor blocker were analyzed for the efficacy in decreasing all cause mortality in heart failure.<sup>28</sup> 2647 patients who had NYHA class III or IV were evaluated; all patients had left ventricular ejection fraction equal or less than 35% and were being treated with ACE inhibitors and diuretics. Patients were randomly assigned to bisoprolol therapy at target dose of 10 mg once daily or to placebo. Again this trial was stopped early when analysis showed a significant reduction in all cause mortality in the bisoprolol group. After follow up, averaging 1.3 years, 156 (11,8%) patients in the bisoprolol group had died, compared with 228 patients (17.350) in the placebo group (34% reduction of mortality with bisoprolol, 95% CI, 19%-46%,  $p < 0.0001$ ).

### **Class I and Class IV Heart Failure**

The major mortality trials have not included patients with NYHA class I symptoms. But in a recent trial the Carvedilol Post Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study, assessed the effect of beta blockers in patient with mild or no symptoms.<sup>5</sup> 1959 patients with proven myocardial infarction and a left ventricular ejection fraction less than 40% were randomized to carvedilol ( $n=975$ ) or placebo ( $n=984$ ) The results showed that all cause mortality was reduced by 23% ( $p = 0.031$ ). Primarily due to the reduction in sudden death ( $p = 0.098$ ). There was also reduction of nonfatal myocardial infarction of 41% ( $p = 0.014$ ) and the combined end point of all cause mortality and nonfatal MI was reduced by 29% ( $p = 0.002$ ). The ACC/AHA guidelines suggested that beta blockers should be prescribed to patients with asymptomatic left ventricular dysfunction with a recent myocardial infarction

regardless of ejection fraction or patients with reduced ejection fraction with or without recent myocardial infarction.<sup>29</sup>

The benefit of beta blockade appears to extend to patients with severe class III and stable class IV NYHA. In a subgroup analysis of 795 patients with severe heart failure (NYHA class III/IV) in MERIT-HF study, the benefit of metoprolol for severe heart failure was similar to that seen in the entire study population. Metoprolol reduced total mortality (11.3 vs 18.2% for placebo), sudden cardiac death (5.5 vs 9.8%), death from heart failure (3.3 vs 7% and the number of hospitalization (15% vs 25%).<sup>21,22</sup> Similar results were seen with carvedilol in COPERNICUS trial, which specifically assessed the efficacy of beta blockade in 2289 patients with class IV heart failure and LVEF less than 25%. The trial was prematurely terminated because a significant mortality reduction from carvedilol compared with placebo (annual mortality rate 11.4% vs 18.5%). The patients treated with carvedilol also spent fewer days in the hospital and were less likely to develop serious adverse effects such as sudden death, ventricular tachycardia, or cardiogenic shock.<sup>4</sup>

These findings were confirmed in a pooled data analysis of 3836 patients NYHA functional class III/IV and LVEF less than 25% enrolled in COPERNICUS. MERIT-HF, CIBIS II. Beta- blockade was associated with a significant reduction in total mortality (13 vs 18% with placebo, relative risk 0.72) however initial worsening of symptoms may be more common in patients with severe disease.

### **INDICATIONS FOR BETA BLOCKERS**

Beta blockers should be administered in all patients with mild, moderate and severe heart failure due to left ventricular systolic dysfunction in the absence of contraindications or tolerance.<sup>29</sup> Beta blocker therapy should be initiated in patients after adequate diuresis and generally following ACE inhibitor treatment and the patient should be stabilized and in compensated condition. Contraindications for beta blocker treatment: cardiogenic shock, symptomatic bradycardia without pacemaker, second and third degree AV block; severe asthma and severe chronic obstructive pulmonary disease.

### **INITIATION OF THERAPY**

If a patient is considered suitable for beta blocker therapy, a careful initiation and gradual increases of beta blocker dose are crucial to avoid clinical deterioration.<sup>30</sup> Patients should first be stable on standard therapy for congestive heart failure, including diuretics, ACE

inhibitors and digoxin. A beta blocker is then added at low starting dose that is gradually increased until the maintenance level derived from the mortality trials are achieved. The increases of the dose should generally occur at 2-3 weeks interval and patients should undergo reevaluation before any adjustments are made.<sup>31</sup>

Carvedilol therapy is usually started with 3.125 mg twice daily for two weeks then the dose is increase every two weeks until target level of 25 mg twice daily for patients who weigh less than 85 kg. Bisoprolol is started at 1.25 mg daily and the dose is increased by 1.25 mg every 1 to 2 weeks to a target dose of 10 mg once daily. Metoprolol CR/XL is usually started at 25 mg once daily and the dose is increased at 2 week intervals until a goal of 200 mg once daily is reached. For patients with relatively severely symptoms (NYHA class III or IV) a starting dose of 12.5 mg once daily may be appropriate.<sup>32</sup> In the beginning of treatment with beta blockers some patients may notice the signs of fatigue. This is due to drop in sympathetic drive.

### PRACTICAL GUIDELINES

Guidelines from the American College of Cardiology and the American Heart Association, the European Society of Cardiology and the Heart Failure Society of America all strongly support the use of beta blockers in patients with heart failure.<sup>33-35</sup> The recently published, revised heart failure guidelines of the American College of Cardiology-American Heart Association and the European Society of Cardiology clinical practice guidelines recommend the use of beta blockers in a broader range of heart failure patients, including those asymptomatic LV systolic dysfunction and those with severe symptomatic disease.<sup>35</sup> These guidelines emphasize that the majority of patients with heart failure are candidates for beta blockers therapy, with few exceptions. Currently, only patients with absolute contraindications to these drugs or patients with severe heart failure requiring inotropes or mechanical support should not receive these agents. Not only these agents beneficial in patients with mild to moderate symptomatic heart failure caused by systolic dysfunction but also they improve survival in patients with severe symptomatic heart failure.

### CONCLUSION

At present beta blockers are well established as a part of standard therapy in patients with congestive heart failure. They have been shown to reduce mortality and to improve quality of life by decreasing sympathetic drive, which is chronically increased in heart failure, by

disturbing and interrupting neurohormonal pathways. Because beta blockers administration may induce acute hemodynamic effects, the initial dose should be very low and gradually the dose can be titrated up carefully. Most of the large clinical trials were done in patients with mild to moderate heart failure. But the COPERNICUS study demonstrated that beta blocker was also beneficial in patients with stable severe heart failure in reducing mortality and improving symptoms.

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