



Beta Blockers Rather Than ACEI Should be the First Line Therapy In CHF

CN Manjunath

Professor of Cardiology, Sri Jayadeva Institute of Cardiology, Bangalore.

10

INTRODUCTION

Heart failure is a condition where the heart is incapable of maintaining a cardiac output adequate to accommodate the metabolic needs and the venous return. It is a disease in which the heart weakens and gradually loses the ability to pump blood effectively.

Heart failure (HF) is a common condition and carries a high mortality rate. The prevalence is increasing as the population ages, and the disorder exacts greater costs than any other medical condition.

Management of HF should address the goals of relieving symptoms, improving the quality of life and slowing or preventing heart failure progression. Recommended therapies include medication, diet, and exercise.

The primary recommended therapies are beta-blockers and angiotension converting enzyme inhibitors (ACEI). These drugs impede long-term disease progression. Several large, long-term studies have shown that beta-blockers significantly reduce the risk of morbidity and mortality.

ROLE OF SYMPATHETIC NERVOUS SYSTEM IN HF

Chronic heart failure due to systolic dysfunction is a progressive disease characterized by left ventricular dysfunction and cardiac remodeling. Patients with heart failure have increased sympathetic nervous system activity, which initially supports cardiac function through an increase in heart rate, myocardial contractility and systemic vascular resistance. However, prolonged adrenergic activation leads to downregulation and desensitization of beta-adrenergic receptors. These processes, in turn, cause deterioration of cardiovascular function and exercise tolerance. Additionally, continued exposure of excess norepinephrine contributes to the development of cardiac hypertrophy, arrhythmia and myocardial cell apoptosis.

HEMODYNAMIC BENEFITS OF BETA BLOCKER THERAPY

Beta-Blockers

1. Increase ejection fraction
2. Reduce end-systolic volume
3. Improve ventricular in coordination
4. Improve ventricular filling time

5. Help to prevent the remodeling process.

Beta-1 blockade inhibits apoptosis beta-2 antagonism increases apoptosis. However, because of beta-1 receptor predominate even in failing heart the net effect of selective and non-selective beta-blockade is attenuation of apoptosis.

Beta-blockers act principally by inhibiting the effects of sympathetic nervous system, through blockade of beta-1 adrenergic receptors. A number of trials showed that patients on long-term beta-blocker therapy have reduced risk of cardiovascular morbidity and mortality. A meta analysis of small and medium sized placebo controlled trials found that beta blockers are safe in patients with heart failure, when therapy is initiated at low dose and gradually uptitrated to the target dosage. Therapy increases left ventricular ejection fraction (LVEF) survival and reduces hospitalization.

Recently three large-scale trials with bisoprolol (CIBIS II), carvedilol (COPERNICUS), and extended release (ER) - metoprolol succinate (MERIT-HF) all showed to reduce mortality by 35%.

CIBIS-II¹ (Cardiac insufficiency Bisoprolol study) - This randomized double blind placebo controlled study included 2647 patients aged between 18-80 yrs, with NYHA class III-IV symptoms and LV EF upto 35%. The study was stopped early because patients treated with bisoprolol had a 34% reduction in mortality compared with placebo. It also reduced secondary end-points like all-cause hospitalization and sudden death.

COPERNICUS² (Carvedilol Prospective Randomized Cumulative Survival Trial)

Total of 2289 patients with severe HF and EF <25% were included in this study. Carvedilol was titrated to a maximum dose of 25mg twice daily. There was a significant 35% reduction in all-cause mortality, compared with placebo.

MERIT HF³ (Metoprolol CR/XL Randomized Intervention Trial in heart failure)

Total of 3991 patients with NYHA class II-IV with EF<40% were randomized to either Metoprolol CR/XL or placebo. Dose was gradually titrated upto a tolerated dose of 200 mg once daily. The study was stopped 1 year early because of 34% reduction in total mortality with Metoprolol.

WHICH DRUG SHOULD BE INITIATED FIRST?

Several arguments argue in favor of the initiation of beta-blocker treatment at the early stages of LV dysfunction, before the introduction of ACE inhibitor therapy. Indeed, early clinical trials⁴, even before the ACE inhibitor era, established the efficacy of beta-blocker treatment in secondary prevention after MI, especially in patients with altered LV function

There is accumulating data indicating that beta-blocker may be the initial choice than ACEI for the treatment of chronic heart failure, however both the drugs have become integral part of standard therapy of HF

ACEI reduce mortality by 20-25% on top of diuretics (+/- digoxin) in chronic HF. Beta-blockers reduce mortality by an additional 34-35% on top of ACEI, as shown in CIBIS II, MEREIT-HF, and COPERNICUS trials. This suggests that beta-blocker may have a superior effect on survival compared to ACEI.

In patients with newly diagnosed HF, mortality is particularly high in the first weeks after diagnosis, mainly due to sudden death. The prevalence of sudden death is more in class II-III heart failure, while worsening of heart failure is the predominant cause of death in class IV (severe) HF. Beta-blockers, in contrast to ACEI, are highly effective in reducing sudden death, suggesting that a beta-blocker should be on board early after the diagnosis of heart failure,

The sympathetic system is activated early in the disease whereas the RAAS is usually triggered at a later stage. Since beta-1 stimulation increases renin release, the administration of beta-blockade first should further delay renin release and stimulation of Angiotensin II receptors. Therefore, from the pathophysiological point of view it might be reasonable to start treatment with a beta-blocker before an ACEI.

Pre-treatment with beta-blocker may reduce the risk of worsening of renal function, frequently observed with ACEI.

Beta-blockade in combination with ACEI results in more effective suppression of serum angiotensin II concentration compared to ACEI alone.

Beta-blocker treatment appears to prevent sudden death more efficiently than ACE inhibitor treatment. In CIBIS II, most of the mortality reducing effect of bisoprolol was attributable to a 44% reduction in the risk of sudden death, whereas in ACE inhibitor studies, mortality reduction was mainly due to a reduction in heart failure worsening.

CIBIS III trial – the above arguments favor the initiation of beta-blocker therapy before that of ACE inhibition in the early stages of heart failure. The hypothesis that beta-blockers should be initiated first will be tested in the CIBIS III trial. This open study will compare starting with bisoprolol vs. enalapril, followed by a combination of both. CIBIS III will include about 1000 patients in NYHA II-III, with an LV ejection fraction <35% who are not yet receiving ACE inhibitors or beta-blockers. The primary end-point will be all-cause mortality and all-cause hospitalization (time to first event). Secondary end-points will be all-cause mortality and all-cause hospitalization at the end of monotherapy, and early introduction of the second drug due to poor control of CHF.

CONCLUSION

It goes without saying that both beta-blockers and ACEI are indicated because of additive morbidity and mortality benefits. Accumulating data indicate that beta-blocker therapy may be the initial choice especially in class II and III HF. CIBIS III trial will guide us regarding the initial sequence of therapy in HF.

REFERENCES

1. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study, a randomized trial. *Lancet* 1999;353:9-13.
2. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effects of Carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651-8.
3. MERIT – HF study Group. Effect of Metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure. *Lancet* 1999;353:2001-7.
4. Beta-Blocker Heart Attack Study Group. A randomized trial of propranolol in patients with acute myocardial infarction. *JAMA* 1983;250:2814-9.
5. Consensus recommendation for the management of chronic heart failure. On behalf of the membership of the advisory council to improve outcome nationwide in heart failure. *Am J Cardiol* 1999;83(2A):1A-38.