β-blocker in Heart failure with reduced ejection fraction: A review

Chandra Mani Adhikari

Department of cardiology, Shahid Gangalal National Heart Centre,Kathmandu,Nepal

Citation

Adhikari CM. β-blocker in Heart failure with reduced ejection fraction: A review. Nepalese Heart Journal 2013;10(1):38-45.

Keywords

β-blocker, heart failure,medical management

ABSTRACT

Heart failure, a major public health problem is associated with high mortality, poor quality of life, and frequent hospitalization. It is a complex syndrome characterized by neurohumoral activation. Activation of sympathetic nervous system plays an important role in its pathogenesis. Randomized trials have show that β-blockers reduce mortality, hospitalization and improves quality of life. One of the three β-blockers (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) is recommended for all patients with current or prior symptoms of Heart Failure, unless contraindicated, to reduce morbidity and mortality. β-blockers are underused in patients with heart failure. If a patient is considered suitable for β-blocker therapy, a careful initiation and gradual increases of β-blocker dose are crucial to avoid clinical deterioration. Initiating the Angiotensin Conventing Enzyme inhibitor first is traditional but studies have proven similar safety with a β-blocker-first strategy. Emerging evidence suggests that the order of initial ACEI or β-blocker therapy may not matter.

INTRODUCTION

Heart failure (HF), a major public health problem is associated with high mortality, poor quality of life, and frequent hospitalization.[1] Prognosis of moderate to severe HF is worse than most malignancies. When the four most common sites of cancer registered in Scottish men during 1991, they were in rank order, lung (30%), large bowel (12%), prostate (11%) and bladder (8%). The equivalent figures for women were breast (24%), large bowel (14%), lung (10%) and ovarian cancer (5%) , these malignancies were compared with heart failure. For both men and women, lung cancer was associated with the poorest unadjusted survival rate with a median survival time of 3–4 months and only 5% of patients surviving to 5 years. However, heart failure was associated with the second poorest unadjusted survival rate with a median survival time of 16 months and only 25% of men and women survived to 5 years.[2]

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood[3] and characterized by neurohumoral activation.[4] Activation of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS)

Address of Corresponence

Chandra Mani Adhikari

Shahid Gangalal National Heart Centre,

Bansbari,Kathmandu,Nepal

Email:topjhap@hotmail.com

play an important role in the pathogenesis of HF[5]. Despite the evidence that angiotensin converting enzyme inhibitor (ACEI) improves the morbidity and mortality of HF, the prognosis of HF has improved little over the past 30 years.[6] Evidences show that β-blockers, when used in addition to ACEI, also reduce mortality in HF. Along with ACEI, β-blockers has become essential first-line therapy in patients with HF, regardless of the cause.[7,8] Treatment with β-blockers improves systolic function, reduces symptoms and mortality.[9] The demonstration of the beneficial effects of β-blocker therapy in patients with HF is one of the most important steps forward in the treatment.

Randomized trials with Carvedilol (U.S. Carvedilol Study[10] and COPERNICUS [Carvedilol Prospective Randomized Cumulative Survival],[8,11] metoprolol (MERIT-HF [Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure][12] ,bisoprolol (CIBIS-II [Cardiac Insufficiency Bisoprolol Study II][13] showed that β-blockers reduce morbidity and mortality in HF patients when added to standard therapy. As a result, these agents have received a Class IA recommendation in current HF guidelines.[3,7]

Rationale for β-blocker therapy in heart failure

Left ventricular systolic dysfunction in HF will be compensated by activating the SNS and increasing adrenergic activity to improve cardiac performance.[14,15] 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.[16] 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 HF.[17] Attenuation of these mechanisms is associated with improvement in survival.

Adrenergic stimulation will affect the heart via three adrenergic receptors: β-1, β-2 and α-1, which are present in human cardiac myocytes. β-blockers function by reversibly binding with β- receptors to block the response to sympathetic nerve impulses or catecholamines.[18] Elevated norepinephrine level causes long-term β-receptor down-regulation which results in attenuation of inotropic activity, while α-receptor stimulation leads to myocyte hypertrophy via activation of C-MYC oncogene regulating system [19] thus contributing to a great extent in the remodeling process. It is known that some β-blockers (metoprolol and bisoprolol) cause up-regulation of these receptors carvedilol does not do so, the point which stresses the importance of other mechanisms by which β-blockers improve the situation in HF patients. As the up-regulation process occurs within hours to days of treatment with β-blockers, clinical improvement may take several months to take place. Even it is noticed that ventricular improvement may occur without an increase in β-receptors density.[20]

β-blockers in addition act as anti-ischemic drugs, they prolong coronary diastolic time, inhibit stimulatory anti β1-receptor auto antibodies, augment atrial and brain naturetic peptide, lower plasma endothelin-1 levels (carvedilol), and stimulate the endothelial L-arginine/nitric oxide pathway (nebivolol).[21] Catecholamines cause shifting of substrate utilization from glucose to fatty acids reducing the efficiency of the heart, the process can be reversed by β-blockers.

Low output status and the increased afterload due to vasoconstriction can accelerate the rate of myocardial cell death in the failing heart in addition to apoptosis[22] caused by the direct effect of catecholamines on heart muscles cells. Secondary to sympathetic stimulation vasoconstriction occurs in kidneys thus elevating level of renin-angiotensin, which can contribute further to ventricular remodelling by promoting smooth muscle cell growth via C-FOS oncogene pathway[18], causing smooth muscle cell growth in peripheral vascular network impairing arteriolar dilating ability by inhibiting distensibility, enhancing norepinephrine release and its systemic effect and increasing interstitial deposition of collagen.[23] When all the data were put together, β-blockers exert their greatest beneficial effects through the reduction of SNS activity. Treatment is aimed at halting this increased sympathetic drive and stopping the adverse effects of chronic adrenergic stimulation in chronic HF is being the fundamental basis for the use of β-blockers.

Mechanism of β-blockade in heart failure [23,24]
Upregulation of β-receptors and improved β adrenergic signaling.
Bradycardia (↑coronary blood flow and decreased myocardial oxygen demand).
Protection from catecholamine myocyte toxicity.
Antiarrhythmic effect
Inhibition of RAAS.
Improved ventricular contractility and synchrony
Inhibition of norepinephrine-mediated muscular hypertrophy
Prevention of norepinephrine-mediated apoptosis
Decreased central sympathetic outflow
Increased myocardial catecholamine stores

The Evidence of β-blocker in heart failure

Number of patients with systolic HF assessed in placebo controlled trials for β-blockers exceeds that of patients in trials for ACEI.[25] Three major randomized controlled trials of β-blockers in mild to moderate systolic chronic HF were stopped early because of overwhelming evidence of mortality benefits and concern that patients receiving placebo should not be denied active therapy.[10]

Metoprolol

The first major placebo-controlled multicenter trial of β-blocker on HF, conducted between 1985 and 1991 was the Metoprolol in Dilated Cardiomyopathy (MDC) trial.[26] A total of 383 subjects with HF from idiopathic dilated cardiomyopathy (ejection fraction < 0.40) were randomly assigned to placebo or metoprolol. Most patients (94%) were in NYHA functional classes II and III, and 80% were receiving background treatment. The trial was powered on an expected 50% reduction by metoprolol in the combined end point of all-cause mortality and deterioration of the patient to the point of requiring listing for heart transplantation. MDC also had numerous prespecified secondary end points, which included mortality alone, hospitalizations, left ventricular function, quality of life, and exercise tolerance.[26] During the mean follow-up of 14 months, metoprolol reduced the prevalence of the primary end point of death; or need for cardiac transplantation by 34%, which was not statistically significant.[26] The benefit was entirely due to a reduction in the morbidity end point , in as much as all-cause mortality actually trended greater in the treatment group.[26] In addition, metoprolol improved left ventricular function, quality of life, hospitalizations, and exercise tolerance at 12 months.[26] The results of the MDC trial were viewed as non definitive but quite promising, and they led to a more traditional placebo-controlled mortality trial MERIT-HF.

In MERIT-HF trial, extended release metoprolol was compared with placebo.[12,27] It began enrolling subjects in early 1997 and was stopped prematurely.[12] A total of 3991patients with ischemic and nonischemic dilated cardiomyopathies with NYHA class II to IV and Left ventricular ejection fraction of <40 percent who were receiving digoxin, ACEI and a diuretics were randomly assigned to 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% in one year. This study was terminated early because significant benefits noted in the treatment group. The results showed that in the metoprolol group there was 34% decrease in all cause mortality at 12 months, there was also reduction in the combined end point of death, need for transplant and reduction in the hospitalization for cardiovascular causes or HF. The NYHA class and quality of life also improved. When analyzed by mode of deaths, there were significantly fewer sudden cardiac deaths and fewer deaths from worsening of heart failure in the treatment group.[12, 27]

Carvedilol

Carvedilol is a nonselective β-blocker that also blocks α- receptors and has unique antioxidant properties.[28] The benefits of carvedilol for the treatment of HF have been shown in the 1996 US Carvedilol Heart Failure Study.[29] This study was a compilation of results from four smaller trials that evaluated the effect of carvedilol on morbidity and mortality in patients with HF.[30,31,32] A total of 1094 patients with left ventricular systolic dysfunction (LVEF< 35%) and NYHA class II and IV were enrolled. Patients continued to receive digoxin, diuretics and ACEI, 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. There was 65% reduction of death and 27% risk reduction for hospitalization for cardiovascular causes in the treatment group.

In COPERNICUS, 2,289 patients with severe CHF and a LVEF < 25% were randomized to carvedilol or placebo. Patients were followed for 10.4 months, during which standard treatment for heart failure was continued. Compared with placebo, carvedilol significantly reduced all-cause mortality by 35%[33] combined risk of mortality or hospitalization for any reason by 24%.The trial was prematurely terminated because a significant mortality reduction from carvedilol compared with placebo. 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.[8]

Bisoprolol

Bisoprolol, a highly selective β1-blocker[8] was tested in HF too.CIBIS-1, which was a placebo-controlled trial of the effects of bisoprolol on mortality in symptomatic ischemic or nonischemic cardiomyopathy subjects treated for an average follow-up of 22.8 months.[34] This trial, powered on an unrealistically high expected event rate in the control group, ended up with a statistically insignificant 20% mortality reduction.[34] In addition, the benefit in this trial was confined to subjects with nonischemic cardiomyopathy , compared with those receiving placebo, had a 47% reduction in mortality.[34] Despite the lack of overall statistical significance in the

CIBIS-I trial, the reduction in mortality was similar to that accomplished with ACEI and was viewed as encouraging. This prompted a follow-up trial, CIBIS-II.[13]

The CIBIS-II trial was stopped 18 months early because of a 32% reduction in all-cause mortality in the treatment group.[13] A total of 2647 patients with class III or IV heart failure from ischemic and nonischemic cardiomyopathies were enrolled and followed for a median of 1.3 years.[13] In addition to the reduction in mortality, bisoprolol also reduced hospitalizations and cardiovascular deaths by 20% and 29% respectively. In CIBIS-II, [13] deaths classified as sudden were statistically reduced by 44% in the treatment group, whereas pump failure deaths were nonsignificantly reduced by 26%. This trend in a greater reduction in sudden versus pump failure deaths was opposite to that obtained in CIBIS-I.[34] Another difference between CIBIS-I and CIBIS-II was the effect on ischemic versus nonischemic cardiomyopathy, which also demonstrated opposite trends. In CIBIS-I, [34] the reduction in mortality in the nonischemic group was by 47%, whereas in patients with a history of myocardial infarction, there was a trend to an increase in mortality (by 11%) in the bisoprolol group. One possible explanation for the differences between CIBIS-I and CIBIS-II is the average target doses of bisoprolol used: 10 mg/d in CIBIS-II[13] and 5mg/d in CIBIS-I.34Although CIBIS-II enrolled subjects with NYHA class III (90%of the total) or IV symptoms, the annualized placebo mortality was only 13.2%.[13] Nevertheless, the results of CIBIS-II were internally consistent through all major demographic groups,[13] and the impressive results constitute a landmark clinical trial in the development of β-blockade as a treatment for chronic HF.

Indication of β-blockers

Despite the fact that clinical evidence clearly demonstrates β-blockers reduce morbidity and mortality in patients with HF, still β-blockers are underused in patients with HF.[35] All patients with stable, mild, moderate and severe chronic HF from ischaemic or non-ischaemic cardiomyopathies and reduced left ventricular ejection fraction, in NYHA class II–IV, should be treated with β-blockers, in the absence of contraindication or intolerance.[36,37,38]

β- blocker therapy should be initiated in patients after adequate diueresis and generally following ACEI treatment and the patient should be stabilized and in compensated condition. Contraindications for β-blocker treatment include cardiogenic shock, symptomatic bradycardia without pacemaker, second and third degree AV block; severe asthma and severe chronic obstructive pulmonary disease (COPD).

Initiation of β-blocker

If a patient is considered suitable for β-blocker therapy, a careful initiation and gradual increase of β-blocker dose are crucial to avoid clinical deterioration.[39] Patients should be stable first on the standard therapy, including diuretics, ACEI. Unlike the results of clinical trials with ACE inhibitors, which indicated that the beneficial effects of these drugs could be considered a "class effect." So 2013 ACCF/AHA Heart Failure Guideline recommended using of one of the three beta blockers proven to reduce mortality (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) for all patients with current or prior symptoms of HF, unless contraindicated, to reduce morbidity and mortality.[3]

A β-blocker is added at low starting dose that is gradually increased until the maintenance dose derived from the mortality trials is achieved. The increases of the dose should generally occur at 2-3 weeks interval and patients should undergo reevaluation before any adjustments are made.[40,41]

Table 2: Titration and doses of Different β-blockers (mg)[42]

B-blocker	1st Dose	3rd Week	5th-6th week	Final Dose
Carvedilol	3.125	6.25×2	12.5×2	25×2*
Metoprolol SR	25**	50	100	200
Bisoprolol	1.25	2.5	5	10

*50mg twice daily in patients>85kg, **Reduce initial dose 12.5mg in severe HF

In the beginning of treatment with β-blockers some patients may notice the signs of fatigue. This is due to drop in sympathetic drive.[43]

The Initiation Management Predischarge process for Assessment of Carvedilol Therapy for HeartFailure (IMPACT-HF) trial confirmed that β-blocker can be safely initiated in patients hospitalized for HF prior to discharge.[44] Predischarge initiation significantly increased β-blocker utilization when compared to initiation in the ambulatory setting. The criteria for introduction of a β-blocker are the same as in the outpatient setting. Thus, the drugs can and should be started in all patients with symptomatic HF as soon as they reach the euvolemic state in the absence of contraindications. Patients who do not tolerate the initial dose due to increasing fluid retention, bradycardia (<60 beats/min) or symptomatic hypotension, or SBP <80 mm Hg, can be challenged with half of the initial dose. The dose should be uptitrated approximately every 2 weeks, but some patients will require a longer titration period. It is not uncommon for patients with severe HF to become more symptomatic before improving. A period of 3–6 months to achieve maximal tolerated or target dose

is not uncommon in these severely ill patients. Most patients, however, can be easily titrated up to target dose and surprisingly few experience even transient symptoms of worsening HF as catecholamine stimulation of the heart is progressively blocked. During titration, the patient should be monitored for CHF symptoms, fluid retention, hypotension and bradycardia.[45] In patients who develop evidence of decompensation secondary to fluid retention, it is recommended to reduce the dose of β-blocker by half and double their diuretic dose for 3 days with careful monitoring of body weight, creatinine, and electrolytes. Then uptitration of the β-blocker over the next 2–3 weeks is resumed. In rare cases, patients will develop hypotension, fluid retention, and rapid progression of HF during the initiation/ uptitration phase. These individuals usually require hospitalization for acute HF exacerbation.

In patients with symptomatic hypotension, it is recommeneded to treat this side effect using one or more of the following approaches[46,47]: (1) stop or reduce the dose of other nonessential vasodilators (2) alternate the dosing of RAS blockers in the morning with β-blockers in the evening (when once daily formulations of these agents are being used) or, when both drugs are given on a bid regimen, separate the dosing of the agents by 1–2 hours; (3) administer the β-blocker with meals when its absorption can be delayed by this approach; (4) consider reducing the diuretic dose if the patient is euvolemic; and (5) temporarily reduce the dose of RAS blockers.

Since blood pressure often improves over time with β-blockers, the RAS blockers can often be increased to target dose at a later date. Patients who develop bradycardia should be queried for a history of syncope or presyncope. Asymptomatic patients without AV block and exertional HR >55 require no further intervention. Patients with severe HF and symptomatic bradycardia, or evidence of AV block that limits initiation and/or uptitration of a β-blocker can be considered for a permanent pacemaker.[48]

ACEI or β-blocker; Which One to Start First in Heart Failure Patients?

In patients with HF, measurements of circulating neurohormones indicate an earlier rise of SNS activity than that of RAAS.[49] This temporal sequence of activation of these different neurohormonal systems and their timely blockade are the key to achieve optimal HF therapy.[49] As the SNS appears to become activated before RAAS, it is logical to start with β – blocker before an RAS blocker. Guidelines indicate that ACEI should be used with or without diuretics as first line therapy before treatment with other neurohormonal antagonists. This choice is based upon historical grounds as ACEI are the first drugs to be evaluated and approved for clinical practice. β-blocker should be the first drug to consider in the view of the early activation of the SNS in heart failure, before that of the RAAS.[50] Pretreamtment with a β-blocker prevents ACEI escape and contributes to a greater suppressing effect of ACEI on angitensin II production.[49] Increased renal sympathetic drive promotes salt and water retention; β-blocker may prevent this.[51] It may decrease untoward increase in serum creatinine during ACEI therapy, therby preventing cardiorenal complication.[52] In contrast to ACEI inhibition, β-blocker results in a significant inhibition of ventricular tachy-arrythmias and reduction of sudden death. The latter is particularly important in mild to moderate HF, where a first-line drug will be typically prescribed. Sudden cardiac death is more prominent as a mode of death in these early stages than in more advanced HF.[49]

Data supporting the use of β-blockers in HF patients are relatively more recent and therefore, in practice, these agents are commonly instituted after the ACE inhibitor. However, clinical trial data indicate that the overall impact of β-blockers on the clinical course may be of greater magnitude than that of the RAS blockers and there is evidence from a small recent study that NYHA Functional Class II–III HF patients with idiopathic dilated cardiomyopathy may actually have better outcomes when initially treated with a β-blocker. In this study, patients receiving digoxin and diuretics were randomized to initial therapy of either carvedilol or perindopril, an ACE inhibitor. After 6 months, the carvedilol group was additionally treated with an ACE inhibitor and the perindopril group was started on carvedilol. A functional assessment at 6 and 12 months favored the group initially receiving carvedilol as these patients tolerated a higher dose of the b-blocker and required a lower dose of diuretic, and experienced significant symptomatic improvement and lower plasma NT-BNP.[53]

However, in some recent studies[54,55] β-blockers were given before ACEI which is logical, considering that excess baroreflex-mediated adrenergic activation may be an important initial event in HF.

Initiating the ACE inhibitor first is traditional, the findings of CIBIS III show that it is not the only option. On the contrary, the findings of CIBIS III support a free choice between Bisoprolol and Enalapril as initial therapy. Both strategies have similar safety, and there is no increased risk of worsening of HF associated with a β-blocker-first strategy.[56]

Many clinicians initiate a low dose of ACEI followed by full up-titration of a β-blocker prior to up-titrating the ACEI.[41] In addition; some emerging evidence suggests that the order of initial ACEI or β-blocker therapy may not matter.[57]

CONCLUSIONS

Though the safety and effectiveness of β-blocker in reducing mortality and morbidity in patients with heart failure were proven by multiple randomized controlled trails and were given class I A recommendation in heart failure guidelines it is still underused. A careful initiation and gradual increases of β-blocker dose are crucial. Initiating the ACE inhibitor first is traditional. Recent studies suggest that the order of initial ACEI or β-blocker therapy may not matter. It is recommended that one of the three β-blockers (i.e., bisoprolol, carvedilol, and sustained-release metoprolol succinate) should be used in heart failure patients, unless contraindicated, to reduce morbidity and mortality

REFERENCES

1. Krum H, Jelinek MV, Stewart S, Sindone A, Atherton JJ, Hawkes AL,et al.CHF Guidelines CoreWriters. Guidelines for the prevention, detection and management of people with chronic heart failure in Australia 2006. Med J Aust. 2006; 185:549-57.
2. Stewart S, MacIntyre K, Hole D, Capewell S, McMurray J. More malignant than cancer? Five year survival following a first admission for heart failure. Eur J Heart Failure. 2001; 3:315-22.
3. Yancy CW, Jessup M, Bozkurt B, Masoudi FA, Butler J, McBride PE,et al. ACCF/AHA Task ForceMembers. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice.J Am Coll Cardiol. 2013; 2013; 128: e240-e327.
4. Alan B Miller. Aldosterone antagonism in heart failure. Vasc Health Risk Manag. 2007 October; 3(5): 605–609.
5. Lukasz Dobrek,Piotr Thor. Neuroendocrine activation as a target of modern chronic heart failure pharmacotherapy. Acta Poloniae Pharmaceutica and Drug Research.2011; 68(3): 307-316.
6. Cleland JGF, Swedberg K, PooleWilson PA. Successes and failures of current treatment of heart failure. Lancet.1998; 352 :(suppl 1):1928.
7. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail. 2008; 10:933-89.
8. Packer M, Coats AJ, Fowler MB, et al.Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001; 344:1651-8.
9. John J.V. McMurray. Systolic Heart Failure. N Engl J Med. 2010; 362:228-38.
10. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S.Carvedilol Heart Failure Study Group. N Engl J Med. 1996; 334:1349–55.
11. Packer M, Fowler MB, Roecker EB, et al. Effect of carvedilol on the morbidity of patients with severe chronic heart failure: results of the carvedilol prospective randomized cumulative survival (COPERNICUS) study. Circulation. 2002; 106:2194–9.
12. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353:2001–2006.
13. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353:9 –13.
14. Ferrari R, Ceconi C, Curello S, et al. Activation of the neuroendocrine response in heart failure:adaptive or maladaptive process? Cardiovasc Drugs Ther. 1996:Suppl2:623-9.
15. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart:the new era in the treatment of heart failure. Circulation. 1996;94(9):2285-96.
16. Metra M, Nodari S, D'Alola A, et al. A rationale for the use of beta blockers as standard treatment for heart failure. Am Heart J. 2000;139(3):511-21.
17. Böhm M, Kilter H, Kindermann M. Mechanisms contributing to the progression of left ventricular dysfunction to end-stage heart

failure. Eur Heart J. 2003; 5(1):114-21.

18. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. Circulation. 2000; 101(5):558-69.
19. Colucci W.S., Braunwald E.: Pathophysiology of heart failure. In: Braunwald E. (Ed.): Heart disease. Philadelphia, Saunder 1997.
20. Eichhorn E.J.: The paradox of beta-adrenergic blockade for the management of congestive heart failure. Amer J Cardiol. 1992; 92: 527.538.
21. Cruickshank J.M.: Beta-blockers continue to surprise us. Europ Heart J 2000; 21: 354.364.
22. Metra M., Nodari S., DAloia A. et al. A rationale for the use of betablockers as standard treatment for heart failure. Amer Heart J. 2000; 139; 511—521.
23. Sleiman OI, Murin J, Ghanem WM. Benefits of beta-blockers in heart failure. Bratisl Lek Listy. 2001; 102 (8): 365-369.
24. Opie LH, Gersh BJ . Drugs for the Heart, 7th edn. Philadelphia:Elsevier, 2008.
25. Henry Krum. Consider β blockers for patients with heart failure. BMJ. 2009;338:b1728.
26. Waagstein F, Bristow MR, Swedberg K, Camerini F, Fowler MB,Johnson M, Silver MA, Gilbert EM, Hjalmarson Å. Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet. 1993;342:1441–1446.
27. Hjalmarson A, Goldstein S, Fagerberg B, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations,and well-being in patients with heart failure: the Metoprolol CR/XL randomized intervention trial in congestive heartfailure (MERIT-HF). MERIT-HF study group. JAMA.2000;283:1295.
28. Frishman WH. Carvedilol. N Engl J Med. 1998;339(24):1759-65.
29. Packer M, Bristow MR, Cohn JN, et al. For the US carvedilol heart failure study group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl JMed. 1996;334(21):1349-55.
30. Packer M, Colucci WS, Sackner Bernstein JD, et al. Double blind placebo controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE trial. Prospective randomized evaluation of carvedilol on symptoms and exercise. Circulation. 1996;24:2793-9.
31. Colluci WS, Packer M, Bristow MR, et al. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. Circulation. 1996;94(11):2800-6.
32. Cohn JN, Fowler MB, Bristow MR, et al. Safety and efficacy of carvedilol in severe heart failure. The US Carvedilol HeartFailure Study Group. J Cardiol Fail. 1997;3(3):173-9.
33. Packer M, Coats AJS, Fowler MB, et al. Effect of carvedilol on survival in chronic heart failure. N Engl J Med. 2001;344:1651-8.
34. CIBIS Investigators and Committees. A randomized trial of betablockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation. 1994;90:1765–1773.
35. Komajda M, Follath F, Swedberg K et al. for the study group of diagnosis of the working group on heart failure of the European Society of Cardiology. The Euro heart failure survey programme – asurvey on the quality of care among patients with heart failure in Europe: Part 2: treatment, Eur Heart J. 2003;24:464–74.
36. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult executive summary and recommendations. J Am Coll Cardiol. 2001;38:2101-13.
37. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure) ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult 2002. Available from: http://www.acc.org.
38. Remme WJ, Swedberg K et al for the task force for the diagnosis and treatment of chronic heart failure, European Society of Cardiology.Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J. 2001;22:1527–60.
39. Eichhorn EJ, Bristow MR. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure.Am J Cardiol. 1997;79:794-8.
40. Gottlieb SS, Fisher ML, Kjekshus J, et al. Tolerability of beta-blocker initiation and titration in the Metoprolol CR/XL randomized intervention trial in congestive heart failure (MERIT-HF). Circulation. 2002;105:1182.
41. Wikstrand J, Hjalmarson A, Waagstein F, et al. Dose of metoprolol CR/XL and clinical outcomes in patients with heart failure.

Analysis of the experience in Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure (MERIT-HR). J Am Coll Cardiol. 2002;40:491.

42. Opie LH, Gersh BJ . Drugs for the Heart, 8th edn. Philadelphia:Elsevier, 2013.
43. Daulat Manurung, et al. Beta Blockers for Congestive Heart Failure. Acta Med Indones-Indones J Intern Med.2007; 39(1):44-48.
44. Gattis WA, et al. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACTHF) trial. J Am Coll Cardiol. 2004;43(9):1534–1541.
45. Task Force for the Diagnosis and Treatment of Chronic Heart Failure,European Society of Cardiology: W. J. Remme and K. Swedberg (Co-Chairmen). Guidelines for the diagnosis and treatment of chronic heart failure. Eur Heart J 2001; 22:1527-60.
46. William T.Abraham, Henry Krum. Heart Failure A Practical Approach to Treatment. McGRAW-HILL.2007.
47. Mann D L. Heart failure a companion to Braunwald's heart disease.2nd edn. Saunders:Elsevier,2011.
48. Gregoratos G, et al. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association task Force on Practice Guidelines (ACC/ AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). Circulation. 2002;106(16): 2145–2161.
49. Willem J Remme.bera blockers or Angiotensin-coverting-enzyme Inhibitor/angiotensin receptor blocker:what should be first?.Cardiol Clin.2007; 25: 581-594.
50. Francis GS,Benedict C,Johnston DE, et al .Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure:a substudy of the studies of left ventricular dysfunction (SOLVD).Circulation 1990;82:1724-9.
51. Schrier RW,Abraham WT.Hormones and hemodynamics in heart failure.N Engl J Med 1999;341:577-85.
52. Knight EL,Glynn RJ,McIntyre KM et al.Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy:results from the studies of left ventricular dysfunction(SOLVD).Am Heart J. 1999;138:849-55.
53. Poole-Wilson PA, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. Lancet. 2003;362(9377):7–13.
54. Sliwa K,et al. Impact of initiating carvedilol beforeangiotensin-converting enzyme inhibitor therapy on cardiac function in newly diagnosed heart failure.J Am Coll Cardiol. 2004;44:1825-1830.
55. Willenheimer R, et al.Effect on survival and hospitalization of initiating treatment for chronic heart failure with bisoprolol followed by enalapril,as compared with the opposite sequenc:results of the randomized Cardiac Insufficiency Bisoprolol Study (CIBIS) III. Circulation. 2005;112:2426-35.
56. Ronnie Willenheimer. The current role of beta-blockers in chronic heart failure: with special emphasis on the CIBIS III trial. European Heart Journal Supplements.2009; 11 (Supplement A), A15–A20.
57. Funck-Brentano C, et al. CIBIS-III investigators, Influence of order and type of drug (bisoprolol vs. enalapril) on outcome and adverse events in patients with chronic heart failure: a post hoc analysis of the CIBIS-III trial.Eup J Heart Fail. 2011;13:765-72.