

Beta-Adrenergic Blocking Agents in Heart Failure

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Cardiac dysfunction in heart failure is widely recognized as a progressive process, regardless of the clinical signs and symptoms. An increase in cardiac sympathetic drive is one of the earliest neurohormonal responses occurring in patients with heart failure and may be one of the major causes of the progressive remodeling leading to the decline in myocardial function, and responsible for the poor prognosis of patients with heart failure. Therefore, recent data provided by several appropriately designed clinical trials clearly indicate the benefits of β -adrenoceptor blocking agents, combined with diuretics, ACE inhibitors, and digoxin in chronic heart failure class II to IV due to systolic ventricular dysfunction. The benefits are related to symptoms, functional capacity, remodeling, and improvement in left ventricular function, reduction in cardiovascular hospitalization, a decrease in the overall and sudden cardiac death rate, and are similar in patients with ischemic or nonischemic cardiomyopathy, independent of age, gender, or functional class. In this review we describe the cardiovascular effects of the increase in sympathetic drive, the pharmacological properties of the beta-blockers most evaluated in heart failure therapy (metoprolol, bisoprolol, and carvedilol), the major clinical trials related to these agents in heart failure, the recommendations for their appropriate use in clinical practice, the precautions to be adopted, and how to handle the more common adverse reactions.

For the last few years, β -adrenergic blocking agents have been contraindicated in the presence of overt heart failure or systolic ventricular dysfunction, even though patients were asymptomatic. Such contraindication was based on inotropic and chronotropic negative activity of β -blocking drugs and their adverse acute hemodynamic effects.

As the failing heart depends on β -adrenergic support to maintain its performance, acute pharmacological effects of any antiadrenergic compound may induce myocardial depression and a decrease in cardiac output. Although such effects may be counteracted by the vasodilatory properties of some β -blocking drugs, which by reducing systemic vascular resistance could counteract myocardial depres-

sion, an abrupt suppression of adrenergic support may initially precipitate a clinical worsening of heart failure. Nevertheless, this negative pharmacological response is transitory and manageable by administration of initial low doses and gradual dosage increase¹. Additionally, chronic effects of β -blocking agents differ from the acute effects because they result essentially from the inhibition of neurohormonal responses that aggravate heart failure, favorably changing myocardium biology².

For many years, the purely hemodynamic concept of heart failure has prevailed, with reflex vasoconstriction yielding a pre- and afterload increase, resulting in additional hemodynamic worsening. Based on this concept, it has been recognized that the effective therapy for heart failure should be based on positive inotropic agents and reduction in excessive overload, with vasodilating and diuretic agents. This strategy, intended only to correct hemodynamic disturbances, may improve symptoms, functional capacity, and quality of life, but neither prevents long-term progression of heart failure nor decreases mortality.

It has been recently hypothesized that heart failure is an entity with a progressive decline in ventricular function due to progressive myocyte dysfunction (caused by gene expression changes), loss of cells (due to necrosis and apoptosis), and subsequent cell and cardiac chamber remodeling³. The remodeling process results in ventricular enlargement, an increase in wall stress, relative myocardial ischemia, energy depletion, progressive interstitial fibrosis, and additional activation of sympathetic nervous and renin-angiotensin-aldosterone systems³.

This sequence of events is essentially mediated by activation of neurohormonal and autocrine/paracrine systems that provoke vasoconstriction, sodium and water retention, and stimulate growth promotion pathways. Of these, the sympathetic nervous system and the renin-angiotensin-aldosterone system play a crucial role. The knowledge of these data led to a change in the paradigm of exclusively hemodynamic and symptomatic control to the treatment of subsequent remodeling pathophysiological processes, which aggravate myocyte biology and heart failure evolution.

Effects of sympathetic hyperactivity

Cardiac sympathetic activity increase and elevated

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plasma norepinephrine levels are reactions that occur early in heart failure patients. They may be already detected in asymptomatic left ventricular dysfunction⁴ and increase as the syndrome progresses⁵⁻⁸. At the same time, myocardial catecholamines become depleted due to norepinephrine synthesis and the captation defect.

Sympathetic activation leads to an increase in heart rate, arteriolar vasoconstriction, and peripheral vascular resistance and to a decrease in blood flow and sodium excretion, consequently increasing ventricular volume and pressure. Cardiac work and oxygen consumption increase. Norepinephrine may induce myocardial hypertrophy, but reduces coronary circulation's ability to adequately supply blood to an enlarged ventricular wall, leading to myocardial ischemia⁹. Sympathetic activation may also provoke arrhythmias by enhancing cardiac automaticity and β_2 -mediated ischemia and hypocalcemia¹⁰. Additionally, norepinephrine exerts direct toxic effects on the myocardium, causing myocyte dysfunction and necrosis by several mechanisms. β_1 - and β_2 -receptor stimulation provokes cyclic adenosine monophosphate (cAMP)-mediated calcium overload in cardiac myocytes, and activates calcium-dependent ATPases, decreasing the availability of highly energetic phosphates, further worsening mitochondrial function¹¹. In addition, by stimulating growth and oxidative stress in terminally differentiated cells, norepinephrine can trigger apoptosis^{12,13}.

Several studies have demonstrated that elevated cardiac sympathetic activity is one of the leading causes of the progressive decline in myocardial function and of a poor prognosis in heart failure patients^{8,14}. Plasma norepinephrine levels have a high prognostic value, independent of other variables related to left ventricular function^{14,15}.

Finally, β_1 -receptor activation stimulates renin secretion by nephron juxtaglomerular cells and augments angiotensin II synthesis, which is also toxic to cardiac myocytes¹⁶, besides causing venous and arterial vasoconstriction, sodium and water retention, and pre- and afterload increase¹⁷. On the other hand, the activated renin-angiotensin-aldosterone system further stimulates norepinephrine release, establishing a vicious circle that adversely affects hemodynamic parameters and enhances remodeling¹⁸.

The recognition of deleterious effects provoked by the sympathetic nervous system in left ventricular systolic function and the potential inhibition of sympathetic-adrenergic stimulation by chronic therapy with β -blocking drugs led to an increased administration of such drugs in heart failure management.

β_1 -adrenergic receptor selectivity and regulation

Approximately 80% of adrenergic receptors in normal myocardium are subtype β_1 . Their stimulation regulates the activity of adenylate cyclase via G proteins, increasing intracellular concentration of cyclic adenosine monophosphate (cAMP), responsible for most effects of beta-adrenergic hyperactivity. In heart failure, chronic sympathetic activation leads to a down-regulation of β_1 -receptors, accompanied by a proportional reduction in agonist-induced

adenylate cyclase activity and myocardial contraction, whereas the density of β_2 -receptors remains constant¹⁹⁻²¹. Consequently, in the failing heart, the proportion of β_2 -receptors increases up to 40%²².

The density of β_1 -receptors increases with the use of selective agents, but does not change with carvedilol²³. The up-regulation of β_1 -adrenergic receptors observed with metoprolol may allow the persistence of sufficient sensitivity to sympathetic stimulation, when increased (e.g. during maximum exercise). However, it can diminish cardiac protection to the undesirable effects of such stimulation²². Pathophysiological evidence indicates that β_2 - and α_1 -adrenergic receptors also play an important role in the pathogenesis of heart failure.

β_2 - and α_1 -adrenergic receptor blockade

Adrenergic receptor subtype β_2 may represent up to 40% of the total adrenergic receptors in the failing heart secondary to β_1 -receptor down-regulation. In addition, these receptors may mediate all cAMP-dependent sympathetic stimulation effects, generally attributable only to β_1 -receptors²². Presynaptic β_2 -receptors facilitate norepinephrine release²⁴. Thus, nonselective agents, which primarily block presynaptic β_2 -receptors, may decrease cardiac release of norepinephrine²³ and plasma norepinephrine levels, not observed with selective agents. β_2 -adrenergic receptors may be responsible for arrhythmogenic effects of sympathetic stimulation, as well as by facilitating secondary hypocalcemia due to potassium deviation into cells²².

The stimulation of α_1 -receptors, which represent the near totality of α -receptors in the myocardium, induces phosphatidylinositol hydrolysis, resulting in inositol triphosphate formation and calcium release from intracellular deposits^{23,24}. The percentage of α_1 -receptors in the heart's total population of adrenergic receptors ranges from 2% to 23% and increases in heart failure, although it remains much lower than the β -receptor percentage.

Deleterious effects of sympathetic hyperactivity mediated by β_1 -, β_2 - and α_1 -receptors are summarized in Table I.

Classification of β -blocking agents

β -blocking drugs constitute a heterogeneous class of agents. The most important differences are related to the degree of selectivity of β_1 -adrenergic receptors and the presence of additional properties. Based on these characteristics, β -blocking agents have been categorized into three classes^{24a}. *First generation agents*, such as propranolol and timolol, block both β_1 - and β_2 -receptors and do not exhibit any particular property. These agents are not well tolerated in heart failure because they exhibit negative inotropic effects associated with an increase in peripheral vascular resistance, secondary to β_2 -blockade^{24a}. *Second generation agents*, such as metoprolol, atenolol, and bisoprolol produce a selective β_1 -blockade and do not have additional properties. They do not increase peripheral vascular resistance and are better tolerated by heart failure patients. Ho-

Table I – Effect of different adrenergic receptor activation in heart failure

β_1-adrenergic receptor	
-	cAMP-mediated effects
-	Enhanced excitability and contractility – Tachycardia
-	Tachyarrhythmia induction
-	Myocardial hypertrophy and remodeling
-	Accelerated cellular death
-	Renin release stimulation
β_2-adrenergic receptor	
-	cAMP-mediated effects (less intense)
-	Tachyarrhythmia induction
-	Presynaptic norepinephrine release stimulation
α_1-adrenergic receptor	
-	Vasoconstriction (systemic, coronary and renal)
-	Tachyarrhythmia induction
-	Myocardial hypertrophy and remodeling
-	Sodium and water retention

wever, acute administration may produce a decline in cardiac output and an increase in ventricular filling pressure due to negative inotropic effects^{24b}. *Third generation agents*, such as bucindolol and carvedilol, are not selective but exhibit ancillary properties, which may be important to their tolerability and efficacy in heart failure patients^{24a}.

Mechanism of action of b-blocking agents

The potential benefit of β -blocking agents as a group in heart failure results from their hemodynamic, electrophysiological, and most of all, neurohormonal action.

Hemodynamic effects during chronic administration differ in many aspects from the acute effects. A reduction in myocardial oxygen consumption associated with a decrease in heart rate may prolong coronary perfusion time by prolonging diastole, with favorable effects on myocardial ischemia. Initially, systolic blood pressure tends to fall, but subsequently stabilizes²⁵.

By preventing an increase in cAMP and calcium myocardial overload, as well as calcium-dependent ATPases activation, and consequently, the reduction in highly energetic phosphates resulting from β -receptor activation, β -blocking agents may preserve myocardial structure and function. These benefits are probably independent of the hemodynamic effects and occur after chronic administration, so clinical benefits may take weeks or even months to become apparent. β -adrenergic blockade may, in addition, reduce cardiac arrhythmias, by reducing heart rate, improving ventricular function and through electrophysiological effects (automaticity reduction), besides preventing the occurrence of hypocalcemia¹⁰.

Long-term administration of β -blocking agents in heart failure determines an increase in left ventricle ejection fraction^{1,26-35}, the magnitude of which is greater than that observed with any other drug, progressive reduction in left ventricular volumes²⁶⁻³⁰ and myocardial mass^{1,27}, further improving left ventricular geometry, which becomes less spherical in shape, and decreasing mitral regurgitation³⁶. In this

way, β -blocking agents may reverse all ventricular remodeling-associated changes³⁷. In general, such a process begins two months after the introduction of therapy and continues for 12 to 18 months³⁸. Some authors have postulated that β -blocking agents reverse intrinsic systolic dysfunction through time-dependent biological effects in cardiac myocytes^{2,3}.

Parasympathetic activity is reduced in heart failure. β -adrenergic blocking agents reset baroreceptor sensitivity, increasing parasympathetic tonus³⁸, reducing tachycardia and arrhythmias, and improving the energy reserve of the heart.

The blockade of β_1 -adrenergic receptors inhibits renin formation and renin-angiotensin-aldosterone system activity, partly counteracting its deleterious effect in heart failure¹⁷. Angiotensin-converting enzyme inhibitors and β -blocking agents act synergically.

In the Caribe Study^{38a} the carvedilol effects on adrenergic neuronal function were investigated in 30 patients with congestive heart failure (functional class II/III) due to dilated cardiomyopathy. The adrenergic neuronal function was evaluated by iodine-123 metaiodobenzylguanidine (norepinephrine analogue) myocardial scintigraphy (MIBG) with early and delayed uptakes to determine the early heart to mediastinum (H/M) activity ratio. The beneficial effects on left ventricular ejection fraction with carvedilol were observed in early (2 or 3 months) and late follow-up (6 months); however, increments in cardiac MIBG uptake were found only in late follow-up. Carvedilol treatment is associated with changes in cardiac adrenergic neuronal function in congestive heart failure.

Pharmacological properties of the most common b-blocking agents used in heart failure therapy

Relevant pharmacological properties of the most commonly used β -blocking agents in the management of heart failure are summarized in Table 2. These properties may be important in the beginning of therapy, as well as in long-term treatment.

β_1 selectivity – In usual dosages, β_1 selective agents do not block peripheral β_2 -receptors (vasodilators) and do not increase peripheral vascular resistance, representing a favorable property in heart failure. However, as up to 40%

Table II - Pharmacological properties of most used b-blocking agents in heart failure therapy

	β_1 -blockade	β_2 -blockade	α_1 -blockade vasodilation	Antioxidative activity
Metoprolol	++	-	-	-
Bisoprolol	++	-	-	-
Bucindolol	++	+	+(dv)	-
Carvedilol	++	++	+(α 1)	+

dv- direct vasodilation.

of receptors in the failing myocardium are subtype β_2 , it has been proposed that blockade of β_2 -receptors may be important in the management of heart failure and that non-selective compounds are more effective³⁹.

α_1 -adrenergic receptor blockade—Blockade of α_1 -receptors in the systemic vascular bed produces vasodilation, reduces preload, afterload, and myocardium oxygen consumption. As α_1 -receptors' proportion in the human heart, even though failing, is small, α_1 -blockade may reduce cardiac overload without causing significant inotropic or chronotropic effects⁴⁰. At the beginning of therapy, peripheral vasodilation is important, because it may counteract the negative inotropic effect of β -blockade. Such an effect may explain why, contrary to second generation agents, the acute administration of carvedilol does not produce a decrease in cardiac output⁴¹. At the level of the coronary bed, stimulation of α_1 -receptors induces vasoconstriction; blockade of those receptors induce vasodilation and may counteract vasoconstriction provoked by chronic sympathetic activation, improving coronary blood flow.

Chronic α_1 -receptor stimulation results in cardiac myocyte hypertrophy and may contribute to the development of catecholamine-induced cardiomyopathy⁴². Findings of recent studies in cultured myocytes of newborn rats have shown that carvedilol may prevent the development of phenylephrine-induced hypertrophy, most probably because of its antagonist effect at the level of α -adrenergic receptors⁴³. In the kidney, stimulation of α_1 -receptors may increase tubular reabsorption of sodium and provoke ion retention. It has been shown in a double-blind study that carvedilol increases blood flow and improves renal hemodynamics, not observed with placebo or metoprolol⁴⁴. These data suggest that agents that are able to block both β_2 - and α_1 -receptors may have an additional advantage for the management of heart failure and may exert greater protection against toxic and arrhythmogenic effects of catecholamines³⁷.

Antiproliferative activity - Both carvedilol and propranolol inhibit vascular smooth muscle cell proliferation in the rat aorta, both in baseline conditions and after endothelin-1 stimulation⁴⁵. *In vitro*, carvedilol inhibits human vascular smooth muscle cell proliferation⁴⁶. The observation that some β -blocking agents, but not others, have antiproliferative activity suggests that such property is independent of β -blockade.

Antioxidative activity—Although the precise mechanism of cardiac alteration caused by an increased production of free radicals of oxygen have not been fully clarified, increasing data point to the role of oxidative stress in heart failure⁴⁵. Free radicals of oxygen have been involved in myocardial injury that occurs during ischemia and reperfusion⁴⁷, but may be important in heart failure even in the absence of myocardial ischemia⁴⁸. A possible effect of oxidative stress is the induction of apoptosis, which may fur-

ther deteriorate structure and cardiac function. Experimentally, several studies have reported increased apoptosis in myocardial infarction, cardiomyopathy, and advanced heart failure, through an up-regulation of different genes, like p53, Fas, or p38 MAP kinase^{49,50}. Mitochondria, as the main source of free radicals of oxygen in every cell, may cause apoptosis via caspase-activating protein release, particularly C-cytochrome and associated-cytosolic factors⁵¹.

Endothelium is a particularly susceptible structure in heart failure. Oxidative stress-mediated apoptosis may play a role in the pathogenesis of endothelial dysfunction, although it may also be related to many other causes, such as abnormal regional blood flow, cytokines, and neurohormonal activation^{52,53}.

Carvedilol is a potent antioxidative agent, with a 10-fold greater activity than vitamin E; this property derives from the carbazole portion of its chemical structure. Some carvedilol metabolites found in human plasma exhibit an antioxidative activity approximately 50- to 100-fold greater to inhibit LDL-oxidation by macrophages^{53,54}. Physicochemical, biochemical, and cellular studies and *in vivo* experimental models have established the antioxidative ability of carvedilol that may be summarized as follows:^{43,55}.

1) Based on paramagnetic electron resonance studies, carvedilol, directly and in a dose-dependent mode, removes free radicals of oxygen and protects cardiac membranes from lipid peroxidation induced by them, both *in vivo* and *in vitro*⁵⁶.

2) Carvedilol prevents vitamin E, glutathion and SH protein depletion induced by oxidative stress, the main defense mechanisms against tissue injury caused by free radicals⁵⁷.

3) In equivalent concentrations to those obtained from plasma with therapeutic doses, 25 to 50mg OD, this compound may block bovine and human endothelial cell injury and death, caused by exposure to hydroxide and hydrogen peroxide radicals⁵⁵.

4) Carvedilol also exerts cardioprotective effects during ischemia-reperfusion injury, with marked inhibition of apoptosis in several experimental models⁵⁵. However, it must be noted that the clinical importance of antiproliferative and antioxidative properties of carvedilol have not been demonstrated yet.

These unique properties of carvedilol, a third generation agent, which causes multiple adrenergic (β_1 , β_2 and α_1) blockade, besides its antioxidative and antiproliferative effects, may be important in preventing progressive deterioration of left ventricular dysfunction and heart failure.

Heart failure clinical trials

The favorable clinical effects of β -adrenergic blockade in heart failure were initially reported by Waagstein et al⁵⁸ and Swedberg et al^{59,60} in patients with dilated cardiomyopathy. Results of these studies were initially accepted with skepticism because the number of patients was too small, the studies were not controlled, and the

hemodynamic concept still predominated over the importance of sympathetic activity to maintain cardiac function in heart failure. However, beneficial effects obtained through β -blockade in postmyocardial infarction, including patients with left ventricular dysfunction, have encouraged researchers to carry out multiple double-blind, randomized, controlled trials in heart failure, some of them small, others involving great numbers of patients, mainly in the last decade. These studies have consistently shown that the chronic addition of a β -blocking agent to the standard heart failure therapy with diuretics, ACE inhibitors, and digoxin leads to improvement in symptoms, functional class, and left ventricular function. The increase in left ventricular ejection fraction after long-term β -blockade is greater than that observed with any other drug used in heart failure therapy^{3,8}. Moreover, despite an initial clinical worsening, in a few cases, probably because of withdrawal of adrenergic support, the studies demonstrate long-term clinical improvement in the course of heart failure, with a reduction in worsening episodes and need of hospitalization in patients treated with β -blocking agents^{3,8}. Subsequently, a significant reduction in mortality rates has also been demonstrated after the introduction of β -blocking therapy.

The most commonly used drugs in such trials, which included around 10,000 patients, were metoprolol, bisoprolol, and carvedilol. We will only describe trials with the greatest number of patients and of clinical relevance.

Metoprolol trials

The, Metoprolol in Dilated Cardiomyopathy study (MDC)²⁸, included 383 patients with nonischemic dilated cardiomyopathy and mild-to-moderate heart failure, randomized to receive either placebo or metoprolol in addition to standard therapy during 12-18 months. The initial dosage of metoprolol was 5mg BID, gradually increased up to 50-75mg BID. The primary endpoint in this study was combined risk of death and worsening heart failure sufficient enough to refer these patients for heart transplantation. The percentage of patients that reached the combined objective was lower in the metoprolol group (13% vs. 20%), i.e., risk reduction of 34% with a boundary significance ($p=0.058$). The overall mortality between groups was not different.

The Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF)⁶¹ involved 3,991 heart failure patients predominantly with New York Heart Association functional class II-III and a few with functional class IV, of both ischemic and nonischemic etiology. Subjects were randomized to receive either placebo or metoprolol (increasing dosages up to a maximum of 200mg daily), in addition to standard therapy during 6 to 20 months. All-cause mortality, the primary endpoint of the study, was reduced by 34% in the metoprolol group ($p=0.00015$).

Bisoprolol trials

The efficacy of bisoprolol, a selective β_1 -adrenergic receptor blocker for the treatment of heart failure, has been evaluated in two major trials. The first one, Cardiac Insuf-

iciency Bisoprolol Study (CIBIS I)⁶², included 641 patients with ischemic or nonischemic, mild-to-moderate heart failure, randomized to receive either placebo or bisoprolol (1.25mg daily up to 5.0mg daily) in addition to standard therapy for a period of 4 to 44 months (mean 23 months). The treatment with bisoprolol was associated with a 20% reduction ($p=0.22$) in all-cause mortality, the primary endpoint of the study, and to a 34% reduction ($p<0.01$) in hospitalization risk due to heart failure, an important secondary endpoint.

The second Cardiac Insufficiency Bisoprolol Study (CIBIS II)⁶³, included 2,647 patients with left ventricular ejection fraction ≤ 0.35 and moderate-to-severe heart failure (most functional class III) due to ischemic cardiomyopathy or not. Patients were randomly assigned to either placebo or bisoprolol (1.25mg up to a maximum of 10mg daily) in addition to standard therapy. The mean follow-up period was 1.3 years. Therapy with bisoprolol was associated with a 34% reduction in all-cause mortality (11.8% vs. 17.3%, $p<0.0001$); 44% reduction in sudden death (3.6% vs. 6.3%, $p=0.0011$); and 32% risk reduction in hospitalization for worsening heart failure ($p<0.0001$). The study was terminated early after a second interim analysis.

Carvedilol trials

Many studies have been conducted with carvedilol, but we will report results of only five prospective, randomized, controlled trials with adequate numbers of subjects. The Australia New Zealand Heart Failure Research (ANZ)³⁴ involved 415 patients with mild-to-moderate heart failure of ischemic etiology. Placebo or carvedilol (3.125 mg BID up to 25 mg BID) were administered concomitantly with the standard therapy for a 15- to 24-month period (mean 19 months). The primary objective of the study was to evaluate the efficacy of therapy in clinical progression of the syndrome, as defined by combined risk of all-cause mortality and need of hospitalization. In the carvedilol group, clinical progression was reduced by 26% ($p=0.02$) and hospitalization risk by 23% ($p=0.05$).

A multicenter program conducted in the United States – US Heart Failure Study⁶⁴ – included 1,094 patients with LVEF $\leq 0.35\%$, heart failure class II-IV, distributed into 4 protocols depending on patients' performance in a 6-minute walk test. All patients were receiving diuretics, ACE inhibitor, and digoxin and were randomly assigned to receive either placebo or carvedilol (6.25 mg to 25 mg BID).

In the mild-to-moderate heart failure study, 366 patients capable of walking 450 to 550 m in 6 minutes, while receiving optimal standard therapy, were randomized to receive carvedilol or placebo and followed for a 12-month period. The primary objective was clinical progression as defined by heart failure death, need of hospitalization, or increasing need of a specific medication. Clinical progression occurred in 21% of patients in the placebo group and in 11% of patients in the carvedilol group, a risk reduction of 48% (RR, 0.52; 95% CI, 0.32-0.85; $p=0.008$). Moreover, therapy with carvedilol has been associated with a 77% decrease in

overall mortality ($p=0.048$).

The PRECISE trial – Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise³¹ – involved 278 patients with moderate-to-severe heart failure (6-minute walk test, 150 to 450m). Patients were randomly assigned to receive either placebo or carvedilol, added to the standard therapy, during a 6-month period. Compared with placebo, carvedilol-treated patients demonstrated higher symptomatic improvement rates and lower risk of clinical worsening, as assessed by functional class shift ($p=0.014$). In addition, therapy with carvedilol was associated with a significant increase in ejection fraction ($p<0.001$) and to a significant reduction in the combined endpoint of morbidity and mortality ($p=0.029$), with a small increase in exercise tolerance, but no differences in quality of life scores. Effects were similar in patients with both ischemic and idiopathic dilated cardiomyopathy.

In another moderate-to-severe heart failure study, Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA)³³, 345 patients with both ischemic and non-ischemic cardiomyopathy were randomly assigned to either placebo or carvedilol (6.25mg, 12.5mg, or 25mg BID) for a 6-month treatment period. Results demonstrated that carvedilol did not exert a significant effect on submaximal exercise (primary endpoint). However, it was associated with a dose-dependent increase in ejection fraction (5, 6, and 8 units in low, medium, and high dosages, respectively, compared with 2 units in the placebo group; $p<0.001$ for a dose-dependent response) and survival rates (mortality rates 6.0%, 6.7%, and 1.1% with increasing carvedilol dosage vs. 15.5% in the placebo group; $p<0.001$). For the three combined carvedilol groups, all-cause mortality risk was reduced by 73% ($p<0.001$) and hospitalization risk by 58% to 64% ($p=0.01$).

In a severe heart failure⁶⁶ study (6-minute walk test less than 145m), 105 patients were randomly assigned to either placebo or carvedilol (up to 25mg BID), added to the standard therapy for up to an 8-month treatment period (mean 3 months). Carvedilol therapy was associated with a lower risk of worsening heart failure, but the number of deaths and hospitalizations was too small to allow an expressive analysis in this class IV group.

Results of combined data derived from these four multicenter studies that involved 1,094 patients with chronic HF have shown that the overall mortality rate was 7.8% in the placebo group and 3.2% in the carvedilol group (a 65% risk reduction; 95% CI, 39-80; $p<0.001$)⁶⁴. Moreover, carvedilol treatment was associated with a 27% reduction in hospitalization risk for cardiovascular cause ($p=0.036$) and to a 38% reduction in the combined risk of death and hospitalization ($p<0.001$). Analysis of these data led to an early termination of the study. Subsequently, the Food and Drug Administration approved the drug for use in chronic heart failure.

Bucindolol trial

The Beta-Blocking Evaluation of Survival Trial – BEST has evaluated bucindolol's efficacy in reducing mortality in chronic heart failure patients. The study was interrupted

early because bucindolol did not show a beneficial effect compared with placebo. Although bucindolol exhibits both β_1 - and β_2 -adrenergic blocking and vasodilating effects, it seems to also exhibit intrinsic sympathomimetic activity, which could be responsible for the absence of a mortality benefit in the BEST trial.

b-blocking agents in clinical practice

Patients with chronic stable class II or III heart failure (EF <35-45%) due to left ventricular systolic dysfunction should receive a β -adrenergic blocking agent, additionally to diuretics and ACE inhibitors, with or without digoxin, except if unable to tolerate the drug or in the presence of a contraindication to its use^{6,67}. Therapy with β -blocking agents must not be delayed until patients develop resistance to standard drugs because such patients may die during this delay period, and mortality could be reduced if treatment were introduced early⁶.

Carvedilol's efficacy and tolerability were both assessed in another study in 63 heart failure patients in NYHA class IV compared with 167 patients with other functional classes. Although class IV patients experienced more adverse effects during the initial and dose titration period, they also experienced long-term symptom improvement as well as a significant improvement in left ventricular function and measurements⁶⁸. However, the number of NYHA class IV patients included in major trials until recently was too small to permit any conclusion or recommendation.

The Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) included 2,200 patients and evaluated carvedilol's comparative efficacy versus placebo on mortality in class IV heart failure patients. Its results were expected in 2001. However, on March 2000, the Data and Safety Monitoring Board of the COPERNICUS study recommended the termination of the trial because of overwhelming evidence of a favorable effect on survival. Preliminary estimates suggest that the magnitude of the survival effect is larger than that reported in other beta-blocker survival trials, exceeded the prespecified boundaries that were set up at the start of the study, and was similar across all predefined subgroups (www.theheart.org/documents, March 21, 2000).

Nevertheless, the use of a beta-blocker in such patients should be done carefully and restricted to physicians with sufficient experience in heart failure management, preferably initiated during an in-hospital stay.

Although some hypoglycemia signs may be blunted by β -adrenergic blocking agents, patients with diabetes mellitus have also demonstrated a significant reduction in morbidity and mortality⁶⁷.

Contraindications to β -adrenergic blocking agent use are bradycardia, especially symptomatic, advanced atrioventricular (AV) block (except patients with a pacemaker), hypotension (systolic blood pressure <90 or 85mmHg), and the presence of bronchospastic disease. β -blocking agents should not be introduced to patients with overt heart failure,

especially acute or that requiring treatment with i.v. β -agonist inotropic agents, to support circulatory function.

Dosage

Therapy with β -blocking agents should be introduced in very low doses: carvedilol, 3.125mg BID; metoprolol extended release, 12.5mg once daily; bisoprolol, 1.25mg once daily. Dosage increase should be performed gradually, doubling dose (if well tolerated) every 2 to 4 weeks. Should any adverse effect occur, dosage increase must be postponed until the side effects have disappeared. Maximum daily doses are: carvedilol, 25mg BID; however, in some studies the target dose was 50mg BID in patients above 85kg in weight; metoprolol ER 200mg OD; bisoprolol, 10mg OD^{66,69}.

It is advisable to follow up patients for up to two hours after the initial dose has been administered and at each dosage increase. Alternatively, administration of a β -blocking agent may be at bedtime.

The patients must be strictly monitored for blood pressure, heart rate, fluid retention (body weight), or worsening heart failure, during initial and titration periods. As fluid depletion may potentiate the risk of hypotension and fluid retention may enhance the possibility of worsening heart failure, diuretic doses (as well as ACE inhibitor and digoxin) must be optimized before and during treatment with a β -blocking agent. Compliance with these items permits early management of β -blocking-associated adverse effects while maintaining its administration⁶⁶. In major carvedilol trials, approximately 90% of patients have tolerated both short- and long-term treatment⁶⁴. Therefore, after the maximum individual dose has been achieved, patients may be kept on long-term treatment without difficulty.

Similarly to ACE inhibitor trials, in β -adrenergic blocking drugs trials, the dose has not been defined by the patient's therapeutic response, but has been increased up to a predetermined target dose, except in cases in which lower doses have not been well tolerated. Although in the MOCHA³³ study, the target dose of carvedilol (25mg BID) was more effective than lower doses, the latter were also associated with significant benefit in left ventricular function, morbidity, and mortality. Therefore, if the patient cannot achieve the target dose, lower doses of carvedilol, 6.25 or 12.5mg BID, have been demonstrated to be effective and should be maintained if higher doses are not tolerated.

Two relevant aspects of therapy with β -blocking agents in heart failure must be emphasized and told to patients: 1) initial adverse effects are usually transitory and in general do not lead to treatment interruption; 2) clinical response may take weeks or up to 2-3 months to become apparent¹. Although patients' symptoms do not improve over a short-term period, therapy should be continuously maintained to reduce the risk of important clinical events. Therapy with β -blocking agents must not be abruptly interrupted in patients with ischemic cardiomyopathy.

In major controlled trials, the proportion of patients

who withdraw from studies of β -blocking agents was similar or even lower than in placebo groups (Table III).

These data demonstrate that if initial therapy and titration, as well as other usage recommendations, are strictly observed, these drugs are much better tolerated than once supposed.

Management of adverse effects and warnings

Most common adverse effects, especially during the initial therapy or titration period, which require careful attention and appropriate management, are: hypotension, bradycardia and AV block, fluid retention, and worsening heart failure.

Hypotension – Hypotension, especially orthostatic, may occur during β -blocking therapy, mainly with agents that also block α_1 -adrenergic receptors, like carvedilol, or if blood pressure is already low. This effect may occur with initial dosage administration or during dosage increase and tends to disappear after multiple doses, between 1 and 5 days, not requiring dose reduction or subsequent medication adjustment. In the US Carvedilol Heart Failure Study⁶⁴, less than 1% of patients required interruption of carvedilol therapy due to hypotension or dizziness. The risk of hypotension may be lessened by administering vasodilatory drugs in a different hour and the β -blocking agent after meals to delay absorption and reduce maximum plasma peak concentration. Occasionally, a temporary reduction in ACE inhibitor and vasodilatory agent doses may be necessary. Eventually diuretics may be reduced with caution, as fluid retention must be avoided.

Bradycardia and AV block – Amongst pharmacological effects of β -blocking agents are a decrease in heart rate and a delay in atrioventricular (AV) conduction, which may induce bradycardia and AV block. Such changes rarely occur with lower doses and usually do not cause symptoms, but the risk increases to 5-10% with increasing doses⁶⁴. If the heart rate falls to less than 55-60 bpm or a 2nd or 3rd AV block develops, β -blocking dosage must be reduced. Additionally, drugs that may potentially induce bradycardia or cardiac block, like digitalis and amiodarone, must be discontinued or the dose must be reduced. Bradycardia as a cause for discontinuation of therapy is uncommon (less than 1%)⁶⁴.

Fluid retention and worsening heart failure – The introduction of a β -blocking agent or an inappropriate dosa-

Table III – Percentage of drop out patients from placebo and β -blocking groups due to adverse effects

Study	Placebo group Drop outs (%)	β -blocking group Drop outs (%)
US HF Study ⁶⁴ (n=1094)	7.8	5.7
MDC ²⁸ (n=383)	16	12
CIBIS ⁶² (n=641)	26	23

ge increase may transiently worsen heart failure symptoms, indicated by fluid retention, pulmonary or peripheral congestion, and body weight increase. Patients should be instructed to weigh themselves daily and to correct any eventual increase in body weight by increasing diuretic dose intake until weight returns to pretreatment levels. As this risk is greater in patients who have already experienced fluid retention before treatment, diuretic dosage must be optimized prior to the introduction of a β -blocking agent. By acting in α_1 -adrenergic receptors, carvedilol causes systemic and renal vasodilation, increasing kidney blood flow⁴⁴. However, it remains unknown whether this property may reduce the risk of fluid retention. Approximately 1.6% of patients have been withdrawn from carvedilol therapy versus 2.3% in placebo groups, because of worsening heart failure in the US Carvedilol Heart Failure Study⁶⁴.

The effective and safe use of β -adrenergic blocking drugs in heart failure requires insight into the selection of patients, the potential benefits of treatment, and recognition and management of side effects. Such insight can be gained by any physician who is interested in the care of patients with heart failure and is willing to commit him/herself to the monitoring that such patients require. These physicians need not be cardiovascular specialists. The ease and success of initiating and titrating β -blockers to target doses increase with experience

Topics to be elucidated

The role of β -adrenergic blocking drugs in reducing morbidity and mortality in heart failure patients with functional class II and III has been consistently demonstrated recently in major published trials. However, many questions remain to be better clarified: 1) Are the effects of all β -blocking agents similar in heart failure? 2) What are the real benefits of these drugs in severe heart failure (class IIIB-IV)? 3) Are β -blocking agents beneficial (when used in addition to ACE inhibitors) in patients with systolic left ventricular dysfunction when administered in the immediate post-MI period?

Are all β -blocking agents similar in heart failure?

Both selective – metoprolol and bisoprolol – and nonselective – carvedilol – β -adrenergic blocking agents have demonstrated beneficial effects in heart failure. However, β -blocking agents differ in the magnitude in which they interfere with effects of the sympathetic nervous system on the heart and circulation⁷⁰⁻⁷². In heart failure, the number of β_1 -receptors is decreased, but the number of β_2 -receptors is increased²². Multiple blockade of adrenergic receptors, at least in theory, would be favorable because if excess catecholamines contribute to the progressive ventricular remodeling, complete blockade of these adrenergic receptors may be necessary for the maximum benefit of sympathetic blockade. Moreover, contrary to that which occurs with selective β_1 -adrenergic receptors, carvedilol does not promote an up-regulation of β -adrenergic receptors^{73,74}.

Such properties, besides the peculiar effects of carvedilol, as α_1 -blockade and antioxidative and antiproliferative effects, could explain the better results obtained with this drug compared with selective β_1 -adrenergic blocking agents.

Overall mortality reduction in the US Carvedilol Heart Failure Study⁶⁴ (65%) was greater than reduction obtained in MERIT-HF⁶¹ with metoprolol (34%) and in CIBIS-II⁶³ with bisoprolol (34%). However, no direct comparison between these drugs has been made. In a recent trial involving a selected population of patients with idiopathic dilated cardiomyopathy who had not adequately responded to optimal long-term heart failure treatment, including metoprolol, therapy with carvedilol was associated with favorable effects on left ventricular function, ventricular remodeling, and arrhythmia, although with a negative effect on maximum oxygen consumption⁷⁵.

Direct Prospective comparisons concerning the different β -blockers' effects on heart failure are scarce, with small number of patients and also evaluating only surrogate end points.

In one study⁷⁶, 67 patients with heart-failure class II/IV were randomly assigned to receive either carvedilol or metoprolol in addition to standard therapy for congestive heart failure. Measured variables included symptoms, exercise, ejection fraction, and thiobarbituric acid-reactive substances (TBARS) as an indirect marker of free-radical activity. Metoprolol and carvedilol were well tolerated, and both patient groups showed significant beneficial effects of β -blocker therapy in each of the measured parameters with no between-group differences over 6 months of follow-up.

In another study⁷⁷, 51 patients with chronic heart failure and mean left ventricular ejection fraction of $26\% \pm 1.8\%$ were randomly assigned treatment with metoprolol 50mg twice daily or carvedilol 25mg twice daily, in addition to standard therapy, after a four-week dose titration period for a total of 12 weeks. Both carvedilol and metoprolol produced highly significant improvement in symptoms ($p < 0.001$), exercise capacity ($p < 0.05$), and left ventricular ejection fraction ($p < 0.001$), and no significant differences existed between the two groups. Carvedilol had a significantly greater effect on sitting and standing blood pressure, left ventricular end-diastolic dimension, and normalization of the mitral E-wave deceleration time.

The hypothesis that multiple adrenergic blockade is more effective than selective β_1 -adrenergic blockade is now being prospectively evaluated in a clinical trial – Carvedilol and Metoprolol European Trial (COMET) – which will directly assess survival efficacy of both drugs in 3,000 patients with heart failure in a 4-year treatment period.

Are β -blocking agents beneficial in severe heart failure therapy (class IIIB/IV)?

Patients with severe heart failure are most dependent on sympathetic activation to maintain cardiac performance. Some reluctance exists to introducing β -blocking agents in such patients because of a concern related to initial tolera-

bility, worsening heart failure, hypotension, and bradycardia. Considering the limited life expectancy in this functional class, it is genuine to call into question the time interval usually necessary to achieve β -blockade related benefits.

Data provided by use of β -blocking agents in heart failure class IV was limited until recently. In the US Heart Failure Study,⁶⁴ 105 out of 1,094 (9.6%) patients had severe heart failure and in the CIBIS-II⁶³ study, 445 out of 2,647 (17%) did. Although these subgroups of patients had shown a trend in symptom and ejection fraction improvement, the results could not allow drawing any conclusion about morbidity and mortality. However, meta-analysis data⁷⁸ have shown that class IV heart failure patients adequately selected may benefit from β -blockade.

In our country, the effects of carvedilol were evaluated in 21 patients with refractory heart failure, in functional class IV or III (intermittently with functional class IV), and mean left ventricular ejection fraction of 0.22 ± 0.06 , under optimized conventional treatment⁷⁹. Carvedilol was well tolerated by 16 patients, with a mean dose of 42 ± 11 mg. After 196 ± 60 days of follow-up significant improvement occurred in functional class, left ventricular end diastolic diameter reduced from 73 ± 13 to 66 ± 12 mm ($p < 0.009$), and left ventricular ejection fraction increased from 0.21 ± 0.06 to 0.34 ± 0.12 ($p < 0.0003$).

As mentioned before, the COPERNICUS study enrolling 2,200 patients with functional class IV heart failure, was terminated early due to the significant survival benefit shown with carvedilol.

Systolic ventricular dysfunction in immediate post-myocardial infarction

It is well established that ACE inhibitors are beneficial in treating post-myocardial infarction (MI) systolic ventricular dysfunction both in symptomatic (AIRE study)⁸⁰ and asymptomatic (SAVE⁸¹, TRACE⁸²) patients. β -blocking

agents are known to prevent sudden death and post-MI reinfarction⁸³. The presence of post-MI ventricular dysfunction has been previously considered a contraindication to their use. Nevertheless, a retrospective analysis of post-MI studies where β -blocking agents have been used (before the ACE inhibitor era) suggests that β -blocking's beneficial effects remain or are even greater in such circumstances⁸⁴. The ongoing study CAPRICORN – Carvedilol Post-Infarction Survival Control in Left Ventricular Dysfunction – has been designed to test the hypothesis that carvedilol is superior to placebo when added to ACE inhibitors in patients with post-MI ventricular dysfunction.

Conclusion

Data provided by several appropriately designed clinical trials involving approximately 10,000 patients clearly indicate the benefits of β -blocking agents in chronic heart failure functional class II to IV due to systolic ventricular dysfunction, combined with diuretics, ACE inhibitor, and digoxin. The benefits are related to symptoms, functional capacity, remodeling, and left ventricular function improvement, cardiovascular hospitalization reduction, overall and cardiac sudden death rate decrease, and are similar in patients with cardiomyopathy of any etiology, independent of age, gender, functional class, left ventricular ejection fraction, or exercise tolerance. It should be noted, however, that the clinical experience with these drugs in heart failure due to Chagas' disease is limited⁸⁵.

Despite the Consensus for Treatment of Heart Failure's recommendation that every patient with heart failure class II and III due to left ventricular systolic dysfunction should receive a β -adrenergic blocking agent, except if the drug is not tolerated or in the presence of a contraindication, less than 10% of eligible patients are receiving such drugs. Therefore, a need exists to further disseminate this new concept to cardiologist and general practice professionals.

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