Beta-Blocker Therapy for Heart Failure: The Standard of Care

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Sympathetic nervous system activation plays an important role in the genesis of symptoms, functional impairment, progressive ventricular dysfunction, and mortality in patients with heart failure. Prospective, randomized clinical trials of beta-blockers in patients with heart failure have demonstrated mortality reductions in patients across the spectrum of clinical presentations and etiologies. Additionally, these trials have provided important information regarding the indications, dosing, and extent of therapeutic benefits of the different beta-blockers studied in patients with heart failure. The recognition that beta-blockers relieve symptoms, reduce hospitalizations, and prolong survival in patients with heart failure represents one of the most important therapeutic advances in the treatment of this complex disorder. Beta-blockers, along with angiotensin-converting enzyme inhibitors and aldosterone antagonists, now represent the standard of care for patients with heart failure.
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Congestive heart failure is a complex syndrome defined by abnormalities of left and/or right ventricular function and changes in neurohumoral regulation, accompanied clinically by effort intolerance, fatigue, and shortness of breath resulting from inadequate tissue perfusion and fluid retention. Because of their negative inotropic actions, beta-blockers were long felt to be contraindicated in patients with congestive heart failure. However, the finding that sympathetic nervous system activation adversely affects the course of chronic heart failure provided a physiologic rationale for the use of beta-block-

ers in these patients.[1,2] Based on this rationale, a number of large-scale, randomized clinical trials using beta-blockers in the treatment of congestive heart failure have been conducted over recent years. The overwhelmingly positive results of these studies have established beta-blockers as essential, life-saving therapy for all patients with heart failure in the absence of contraindications. This article will provide a review of the physiologic rationale for beta-blocker treatment in heart failure, a synopsis of the existing trial evidence for the use of beta-blockers in congestive heart failure, a comparison of the various available beta-blockers, and finally, current recommendations for beta-blocker therapy in this patient population.

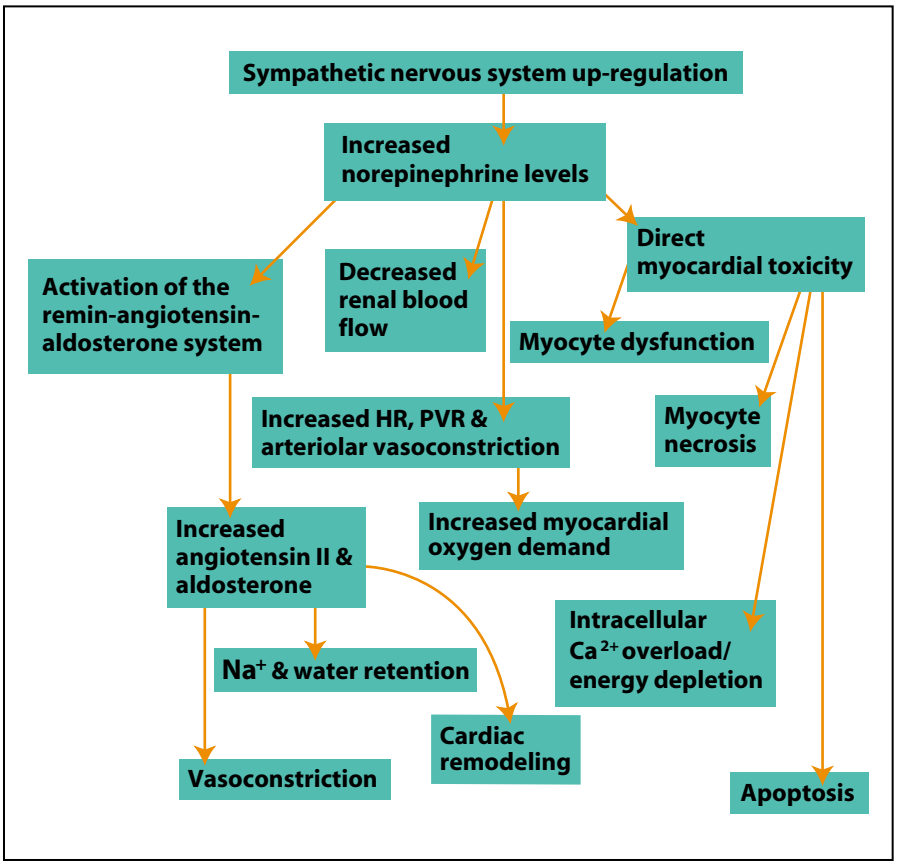

Figure 1. *Deleterious effects of the activation of the sympathetic nervous system. HR, heart rate; PVR, peripheral vascular restistance.*

Neurohumoral Activation as a Treatment Target

Numerous hormonal and neuroendocrine changes have been described in patients with congestive heart failure. One of the earliest detectable changes in patients with heart failure is the activation of the sympathetic nervous system. This neurohormonal activation can be detected by measuring plasma norepinephrine levels, which are elevated early in patients with heart failure and increase as the disease progresses.[3,4] Plasma norepinephrine levels have been shown to correlate with symptom progression, peak oxygen consumption during cardiopulmonary exercise testing, and adverse outcomes in heart-failure patients.[1,5,6] This chronic activation of the sympathetic nervous system in patients with congestive heart failure provides inotropic support to the failing myocardium. Unfortunately, this increased adrenergic output also produces numerous deleterious effects, shown in Figure 1. Elevated norepinephrine levels can result in increased heart rate, arteriolar and venous vasoconstriction, increased peripheral vascular resistance, and decreased renal blood flow.[7,8] Ultimately, these effects increase myocardial oxygen demand and can result in myocardial ischemia.

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Additionally, norepinephrine can be directly toxic to the myocardium, resulting in contractile dysfunction, necrosis, and apoptosis of cardiomyocytes. High concentrations of the beta-agonist isoproterenol have been demonstrated to result in increased calcium entry into cells, and the resultant overactivation of the calcium-dependent, intracellular adenosine triphosphatases (ATPases) leads to energy depletion, mitochondrial damage, and cell necrosis, all of which were prevented with beta-blocker treatment.[8] Catecholamines also increase myocyte susceptibility to triggers of programmed cell death.[9] Finally, increased sympathetic nervous system activity contributes to the activation of the renin–angiotensin–aldosterone system, resulting in sodium and water

Table 1
Major Placebo-Controlled Trials of Beta-Blockers in Patients with Chronic Heart Failure

Study (Reference)	Patients	Sample Size	Beta-Blocker Studied	Mean Dosage Achieved	Results
MDC[18]	Patients with dilated cardiomyopathy and LVEF ≤ 40%	383	Metoprolol	108 mg/d	No significant reduction in mortality (*P* = NS).
CIBIS-I[19]	Patients aged 18–80 with Class II–III* heart failure and LVEF ≤ 35%	641	Bisoprolol	3.8 mg/d	No significant reduction in mortality (*P* = NS); reduction in hospitalizations for heart failure
USCS[21]	Patients with chronic heart failure and LVEF ≤ 35%	1094	Carvedilol	45 mg/d	65% risk reduction in mortality (*P* = .0001); reductions in sudden deaths, progressive heart failure deaths, and hospitalizations
CIBIS-II[24]	Patients aged 18–80 with Class III* heart failure and LVEF ≤ 35%	2647	Bisoprolol	7.5 mg/d	34% risk reduction in mortality (*P* = .0001); reductions in sudden deaths and heart failure hospitalizations
MERIT-HF[25]	Patients aged 40–80 with Class II and III* heart failure and LVEF ≤ 40%	3991	Metoprolol CR/XL	159 mg/d	34% risk reduction in mortality (*P* = .006); reductions in sudden deaths, progressive heart failure deaths, and heart failure hospitalizations
COPERNICUS[26]	Patients with Class IV* heart failure and LVEF ≤ 25%	2289	Carvedilol	37 mg/d	35% risk reduction in mortality (*P* = .0001); reductions in sudden deaths, progressive heart failure deaths, and hospitalizations

*New York Heart Association (NYHA) functional classification.
LVEF, left ventricular ejection fraction; CR, controlled release; XL, extended release.

retention and vasoconstriction.[10] Angiotensin II and aldosterone have been demonstrated to play a major role in the pathophysiology of heart failure, contributing to cardiac remodeling and a progressive decline in ventricular function.[11]

The cardiovascular effects of norepinephrine are mediated through the activation of myocardial alpha$_1$-adrenergic and beta-adrenergic receptors.[3] Approximately 80% of the adrenergic receptors in normal myocardium are beta$_1$-G protein–coupled receptors, which activate adenylate cyclase, resulting in increased intracellular levels of cyclic adenosine monophosphate (cAMP).[12] As heart failure progresses, chronic sympathetic stimulation leads to a down-regulation of beta$_1$-adrenergic receptors. The density of beta$_2$-receptors remains the same, but these receptors become functionally uncoupled.[12,13] Additionally, the percentage of alpha$_1$-receptors increases in heart failure, but remains low relative to the percentage of beta-receptors in the myocardium.[13]

As the understanding of the pathophysiologic mechanisms behind chronic heart failure advanced, it became increasingly clear that neurohormonal activation of the renin–angiotensin–aldosterone and sympathetic nervous systems plays

a critical role in the progression of this disease. Because beta-blockers would be expected to mitigate the deleterious effects of chronic neurohormonal activation, it was logical to assume that these agents might have a beneficial role in the treatment of heart failure. A large number of clinical trials have been conducted over the past few years providing proof of this concept.

Clinical Trials of Beta-Blockers

The earliest studies of beta-blockers in the treatment of heart failure were conducted by Swedish investigators in the early 1970s. These investigators gave beta-blockers to patients with idiopathic-dilated cardiomyopathy to treat resting tachycardia, and the results were encouraging.[14] In the mid-1980s, a number of small-scale trials showed increased ejection fraction, improved symptoms, and improved duration in exercise in heart-failure patients treated with beta-blockers.[15–17] These encouraging results led to trials involving a few hundred patients (Table 1).

The Metoprolol in Dilated Cardiomyopathy Trial

The Metoprolol in Dilated Cardiomyopathy (MDC) study group randomized 383 subjects with idiopathic-dilated cardiomyopathy and ejection fractions ≤ 40% to receive metoprolol, a $beta_1$-selective agent, or placebo.[18] Prior to enrollment, the subjects were required to be maintained in compensated heart failure on conventional treatments, including digoxin, diuretics, nitrates, and angiotensin-converting enzyme (ACE) inhibitors. Treatment with metoprolol significantly improved cardiac function in these patients, as measured by ejection fraction and exercise time.[18] Progressive heart-failure death and all-cause mortality were not, however, reduced in this study.

The Cardiac Insufficiency Bisoprolol Study

In the Cardiac Insufficiency Bisoprolol Study (CIBIS), 641 patients with chronic heart failure of various etiologies, a left ventricular ejection fraction (LVEF) ≤ 40%, and New York Heart Association (NYHA) functional Class III (95%) or IV (5%) were enrolled and randomized to treatment with bisoprolol, another $beta_1$-selective agent, or placebo.[19] Bisoprolol, at a target dose of 5 mg q.d., significantly improved functional status, decreased hospitalizations for decompensated heart failure, and increased the number of patients improving by at least one NYHA functional class; however, the observed difference in mortality between bisoprolol-treated patients and the placebo group failed to reach statistical significance.[19] Thus, although these studies had demonstrated that therapy with beta-blockers could be tolerated in patients with heart failure and that these patients' ventricular function improved, a reduction in mortality had not yet been established.

Carvedilol Clinical Trials

A major advancement in the use of beta-blockers in heart-failure patients occurred with the clinical trials involving carvedilol. Carvedilol is a nonselective beta-adrenoreceptor antagonist with $alpha_1$-adrenoreceptor–blocking properties and no intrinsic sympathomimetic activity.[20] The U.S. Carvedilol Heart Failure Study (USCS) was composed of 4 individual studies randomizing 1094 patients with mild, moderate, or severe heart failure on standard background heart-failure therapy to carvedilol at a target dose of 25 mg b.i.d. or placebo. All-cause mortality was reduced by 65% ($P < .0001$) with significant reductions in progressive heart-failure death and sudden death.[21] The Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) trial enrolled 278 patients with moderate to severe heart failure and a LVEF ≤ 35% to treatment with carvedilol or placebo for 6 months.[22] Carvedilol-treated patients had greater symptomatic improvement, less risk of clinical deterioration, a significant increase in ejection fraction, and a significant decrease in the combined risk of morbidity and mortality; however, carvedilol had little effect on exercise tolerance. The Multi-Center Oral Carvedilol Heart Failure Assessment (MOCHA) trial demonstrated dose-related improvements in left ventricular function and survival in patients with moderate heart failure treated with carvedilol.[23] Compared to placebo, a dose of carvedilol as low as 6.25 mg b.i.d. produced clinically relevant improvements in LVEF and a significant reduction in mortality.

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Beta-Blocker Trials with Mortality Benefits

Subsequently, trials with other beta-blocking agents demonstrated significant mortality benefits in the heart-failure population (Table 1). A CIBIS-II study was conducted, using a higher target dose of bisoprolol (10 mg q.d.)

than the CIBIS-I trial did.[24] This study enrolled 2647 heart-failure patients with NYHA functional Class III or IV symptoms, and a LVEF ≤ 35%, who were already receiving standard therapy with diuretics and ACE inhibitors. This trial was stopped early, because bisoprolol showed a significant all-cause mortality benefit. Additionally, there were significantly fewer sudden deaths in the bisoprolol group compared with the group taking placebo.[24] This was soon followed by the MERIT-HF trial, which enrolled 3991 patients with chronic heart failure, NYHA Class II-IV, and ejection fractions ≤ 40%, who were stabilized on standard medical therapy.[25] The patients were randomized to treatment with controlled-release (CR)/extended-release (XL) metoprolol, with a target dose of 200 mg q.d. or placebo. Again, this study was stopped early, because all-cause mortality was lower in the metoprolol CR/XL group than in the placebo group. Additionally, there were significantly fewer sudden deaths and deaths from worsening heart failure in the metoprolol-treated patients.[25] Because both CIBIS-II and MERIT used high doses of $beta_1$-selective beta-blockers, doses at which these agents have a significant $beta_2$ effect, it remains unknown whether lower doses of $beta_1$-selective beta-blockers would provide a reduction in mortality.

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Severe Heart Failure

The vast majority of subjects in the heart-failure trials discussed up to this point demonstrated NYHA Class II or III symptoms, because many physicians were concerned that patients with severely symptomatic heart failure would not tolerate the initiation of beta-blocker therapy. This important clinical question about the risks and benefits of beta-blocker therapy in patients with NYHA Class IV heart failure was answered in a recently published trial. The Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) studied the impact of beta-blockade in patients with NYHA Class IV symptoms.[26] This trial enrolled 2289 patients with heart-failure symptoms at rest or on minimal exertion and an ejection fraction of ≤25%. The study drug could be started while the patient was still hospitalized, but the patients could not be in a critical care unit, an intensive care unit, or on intravenous inotropic agents within the past 4 days. Treatment with carvedilol resulted in a significant 35% reduction in all-cause mortality rates and a significant reduction in the combined risk of death or hospitalization in this severely symptomatic heart-failure population (Figure 2).[26] Benefits were seen across all subgroups of patients examined. Carvedilol was very well tolerated in this population, and more patients were withdrawn from the placebo group because of adverse events than from the carvedilol group. Taken together, these results firmly established that beta-blockade has long-term beneficial effects across a wide spectrum of heart-failure patients with symptoms ranging from mild to severe.

Figure 2. *Results from the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNUCUS): Effect of carvedilol versus placebo on survival in 2289 patients with severe heart failure (New York Heart Association Class IV) receiving standard therapy.*

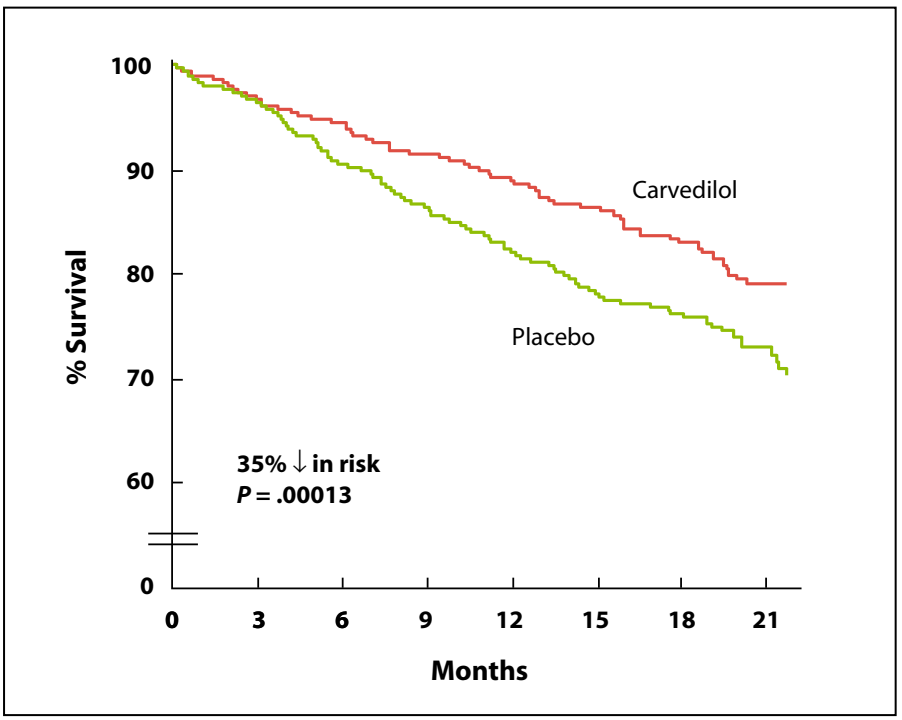

Table 2
Beta-Blockers Used for Heart-Failure Management

Generic Name	Trade Name	Starting Dose	Target Dose
Bisoprolol fumarate	Zebeta	1.25 mg q.d.	10 mg q.d.
Carvedilol	Coreg	3.125 mg b.i.d.	25 mg b.i.d.*
Metoprolol	Lopressor	6.25 mg b.i.d.	100 mg b.i.d.
Metoprolol CR/XL	Toprol XL	12.5–25 mg q.d.	200 mg q.d.

*Carvedilol in doses of 6.25 mg and 12.5 mg b.i.d. also demonstrated that it reduced mortality compared to placebo.
CR, controlled release; XL, extended release.

Subgroups

The effects of beta-blockade on various subpopulations of heart-failure patients have also been examined. Subgroup analysis of the USCS data demonstrated all-cause mortality benefits in both diabetic and nondiabetic heart-failure patients treated with carvedilol.[21] Carvedilol treatment also resulted in significant survival benefits in both men and women.[21,26] Additionally, patients with severe heart failure of both ischemic and nonischemic etiologies demonstrated benefit from beta-blockade with respect to the combined endpoint of death and hospitalization for any reason.[26] Finally, despite early reports of differential benefits between races, the COPERNICUS and USCS trials demonstrated the beneficial effects of beta-blockade with carvedilol in both black and nonblack heart-failure patients.[21,26]

Comparative Effects of Beta-Blockers

The clinical benefits resulting from using various beta-blockers in heart failure led many investigators to argue that these improvements were a class effect caused by $beta_1$-adrenoreceptor antagonism. However, others argued that the additional pharmacological properties of certain beta-blockers increased their efficacy and might result in additional benefits in the treatment of heart failure. In fact, the Beta-blocker Evaluation Survival Trial (BEST) failed to show a mortality reduction with the use of the beta-blocker bucindolol, indicating that there might be important differences between beta-blockers in the treatment of heart failure.[27] Further, at lower doses, both metoprolol and bisoprolol failed to reduce mortality, but at higher doses, at which both $beta_1$- and $beta_2$-receptor blockade is achieved, the two drugs significantly increased survival in the heart-failure population. This debate led to direct comparisons of "second-generation" $beta_1$-adrenoreceptor selective agents, such as metoprolol, with "third-generation" nonselective beta/alpha-blockers, such as carvedilol. The largest comparison trial to date enrolled 150 patients with heart failure (LVEF < 35%), who were subsequently treated with either metoprolol or carvedilol.[28] The carvedilol-treated patients showed larger increases in LVEF and in left ventricular stroke volume and stroke work during exercise than did the metoprolol-treated patients. Additionally, carvedilol produced greater decreases in mean pulmonary artery pressure and pulmonary wedge pressure than metoprolol did. However, metoprolol produced greater increases in maximal exercise capacity than carvedilol did; but the two drugs improved symptoms, submaximal exercise tolerance, and quality of life to a similar degree. Further, there were no detectable differences between these two agents in the clinical endpoints measured; however, this may have resulted from the small sample size.[28] A recently published meta-analysis comparing the effects of carvedilol to metoprolol on LVEF in heart-failure patients revealed that carvedilol produces greater effects on LVEF than metoprolol does at similar doses.[29]

These diverse trials demonstrate the potential differences between the various beta-blockers and illustrate the need for further large-scale trials to directly compare beta-blocking agents. The results of ongoing large-scale direct comparison trials, such as the Carvedilol and Metoprolol European Trial (COMET), are eagerly awaited to determine whether clinically important differences exist between these two agents. Until these results are available, either a second-generation $beta_1$-selective compound, such as metoprolol or bisoprolol (titrated to a high dose), or a third-generation, nonselective beta/alpha-blocker, such as carvedilol, is a reasonable choice in patients with heart failure (Table 2).

Clinical Guidelines for Beta-Blockers

There is compelling clinical trial evidence that all patients with heart failure, from asymptomatic left ventricular dysfunction to Class IV symptoms of any etiology, should be treated with beta-blocker therapy in addition to ACE inhibitors, in the absence of contraindications.[30-32] Patients with acutely decompensated heart failure and those dependent on intravenous inotropic medications should not have beta-blockers initiated until they are in a compensated state on oral agents. Frequently, hospitalized patients with heart failure become stabilized within a few days, and beta-blocker therapy may be safely initiated prior to hospital discharge. For patients admitted to the hospital with acutely decompensated heart failure who were previously receiving beta-blockers, therapy may be continued during the hospitalization so long as the patient is not in cardiogenic shock or showing signs of systemic hypoperfusion. Beta-blockers should be avoided in patients with severe bronchial asthma, but may be used with closer monitoring in patients with mild to moderate asthma or chronic obstructive airway disease.

Approximately 90%–95% of heart-failure patients who are thought suitable for beta-blockade will tolerate the initiation and maintenance of the therapy.

When beta-blocker therapy is initiated in patients with heart failure, it is important to start at a low dose and titrate the dose of beta-blocker upwards slowly. The starting doses used in major clinical trials are shown in Tables 1 and 2. The beta-blocker dose should be doubled at 2- to 8-week intervals, so long as the patient remains compensated. Further studies are needed to determine the optimal dose for $beta_1$-selective beta-blockers. Until this data is available it is appropriate to use the doses shown to be effective in the large-scale clinical trials, depicted in Tables 1 and 2, as a general treatment target.

In our experience at the Ahmanson-UCLA Cardiomyopathy Center and in the clinical trials described above, approximately 90%–95% of heart-failure patients who are thought suitable for beta-blockade will tolerate the initiation and maintenance of the therapy. Worsening heart-failure symptoms should prompt an increased dose of ACE inhibitor, diuretic, or both; alternatively, symptomatic hypotension should result in a decreased dose of these agents. If the dose adjustment of other medications fails to relieve adverse side effects, reduction or withdrawal of beta-blocker therapy should be consid-

Main Points

- The neurohormonal activation of the renin–angiotensin–aldosterone and sympathetic nervous systems plays a key role in the development of congestive heart failure.
- This neurohormonal activation can be detected early in patients with congestive heart failure by measuring plasma norepinephrine levels. These levels increase as the disease progresses and induce a variety of symptoms.
- Because beta-blockers mitigate many of these neurohormonal changes, a number of large-scale, randomized trials were conducted to test whether beta-blockers would be beneficial in treating myocardial dysfunction.
- Initial trials using metoprolol and bisoprolol showed improvement in cardiac function, measured by the left ventricular ejection fraction (LVEF), the New York Heart Association (NYHA) functional class, and exercise time, but failed to provide a reduction in mortality.
- Trials with the nonselective beta-adrenoreceptor antagonist carvedilol resulted in clinically relevant improvements in LVEF in patients with NYHA Class II, III, or IV (mild to severe) heart failure and a significant reduction in mortality. Carvedilol also demonstrated all-cause mortality benefits in diabetic heart-failure patients.
- Later trials using higher target doses of bisoprolol and metoprolol—doses with a notable $beta_2$ effect—showed significant reductions in all-cause mortality and sudden death.
- Beta-blockers for the treatment of heart failure represent a major, life-saving therapeutic advance. The evidence is compelling that all patients with heart failure and no contraindications to using beta-blockers should receive beta-blocker treatment in addition to standard therapy. Beta-blocker treatment should be initiated at low doses and titrated upwards slowly.

ered, followed by a second attempt to reinitiate beta-blockers at a later date. Symptomatic bradycardia requiring withdrawal of beta-blockers or a pacemaker is rare.[21,24,25]

Conclusion

The benefits of beta-blockers are additive to other proven heart failure treatments. Beta-blockers should thus be used in combination with other proven treatments, including ACE inhibitors and aldosterone blockade with spironolactone. The beneficial effects of these agents in heart-failure patients include improvements in left ventricular function and quality of life, a delay in clinical progression, reduced hospitalizations, and a reduction in overall mortality. The evidence demonstrating the benefits of beta-blockers in patients with heart failure is compelling enough to make this the standard of care.[30,31] A team-management approach, as outlined by the American Heart Association, may be extremely helpful in the successful initiation and continued use of beta-blockers in the chronic heart-failure population.[33] Beta-blockers for the treatment of heart failure represent a major therapeutic advance, and every effort should be made to apply this life-saving therapy in all heart-failure patients, if there are no contraindications or documented intolerance. ■

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