β-Blockers in Chronic Heart Failure: Considerations for Selecting an Agent

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Patients with chronic heart failure have increased sympathetic nervous system activity that contributes to deterioration of cardiovascular function over time. Long-term β-blocker therapy prevents such deterioration through inhibition of this neurohormonal pathway. The impressive survival data collected from several large studies have made β-blockers a component of standard therapy for New York Heart Association class II to III heart failure. Although there are differences in the pharmacological properties of the β-blockers shown to improve morbidity and mortality in heart failure, there is little evidence to suggest that such properties constitute any major advantages in clinical outcome. Carvedilol and extended-release metoprolol succinate are 2 β-blockers currently approved in the United States for the treatment of patients with heart failure. Both agents have shown similar risk reductions in overall and cause-specific mortality; however, no outcome data from a comparative trial are available to support the use of one agent over the other. Regardless of the agent chosen, appropriate dosing and titration of β-blockers are essential for successful therapy.

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ACE = angiotensin-converting enzyme; BEST = Beta-Blocker Evaluation of Survival Trial; CHF = chronic heart failure; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; COMET = Carvedilol or Metoprolol European Trial; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; ER = extended release; LVEF = left ventricular ejection fraction; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NYHA = New York Heart Association; RR = risk reduction

C hronic heart failure (CHF) due to systolic dysfunction is a progressive disease characterized by left ventricular dysfunction and cardiac remodeling.1,2 Patients with heart failure have increased sympathetic nervous system activity, which initially supports cardiac function through an increase in heart rate, myocardial contractility, and systemic vascular resistance.2,3 However, prolonged adrenergic activation leads to down-regulation and desensitization of β-adrenergic receptors. These processes, in turn, cause deterioration of cardiovascular function and exercise tolerance.2,3 Additionally, continued exposure to excess norepinephrine contributes to the development of cardiac hypertrophy, arrhythmia, and myocardial cell apoptosis.1

Long-term β-blocker therapy prevents such adverse biological effects and reduces cardiac remodeling by inhibiting this neurohormonal pathway. Cardiac remodeling is characterized by progressive ventricular hypertrophy, altered gene expression on cardiac myocytes, and subsequent deterioration in cardiac contractility; it is a strong predictor of adverse clinical outcome. Studies have shown that use of β-blockers in patients with mild to moderate heart failure substantially improves left ventricular ejection fraction (LVEF), symptoms, and overall mortality.4,7 According to professional practice guidelines, β-blockers should be administered to all patients with New York Heart Association (NYHA) class II or III heart failure who are clinically stable while taking a diuretic, an angiotensin-converting enzyme (ACE) inhibitor, and, in some cases, digoxin.8

β-BLOCKERS IN CHF: OVERVIEW OF CLINICAL EFFICACY

Initial randomized trials conducted to evaluate the efficacy of various β-blockers in the treatment of heart failure did not include sufficient sample sizes, had short follow-up durations, and had different primary end points, which make interpretation of their results difficult.9,11 In some studies, LVEF was the primary end point; in other studies, the primary end points were a combination of a mortality (eg, all-cause mortality) and a morbidity component (eg, need for hospitalization or cardiac transplantation).9,11 Although these trials provided no definitive evidence of mortality reduction, they suggested that β-blockers could be used safely in heart failure patients, and the results were sufficiently encouraging to warrant further evaluation.12 Two meta-analyses,13,14 each including more than 3000 patients, have evaluated results of heart failure trials analyzing numerous β-blockers, including bisoprolol,
bucindolol, carvedilol, metoprolol, and nebivolol. Both meta-analyses showed a risk reduction (RR) for mortality, hospitalization due to heart failure, and the combined end points of mortality and hospitalizations with β-blocker use.

Several larger randomized trials have firmly established the benefits of β-blockers in heart failure, including the US Carvedilol Program and 4 large mortality trials: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II), the Beta-Blocker Evaluation of Survival Trial (BEST), and the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial (Table 1). The US Carvedilol Program consisted of 4 separate protocols, which were not designed to assess mortality prospectively, and enrolled 1094 patients with mild, moderate, or severe CHF (LVEF ≤ 35%).6 End points for these studies differed and included hospitalization rate for cardiovascular disease and exercise tolerance. All patients received carvedilol, 6.25 mg twice daily, for a 2-week, open-label, run-in period; patients who tolerated this dose were then randomly assigned to receive carvedilol (to a target maximum dose of 25-50 mg twice daily) or placebo in addition to their current therapies. The safety committee terminated the program early because of a significant RR for mortality (P < .001) observed among patients treated with carvedilol; overall mortality rates were 3.2% and 7.8% in the carvedilol and placebo groups, respectively. The total number of deaths was small: 22 deaths in the carvedilol group and 31 deaths in the placebo group. The mortality benefits observed in this trial were initially questioned because mortality was not a predefined end point in all the protocols and the length of follow-up was short (mean follow-up, 6.5 months).17 In addition, pooling the 4 protocols, which had different inclusion criteria and end points, and the nature of the run-in period (in which patients who could not tolerate carvedilol were excluded) have been criticized.15 The outcomes of the US Carvedilol Program provided a strong rationale for conducting large, randomized mortality trials.

### Table 1. Summary of Major Mortality Trials Evaluating β-Blockers in Patients With Heart Failure*

<table>
<thead>
<tr>
<th>Study</th>
<th>β-Blocker</th>
<th>No. of patients</th>
<th>NYHA class</th>
<th>LVEF (%)</th>
<th>Annual RR vs placebo in all-cause mortality (%)</th>
<th>P value</th>
<th>Annual mortality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MERIT-HF†,**</td>
<td>ER metoprolol succinate</td>
<td>3991</td>
<td>II-IV</td>
<td>≤ 40</td>
<td>34</td>
<td>&lt; .001</td>
<td>7.2</td>
</tr>
<tr>
<td>CIBIS-II‡</td>
<td>Bisoprolol</td>
<td>2647</td>
<td>III-IV</td>
<td>≤ 35</td>
<td>34</td>
<td>&lt; .001</td>
<td>11.8</td>
</tr>
<tr>
<td>BEST³</td>
<td>Bucindolol</td>
<td>2708</td>
<td>III-IV</td>
<td>≤ 35</td>
<td>… †</td>
<td>.13</td>
<td>15.0</td>
</tr>
<tr>
<td>COPERNICUS trial⁴</td>
<td>Carvedilol</td>
<td>2289</td>
<td>III-IV</td>
<td>≤ 25</td>
<td>35</td>
<td>&lt; .001</td>
<td>11.4</td>
</tr>
</tbody>
</table>

*BEST = Beta-Blocker Evaluation of Survival Trial; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; ER = extended release; LVEF = left ventricular ejection fraction; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NYHA = New York Heart Association; RR = risk reduction.

†RR for total mortality, 10% (33% placebo, 30.2% bucindolol; P = .13; 2-year follow-up).

**MERIT-HF was a randomized, double-blind, placebo-controlled study that included 3991 patients with NYHA class II to IV heart failure and an LVEF of 40% or less.5,15 After a 2-week, single-blind, placebo, run-in period, patients were randomized to extended-release (ER) metoprolol succinate at a starting dose of 12.5 mg/d (class III and IV patients) to 25 mg/d (class II patients) or placebo in addition to their conventional therapies. The ER metoprolol succinate dose was doubled every 2 weeks as tolerated up to a maximum target dose of 200 mg/d; doses could be adjusted at the discretion of the investigator. The 2 primary study end points were all-cause mortality and the combined end point of all-cause mortality plus all-cause hospitalization (time to first event). The independent safety committee terminated the trial early, approximately 18 months after start of randomization, because ER metoprolol succinate significantly reduced all-cause mortality. Results showed a 34% RR for all-cause mortality (P < .001, Figure 1) and a 19% RR for total mortality or all-cause hospitalization (P < .001). The median follow-up at study termination was 12 months. The ER metoprolol succinate therapy resulted in a 31% RR for all-cause mortality or hospitalization for worsening heart failure (P < .001), a 41% RR for sudden death (P < .001), and a 49% RR for death due to worsening heart failure (P = .002). Several predefined subgroups were analyzed to determine any difference in outcome, including elderly patients, smokers and nonsmokers, and those with a history of hypertension, prior myocardial infarction, or diabetes mellitus; the benefits observed with ER metoprolol succinate in the overall study population were consistent across all predefined subgroups.15 In addition, ER metoprolol succinate significantly reduced the number of all-cause hospitalizations (P = .005) and the total number of days in the hospital due to all causes (P = .004).
relative to placebo.15 This difference was primarily related to a reduction in the number of hospitalizations for worsening heart failure.

A post hoc subgroup analysis of MERIT-HF evaluated patients with NYHA class III and IV heart failure and an ejection fraction less than 25% (n=795).19 Treatment with ER metoprolol succinate in this subgroup resulted in significant RRs for total mortality (RR, 39%; \( P = .009 \)), sudden death (RR, 45%; \( P = .02 \)), and death due to worsening heart failure (RR, 55%; \( P = .01 \)) relative to placebo. The ER metoprolol succinate treatment significantly reduced hospitalizations due to worsening heart failure by 45% compared with placebo (\( P < .001 \)). This subgroup analysis suggests that patients with more severe heart failure had a mortality benefit and reduction in hospitalizations similar to those observed in the overall population of MERIT-HF.

CIBIS-II

CIBIS-II, a randomized, double-blind, placebo-controlled study, included 2647 patients with NYHA class III to IV heart failure and an LVEF of 35% or less.4 Patients were randomized to receive bisoprolol, 1.25 mg/d (titrated to a maximum target dose of 10 mg/d), or placebo in addition to standard heart failure therapies. The primary study end point was all-cause mortality; secondary end points included all-cause hospitalizations, cardiovascular mortality, and the combined end point of cardiovascular mortality and cardiovascular hospitalizations. The trial was discontinued because of the substantial reduction in total mortality (34%) observed among patients in the bisoprolol group (Figure 2, \( P < .001 \)).4 In addition, there were significantly fewer cardiovascular deaths (\( P = .005 \)) and all-cause hospitalizations (\( P < .001 \)) reported among patients treated with bisoprolol vs those who received placebo.4 Thus, the CIBIS-II mortality data are consistent with the data from MERIT-HF.

The COPERNICUS Trial

Although a substantial body of evidence in the medical literature supports the use of \( \beta \)-blockers in patients with mild to moderate heart failure, data regarding the long-term safety and efficacy of \( \beta \)-blockers in patients with severe heart failure are limited.6 The COPERNICUS trial evaluated carvedilol in 2289 patients with severe heart failure and an LVEF of 25% or less.7 Patients randomized to carvedilol treatment received an initial dose of 3.125 mg twice daily for 2 weeks, which was doubled at 2-week intervals to a maximum target dose of 25 mg twice daily as tolerated. The Data and Safety Monitoring Board discontinued the trial early because of the mortality benefits observed with carvedilol. Final analysis of the data showed that patients in the carvedilol group had a 35% RR in total mortality (Figure 3, \( P = .001 \)), with cumulative risk of death at 1 year of 18.5% in the placebo group and 11.4% in the carvedilol group. These data are consistent with the results of MERIT-HF and CIBIS-II and extend the results of \( \beta \)-blocker trials to the sickest group of patients. The post hoc analysis of the MERIT-HF study of a comparable severe heart failure subgroup also supports this conclusion.19

BEST

The efficacy of bucindolol, a nonselective \( \beta \)-blocker, was evaluated in patients with severe heart failure in the BEST.16 This randomized placebo-controlled study included 2708 patients with NYHA class III to IV heart failure (LVEF \( \leq 35\% \)). Patients were randomly assigned to receive placebo or bucindolol titrated to a target maximum daily dose of 50 to 100 mg twice daily in addition to standard therapies. The primary end point was all-cause mortality. In contrast to previous mortality studies in heart failure, this study was terminated after 2 years because no significant differences were observed between the 2 groups with regard to all-cause mortality. However, a post hoc analysis of causes of death showed a significant decrease in cardiovascular deaths among patients treated with bucindolol (\( P = .04 \)). Additionally, hospitalization due to heart failure (\( P < .001 \)) and progression to death or transplantation.
SELECTING THE APPROPRIATE β-BLOCKER

β-Blockers are categorized into 3 classes. First-generation agents (eg, propranolol) are nonselective in their blockade of β-adrenergic receptors. Second-generation β-blockers (eg, metoprolol and bisoprolol) are β₁-selective and have no ancillary vasodilatory effects. Third-generation agents (eg, carvedilol and bucindolol) are nonselective β-blockers and have ancillary vasodilating properties, attributable to α₁-blocking activity in the case of carvedilol.

Three β-blockers, ER metoprolol succinate, carvedilol, and bisoprolol, have proven mortality and morbidity benefits in patients with CHF and therefore can be considered for heart failure treatment. Only ER metoprolol succinate and carvedilol are approved in the United States to treat CHF. Whether differences in the pharmacological properties of these β-blockers have practical importance in determining clinical response and tolerability in heart failure patients is debatable.

β₁-Selective vs Nonselective β-Blockers

Currently, no convincing clinical trial data support the preferential use of a nonselective β-blocker over a β₁-selective agent in CHF. It has been speculated that comprehensive adrenergic blockade provided by the third-generation agent carvedilol offers some clinical advantage in the treatment of heart failure. However, this hypothesis is inconsistent with the similar mortality benefits observed in MERIT-HF, CIBIS-II, and the COPERNICUS trial. In addition, bucindolol, which blocks both β₁- and β₂-receptors, showed no beneficial effect on mortality in patients with CHF in a randomized trial. β₁-Selective agents may be better tolerated because they leave the β₂-receptors unblocked, allowing them to support myocardial function and mediate peripheral vascular vasodilation.

Soriano et al conducted a meta-analysis of 71 randomized controlled trials to assess the importance of ancillary properties of β-blockers and their effects on mortality after myocardial infarction. This analysis showed that β₁-selective agents were more effective than nonselective β-blockers in reducing 1-week mortality, long-term mortality, reinfarction, and sudden death. Lipophilic β-blockers were associated with greater RRs compared with hydrophilic agents, and β-blockers without intrinsic sympathomimetic activity were associated with greater RRs than those possessing intrinsic sympathomimetic activity. However, differences in the clinical efficacy of selective and nonselective β-blockers can be determined only through direct comparative studies.

No large-scale mortality trial directly comparing β₁-selective and nonselective agents has been completed yet. The Carvedilol or Metoprolol European Trial (COMET) is currently ongoing and may help resolve this issue in the future. However, there are already questions about the target dose of metoprolol tartrate (50 mg twice daily) in COMET because the target dose in MERIT-HF using ER metoprolol succinate was 200 mg/d. Furthermore, COMET is not comparing carvedilol to either of the 2 β₁-selective preparations that have shown a significant 34% reduction in mortality (bisoprolol and ER metoprolol succinate).

Vasodilating Properties

Myocardial remodeling is an important pathophysiologic component of heart failure. The pathogenesis of myocardial remodeling is multifactorial and includes mechanical stress, angiotensin II, and norepinephrine as potential mediators of this process. A reduction in myocardial mass and normalization of ventricular geometry (reverse remodeling) have been reported after treatment with β-blockers. β-Blockers with vasodilating effects may further attenuate myocardial remodeling by reducing wall tension,
filling pressure, and mechanical stress. However, head-to-head comparisons of immediate-release metoprolol tartrate (β1-selective) and carvedilol (nonselective, vasodilating) in 3 trials showed overall improvement in LVEF with both drugs.33-35

β-Blockers with vasodilatory properties reduce afterload and counteract the observed negative inotropic properties (ie, decreased cardiac output) due to adrenergic blockade.18 Thus, these agents (eg, bucindolol and carvedilol) may be better tolerated during treatment initiation.36

Antioxidant Activity

Increased lipid peroxidation has been observed in patients with heart failure and has the potential of further damaging the myocardium via oxygen free radical generation,37,38 which has been associated with decreased LVEF.35 Carvedilol has documented antioxidant activity in vitro,39,40 and studies in experimental models of myocardial ischemia have shown that it inhibits oxygen radical–induced endothelial cell injury and death.40 However, both carvedilol and metoprolol similarly reduced the concentration of thiobarbituric acid–reactive substances, a specific marker of lipid peroxidation and oxidative stress.33,41,42 In a randomized clinical trial, metoprolol, a β-blocker with no documented antioxidant properties, and carvedilol produced similar improvements in symptoms, LVEF, and exercise capacity in patients with symptomatic heart failure and LVEFs of 35% or less.33

Apoptosis

Studies evaluating heart tissues from animals and humans with heart failure have shown ongoing myocyte degeneration.43 The 2 mechanisms through which this process occurs are (1) cell necrosis characterized by membrane disruption and inflammation and (2) apoptosis associated with cell shrinkage and organized degradation of DNA.43 Several factors, including cytokines,44 mechanical stress,45 oxygen free radicals, elevated norepinephrine concentrations, and cardiomocyte hypoxia, may be inducers of apoptosis.2 Treatment with β-blockers inhibits several of these factors, thereby reducing myocyte loss.2

Communal et al46 showed that although β1-blockade inhibits apoptosis, β2-antagonism increases apoptosis. However, because β2-receptors predominate even in the failing heart, the net effect of selective and nonselective β-blockade is attenuation of apoptosis. Antiapoptotic effects of both metoprolol and carvedilol have been shown in various animal models.47

SAFETY AND TOLERABILITY

Institution of β-blocker therapy for patients with CHF may initially produce negative chronotropic and inotropic effects on the myocardium.20,36 During initiation and up-titration, some patients may experience a reduction in cardiac output characterized by hypotension and worsening heart failure.48 By starting with a low dose and up-titrating slowly, most patients tolerate dose escalation well.

β-Blockers, particularly nonselective agents with vasodilating properties, can produce hypotension. For example, initiation of carvedilol can result in symptomatic hypotension, including dizziness and blurred vision.6 These vasodilatory effects typically occur within 24 to 48 hours after the initial dose or dose titration but tend to diminish with continued treatment.1 In some cases, hypotension can be managed by a temporary reduction in the dose of ACE inhibitors or other vasodilatory medications. Reduction in the dose of diuretics is discouraged because it may increase the risk of fluid retention.1

β-Blocker therapy should be initiated in patients who are clinically stable. In some patients, fluid retention and symptoms of worsening heart failure may occur after treatment initiation with a β-blocker. Patients may experience weight gain within the first 3 to 5 days of treatment; therefore, they should be advised to weigh themselves on a daily basis. Weight gain is managed through an increase in the diuretic dose until weight returns to baseline and should not preclude future up-titration of the β-blocker.

Initiation of β-blocker therapy also may lead to bradycardia or heart block, but most patients are asymptomatic. Patients receiving low doses of β-blockers rarely experi-
ence these adverse events, but the risk appears to increase to 5% to 10% with dose titration. Dose reduction is required if second- or third-degree heart block develops. For a resting asymptomatic heart rate of less than 50 beats/min, measuring heart rate response to a short walk can be helpful in determining continuation of therapy.

Overall, most patients tolerate β-blockers well. Results from large clinical trials showed that the discontinuation rate for β-blockers did not differ from that observed with placebo.

**DOsing AND TItRAtION**

Before β-blocker therapy is initiated, it is recommended that patients be clinically stable while taking appropriate doses of diuretics and ACE inhibitors for at least 2 to 4 weeks without evidence of volume overload (peripheral edema or rales). β-Blocker therapy should be initiated at low doses and gradually titrated upward to the maximum tolerated dose or until the target dose is achieved. For carvedilol, the recommended starting dose in patients with CHF is 3.125 mg twice daily, and the dose is doubled every 2 to 4 weeks, as tolerated, to a maximum dose of 25 mg twice daily in patients weighing less than 85 kg and 50 mg twice daily in patients weighing 85 kg or more. For metoprolol succinate, the recommended starting dose is 25 mg/d in patients with NYHA class II heart failure or 12.5 mg/d in patients with more severe heart failure. The dose should then be doubled every 2 weeks as tolerated to a maximum target dose of 200 mg/d. With this strategy, most doses can be up-titrated to be effective. In MERIT-HF, the mean dose achieved with ER metoprolol succinate was 159 mg; in the COPERNICUS trial, the mean dose achieved with carvedilol was 37 mg.

Immediate-release metoprolol (tartrate) may not be considered therapeutically interchangeable with ER metoprolol succinate in patients with CHF. MERIT-HF showed a 34% RR in mortality with ER metoprolol succinate, but there are no positive outcome studies in heart failure with immediate-release metoprolol. In the Metoprolol in Dilated Cardiomyopathy Trial, immediate-release metoprolol did not show a significant reduction in mortality compared with placebo (P = .06). Kukin et al compared both hemodynamic effects and tolerability of ER metoprolol succinate and immediate-release metoprolol during initiation and up-titration of β-blocker therapy in patients with heart failure. Patients were randomized to immediate-release metoprolol, 6.25 mg twice daily, or ER metoprolol succinate, 25 mg/d, with dose titration throughout several weeks to a target of 50 mg twice a day or 100 mg/d, respectively. Similar acute and chronic hemodynamic and clinical effects were observed, despite the 4-fold greater starting dose of ER metoprolol succinate. The results suggest that ER metoprolol succinate may facilitate easier initiation and up-titration to the target dose compared with immediate-release metoprolol (tartrate). Equally important is the availability of the requisite low starting dose, for example, a scored 25-mg tablet that can be easily split to make a 12.5-mg dose.

Heart failure treatment guidelines recommend that patients intolerant of higher doses should continue with low-dose β-blocker therapy. Although greater doses of these agents appear to be more beneficial, administration of low doses also has resulted in significant improvement in LVEF and clinical outcomes. Therefore, patients are encouraged to continue with low-dose β-blocker therapy if they are intolerant of the titration process. Additionally, patients must be informed that clinical response may not be observed for approximately 2 to 3 months after treatment initiation. Studies conducted in patients with dilated cardiomyopathy have shown that continuous treatment with a β-blocker is essential to the survival of these patients and that withdrawal of such therapy can cause clinical deterioration. Therefore, patients should be advised to continue β-blocker therapy even if their symptoms do not improve in order to reduce the risk of sudden death and other clinical complications. Furthermore, because ischemic heart disease is a common cause of heart failure, use of β-blockers should not be discontinued abruptly because this may result in exacerbations of angina pectoris and potentially myocardial infarction. Even in patients with hypotension, it may be prudent not to discontinue β-blocker therapy abruptly because coronary artery disease may be unrecognized in these patients. The dose of β-blocker should be gradually decreased throughout 1 to 2 weeks.

The significant peak-to-trough variation in plasma levels observed with immediate-release metoprolol (tartrate) twice daily may predispose the heart to withdrawal phenomena at trough levels or if a dose is missed. The more even plasma concentration achieved with ER metoprolol succinate, however, ensures consistent 24-hour β-blockade.

Patients who generally should not receive a β-blocker for heart failure therapy include those with bronchial asthma and chronic obstructive pulmonary disease requiring β-agonist therapy, symptomatic hypotension, resting heart rate of less than 60 beats/min, or advanced heart block without a pacemaker and those with general contraindications to β-blocker therapy. Additionally, volume-overloaded patients should not receive β-blockers until fluid retention has been treated effectively.

**CONCLUSION**

Use of certain β-blockers in patients with mild to moderate heart failure has been shown to improve both morbidity

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and mortality significantly. Recent clinical guidelines strongly recommend initiation of β-blocker therapy for all patients with NYHA class II to III heart failure who are clinically stable with standard treatment. Carvedilol, ER metoprolol succinate, and bisoprolol have all been studied in such settings; both carvedilol and ER metoprolol succinate are approved in the United States for the management of CHF. Treatment with β-blockers may produce adverse events, such as hypotension, symptoms of worsening heart failure, and symptomatic bradycardia. However, careful initiation along with appropriate dosing and titration allows patients to reach target doses with acceptable tolerability. When the maintenance dose is achieved, treatment should be continued indefinitely.8

Although β-blockers exhibit various pharmacological properties, no data support the preferential use of one agent over another. Therefore, selection of β-blockers should be based on individual patient characteristics, cost, convenience, and potential for compliance with therapy. Regardless of the agent used, appropriate dosing and titration of β-blockers are essential for successful therapy. To achieve successful therapy, clinicians need to be educated regarding the appropriate dosing and titration of β-blockers and encouraged to use these life-saving medications in clinically stable patients with mild to moderate heart failure.25

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