

β -Blockers: New Standard Therapy for Heart Failure

ALLISON M. PRITCHETT, MD, AND MARGARET M. REDFIELD, MD

Despite recent advances in the diagnosis and treatment of cardiovascular disease, the prevalence of heart failure, a highly morbid and lethal condition, is increasing. Because of recent advances in basic and clinical research, β -blockade is now established as a highly effective therapy that reduces morbidity and mortality dramatically in patients with heart failure associated with reduced systolic function. The new guidelines from the American College of Cardiology-American Heart Association recommend use of β -blockers in all patients with symptomatic left ventricular systolic dysfunction. Now clinicians need to incorporate use of β -blockers into their standard approach to

the treatment of heart failure. We briefly summarize the basic and clinical evidence establishing the benefit of β -blockers for heart failure and provide practical information to assist clinicians in deciding when and how to use β -blockers in patients with heart failure.

Mayo Clin Proc. 2002;77:839-846

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; CHF = congestive heart failure; EF = ejection fraction; NYHA = New York Heart Association; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system

Congestive heart failure (CHF) is a clinical syndrome that represents the final common pathway for nearly all forms of cardiovascular disease, including hypertension, coronary artery disease, valvular disease, cardiomyopathies, and congenital heart disease. The prevalence of CHF is increasing, as are the costs related to treatment of this highly morbid condition. It is now well recognized that CHF represents a progressive disorder. Indeed, new practice guidelines from the American College of Cardiology (ACC)-American Heart Association (AHA) have reclassified CHF, emphasizing that CHF progresses from cardiovascular disease without cardiac dysfunction (stage A), to asymptomatic cardiac dysfunction (stage B), to overt CHF (stage C), and then to refractory CHF (stage D).¹ Although it is now clear that nearly 50% of individuals with the clinical syndrome of CHF have preserved systolic function, optimal therapy for CHF in this setting has not been established.² This review concentrates on medical therapy for CHF associated with a reduced ejection fraction (EF).

In the 1970s, CHF treatment consisted of bed rest, diuretics, and digoxin. Despite these therapies, outcome remained bleak. In the 1970s and 1980s, studies in human and experimental CHF established that CHF is associated

with the activation of several humoral systems, most notably the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS). These studies showed that circulating levels of renin, angiotensin II, aldosterone, and norepinephrine were increased in patients with CHF in proportion to the severity of CHF and risk of mortality.³ With the advent of drugs capable of antagonizing RAAS, these experimental observations were ultimately translated into clinical trials that conclusively showed that angiotensin-converting enzyme (ACE) inhibitors reduced mortality and morbidity in patients with CHF. Thus, since the early 1990s, ACE inhibitors have been considered standard therapy for all patients with reduced EF with or without symptoms of CHF (stage B-D). Angiotensin-receptor blockers may be used for patients intolerant of ACE inhibitors. However, subgroup analysis from the Valsartan Heart Failure Trial (Val-HeFT) showed a significant increase in mortality and a trend toward worsening morbidity when the angiotensin-receptor blocker valsartan was added to ACE inhibition and β -blockade.⁴ Current ongoing trials should help clarify how complete neurohormonal antagonism should be. Until these data are available, either an ACE inhibitor *or* an angiotensin-receptor blocker should be added to β -blockade.

Despite clear evidence of SNS activation and its association with increased mortality in patients with CHF, antagonism of SNS activation as a therapy for CHF was not embraced because it appeared counterintuitive to clinical management and known physiologic mechanisms. Catecholamines are potently inotropic and enhance diastolic function by promoting left ventricular relaxation (positive lusitropism), thereby supporting the circulation in the set-

From the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic, Rochester, Minn.

A question-and-answer section appears at the end of this article.

Address reprint requests and correspondence to Margaret M. Redfield, MD, Division of Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (e-mail: redfield.margaret@mayo.edu).

Table 1. Summary of Clinical Trials of β -Blocker Use in Patients With CHF*

| Trial | Drug | No. of patients | Duration (mo) | NYHA class | Total mortality (%) | | Change in hospitalization rate for CHF [†] (%) |
|--------------------------------------------------------------------------------------------------------|---------------|-----------------|--------------------|------------|---------------------|---------|---------------------------------------------------------|
| | | | | | β -Blocker | Placebo | |
| US Carvedilol Heart Failure Study Group ⁸ | Carvedilol | 1094 | 6; 12 for mild CHF | II-IV | 3.2 | 7.8 | -5.5 for all cardiac causes |
| Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN) ⁹ | Carvedilol | 1959 | Mean, 15.6 | NA | 12 | 15 | -2.0 |
| Carvedilol Prospective Randomized Cumulative Survival Study Group (COPERNICUS) ¹⁰ | Carvedilol | 2289 | Mean, 10.4 | IV | 11.2 | 16.8 | NA |
| Metoprolol in Dilated Cardiomyopathy (MDC) ¹¹ | Metoprolol | 383 | 12-18 | II-III | 11.9 | 10.1 | NA |
| Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) ^{12,13} | Metoprolol XL | 3991 | 12 | II-IV | 7.3 | 10.8 | -4.7 |
| Cardiac Insufficiency Bisoprolol Study (CIBIS I) ¹⁴ | Bisoprolol | 641 | 22.8 | III-IV | 16.6 | 20.9 | -9 |
| CIBIS II ¹⁵ | Bisoprolol | 2647 | 15.6 | III-IV | 11.8 | 17.3 | -6 |
| Beta-Blocker Evaluation of Survival Trial (BEST) ¹⁶ | Bucindolol | 2708 | 24 | III-IV | 30 | 33 | -7 |

*CHF = congestive heart failure; NA = not available; NYHA = New York Heart Association.

[†]Percent change in number of treated patients hospitalized for CHF vs placebo patients.

ting of reduced systolic function. Indeed, β -adrenergic receptor agonists are used to treat patients with cardiogenic shock. Furthermore, therapy with β -adrenergic receptor blockers can precipitate CHF episodes in patients with reduced systolic function. However, early anecdotal reports of benefits of β -blockers in patients with CHF began to emerge.^{5,6} These reports were viewed with skepticism until a seminal study by Mann⁷ showed that catecholamines had a toxic effect on the cardiomyocyte in vitro. This study suggested that SNS activation was not merely a marker of CHF severity, but rather it contributed to the progression of CHF. This theory was recently confirmed in murine models in which overexpression of any of the adrenergic signaling components may initially lead to enhanced systolic performance but will ultimately lead to cardiac dilatation, systolic and diastolic dysfunction, and the syndrome of CHF. A large number of clinical trials have shown that β -adrenergic blockade, when added to ACE inhibitor therapy, reduces morbidity and mortality in CHF associated with systolic dysfunction (Table 1). The bulk of clinical evidence to date has resulted in the unequivocal endorsement of β -blockers as standard therapy for patients with CHF. The ACC and the AHA have articulated this policy in their 2001 revision of CHF management guidelines.^{1,17}

Unfortunately, overcoming a previously accepted "dogma" is often difficult. There is considerable delay among establishment of efficacy of a new therapy, endorsement by professional medical societies, and integration into clinical practice. Indeed, utilization rates for ACE

inhibitors for patients with CHF remain disappointingly low. Integration of β -blockers into standard clinical practice may be even slower because these agents may precipitate CHF and cause several other adverse effects. It is only since the 1990s that heart failure survival rates have begun to improve. Data from the Scottish National Health Service database from 1986 through 1995 showed an increase in median survival from 1.23 to 1.64 years in heart failure patients.¹⁸ These benefits coincide with the incorporation of ACE inhibitor therapy into the standard heart failure regimen. Because of the apparent importance of neurohormonal modulation and the ability of β -blockers to reduce hospitalization rates, morbidity, and mortality in a clinical syndrome with a dismal prognosis, cardiologists and noncardiologists alike must become comfortable with the use of these agents in patients with CHF. The purpose of this review is to provide practical guidelines to assist noncardiologists in the integration of β -blockers into their approach to the patient with CHF.

WHY DO β -BLOCKERS BENEFIT PATIENTS WITH CHF?

Multiple mechanisms contribute to the beneficial effects of β -blockers in CHF. Simply, the reduction in heart rate serves to lower myocardial energy expenditure, prolongs diastolic filling, and hence lengthens coronary perfusion. β -Blockers possess antihypertensive, anti-ischemic, and antiarrhythmic properties. This pharmacological class also works adjunctively with ACE inhibitors as β_1 -adrenergic stimulation activates the renin-angiotensin cascade.¹⁹ As

Table 2. β -Blockers and Their Effect on EF*

| Trial | Drug | No. of patients | Change in EF (%) | | Duration (mo) |
|--------------------------------------------------------------------------------------------------|------------|-----------------|-------------------|-----------|---------------|
| | | | β -Blockers | Placebo | |
| Krum et al ²² | Carvedilol | 56 | 6.5 | -0.4 | 3.5 |
| Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) ²³ | Carvedilol | 345 | 6.3 | 2 | 6 |
| Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (PRECISE) ²¹ | Carvedilol | 278 | 8.0 | 3.0 | 6 |
| Australia/New Zealand Heart Failure Research Collaborative Group (ANZ) ²⁴ | Carvedilol | 415 | 5.1 | -0.2 | 12 |
| Beta-Blocker Evaluation of Survival Trial (BEST) ¹⁶ | Bucindolol | 2708 | 7.3 | 3.3 | 12 |
| Metoprolol in Dilated Cardiomyopathy (MDC) ¹¹ | Metoprolol | 383 | 12.0 | 6.0 | 12 |
| Total | ... | 4185 | Mean, 7.5 | Mean, 2.3 | ... |

*EF = ejection fraction.

aforementioned, β_1 -adrenergic stimulation exerts a toxic effect on the myocardium by activating calcium channels that cause myocyte calcium overloading and finally apoptosis or cell necrosis.⁷ Preventing myocyte loss may be a mechanism by which β -blockers inhibit detrimental left ventricular remodeling.

WHAT IS THE CLINICAL EVIDENCE OF BENEFIT FROM β -BLOCKERS?

Initial studies analyzing β -blocker utility were performed in the 1970s in Sweden^{5,6} in a small number of young patients with dilated cardiomyopathy and moderate to severe heart failure and in the absence of ACE inhibitors. Findings showed significant symptomatic improvement, improved exercise capacity, increased EF, and survival. Since then, many large randomized, placebo-controlled trials have analyzed β -blockers in heart failure of all etiologies (Table 1). Of importance, these trials have been performed in the modern arena of heart failure, seeking benefit in the setting of accepted optimal medical management. Thus, in all clinical trials of β -blockers, β -blocker therapy was added to standard therapy that included ACE inhibition. Cleland et al²⁰ summarized the mortality benefits of large placebo-controlled trials as follows: β -blockers reduce the *absolute* risk of death over an average 13-month follow-up by 4.5%, decreasing the 12.8% placebo mortality rate to 8.3% in the treated group. This translates into 45 lives saved for every 1000 persons treated. In analyzing the etiology of death, sudden cardiac death and death due to progressive heart failure are both reduced with β -blocker therapy. Hospitalization rates are significantly decreased as well. Specifically, the number of patients hospitalized, total hospitalizations, and duration of hospitalization were lower in patients taking β -blockers.¹²

In addition to the dramatic effects on mortality and morbidity (Table 1), numerous studies have investigated the effect of β -blockers on functional status and quality of

life. Most, but not all, studies using carvedilol, metoprolol, bucindolol, and bisoprolol have shown an improvement in New York Heart Association (NYHA) class with treatment. The effects of β -blockers on quality of life have varied. Submaximal and maximal exercise performance, as assessed by the 6-minute walk and treadmill test, respectively, have generally failed to improve with β -blocker therapy. Exercise capacity may not be a useful measure of the efficacy of β -blockers.²¹ With a lowering of the maximal achievable heart rate, the increase in cardiac output with exercise may be blunted, thus limiting maximum exertion.

The effect of β -blocker therapy on indices of systolic function such as EF has also been studied. Early administration of a full dose of β -blockade reduces EF. However, this effect is transient, and prolonged (>3-6 months) β -blockade has been consistently shown to improve EF (Table 2). This observation emphasizes the necessity of long-term maintenance therapy. Other hemodynamic observations with therapy include lower pulmonary wedge pressures, decreased systemic vascular resistance, and increased stroke volume index.^{22,25,26}

WHICH PATIENTS SHOULD RECEIVE β -BLOCKERS?

Criteria for β -blocker therapy are summarized in Table 3. Although it was initially thought that β -blockers would be most beneficial in patients with nonischemic dilated cardiomyopathy, clinical trials have shown benefit in patients with ischemic and nonischemic dilated cardiomyopathy.

Most of the trials used β -blockade for patients in NYHA class II and III (mild to moderate symptoms). Previously, the number of class IV patients in the trials was small, making conclusions difficult. However, the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) randomized 2289 class IV patients to either carvedilol or placebo, with a mean follow-up of 10.4 months. The treatment group had a 35% reduction in the risk of death, supporting the use of β -blocker therapy in

Table 3. Patient Criteria for β -Blocker Therapy*

| |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Age ≥ 18 y [†] |
| Ejection fraction $<40\%$, with or without coronary artery disease |
| Already taking an ACE inhibitor or angiotensin-receptor blocker |
| Use of diuretics and digoxin as needed |
| Systolic blood pressure >85 mm Hg |
| Heart rate >60 beats/min without sick sinus syndrome or advanced heart block [‡] |
| NYHA class I§ |
| NYHA class II or III |
| NYHA class IV |
| If systolic blood pressure >85 mm Hg, heart rate >68 beats/min, creatinine level <2.8 mg/dL, "clinical euolemia," and taking standard conventional therapy ¹⁰ |

*ACE = angiotensin-converting enzyme; NYHA = New York Heart Association.

[†]This concise review did not address the pediatric population.

[‡]Can consider β -blocker use in selected patients with heart rate ≤ 60 beats/min.

[§]No randomized trials have specifically addressed NYHA class I patients.

patients with class IV CHF.¹⁰ Although this trial had the highest mortality rate in the placebo group compared with other published studies, confirming the severity of CHF in these patients, restrictions were stringent on what type of class IV patients were enrolled (Table 3). These characteristics must be considered when patients with severe CHF are selected for β -blocker therapy. Of importance, many patients present with class IV symptoms and quickly experience compensation with digoxin, diuretics, and ACE inhibitors. These patients are no longer in class IV and can be treated promptly with β -blocker therapy. Patients who remain in class IV while receiving aggressive medical therapy, particularly those with refractory volume overload, must be treated carefully. Some groups have advocated use of inotropic therapy with phosphodiesterase inhibitors as a bridge to allow tolerance of β -blockers.²⁷ This strategy remains investigational.

At the other end of the spectrum, little is known about the benefit of early β -blockade in asymptomatic patients with left ventricular dysfunction (stage B heart failure). Because heart failure is truly a progressive disease, it seems rational that asymptomatic patients identified early in the stage of disease may benefit from prompt initiation of β -blockade. A retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD), a prevention trial that enrolled 4223 asymptomatic and mildly symptomatic patients with an EF of 35% or lower, showed that the lowest mortality was in patients randomized to enalapril and already taking a β -blocker.²⁸ However, prospective data are lacking because clinical trials in patients with asymptomatic left ventricular dysfunction require large patient numbers and longer follow-up due to lower event rates. Whether prospective trials will be performed in patients with asymptomatic left ventricular dysfunction is unclear.

The new heart failure treatment guidelines from the ACC-AHA recommend that all "eligible" patients with asymptomatic systolic dysfunction (stage B CHF) take both an ACE inhibitor and a β -blocker.¹ Eligibility is loosely defined as an alternative indication for β -blockade (ie, coronary disease or hypertension).

Because older patients are often not included in clinical trials, there is concern that efficacy established in younger populations may not be observed in elderly populations. However, subgroup analyses of clinical trials suggest benefit across all age groups.^{8,13} Female patients have comprised approximately 20% of trial populations. Because of small numbers, subgroup or post hoc analyses, and inconsistent results between trials, sex-specific benefits are unclear.²⁹ A post hoc analysis of the Cardiac Insufficiency Bisoprolol Study (CIBIS II) using bisoprolol in 2647 patients with NYHA class III or IV failure showed that women (n=515) benefited from β -blockade and had an overall lower risk of death compared with men.³⁰ However, the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) subgroup analysis showed mortality reduction for men, not women.¹³ Larger meta-analyses need to be performed for a more definitive answer.

Racial differences have not been well studied, but the Beta-Blocker Evaluation of Survival Trial (BEST) using bucindolol in class III and IV heart failure patients noted the lack of a mortality benefit in black participants (n=627; hazard ratio, 1.17) compared with nonblack persons (hazard ratio, 0.82).¹⁶ The reasons for this have not been clearly delineated. The trial itself was terminated prematurely because of the dramatic mortality benefits seen in other β -blocker trials. In contrast, a retrospective review of the US carvedilol trials showed that carvedilol reduced the risk of death from any cause by 56% in black persons (n=217) and 68% in nonblack persons (n=877).³¹ Also, there were similar reductions in hospitalization rates and progression of heart failure for both groups. The lack of racial-specific response may be attributed to the pharmacological characteristics of carvedilol, but studies with larger cohorts are needed to support this conclusion.

Published clinical trials suggest that β -blockers are tolerated by 85% to 90% of patients with CHF. However, these data can be misleading because most of the clinical trials had an open-label run-in period. Therefore, the trials included only those patients who initially tolerated the medication. A recent retrospective analysis of community practice records in Australia confirmed an 88% tolerance rate.³² No one variable predicted intolerance, but rates of drug withdrawal increased with age, worsening NYHA class, elevated blood urea nitrogen, and lower diastolic blood pressure. Although caution is advised when β -

Table 4. Pharmacology and Dosing of β -Blockers*

| Drug | β_1 -Blockade | β_2 -Blockade | Other properties | Lipophilic | FDA approved for CHF | Initial dose (mg) | Goal dose (mg) |
|---------------|---------------------|---------------------|---------------------------|------------|----------------------|-------------------|----------------|
| Carvedilol | Yes | Yes | Vasodilatory, antioxidant | Yes | Yes | 3.125 bid | 25 bid† |
| Metoprolol XL | Yes | No | None | Yes | Yes | 12.5 qd | 200 qd |
| Bisoprolol | Yes | No | None | Yes | No | 1.25 qd | 10 qd |

*bid = twice daily; CHF = congestive heart failure; FDA = Food and Drug Administration; qd = every day.

†50 mg bid if patient's weight is more than 85 kg.

blockers are being considered in patients with bradyarrhythmias, advanced heart block, and asthma or chronic obstructive pulmonary disease, each patient should be considered individually. Specifically, evidence shows that the benefits seen with β -blockers may outweigh the risks associated with relative contraindications. For example, Chen et al³³ recently showed that patients with asthma or chronic obstructive pulmonary disease who were not taking bronchodilators and those with mild disease controlled with β -agonists had a survival benefit with β -blockade after myocardial infarction. Cardioselective agents may be better tolerated in patients with pulmonary disease.

WHICH β -BLOCKER SHOULD BE USED?

Currently, only carvedilol and long-acting metoprolol are approved by the Food and Drug Administration for the indication of heart failure. Second- and third-generation β -blockers, metoprolol, carvedilol, bucindolol, and bisoprolol, have been studied more extensively than earlier drugs such as propranolol and atenolol. Although all β -blockers share blockade of the β_1 -receptor, there is considerable variability in the agents in regard to other properties that they possess (Table 4). Whether these differences translate into significant differences in efficacy in CHF is the subject of considerable debate. The most fundamental issue is whether a nonselective agent that blocks both the β_1 - and β_2 -receptors is superior to an agent that blocks only the β_1 -receptor. The ratio of β_2 -/ β_1 -receptors is increased in patients with CHF because of the greater down-regulation of β_1 -receptors. This suggests that nonselective agents may provide more complete antagonism of the SNS and more potent clinical effects. One prospective study³⁴ suggested that increases in EF are greater with nonselective agents, whereas a meta-analysis of 18 trials showed no difference in effect on EF.³⁵ Nonselective β -blockers decreased mortality more robustly than did selective agents. The ongoing Carvedilol and Metoprolol European Trial (COMET) was designed to further clarify this issue by randomizing patients to a nonselective (carvedilol) or β_1 -selective (metoprolol) agent. Pindolol and acebutolol are 2 β -blockers that possess intrinsic sympathomimetic qualities. This si-

multaneous stimulation and blockade of the β -receptors result in less slowing of the heart rate, increased norepinephrine levels, and hence acutely higher peripheral vascular resistance.³⁶ Because of these detrimental effects, these agents are not currently recommended for use in patients with heart failure. In addition to differences in β -receptor selectivity, many agents possess other ancillary properties, such as α -blockade, direct arterial vasodilatation, and antioxidant properties. Few data suggest that these effects are important clinically, and the potential advantage provided by these agents requires further study.

HOW SHOULD β -BLOCKERS BE INITIATED AND ADJUSTED IN CHF?

Before a β -blocker is initiated, patients should be taking other conventional heart failure treatments (ACE inhibitors, diuretics with or without digoxin), they should be clinically euvolemic, and they should not recently have required intravenous inotropes. The key to dosing in these patients is to start low and titrate up slowly. Typically, the dose is doubled every 2 weeks until the goal dose is reached or intolerable adverse effects are apparent. The initial and goal doses for the β -blockers approved for use in heart failure are listed in Table 4. Patients with more severe heart failure, those with "borderline" blood pressure or heart rate, or those who experience adverse effects may need a much slower titration, with smaller increments in dose every 2 weeks. Patients should be seen or contacted by telephone before each step in the titration upward. Nurses can telephone stable patients and ask them about their blood pressure, heart rate, weight, CHF symptoms, and adverse effects before each dose adjustment. Unstable patients are seen by a physician before each adjustment. Patients should be encouraged to call with questions regarding the titration process because some adverse effects are transient or will respond to adjustment of other medications. Common adverse effects and the recommended responses are listed in Table 5. Of importance, fatigue can be due to the central effects of β -blockade or to worsening CHF during dose titration. This distinction must be made clinically because fatigue not associated

Table 5. Common Adverse Effects of β -Blockers*

| Effect | Recommended action |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Fatigue without CHF | Encourage continuation as fatigue may improve |
| Worsening CHF | Adjust diuretics and ACE inhibitor; consider a vasodilatory β -blocker; decrease dose transiently |
| Hypotension | Alter doses of other medications (ACE inhibitors, diuretics) or decrease dose |
| Bradycardia | May require a decrease in dose or placement of a pacemaker |
| Bronchospasm | Try a β_1 -selective agent plus inhaled β_2 -agonists; β -blockers are contraindicated in moderate to severe asthma |
| Cold extremities | Avoid nonselective agents |
| Worsening claudication | Reduce dose; consider a vasodilatory β -blocker; or discontinue β -blocker |
| Sexual dysfunction | Discuss relative risk-benefit with patient |
| Nightmares | Give medication in the morning |

*ACE = angiotensin-converting enzyme; CHF = congestive heart failure.

with CHF often will improve with time, but fatigue due to low blood pressure, low heart rate, or worsening CHF must be treated.

Although the goal of therapy is to achieve the maximally tolerated dose, it is important to recognize that lower doses of β -blockers improve mortality. The Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) dose-ranging carvedilol study showed progressively lower mortality with increasing dosage. Compared with placebo, a low dose (6.25 mg twice daily) provided an absolute reduction in mortality of 9.5% compared with 14.4% with the highest dose (25 mg twice daily).²³ Interestingly, preliminary data from CIBIS II indicate that the higher the dose of β -blockers tolerated, the better the prognosis. However, survival was improved with all doses of β -blockade.³⁷

HOW SHOULD β -BLOCKER THERAPY BE MONITORED?

Patients should be seen and examined regularly for signs and symptoms of heart failure or adverse effects due to β -blockade. Because at least 3 months of therapy are required to observe the full benefit of β -blockade, systolic function should be reanalyzed approximately 6 to 12 months after initiation of therapy. Dramatic improvements may be seen, but this outcome should not prompt an assumption of "cure" and discontinuation of the β -blocker. If a patient is able to tolerate a submaximal dose or the dosage needs to be decreased because of adverse effects, retitration can be attempted after several weeks of stabilization.

In conclusion, β -blockers are proved to reduce mortality and morbidity dramatically in patients with CHF. Although initiating and titrating therapy require an investment from both patient and physician, clinical evidence has shown a magnitude of benefit for patients with CHF. In many patients with CHF, β -blocker therapy can be initiated by

noncardiologists. If initial attempts are not tolerated or if there are concerns regarding possible contraindications or instability, referral to a cardiologist or heart failure clinic may be warranted.

REFERENCES

- Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol*. 2001;38:2101-2113.
- Hart CY, Redfield MM. Diastolic heart failure in the community. *Curr Cardiol Rep*. 2000;2:461-469.
- Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. *Circulation*. 2000;102(20, suppl 4):IV14-IV23.
- Cohn JN, Tognoni G, Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667-1675.
- Swedberg K, Hjalmarson A, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. *Lancet*. 1979;1:1374-1376.
- Waagstein F, Hjalmarson A, Varnauskas E, Wallentin I. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. *Br Heart J*. 1975;37:1022-1036.
- Mann DL. Basic mechanisms of disease progression in the failing heart: the role of excessive adrenergic drive. *Prog Cardiovasc Dis*. 1998;41(1, suppl 1):1-8.
- Packer M, Bristow MR, Cohn JN, et al, U.S. Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *N Engl J Med*. 1996;334:1349-1355.
- CAPRICORN Investigators. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385-1390.
- Packer M, Coats AJS, Fowler MB, et al, Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001;344:1651-1658.
- Waagstein F, Bristow MR, Swedberg K, et al, Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group. Beneficial ef-

- fects of metoprolol in idiopathic dilated cardiomyopathy. *Lancet*. 1993;342:1441-1446.
12. Hjalmarson A, Goldstein S, Fagerberg B, et al, MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA*. 2000;283:1295-1302.
 13. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-2007.
 14. CIBIS Investigators and Committees. A randomized trial of beta-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study (CIBIS). *Circulation*. 1994;90:1765-1773.
 15. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9-13.
 16. Beta-Blocker Evaluation of Survival Trial Investigators. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N Engl J Med*. 2001;344:1659-1667.
 17. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Circulation*. 2001;104:2996-3007.
 18. MacIntyre K, Capewell S, Stewart S, et al. Evidence of improving prognosis in heart failure: trends in case fatality in 66 547 patients hospitalized between 1986 and 1995. *Circulation*. 2000;102:1126-1131.
 19. Eichhorn EJ, McGhie AL, Bedotto JB, et al. Effects of bucindolol on neurohormonal activation in congestive heart failure. *Am J Cardiol*. 1991;67:67-73.
 20. Cleland JG, Bristow MR, Erdmann E, Remme WJ, Swedberg K, Waagstein F. Beta-blocking agents in heart failure: should they be used and how? *Eur Heart J*. 1996;17:1629-1639.
 21. Packer M, Colucci WS, Sackner-Bernstein JD, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure: the PRECISE Trial. *Circulation*. 1996;94:2793-2799.
 22. Krum H, Sackner-Bernstein JD, Goldsmith RL, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation*. 1995;92:1499-1506.
 23. Bristow MR, Gilbert EM, Abraham WT, et al, MOCHA Investigators. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation*. 1996;94:2807-2816.
 24. Australia/New Zealand Heart Failure Research Collaborative Group. Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. *Lancet*. 1997;349:375-380.
 25. Pollock SG, Lystash J, Tedesco C, Craddock G, Smucker ML. Usefulness of bucindolol in congestive heart failure. *Am J Cardiol*. 1990;66:603-607.
 26. Woodley SL, Gilbert EM, Anderson JL, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation*. 1991;84:2426-2441.
 27. Shaker SF, Bristow MR. Low-level inotropic stimulation with type III phosphodiesterase inhibitors in patients with advanced symptomatic chronic heart failure receiving beta-blocking agents. *Curr Cardiol Rep*. 2001;3:224-231.
 28. Exner DV, Dries DL, Waclawiw MA, Shelton B, Domanski MJ. Beta-adrenergic blocking agent use and mortality in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a post hoc analysis of the Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol*. 1999;33:916-923.
 29. McMurray JJV. Major β blocker mortality trials in chronic heart failure: a critical review. *Heart*. 1999;82(suppl IV):IV14-IV22.
 30. Simon T, Mary-Krause M, Funck-Brentano C, Jaillon P. Sex differences in the prognosis of congestive heart failure: results from the Cardiac Insufficiency Bisoprolol Study (CIBIS II). *Circulation*. 2001;103:375-380.
 31. Yancy CW, Fowler MB, Colucci WS, et al, U.S. Carvedilol Heart Failure Study Group. Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. *N Engl J Med*. 2001;344:1358-1365.
 32. Krum H, Ninio D, MacDonald P. Baseline predictors of tolerability to carvedilol in patients with chronic heart failure. *Heart*. 2000;84:615-619.
 33. Chen J, Radford MJ, Wang Y, Marciniak TA, Krumholz HM. Effectiveness of beta-blocker therapy after acute myocardial infarction in elderly patients with chronic obstructive pulmonary disease or asthma. *J Am Coll Cardiol*. 2001;37:1950-1956.
 34. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. *Circulation*. 2000;102:546-551.
 35. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation*. 1998;98:1184-1191.
 36. Majid PA, Niznick J, Nishizaki S, Morris WM, Sole MJ. Acute hemodynamic and neurohumoral effects of pindolol: a beta-adrenoceptor antagonist with high intrinsic sympathomimetic activity in patients with dilated cardiomyopathy. *J Cardiovasc Pharmacol*. 1987;10:309-314.
 37. Tabassome S, Krause MM, Funck-Brentano C, Jaillon P. Bisoprolol dose-response in the Cardiac Insufficiency Bisoprolol Study (CIBIS II) [abstract]. *Circulation*. 2000;102(suppl 2):II-629. Abstract 3051.

Questions About Treatment of CHF

1. Which one of the following statements is false regarding β-blocker use in patients with CHF and reduced systolic function?
 - a. Mortality from worsening CHF and sudden cardiac death decreases
 - b. New York Heart Association class improves
 - c. Exercise performance improves
 - d. Ejection fraction improves
 - e. Hospitalization rates and duration of stay decrease
2. Which one of the following is not a detrimental effect of adrenergic stimulation on the myocardium?
 - a. Stimulation of the renin-angiotensin system
 - b. Shortening of coronary perfusion
 - c. Increase in myocardial oxygen demand
 - d. Increase in intracellular calcium that may lead to apoptosis
 - e. Lengthening of diastolic filling

3. Which *one* of the following patients would *not* be a candidate for a β -blocker?
- An 80-year-old man with an EF of 25%, first-degree atrioventricular block, and a heart rate of 62 beats/min
 - A 55-year-old woman with idiopathic dilated cardiomyopathy, atrial fibrillation, and a heart rate of 90 beats/min
 - A 65-year-old man with chronic obstructive pulmonary disease who is using no bronchodilators, has a previous myocardial infarction and EF of 20%, and is euvolemic while taking diuretics and ACE inhibitors
 - An asymptomatic 40-year-old woman in whom echocardiography shows an EF of 35%
 - A 70-year-old man with dyspnea at rest, rales, edema, and systolic blood pressure of 75 mm Hg
4. Which *one* of the following statements about β -blocker use in CHF is *false*?
- If adverse effects necessitate a decrease in dosage, do not try to retitrate the dose once the patient is stabilized
 - β -Blockers should be continued even if EF improves
 - Metoprolol XL and carvedilol are approved for treatment
 - Mortality benefit has been shown even with small doses of β -blockade
 - Patients should be questioned about their weight, blood pressure, heart rate, and adverse effects before a dosage is changed
5. Which *one* of the following is *not* a possible adverse effect of β -blockers?
- Worsening claudication
 - Bradycardia
 - Hypotension
 - Tremor
 - Bronchospasm
- Correct answers:
1. *c*, 2. *e*, 3. *e*, 4. *a*, 5. *d*