Overview of Beta Blockers for Systolic Heart Failure

Steven D. Hanks, MD, MMM, FACP

Introduction

Congestive heart failure (CHF) is one of the costliest chronic conditions in the U.S., with direct and indirect expenditures of approximately $27.9 billion in 2005.1 It is estimated that more than 4.5 million Americans have this condition.2 Each year, more than 500,000 new cases of heart failure are diagnosed in the U.S.1 Data from the Framingham Heart Study indicate that 20% of both men and women, at 40 years of age, will develop CHF at some point in their lifetime.3

Given this significant burden, it is incumbent upon health care providers to ensure that patients with systolic dysfunction are receiving optimal therapy. Until recently, such therapy was directed toward volume control, afterload reduction, inotropic support, and avoidance of negative inotropes. More recently, the focus has changed to include therapy aimed at some of the underlying neurohormonal adaptations associated with CHF.

Few paradigm shifts have been as striking as that regarding the use of beta blockers in patients with systolic dysfunction. Just 15 years ago, trainees were still being taught, in many cases quite dogmatically, that heart failure was an absolute contraindication to beta blockade. This belief was based on the known negative inotropic effects of these agents and the predominant pathophysiological view that heart failure was primarily a hemodynamic disorder. Since the 1980s, a new understanding of the pathophysiology of CHF has emerged. This new view emphasizes the deleterious effects of enhanced sympathetic tone and the neurohormonal system.4

The demonstration that plasma noradrenephrine levels were independently related to mortality in patients with heart failure was one of the first lines of evidence in support of the deleterious role of sympathetic activation in this disorder.5 Activation of compensatory vasoconstriction in these patients via mediators of the sympathetic system (the renin–angiotensin–aldosterone system and arginine vasopressin) was postulated to eventually add to the burden of a failing myocardium.6 This led to the recognition that inhibiting these neurohormonal systems in heart failure might prove beneficial,6 a view that has endured for the ensuing 15 years. This expanded understanding of the pathophysiology of CHF has resulted in the paradigm shift. As a result, beta blockers are now seen as an integral part of the proper management of patients with symptomatic systolic dysfunction.

Educational Objectives

After reviewing this article, the reader should be able to:

- Describe the pharmacology of the various types of beta blockers.
- Understand the rationale for treating systolic heart failure with beta blockers.
- Identify patient selection for using beta blockers in systolic heart failure.

Brief Overview of Beta Blockers

In 1948, Ahlquist demonstrated that adrenergic receptors can be divided into two types: alpha and beta.7 A decade later, a specific inhibitor of the beta class of adrenergic receptors was identified.8 There are at least three subtypes of beta receptors:

- Beta 1 receptors are found primarily in heart myocytes. Blockade of beta 1 receptors slows the heart rate, reduces contractility, and delays atrioventricular (AV) conduction.9
- Beta 2 receptors are also found in heart tissue, but they are more numerous in bronchial and peripheral vascular smooth muscle.10 These receptors mediate bronchodilation and vasodilation.10

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is what gives nonselective beta blockers their bronchospastic potential.

- Beta 3 receptors are found in heart and adipose tissue and may serve to reduce cardiac contractility.11

The recognition of the different beta receptors gave rise to the development of beta blockers that were relatively selective at one of the receptor subtypes.12 In addition to being classified as selective or nonselective, beta blockers are also characterized according to whether they have intrinsic sympathomimetic activity. This is the characteristic of a beta blocker that induces a slight cardiac stimulation that can be blocked by propranolol (e.g., Innopran, Reliant; Inderal, Wyeth).13

The reduced contractility mediated by beta 1 blockade was the principal reason why beta blockers were historically considered to be contraindicated in patients with CHF. It seemed sensible to avoid anything that could further weaken an already weakened muscle. This sentiment began to change in the early 1990s as a better understanding of the role of neurohormonal systems in the pathophysiology of CHF took hold.

**Beta Blockers in Systolic Dysfunction**

Despite the relatively recent change in attitudes about beta-blocker usage in heart failure, the idea that beta blockade might actually benefit patients with CHF is three decades old. In 1975, Waagstein et al. reported that beta blockade improved ejection fraction and clinical status in seven patients with congestive cardiomyopathy and that withdrawal of beta-blocker therapy resulted in clinical deterioration.14 In the 1990s, a series of studies demonstrated the positive effects of various beta blockers on contractility and hemodynamics.15–21

The concept that beta blockers might prolong survival in CHF patients was first reported in 1979.22 In the past 10 years, a number of large, well-designed studies have confirmed improvement in overall survival in patients with CHF who were treated with long-acting metoprolol,16,23,24 carvedilol (Coreg, GlaxoSmithKline),25 and bisoprolol (Zebeta, Duramed).26,27 Bucindolol also improves cardiovascular, but not overall, mortality in patients with CHF.28

In these studies, the effects of beta blockade were additive to that of standard heart failure therapy. As a result of these accumulating data, beta blockade for symptomatic systolic dysfunction was graded a class IA recommendation in the 2001 updated American College of Cardiology/American Heart Association (ACC/AHA) guidelines for CHF.29

**Reduced Mortality with Beta Blockade As Shown in Major Trials**

Since 1996, major mortality benefits for patients with systolic dysfunction have been demonstrated in several large trials involving bucindolol, carvedilol, and the long-acting form of metoprolol succinate (Toprol XL, AstraZeneca).

**Packer et al.**25

The first major report came from the U.S. Carvedilol Heart Failure Program. The program enrolled nearly 1,100 patients with New York Heart Association (NYHA) class II or III heart failure. The patients had already been treated with diuretics, digoxin, and angiotensin-converting enzyme (ACE)–inhibitors. They were randomly selected to receive placebo or carvedilol at an initial dose of 6.25 mg twice daily and gradually increased to a maximum of 25 mg twice daily. The Data and Safety Monitoring Board terminated the study prematurely because the carvedilol group experienced a 65% reduction in the risk of mortality.25

**MERIT-HF**23

The Metoprolol Controlled-Release/Extended-Release (CR/XL) Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) enrolled almost 4,000 patients with NYHA class II–IV heart failure. These patients were already receiving placebo or standard therapy with long-acting metoprolol, starting at 12.5 or 25 mg daily, with the dose titrated to a maximum of 200 mg daily. As with the earlier carvedilol study, MERIT-HF was stopped early because of the significant benefit derived from active treatment. Long-acting metoprolol resulted in a 34% reduction in the relative risk of all-cause mortality at 12 months.23

**CIBIS II**26

The efficacy of bisoprolol for mortality reduction in heart failure was demonstrated in the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). In this study, nearly 2,700 patients with NYHA Class III or IV heart failure already receiving diuretics and ACE-inhibitors were randomly assigned to take either bisoprolol (starting at 1.25 mg daily, titrated to a maximum of 10 mg daily) or placebo. As with the carvedilol and metoprolol studies, CIBIS II was also prematurely terminated because of the positive treatment effect. All-cause mortality was 11.8% for patients receiving bisoprolol and 17.3% for those taking placebo (hazard ratio, 0.66).26

**Brophy et al.**30

How significant is the effect of beta blockers overall? A Bayesian meta-analysis of 22 trials involving 10,135 patients with heart failure who took ACE-inhibitors estimated that 3.8 lives were saved and four hospitalizations were avoided in the first year for every 100 patients receiving additional beta-blocker therapy. The mortality rate with beta blockade was reduced at both one year (odds ratio, 0.65; 95% confidence interval [CI], 0.53–0.80) and at two years (odds ratio, 0.72; 95% CI, 0.61–0.84).30

**Who Should Be Treated?**

An analysis of the major trials and subsequent smaller studies of beta blockers in heart failure generally shows that the effects of beta blockade extend to almost all subgroups of patients with systolic dysfunction. This includes elderly
Patients, women, diabetic patients, those with advanced disease (NYHA class III/IV), and patients outside the context of clinical trials.

In black patients, the effects of beta blockade have varied, according to the specific agent used. Carvedilol and long-acting metoprolol appear to be equally efficacious in blacks and whites. However, bucindolol appears to show no benefit in black patients. The reasons for this are not clear, but in recent trials of beta blockers for heart failure, bucindolol seemed to have the weakest effect, showing no benefit for overall mortality in the populations studied.

Most of the major trials excluded patients with absolute and relative contraindications to beta-blocker therapy (Table 1). Health care providers should prescribe beta blockers in patients with relative contraindications only with the appropriate input and full informed patient consent, and they should proceed cautiously and with close, ongoing patient monitoring.

Unfortunately, there is often a lag between the publication of evidence-based guidelines and the adoption of such practices in routine clinical care. Limited evidence suggests that this is the case with beta-blocker use for symptomatic heart failure.

The American College of Cardiology Foundation recently reported the results of the Guidelines Applied in Practice (GAP) project, which examined, among other things, compliance with the 2001 ACC/AHA heart failure guidelines. This 18-month project was a quality-improvement initiative, conducted in six outpatient cardiology practices in Oregon.

At the baseline measurement, it was found that compliance with the recommendation for appropriate beta-blocker therapy was just above 60%, improving to just over 70% in the course of the project. It would not be unreasonable to presume that the numbers would be lower among primary care practices, in which a good portion of the chronic care for CHF patients takes place. On the basis of these considerations, there is likely to be a large population of patients with systolic dysfunction in whom beta blockers are indicated but who are not receiving such therapy.

### Which Beta Blocker Should Be Used?

Beta blockers with intrinsic sympathomimetic activity, such as acebutolol (Sectral, ESP Pharma) and pindolol (Visken, Novartis), should be avoided, because this property may increase mortality. As for beta blockers without intrinsic sympathomimetic activity, it seems prudent to use those agents that do improve survival. These include both the nonselective beta blocker carvedilol and the cardioselective beta blockers metoprolol succinate (the long-acting form of metoprolol) and bisoprolol.

Bucindolol should probably not be used, because it has not been shown to improve overall mortality; it is also of questionable value in black patients. These limitations may be partly a result of the fact that bucindolol does have some weak intrinsic sympathomimetic activity.

Only one major trial has been designed to address whether there is an advantage to one beta blocker over another in patients with heart failure. In the Carvedilol Or Metoprolol European Trial (COMET), 3,029 patients with chronic heart failure were randomly assigned, in a double-blind fashion, to receive carvedilol or metoprolol tartrate (Lopressor, Novartis), the short-acting form of metoprolol. Although the COMET investigators suggested that carvedilol was more effective, their conclusion drew significant criticism, because the formulation (short-acting vs. long-acting metoprolol) and the target dose (50 mg twice daily) of metoprolol were not consistent with those used in the MERIT-HF study. This is of particular concern, because the degree of beta blockade achieved in the COMET trial differed between the two groups; the carvedilol arm showed consistently greater reductions in heart rate as well as in systolic blood pressure.

A more appropriate and relevant comparison would have been to compare carvedilol at the dosages used with extended-release metoprolol in the dosages used in MERIT-HF, the largest and most significant of the trials involving metoprolol for heart failure to date. Until further information is available from well-designed comparative studies, any of the three aforementioned agents can be used. The more important issue is to give beta-blocker therapy to patients with heart failure, irrespective of the choice of agent.

### Dosage and Titration

Data are limited in terms of the most appropriate doses of beta blockers for heart failure. In a small study of Japanese patients with chronic heart failure, the benefits of carvedilol at all endpoints were found to be dose-dependent. However, the benefits of carvedilol over placebo were found at even at the lowest doses (2.5 mg twice daily) in the trial.

One analysis of the MERIT-HF study showed that mortality outcomes were similar regardless of the degree of reduction in heart rate achieved with metoprolol. This suggests that the appropriate approach should consist of careful initiation of therapy at low starting doses, with titration to the doses targeted in the major clinical trials (Table 2). However, even for patients who can tolerate only doses lower than those targeted in the clinical trials, the evidence

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**Table 1: Contraindications to Beta-Blocker Therapy**

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
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<tbody>
<tr>
<td>Severe bradycardia</td>
<td>Hypotension</td>
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<tr>
<td>Heart block greater than first-degree</td>
<td>History of asthma</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>History of chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Decompensated heart failure</td>
<td>Severe peripheral vascular disease</td>
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* Unless a permanent pacer is in place.
supports the continuation of beta blockers.

Because of the immediate negative inotropic and chronotropic effects of these agents, beta-blocker therapy should not be initiated in patients with acutely decompensated heart failure or who have recently discontinued inotropic support therapies.38 Because it typically takes four or more weeks for hemodynamic improvements to take hold,39 patients should be warned that their condition might temporarily worsen during the initial phases of beta blocker therapy. Patients should be instructed to contact their physicians if they experience signs and symptoms such as weight gain and dyspnea.

For stable patients who are tolerating initial beta-blocker therapy, published guidelines suggest doubling of the dose each week or two until either the target dose is reached or until intolerance develops.38

Health care providers should warn patients of the signs and symptoms associated with the sudden cessation of beta-blocker therapy, and they should advise patients that the drugs should be tapered over time rather than abruptly withdrawn.

Conclusion

In less than two decades, beta-blocker therapy for patients with CHF has gone from something to be avoided at all costs to a mainstay of modern therapy. All patients with symptomatic systolic dysfunction who can tolerate beta blockade should be offered treatment. Beta blockers are probably underutilized in heart failure, and better compliance with published guidelines and evidence-based practices may result in significant benefits for these patients. Long-acting metoprolol, carvedilol, and bisoprolol are all acceptable choices for treatment. It is hoped that future studies will help us further distinguish between these agents.

References


Table 2 Dosing of Beta Blockers for Congestive Heart Failure

<table>
<thead>
<tr>
<th>Beta Blocker</th>
<th>Starting Dose</th>
<th>Target Dose</th>
<th>Retail Cost‡</th>
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<tbody>
<tr>
<td>Carvedilol (Coreg)</td>
<td>3.125–6.5 mg b.i.d.</td>
<td>25–50 mg b.i.d.</td>
<td>$189.98</td>
</tr>
<tr>
<td>Metoprolol succinate (Toprol XL)</td>
<td>12.5–25 mg q.d.</td>
<td>200 mg q.d.</td>
<td>$58.99</td>
</tr>
<tr>
<td>Bisoprolol (Zebeta)</td>
<td>1.25 mg q.d.</td>
<td>5–10 mg q.d.</td>
<td>$68.86</td>
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<tr>
<td>Nebivolol†</td>
<td>0.25 mg q.d.</td>
<td>10 mg q.d.</td>
<td>NA</td>
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* Specific FDA indication for congestive heart failure.
† Not available in the U.S.
b.i.d. = twice daily; NA = not applicable; q.d. = once daily.


Continuing Education Questions for Physicians and Pharmacists

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ACPE Program # 079-999-06-014-H01
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**TOPIC:** Overview of Beta Blockers for Systolic Heart Failure

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Multiple Choice
Select the one correct answer.

1. MERIT-HF was terminated prematurely because of a 34% reduction in relative risk of all-cause mortality at 12 months. The intervention drug in this trial was which of the following?
   a. short-acting metoprolol
   b. long-acting metoprolol
   c. carvedilol
   d. bisoprolol

2. Which of the following drugs appears to show no benefit for overall mortality in heart failure?
   a. bisoprolol
   b. metoprolol
   c. carvedilol
   d. bucindolol

3. According to the “Guidelines Applied in Practice” Project, compliance with the evidence-based ACC/AHA recommendation regarding beta-blocker therapy is an issue. At approximately what rate are these guidelines being followed?
   a. 20%–30%
   b. 40%–50%
   c. 60%–70%
   d. 80%–90%

4. Among heart failure patients treated with ACE-inhibitors, approximately how many lives can be saved by treating 100 patients additionally with beta blockers?
   a. 0.5
   b. 2
   c. 3
   d. 4

5. What were the approximate direct and indirect expenditures associated with congestive heart failure in 2005?
   a. $58.3 million
   b. $796 million
   c. $18.7 billion
   d. $27.9 billion

6. According to the Framingham Heart Study, at age 40 years, what percentage of Americans will develop congestive heart failure at some point during their lifetimes?
   a. 5%
   b. 20%
   c. 35%
   d. 60%

7. Which beta receptor would need to be blocked in order to slow the heart, reduce contractility, and slow atrioventricular conduction?
   a. beta 1
   b. beta 2
   c. beta 3
   d. beta 4

8. What was the principal reason why beta blockers were historically considered to be contraindicated in patients with congestive heart failure?
   a. Increased contractility mediated by beta 1 blockade
   b. Reduced contractility mediated by beta 1 blockade
   c. Increased contractility mediated by beta 2 blockade
   d. Reduced contractility mediated by beta 2 blockade

9. Which beta blocker is contraindicated in heart failure?
   a. bisoprolol
   b. carvedilol
   c. metoprolol
   d. acebutolol

10. For which of the following groups of patients is beta blockade indicated?
    a. patients with acutely decompensated heart failure
    b. patients who have recently used inotropic agents
    c. patients with brittle asthma and uncontrolled heart failure
    d. patients with compensated New York Heart Association class III heart failure
CE Registration and Evaluation Form

Date of publication: February 2006
Title: Overview of Beta Blockers for Systolic Heart Failure
Author: Steven D. Hanks, MD, MMM, FACP
Submission deadline: February 28, 2007
ACPE Program # 079-999-06-014-H01

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Answer Sheet
Please fill in the box next to the letter corresponding to the correct answer

1.   a   b   n   c   n   d   n
2.   a   b   n   c   n   d   n
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10.  a   b   n   c   n   d   n

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Rate the extent to which:

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Which ONE of the following best describes the impact of this activity on your performance:

n This program will not change my behavior because my current practice is consistent with what was taught.
n This activity will not change my behavior because I do not agree with the information presented.
n I need more information before I can change my practice behavior.
n I will immediately implement the information into my practice.

10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)

n Discuss new information with other professionals
n Discuss with industry representative(s)
Consult the literature
n Participate in another educational activity
n Other ____________________________________________

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