β-Blockers in Chronic Heart Failure

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**Case 1:** A 54-year-old man with a history of myocardial infarction (MI) presented with exertional dyspnea. Physical examination was unremarkable. Left ventricular ejection fraction (LVEF) by Doppler echocardiography was 35%, and a stress test was negative for ischemia. The patient was taking aspirin, a statin, and an angiotensin converting enzyme (ACE) inhibitor. He was started on 12.5 mg/d metoprolol controlled-release/extended release (CR/XL) and titrated to a target dose of 200 mg/d over several weeks.

**Case 2:** A 65-year-old woman with a history of heart failure (HF) due to hypertension (HTN) continued to have dyspnea with exertion and occasionally at rest. On physical examination, there was no jugular venous distention or ankle edema. Her LVEF was 10%. She was taking a loop diuretic, digoxin, and an ACE inhibitor; 3.125 mg twice/d carvedilol was added and slowly titrated to a target dose of 25 mg twice/d.

Chronic HF is a common clinical syndrome resulting from coronary artery disease (CAD), HTN, valvular heart disease, and/or primary cardiomyopathy. There is now conclusive evidence that β-blockers, when added to ACE inhibitors, substantially reduce mortality, decrease sudden death, and improve symptoms in patients with HF. Despite the overwhelming evidence and guidelines that mandate the use of β-blockers in all HF patients without contraindications, many patients do not receive this treatment.

**Demographics of HF**

In the United States, approximately 70% of patients with HF have CAD. Hypertension is a major risk factor for HF, particularly in blacks. An increasing number of HF patients have diabetes. Although the term “congestive” HF continues to be used, most patients, even those with severe symptoms, may have few or no signs of congestion. Often, if signs of congestion are not present, HF is not diagnosed, and these patients are therefore not considered for treatment.

Approximately 40% of patients with HF have preserved systolic function, frequently associated with HTN, CAD, diabetes, and/or atrial fibrillation. Such patients have diastolic dysfunction that is age related (for more information, see the Clinician Update by Grossman and Angeja). Sudden death accounts for the majority of deaths in HF patients, is more common (versus progressive circulatory failure) in patients with milder symptoms, and can occur before the development of symptoms or after symptoms have been well controlled.

Because of its diverse pathophysiology and presentations, there is no uniform classification for all the clinical manifestations of HF. However, the American College of Cardiology/American Heart Association recently released guidelines that described the 4 stages of HF (Table 1).

**Mechanism of Beneficial β-Blocker Effects in HF**

After a myocardial insult — acute (eg, MI) or chronic (eg, HTN) — that results in LV dysfunction, there is an increased activity of the renin-angiotensin and sympathetic nervous systems. Sympathetic nervous system activation may accelerate LV remodeling, worsen myocardial function, and lower the threshold for life-threatening arrhythmias. Progression of CAD also may contribute to worsening of HF.

It is possible that by reducing the harmful effects of excessive and continuous increased adrenergic drive on the myocardium, β-blockers cause time-dependent improvements in ventricular structure and function. Other likely beneficial actions include reductions in heart rate and blood pressure,
inhibition of the renin-angiotensin system, reduction of atrial and ventricular arrhythmias, and anti-ischemic effects. β-Blockers improve the contractility of viable but not contractile myocardial regions in patients with ischemic (hibernating myocardium) and nonischemic etiology. The beneficial effects of chronic β-blockade in HF occur despite an initial and transient decrease in contractility.

### Evidence Supporting the Use of β-Blockers in HF

#### Background

The initial experience with β-blockers in HF was reported in 1975, and the first observations on survival were made in 1979. However, the first multicenter randomized trial was not published until 1993, and it was 1997 before a β-blocker (carvedilol) was first approved for the treatment of HF. The reason for the slow acceptance of β-blocker therapy for HF seems to be related to the transient negative inotropic effect of acute β-blockade and the attendant risk of decompensation in patients with HF.

#### Randomized Clinical Trials

The available randomized data overwhelming show that carvedilol, metoprolol CR/XL, and bisoprolol reduce

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**TABLE 1.** Heart Failure Stages, Indications, Contraindications, and Relative Contraindications to β-Blockers

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>No. of Patients (United States Estimate)</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Relative Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Patients at high-risk of developing HF. These are patients with CAD, diabetes, HTN, and/or valvular heart disease.</td>
<td>~50 million</td>
<td>In addition to ACE inhibitors, β-blockers should be considered in patients with CAD, particularly if they are post-MI and/or have angina, and in patients with hypertension.</td>
<td>β-blockers are contraindicated in patients with:</td>
<td>● advanced heart block ● asthma or reactive airways disease that is not related to HF and requires bronchodilator therapy ● a heart rate &lt;50 bpm (unless a pacemaker is present) ● systolic blood pressure &lt;85 mm Hg.</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without clinical HF symptoms, many of whom have decreased systolic function.</td>
<td>~8 to 10 million</td>
<td>Should be prescribed to all patients with systolic dysfunction, regardless of its etiology.</td>
<td></td>
<td>● β-blockers can be used with caution in HF patients with COPD, diabetes, and peripheral vascular disease. ● The available data suggest that these patients are at particularly high risk for major cardiovascular events and derive a significant benefit from β-blocker therapy. ● β-blockers can also be used with caution in patients with HF associated with asymptomatic hypotension, sinus bradycardia (50 to 60 bpm), depression, and cocaine abuse.</td>
</tr>
<tr>
<td>C</td>
<td>Patients who have prior or current symptomatic HF due to systolic or diastolic dysfunction and who are responding to therapy.</td>
<td>~5 million</td>
<td>Should be used in all patients with systolic dysfunction in addition to diuretics, ACE inhibitors, and, depending on symptoms, digoxin and low-dose spironolactone. Patients with HF and preserved systolic function should also receive a β-blocker if they have hypertension, CAD, or atrial fibrillation.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Patients with end-stage or refractory-to-therapy HF.</td>
<td>~200 000</td>
<td>In selected patients who are not dependent on intravenous inotropes or intravenous diuretics.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**TABLE 2.** Major Placebo-Controlled Trials of β-Blockade in Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>HF Severity</th>
<th>Patients, n</th>
<th>Follow-up, mean years</th>
<th>Target Dosage, mg</th>
<th>Mean Dosage Achieved, mg/d</th>
<th>Effect on All-Cause Mortality</th>
<th>Effect on All-Cause Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Carvedilol†</td>
<td>Carvedilol</td>
<td>Mild/Moderate</td>
<td>1094</td>
<td>6.5 months</td>
<td>6.25 to 50 bid</td>
<td>45</td>
<td>↓ 65% (P=0.001)†</td>
<td>↓ 27% (P=0.036)</td>
</tr>
<tr>
<td>CIBIS-II</td>
<td>Bisoprolol*</td>
<td>Moderate/Severe</td>
<td>2647</td>
<td>1.3</td>
<td>10 qd</td>
<td>7.5</td>
<td>↓ 34% (P=0.0001)</td>
<td>↓ 20% (P=0.0006)</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Metoprolol CR/XL</td>
<td>Mild/Moderate</td>
<td>3991</td>
<td>1</td>
<td>200 qd</td>
<td>159</td>
<td>↓ 34% (P=0.0062)</td>
<td>↓ 18% (P=0.004)</td>
</tr>
<tr>
<td>BEST</td>
<td>Buclidol*</td>
<td>Moderate/Severe</td>
<td>2708</td>
<td>2</td>
<td>50 to 100 bid</td>
<td>152</td>
<td>NS</td>
<td>↓ 8% (P=0.08)</td>
</tr>
<tr>
<td>COPERNICUS†</td>
<td>Carvedilol</td>
<td>Severe</td>
<td>2289</td>
<td>10.4 months</td>
<td>25 bid</td>
<td>37</td>
<td>↓ 35% (P=0.0014)</td>
<td>↓ 20% (P=0.002)</td>
</tr>
</tbody>
</table>

*Not FDA approved in United States.
†Mortality not a planned end point.
Practical Aspects of Using \( \beta \)-Blockers for HF Treatment

**Indications/Contraindications to \( \beta \)-Blocker Therapy/Relative Contraindications**

Table 1 describes the stages of HF, indications for therapy, contraindications, and relative contraindications.

### Starting Dose and Titration

Carvedilol, metoprolol CR/XL, and bisoprolol have been shown to reduce mortality and morbidity in HF. However, only carvedilol and metoprolol CR/XL are approved for HF in the United States, whereas bisoprolol is approved in several European countries. The Figure describes the initiation, titration steps, and target doses.

**Target doses should be achieved and are strongly recommended.** A study showing clinical benefit of carvedilol at lower doses and retrospective subgroup analyses with metoprolol CR/XL suggest that if a higher (target) dose is not tolerated, then the highest tolerated dose should be maintained.

### Which \( \beta \)-Blocker?

Studies have shown that carvedilol, metoprolol CR/XL, and bisoprolol are efficacious in patients with moderate and mild-to-moderate HF. Carvedilol was also shown to benefit post-MI patients with LV systolic dysfunction and patients in New York Heart Association functional class IV (symptoms at rest) without signs of congestion. These agents are recommended for the treatment of HF. Other \( \beta \)-blockers, such as atenolol or propranolol, have not been adequately tested in HF and should not be considered as primary therapy.

Although \( \beta \)-blockers share a common “class effect” in that they all block the \( \beta_1 \)-adrenergic receptor, they can also differ markedly in their pharmacological profiles. Metoprolol CR/XL and bisoprolol are selective for the \( \beta_1 \)-receptor. Carvedilol blocks both the \( \beta_1 \)- and \( \beta_2 \)-receptors and the \( \alpha_1 \)-adrenergic receptor, thereby resulting in peripheral vasodilation. Carvedilol increases insulin sensitivity, whereas metoprolol does not. A potentially beneficial direct antioxidant effect of carvedilol was shown, although there is evidence that \( \beta \)-blockade per se reduces oxidative stress in patients with HF. \( \beta \)-Blockers may differ with regard to intrinsic sympathomimetic

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**Heart Failure**

All patients will exhibit moderate- or severe symptoms.^

**Patient Exclusions**

Based on Patients’ Current Clinical Status:
- Cardiogenic shock
- Signs of systemic hypoperfusion (ordered mental status, narrow pulse pressure, cold or clammy skin, urine output < 0.5 ml/kg)
- SBP < 80 mm Hg
- Significant volume overload (delayed initiation until adequately diuresed)
- Absolute contraindications: symptomatic bradyarrhythmia, 2nd- or 3rd-degree heart block without pacemaker, reactive airways disease

**Initiation and Titration**

Begin patient on low initial starting dose. Increase dose at 2-4 week intervals until the target dose is achieved.

**\( \beta \)-Blocker therapy should not be initiated in patients receiving \( \beta \)-blockers.**

**Weight**

- Daily weights should be obtained and recorded
- Although infrequent, some patients may note increased fatigue or right-sidedness, weight gain, or bradycardia. This is not an indication for discontinuation (see text)

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**\( \beta \)-Blocker treatment algorithm for chronic heart failure (ACC/AHA stages C and D in patients with reduced systolic function).** ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BUN/Cr, Blood urea nitrogen/creatinine; HR, heart rate; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; and SBP, systolic blood pressure. Most patients with HF and preserved systolic function will benefit from \( \beta \)-blockade therapy (eg, those with coronary artery disease, atrial fibrillation, and hypertension). ^Not FDA approved in United States.
activity and lipophilicity. Because it is not yet clear whether these or other pharmacological distinctions translate into meaningful clinical differences, it cannot be assumed that all β-blockers will exert similar beneficial effects in HF. The Carvedilol and Metoprolol European Trial (COMET),24 which compares the effects of metoprolol tartrate and carvedilol in >3000 patients, should yield relevant data later this year.

Using β-Blockers in Combination With Other HF Therapies

β-Blockers should be used in patients already receiving an ACE inhibitor; however, it is likely that they also benefit patients not taking an ACE inhibitor.25 If there are signs and symptoms of HF, diuretics, digoxin, and low-dose spironolactone should be included when appropriate.1,3,4,26 Patients need not take target doses of ACE inhibitors before initiating therapy with β-blockers. However, the doses of both ACE inhibitors and β-blockers should ultimately be maximized.26 Because their use may predispose the patient to sodium accumulation, β-blocker should not be initiated if patients are fluid-overloaded. They should always be prescribed with a diuretic in patients that are likely to develop fluid retention.26 The triple combination of an ACE inhibitor, β-blocker, and angiotensin receptor blocker may increase mortality and should be avoided.1,27

Using β-Blockers in HF Patients With Comorbidities

• Peripheral vascular disease: Using lower than target doses, β1-selectivity (eg, metoprolol CR/XL or bisoprolol) or concomitant α1-blockade (eg, carvedilol) may increase tolerability in patients with symptomatic claudication.
• Diabetes mellitus: Diabetic patients with HF have a worse prognosis than non-diabetics with HF.29 Although in general, β-blockade exerts adverse effects on the metabolic profile in diabetic patients, subgroup analyses from bisoprolol,4 metoprolol CR/XL,5 and carvedilol trials suggest that diabetic patients with HF derive significant morbidity and mortality benefits with these agents. Because of its α1-blocking effects, carvedilol may have neutral effects with respect to lipid profile and insulin sensitivity.22,30

Clinical Management Issues

Volume Overload

Incidence of adverse effects are listed in Table 3. β-blockers should not be initiated in patients with moderate to severe fluid retention. HF is a progressive disease, and it is likely that during its course, many patients will develop signs and symptoms related to fluid retention. The initial approach to such patients should be to intensify fluid management, most often by increasing the dose or adding a second diuretic. Uptitration of a β-blocker should be delayed when volume overload is present. Daily weighing is important, as weight gain often precedes the development of symptoms by several days. If there is a gain in weight (2 to 3 lbs/d or 4 to 5 lbs over a few days), the diuretic dose should be increased even before symptoms develop.

Hypotension

Asymptomatic hypotension is common in patients with severe HF, and in itself it is not a contraindication to β-blocker therapy.6 It is important to determine by obtaining supine and standing blood pressures that the hypotension is not caused by an inadequate preload related to aggressive use of diuretics or ACE inhibitors. In some cases, it may be necessary to adjust the dose and/or timing of concomitant therapy with ACE inhibitors, other vasodilators, and/or diuretic.

Bradycardia

β-Blockers can be used in patients who have asymptomatic and mild bradycardia, particularly when the heart rate increases with exercise. The possibility of drug interactions that may lower heart rate (eg, digoxin and amiodarone) should also be considered. Given the substantial benefits of β-blockers in HF, cardiac pacing should be considered on an individual basis.1 Asymptomatic bradycardia during β-blocker therapy is not a reason for its discontinuation.

β-Blocker Discontinuation

Abrupt discontinuation of β-blocker therapy in HF should be avoided be-
cause it may be associated with rebound effects and increased morbidity and mortality, even in patients without overt HF.

In patients presenting with worsening HF while taking β-blockers, the first consideration should be to achieve compensation by adjusting other medications, including diuretics, digoxin, and ACE inhibitors, before decreasing the dose or discontinuing the β-blocker. Most patients admitted for HF have congestion without signs of hypoperfusion and will respond to standard HF therapy.33 An important exception is the patient presenting with hypotension and signs of organ hypoperfusion. In such patients, β-blockers should be decreased or discontinued and supportive therapy with a phosphodiesterase inhibitor (eg, milrinone) may be considered.

Initiating β-Blocker Therapy in the Hospital

One approach to increasing the overall implementation of β-blocker therapy is the initiation of therapy before discharge from the hospital. Preliminary evidence suggests that, with proper caution and patient selection, this can be accomplished safely.14

Conclusion

More than 5 years after the first approval of a β-blocker for the treatment of HF by the Food and Drug Administration, this life-saving therapy continues to be underutilized. Given the recommendation to use β-blockade in all HF patients without a contraindication, more effort is needed to improve the dissemination of the scientific, clinical, and practical aspects of β-blocker therapy for HF to physicians, healthcare providers, and patients.

References


7. Heart Failure Society of America (HFSA) practice guidelines. HFSA guidelines for management of patients with heart failure caused by left ventricular systolic dys-


cardiomyopathy by beta-receptor blockade. 


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Circulation. 2003;107:1570-1575
doi: 10.1161/01.CIR.0000065187.80707.18
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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