β-Blockers in Chronic Heart Failure

Mihai Gheorghiade, MD; Wilson S. Colucci, MD; Karl Swedberg, MD

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.1,2

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 evidence3–6 and guidelines7,8 that mandate the use of β-blockers in all HF patients without contraindications, many patients do not receive this treatment.9

Demographics of HF

In the United States, approximately 70% of patients with HF have CAD.10,11 Hypertension is a major risk factor for HF,11 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.9 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,12 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 Angeja13).

Sudden death accounts for the majority of deaths in HF patients, is more common (versus progressive circulatory failure) in patients with milder symptoms,2 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 Association1 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.1 Sympathetic nervous system activation may accelerate LV remodeling, worsen myocardial function, and lower the threshold for life-threatening arrhythmias.1 Progression of CAD also may contribute to worsening of HF.10

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 non-ischemic 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...
morbidity and mortality in minimally, moderately, or severely symptomatic patients with HF (Table 2). It is noteworthy that β-blockers were used in addition to ACE inhibitors in all of these trials. Even so, the incremental mortality benefits observed with these β-blockers are greater than those observed with ACE inhibitors alone or with other classes of agents.

**Practical Aspects of Using β-Blockers for HF Treatment**

**Indications/Contraindications to β-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 β-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 β-blockers, such as atenolol or propranolol, have not been adequately tested in HF and should not be considered as primary therapy.

Although β-blockers share a common “class effect” in that they all block the β₁-adrenergic receptor, they can also differ markedly in their pharmacological profiles. Metoprolol CR/XL and bisoprolol are selective for the β₁-receptor. Carvedilol blocks both the β₁- and β₂-receptors and the α₁-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 β-blockade per se reduces oxidative stress in patients with HF. β-Blockers may differ with regard to intrinsic sympathomimetic activity.
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. Up-titration 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.

Bradydcardia

β-Blockers can be used in patients who have asymptomatic and mild bradydcardia, 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 bradydcardia 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-
 continues to be underutilized. Given the
limitations of other medications, including diuretics, digoxin, and ACE inhibitors, before decreasing the
cer dose or discontinuing the β-blocker. Most patients admitted for HF have con-
gestion without signs of 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 dis-
charge from the hospital. Preliminary evidence suggests that, with proper
caution and patient selection, this can be accomplished safely.34

Conclusion
More than 5 years after the first ap-
proval of a β-blocker for the treatment of
HF by the Food and Drug Admin-
istration, this life-saving therapy con-
tinues to be underutilized. Given the
recommendation to use β-blockade in
all HF patients without a contraindica-
tion, more effort is needed to improve
the dissemination of the scientific, clini-
cal, and practical aspects of
blocker therapy for HF to physi-
cians, healthcare providers, and
patients.

References
1. 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
2. American Heart Association. 2003 Heart and Stroke Statistical Update. Available at:
3. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mor-
tality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group.
4. The CBIS-II Investigators. The Cardiac Insufficiency Bisoprolol Study II (CBIS-II): a
5. The MERIT-HF Investigators. Effect of metoprolol CR/XL in chronic heart failure:
Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF).
7. Heart Failure Society of America (HFSA) practice guidelines. HFSA guidelines for
management of patients with heart failure caused by left ventricular systolic dys-
8. Remme WJ, Swedberg K. Comprehensive guidelines for the diagnosis and treatment of
chronic heart failure. Task force for the diagnosis and treatment of chronic heart
9. Gheorghiade M, Bonow RO. Introduction and overview: beta-blocker therapy in the
10. Gheorghiade M, Bonow RO. Chronic heart failure in the United States: a manifestation
temporal trends in drug-prescribing practices, hospital readmissions, and survival
ventricular function predict increase of left ventricular ejection fraction after beta-
blocker therapy in nonischemic cardiomyo-
15. Hall SA, Cigarroa OG, Marcus L, et al. Time course of improvement in left ventricu-
lar function, mass and geometry in patients with congestive heart failure treated with
receptor blockade in congestive cardiomyo-
HF.


β-Blockers in Chronic Heart Failure
Mihai Gheorghiade, Wilson S. Colucci and Karl Swedberg

Circulation. 2003;107:1570-1575
doi: 10.1161/01.CIR.000065187.80707.18
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/107/12/1570

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org/subscriptions/