

# Beta-Blockers: Class Effect in Heart Failure—Fact or Fiction?

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## Summary

Heart failure (HF) is a significant national problem, in terms of morbidity, mortality, and costs. Today, a number of beta-blockers are being used to improve symptoms, reduce remodeling, reduce hospitalization, reduce sudden death, and improve HF survival rates. Three agents have been extensively studied and shown to be effective in treating HF. These include metoprolol succinate extended release (Toprol-XL<sup>®</sup>), bisoprolol (Zebeta<sup>®</sup>), and carvedilol (Coreg<sup>®</sup>). Although beta-blockers are currently underused in HF treatment, increasing appropriate use should improve clinical outcomes and reduce costs.

## Key Points

- Beta-blockers are underused in HF, especially in the elderly.
- Three agents (bisoprolol, sustained-release metoprolol succinate, and carvedilol) have proven effects on reducing morbidity and mortality related to HF.
- Based on current data, all beta-blockers do not appear to be effective for HF.
- Improved use of beta-blockers would reduce costs related to HF.

HEART FAILURE IS A SIGNIFICANT problem, with 5 million people affected in the United States.<sup>1</sup> The incidence of HF in the U.S. has doubled in the last decade. The prevalence is particularly high in people over 65 years of age, with 6 percent to 10 percent having some degree of heart failure.<sup>2</sup> It accounts for about 6.5 million hospital days a year and 300,000 deaths per year.<sup>1</sup> Heart failure also causes two thirds of all cardiovascular disease deaths.<sup>1</sup> Eighty percent of men and 70 percent of women who have heart failure under the age of 85 will die within eight years.<sup>3</sup> Heart failure accounts for \$30 billion in annual costs.<sup>1</sup>

## Overview of Heart Failure

Fifty percent of patients with HF have hypertension as a contributing factor.<sup>4</sup> In addition to hypertension, smoking, obesity, diabetes, and lipid disorders contribute to the development of left ventricular hypertrophy or myocardial infarctions, which both lead to HF. Numerous factors aggravate HF (see Exhibit 1), while Exhibit 2 illustrates the pathologic progression from an insult to the myocardium to the development of HF, arrhythmias, and, ultimately, death.<sup>5</sup> The American College of Cardiology/American Heart Association (ACC/AHA) has characterized symptoms,

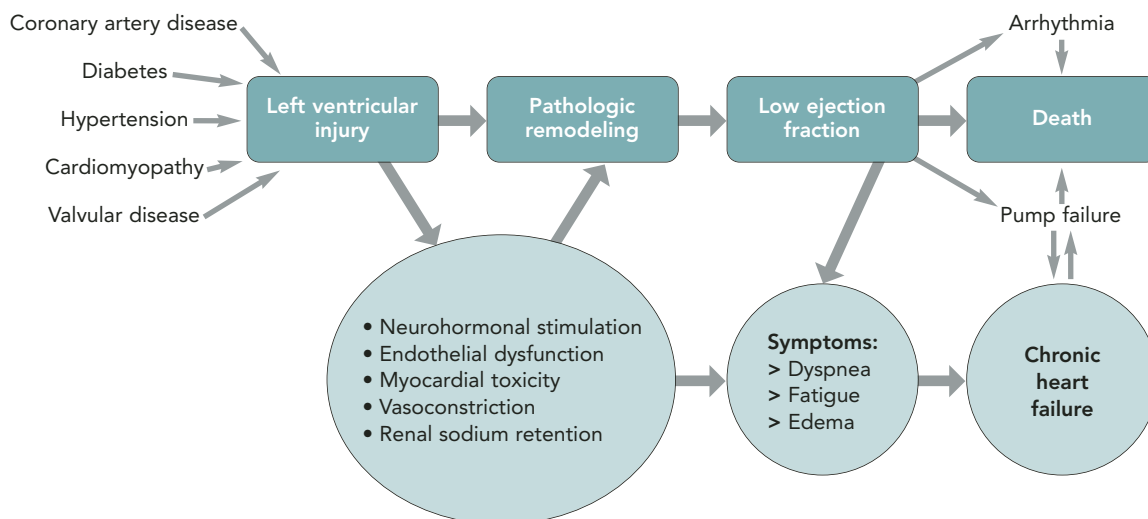
clinical characteristics, and treatment for the evolutionary stages of heart failure (see Exhibit 3).<sup>7</sup> In this example, the A and B groups are asymptomatic, while the C and D groups are symptomatic. Group A is at risk of HF. Group B has heart disease with left ventricular dysfunction but does not yet exhibit symptoms. Group C is the typical heart failure group, exhibiting symptoms as well as structural heart disease or a history of symptomatic HF. Group D has severe refractory HF.

Although evidence-based guidelines for HF have existed for several years, there is still variation in

### Exhibit 1: Aggravating Factors

- Medications
  - New heart disease
  - Myocardial ischemia
- |                        |                     |
|------------------------|---------------------|
| > Pregnancy            | > Endocarditis      |
| > Arrhythmias (AF)     | > Obesity           |
| > Infections           | > Hypertension      |
| > Thromboembolism      | > Physical activity |
| > Hyper/hypothyroidism | > Dietary excess    |

**Exhibit 2: Pathologic Progression of CV Disease<sup>6</sup>**



**Exhibit 3: Stages of the Evolution of Heart Failure<sup>7</sup>**

AHA/ACC HF Guidelines 2001			
Stage	Description	Clinical Characteristics	Treatment
A	HF risk factors, no heart disease, no symptoms	Hypertension, diabetes, hyperchol, family history, cardiotoxins	Treat risk factors, avoid toxics, ACE-I in selected patients
B	Asymptomatic heart disease, liver dysfunction	Systolic or diastolic dysfunction	ACE-I beta-blockers in selected patients
C	Prior or current HF symptoms	Dyspnea, fatigue, reduced exercise capacity	ACE-I beta-blockers diuretics/digitalis
D	Refractory HF symptoms	Marked symptoms at rest, despite maximum therapy	Palliative therapy, mechanical assistance device, heart transplant

HF (heart failure)  
ACE-I (angiotension converting enzyme inhibitor)

actual heart failure management. A study of 2,000 patients with heart failure found that 23 to 79 percent of eligible HF patients had standard therapy with an angiotension converting enzyme inhibitor (ACE-I) prescribed.<sup>8</sup> A similar trend was seen in terms of counseling on salt intake. Other studies have shown that only 30 percent of post-MI patients with HF actually receive beta-blocker therapy.<sup>9</sup>

In general, the treatment objectives in HF are to

- increase survival
- decrease morbidity
- increase exercise capacity
- increase quality of life

- decrease neurohormonal changes
- decrease progression of CHF<sup>7</sup>

All HF patients should have risk factors controlled, lifestyle changes, treatment for underlying causes, and standard medications. As noted in Exhibit 3, standard medications include ACE inhibitors and beta-blockers as tolerated. Additional agents that may be used include diuretics, digoxin, aldosterone inhibition, vasodilators, and angiotension receptor blockers. For patients with severe disease, other therapies that may be used include revascularization, implantable cardiac defibrillator, ventricular resynchronization, ventricular assist devices, heart transplant, and artificial heart.

## Beta-Blocker Under-Use

Although beta-blocker use after a heart attack is one of the most scientifically substantiated, cost-effective medical services, they are substantially underused, especially in the elderly.<sup>10</sup> A beta-blocker used after a heart attack decreases cardiovascular mortality and reinfarctions by 20 to 40 percent.<sup>7</sup> Beta-blocker under-use leads to excess two-year mortality and re-hospitalization for cardiovascular disease.

In a survey of New Jersey Medicare beneficiaries, only 21 percent received beta-blocker therapy post-MI.<sup>10</sup> Calcium channel blockers were used almost three times more often than beta-blockers despite a lack of efficacy evidence. The use of a calcium channel blocker instead of a beta-blocker doubled the risk of death. Patients on beta-blockers were re-hospitalized 22 percent less often and had 43 percent lower mortality.<sup>10</sup>

## Efficacy of Beta-Blockers in Heart Failure

In HF, beta-blockers improve symptoms, reduce remodeling, reduce hospitalization, reduce sudden death, and improve survival. Not all beta-blockers are effective for, or have been studied for, HF. Three agents have been extensively studied and shown to be effective in treating HF. These include metoprolol extended release (Toprol-XL<sup>®</sup>), bisoprolol (Zebeta<sup>®</sup>), and carvedilol (Coreg<sup>®</sup>). As noted in the ACC/AHA guidelines, positive findings with these three agents, however, should not be considered indicative of a beta-blocker class effect, as shown by the lack of effectiveness of bucindolol and the lesser effectiveness of short-acting metoprolol in clinical trials.<sup>7</sup>

Data from landmark beta-blocker studies in HF appear in Exhibits 4-7. The U.S. Carvedilol Heart Failure Trials Program study showed a 65 percent

reduction in death for patients with class I and class II heart failure.<sup>11</sup> The Cardiac Insufficiency Bisoprolol Study (CIBIS)-II and Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) trials showed a 34 percent reduction in all-cause death with bisoprolol and metoprolol therapy in patients with class II-III heart failure.<sup>12,13</sup> Data from Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), with a 35 percent mortality reduction, extended this benefit to class IV patients treated with carvedilol who do not require intravenous diuretics or positive inotropes.<sup>14</sup>

Metoprolol extended release, bisoprolol, and carvedilol are indicated for symptomatic heart failure, asymptomatic ventricular dysfunction (left ventricular ejection fraction [LVEF] < 35 to 40 percent) and recent or remote MI regardless of LVEF.<sup>7</sup> Patients who have Stage C HF should be treated with one of these three beta-blockers. The relative efficacy among these three agents is not known, but available evidence does suggest that beta-blockers can differ in their effects on survival. In the COMET trial, carvedilol (target dose 25 mg twice daily) was compared with immediate-release metoprolol tartrate (target dose 50 mg twice daily).<sup>15</sup> In that trial, carvedilol was associated with a significantly reduced mortality rate compared with metoprolol tartrate.

Although both the dose and the formulation of metoprolol (metoprolol tartrate) used in the above-referenced trial are commonly prescribed by physicians for the treatment of HF, they were neither the dose nor the formulation used in the controlled trials that show that sustained-release metoprolol (metoprolol succinate) reduces the risk of death.<sup>7,13</sup> To date, there are no published head-to-head comparisons with any of the three preferred agents.

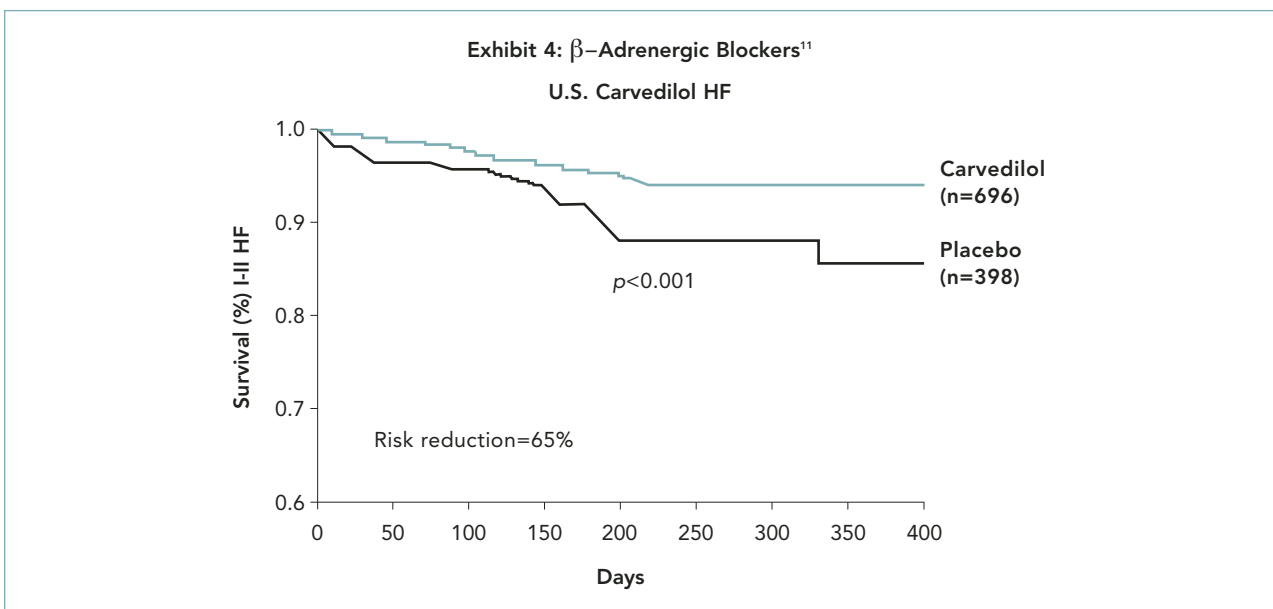


Exhibit 5:  $\beta$ -Adrenergic Blockers<sup>12</sup>

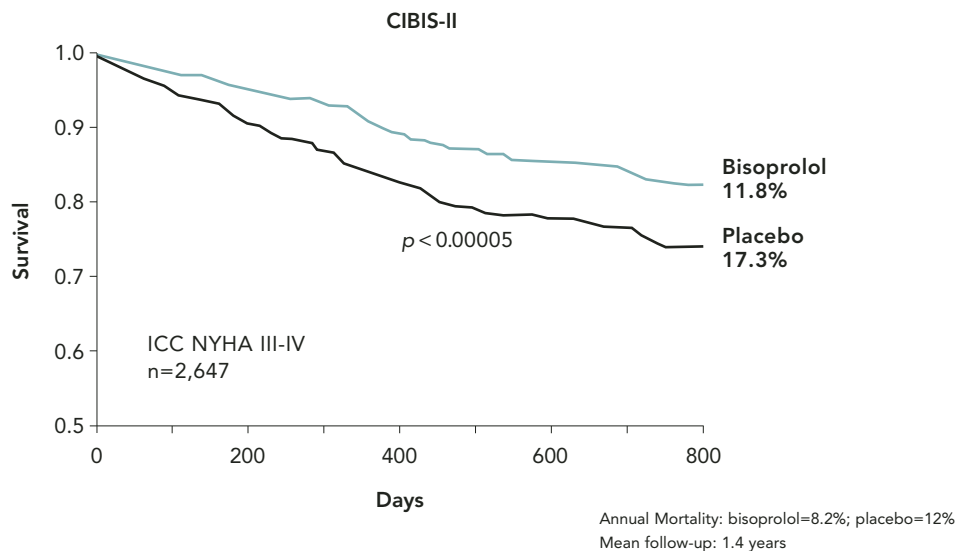
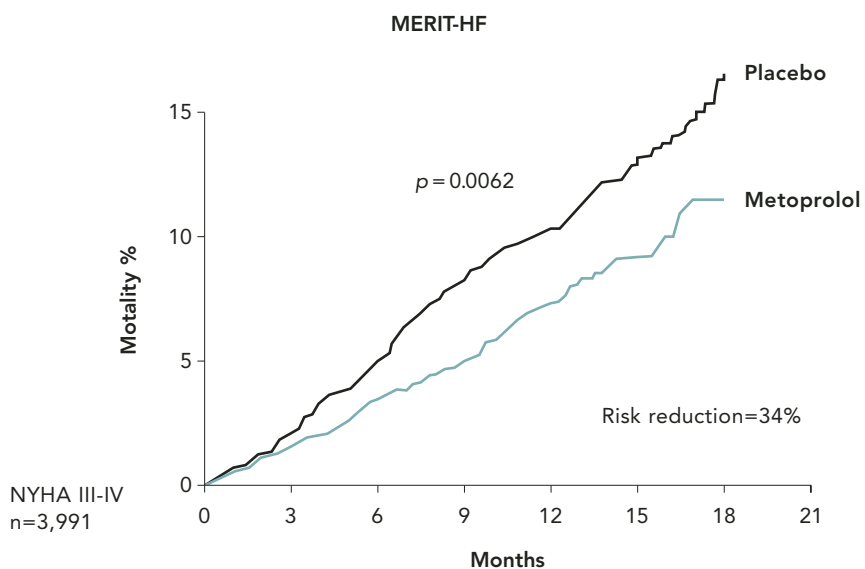


Exhibit 6:  $\beta$ -Adrenergic Blockers<sup>13</sup>



Beta-blockers should be prescribed to all patients with stable HF due to reduced LVEF unless they have a contraindication to their use or have been shown to be unable to tolerate treatment with these drugs.<sup>7</sup> Because of the favorable effects of beta-blockers on survival and disease progression, treatment with a beta-blocker should be initiated as soon as LV dysfunction is diagnosed.<sup>7</sup> Even when symptoms are mild or have responded to other therapies, beta-blocker therapy is important and should not be delayed until symptoms return or disease progression is documented during treatment with other drugs. Therefore, even if patients

do not benefit symptomatically because they have little disability, they should receive treatment with a beta-blocker to reduce the risk of disease progression, future clinical deterioration, and sudden death.<sup>7</sup>

#### Cost Effectiveness of Beta-Blockers

Several studies have examined the cost effectiveness of beta-blocker therapy in HF.<sup>16-20</sup> Two of these analyzed data from two carvedilol studies, COPENICUS and U.S. Carvedilol Heart Failure Trials Program.<sup>16,17</sup> One estimated an 11.1 percent reduction in healthcare costs in favor of carvedilol.<sup>17</sup> The

Exhibit 7:  $\beta$ -Adrenergic Blockers<sup>14</sup>

COPERNICUS

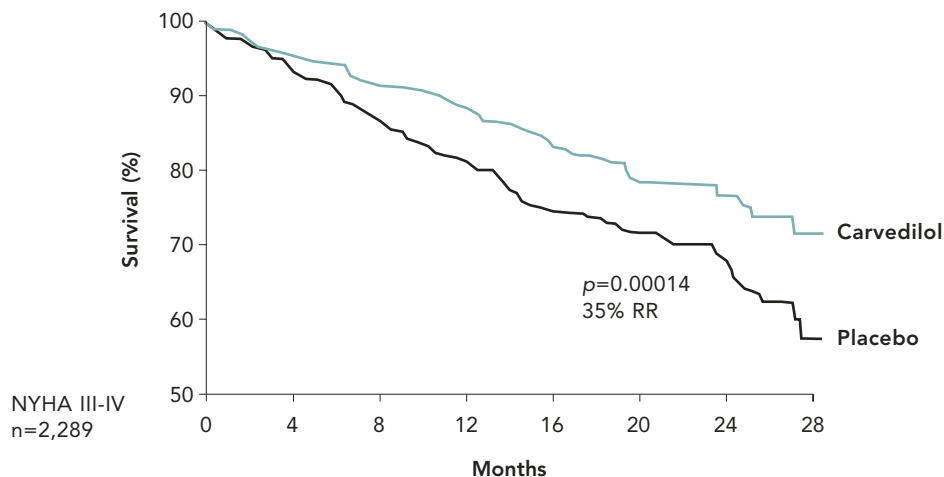
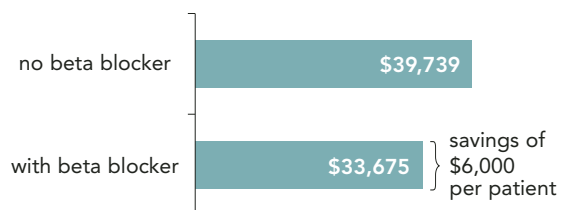


Exhibit 8: AHRQ Study—Cost of Beta-Blockers in CHF<sup>20</sup>

**Major Finding:** Decision model indicates that Medicare costs would decrease if the use of beta-blockers were more widespread for patients with heart failure.

Estimated cost for Medicare to treat heart failure per-person over a five-year period



Source: Duke Center for Education and Research on Therapeutics, Economic effects of beta-blocker therapy in patients with heart failure, *American Journal of Medicine*, January 2004.

Exhibit 9: Cost Savings With Beta-Blocker<sup>20</sup>

	No BB	+BB	Difference
Inpatient	\$37,294	\$29,697	-\$7,597
Outpatient	\$12,817	\$14,000	\$1,183
Medication	\$2,888	\$5,343	\$2,455
<b>TOTAL</b>	<b>\$52,999</b>	<b>\$49,040</b>	<b>-\$3,959</b>

Total societal costs over five years

cost effectiveness of carvedilol for HF compared favorably to that of other generally accepted medical interventions, even under conservative assumptions regarding the duration of therapeutic benefit.

In a retrospective cohort study based on claims and medical chart data, carvedilol use in HF resulted in a significant economic reduction in the overall expenditures by approximately \$14,530. Hospital expenditures were approximately \$9,000 lower for the carvedilol group than for the control group. Carvedilol-treated patients had less frequent hospital admissions and shorter lengths of stay compared with patients not receiving carvedilol.

In a cost analysis by Cowper and colleagues, beta-blocker therapy increased survival in HF patients by 0.3 years per patient and reduced societal costs by \$3,959 per patient over five years (see Exhibit 8).<sup>20</sup> Medicare costs declined by \$6,064 per patient, due primarily to lower hospitalization rates (see Exhibit 9).<sup>20</sup>

Hospitalization contributes between 60 and 75 percent of the total expenses related to HF. The addition of  $\beta$ -blockers to conventional HF therapy results in a significant reduction in hospitalization. Beta-blocker therapy in heart failure is cost-effective and compares favorably to that of other generally accepted medical interventions.

## Conclusion

Long-term treatment with beta-blockers can lessen the symptoms of HF, improve the clinical status of patients, and enhance patients' overall sense of well being. Like ACE-I's, beta-blockers can reduce the risk of death and the combined risk of death or hospitalization. These benefits are seen in patients with or without coronary artery disease and in patients with or without diabetes mellitus, as well as in female and black patients. The favorable effects of beta-blockers are also observed in patients already taking ACE-I's, which suggests that a combined blockade of the two neurohormonal systems can produce additive effects. **JMCM**

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