

# β-Blocker Therapy in Heart Failure

## Scientific Review

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**A** MEDICATION ONCE THOUGHT to be dangerous<sup>1-3</sup> for patients with heart failure, β-blockers have been shown to reduce morbidity and mortality<sup>4-9</sup> and are strongly supported by consensus recommendations and clinical guidelines.<sup>10-12</sup> Clinicians are now challenged to translate this important new information into clinical practice.

For half a century, β-blockers have been an important therapy for patients with cardiovascular disease. Originally developed as a drug to treat angina and hypertension, β-blockers have also become essential therapies for patients with acute myocardial infarction (AMI) and those with tachyarrhythmias. Even before β-blockers were shown to benefit patients with heart failure, the Nobel Committee declared James W. Black's development of propranolol as the greatest breakthrough in pharmaceuticals to treat heart illness since the discovery of digitalis 200 years earlier.<sup>13,14</sup>

Enthusiasm for the use of β-blockers as a treatment for heart failure emerged slowly. Conventional wisdom held that heart failure was solely due to a decline in systolic function and was an absolute contraindication for the prescription of any medication with negative inotropic action. Initial small studies demonstrating the significant negative inotropic effects and poor clinical response to β-blockers<sup>15,16</sup> only re-

**Context** Care of patients with heart failure has been revolutionized throughout the past decade. A paradigm shift in the strategy for treating heart failure caused by systolic dysfunction is in progress. Despite the initial perception about β-blockers' safety, they are now the most extensively studied class of agents in the treatment of heart failure and have emerged as an important intervention to improve the clinical outcomes of heart failure patients.

**Objective** To provide scientific rationale for the use of β-blockers for patients with heart failure.

**Data Sources** All English-language articles of large, randomized controlled clinical trials assessing the mortality benefits of β-blockers in patients with heart failure were identified to provide the scientific rationale for the use of β-blockers in heart failure. Basic science studies were reviewed to provide an overview of the potential physiologic role of β-blockers in heart failure. Finally, clinical guidelines for the treatment of patients with heart failure were assessed to determine current recommendations for the use of these agents.

**Study Selection and Data Extraction** Randomized controlled clinical trials of β-blockers that included more than 300 subjects and assessed mortality as a primary end point.

**Data Synthesis** Of the 4 β-blockers tested in large randomized controlled clinical trials of patients with heart failure, 3 are available in the United States, bisoprolol, carvedilol, and metoprolol; 2 of these, carvedilol and metoprolol, have Food and Drug Administration indications for the treatment of heart failure. Compared with placebo treatment, β-blocker use is associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations in patients with class II and III heart failure.

**Conclusions** Tested in more than 10 000 patients, β-blockers reduce morbidity and mortality in class II through IV heart failure. Along with angiotensin-converting enzyme inhibitors, digoxin, and diuretics, β-blockers have strengthened the armamentarium to improve clinical outcomes of heart failure patients. The science supporting β-blockers must be translated into practice safely and rationally if the agents are to achieve their full potential.

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inforced this view. Consequently, early trials of β-blockers in hypertension or AMI excluded patients with heart failure. Until recently, national guidelines,<sup>17-20</sup> the US Food and Drug Administration, and package inserts stated

that β-blockers were contraindicated in patients with heart failure.

In 1973, Finn Waagstein et al,<sup>21</sup> convinced that the heart-rate-lowering properties of β-blockers could provide benefit to patients with heart failure,

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administered practolol to a 59-year-old woman with heart failure, with dramatic improvement in the patient's clinical status.<sup>22</sup> In another study,<sup>23</sup> Waagstein and colleagues demonstrated that  $\beta$ -blockers were well tolerated by patients with heart failure. Subsequent studies from his group demonstrated the clinical benefits of  $\beta$ -blockers in patients with heart failure.<sup>24,25</sup> These studies, however, did not influence mainstream medical culture, and concerns about the potential adverse effects of  $\beta$ -blockers for these patients remained.

Throughout the next 30 years, experts began to perceive that heart failure was a complex disorder characterized not only by declines in systolic function, but also by a maladaptive increase in adrenergic drive.<sup>26,27</sup> Only after decades of laboratory science demonstrating biological plausibility,<sup>26-35</sup> mechanistic studies showing direct cardiovascular effects,<sup>36-41</sup> and large randomized clinical trials<sup>4-9</sup> demonstrating mortality benefits did  $\beta$ -blockers become accepted as a treatment for heart failure.

This article reviews the scientific rationale supporting the use of  $\beta$ -blockers for patients with heart failure and presents current therapy recommendations<sup>10-12</sup> based on guidelines from professional organizations. Our goal is to provide information for clinicians caring for patients with heart failure to accelerate the appropriate use of  $\beta$ -blockers for their patients.

### Laboratory Science

After the discovery of propranolol, laboratory science laid the groundwork for  $\beta$ -blocker use for patients with heart failure<sup>28-35</sup> as it came to be understood that the pathophysiology of heart failure was related to activation of the adrenergic nervous system. Early in heart failure, drops in cardiac output lead to decreased organ perfusion, a compensatory increase in adrenergic drive, and the subsequent release of neurohormones such as norepinephrine.<sup>35,42</sup> In turn, norepinephrine stimulates ventricular contraction and increases vascular resistance, thereby increasing cardiac output

and blood pressure. This increase in the cardiac adrenergic drive, initially a compensatory mechanism for the failing heart, is one of the earliest measurable responses in heart failure<sup>43,44</sup> occurring while patients are still asymptomatic.<sup>45,46</sup>

This chronic activation of the adrenergic nervous system leads to several potentially deleterious effects on the heart.<sup>47-51</sup> Sustained adrenergic activation and norepinephrine release raise cardiac output and heart rate, which then increase myocardial oxygen demand, ischemia, and oxidative stress. At the same time, peripheral vasoconstriction increases both preload and afterload, causing additional stress on the failing ventricle. This long-term mechanical stress in conjunction with cardiac fibrosis<sup>52-55</sup> and necrosis<sup>28-35</sup> promoted by norepinephrine contributes to cardiac remodeling and a dilated, less contractile cardiac chamber. Norepinephrine downregulates the  $\beta_1$ -adrenergic receptor and uncouples the  $\beta_2$ -adrenergic receptor,<sup>56-58</sup> leaving the myocyte less responsive to adrenergic stimuli, and further decreases contractile function. Thus, prolonged activation of the adrenergic system may be maladaptive,<sup>46,59-62</sup> causing progressive deterioration of myocardial function and portending a poor prognosis.<sup>37,41,63</sup>

As the neurohormonal hypothesis emerged, so too did a new understanding of the potential role of  $\beta$ -blockers in heart failure. Although acute treatment with  $\beta$ -blockers decreases blood pressure and cardiac index, long-term administration of  $\beta$ -blockers is associated with significant increases in ejection fraction<sup>64-77</sup> and cardiac index and a decrease in left ventricular (LV) end diastolic pressure.<sup>61,77-87</sup>  $\beta$ -Blockers reverse the deleterious changes associated with LV remodeling and decrease myocardial mass and LV volume, leading to improved hemodynamics. Finally,  $\beta$ -blockers may also mediate benefit via regulating heart rate and decreasing cardiac arrhythmias.<sup>67</sup> These direct cardiac effects led to the hypothesis that  $\beta$ -blockers would provide substantial clinical benefits in patients with heart failure.

### Clinical Trials

$\beta$ -Blockers have been evaluated in more than 10 000 patients with mild, moderate, or severe heart failure and ejection fractions less than 40% in randomized clinical trials. Five meta-analyses<sup>88-92</sup> have arrived at the same conclusions: the use of  $\beta$ -blockers was associated with a consistent 30% reduction in mortality and a 40% reduction in hospitalizations in patients with heart failure. In the most recent of these meta-analyses,<sup>92</sup> it was estimated that 26 patients would need to be treated to avoid 1 death; 25, to avoid 1 hospitalization. Despite differences in patient selection, target doses, methodology, and clinical end points, results were remarkably consistent across these trials. The evidence suggests that virtually all patients with heart failure caused by LV systolic dysfunction benefit from  $\beta$ -blockers.

Seven mortality trials with more than 300 subjects evaluated the impact of the second- and third-generation  $\beta$ -blockers (metoprolol, bisoprolol, bucindolol, or carvedilol) on patients with symptomatic LV systolic dysfunction (TABLE 1). These trials included the Metoprolol in Dilated Cardiomyopathy (MDC)<sup>93,94</sup> study, the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF),<sup>6,9</sup> the Cardiac Insufficiency Bisoprolol Studies (CIBIS I and II),<sup>4,5</sup> the Australia, New Zealand, and United States Carvedilol Clinical Trial<sup>8</sup> program, the Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS),<sup>95</sup> and the Beta-Blocker Evaluation of Survival Trial (BEST)<sup>96</sup> (TABLE 2).

One of the earliest controlled trials of  $\beta$ -blockers in heart failure, MDC,<sup>93,94</sup> was designed to assess the impact of metoprolol on the combined end point of death or progression to heart transplantation. In this trial, 383 patients with mild to moderate heart failure and an ejection fraction less than 40% were randomized to placebo or metoprolol. Metoprolol initiated at a dose of 5 mg twice daily and titrated to a high dose of 100 to 150 mg/d was associated with a 34% decrease in the combined primary end point. Although the improve-

ment was due entirely to a reduction in the need for cardiac transplantation without a significant difference in mortality ( $P=.12$ ), this study was the first larger-scale trial to add support to the role of β-blockers in heart failure therapy. Despite its limitations and negative mortality results, the MDC trial sparked renewed interest in β-blockers as a therapy for heart failure.

In follow-up to the MDC trial, the MERIT-HF<sup>6,9</sup> was designed to determine whether therapy with the long-acting metoprolol CR/XL was associated with a reduction in all-cause mortality. Larger than the MDC trial, this study randomized 3991 patients with stable New York Heart Association class II through IV heart failure and already receiving standard medical treatment (including angiotensin-converting enzyme [ACE] inhibitors, diuretics, and digitalis) to increasing doses of metoprolol CR/XL or placebo. The MERIT-HF trial featured a 2-week placebo run-in period to assess clinical stability. The starting dosage of metoprolol CR/XL was 12.5 or 25 mg/d and was gradually increased every 2 weeks to the target dose of 200 mg/d. At the conclusion of the study, 64% of the patients were receiving 200 mg of metoprolol per day. Planned follow-up was 2 years, but the study was stopped early because of a significant decrease in all-cause mortality in the metoprolol treatment arm. Treatment with metoprolol was associated with a 34% decrease in all-cause mortality, a 38% decrease in cardiovascular mortality, a 41% decrease in sudden death, a 49% decrease in death caused by progressive heart failure, and a 35% reduction in hospitalizations caused by heart failure. Treatment of 27 patients with metoprolol for 1 year could prevent 1 death.

At approximately the same time, the CIBIS-I<sup>4</sup> sought to determine whether bisoprolol therapy was associated with an improvement in survival and functional status in patients with moderate heart failure and already receiving diuretics and ACE inhibitors. Although patients treated with bisoprolol had marked improvements in func-

**Table 1.** β-Blockers Used in Mortality Trials in Patients With Left Ventricular Systolic Dysfunction

Drug	Pharmacologic Action	Ancillary Properties
Bisoprolol (Zebeta)	β <sub>1</sub> -receptor blockade	None
Bucindolol (Bextra)*	β <sub>1</sub> - and β <sub>2</sub> -receptor blockade	Vasodilatory
Carvedilol (Coreg)†	α <sub>1</sub> -, β <sub>1</sub> -, and β <sub>2</sub> -receptor blockade	Vasodilatory, antioxidant
Metoprolol tartrate (Lopressor) Metoprolol succinate (Toprol XL)†	β <sub>1</sub> -receptor blockade	None

\*Not available in the United States.  
†Approved for use in patients with heart failure.

tional class and reduced readmissions, the observed difference in mortality between groups did not reach statistical significance ( $P=.22$ ; relative risk [RR], 0.80; 95% confidence interval [CI], 0.56-1.15). In general, CIBIS-I demonstrated the safety of bisoprolol in patients with moderate heart failure and its efficacy in improving functional class and decreasing hospitalizations.

The CIBIS-II,<sup>5</sup> with greater statistical power than its predecessor, CIBIS-I, was designed to determine whether bisoprolol at optimal target doses of 10 mg/d would be associated with improved survival. The trial was stopped early after treatment with bisoprolol was found to have a significant mortality benefit: 156 (11.8%) vs 228 (17.3%) deaths with an RR reduction of 0.66 (95% CI, 0.54-0.81;  $P<.001$ ) noted in the β-blocker group. There were significantly fewer sudden deaths among patients receiving bisoprolol than among those receiving placebo (48 [3.6%] vs 83 [6.3%] deaths), with an RR reduction of 0.56 (95% CI, 0.39-0.80;  $P=.001$ ). In addition, all-cause hospital admission was reduced in the treatment group (hazard ratio, 0.80 [95% CI, 0.71-0.91];  $P<.001$ ). Treatment effects were independent of the severity or cause of heart failure. Of note, CIBIS-II did not have a run-in period and thus may be more representative of β-blocker use in clinical practice. According to these findings, treating 23 patients with bisoprolol would prevent 1 death.

Carvedilol, a third-generation β-blocker with α<sub>1</sub>, β<sub>1</sub>, and β<sub>2</sub> blocking properties as well as antioxidant activity, was extensively tested in the US Carvedilol Heart Failure Program, which

consisted of different multicenter trials,<sup>8,81,97</sup> each with a run-in period and including 1094 patients with chronic heart failure. Within each of the trial protocols, patients with mild, moderate, or severe heart failure and LV ejection fractions of 35% were randomized to carvedilol ( $n=696$ ) or placebo ( $n=398$ ). Carvedilol therapy was associated with a significant reduction in overall mortality rate (3.2% vs 7.8% in the placebo group). The reduction in mortality was 65% (95% CI, 39%-80%;  $P<.001$ ). Carvedilol therapy was associated with a 27% reduction in hospitalizations for cardiovascular causes ( $P=.04$ ) and a 38% reduction in the combined end point of hospitalization or death ( $P<.001$ ).

In the COPERNICUS,<sup>95</sup> the first study to target New York Heart Association IIIB to IV patients with heart failure despite optimal medical therapy, there was a significant 35% decrease in all-cause mortality in patients treated with carvedilol. In order to address concerns over the safety of these agents in patients with advanced disease, outcome data were analyzed by high-risk subsets. Even in patients who had fluid retention, used intravenous inotropes or vasodilators within 2 weeks, or had 3 heart failure admissions within 1 year, carvedilol use was associated with a 50% RR reduction in all-cause mortality (95% CI, 27%-90%). Carvedilol was well tolerated at 12 months, with 13% of the carvedilol-treated patients and 16% of the placebo-treated patients withdrawing from therapy. According to these results, administering carvedilol to just 14 patients with severe heart failure would save 1 life.

In contrast to the other recent large trials, the BEST<sup>96</sup> failed to demon-

**Table 2.** Overview of Large Mortality Trials of β-Blockers in Heart Failure\*

	MDC, <sup>8,9</sup> 1993		MERIT-HF, <sup>9</sup> 1999		CIBIS I, <sup>4</sup> 1994	
	Placebo (n = 189)	Metroprolol Tartrate (n = 194)	Placebo (n = 1995)	Metroprolol Succinate (n = 1996)	Placebo (n = 321)	Bisoprolol (n = 320)
Mean age, y	49	49	64	64	59	60
Male, %	75	70	78	78	83	83
Mean LVEF, %	22	22	<40	<40	26	25
NYHA class, %						
I	0	0	0	0	0	0
II	47	42	41	41	0	0
III	47	51	55	55	95	95
IV	4	4	4	4	5	5
β-Blocker dosage, mg/d						
Starting	10		12.5 or 54		1.25	
Target	100-150		200		5	
β-Blocker run-in	2-7 days		None		None	
Primary end point	Mortality and need for transplantation		Mortality		Mortality	
Mortality, %	11	12	11	7	21	17
Mortality difference, %	...		35		20 (NS)	
Interpretation	Improved clinical status and decreased need for heart transplantation with metoprolol but no mortality benefit		Significant reduction in primary end point of all-cause mortality with metoprolol. Stopped early. Significant decrease in sudden death and death from pump failure.		No significant mortality benefit with bisoprolol. Lower than expected mortality in placebo group decreased statistical power.	

\*See the "Clinical Trials" section for definitions of the trial abbreviations. LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association; and NS, nonsignificant. Ellipses indicate that values were not computed.

strate that bucindolol improved overall survival in patients with New York Heart Association class III to IV heart failure. The data and safety monitoring board halted this study, which randomized 2708 patients. Patients receiving bucindolol, a nonselective β-blocker with vasodilatory properties, showed a significant decrease in cardiovascular mortality as well as significant decreases in norepinephrine levels and significant increases in LV function. Subgroup analysis suggested that black patients may have fared worse with bucindolol. This result raised questions regarding efficacy of bucindolol in patients with heart failure as well as concerns that β-blockers may not be an effective therapy for black patients with advanced heart failure.

Heart failure patients with recent AMI have also not been extensively studied. Patients with heart failure were generally excluded from post-AMI β-blocker trials, and heart failure patients with recent AMI were excluded from heart failure β-blocker trials. The

CAPRICORN study<sup>98</sup> was the first large mortality trial to specifically randomize patients with LV dysfunction following AMI to assess whether carvedilol in addition to ACE inhibition would improve all-cause mortality in an era of aggressive reperfusion therapy. Patients with LV dysfunction (ejection fraction <40%) with or without heart failure were randomized to carvedilol or placebo early after an AMI. Patients receiving carvedilol had a lower rate of all-cause mortality (12% vs 15%), with a hazard ratio of 0.77. The original primary end point for this study was all-cause mortality. However, because of a lower-than-anticipated overall mortality in the study sample, a new combined end point of all-cause mortality or hospital admission for cardiovascular events was adopted. Although there was no difference in the new primary end point (35% carvedilol vs 37% placebo), all-cause mortality was lower in patients receiving carvedilol than in those receiving placebo (12% vs 15%; *P* = .03). Although nominally signifi-

cant for the outcome of all-cause mortality, *P* = .03 does not meet the higher level of significance (.005) established when the primary end point was changed from all-cause mortality to a combined end point of all-cause mortality and cardiovascular hospitalizations. In practical terms, however, the observed 23% reduction in mortality represents a clinically important outcome.

**Practice Guidelines**

With the emergence of strong new evidence demonstrating that β-blockers decrease morbidity and mortality in a broad range of patients with heart failure, guidelines from the American College of Cardiology and the American Heart Association,<sup>12</sup> the European Society of Cardiology,<sup>11</sup> and the Heart Failure Society of America<sup>10</sup> all strongly support the use of β-blockers in patients with heart failure. The recently published, revised heart failure guidelines of the American College of Cardiology–American Heart Association<sup>12</sup> and the

CIBIS II, <sup>5</sup> 1999		US Carvedilol, <sup>8</sup> 1996		COPERNICUS, <sup>95</sup> 2001		BEST, <sup>96</sup> 2001	
Placebo (n = 1224)	Bisoprolol (n = 1222)	Placebo (n = 398)	Carvedilol (n = 696)	Placebo (n = 1133)	Carvedilol (n = 1156)	Placebo (n = 1354)	Bucindolol (n = 1354)
61	61	58	58	63	63	60	60
80	80	76	77	80	79	77	79
25	25	22	23	20	20	23	23
0	0	0	0	0	0	0	0
0	0	52	54	0	0	0	0
83	83	44	44	0	0	92	92
17	17	3	3	100	100	8	8
1.25		3.125 or 6.35		3.125		3	
10		50-100		50		100 (<75 kg), 200 (≥75 kg)	
None		2 weeks		None		None	
Mortality		Mortality, exercise tolerance, quality of life, progression of disease		Mortality, combined death and hospitalization		Mortality	
17	12	8	3	19	11	33	30
34		65		35		10 (NS)	
Significant reduction in primary end point of all-cause mortality with bisoprolol. Greatest reduction in sudden death. No benefit in death from pump failure.		Significant reduction in all-cause mortality with carvedilol. Stopped early because of mortality benefit. No effect on exercise tolerance or quality of life.		Significant reduction in primary and secondary end points in patients with severe heart failure with carvedilol		No significant mortality benefit with bucindolol	

European Society of Cardiology clinical practice guidelines<sup>11</sup> recommend use of β-blockers in a broader range of heart failure patients, including those with asymptomatic LV systolic dysfunction and those with severe symptomatic disease.

These guidelines emphasize that the majority of patients with heart failure are candidates for β-blockers, with few exceptions. Currently, only patients with absolute contraindications to these drugs or patients with severe heart failure requiring intravenous inotropes or mechanical support should not receive these agents. Not only are these agents beneficial in patients with mild to moderate symptomatic heart failure caused by systolic dysfunction, but also they improve survival in patients with severe symptomatic heart failure.

**Conclusions**

Developed nearly half a century ago by Sir James Black, β-blockers have become the most extensively scrutinized treatment for heart failure. Basic sci-

ence, mechanistic studies, and large, randomized controlled clinical trials support the value of β-blockers for patients with heart failure caused by systolic dysfunction. Tested in more than 10 000 patients, they reduce morbidity and mortality in class II through IV heart failure. Along with ACE inhibitors, digoxin, and diuretics, β-blockers have strengthened the armamentarium to improve clinical outcomes of heart failure patients. The science supporting β-blockers must be translated into practice safely and rationally if the agents are to achieve their full potential.

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You can hold back from the suffering of the world, you have free permission to do so and it is in accordance with your nature, but perhaps this very holding back is the one suffering that you could have avoided.

—Franz Kafka (1883-1924)