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Carvedilol for heart failure: Renewed interest in beta blockers

ON FIRST BLUSH, the idea of using beta blockers to treat heart failure seems counterintuitive. Beta blockers lower blood pressure, yet many patients with heart failure are already hypotensive. In addition, beta blockers are negatively inotropic, which seemingly should worsen the diminished cardiac function of heart failure.

Nonetheless, beta blockers, once contraindicated in heart failure, are gaining acceptance as part of the regimen. In fact, carvedilol, the latest beta blocker to be approved by the Food and Drug Administration, carries an indication for use in heart failure, as clinical studies have shown it to reduce morbidity and mortality and, perhaps, to slow the progression of heart failure.

The reason for this resurgence of interest in beta blockers in heart failure is that treatment has changed dramatically over the last several years as knowledge about its pathophysiology has increased.¹⁻³ The focus of treatment has moved from the edema of congestive heart failure, to the neurohumoral and inflammatory responses that occur in the face of cardiac injury and impaired blood flow.⁴

This article summarizes some of the current thinking in the treatment of heart failure, including why, when, and how to use carvedilol.

■ WHY USE A BETA BLOCKER?

Heart failure begins with myocardial injury from a variety of causes, leading to ventricular dysfunction and a decrease in peripheral organ

■ ABSTRACT

Although beta blockers were once contraindicated in patients with heart failure, a growing understanding of the role of the sympathetic nervous system in heart failure is rekindling interest in these drugs. In particular, the beta blocker carvedilol is a valuable adjunctive treatment for mild-to-moderate compensated congestive heart failure, regardless of etiology. The utility of carvedilol appears to be related to its specific properties.

■ KEY POINTS

Clinical trials have found that carvedilol reduces mortality and morbidity when added to an angiotensin-converting enzyme inhibitor, a diuretic, and digoxin. It also may slow the progression of heart failure.

The initial dosage is 3.125 mg twice a day, gradually increased to 25 to 50 mg twice a day, if tolerated. Patients should be observed for or cautioned about side effects after the initial dose and each subsequent dose increase.

The principal side effects of carvedilol—dizziness, worsening heart failure, and bradycardia—can generally be managed by adjusting the dosage of carvedilol, digitalis, or diuretic.

Unlike other heart-failure medications, carvedilol may not begin to relieve symptoms immediately—long-term administration is required to induce substantive benefit.

TABLE 1

POTENTIAL BENEFITS OF BETA BLOCKERS IN PATIENTS WITH HEART FAILURE

Reduce norepinephrine release by prejunctional beta receptors
Reduce peripheral vascular resistance (with agents having alpha-blocking effects)
Reduce venomotor tone
Reduce plasma volume
Reset carotid baroreceptors
Attenuate the response to catecholamines during exercise
Inhibit renin secretion
Reduce heart rate
Restore heart-rate variability
Attenuate potentially malignant ventricular arrhythmias
Control atrial arrhythmia rate
Reduce ventricular wall stress
Ameliorate myocardial ischemia

perfusion. The body attempts to maintain adequate peripheral flow with homeostatic compensatory mechanisms, such as vasoconstriction, mediated by various neurohormones, principally those of the renin-angiotensin-aldosterone system and the sympathetic nervous system. Although these responses may be beneficial early on, they ultimately impair ventricular performance further as the syndrome progresses.

Therapies directed at impaired left ventricular function (such as positive inotropic agents) or at the peripheral circulation (such as direct-acting vasodilators) have not proven as effective at increasing survival as have drugs such as angiotensin-converting enzyme inhibitors, which address the neurohormonal imbalances.

Conventional therapy for heart failure now includes³:

- Angiotensin-converting enzyme inhibitors, as first-line drugs.
- Diuretics, to relieve volume overload and edema and thus attenuate symptoms.
- Digoxin, which is inotropic and has some neurohormonal antagonizing

actions and also helps attenuate symptoms.⁵

- Dietary salt restriction.
- Treatment of the underlying etiologic or precipitating disease.
- Patient education, to assure compliance with treatment.

However, even with such aggressive treatment, the morbidity and mortality rates in heart failure remain extremely high: in some cohorts, 50% to 80% of patients die within 2 to 5 years after symptoms first appear. For this reason, new strategies are constantly being designed and tested. And one such strategy is to use drugs to block pathologic stimulation of the adrenergic nervous system.

Alpha blockers tried, discarded

The idea of using adrenergic-blocking drugs to treat heart failure is not new. For example, alpha blockers such as phentolamine and prazosin were tested in heart failure in the 1970s. Although these drugs, which are very effective vasodilators, reduced afterload and thereby improved ventricular performance,^{6,7} they did not decrease the mortality rate,⁸ and they have largely been abandoned in treating heart failure.

Early trials of beta blockers promising

Beta blockers are another story. In studies in the 1970s, Waagstein et al⁹ and Swedberg et al¹⁰ found that beta blockers could help relieve the symptoms of heart failure, even though the concept seemed counterintuitive, since beta blockers can *worsen* the symptoms of congestive heart failure and generally carry warnings against their use in heart failure.¹¹ Several subsequent studies failed to demonstrate any benefit with beta blockers in heart failure. However, these studies used agents with intrinsic sympathomimetic activity (that is, they blocked the effects of catecholamines while themselves mildly stimulating the beta receptors) and had short follow-up periods, both of which may have precluded any positive results.

Beta blockers and the sympathetic nervous system

Nevertheless, beta blockers have many effects that, at least in theory, should be beneficial (TABLE 1), and greater insight into the role of

Beta blockers interdict the abnormal neurohormonal activation

**TABLE 2****PHARMACODYNAMIC PROPERTIES OF BETA BLOCKERS USED IN RANDOMIZED TRIALS IN HEART FAILURE**

Agent	Beta ₁ selectivity*	Alpha ₁ antagonism	Partial agonist activity	Peripheral vascular resistance
Acebutolol	Modest	None	Modest	Increase or no change
Bisoprolol [†]	Strong	None	None	Increase or no change
Bucindolol	None	None	Modest	Decrease
Carvedilol	None	Modest	None	Decrease
Labetalol	None	Modest	Modest	Decrease
Metoprolol	Strong	None	None	Increase or no change
Nebivolol [†]	Modest	None	None	Data not available
Propranolol	None	None	None	Increase

*Selectivity seen only with low therapeutic doses

[†]Not clinically available

adrenergic activation in heart failure has rekindled interest in using beta blockers in this condition. We now know that:

- Sympathetic activation correlates closely with the severity of heart failure¹² and survival.¹³ Indeed, plasma norepinephrine levels correlate directly with New York Heart Association (NYHA) functional class.

- Sympathetic neurotransmitters can cause cardiac myocyte death and impair normal myocyte function.¹⁴

- Antagonism of the sympathetic nervous system improves myocardial function and oxygen delivery in patients with nonischemic dilated cardiomyopathy.¹⁵

■ ACTION AND EFFECTS

Useful properties

Carvedilol, the first beta blocker approved for treating congestive heart failure, has several properties that may make it more appropriate for treating this condition than other beta blockers (TABLE 2).¹⁶

Alpha blocking activity. Drugs with alpha blocking activity, such as carvedilol, reduce systemic vascular resistance, thereby reducing afterload. This effect might compensate for the initial negative inotropic effects of

beta blockade, which seemingly caused difficulties during other trials of beta blockers in heart failure.

Nonselectivity for both types of beta receptors. There are two types of beta receptors: beta₁ receptors, which normally predominate in the heart muscle; and beta₂ receptors, which predominate in bronchial and vascular smooth muscle. However, in heart failure, the number of beta₁ receptors in the heart decreases, until there are approximately equal numbers of both types of receptors there.¹⁷ Therefore, in theory, beta blockers such as metoprolol that are selective for beta₁ receptors may not be as effective in congestive heart failure as a nonselective beta blocker would be. However, this hypothesis is unproved and contentious.

No intrinsic sympathomimetic activity. Unlike beta blockers used in some previous trials, carvedilol has no intrinsic sympathomimetic activity—it blocks the beta receptors without stimulating them. Thus, carvedilol maximizes the benefits of adrenergic blockade by more completely antagonizing the sympathetic nervous system.

Together, these properties counteract the increased sympathetic tone responsible for progressive myocardial damage and dysfunc-

Sympathetic activation correlates closely with the severity of heart failure

TABLE 3

EFFECTS OF CARVEDILOL IN CONGESTIVE HEART FAILURE (PLACEBO-CONTROLLED TRIALS)

Study	No. of patients	Follow-up (months)	Effect on ejection fraction	Effect on exercise tolerance	Effect on NYHA classification	Effect on global assessment
Olsen et al ¹⁸	60	4	Increased	No change	Improved	Improved
Metra et al ¹⁹	40	4	Increased	Increased	Improved	Improved
Krum et al ²⁰	49	3	Increased	Increased	Improved	Improved
US mild CHF ²²	366	12	Increased	Not available	Improved	Improved
PRECISE ²³	278	6	Increased	Increased	Improved	Improved
MOCHA ²⁴	346	6	Increased	No change	No change	No change
US severe CHF ²⁵	105	6	Increased	Increased	Improved	Improved
AUS-NZ ²⁶	415	20	Increased	No change	No change	No change

US mild CHF=United States Carvedilol Heart Failure Program mild-heart-failure study

PRECISE = Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise (United States Carvedilol Heart Failure Program moderate-heart-failure study)

MOCHA = Multicenter Oral Carvedilol Heart Failure Assessment (United States Carvedilol Heart Failure Program dose-ranging study)

US severe CHF = United States Carvedilol Heart Failure Program severe-heart-failure study

AUS-NZ = Australia-New Zealand Carvedilol Heart Failure trial

tion in heart failure. Carvedilol is also a potent antioxidant, but the clinical importance of this effect is unknown.

Studies with carvedilol

Three small, short-term studies¹⁸⁻²⁰ showed that carvedilol increased the ejection fraction and improved the general condition of patients with heart failure, as reflected by the patients' own overall ("global") assessment and by the New York Heart Association (NYHA) functional class. In addition, two of these studies suggested that carvedilol could improve exercise tolerance (TABLE 3).

The United States Carvedilol Heart Failure Trials Program²¹ enrolled 1094 patients. All had been in heart failure for at least 3 months and had a left ventricular ejection fraction less than 35%, systolic blood pressure ranging from 85 to 160 mm Hg, diastolic blood pressure less than 100 mm Hg, and a resting heart rate greater than 68 beats per minute. Patient entry was not limited on the basis of disease etiology.

Depending on how far the patients could walk in 6 minutes, they entered one of four randomized, placebo-controlled studies: a mild-heart-failure study (patients who could walk 426 to 550 meters in 6 minutes)²²; a moderate-heart-failure study (those who could walk 150 to 425 meters)²³; a dose-ranging study (also 150 to 425 meters)²⁴; or a severe-heart-failure study (those walking less than 150 meters).²⁵ The planned duration of the study was 6 months (12 months for the group with mild heart failure). The findings were:

- The program was terminated early when the Data and Safety Monitoring Board found that carvedilol imparted a significant survival advantage (FIGURE 1). The overall mortality rate was 7.8% in patients receiving placebo vs 3.2% in patients receiving carvedilol, a risk reduction of 65% (95% confidence interval 39% to 80%, $P < .001$).²¹

- The probability of survival free of hospitalization was significantly greater in patients receiving carvedilol than with placebo in the dose-ranging trial ($P = .002$), repre-

More patients who received carvedilol improved and fewer worsened

senting a 49% risk reduction.²⁴ The difference in hospitalization rates began to appear at approximately 50 days of therapy, suggesting an early and sustained effect.

- The moderate-heart-failure study demonstrated a 39% risk reduction in survival free of death or any hospitalization with carvedilol ($P = .019$).²³

- In the mild-heart-failure trial, there was a 48% reduction in the combined endpoint of congestive heart failure death or hospitalization, or the need for a sustained increase in other medications for congestive heart failure with carvedilol ($P = .008$).²² The reduction of each component endpoint was similar to the overall reduction in the combined endpoint. The benefit appeared after approximately 50 days of therapy in this study, and the benefit on progression of heart failure was apparent regardless of sex, age, race, cause of heart failure, or baseline left ventricular ejection fraction.

The Australia-New Zealand Carvedilol Heart Failure trial (TABLE 3)²⁶ enrolled 415 patients who had heart failure due to coronary artery disease, an ejection fraction less than 45%, and who were receiving diuretics and angiotensin-converting enzyme inhibitors. These patients were randomized to receive either carvedilol or placebo in addition to their baseline medications. At 18 months, a 26% reduction in mortality risk or heart failure hospitalization was observed ($P = .02$). At a mean of 23 months, the risk reduction was 23% ($P < .05$).

Improvement seen in all trials

Of note, in all these trials more patients who received carvedilol seemed to improve clinically and fewer worsened (as assessed by NYHA functional class and global heart failure scores) than with placebo. These “soft” endpoints are mirrored by improvements in the “hard” endpoints of hemodynamic improvement. In the United States Carvedilol Heart Failure Trials Program, the average ejection fraction increased by 6.5 percentage points more in patients receiving carvedilol than with placebo. Further, in smaller studies¹⁹ there were significant reductions in mean pulmonary artery pressure and systemic vascular resistance.

EFFECT OF CARVEDILOL ON THE MORTALITY RATE IN THE UNITED STATES CARVEDILOL HEART FAILURE PROGRAM

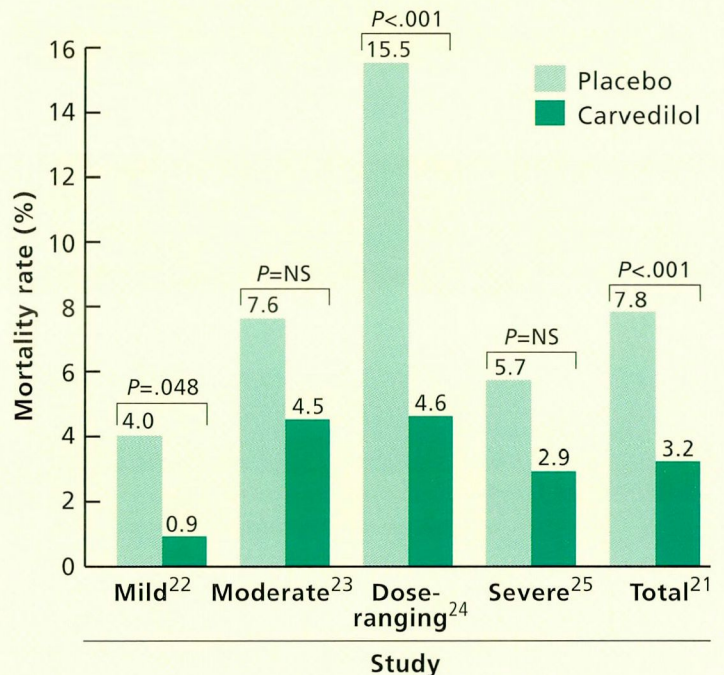


FIGURE 1 Although the four studies comprising the United States Carvedilol Heart Failure Program were not designed to assess the mortality rate primarily, they were terminated early when the Data and Safety Monitoring Board found that adding carvedilol to a standard regimen of an angiotensin-converting enzyme inhibitor, a diuretic, and digoxin conferred a significant survival advantage.

TREATMENT

Who should receive carvedilol?

Carvedilol appears to be a reasonable addition to standard therapy for patients with mild-to-moderate symptomatic congestive heart failure. At the outset of therapy, patients should be clinically stable and, for the most part, receiving an angiotensin-converting enzyme inhibitor, a diuretic, and a digitalis preparation (TABLE 4).

Not enough studies have been performed in patients with severe congestive heart fail-

ure to permit any recommendations; therefore, carvedilol should not be started in patients hospitalized for heart failure decompensation or who are significantly hypotensive or in a volume overloaded state. Furthermore, carvedilol has also not been carefully evaluated in patients with asymptomatic systolic left ventricular dysfunction.

Dosage

The initial dosage is 3.125 mg twice daily for 2 weeks regardless of disease severity, weight, or age. Patients should be observed for 1 to 2 hours after the initial dose and each increase in dosage. An alternative strategy that appears successful and safe is to have patients take their first dose or dose increase at bedtime. If the initial dosage is tolerated reasonably well after 1 to 2 weeks, it can be increased to 6.25 mg twice daily. Doses should then be doubled every 1 to 2 weeks to the highest level tolerated, with a target dosage of 25 mg twice daily in patients weighing 85 kg or less and 50 mg twice daily in patients weighing more than 85 kg.

Carvedilol should be taken with food to slow its absorption and to decrease the incidence of orthostatic effects; some authorities also recommend giving carvedilol a few hours before other vasodilating drugs for the same reason.

Like other beta blockers, carvedilol should not be discontinued abruptly in patients with ischemic heart disease, but rather tapered over 1 to 2 weeks if side effects develop.

Side effects

Throughout the titration period, patients may experience side effects that require dosage adjustments, although most patients do not, and the side effects that do occur can usually be managed successfully.

Dizziness. Carvedilol has been observed to lower the blood pressure significantly during the period of initial titration, and this effect likely accounts for some of the orthostatic dizziness described. In the United States Clinical Trials Program, 19% of patients receiving placebo complained of dizziness, compared with 32% of patients receiving carvedilol. Still, only 0.4% of patients had to stop taking carvedilol because of dizziness.

The vasodilator side effects of dizziness and light-headedness are often self-limiting. Patients who experience this problem should be reassured that it often resolves spontaneously. If the dizziness is more severe, one should assess the extent of diuresis and consider decreasing the dosage of the diuretic or of other vasodilators.

Worsening heart failure is less frequent than dizziness. However, in the United States Clinical Trials Program, it was the most common reason for stopping therapy, accounting for 1.6% of patients stopping active treatment.

Increasing the diuretic dosage may compensate for any edema, weight gain, or shortness of breath that develops during upward titration of carvedilol.

Bradycardia. In the United States Clinical Trials Program, 1% of the placebo group experienced bradycardia vs 9% of the carvedilol group. Nevertheless, only 0.8% of the patients had to stop taking carvedilol because of bradycardia.

If bradycardia or prolonged atrioventricular conduction delays occur, the dose of carvedilol should be reduced. Some bradycardia may be due to increased digoxin levels, which carvedilol has been shown to cause. In this situation, one might consider monitoring digoxin levels more closely or routinely reducing the digoxin dose.

Long-term therapy needed

Unlike other heart-failure medications, carvedilol may not begin to relieve symptoms immediately—long-term administration is required to induce substantive benefit. Although most patients do not experience clinical problems within the first 1 to 2 months, deterioration in clinical status can occur and patients must, therefore, be followed very carefully, with dosages adjusted on the basis of clinical presentation. Of note, in clinical trials more than 90% of patients were able to undergo upward titration of carvedilol to target doses.

■ UNSETTLED ISSUES

Two recent meta-analyses^{27,28} concluded that beta blockers reduce the mortality rate in heart failure; one suggested that the effect is

Carvedilol should not be started in patients hospitalized for uncompensated heart failure, ie, NYHA class IV

**TABLE 4****HOW TO USE CARVEDILOL IN HEART FAILURE*****Patient selection**

- Mild to moderate heart failure
- Already receiving angiotensin-converting enzyme inhibitors, a diuretic and digoxin
- Not recommended in patients hospitalized for decompensated heart failure, or who have significant hypotension or pulmonary congestion

Dosage

- Start with 3.125 mg twice a day for 2 weeks
- Observe the patient for side effects 1 to 2 hours after initial dose and each dose increase or have the patient take these doses at bedtime
- If first dose is tolerated well, increase to 6.25 mg twice a day after 2 weeks
- Double the dose every 1–2 weeks until target reached
 - 25 mg twice a day in patients weighing 85 kg or less
 - or 50 mg twice a day in patients weighing more than 85 kg
- Tell the patient to take carvedilol with meals

Side effects during upward titration

- Vasodilator effects (dizziness or light-headedness)
 - Give the drug with food
 - Give drug 2 hours before other agents
 - Consider reducing diuretic or vasodilator doses temporarily
 - Reduce carvedilol dose
 - May require no attention, as symptoms are often self-limiting
- Worsening heart failure (edema, weight gain, dyspnea)
 - Intensify salt restriction
 - Increase diuretic dose
 - Reduce carvedilol dose
- Significant bradycardia (consistently < 60–65/minute with symptoms)
 - Reduce carvedilol dose
 - Monitor digoxin levels
 - Reduce digoxin dose

*See reference 29 for detailed instructions and commentary

The starting dosage is 3.125 mg twice daily for 2 weeks regardless of disease severity, weight, or age

greater with carvedilol than with other beta blockers (although the trend was not statistically significant),²⁸ the other found carvedilol no better than other beta blockers.²⁷ Additional trials are required to settle this issue. Carvedilol is nonselective for beta₁ receptors; whether beta₁ selectivity is important when prescribing beta blockers in heart failure will likely become clear when the results of clinical trials now ongoing become available.

These investigators also point out that

most of the trials to date were very short-term, and were not designed to assess mortality as a primary endpoint. Further, carvedilol did not seem to have any effect on exercise tolerance in some of the trials that were designed primarily to measure this endpoint.²⁹ Still, the probability that beta blockers in general, and carvedilol specifically, decrease the mortality rate in heart failure is high, and the evidence supporting this therapeutic approach is growing.

Several clinical trials currently underway will give greater insight into these issues. The



Beta Blocker Evaluation in Survival Trial (BEST), using bucindolol, and the Cardiac Insufficiency Bisoprolol Study II (CIBIS II) will soon be available for analysis. These are

large-scale trials and use mortality as a formal endpoint. In addition, carvedilol is being directly compared with metoprolol in the COMET trial now ongoing in Europe.³⁰

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Increasing the diuretic dosage may compensate for worsening heart failure