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Marie Taccetta-Chapnick

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# Using Carvedilol to Treat Heart Failure

Marie Taccetta-Chapnick, MSN, RNC, CCRN

**T**he prevalence of heart failure in the United States is increasing.<sup>1</sup> In 1990, heart failure was the primary diagnosis in more than 700 000 hospital discharges, a 4-fold increase since 1971. Heart failure is the primary cause of hospitalization for persons older than 65 years old.<sup>2</sup> Hospital admissions for heart failure in the elderly (>65 years old) increased from 55 per 10 000 to 150 per 10 000 between 1972 and 1990.<sup>2</sup> Heart failure affects about 2 to 4 million persons in the United States, with 400 000 new cases diagnosed annually.<sup>3</sup> Approximately 35% of patients with newly diagnosed heart failure are hospitalized annually, and once discharged, 47% of these patients are readmitted to the hospital within 3 months.<sup>2</sup>

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*Marie Taccetta-Chapnick is a staff nurse in cardiac critical care at Victory Memorial Hospital, Brooklyn, NY, and an adjunct lecturer at New York City Technical College in Brooklyn. Currently, she is a postgraduate nurse practitioner student at Wagner College, Staten Island, NY.*

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Despite current treatments, including use of angiotensin-converting enzyme (ACE) inhibitors, digoxin, and diuretics, morbidity and mortality remain alarmingly high. An estimated 50% of patients with severe signs and symptoms of heart failure will die within 1 year and 70% within 3 years.<sup>3,4</sup> Additional pharmacological therapies to mitigate this disorder, such as  $\beta$ -blockers, continue to be investigated.  $\beta$ -Blockers were thought to be contraindicated in patients with heart failure because of the drugs' negative chronotropic (heart rate) and inotropic (contractility) actions on the heart.<sup>5</sup> However, the findings of several recent studies<sup>6-10</sup> indicate that  $\beta$ -blockers decrease morbidity and mortality and improve signs and symptoms and quality of life for patients with heart failure.

In this article, I review the pathophysiology and compensatory mechanisms in patients with heart failure and discuss the beneficial effects of  $\beta$ -blockers, especially carvedilol, in the treatment of heart failure. Nursing diagnoses and interventions provide nurses with information on how to safely administer carvedilol and monitor its clinical effects. The included guide for teaching patients is a tool nurses can use to instruct patients being treated with carvedilol.

## DEFINITIONS AND CLASSIFICATIONS

Heart failure is classified as systolic and/or diastolic dysfunction. Systolic ventricular dysfunction is a defect in the expulsion of blood (ie, systolic/forward failure) from the ventricles into the aorta and pulmonary artery caused by an impaired inotropic state. The principal manifestations of systolic failure are due to inadequate forward output, causing an increase in end-diastolic volume, and a normal or reduced stroke volume, resulting in a decreased ejection fraction of 0.45 or less. Causes of systolic failure include hypertension, coronary artery disease, valvular disease, pulmonary embolism, and idiopathic cardiomyopathy.<sup>11-13</sup>

Diastolic ventricular dysfunction occurs when the filling of one or both ventricles is impaired, causing inadequate emptying of the venous reservoir (ie, diastolic/backward failure). The transient inability of the ventricles to accept blood may occur because of slowed or incomplete ventricular relaxation (lusitropic properties), such as acute ischemia, or may be sustained, as in restrictive cardiomyopathy or concentric myocardial hypertrophy. Diastolic failure due to increased diastolic stiffness causes high ventricular filling pressure and

high venous pressure, resulting in pulmonic and/or systemic congestion. Causes of diastolic dysfunction include hypertrophic cardiomyopathy, subendocardial fibrosis, coronary artery disease, and arterial hypertension.<sup>14</sup>

In many patients, systolic and diastolic dysfunction coexist. The most common cause is coronary atherosclerosis. In this condition, systolic dysfunction is the result of decreased myocardial contractility associated with myocardial infarction. Diastolic failure is due to replacement of normal, distensible myocardium by nondistensible fibrous scar tissue.<sup>12</sup>

## **PATHOPHYSIOLOGY OF HEART FAILURE AND COMPENSATORY MECHANISMS**

A primary disturbance in myocardial contractility, an excessive hemodynamic burden placed on the ventricles, or both initiate compensatory mechanisms that attempt to sustain cardiac output and arterial blood pressure. Compensatory mechanisms include the Frank-Starling mechanism, ventricular myocardial hypertrophy, and activation of neurohormonal systems.

### **Frank-Starling Mechanism**

When the ventricles do not eject a normal quantity of blood during each contraction, the residual volume is added to the blood volume entering the ventricle during the next diastole, increasing the end-diastolic volume. As the preload increases, the left ventricle distends, causing elevated left ventricular pressure. According to the Frank-Starling law, the greater the volume of blood in the ventricle during diastole, up to a point, the greater is

the force of contraction during systole. The increase in contractile force is related to the lengthening of sarcomeres.<sup>13</sup> When the ventricles are stretched by a pressure or volume overload, the length of the sarcomeres within the ventricular walls increases, causing optimal overlapping between myofilaments (contractile structures). This increase results in an increased force of muscle contraction as actin and myosin filaments are brought to a more optimal degree of interdigitation.<sup>14</sup> The sarcomere length associated with the most forceful contraction is approximately 2.2  $\mu\text{m}$ .<sup>11,13</sup> The deterioration in cardiac function is not due to a loss of optimal overlap of actin or myosin (due to further distortion) but rather to a failure of the latching mechanism itself. Increased sarcomere length enhances the concentration of calcium ions released into the myocyte, potentiating the force of contraction.<sup>15</sup>

### **Myocardial Hypertrophy**

Increased systolic stress (myocardial workload and oxygen requirements) causes the heart to increase muscle mass and contractile strength, similar to the hypertrophy in skeletal muscles caused by exercise.<sup>16</sup> The development of ventricular hypertrophy is the primary mechanism by which the heart compensates for an increased load.<sup>11</sup> When hypertrophy is the result of pressure overload, the resultant increase in systolic wall stress leads to parallel replication of myofibrils and thickening of myocytes. When the primary stimulus is volume overload, increased diastolic wall stress leads to replication of sarcomeres, elongation of myocytes, and ventricular dilatation. In both

types of hypertrophy, ventricular remodeling occurs to maintain a normal level of systolic stress, improve cardiac output, and minimize pulmonary edema. However, as left ventricular failure progresses, lysis of myofibrils occurs, the number of lysosomes increases (to digest worn-out cells), and fibrous tissue replaces cardiac cells. The resulting ischemia may contribute further to the impairment of cardiac function.<sup>11</sup>

### **Activation of Neurohormonal Systems**

A series of neurohormonal changes occurs as a result of reduced cardiac output and arterial hypertension. Many of these changes occur in response to inadequate arterial blood volume, a characteristic of systolic heart failure. In the early stages of systolic failure, activation of the sympathetic nervous system and the renin-angiotensin system maintains perfusion to vital organs and expands the arterial blood volume. However, as heart failure becomes chronic, these mechanisms cause undesirable effects such as excessive vasoconstriction, increased afterload, excessive retention of sodium and water, electrolyte abnormalities, and arrhythmias.<sup>11</sup>

#### *Increased Sympathetic Activity.*

Activation of the sympathetic nervous system, with a concomitant decrease in parasympathetic tone, causes the release of norepinephrine from adrenergic nerve fibers, resulting in venous and arterial vasoconstriction. Vasoconstriction, mediated through the  $\alpha$ -adrenergic fibers, causes constriction of the splanchnic and cutaneous veins. Constriction of these highly capacious vascular beds causes translocation of blood

back into the central circulation, increasing preload in accordance with the Frank-Starling law. Increased preload predisposes patients to pulmonary congestion and worsening of heart failure.<sup>11,13</sup>

Chronic arterial vasoconstriction caused by norepinephrine increases afterload (the force a ventricle must overcome while it contracts during ejection) and peripheral vascular resistance, making ejection of blood by the failing heart more difficult.<sup>13</sup> Increased filling pressures and ventricular wall stress accelerate cell death due to the increased workload of the ventricles. Norepinephrine causes  $\beta$ -adrenergic stimulation, increasing the heart rate and myocardial contractility. Tachycardia decreases the time available for diastolic filling, decreases coronary artery perfusion, increases myocardial

oxygen demand, and may trigger ventricular tachycardia or sudden cardiac death.<sup>11</sup>

*Renin-Angiotensin System.* Compensatory mechanisms to restore circulatory volume include activation of the renin-angiotensin system. Renin is released because of increased activation by the sympathetic nervous system of the afferent and efferent arterioles in the renal glomeruli, decreased renal perfusion, and decreased sodium concentration in the macula densa. Renin is secreted from the renal juxtaglomerular cells, increases blood flow to the kidneys, and maintains arterial blood pressure. Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by ACE. Angiotensin II is a potent arterial vasoconstrictor that causes increased systemic vascular

resistance (SVR) and maintenance of blood pressure. It also stimulates the release of aldosterone from the adrenal gland, causing sodium and water reabsorption by the renal tubules, ultimately increasing intravascular volume. However, the increased sodium and water retention predisposes patients to fluid overload and electrolyte imbalances.<sup>12</sup> Fluid retention and the inability of the heart to pump blood adequately cause elevated filling pressures. Eventually, the heart is so overstressed that the pump fails.

Failure to pump blood into the systemic circulation increases the volume of blood in the lungs, increasing the pulmonary capillary pressure. If the pressure increases to levels greater than that of plasma colloid osmotic pressure (approximately 18 mm Hg), fluid begins to filter out of

the capillaries into the interstitial spaces and alveoli, resulting in pulmonary edema and/or systemic congestion.<sup>12</sup> Signs and symptoms of pulmonary congestion include dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. The same pathophysiological factors are responsible for systemic edema. Signs and symptoms of systemic congestion include edema, ascites, and hepatic congestion.<sup>12</sup>

### Summary

Compensatory mechanisms such as the Frank-Starling mechanism, myocardial hypertrophy, and activation of neurohormonal systems are finite, and they become maladaptive when chronically maintained. A vicious cycle of neurohormonal secretions, excessive vasoconstriction,

and tachycardia compromises the balance between myocardial oxygen demand and supply. The resultant increased SVR, fluid and electrolyte imbalance, and arrhythmias ultimately lead to deteriorating ventricular function, cardiac failure, and death.<sup>17</sup>

### CARDIOVASCULAR DISABILITY

The best measure of a patient's cardiovascular disability is an assessment of his or her status over time and an evaluation of the effects of therapeutic intervention. The New York Heart Association (NYHA) classification of functional ability in patients with heart failure has 4 classes: I, asymptomatic; II, symptomatic with moderate exertion; III, symptomatic with minimal exertion; and IV, symptomatic at rest.<sup>18,19</sup>

### CURRENT STANDARDS OF CARE FOR TREATMENT OF HEART FAILURE

Traditional treatment of heart failure includes the use of diuretics, which reduce fluid overload and relieve signs and symptoms. The addition of cardiac glycosides was initiated to increase cardiac contractility. However, treatment with diuretics and cardiac glycosides improved signs and symptoms but did not improve mortality rates.<sup>20</sup> This situation prompted an investigation of new drugs during the past decade, as cardiologists continue to gain new understanding of the role of neurohormonal systems and vascular endothelium in heart failure. Current treatment of heart failure, in addition to diuretics and inotropic drugs, includes ACE inhibitors and  $\beta$ -blockers.<sup>20</sup>

## Diuretics

Diuretics reduce extracellular fluid volume and ventricular filling pressures by inhibiting reabsorption of solutes by the renal tubules and inducing sodium and water excretion. In addition to reducing signs and symptoms of heart failure, diuretics are also associated with a decreased rate of hospitalization.<sup>20</sup> The most commonly used diuretics are the loop diuretics (ie, furosemide and ethacrynic acid) because of their rapid onset of action, high potency, and ability to induce diuresis when renal blood flow is reduced.<sup>21,22</sup> Loop diuretics are preferred in patients with compromised renal function and decompensated heart failure.<sup>20,21</sup> Thiazide diuretics and potassium-sparing diuretics are useful for volume retention in patients with mild heart failure, because these agents have a weak diuretic action.<sup>23</sup> A combination of diuretics, such as thiazides (metolazone) plus loop diuretics, can have a synergistic effect.<sup>22</sup> Combination therapy is highly beneficial for patients refractory to loop diuretics alone. Similarly, potassium-sparing diuretics (spironolactone, triamterene, amiloride) greatly augment diuresis when combined with thiazide or loop diuretics.<sup>20,22</sup>

The use of diuretics predisposes patients to electrolyte abnormalities, including hyponatremia, hypochloremic metabolic alkalosis, hypomagnesemia, and hypokalemia. Potassium depletion can be prevented by administration of oral potassium chloride supplements or by use of a potassium-sparing diuretic. Patients on long-term diuretic therapy need routine monitoring of serum levels of potassium, particularly when they are taking agents that limit

renal potassium losses (ie, nonsteroidal anti-inflammatory drugs and ACE inhibitors).<sup>23</sup>

## Cardiac Glycosides

Digoxin has a negative chronotropic effect and a positive inotropic effect.<sup>21</sup> The inotropic effects are mediated by inhibition of sodium and potassium ATPase activity. This inhibition increases sodium influx in the cells and, in turn, increases calcium accumulation in exchange for sodium through the sodium-calcium exchange system. The increased amount of cytosolic calcium interacts with contractile proteins, increasing the velocity of sarcomere shortening, changes that augment contractility.<sup>22</sup>

In several randomized controlled trials, withdrawal of digoxin in patients with stable mild to moderate heart failure caused significant worsening of signs and symptoms, even in patients receiving an ACE inhibitor.<sup>21</sup> Therefore, even though cardiac glycosides have not been proven to decrease mortality, they improve contractility, improve diastolic filling, and augment left ventricular function.<sup>21</sup> A disadvantage of digoxin treatment is a small therapeutic-toxic ratio. Signs and symptoms of toxic reactions include anorexia, nausea, vomiting, confusion, seizures, visual manifestations (blue-green-yellow vision, halos), dysrhythmias, and increased severity of heart failure.<sup>22</sup>

## ACE Inhibitors

Patients with chronic heart failure have increased renin-angiotensin-aldosterone activity, resulting in excessive vasoconstriction and water and sodium retention. ACE inhibitors reverse

the effects of the renin-angiotensin system by reducing the production of angiotensin II and decreasing the release of aldosterone.<sup>20,24</sup> The cumulative effect is improved hemodynamic function, including reduced mean arterial pressure and SVR, thus decreasing afterload and myocardial oxygen consumption. In addition, ACE inhibitors decrease plasma levels of norepinephrine. Circulatory levels of norepinephrine are inversely correlated with signs and symptoms and prognosis of heart failure.<sup>25</sup>

Despite the benefits observed with ACE inhibitors, many patients with heart failure remain markedly symptomatic, and mortality rates remain relatively high.<sup>26-28</sup> This situation has led to further investigation of additional pharmacotherapeutic treatment for heart failure, such as the use of  $\beta$ -blockers.

## $\beta$ -Blockers

*Clinical Trials.* During the past 30 years,  $\beta$ -blockers have been used to treat hypertension, prevent myocardial infarction, and treat arrhythmias.<sup>29,30</sup> Treatment with  $\beta$ -blockers for heart failure has been controversial because of the negative chronotropic and inotropic actions of these drugs. Recent studies<sup>3,6-9</sup> indicated that  $\beta$ -blockers improve signs and symptoms, exercise tolerance, and hemodynamics and reduce mortality in patients with heart failure. The Cardiac Insufficiency Bisoprolol Study II<sup>31</sup> and the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure<sup>32</sup> were done to determine the survival benefits of  $\beta$ -blockers in patients with heart failure. In the Cardiac Insufficiency Bisoprolol Study II, 2647

patients with heart failure (83% with NYHA class III and 17% with class IV) were randomized to receive bisoprolol (a  $\beta_1$ -selective nonvasodilatory  $\beta$ -blocker) or a placebo. The bisoprolol group had 34% fewer deaths than the control group did ( $P < .001$ ). Further subgroup analysis indicated that most of the benefit from bisoprolol was attributable to a reduction in sudden death. The Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure was a placebo-controlled mortality study of metoprolol in 3991 patients with systolic heart failure (ejection fraction,  $< 0.40$ ). The number of deaths due to all causes was 145 in the 1990 patients in the metoprolol group and 217 in the 2001 patients in the placebo group, a 34% decrease in mortality ( $P < .001$ ). In addition, both sudden death and death due to progressive heart failure were significantly reduced, by 41% and 49%, respectively, in the metoprolol group ( $P < .001$ ).

**Classification of  $\beta$ -Blockers.**  $\beta$ -Blockers are classified according to their affinity for adrenergic receptors<sup>33</sup> (Table 1) and according to their generation<sup>7</sup> (first, second, third; Table 2). The 2 types of identified adrenergic receptors are  $\alpha$  and  $\beta$ .  $\beta$ -Adrenergic receptors are subclassified as  $\beta_1$  and  $\beta_2$  and  $\alpha$ -adrenergic receptors as  $\alpha_1$  and  $\alpha_2$ . Stimulation of  $\beta_1$ -receptors causes an increase in heart rate, cardiac contraction, and conduction velocity (dromotropic).  $\beta$ -Blockers interrupt these effects by occupying  $\beta$ -receptor sites, preventing the binding of norepinephrine and epinephrine. The resultant decrease in inotropic, chronotropic, and dromotropic states reduces myocardial oxygen

**Table 1** Main responses of adrenergic receptors<sup>33</sup>

System affected	Receptor	Response to stimulation
Heart	$\alpha_1$ $\beta_1$	Increased contractility Increased conduction velocity, heart rate, excitability, force of contraction
Blood vessels	$\alpha_1$ and $\alpha_2$ $\beta_2$	Arterial vasoconstriction Arterial vasodilation
Lungs	$\beta_2$	Bronchodilation
Kidneys	$\alpha_1$ and $\alpha_2$ $\beta_2 > \beta_1$	Vasoconstriction Stimulation of renin release
Glycogenolysis	$\beta_1$ (heart) $\beta_2$ (skeletal muscle, liver)	Promotion of glycogen breakdown Promotion of glycogen breakdown

consumption, enhances coronary blood flow, and improves myocardial perfusion.<sup>17,29</sup> Stimulation of  $\beta_1$ -receptors in the kidneys causes the release of renin during heart failure. Blockade of  $\beta_1$ -receptors inhibits the activation of the renin-angiotensin system, thereby decreasing water and sodium retention. Activation of  $\beta_2$ -receptors causes arterial dilatation. Blockade of these receptors produces vasoconstriction.

First-generation  $\beta$ -blockers block both  $\beta_1$ - and  $\beta_2$ -receptors but do not have ancillary properties such as vasodilating effects. The first-generation drugs are generally not well tolerated because they have a potent negative inotropic effect, which decreases stroke volume and cardiac index. Second-generation  $\beta$ -blockers are selective for the  $\beta_1$ -receptors and also do not cause vasodilation. Because they do not affect  $\beta_2$ -receptors, second-generation agents cause less cardiac depression and vasoconstriction than do first-generation agents.

Third-generation  $\beta$ -blockers that also block  $\alpha_1$ -receptors cause arterial vasodilation in addition

to the actions associated with blocking of  $\beta$ -receptors. Because of their greater vasodilating properties, third-generation  $\beta$ -blockers are better tolerated by patients during the initiation and titration of treatment than are the first- and second-generation drugs. The vasodilatation caused by the third-generation blockers reduces the afterload, which offsets the transient decrease in cardiac output related to the withdrawal of adrenergic support from the failing heart. In addition, third-generation agents produce less bradycardia than do

**Table 2** Classification of  $\beta$ -blockers<sup>7</sup>

Generation	Drug
First	Propranolol Timololol
Second	Metoprolol Atenolol Bisoprolol Betaxolol
Third	Pindolol Dilevalol Celiprolol Labetolol Carvedilol Bucindolol

second-generation agents, a characteristic that may be beneficial in patients with low heart rates.<sup>14,16</sup>

Although a variety of  $\beta$ -blockers exist and are associated with decreased mortality and morbidity, it is not clear which agent provides the greatest benefit. The differences between the  $\beta$ -blockers, including carvedilol (Coreg), a promising new third-generation  $\beta$ -blocker, are being investigated in clinical trials.

## CARVEDILOL

Carvedilol was approved by the Food and Drug Administration in 1997 for treatment of mild or moderate heart failure of ischemic or cardiomyopathic origin.<sup>17</sup> Its approval was based on the results of large clinical trials in which use of carvedilol reduced the number of hospitalizations for cardiovascular reasons and

decreased disease progression and mortality.<sup>7,34</sup>

Carvedilol is a nonselective  $\beta$ -blocker without intrinsic sympathomimetic activity. Drugs with intrinsic sympathomimetic activity not only prevent the binding of endogenous catecholamines but also act as weak agonists. As a result,  $\beta$ -blockers with intrinsic sympathomimetic activity cause a smaller decline in heart rate, cardiac output, and renin levels than do agents without this activity.<sup>12</sup>

Carvedilol blocks  $\beta_1$ -,  $\beta_2$ -, and  $\alpha_1$ -adrenergic receptors. The vasodilating effects of carvedilol, exerted primarily through blockade of  $\alpha_1$ -receptors, lower cardiac filling pressure and SVR. Compared with second-generation  $\beta$ -blockers, third-generation drugs (labetalol, carvedilol) are better tolerated during initiation and titration of therapy because the vasodilating

properties of the third-generation agents decrease afterload and offset the negative inotropic effects associated with the initiation of  $\beta$ -blocker treatment.<sup>7,27,35</sup>

Labetalol and carvedilol both block  $\alpha$ -receptors and thus have vasodilating properties. However, long-term treatment with labetalol may result in the loss of blockade of  $\alpha_1$ -receptors, leaving blockade of  $\beta$ -receptors as the major action. This effect does not occur with carvedilol. Labetalol has also been associated with excessive vasodilation in patients with heart failure. Carvedilol produces a less potent vasodilator response than does labetalol because of the former's modest  $\alpha_1$ -adrenergic blocking ability.<sup>35</sup> In addition, unlike the effects of carvedilol, the effects of labetalol on long-term morbidity and mortality are unknown.<sup>7,34</sup>

The superior cardiac protection provided by carvedilol is not a consequence of hemodynamic variances but rather is due to the additional antioxidant effects of carvedilol. Studies in animals suggest that antioxidant effects may be protective in myocardial ischemia and may help retard the progression of atherosclerosis. Carvedilol decreases nitric oxide, the chemical that causes endothelial dysfunction and apoptosis (programmed cell death). In addition, carvedilol decreases the expression of structural extracellular proteins, an effect that reverses cardiac remodeling.<sup>36-40</sup>

Carvedilol has been evaluated in the treatment of patients with heart failure in a series of randomized, double-blind, placebo-controlled trials that included more than 1600 patients. The studies included a series of 3 pilot trials<sup>9,41,42</sup>

and 2 large-scale phase 3 programs.<sup>34,43</sup> Beneficial effects reported from the trials include improved signs and symptoms, improved exercise tolerance, decreased number of hospitalizations for cardiovascular reasons, and reduced mortality rates when carvedilol was added to conventional drug therapy (diuretics, cardiac glycosides, and ACE inhibitors).

#### Effects on Left Ventricular Ejection Fraction, Signs and Symptoms, and Exercise Tolerance

Long-term treatment with carvedilol improves cardiac function by decreasing pulmonary artery wedge pressure, right atrial pressure, left ventricular end-systolic and end-diastolic volumes, heart rate, and SVR. The resultant reductions in preload and afterload increase the stroke

index and cardiac output.<sup>9,41,44</sup> The cumulative effect is improved signs and symptoms and improved exercise tolerance, findings in several placebo-controlled trials (Table 3).<sup>9,34,41-43</sup>

#### Effects on Mortality

In the combined trials of the US program,<sup>34</sup> after 6 months of treatment, 7.8% of patients in the placebo group died compared with 3.2% of patients who received carvedilol, a 65% reduction in mortality ( $P<.001$ ). Carvedilol lowered the risk of death from both progression of heart failure (0.7% of carvedilol patients compared with 3.3% of placebo patients) and the occurrence of sudden death (1.7% of carvedilol patients compared with 3.8% of placebo patients,  $P<.001$ ). The reduction in mortality was similar regardless of disease severity,

**Table 3** Randomized placebo-controlled trials of carvedilol

Trial	No. of patients	NYHA class	Mean	Change	Improved signs and symptoms	Submaximum exercise improvement
Metra <sup>41</sup>	40	II/III	0.20	+ 0.10	Yes	Yes
Packer et al <sup>34</sup>	276	II-IV	≤0.35	+ 0.07	Yes	Yes
Krum et al <sup>9</sup>	49	II-IV	0.16	+ 0.07	Yes	Yes
Australia/New Zealand group <sup>43</sup>	415	I-III	0.29	+ 0.05	No	No
Olsen et al <sup>42</sup>	60	II/III	0.20	+ 0.11	Yes	Yes

cause of heart failure, left ventricular ejection fraction, exercise tolerance, age, sex, systolic blood pressure, or heart rate.<sup>9,34,41,42</sup> In the Australia-New Zealand trial,<sup>43</sup> morbidity was assessed after 19 months of treatment. A total of 50% of the patients who received carvedilol died compared with 63% of patients who received placebo ( $P=.02$ ).

### Effect on Hospitalization

In one study,<sup>34</sup> compared with placebo, carvedilol was associated with a 27% reduction in the risk for hospitalization for cardiovascular reasons ( $P=.04$ ). The cost of hospitalizations for cardiovascular problems was also assessed. The cumulative costs for all protocols in the US program were 62% lower for patients receiving carvedilol than for those receiving placebo ( $\$1664 \pm \$6867$  compared with  $\$4327 \pm \$20\,507$ ;  $P<.001$ ). Reduced numbers of admissions accounted for 44% of hospital savings.<sup>34</sup>

### Current Studies

The Mt. Sinai School of Medicine recently conducted a clinical study comparing the effects of long-term treatment

with metoprolol and carvedilol.<sup>45</sup> The variables investigated in this study included signs and symptoms, exercise tolerance, ejection fraction, and oxidative stress in heart failure. A total of 67 patients with symptomatic stable heart failure were randomly assigned to receive carvedilol or metoprolol in addition to standard therapy. Metoprolol is a  $\beta_1$ -selective agent, whereas carvedilol combines nonselective blockade of  $\beta$ -receptors with blockade of  $\alpha$ -receptors and antioxidant effects.

The 53 patients who completed the protocol in the Mt. Sinai study (23 in the metoprolol group and 30 in the carvedilol group) had significant improvements in all clinical and exercise parameters, with a mild improvement in NYHA class ( $P<.001$ ). Initial numbers of patients in the various NYHA classes (I/II/III/IV) in the metoprolol group were 0/5/17/1 at baseline and 1/11/11/0 at 6 months. With carvedilol, the numbers were 0/5/22/3 at baseline and 0/9/21/0 at 6 months. With both metoprolol and carvedilol, heart failure symptom scores improved (for metoprolol, from  $10 \pm 4.7$  at baseline to  $7.0 \pm 4.4$ ,  $P<.001$ ; for carvedilol, from

$9.9 \pm 4.5$  to  $7.3 \pm 3.8$ ,  $P<.001$ ). For exercise parameters, both groups had an improvement in the 6-minute walk, but the differences were not significant. The ejection fraction improved significantly in both groups, with no difference between the groups. Ejection fraction improved from  $0.18 \pm 0.06$  to  $0.23 \pm 0.07$  ( $P<.005$ ) for patients treated with metoprolol and from  $0.19 \pm 0.08$  to  $0.25 \pm 0.10$  ( $P<.001$ ) for patients treated with carvedilol.

In addition, no significant change was reported within or between the groups in norepinephrine levels. With metoprolol, plasma levels of norepinephrine were  $500 \pm 304$  pg/mL at baseline and  $486 \pm 324$  pg/mL at 6 months; with carvedilol, the levels were  $651 \pm 338$  pg/mL at baseline and  $532 \pm 312$  pg/mL at 6 months.

In conclusion, the study<sup>45</sup> indicated parallel beneficial effects in the measured parameters. The only difference reported between the 2 drug groups was a lower heart rate with carvedilol. This difference may reflect the greater degree of blockade achieved with a higher equivalency dose of carvedilol.

## NURSING IMPLICATIONS FOR ADMINISTRATION OF CARVEDILOL

The use of  $\beta$ -blockers in heart failure is becoming common practice. However, because carvedilol was only recently approved by the Food and Drug Administration for use in treatment of heart failure, nurses may need to update their current knowledge of this medication in order to safely administer the drug and monitor clinical effects.<sup>7,36,44,47</sup>

### Indications for Use

Carvedilol has previously been used for the treatment of hypertension and angina pectoris. It is now also indicated for the treatment of mild to moderate (NYHA class II or class III) heart failure of

cardiomyopathic origin and can be used in conjunction with digoxin, diuretics, and ACE inhibitors to reduce the progression of disease and to decrease the number of hospitalizations and deaths due to cardiovascular conditions.<sup>7,46,47</sup>

### Pharmacodynamics

Carvedilol is a racemic lipophilic aryloxypropranolamine that blocks  $\alpha_1$ - and  $\beta$ -adrenergic receptors. Carvedilol significantly decreases systemic blood pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure because of the vasodilatation that occurs with blocking of  $\alpha_1$ -receptors. Blocking of  $\beta$ -receptors reduces the heart rate and increases diastolic filling time. The combined effects of blocking both  $\alpha$ - and  $\beta$ -adrenergic receptors are decreases in

preload, afterload, and myocardial oxygen consumption.<sup>36,48,49</sup>

### Pharmacokinetics

Carvedilol is a white, oval tablet available in doses of 3.125, 6.25, 12.5, and 25 mg. It is rapidly absorbed after oral administration (onset of action, 1 hour), has a plasma half-life of 7 to 10 hours, and reaches peak levels in 7 to 14 days. Carvedilol is metabolized by the liver and excreted via bile into the feces. In serum, 98% of carvedilol is bound to protein, primarily albumin.<sup>7,46,47</sup>

The primary cytochrome P-450 enzymes responsible for the metabolism of carvedilol are microsomal CYP2D6 and CYP2C9. Inhibition of carvedilol metabolism via the CYP2D6 isozyme causes greater  $\alpha_1$ -adrenergic blockade than does metabolism via CYP2C9

and increases the risk of episodic hypotension. In contrast, inhibitors of CYP2C9 produce greater  $\beta$ -adrenergic blockade, increasing the risk of more profound bradycardia or overt heart failure.<sup>48,50</sup>

### Drug Interactions

Patients' drug profiles should be reviewed for possible interactions between carvedilol and other medications<sup>7,36,46,47,50</sup> (Table 4) before carvedilol is administered, and when necessary, drugs that interact with it should be discontinued or their dosages decreased. When an interacting drug cannot be discontinued or the dosage decreased, the maximum target serum level of carvedilol may not be attainable. Although carvedilol may interact with other medications, causing an increase or decrease in serum levels of both carvedilol and the other drugs, routine measurement of serum levels of carvedilol is not done. In fact, such measurement requires specific equipment in a research laboratory, and few clinical laboratories have the capacity to perform this test.

**Cimetidine.** Concurrent use of cimetidine can increase plasma levels of carvedilol by 30% but causes no change in the peak plasma concentration of carvedilol.<sup>7,36,46,47</sup>

**Clonidine.** Concurrent treatment with clonidine and carvedilol may potentiate hypotension and bradycardia. When treatment is discontinued, carvedilol should be discontinued first. Clonidine can then be tapered off during the course of several days.<sup>7,36,46,47</sup>

**Digoxin.** The concomitant use of digoxin and carvedilol increases digoxin levels by 15%. This interaction may lead to greater atrioventricular nodal conduction blockade, causing lower heart rates. Increased monitoring of digoxin

**Table 4** Suspected or known drug interactions with carvedilol in patients with heart failure

Drug	Interaction	Potential outcome
Quinidine*	CYP2D6 inhibition	Hypotension
Fluoxetine*	CYP2D6 inhibition	Hypotension
Paroxetine*	CYP2D6 inhibition	Hypotension
Sertraline*	CYP2D6 inhibition	Hypotension
Cimetidine†	CYP2D6 inhibition	Hypotension
Mibefradil*	CYP2D6 inhibition	Hypotension
Amiodarone*	CYP2D6 inhibition	Hypotension
Fluoxetine*	CYP2C9 inhibition	↓HR, hypotension
Cimetidine†	CYP2C9 inhibition	↓HR, hypotension
Omeprazole*	CYP2C9 inhibition	↓HR, hypotension
Rifampin†	CYP2C9 induction	↑HR (↓carvedilol plasma concentration 70%)
Digoxin†	Unknown	↑Digoxin serum concentration 15% (↑AV nodal blockade, ↓HR)
Verapamil*	Pharmacodynamic	↑AV nodal blockade, ↓HR, hypotension
Diltiazem†	Pharmacodynamic	↑AV nodal blockade, ↓HR, hypotension
Clonidine†	Pharmacodynamic	↓HR, hypotension
Catecholamine-depleting agents (reserpine)	Pharmacodynamic	↓HR, hypotension
Mibefradil*	Pharmacodynamic	↑AV nodal blockade, ↓HR, hypotension
Insulin*	Pharmacodynamic	Potentiate ↓blood sugar
Oral hypoglycemics		

\*Suspected drug interaction.

†Known drug interaction.

AV indicates atrioventricular; HR, heart rate; ↑, increased; ↓, decreased.

Adapted from Bleske et al,<sup>50</sup> with permission.

levels is recommended when initiating, adjusting, or discontinuing treatment with carvedilol.<sup>7,36,46,47</sup>

**Diltiazem.** Conduction disturbances may occur if carvedilol is

coadministered with drugs that have sinoatrial or atrioventricular nodal properties, such as diltiazem, mibefradil, and verapamil. Drugs with negative inotropic

properties such as diltiazem and verapamil should generally be avoided in patients with heart failure, especially patients receiving carvedilol. When carvedilol is used with diltiazem, electrocardiographic findings and blood pressure should be monitored.<sup>7,36,46,47</sup>

*Glyburide.* Combined administration of carvedilol and glyburide does not cause relevant pharmacokinetic interactions.<sup>7,36,46,47</sup>

*Hydrochlorothiazide.* Concurrent administration of hydrochlorothiazide and carvedilol has no effect on the pharmacokinetics of either agent.<sup>7,36,46,47</sup>

*Rifampin.* Concurrent use of rifampin reduces plasma levels of carvedilol by 70%.<sup>7,36,46,47</sup>

*Vasodilators.* Hypotension is more likely if carvedilol is administered with other vasodilator drugs (hydralazine, ACE inhibitors),

especially if the drugs are taken at the same time each day. In order to decrease the likelihood of hypotension, carvedilol and other vasodilators should be taken approximately 2 hours apart.<sup>7,36,46,47</sup>

*Warfarin.* Coadministration of warfarin and carvedilol does not affect the prothrombin time ratios and does not change the pharmacokinetics of warfarin.<sup>7,36,46,47</sup>

### Dosage and Administration

The recommended starting dose of carvedilol is 3.125 mg twice a day. Thereafter, the dose is titrated upward every 2 weeks, according to the patient's tolerance, to a maximum dosage of 25 to 50 mg twice a day. In a large placebo-controlled trial, patients who were given lower than maximum dosages of carvedilol still derived benefits compared with

patients who received a placebo. However, benefits were greater in those patients who were able to achieve the maximum target dose of carvedilol. Therefore, the goal of therapy should be to reach maximum target dosages. Initial difficulties with increasing the dosage of carvedilol do not preclude later attempts to up-titrate the dosage once a patient's clinical condition is stable.<sup>34,43,51</sup> At the initiation of each higher dose, the patient should be observed for 1 hour for hypotension, dizziness, and lightheadedness. If the systolic blood pressure is less than 85 mm Hg, the medication should be withheld, and a physician should be notified. In addition, as with any agent that affects heart rate and blood pressure, combining carvedilol with other cardiovascular agents may lead to bradycardia

and/or hypotension. In order to minimize the occurrence of orthostatic effects, carvedilol should be taken with food.<sup>7,46,47</sup>

Excessive hypotension or syncope and signs or symptoms of vasodilatation can be treated by reducing the dose of diuretics or ACE inhibitors. Transient worsening of heart failure (peripheral edema, weight gain, shortness of breath) often responds to increased dosages of diuretics or ACE inhibitor. If the problem persists, the dose of carvedilol may need to be decreased or discontinued. Patients receiving carvedilol who are hospitalized for exacerbation of heart failure and/or cardiogenic shock should not receive carvedilol until the condition is stabilized.<sup>50,52</sup>

### Contraindications

Carvedilol may cause an initial decrease in chronotropic and inotropic states and is therefore contraindicated in patients with NYHA class IV heart failure. It is also contraindicated in patients with cardiogenic shock, volume overload, or severe bradycardia and in those with second- or third-degree atrioventricular block who do not have a pacemaker.<sup>7,36,46,47</sup> Patients who have clinical evidence of bronchitis or asthma maintained with bronchodilators or corticosteroids and/or whose forced vital capacity/forced expiratory volume in 1 second is less than 0.60 also should not receive this agent. Other contraindications include symptomatic peripheral vascular disease, because  $\beta$ -blockers may precipitate or aggravate signs and symptoms of arterial insufficiency. Use of carvedilol in patients with hepatic impairment (defined as an increase in the serum level of transaminase 3 times the upper

limit of the reference range) is not recommended because the drug is metabolized by the liver.<sup>50</sup>

$\beta$ -Blockers may mask signs and symptoms of hypoglycemia and/or hyperglycemia. However, in several trials,<sup>39,53</sup> patients with type 2 diabetes mellitus treated with carvedilol had no significant differences in fasting or postprandial glucose concentrations or in levels of glycosylated hemoglobin. In addition, in 2 double-blinded comparative trials,<sup>38,54</sup> hypertensive patients treated with carvedilol had improved insulin sensitivity. In these trials,<sup>38,54</sup> neither prolonged hypoglycemia nor delayed recovery of

glucose concentrations occurred. Despite the results reported in the studies,<sup>38,39,53,54</sup> blood glucose monitoring should be increased when treatment with carvedilol is initiated, adjusted, or discontinued.

### Adverse Reactions

Common adverse reactions associated with use of carvedilol include hypotension, bradycardia, dizziness, fatigue, hyperglycemia, and diarrhea. Less common are syncope, fluid overload, respiratory distress, thrombocytopenia, and urinary tract infection (Table 5). Nursing diagnoses and interventions are reviewed in Table 6.

**Table 5** Adverse reactions associated with use of carvedilol in US placebo-controlled heart failure trials<sup>36</sup>

Adverse reaction	Occurrence*	Withdrawal†
Cardiovascular		
Peripheral edema	2.2	0.1
Hypotension	8.5	0.4
Bradycardia	8.8	0.8
Syncope	3.4	0.3
Fluid overload	2.0	0.0
Respiratory		
Dyspnea	1.4	0.4
Sinusitis	5.4	0.0
Bronchitis	5.4	0.0
Pharyngitis	3.1	0.0
Central nervous system		
Dizziness	32.4	0.4
Fatigue	23.9	0.7
Hematologic		
Thrombocytopenia	2.0	0.1
Metabolic		
Hyperglycemia	12.2	0.1
Gastrointestinal		
Diarrhea	11.8	0.3
Urinary/renal		
Urinary tract infection	3.1	0.0

\*Numbers in occurrence column are percentages of patients who experienced each adverse reaction.

†Numbers in withdrawal column are percentages of patients who withdrew from the trial because of the adverse reaction.

**Table 6** Nursing plan of care for patients receiving carvedilol<sup>46,47,55</sup>

Adverse reaction	Nursing diagnosis	Interventions
Cardiovascular Peripheral edema Hypotension Bradycardia Syncope Fluid overload	Potential for alteration in peripheral perfusion and decreased cardiac output	Check blood pressure every 2 hours with patient lying down and then standing (wait 2 minutes after patient stands before measuring). Report systolic blood pressure < 90 mm Hg (mean arterial pressure < 80 mm Hg). Note narrowing of pulse pressure. Assess alternations in strong and weak pulsations (pulsus alternans). Report heart rate < 50/min. Auscultate heart sounds every 4-8 hours for presence of rales, S <sub>3</sub> or S <sub>4</sub> gallop. (S <sub>3</sub> is heard best when patient is lying on his or her left side.) Monitor electrocardiograms for premature ventricular beats. Observe patient for decreased peripheral perfusion (cool, pale skin, capillary refill < 3 seconds). Report cough, pink frothy secretions, and dyspnea. Monitor patient for change in mental status. Assess patient for jugular venous distention and hepatjugular reflux. Monitor pulmonary artery wedge pressure (normal, 4-12 mm Hg), if applicable. A change of 4 mm Hg is clinically important in most patients. Check dependent areas for edema (ie, ankles, sacral area, buttocks).
	Potential for fluid and electrolyte imbalance	Document intake and output every hour. Report urinary output < 30 mL/h. Obtain weight at same time daily. Report weight gain > 0.9 kg (> 2 lb). Report central venous pressure > 10 mm Hg, if applicable.
Respiratory Dyspnea Sinusitis Bronchitis Pharyngitis	Potential for impaired gas exchange	Monitor rate and depth of respirations. Report dyspnea and use of accessory muscles. Auscultate lung fields for wheezing, rhonchi, stridor, and rales. Assess symmetry of breath sounds. Provide oxygen therapy as ordered if respiratory distress occurs. Obtain sample for arterial blood gas analysis if oxygen saturation < 90%. Document effects of bronchodilators/corticosteroids within 30 minutes after administration, if ordered. Report confusion/restlessness, and decreased level of consciousness. Provide fluids to liquefy secretions. Suction airway as needed.
Central nervous system Dizziness Fatigue	Potential for injury	Keep side rails up and call bell within patient's reach. Encourage patients to call for assistance to get out of bed. Encourage patients to report dizziness or syncope. Encourage patients to stand slowly, dangle at bedside before getting out of bed, and avoid sudden changes in position (ie, bending over).
Hematologic Thrombocytopenia	Potential for bleeding	Check complete blood cell count regularly, especially at the initiation of therapy, and then less frequently when a stable dose of carvedilol is reached. Report platelet count < 140 x 10 <sup>9</sup> /L. Report petechiae or ecchymotic areas.

*Continued*

**Table 6** *Continued*

Adverse reaction	Nursing diagnosis	Interventions
Metabolic Hyperglycemia	Potential for elevated serum glucose level	Observe patient for oozing from intravenous sites. Assess urinary drainage for hematuria. Report bleeding of gums, and provide gentle mouth care. Monitor secretions for occult blood. Report hemoptysis. Report tarry stools and test for presence of occult blood.  Increase glucose monitoring (4 times daily) in diabetic patients in whom carvedilol therapy is started.* Report fasting serum glucose levels > 7.2 mmol/L (> 130 mg/dL). Assess urine for sugar and acetone when serum glucose level > 10.0 mmol/L (> 180 mg/dL).
Gastrointestinal Diarrhea	Potential for altered bowel elimination	Monitor regularity and frequency of stools. Note consistency, amount, and color of stools. Auscultate frequency of bowel sounds. Notify physician if loose, liquid stools occur (may require change in medication). Hold laxative and stool softeners if diarrhea occurs. Provide binding foods (ie, toast, tea, and rice). Collaborate with dietician regarding low-fiber, low-residue, soft diet. Avoid giving patients foods described by them as irritants. Provide perineal care and monitor skin integrity. Avoid hot/cold fluids (tepid only).
Urinary/renal Urinary tract infection	Potential for fluid and electrolyte imbalance	Provide adequate hydration. Increase electrolyte supplement fluids during diarrhea.
	Potential for infection	Monitor patient for signs and symptoms of infection. Report burning, pain, and frequency. Observe urine for color, sediment, and occult blood. Palpate bladder for distention and tenderness. Report temperature every 4 hours. Send urine for analysis, including urine culture, on admission and thereafter if patient is symptomatic.

\*Because  $\beta$ -blockers reduce the heart rate, in states of hypoglycemia, the tachycardia effect may be masked.

### Teaching of Patients and Their Families

Before discharge from the hospital, patients and their families should be instructed about the proper use of carvedilol. It should be emphasized that to prevent the acute onset of heart failure, patients should never suddenly stop taking this drug unless directed to do so by a physician. Patients should be taught about the classical signs and symptoms of heart failure that should be

reported. In addition, subtle signs and symptoms and ways to lessen them should be discussed, including increasing the number of pillows used during sleep to decrease shortness of breath. Patients should also be taught how to take their pulse and should show that they can do it properly. Verbal information should be reinforced with written information in easily understandable terms that exclude medical jargon.<sup>46,47,55,56</sup> The teaching guide

(Table 7) is a tool nurses can use to educate patients and patients' families during discharge planning. In addition, patients should be encouraged to discuss carvedilol and all other medications they are taking (including over-the-counter products) with their physicians and pharmacist.

### CONCLUSION

In conclusion, the use of  $\beta$ -blockers in addition to standard therapy including cardiac glyco-

**Table 7** Teaching guide for patients taking carvedilol<sup>46,47,55,56</sup>

This medication may slow your heart rate and lessen the work load of your heart. Take your medication as directed. Side effects may occur and may be a temporary reaction until your body adapts to the new medication. Do not stop taking this medication without consulting your physician.

**Medication:** Carvedilol (Coreg). Do not take this medication if you have severe congestive heart failure, liver disease, or lung diseases such as asthma, chronic bronchitis, or emphysema without talking with your doctor.

**Side effects to report**

Dizziness	Asthma attacks
Fainting	Difficulty in breathing
Difficulty sleeping	Frequent painful urination
Diarrhea	Unusual bleeding
Swelling of hands or feet	Weight gain of 0.9 kg (2 lb) or more within a few days
Increase in the number of pillows needed to achieve comfortable sleep and decrease shortness of breath	Memory loss
	Fatigue

**Instructions**

1. Take this medication during or after meals.
2. Do not use hazardous machinery or drive when first taking this medication because dizziness may occur.
3. To prevent dizziness, avoid sudden changes in body position (bend over slowly, stand slowly, and sit at bedside 2-3 minutes before getting out of bed).
4. Weigh yourself the same time every day wearing the same amount of clothing.
5. Take your radial pulse. If your heart rate is 50 beats per minute or lower, do not take this medication without calling your physician.
6. Eat toast and rice and drink tea if diarrhea occurs. Contact your doctor or pharmacist if diarrhea becomes severe or continues.

Before taking this medication, alert your physician and pharmacist if you are taking diltiazem, digoxin, clonidine, rifampin, cimetidine, or any of the following antidepressants: tranylcypromine (Parnate), phenelzine (Nardil), isocarboxizid (Marplan), paroxetine (Paxil), fluoxetine (Prozac).

sides, diuretics, and ACE inhibitors, can decrease signs and symptoms, number of hospitalizations for cardiovascular reasons, and mortality in patients with heart failure. Carvedilol is a promising new  $\beta$ -blocker that has been specifically approved by the Food and Drug Administration for use in the treatment of heart failure. Its antioxidant properties and its ability to cause arterial vasodilation distinguish it from other  $\beta$ -blockers.

As with any  $\beta$ -blocker, initial administration may cause a transient decrease in myocardial contractility. Therefore, patients

should be monitored for further cardiac decompensation, in addition to other reported adverse reactions. Information given to the patients and their families about the patients' medications should be reinforced by written material, and discussions with patients' physicians and pharmacist should be encouraged. †

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