Carvedilol: Therapeutic Application and Practice Guidelines

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Current knowledge of the mechanisms contributing to progression of heart failure suggests that therapies that limit or interfere with the consequences of neurohormonal activation and improve myocardial energetics appear to be most beneficial. Carvedilol, a nonselective β-adrenergic blocker with peripheral vasodilating properties, reduces mortality, slows progression of disease, and improves quality of life in patients with heart failure when added to standard therapy. When administered according to recommended guidelines, carvedilol is well tolerated. Clinical guidelines on the use of carvedilol in heart failure are provided.
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OUTLINE

"It should be the function of medicine to have people die young as late as possible."

Ernest L. Wynder

Heart failure increases myocardial energy expenditure, thereby promoting pathologic remodeling, which accelerates cell death in the human failing heart by overactivity of neurohormonal systems.[1] Given this understanding of the pathophysiology of heart failure, treatments that limit or interfere with neurohormonal activation or improve the balance between myocardial oxygen supply and demand appear to be most promising.[2] Results of 2 decades of basic and clinical research suggest that β-adrenergic blockers can prevent disease progression and are tolerated in selected patients.

Carvedilol is the first β-adrenergic blocker approved for the treatment of heart failure. It improves ejection fraction, cardiac hemodynamics, New York Heart Association (NYHA) functional class, and well-being.[3–9] It slows the progression of the disease when added to conventional therapy, as evidenced by risk reductions for hospitalization and mortality.[6] Therapy must be managed carefully, however, to ensure these outcomes.

Like other β-adrenergic blockers, carvedilol reduces adrenergic drive from the failing human heart, resulting in early clinical deterioration in many patients. With proper understanding of the common symptoms associated with initiation and up-titration of therapy, this short-lived deterioration can be managed safely. Thereafter, patients experience long-term benefits from the agent.

Rationale for β-Adrenergic Blockade in Heart Failure

Heart failure prognosis has remained dismal over the past 4 decades despite reductions in

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morbidity and mortality for most cardiovascular diseases. Results of large placebo-controlled clinical trials show that annual mortality ranges from approximately 15% in mild to moderate disease to 54% in severe disease.[10, 11] An angiotensin-converting enzyme (ACE) inhibitor is considered the mainstay of therapy, but these agents result in only an approximate 10% annual reduction in mortality.[10–12] Therefore, the challenge is to develop new treatment strategies that will decrease the high risk of dying from this syndrome.

The rationale for prescribing β-adrenergic blocking agents is founded on knowledge that heart failure is a chronically activated adrenergic state. Over the past 2 decades, studies described an association between progression of left ventricular dysfunction and greater norepinephrine spillover.[13] As a result of increased myocardial interstitial norepinephrine concentration, poor left ventricular dysfunction is associated with several changes in the β-adrenergic receptor complex. These include β_1-receptor down-regulation, uncoupling of the β_2-receptor, increases in α_1-receptor density, and decreased density of the AT_1-receptor (angiotensin II).[13, 14] In patients with heart failure, the outcome of these β-adrenergic system changes is a reduction in myocyte contractility with an associated diminished ability to respond to dynamic stress,[15] resulting in chronic fatigue. In addition, norepinephrine is directly toxic, thereby accelerating cardiac myocyte death.[16] The end result of these changes is progression of disease and poor survival.

In theory, β-adrenergic blockade could attenuate changes in the cardiac sympathetic nervous system and slow disease progression. Potential benefits include reduced autonomic tone, resulting in a decrease in resting energy demands of the failing human heart, improved cardiac metabolic and hemodynamic status, attenuation of myocyte necrosis, and prevention of sympathetic-mediated arrhythmogenesis. In long-term clinical trials, carvedilol was associated with improvements in heart failure when added to ACE inhibitors with or without diuretics and digoxin.[3–9]

Pharmacology

Carvedilol is a racemic arylethanolamine with nonselective β-adrenergic-blocking and peripheral vasodilating properties. The β-adrenergic-blocking activity occurs without intrinsic sympathomimetic activity and only with the levorotatory configuration.[17] Moderate arteriolar dilation and reductions in peripheral vascular resistance occur through α_1-adrenergic receptor blockade.[18–20] The α_1-antagonist properties occur at equal potency from both dextrorotatory and levorotatory enantiomers.[21] At therapeutic dosages, carvedilol inhibits $\beta_1 > \alpha_1 > \beta_2$-receptors at a ratio of 1:3:7, respectively.[22]

Blockade of β-receptors should result in normal β-adrenergic receptor biology. Carvedilol, however does not up-regulate β-adrenergic receptors. This may be due to guanine nucleotide binding, a process whereby high concentrations of guanine nucleotides (similar in structure to carvedilol) competitively antagonize β-adrenergic-blocker receptor binding.[20, 23] Despite competitive pharmacologic binding, adenylate cyclase activity is not elevated with carvedilol, suggesting signal transduction is not restored and therefore the heart is protected from adrenergic stimulation.[22] Further protection against chronic adrenergic activation is evidenced by a decrease in transmyocardial norepinephrine production with long-term dosing.[24]

β-Adrenergic blockers also reduce adrenergic drive to the heart through inverse agonism.[22, 25, 26] Unoccupied or nonstimulated adrenergic receptors retain intrinsic activity that can support myocardial contractility. Inverse agonism is a process whereby β-adrenergic blockers inactivate these unoccupied receptors.[22, 27, 28] Carvedilol has the least amount of this property among commercially available β-adrenergic blockers. Independent of the degree of inverse agonism, this property contributes to myocardial depression on starting carvedilol therapy.

Ancillary Properties

Carvedilol has a number of cardioprotective properties that may be beneficial in heart failure. It reduces hypoxic stress-induced glycogen loss from myocardial tissue compared with equivalent doses of propranolol in vitro.[29] Although the exact mechanism of these effects is unknown, carvedilol inhibits oxygen free radical lipid oxidation in rat brain and heart tissue and in human in vitro studies, and inhibits superoxide release from phorbol ester-activated neutrophils.[30–32] These antioxidant properties occur in clinically observed plasma concentrations.[33]

Results of animal studies indicate that the drug inhibits vascular smooth muscle cell proliferation and migration.[34] This suggests that it has cardio-

protective effects in patients with underlying atherosclerosis. The clinical significance of these findings is unknown.

Pharmacokinetics

The agent undergoes rapid and extensive absorption with a large first-pass metabolic effect resulting in only 25% absolute bioavailability.[35] A 2-fold bioavailability difference exists between the dextrorotatory (31%) and the levorotatory configurations (15%).[36] The compound is highly lipophilic, thereby exhibiting a large volume of distribution.[37] Carvedilol is highly protein bound to albumin.[38] It is extensively metabolized by cytochrome P450 (CYP) 2D6 and CYP2C9 microsomes, which show genetic polymorphism. The result is three active metabolites, of which the 4′-hydroxyphenyl metabolite has 13-fold greater β-adrenergic-blocking activity than the parent compound.[39] The predominant excretion pathway is through bile.

Clinical Outcomes

Most clinical trials of carvedilol employed consistent research methods. The agent was added to a background therapy of ACE inhibitors plus diuretics and/or digoxin. Calcium channel blockers, other β-adrenergic blockers, and vasodilators, with the exception of long-acting nitrates and hydralazine, were excluded. Patients were first enrolled in an open-label run-in phase lasting from 24 hours–3 weeks to evaluate tolerance. If they tolerated the β-adrenergic blocker, they moved to a dose-escalation phase of 4–6 weeks. Exposure to carvedilol was generally 3–6 months. Most patients were in NYHA functional class II–III heart failure with relatively even distribution between idiopathic dilated and postinfarction cardiomyopathy.

Cardiac Hemodynamics and Left Ventricular Effects

Carvedilol therapy in patients with heart failure results in significant improvement in left ventricular hemodynamics, which occurs at a substantially lower double product (systolic blood pressure x heart rate) than baseline values. Significant increases occur in cardiac output and are associated with improvements in stroke volume and stroke work indexes.[3, 4] The drug causes in modest falls in systemic vascular resistance and mean arterial pressure.[3, 4, 6] Heart rate decreases in a dose-related manner, with a mean decrease of approximately 12–13 beats/minute at a mean dosage of 45 mg/day.[40]

Long-term administration of the agent results in significant improvement in left ventricular ejection fraction. Improvement occurs only with long-term dosing, is dose dependent, with greater increases occurring with dose escalation, and is independent of heart failure etiology.[9] The exact mechanisms related to the improvement in ejection fraction are unknown.

Exercise Tolerance

Results of clinical exercise tolerance studies with carvedilol reported minimal improvement in exercise capacity. In tests of maximum energy expenditure the drug led to no change in exercise tolerance, perhaps due to blunting of maximum heart rate.[3, 4] Submaximum tests yield mixed results, confirming the limitation of these tests is due to patient effort.[3–6, 9, 24] Although peak exercise remains stable with carvedilol therapy, exercise performance is maintained at a significantly lower double product, suggesting improved cardiac efficiency.

Symptom and Global Assessment Outcomes

Carvedilol was extensively evaluated by symptom measures and global assessment outcomes. It significantly improves NYHA functional class.[3, 4, 6–9] It also improves symptom scores[3, 4, 7] and patient and physician global assessments of the heart failure state.[7–9] Quality of life measured by the Minnesota Living with Heart Failure questionnaire showed no change.[8, 9] This may reflect length of therapy, problems with measuring quality of life with this instrument, differences in clinical experience among investigators, or unfavorable effect on quality of life of β-adrenergic blockers. Since other studies showed β-adrenergic blockers improved quality of life after 12–18 months, length of follow-up is the most probable explanation.

Morbidity and Mortality

Clinical progression of heart failure may be defined by death, hospitalization, increased drug requirements, and decline in left ventricular function or exercise tolerance. A stratified analysis of four studies randomizing 1094 patients with NYHA functional class II–IV heart failure followed for a mean of 6.5 months showed a significant 65% reduction in mortality, 7.8% in the placebo group and 3.2% in the carvedilol

group.[6–8, 41] The mortality risk reduction was due to decreases in both progressive heart failure and sudden death. The risk of hospitalization for the disease was reduced 36% and length of stay per patient decreased by 1.4 days. Reductions were also noted in the need for sustained increases in heart failure drugs. Benefits were seen in all subgroups stratified by age, sex, race, severity and etiology of disease, and concomitant therapy.

Clinical Guidelines

Carvedilol is indicated for the treatment of mild to moderate (NYHA functional class II–III) disease due to left ventricular systolic dysfunction. It had clinical benefit in patients receiving standard therapy with an ACE inhibitor with or without diuretics and digitalis, and it should therefore be prescribed in combination with these drugs. Carvedilol, however, should not be considered as a fourth-line agent, since reduction of disease progression is not firmly established with all the standard drugs.[42] Once the decision is made to start carvedilol therapy, clinical guidelines must be understood and followed to ensure the best clinical outcomes (Figure 1).

This drug should be prescribed only for patients whose heart failure is clinically stable, defined by stable dosing of standard agents (i.e., no dosage changes in ACE inhibitors for 1 mo and diuretics for 2 wks) and without the need for intravenous inotropic support for at least 30 days, those with optimal filling pressures, and those with an absence of contraindications to β-adrenergic blockers. Experience with carvedilol is limited in patients with severe, NYHA functional class IV disease; these patients are the subject of an ongoing trial (COPERNICUS). The agent can be prescribed for these patients, but only by cardiologists experienced in the management of β-adrenergic blockers in heart failure. Patients considered for carvedilol therapy should have no evidence of low volume status (dry mucous membranes, orthostatic blood pressure changes, decreased urinary output) or signs and symptoms of excessive fluid volume (weight gain, radiographic evidence of pulmonary edema, increased jugular venous pressure, enlarged or tender liver, peripheral edema).

Several contraindications to carvedilol therapy exist. Briefly, decompensated heart failure, patients with clinical evidence of bronchitis or asthma maintained with bronchodilators or steroids and/or forced vital capacity (FVC)/forced expiratory volume in 1 second (FEV_1) below 60%, symptomatic peripheral vascular disease, brittle insulin-dependent diabetes (repeated episodes of ketoacidosis, hyperglycemic coma, hypoglycemic shock), severe bradycardia, sick sinus syndrome, second- or third-degree heart block unless paced, standing systolic blood pressure below 85 mm Hg, and hepatic injury defined by a rise in transaminase level 3 times upper limit of normal should generally not receive the agent.

The patient's drug profile should be examined for possible interactions (Table 1). Carvedilol is metabolized by CYP2D6 and CYP2C9 microsomes. Inhibition of the clearance of its metabolism through the CYP2D6 isozyme would be expected to increase the dextrorotatory enantiomer concentration, producing greater α_1-adrenergic blockade and leading to an increased likelihood of episodic hypotension. Inhibitors of CYP2C9 increase the levorotatory enantiomer concentration, producing greater β-adrenergic blockade, and result in the possibility of more profound bradycardia or overt heart failure. Carvedilol increases serum digoxin concentrations by 15%.[43] This interaction may lead to greater atrioventricular nodal conduction blockade, resulting in lower heart rates. Strong inducers of CYP2C9 such as rifampin decrease carvedilol serum concentrations by approximately 70%.

These interactions should be anticipated before carvedilol is administered and if necessary, contributing agents should be discontinued or their dosages decreased. When the interacting drug may not be discontinued or its dosage decreased, it should be understood that reaching the target dosage of carvedilol may not be possible or perhaps reasonable.

Pharmacodynamic interactions also should be evaluated. Conduction disturbances may occur if carvedilol is coadministered with drugs with sinoatrial or atrioventricular nodal-blocking properties such as verapamil, diltiazem, and mibefradil. Drugs that have negative inotropic properties such as verapamil and diltiazem should generally be avoided in patients with heart failure, and especially in those who are candidates for carvedilol. Symptomatic hypotension is more likely to occur if carvedilol is coadministered with other vasodilating agents (ACE inhibitors, calcium channel blockers, hydralazine), especially at the same time of day. Although this is patient and drug specific, separating drug administration times may be prudent at the start of carvedilol therapy in patients receiving one or, especially, two or more

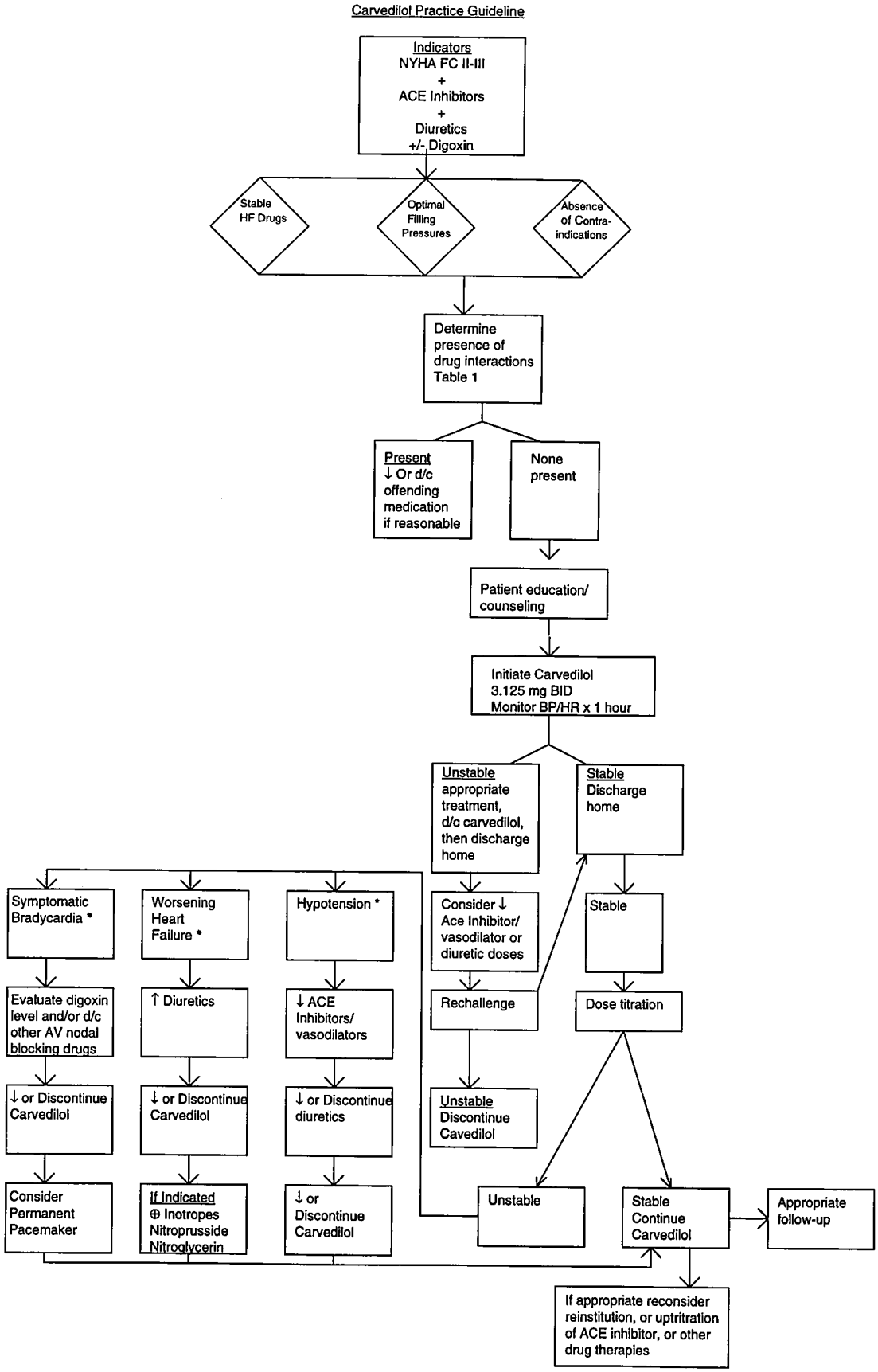

Figure 1. Guidelines for starting and titrating carvedilol therapy. *The order of intervention should be based on clinical presentation.

Table 1. Suspected or Known Drug Interactions with Carvedilol Therapy in Heart Failure

Drug	Interaction	Potential Outcome
Quinidine[a]	CYP2D6 inhibition	↑ R(+) enantiomer, hypotension
Fluoxetine[a]	CYP2D6 inhibition	↑ R(+) enantiomer, hypotension
Paroxetine[a]	CYP2D6 inhibition	↑ R(+) enantiomer, hypotension
Sertraline[a]	CYP2D6 inhibition	↑ R(+) enantiomer, hypotension
Cimetidine[b]	CYP2D6 inhibition	↑ R(+) enantiomer,[39] hypotension
Mibefradil[a]	CYP2D6 inhibition	↑ R(+) enantiomer, hypotension
Amiodarone[a]	CYP2D6 inhibition	↑ R(+) enantiomer, hypotension
Fluoxetine[a]	CYP2C9 inhibition	↑ S(-) enantiomer, ↓ HR, hypotension
Cimetidine[b]	CYP2C9 inhibition	↑ S(-) enantiomer,[39] ↓ HR, hypotension
Omeprazole[a]	CYP2C9 inhibition	↑ S(-) enantiomer, ↓ HR, hypotension
Rifampin[b]	CYP2C9 induction	↓ S(-) enantiomer, ↑ HR (↓ carvedilol plasma conc 70%)[39]
Digoxin[b]	Unknown	↑ digoxin serum conc 15%[43] (↑ AV nodal blockade, ↓ HR)
Verapamil[a]	Pharmacodynamic	↑ AV nodal blockade, ↓ HR, hypotension
Diltiazem[b]	Pharmacodynamic	↑ AV nodal blockade, ↓ HR, hypotension
Clonidine[b]	Pharmacodynamic	↓ HR, hypotension
Catecholamine-depleting agents (reserpine)	Pharmacodynamic	↓ HR, hypotension
Mibefradil[a]	Pharmacodynamic	↑ AV nodal blockade, ↓ HR, hypotension
Insulin[a]	Pharmacodynamic	Potentiate ↓ blood sugar
Oral hypoglycemics		

HR = heart rate; AV = atrioventricular; C_{max} = maximum concentration.
[a]Suspected drug interaction.
[b]Known drug interaction.

vasodilating drugs. A reasonable suggestion is to administer carvedilol and other vasodilators approximately 2 hours apart.

An important step before starting carvedilol therapy is patient education. The drug does not typically result in short-term symptomatic benefit due to withdrawal of adrenergic drive to the heart. Rather, it reduces chronotropic and inotropic support, potentially leading to deterioration in many patients. Typically, long-term benefit occurs after 1–2 months, so patient education is absolutely necessary to avoid premature discontinuation. Patients should understand common symptoms that occur, and that in some cases reassurance is all that is necessary, whereas in others symptoms can be effectively managed by adjustments in dosages of other drugs.

It is extremely important that patients know that it may be several weeks before they experience improvement in heart failure. Education will diminish the number of patients who become noncompliant when beginning therapy or up-titrating the dose, and lead to fewer therapeutic failures.

The initial dosage of carvedilol is 3.125 mg twice/day for 2 weeks. It may be doubled (6.25, 12.5, and 25 mg) every 2 weeks to a maximum of 50 mg twice/day in patients weighing more than 85 kg, or 25 mg twice/day in those weighing under 85 kg. Clinical trials suggest that more than 90% of patients can be successfully titrated to target dosages.[39] Patients may be managed in a clinic setting for evaluation of response, with orthostatic blood pressure and heart rate measured at peak concentrations (30 min–1 hr) before the dosage is changed. The dosage may be titrated upward based on standing systolic blood pressure and heart rate responses.

At the start of therapy or during titration, patients should be observed for signs of dizziness or lightheadedness for at least 1 hour after dosing. With each dosing change patients should be cautioned about driving or other hazardous activities. These recommendations are in the package insert and therefore should be followed, without exception, to avoid legal problems. If systolic blood pressure is above 85 mm Hg, heart rate is greater than 55 beats/minute, and the patient is asymptomatic, titration may proceed and continue until target dosages or intolerable adverse effects occur. To avoid intolerance associated with peak drug concentrations, carvedilol should be taken with food, which slows absorption but does not affect the extent of bioavailability.

Similar to other β-adrenergic blockers,

carvedilol should not be discontinued abruptly and should be tapered off. Before surgery, the dosage may be halved, but therapy should be continued to avoid reverting to dosages at the start of therapy and up-titration schedules.

In clinical trials the discontinuation rate of carvedilol was approximately 5%.[40] The primary reasons were bradycardia, episodic hypotension (dizziness), and worsening heart failure. If the heart rate drops below 55 beats/minute, the dosage should be adjusted (decreased one-half) or discontinued, and the patient should undergo further medical evaluation. If the patient is taking other arteriovenous nodal conduction drugs, consideration should be given to discontinuing those agents. Digoxin serum concentrations should be assessed. An alternative to discontinuation is permanent pacemaker placement, which is well tolerated with carvedilol.

Excessive hypotension or syncope can be treated by discontinuing diuretics or reducing dosages of ACE inhibitors or other vasodilators by half. If hypotension or syncope requires ACE inhibitor dosage reduction or discontinuation, it is important to reinstitute the ACE inhibitor after the patient has been stabilized with carvedilol. Worsening heart failure typically is associated with excessive fluid retention (peripheral edema, weight gain, shortness of breath). Fluid retention often responds to increased dosages of the diuretic or ACE inhibitor. These changes can often be handled in an outpatient setting. If symptoms persist, the carvedilol dosage may also have to be decreased or, occasionally, the drug discontinued. If cardiogenic shock occurs, the patient may be hospitalized and intermittent low-dose inotropic (dobutamine) or vasodilator (nitroprusside, nitroglycerin) therapy with concomitant carvedilol may be prescribed, or carvedilol may be discontinued.[44] Carvedilol should not be reinstituted or the dosage titrated up until bradycardia, hypotension, or worsening heart failure is stabilized.

Guidelines for reinstituting the drug are listed in Table 2.[44] In patients who develop worsening heart failure when beginning carvedilol, reinstitution of the agent results in clinical improvement similar to that in patients who tolerated the initial dosage.[45] Therefore, the chances for clinical success appear to be equivalent for patients who are tolerant and intolerant to the first dose. Renal insufficiency occasionally develops in patients with preexisting vascular disease, renal disease, and low blood pressure (systolic blood pressure < 100 mm Hg). Dosage reduction or discontinuation of diuretics or other vasodilators and weekly monitoring of serum creatinine should be considered.

Table 2. Guidelines for Reinstituting of Carvedilol after Discontinuation[44]

Time off Carvedilol	Guideline
< 72 hrs	Restart at same dosage before discontinuation.
> 72 hrs to < 7 days	Restart at half dosage before discontinuation.
≥ 7 days	Restart at 3.125 mg b.i.d.

A question clinicians may face is whether or not patients who are taking another β-adrenergic blocker should be changed to carvedilol. Clinical trials suggest an affirmative answer, although several courses of action may be considered. If patients have a positive clinical response to the current β-adrenergic blocker (increased left ventricular ejection fraction > 5 ejection units, no progression of disease defined by need for hospitalization or sustained increases in dosage), changing to carvedilol will most likely add little benefit. If patients have not shown these responses, tolerance to the current β-blocker should be assessed. If patients demonstrated intolerance at the start of therapy or during titration of the current β-adrenergic blocker, carvedilol 3.125 mg may be prescribed and dosing guidelines followed. For those who tolerate the current β-adrenergic blocker, carvedilol should be started at the next lowest dosage level; that is, if the dose of metoprolol is 50 mg or greater, then start carvedilol dosage at 6.25 mg twice/day due to combined β- and α_1-adrenergic blockade; titrate to target dosages. The change to carvedilol may be begun the day after discontinuing metoprolol.

Conclusion

Carvedilol is an important agent for the treatment of heart failure. Clinical trials showed that when added to standard heart failure therapy, it reduces the risk of mortality, slows progression of disease, and improves quality of life measures. Providing patient education, following prescribing guidelines, and performing appropriate monitoring will minimize intolerance while providing maximum benefit of this drug.

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