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Carvedilol

A new agent for chronic heart failure

In this installment of Pharmacotherapy Perspectives, Michael Vela, Pharm.D. presents a review of a new cardiovascular agent, carvedilol. As this product was presented to the University of Wisconsin Hospital and Clinics' Pharmacy and Therapeutics Committee, two significant questions were raised. The first was how to limit the use of this expensive new agent to patients with congestive heart failure (the only indication for which the drug has shown benefit over less expensive alternatives). The second was how to select patients who are appropriate candidates for therapy (to avoid its use in patients whose CBF symptoms may actually worsen with therapy). Our solution in response to these questions was the development of carvedilol prescribing guidelines. These clinical practice guidelines (also presented in this issue), were written by Peter Rahko, M.D. with contributions from several other LTW physicians and pharmacists.

The goals of clinical practice guidelines vary, depending on the problem for which they were developed. For example, the carvedilol guideline was written to enhance prescriber education, to prevent potential adverse drug reactions, and to ensure the cost-effective use of a new medication. Other guidelines have been developed to reduce unexplainable and expensive variation in practice (e.g., weight-based heparin dosing guidelines), to reduce the use of inexpensive but unsafe medications (e.g., potassium chloride injection, meperidine), or to guide the selection of medications from among many alternatives (e.g., treatment of migraine headache, use of hypnotic medications). Invariably, cost is an issue; if medications were free, guidelines would not be necessary.

Opponents of guidelines claim that they impinge on the freedom of prescribers to select medications best suited to their patient's needs. They suggest guidelines introduce a "cookbook" approach to medical care and may actually increase the cost of treating individual patients. I suggest that there are many other things more onerous than guidelines impinging on the autonomous practice of medicine (such as prior approval requirements for inpatient admissions and other utilization and peer review requirements). Guidelines are meant to increase the efficiency of prescribing

ers by summarizing an exhaustive review of the medical literature and incorporating expert opinion, both contributing knowledge that may not be readily accessible to the average prescriber. It is important to recognize that guidelines may not be appropriate for every patient, but rather reflect the best approach to care for most patients. Applying guidelines without exercising professional judgement would indeed be a cookbook approach to care. Combining a guideline with the consideration of patient-specific information may be the most efficient strategy. The cost associated with guidelines may indeed increase. The fact that guidelines suggest appropriate care could reduce cost by recommending that patients not receive expensive treatments, but could in other cases increase cost by recommending expensive therapies for patients currently not receiving them. As guidelines are developed, consideration is given to the system-wide cost of care which includes not only the cost of specific medications, but also the long-term costs that might be avoided by using more expensive alternatives. It is in this framework that the financial effect of guidelines must be assessed.

I hope that this guideline will help you work with prescribers and patients to maximize the cost-effective use of carvedilol while avoiding potentially dangerous and expensive adverse effects. As always, I welcome comments about this article (and guideline) as well as suggestions regarding future installments in this column. Comments can be sent to me via E-mail at lc.vermeulen@hosp.wisc.edu.

Summary

Indications: Carvedilol is indicated in the treatment of mild to moderate congestive heart failure in combination with other agents (e.g., digitalis, diuretics and ACE inhibitors). While carvedilol has also been used for the management of essential hypertension, its high cost makes it a poor choice for this indication.

Monitoring parameters: Blood pressure and pulse during therapy of hypertension, treadmill exercise testing and ECG monitoring periodically during therapy of angina, and signs and symptoms of worsening CHF such as weight gain or increasing shortness of breath.

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Dose: The initial dose of carvedilol is 6.25 mg by mouth twice a day with dose increases as tolerated. Maintenance doses range from 25 mg to 50 mg twice daily.

Pregnancy category: C

Breast feeding: It is not known whether this drug is excreted in human milk.

Pediatrics: The safety and efficacy of carvedilol in pediatric patients have not been established.

Geriatrics: The elderly can be more susceptible to the postural hypotensive effects of carvedilol which suggests initial doses be should lowered.

Cost: All tablet strengths of carvedilol are priced equally. The Average Wholesale Price is \$1.50 per 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablet.

Introduction

Carvedilol (Coreg[®], SmithKline Beecham Pharmaceuticals) is a non-selective beta-adrenergic receptor antagonist, an alpha₁-adrenergic receptor antagonist and a potent antioxidant. In recent years, the place of adrenergic blockade in the treatment of chronic congestive heart failure (CHF) has been a topic of research. It is thought that drugs which interfere with the compensatory actions of the sympathetic nervous system may reduce the progression of CHF.^{1,2,3} Studies with carvedilol have primarily focused on its role in the management of CHF.

Pharmacokinetics/Pharmacology

Carvedilol is a racemic agent with non-selective beta-adrenoreceptor blockade due to the S(-) enantiomer and alpha-adrenoreceptor blockade present in both the R(+) and the S(-) forms.^{4,6}

Carvedilol is rapidly and extensively absorbed after oral administration. Absolute bioavailability is 25 percent to 35 percent due to a significant degree of first-pass metabolism. Carvedilol undergoes stereo-selective first-pass metabolism with plasma levels of R(+)-carvedilol approximately two to three times higher than those of S(-)-carvedilol following oral administration. Following oral administration peak serum levels of carvedilol are observed in 1 to 1.5 hours. The drug is metabolized in the liver and primarily excreted in the feces. The primary P450 enzymes responsible for the metabolism of carvedilol are CYP2D6 and CYP2C9 and to a lesser extent CYP3A4, 2C19, 1A2, and 2E1.^{1,5,6} Less than 2 percent of a dose is excreted unchanged in the urine. The elimination half-life is 6 to 8 hours. Carvedilol is more than 98 percent bound to plasma proteins, primarily albumin.^{1,5,6}

Drug interactions have been seen with co-administration of carvedilol and digoxin, resulting in an increased

bioavailability of digoxin. This increase is not clinically significant and does not correlate with pharmacologic response.⁷ Pharmacokinetics studies demonstrated a lack of drug interaction between carvedilol and hydrochlorothiazide, cimetidine, torsemide and warfarin.⁸

Clinical Trials

Hypertension

A randomized single-blind trial of 24 patients, 12 male and 12 female, ages 36 to 68 years with uncomplicated sustained hypertension was published by Weber et al.² The comparative effects of carvedilol and metoprolol on heart rate, systemic blood pressure and echocardiographically determined aortic and femoral artery blood flow were measured at rest, at 2 hours and 24 hours after the first dose and after 4 weeks on sustained monotherapy. Carvedilol patients experienced significantly greater reduction of heart rate and systolic pressure 2 hours after the initial dose when compared to metoprolol. Metoprolol significantly reduced cardiac output and significantly increased systemic and femoral vascular resistances compared to carvedilol. All patients in both groups achieved the target diastolic blood pressure of less than 90 mmHg. At 4 weeks, the mean diastolic blood pressure was significantly lower in patients receiving carvedilol compared to control (86 vs 95 mmHg, $p < 0.05$).

In a double-blinded placebo study, 325 patients with stable hypertension were treated with 25 mg carvedilol once daily or 50 mg atenolol once daily in a double-blind 8-week treatment phase.³ The dose was doubled after 4 weeks, if the response was inadequate. Sitting blood pressure, heart rate, body weight, adverse effects, compliance and use of concomitant medications were evaluated after 2, 4 and 8 weeks of treatment. After 8 weeks, the rates of blood pressure response for carvedilol and atenolol were 75 percent and 82 percent, respectively. Compared to baseline, the mean sitting blood pressure was significantly reduced by carvedilol from 165/104 mmHg to 147/89 mmHg ($p < 0.05$), and with atenolol from 167/104 mmHg to 150/90 mmHg ($p < 0.05$).

Chronic CHF

Sixty patients with idiopathic or ischemic New York Heart Association (NYHA) classes II-IV CHF and left ventricular ejection fraction (LVEF) greater than 0.35 were enrolled in a 4-month, prospective, randomized, double-blind, placebo-controlled trial.⁹ The trial consisted of four phases: a 4-week run-in period, a 1-week challenge period with carvedilol 3.125 mg twice a day, an up-titration period to a target dose of 25 to 50 mg twice daily and a double-blind treatment phase that continued for 3 months. Exercise tolerance, left ventricular dimensions, cardiac function and functional class were evaluated during the course of the

trial. Right atrial, pulmonary artery and pulmonary capillary wedge pressures, cardiac output, systemic arterial pressures, heart rate and stroke work were also measured. The endpoints of the study included completion of the study, significantly worsening CHF not improved with adjustments in conventional medications, cardiac transplantation or death. Digitalis, diuretics, angiotensin converting enzyme (ACE) inhibitors, nitrates and hydralazine were allowed; however, these medications and their doses could not be adjusted during the screening and baseline phases of the trial.

Patients in the carvedilol group reported significant improvement in CHF symptoms ($p=0.0277$). There was also significant improvement in functional class in 15 of 18 carvedilol-treated patients compared to 4 of 10 placebo-patients ($p=0.0170$). Resting LVEF improved by 52 percent in the carvedilol group compared to no improvement in the placebo group ($p=0.0001$). There was significant improvement in exercise LVEF ($p=0.0001$). Compared to placebo, carvedilol significantly decreased heart rate ($p=0.0001$), pulmonary artery pressure ($p=0.025$), pulmonary capillary wedge pressure ($p=0.0213$) and stroke volume index ($p=0.0004$). There were no significant changes in systemic arterial and venous pressures, left ventricular dimensions or maximal and submaximal exercise tolerance; however, patients on carvedilol did demonstrate a trend toward improved submaximal exercise duration.

A study by Krum et al. enrolled 56 patients with chronic CHF.¹⁰ The patients remained symptomatic despite LVEF less than 0.35 and NYHA class III or IV symptoms, maximal oxygen consumption of less than 14 ml/kg/min or pulmonary capillary wedge pressure greater than 18 mmHg despite more than 2 months of therapy with digoxin, diuretics and ACE inhibitor. These background medications were kept constant for at least 2 weeks before entry into the study. Effort tolerance was evaluated by measuring peak oxygen consumption during bike exercise and submaximal exercise tolerance as determined by six-minute walk. Left ventricular function was also assessed. At enrollment, right heart catheterization was performed to measure cardiac output and intracardiac and pulmonary pressures. Left ventricular ejection fraction and norepinephrine, epinephrine and aldosterone blood levels were also measured. Patient symptoms were evaluated through a questionnaire. After the 2 week baseline period, patients entered the open-label phase receiving 3.125 mg twice a day for 1 week, 6.25 mg twice a day for 1 week and 12.5 mg twice a day for 1 week. If carvedilol was tolerated, patients were randomized to receive either carvedilol 12.5 mg twice daily for 1 week then 25 to 50 mg bid for a total of 14 week or placebo. During this period, treatment with digoxin, diuretics and ACE inhibitors was kept constant

Patients treated with carvedilol showed improvement in symptom scores from baseline (11.4 to 5.4; $p=0.003$) and functional class (2.8 to 1.9; $p<0.0001$). There was little change in the placebo group. Carvedilol patients also demonstrated increased six-minute walk tolerance over placebo (+53 vs -51; $p=0.006$). No change in maximal oxygen consumption was seen. Other improvements seen with carvedilol patients compared to placebo patients include stroke volume index (+10.4 vs -0.3 ml/m²; $p=0.015$), left ventricular function (+6.5 vs. -0.4 units; $p=0.005$) and decreases mean arterial pressure (-11.4 vs +5.3 mmHg; $p<0.001$), mean pulmonary arterial pressure (-7.6 vs +3.3 mmHg; $p=0.009$), pulmonary capillary wedge pressure (-7.8 vs +2.6 mmHg; $p=0.004$), mean resting arterial pressure (-4.1 vs +4.0 mmHg; $p=0.001$), systemic vascular resistance (-17% vs +11%, $p=0.017$), and heart rate (-25 vs -1 beats per minute; $p<0.001$). Declines in plasma epinephrine ($p=0.014$), aldosterone ($p=0.065$) and norepinephrine (NS) were also seen. Finally, the combined risk of major cardiovascular events (death, worsening CHF requiring IV therapy or discontinuation of study medication) was significantly lowered in carvedilol versus placebo (18% vs 44%; $p=0.028$).

Patients from 20 hospitals in Australia and New Zealand with chronic stable CHF class II or III with LVEF of less than 0.45 were enrolled in another study.^{11,12} Eligible patients began the trial with an open-label section that lasted 2 to 3 weeks to determine if carvedilol treatment could be tolerated. Patients who tolerated the open-label section were randomized placebo or carvedilol. Those on the carvedilol arm underwent a 2 to 5 week up-titration period to reach 25 mg twice a day. Once the target dose was reached, patients were assessed at 5 weeks and 3 months during the trial. Patients were enrolled for a minimum of 15 months and an average of 19 months. Outcomes assessed were LVEF, treadmill exercise duration and 6-minute walk distance, symptoms of CHF described by class and frequency of death, hospital admission or worsening CHF. Worsening CHF was defined as clinically significant deterioration in a patients condition requiring an increase in treatment medications, a hospital admission for worsening symptoms of CHF, an increase in NYHA class, or a non-sudden death from worsening CHF. After 6 months, LVEF increased by 5.2 percent in carvedilol patients compared to placebo patients ($p<0.001$). After 12 months of treatment the carvedilol group showed an increase in LVEF from 28.4 percent at baseline to 33.5 percent. The placebo group showed little or no change. At 6 months patients in the carvedilol group showed less improvement and more frequent worsening of NYHA class than placebo. At 12 months, no significant differences were found between the groups.

After 19 months of treatment, the risk of death alone was not significantly different between the groups, but there was a 23 percent decreased risk of hospitalization among carvedilol patients. When taken as a combined endpoint the risk of death or hospitalization was 26 percent lower in carvedilol patients than for placebo patients ($p=0.02$).

Packer et al. summarized the inclusion and exclusion criteria, incidence of adverse reaction, and results of the following three studies, which are collectively known as the US Carvedilol CHF Program.¹³ One thousand and ninety-four patients with chronic CHF were enrolled in these double-blind, placebo-controlled, stratified studies. Eligible patients had to have symptoms of CHF for at least 3 months and ejection fractions less than 0.35, even after 2 months of treatment with diuretics and ACE-inhibitor. The use of digoxin, hydralazine or nitrates was permitted, but not required. Each patient's exercise capacity was measured by a 6-minute corridor walk test. Patients were then stratified to one of four treatment protocols based on the results of the exercise test: mild-CHF, moderate-heart-failure, dose-ranging protocol, and severe-heart-failure. Within each of the four groups, patients with mild, moderate or severe CHF with left ventricular ejection fractions less than 0.35 were randomly assigned to receive either placebo or the carvedilol in addition to concurrent treatment with diuretics and ACE-inhibitor. Patients in the mild, moderate, or severe patient groups started on 6.25 mg twice a day for 2 weeks in the open-label portion of the study. If the carvedilol was tolerated, patients were assigned to receive placebo or carvedilol. Patients in the carvedilol groups underwent a 2 to 6 week up-titration period with doses starting at 12.5 mg twice daily. The doses increased weekly as tolerated to target doses of 25 mg to 50 mg twice a day. Patients in the dose-ranging protocol were randomly assigned to one of four treatment groups: placebo, 6.25 mg, 12.5 mg or 25 mg all dosed twice a day. Patients were then observed for 6 months (12 months for patients with mild CHF). Factors measured were functional capacity (submaximal exercise testing), LV function, the occurrence of death or hospitalization due to cardiovascular reasons and the need for a sustained increase in CHF medications.

Patients receiving carvedilol had a 65 percent decrease in the risk of death (3.2% carvedilol vs 7.8% placebo; $p<0.001$). Cause of death included progressive CHF, sudden death, myocardial ischemia, other cardiovascular causes and noncardiovascular causes. The reduction in mortality was similar in carvedilol patients regardless of age, sex, the cause of CHF, ejection fraction, exercise tolerance, systolic blood pressure, heart rate or protocol assignment. There was also a 27 percent reduction in the risk of hospitalization in

patients in the carvedilol group (14.1% risk vs 19.6% placebo; $p=0.036$). The combined risk of either dying or being hospitalized for cardiovascular reasons was decreased in the carvedilol group by 38 percent versus the placebo group (15.8% carvedilol vs 24.6% placebo; $p<0.001$).

In the PRECISE trial, 275 patients with moderate to severe CHF were enrolled.¹⁴ CHF severity was assigned on the basis of a 6-minute corridor walk and a radionuclide ventriculography assessed LVEF of less than 0.35. Patients underwent a baseline clinical evaluation and entered an open-label period to evaluate tolerance of the carvedilol as in the above study. Following this open-label period, each patient was randomly assigned to either placebo ($n=145$) or carvedilol ($n=133$) 12.5 mg twice daily with a target dose of 25 to 50 mg twice daily, in addition to their current CHF regimen. Once the target dose was reached, therapy was continued for 6 months. Both direct and indirect measures of patient response were conducted. Direct measures consisted of assessment of symptoms of CHF by patient and physician, functional capacity as classified by NYHA class and LVEF. Indirect measures included quality of life scores and exercise tolerance testing. Compared with placebo, carvedilol produced greater symptomatic improvement and lower clinical deterioration as determined by NYHA functional class ($p=0.014$). The carvedilol group showed an improvement in disease severity compared to placebo when reported by the patient ($p=0.002$), or by the physician ($p<0.001$). Carvedilol patients also had a significant increase in ejection fraction (+0.08 carvedilol vs +0.03 placebo; $p<0.001$). In addition, patients on carvedilol had a significant decrease in hospitalizations due to cardiovascular causes (14.5% carvedilol vs 24.4% placebo; $p=0.029$). Carvedilol also decreased the combined risk of hospitalization and death (19.6% carvedilol vs 31.0% placebo; $p=0.029$). Carvedilol therapy also resulted in some improvements in indirect measures when compared to placebo. The 6-minute walk distance increased by 9 meters in the carvedilol group. There was a decrease of 3 meters in the placebo group ($p=0.048$). In the 9-minute treadmill test there was no significant change. Carvedilol had no effect on exercise tolerance or quality-of-life scores.

Colluci et al. focused on patients with mild or NYHA functional class II CHF and contributed to the US carvedilol CHF program in evaluating the effects of carvedilol on this specific group of patients.¹³ As in the above studies, patients were evaluated then placed on carvedilol for a 2 week open-label dosing period. Following this period, patients were randomized in a double-blind fashion to receive placebo ($n=134$) or carvedilol ($n=232$) 25 mg to 50 mg twice daily for a 12-month maintenance phase. During the maintenance

phase patients were assessed for NYHA class, CHF symptoms and changes in LVEF, quality of life and 9-minute self-powered treadmill test. Patients in the carvedilol group had a 48 percent decrease in clinical progression of CHF compared to placebo ($p=0.008$). There were no deaths in the carvedilol group due to CHF, the placebo group had four deaths due to CHF. The carvedilol patient group also experienced less hospitalizations (4% vs 6%) and fewer increases in CHF medications (6.9% vs 11.9%). Changes in functional class were significantly favorable in the carvedilol group ($p=0.003$). Improvement from baseline was seen in 12 percent of carvedilol patients versus 9 percent of placebo. Deterioration was seen in 4 percent and 15 percent of carvedilol patients and placebo patients, respectively. More carvedilol patients than placebo patients rated their CHF symptoms as improved ($p=0.013$) and physicians rated a greater improvement with carvedilol than placebo ($p<0.001$). The change in LVEF was larger with carvedilol (0.10) than placebo (0.03) ($p<0.001$). Quality of life scores and nine-minute treadmill tests did not show significantly statistic changes.

A trial by Bristow et al. enrolled 345 patients with mild to moderate CHF.¹⁶ It follows the same patient inclusion and exclusion criteria as the other studies. Following the open-label dosing period, patients were randomized to receive either placebo, low dose (6.25 mg twice daily), medium dose (12.5 mg twice daily) or high dose (25 mg twice daily) carvedilol. Patients were given 2 to 4 weeks to reach their target dose in an up-titration period, after which the patients were followed for a period of 6 months. Efficacy was evaluated on the basis of patients' functional capacity, LV function, CHF symptoms, CHF morbidity and survival. Exercise testing and quality of life measurements were performed at baseline, at 2, 4 and 6 months during the maintenance period. Carvedilol had no significant difference over placebo on exercise function, quality of life or changes in classification. Carvedilol treatment did exhibit a trend toward improvement in global assessment by patient

and physician. When compared to placebo, carvedilol demonstrated a statistically significant dose-related improvement in LVEF (6.25 mg BID and 12.5 mg BID, $p<0.006$; 25 mg BID, $p<0.0001$). Carvedilol produced a significant, dose-related decrease in mortality rate compared to placebo. Patients in the 6.25 mg, 12.5 mg, and 25 mg dosing protocols had mortality rates of 6.0 percent ($p<0.05$), 6.7 percent ($p=0.07$) and 1.1 percent ($p<0.001$) respectively, versus a mortality rate of 15.5 percent for the placebo group.

Adverse Effects

The most commonly reported adverse reactions associated with carvedilol are dizziness and symptoms of worsening CHF. Symptoms such as dizziness, bradycardia and abnormal vision are usually seen early in treatment and are dose-related.¹³ Table 1 lists the adverse effects reported during placebo-controlled clinical trials of carvedilol.

Cost, Dose and How Supplied

The initial dose of carvedilol should be 3.125 mg twice a day for 2 weeks. Increase the dose by 6.25 mg twice daily if tolerated. The maximum dose is 25 mg twice a day in patients weighing less than 85 kg, and 50 mg twice a day in patients weighing more than 85 kg. Carvedilol should be given with food to slow the rate of absorption and reduce the incidence of orthostatic hypotension.^{5,6}

Carvedilol is available in tablet form in strengths of 3.125 mg, 6.25 mg, 12.5 mg and 25 mg in bottles of 100. All tablet strengths of carvedilol are priced equally. The Average Wholesale Price is \$1.50 per 3.125 mg, 6.25 mg, 12.5 mg and 25 mg tablet.

Conclusion

Chronic CHF continues to be a leading cause in hospital admissions in patients older than 65.¹⁹ Mortality rates of CHF patients with decreased left ventricular function are 20 percent over 3.5 years despite current therapy with diuretics and ACE inhibitors. Rates can exceed 26 percent over 6 months for patients with more severe disease. Recently, more focus has been placed on the abnormal neurohormonal activation that occurs in the disease. Evidence supports the use of beta blockers in counteracting these abnormal levels. Clinical trials have been conducted with metoprolol, acebutolol, propranolol, bucindolol, nebivolol, bisoprolol and carvedilol.¹⁷ Carvedilol has been the only beta blocker to demonstrate a decrease in mortality and hospitalization. The trials in the US Carvedilol CHF Program were stopped approximately 6 months early by the data and safety monitoring board due to a decrease in the rates of hospitalizations and mortality among patients treated with carvedilol.

Table 1. Adverse Effects of Carvedilol vs Placebo in Clinical Trials¹³

Adverse Effect	Carvedilol	Placebo
Dizziness	32%	20%
CHF	16%	21%
Hypotension	8.5%	3.4%
Diarrhea	11.8%	5.9%
Bradycardia	8.8%	0.9%
Generalized edema	5.1%	2.5%
Abnormal vision	5.0%	1.8%

Carvedilol is the first beta blocker to demonstrate a reduction in the rates of hospitalization and death in patients with chronic CHF. Further research is needed to determine if other beta adrenergic antagonists can also benefit CHF patients and to establish the optimal place of beta blockers in therapy. The cost of carvedilol does not warrant use as a first line agent in hypertension or angina where other less expensive and equally efficacious agents are available.

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University of Wisconsin Hospital and Clinics Guidelines for use of Carvedilol (Coreg[®])

A. Indications

Use of carvedilol should be limited to the following circumstances:

- 1.0 Adjunctive therapy for patients with symptomatic heart failure and documented systolic dysfunction. *The alpha-beta blocker carvedilol (Coreg[®]) represents a significant advance in heart failure therapy. It is a logical additional step for medical therapy of patients with documented systolic dysfunction and symptomatic heart failure. Patients who may benefit are those who have mild to moderate heart failure which is clinically stable on optimal background medications, typically including appropriate doses of diuretics, digoxin and ACE inhibitors or other combinations of vasodilating drugs.*
- 2.0 Antihypertensive therapy in patients with concomitant left ventricular dysfunction. *Although carvedilol is officially approved for use as an antihypertensive agent, there is no definite evidence at the present time that this agent is superior to conventional beta-blockers already carrying an indication for antihypertensive therapy. Since the cost of carvedilol is considerably higher than many other beta-blockers, carvedilol should not be used for routine antihypertensive therapy, unless the patient has concomitant left ventricular dysfunction that may clearly benefit from this agent.*
- 3.0 Anti-anginal therapy in patients with significant left ventricular dysfunction. *Carvedilol has known anti-anginal properties. It does not have an anti-anginal indication at the present time. Because it is expensive carvedilol should not be used*

as a conventional beta-blocking anti-anginal drug, unless the patient has significant left ventricular dysfunction.

- 4.0 Post-myocardial infarction in patients with large infarcts or who have significant left ventricular dysfunction. *Preliminary evidence suggests carvedilol has significant beneficial effects post myocardial infarction. There is no evidence to date to suggest that these beneficial effects are superior to other beta blockers currently used for this indication. Carvedilol should only be used in patients with large infarcts or patients who have significant left ventricular dysfunction post-myocardial infarction, i.e. ejection fraction below 40%.*
- 5.0 Patients on carvedilol prior to admission to the hospital.
- 6.0 Due to the initial worsening of heart failure which some patients experience when beginning carvedilol therapy, the drug should only be prescribed by a cardiologist or other physician with expertise in the management of heart failure.
- 7.0 Carvedilol is contraindicated in patients with NYHA Class IV decompensated cardiac heart failure; bronchial asthma or related bronchospastic conditions; second- or third-degree AV block; sick sinus syndrome, unless a permanent pacemaker is placed; cardiogenic shock; severe bradycardia; hypersensitivity to the drug.

B. Patient Selection

Suitable patients for carvedilol therapy should have the following characteristics:

- 1.0 Mild to moderate heart failure which is clinically

stable on optimal background medications. These background medications typically would be appropriate doses of diuretic, digoxin and ACE inhibitors or other combinations of vasodilating drugs.

- 2.0 Stable background medication doses; only minor recent dose adjustments in a stable regimen.
- 3.0 No fluid overload.
- 4.0 A standing systolic blood pressure of greater than 90 mmHg in patients with stage II or III heart failure. In patients with stage IV heart failure and cardiomyopathy who are awaiting a heart transplant, the minimum systolic blood pressure should be at least 80 mmHg.
- 5.0 Any patients with evidence of significant bradycardia or heart block should be carefully screened before initiation of carvedilol. As with all beta blockers, heart rate tends to fall 10 to 15 beats per minute as the drug is titrated up to maximum doses. It is therefore suggested that the initial resting heart rate of at least 60 beats per minute.

C. Dosing

- 1.0 For most patients, begin carvedilol at the lowest dose of 3.125 mg twice daily (BID). Continue this dose for 1 to 2 weeks and monitor carefully. Patients with lower blood pressure or more severe forms of failure should be monitored for hypotension for one hour after the initial dose.
- 2.0 Titrate the dose upward gradually in 1 to 2 week intervals after the initiation. Monitor patients either by direct telephone contact or by follow-up office visits. Doses for stable hospitalized inpatients should not be adjusted any more frequently than once per week.
- 3.0 Titrate upward to the maximum dose of 25 mg BID or as close as possible. There is an incremental dose-related effect on mortality reduction and efficacy. Patients weighing more than 85 kg may be titrated to 50 mg BID. This will double the cost of the drug because two 25 mg tablets will have to be used for each dose.

D. Adverse Effect Management

The most frequently exhibited side effects during dose titration are vasodilator side effects like dizziness and lightheadedness, or symptoms of worsening congestive heart failure with edema, weight gain, fatigue and shortness of breath. Patients should be asked specifically about these side effects and changes in heart rate or blood pressure. To reduce some of the potential problems of adverse effects,

consider the following suggestions:

- 1.0 Explain that initially symptoms may actually be worse. Patients may not experience improvement at all during their first 2 to 3 months of therapy.
- 2.0 Carvedilol is best taken with meals to slow the absorption rate and reduce some of the hypotensive effects.
- 3.0 If patients have relatively low blood pressure at the initiation of the drug, take the drug at least 2 hours before or after other vasodilators to decrease possible additive effects. In some situations, long acting ACE inhibitors can be switched to bedtime dosing to reduce hypotensive effects during the morning.
- 4.0 If carvedilol must be discontinued, down-titration rather than abrupt discontinuation is suggested. A 1 to 2 week taper is recommended. ■

E. Economic Impact

Cost of Selected UWHC Formulary Agents Used to Treat Hypertension/CHF

Cost	Drug	Cost (\$) per Month of Therapy (Based on Cost to Unity Health Plans)
Atenolol*	50 mg QD	2.00
Metoprolol*	50 mg BID	3.75
Carvedilol	25 mg BID	90.00
Captopril	50 mg TID	8.00
Lisinopril	20 mg QD	26.10
Hydrochlorothiazide	50 mg QD	1.20
Furosemide	40 mg QD	1.98
Digoxin	0.25 mg QD	3.63

*Atenolol and metoprolol are not used in the management of heart failure.

Author: Peter Rahko, MD Reviewed by: James Stein, MD, Gerald Ryan, MD, Craig January, MD, PhD, MaryAnn Steiner, PharmD, Lorna Goshman, RPh, Timothy Hoon, PharmD Approved by DUE Committee: January 30, 1998 Approved by P&T Committee: February 19, 1998 Scheduled for review: February 2000