Appropriate Dose Transition to a Controlled-Release Formulation of Carvedilol in Patients With Hypertension

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Few patients with hypertension meet recommended target blood pressure goals, and most hypertensive patients require at least 2 antihypertensive medications from different pharmacologic classes to adequately lower blood pressure. β-Blockers are guideline-recommended for the treatment of hypertension with compelling indications. β-Blockers differ with respect to pharmacology (particularly receptor biology and ancillary properties), hemodynamic effects, and tolerability. In clinical practice, the choice of β-blockers for individual patients with hypertension is often based on practical issues such as convenience and cost. However, given the pharmacologic and clinical trial data demonstrating differences, the choice of β-blocker for the treatment of high-risk hypertension should be evidence-based. Vasodilating β-blockers, such as carvedilol, decrease blood pressure without the concerning hemodynamic, renal, and metabolic responses associated with most β-blockers. The use of carvedilol CR (once daily) may be preferable to a twice-daily regimen.

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Key words: Hypertension • Diabetes • β-Blockers • Carvedilol CR

Although blood pressure (BP) control rates have improved according to the most recent National Health and Nutrition Examination Survey (NHANES) 2001 to 2004 report, they are still below 50%.[1] More than 66% of patients with hypertension require at least 2 antihypertensive medications from different pharmacologic classes to achieve adequate BP control,[2] and initiation of therapy with 2 antihypertensive agents with complementary mechanisms should be strongly considered in patients who are more than

20/10 mm Hg above their BP goal.[2] Moreover, the selection of antihypertensive medications should be individually tailored based on compelling indications.[2,3]

Many drug classes are used in combination with diuretics and calcium antagonists, but there is limited acceptance of β-blocker use either alone or in combination because of the expectation of negative metabolic effects.[4-6] Recent data from a meta-analysis also suggest that vasoconstricting β-blockers such as atenolol may not significantly reduce cardiovascular events.[7] For this reason, we have reviewed the utility of β-blockade in hypertensive patients with no compelling cardiovascular indications for β-blocker use, noting the different pharmacological profiles of various β-blockers used for the treatment of hypertension.

Assuming that a therapeutic regimen for a patient with complicated hypertension may include a β-blocker, then one of the vasodilating β-blockers may be a reasonable option. However, many patients currently being treated with β-blockers may experience metabolic consequences and other adverse effects of treatment. It is therefore important to prescribe a β-blocker that will not produce undesirable side effects in patients with hypertension, especially those who also have diabetes. To aid clinicians, we present practical protocols based on recent studies to facilitate and maximize ease of conversion from carvedilol twice daily to the once-daily carvedilol CR (controlled release) and conversion from a vasoconstricting β-blocker to a once-daily vasodilating agent.

Role of β-Blockers in High-Risk Hypertensive Patients

High-risk hypertensive patients (ie, those with compelling indications), including patients with heart failure, myocardial infarction, high coronary disease risk, diabetes, chronic kidney disease, and recurrent stroke, warrant particularly aggressive treatment and careful selection of specific antihypertensive medication classes (Table 1).[2] β-Blockers are indicated in patients with heart failure, high coronary disease risk, or diabetes, and following myocardial infarction.[8-12] In addition to having a powerful BP-lowering effect, β-blockers are: (1) antiatherogenic: they reduce inflammation, endothelial dysfunction, and risk for plaque rupture; (2) antiarrhythmic: they decrease heart rate and sympathetic activity; and (3) anti-ischemic: they decrease heart rate and BP, and reverse cardiac remodeling.[13-15] Because of these benefits, β-blockers should not be relegated to second- or third-line agents in the high-risk hypertensive patient. Recent literature has questioned the efficacy of β-blockers in patients with hypertension,[7,16] however, the implication that all β-blockers lack benefit is based almost exclusively on data from atenolol. Both the European Society of Hypertension/European Society of Cardiology and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) recommend β-blockers for patients with hypertension and previous myocardial infarction, concomitant heart failure, diabetes, or coronary artery disease.[2,17] Because negative side effects (along with complexity of the regimen) are a frequent cause of patient nonadherence to therapy, the optimal choice of β-blocker and how to switch to an optimal β-blocker are discussed below.

Choice of β-Blocker in Antihypertensive Therapy

Currently, atenolol, propranolol, metoprolol (short- and long-acting formulations), timolol, labetalol, and carvedilol (short- and long-acting) are approved by the US Food and Drug Administration for use in hypertension and are often used in practice (Table 2).[18] However, β-blockers differ with respect to pharmacology (particularly receptor biology and ancillary properties), hemodynamic effects, and tolerability.[19-21] In clinical practice, the choice of β-blockers for individual patients with hypertension is often based on practical issues such as convenience and cost. However, given the pharmacologic and clinical trial data demonstrating differences,[22,23] the choice of β-blocker for the treatment of high-risk hypertension should be evidence-based.

Atenolol is the most frequently prescribed β-blocker in patients with hypertension, but it has not been shown to reduce heart failure or mortality in this population over the long-term when compared with other active agents.[7] A meta-analysis of 4 studies comparing atenolol with placebo or no treatment showed that, despite a clear BP-lowering effect from atenolol, there were no differences in outcomes (all-cause mortality, myocardial infarction, or cardiovascular mortality) between atenolol and placebo.[24] The same authors also performed a meta-analysis of 5 studies comparing atenolol with other antihypertensive drugs; although there were no major differences in BP lowering between the treatment arms, there were significantly higher mortality rates (relative risk 1.13; 95% confidence interval [CI], 1.02-1.25) with atenolol than with other antihypertensive drugs.[7,24]

β_1-Selective blockers, such as atenolol and metoprolol, and β_1-, β_2-blockers, such as propranolol, are also associated with negative metabolic effects, including decreased

Table 1
Clinical Trial and Guideline Basis for Compelling Indications for Individual Drug Classes

High-Risk Condition With Compelling Indication*	Thiazide-Type Diuretic	β-Blocker	ACEI	ARB	CCB	Ald Ant	Guideline and/or Clinical Trial Basis†
Heart failure	X	X	X	X		X	ACC/AHA heart failure guidelines,[18] MERIT-HF,[55] COPERNICUS,[56] CIBIS,[9] SOLVD,[57] AIRE,[58] TRACE,[59] Val-HeFT,[60] RALES[61]
Postmyocardial infarction		X	X			X	ACC/AHA post-myocardial infarction guidelines,[62] BHAT,[63] SAVE,[64] CAPRICORN,[10] EPHESUS[65]
High coronary disease risk	X	X	X		X		ALLHAT,[12] HOPE,[66] ANBP2,[67] LIFE,[68] CONVINCE[69]
Diabetes	X	X	X	X	X		NKF-ADA guidelines,[70] UKPDS,[11] ALLHAT[12]
Chronic kidney disease			X	X			NKF guidelines,[71] Captopril Trial,[72] RENAAL,[73] IDNT,[74] REIN,[75] AASK[76]
Recurrent stroke prevention	X		X				PROGRESS[77]

*Compelling indications for antihypertensive drugs are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed in parallel with the blood pressure.
†Conditions for which clinical trials demonstrate benefit of specific classes of antihypertensive drugs used as part of an antihypertensive regimen to achieve blood pressure goal to test outcomes.
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; Ald Ant, aldosterone antagonist; ACC/AHA, American College of Cardiology/American Heart Association; MERIT-HF, Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; CIBIS, Cardiac Insufficiency Bisoprolol Study; SOLVD, Studies of Left Ventricular Dysfunction; AIRE, Acute Infarction Ramipril Efficacy; TRACE, Trandolapril Cardiac Evaluation; Val-HeFT, Valsartan in Heart Failure Trial; RALES, Randomized Aldactone Evaluation Study; BHAT, Beta-Blocker Heart Attack Trial; SAVE, Survival and Ventricular Enlargement; CAPRICORN, Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction; EPHESUS, Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; HOPE, Heart Outcomes Prevention Evaluation; ANBP2, Second Australian National Blood Pressure Study; LIFE, Losartan Intervention For Endpoint Reduction; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular Endpoints; NKF-ADA, National Kidney Foundation–American Diabetes Association; UKPDS, UK Prospective Diabetes Study; RENAAL, Reduction in End Points in Noninsulin-Dependent Diabetes Mellitus With the Angiotensin II Antagonist Losartan; IDNT, Irbesartan in Diabetic Nephropathy Trial; REIN, Ramipril Efficacy in Nephropathy; AASK, African American Study of Kidney Disease and Hypertension; PROGRESS, Perindopril Protection Against Recurrent Stroke Study.
Adapted with permission from Chobanian AV et al.[2]

insulin sensitivity and lipid metabolism.[22,25-27] Carvedilol, a vasodilating β-blocker (β:α ratio 7.6:1),[28] does not exhibit the carbohydrate and lipid disturbances that may underlie the apparent failure of some β-blockers to reduce cardiovascular morbidity and mortality.[22,26] The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study also demonstrated that carvedilol does not worsen microalbuminuria, whereas metoprolol tartrate has a negative effect on it.[29] Small studies have shown that carvedilol improves decreased left ventricular hypertrophy in patients with hypertension,[30,31] and in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, a subgroup analysis of the post–myocardial infarction (MI) left ventricular dysfunction (LVD) patients with hypertension showed a 23% risk reduction in all-cause mortality or nonfatal MI with carvedilol versus placebo that was equivalent to the overall population.[32]

β-blockers may not be tolerated as well as other antihypertensive classes, with side effects including fatigue, reduced exercise capacity, and impotence that lead to a greater likelihood of discontinuation and, subsequently, less successful BP control.[33] Nonselective β-blockers (vasoconstricting β-blockers) may also further reduce already compromised renal blood flow

Table 2
ACC/AHA HF Guidelines: Evidence-Based β-Blocker Indications for Treatment of Cardiovascular Disease

Acebutolol	HTN		
Atenolol	HTN	Post-MI	
Betaxolol	HTN		
Bisoprolol	HTN		HF
Carteolol	HTN		
Carvedilol	HTN	Post-MI	HF; post-MI
Labetalol	HTN		
Metoprolol succinate	HTN		HF
Metoprolol tartrate	HTN	Post-MI	
Nadolol	HTN		
Penbutolol	HTN		
Pindolol	HTN		
Propranolol	HTN	Post-MI	
Timolol	HTN	Post-MI	

ACC/AHA, American College of Cardiology/American Heart Association; HF, indicated for heart failure and asymptomatic left ventricular dysfunction; HTN, indicated for hypertension; Post-MI, indicated for reduction in heart failure or other cardiac events following myocardial infarction.
Adapted with permission from Hunt SA et al.[18]

in patients with hypertension and may even cause slight decreases in the glomerular filtration rate.[34] In contrast, carvedilol has been shown to increase renal blood flow and decrease peripheral resistance in patients with hypertension.[34-38]

For patients with hypertension and diabetes, the American Association of Clinical Endocrinologists (AACE) guidelines recommend using an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker as a first- or second-line agent, a thiazide diuretic as a first- or second-line agent, and a β-blocker as a second- or third-line agent in order to reduce BP to less than 130/80 mm Hg.[39] These guidelines, along with those of the National Kidney Foundation, recommend that the chosen β-blocker target both the α- and β-receptors, which carvedilol does.[39,40] Another α-/β-blocker, labetalol, has a β:α ratio estimated to range from 3:1 to 7:1 but has no outcome data to support its use.[41] The ratio of β to α is important because it impacts cardiac output and tolerability. Although labetalol has α_1-blocking properties, it has been associated with vasodilating side effects such as postural hypotension and dizziness.[42] This higher β:α ratio has demonstrated effects on blood glucose similar to those of metoprolol succinate, thus supporting a predominantly β effect.[42-44]

Until recently, carvedilol was available only as an immediate-release formulation requiring twice-daily dosing, which can be an inconvenience for patients. Hypertension treatment requires daily lifelong treatment with rigid adherence to therapy; proper BP control is crucial for the avoidance of hypertensive complications. Use of once-daily hypertension drug formulations has been shown to improve medication adherence.[45] Carvedilol CR, a once-daily formulation of carvedilol, was approved by the US Food and Drug Administration for use in patients with hypertension, heart failure, and post–MI left ventricular dysfunction. With the once-daily dosing of carvedilol CR, there is an opportunity to improve patient care by increasing the likelihood of medication adherence.[46]

Conversion to Vasodilating β-Blockers in Patients With Hypertension

Because carvedilol CR is the only once-daily vasodilating β-blocker available in the United States, the focus on conversion will be from a twice-daily to a once-daily preparation. Practical protocols for switching to carvedilol CR from carvedilol BID or from other β-blockers are outlined below.

Switching From Carvedilol to Carvedilol CR

Carvedilol CR is a once-daily agent with dosage strengths of 10, 20, 40, and 80 mg. Prescription of a once-daily agent may make adherence easier for many patients, and therefore it may be prudent to switch patients who are currently on a stable dose of carvedilol twice daily to carvedilol CR. A pharmacokinetic/pharmacodynamic study of carvedilol CR showed that the pharmacokinetics (area under the curve, maximum plasma concentration, and trough drug concentration) of carvedilol were equivalent (carvedilol CR is less bioavailable than carvedilol per the labeling) after administration of carvedilol CR once daily and immediate-release carvedilol twice daily in all doses used in hypertension (20, 40, and 80 mg).[47] The bioequivalent doses of carvedilol and carvedilol CR are noted in Table 3. Figure 1 shows

Table 3
Dose Conversion Chart for Carvedilol and Carvedilol CR*

Dose of Carvedilol	Dose of Carvedilol CR
3.125 mg BID	10 mg QD
6.25 mg BID	20 mg QD
12.5 mg BID	40 mg QD
25 mg BID	80 mg QD

*Dose strengths are based on the use of carvedilol phosphate (which has a higher molecular weight than carvedilol) and contain an additional amount of immediate-release carvedilol compared with the BID formulation (approximately 30% higher to adjust for bioavailability). The relative bioavailability (area under the curve, maximum plasma concentrations, and trough drug concentration) of carvedilol is equivalent after administration of the once daily formulation and the twice-daily formulation.
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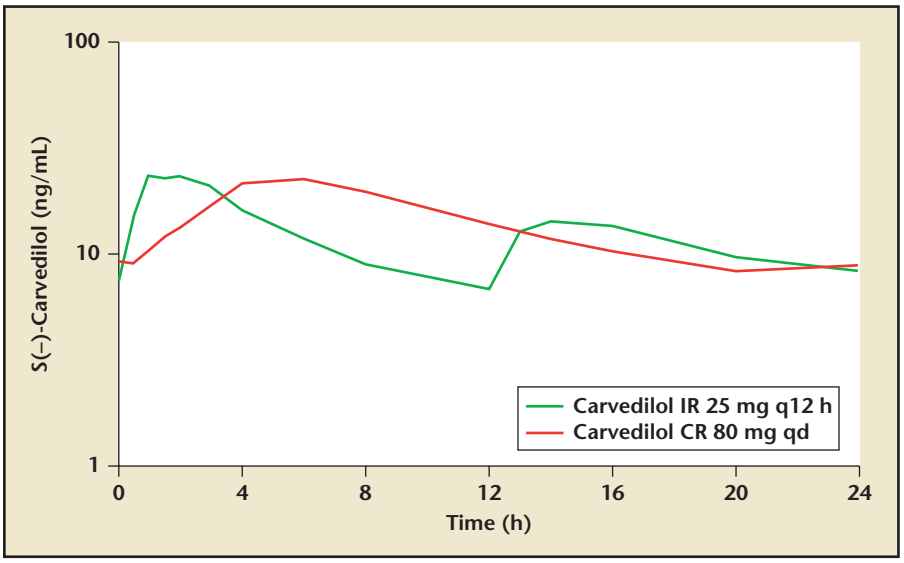

Figure 1. *Mean steady-state concentration-time profile for S(–)-carvedilol after administration of carvedilol BID and carvedilol CR in patients with hypertension. Reprinted with permission from Tenero DM et al.*[47]
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the mean steady-state concentration-time profile for S(–)-carvedilol, the enantiomer responsible for β-blockade, after administration of carvedilol twice daily and carvedilol CR. The maximum concentration is reached approximately 3.5 hours later following administration of the carvedilol CR capsule compared with the twice-daily formulation, as expected from a controlled-release agent.[47]

A randomized, double-blind, repeat crossover study in 122 patients with newly diagnosed controlled or uncontrolled hypertension demonstrated the side effect profile of patients switching from carvedilol twice daily to carvedilol CR.[48] Subjects assigned to the lowest dosage of carvedilol (6.25 mg BID) for 22 days were switched to the comparable lowest dosage of carvedilol CR (20 mg/d) for 8 days, and subjects assigned to the high target dosage of carvedilol (25 mg BID) for 22 days were switched to the comparable high dosage of carvedilol CR (80 mg QD) for 8 days. The number of subjects experiencing adverse events did not increase following the switch from the immediate-release twice-daily formulation to the CR formulation for either the lower or higher doses of carvedilol (Table 4).[48] Although there was no comparison for statistical significance, patients seemed to experience fewer adverse events on the CR formulation, perhaps due to its slower rate of rise. The adverse event profile of carvedilol CR indicates that patients can be safely switched from twice-daily to once-daily carvedilol. Further clinical trial

Table 4
Patients Reporting Adverse Events Before and After Switch From Carvedilol to Carvedilol CR

	Regimen			
	Switching at Low Dose (n = 18)		Switching at High Dose (n = 26)	
Adverse Event	Carvedilol 6.25 mg BID (%)	Carvedilol CR 20 mg QD (%)	Carvedilol 25 mg BID (%)	Carvedilol CR 80 mg QD (%)
Headache	7 (38.9)	4 (22.2)	10 (38.5)	6 (23.1)
Dizziness	1 (5.6)	2 (11.1)	4 (15.3)	1 (3.8)
Orthostatic hypotension	2 (11.1)	2 (11.1)	2 (7.7)	2 (7.7)
Any adverse event	10 (55.6)	6 (33.3)	14 (53.8%)	9 (34.6)

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Table 5
Recommended Algorithm for Switching From Carvedilol to Carvedilol CR in Patients With Hypertension

Current Dose of Carvedilol		Starting Dose of Carvedilol CR
6.25 mg BID		20 mg QD
12.5 mg BID	**Wait 12 hours***	40 mg QD
25 mg BID		80 mg QD

*Suggestion for patients: take the night-time dose of carvedilol BID and start carvedilol CR the next morning.
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data and use in the community will determine if the potential for improved tolerability with the long-acting formulation is realized.

Because patients who do not adhere to antihypertensive medication have been shown to exhibit poor BP control,[49,50] it may be worth switching patients to carvedilol CR to improve adherence with a simpler regimen and potentially decrease side effects. Switching patients from twice-daily carvedilol to once-daily carvedilol CR is straightforward. Patients should start the equivalent dose of carvedilol CR the following day after their last evening dose of carvedilol (Table 5).[51]

Switching From Other Agents to Carvedilol CR

As mentioned above, there are practical reasons to consider switching many patients from a β-blocker such as atenolol or metoprolol tartrate to carvedilol; patients with hypertension and concomitant diabetes should be switching from a vasoconstricting β-blocker such as atenolol or metoprolol tartrate to carvedilol CR, and post-MI LVD patients with hypertension and those with hypertension and heart failure should also be switched to carvedilol CR. To help physicians switch β-blockers in a hypertensive patient, we have provided an algorithm to help ensure that patients who are switched maintain an adequate level of BP lowering and avoid any negative changes in tolerability. Switching from one β-blocker to another is generally safe and well tolerated, but physicians should use their judgment regarding individual patient tolerance at all times. Patients should not be switched to carvedilol if they have a contraindication to the agent, such as reactive airway disease; these patients should remain on a β_1-selective agent, preferably metoprolol succinate.

As would be the case with switching any medication, all other medications should be stable prior to the switch to carvedilol CR. It would also be prudent to avoid adding other agents with vasodilatory properties, such as calcium channel blockers, nitrates, or other antihypertensives, to the patient's regimen directly prior to or during a switch. A practical algorithm for switching patients with hypertension from atenolol and metoprolol to carvedilol CR is shown in Table 6. The dose equivalencies for this algorithm are derived both from clinical experience and the degree of BP lowering that can be expected with each dose as well as the potential for α-blocker–related side effects. In order to avoid postural hypotension or dizziness, the algorithms suggest that patients on a medium to high dose of a previous β-blocker may be switched to a low to medium dose of carvedilol CR and then uptitrated to the equivalent dose as tolerated. We have erred on the side of a lower dose of carvedilol CR to ensure that patients tolerate the side effects prior to uptitration.

Previous studies of β-blockers provide a basis for expected equivalencies. In the GEMINI trial, doses of carvedilol and metoprolol tartrate were titrated to the BP target.[22] To lower BP similarly with the 2 drugs, each patient's dose was titrated progressively, from 6.25 mg BID of carvedilol or 50 mg BID of metoprolol to a maximum dose of 25 mg carvedilol BID or 200 mg metoprolol BID at 1- to 2-week intervals, toward target BP levels, for a total of 2 to 7 weeks. To achieve target BP, the mean dose required for carvedilol was 17.5 mg BID; for metoprolol it was 128 mg BID. Approximately half of each group required the highest dose.[22] Based on that experience, 40 mg/d of carvedilol CR would lower BP to the same degree as approximately 100 to 200 mg BID of metoprolol tartrate.

In previous studies, dosing with 100 mg metoprolol succinate following 6 weeks of treatment (measured by cuff) was associated with mean reductions at 24 hours in systolic BP, diastolic BP, and heart rate of −15 mm Hg, −12 mm Hg, and −7 beats per minute, respectively.[52] Mean reductions in systolic BP and diastolic BP at 24 hours after dosing with 40 mg of carvedilol CR following 6 weeks of therapy (measured by cuff) were −9.1 mm Hg and −7.6 mm Hg, respectively.[53] These prior studies provide data relevant for guidance for switching and expected BP-lowering outcomes. However, no study has provided data on the direct comparison of carvedilol CR and metoprolol succinate or atenolol; these studies are ongoing, as described below.

Table 6
Suggested Algorithm for Switching From Other β-Blockers to Carvedilol CR in Hypertension*

When Switching From:		To Carvedilol CR: Starting Dose†	To Carvedilol CR: Uptitration (after several days to 1 week) as tolerated‡
Atenolol	**Wait 24 hours from last dose of once-daily atenolol**	**Carvedilol CR**	**Carvedilol CR**
50 mg daily§		20 mg daily	40 mg daily
≥ 75 mg daily		40 mg daily	80 mg daily
Metoprolol Tartrate	**Wait 12 hours from last dose of metoprolol tartrate**		
25-50 mg twice daily		20 mg daily	40 mg daily
75-100 mg twice daily		40 mg daily	80 mg daily
> 100 mg twice daily		40-80 mg daily	80 mg daily
Metoprolol Succinate	**Wait 24 hours from last dose of metoprolol succinate**		
50-100 mg daily		20 mg daily	40 mg daily
150-200 mg daily		40 mg daily	80 mg daily
> 200 mg daily		40-80 mg daily	80 mg daily

*Physicians should be guided by their own judgment and experience in choosing doses when switching among drugs.
†In clinical trials, carvedilol CR was initiated in β-blocker-naïve patients at 20 mg. The recommendations in this table are based on the authors' clinical and research experience, and advise switching patients already on a medium-to-high dose of another β-blocker to a medium-to-high dose of carvedilol CR. A caveat, however: older patients (> 65 years), patients with diabetic neuropathy, or those predisposed to orthostatic hypotension should generally start at 20 mg if on a low dose of another β-blocker and 40 mg if on a high dose of another β-blocker. Such patients may then be uptitrated as tolerated; switching directly to 80 mg is not recommended in these patients. Physicians should closely monitor all patients to avoid possible worsening of blood pressure and increases in heart rate after switching to 20 or 40 mg of carvedilol CR, which would call for a quicker uptitration.
‡Uptitrate to achieve BP goal. Maximal dose is 80 mg/d (equivalent to 25 mg of carvedilol BID).
§For patients on a dose of atenolol lower than 50 mg (eg, 25 mg/d), it is unclear what the exact dose of carvedilol CR would be; however, patients at this low a dose should not be started on higher than 20 mg of carvedilol CR.

The goal for switching is to keep, or improve, BP control without increasing the likelihood that vasodilation symptoms will occur due to the initiation of α-blockade. The first part of this goal may best be achieved by switching to a dose of carvedilol CR that, based upon the GEMINI experience, is likely to reduce BP to the same extent or more than the dose of the β_1-selective agent. This approach would minimize the occurrence of increases in heart rate or BP while the switch is being made. However, if the physician decides to switch the patient at higher doses of carvedilol CR (40-80 mg), the patient should be counseled to be aware of the potential for symptoms such as dizziness (which is generally transient).

In at least some patients—such as the elderly, patients with diabetic neuropathy, or those prone to orthostatic hypotension—switching at higher doses might result in dizziness or other unwanted symptoms of vasodilation. Patients such as these would likely benefit from the switch initially being made to a lower dose of carvedilol CR than would be expected to produce the same BP results as the β_1-selective blocking dose. In this case, uptitrating back to the higher dose could generally be done at intervals of several days, rather than of a week or more.

In summary, in the absence of specific clinical trial data on switching and until further experience with carvedilol CR is gained, these recommendations coupled with physician judgment should allow an uncomplicated switch to carvedilol CR.

Future Studies

Two studies are currently underway to directly assess the effect of carvedilol CR vs metoprolol succinate or atenolol on cardiovascular risk factors in patients with hypertension.[54] These studies will help determine whether the metabolic and cardiovascular profiles of atenolol and metoprolol succinate warrant a switch to carvedilol CR in hypertensive patients. In the Randomized, Double-Blind, Multicenter Study Comparing the Effects of Carvedilol Controlled-Release Formulation (Carvedilol CR) and Atenolol in Combination with and Compared to an Angiotensin Converting Enzyme Inhibitor (Lisinopril) on Left Ventricular Mass Regression in Hypertensive Subjects with Left Ventricular Hypertrophy (CLEVER) trial, atenolol and carvedilol CR will be compared to determine the effect on left ventricular mass regression and left ventricular hypertrophy as well as on secondary endpoints, such as BP, heart rate, lipid profile, and new-onset diabetes. The β-blocker doses chosen for this trial are carvedilol CR 20 mg versus

atenolol 50 mg, carvedilol CR 40 mg versus atenolol 75 mg, and carvedilol 80 mg versus atenolol 100 mg (both arms will have background therapy of lisinopril). In the Lipids Trial (Randomized, Double-Blind, Multicenter Study Comparing the Effects of Carvedilol CR Formulation with Metoprolol Succinate on the Lipid Profile in Normolipidemic or Mildly Dyslipidemic Hypertensive Subjects), metoprolol succinate and carvedilol CR will be compared to determine the effects of both agents on lipid profile. In addition, BP, heart rate, and occurrence of new-onset diabetes will be measured. The doses chosen are consistent with the switching equivalencies shown in Table 6. These 2 trials will better define the effects of these agents in patients with hypertension and will definitively determine if switching to carvedilol CR from atenolol or metoprolol is warranted to the degree suggested by other studies.

Nebivolol (Forest Laboratories, New York, NY/Mylan, Inc, Canonsburg, PA), a new beta-blocker, has recently been approved by the US Food and Drug Administration (FDA) for the treatment of hypertension. It has been shown to produce vasodilation and reduce total peripheral resistance brought about by modulation of nitric-oxide release. Ongoing studies show that nebivolol has efficacy similar to that of other approved beta-blockers and a favorable side effect profile.

Conclusion

Not all patients with hypertension achieve the recommended BP goal of less than 140/90 mm Hg, and many patients with hypertension and diabetes do not achieve the more stringent recommended goal of 130/80 mm Hg. A re-evaluation of the benefit of β-blockers in patients with hypertension may result in more frequent use of these BP-lowering agents and, subsequently, better outcomes for patients. However, β-blockers are heterogeneous and should not be used interchangeably. Vasoconstricting β-blockers such as atenolol or metoprolol lower cardiac output and induce an increase in peripheral vascular resistance. They may also lead to metabolic consequences that can promote coronary artery disease: decreased insulin sensitivity and glucose utilization as well as increased triglyceride levels and decreased high-density lipoprotein cholesterol levels.

The availability of vasodilating β-blockers, such as the combined nonselective β- and α_1-blocker carvedilol, represents the opportunity to use a β-blocker in patients with hypertension without the concerning hemodynamic, renal, and metabolic responses associated with most β-blocker therapy. Furthermore, carvedilol increases insulin sensitivity and glucose disposal and has a neutral effect on lipid profile. The availability of once-daily carvedilol CR should increase the probability of good adherence to therapy.

In light of the proven benefits of vasodilating β-blocker therapy, the previous limitations on β-blocker use for the treatment of hypertension should now be reappraised. Patients on carvedilol twice daily may be switched to the once-daily formulation to ensure adherence and, perhaps, reduce side effects. Patients with hypertension taking vasoconstricting β-blockers should be switched to carvedilol CR following practical protocols. Ongoing head-to-head studies will add to the literature that suggests patients would benefit from switching from a nonvasodilating β-blocker to a vasodilating one, such as carvedilol CR. ■

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Main Points

- Because of their many benefits, β-blockers should not be relegated to second- or third-line agents in the high-risk hypertensive patient.
- β-blockers differ with respect to pharmacology (particularly receptor biology and ancillary properties), hemodynamic effects, and tolerability.
- Use of once-daily hypertension drug formulations has been shown to improve medication adherence.
- The adverse event profile of carvedilol CR indicates that patients can be safely switched from twice-daily to once-daily carvedilol.
- In order to avoid postural hypotension or dizziness, patients on a medium to high dose of a previous β-blocker may be switched to a low to medium dose of carvedilol CR and then uptitrated to the equivalent dose as tolerated.

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