Practical Considerations for Switching ß-Blockers in Heart Failure Patients

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The use of ß-blocker therapy has proven extremely useful in a variety of clinical settings, including the management of hypertension, acute- and post-myocardial infarction, and in congestive heart failure (HF). However, there are noticeable differences among individual ß-blockers in regard to efficacy of treatment and clinical outcomes in many of these conditions. These differences are particularly apparent in the treatment of HF, where effects on reverse remodeling and interactions on the periphery are potential factors that can differentiate between the efficacy of one drug versus another. In fact, ß-blockers are not a singular, homogeneous group, but rather a class made up of a number of agents with individual differences in pharmacology, receptor biology, hemodynamic effects, and tolerability. In the event of ongoing disease progression, the onus of choosing the most appropriate ß-blocker falls on the clinician's shoulders. Given the baseline differences among medications of this class, the rationale and manner for transitioning to a different ß-blocker should take into account the specific receptor-blockade subtype of any given agent, as well as any other intrinsic effects attributed to a specific drug. This article includes 2 protocols for switching between carvedilol, a third generation non-selective agent with vasodilatory properties through α_1-blockade, and a $ß_1$-selective agent (e.g., metoprolol, atenolol). The aim is to simplify and maximize the safety and tolerability of performing this exchange. With the increasing amount of clinical evidence supporting the use of one ß-blocker over another in the treatment of HF, it behooves physicians treating this patient population to utilize the adrenergic blocking agent that provides optimal therapy with minimal side effects and intolerability.

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The current uses of ß-blockers in treating medical conditions vary beyond the spectrum of heart failure (HF) to include both cardiovascular and non-cardiovascular indications, such as hypertension, angina, and the treatment of migraine headache. Over the last 10 years, numerous large-scale randomized controlled trials (RCTs) have demonstrated the significant mortality

and morbidity benefits of ß-blocker therapy in the management of mild to moderate HF.[1-6] In fact, over 5000 patients evaluated in over 20 trials have manifested a variety of benefits, including reductions in rates of death, hospitalization, and progression of HF, as well as improved left ventricular (LV) function, when ß-blockers are combined with angiotensin-converting enzyme (ACE) inhibitors and diuretics.[7,8] Indeed, the majority of ß-blocker mortality trials have consistently shown favorable survival benefits, with a relative decrease in mortality at least as great as that produced with ACE inhibitors.[9,10] This increasing wealth of clinical evidence has escalated ß-blockers to the forefront of HF management.

Currently, both the Heart Failure Society of America Practice Guidelines and the Consensus Recommendations for the Management of Chronic Heart Failure mandate that all patients with New York Heart Association (NYHA) Class II-III HF should be treated with a ß-blocker unless there is a contraindication in a particular patient, or if the patient has been shown to be intolerant of treatment with the drug.[11,12] There have also been 2 studies extending the ß-blocker spectrum in HF to incorporate patients with more or less severe disease. The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial showed that the benefits of carvedilol with respect to mortality as well as morbidity could be extended to patients with severe HF, those with symptoms at rest or on minimal exertion, and with an ejection fraction (EF) less than 25%.[13] In patients who have suffered an acute ischemic event, the Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial showed that carvedilol improved outcomes in patients with LV dysfunction (LVEF < 40%) following acute myocardial infarction, with or without symptoms.[14] Carvedilol's U. S. Food and Drug Administration-approved indication has widened to encompass all patients from NYHA class I (post-MI patients with LV dysfunction) through stable patients with NYHA class IV HF.

Though clinical data supports the use of ß-blockers in the treatment of HF, it is prudent to remember that not all ß-blockers are alike and that benefits and side effects can differ among individual agents. Also, the use of a specific ß-blocker in acute HF may not indicate use of the same medication for the treatment of chronic HF. Currently, there are only 2 ß-blockers that have regulatory approval in the United States for the treatment of patients with HF: carvedilol and the long-acting form of metoprolol (metoprolol CR/XL). Also, while some ß-blockers (carvedilol, bisoprolol, and metoprolol succinate [CR/XL]) have been proven to reduce mortality and morbidity in HF, others do not (bucindolol, xamoterol).[15,16] As a class, ß-blockers are a diverse group of agents with intrinsic differences in pharmacology (receptor biology and important ancillary properties), hemodynamic effects, and tolerability.[17,18] It is these differences that provide a rationale for varying clinical trial results, in patients with both ischemic and nonischemic HF.[19,20]

There are a number of factors that should be taken into consideration when deciding which ß-blocker to use in clinical practice. The choice of ß-blocker for an individual patient with HF is often based on answers to several practical questions: (1) Has the patient been on a ß-blocker for a prior indication (hypertension, angina, arrhythmia, migraine) when HF is first diagnosed? (2) Is there a history of intolerance or poor response to a specific agent? (3) Are there any other comorbid disease processes (pulmonary disease, peripheral vascular disease, diabetes mellitus, disorders of cardiac conduction) present? (4) What medication has provided the physician with positive outcomes in the past? (5) Can the patient afford the medication? This last may be the most important consideration.

With the knowledge that ß-blockers can differ on the pharmacologic as well as the clinical level and that only certain ß-blockers are indicated for different phases of HF (as recent trials have shown), it follows that the choice of ß-blocker for the treatment of chronic HF should be made on the current body of evidence available. To this end, only 2 agents should be considered to treat chronic HF in the United States: carvedilol and metoprolol CR/XL. Between these 2, there are a number of considerations that support the selection of carvedilol in certain subpopulations of HF patients and the use of metoprolol CR/XL in others. The results of the Carvedilol and Metoprolol European Trial (COMET), which was designed as a direct comparison between metoprolol and carvedilol, reveal that carvedilol is clearly superior to metoprolol in reducing mortality in patients with chronic HF. It is worth noting that the study investigators used metoprolol tartrate in COMET and not the longer-acting version, metoprolol succinate (CR/XL).

Given the varying pathways through which a patient can develop HF, possible previously-diagnosed cardiovascular disease processes (i.e. hypertension, post-MI), and that some physicians will electively decide to switch their HF patients from an alternative ß-blocker to carvedilol, there should be an ordered process for this exchange between

agents. This review will shed some light on the rationale behind switching HF patients from another ß-blocker to carvedilol (as well as vice versa) and to propose a method that will be both safe and practical.

Rationale for Switching ß-Blockers

Undeterred chronic sympathetic stimulation of the cardiac, circulatory, and renal systems has been demonstrated to have long-term detrimental effects, especially in patients with HF.[21-24] From these observations, the rationale behind the use of ß-blockers in HF was founded. Adrenergic stimulation (measured by increased cardiac and systemic norepinephrine[25,26] along with the chronic activation of the renin-angiotensin-aldosterone system [RAAS],[27]) has been shown to increase left ventricular (LV) wall stress by promoting peripheral vasoconstriction (increased ventricular afterload) and renal sodium and water retention (increased cardiac preload). This continuous onslaught of hormones results in pathologic changes in the myocardium, eventually leading to adverse ventricular remodeling.[28,29] Studies conducted on both transgenic mice over-expressing $ß_1$-adrenergic receptors and human cardiac tissues have shown that adrenergic stimulation is also directly injurious to the cardiac myocyte on the cellular level,[30,31] promoting changes in gene expression,[32,33] oxidative stress,[34] hypertrophic cell growth,[35] and coronary vasoconstriction,[36] as well as being proarrhythmic[37] and proapoptotic.[38] The detrimental effects of chronic adrenergic stimulation in the pathophysiology of progressive HF have been extensively reviewed previously.[39]

Though these concepts of using ß-blockers in HF have been examined for nearly 25 years (beginning with small, uncontrolled studies conducted in Sweden in the 1970s, on patients with congestive cardiomyopathy[40,41]), it was only recently that large RCTs have confirmed the morbidity and mortality benefit of ß-blockers in HF.

Bisoprolol and metoprolol, both studied for their use in HF, are $ß_1$-selective agents. However, $ß_1$-selectivity is associated with certain potential biological disadvantages. $ß_1$-Receptor density is usually down-regulated by nearly half in HF, desensitizing the myocardium against the deleterious effects of chronic sympathetic over-stimulation.[42] ß-Blockade with metoprolol during HF reverses this effect with a resulting increase or up-regulation of $ß_1$-receptor density.[43,44] At the same time, metoprolol treatment is associated with increased central venous norepinephrine levels which might potentially result in a spike of adrenergic signal transduction, especially during trough plasma concentrations of the drug. The selective blockade of only $ß_1$-receptors may facilitate continuous sympathetic signal transductions through the unblocked cardiac $ß_2$-receptor, which is not only cardiostimulatory but may also increase the likelihood of arrhythmias.[45,46] Cardiac and peripheral α_1-receptors, which are not blocked by $ß_1$-selective agents, become key players in the setting of HF, due to their relative increase in receptor density. α_1-Receptors contribute to cardiac remodeling by inducing myocyte hypertrophy and injury, and their role in deadly arrhythmias such as ventricular fibrillation has been examined.[47] The progression of HF is hastened by the continuous stimulation of α_1-receptors, which results, systematically, in both increased peripheral vasoconstriction and impaired renal perfusion.

Third-generation ß-blocking agents are non-selective ß-blockers with ancillary vasodilating properties.[48,49] Vasodilation mediates a reduction in ventricular afterload, physiologically counterbalancing the negative inotropic effects of acute cardiac ß-sympathetic withdrawal.[50] When tested in HF, carvedilol, which inhibits α_1- as well as $ß_1$- and $ß_2$-adrenergic receptors, was found in double-blind, randomized placebo-controlled studies to improve a number of cardiac hemodynamics, including reducing heart rate and pulmonary capillary wedge pressure while increasing stroke volume, LV stroke work, and ejection fraction (EF).[51] Carvedilol has also been found to be more effective in improving ventricular function when compared with metoprolol.[52-54] These results have been attributed to carvedilol's wider degree of adrenergic blockade, when compared to $ß_1$-selective agents.

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$ß_1$-Receptor density does not increase with the use of carvedilol in HF and a decrease, rather than an increase, in coronary sinus norepinephrine levels is associated with its use. As was mentioned earlier, carvedilol possesses a number of other biologically active properties in addition to α_1-inhibition. Antioxidant protection, in the form

of its carbazole moiety, may be a factor in preventing cardiac remodeling induced by oxygen free radicals.[55-57] Antiproliferative,[58,59] anti-apoptotic,[60,61] and anti-arrhythmic properties (G. Cice, E. Tagliamonte, L. Ferrara, A. Iacono; Internet communication, August 2001) have also been attributed to carvedilol. And lastly, carvedilol, but not metoprolol, inhibits vascular endothelin production.[62]

With the current evidence from RCTs, one could make the connection between carvedilol's distinguishing properties and the potential advantages they might offer in the treatment of HF. In one open label study involving 30 subjects who had been considered stable on chronic metoprolol therapy, a 7-unit improvement in LVEF was reported in metoprolol-treated patients who were randomly switched to carvedilol, versus those who remained on metoprolol therapy. This study demonstrates the additional benefit of adding $ß_2$- and α_1-receptor blockade to preexisting $ß_1$-blockade on LV reverse remodeling. In a recent meta-analysis of 19 placebo-controlled trials of at least 3 months duration, involving over 2000 Class II-IV ischemic and non-ischemic HF patients receiving carvedilol or metoprolol, Packer and associates[54] found that the increase in EF with carvedilol was almost twice that observed with metoprolol (7 vs 4 units, respectively). Interestingly enough, it was noted that this difference represented a greater therapeutic effect than had been seen with captopril or enalapril in HF patients. The COMET trial demonstrated a reduction in all-cause mortality with carvedilol, when compared to metoprolol in 3029 patients with chronic HF.[63] The survival benefits seen with carvedilol in this study were not directly related to baseline heart rates nor change in blood pressure.[64,65] Carvedilol was also shown to decrease the number of adverse cardiovascular events as well as deaths due to stroke when compared with metoprolol.[66,67]

In addition to the previously mentioned clinical trials, there are other reasons why carvedilol is the most suitable ß-blocker for use in HF. For example, lower doses of metoprolol CR/XL have not demonstrated efficacy in reducing mortality, while carvedilol reduces mortality and morbidity across the dose range from 6.25 mg to 25.0 mg, twice daily.[1] The ancillary properties that carvedilol possesses may also add hormonal antagonism that could possibly be beneficial in patients in whom the progression of disease is occurring, despite adequate therapy with maximally tolerated doses of another ß-blocker along with ACE inhibitors and diuretics.

Important subgroup differences that favor the use of one ß-blocking agent over another may also be present in this patient population. HF patients with diabetes, peripheral vascular disease, Raynaud's phenomenon with vasospasm in the periphery, or renal dysfunction may be better suited for carvedilol given its favorable effects on insulin sensitivity/glycemic control and lipid metabolism, peripheral vascular tone, and renal hemodynamics, respectively.[68-73] Conversely, patients with true reactive airway disease requiring treatment with $ß_2$-agonists, or those with excessive hypotension or abnormal peripheral vasodilation, may benefit from treatment with a $ß_1$-selective agent.

Protocols for Switching to Carvedilol

Currently, there is no data from the large RCTs on how to go about an ideal exchange between cardioselective ß-blockers such as metoprolol or atenolol and carvedilol. At the conclusion of the COMET trial, patients were prescribed open-label ß-blockade with the switch from study medication to an open-label drug involving a halving of the dose. The efficacy of this approach awaits peer review. Thus, the recommendations we have presented here are primarily from the observational experience of physicians who specialize in treating the HF population and are familiar with the use of carvedilol and performing the exchange of ß-blockers in these patients. To give a complete overview, the regimens used in 2 publications in which switching was performed are also reviewed.[53,74]

General Principles

Switching ß-blockers is usually safe and well tolerated, although the prescribing physician's judgment concerning individual patient requirements plays a key role. The dose of the first- or second-generation ß-blocker that the patient is receiving is an important consideration for the switching regimen chosen.

Some important questions that a physician has to ask him or herself prior to the exchange are: (1) Am I maintaining an adequate ß-blockade to avoid the potential for precipitating ischemia or arrhythmias? (2) Am I choosing an initial dose with a low potential for producing any vasodilating side effects (e.g., dizziness or hypotension)? (3) Am I aware of possible changes in HF status due to changes in receptor sensitivity and density?

In addition, as in any patient initiating ß-blockade, there should be a stable HF regimen already in place (ACE inhibitors; diuretics, digoxin, nitrates as warranted) and the patient should be relatively euvolemic. A switch between ß-blockers should not be made if the patient is

acutely decompensated; these patients are best suited to treatment with positive inotropic agents, vasodilators, and, possibly, mechanical support. If a patient is having a chronic, progressive deterioration of HF or if they have not shown a response to their currently prescribed ß-blocker, then a switch to carvedilol might be appropriate. It must be re-emphasized that a stable HF regimen prior to switching ß-blockers is of the utmost importance and that severe decompensation episodes of HF are not suitable times to perform these exchanges.

Prior to switching to carvedilol, patients should be well-informed of the possible side effects that may occur after they start taking the medication. The hypotension that might result from the vasodilatory actions of carvedilol may be ameliorated somewhat by spacing out the dosing at least 2 hours from when the ACE inhibitor is given. Patients should be reassured that these effects are usually self-limiting and rarely require any further intervention. If signs or symptoms of excessive vasodilation appear, dose adjustments to the patient's other HF medications should be attempted before discontinuing carvedilol. No other vasodilatory agents (ie, calcium-channel blockers, nitrates) should be started at the same time when performing the switch between ß-blockers, as side effects are more likely to occur.

Switching Algorithms

There are 2 schools of thought on how to go about switching from other ß-blockers to carvedilol: (1) an immediate change which involves stopping the existing ß-blocker and initiating carvedilol within 24 hours, followed by up-titration of the carvedilol; and (2) an overlapping method in which a first- or second-generation ß-blocker is weaned while carvedilol is simultaneously initiated and up-titrated.

Di Lenarda and coworkers[53] reported on switching from metoprolol to carvedilol in HF patients who have failed to respond adequately to metoprolol. From a total of 154 stable, dilated cardiomyopathy patients, 20% were identified as having persistent LV dysfunction (EF < 40% and reduced exercise tolerance) despite more than 1 year of adequate metoprolol therapy (mean dose of 142 mg/day). Half of these patients were switched immediately to carvedilol beginning 18 hours after their last metoprolol dose. For metoprolol doses at or above 100 mg (i.e., medium to high doses) and systolic blood pressure greater than 100 mmHg, carvedilol was started at 12.5 mg, twice daily; otherwise (i.e., for patients receiving low- to medium-sized doses of metoprolol) it was begun at 6.25 mg twice daily and titrated rapidly every 3 days to a maximum dose of 50 mg twice daily, based on a target of achieving a heart rate of 60 bpm or systolic blood pressure of 100 mm Hg. The mean administered carvedilol dose was 74 mg/day. Mild symptomatic hypotension occurred rarely during carvedilol titration and was treated with adjustment of diuretic or ACE inhibitor dose.[53]

Maack and associates[74] recently reported on switching between ß-blockers (metoprolol and carvedilol) in 68 patients treated with either agent for 1 year, who had improved in terms of LVEF and NYHA class. Patients were switched if they were stable on a minimum dose of 25 mg, twice daily, of carvedilol or 100 mg of metoprolol. The crossover was performed within 1 day during monitoring of blood pressure and heart rate in the outpatient clinic. Switching was initially done between patients receiving 25 mg doses of carvedilol and 100 mg of metoprolol. The authors reported that the change from metoprolol to carvedilol was tolerated well. Interestingly enough, the first patients switched from carvedilol to metoprolol frequently experienced hypotension or bradycardia. The metoprolol dose was then reduced to 50 mg. However, despite this lower initial dose, 25% of patients still experienced hypotension or bradycardia. The authors felt that this was probably related to the greater inverse agonist activity and more pronounced negative inotropic effects of metoprolol.

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In clinical practice, most patients seem to tolerate a simple approach without an "overlap" period; that is the discontinuation of the existing ß-blocker upon initiation of carvedilol, particularly if they are receiving relatively low doses of the first- or second-generation agent. In attempting this form of switch, the current ß-blocker should be discontinued approximately 12 hours before the first dose of carvedilol. As mentioned above, most patients can be initially switched to 6.25 mg or 12.5 mg, twice daily, and then up-titrated at 1- to 2-week intervals (Table 1).

In some instances, where the pos-

Table 1
Non-Overlapping Protocol* for Switching ß-Blockers

	Carvedilol (bid)			
Metoprolol (daily)	**Week 0**	**Week 2**	**Week 4**	**Week 6**
50 mg	6.25 mg	12.5 mg	25.0 mg	25.0 mg†
100 mg, 150 mg, 200 mg	12.5 mg	25.00 mg	25.0 mg†	25.0 mg†

	Carvedilol (bid)			
Atenolol (daily)	**Week 0**	**Week 2**	**Week 4**	**Week 6**
50 mg	6.25 mg	12.5 mg	25.0 mg	25.0 mg†
100 mg, 150 mg, 200 mg‡	12.5 mg	25.0 mg	25.0 mg†	25.0 mg†

*For non-overlapping switching, the current ß-blocker should be discontinued approximately 12 hr before the first dose of carvedilol.
†50 mg b.i.d. for body weight ≥ 85 kg.
‡This dose is recommended only for angina.

sibility of inducing ischemia or cardiac arrhythmias is of greater concern, and especially in patients receiving higher doses of the first- or second-generation agent, an overlapping schedule for initiating and up-titrating a change to carvedilol may be used (Table 2). There should not be any significant additional ß-blocking effect with the addition of low-dose carvedilol in patients who are already maximally ß-blocked on their first agent. This overlap period will allow time for the patient to become more adjusted to the vasodilatory effects of carvedilol.

Given the additional adrenergic-blocking effects of carvedilol, an immediate switch from another ß-blocker to high doses of carvedilol would not be prudent. However, the starting dose of carvedilol in currently ß-blocked patients can be higher than the usually recommended starting dose of 3.125 mg, twice daily. Patients who are already tolerating high-dose $ß_1$-blockade with a stable heart rate and blood pressure, for example, may be started on a dose of carvedilol at 12.5 mg twice daily and subsequently up-titrated to a target dose. Those treated with lower doses of $ß_1$-selective agents and/or those with marginal blood pressures may be initially switched to 6.25 mg of carvedilol twice daily, followed by up-titration or as tolerated.

Widely used $ß_1$-selective agents such as metoprolol and atenolol were used as examples for switching in this paper (Tables 1 and 2), but comparable steps can be used to exchange other ß-blockers as well. In patients for whom the physician chooses not to titrate to higher doses due to side effects, clinical benefit may still be expected at carvedilol doses of 6.25 mg or 12.5 mg, twice daily, as previously mentioned.

Switching From Carvedilol to a $ß_1$-Selective Agent

Of course, there are situations where the exchange can be done in reverse, switching carvedilol to a $ß_1$-selective agent. Other than carvedilol, the ß-blockers of choice in treating HF are metoprolol CR/XL in the United States and bisoprolol outside of the United States, (given the evidence from recent RCTs and U. S. Food and Drug Administration approval). Patients who are truly intolerant of carvedilol (for any reason) might benefit from performance of this change of medications. Indeed, some of these patients might actually have an underlying form of reactive airway disease which is exacerbated by the $ß_2$-receptor blocking property of carvedilol. Tables 1 and 2 could be followed in reverse when switching from carvedilol (or any non-selective adrenergic antagonist with α_1-receptor blocking effects) to a $ß_1$-selective blocking agent. There should not be a significant concern regarding peripheral vasodilation when the exchange is performed in this manner. Titration should be closely monitored as there are inherent differences in the biological and pharmacological properties between selective and non-selective agents, especially in relation to dose-equivalency of ß-blockade and on glycemic control.

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Summary

In performing the exchange from a first- or second-generation ß-blocker to carvedilol:

1. A direct switch is possible, but it must be appropriately adjusted to the ß-blocker dose the patient is currently receiving.
2. Hypotension and other related

Table 2
Overlapping Protocol for Switching ß-Blockers

Carvedilol (bid)	Metoprolol (daily)		
Add to usual dose of:			
Week 0 at 3.125 mg	100 mg	150 mg	200 mg
Week 2 at 6.25 mg	50 mg	100 mg	150 mg
Week 4 at 12.5 mg	—	50 mg	100 mg
Week 6 at 25.0 mg	—	—	50 mg
Week 8 at 25.0 mg*	—	—	—
Carvedilol (bid)	**Atenolol (daily)**		
Add to usual dose of:			
Week -2 at 3.125 mg	—	—	200 mg†
Week 0 at 3.125 mg	50 mg	100 mg	150 mg
Week 2 at 6.25 mg	25 mg	50 mg	100 mg
Week 4 at 12.5 mg	—	25 mg	50 mg
Week 6 at 25.0 mg	—	—	25 mg
Week 8 at 25.0 mg*	—	—	—

*50 mg for body weight ≥85 kg.
†This dose is only recommended for angina.

side effects might be precipitated by a sudden or abrupt switch to a high dose of carvedilol and could possibly be avoided by a slower up-titration of dosing.

3. If the underlying principles of HF management are maintained during this switch, this exchange is generally well tolerated.

Conclusion

The use of ß-blocking agents has been clearly proven to provide significant survival benefit in patients being treated for HF when used in combination with ACE inhibitors and diuretics. As recent evidence has shown, there are significant differences between individual ß-blockers in their inherent biological and pharmacologic properties that may result in varied clinical responses. Carvedilol, a third-generation ß-blocker, has been approved for use in mild to moderate HF since 1996, and has been gradually accruing increased amounts of clinical evidence solidifying its role as a potent agent in the treatment of HF. Recently, carvedilol's U. S. Food and Drug Administration-approved indication has been extended to include all patients from NYHA class I (post-MI patients with LV dysfunction) through stable patients with NYHA class IV HF. The rationale in switching a patient from a $ß_1$-selective agent to carvedilol can be rooted in the strength of its performance in recent RCTs as well as its baseline pharmacologic differences which might make it more suitable for certain patients. There will be patients who will need the reverse exchange, from carvedilol to a $ß_1$-selective

Main Points

- Currently, both the Heart Failure Society of America Practice Guidelines and the Consensus Recommendations for the Management of Chronic Heart Failure mandate that all patients with New York Heart Association (NYHA) Class II-III HF should be treated with a ß-blocker unless there is a contraindication in a particular patient, or if the patient has been shown to be unable to tolerate treatment with the drug.
- HF patients with diabetes, peripheral vascular disease, Raynaud's phenomenon with vasospasm in the periphery, or renal dysfunction may be better suited for carvedilol given its favorable effects on insulin sensitivity/glycemic control and lipid metabolism, peripheral vascular tone, and renal hemodynamics, respectively.
- Carvedilol, a third-generation ß-blocking agent with additional vasodilatory $ß_1$-blocking properties, may provide added benefit to patients with chronic heart failure who are already undergoing treatment with a $ß_1$-selective antagonist.
- The switch from other ß-blockers to carvedilol can be made in one of two ways: an immediate change, which involves stopping the existing ß-blocker and initiating carvedilol within 24 hours, followed by up-titration of the carvedilol; or an overlapping method in which a first- or second-generation ß-blocker is weaned while carvedilol is simultaneously initiated and up-titrated.
- For patients who are truly intolerant of carvedilol, a similar switch in the opposite direction can be safely performed, preferably to metoprolol CR/XL, the only other ß-blocker with an approved indication for heart failure.

agent, as well. The ability to perform both types of exchanges safely and effectively, as well as for practical considerations, are important reasons why protocols highlighting this management strategy are needed in clinical practice. ■

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