Carvedilol: ß-Blockade and Beyond

Alice F. Stroe, MD, Mihai Gheorghiade, MD

Division of Cardiology, Northwestern University Feinberg School of Medicine, Chicago, IL

Carvedilol is an adrenergic antagonist with nonselective ß- and α_1-receptor blocking properties that has demonstrated significant clinical benefit in the management of patients with heart failure and in the post-myocardial infarction setting. It also possesses unique ancillary properties that may account for positive results in a number of clinical trials. It appears to offer particular advantages in the treatment of comorbid conditions, including coronary artery disease, stroke, hypertension, renal failure, diabetes, and atrial fibrillation, that can independently contribute to the progression of heart failure.

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Carvedilol is an adrenergic antagonist with nonselective ß- and α_1-receptor blocking properties that has demonstrated significant clinical benefit in the management of patients with heart failure and in the post-myocardial infarction (MI) setting.[1,2] It also possesses unique ancillary properties that may help account for positive results in a number of clinical trials when compared to other ß-blockers.[3-6] Carvedilol has proven beneficial not only in heart failure and in post-MI patients, but has also been shown to provide benefit in common comorbid conditions such as coronary artery disease, stroke, renal failure, diabetes, and atrial fibrillation.

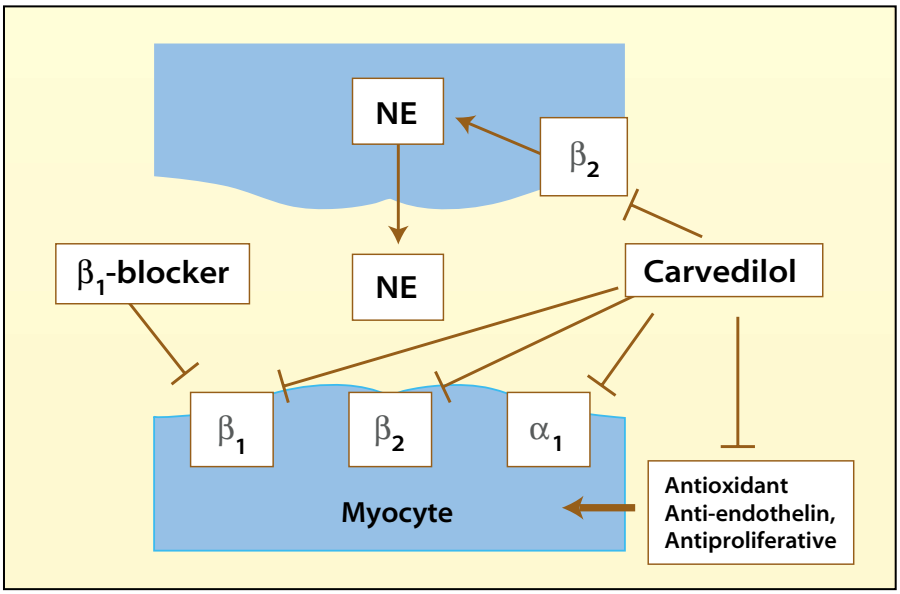

Figure 1. *Carvedilol has broad-based antiadrenergic activity and ancillary properties. NE, norepinephrine.*

Pharmacologic Properties

Adrenergic Receptor Blockade

First generation ß-blockers, such as propranolol and timolol, are nonselective $ß_1$-/$ß_2$-antagonists used for the treatment of hypertension and post-MI patients without heart failure. Second generation ($ß_1$-selective) ß-blockers, including atenolol, metoprolol, and bisoprolol were developed in response to problems related to unopposed α-adrenergic activity, particularly peripheral vasoconstriction exacerbated by $ß_2$-blockade. Carvedilol is a third-generation, vasodilating ß-blocker that acts at all 3 major adrenergic receptors: $ß_1$, $ß_2$, and $α_1$.[7-9] Carvedilol is devoid of intrinsic sympathomimetic activity and does not produce a high level of inverse agonist activity.[8,10]

Chronic heart failure is associated with increased activity of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) aimed at supporting cardiac output and systemic pressure.[11] However, these short-term compensatory mechanisms may lead to long-term deterioration in cardiac function.[12] Increased SNS activity can result in progressive left ventricular (LV) systolic impairment through direct catecholamine toxicity on cardiomyocytes,[13] as well as the detrimental effects of increased LV afterload and wall stress, promoting myocardial ischemia and oxidative stress.[12,14] Chronic heart failure is also associated with selective down-regulation of myocardial $ß_1$-receptors, increasing the relative importance of $ß_2$ and $α_1$ stimulation in the progressive deterioration of cardiac function.[7,15]

Because stimulation of all 3 adrenergic receptors may be involved in promoting myocardial toxicity, carvedilol blocks increased sympathetic activity more completely than previous ß-antagonists.[16] Carvedilol also blocks presynaptic $ß_2$-stimulation of norepinephrine release (Figure 1).[9] Furthermore, carvedilol does not increase myocardial $ß_1$-receptor density and the resulting exposure to harmful effects of SNS hyperactivity in patients with heart failure like $ß_1$-selective blockers do.[15,17] Finally, the vasodilating activity of carvedilol can minimize the increase in peripheral vascular resistance and LV afterload associated with chronic heart failure, although it is not certain that this property is maintained during long-term treatment.[16]

Ancillary Properties

Carvedilol possesses important ancillary properties that may help explain its beneficial clinical effects (antioxidant, antiarrhythmic, antiapoptotic, and antiproliferative) demonstrated in heart failure patients. It also has unique effects on carbohydrate and lipid metabolism that significantly differ from other ß-blockers.

Heart failure is associated with an increase in myocardial oxidative stress and a decrease in antioxidant reserve, induced in part by SNS and RAAS hyperactvity.[18-20] Reactive oxygen species (ROS) are generated by the mitochondria, cardiomyocyte xanthine oxidase, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity.[21,22] Oxidative stress, particularly increased NADPH oxidase activity,[23] is stimulated by elevated catecholamine and angiotensin-II,[22,24,25] resulting in myocardial lipid peroxidation in sarcolemmal membranes impairing cardiomyocyte integrity and function and decreased vascular nitric oxide synthesis, with subsequent reductions in endothelium-depend-

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ent vasodilation.[18,26,27]

Carvedilol acts as a potent antioxidant due to the unique carbazol moiety contained in its structure.[18,28] It may directly inhibit oxidative stress by scavenging oxygen free radicals or by reducing their generation through sequestration of the ferric ions needed for the non-enzymatic production of hydroxyl radicals.[28,29] Carvedilol significantly increases myocardial levels of the antioxidant enzymes superoxide dismutase and glutathione peroxidase, whereas the $ß_1$-selective blocker metoprolol does not.[30] Carvedilol has been shown to decrease myeloperoxidase activity and cardiac-membrane lipid peroxidation, an effect not produced by the $ß_1$-selective agent bisoprolol.[31] In patients with dilated cardiomyopathy, endomyocardial biopsies have demonstrated that carvedilol decreases the evidence of oxidative stress ordinarily associated with heart failure.[32]

Oxidative stress is a potent stimulus for cardiomyocyte apoptosis; ROS upregulates redox-sensitive genes for such proapoptotic proteins as Bax and caspases.[21,33] Carvedilol's antioxidant properties may provide a demonstrable cardioprotective effect by inhibiting apoptosis, thereby protecting against myocardial cell loss that is a part of progressive heart failure.[34,35] In a canine model of LV injury, carvedilol significantly reduced cardiomyocyte apoptosis with down regulation of Fas and Fas ligand expression, as well as caspase-3, in association with a reduction in reactive oxygen free radicals.[36]

Compensation for the hemodynamic consequences of heart failure also results in cardiac remodeling with changes in LV size, mass, and shape.[37] Decreased LV contractility is marked by an increase in end-systolic volume and a decrease in ejection fraction. End-diastolic volume increases to increase stroke volume and cardiac work. However, increasing ventricular volumes also potentiates mitral regurgitation, raises wall stress, and degrades myocardial energetics, promoting ischemia and exacerbating oxidative stress.[35,38] Increases in cardiac size are mediated through myocardial hypertrophy and interstitial fibrosis.[37] Carvedilol has been shown to have antiproliferative effects that may partly explain its ability to limit cardiac remodeling in clinical heart failure.[39] Treatment with carvedilol significantly reduces LV mass, improves LV geometry, and decreases mitral regurgitation in patients with chronic heart failure.[40] A meta-analysis of 19 clinical trials of carvedilol or metoprolol in over 2000 patients with chronic heart failure showed a significantly greater improvement in ejection fraction with carvedilol after a mean of 8 months of treatment.[41] Combination carvedilol and angiotensin-converting enzyme (ACE) inhibitor therapy has been shown to reverse left ventricular remodeling to a greater extent than ACE inhibitor use alone.[42,43]

Chronic heart failure is associated with an increase in both atrial and ventricular arrhythmias. Carvedilol has a demonstrated antiarrhythmic effect,[44] especially in patients with ischemic cardiomyopathy,[45] which may result from several different electrophysiological mechanisms. Adrenergic receptor blockade itself is well recognized to reduce myocardial ischemia and to improve arrhythmic thresholds.[46] In addition, carvedilol possesses membrane-stabilizing characteristics,[47] as well as the ability to selectively block important electrophysiologic calcium, sodium, and various potassium channels, including both the rapid and slow components of the delayed rectifier current and the transient outward potassium current.[48]

The use of ß-blockers in diabetic patients has been limited by adverse effects on glucose and lipid metabolism.[49] Unlike the $ß_1$-selective blockers atenolol and metoprolol, carvedilol does not reduce insulin sensitivity and glucose utilization; consequently, insulin and glycosylated hemoglobin levels are not raised. In fact, peripheral insulin sensitivity is increased during treatment with carvedilol (Figure 2).[3,5,49] Similarly carvedilol does not promote atherogenic dyslipidemia like the $ß_1$-selective agents; nor does it raise triglyceride levels or

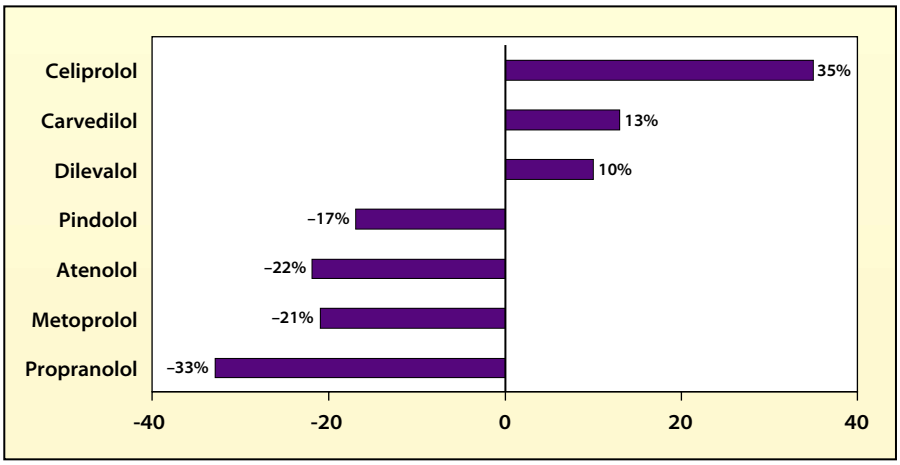


Figure 2. *The effect of ß-blockers on insulin sensitivity in hypertensive patients. Traditional ß-blockers reduce insulin hypersensitivity while vasodilating ß-blockers increase sensitivity. Reproduced with permission from Jacob et al.[86]*

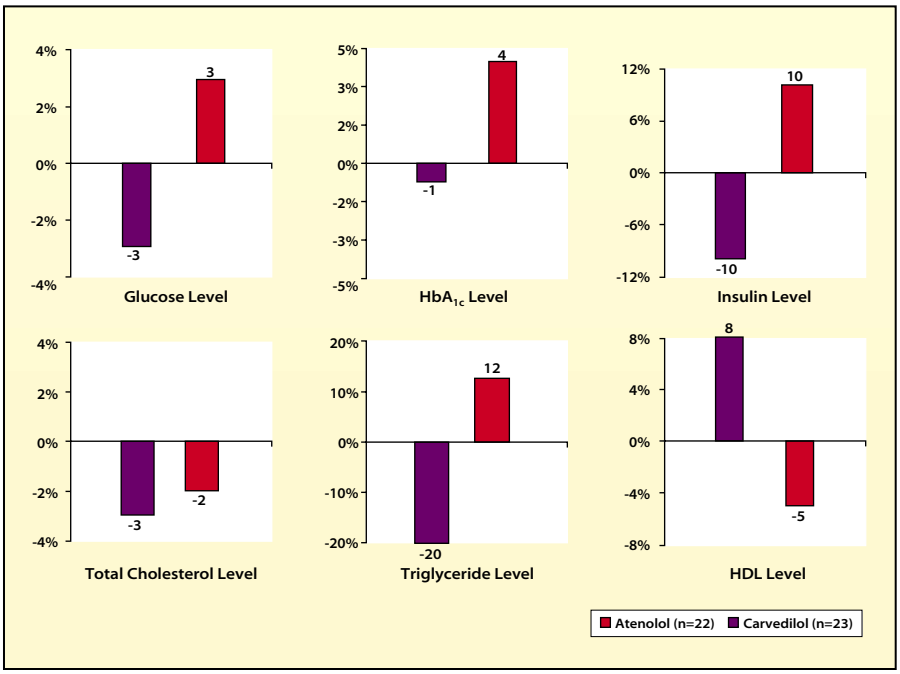


Figure 3. *The metabolic effects of atenolol and carvedilol in diabetic hypertensive patients: percent change from baseline to 6 months in 45 patients. HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein. Reproduced with permission from Giugliano et al.*[3]

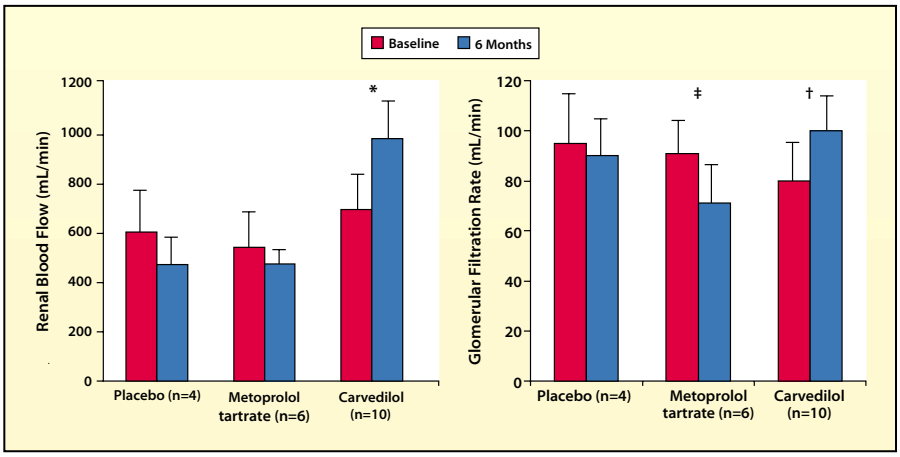
reduce high-density lipoprotein cholesterol levels like atenolol and metoprolol (Figure 3).[3,5] The differences in metabolic effects between carvedilol and $ß_1$-selective blockers are likely due to increases in peripheral glucose and insulin delivery caused by α_1–mediated vasodilation of skeletal muscle.[5] In addition, α_1-blockade has the opposite effect from $ß_1$-blockade on several key enzymes involved in lipid metabolism (lipoprotein lipase and lecithin-cholesterol acyltransferase), resulting in the promotion of a less atherogenic pattern of blood lipids.[50]

Carvedilol's vasodilating property also differentiates it from other ß-blockers in effect on renal function in heart failure. ß-Blockade ordinarily exacerbates the reduction in cardiac output due to impaired LV function, which in turn diminishes renal blood flow and sodium excretion. α_1-Blockade, on the other hand, antagonizes this effect on sodium excretion while decreasing peripheral resistance to cardiac output. Compared to metoprolol, carvedilol significantly increases renal blood flow and glomerular filtration rate in patients with heart failure (Figure 4).[16,51]

Carvedilol Versus Other ß-Blockers

Carvedilol, long-acting metoprolol succinate, and bisoprolol (used only in Europe) have all been found effective for the treatment of patients with heart failure due to LV systolic dysfunction.[9] Large, randomized, placebo-controlled clinical trials with metoprolol succinate (Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure [MERIT-HF]), bisoprolol (Cardiac Insufficiency Bisoprolol Study [CIBIS]-II), and carvedilol (U. S. Carvedilol Heart Failure Study)[52,53,54] have all shown a significant reduction in all-cause mortality in heart failure patients. Although the MERIT-HF and CIBIS-II trials included some patients with New York Heart Association (NYHA) class IV heart failure, carvedilol is the only ß-blocker shown to reduce mortality in a large, randomized, placebo-controlled trial involving only patients with severe, advanced heart failure.[52,53,55,56] It has been suggested that the more complete adrenergic blockade produced by carvedilol as well as its ancillary properties might confer a greater survival benefit

Figure 4. *The renal effects of carvedilol and metoprolol in heart failure. Carvedilol was titrated from 3.125 mg, twice daily, to 25 mg, twice daily (patients < 85 kg) or 50 mg, twice daily (patients > 85 kg). Metoprolol tartrate was titrated from 6.25 mg, twice daily, to 50 mg, twice daily (patients < 85 kg) or 100 mg, twice daily (patients > 85 kg). *P = .01 versus baseline; †P = .04 versus baseline; ‡P = .03 versus baseline. Reproduced with permission from Abraham et al.*[51]



than seen with α_1-selective agents.[9,57]

In order to test the relative effects of carvedilol and metoprolol on clinical outcomes, the Carvedilol or Metoprolol European Trial (COMET) randomized 3000 heart failure patients to treatment with either carvedilol or short-acting metoprolol at comparable ß-blocking doses.[1] The long-acting metoprolol succinate used in the MERIT-HF trial had not yet become available for use during this trial. In this head-to-head trial, carvedilol treatment was associated with a nearly 20% survival advantage compared to metoprolol over a 5-year period.[1] CIBIS-II results associated bisoprolol with a greater rate of stroke than placebo. Equivalent average heart rates after 16 months indicated that the actual carvedilol and metoprolol doses used in COMET achieved comparable ß-blockade.[1] However, the formulation and dosage of metoprolol used in COMET have been the subject of continuing debate.[58,59]

Clinical trials have shown that carvedilol, metoprolol succinate, and bisoprolol are efficacious in patients with mild-to-moderate heart failure. Carvedilol was also shown to benefit patients with severe (NYHA class IV) heart failure as well as patients with post-MI LV dysfunction.[2,55] Only carvedilol and metoprolol, but not bisoprolol, have been shown to be effective in heart failure accompanied by atrial fibrillation.[60,61] In contrast to metoprolol, carvedilol has demonstrated a beneficial effect on renal hemodynamics in patients with impaired renal function.[51]

It has been suggested that the more complete adrenergic blockade produced by carvedilol as well as its ancillary properties might confer a greater survival benefit than seen with α1-selective agents.

Carvedilol in Clinical Trials

Carvedilol in Patients With Severe Heart Failure: The COPERNICUS Trial

The morbidity and mortality benefits of carvedilol in severe heart failure were investigated in the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial.[55] This large, multicenter, double-blind trial randomized 2289 patients with heart failure symptoms at rest or minimal exertion (NYHA class IV) and a left ventricular ejection fraction (LVEF) less than 25% to treatment with carvedilol or placebo. Patients were required to be clinically euvolemic on stable doses of ACE inhibitors and diuretics. The study was stopped early because carvedilol conferred a statistically significant survival benefit that exceeded the predefined stopping criteria set by the study's data and safety monitoring board.[55]

Compared to placebo, patients receiving carvedilol had a 35% reduction of risk of death after a mean follow-up of 10.4 months. There was also a 24% reduction in the combined rate of all-cause death or hospitalization, and a 27% reduction in the combined rate of cardiovascular death or hospitalization.[55,62] In a subgroup of patients at particularly high risk of cardiac events, carvedilol treatment provided a 39% reduction in the risk of death and a 29% reduction in the rate of death or hospitalization, when compared to placebo.[55] These findings are particularly important since they negate the long-standing impression that heart failure patients at high risk respond poorly to ß-blockade.[56,63] Moreover, the benefit obtained during the first 8 weeks in COPERNICUS was similar to that obtained throughout the entire study, suggesting that initiation of carvedilol treatment is not harmful but has immediate beneficial effects in patients with heart failure.[64]

Carvedilol in Post-MI Patients With LV Dysfunction: The CAPRICORN Trial

Although the benefit of ß-blocker therapy on mortality rates after MI was established in the early 1980s,[65] clinical trials demonstrating this benefit had generally excluded patients with significant heart failure,[66] and ß-blocker use has specifically been avoided in these patients due to the fear of precipitating pulmonary edema or cardiogenic shock following the withdrawal of sympathetic support.[7,67,68] Since then, ß-blocker use has become further marginalized by the emergence of other mortality-reducing treatments including thrombolysis, angioplasty, and ACE inhibitor, intravenous-nitrate, aspirin, heparin, and statin therapies. However, significant survival benefits from ß-blocker use in patients with heart failure, such as ischemic cardiomyopathy and prior MI, have renewed interest in ß-blocker therapy for post-MI patients with LV impairment.[2,52,53]

CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction) was the first clinical trial specifically designed to study post-MI patients with confirmed LV systolic dysfunction, with or without clinical heart failure, and the only large-scale post-MI ß-blocker trial performed in the modern, post-thrombolytic era.[2] The trial randomized nearly 2000 acute MI patients with an ejection fraction less than 40% to carvedilol or placebo; patients were also required to receive an ACE inhibitor for at least 48 hours. Nearly half underwent thrombolytic thera-

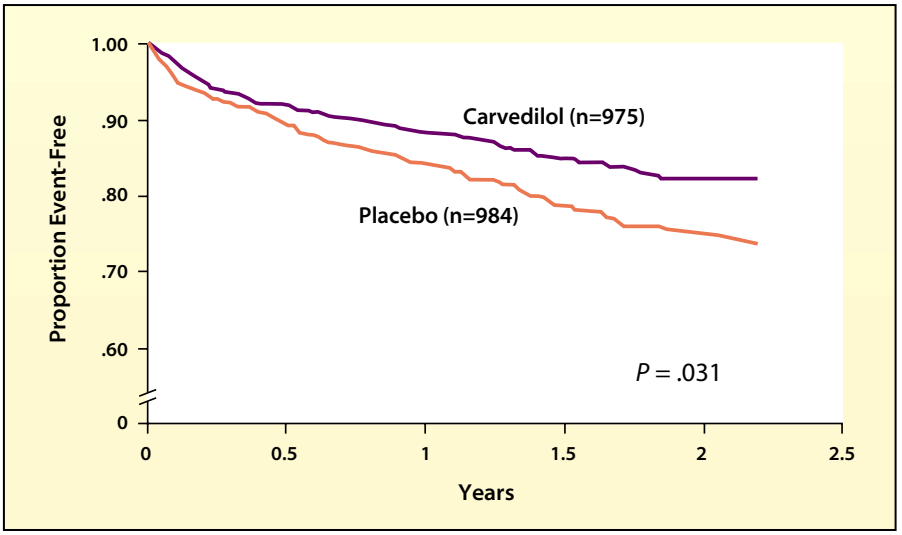


Figure 5. *Rates of death or reinfarction in CAPRICORN. A 29% risk reduction was seen (placebo 20%; carvedilol 14%) (P = .002). Reproduced with permission from CAPRICORN Investigators.*[2]

py or angioplasty and the majority was treated with aspirin, heparin, and nitrates. Only 10% received immediate intravenous ß-blockers.[2]

Carvedilol reduced all-cause mortality by 23%, similar to earlier ß-blocker trials that did not include heart failure patients.[69,70] Carvedilol treatment was also associated with a significantly lower incidence of cardiovascular mortality (25%), recurrent nonfatal MI (41%), and the combined end point of death or reinfarction (29%) (Figure 5).[2] Both atrial and ventricular arrhythmias occurred significantly less frequently in patients randomized to carvedilol than to placebo (52% and 63%, respectively).[71] However, there were no significant differences from placebo in the rate of sudden death, death due to heart failure, heart failure hospitalizations, or the combined endpoint of all-cause mortality or cardiovascular hospitalizations.[2]

A 6-month echocardiographic substudy of CAPRICORN found that carvedilol treatment had a beneficial effect on LV remodeling, with significantly greater improvements in LV end systolic volume and LVEF, the 2 most potent predictors of post-MI survival. Changes in LV end-diastolic volume and wall motion score index were not statistically different from placebo.[72]

CAPRICORN has provided an evidence-based template for the management of patients with LV dysfunction post-MI. The study reaffirms that these patients remain at high risk of death and major coronary events, despite the benefits afforded by modern drugs and interventions. The results of CAPRICORN suggest that long-term carvedilol, in association with ACE inhibitors, aspirin, statins, and acute revascularization, is the drug of choice for post-acute MI patients with LV dysfunction. Carvedilol has recently received U. S. Food and Drug Administration approval for this indication.

Carvedilol in Patients With Chronic Heart Failure and Atrial Fibrillation: The CAFE Trial

Atrial fibrillation (AF) confers an increased mortality and morbidity risk in patients with heart failure, especially from sudden death. AF may directly contribute to sudden death by increasing the dispersion of refractoriness or may be a surrogate for severe LV dysfunction.[73] ß-Blockers, as well as digoxin, are well known to control the ventricular response rate in AF; whereas digoxin alone increases vagal tone and controls the nocturnal ventricular rate, ß-blockade moderates the ventricular rate during exercise or when sympathetic tone is otherwise increased. However, there is limited information regarding the benefit of ß-blockers in the subgroup of patients with heart failure and AF.[74] In a retrospective analysis of the US Carvedilol Heart Failure Trials Program of patients with AF, carvedilol improved ejection fraction and physician-determined global assessment and probably reduced the combined endpoint of death or hospitalization compared to placebo.[74] Moreover, the adverse events database analysis of the CAPRICORN trial showed a 59% risk reduction of developing atrial fibrillation/flutter in heart failure patients.[71]

The Carvedilol in Atrial Fibrillation Evaluation (CAFE) trial was a randomized, double-blind, parallel-arm study investigating the effects of carvedilol and digoxin, separately and together, in the treatment of patients with heart failure and AF.[74] The study enrolled 47 patients with persistent AF (> 1 month) and heart failure (mean LVEF = 24%) who were receiving digoxin and diuretics. In the first 4 months of the study, continuing digoxin monotherapy was compared to digoxin plus carvedilol. The second 6 months of the study compared digoxin and carvedilol monotherapies by withdrawing digoxin from half of the carvedilol-treated cohort. This study design avoided the potential hazard of withdrawing digoxin at the same time as initiating ß-blockade in patients with established heart failure.

Ventricular response was measured by 24-hour ambulatory monitoring and during submaximal exercise.

The combination of carvedilol plus digoxin was superior to digoxin alone in slowing ventricular rate as well as in improving LV ejection fraction and overall symptom score (Figure 6).[75] When patients were switched from combination therapy to carvedilol alone, mean ventricular rate rose and ejection fraction regressed. However, there were no significant differences from baseline in any of the measured variables between continuing or withdrawing digoxin. The study also found no significant differences in any of the variables between carvedilol and digoxin when used as single agents.[75]

The CAFE Trial suggests that adding carvedilol to digoxin therapy in patients with heart failure and AF provides enhanced rate control as well as improvement in ventricular function and clinical status.

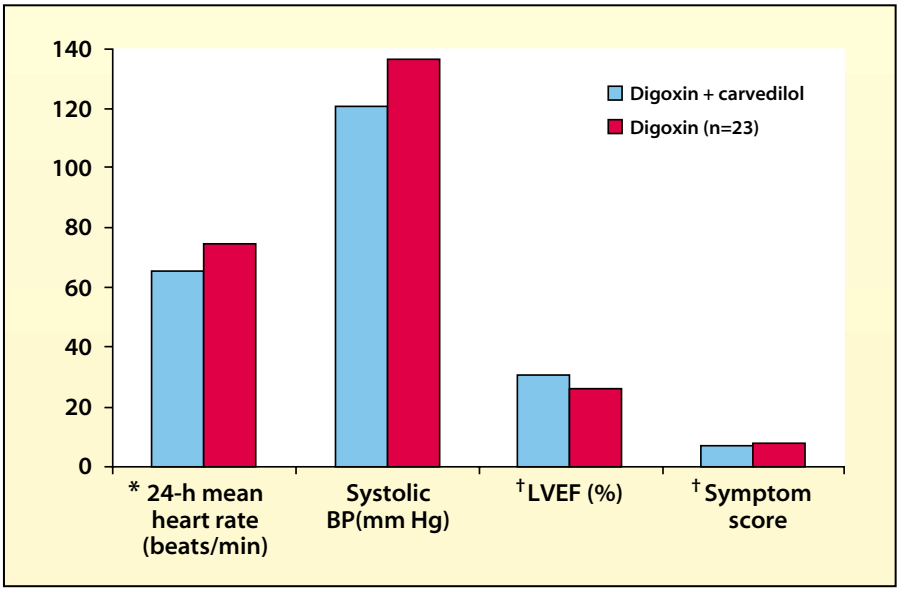


Figure 6. *Ventricular rate control and left ventricular function in heart failure patients treated with carvedilol and digoxin, or digoxin alone, in the CAFE trial. *P < .0001 change from baseline between groups. †P < .05 change from baseline between groups. BP, blood pressure; LVEF, left ventricular ejection fraction. Data from Khand et al.*[75]

Carvedilol in Patients With Heart Failure and Diabetes

Despite evidence that diabetes confers added mortality and morbidity risk to patients with heart failure, physicians are reluctant to prescribe ß-blockers in patients with diabetes because these agents may complicate therapy or worsen glycemic control by masking hypoglycemic symptoms, interfering with insulin release, and degrading insulin sensitivity.[76]

The efficacy and tolerability of the long-term administration of carvedilol was compared in 193 heart failure patients, 68 with and 125 without concomitant diabetes. Treatment with carvedilol was associated with comparable improvements in LV function, clinical symptoms, and resting and exercise hemodynamic parameters in the diabetic and the non-diabetic patients. The incidence of adverse events was also similar between the 2 groups.[76] The results of this trial suggest that carvedilol is equally beneficial in diabetic as in non-diabetic patients.

A meta-analysis of 6 ß-blocker trials, 3 with carvedilol (Australia and New Zealand [ANZ]-Carvedilol, Carvedilol US Trials, COPERNICUS), showed that there is prognostic benefit for diabetic heart failure patients treated with ß-blocker therapy, although the magnitude of the effect is not as great as in heart failure patients without diabetes.[77] This meta-analysis of more than 13,000 patients extends previous observations that diabetes is associated with increased mortality in heart failure into the modern treatment era, and indicates that heart failure patients with and without diabetes can derive significant prognostic benefit from ß-blockade.

ß-Blockers have been associated with an increased incidence of new-onset diabetes in previously nondiabetic individuals, compared with other classes of drugs used in the treatment of hypertension.[78] This phenomenon may be related to peripheral vasoconstriction with first- and second-generation ß-blockers because the COMET trial found that carvedilol, a vasodilating ß-blocker, was associated with a 22% lower risk than metoprolol of developing complications related to new-onset diabetes including hyperglylcemia, diabetic coma, and peripheral gangrene.[1]

The Role of Carvedilol in the Prevention of Arrhythmia and Sudden Death

The antiarrhythmic properties of carvedilol are due to blockade of ß-adrenergic receptors, and calcium, sodium, and potassium channels, as well as through lipophilic and membrane-stabilizing activity.[48] The analysis of the adverse events database from CAPRICORN shows a 63% risk reduction of any ventricular arrhythmia and, in particular, a 76% risk reduction in malignant ventricular arrhythmia (ventricular tachycardia

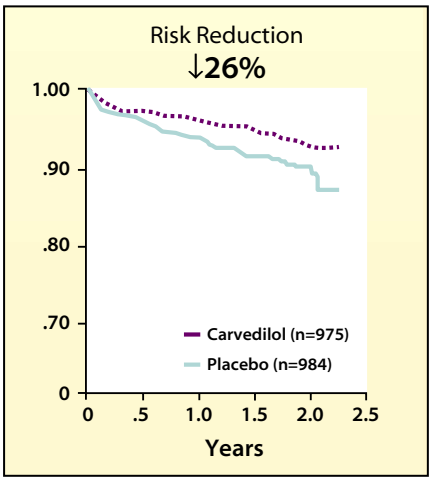


Figure 7. *Sudden death in the CAPRICORN trial. Carvedilol use resulted in a 26% risk reduction versus placebo. (P = .098). Data from CAPRICORN Investigators.*[2]

Table 1
Antiarrhythmic Effects of Carvedilol in the CAPRICORN Trial

	Placebo (n = 984)	Carvedilol (n = 975)	Risk Reduction (95% CI)	*P* value
Any supraventricular arrhythmia	54	26	52% (24%–70%)	.0015
Atrial flutter or atrial fibrillation	53	22	59% (32%–75%)	.0003
Any ventricular arrhythmia	69	26	63% (42%–76%)	<.0001
Malignant ventricular arrhythmia Ventricular fibrillation/ ventricular tachycardia	38	9	76% (51%–89%)	<.0001

Data from CAPRICORN Investigators.[2]

or fibrillation) (Table 1).[71] Patients treated with carvedilol had a 26% reduction in risk of sudden death in the CAPRICORN trial (Figure 7).[2] Carvedilol acts to ameliorate hemodynamic abnormalities accompanying heart failure by increasing ejection fraction and reducing remodeling, thereby diminishing the physiologic substrate responsible for arrhythmogenesis.[79]

The Antihypertensive Effect of Carvedilol

Although ß-blockers have been approved as first-line therapy for hypertension, traditional ß-blockers are not always the best choice. In effect, they act as though patients were made hemodynamically "older" by decreasing cardiac output and increasing systemic vascular resistance.[80] They are less effective in reducing LV hypertrophy than angiotensin receptor antagonists[81] and do not reduce pulse pressure or arterial compliance.[82] These properties make them less effective in treating systolic hypertension and relatively ineffective and poorly tolerated in the elderly patient.[80] Commonly used ß-blockers are ineffective in reducing coronary heart disease, cardiovascular mortality, and all-cause mortality in elderly patients with hypertension.[80] On the other hand, carvedilol, as a vasodilating ß-blocker, contrasts with the hemodynamic profile of traditional ß-blockers in hypertensive patients; it maintains cardiac output, decreases blood pressure by decreasing systemic vascular resistance and increases renal blood flow,[83,84] and appears to exert a regressive effect on LV hypertrophy.[85]

Conclusion

Carvedilol blocks $ß_1$-, $ß_2$-, and α_1-adrenoceptors and has a unique pharmacological profile. Ancillary pharmacologic properties of carvedilol (antioxidant, antiapoptotic, antiproliferative, electrophysiologic, and metabolic) may contribute to its beneficial effects in patients with chronic heart failure. Carvedilol improves ventricular function and reduces mortality and morbidity in patients with mild to severe heart failure and should be considered a standard treatment option in this setting. Administering carvedilol in addition to conventional therapy reduces mortality and attenuates myocardial remodeling in patients with LV dysfunction following acute MI. In addition to its usefulness in patients with mild to moderate and severe heart failure, carvedilol is beneficial in the treatment of common comorbid conditions. ■

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Main Points

- Carvedilol possesses unique ancillary properties with clinical effects (antioxidant, antiarrhythmic, antiapoptotic, antiproliferative) that are beneficial to heart failure patients.
- Unlike the ß$_1$-selective blockers atenolol and metoprolol, carvedilol does not reduce insulin sensitivity and glucose utilization; consequently, insulin and glycosylated hemoglobin levels are not raised.
- Carvedilol does not promote atherogenic dyslipidemia like the ß$_1$-selective agents; nor does it raise triglyceride levels or reduce high-density lipoprotein cholesterol levels like atenolol and metoprolol.
- Compared to metoprolol, carvedilol significantly increases renal blood flow and glomerular filtration rate in patients with heart failure.
- The COPERNICUS trial compared carvedilol to placebo in the treatment of patients with severe (New York Heart Association Class IV) heart failure and left ventricular ejection fraction less than 25%. In the highest risk group, carvedilol provided a 39% reduction in risk of death and a 29% reduction in the combined risk of death or hospitalization. This level of benefit was seen throughout the trial, including the initial 8 weeks of therapy.
- The CAPRICORN and CAFE trials, and a meta-analysis of three trials from the U. S., Australia, and New Zealand have all shown benefit from carvedilol therapy in the settings of left ventricular dysfunction following myocardial infarction, heart failure complicated by atrial fibrillation, and the prevention of new-onset diabetes in patients with heart failure.
- As a vasodilating ß-blocker, carvedilol contrasts with the hemodynamic profile of first- and second-generation ß-blockers, thereby conferring benefit in hypertensive patients by maintaining cardiac output, decreasing blood pressure, and increasing renal blood flow.

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