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Reviews

Carvedilol's Antiarrhythmic Properties: Therapeutic Implications in Patients with Left Ventricular Dysfunction

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Summary: Carvedilol is a beta- and alpha-adrenergic-blocking drug with clinically important antiarrhythmic properties. It possesses anti-ischemic and antioxidant activity and inhibits a number of cationic channels in the cardiomyocyte, including the HERG-associated potassium channel, the L-type calcium channel, and the rapid-depolarizing sodium channel. The electrophysiologic properties of carvedilol include moderate prolongation of action potential duration and effective refractory period; slowing of atrioventricular conduction; and reducing the dispersion of refractoriness. Experimentally, carvedilol reduces complex and repetitive ventricular ectopy induced by ischemia and reperfusion.

In patients, carvedilol is effective in controlling the ventricular rate response in atrial fibrillation (AF), with and without digitalis, and is useful in maintaining sinus rhythm after cardioversion, with and without amiodarone. In patients with AF and heart failure (HF), carvedilol reduces mortality risk and improves left ventricular (LV) function. Large-scale clinical trials have demonstrated that combined carvedilol and angiotensin-converting enzyme inhibitor therapy significantly reduces sudden cardiac death, mortality, and ventricular arrhythmia in patients with LV dysfunction (LVD) due to chronic HF or following myocardial infarction (MI).

Despite intensive neurohormonal blockade, mortality rates remain relatively high in patients with post-MI and nonischemic LVD. Recent trials of implantable cardioverter-defibrillators added to pharmacologic therapy, especially beta blockers, have shown a further reduction in arrhythmic deaths in these patients.

Key words: carvedilol, antiarrhythmic drugs, left ventricular dysfunction, atrial fibrillation, ventricular arrhythmias, sudden cardiac death

Introduction

Heart failure (HF) due to left ventricular dysfunction (LVD) is associated with poor long-term survival, with approximately one half of deaths being sudden and unexpected.[1] Atrial fibrillation (AF) occurs in 15–30% of patients with HF and is associated with an increased risk of death.[2, 3] In addition, over 60% of patients with LVD have concomitant nonsustained ventricular tachycardia.[2] Carvedilol, long-acting metoprolol, and bisoprolol have all been found to reduce the risk of all-cause mortality significantly in HF, including the risk of sudden arrhythmic death.[4] However, carvedilol is a beta-blocking agent with other unique properties, and its electrophysiologic effects and antiarrhythmic potential have been underappreciated. This paper discusses the multiple antiarrhythmic mechanisms by which carvedilol may suppress ventricular and atrial arrhythmias and reviews the experimental and clinical evidence supporting its antiarrhythmic efficacy in patients with LVD.

Electrophysiologic Effects and Antiarrhythmic Mechanisms

Adrenergic blockers have well-established antiarrhythmic effects for which a number of mechanisms have been proposed. The anti-ischemic activity of beta blockade may reverse the nonuniformity in refractoriness, excitability, and conduction, and reduce vagal tone caused by myocardial ischemia. Beta blockade can increase the threshold for ventricular fibrillation (VF) that accompanies high sympathetic and low vagal tone and may diminish the attenuation of Class IA or

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Class III antiarrhythmic drug action caused by sympathetic stimulation. Acting through $beta_1$ receptors, beta-blockade may exert an antiarrhythmic effect by ameliorating underlying arrhythmogenic processes such as reinfarction in coronary artery disease (CAD) and LVD in ischemic and nonischemic cardiomyopathy.[5] $Beta_2$ blockade may limit increases in automaticity, and $alpha_1$ blockade may inhibit delayed afterdepolarizations and triggered activity, all of which are induced by norepinephrine.[6]

Carvedilol is an adrenergic antagonist that blocks $beta_1$, $beta_2$, and $alpha_1$ receptors in cardiomyocytes, and that demonstrates important antiarrhythmic properties both experimentally and clinically (Fig. 1).[6] Specifically, it is a nonselective, competitive, adrenergic inhibitor with 7-fold and 2-fold greater affinity for $beta_1$ than $beta_2$ and $alpha_1$ receptors, respectively, and it diminishes sympathetic-induced ischemia by attenuating myocardial contractility, vasoconstriction, and tachycardia.[7] The lipophilicity of carvedilol increases its activity in the central nervous system, which is important in relation to its vagotonic action.[5, 8]

Carvedilol possesses complex electrophysiologic properties. Its predominant electrophysiologic effects relate to the drug's Vaughan Williams Class II dose-related antiadrenergic effects. Carvedilol's other electrophysiologic effects are underappreciated and include direct membrane-stabilizing activity (Class IA); prolonging repolarization by blocking potassium channels (Class III); and inhibiting L-type calcium channels (Class IV).[9–13] These effects appear to be without any known ventricular proarrhythmic activity.

Carvedilol inhibits several native potassium channels responsible for repolarization in cardiomyocytes, including the rapidly and slowly activating components of the delayed rectifier current (I_{Kr} and I_{Ks}) and the transient outward current (I_{to}), but not the inward rectifier current (I_{KI}), which prolongs the action potential duration (APD) and effective refractory period to repeat excitability (Fig. 2).[9] The major impact of clinically utilized levels of carvedilol (0.1–0.6 μM)[9] on the APD in rabbit papillary muscle is due to a concentration-dependent inhibition of I_{Kr}, the channel encoded in humans by the ether-a-go-go-related gene (HERG).[9, 10] At a comparably adjusted concentration, carvedilol can similarly block cloned HERG channels expressed in *Xenopus* oocytes.[10] In spite of this measured activity, patients treated with carvedilol do not demonstrate a significantly prolonged QT interval on the surface electrocardiogram (ECG).[10] Although poorly understood, the mechanism responsible for this lack of QT-prolonging effect may include the fact that carvedilol is a weak I_{Kr} blocker; blockade of I_{Ks} may minimize the QT-prolonging effect; or that blocking the L-type calcium channel or the beta-blockade effect predominates with a resultant shortening of the QT interval.

The effect on I_{Kr} is shared by other antiarrhythmic drugs with Class III activity, including the pure Class III agents d-sotalol and dofetilide, as well as the multichannel blocker amiodarone. However, both d-sotalol and dofetilide demonstrate reverse frequency dependence and can be associated with torsade de pointes.[14] Carvedilol, on the other hand, demonstrates no significant reverse frequency dependence and, in its low ventricular proarrhythmic potential, more closely resembles amiodarone.[9] At concentrations of 1 and 3 μM, carvedilol prolonged the APD in rabbit papillary muscle 7–12% and 12–24%, respectively, at stimulation frequencies of 0.1–3.0 Hz.[9] This electrophysiologic effect of carvedilol appears to be due to a balanced inhibition of L-type calcium channels (more prominent at lower stimulation frequencies) as well as potassium channels, resulting in a moderately prolonged APD with minimal reverse frequency dependence compared with pure Class III agents.[9, 14] The inhibition of L-type calcium channels at concentrations > 0.3 μM not only protects against the potentially hazardous effects of prolonged APD, but also decreases sinus node firing that can mitigate the tachycardia-induced ischemia in myocardial infarction (MI).[9, 15]

Prolonged APD may be particularly proarrhythmic in the setting of a decreased sodium current in which the refractory and vulnerable periods are increased.[10] Downregulation of the sodium channel that carries the initial depolarizing in-

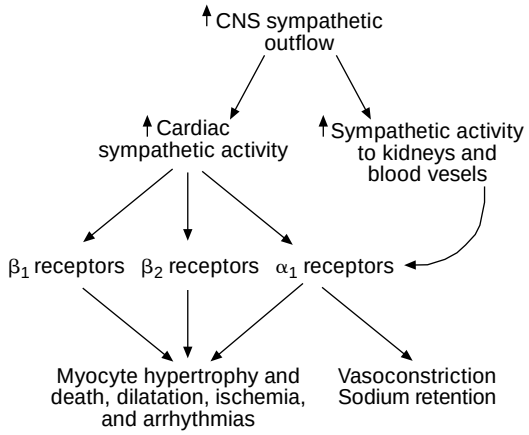

FIG. 1 The deleterious effects of an increase in sympathetic activation are mediated by three adrenergic receptors (β_1, β_2, α_1). CNS = central nervous system. Adapted from Ref. No. 6 with permission.

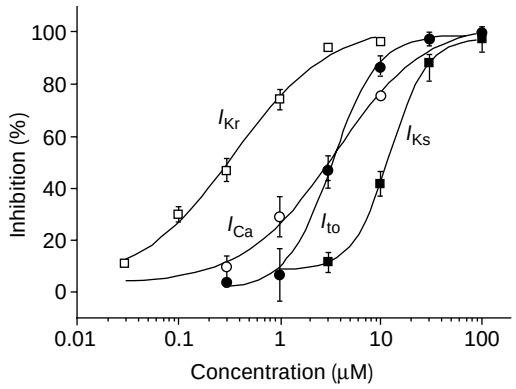

FIG. 2 Effect of carvedilol on inhibiting I_{Kr}, I_{Ca}, I_{to}, I_{Ks}. Adapted from Ref. No. 9 with permission.

ward sodium current (I_{Na}) has been associated with AF, MI, and chronic HF. By reducing the rate of Phase 0 depolarization, changes in I_{Na} can slow conduction and promote reentrant arrthythmias.[11]

In a canine model of chronic HF associated with a decrease in sodium current, long-term carvedilol treatment resulted in a recovery in the density of I_{Na}.[11] Because changes in intracellular calcium modulate the expression of sodium channels in cardiomyocytes,[16] it is believed that chronically heightened sympathetic beta-receptor stimulation, which increases intracellular calcium, may downregulate sodium channels in chronic HF. Carvedilol may increase sodium-channel expression and I_{Na} density by ameliorating the abnormal calcium handling found in the failing cardiomyocyte (spontaneous sarcoplasmic reticulum sodium release, upregulated sodium–calcium exchange, and increased L-type channel activity), resulting in improved myocardial conduction.[11]

Treatment with carvedilol causes electrophysiologic changes in conduction and repolarization; these changes are manifested by improvements in several important parameters. Nonuniform myocardial repolarization that leads to dispersion of refractoriness is well recognized as an important predisposing factor in the genesis of reentry and malignant ventricular arrhythmias.[17] QT dispersion on the 12-lead surface ECG provides an indirect estimate of arrhythmogenicity and has been used as a potential indicator for predicting sudden cardiac death and drug effects on cardiac mortality.[18, 19] In a study of patients with ischemic and nonischemic cardiomyopathy, long-term treatment with carvedilol significantly reduced QT dispersion in both etiologic categories. It is interesting that improved repolarization homogeneity paralleled enhanced left ventricular (LV) function, which is associated with carvedilol use in chronic HF.[20] When compared with the $beta_1$-selective blocker metoprolol in patients with clinical HF, long-term carvedilol treatment significantly reduced QT temporal dispersion.[21]

A second indicator of improved conduction with carvedilol was observed in a study of intracardiac conduction intervals. The effects of propranolol and carvedilol on atrioventricular conduction were compared in isolated rat heart preparations. Carvedilol produced 10-fold greater increases in the atrial-His interval than propranolol and also suppressed His-ventricular conduction at high doses. The differences between the two drugs were unrelated to the $alpha_1$-blocking property of carvedilol or to differences in direct membrane-stabilizing activity between the two agents.[22]

Carvedilol is a unique beta blocker because a carbazole moiety in its structure confers an antioxidant property that allows carvedilol to protect biological membranes against oxygen-free radicals in vitro and in vivo.[23] Carvedilol possesses approximately 10-fold greater antioxidant activity than vitamin E, and several of its metabolites are 50–100 times more potent than the parent drug itself.[14] Because oxidative stress can be a factor in ventricular arrhythmias, the antioxidant property of carvedilol may be responsible for some of its antiarrhythmic activity.[24] Reperfusion arrhythmias, in particular, have been linked to a burst of oxygen-free radicals released on resumption of coronary blood flow. In an anesthetized rat model of coronary reperfusion, the effects of carvedilol, propranolol, and the combined antioxidant enzymes superoxide dismutase (SOD) plus catalase were compared in ventricular arrhythmogenesis.[24] The incidence of reperfusion-induced ventricular tachycardia (VT) or VF was 100% in control animals. Whereas carvedilol alone and propranolol plus SOD/catalase significantly reduced VT and VF, neither propranolol alone nor SOD/catalase alone diminished these arrhythmias. The combined beta-blocking and antioxidant activities of carvedilol appeared to help suppress these lethal ventricular arrhythmias.[24] The same mechanisms may also aid in the effects of carvedilol in AF because this arrhythmia is also associated with oxidative injury. Atrial tissue removed from patients with persistent AF have demonstrated increased levels of protein oxidation compared with patients in sinus rhythm.[25]

Clinical Data

Atrial Arrhythmias

Sympathetic stimulation is a well-established cause of the induction and perpetuation of AF.[26] Although digoxin is considered a standard AF treatment, it is significantly less effective for controlling ventricular response during daily activity (especially during exercise) than a beta blocker or a calcium blocker alone or in combination with digoxin.[27] Recently, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators reported that beta blockers were the class of drugs most likely to result in effective rate control when compared with calcium blockers or digoxin.[28] Compared with patients in sinus rhythm, those with HF and AF have nearly twice the risk of dying from pump failure.[3] Digoxin does not reduce mortality in patients with chronic HF, whereas certain beta blockers (carvedilol, bisoprolol, metoprolol) have been associated with significant mortality reductions in this high-risk population.[4, 29–31]

Retrospective analysis of large randomized, placebo-controlled HF trials have found that, in patients with AF at baseline, carvedilol treatment significantly improved LV function and clinical status. Carvedilol improved LV ejection fraction (EF) by 10% (23–33%), compared with 3% with placebo. Carvedilol treatment was also associated with a 65% reduction in death or hospitalization for HF (carvedilol 7%, placebo 19%; $p = 0.055$).[32] While the beneficial effects of carvedilol were found to extend to patients in AF, a similar large-scale trial of the $beta_1$-selective blocker bisoprolol did not find a mortality benefit or reduction in HF hospitalizations in patients with HF and AF, suggesting a clinical difference between beta blockers.[33]

Digoxin and beta blockers are commonly used for rate control in chronic AF. A randomized, double-blind comparison of carvedilol alone, digoxin alone, or their combination in patients with chronic HF and persistent AF found the combination to be generally superior to either drug alone. Adding carvedilol to digoxin significantly reduced the ventricular re-

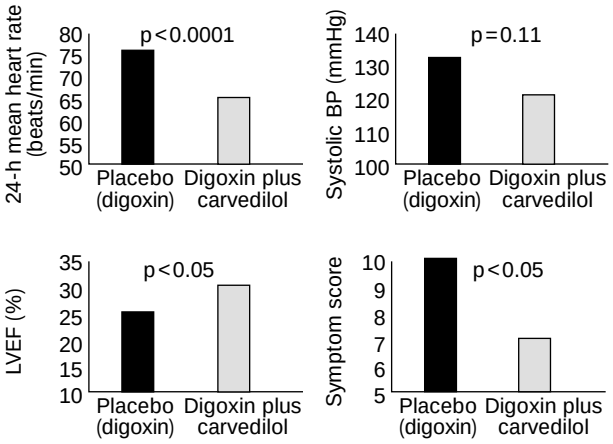

FIG. 3 Carvedilol in Atrial Fibrillation Evaluation (CAFE): Effect of carvedilol and digoxin on ventricular control rate. BP = blood pressure, LVEF = left ventricular ejection fraction. Source: Ref. No. 34.

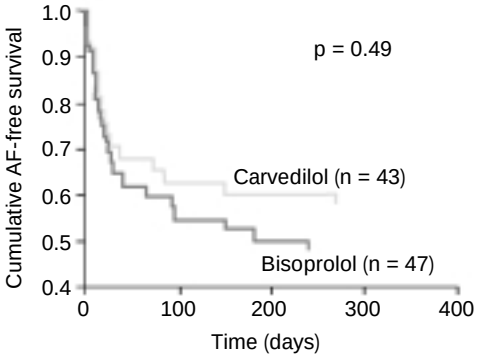

FIG. 4 Effect of carvedilol and bisoprolol in maintaining sinus rhythm after cardioversion for atrial fibrillation (AF). Adapted from Ref. No. 36 with permission.

sponse on 24-h Holter monitoring and during submaximal exercise. However, no significant differences were demonstrated between the two drugs when used alone for rate control (Fig. 3).[34]

After cardioversion of persistent AF, 1-year recurrence rates are as high as 75% in untreated patients or those receiving placebo. Although Class IA and III antiarrhythmic drugs can suppress AF recurrences, rate control drugs usually have little suppressive effects on recurrences. However, recent data suggest that metoprolol and carvedilol may have added antiarrhythmic effects. A recent study demonstrated that long-acting metoprolol was superior (p = 0.005) to placebo in preventing recurrences post cardioversion.[35] In the metoprolol group, relapses occurred in 48.7% of patients compared with 59.9% of patients in the placebo group. When AF recurred, the ventricular response was statistically lower in the metoprolol-treated group (p = 0.015).[35] In a postcardioversion trial comparing carvedilol with bisoprolol, carvedilol had a 14% lower rate of AF relapse during the 1-year period following cardioversion (Fig. 4).[36]

Carvedilol was also compared with two other beta$_1$-selective blockers, metoprolol and atenolol, in a study of postoperative AF as a complication of cardiac surgery. Postoperative AF occurred in 8% of carvedilol-treated patients versus 32% of metoprolol- or atenolol-treated patients, for a 75% risk reduction. This occurred despite significantly poorer baseline LV function in the carvedilol group (Fig. 5).[37] Carvedilol was compared with amiodarone in a placebo-controlled trial of patients with chronic AF undergoing electrical cardioversion.[38] Patients were randomized to receive carvedilol, amiodarone, or no antiarrhythmic drug for 6 weeks before and after external transthoracic cardioversion. Successful cardioversion was achieved with carvedilol and amiodarone pretreatment (87 and 94%, respectively) versus no antiarrhythmic prophylaxis (69%). Patients in both drug-treated groups immediately had longer fibrillatory cycle-length intervals pre conversion and longer atrial effective refractory periods 5 min post conversion than unprotected patients. More patients who experienced an AF relapse by 7 days were untreated (44%) compared with those receiving either carvedilol (29%) or amiodarone (19%) treatment (Fig. 6).[38] The similarities in electrophysiologic and clinical responses to the two agents suggest that carvedilol may have a beneficial role in the management of chronic AF.

The effect of long-term carvedilol therapy on atrial arrhythmia in patients with impaired post-MI LV function was

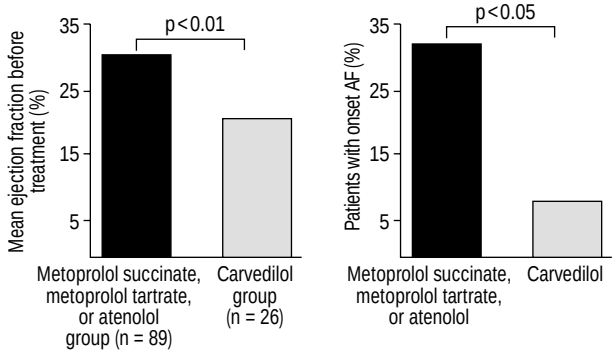

FIG. 5 Effect of carvedilol, metoprolol, and atenolol on postoperative atrial fibrillation (AF). Source: Ref. No. 37.

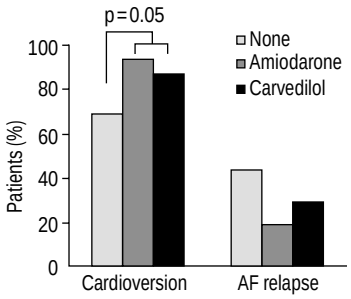

FIG. 6 Effect of carvedilol and amiodarone on atrial fibrillation (AF) conversion and recurrence. Source: Ref. No. 38.

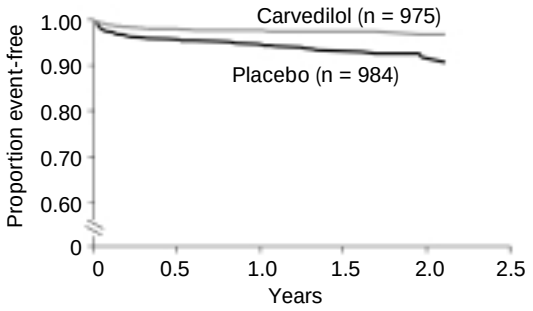

FIG. 7 Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN): Effect of carvedilol on atrial flutter/fibrillation. Treatment with carvedilol resulted in a 59% risk reduction compared with placebo (CI 32%, 75%; $p < 0.0003$). Source: Ref. No. 39.

reported from the recent Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. Almost 2000 survivors of MI with an EF ≤ 40%, with or without clinical HF, were randomized to carvedilol or placebo treatment in addition to an angiotensin-converting enzyme (ACE) inhibitor. Although the occurrence of AF or flutter was low, carvedilol-treated patients experienced 52% fewer supraventricular arrhythmias, including 59% fewer episodes of AF or atrial flutter (Fig. 7).[39] It remains to be determined whether carvedilol's unique electrophysiologic, alpha blockade, and antioxidant properties add to the drug's efficacy over other beta-blocking agents.

Ventricular Arrhythmias

Sudden cardiac death, in the vast majority of cases, results from VT that degenerates into VF.[40, 41] Despite improved management strategies, ventricular arrhythmias remain important markers of electrical instability and contribute to the identification of patients at increased risk of sudden cardiac death due to LVD or following MI.[42–45] Clinical trials have demonstrated that beta blockers reduce simple and complex ventricular ectopy and decrease sudden cardiac death.[12]

The clinical antiarrhythmic efficacy of carvedilol was demonstrated by Holter monitoring in an uncontrolled open study of 65 patients who were treated for hypertension, HF, or angina.[13] After 4–8 weeks of carvedilol treatment, the number of premature ventricular contractions (PVCs) had decreased from 26 to 6/h, and 23% of patients with multifocal PVCs converted to a unifocal morphology. Nonsustained VT that had been present in four patients was absent at follow-up. An improvement in Lown classification occurred in 50% of the patients (Fig. 8).[13]

The effect of carvedilol on complex, nonsustained ventricular arrhythmias was more rigorously evaluated in a randomized, placebo-controlled clinical trial in patients with dilated cardiomyopathy.[46] In this study, carvedilol or placebo was added to conventional therapy that included digitalis, diuretics, and ACE inhibitors in 168 patients with ischemic or nonischemic cardiomyopathy and Lown class III–V ventricular arrhythmias (multifocal or repetitive PVCs, VT, or R-on-T). All participants had New York Heart Association (NYHA) class II–IV HF and echocardiographically measured EF < 35%. Forty-eight-h Holter recordings were performed at baseline and after 1, 3, and 6 months of treatment. Suppression of ventricular ectopy was seen after 1 month in both ischemic and nonischemic groups, with significant decreases in total PVCs, repetitive PVCs, and nonsustained VT. Further reductions were seen at 3 months but remained stable at 6 months. At 1 month, patients with ischemic cardiomyopathy experienced significantly greater arrhythmia suppression than patients with nonischemic cardiomyopathy despite no EF differences. At 3 months, when both groups had improved ventricular function, the degree of ventricular ectopy suppression was comparable, suggesting that the early improvement had been caused primarily by the anti-ischemic effect of carvedilol. This benefit was augmented by the subsequent beneficial effects of carvedilol on ventricular remodeling in both groups.[46]

While carvedilol has been shown to improve mortality and morbidity risk in a wide range of patients with chronic HF due to mild to severe LVD,[47–49] treatment with amiodarone has not shown consistent benefit in death reduction.[50, 51] In a retrospective subgroup analysis of the European Myocardial Infarction Amiodarone Trial (EMIAT) in patients with post-MI LVD, amiodarone-treated patients who had been receiving concomitant beta-blocker therapy did experience a significant survival advantage over untreated patients.[52] A prospective clinical trial was subsequently reported, in which patients with severe HF treated for 1 year with carvedilol plus amiodarone experienced significant clinical benefits.[53] Compared with entry, 26% more patients were in sinus rhythm at the end of 1 year, the average heart rate was reduced from 90 to 59 beats/min, and the number of PVCs and episodes of tachycardia was significantly suppressed. Left ventricular EF increased from 26 to 39% and the average NYHA clinical class improved from 3.17 to 1.8. Compared with historic controls of similar patients receiving neither test drug, transplantation-free survival increased by 36% (Fig. 9).[53] However, the possibility of

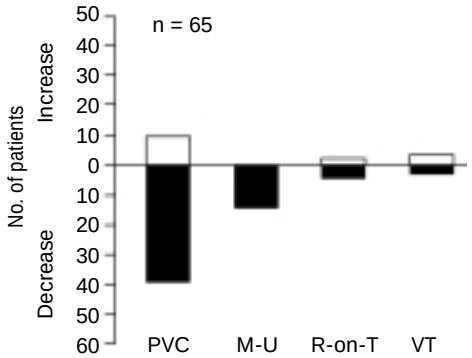

FIG. 8 Effect of carvedilol on arrythmias. M = multifocal, PVC = premature ventricular contraction, U = unifocal, VT = ventricular tachycardia. Source: Ref. No. 13.

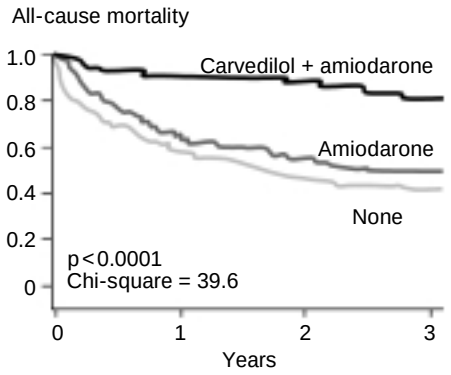

FIG. 9 Effect of carvedilol and amiodarone on death and sudden death. Source: Ref. No. 53.

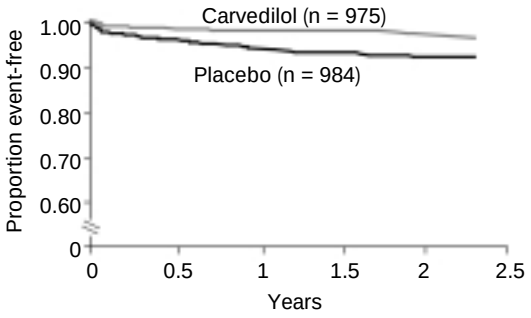

FIG. 10 Carvedilol Post-Infarct Survival Control in LV Dysfunction (CAPRICORN): Effect of carvedilol on any ventricular arrhythmia. Treatment with carvedilol resulted in a 63% risk reduction compared with placebo (CI 42%, 76%; $p < 0.001$). Source: Ref. No. 39.

severe bradycardia must be anticipated with this combination of two negatively chronotropic drugs. In this population, approximately 6% of patients became pacemaker dependent within 1 year.[53]

The effects of carvedilol on ventricular arrhythmias in patients with post-MI LVD were reported in the CAPRICORN trial.[39] Survivors of MI with an EF ≤ 40% (n = 1959) were randomized to treatment with either carvedilol or placebo. During over 1 year of follow-up, carvedilol significantly reduced supraventricular arrhythmias, ventricular arrhythmias, and VF (Fig. 10).[39]

In the Carvedilol Or Metoprolol European Trial (COMET), carvedilol was compared in a head-to-head clinical trial with metoprolol tartrate in patients with chronic HF. Metoprolol tartrate is a $beta_1$-selective beta blocker that does not possess either $alpha_1$-blocking or antioxidant properties. Over a mean follow-up of nearly 58 months, total mortality was 17% lower with carvedilol.[54]

Implantable Cardioverter-Defibrillators and Beta Blockers

Recent advances in the pharmacologic approach to LVD have significantly improved clinical outcomes in patients with ischemic and nonischemic cardiomyopathy, with recent or distant MI, and with or without symptomatic HF. Neurohormonal blockade has evolved since the 1990s with the stepwise demonstration of the additive benefits achieved from treatment with ACE inhibitors, beta blockers, aldosterone antagonists, and angiotensin-receptor blockers (ARBs) as an alternative to ACE inhibitors. Nevertheless, in the recent Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), all-cause mortality after 16 months was 14% in the eplerenone-treated group, in which 40% of cardiovascular deaths were sudden. In this study of survivors of acute MI with impaired LV function, the majority of patients were also receiving an ACE inhibitor (or ARB) and a beta blocker in addition to eplerenone.[55]

Unresolved mortality in HF has led to the evaluation of implantable cardioverter-defibrillators (ICDs) in addition to optimal pharmacologic therapy. A significant mortality benefit of ICD added to conventional therapy versus conventional therapy alone has been documented in a number of diverse randomized clinical trials in patients with CAD or nonischemic cardiomyopathy (Table I).[56–63] The Multicenter Automatic Defibrillator Implantation Trial (MADIT),[56] MADIT-II,[57] and the Multicenter UnSustained Tachycardia Trial (MUSTT)[58] selected high-risk, postmyocardial infarction patients based on impaired LV function; in MADIT and MUSTT, nonsustained VT and inducible sustained VT during electrophysiologic studies with programmed stimulation was also present. The other trials selected survivors of MI or patients with nonischemic cardiomyopathy based on poor LV function alone. Except for the early trials (MADIT and Coronary Artery Bypass Graft-Patch [CABG-Patch]), patients in the remainder of trials were concomitantly receiving a full range of pharmacologic therapy that could include an ACE inhibitor or ARB, a beta blocker, an aldosterone inhibitor, diuretics, digitalis, and amiodarone (Table I).

Table I lists a variety of features of each study, including the total mortality reduction of ICD therapy compared with conventional medical management alone. In the positive studies, ICD therapy was associated with about one-third to one-half fewer deaths. An even greater reduction in the rate of sudden or arrhythmic deaths occurred with ICD use. In MUSTT[58] and in the DEFibrillator In Non-Ischemic cardiomyopathy Treatment Evaluation (DEFINITE),[60] the rate of cardiac arrest or arrhythmic death was reduced by 72 and 80%, respectively. The Defibrillator In Acute Myocardial Infarction Trial (DINAMIT)[63] also showed a marked decrease (58%) in arrhythmic deaths, although the effect on total mortality was cancelled by a significant unexplained increase in the number of patients who died from nonarrhythmic causes (overall mortality hazard ratio = 1.08, $p = 0.66$).

Beta-blocker use varied widely in these studies, from 18 to 86%, with use lowest in the older trials such as MADIT-I and highest in more recent trials (MADIT-II-70%). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) are two studies that reported a

TABLE I Randomized implantable cardioverter-defibrillator trials in patients with left ventricular dysfunction

	MADIT[56]	MADIT-II[57]	MUSTT[58]	SCD-HeFT[59]	DEFINITE[60]	COMPANION[61]	CABG-Patch[62]	DINAMIT[63]
Number of patients	196	1,232	704	2,521	485	1,520	900	674
Months of follow-up	27	20	39	40	29	16	32	30
NYHA class I or II, %	63	30	63	100	75	83	74	
Mean ejection fraction, %	27	23	30	< 35	21	22	27	28
Etiology, %								
CAD/ICM	100	100	100	53	—	55	100	100
NICM	—	—	—	47	100	45	—	—
Medication, % [a]								
ACE inhibitor	60	68	72	85	84	69	55	95
Beta blocker	26	70	29	69	86	68	18	87
ARB				11	31	21		
Aldosterone antagonist				19	14	55		
Diuretic	53	72	58	82	87	97	57	
Digitalis	58	57	52	70	42		69	
Amiodarone	2	13		0	4		4	
Total mortality reduction, % [b]	54	31	51	23	35	36	NS	NS

[a] In patients receiving ICD.

[b] Compared with control group.

Abbreviations: ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker, CABG-PATCH = Coronary Artery Bypass Graft, CAD = coronary artery disease, COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure, DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation, DINAMIT = Defibrillator in Acute Myocardial Infarction Trial, ICM = ischemic cardiomyopathy, MADIT = Multicenter Automatic Defibrillator Implantation Trial, MUSTT = Multicenter Unsustained Tachycardia Trial, NICM = nonischemic cardiomyopathy, NS = not significant, NYHA = New York Heart Association, SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.
Sources: Refs. 56–63.

synergy between ICD and beta-blocker use. In SCD-HeFT,[59] the survival benefit of ICD therapy was greater for the population of patients receiving concomitant beta blockers (32%) compared with those who did not (8%). Similarly, in COMPANION,[61] a significant reduction in total deaths was demonstrated for patients randomized to ICD therapy who were also taking beta blockers, but not for patients who did not. Of particular note, the proportion of total deaths due to arrhythmia (one-third) in the conventional therapy group in DEFINITE[60] was lower than has ordinarily been reported (one-half) for this population of patients. This disparity may have been due to the comparatively high use of ACE inhibitors and beta blockers (mostly carvedilol) encountered in this trial. Carvedilol is the only beta blocker that has been shown to reduce the risk of death in patients with impaired LV function, both with chronic HF and following acute MI.[4, 48, 64]

Data for the above trials confirm that in patients with an EF < 30–35%, the addition of an ICD can significantly reduce the risk of sudden arrhythmic death and decrease overall mortality; ICDs should be implanted in appropriate patients, but only after optimal medical therapy with beta blockers, ACE inhibitors, and aldosterone antagonists has also been used. The implantation of pacemakers, pacemaker/ICDs, and biventricular pacing devices is often useful for avoiding significant bradycardia secondary to high beta-blocker doses. Thus, patients with such pacing devices can often be treated more aggressively with beta blockers and their medical management can be optimized.

Conclusions

Carvedilol is an adrenergic blocker with antiarrhythmic, anti-ischemic, and antioxidant properties that inhibits alpha- and beta-adrenergic receptors as well as potassium, calcium, and sodium ion channels in cardiomyocytes. It shares many electrophysiologic properties with amiodarone and lacks the QT-prolonging proarrhythmic potential of dofetilide, d-sotalol, or the Class IA antiarrhythmic agents.

Carvedilol treatment decreases mortality in patients with AF and reduced LV function. Carvedilol improves cardioversion success in patients with persistent AF and reduces the occurrence of postoperative AF after cardiac surgery. Carvedilol is also highly effective for ventricular rate control and is clinically useful for AF in the presence of LVD due to chronic HF or an MI.

Clinical trial evidence has demonstrated that carvedilol reduces ventricular ectopy, including total, multifocal, and repetitive PVCs, as well as nonsustained VT in patients with HF due to LVD and in patients with VT and VF post MI. Carvedilol improves the likelihood of survival in patients with LVD due to chronic HF or following MI. In patients receiving opti-

mal pharmacologic therapy with ACE inhibitors, beta blockers, and aldosterone antagonists, the appropriate addition of an ICD further reduces total mortality and sudden cardiac death.

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