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Real-World Long-Term Metabolic and Renal Protective Effects of Combination Therapy of Carvedilol, Statins and Other Antihypertensive Agents with Diet and Exercise in Patients with Hypertension and Hyperlipidemia. A 21-Year Experience in a Private Cardiologist's Practice

Richard E. Katholi[1*], Eugene A. Stormer[2], Yaniel Castro-Torres[3] and Marcella R. Ervin[2]

[1]*Department of Pharmacology, Southern Illinois School of Medicine, USA*
[2]*Prairie Educational and Research Cooperative, USA*
[3]*Hospital Universitario Celestino Hernández Robau, Cuba*

Abstract

Carvedilol is a third generation, fat soluble molecule that combines the properties of a nonspecific beta-blocker and a specific alpha-1 blocker in a ratio of 2:3. Carvedilol also possesses antioxidant properties and has no intrinsic sympathomimetic activity. Carvedilol has been approved for the treatment of Hypertension (HT). Traditional beta-blockers have been shown to worsen insulin resistance, facilitate weight gain and increase triglycerides. Carvedilol in hypertensive patients with Diabetes Mellitus (DM) already receiving renin-angiotensin system blockade has been found during a 6-month trial to have a neutral effect on insulin resistance, weight and triglycerides. In these hypertensive, diabetic patients already receiving renin-angiotensin system blockade, progression to microalbuminuria was less frequent with carvedilol than metoprolol tartrate. These favorable metabolic and renal protective effects suggest that carvedilol is a better choice compared to traditional beta-blockers in the long-term management of high risk patients. This manuscript reports results using a 21-year, real-world experience database from a private cardiologist's practice to determine carvedilol's long-term (5 years) impact on body weight, lipids, risk of developing type 2 DM and preservation of renal function in patients with HT and hyperlipidemia.

Keywords: *hypertension, carvedilol, hyperlipidemia, statins, type 2 diabetes mellitus, chronic kidney disease, creatinine, eGFR, heart rate, magnesium, potassium*

Introduction

Since the release of carvedilol in 1997, there has been much research interest in the use of this beta-blocker. Carvedilol is a third generation, fat soluble molecule that combines the properties of a nonspecific beta-blocker and a specific alpha-1 blocker in a ratio of 2:3. Carvedilol also possesses antioxidant properties and has no intrinsic sympathomimetic activity [1]. Carvedilol has been approved for treatment of NYHA class I, II, III and IV Congestive Heart Failure (CHF) patients and post-myocardial infarction patients, if the patient's Ejection Fraction (EF) is less than 40%. Carvedilol is also approved for the treatment of HT. Diabetes mellitus is an important and independent predictor of cardiovascular morbidity and mortality in patients with HT. Increased sympathetic nervous system activity has been implicated in the pathogenesis of HT and type 2 DM [2]. Traditional beta-blockers have been shown to worsen insulin resistance, facilitate weight gain and increase triglycerides. Carvedilol in hypertensive patients with DM already receiving renin-angiotensin system blockade has been found during a 6-month trial to have a neutral effect on insulin resistance, weight and triglycerides [3]. In this hypertensive, diabetic patients, progression to microalbuminuria was less frequent with carvedilol than metoprolol tartrate. These favorable metabolic and renal protective effects suggest that carvedilol is a better choice compared to traditional beta-blockers in the long-term management of high risk patients. In addition, in patients with renal impairment, dose adjustment of carvedilol is not necessary. While clinical trials have demonstrated the metabolic and renal protective benefits of carvedilol, translating carvedilol's efficacy and usefulness in clinical practice requires understanding of its side effect profile and the importance of dosage in long-term monitoring [3,4]. This manuscript reports results using a 21-year, real-world experience database from a private cardiologist's practice to determine carvedilol's long-term impact on body weight, lipids, risk of developing type 2 DM and preservation of renal function in patients with HT and hyperlipidemia.

Methods

The database was begun in 1997 and concluded at the end of 2018. The study was conducted in accordance with the principles of the Declaration of Helsinki. In 1997, after local ethics committee (Southern Illinois School of Medicine) approval, a computer was purchased and designated for the database. The computer was kept locked in a cabinet and never connected to the internet. The database was password-protected, and over the 21 years, the same three individuals (E.A.S., M.W.K. and D.J.W.), who were employed by Prairie Educational Research Cooperative, independently extracted and entered data each week from clinical

records. Patient data was entered into the database according to HIPAA guidelines. Patients who were referred to a private practice cardiologist and had indication for treatment with carvedilol were entered and followed. All patients gave informed consent for medical information to be used for research studies. Clinical management was based on treatment recommendations and patient indications for followup and testing (i.e., there was no research protocol, and no testing was ordered unless clinically indicated). This report represents a retrospective analysis from a database started and maintained weekly over many years on the long-term effects of therapies in a real-world setting. If a patient when sent for consultation was already on a beta-blocker, they were converted after patient consent to carvedilol as a preferred beta-blocker with metabolic and renal protective benefits. Immediate-release carvedilol was prescribed as every 12 hours to accomplish beta-receptor blockade over each 24-hour period. If sustained-release carvedilol was prescribed, it was prescribed as daily in the morning with food. The goal of carvedilol dosage was to increase the dose every 1-2 weeks until each patient was pharmacologically "beta-blocked" (i.e., resting heart rate in the 60s). Since the average patient in this referral practice lived 80 miles from the cardiologist's office, up-titration of carvedilol dose was often done by telephone. Over the years, carvedilol dose was adjusted based on heart rate. For data analysis on dosage, sustained-release carvedilol patient dosage was converted to immediate-release carvedilol doses. This analysis focused on patients who had HT and had serial lipid profiles and renal function measurements over the years. Besides carvedilol, many hypertensive patients were treated with Angiotensin-Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), dihydropyridine calcium channel blockers, thiazide-type diuretics and aldosterone receptor blockers. Creatinine, potassium and magnesium were monitored periodically, as indicated [5]. Goal for potassium supplementation was to keep the serum potassium between 4 and 5 mEq/L, and goal for magnesium supplementation was to keep the serum magnesium greater than 2 mg/dL. GFR was estimated by the Modification of Diet in Renal Disease (MDRD) 4-component study equation. Nonpharmacological therapy to treat HT included counseling the patient on weight loss strategies combining moderate calorie restriction with regular low resistance exercise. Goal for overweight and obese patients was to lose, at least, 10% of baseline body weight. Goal for systolic blood pressure was 130 mmHg or lower. Systolic blood pressures recorded in the database included resting blood pressures measured in the office and/or taken by the patient at home. Patients were educated on how to measure a resting blood pressure, and home cuffs were often checked for accuracy during office visits. Goals for risk factor modification for patients with hyperlipidemia were an LDL Cholesterol (LDL-C) of less than 100 mg/dL as primary prevention and LDL-C of less than 70 mg/dL as secondary prevention. When measured, lipid profile was drawn after, at least, 12 hours fasting. Evaluation of patients with HT and hyperlipidemia included identifying and treating associated comorbidities, including coronary artery disease, DM, obesity and Chronic Kidney Disease (CKD). Type 2 DM was defined as a hemoglobin A1C greater than 6.5%, CKD was defined as an Estimated Glomerular Filtration Rate (eGFR) less than 60 mL/min/1.73 m^2. The majority of patients were referrals to a cardiologist and managed over the years by both the cardiologist and a primary care provider. Once stable, the patients were seen annually by the cardiologist. Medicines were changed based on updated guideline recommendations. "Age" was the age of the patient when started on carvedilol. Carvedilol dosing information was the last available dose at the time of data analysis. Numerical results are expressed as means ± standard error of the mean. Statistical analysis of changes in weight, blood pressure, lipids and renal function was performed using analysis of variance based on split-plot in time model.

Results

The database was begun in 1997 and concluded at the end of 2018 and has 4,955 patients who were treated with carvedilol. The focus of this research analysis is patients with HT and hyperlipidemia who were managed long-term over the years on carvedilol and other antihypertensive medicines and statins and were encouraged to walk, at least, 30 minutes daily and to lose weight. A total of 1,971 patients were identified with HT and serial lipid profile measurements. On initial Cardiology Clinic visit, 46% were female with an average age of 50±7 years, and 54% were males with an average age of 54±7 years. The initial weight of females ranged between 126 and 425 pounds with a mean weight of 172±9 pounds. The initial weight of males ranged between 158 and 446 pounds with a mean weight of 207±7 pounds. (Table 1) shows population overview of hypertensive patients with hyperlipidemia on initiation of carvedilol therapy. (Table 2) shows final carvedilol dosage, age range and final therapeutic heart rate of patients in sinus rhythm. Seventeen of the 1,971 patients claimed intolerance to carvedilol and were changed to metoprolol succinate, verapamil or diltiazem and excluded from further analysis.

At the time of 5-year analysis, 99% of patients were still on carvedilol, 88% were on a statin, 73% were on ACE inhibitor or ARB, 40% were on amlodipine, 46% were on a mineralocorticoid receptor blocker, and 25% were on a thiazide-type diuretic. Mean systolic blood pressure of patients at 5-year analysis was 126±9 mmHg. The mean weight of females at 5-year analysis was 174±10 pounds, which was not significantly different from the initial weight when carvedilol was started. The mean weight of males at 5-year analysis was 210±11 pounds, which was not statistically significantly different from initial weight when carvedilol was started.

The long-term effects of combination therapy of carvedilol, statins and other antihypertensive agents with diet and exercise on lipid profile in patients with HT was examined as a measurable factor. When patients were started on carvedilol (initial measurement) men had significantly ($P<0.05$) lower HDL Cholesterol (HDL-C), and women had significantly ($P<0.05$) higher triglycerides when comparing men and women (Table 3). After 5 years on combination therapy of carvedilol, statins and other antihypertensive agents with diet and exercise, lipid profile in patients with HT revealed a significant ($P<0.01$) increase in HDL-C in men with no change in women. Triglycerides were mildly decreased after 5 years compared to initial measurements in both men and women. Systolic blood pressures were similar, and heart rates when in sinus rhythm were in the 60s suggesting similar degrees of clinical beta-blocker effect when comparing men and women.

The long-term effects of combination therapy of carvedilol, statin and other antihypertensive agents with diet and exercise on risk of developing type 2 DM in nondiabetic patients with HT was also examined as a measurable factor. After 5 years, a similar number of men (33 of 649) and women (30 of 535) had developed type 2 DM. After adjusting for changes in weight and whether on thiazide-type diuretics and/or statins, carvedilol-treated patients in this database had a significantly ($P<0.05$) lower incidence over 5 years of developing type 2 DM compared to previous reports of similarly matched patients with HT on other beta-blockers [6].

The long-term effect of combination therapy of carvedilol, statins and other antihypertensive agents with diet and exercise on

Table 1: *Baseline characteristics of patients with HT at the initiation of carvedilol therapy*

Population Overview				
	Total Patients	Male	Female	mg/dL
Patients with HT	1,971	1,064	907	
Patients with HT and CAD		904	562	
Patients with HT and DM		415	372	
Patients with HT and CKD		415	317	
Serum creatinine		344 51 12 8	254 51 6 6	1.1-1.9 2.0-2.9 3.0-3.9 Above 4.0

CKD: chronic kidney disease; HT: hypertension

Table 2: *Final dose, age range and final therapeutic heart rates of patients in sinus rhythm with HT treated with carvedilol*

Final Carvedilol Dose in Patients with HT				
Dosage	3.125 mg q.12h	6.25 mg q.12h	12.5 mg q.12h	25 mg q.12h
Number of Patients	453	436	388	339
Age Range (Years)	31-98	33-95	30-91	28-94
Therapeutic Heart Rate (bpm)	63±8	62±7	62±7	61±9

Table 3: *Change in lipids over 5 years in patients with HT on carvedilol*

	Males (n=1,053)		Females (n=898)	
	Initial (mg/dL)	Last (mg/dL)	Initial (mg/dL)	Last (mg/dL)
HDL-C	29±8†	54±6*	51±6	51±5
LDL-C	108±7	94±7	119±7	103±7
TG	177±9	155±8	201±9†	175±8

*P<0.01 comparing initial to last

†P<0.05 comparing males to females

Table 4: *Change in renal function over 5 years in patients with HT and CKD (DM and nondiabetic) on carvedilol.*

	Patients with HT, DM and CKD	Patients with HT and CKD, non-DM
	n=503	n=229
Baseline patient characteristics		
Men, %	53	62
White, %	98	99
Carvedilol, %	99	99
ACE or ARB, %	82	74
Serum creatinine (mg/dL)	1.75	1.73
Outcomes		
Doubling of baseline serum creatinine	45	21
ESRD	31	14
Slope of decreasing GFR, mL/min/1.73 m^2	1.9	1.7

ESRD: End-Stage Renal Disease

preservation of renal function in nondiabetic and type 2 diabetic patients with HT was also examined as a measurable factor (Table 4). Nondiabetic patients with HT and CKD over 5 years had similar decreases in renal function (slope eGFR) comparing carvedilol versus carvedilol plus ACE inhibitor or ARB. In patients with CKD, type 2 DM and HT over 5 years, carvedilol plus ACE inhibitor or ARB showed significantly ($P<0.05$) better preservation of renal function compared to carvedilol without ACE inhibitor or ARB. After adjusting for age and weight, carvedilol-treated patients with CKD and HT, nondiabetic and type 2 diabetic, in this database had a slower decline in renal function (slope eGFR) and significantly ($P<0.05$) lower incidence of requiring dialysis over 5 years compared to previous reports of similarly matched patients with HT and CKD on other beta-blockers [7].

Because of the referral population being from rural farming communities in Central Illinois, subanalysis of African American, Hispanic or Asians could not be done because of small numbers.

Discussion

A review of the Global Burden of Diseases, Injuries and Risk Factors study of 2019 described the global rise in Cardiovascular Disease (CVD) and mortality since 1990 [8]. Total CVD nearly doubled, and CVD deaths increased from 12.1 million in 1990 to 18.6 million in 2019. Approximately 6.1 million deaths were among individuals aged 30 to 70 years. Moreover, CVD was the underlying cause of death among approximately one-third of all deaths globally. Analysis of the Burden of Diseases, Injuries and Risk Factors study also yielded a ranking of modifiable risk factors associated with these concerning trends in CVD and mortality: high systolic blood pressure, dietary risk, high LDL-C, air pollution, high BMI, tobacco smoking, high blood glucose and kidney dysfunction. Thus, HT remains the greatest modifiable risk factor [9].

In the treatment of patients with HT, guidelines for goal of therapy have been developed based on the patient's risk. The Joint National Committee (JNC-6) recommended thiazide-type diuretics or beta-blockers as initial therapy for treating patients with HT in 1997, which is the year carvedilol was released and this database was started [10]. JNC-7 (2003) and JNC-8 (2014) provide further support for the importance of long-term treatment of HT to decrease strokes, heart attacks, renal failure, atrial fibrillation and both CHF with reduced ejection fraction and CHF with preserved ejection fraction [11,12]. While in men the most common predisposing risk factor for heart failure is coronary artery disease, in women, it is HT [13]. In an analysis of data from the Systolic Blood Pressure Interventional Trial (SPRINT), participants who were randomized to the intensive blood pressure group (target systolic blood pressure less than 120 mmHg) had a 38% lower risk of developing CHF and a 26% lower risk of developing new atrial fibrillation than those randomized to the standard blood pressure lowering group (target systolic blood pressure less than 140 mmHg) [14,15]. Our patients' mean systolic blood pressure was 126 mmHg. A post-hoc analysis of SPRINT found that greater time with systolic blood pressure within target range predicted reduced risk of major cardiovascular events independent of traditional cardiovascular risk factors [16]. Thus, time in target range provides incremental value beyond mean systolic blood pressure to population-based HT quality monitoring and clinical trial-based blood pressure interventions. Since most of our patients were seen in the office annually, this report emphasizes the need for patients to monitor blood pressure at home periodically to be certain their blood pressure is well controlled the majority of time under normal living circumstances.

In the long-term management of patients, choice of pharmacological agents has important implications. For example, if a physician starts a beta-blocker, how much weight has the patient gained, has the patient developed type 2 DM, has the patient's triglycerides increased, and how much decline has occurred in renal function over the years? A 6-month trial comparing the beta-blockers carvedilol and metoprolol tartrate in hypertensive, diabetic patients already receiving renin-angiotensin system blockade found a neutral effect in carvedilol-treated patients on weight, insulin resistance and lipids [3]. Development of microalbuminuria was less frequent in carvedilol-treated patients compared with metoprolol tartrate. The alpha-blocking and antioxidant properties of carvedilol are thought to explain these beneficial metabolic and renal protective effects.

The hypothesis tested in this retrospective analysis using a 21-year real-world database from a private cardiology practice was whether carvedilol shows metabolic and renal protective benefits over 5 years in patients with HT.

The use of carvedilol as a preferred beta-blocker in the long-term treatment of patients with HT and the comorbidities of hyperlipidemia, type 2 DM, coronary artery disease and CKD was well tolerated and clinically easy to manage. With the availability of automatic blood pressure-heart rate monitors, most patients can have carvedilol dose up-titrated or adjusted by phone. Using a resting heart rate in the 60s as a guide for maintaining pharmacological beta-blockade appears to be a useful practical approach for long-term antihypertensive therapy with carvedilol. Once a heart rate in the 60s is achieved, heart rate measurement on followup visits reflects medication adherence.

Blood pressure is commonly monitored by using office and/or self-measured home readings. The 24-hour ambulatory blood pressure monitoring is considered as the gold-standard noninvasive method, but, due to its high cost and inconvenience for patients, it is only indicated in cases of suspicion for white coat or masked HT, noncompliance, drug-resistant or hypotensive symptoms while on antihypertensive therapy [12].

A consensus statement has recently been issued that offers guidance on personalized exercise programs as part of an overall management approach for patients with or at risk of hypertension [17]. In patients with HT, aerobic training is recommended as a first-line exercise therapy, and low- to moderate-intensity resistance training, both dynamic and isometric, as second-line therapy. The consensus statement explains how valuable aerobic exercise is with expected range of blood pressure lowering in hypertensive patients from -4.9 to -12 mmHg systolic and -3.4 to -5.8 mmHg diastolic. The consensus statement noted that further research is needed to determine whether men and women respond to exercise differently and whether there should be a different exercise prescription based on ethnicity.

Evidence in Support of Combination Therapy of Carvedilol, Statins and Other Antihypertensive Agents with Diet and Exercise for Long-term Treatment of Hypertension in Patients with Hyperlipidemia

Hyperlipidemia is an important independent predictor of cardiovascular morbidity and mortality in patients with HT. An often referenced study on the effects of antihypertensive medications on plasma lipids in 1,292 men compared hydrochlorothiazide, atenolol, captopril, clonidine, diltiazem and prazosin over one year [18]. Patients with total cholesterol over 300 mg/dL, patients with type 2 DM requiring insulin and patients with symptomatic coronary artery disease were excluded. In contrast, our retrospective analysis of real-world data of patients with HT and hyperlipidemia included women and men, nondiabetic and diabetic, with no exclusions.

Beta-blockers are a heterogeneous class of antihypertensive medications. The effect of beta-blockers on serum lipids varies with their characteristics and may be more prominent among smokers [19]. Both cardioselective and non-cardioselective beta-blockers, such as atenolol, metoprolol and propranolol, lead to a fairly modest increase in triglycerides (20-40%), a decrease in HDL-C (approximately 10%) and little effect on total cholesterol or LDL-C.

Carvedilol has a more favorable metabolic profile because of its combined nonselective beta-blockade and alpha-1 blockade and, thus, less of a deleterious effect on triglyceride levels than metoprolol or atenolol. The selective alpha-1 adrenergic blockers, specifically prazosin, doxazosin and terazosin, improve lipoprotein lipase activity and consistently demonstrate favorable effects on plasma lipids [20]. The drugs lower total cholesterol by approximately 3-5%, reduce triglyceride levels by 3-4% and mildly raise HDL-C. High-dose thiazide diuretics increase triglycerides 5-10% and LDL 5-10%. The hyperlipidemic effects of thiazides are dose-dependent [21]. Little or no effect on metabolism is seen with a daily dose of 12.5 mg of hydrochlorothiazide, and the antihypertensive effect is nearly as great as the higher doses. The effects of combination antihypertensive therapy on lipids in most cases appears to reflect the sum of the effects of the individual medications.

A focus of interest in this retrospective analysis was to determine carvedilol's long-term effect on HDL-C and triglycerides given its alpha-1 adrenergic receptor blocker and antioxidant properties. Men and women were analyzed separately because it has been shown that exercise increases HDL-C more in men than women. Typically, beta-blockers cause a decrease in HDL-C and an increase in triglycerides. In men with baseline HDL-C of less than 35 mg/dL, 12 weeks of exercise increased HDL-C similarly whether on nonselective beta-blocker or not [22]. In the GEMINI trial, the effects of carvedilol versus metoprolol tartrate on lipids were compared over 35 weeks [3]. Metoprolol tartrate increased triglycerides by 13% ($P<0.001$) whereas carvedilol had no effect; no treatment difference for LDL-C or HDL-C was noted between groups. Of note, in GEMINI, men and women were not analyzed separately. Our results reveal a significant increase in HDL-C in men over 5 years of therapy with the combination of carvedilol, statins and other antihypertensive agents with diet and exercise. The mechanism for an increase in HDL-C is increased lipoprotein lipase activity (i.e., the enzyme moves from the interstitial to endothelial capillary space). Statins improve endothelial function lowering blood pressure and increasing lipoprotein activity and consistently demonstrate favorable effects on plasma lipids. At 6 months, 40 mg of pravastatin has been shown to modestly reduce systolic and diastolic blood pressure by 2.2 and 2.4 mmHg respectively [23]. In contrast, decreased lipoprotein lipase activity is seen secondary to increased insulin resistance. Further, chronic kidney disease causes a decreased synthesis in lipoprotein lipase and retention of other circulating inhibitors of lipoprotein lipase.

In general, experts do not consider effect on lipid profile when choosing antihypertensive therapy. Experts would not avoid using thiazide or older beta-blockers in patients with dyslipidemia, if otherwise indicated, and similarly would not discontinue thiazide or beta-blocker in a patient just to improve the lipid profile [24]. New data from carvedilol studies may change that concept. Some medications, such as first and second generation beta-blockers, are associated with a decrease in HDL-C and increased triglycerides. Past recommendations do not stop these drugs if they are important to the treatment of other medical conditions. HDL-C is a biomarker and virtually associated with an increased risk of cardiovascular disease events. However, low levels of HDL-C have not been established as causative in this increase in risk. Low HDL-C is also felt to be a precursor of the metabolic syndrome or type 2 DM sometimes by many years.

The HDL-C particle's complexity as a mediator of cardiovascular risk was recently examined in a case-control study pointing to its anti-inflammatory capacity as potentially another addition to standard CV risk assessments [25]. A measure of HDL-C anti-inflammatory capacity in a prospective community cohort was inversely related to future CV risk independent of HDL-C's role in cholesterol transport, total cholesterol and other established biomarkers, as well as any lipid-modifying therapy. The current analysis identified an impaired HDL-C anti-inflammatory capacity as a functional metric prospectively associated with increased cardiovascular risk in the general population.

The recommendation is not to specifically target low HDL-C with drug therapy. There is no firm evidence of benefit from drug therapy to target low HDL-C. Evidence does not support a beneficial clinical impact with efforts to raise HDL-C. A 2009 meta-analysis of 108 randomized trials involving nearly 300,000 patients at risk for cardiovascular events found no association between treatment-induced increases in HDL-C with risk ratios for coronary heart disease deaths, coronary heart disease events or total deaths after adjustment for changes in LDL-C [26]. Exercise, weight loss in overweight subjects, smoking cessation and substitution of monosaturated for saturated fatty acids raise HDL-C. As multiple health benefits are associated with each of these lifestyle changes, these lifestyle changes are recommended in patients with low HDL-C. Irrespective of HDL-C level, all adults should have an LDL-C target established and a plan to reach that target in place.

Evidence in Support of Combination Therapy of Carvedilol, Statins and Other Antihypertensive Agents with Diet and Exercise for Decreasing the Risk of Developing Type 2 Diabetes Mellitus in Nondiabetic Patients with Hypertension

Type 2 DM and HT represent two common conditions worldwide. They increase the risk for the development of cardiovascular disease with adverse clinical outcomes, including disabilities and mortality. In the absence of cardiac comorbidities, traditional beta-blockers, which increase Insulin Resistance (IR) do not constitute an initial choice for the treatment of HT. However, carvedilol, which is a third generation beta-blocker, in some studies has demonstrated efficacy to reduce plasma glucose levels and IR in patients with and without type 2 DM [3,4]. The reduction in blood pressure and fall in plasma glucose concentration seen with carvedilol is likely due to an attenuation in sympathetic nervous system activity [2]. Thus, the benefit of lowering a patient's blood pressure with carvedilol would be complemented with an IR reduction decreasing significantly the risk of future metabolic complications.

The use of statins is associated with reduced cardiovascular risk in studies of primary and secondary prevention, and the reduction is directly proportional to the reduction in LDL-C. However, in both observational studies and randomized trials, statin use has been associated with increased risk of diabetes, particularly in a population at high risk for type 2 DM [27,28]. Additional studies are needed to explore the mechanism for statin-associated diabetes, but it is accompanied by a decline in insulin secretion. Thus, patients at high risk for type 2 DM should be monitored during statin therapy. Since the benefit of cardiovascular risk reduction prevails even in statin-associated diabetic patients, there is no evidence to date that this risk should change the recommendation

of starting statin therapy when indicated based on guidelines [29].

ACE inhibitors and ARBs tend to decrease the risk of type 2 DM in patients with HT. Dihydropyridine calcium channel blockers and mineralocorticoid receptor blockers have a neutral effect on risk of type 2 DM in patients with HT. If thiazide-type diuretics are used in lower doses and serum potassium is kept in the 4-5 mEq/L range and serum magnesium is kept above 2 mg/dL, the risk of developing hyperglycemia from thiazide-type diuretics is low [30]. Both weight loss and regular low resistance exercise, such as walking 30 minutes a day, decrease the risk of patients with HT of developing type 2 DM [31].

Evidence in Support of Combination Therapy of Carvedilol, Statins and Other Antihypertensive Agents with Diet and Exercise on Preservation of Renal Function in Nondiabetic and Type 2 Diabetic Patients with Hypertension

Measures to reduce the risk of worsening renal function include avoiding concomitant nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, limiting exposure to contrast medium, avoidance of volume depletion and counseling patients not to smoke.

Hypertension is a leading cause of end-stage renal disease [32]. ACE inhibitors or ARBs are highly effective in slowing the progression of renal disease due to type 1 DM, and there is much evidence for their efficacy in type 2 DM. There is also strong and consistent evidence of the beneficial effect of ACE inhibitors or ARBs in nondiabetic kidney disease that are similar to their effects in diabetic renal disease [7,33,34]. Current guidelines recommend ACE inhibitor or ARB therapy in most patients with chronic kidney disease. ACE inhibitors or ARBs appear to be more effective than traditional beta-blockers or dihydropyridine calcium channel blockers in slowing GFR decline.

The Glycemic Effects in Diabetes Mellitus, Carvedilol-Metoprolol Comparison in Hypertension (GEMINI) trial excluded patients with kidney disease having a serum creatinine greater than 2.5 mg/dL and did not report eGFR [3].

However, post-hoc analysis of the GEMINI trial demonstrated that despite similar levels of blood pressure in the presence of renin-angiotensin system blockade, carvedilol over 6 months retarded development of new onset microalbuminuria in patients with type 2 DM to a greater extent than metoprolol tartrate. Of note, in experimental studies, carvedilol has been shown to preserve kidney structure and function [35,36]. The renal protective effect is thought to be, at least, in part, attributable to the antioxidant activity of carvedilol [37]. In patients with renal impairment, dose adjustment of carvedilol is not necessary.

The accuracy and precision of longitudinal changes in eGFR are imperfect and not necessarily equivalent to longitudinal changes in measured or true GFR [38]. Studies of the natural history of GFR decline frequently involve clinical trial participants. Trial participants tend to have a better prognosis than those not enrolled in trials, and, therefore, these studies may provide a lower-range estimate of GFR decline compared with the general population. The average annual rate of decline in eGFR due to age-related senescence of the kidney in otherwise healthy individuals is 0.5 to 1 mL/min/1.73 m2 per year. In type 2 DM patients, the rate of eGFR decline varies, but it is typically more rapid, such as a loss of more than 3 mL/min/1.73 m2 per year, particularly with a long duration of DM, such as >10 years, severely increased albuminuria or low baseline eGFR of <60 mL/min/1.73 m2.

Registry data from Denmark demonstrate a 4-5 year delay to end-stage kidney failure in those individuals receiving renin-angiotensin system inhibitors [39].

A multicenter, double-blind, randomized, controlled study of 1448 patients with type 2 DM, a urinary albumin-to-creatinine ratio of, at least, 300 and an eGFR of 30.0-89.9 mL/min/1.73 m2 found during a median followup of 2.2 years a twofold increased risk of hyperkalemia and acute kidney injury with combination ACE inhibitor and ARB therapy versus monotherapy with losartan [40]. No significant difference was seen between the groups in the renal endpoint of first occurrence of a decline in eGFR or ESRD, mortality or rate of cardiovascular events. We found no evidence of hyperkalemia or acute kidney injury combining ACE inhibitor or ARB with carvedilol in patients with diabetic nephropathy over 5-year followup.

Our results demonstrate the long-term protective benefit of combination therapy of carvedilol, statins and other antihypertensive agents with diet and exercise on preservation of renal function in nondiabetic and type 2 diabetic patients with HT and CKD. Many studies demonstrate that in patients with HT and CKD receiving renin-angiotensin system inhibitors is more effective than traditional beta-blockers in slowing GFR decline. Our 5-year data suggests that carvedilol appears to be more effective in patients with HT and CKD in slowing eGFR decline than traditional beta-blockers [32]. In addition, carvedilol is easily administered when given to hypertensive patients already receiving renin-angiotensin system blockade.

Strengths of the Data

These data give insight into carvedilol's use combined with statins and other antihypertensive agents with weight loss and exercise in patients with HT in a real-world setting with long-term followup. These data reflect the importance of continuity of care to accomplish therapeutic goals for patients with HT. These data demonstrate the long-term benefit of carvedilol in high risk patients with multiple comorbidities of hyperlipidemia, coronary artery disease, type 2 DM and CKD. These data were extracted weekly by chart reviewers, and there was no stated hypothesis, thus, decreasing recall bias.

Limitations of the Data

This is a database and not a clinical trial, so available data for analysis are limited to clinical decisions. Fasting lipid profiles, creatinine, potassium and magnesium were measured at local hospitals and not run in a core lab. When the database was started, patients had paper charts; later, patient information was in electronic medical records. Both represent challenges for chart reviewers. In retrospect, some data were not thought of in 1997 when the database was started and, thus, not collected, such as microalbuminuria or whether the patient had obstructive sleep apnea. These data were obtained from a predominantly rural white population living in Central Illinois. Given the homogeneity of this population, it may not reflect clinical responses in African American, Hispanic or Asian populations. However, despite the homogeneity, this current study confirms and expands previous data on patients with HT, hyperlipidemia, type 2 DM and CKD. While the number of patients examined in this study is somewhat small, the duration of data retrieval allows for long-term clinical consequences of patients with HT to be defined further.

Summary and Conclusions

Our retrospective analysis from a 21-year real-world experience database from a private cardiologist's practice reveals carvedilol's long-term benefits on body weight, lipids, risk of developing type 2 DM and preservation of renal function in patients with HT and hyperlipidemia. The use of carvedilol as a preferred beta-blocker in the long-term treatment of patients with HT and comorbidities

of hyperlipidemia, DM, coronary artery disease and CKD was well tolerated. Carvedilol was clinically easy to manage using a resting heart rate in the 60s as a guide for maintaining pharmacological beta-blockade. Our retrospective analysis from a database resulted in similar patient profiles to other clinical trials but did not allow for assessing quality of life, cardiovascular events or mortality in the treatment of patients with HT. The hypothesis tested in this retrospective analysis was whether carvedilol as the preferred beta-blocker combined with other guideline-directed therapies shows long-term metabolic and renal protective benefits. We found that carvedilol can be used successfully in patients with HT irrespective of age and sex with significant long-term improvement in lipid profile, lower risk of developing type 2 DM and preservation of renal function compared to traditional beta-blockers. Findings from our 5-year analysis confirms and extends previous studies on carvedilol's beneficial effects. Thus, carvedilol therapy results in improved cardiovascular risk factors. These results provide support for the concept that choice of pharmacological agents has important implications in the long-term management of patients. Our long-term findings demonstrate that carvedilol's unique pharmacological properties give long-term metabolic and renal protective benefits to patients with HT.

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***Correspondence:** Richard E. Katholi, M.D, Prairie Cardiovascular Consultants, Ltd., P.O. Box 19420, Springfield, IL 62794-9420, USA, E-mail: rkatholi@aol.com

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