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Is Real World Use of Carvedilol in Patients with HFrEF Consistent with Clinical Trial Data? A 21-Year Experience in a Private Cardiologist's Practice

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Abstract

Carvedilol has been approved for treatment of New York Heart Association (NYHA) Class I, II, III and IV patients and post-Myocardial Infarction (MI) patients, if the patient's Ejection Fraction (EF) is less than 40% because this third-generation beta-blocker demonstrated a decrease in mortality. While clinical trials demonstrated the survival benefits of carvedilol, translating carvedilol's efficacy and usefulness in clinical practice requires understanding of its side effect profile and the importance of dosage and long-term monitoring.A database on use of carvedilol in a private cardiologist's practice was begun in 1997 and concluded at the end of 2018.We report analysis of 642 patients with HFrEF. Initial EF's ranged between 8 and 47% with mean EF 32 ± 6%. The average age of the patient when started on carvedilol was 69 ± 7 years. Only 7 patients were changed to metoprolol succinate because of adverse side effects. After up-titration of carvedilol, the average resting heart rate was 61 ± 8 beats per minute. Two hundred and forty patients with HFrEF on carvedilol for greater than 5 years had a significant mean increase in EF of 5.5 ± 8% ($p < 0.05$). Two hundred of the patients with HFrEF also had or developed type 2 diabetes and chronic kidney disease during followup. Thirty-one percent of these patients with type 2 diabetes and chronic kidney disease lived longer than 10 years. Carvedilol remains a well-tolerated beta-blocker which demonstrates long-term benefits in a real-world setting.

Keywords: *Carvedilol, HFrEF, Type 2 diabetes, Chronic kidney disease, Ejection fraction, Mortality, Creatinine, eGFR, Heart rate*

Introduction

Since the release of carvedilol in 1997, which demonstrated a decrease in mortality in the treatment of patients with congestive heart failure with reduced ejection fraction (HFrEF), there has been much research interest in the use of this unique beta-blocker [1-4]. The beneficial effect of carvedilol on survival was found in a decrease in the risk of sudden death as well as a decrease in the risk of death from progressive heart failure. Carvedilol is a third-generation fat soluble beta-blocker that has $beta_1$-, $beta_2$- and $alpha_1$-blocking properties and also has strong antioxidant effects [5]. Carvedilol has no intrinsic sympathomimetic activity. Carvedilol has been approved for treatment of NYHA Class I, II, III and IV patients and post-MI patients, if the patient's EF is less than 40% [6]. Carvedilol is also approved for the treatment of hypertension. While clinical trials demonstrated the survival benefits of carvedilol, translating carvedilol's efficacy and usefulness in clinical practice requires understanding of its side effect profile and the importance of dosage and long-term monitoring.

Methods

A 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 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, extracted and entered data each week from clinical records. Patients who were referred to a private practice cardiologist and had indication for treatment with carvedilol were entered and followed. Clinical management was based on treatment guidelines and patient indications for followup and testing (i.e., there was no research protocol, and no testing was ordered unless clinically indicated). This database represents a prospective-retrospective study (i.e., prospectively

started a database and maintained it weekly over the years with a real-world setting). 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 2-4 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 but never discontinued. For data analysis on dosage, sustained-release carvedilol patient dosage was converted to immediate-release carvedilol doses. Besides carvedilol, HFrEF patients were treated with Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARB), isosorbide dinitrate/hydralazine or sacubitril/valsartan for afterload. If symptomatic hypotension occurred during up-titration of carvedilol, the dose of afterload was decreased to accomplish a "beta-blocking" goal of carvedilol. HFrEF patients with New York Heart Association Class II-IV were also treated with aldosterone receptor blockers (spironolactone or plans to eventually analyze the long-term benefits of carvedilol in eplerenone). Loop diuretics were used to relieve symptoms. Digital is was used to relieve symptoms and for ventricular rate control in HFrEF patients with atrial fibrillation after beta-blocker therapy. Ejection fractions for data entry were from echocardiograms or Left Ventricular (LV) angiograms. Ejection fractions measured during nuclear stress testing tend to be lower, and so EFs from nuclear stress testing were not used, and MUGA scans were rarely ordered. For this analysis, HFrEF was defined as patients with EF less than 50%. Type 2 diabetes mellitus was defined as hemoglobin A1C greater than 6.5%. Chronic kidney disease was defined as 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, patients were seen annually by the cardiologist. Medicines were changed based on updated guidelines. Age was the age of the patient when carvedilol was started. 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 the EF data was performed using analysis of variance based on a split-plot in time model.

Population Overview						
	Total Patients	**Male**	**Female**	**EF%**	**mg/dL**	**Age (years)**
Patients with HFrEF	642	385	257			
Initial EF	2			0-10		
	11			11-15		
	53			16-20		
	74			21-25		
	121			26-30		
	95			31-35		
	124			36-40		
	79			41-45		
	83			46-50		
Patients with HFrEF and diabetes mellitus	348	205	143			
Patients with HFrEF, diabetes mellitus and chronic kidney disease	200	124	76			
Serum creatinine	118				1.4-1.9	
	65				2.0-2.9	
	13				3.0-3.9	
	4				Above 4.0	
Mean age at carvedilol start						69 ± 7

Table 1. Baseline characteristics of patients with HFrEF at the initiation of carvedilol therapy.

Final Carvedilol Dose in HFrEF Patients					
Dosage	1/2 of 3.125 mg q.12h	3.125 mg q.12h	6.25 mg q.12h	12.5 mg q.12h	25 mg q.12h
Number of Patients	2	176	176	155	126
Age Range (years)	49-84	48-96	34-95	39-94	35-99
Therapeutic Heart Rate	62 ± 4	62 ± 8	62 ± 7	62 ± 9	59 ± 9

Table 2. Final dose, age range and final therapeutic heart rates of patients with HFrEF treated with carvedilol.

Change in Ejection Fraction (EF) Over Time on Carvedilol 154 Patients Showed Increased EF	
Ejection Fraction	Number of Patients
50% or more	2
40% or more	4
30% or more	10
20% or more	21
10% or more	63
Between 1-9%	54

Table 3. Variation in improvement in EF in HFrEF patients on carvedilol for greater than 5 years.

Trial	Baseline EF	Design	Final Dose	Duration	Decrease in Mortality Risk
US CARVEDILOL n = 696	23 ± 7%	vs placebo	22.5 mg q.12h	6.5 m median	65%
COMET n = 1511	26 ± 7%	vs metoprolol	20.9 mg q.12h	58 m mean	5.7%
CAPRICORN n = 975	33 ± 6%	vs placebo	74% on 25 mg q.12h	15 m mean	23%
COPERNICUS n = 1156	20 ± 4%	vs placebo	18.5 mg q.12h	10.4 m mean	35%

Table 4. Landmark carvedilol trials which resulted in approval for treatment of NYHA Class I, II, III and IV and post-MI patients if the patient's EF is less than 40%.

Results

The database was begun in 1997 and concluded at the end of 2018 and has 4,955 patients who had indications for treatment with carvedilol. The focus of this research analysis is patients with HFrEF who were started on carvedilol and managed long-term over the years. A total of 977 patients were diagnosed with congestive heart failure; of these patients, 642 or 66% (385 males and 257 females) had EF's less than 50% at the initiation of carvedilol. Seventy-three percent of these patients had ischemic cardiomyopathy and underwent revascularization as indicated. Table 1 shows population overview in HFrEF patients with EFs at the initiation of carvedilol therapy. Mean baseline EF for the 642 patients was 32 ± 6%. Table 2 shows final carvedilol dosage, age ranges and final therapeutic heart rates. There did not appear to be a correlation between carvedilol dosage needed to achieve a

resting heart rate in the 60s and a patient's age. The mean systolic blood pressure when at final carvedilol dosage was 125 ± 7 mmHg. Of 642 patients, 46 patients only had an initial EF and, thus, were excluded in the analysis of change in EF. Seven of the 642 patients claimed intolerance to carvedilol and were changed to metoprolol succinate and excluded from further analysis. To examine the long-term effects of carvedilol, change in EF was analyzed in patients who were on carvedilol for greater than 5 years. Table 3 shows a subgroup of 154 patients with long-term increased EF with variation in improvement between 1% to greater than 50%. There was a significant mean increase in EF in these 154 patients of 12 ± 7% ($p < 0.01$). Another group of 12 patients followed on carvedilol for greater than 5 years showed no change in EF. A third subgroup of 74 patients' followup on carvedilol for greater than 5 years eventually showed a decrease in EF varying between 1 and 21%.There was a significant mean decrease in EF in these 74 patients of 7 ± 5% ($p < 0.01$) and often found after patients had suffered an acute MI or developed left bundle branch block. In summary, averaging the 3 subgroups totaling 240 HFrEF patients on carvedilol for greater than 5 years had an overall mean significant increase in EF of 5.5 ± 8% ($p < 0.05$). Heart rate in these three groups were in the 60s suggesting similar degrees of clinical beta-blocker effect. Presently, 99% of patients are on carvedilol, 72% are on ACE inhibitor, ARB or sacubitril/valsartan and 55% on a mineralocorticoid receptor blocker. Similar improvements in EF were seen comparing males versus females or nondiabetic versus diabetic patients or patients with ischemic versus nonischemic cardiomyopathy. Because of the referral population being from small rural farming communities in Central Illinois, subanalysis of African-Americans or Hispanics could not be done because of small numbers. Because of more recent approval and small numbers, interaction of carvedilol and sacubitril/valsartan could not be analyzed.

Over the years, 200 of the patients with HFrEF had or developed type 2 diabetes and chronic kidney disease. This subgroup was analyzed for survival. Thirty-one percent of this subgroup lived greater than 10 years.

Discussion

Long-term therapy with an evidence-based beta-blocker improves symptoms and clinical outcomes in patients with HFrEF [1-4,7,8]. Carvedilol, metoprolol succinate and bisoprolol have been shown to reduce the rates of hospitalization and death in patients with HFrEF. Bisoprolol is not approved by the FDA for treatment of heart failure. Unlike metoprolol and bisoprolol, carvedilol blocks both $alpha_1$ and $beta_2$ adrenergic receptors, reduces cardiac norepinephrine levels and does not elicit up-regulation of cardiac beta-receptors. Furthermore, unlike other beta blockers, carvedilol has potent antioxidant effects which may protect against the continuing loss of cardiac myocytes that characterize the progression of heart failure [5]. Beta-blocker therapy for patients with HFrEF should be started early at low dosage and gradually increased to the highest tolerated dose [6]. Full clinical benefits may not occur for 3-6 months or longer, and transient worsening of symptoms can occur during dose increases.

As shown in Table 4, the initial carvedilol trials' primary endpoint was decrease in mortality risk [1-4]. When this endpoint was accomplished, the trial was concluded, resulting in trials of varying duration (6.5 months medium to 58 months mean). The final dosage of carvedilol was reported but often not mean heart rate. Also, these initial trials did not report change in EF. Comparing this real-world carvedilol database to the landmark carvedilol trials, differences include older patients (69 ± 7 versus 62 ± 12 years), more patients with diabetes (54% versus 21-24%) and longer duration of followup.

As a clinical guide to achieving beneficial dosage in the patients in this referral practice, a heart rate in the 60s was used since up-titration was often done by phone because the average patient lived 80 miles from the cardiology clinic. Guidelines recommend that patients with HFrEF have evidence-based medical therapy titrated to target doses derived from clinical trials as tolerated. In a contemporary U.S. registry, most eligible HFrEF patients did not receive target doses of evidence-based beta-blocker at any point during followup, and few patients had doses increased over time [9,10]. In this real-world experience, these patients with HFrEF had carvedilol up-titrated because it was the goal of a single cardiologist committed to long-term follow up of his patients. With availability of automatic blood pressure-heart rate monitors, most patients can be up-titrated with evidence-based beta-blockers by phone. Using resting heart rate in the 60s as a guide for achieving pharmacological beta-blockade appears to be a useful practical approach for managing patients with HFrEF.

Evidence-based beta-blocker therapy benefits may be mediated, in part, by heart rate lowering. Heart rate reduction is a potential therapeutic target in patients with HFrEF since an elevated heart rate is associated with worse clinical outcomes [11,12]. While the relative contribution of increased heart rate versus underlying neurohormonal abnormalities is difficult to determine, the beneficial effects of ivabradine, an agent that acts solely by decreasing heart rate, suggest that an elevated heart rate per se contributes to an adverse outcome in patients with HFrEF [13]. Possible detrimental effects of elevated heart rate include heart rate-related increase in myocardial oxygen consumption and decrease in myocardial perfusion.

Initial EF determines therapy in heart failure patients, but information is scarce about incident, determinants and prognostic implications of EF over time [14]. Having been used in clinical trials of heart failure therapy, decreased Left Ventricular Ejection Fraction (LVEF) is the deciding factor for initiating guideline-directed medical therapy for patients with HFrEF. Together with increased LV volumes, falling EF identifies pathological LV remodeling, a deleterious process that represents a target for guideline-directed medical therapy and device therapy that decreases hospitalizations and saves lives in patients with HFrEF.

In general, when patients are initially diagnosed with congestive heart failure, 50% have HFpEF and 50% have HFrEF. In this database of a single cardiologist in private practice, 66% of patients referred for congestive heart failure had HFrEF. This may reflect primary care physician request for assistance in guideline-directed pharmacological and device management and followup in patients with HFrEF. Present guidelines strongly recommend treating patients with HFrEF with multiple medications proven to improve clinical outcome as well as survival [15]. Use of these medications require proper dosing to achieve results, as found in carefully performed multicenter trials

[16]. Patients must be "beta-blocked" with evidence-based beta-blockers, afterload must be advanced as tolerated, and renal function, potassium and magnesium must be monitored. After achieving beta-blockade, some HFrEF patients have a low blood pressure which limits advancing afterload. Of note, sacubitril/valsartan has shown efficiency at lower than target doses in patients with HFrEF [17]. If patients cannot tolerate blockade of the renin-angiotensin system, carvedilol alone has been shown to attenuate pathological remodeling [18].

As shown in clinical trials, improvement in EF to beta-blocker therapy with carvedilol occurs over 3 to 6 months. The Multicenter Oral Carvedilol Heart Failure Assessment (n = 261) demonstrated improved EF with higher doses of carvedilol increasing to 8% at 6 months [19]. Meta-analysis of 19 randomized control trials of carvedilol (n = 668) reported 7% increase of EF after an average of 8.3 months of treatment [20]. The Australia/New Zealand trial (n = 207) reported an increase of EF of 5.3% after 12 months [21]. The overall improvement in EF seen in this real-world setting using carvedilol for greater than 5 years was 5.5%.Analyzed by subgroups, after greater than 5 years of carvedilol, 154 patients showed improved EF of 12%, 12 patients showed no change, and 74 patients showed decrease in EF of 7%.The subgroup with a 12% improvement in EF likely is due to coronary revascularization and/or duration of carvedilol therapy. When patients' EF decreased, there was often a reason, such as acute MI or the development of left bundle branch block. When patients' EF stayed the same or decreased somewhat, it was thought that beta-blocker therapy with carvedilol delayed or attenuated pathological LV remodeling.

Both nonselective and traditional beta-blockers have been shown to increase insulin resistance, facilitate weight gain of approximately 1 kilogram per six months and worsen hypertriglyceridemia by approximately 13%. In contrast, carvedilol in hypertensive, diabetic patients had been found to have a neutral effect on insulin resistance, weight and triglycerides [22]. This favorable metabolic profile also suggests that carvedilol is a better choice compared to metoprolol succinate or bisoprolol in HFrEF patients who also have type 2 diabetes mellitus.

Management of patients with HFrEF is more challenging if the patients also have chronic kidney disease [23-25]. Of note, carvedilol, metoprolol succinate and bisoprolol are metabolized by the liver and, thus, require no dosage adjustment in patients with chronic kidney disease. Patients with HFrEF should receive beta-blocker therapy even with moderate or moderately severe renal dysfunction. Initial beta-blocker (cardioselective or nonselective) therapy in patients with HFrEF causes increased renovascular resistance due to unopposed $alpha_1$-mediated vasoconstriction [26]. In contrast, renovascular resistance is maintained or decreased during initiation of therapy with carvedilol, which blocks $alpha_1$ receptors as well as $beta_1$ and $beta_2$ receptors [27].This gives insight into the contribution of renal sympathetic efferent nerve activity to heart failure but likely does not explain the possible carvedilol mortality benefits compared to metoprolol tartrate. Increased $alpha_1$ activity causes peripheral and renal vasoconstriction and myocardial hypertrophy. However, it is unlikely that carvedilol's $alpha_1$ adrenergic-blocking property is important in the long-term treatment of HFrEF. Pure $alpha_1$ antagonists have not been associated with favorable effects on either the incidence of heart failure or its outcome. There are also important data comparing the effects of metoprolol versus carvedilol in systemic and cardiac norepinephrine spillover demonstrating that carvedilol, but not metoprolol, decreased both measures without changes in muscle sympathetic nerve activity indicating that the effect may be due to blocking peripheral prejunctional beta-adrenergic receptors [28]. In addition, there are data showing the development of tolerance to the peripheral and renal hemodynamic $alpha_1$-mediated effects of carvedilol in patients with congestive heart failure. However, carvedilol appears to have renal protective properties in patients with chronic HFrEF as evidenced by increases in GFR. The improvement in GFR with carvedilol is independent of the improvement in LVEF. Proposed renal protective mechanisms of carvedilol include antagonizing prejunctional beta-adrenergic receptors, which facilitate renal neural norepinephrine release. Carvedilol has also been shown to reduce urinary albumin excretion and expression of profibrotic factors, such as renal tissue growth factor-beta, likely due to its antioxidant properties [22,29].

Strengths of these data

These data give insight into carvedilol's use and benefit in a robust number of patients in the real-world setting with long-term followup. These data reflect the importance of continuity of care to accomplish therapeutic goals as recommended in guidelines for patients with HFrEF. These data demonstrate the long-term benefit of carvedilol in high risk patients with multiple comorbidities of HFrEF, type 2 diabetes mellitus and chronic kidney disease. These data were extracted weekly by chart reviewers, and there was no stated hypothesis, thus, decreasing recall bias.

Limitations of these Data

This is a database and not a clinical trial, and so available data for analysis is limited to clinical decisions. 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 collected because it was not thought of 21 years ago when the database was started, such as rates of hospitalization or presence of iron deficiency.

Summary and Conclusions

Carvedilol can be used successfully in patients with HFrEF irrespective of age and sex with significant long-term clinical benefit in the real-world setting. As shown in clinical trials, starting this evidence-based beta-blocker should not be delayed, beneficial results require increasing the dose of carvedilol until patients are "beta-blocked," meaning a resting heart rate in the 60s, and therapy should not be discontinued. An increase in LVEF and a decrease in LV dimensions suggest a sustained improvement in intrinsic myocardial function. This 21-year database found that most patients tolerate carvedilol with long-term benefit, patients who cannot tolerate ACE or ARB benefit on carvedilol alone, and women respond similar to men. This

long-term database demonstrates that effects of carvedilol on LV systolic function were maintained for years from the start of treatment, with no apparent loss of the initial improvement unless factors, such as MI or left bundle branch block, occurred.

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