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Using A 21-Year Real-World Database from a Private Cardiologist's Practice to Test the Hypothesis that Combining Pharmacological Therapies (Carvedilol, Spironolactone and Statins) with Weight Loss May Benefit Patients with HFpEF

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Abstract

Heart Failure with preserved Ejection Fraction (HFpEF) is a clinical syndrome in which patients have symptoms of Heart Failure (HF), such as dyspnea and fatigue, a Left Ventricular Ejection Fraction (LVEF) ≥ 50% and evidence of cardiac dysfunction as a cause of symptoms, such as abnormal Left Ventricular (LV) diastolic dysfunction with elevated filling pressures. Besides LV diastolic dysfunction, recent investigations suggest a more complex and heterogeneous pathophysiology, including systolic reserve abnormalities, chronotropic incompetence, stiffening of ventricular tissue, atrial dysfunction, secondary Pulmonary Arterial Hypertension (PAH), impaired vasodilatation and endothelial dysfunction. Unlike Heart Failure with Reduced Ejection Fraction (HFrEF), clinical trials over the years have not yet identified effective treatments that reduce mortality in patients with HFpEF. A database on use of carvedilol in a private cardiologist's practice was begun in 1997 and concluded at the end of 2018. We used this database to test the hypothesis that combining pharmacological interventions to address diastolic dysfunction (carvedilol), volume overload (spironolactone/eplerenone) and endothelial dysfunction (statins) with weight loss may benefit patients with HFpEF. We report analysis of 335 patients with HFpEF comprised of 61% female (mean age 74 ± 8) and 39% males (mean age 72 ± 7). Initial EF ranged between 50 and 77% with mean EF of 57 ± 6%. Only 15 patients were changed to metoprolol succinate, verapamil or diltiazem because of adverse side effects. Two hundred and twenty of the patients were in normal sinus rhythm when started on carvedilol, spironolactone/eplerenone and statin therapy with weight loss counseling. After 5 years, 191 patients were still on combination therapy, and only 31 (17%) had developed Atrial Fibrillation (AF). Compared to previous HFpEF trials reporting a 32% risk of developing atrial fibrillation after 4 years, our combination therapy significantly ($p < 0.05$) reduced the risk of developing AF over 5 years. Thus, irrespective of age and sex with comorbidities of type 2 Diabetes Mellitus (DM) and Chronic Kidney Disease (CKD), patients with HFpEF can be managed successfully with carvedilol, spironolactone/eplerenone and statins with a clinical benefit being a reduced risk of developing AF. We consider these data hypothesis-generating and hope these results will be tested further in database analyses and clinical trials.

Keywords: *HFpEF, Carvedilol, Spironolactone, Eplerenone, Statins, Sacubitril/valsartan, LVH, Atrial fibrillation, Type 2 diabetes mellitus, Chronic kidney disease, Ejection fraction, Diastolic dysfunction, Mortality, Creatinine, eGFR, Heart rate, Atrial myopathy*

Introduction

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome in which patients have symptoms of HF, such as dyspnea and fatigue, LVEF ≥ 50%, and evidence of cardiac dysfunction as a cause of symptoms, such as abnormal LV diastolic dysfunction with elevated filling pressures [1]. Among all patients with HF worldwide, roughly half have an LVEF ≥ 50%. The major contributors to HFpEF are systemic Hypertension (HT), female sex, aging, Coronary Artery Disease (CAD), type 2 DM and metabolic syndrome, obesity and CKD. Besides LV diastolic dysfunction, recent investigations suggest a more complex and heterogeneous pathophysiology, including systolic reserve abnormalities, chronotropic incompetence, stiffening of ventricular tissue, atrial dysfunction, secondary PAH, impaired vasodilatation and endothelial dysfunction. Frequently, these abnormalities are noted only when the circulatory system is stressed [2]. Unlike HF with HFrEF, clinical

trials over the years have not yet identified effective treatments that reduce mortality in patients with HFpEF. This manuscript reports results from using a 21-year real-world experience database from a private cardiologist's practice to test the hypothesis that combining pharmacological interventions to address diastolic dysfunction (carvedilol), volume overload (spironolactone/eplerenone) and endothelial dysfunction (statins) with weight loss may benefit patients with HFpEF [3-7].

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 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 recommendations 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 plans to eventually analyze 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 to carvedilol. 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, many HFpEF patients were treated with aldosterone receptor blockers (spironolactone or eplerenone) and statins, if indicated. Doses of spironolactone were 25 mg or 12.5 mg daily. Some patients with CKD were given spironolactone 12.5 mg every other day. Creatinine and potassium were monitored periodically, as indicated [8]. HFpEF patients were also treated with Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor Blockers (ARB) or dihydropyridine calcium channel blockers as additional antihypertensive therapy. Nonpharmacological therapy to treat HT and facilitate regression of Left Ventricular Hypertrophy (LVH) 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 better. Loop diuretics were used to relieve symptoms. Digitalis was used to relieve symptoms and for ventricular rate control in HFpEF patients with AF after beta-blocker therapy. Ejection fractions for data entry were from echocardiograms or LV angiograms. Ejection fractions measured during nuclear stress testing tend to be lower, and so EF's from nuclear stress testing were not used and MUGA scans were rarely ordered.

For this analysis, HFpEF was defined as patients accepted in referral complaining of dyspnea and fatigue with elevated Brain Natriuretic Peptide (BNP) level ≥ 100 pg/mL and with EF ≥ 50% with echocardiographic findings showing diastolic dysfunction, LVH and other structural abnormalities, such as left atrial enlargement and PAH. Coronary angiography was performed to eliminate myocardial ischemia as a cause of diastolic dysfunction. Causes of HF in patients with an LVEF ≥ 50% other than HFpEF are not the subject of this report, such as hypertrophic or restrictive cardiomyopathy, cardiac amyloidosis or LV non-compaction. Also, excluded from this analysis were causes of HF with LVEF ≥ 50%, such as valvular heart disease or primary PAH. Evaluation of patients with HFpEF included identifying, evaluating and treating associated comorbidities, including HT, CAD, DM, obesity and CKD. Type 2 DM was defined as a 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 recommendations. "Age" was the age of the patient when diagnosed with HFpEF. 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 the AF and EF data 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 HFpEF who were managed long-term over the years on combination therapy of carvedilol, spironolactone/eplerenone and statins and encouraged to lose weight. A total of 335 patients were identified with HFpEF. On initial clinic visit, 61% were females with an average age of 74 ± 8 years and 39% were males with an average age of 72 ± 7 years. The EF ranged between 50% and 77% with mean EF of 57 ± 7%. The initial weight of females ranged between 100 and 450 pounds with mean weight of 181 ± 8 pounds. The initial weight of males ranged between 130 and 380 pounds with mean weight of 219 ± 9 pounds. Females (83%) and males (82%) had similar incidence of HT. Females had more LVH (57% versus 45%). Males had more CAD (64% versus 55%). Initial BNP's ranged from 195 to 4799 with a mean of 859 ± 125 pg/mL. Table 1 shows population overview of HFpEF patients at initiation of carvedilol therapy. Table 2 shows final carvedilol dosage, age ranges and final therapeutic heart rates of HFpEF patients in sinus rhythm.

Fifteen of the 335 patients claimed intolerance to carvedilol and were changed to metoprolol succinate, verapamil or diltiazem

and excluded from further analysis. Thirty-one of the 335 patients claimed intolerance (gynecomastia and/or gastritis) to spironolactone and were changed to eplerenone. At the time of 5-year analysis 95% of patients were on carvedilol, 79% were on a mineralocorticoid receptor blocker, 88% were on a statin and 71% were on ACE inhibitor, ARB or amlodipine. Mean systolic blood pressure of patients at 5-year analysis was 126 ± 7 mmHg. Mean EF of patients at 5-year analysis was 55 ± 7%, which was not statistically significantly different from baseline EF.

The long-term effects of combination therapy of carvedilol, spironolactone/eplerenone and statin with weight loss on AF in patients with HFpEF was examined as a measurable factor. One hundred (30%) of the 335 patients on initial evaluation were diagnosed with AF before starting carvedilol, spironolactone/eplerenone and statins and recommending weight loss. Over the next 5 years, 83 were still on carvedilol, spironolactone/eplerenone and statins, and 9 of these patients had spontaneously converted to normal sinus rhythm. None of these 9 patients had been cardioverted, treated with amiodarone or had AF ablation. Ten of the 83 patients had dieted off, at least, 10% of baseline body weight, and 5 of those had converted to normal sinus rhythm.

Two hundred and twenty of the 335 patients on initial evaluation were in normal sinus rhythm when started on carvedilol, spironolactone/eplerenone and statins with recommended weight loss. After 5 years, 191 were still on carvedilol, spironolactone/eplerenone and statins, and only 32 (17%) had developed AF. Compared to previous HFpEF trials reporting a 32% risk of developing AF after 4 years, our combination therapy significantly ($p < 0.05$) reduced the risk of developing atrial fibrillation over 5 years [9]. Twenty-nine (15%) of the 191 patients had dieted off, at least, 10% of baseline body weight, and 4 had developed AF. Of the patients that developed AF compared to patients that remained in normal sinus rhythm, systolic blood pressures were similar and heart rates when in sinus rhythm were in the 60s suggesting similar degrees of clinical beta-blocker effect. Patients returning to sinus rhythm or developing AF were similar comparing males versus females or nondiabetic versus diabetic patients. Because of the referral population being from small rural farming communities in Central Illinois, subanalysis of African-American, Hispanic or Asians could not be done because of small numbers.

Population Overview				
	Total Patients	**Female**	**Male**	**mg/dL**
Patients with HFpEF	335	204	131	
Patients with HFpEF and AF	100	61	39	
Patients with HFpEF and DM	168	102	66	
Patients with HFpEF, DM and CKD	107	65	42	
Serum creatinine	63 35 6 3			1.1-1.9 2.0-2.9 3.0-3.9 Above 4.0

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

Final Carvedilol Dose of HFpEF Patients				
Dosage	3.125 mg q.12h	6.25 mg q.12h	12.5 mg q.12h	25 mg q.12h
Number of Patients	69	63	45	43
Age Range (years)	49-98	48-99	50-95	46-94
Therapeutic Heart Rate	62 ± 6	62 ± 7	63 ± 9	61 ± 8

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

Trial	Year	Design	EF Criteria	Patients with AF	Final Dose	Final HR	Duration	Main Outcome
carvedilol SWEDIC n = 113	2004	vs placebo	> 45%	0 (excluded)	25 mg q12h	60 bpm	6 m	Significant improvement in diastolic dysfunction
nebivolol SENIORS n = 643	2005	vs placebo ≥ 70 y	> 35% ≥ 40%	36%	7.6 mg q.d. (goal 10 mg qd)	71 bpm	21 m	Primary outcome nonsignificant
carvedilol J-DHF n = 245	2013	vs placebo	> 40%	34%	3.75 mg q12h (goal 10 mg q12h)	66 bpm	3.2 y median	Higher doses might improve prognosis
nebivolol ELANDD n = 116	2014	vs placebo	> 45%	0 (excluded)	At least 5 mg qd (goal 10 mg qd)	67 bpm	6 m	No significant improvement in exercise capacity
carvedilol J-nonischemic HF n = 962	2020	survival rate	≥ 40%	25%	3.75 mg q12h	72 bpm	5.5 y	Higher doses and lower HR did not improve survival

Table 3. Beta-blocker trials of patients with diastolic HF having mid-range and normal EF.

Acknowledgements

Asymptomatic diastolic dysfunction is a common form of ACC/AHA stage B HF, which is not encompassed by the term "HFpEF," but is associated with increased risk of developing HFpEF [10]. Unlike treating HFrEF patients with multiple medications proven to improve survival, no medical treatment has been identified that reduces mortality in patients with HFpEF [1]. Some evidence indicates that ACE inhibitors improve ventricular relaxation, but this improvement did not seem to be translated into benefit when studied in patients with HFpEF [11]. Two clinical trials comparing ARB agents (candesartan and irbesartan) to placebo demonstrated a small reduction in HF hospitalizations without a beneficial effect on the primary endpoint (cardiovascular death or HF hospitalizations) or on total mortality [12,13]. Phosphodiesterase inhibitors have been shown to improve diastolic function acutely, but there has been no control experience with these agents in chronic therapy [14].

The hypothesis tested in this retrospective analysis using a 21-year real-world database from a cardiologist in private practice is whether combining pharmacologic interventions to address diastolic dysfunction (carvedilol), volume overload (spironolactone/eplerenone) and endothelial dysfunction (statins) with weight loss results in improved outcomes in patients with HFpEF [3-7].

Evidence in support of carvedilol for treatment of diastolic dysfunction, HT, to facilitate regression of LVH and decrease risk of AF

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 [15]. Carvedilol has no intrinsic sympathomimetic activity. A beneficial effect of carvedilol on survival in patients with HFrEF was found in a decrease in the risk of sudden death as well as a decrease in the risk of death from progressive HF [16-19]. Carvedilol in patients with HFpEF has been shown to restore physiologic early diastolic filling. An early controlled trial of carvedilol as a beta-blocking agent (see Table 3) to assess the effect on diastolic function in patients with HFpEF showed that treatment with carvedilol for 6 months produced a significant improvement in diastolic function compared to placebo, particularly in patients with baseline heart rate above 71 bpm [3]. By significantly reducing heart rate towards 60 bpm, carvedilol allows more time for physiological diastolic filling of the heart through a shift of diastolic volume from late to early diastole. It appears that this redistribution of filling volumes toward a more normal pattern is brought about by an improvement in early filling [20].

Current treatment recommendations for hypertensive patients with LVH are based on blood pressure lowering and do not specifically favor selection of a particular beta-blocker over another except to avoid beta-blockers with intrinsic sympathomimetic activity which may increase LV mass and increase the risk of sudden death [5]. However, recent trials emphasize class heterogeneity that exists for beta-blockers and provide a strong basis for preferred use of carvedilol in these high-risk patients. Several studies have shown that carvedilol significantly reduced LV mass and myocardial fibrosis in both animals and humans [5]. In patients with hypertensive LVH and decreased coronary flow reserve, carvedilol treatment compared to metoprolol treatment over 6 months showed a greater decrease in LV mass index and a greater recovery in coronary flow reserve.

Patients with LVH are at an increased risk of progressing to HFrEF. Studies have shown that ACE inhibitors delay the development of Congestive Heart Failure (CHF). Animal studies

indicate a role of oxidative stress causing myocyte apoptosis and the transition of hypertrophy to systolic HF [5]. Carvedilol with its complete sympathetic blockade and antioxidant properties may be an appropriate choice for the prevention of progression from HFpEF to HFrEF in patients. This concept is reinforced by the beneficial effects of carvedilol for the reduction of morbidity and mortality in patients after Myocardial Infarction (MI) and with HFrEF [16-19].

Left ventricular hypertrophy and dyslipidemia are important and independent predictors of cardiovascular morbidity and mortality with HT. Traditional beta-blockers have been shown to worsen insulin resistance, facilitate weight gain and increase triglycerides. Carvedilol in hypertensive patients with DM has been found to have a neutral effect on insulin resistance, weight and triglycerides. This favorable metabolic profile also suggests that carvedilol is a better choice compared to traditional beta-blockers in these high-risk patients [21]. In patients with renal impairment, dose adjustments of carvedilol are not necessary.

Carvedilol has been shown to exert beneficial effects in the management of AF. Treatment with carvedilol is associated with the reduction in the occurrence of AF in patients following coronary artery bypass grafting or cardiac valve operation compared to metoprolol tartrate, metoprolol succinate or atenolol [22]. A retrospective analysis of patients with AF from the US Carvedilol HF Trials Program found that treatment with carvedilol resulted in a statistically significant improvement in LVEF (23% to 33%) with a greater percentage converting to normal sinus rhythm and a trend toward a reduction in the combined endpoint of death or HF hospitalization compared to placebo [16]. In the Carvedilol or Metoprolol European Trial (COMET), all-cause mortality was reduced in patients with AF by 17% with carvedilol compared to metoprolol tartrate [17]. However, treatment with carvedilol or metoprolol tartrate did not affect the incidence of new-onset AF. In patients, post-MI with LV dysfunction, treatment with carvedilol was associated with a reduction in supraventricular arrhythmias, including AF and atrial flutter [18].

Evidence in support of spironolactone/eplerenone treatment of HT, volume overload, to facilitate regression of LVH and decrease the risk of AF

Aldosterone is produced locally in the adrenal gland, brain, smooth muscle cells of blood vessels and the myocardium. Higher plasma levels of aldosterone have deleterious effects on the cardiovascular system; in HF, they are known to be positively linked to mortality. Aldosterone has also been found to cause myocardial and aortic fibrosis in animals, induce coronary inflammation and LVH and cause glomerular damage [8]. Spironolactone and eplerenone are both mineralocorticoid receptor antagonists.

Spironolactone has been proven to be beneficial for patients with HFrEF. The Randomized Aldactone Evaluation Study (RALES) demonstrated a 30% reduction in mortality for HF compared with placebo [4]. The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) found a 15% reduction in mortality compared with placebo in patients with LV systolic dysfunction after MI [23]. The EPHESUS trial did not show as large a decrease in mortality, but it did demonstrate gynecomastia at rates similar to placebo and was one of the first to demonstrate a reduction in mortality with the combined use of beta-blockers and mineralocorticoid antagonists. Multiple other studies have demonstrated the beneficial effects of spironolactone, including improved nitric oxide-induced vasodilatation in the peripheral arteries and improved LVEF, LV end systolic volume and exercise tolerance, as well as decrease in frequency of premature ventricular contractions and episodes of ventricular tachycardia in patients with HFrEF.

The mechanism that results in mineralocorticoid receptor antagonists improving survival is yet to be determined [8]. A substudy of the RALES group found that plasma procollagen type III amino terminal peptide was higher before treatment and that spironolactone reduced these levels, suggesting that the mineralocorticoid receptor antagonist may reduce cardiac fibrosis; the marker was also found to correlate negatively with survival. Other studies have found improvement in norepinephrine uptake, leading to more rapid norepinephrine breakdown as a possible explanation for the decrease in cardiac sudden death via decreased arrhythmias seen in RALES. Aldosterone blockade also improves baroreceptor function in patients with HFrEF, thus, increasing parasympathetic activity and decreasing central sympathetic outflow.

Evidence indicates that aldosterone receptor blockers are effective in facilitating regression of LVH [5]. High aldosterone levels in experimental animals have been found with increased fibrosis in the cardiac interstitial space and fibrosis is part of the process of pathologic LVH. In experimental animals with LVH, the use of spironolactone or eplerenone decreases the development of fibrosis in pathologic LVH and even seems to facilitate its regression.

Among patients with HFpEF, the development of secondary PA and right HF increases the risk of AF. There are data from animal and human studies to suggest that spironolactone may reduce the risk of paroxysmal AF. Eplerenone was shown in the randomized Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) study to reduce new onset AF in patients with HFrEF and mild HF symptoms [23]. In the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) randomized trial of patients with HFpEF, spironolactone did not reduce the incidence of AF [24]. A 2016 meta-analysis did suggest reduced AF in patients treated with aldosterone antagonist based on three randomized control trials and two observational studies. This effect was evident for eplerenone but not spironolactone. Presently, aldosterone inhibitors are not specifically recommended for prevention of new or recurrent AF.

Evidence in support of using statins in patients with HFpEF with endothelial dysfunction and to decrease the risk of AF

A future potential therapeutic concept for the treatment of HT and to facilitate regression of LVH is inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins) [5]. Statins have been shown to facilitate the regression of LVH in various animal

models of pathological myocardial growth. In addition to the reduction in LV mass, statins have been shown to reduce myocardial fibrosis, increase capillary density network and attenuate electrical instability of the hypertrophied heart. Most importantly, statins improve systolic and diastolic LV function and even decrease mortality. The mechanism of these beneficial effects is still under investigation. As statins lower LDL cholesterol, endothelial function improves and systolic blood pressure decreases by 2-4 mmHg [6]. The inhibition of hypertrophic growth by statins is only partially achieved by the reduction of hemodynamic afterload. Direct mechanisms, such as inhibition of neurohumoral activation in the myocardial tissue, attenuated production of growth factors and markers of inflammation, and reduction in oxidative stress also seem to participate. Thus, statins appear to exert biologic effects other than their cholesterol lowering actions [5]. Additional protective effect of statins is associated with inhibition of expression and activation of small guanosine triphosphate-binding proteins, such as Ras and Rho, which control the intensity of oxidative stress, the production and availability of nitric oxide and the expression of genes involved in myocardial growth. The data from these carefully done animal studies document novel effects of statins on LVH and open a potential new therapeutic strategy for patients with LVH [5]. Clinical trials to test statins' benefit in patients with HFpEF warrant further study. An early study reported a significant relative risk reduction in mortality in patients with HFpEF treated with statins and followed for 21 months [25]. More recent studies also suggest that statin therapy seems to be associated with improved survival benefit in patients with HFpEF [26-28].

There is some evidence that statins may prevent recurrence in patients with lone AF and with ischemic heart disease [29]. Some, but not all, studies have shown that statins lower the incidence of postop AF after coronary artery bypass surgery.

Evidence for weight loss to facilitate regression of LVH

Effective long-term antihypertensive therapy focused on regression of LVH is indicated in patients with HFpEF and requires nonpharmacologic consideration in combination with pharmacologic treatment. With regression of LVH, diastolic function and coronary flow reserve usually improve, and risk of AF, CHF and cardiovascular mortality decreases [5]. Goal of therapy is an arterial systolic pressure of < 130 mmHg. Left ventricular hypertrophy regression necessitates effective arterial pressure lowering 24 hours a day. In patients who appear to be at goal but fail to regress, 24-hour blood pressure ambulatory monitoring can be used to determine whether arterial pressure is, in fact, effectively controlled.

In addition to controlling arterial pressure, sodium restriction and weight loss independently facilitate regression of LVH [5]. If the patient loses even 10 pounds, it enhances the antihypertensive effect of medications, and associated weight loss speeds up the potential for regression. Weight loss facilitating regression of LVH has been accomplished through moderate calorie restriction in combination with regular low resistance exercise, such as walking 30 minutes a day.

Both obesity and inflammation are risk factors for AF. Obese individuals are significantly more likely to develop AF than those with a normal BMI.

Discussion of the findings from the database

A major finding of this database analysis is that combining pharmacological interventions to address diastolic dysfunction (carvedilol), volume overload (spironolactone/eplerenone) and endothelial dysfunction (statins) with weight loss may benefit patients with HFpEF by reducing the risk of AF. A previous study of HFpEF reported that 32% of patients developed AF within 3-4 years of followup [9]. We report that only 17% of HFpEF patients on combination therapy developed AF during 5-year followup. Further, of HFpEF patients with AF when started on combination therapy, 9 returned to normal sinus rhythm during 5-year followup. These results also suggest that combining carvedilol, spironolactone/eplerenone and statins was tolerated with usual outpatient monitoring. Of note, discussing weight loss strategies during annual followup visits resulted in only limited success. Only 12% of patients in AF and 15% of patients in normal sinus rhythm combined weight loss and low resistance exercise to achieve the recommended goal of losing, at least, 10% of body weight from baseline.

Atrial fibrillation is one of the most common comorbidities in patients with HFpEF. Our finding that 30% of patients were in AF at the time of referral and diagnoses is typical of large registries and of HFpEF clinical trials (see Table 3). Most drugs targeting HFpEF may not impact patients with a primary problem of AF. The fact that 9 of the patients spontaneously converted to normal sinus rhythm and only 17% of patients who were in normal sinus rhythm at baseline over 5 years developed AF suggests that the combination of carvedilol, spironolactone/eplerenone and statins may reverse or, at least, attenuate the development of atrial myopathy [30,31].

Guidelines give a Class IA recommendation regarding the use of carvedilol, bisoprolol or metoprolol succinate in patients with HFrEF who are in sinus rhythm and discourage the practice of withholding therapy in women and elderly patients [10]. In contrast, use of beta-blockers and specifically carvedilol in the treatment of patients with HFpEF needs further study. With availability of automatic blood pressure-heart rate monitors, most patients can have carvedilol dose up-titrated or adjusted by phone. Using resting heart rate in the 60s as a guide for maintaining pharmacologic beta-blockade appears to be a useful practical approach for many patients with HFpEF. As mentioned earlier, in a controlled trial of carvedilol (see Table 3) as a beta-blocking agent to assess the effect of diastolic dysfunction in patients with HFpEF showed that treatment with carvedilol for 6 months produced evidence of a significant improvement in diastolic function when reducing heart rate towards 60 bpm [3]. This benefit was observed particularly in patients with heart rates above 71 bpm at baseline.

Table 3 also reviews other beta-blocker trials of patients with diastolic heart failure having mid-range and normal EF [32-35]. Neither carvedilol ($beta_1$.$beta_2$-$alpha_1$ with antioxidant properties) nor nebivolol ($beta_1$ with nitric oxide-mediated vasodilatory

activity) had a major impact on survival on the degree of beta-blockade achieved based on final heart rates. More recent analysis of data suggests that patients with mid-range EF respond to beta-blockade and sacubitril/valsartan, like HFrEF patients [32,36]. Future HFpEF trials should use EF criteria of ≥ 50% and consider heart rate goal closer to 60 bpm. Subanalysis of TOPCAT suggests use of beta-blockers in HFpEF patients may increase the frequency of hospitalizations [37,38]. In the TOPCAT trial, 78% of patients were on beta-blockers, but the choice of beta-blocker and the dose of beta-blocker were not reported [24]. The choice of beta-blocker and the dose of beta-blocker may be important to benefit HFpEF patients as they are in the management of patients with HFrEF. Using carvedilol in combination with spironolactone/eplerenone, statins and weight loss appears to benefit HFpEF patients suggesting the need for future double-blind robust clinical trials. If our combination therapy maintains EF and reduces the risk of AF and beta-blockade may decrease the risk of sudden death in patients with HFpEF, they will have benefited [39]. A lower risk of AF might decrease the risk of HF decompensation requiring hospitalization and decrease morbidity and mortality due to embolic stroke [40].

Strengths of these data

These data give insight into carvedilol, spironolactone/eplerenone and statin use combined with weight loss in patients with HFpEF in the real-world setting with long-term followup. These data reflect the importance of continuity of care to accomplish therapeutic goals for patients with HFpEF. These data demonstrate the long-term benefit of carvedilol, spironolactone/eplerenone and statins in high risk patients with multiple comorbidities of HFpEF, type 2 DM and CKD [41]. 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 in 1997 when the database was started, such as rates of hospitalization or whether the patient had obstructive sleep apnea [42]. Methods to detect AF are becoming increasingly sensitive revealing that patients may have episodes of AF that are not detected by intermittent assessment [43]. Intermittent assessment could randomly impact both our AF and sinus rhythm patient groups. More effective AF detection strategies should be used in future clinical trials. 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 HFpEF, HT, DM and CKD. While the number of patients examined in the study is somewhat small, the duration of data retrieval allows for long-term clinical consequences for patients with HFpEF to be defined further.

Summary and Conclusions

Our retrospective analysis from a database resulted in similar patient profile to other clinical trials but did not allow for assessing mortality, frequency of hospitalizations or quality of life in the treatment of patients with HFpEF. However, it did allow the testing of the hypothesis that carvedilol, spironolactone/eplerenone and statins can be combined successfully in patients with HFpEF irrespective of age and sex with comorbidities of DM and CKD with the clinical benefit being a reduced risk of AF during 5-year followup. A lower risk of AF might decrease the risk of heart failure decompensation requiring hospitalizations and decrease morbidity and mortality due to embolic strokes. Meta-analyses from some studies suggest that eplerenone may be more effective than spironolactone in reducing the risk of AF. This possibility could not be determined from this database because most patients were on spironolactone as the preferred medicine on medical insurance plans.

The role of the Angiotensin Receptor-Neprilysin Inhibitor (ARNI) sacubitril/valsartan in the treatment of patients with HFpEF is yet to be fully defined [36]. Use of sacubitril/valsartan was associated with modest but nonsignificant ($p = 0.058$) reductions in the risk of total HF hospitalizations and cardiovascular death compared with valsartan alone, specifically in women and patients with mildly reduced EF. Subgroup analysis showed an apparent 27% relative risk reduction in women driven primarily by reduction in HF hospitalizations. Of note, the Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction (PARAGON-HF) trial included patients with EF as low as 45% and excluded patients with obesity. Further analysis of PARAGON-HF also found that the lowest rates of major adverse cardiovascular and renal events in patients with HFpEF occurred when systolic blood pressure was in the 120-129 mmHg range.

New analysis may have identified three variations (phenotypes) of this single clinical entity HFpEF that are based on how some biochemical markers relate to traditional echocardiographic criteria. Proposed HFpEF phenotypes may point toward distinctive treatment approaches in the future [44].

In summary, combining pharmacological interventions to address diastolic dysfunction, (carvedilol), volume overload (spironolactone/eplerenone) and endothelial dysfunction (statins) may reduce the risk of HFpEF patients developing AF. We consider these data as hypothesis-generating and hope these results will be tested further in database analyses and clinical trials. ic

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