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Comparing nebivolol and spironolactone in the treatment of heart failure with a preserved ejection fraction

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Abstract

Objective: To assess the efficacy of improving diastolic dysfunction with the use of nebivolol, a selective beta-1 adrenergic receptor antagonist, as compared to spironolactone, a mineralocorticoid receptor antagonist, in the treatment of diastolic heart failure. To assess whether or not these medications have a favorable outcome in terms of improving exercise capacity in patients with Heart Failure with Preserved Ejection Fraction (HFpEF). ***Design***: Systematic Literature Review. ***Methods:*** Searches in PubMed and the JMU online library database using mesh terms that included "diastolic heart failure", "nebivolol", and "spironolactone". In order to narrow down relevant articles, filter terms included "humans", "published in the last 5 years", "full text" and "English." This literature review includes three separate studies pertaining to different treatment modalities for diastolic heart failure. We focused on the use of nebivolol as compared to spironolactone as mainstay therapies in the treatment regimen for heart failure with a preserved ejection fraction. The Aldo-DHF randomized control trial was included for its research in assessing the efficacy of improving diastolic function and maximizing exercise capacity in patients with HFpEF. The study with a focus on treatment with spironolactone in elderly women with HFpEF was included because it focused on baseline and endpoint data concerning improvement in exercise capacity as well as left ventricular (LV) structure and function on echocardiogram and biomarkers such as brain natriuretic peptide (BNP). The ELANDD study was included because it discussed mechanisms of nitric oxide release and subsequent peripheral vasodilation, which was hypothesized to improve aortic and ventricular compliance and thus improve diastolic filling. ***Results*** – spironolactone was found to improve left ventricular diastolic function, but had no effect on maximal exercise capacity and did not improve patient symptoms or quality of life. Spironolactone was also shown to have beneficial effects on the remodeling of the ventricle. The selective beta-1 adrenergic receptor antagonist, nebivolol, was found to have no improvement in maximal exercise capacity and was found to have a neutral effect on both peak oxygen uptake during exercise and pro brain natriuretic peptide plasma levels (pro-BNP). Nebivolol did decrease resting and peak blood pressure and heart rate as compared to the placebo.

Introduction

Heart failure is characterized by an inability to produce a cardiac output sufficient enough to perfuse and oxygenate vital organs and tissues while maintaining adequate and normal filling pressures in the heart. It is broken down into two distinct phenotypes, including systolic failure (reduced ejection fraction) and diastolic failure (preserved ejection fraction).

Systolic heart failure is characterized by impaired contractility of the myocardium, which allows for normal diastolic filling but results in a reduced volume of blood ejected from the ventricle. This combination of normal filling with reduced ejection results in increased end systolic volumes and thus volume overload in the ventricle. Systolic failure is typically associated with dilation of the left ventricle (LV), or eccentric remodeling, as a result of volume overload. This type of failure is typically defined by an ejection fraction (EF) < 45%. [3]

Diastolic heart failure is characterized by stiffened ventricles, which result in an inability of the ventricles to relax and amounts to poor diastolic filling and a reduced end diastolic volume (EDV). The preservation of the ejection fraction in diastolic failure is a result of initially low EDV with a normal contractile force during systole, which allows for full emptying of the ventricle upon contraction. Diastolic failure is typically associated with hypertrophy of the left ventricle as a result of concentric remodeling due to pressure overload. This type of failure is typically defined by an ejection fraction of >45 %. [1]

The distinction between systolic and diastolic heart failure is important, as each is phenotypically different from the other and thus have differing etiologies and treatment modalities. It is also important to note the difference between diastolic "dysfunction" and "failure". Dysfunction describes the mechanical properties, referring only to abnormal relaxation or filling, regardless of EF. Diastolic "failure" refers to diastolic dysfunction in the presence of a preserved EF and clinical symptoms of heart failure. [1]

In diastolic failure, inadequate relaxation of the LV in addition to loss of ventricular wall compliance results in poor filling, a low stroke volume, and a pressure increase in the left atrium as well as the pulmonary veins. This increase in LV pressure ultimately causes increased pulmonary pressures and manifests clinically as dyspnea and limitations in exercise as a result of pulmonary congestion and fluid overload. [1]

The etiology among patients with heart failure with preserved ejection fraction (HFpEF) is different from those patients with a reduced ejection fraction. Notably, chronic systemic hypertension is one of the most common causative factors in patients with HFpEF, with obesity as another significant causative factor. Etiologies that commonly result in ischemic conditions cause poor oxygenation of myocytes, an inability to make sufficient amounts of ATP for the process of calcium removal by the sarcoplasmic reticulum (SR) and thus poor relaxation of the myocardium. LV chamber stiffness and increased resistance to filling results in increased LV filling pressures and higher pressures in the lung capillary beds. See Table 1 to distinguish etiologies, pathophysiology, and signs and symptoms of systolic and diastolic heart failure. [1][8]

Table 1. Comparison between Systolic and Diastolic Heart Failure

	Heart Failure with Reduced Ejection Fraction ***"Systolic Heart Failure"***	Heart Failure with Preserved Ejection Fraction ***"Diastolic Heart Failure"***
Common Etiologies	• Coronary artery disease • Diabetes mellitus • Hypertension • Valvular heart disease • Arrhythmia (SVT or ventricular) • Ischemic cardiomyopathy • Dilated cardiomyopathy • Congenital heart disease • Drugs and alcohol • Idiopathic	• Coronary artery disease • Diabetes mellitus • Hypertension • Valvular heart disease • Hypertrophic cardiomyopathy • Restrictive cardiomyopathy • Constrictive pericarditis • Aging • Obesity
Pathophysiology	• Normal relaxation/filling • Poor contractility, impaired emptying • Normal EDV with increased ESV • Increased diastolic pressure • Ventricular dilation • EF < 45%	• Impaired relaxation - Loss of LV wall compliance • Low EDV • Increased end diastolic pressure • LV Hypertrophy • EF > 45% • Elevated left atrial pressure
Symptoms	• Dyspnea, Cough • Orthopnea and paroxysmal nocturnal dyspnea • Peripheral edema (ankle swelling) • Fatigue and weakness • Reduced exercise performance	
Signs	• Pulmonary congestion (edema, crackles) • Elevated jugular venous pressure • Hepatosplenomegaly, ascites • Displaced PMI • Renal hypoperfusion • Rapid/irregular heart rate	

Table 1 *depicts basic similarities and differences between systolic and diastolic heart failure. Common etiologies and pathophysiology behind each type of heart failure often differ significantly, while signs and symptoms associated with heart failure in general are often similar, regardless of ejection fraction. [1][8]*

The diagnosis of HFpEF may be made based on a clinical picture consistent with diastolic failure, an EF > 45%, and evidence of LV dysfunction on echocardiogram. On physical exam, pulmonary congestion manifested as adventitious lung sounds (crackles, rales, rhonchi) and jugular venous distention may be present. An echocardiogram may reveal abnormal LV filling and left atrial enlargement. Cardiac catheterization may reveal elevations in filling (diastolic) pressures either at rest or during exercise and strenuous activity. The NYHA functional classification system is used to assess both the severity and limitations of heart failure patients. It refers to heart failure in general, regardless of ejection fraction. This system is explained in Table 2. [2]

Table 2. New York Heart Association (NYHA) Heart Failure Symptom Classification System

NYHA Class	Level of Functional Impairment
I	No limitation with ordinary physical activity (no dyspnea, undue fatigue, palpitation)
II	Ordinary physical activity somewhat limited by symptoms (long walks, climbing two flights of stairs)
III	Physical activity markedly limited by symptoms (short walks, climbing one flight of stairs)
IV	Symptoms of heart failure at rest or with very little exertion

Table 2 *refers to the New York Heart Association (NYHA) functional classification system. It is the most commonly used system to classify heart failure patients based on the severity of their symptoms. Patients are placed in one of four categories based on their level of limitation and symptom onset during exercise.* [2]

In terms of treating diastolic heart failure, concrete treatment regimens have not yet been established like they have been for systolic heart failure. As the physiology behind diastolic failure differs substantially from that of systolic failure, the pharmacologic treatments that are effective in patients with a reduced EF are not necessarily successful in patients with a preserved EF. Due to the lack of a proven regiment, treatment at this time is directed towards contributing factors and comorbidities including hypertension and coronary artery disease, in addition to symptom relief with diuretics. [1]

Clinical Scenario

Ms. AC is a 72-year-old Caucasian female with a body mass index (BMI) of 28.5 who presents today with signs and symptoms consistent with heart failure. Ms. AC has been short of breath for the past 72 hours and her dyspnea is worse with exertion, while lying flat, and at night, but gets a little better when she sits up-right and rests. Ms. AC complains of constant fatigue that has been worse in the last two days and reports that her legs and ankles have been “puffier than normal” this past week. Ms. AC reports no recent illness, but states she has had a cough for months and just always feels a little run-down, especially when she cleans the house or walks up even a few stairs. Ms. AC reports no chest pain or discomfort today, but states that her heart “feels a little fast” and she’s anxious this morning because she’s worried about her health. Ms. AC is a 20-pack-year smoker and her diet is high in fat and sugary beverages, but she reports cutting down significantly in the past 2 months.

Ms. AC’s past medical history is significant for type 2 diabetes mellitus for 20 years, hypertension for 20 years, osteoporosis for 10 years, and dyslipidemia for 10 years, which are all well controlled with 2g of metformin BID and 16 units of lantus with breakfast, 40 mg of lisinopril BID, 5 mg of alendronate QD, and 40 mg atorvastatin QD.

Clinical Question

In adults with HFpEF (LVEF >45%) who are 40 years of age or older, does spironolactone as compared to a selective B1 beta blocker (nebivolol) improve exercise capacity and reduce diastolic dysfunction, therefore improving diastolic filling and thus cardiac output.

Methods

An initial investigation for research articles was performed in September 2016 using the PubMed search engine and the James Madison University online library database. Search terms included "heart failure with preserved ejection fraction", "spironolactone", "nebivolol", "diastolic heart failure", "beta blockers", and "mineralocorticoid receptor antagonists." These terms produced 482 results and after duplicates were removed, 375 articles remained. Excluding articles that were not in full text, not in English, not using human subjects, and articles that were published more than 5 years ago allowed us to further narrow our search. The remaining 180 articles were assessed for eligibility. Of these articles, 89 were excluded if the population study included participants less than 40 years of age, if left ventricular ejection fraction was less than 45%, and if the studies were looking at populations with less than class II heart failure, based on the New York Heart Association (NYHA) classification. Meta-analyses research articles were also excluded, leaving 91 articles for qualitative synthesis. See Table 3 for study criteria.

Table 3. Study Criteria

Inclusion Criteria	Exclusion Criteria
• Cohort • Randomized Control Trial • English • Humans • Class II or III Heart Failure • Full-text • Evidence of diastolic failure on echocardiogram • 6-Minute walking distance • Double-blind	• Studies older than 5 years • Non-human populations • Class I Heart Failure • Less than 40 years of age • LVEF < 45% • Meta-analysis

The qualitative synthesis was then further narrowed to the final 3 articles. This was done so using the specific inclusion criteria of patient population of greater than or equal to 40 years of age, left ventricular ejection fraction of greater than 45%, and a diagnosis of heart failure with preserved ejection fraction in NYHA function class II-III. We also consider the year each article was published, sample size, and the journal from which our articles were published. See Table 4 below for details on quality assessment.

Articles with double-blinded randomized control trials and monitoring of diastolic dysfunction with an echocardiogram were also included in our analysis. In addition to the echocardiogram, we included articles that used a 6-minute walk distance test and measured peak VO2. Since there are no studies to date directly comparing nebivolol and spironolactone, we used studies comparing each medication against a placebo. The process of article selection is detailed in appendix 1. See Table 4 for details on the quality assessment for each article included in this literature review. [4][5][6]

Table 4. Quality Assessment			
	Study 1	**Study 2**	**Study 3**
Year Published	2013	2014	2011
Sample Size	422	48	116
Journal	Journal of the American Medical Association	Journal of Cardiac Failure Vol. 20 No. 8	European Journal of Heart Failure

Table 4 *displays publishing dates, sample sizes and the journal from which each article was selected.* [4][5][6]

Results

Table 5. Overview of Studies Included in Literature Review			
	Study #1: Spironolactone vs Placebo	**Study #2: Spironolactone vs Placebo**	**Study #3: Nebivolol vs Placebo**
Study Design	Double-blind, Randomized, Placebo-controlled		
Duration of Study	12 months	6 months	6 months
Efficacy Outcomes	6-Minute Walking Distance E/e' Velocity Ratio E/A Velocity Ratio Peak VO_2 Levels NT-proBNP Levels	6-Minute Walking Distance E/e' Velocity Ratio E/A Velocity Ratio BNP Levels PIIINP Levels	6-Minute Walking Distance Peak VO_2 Levels NT-proBNP Levels
Treatment Groups	Spironolactone (25 mg QD) n = 213 Placebo (25 mg QD) n = 209	Spironolactone (25 mg QD) n = 24 Placebo (25 mg QD) n = 24	Nebivolol (2.5 mg QD) n = 57 Placebo (2.5 mg QD) n = 59

Table 5 *depicts an overview of each article included in this literature review including the type of study design and duration of each study, as well as primary and secondary outcomes for each study. This table also provides a breakdown of participants between study and control groups, as well as medications and the dose used.* [4][5][6]

E wave = early diastolic filling; A wave = late diastolic filling. Both refer to mitral inflow. Normally the E wave should be taller than the A wave, as more filling occurs passively (E) than during the atrial kick (A) at the end of diastole. The E/e' ratio is derived by dividing the max flow velocity of the mitral valve inflow (early filling) by the max velocity of E.VO_2 refers to the maximal oxygen consumption or use during exercise. NT-pro BNP, or BNP, refers to the brain natriuretic peptide which is secreted from the ventricles in response to over stretching. When elevated, the BNP may be suggestive of heart failure.

Study 1.

Effect of Spironolactone on Diastolic Function and Exercise Capacity in patients with Heart Failure with Preserved Ejection Fraction [5]

Objective:

The objective of the study was evaluating the use of spironolactone as compared to placebo in the treatment of heart failure with preserved ejection fraction. The primary outcomes that were investigated include the effects on diastolic function and exercise capacity while assessing the long term efficacy and safety of mineralocorticoid receptor antagonists.

Study 1 Design

This was a randomized controlled double-blinded study with 422 patients from ten different sites in Germany and Austria. All 422 patients were randomized using the Pocock's minimization algorithm on a 1:1 basis to receive spironolactone (n = 213) or placebo (n = 209).

Patients in the spironolactone group received 25 mg/day for a total of 12 months in duration. The primary endpoints in this study included change in maximum exercise capacity (Peak VO_2 on spiroergometry) and the E/e' ratio (ratio of peak early transmitral ventricular filling velocity to early diastolic tissue Doppler velocity) measured on an echocardiogram at 12 months and compared to baseline. The exercise test and echocardiogram were performed twice, once at screening and once at baseline, to ensure reproducibility. All echocardiogram data were reviewed by a blinded lab tech that was trained by two national echocardiogram coordinators acting as blinded reference centers. An echocardiogram operating procedure was constructed to provide standard parameters for the data. Diastolic function was classified into four grades based on E/e' ratio and E/A ratio, or the ratio between early diastolic filling and late diastolic filling (or the atrial kick). See Table 6 for grading classifications based on echocardiogram measurements (E/e' and E/A ratios, specifically). [5][7]

Table 6. Classification of Diastolic Function in the Aldo-DHF study (Study 1 – spironolactone vs placebo)

	Normal Diastolic Function	Delayed relaxation – Grade I	Pseudonormal Filling – Grade II	Restrictive Filling	
				Reversible – Grade III	Not Reversible – Grade IV
E/A Ratio	≥ 1	< 1	≥ 1 and < 2	≥ 2	≥ 2
E/e' Ratio	< 10	Not graded	≥ 10	≥ 10	≥ 10

Table 6 *depicts the classification of diastolic function based on the E/A and E/e' ratios obtained from echocardiography. E wave = early diastolic filling; A wave = late diastolic filling. Both refer to mitral inflow; that is, filling of the left ventricle via the mitral valve. The E/e' ratio is derived by dividing the max flow velocity of the mitral valve inflow (early filling) by the max velocity of E. Study 1 defines a normal E/e' ratio of <10. The ratio will increase if there is diastolic dysfunction, which results in an E-wave that increases with higher filling pressures. Under normal conditions (no diastolic dysfunction), the filling of the left ventricle is passive. The E wave (early filling) is taller than the A wave (later filling). In the presence of diastolic dysfunction, the ventricle becomes stiff, cannot relax properly during diastole, and thus impairs early filling, resulting in a decreased magnitude of the E wave. As less blood fills the ventricle during passive filling (early diastole), more blood is left in the atrium. When late filling occurs, more blood is ejected from the atrium and thus an increase in the magnitude of the A wave occurs. This results in an E/A ratio of <1 (delayed relaxation, grade I).* [5][7]

Similarly to the echocardiogram operations, the spiroergometry testing also used a blinded reference lab to train investigators on the procedures of the instrumentation and evaluation of any related cardiopulmonary exercise testing. The exercise testing consisted of bicycle ergometer starting with a workload of 20 watts and increasing 20 watts in 2-minute intervals. An ECG was used to record continuous heart rate, monitor for arrhythmias, and observe for and ST-segment changes. Blood pressure was measured at baseline and every 2 minutes thereafter. Ventilatory exchange (peak VO_2) was calculated by averaging breath-by breath measurements over 10 second intervals. The peak VO_2 is defined as the maximum value of the last three 10 second averages during exercise. Blood samples of N-terminal pro-brain-type natriuretic peptide (NT-proBNP), sodium, potassium, hemoglobin, and estimated glomerular filtration rate (eGFR) were collected after 20 minutes of lying in the supine position following the cardiopulmonary exercise test.

Office visits for the study included the screening visit, baseline visit, follow up after one week, and continued follow up at 3, 6, 9, and 12 months. At 6 and 12 month follow up visits, an echocardiogram, cardiopulmonary exercise test, 6-minute walking test, and blood sample were obtained. See Table 7 for inclusion and exclusion criteria for this study. [5]

Table 7. Inclusion and Exclusion Criteria for Study 1: Edelmann et al.

Inclusion	Exclusion
• Males and females age ≥ 50 years of age • NYHA class II or III • LVEF > 45% • Echocardiographic evidence of diastolic dysfunction of grade ≥ 1 OR atrial fibrillation at presentation • Peak VO_2 of ≤ 25 mL/kg/min	• Prior documented reduced LVEF <45% • Significant coronary artery disease (CAD) • Myocardial infarction OR coronary artery bypass surgery ≤ 3 months prior to enrollment • Relevant pulmonary disease (Vital capacity < 80% or FEV_1 < 80% predicted) • Significant Lab Abnormalities • Known contraindications or known intolerance to therapy with MRA's in last 3 months. • Concomitant therapy with potassium-sparing diuretic *(Triamterene, Amiloride)* • Potassium supplementation

Significant Lab Abnormalities *- (K+ ≥ 5.1 mmol/L; Hgb ≤ 11 g/dL; Hct ≤ 33%; Serum creatinine > 1.8 mg/dL; Estimated GFR < 30 mL/min/1.73 m²)* ***Significant CAD*** *- current angina pectoris or ischemia on stress test, or untreated coronary stenosis > 50%* ***MRA*** *– mineralcorticoid receptor antagonists (like spironolactone)*

Study 1 Results

Demographics

Of the 422 patients that underwent the study, the mean average age of the patient population was 67 and of those 422 patients, 52% were women. Characteristics of the patients' medical histories included 92% of the patients having a current history of hypertension, 65% with hyperlipidemia, 40% with coronary artery disease, 17% diabetes mellitus, 3% chronic obstructive pulmonary disease, and 5% with a history of atrial fibrillation. On average, the total BMI for the study was 28.9; indicating most of the patients were overweight or obese. The study included NYHA functional classes II and III of 86% and 14%, respectively. [5]

Treatment Efficacy

Results from the study indicated that diastolic function was improved with the use of spironolactone as compared to placebo. Measurements from the echocardiogram proved so with a decrease in the E/e' from 12.7 at baseline to 12.1 after 6 months. On the other hand, patients taking placebo had an increase in E/e', starting at 12.8 at baseline and then increasing to 13.6 after 12 months. These results carried a P value of < .001, suggesting statistical significance.

E/A velocity ratio on echocardiogram was 0.90 for spironolactone and 0.92 for the placebo group at baseline. After 12 months of treatment the spironolactone group E/A velocity ratio increased to 0.91 and the placebo group increased to 0.96. The P value was .08, indicating no true statistical significance, however, improvement in the E/A ratio with the use of spironolactone may be significant with a study that is longer in duration because there would be more time for structural changes of the heart. See Figures 1 and 2 at the end of this section for E/e' and E/A ratio measurements, respectively.

A co-primary endpoint was the peak VO_2 Patients taking spironolactone improved from baseline scores, increasing from 16.3 mL/min/kg to 16.8 mL/min/kg. Patients taking placebo also increased their Peak VO_2 from 16.4 mL/min/kg to 16.9 mL/min/kg. These measurements suggest no significant difference between study and control groups, with a P value of 0.81. See Figure 3 for peak VO_2 measurements in both the study and control groups.

Secondary endpoints included a decrease in left ventricular mass index (LVMI), as seen on the echocardiogram, and a decrease in the levels of NT-proBNP. At baseline, LVMI of patients on spironolactone were 108 g/m^2, eventually decreasing to 100 g/m^2 after 12 months of treatment. The LVMI for patients in the placebo group were 109 g/m^2 at baseline and decreased to 106 g/m^2 after 12 months. Similarly, patients taking showed a decrease in NT-proBNP, from 2.22 ng/L to 2.18 ng/L, whereas patients on placebo had increased levels from 2.19 ng/L to 2.22 ng/L after 12 months. The P values for LVMI and NT-proBNP were 0.16 and 0.8, respectively. This suggests that, while there was a difference between the use of spironolactone vs placebo, neither the decrease in pro-BNP levels or LVMI were statistically significant. Patients taking spironolactone, as compared to placebo, did see a reduction in systolic blood pressure after 12 months. There was a slight decrease in the 6-minute walking distance for patients in the spironolactone study group. Neither finding was statistically significant. See Figures 4 and 5 for NT-proBNP levels and 6-minute walking distances, respectively.

In patients assigned to the spironolactone study group, there was a mild increase in potassium levels at 1 week, which remained stable throughout the duration of the study. A significant number of patients in the spironolactone group (13 as compared to 7 in the placebo group) had potassium levels >5.5 mmol/L. This finding was expected, as spironolactone is a potassium sparing diuretic and increased serum potassium levels are common in patients taking this medication. However, the group taking placebo also saw an increase in serum potassium in 7 patients, which, while not due to use of a potassium sparing diuretic, could be due to the concomitant use of ACE inhibitors, which also raise serum potassium levels. These findings could also be due to pseudo hyperkalemia. [5]

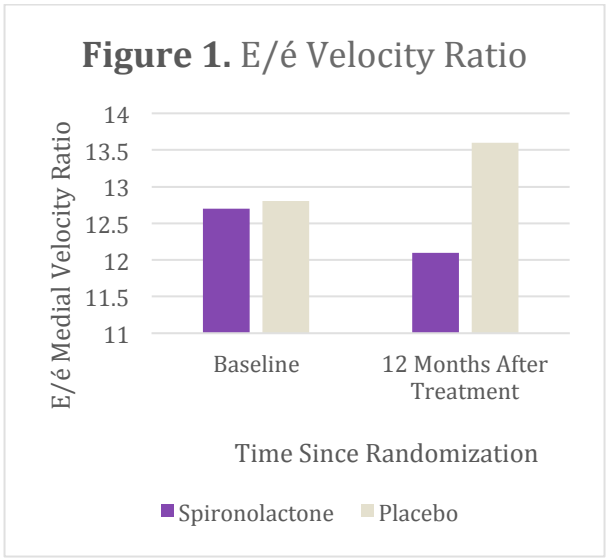

Figure 1 – Edelmann et al (Study 1) – E/e' ratio

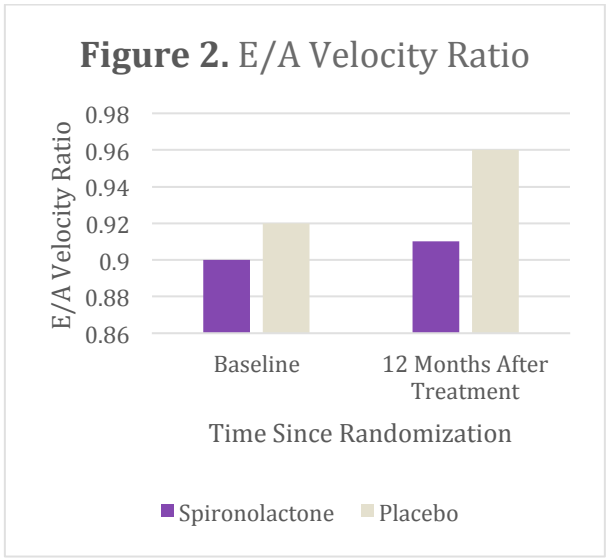

Figure 2 – Edelmann et al (Study 1) – E/A ratio

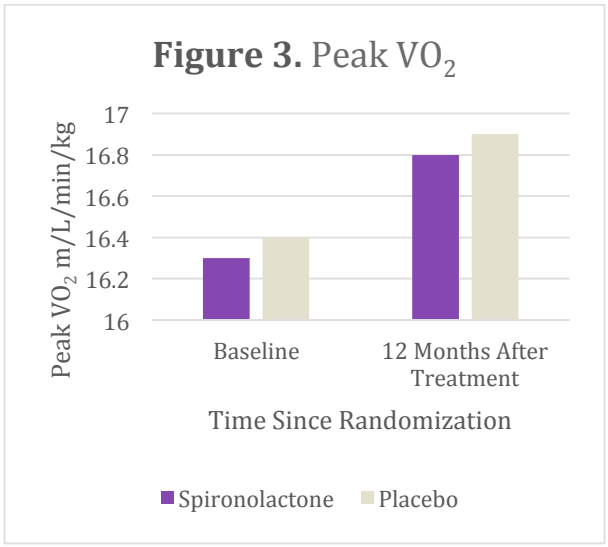

Figure 3 – Edelmann et al (Study 1) – Peak VO_2

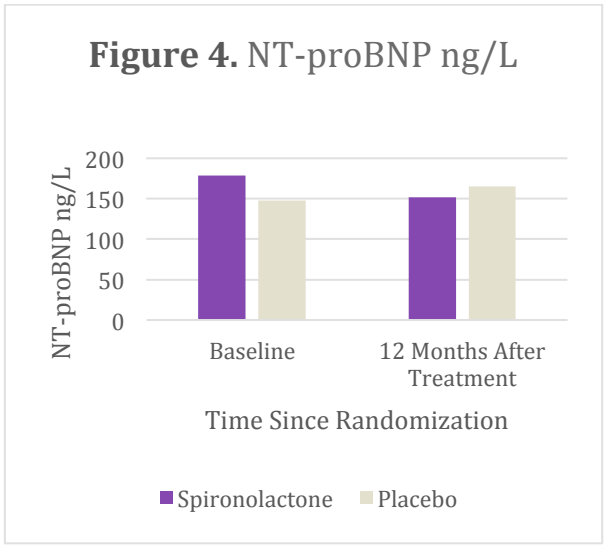

Figure 4 – Edelmann et al (Study 1) – NT-proBNP

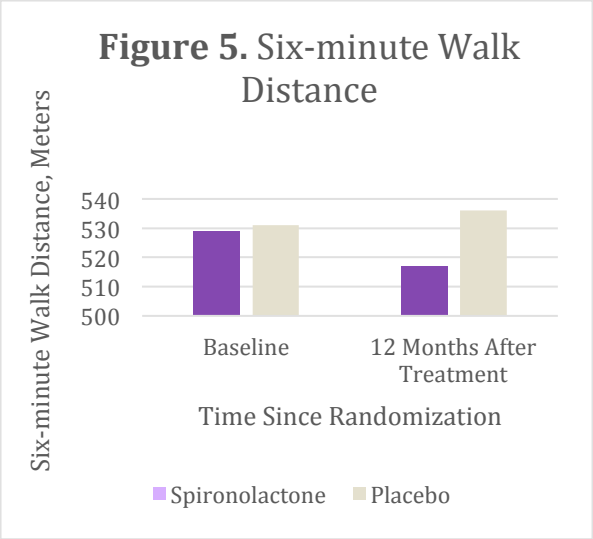

Figure 5 – Edelmann et al (Study 1) – six-minute walking distance

Study 1 Critique

This study was a double blind, randomized control trial that included 422 participants from 10 different sites in Germany and Austria. The patient population was much larger than comparative studies and it is diverse in its participant pool. However, considering the local population in Harrisonburg, VA, or even surrounding areas in Virginia and the rest of the United States, the populations may vary tremendously. While the study is diverse, including 10 different countries, it may not be as applicable locally. The mean age was 67 with 52% of participants being female, which is representative of the general population with HFpEF. All participants had similar baseline characteristics including a designation by the NYHA of class II or III heart failure and a preserved ejection fractions of ≥ 45%. While all patients did present with similar baseline findings, this study did allow for the inclusion of patients with either evidence on echocardiogram of diastolic dysfunction or atrial fibrillation at presentation. This inclusion criterion is acceptable, as atrial fibrillation can cause a rapid ventricular response, which results in a reduction of left ventricular filling during diastole and thus poor cardiac output. However, patients with atrial fibrillation may or may not go on to develop true diastolic dysfunction in the long term in the event that a patient spontaneously converts to normal sinus rhythm and thus no longer meets inclusion criteria for diastolic heart "failure."

This study chose to focus equally on co-primary endpoints including changes in diastolic function, based on E/e' values, as well as maximal exercise capacity, based on peak VO2 and a 6 minute walking distance. This co-ranking of end points allowed for maximal focus to be put on both exercise capacity and structural changes in the heart, where as other studies may only focus on one or the other.

The exclusion criteria is also significant, deeming participants not eligible in the case of significant CAD, MI or CABG surgery in 3 months prior to enrollment, significant lung disease based on FEV_1 values of <80%, in addition to elevated potassium and serum creatinine, low GFR, and hematocrit < 33%. These exclusion criteria, while probably necessary in order to ensure the safety of study participants, does exclude a large majority of heart failure patients, many of whom have multiple comorbidities, especially those involving the renal and cardiopulmonary organ systems.

Study 2.

Effects of Spironolactone Treatment in Elderly Women with Heart Failure and Preserved Left Ventricular Ejection Fraction [6]

Objective:

To explore the effects of spironolactone in elderly women as compared to placebo in combination with patients who chronically taking angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) therapy for heart failure with preserved ejection fraction. The study examined short-term primary outcomes of diastolic function.

Study 2 Design

This was a randomized, placebo controlled trial with 48 female patients from the Methodist Hospital in Houston Texas. Randomization of 48 patients took place on a 1:1 to basis to receive spironolactone (n=24) or placebo (n=24). The patients in the spironolactone group received 25 mg/day for a total of 6 months in duration.

Throughout the study, serum electrolytes including potassium, sodium, chloride, and bicarbonate, as well as blood urea nitrogen (BUN) and serum creatinine, were monitored. Monitoring took place at weeks 2, 6, 13, 25, and 27. The study measured a 6-minute walking distance, performed an echocardiogram, measured serum biomarkers levels, and administered the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ score), interpreted at 3 and 6 months to evaluate the effects of spironolactone on exercise tolerance, functional capacity, symptoms, and echocardiographic doppler measurements. The Doppler echocardiogram was a two-dimensional study and was performed by an experienced echocardiographer who was blinded to the study. The evaluation of biomarkers included troponin and brain natriuretic peptide (BNP). A commercial lab, that was also blinded, collected these measurements. Since the patients were previously on an angiotensin-converting-enzyme inhibitor (ACE-I) in addition to the study drug, spironolactone, serum potassium was monitored for the duration of the study, at weeks 2, 6, 13, and 25. Inclusion and exclusion criteria are outlined in Table 8 below. [6]

Table 8: Inclusion and Exclusion Criteria for Study 2: Kurrelmeyer et al.

Inclusion	Exclusion
• Age ≥ 18 years of age • NYHA class II or III • LVEF > 45% • Diastolic dysfunction with elevated left ventricular filling pressure *(E' < 10 cm/s and lateral E/e' >15)* • BNP > 62 pg/mL • BP ≤ 150/95 mmHg for 4 weeks prior to enrollment • Ability to walk ≥ 50 meters at time of enrollment • Treatment with ACEI or ARB for at least ≥ 4 weeks *(prior to enrolling)*	• Current treatment with Spironolactone or Eplerenone • Previous intolerance to Spironolactone • SCr > 2.5 mg/dL • Serum K+ > 5.0 mEq/L • Significant valvular heart disease • Pericardial disease • Severe chronic lung disease w/ cor pulmonale • Unstable angina OR MI ≤ 4 weeks prior to enrollment • Severe PVD w/ claudication that limits walking distance • Severe comorbidities with life expectancy < 6 months duration • Pregnant • Lactating female

***NYHA** = New York Heart Association (classification of heart failure); **LVEF** = Left Ventricular Ejection Fraction; **ACEI** = angiotensin-converting-enzyme inhibitor; **ARB** = Angiotensin II receptor blockers; **PVD** = peripheral vascular disease; **MI** = Myocardial Infarction; **BP** = blood pressure; **SCr** = serum creatinine; **K**+ = Potassium* [6]]

Study 2 Results

Demographics

This study had a sample size of 48, with the average age being 70 and with 100% of the patients being female. Baseline health status included 83% of the patients with a history of chronic hypertension, 35% with coronary artery disease, 37.5% with diabetes mellitus, and 25% with atrial fibrillation. Patients in the NYHA functional classes II and III were included in the study, with 42% of the patient population falling into class II and 58% into class III. The average BMI for patients in this study was 27.85, which classifies most patients as "overweight" based on BMI alone. All of the patients were also previously taking either an ACEI or ARB, with one patient taking both. [6]

Treatment efficacy

Results from echocardiogram measurements showed a benefit from taking spironolactone as compared to the placebo. The lateral E/e' ratio decreased from 16.5 ± 1.2 at baseline to 14.0 ± 0.8 at 6 months for patients taking spironolactone and remained essentially the same, with values of 12.5 ± 0.5 at baseline and 12.0 ± 0.5 after 6 months. These results produced a P value of 0.0001, which suggests statistical significance.

The mitral E/A ratios at baseline produced values of 1.5 ± 0.1 and 1.6 ± 0.1 for patients in the spironolactone and placebo groups, respectively. After six months of treatment, E/A ratios of 1.6 ± 0.1 and 1.9 ± 0.2 were produced for patients in the spironolactone and placebo groups, respectively. Mitral E/A ratio had a significant change overall in both treatment groups with a P value of < 0.05, which is statistically significant. See figures 6 and 7 for results of E/e' and E/A ratios, respectively.

The six-minute walking distance test was significantly improved in both treatment groups. The patients taking spironolactone walked 250 meters ± 20 at baseline and improved to 272 meters ± 22 after 6 months of treatment. The placebo group walked 228 meters ± 12 at baseline and improved to 256 meters ± 13 after 6 months. Both were significant ($P < 0.05$). See figure 8 for 6-minute walking distance measurements.

At baseline, serum BNP was measured at 215.4-pg/mL ± 19.0 and 139.4 pg/mL ± 10.6 for the placebo and spironolactone groups, respectively. The significantly higher baseline BNP levels in the placebo group were likely due to the age difference in the two groups. After 6 months of treatment, BNP levels decreased, measuring 166.9 pg/mL ± 13.3 and 119 pg/mL ± 10.9 for the placebo and spironolactone groups, respectively. After adjusting for age, the statistics favored spironolactone as compared to placebo, but did not reach statistical significance, with a P value of 0.074. See figure 9 for BNP measurement comparisons.

Measurements for type III procollagen (PIIINP) were also measured and decreased from 5.6-µg/L ± 0.4 at baseline to 5.1-µg/L ± 0.4 at 6 months in patients taking spironolactone. Levels in the placebo group increased from 5.6-µg/L ± 0.3 at baseline to 6.6-µg/L ± 0.4 after 6 months. These changes were significant ($P = 0.035$) and indicate that treatment with spironolactone may decrease myocardial fibrosis by significantly reducing the synthesis of type III procollagen. There was no difference between the study groups for systolic or diastolic blood pressures over the duration of the study. See figure 10 for type III procollagen measurements.

Three participants in the spironolactone treatment group had to withdrawal from the study due to hospitalization for hyperkalemia (serum potassium ≥ 6.0 mEq/L). Transient hyperkalemia (≥ 5.5 mEq/L but < 6.0 mEq/L) occurred in 2 patients, one from each of the treatment groups. [6]

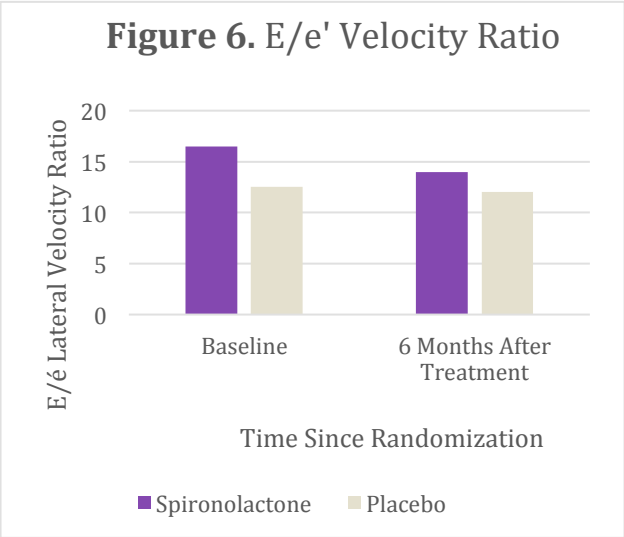

Figure 6 – Kurrelmeyer et al (Study 2) – E/e' ratio

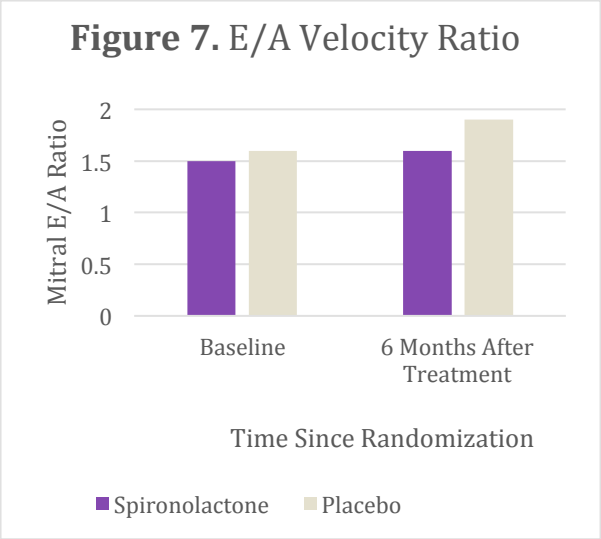

Figure 7 – Kurrelmeyer et al (Study 2) – E/A ratio

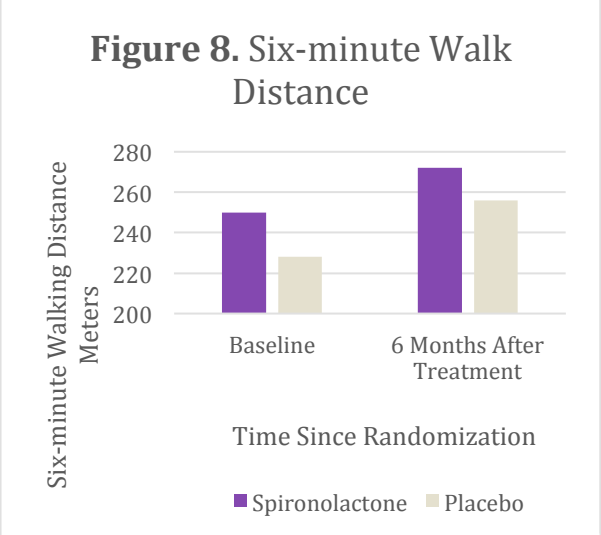

Figure 8 – Kurrelmeyer et al (Study 2) – six-minute walking distance

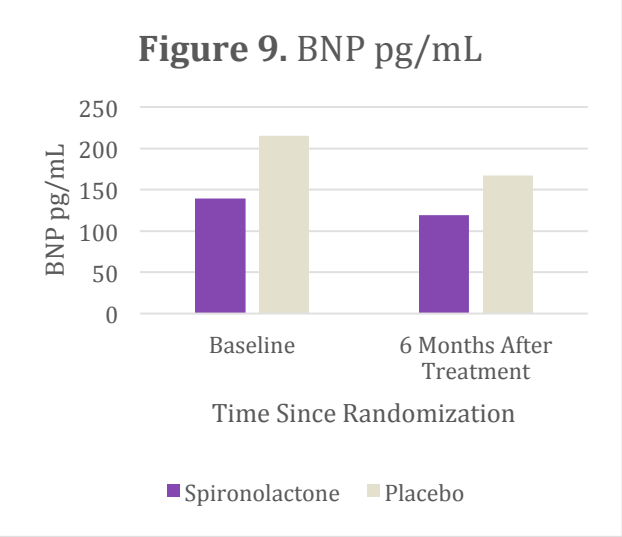

Figure 9 – Kurrelmeyer et al (Study 2) – BNP levels

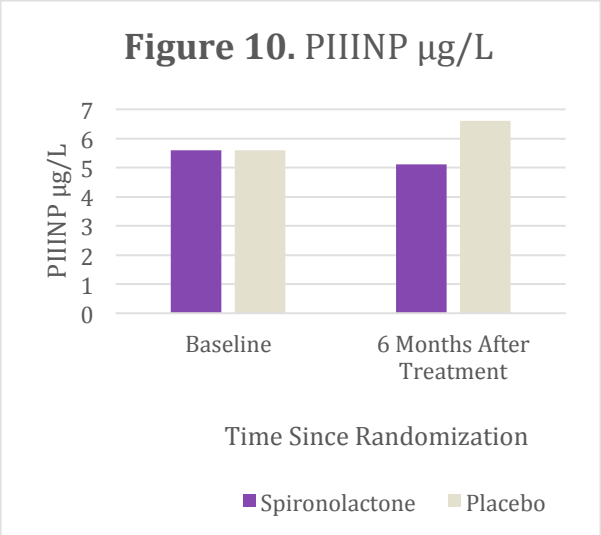

Figure 10 – Kurrelmeyer et al (Study 2) – type III procollagen (PIIINP)

Study 2 Critique

This study was a double blind, randomized control trial, which allowed for blinding of both the study group and the researchers in order to eliminate bias. All participants had similar baseline characteristics in terms of a previous diagnosis of heart failure with ejection fraction ≥ 45% and all were considered to be heart failure class II or III by the New York Heart Association (NYHA) classification system.

While this study adequately randomized and blinded all allocation of study drug vs placebo, the number of study participants was low, at 48, all of whom were female. This is not uncommon, as a majority of heart failure patients with preserved ejection fraction are women, however, study results may not apply to the general population of both males and females. All participants were also from the same hospital in Houston, TX, accounting for minimal variability in terms of patient demographics.

This study conducted a 4 week "open label" phase, in which baseline serum creatinine and potassium were followed to ensure levels were below 2.5 mg/dL and 5.0 mEq/L, respectively. Serum potassium was also checked consistently at weeks 2, 6, 13, 25, and 27 to ensure no hyperkalemia develops, in which case the patient would not continue with the drug treatment. Safety measures taken to ensure control of serum potassium were extensive, but necessary, as this medication is known to increase serum potassium levels, which can be fatal if ignored.

The exclusion criteria for this study were extensive, excluding patients with valvular disease, pericardial disease, COPD, cor pulmonale, and unstable angina. This is problematic, considering the multitude of comorbidities this particular population may suffer from, in addition to heart failure. The results of this study may in fact be skewed towards a particular population of heart failure patients in which no other cardiac comorbidities exist, which is not necessarily the norm.

Patients were also screened for intolerance to the use of an ACEI or ARB and then treated with these medications during the 4-week open label phase. Patients were also required to have a blood pressure of ≤ 150/95 mmHg for 4 weeks prior to the start of enrollment. This extensive screening process and pre-treatment regimen required during the open-label phase of this clinical trial effectively removes potentially eligible candidates from enrollment in order to study only a specific subset of heart failure patients, therefore does not accurately represent the general population.

Another limitation of this study includes age difference between spironolactone and placebo groups. Even with randomization, the small sample size allowed for possible allocation bias. This age difference may account for differences in primary and secondary endpoints including the 6 minute walking distance, ECHO measurements, and biomarker levels, which are known to vary depending on patient age.

Study 3.

Effects of the Long-Term Administration of Nebivolol on the Clinical Symptoms, Exercise capacity, and Left Ventricular Function of Patients with Diastolic Dysfunction: Results of the Conraads et al Study [4]

Objective:

To assess the effects of nebivolol as compared to placebo on exercise capacity in patients with heart failure with preserved ejection fraction. Diastolic function and exercise tolerance were the primary outcomes analyzed.

Study 3 Design

This was a randomized controlled, double-blinded, parallel group study design with a total of 116 patients. All 116 patients were randomized on a 1:1 basis to receive nebivolol (n = 57) or placebo (n = 59). Patients in the nebivolol group received 2.5 mg/day and were gradually titrated up to 10 mg/day over a 5-week period. Treatment was administered for a total duration of 6 months, or 21 weeks in addition to the 5-week titration period. The primary endpoint that was evaluated in this study was the 6-minute walking test (6MWT), which was measured at baseline and at 6 months. Secondary endpoints include patient symptoms, exercise capacity assessing peak VO_2 and parameters of left ventricular function. The Conraads et al study also observed major outcomes such as mortality, hospitalizations, and unexpected visits to the heart failure clinic as well as other adverse events. Inclusion and exclusion criteria are outlined in Table 9. *[4]*

Table 9: Inclusion and Exclusion Criteria for Study 3: Conraads et al.

Inclusion	Exclusion
• Willing and able to sign informed consent • Age ≥ 40 years • Documented history of heart failure • Persistent symptoms during effort • NYHA class II or III • LVEF > 45% • LV end diastolic internal diameter < 3.2 cm/m^2 OR LV end diastolic volume index < 102 mL/m^2 • Any LV diastolic dysfunction (documented by ECHO) • E/E' > 15 (on tissue doppler ECHO) • E/E' ratio of 8 to 15 with other diastolic dysfunction	• Acute coronary or cerebrovascular ischemic event in 3 months prior to enrollment • Exercise-induced myocardial ischemia in 3 months prior to enrollment • Contraindications to beta blocker treatment • Ongoing treatment with beta blocker therapy, verapamil, diltiazem

***NYHA** = New York Heart Association (classification of heart failure); **LVEF** = Left Ventricular Ejection Fraction; **LV** = left ventricular; **ECHO** = echocardiogram; **ms** = milliseconds **"Other Diastolic Dysfunction"** = E/A < 0.5 and/or deceleration half-time > 280 ms in patients > 50 years of age and/or duration of reverse pulmonary vein atrial systole flow – mitral valve atrial wave flow > 30 ms, and/or left atrial volume index >40 mL/m^2, and/or increased LV mass index*

Study 3 Results

Demographics

A total of 116 patients were enrolled in the study for a total duration of 6 months. Only 93 patients were evaluated at their 6-month follow up due to poor tolerance, side effects, or lack of compliance. The mean patient age was 66 with 65% of them being women. Patient comorbidities included 86% with a chronic history of hypertension, 56% with hyperlipidemia, 20.5% with diabetes, 18.5% with coronary artery disease, and 11.5% with chronic obstructive pulmonary disease. The average BMI of the patients in the study was 30, with a majority of patients being classified as overweight or obese. [4]

Treatment Efficacy

The primary end point for the Conraads et al study was the 6-minute walking distance test. Patients randomized to the nebivolol treatment group had a walk distance of 420 meters ± 143 at baseline and improved to 428 meters ± 141 after 6 months of treatment, but did not reach statistical significance (P = 0.094). The placebo group walk distances also improved, with 412 meters ± 123 at baseline and 446 meters ± 119 after 6 months.

Peak VO_2 values for patients in the Nebivolol study group measured 17.02-mL/kg/min ± 4.79 at baseline and decreased to 16.32-mL/kg/min ± 3.76 after 6 months. Baseline measurements in the placebo group increased from 17.79-mL/kg/min ± 5.96 at baseline to 18.59-mL/kg/min ± 5.64 after 6 months. Peak VO_2 levels at baseline, as compared to 6 months, were not statistically significant (P = 0.63). See figures 11 and 12 for 6-minute walking distance results and peak VO_2 measurements, respectively.

Resting systolic blood pressure for patients taking nebivolol decreased from 128 ± 17 at baseline to 122 ± 18 at 6 months, which did reach statistical significance (P <0.05). Systolic blood pressure measured during peak exercise decreased from 176 ± 29 at baseline to 167 ± 31 after 6 months of treatment, which also reached statistical significance (P < 0.05). In contrast, patients in the placebo group had no significant decrease in either resting or peak systolic blood pressure.

The biomarker NT-proBNP was measured at baseline and at 6 months. The nebivolol treatment group had a slight increase in levels, from 147 pg/ml at baseline to 162 pg/mL after 6 months of treatment. Patients in the placebo group had a decrease in values, from 126 pg/mL at baseline to 99 pg/mL after 6 months of treatment. These measurements did not reach statistical significance (P = 0.878). See figure 13 for NT-proBNP measurements at baseline and after 6 months.

The numbers of adverse events affecting the nebivolol and placebo study groups were 20 and 13, respectively. This resulted in the withdrawal of nine patients in the nebivolol group as compared to zero patients in the placebo group. [4]

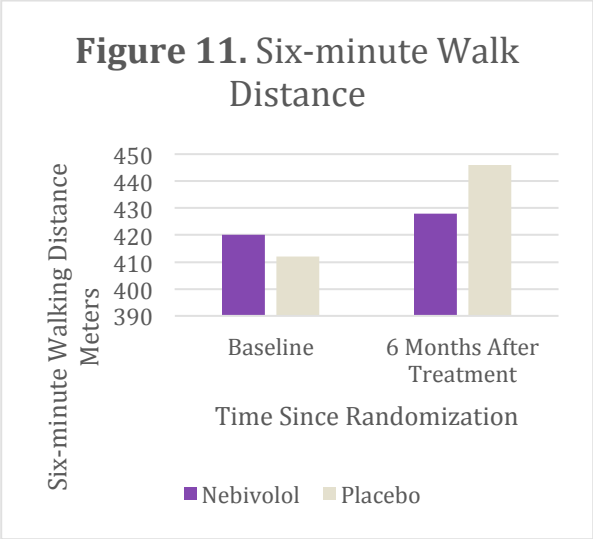

Figure 11 – Conraads et al (Study 3) – 6-minute walking distance

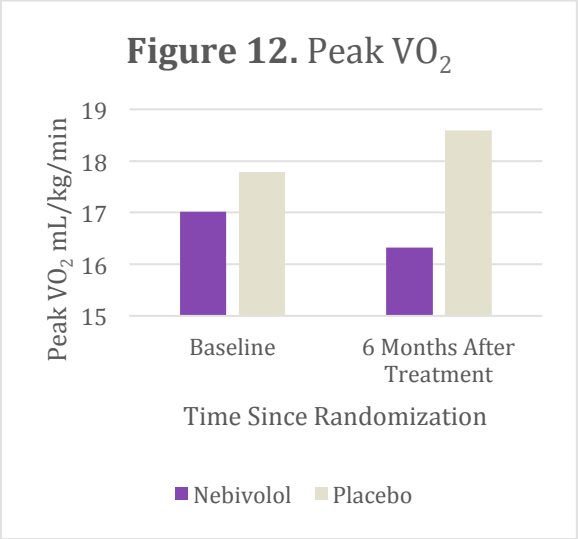

Figure 7 – Conraads et al (Study 3) – Peak VO_2

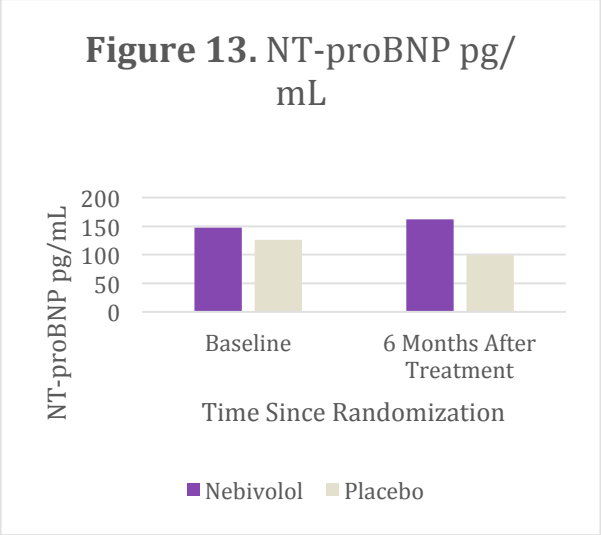

Figure 7 – Conraads et al (Study 3) – NT-proBNP levels

Study 3 Critique

Strengths of this study included double-blinding using computer-generated, 1:1 randomization to ensure complete blinding for both participants and researchers. The study participants were also diverse, as enrollment stemmed from 12 hospitals in 8 different countries. Minimal differences in baseline characteristics between the nebivolol and placebo groups were found, as most participants were female (65%), with a history of hypertension and an average BMI of 30.

While a majority of study participants being female did allow for similar baseline findings, it also means that there was an uneven distribution of participants in terms of gender. This may affect the results of the study, but should be expected, as heart failure with a preserved ejection fraction is more common among women than men. Although random assignment to study and control groups was used, more patients assigned to the nebivolol group (16% vs 7% in the placebo group) had a history of COPD, which may have affected the baseline health of those particular patients. While it is good that all participants were either classified as having heart failure class II or III, it should be noted that the majority of patients (78%) were considered only class II at the start of the study. This may suggest that patients were not sick enough to truly benefit from the effects of nebivolol in terms of beta blockade and nitric oxide (NO) release. Nitric oxide is a potent vasodilator that is associated with a decrease in afterload, which may contribute to the LV remodeling in terms of lowering the pressure at which the LV pumps against. Less pressure to pump against may mean less LV hypertrophy, or less cardiac muscle mass in the LV.

In order to further support findings of this study, an intention-to-treat analysis was performed in order to evaluate efficacy endpoints, which allowed for evaluation using the “last observation carried forward” method in patients who were initially enrolled, but not assessed at the end of the 6 month period.

This study did have a very low loss to follow-up, with only 1 in the nebivolol group and none in the placebo group. However, the nebivolol group did lose a total of 14 participants due to adverse drug side effects and consent withdrawals, compared with only 8 in the placebo group.

Discussion

Heart failure with preserved ejection fraction (HFpEF) is a common clinical syndrome in which patients have signs and symptoms of heart failure in addition to a normal ejection fraction (> 45%). These patients also have evidence of LV diastolic dysfunction, suggested by physical exam and echocardiogram. Also known as diastolic heart failure, this condition has a multitude of etiologies, most commonly chronic systemic hypertension, ischemic heart disease, and hypertrophic or restrictive cardiomyopathies. HFpEF tends to affect women more than men. This finding may be related to females having abnormal presentation of myocardial infarction, leading to undetected ischemic heart disease and thus comorbid heart disease that leads to heart failure because it was never treated to begin with. It is also more commonly seen in older adults who have chronic systemic hypertension. It is less likely to be seen in patients with prior myocardial infarction. HFpEF is often associated with comorbidities including coronary heart disease, diabetes mellitus, obesity, sleep apnea, and kidney disease. [1][3][8]

It is important to distinguish asymptomatic diastolic “dysfunction” from “failure.” Evidence of LV dysfunction, as seen on echocardiogram, in addition to a normal ejection fraction (>45%), is not sufficient to diagnose a patient with heart “failure”, which requires the presence of signs and symptoms such as dyspnea, orthopnea, pulmonary congestion, peripheral edema, and jugular venous distension.

In terms of the treatment of heart failure, proven pharmacologic regimens have only been established for those patients with a reduced ejection fraction. HFpEF differs significantly in terms of etiology, pathophysiology, and heart structure and dysfunction. Unlike systolic failure, in which poor contractility is the main concern, diastolic failure involves normal contractile force with poor ability to relax, thus poor diastolic filling. [1][3][8]

Initial treatment of patients with reduced ejection fraction includes loop diuretics such as furosemide, which target symptom relief related to volume overload. Angiotensin converting enzyme inhibitors (ACEI),

angiotensin II receptor blockers (ARBs) and beta-blockers are also used as initial therapy in addition to the loop diuretics. Mineralocorticoid receptor antagonists may also be added to the initial regimen.

It is thought that this treatment regimen might also be successful if used for patients with a preserved ejection fraction, or patients with diastolic failure. However, in reviewing the current literature pertaining to the treatment of patients with preserved ejection fraction, studies suggest otherwise.

In study 1, Edelmann et al, spironolactone was compared to placebo and results suggest an improvement in diastolic dysfunction as seen by a decreased in the E/e' ratio in the spironolactone group with an increase in the placebo group. Additionally, results suggest an improvement in neuroendocrine activation, as seen by a decrease in NT-proBNP levels from baseline to the end of the trail 12 months later. While endpoint data do suggest improved diastolic function, there was no improvement in exercise capacity, no improvement of patient symptoms, and no improvement in overall quality of life. [5]

Study 2, Kurrelmeyer et al, which studied the effects of Spironolactone as compared to placebo in the treatment of elderly women with HFpEF, produced results that suggest an improvement in diastolic dysfunction, suggested by a decrease in the E/'e ratio, as well as an improvement in BNP levels in the spironolactone group. Results showed no improvement in exercise capacity and no significant difference in blood pressures or heart rates between Spironolactone and placebo groups. [6]

In study 3, Conraads et al, results suggest no improvement in exercise capacity, as suggested by no change in the 6-minute walking distances or peak VO_2 levels. Resting and peak blood pressure and heart rate did decreased more in the Nebivolol group. Quality of life and NT-proBNP levels were unchanged in both groups. This suggests that the use of Nebivolol, a beta-1 adrenergic receptor antagonist, is not effective in the improvement of exercise capacity and likely inhibits the chronotropic response to exercise. Changes in the peak exercise capacity are thought to be related solely to the negative chronotropic effect of nebivolol. It should be noted that patients in this study had mild LV diastolic dysfunction, with 78% of participants deemed class II heart failure. These patients had only mild exercise limitations, which mean their baseline was not diminished enough to really show any benefit from the administration of a beta-blocker during exercise. [4]

See figures 14-18 for information regarding overall results of the six-minute walking distance, serum BNP levels, Peak VO2 measurements, E/e' ratios, and E/A ratios for each study, comparatively.

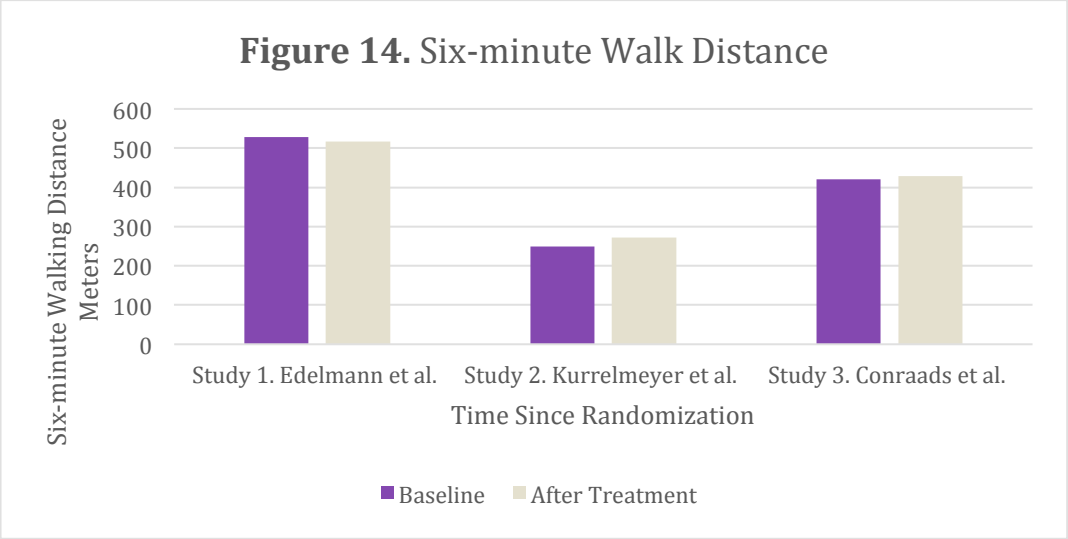

Figure 14 – comparison of six-minute walking distances between studies 1, 2, and 3 as measured at baseline and at the end of the study durations.

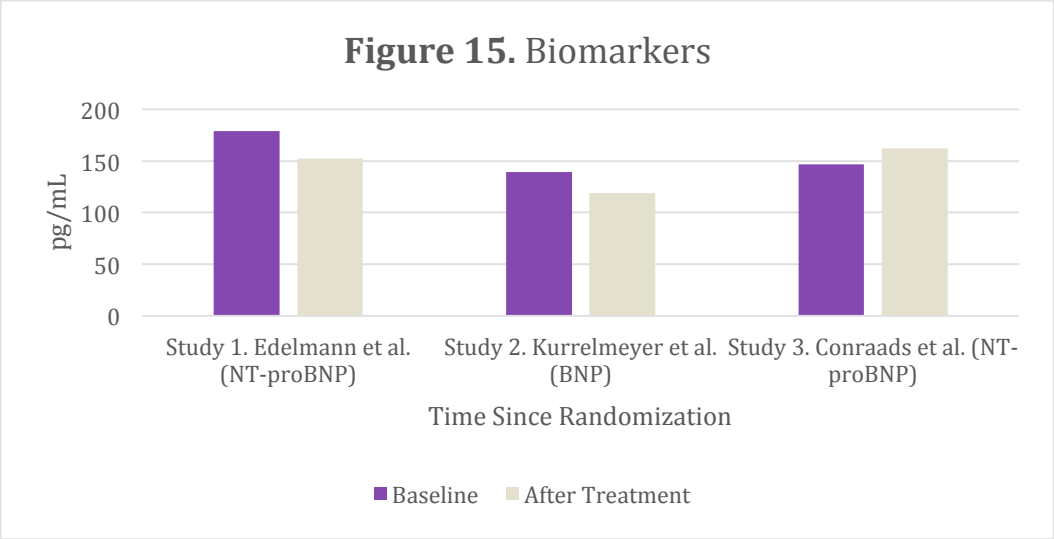

Figure 15 – Comparison of serum BNP levels between studies 1, 2, and 3 as measured at baseline and after full duration of studies.

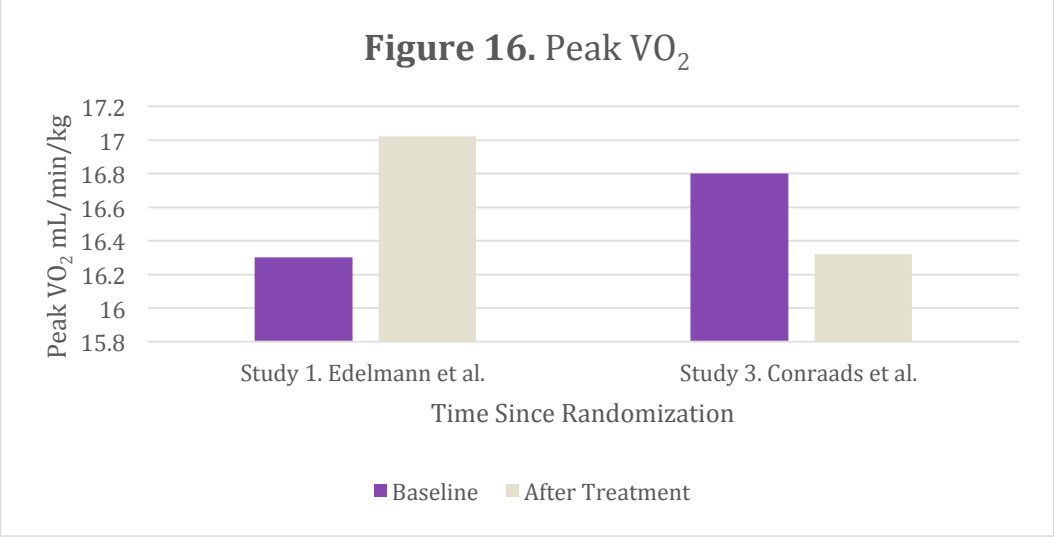

Figure 16 – Comparison of peak VO_2 levels between studies 1 and 3 as measured at baseline and after full duration of studies.

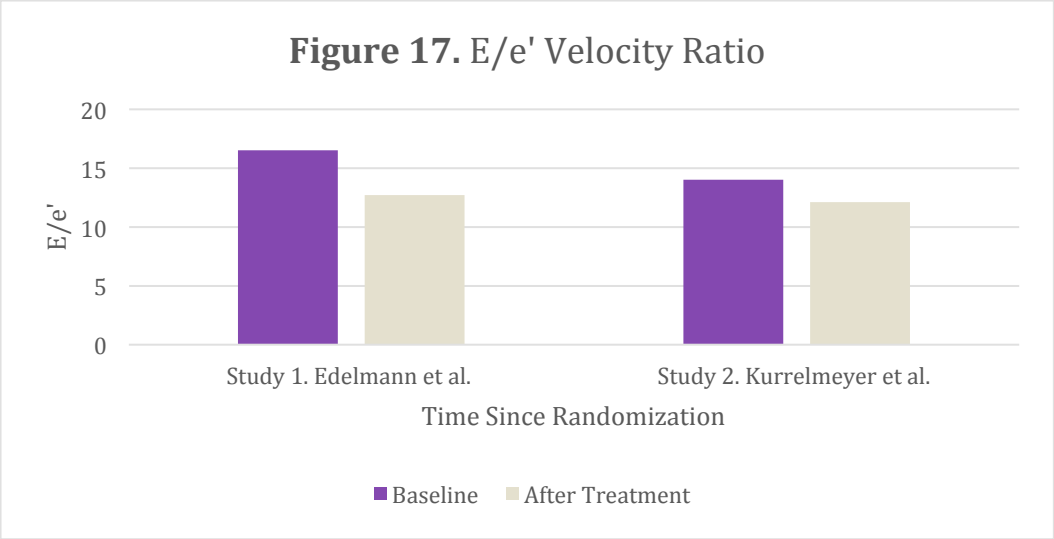

Figure 17 – Comparison of the E/e' velocity ratios between studies 1 and 2 as measured at baseline and after full duration of studies.

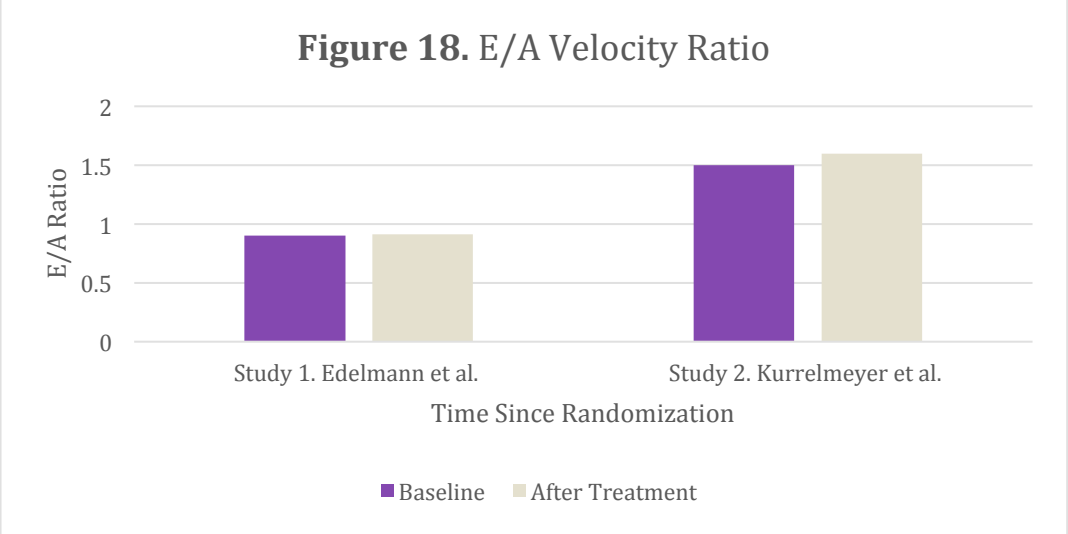

Figure 18 – Comparison of E/A velocity ratios between studies 1 and 2 as measured at baseline and after full duration of studies.

Conclusion

While there is an established, proven treatment regimen for the management of heart failure in patients with a reduced ejection fraction, successful treatment regimens for patients with preserved ejection fraction have not yet been proven. Among heart failure patients, nearly half of all diagnosed cases are in patients with diastolic failure, which is why there is such a high demand for further research and proven methods of treating this type of failure. [1][3][8]

In reviewing the literature, Nebivolol, a cardio-selective beta-1 adrenergic receptor antagonist, had no favorable effect on exercise capacity and was not reported to improve diastolic function. Nebivolol did lower heart rate and blood pressure as compared to patients in the placebo group. Spironolactone, a mineralocorticoid receptor antagonist, was shown to improve diastolic function, but had no favorable effect on exercise capacity. [4][5][6]

In addition to primary endpoints of increase in six-minute walking distance and improvement of diastolic function, study 2, which considered treatment of elderly women with HFpEF, it was found that after 6 months of Spironolactone use, there was a significant decrease in the levels of PIIINP, which is a N-terminal propeptide of type III procollagen. Elevations of this biomarker are associated with increased levels of the type III collagen and thus fibrotic changes, leading to increased ventricular stiffness. [4][5][6]

With no proven treatment regimen in the management of HFpEF, it is widely accepted that prevention of disease development and progression is the best course of action. Treatment is targeted at management of comorbidities and contributing factors, with tight blood pressure control as a main focus. The use of diuretics for symptom management and encouraging exercise to promote weight loss and cardiovascular health are also helpful in preventing disease development. Weight loss, glycemic control, management of diabetes, and management of atherosclerotic coronary artery disease are also key in prevention of disease progression. [8]

In prescribing mineralocorticoid receptor antagonists (MRA's) such as Spironolactone, it is important to routinely check electrolyte levels and monitor renal function, as this medication can result in hyperkalemia, which may manifest as deadly arrhythmias. Additionally, the use of MRA's with concomitant ACE inhibitor use should be done so with caution, as both may contribute to high serum potassium levels, especially in combination. [5][6][8]

Further research is needed to devise proven methods for treating heart failure in patients with preserved ejection fraction and diastolic dysfunction. Current research is lacking in both duration of study and endpoints including mortality. This literature review includes articles following participants for only 6 to 12 months in duration and does not include statistics concerning rates of mortality associated with use of MRA's and beta-blockers.

Further studies need to be performed that include clinical end points of morbidity and mortality. In addition the monitoring and treatment of surrogate endpoints such as hypertension and obesity should also play a major role in the data that is collected in further studies. The spironolactone studies may also benefit from a study that is longer than 6-12 months to further evaluate the effect on diastolic function and ultimately improving symptoms and clinical end points of patient with heart failure with preserved ejection fraction.

Clinical Recommendations

In terms of managing patients in heart failure with a preserved ejection fraction, treatment modalities that exist for systolic failure are typically not accepted as being successful in those with diastolic failure. Results of clinical trials, including the studies in this literature review, suggest that neurohormonal antagonists such as beta-blockers, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers do not decrease the morbidity and mortality of patients in diastolic failure.

At this point, based on results from this literature review and on recommendations made by UpToDate and the American Heart Association, we suggest using pharmacologic treatment with diuretics to target symptom management. We also suggest focusing on lifestyle changes such as diet modification, smoking cessation, and

weight loss with structured exercise plans in order to prevent progression of diastolic dysfunction to HFpEF, which lacks specific treatment regimens. [1]

In addition to lifestyle modifications, tight blood pressure control is warranted, as is the treatment of all lung disease, coronary artery disease, atrial fibrillation, diabetes mellitus, sleep apnea, and renal disease. These comorbid conditions, which are commonly associated with those in HFpEF, should be controlled, as they have significant impact on clinical outcomes.

Currently, UpToDate, which is a well trusted academic resource that many providers use to research evidence-based data to help them with decisions in point of care, recommends the use of mineralocorticoid receptor antagonists such as Spironolactone in the treatment of patients with diastolic failure. [1]

Acknowledgements

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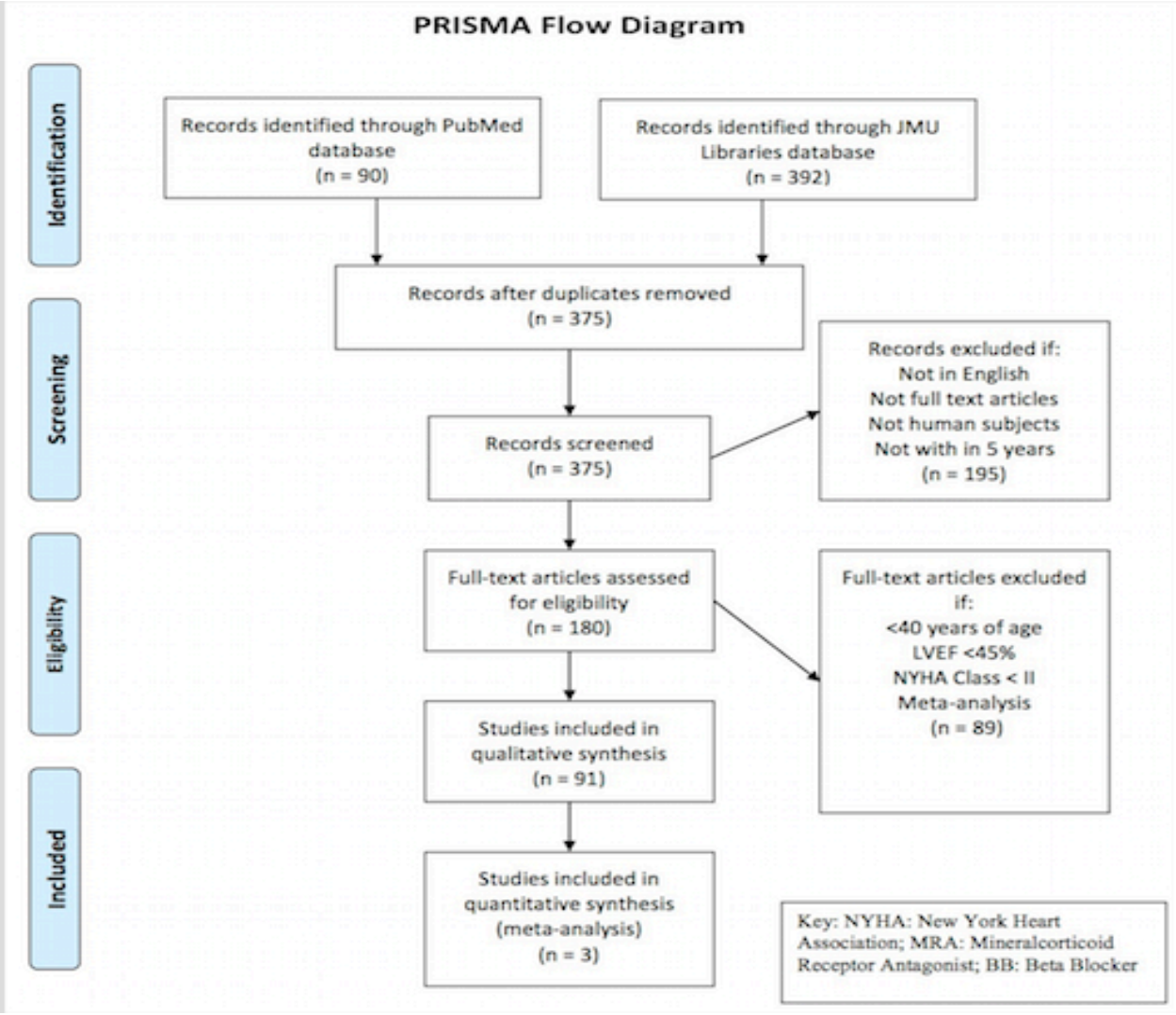
Appendix 1.


PRISMA Flow Diagram
Identification
Screening
Eligibility
Included
Records identified through PubMed database (n = 90)
Records identified through JMU Libraries database (n = 392)
Records after duplicates removed (n = 375)
Records screened (n = 375)
Records excluded if: Not in English Not full text articles Not human subjects Not with in 5 years (n = 195)
Full-text articles assessed for eligibility (n = 180)
Full-text articles excluded if: <40 years of age LVEF <45% NYHA Class < II Meta-analysis (n = 89)
Studies included in qualitative synthesis (n = 91)
Studies included in quantitative synthesis (meta-analysis) (n = 3)
Key: NYHA: New York Heart Association; MRA: Mineralcorticoid Receptor Antagonist; BB: Beta Blocker

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