ISSN: 2577 - 8005

Research Article

Medical & Clinical Research

Impact of beta blockade therapy on heart failure with preserved ejection fraction

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Submitted: 19 Mar 2022; **Accepted**: 26 Mar 2022; **Published**: 11 Apr 2022

Citation: *Miguel Rodriguez-Guerra, Neelanjana Pandey, Mohammed Shaban, Nisha Ali, Singh Tushi, Rahul Anand, Timothy J Vittorio (2022) Impact of beta blockade therapy on heart failure with preserved ejection fraction. Medical & Clinical Research 7(4):38-44.*

Abstract

Background: *Heart failure preserved ejection fraction does not have clear guidelines. Because of past meta-analyses investigations, the Beta-blockade has sparked the most attention.*

Method & Results: *We performed a retrospective observational where 1500 adult patients were studied from the period January 1, 2012 to December 31, 2017. After the review, 625 met the criteria to be included in the study. Cardiac reasons for inpatient admission between patients on beta-blockers vs. not on beta-blockers do not differ. The likelihood of requiring critical care admission was similar, and the likelihood of death due to cardiovascular causes between both groups did not differ.*

Conclusion: *The use of beta-blockade therapy is still a subject of debate, especially in the minority (Hispanic and African American) population.*

Keywords: Heart Failure, HFrEF, HFpEF, Beta Blockers, Mortality.

Introduction

Heart failure with reduced ejection fraction (HFrEF) is known to have well-established clinical guideline-directed medical therapy (GDMT) [1]. However, patients with preserved ejection fraction (HFpEF) do not have clear guidelines. The Beta-blockade because of past meta-analyses investigations, it has sparked the most attention. We performed a retrospective observational analysis to study the effect of beta-blockade in patients with preserved ejection fraction.

Methods

This was a retrospective observational study of 1500 patients from January 1, 2012 to December 31, 2017. We included patients that underwent transthoracic echocardiogram (TTE) with left ventricular ejection fraction (LVEF) above 50% and evidence of diastolic dysfunction, who were followed at least 3 times.

Results

After the review, 625 met the criteria to be included in the study. Approximately 55% were Hispanic, 39% African-American, 5% Caucasian and the remaining 1% Asian. The 90% had grade 1-2 diastolic dysfunction and 15% had baseline arrhythmias (Figure 1). Overall, 27% had the heart rate below 70 bpm at baseline. Overall, the 62% were on beta-blockers. Cardiac reasons for inpatient admission between patients on beta-blockers vs not on beta blockers not differ. The likelihood of requiring critical care admission was similar and the likehood death due to cardiovascular causes between both groups did not differ (Figure 2).

Discussion

HF is a cardiovascular disease with rising incidence and is associated with significant mortality [2]. The main terminology used to describe heart failure (HF) is based on measuring the left ventricular ejection fraction (LVEF). LVEF in the range of 40-49% was recently defined as HF with mid-range EF (HFmrEF) by the 2016 European Society of Cardiology guidelines [3]. HFpEF accounts for more than three-fourths of the HF population [4]. Delepaul et al. Performed a retrospective study including 482

completions with heart failure. They were 258 (53%), 115 (24%), and 109 (23%) patients with HFrEF, HFmrEF.

Beta Blockers and HFpEF

Traditionally, beta blockers (BB) has been considered to be contraindicated in patients with heart failure exacerbation. However, multiple large randomized trials have been stopped early because of significant improvement in mortality rates in patients with HF who received BB in addition to angiotensin-converting enzyme inhibitors(ACIE), diuretics, and digoxin in particular cases [5].The progression of the disease is driven by the neurohormonal cascade, which is blocked by beta-blockade therapy but does not provide symptomatic relief. The BB is now considered the standard therapy in patients with NYHA-fc II or III HfrEF [6]. The COMET trial compared the mortality in New York Heart Association-functional class (NYHA-fc) II HFrEF patients receiving carvedilol vs. metoprolol. It shows the superiority of carvedilol [7]. The CIBIS-II trial showed mortality benefits and reduced hospitalizations in patients with NYHA-fc III-IV receiving bisoprolol [8].

BBs improve survival in patients with heart failure (HF) with reduced ejection fraction, but their effect is inconclusive in those with HF with preserved ejection fraction (HFpEF) [9]. BBs are still widely prescribed to most patients with HFpEF, but their effect on those patients remains questionable [10,11].

Silverman et al. used data of 1761 participants from North and South America in the TOPCAT Trial to determine the association of BB use with HF hospitalizations and cardiovascular disease (CVD) mortality. The BB use was associated with a higher risk of HF hospitalization among patients with an EF of 50% or greater (HR=1.74) but not among those with 45%-49% (HR=0.68). There was a significant interaction between BB use and EF threshold for incident HF hospitalizations. The use of BBs was not associated with a change in CVD mortality [10].

In the CIBIS-ELD trial, 626 patients older than 65 years with HFrEF and 250 with HFpEF were randomized to the maximum tolerated dose of bisoprolol or carvedilol. A twelve-week follow-up was performed to assess the tolerability, HR, blood pressure, LV parameters, 6-minute-walk distance, quality of life, change of NYHA-fc, and NT-proBNP. It showed that HFpEF patients demonstrated higher rates of dose escalation delays and treatment-related side effects. Similar blood pressure and HR reductions were observed in both groups, whereas more remarkable NYHA-fc improvement was reported in HFrEF (HFpEF: 23% vs. HFrEF: 34%). Only HFrEF patients exhibited clinical parameters and left ventricular function improvement. Interestingly, beta-blockade did not affect the established and prognostic markers of diastolic function in either group. Left atrial volume index and Mean E/e' had no significant change in both groups, although E/A increased in HfpEF [11]. Using the data from the CIBIS-ELD trial, Loncar et al. evaluated the effect of BB up-titration on copeptin and NT-proBNP serum levels in 219 elderly patients with HFrEF or HFpEF. After 12 weeks of BB optimization, they found that copeptin correlates faster with BB successful up-titration than NT-proBNP in HFrEF, while the opposite was found in patients with HfpEF [12].

Chronotropic incompetence (CI) is typical in HFpEF and maybe a fundamental reason for exercise intolerance. Althought, the determinants of CI in HFpEF are unknown [13]. Recently in 2021, Palau et al. published their study that aimed to evaluate the effect of BB withdrawal on peak oxygen consumption (peak Vo2) in patients with HFpEF and chronotropic incompetence. They performed a crossover clinical trial consisting of 2 treatment periods of 2 weeks separated by a washout period of 2 weeks. Fifty-two patients with stable HFpEF, NYHA-fc II and III, previous treatment with BBs, and chronotropic incompetence were first randomized to withdrawing from versus continuing BB treatment. They were then crossed over to receive the opposite intervention. Despite no significant baseline differences across treatment arms, Peak Vo2 and peak Vo2% increased significantly after BB withdrawal. In other words, BB withdrawal improved maximal functional capacity in patients with HFpEF and chronotropic incompetence [14].

Klein et al. performed cardiopulmonary exercise testing for 157 patients with HFpEF. CI was diagnosed with a percent heart rate reserve (%HRR) <80 if not a BB and <62 if taking β blockers. Only 108 (69%) achieved a respiratory exchange ratio >1.05 and were included in the final analysis. 70% were women, 62% were taking β blockers, 38% had chronic kidney disease, and 75% of patients had CI. CI was associated with higher BNP, lower estimated glomerular filtration rate (GFR),and more elevated pulmonary artery systolic pressure. After multivariable adjustment, a 1-standard deviation(SD) decrease in GFR was independently associated with CI [13].

In the analysis of the Aldo-DHF trial that included 422 patients with HFpEF, after multiple adjustments, older age was significantly related to decreased peakVO2 and increased E/e', NT-proBNP. Female gender, CAD, BMI, sleep apnea, and CI were significantly associated with lower peakVO2 values. Higher pulse pressure, lower HRs, CI, and BB treatment were associated with higher E/e'. BB treatment was also associated with higher NT-proBNP. After multiple adjustments for demographic and clinical variables, the associations of E/e' with NT-proBNP, LAVI, and LVMI were the only significant ones. They concluded that exercise intolerance in HFpEF is multi-factorial with widely variable interactions with the therapeutic approaches [15].

Böhm et al. analyzed the relationship between heart rate and outcomes in theI-Preserve trial in HFpEF patients older than 60 years of age. Three thousand two hundred seventy-one patients with sinus rhythm and 696 with atrial fibrillation (AF) were analyzed separately. Higher HR was associated with worse outcomes for patients in sinus rhythm, even after adjustment for other prognostic variables as NT-proBNP. Each standard deviation increase in HR (12.4 bpm) was associated with an increase in the risk of 13% for CV death or HF hospitalization. No relationship

between HR and outcomes was observed for patients with AF. BB treatment did not reduce the HR-risk relationship. In other words, HR in sinus rhythm is an independent predictor of adverse clinical outcomes and might be a therapeutic target in HfpEF [16].

The SENIORS trial demonstrated that nebivolol has beneficial effects in patients with heart failure. However, the role of BB therapy in patients with HFPEF was unsettled [17]. The Effect of Long-term Administration of Nebivolol on clinical symptoms, exercise capacity and left ventricular function in patients with Diastolic Dysfunction (ELANDD) study was a prospective study started in 2010 to compare nebivolol to placebo based on the clinical symptoms, exercise capacity and parameters of LV function in patients with HFPEF, 120 patients assessed at 1, 2, 5, and 6 weeks (titration phase), then 12 and 26 weeks [17]. The ELANDD study concluded in 2012 that, compared with placebo, six months of nebivolol treatment did not improve exercise capacity in this patients, likely secondary to its negative chronotropic effect [18].

Simpson et al. used the data of patients with AF included in the Global Group in Chronic Heart Failure (MAGGIC) meta-analysis (3259 patients from 17 studies) to investigate the relationship between heart rate and mortality in patients with HF and coexisting AF. The outcome was all-cause mortality at three years. A higher HR was associated with higher mortality in patients with sinus rhythm (SR) but not in AF patients. The HR does not have the same prognostic significance in patients in AF as it does in those in SR, irrespective of ejection fraction or treatment with BB [19].

More in-depth findings were found by Takada et al. after enrolling 2688 patients in Stage C or D HF with sinus rhythm from the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study (Total number of 10,219 patients). Elevated baseline HR was associated with higher all-cause mortality in both groups (HFrEF and HFpEF). However, high HR was associated with CV deaths in HFpEF (HH 2.17), but the association was modest in HFrEF (HH1.49).In particular, the impact on HF death was different between HFpEF (HH 3.79) and HFrEF (HH 1.07). In contrast, the prognostic effect of baseline HR on non-CV mortality was noted only in patients with HFrEF. Elevated HR was associated with higher CV mortality in HFpEF compared with HFrEF. No significant difference between both groups in all-cause mortality [20].

BB and HF Rehospitalizations Around the World

Clinical studies reporting outcomes of mortality or hospitalization for patients with HFpEF were assigned to BBs treatment, and the non-BBs control group was included [21]. However, in this study, they also found that the BBs therapy for the patients with HFpEF was related to a lower risk of all-cause mortality but not a lower risk of hospitalization. These findings were mainly obtained from observational studies, and further investigations are needed to make an assertion [1]. Another registry, the OPTIMISE-HF, studied the outcomes of elderly patients admitted with heart failure; it found that BBs did not significantly change mortality or rehospitalization risks among patients with HfpEF [1]. Yamamoto reported a registry of Swedish 67 hospitals and 95 outpatient clinics that showed lower all-cause mortality in HFpEF patients on BBs. Still, there was no impact in combined all-cause mortality or heart failure hospitalization [22,23].

Fukuta et al. conduct a meta-analysis of the effect of BBs on mortality in HFpEF. They included 28.636 patients from 14 trials; 3 RCTs (1046 patients), 5 OCSs with propensity score (PS) analysis (12,315 patients), and 6 OCSs without PS analysis (15,275 patients). They found that BB use was associated with improved survival in the pooled analysis of OCSs with PS analysis and OCSs without PS analysis. BB use was associated with a non-significant reduced risk for mortality in the pooled analysis of RCTs. Overall, BBs reduced the risk of mortality by 21% [24]. Another meta-analysis was done with almost the same scope and conclusion by Bavishi et al. using data from 15 observational studies and two randomized control trials involving a total of 27,099 patients. A similar finding of BB related reduction of all-cause mortality, but not HF hospitalization. Subgroup analysis revealed that the survival benefits of BB were limited to studies with mean age <75 years. In the two RCTs where the use of BB was not associated with all-cause mortality, Bavishi et al. attributed that to the observation that both trials were not adequately powered and had a high loss to follow-up rates [25]. Also, in the meta-analysis done by Liu et al. using the database of 21.206 patients, they found that BB exposure was associated with a 9% reduction in relative risk for all-cause mortality in patients with HFpEF. However, this treatment did not affect all-cause hospitalization, HF hospitalization, and composite outcomes (mortality and hospitalization) [26].

In our study, in concordance with the previous studies, cardiac reasons for inpatient admission between patients on BBs vs. not on BBs did not differ. In addition, the likelihood of requiring critical care admission was similar.

Vicent et al. reported a multicentre prospective registry in 20 Spanish hospitals, including 583 patients with HFrEF, 227 patients with HFmrEF, and 610 with HFpEF after acute HF hospitalization. Discharge treatment with ACEI /ARB was independently associated with a reduction in mortality and HF admissions (HR 0.61), more evident in HFrEF (HR 0.54) compared with HRmEF (HR 0.64), or HFpEF (HR 0.70). In patients with HFrEF, BB was associated with the lowest mortality risk [27].

Data of 13,687 patients were collected prospectively after hospitalization with HF to find out the HF epidemiology in China. 36% had HFpEF. The systolic blood pressure, age, and body mass index were lower than in other high-income countries compared with previously published literature. Common comorbidities included hypertension (50.9%), coronary heart disease (49.6%), and atrial fibrillation (24.4%). The use of BBs at admission was 25.6%, lower than in other registries. The median hospitalization length of stay was ten days, and in-hospital mortality was 4.1%. Predictors of mortality included low systolic blood pressure, acute

myocardial infarction, infection, right bundle branch block, and elevated total bilirubin and blood urea nitrogen level [28].

Miller et al. performed a retrospective cohort study in 935 patients (55% with preserved LVEF) discharged with concurrent diagnoses of HF and AF. Neither BB dose nor predischarge HR was associated with mortality or cardiovascular rehospitalization over a median of 2.9 years. However, tachycardia at admission (HR>120bpm) was associated with a reduced risk of the composite outcome in patients with both reduced LVEF and preserved LVEF [29].

Khalil et al. conducted a prospective multicentre study of 5005 patients from the middle east after being hospitalized with acute heart failure. It showed that non-withdrawal of BBs in acutely decompensated chronic and de novo HFrEF lowered the intrahospital mortality. However, it does not influence 3-month and 12-month mortality, rehospitalization for heart failure, and the length of hospital stay [30].

In a study trying to identify which HFpEF subgroups would get benefits of BB therapy, Park et al. performed a five years follow-up study in South Korea, including 1,969 patients with LVEF ≥ 40% to assess all-cause mortality. Seven hundred fifty-two patients (38.2%) died within five years. They found that the use of BBs is associated with improved survival in those with global longitudinal strain (GLS) <14% in patients with HF and LVEF ≥ 40%. They suggested stratifying HFpEF patients with GLS to identify those who could benefit from BBs. No significant interaction between BBs and other variables was found except for GLS [9]. HFpEF could also have some unique gender-related dose specifications rather than HFpEF. Bots et al. investigated Heart failure medication dosage and survival in 561 women (49% was HFpEF), compared to 615 men (25% with HFpEF) for a median follow-up period of 3.7 years. The mean target dose was 50% for ACEI/ARBs and BBs in both sexes. The study showed that a lower than 50% dose of ACEI/ARB was associated with less mortality in females with HFrEF but not in males. This difference disappeared in HFpEF. The dosage of BB was not associated with all-cause mortality [31].

Other Therapies in HFpEF

ACEI/ARBs are still widely acceptable therapeutic agents for HFpEF. A combination of both in HFpEF is not recommended yet. Parthasarathy et al. randomized 152 patients with symptomatic HFPEF to receive placebo or valsartan 80 mg, titrated up to 320 mg. Most patients had well-controlled hypertension, and >50% received another ACEI and/or BBs. After 14 weeks, Valsartan had no significant effect on exercise time, 6 min walking test, exertionalsymptoms, brain natriuretic peptide levels, echocardiographic parameters, or quality-of-life scores. Valsartan significantly lowered peak exercise systolic BP and improved ratings of perceived exertion (Borg score). [32]. The supplemental benefit of an angiotensin receptor blocker in hypertensive patients with stable heart failure using olmesartan, the SUPPORT trial, was done by Sakata et al. to assess the clinical values of adding olmesartan in patients with hypertension and chronic heart failure [33]. In this subanalysis study of the SUPPORT Trial, Miura et al. reported 1,147 patients, 429 patients with HFrEF, and 709 with HFpEF observed for a median follow-up of 4.4 years. In HFrEF patients, the addition of olmesartan to the combination of ACEI and BB was associated with increased mortality (HR=2.26) and worsening renal function (HR=2.01); however, its addition to ACEI or BB alone was not. In contrast, in HFpEF patients, the addition of olmesartan to BB alone was significantly associated with reduced mortality (HR=0.32), whereas with ACEIs alone or in combination with BB and ACEI was not [34].

Metformin treatment may be associated with a reduction in mortality in patients with HFpEF. Halabi et al. used data from four studies that reported the proportion of patients with HFpEF to perform a metanalysis to determine the interaction between metformin and HF subgroups on the mortality. Metformin reduced mortality in both HFrEF and HFpEF after the HF therapies such as ACEI and BB. Metformin treatment with insulin, ACEi, and BB therapy was also shown to reduce mortality, especially in males compared to females who had worse outcomes [35].

In the update of CCS/CHFS Heart Failure Guidelines, patient subgroups with HFpEF might benefit from the use of sacubitril/valsartan; however, further data are needed to clarify the effect of this therapy in patients with HFpEF. Sodium-glucose co-transport inhibitors reduce the risk of incident HF, HF-related hospitalizations, and cardiovascular death in type 2 diabetes and cardiovascular disease patients. Clinical trials recently showed that dapagliflozin provides significant outcome benefits in well-treated patients with HFrEF, with or without type 2 diabetes [36].

Experimental Therapies

Clinical trials are ongoing to find new therapies for HFpEF. Beta-3 Agonists are an emerging treatment modality. The third isotype beta-adrenoreceptors, B3AR, were more recently identified in cardiac myocytes and endothelial cells, where their distinctive coupling to nitric oxide and antioxidant pathways suggested potential protective properties. The B3AR agonist, mirabegron, beneficial effects in patients with/at risk of developing HFpEF are investigated in an ongoing clinical trial [37].

Cardiac fibroblasts are essential mediators for fibrotic remodeling in heart failure. They transform into myofibroblasts in the presence of transforming growth factor-β, causing more myocardial fibrosis and accelerating decompensated HF progression. Bradley et al.investigated the effects of a novel inhibitor (NM922) on the transformation of myocardial fibroblasts into the myofibroblast phenotype in the setting of pressure overload-induced HF. NM922 inhibited fibroblast-to-myofibroblast transformation in vitro, preserved left ventricular ejection fraction, and significantly attenuated transverse aortic constriction-induced LV dilation and hypertrophy in a murine model of HFrEF. NM922 treatment after the onset of cardiac hypertrophy and HF resulted in less myocardial collagen formation, less adverse remodeling, and left

ventricular ejection fraction preservation. Future studies aim to elucidate further the molecular and cellular mechanisms by which this novel antifibrotic agent protects the failing heart [38].

Another agent, Si-Miao-Yong-An decoction (SMYAD), was studied by Su et al.. SMYAD was administered to the mice for four weeks after sham or transverse aortic constriction (TAC) surgery to induce heart hypertrophy. SMYAD improved cardiac dysfunction with preserved left ventricular ejection fraction. SMYAD treatment significantly attenuated cardiac hypertrophy as reflected by the inhibition of atrial natriuretic peptide, BNP, β-myosin heavy chain mRNA expression, and by decreasing cardiac myocyte cross-sectional area. SMYAD is thought to exert this effect by inhibiting platelet aggregation and activation, as revealed by CD41/CD61/P-selectin downregulation [39].

Conclusion

Several analyses demonstrated a reduction in mortality. However, observational studies are not able to show similar results. The use of beta-blockade therapy is still a subject for debate especially on in minority (Hispanic and African American) population.

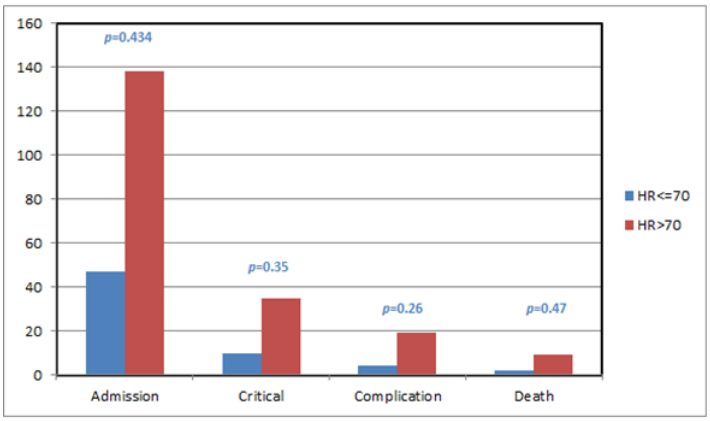

Figure 1:

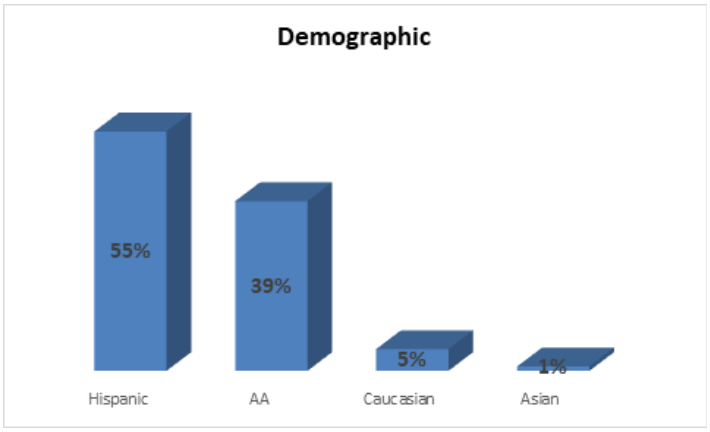

Figure 2:

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