DOI- https://doi.org/10.3329/cardio.v17i1.80000

Editorial

Beta-blockers in Heart Failure with Preserved Ejection Fraction and Comorbidities

Prof. Abdullah Al Shafi Majumder

Prof. Abdullah Al Shafi Majumder, Bangladesh Specialized Hospital, Dhaka, Bangladesh.

Keywords: *Heart failure, beta blocker, Ejection fraction.*

(Cardiovasc j 2024; 17(1): 1-4)

In contrast to universal recommendations for the therapeutic management of heart failure with reduced ejection fraction, role of beta-blockers in heart failure with preserved ejection fraction (HFpEF) is debatable and controversial.[1-3] This is well understood considering the different pathophysiology of the two phenotypes; though both of them present with same clinical features of heart failure.[1,2] In heart failure with reduced ejection fraction (HFrEF), beta-blockers are used to fight back the increased sympathetic activity that results from the compensatory mechanisms; which is initially beneficial and later self-defeating.[1,3] In contrast there is chronotropic incompetence in many cases of HFpEF, thus raising the fear of the use of beta-blockers.[4]

In the setting of HFpEF, beta-blockers exert dual opposing functions. Beta-blockers reduce ventricular rate and prolong the diastolic period thus favorably impact LV diastolic filling by reducing myocardial ischemia and prolonging diastolic period and may thereby improve symptoms and exercise capacity in HFpEF patients, particularly in those with coronary artery disease (CAD) or atrial fibrillation (AF). But negative chronotropic effects may lead to worsened exercise capacity. Balance between the effects on increasing diastolic filling period and increasing chronotropic incompetence will be determinant for beneficial vs. harmful effects of beta-blockers in HFpEF.[5]

A number of discussions centering the use of beta blocker in HFpEF has been made for last many years. A study in 2009 on 7154 hospitalized patients with either HFrEF and HFpEF was done to examine associations between initiation of beta-blocker therapy and outcomes among elderly patients hospitalized for heart failure. While Beta-blocker use was clinically associated with lower risks of death and rehospitalization in HFrEF patients but it was associated with poor outcomes, and beta-blockers did not significantly influence the mortality and rehospitalization risks in HFpEF patients.[4]

In SENIORS trial,[6] 2128 patients, aged >70 years with LVEF >40% were included . Reduction in composite of all-cause mortality or HF hospitalization with the use of nebivolol was noted. Post hoc analysis of TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist), which randomized patients with LVEF >45% to receive spironolactone or placebo, found that beta-blocker use was associated with an increased risk of HF hospitalization in patients with LVEF >50%.[7]

An individual patient-level analysis of double-blind randomized trials from NCDR-PINNACLE (National Cardiovascular Data Registry–Practice Innovation and Clinical Excellence) registry, involving 4,35,897 patients aged >65 years with LVEF >40%, found that there is significant relationship between LVEF and beta blocker use and HF hospitalization, death, and the composite of HF hospitalization and death. There is higher risk of events with higher ejection fraction.[8]

Address of Correspondence: Prof. Abdullah Al Shafi Majumder, Bangladesh Specialized Hospital, Dhaka, Bangladesh. Email: m.abdullaalshafi@yahoo.com

Analysis of the SwedeHF (Swedish Heart Failure) registry that included 6,618 patients with HF with LVEF >50% showed that beta-blockers were neither associated with nor did they modify risk for HF hospitalization or CV death.[9]

In a review Xu X & Wang DW analysed number of studies regarding the use of beta blockers in HFpEF. They pointed that in SWEDEC study, treatment with carvedilol resulted in a significant improvement in E/A ratio in patients with heart failure due to a left ventricular relaxation abnormality. Due to limitation of this echocardiographic index, no conclusion can be derived from this study.[10] The reviewers cited the result of a study that high-dose beta blockers use on discharge of hospitalized HFpEF patients were associated with a significantly lower risk of all-cause mortality, but not with heart failure hospitalization.[11] These data indicate the beneficial effects of beta blockers. Considering all these data the authors conclude that results regarding the use of beta blocker are inconsistent and we have wait for future studies to make a proper decision.

Use of beta blocker in HFpEF with comorbidities

Hypertension is a common association of HFpEF. Recommended therapeutic agents to control hypertension to a level of BP 130/80 mmHg, are diuretics; ARNI; ACEi. ARBs. Beta blockers are not first choice. In presence of tachycardia or ischaemic background. vasodilatory beta-blockers such as nevibolol may be used.

Atrial fibrillation is highly prevalent in HFpEF and its presence indicates more advanced disease with poorer exercise capacity along with increased mortality. Aggressive measures including catheter ablation for rhythm control is recommended.[12] Rate control by beta blockers (metoprolol and carvedilol) vs. calcium channel blockers – diltiazem and verapamil were compared and found that treatment with beta-blockers reduced the exercise capacity whereas that with calcium channel blockers increased the exercise capacity and reduced the NT-proBNP level. Aggressive rate control is deleterious as there is LA dysfunction with low stroke volume and LV output may be compromised on decrease in heart rate.

In a review of hypertension in HFpEF, the authors discussed the use of beta-blockers (along with other anti-hypertensive agents) in hypertension in the setting of HFpEF.[13] They considered the findings of OPTIMIZE HF registry[4] and the ELANDD study[14]. ELANDD study comprised 116 patients and failed to show improvement in 6 minutes walk distance or quality of life. A study on Japanese patients - J-DHF study (245 patients) found that standard-dose carvedilol (> 7.5 mg/day) may be effective in reducing the composite outcome of cardiovascular death and unplanned HF hospitalization; however, the study was underpowered, and the findings were not conclusive.[15] There was no difference in primary outcome of CV death and heart failure hospitalization. At the end the authors opined that although beta-blockers demonstrate some promise in the management of HFpEF, the findings remain inconclusive.

In this year, two observations regarding the effects of beta-blockers on HFpEF are encouraging for use of beta-blockers in the context HFpEF: one is meta-analysis and another one is post hoc analysis.

A systematic review and meta-analysis was conducted by some authors to find out whether use of beta-blockers in HFpEF was beneficial or not. One randomized trial and 15 cohort observational studies were taken for analysis. The studies enrolled 27,188 patients, out of whom 17,232 (63.4 %) were treated with a beta-blocker and 9,956 (36.6 %) without it. This meta-analysis showed beta-blocker therapy has the potential to reduce all-cause mortality in patients with HFpEF based on observational studies, while it did not affect rehospitalization for heart failure or its composite with all-cause mortality.[3]

Recently a post-hoc analysis of the use of beta-blockers in the patients of HFpEF has been made from the data of DELIVER trial, which was done to see the efficacy and safety of a SGLT2 inhibitor dapagliflozin.[16] A total of 6,263 patients with symptomatic heart failure with a left ventricular ejection fraction (LVEF) >40% were randomized to dapagliflozin or placebo. Beta-blockers were used in 5,177 patients (83%) or 4 out of 5 participants were treated with a beta-blocker. Two conclusions have been made by the authors: there

was no worsening of heart failure in those on beta blockers and effectiveness of dapagliflozin was observed whether the patients were on beta-blockers or not. Beta-blocker use was associated with a lower risk of worsening HF or cardiovascular death.

There were important editorial comments on this post-hoc analysis in the same issue of JACC Heart Failure - findings that these drugs are not harmful and that adding an SGLT2i to a medical regimen that already contains a beta-blocker will not adversely affect outcomes are reassuring. And the authors added "It by no means settles the issue."[17]

In a long review on the management of HFpEF, Niyati Grewal et al noted that there is no trial that could show the benefits of beta blockers and thereby there is no recommendation for their use.[18]

What we have learnt?

Beta blockers may be used in the presence of co-morbities that require management by beta – blockers. For the management per se of HFpEF, role of beta blockers is yet to be defined. Rather it is on the negative side till now. It has been recommended that when there is deterioration of clinical conditions on proper management along with beta blockers, withdrawal of beta-blockers is imperative. We have to wait to see further studies to consider the efficacy and safety of the beta blockers in the management of heart failure with preserved ejection fraction.

Conflict of Interest - None.

References:

1 Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(17):1757-1780. doi:10.1016/j.jacc.2021.12.011

2 McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [published correction appears in Eur Heart J. 2021 Dec 21;42(48):4901. doi: 10.1093/eurheartj/ehab670]. *Eur Heart J*. 2021;42(36):3599-3726. doi:10.1093/eurheartj/ehab368

3 Kaddoura R, Madurasinghe V, Chapra A, Abushanab D, Al-Badriyeh D, Patel A. Beta-blocker therapy in heart failure with preserved ejection fraction (B-HFpEF): A systematic review and meta-analysis. *Curr Probl Cardiol*. 2024;49(3):102376. doi:10.1016/j.cpcardiol.2024.102376

4 Hernandez AF, Hammill BG, O'Connor CM, Schulman KA, Curtis LH, Fonarow GC. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. *J Am Coll Cardiol*. 2009;53(2):184-192. doi:10s.1016/j.jacc.2008.09.031

5 Fukuta H, Goto T, Kamiya T. Effects of beta-blocker withdrawal in patients with heart failure with preserved ejection fraction: A protocol for systematic review and meta-analysis. *PLoS One*. 2023;18(11):e0294347. Published 2023 Nov 16. doi:10.1371/journal.pone.0294347

6 Flather MD, Shibata MC, Coats AJ, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur Heart J*. 2005;26(3):215-225. doi:10.1093/eurheartj/ehi115

7 Silverman DN, Plante TB, Infeld M, et al. Association of â-Blocker Use With Heart Failure Hospitalizations and Cardiovascular Disease Mortality Among Patients With Heart Failure With a Preserved Ejection Fraction: A Secondary Analysis of the TOPCAT Trial. *JAMA Netw Open*. 2019;2(12):e1916598. Published 2019 Dec 2. doi:10.1001/jamanetworkopen.2019.16598

8 Cleland JGF, Bunting KV, Flather MD, et al. Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials. *Eur Heart J*. 2018;39(1):26-35. doi:10.1093/eurheartj/ehx564

9 Meyer M, Du Fay Lavallaz J, Benson L, Savarese G, Dahlström U, Lund LH. Association Between â-Blockers and Outcomes in Heart Failure With Preserved Ejection Fraction: Current Insights From the SwedeHF Registry. *J Card Fail*. 2021;27(11):1165-1174. doi:10.1016/j.cardfail.2021.04.015

10 Xu X, Wang DW. The progress and controversial of the use of beta blockers in patients with heart failure with a preserved ejection fraction. *Int J Cardiol Heart Vasc*. 2019;26:100451. Published 2019 Dec 13. doi:10.1016/j.ijcha.2019.100451

11 Lam PH, Gupta N, Dooley DJ, et al. Role of High-Dose Beta-Blockers in Patients with Heart Failure with Preserved Ejection Fraction and Elevated Heart Rate. *Am J Med*. 2018;131(12):1473-1481. doi:10.1016/j.amjmed.2018.07.008

12 Lundström T, Rydén L. Ventricular rate control and exercise performance in chronic atrial fibrillation: effects of diltiazem and verapamil. *J Am Coll Cardiol*. 1990;16(1):86-90. doi:10.1016/0735-1097(90)90461-w

13 Hiraiwa H, Okumura T, Murohara T. Drug Therapy for Acute and Chronic Heart Failure with Preserved Ejection Fraction with Hypertension: A State-of-the-Art

Review. *Am J Cardiovasc Drugs*. 2024;24(3):343-369. doi:10.1007/s40256-024-00641-9

14 Conraads VM, Metra M, Kamp O, et al. 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 ELANDD study. *Eur J Heart Fail*. 2012;14(2):219-225. doi:10.1093/eurjhf/hfr161

15 Yamamoto K, Origasa H, Hori M; J-DHF Investigators. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). *Eur J Heart Fail*. 2013;15(1):110-118. doi:10.1093/eurjhf/hfs141

16 Peikert A, Bart BA, Vaduganathan M, et al. Contemporary Use and Implications of Beta-Blockers in Patients With HFmrEF or HFpEF: The DELIVER Trial. *JACC Heart Fail*. 2024;12(4):631-644. doi:10.1016/j.jchf.2023.09.007

17 Hong KN, Greenberg B. Beta-Blockers in HFpEF: Finding a Role, Easy…Finding the Evidence, Not So Much. *JACC Heart Fail*. 2024;12(4):645-647. doi:10.1016/j.jchf.2024.01.017

18 Grewal N, Grewal JS, Aldhaeefi M, Mehrotra PP, Fatima U. Navigating the evolving landscape of HFpEF management: A detailed look at key ACC/AHA/ESC guideline updates. *Cardiovasc Revasc Med*. 2024;68:79-85. doi:10.1016/j.carrev.2024.04.004

19 Patel K, Fonarow GC, Ekundayo OJ, et al. Beta-blockers in older patients with heart failure and preserved ejection fraction: class, dosage, and outcomes. *Int J Cardiol*. 2014;173(3):393-401. doi:10.1016/j.ijcard.2014.03.005

20 Shah R, Wang Y, Foody JM. Effect of statins, angiotensin-converting enzyme inhibitors, and beta blockers on survival in patients >or=65 years of age with heart failure and preserved left ventricular systolic function. *Am J Cardiol*. 2008;101(2):217-222. doi:10.1016/j.amjcard.2007.08.050

21 Kim SH, Yun SC, Park JJ, et al. Beta-Blockers in Patients with Heart Failure with Preserved Ejection Fraction: Results from The Korea Acute Heart Failure (KorAHF) Registry. *Korean Circ J*. 2019;49(3):238-248. doi:10.4070/kcj.2018.0259

22 Tsujimoto T, Kajio H. Beta-blocker use and cardiovascular event risk in patients with heart failure with preserved ejection fraction. *Sci Rep*. 2018;8(1):9556. Published 2018 Jun 22. doi:10.1038/s41598-018-27799-y

23 European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC) [published correction appears in Eur Heart J. 2011 May;32(9):1172]. *Eur Heart J*. 2010;31(19):2369-2429. doi:10.1093/eurheartj/ehq278

24 Fuster V, Rydén LE, Cannom DS, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011;123(10):e269-e367. doi:10.1161/CIR.0b013e318214876d

25 Kubac G, Malowany L. Functional capacity of patients with atrial fibrillation and controlled heart rate before and after cardioversion. *Can J Cardiol*. 1992;8(9):941-946

26 Ulimoen SR, Enger S, Pripp AH, et al. Calcium channel blockers improve exercise capacity and reduce N-terminal Pro-B-type natriuretic peptide levels compared with beta-blockers in patients with permanent atrial fibrillation. *Eur Heart J*. 2014;35(8):517-524. doi:10.1093/eurheartj/eht429