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Research Article

A Narrative Review of Efficacy, Safety, and Prognostic Role of Beta-Blockers in Patients with Heart Failure with Preserved Ejection Fraction

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Abstract

Background: Medical management of Heart failure with preserved ejection fraction (HFpEF) remains uncertain, especially beta blockers (BBs) had various outcomes in studies. The objective of the present study is to review the efficacy and prognostic role of BBs in patients with HFpEF. *Methods:* A total of 58 articles were chosen for this narrative review from sources including web of science, PUBMED and Google Scholar. *Results:* Patients with HFpEF are more prevalent in female. The average age of patients is usually 70-80 years. The most important risk factors for this condition include advanced age, female gender, hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), and atrial fibrillation (AF). Despite a lack of evidence or indication, BBs are still extensively prescribed in HFpEF. In patients with HFpEF, BBs reduce blood pressure, left ventricular hypertrophy, and diastolic dysfunction by slowing heart rate and myocardial oxygen demand. BBs reduce blood pressure, but despite this, they do not improve the quality of life, cardiovascular events, and all-cause mortality. BBs may even be associated with an increased risk of HF hospitalization. In some studies, Carvedilol and Nebivolol were associated with improvement of functional capacity, NT Pro-BNP levels, and survival. Overally, using the BBs, recommended for patients of HFPEF with atrial fibrillation, hypertension, and coronary artery disease. *Conclusion:* BBs does not have a beneficial effect on quality of life and survival, and is also linked to a higher risk of HF-related hospitalizations. The use of BBs is not recommended for the treatment of HFpEF.

Keywords

Heart Failure with Preserved Ejection Fraction, Beta Blocker, Efficacy, Prognosis, Review

1. Introduction

Heart failure (HF) is regarded as an important healthcare issue all over the world, affecting up to 10 million people in the next 5 years. High hospitalizations, high complications of the disease and medications, and high mortality in these patients are a major issue for healthcare organizations and patients [1, 2]. HF is classified into HF with reduced ejection fraction (HFrEF), within an EF of less than 50% AND HF with preserved ejection fraction (HFpEF), within an EF of 50% or higher [3]. The prevalence of HFpEF is slightly higher than

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that of HFrEF, affecting approximately 32 million people all over the world. These patients have an average of 1.5 times hospitalizations per year and a 15% mortality rate per year [4].

Management of these patients remains challenging. Lifestyle modification is emphasized, similar to patients with HFrEF. However, medication has encountered challenges in various studies. Medication strategies include angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNI), beta blockers (BBs), mineralocorticoid receptor antagonists (MRA), and sodium-glucose cotransporter-2 inhibitors (SGLT-2i) [5, 6]. BBs had various outcomes in studies in patients with HFpEF. In this study, we aim to review the efficacy, safety, and prognostic role of BBs in patients with HFpEF.

2. Methods

In November 2025, we conducted a narrative review to investigate the potential roles of BB in the efficacy, safety, and prognostic role in patients with HFpEF. The review followed the methodological framework for literature reviews proposed by the Scale for the Assessment of Narrative Review Articles (SANRA). articles not in English; articles lacking sufficient data; letters to the editor; editorials; hypothesis articles; congress abstracts; opinion articles; articles discussing other cardiovascular conditions or related factors were excluded. To specify pivotal studies relevant to this topic, searches were guided in the PUBMED, SCOPUS, and EMBASE databases. Our search strategy was terms related to “heart failure,” “diastolic,” “preserved,” “heart failure with preserved ejection fraction,” “beta adrenergic receptor blocking agent,” “beta blockers,” “BBs,” individual beta-blocker agents (acebutolol, alprenolol, atenolol, betaxolol, bisoprolol, carvedilol, esmolol, labetalol, metoprolol succinate, Metoprolol tartarate, nadolol, nebivolol, penbutolol, pindolol, propranolol, sotalol, and timolol). The search produced 428 articles in PubMed, 257 in SCOPUS, and 97 in EMBASE. Studies on the use of BBs in patients with a history of acute coronary events or ischemic cardiomyopathy were excluded. Also, we excluded case reports and letters. Finally after the omission of duplicate articles, 58 articles remained which is given in detail in Table 1. The cut-off LVEF to define HFpEF was EF≥ 50% [3]. In this article, no ethical code was obtained because this study is based on the published literature, and it does not use any original data from human or animal studies led by the author.

Table 1. *Summaries of the studies about efficacy, safety, and prognostic role of Beta-Blockers in patients with heart failure with preserved ejection fraction.*

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
Arnold SV et al/2023 [1]	USA	435,897 patients	52.6	76.1 ± 7.8	29.5 ± 6.0	DM:30.3 CVA:15.6 AF/AFl:45 CAD:70 CKD:9.5	RCT	–	LVEF: 56.8 ± 9.6	lack of survival benefit and a higher risk of HF hospitalization associated with the use of BBs.
Palau P et al /2021 [2]	Spain	52 patients	40.4	72.6 ± 13.1	31.1 ± 4.7	HTN: 88.5 DM:40.4 IHD:23.1 CVA:1.9 AF:38.5 COPD:11.5	RCT	III/IV: 34.6	LVEF: 64.7 ± 7.1 LAVI, mL/m2: 39.8 ± 13.7 LVMI, g/m2: 108.0 ± 31.6 E/e′: 14.6	BBs withdrawal resulted in a short-term improvement of maximal functional capacity and chronotropic incompetence.
Matsumoto S et al/2025 [3]	UK	16951 patients	50.2	71.5±8.7	–	AF: 48.7	Observational Study	–	LVEF: 56.2±8.6	There was no suggestion that BBs use was associated with worse HF outcomes in HFmrEF/HFpEF.
Palau P et al/2024 [4]	Spain	52 patients	40	74.7	31.1	HTN:44.2 DM:20.1 IHD:11.5 AF:19.2	RCT	III/IV	LVEDV, mL/m2: 44.7 LVEF: 64.7 LAVI, mL/m2: 39.8 LVMI, g/m2: 108	Lower iLVESV could identify patients in whom BBs withdrawal was associated with a greater short-term improvement in maximal functional capacity.

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
									E/e': 14.7	
Peikert A et al/2024 [5]	USA	3,131 patients	56.1	71.7 ± 9.6	29.8 ± 6.1	AF:56.7 CVA:9.5 DM:44.8 MI: 26.2 HTN:88.7 CAD:51.4	RCT	I: 0.0 II: 75.3 III: 24.4 IV: 0.3	LVEF,%:54.2 ± 8.8	BBs use was not associated with a higher risk of worsening HF or CV death and QOL.
Fu EL et al/2020 [6]	Netherlands	3775 patients	64.1	80.2	26.8	AF:61.4 COPD:16.5 DM:39.3 HTN:75.4 IHD:74.5 CVA:19.3	Observational Study	I:2.03 II:19.1 III:39.2 IV:8.8	–	In patients with HFpEF in sinus rhythm, BBs use was not related to one-year mortality or mortality plus HF readmission.
Yang Y et al/2020 [7]	China	78 patients	44.9	76	–	HTN:66.5 DM:29.8 AMI:9.4 CVA:25.7	cohort study	–	LAD (mm):44 (40–48) LVEDD (mm):47 (43–51) PAP (mmHg):42.2 ± 12.2	In HFpEF patients with AF, BBs is associated with significantly lower all-cause mortality, but may increase the risk of HF rehospitalization.
Abdel Jawad M et al/2025 [8]	USA	1726 patients	50.1	71.6	33.8	MI: 20.4 PAD:11.8 CVA: 8.9 AF:42.3 OAD:16.7 DM: 44.7 HTN:89.9	RCT	–	EF:57.7% HR: 76 bpm	BBs use was not associated with significantly different concurrent HF–specific health status or modification of the health status.
Tsujimoto T ETAL/2018 [9]	Japan	6834 patients	48.3	68.5	32.1	DM:32.4 HTN:91.4 MI:12.9 CVA:7.7 AF:35.2 COPD:11.6	RCT	I/II:67.04 III/IV:32.96	--------	NYHA functional classification was not significantly different between those on and not on BBs.
Silverman DN et al/2019 [10]	USA	1394 patients	51.8	71.3	34	MI:20.3 HTN:90.1 AF:42.2	RCT	III/IV	EF:58.17 EF ≥50%:88.9 EF ≥60%:48.5	BBs use in the TOPCAT trial cohort was associated with a higher risk for incident HF hospitalization, without an associated change in CVD mortality.
Yum B et al/2019 [11]	USA	207 patients	44	77	–	HTN: 83 CAD: 64 DM: 50 AF/AFl:44 COPD: 43 CKD: 42 CVA: 18	Observational Study	–	–	BBs can worsen function in patients with geriatric conditions and can increase their risk for adverse drug reactions.
Farasat SM et al/2010	USA	66 patients	32	71 ± 13	–	–	Comparative	–	–	BBs may be associated with a higher risk of HF rehospitalization in

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
[12]							Study			women with HFpEF.
Patel K et al/2014 [13]	USA	2553 patients	35.5	81.2±8	_	CAD:40.3 HTN:72.6 DM:36.9 AF:33.4 COPD:24.7 CKD:6.1	RCT	_	_	BBs has not independent associations with long-term outcomes, regardless of evidence class or daily dosages used.
Meyer M et al/2021 [14]	USA	14434 patients	48.6	79.3	BMI ≥30 kg/m^2 : 20.3	HTN:70.6 DM:27.6 PAD:9.5 AF:61.3 COPD:16.4	RCT	I:8.7 II:26.8 III:19.7 IV:1.6	–	No associations between BBs and outcomes. The adverse BBs effects should be considered in a patient group that is prone to polypharmacy.
Lund LH et al/2014 [15]	Sweden	5496 patients	54	78	–	HTN:58 DM:25 MI:32 AF/AFl:52	RCT	I:19 II:46 III:31 IV:4	LVEF%: 40-49: 44 ≥50: 58	BBs was associated with lower all-cause mortality but not with combined all-cause mortality or HFH.
Harada E et al/2022 [16]	Japan	721 patients	25.5	81.8± 8.9	21.49	AF: 18.8 HTN: 80.1 DM: 39.6 DLP: 33.3	RCT	–	LVEF:67.6% E/e′:17.6 E/A:0.76 LVDd,:41.4 mm LVDv:28.9mm/m^2 LAD:36.4mm RWT:0.527	BBs were associated with high-plasma BNP levels in conjunction with the structural and functional alterations of the heart differently in men and women with HFpEF in SR but not in AF.
Maldonado-Martín S et al/2020 [17]	Spain	59 patients	29.7	70.7±6.8	30.9± 4.7	HTN:92.2 DM:18.8	RCT	I: 0 II: 67.2 III: 32.8	–	BBs may favorably alter the biological properties of the cardiac autonomic system regulation in elderly patients with HFpEF, such as HRpeak, HRresv, HRrecov, and Vo2 peak.
Palau P et al/2020 [18]	Spain	28 patients	32.10	74.3 (68-77)	–	–	RCT	–	–	BBs in HFpEF patients has not benefit, even less in those with documented chronotropic incompetence.
Lam PH et al/2018 [19]	USA	1370 patients	34.17	76	_	HTN:80.1 CAD:44.6 MI:17.1 DM:43.9 AF:39 COPD:24.2	RCT	_	LVEF:58.6	In patients with HFpEF and heart rate ≥70 beats/minute, high-dose BBs use was associated with a significantly lower risk of total mortality.
Seko Y et al/2022 [20]	Japan	388 patients	51.1	87.1±12	BMI ≤22 kg/m2: 59.27	HTN:65.7 DM:30.4 AF:40.9 VT/VF:0.2 MI:10.5	observational	_	HFpEF (EF ≥50%):55.6 HFmrEF (EF 40–49%):44.3	Starting both ACE-I/ARB and BBs were associated with a reduced risk of the composite of all-cause death or HFH.

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
Kim SH et al/2019 [21]	Korea	4045 patients	42.6	71.4±13.4	23.6±3.8	HTN:67.7 DM:35.9 IHD:38.4 CHF:39.2 AF:32.9 COPD:12.1 CKD:12.7	cohort study	II:17.7 III:36.8 IV:45.4	EF:53.6±9.1 LAD (mm):48.8±10.7	BBs is associated with reduced all-cause death but not with reduced re-hospitalization.
Harada D et al/2020 [22]	Japan	213 patient	47.41	75.8	23.7	HTN:90.6 DM:23.0 AF:23.9 COPD:7.9	cohort study	–	LVEF:65.3 LVEDD, mm:47.2 IVST, mm:10.63 PWT, mm:10.5 LVMI, g/m2:140.8 E/e′:11.1	BBs were not associated with a reduction in the rate of cardiovascular events but it may have beneficial effects on HFpEF with preserved RV function. RV function may serve as an indicator in patients with HFpEF.
Yamamoto K et al/2014 [23]	Japan	245 patients	57.9	72 ±10.7	24.1±4.2	AF:48.1 HTN:80.4 IHD:26.1 DM:30.6 DLP:40.8	RCT	I:18.3 II:72.2 III:7.7 IV:1.6	LVEF:62±10.2 LVEDD (mm):50±7.7 LVMI (g/m2) 7:63.2±24.8 PWT:0.4±0.1	Carvedilol may exert greater reduction of the incidence of clinical outcomes in the patients with HFPEF and advanced rather than mild diastolic dysfunction.
Uijl A et al/2024 [24]	sweden	20980 patients	48.20	79.0 [71.0–85.0]	28.0 (6.2)	AF: 63.9 HTN: 74.5 COPD: 16.0 DM: 28.6	cohort study	I-III	–	The association with all-cause mortality and non-CV hospitalization was heterogeneous across clusters for BBs. It remains to be elucidated how heterogeneity in HFpEF could influence personalized medicine and future clinical trial.
Conraads VM et al/2012 [25]	Belgium	57 patients	35	66.5 ± 9.8	30.3 ± 4.5	HLP:56 HTN: 86 DM: 21 COPD: 16	RCT	II/III	LVEF:61.9 ± 7.8 E/A ratio: 0.8 ± 0.18 E/e': 11.1±4.2	6 months treatment with Nebivolol did not improve exercise capacity. Its negative chronotropic effect may have contributed to this result.
Tost J et al/2021 [26]	Spain	2312 patients	39.1	83	–	DM: 42.1 DLP: 49.7 CRD: 28.1 AF: 62.8	cohort study	III-IV	LVEF: 60.2	BBs were prescribed in 45.8% of patients. BBs were associated with worse results in some co-primary or secondary endpoints.
Yamamoto K et al/2013 [27]	Japan	120 patients	57.5	73 ± 1	73 ± 10	HTN: 80.0 IHD: 28.3 AF: 50.8 DM: 27.5 DLP: 35.8	RCT	I:22 II:83 III:13 IV:2	LVEF: 62 ± 10 LVMI (g/m2): 126 ± 44 LAD (mm):	Carvedilol did not improve the prognosis of HFPEF patients overall.

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
									44 ± 8	
Edelmann F et al/2016 [28]	Germany	250 patients	66	73.4 ± 6.0	29.5 ± 5.9	HTN:90 CAD: 33 DM: 23 HLP: 66 AF: 10 COPD: 9	RCT	I: 1 II: 76 III: 23	LVEF:58.9± 8.8	The tolerability of BBs was low. Titration delays and non-severe side effects more often occurred in HFpEF than HFrEF.
Ahn MS et al/2020 [29]	Korea	878 patients	62.3	68.3±12.7	23.4± 3.6	HTN:56.1 DM: 32.3 IHD: 23.4 MI: 15.6 CKD: 11.1 COPD:11. 3	cohort study	II:12.7 III:42 IV:45.3	LVEF:27.4± 8 LVEDV, mL:158.9±6 8.7 LVESV, mL:115.6±5 6.3 LAD, mm:50.6±7.8	BBs were not associated with clinical outcome. However, in HFpEF with AF, BBs reduced rehospitalization during the 6-month and 1-year follow-up.
Kim YI et al/2024 [30]	Korea	249 patients	37.3	73.8±11.2	23.69 ±3.94	HTN:75.9 DM:32.5 IHD:16.8 CKD:9.6 COPD:11. 2	cohort study	II:17.6 III:37.7 IV:44.5	LVEF:58.5± 6.5 LVEDVi (mL/m2):63. 8±29.6 LVESVi (mL/m2):26. 6±15.3 LAVI (mL/m2):69. 3±33.6	In HFpEF with AF, in patients with HR over 75 bpm at discharge, BBs was associated with a reduced 60-day rehospitalization rate.
Dobre D et al/2007 [31]	Netherlands	443 patients	44.5	77.6	–	HTN: 49.4 MI: 36.1 DM: 28.7 AF: 44.5 COPD:28. 4	Cohort study	–	–	BBs were associated with a significant mortality reduction.
Formiga F et al/2022 [32]	Spain	531 patients	39	78.9	30.3	HTN: 93 DM:53 IHD:60 CKD:62 COPD:17	observational study	–	–	In patients with HFpEF in sinus rhythm, BBs use was not related to one-year mortality or mortality plus HF readmission.
El-Refai M et al/2013 [33]	USA	741 patients	39.4	71.3 ±12.3	–	AF: 29.8 DM: 46.4 HTN: 73.4 COPD:39. 0	Comparative Study	–	LVEF: 57.2 ±5.4	BBs exposure was associated with a similar protective effect in terms of time to death or HFH.
van Veldhuisen DJ et al/2009 [34]	Netherlands	380 patients	49.2	age ≥70 years	–	CAD:77.1 MI: 32.4 HTN:77.7 HLP: 46.9 AF: 36.0 DM: 24.3	RCT	I: 3.5 II: 62.5 III:32.2 IV: 1.9	LVEF≥50%	The current study provides the first large-scale data for a potentially beneficial effect of BBs in HFpEF, and is the only one in elderly patients.
Park K et al/2016 [35]	South Korea	62 patients	–	over 70 years of age	–	–	RCT	II or III	LVEF ≥40%	There was no difference between carvedilol and nebivolol for improving

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
										diastolic function of elderly HF patients.
Smith DT et al/2010 [36]	USA	534 patients	84	67±11	29±5	DM:29 MI: 60	RCT	–	LVEF: 62±9	BBs is associated with a decreased risk of HFH in patients with diastolic dysfunction and stable CHD.
Mittal N et al/2017 [37]	India	–	–	–	–	–	RCT	–	–	Metoprolol succinate has some beneficial role in HFpEF including QoL parameters.
Cleland JGF et al/2018 [38]	UK	819 patients	60.1	72.2	27	MI: 61.1 DM: 25.1	SRMA	III/IV	LVEF:46.5	LVEF increased with BBs in all HF groups in sinus rhythm except LVEF ≥50%.
Gu, J et al/2016 [39]	China	803 patients	–	–	–	–	cohort study	–	–	BBs was associated with protective effects against incidence of new-onset symptomatic HFpEF, LV diastolic dysfunction and LVH.
Hikoso, S et al/2024 [40]	Japan	1159 patients	44.7	81.4	–	–	propensity-matched analysis	–	–	BBs were significantly associated with worse prognosis specifically in patients with HFpEF and high clinical frailty scale (CFS).
Musse, M et al/2023 [41]	USA	–	–	–	–	–	Observational study	–	–	A significant proportion of physicians prescribing BBs to patients with HFpEF, even without indications, and rarely deprescribe BBs.
Ruiz, G et al/2016 [42]	Spain	2704 patients	–	–	–	–	cohort study	–	–	Commencing treatment with bisoprolol or carvedilol, both at high and at lower doses, is associated with an improved prognosis of patients newly diagnosed with HFpEF.
Yoon, M et al/2024 [43]	South Korea	100 patients	–	aged >= 20	–	–	RCT	–	LVEF ≥50%	Carvedilol improve diastolic dysfunction, cardiac remodeling, or NYHA functional class in HFpEF.
Ibrahim, J et al/2024 [44]	USA	20206 patients	–	–	–	–	cohort study	–	–	BBs use was associated with lower mortality in HFpEF patients with a recent decompensated HF hospitalization.
Wernhart, S et	Germany	99 patients	–	–	–	–	case-control	–	–	BBs reduce exercise ca-

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
al/2023 [45]							study			pacity and O2 pulse increase in HFpEF patients. Direct quantification of O2 pulse increase may help to improve the discrimination of HFpEF patients.
Patel, L et al/2024 [46]	USA	216 patients	51.8	69	–	–	RCT	–	–	BBs use was associated with a higher anaerobic threshold and lower QOL.
Kamp, O et al/2010 [47]	Netherlands	120 patients	–	–	–	–	cohort study	–	–	Nebivolol had no effect on 6MWT.
Nevzorov, R et al/2012 [48]	Israel	154 patients	–	older than 18 years	–	–	cohort study	–	–	BBs may have protective effect on survival.
Park, JJ et al/2019 [49]	South Korea	1277 patients	–	–	–	–	cohort study	–	–	BBs is associated with improved survival in those with GLS < 14%.
Domagoj, M et al/2019 [50]	Croati	-----	–	–	–	–	comparative study	–	–	Long term carvedilol is associated with a higher overall survival rate, improvement in EF and NYHA class in HFpEF.
Horiuchi, Y et al/2016 [51]	Japan	81 patients	–	–	–	–	cohort study	–	–	Effects of BBs on LV remodeling were uncertain in AMI patients with HFpEF, who obtained complete coronary revascularization and received optimal MT.
Gomez-Soto, FM et al/2011 [52]	Spain	1085 adults	–	–	–	–	observational study	–	–	Bisoprolol or carvedilol is associated with a reduced mortality and morbidity of patients with newly diagnosed HFpEF.
Takeda, Y et al/2004 [53]	Japan	40 patients	–	–	–	–	RCT	–	–	Carvedilol decrease neurohumoral activation, decreased symptoms, and increased exercise capacity in patients with HFpEF.
Li S et al/2019 [54]	China	330 patients	52.1	73	–	–	Observational Study	-------	EF ≥ 50%	BBs was associated with reduced mortality and a lower HR was associated with reduced mortality in HFpEF patients with SR.

Author/year	country	Sample	Male (%)	Age (Years)	BMI	RF (%)	Study type	NYHA class	Echo findings	Key finding
Loncar G et al/2012 [55]	Serbia	219 elderly patients	–	–	–	–	RCT	–	–	After 12 weeks of BBs optimization copeptin might reflect successful up-titration faster than NT-proBNP in HFrEF, while the opposite was found in patients with HFpEF.
Verbrugge FH et al/2013 [56]	Belgium	------	–	–	–	–	Comparative Study	–	–	No benefit of RAS- or BBs uptitration was observed in HFpEF.
Kanorsky SG et al/2016 [57]	Russia	126 patients	–	–	–	–	RCT	–	–	Bisoprolol was not improved METs, QOL, and reduced level of NT-proBNP precursor.
Hamdani N et al/2009 [58]	Netherlands	71 patients	–	–	–	–	RCT	–	–	Myocardial effects of BBs was include higher resting force, lower collagen volume fraction, lower cardiomyocyte diameter, and lower expression of stimulatory G protein.

DM, Diabetes mellitus; CVA, Cerebrovascular accident; AF, Atrial fibrillation; AFI, Atrial flutter; CAD, Coronary artery disease; CKD, Chronic kidney disease; LVEF, Left ventricular ejection fraction; HF, heart failure; BBs, Beta blockers; HTN, Hypertension; IHD, Ischemic heart disease; COPD, Chronic obstructive pulmonary disease; LAVI, Left atrial volume index; LVMI, Left ventricular mass index; E/e', Early mitral inflow velocity to early diastolic mitral annular velocity; HFmrEF, Heart failure with mid-range ejection fraction; HFpEF, Heart failure with preserved ejection fraction; LVEDV, Left ventricular end-diastolic volume; iLVESV, indexed Left ventricular end-systolic volume; MI, Myocardial infarction; CV, Cardiovascular; QOL, Quality of life; AMI, Acute Myocardial infarction; LAD, Left anterior descending artery; LVEDD, Left ventricular end diastolic diameter; PAP, Pulmonary artery pressure; PAD, Peripheral artery disease; OAD, Obstructive airway disease; EF, Ejection fraction; HR, Heart rate; CVD, Cardiovascular disease; BMI, Body mass index; HFH, Heart failure hospitalization; DLP, Dyslipidemia; E/A, Early to atrial peak mitral inflow velocities; LVDd, Left ventricular end diastolic diameter; LVDv, Left ventricular end diastolic volume; RWT, Relative wall thickness; BNP, B-type natriuretic peptide; SR, sinus rhythm; VT, Ventricular tachycardia; VF, Ventricular fibrillation; CHF, Congestive heart failure; ARB, Angiotensin-2 receptor blocker; ACE-I, Angiotensin-converting enzyme inhibitors; IVST, Interventricular septum thickness; PWT, Posterior wall thickness; RV, Right ventricular; HLP, Hyperlipidemia; CRD, chronic respiratory disease; HFrEF, Heart failure with reduced ejection fraction; LVESV, Left ventricular end systolic volume; CHD, coronary heart disease; LV, Left ventricular; LVH, Left ventricular hypertrophy; GLS, Global longitudinal strain; RAS, Renin angiotensin system; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York heart association; RCT, Randomized controlled trial

3. Results

3.1. Beta Blockers and HFpEF Prevention and Treatment

BBs are frequently prescribed in patients with HFpEF, although the evidence for a direct therapeutic benefit in HFpEF is lim-ited. Findings from the Japanese Diastolic Heart Failure Study (J-DHF) suggested that the effect of carvedilol may vary ac-cording to patient characteristics rather than being uniform across the HFpEF population [11, 23]. In the reviewed studies, BB therapy generally did not produce consistent improvements in symptoms, functional status, hospitalization, or all-cause mor-tality [1, 3, 6, 8, 13, 15, 27, 33, 34]. Patients with chronotropic incompetence represent a potentially distinct subgroup, as withdrawal of BB therapy has been associated with short-term improvement in maximal functional capacity [2, 4]. In con-trast, some analyses have identified potential benefits in selected patients with lower ejection fraction or particular pheno-types, including those with atrial fibrillation or an elevated heart rate [7, 19, 38, 49]. These findings suggest that the clinical effect of BBs in HFpEF may de-

pend on the underlying phenotype and the indication for treatment rather than on the HFpEF diagnosis alone.

3.2. Beta Blockers and Safety

Despite BBs titration in HFpEF and HFrEF being feasible and safe, titration delays and non-severe side effects more often occurred in HFpEF [28].A recent secondary study from TOPCAT showed that for patients with an EF of 50% or greater, BBs use was associated with an increased risk of HF hospitalizations but not CVD mortality [18]. In some studies, the use of BBs in patients with HFpEF has been associated with worsening clinical symptoms [45], increased risk of hospitalization [1, 10]. These requirementsmay occur following exercise intolerance, possibly due to exacerbation of chronotrophic incompetence [3]. The incidence of complications is higher in elderly patients and those with high frailty scales [40]. In one study, the use of BBs was associated with a reduced incidence of arrhythmia in HFpEF patients by favorably altering the biological properties of the cardiac autonomic system regulation [28].

3.3. Beta Blockers and HFpEF Symptoms, Signs, Functional Capacity, and Quality of Life

BBs could theoretically be useful in HFPEF by lowering blood pressure and reducing left ventricular hypertrophy and diastolic dysfunction, and by slowing heart rate and reducing myocardial oxygen demand. However, their use in HFpEF remains controversial, and BBs are currently not indicated for treating HFpEF [5, 15]. In the PRESERVE-HR trial, in patients with HFpEF and chronotropic incompetence, BBs withdrawal resulted in substantial short-term improvement in peak VO2, which was related to lower LVESV [2]. A large sample study showed no meaningful differences in HRpeak, HRresv, HRrecov, and functional capacity (Vo2 peak) between those with or without BBs therapy [17]. In practice and in studies, the use of BBs has not had an effect on improving clinical symptoms [9, 47] and quality of life (QOL) [5, 46, 53], and in some cases, even their discontinuation has improved symptoms [2, 45]. Evidence from the PRESERVE-HR study suggests that discontinuation of beta-blockers may temporarily improve exercise capacity in selected HFpEF patients with chronotropic incompetence [2]. Similar findings have been reported in subsequent analyses, particularly among patients with lower baseline LVESV [4], a reduction of heart rate response to exercise [25]. In some studies, carvedilol has been useful in improving clinical symptoms and NYHA function class [23, 43, 50, 52, 53]. The mechanism may confer benefits in HFpEF is not clearly understood. The main potential mechanism includes sympathetic antagonism of BBs with the potential benefits of lowering BP and rate, enhancing relaxation, increasing diastolic filling, improving ventricular remodeling, decreasing myocardial oxygen demand, and lowering arrhythmic threshold [16, 23, 28]. Moreover, BBs might confer benefit in HFpEF through improving metabolic activity and endothelial inflammation [43].

3.4. Beta Blockers and HFpEF Hospitalization and Urgent Visits Requiring

There were significant interactions between LVEF and BBs use for HF hospitalization, death, and the composite of HF hospitalization or death, with a higher risk of HF hospitalization and/or death among patients using BBs as LVEF increased [1, 4, 5, 7]. The relationship between beta-blocker therapy and outcomes appears to vary according to LVEF. Available data suggest less favorable hospitalization outcomes among patients with higher-range LVEF, particularly above 60% [1]. In the TOPCAT trial, a higher risk for incident HF hospitalization among patients with an EF of 50% or greater, without an associated change in CVD mortality [10]. A study found a statistical interaction between beta-blocker use and cluster membership for all-cause mortality and non-CV hospitalisation. In the young–low comorbidity burden and atrial fibrillation–hypertensive cluster, BBs use was associated with lower all-cause mortality and non-CV hospitalisation and in the obese–diabetic cluster BBs use was only associated with a lower non-CV hospitalization [24].In HFpEF with AF, the use of BBs was associated with reduced rehospitalization during the 6-month and 1-year follow-up [29]. In HFpEF with AF, BBs reduce 60-day readmission rates in patients with HFpEF and AF, provided that it does not excessively reduce HR in patients with discharge HR higher than 75 bpm. These findings suggest that BBs may be an option for unmet need in patients with HFpEF with AF [30]. In some studies, the use of BBs has not had an effect on reducing or increasing hospitalizations [14, 15].

3.5. Beta Blockers and Co-Morbidities (HTN, DM, CKD, etc)

Most patients with HFpEF are older adults who suffer from multiple comorbid conditions, many non-cardiovascular in nature, which explain the higher rates of non-cardiovascular events in these patients [2]. These suggest that improving outcomes in HFpEF may also require interventions that would need to address noncardiovascular comorbidities in real-world older patients with HFpEF [13]. HFpEF is significantly associated with HTN, DM, CKD, OAD, AF, and IHD [3, 5-7]. The latest European Society of Cardiology and American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Failure Society of America (HFSA) guidelines do not recommend the use of BBs for the treatment of HFpEF. However, these therapies remain widely used in these patients for management of comorbidities, including DM, HTN, OAD, presence of stable angina, IHD, and AF [5]. HF hospitalization related to BBs was not associated with comorbidities, including MI, a history of HTN, and baseline heart rate. By contrast,

a better outcome with BBs use was seen in patients with AF compared to those without AF [3].

3.6. Beta Blockers and Cardiac Structure

The relationship between BB therapy and cardiac structure appears to depend on both treatment and baseline cardiac char-acteristics. In patients undergoing BB withdrawal, the magnitude of improvement in peak VO2 differed according to baseline LVESV, whereas comparable associations were not demonstrated for LVEDV or LVEF [4]. Right ventricular dysfunction may also modify the response to BB therapy, with some data suggesting less favorable effects when RV function is impaired [22]. Regarding the J-DHF population, the association between carvedilol and clinical outcomes was not uniform across patients. Greater benefit was observed among patients with more pronounced left atrial enlargement, a finding interpreted as possible evidence that the degree of diastolic dysfunction may modify the treatment response [23]. This observation should be viewed as a subgroup finding rather than evidence of a general structural benefit from carvedilol in HFpEF. Other studies have re-ported variable or absent changes in ventricular dimensions after BB exposure or withdrawal [2, 4, 51].

3.7. Beta Blockers and Cardiac Biomarkers

BBs were associated with high-plasma BNP levels in females and AF rhythm, but not in males with sinus rhythm, suggesting that the pathogenesis and treatment of HFpEF may vary in males and female in sinus rhythm [16]. In a study, carvedilol was correlated with a decrease in plasma BNP concentration, and an ischemic cause of HF, high plasma concentration of BNP, LV dilation, and use of carvedilol at baseline were predictive of a decrease in plasma concentration of BNP. In conclusion, carvedilol potentially decreased neurohumoral activation and hemodynamic improvement patients with HF and preserved EF [53]. Also, it is thought that BBs potentially improve BP, heart rate, and diastolic filling, and result in protective effects in terms of the LV diastolic dysfunction and LVH, which causes reduced LA and LV strain, which might decrease BNP plasma levels [39].

3.8. Beta Blockers and Major Adverse Cardiovascular Event, Cardiovascular Mortality, and all-Cause Mortality

Studies showed that, in patients with HFpEF and AF, and a heart rate ≥70 bpm, high-dose BBs use was associated with a significantly lower risk of death [7, 19, 23]. BBs have a variety of positive actions in HFpEF patients associated with AF as follows: [1] rate control and prevention of tachycardia-induced cardiomyopathy; [2] blocking adrenergic receptors, which have direct effects on cardiomyocytes; and [3] alteration of vascular function and modification of the neuroendocrine response to HF. BBs could be used in HFpEF patients associated with AF. However, because BBs can be negative inotropic, there should be caution with the initial dosage, and this should be gradually increased [7]. The use of BBs in elderly patients with HFpEF in sinus rhythm does not seem to influence major cardiovascular events (MACE, death or HF readmission) within a year following an AHF admission [32]. In very few studies, there is a potential reduction in all-cause mortality with BBs use in HFpEF, although their effect on cardiovascular mortality or HF hospitalizations is less clear [7, 21, 24, 31, 44]. In some studies, bisoprolol or carvedilol is associated with reduced mortality and morbidity of patients with newly diagnosed HFpEF [29, 42, 50, 52].

4. Conclusion

Overall, the available evidence does not demonstrate a consistent clinical benefit from beta-blockers in HFpEF. Potential benefits appear to be confined to selected clinical settings, including concomitant atrial fibrillation, elevated heart rate, or specific phenotypic characteristics. Conversely, beta-blocker withdrawal may improve exercise capacity in selected patients with chronotropic incompetence. Further prospective studies are needed to identify patients who may derive benefit from continued therapy.

Abbreviations

AF	Atrial Fibrillation
BBs	Beta-Blockers
BNP	B-type Natriuretic Peptide
CAD	Coronary Artery Disease
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
CVD	Cardiovascular Disease
EF	Ejection Fraction
HF	Heart Failure
HFmrEF	Heart Failure with Mildly Reduced Ejection Fraction
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Heart Rate
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Events
NYHA	New York Heart Association
QOL	Quality of Life
RCT	Randomized Controlled Trial

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Conflicts of Interest

The authors declare no conflicts of interest.

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