REVIEW ARTICLE

Role of Bisoprolol in Heart Failure Management: A Consensus Statement from India

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Abstract

In India, heart failure (HF) is an important health concern affecting younger age groups than the western population. A limited number of Indian patients receive guideline-directed medical therapy (GDMT). Selective β-1 blockers (BB) are one of the GDMTs in HF and play an important role by decreasing the sympathetic overdrive. The BB reduces heart rate (HR) reverse the adverse cardiac (both ventricular and atrial), vascular, and renovascular remodeling seen in HF. Bisoprolol, a β-1 blocker, has several advantages and can be used across a wide spectrum of HF presentations and in patients with HF and comorbid conditions such as coronary artery disease (CAD), atrial fibrillation (AF), post-myocardial infarction (MI), uncontrolled diabetes, uncontrolled hypertension, and renal impairment. Despite its advantages, bisoprolol is not optimally utilized for managing HF in India. This consensus builds on updated evidence on the efficacy and safety of bisoprolol in HF and recommends its place in therapy with a focus on Indian patients with HF.

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Introduction

Heart failure (HF) is a global health issue and an important public health concern in India due to its impact on the economic and mortality burden.[1–3] HF is seen in 1% of the Indian population, and its annual incidence is expected to increase by 18% by 2025.[1,2]

Heart failure (HF) encompasses a wide spectrum of presentations (Fig. 1).[3] The recent study from the Cardiology Society of India-Kerala Acute Heart Failure Registry (CSI-KHFR) with the participation of 7,507 patients with acute HF (AHF) reported that more than two-thirds of patients (67.5%) had reduced ejection fraction [heart failure with reduced ejection fraction (HFrEF)]; unfortunately, the disease affected younger population in their sixties.[4] HF with mildly reduced ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) were noted in 17.6% and 14.9% of patients, respectively.[4]

In HF, the cardiac output (CO) decreases and subsequently activates the sympathetic nervous system (SNS), the renin–angiotensin–aldosterone system (RAAS), and the natriuretic peptide system (NPS) (Figs 2 and 3).[5–8] Though initially beneficial, continued SNS, RAAS, and NPS activation develops reverse cardiac remodeling over a period of time.[5,8,9] Sympathetic overdrive is seen in >62% of Indians with HF, especially in those with metabolic syndrome.[10] Therefore, drugs that inhibit SNS, RAAS, and NPS would be beneficial in the management of HF.

Further, HF is commonly associated with various comorbidities such as diabetes mellitus (61.4%), hypertension (53.4%), chronic kidney disease (CKD) with

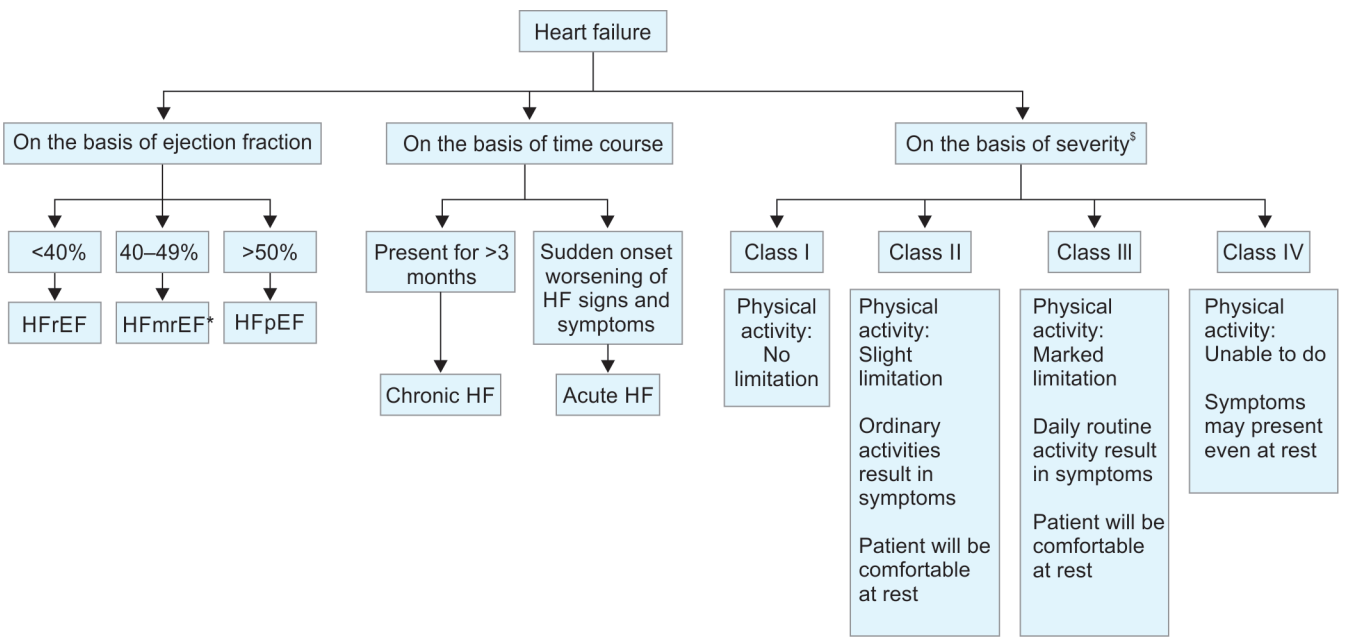

Fig. 1: Different types of HF presentations[3]; *protocol and treatment for this group are unclear but usually follow that of HFrEF; $, New York Heart Association classification (NYHA); HF, heart failure; LVEF, left ventricular ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction

estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2 (15%), anemia (15%), and atrial fibrillation (AF) (14%).[4] Coronary artery disease (CAD) was the most common etiology for HF (65.7%).[3,4]

The CSI-KHFR data showed that the 5-year mortality rate in HF was 59%, and sudden cardiac death occurred in 46% of patients with HF.[4] Presence of comorbidities increases the mortality risk in HF.[3,4] The in-hospital mortality rates of HF were 7%, and 90-day mortality rates were 11%.[4] Drugs that can effectively and safely manage HF in the presence of comorbidities would be beneficial in HF.

The CSI-KHFR data showed that only 28% of these patients received guideline-directed medical therapy (GDMT).[4] Patients who received GDMT at discharge had better survival (25%).[4] β-1 selective β-blockers (BBs) have an important place in the management of HF. As compared to other GDMTs for HF, the use of BBs correlated with 43% lower 90-day mortality risk (lowest among the GDMTs), followed by RAAS blockers (40% lower risk than other GDMTs).[4]

Bisoprolol is one of the guideline-recommended β-1 super-selective BB for HF.[11–14] Bisoprolol inhibits the neurohormonal overdrive in HF that occurs due to activation of the SNS, and RAAS and has several advantages over other BBs (Table 1).[9,15,16]

This consensus from India discusses the evidence-based role of bisoprolol in the current management of HF. The consensus highlights the importance of bisoprolol in the management of HF and aims to improve the use of bisoprolol in the management of HF by identifying and highlighting the patient population and scenarios where bisoprolol can be effectively and safely used in Indian patients with HF.

Sympathetic Overdrive and RAAS Activation in HF

Cardiac injury in HF triggers a number of molecular, cellular, interstitial, mitochondrial, and genetic changes that cause adverse cardiac, renal, and vascular remodeling (Figs 2 and 3).[6,7,9,17] The adverse remodeling is mainly mediated through the overactive SNS, RAAS, and NPS.[6,9,18] The SNS and RAAS are interrelated as SNS activation in HF leads to RAAS activation, while RAAS activates the central angiotensin II type 1 receptor (AT1R), which contributes to sympathetic overdrive in HF.[5,6] Further, activated RAAS initiates the efferent renal sympathetic nerve activity, resulting in salt and water retention.[5,6] The sympathetic overdrive causes vasoconstriction, which increases blood pressure and, if this persists, causes left ventricular (LV) remodeling.[5,6] The NPS is activated in response to SNS and RAAS continued overdrive as a counter-protective mechanism.[8] However, continued SNS overdrive in HF reduces the response to NPS.[6]

Additionally, the increased cardiac sympathetic adrenergic drive in HF correlates with long-term negative impacts on myocardial function, like increased myocardial energy expenditure and possibly ischemia.[19] The stimulation of the cardiac β-1 adrenergic receptors (ARs) accelerates apoptotic cell death.[20] Further, β-1 AR stimulation reduces the contractility of myocardial cells.[21] Additionally, the sarcoplasmic reticulum is not able to properly handle the intracellular calcium.[21] All these mechanisms result in further deterioration of the failing heart.[7] Therefore, a predominant SNS blockade, combined with RAAS blockade, will be beneficial in HF.

Role of Beta-blockers in HF

Guideline-directed medical therapies (GDMTs) in HFrEF include BBs; angiotensin receptor-neprilysin inhibitors (ARNi) or angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB); mineralocorticoid receptor antagonists (MRA) and a sodium-glucose cotransporter 2 inhibitor (SGLT2i).[2,9,11–13,22,23] BBs are the cornerstones in the management of HF.

Reversing the adverse cardiovascular remodeling is critical for improving cardiac function and outcomes in HF.[9] BB has an important place in reversing cardiac remodeling (atrioventricular and vascular remodeling reversal) in HF by suppressing the β-1 AR activation and thus inhibit the neurohormonal activation seen in HF.[18,24] Further, the sympathetic overdrive in HF reduces the response to cardioprotective natriuretic peptides and thereby contributes to adverse cardiac remodeling.[6] However, substantial clinical evidence demonstrated a trend toward higher levels of natriuretic peptides with guideline-directed BB (nebivolol, bisoprolol, and carvedilol) in HF.[25–27]

Table 1: Advantages of bisoprolol over other β-1 selective blockers

Condition/comorbidity	Advantages of bisoprolol over other β-1 selective BBs (carvedilol, metoprolol or nebivolol)
HF with AF	Bisoprolol is more effective in patients with severe congestive HF with AF[69]: • Better HR control • Improved brain natriuretic peptide level • More patients defibrillated from AF to sinus rhythm • More effective in decreasing post-discharge AF incidence after CABG in patients with decreased LV function[70]
HFrEF (CIBIS-J trial)	Better HR reduction[71]
HF with COPD	Dose–response survival benefit of bisoprolol but not for carvedilol or metoprolol[72] Slightly higher peak VO2 with bisoprolol particularly in CHF patients with reduced DLCO[73] Improvement in pulmonary function and fewer adverse events[74] Better protection against inflammation, myocardial injury and better improvement in pulmonary function in chronic systolic HF[36,75]
HF patients on hemodialysis	Lower 2-year risk of death and MACEs, mainly due to lower HF and ischemic stroke risk[76]
Attaining target dose in HF patients with dizziness and hypotension	Switching from carvedilol to bisoprolol may help continue β-blocker treatment and reach target dose[77]
Prognosis in CHF	"bisoprolol > carvedilol = metoprolol succinate = nebivolol > metoprolol tartrate; (" > " means "prior to")"[38]
HF with diabetes	Bisoprolol and carvedilol do not worsen glycemic parameters and can be preferred over other BBs[39]

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CHF, chronic heart failure; CIBIS, Cardiac Insufficiency Bisoprolol Study; COPD, chronic obstructive pulmonary disease; DLCO, diffusing capacity of the lungs for carbon monoxide; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; MACE, major adverse cardiovascular events; VO_2, oxygen consumption

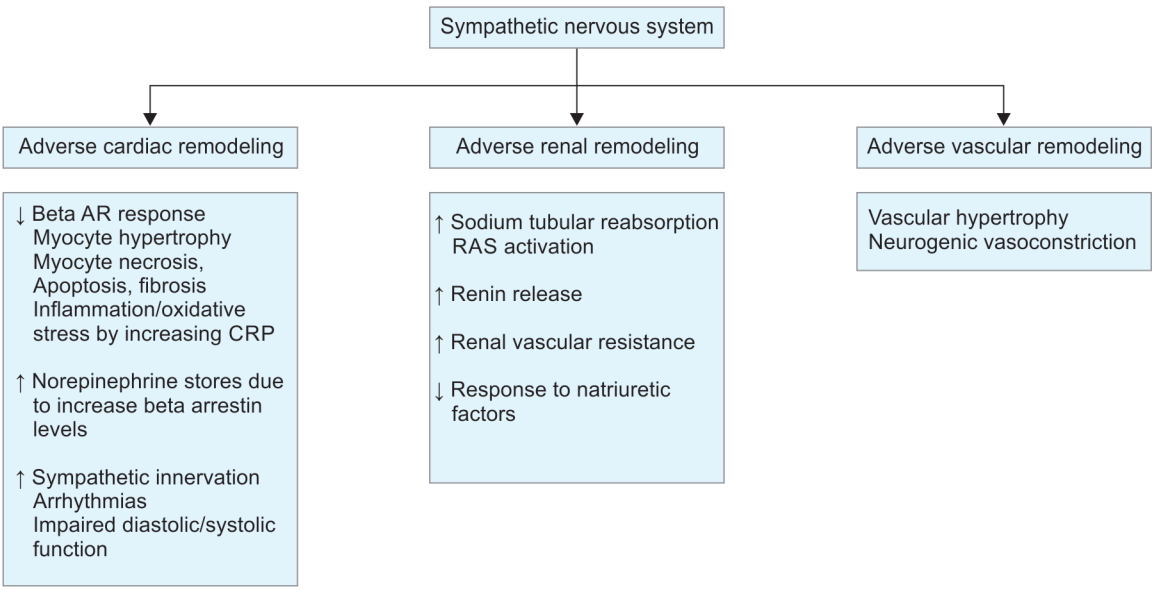

Fig. 2: Adverse cardiac, renal and vascular remodeling due to sympathetic overdrive[6,7,36,37]; AR, adrenergic receptors; NPS, natriuretic peptide system; RAS, renin angiotensin system

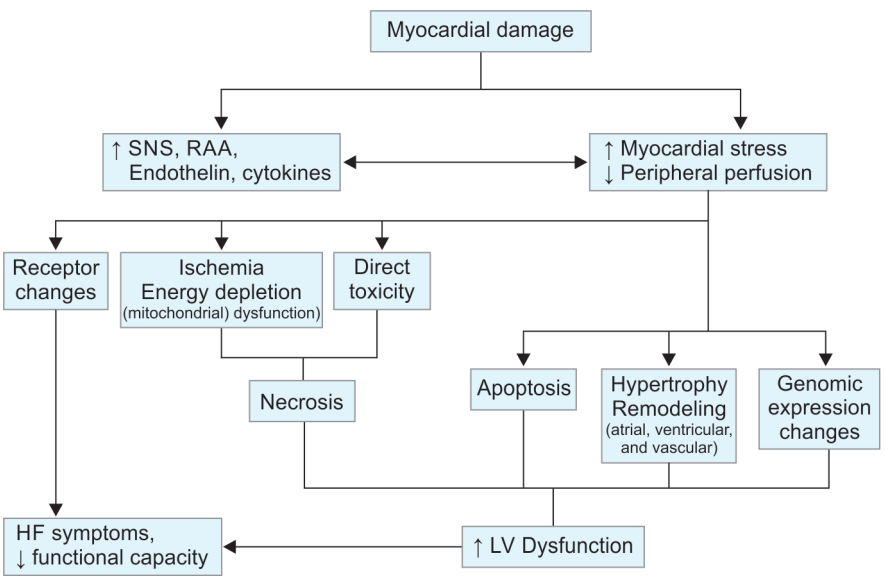

Fig. 3: Myocardial damage (adverse cardiac remodeling) in HF[6,7,17]; HF, heart failure; LV, left ventricular; RAA, renin, angiotensin, aldosterone; SNS, sympathetic nervous system

Multiple studies of BB in HF, such as MERIT-HF (with metoprolol),[28] CIBIS-II (with bisoprolol),[29] and COPERNICUS (with carvedilol)[30] highlight that adding BB to GDMT (ACEi or diuretics) reduces mortality and improves left ventricular (LV) function and volumes.[9] Further, the *post hoc* analysis of the "studies of left ventricular dysfunction" (SOLVD) showed that BB, along with enalapril, was associated with a synergistic reduction in the risk of death as compared to non-BB users.[31]

In view of this evidence, BBs can be initiated immediately in HF along with other GDMTs for rapid titration to optimal dose, thus reducing morbidity and mortality in HF.[32,33]

Guideline Recommendations for Beta-blockers in HF

Indian and International guidelines recommend β-1 blocking BBs such as bisoprolol, carvedilol, metoprolol, or nebivolol as one of the evidence-based selective BB in first-line management of HFrEF, (class I) HF with arrhythmia (class Ia for AF and I for ventricular rate), HFmrEF (class IIB), and HF with CAD (class 1) (Table 2).[2,11–13] These guidelines recommended a variety of BBs, *viz*: second-generation β-1 AR selective BBs including bisoprolol and metoprolol; third generation BB with β-1 blockade and vasodilating properties like carvedilol and nebivolol.[18]

Benefits of Bisoprolol over other Beta-blockers in HF

Current evidence highlights that bisoprolol has several advantages over other BBs recommended in the guidelines for the management of HF (Table 1). Bisoprolol targets both sympathetic overdrive and RAAS activation involved in adverse cardiac remodeling (Fig. 4).[15]

Bisoprolol is a second-generation BB that selectively blocks β_1 AR, which are mainly located in the heart, while β_2 receptors are present in vascular and airway smooth muscle, with a ratio of 119:1.[18,34,35] Bisoprolol, reduces heart contraction and heart rate (HR), leading to reduction in oxygen utilization by the cardiac cells.[15,35] Also, bisoprolol is an inverse agonist at the β_1- receptor and does not have any intrinsic sympathomimetic activity at the β_1- or β_2 ARs.[34]

Bisoprolol inhibits the activation of B1 receptors on juxtaglomerular cells and blocks RAAS, thereby preventing salt and water retention.[15,35] RAAS activation also releases noradrenaline, which has negative effects on the myocardium.[15] Thus, RAAS inhibition by bisoprolol may also reduce noradrenaline-mediated myocardial toxicity. Bisoprolol reverses cell toxicity by increasing the expression of β-arrestin levels; it also has anti-inflammatory action mediated by reduction of CRP.[36,37]

The pharmacokinetic and pharmacodynamic profile of bisoprolol confers several advantages as compared to other BBs. Compared to other BBs, bisoprolol is less lyophilic and, therefore, does not cross the blood–brain barrier and exhibits mixed

Table 2: Guideline recommendations for β-blockers/bisoprolol in HF

Guideline	*Type of HF*	*Recommendation*	*Class of recommendation*	*Level of evidence*
European Society of Cardiology (ESC) 2021[11] and 2023 ESC update[56]	HFrEF	"A β-blocker* is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death"	I	A
	HFmrEF	"A β-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death"	II	B
American Heart Association (AHA)/ACC/Heart Failure Society of America (HFSA) 2022[12]	HFrEF	"In patients with HFrEF, with current or previous symptoms, use of one of the three β-blockers** proven to reduce mortality is recommended to reduce mortality and hospitalizations"	I	A
		In patients with HFrEF, with current or previous symptoms, β-blocker therapy provides high economic value	High value statement	
	HFpEF	BB/bisoprolol is not a recommended GDMT		
ACC 2021 update[14]	HFrEF	Start evidence based BB at their initial dose; bisoprolol to start at 1.25 mg OD Consider increasing dose every 2 weeks until maximum tolerated or targeted dose (10 mg OD) is achieved Monitor HR, blood pressure and look for signs of congestion after initiation and during titration		
Heart Failure Guidelines India: 2017 update[13]	AHF	β-blockers** to be initiated only when the patient is mobile off IV diuretics and inotropes, having no systemic or pulmonary congestion, and is mobilized; Start a very low dose of any approved β-blocker** and very gradually build up the dose		
	CHF	Any approved β- blocker** Bisoprolol to be started at 1.25 mg QD and up titrated to 10 mg QD		
Indian Consensus 2020[2]	Stabilized acute decompensated HFrEF	During hospital stay: follow GDMT#[13] At discharge from hospital: "β-blockers: reduces the risk of all-cause and CV mortality but increase the risk of bradycardia and hypotension; once BP is stable, β-blockers can be safely administered. The dose should be carefully increased to reduce the HR to around 70 beats per minute"		
HFpEF Guidelines (Heart Failure Association of India, Endorsed by Association of Physicians of India) 2022[78]	HFpEF	BB should be avoided except if required for angina relief or AF rate control		
ACC consensus 2023[57]	HFpEF	The guideline notes that BB may be used in patients with "prior MI (for up to 3 years), angina, or AF, but exercise tolerance should be monitored due to the potential for chronotropic incompetence"		

*Bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol; **bisoprolol, carvedilol, sustained-release metoprolol succinate; #, as per ESC guidelines; AHF, acute heart failure; BB, β-blocker; GDMT, guideline directed medical therapy; HFmrHF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not available; OD, once daily

hepatic/renal clearance.[18,35] Additionally, bisoprolol has a lower first-pass metabolism and, therefore, has a high bioavailability of 80%, higher than other BBs.[35] It also has a long half-life of 9–12 hours in healthy patients and approximately 17 hours in HF patients, and therefore suitable for once-a-day doses.[18,35,38] Bisoprolol has no intrinsic sympathomimetic activity and is, therefore, beneficial in patients with tachycardia and in post-myocardial infarction (MI) patients who exhibit increased sympathomimetic drive.[34,38] Based on the abovementioned evidence, it has been noted that bisoprolol is more effective and equally safe compared to other β-1 selective blockers such as carvedilol, metoprolol, and nebivolol.[38]

The maximum benefit of BBs is seen at the target dose.[39] Bisoprolol should be started at a low dose of 1.25 mg OD and up-titrated every 2 weeks until the target dose of 10 mg OD is reached.[11–14]

Methodology

The national consensus meeting was organized on 6th August 2023 to discuss the current evidence-based place of bisoprolol in the management of HF. A total of 77 experts from India in the fields of cardiology, nephrology, endocrinology, and intensive care specialty attended this meeting. One senior cardiologist presents the comprehensive and most updated evidence of BB in HF. The experts discussed the literary and guideline-based evidence on the rationale, benefits, and role of β-blockers, especially bisoprolol, in the management of HF. They also shared their clinical experience in managing HF with bisoprolol. The panel discussion was moderated by leading cardiologists, nephrologists, and endocrinologists. With focused discussion and deliberation, the expert opinion was formulated and accepted by all the participating faculty. This consensus

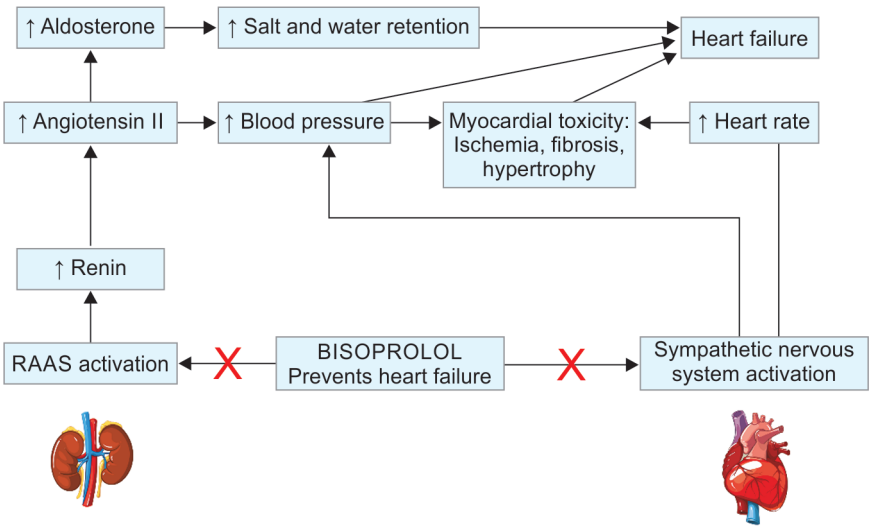

Fig. 4: Bisoprolol blocks the SNS and the RAAS involved in the development and maintenance of HF[15]

was further discussed with one expert from the United States individually by the moderator.

Panel Discussion: Role of Bisoprolol in Different Types of HF

The literary evidence on the efficacy and safety of bisoprolol in different types of HF is represented in Table 3. The randomized placebo-controlled Cardiac Insufficiency Bisoprolol Study (CIBIS) II reported that adding bisoprolol to standard GDMT in HF, such as ACEi and diuretics, improved survival.[29] This study was stopped 18 months earlier as there was a 32% reduction in all-cause mortality ($p < 0.001$).[29] A meta-analysis of the CIBIS-I and CIBIS-II studies (N =3288) confirmed that bisoprolol administration was associated with a significant reduction of overall death, cardiovascular (CV) death, and hospitalizations ($p = 0.0003$ and 0.0001, respectively).[40] The CIBIS-II trials also highlighted that the robust survival benefit with bisoprolol is seen across all dose levels, and bisoprolol withdrawal was associated with a significant increase in mortality risk.[41]

Real-world evidence also highlighted that bisoprolol with GDMT significantly improved left ventricular ejection fraction (LVEF) in patients with HFrEF or HFmrEF recovering in the acute post-acute coronary syndrome (ACS) phase.[42] Additional benefits of reduction in HR and J point ST segment deviation with no adverse effect on lipid profile or glycosylated hemoglobin (HbA1C) were noted.[42] The BISCOR Study showed that bisoprolol can be effectively and safely used at the guideline-recommended maximum doses for outpatient treatment of HF.[24]

Bisoprolol in Chronic HF

Literary evidence from various landmark trials (CIBIS-II[43]; CIBIS III[44]; BISCOR Observational Study[24]) proves the efficacy and safety of bisoprolol in CHF and has been captured in Table 3.

CIBIS-III study highlighted that first-line bisoprolol in CHF could be as efficacious and well tolerated similar to that of ACEi (enalapril), which is usually used as first-line in CHF.[44]

Further, a recent study evaluating the effectiveness and safety of four guideline-recommended BBs (bisoprolol, metoprolol, carvedilol, and nebivolol) in CHF demonstrated improved prognosis with bisoprolol as compared to carvedilol.[38] The study also demonstrated that the efficacy of bisoprolol was superior to other BBs; the effects of carvedilol were similar to metoprolol succinate and nebivolol but superior to metoprolol tartrate.[38] Evidence supports a better reduction in all-cause mortality with bisoprolol compared to carvedilol in patients with CHF. The survival benefit was consistent in Asian patients and in patients with HFrEF.[38] The survival benefit with bisoprolol was higher than that provided by metoprolol but did not reach statistical significance. Hospital readmission rates were significantly lower in patients on bisoprolol than those on metoprolol.[38]

Bisoprolol in Acute Decompensated Heart Failure (ADHF)

There have been concerns regarding the use of BBs in decompensated HF or worsening of HF.[14] However, current literary evidence supports the continued use of evidence-based BBs during acute exacerbation in HFrEF and also raises the possibility of their continued use during compromised renal function.[45,46]

A large study involving 3,817 patients hospitalized for ADHF reported that >90% of them were on evidence-based BBs at admission, of which 33.5% were on bisoprolol.[47] Patients receiving evidence-based BBs at admission had lower in-hospital mortality risk and had lower risk for CV and all-cause mortality.[47] Higher BB dose was associated with lower in-hospital mortality risk.[46] Thus, evidence-based BBs can be safely continued in ADHF.

Patients who were on evidence-based BB (including bisoprolol) at admission had a history of previous HF hospitalization, ventricular tachyarrhythmias, MI, AF, cardiomyopathy, or eGFR <30 mL/minute/1.73 m^2, or they had a history of being on ACEi, ARB, or MRA.[46]

Another retrospective review with 227 patients with ADHF on vasopressors and inotropes (Vs/Is) for cardiogenic shock also reported a lower risk for in-hospital mortality with concomitant use of BBs.[47] The patients who received BBs were younger, had HFrEF, and were more likely to have comorbidities like CAD and AF.[47] ACS was the main reason for hospital admission.

Thus, evidence-based BBs can be safely used in ADHF, confer survival benefits, and can be used across a wide range of patient profiles and combined with many drugs co-prescribed in ADHF.

The dose of evidence-based BB should be carefully monitored to keep the HR 60–70 beats per minute in HF.[2,48] While most patients with ADHF are able to tolerate evidence-based BBs, the dose may need to be down-titrated or the drug withheld if there is marked volume overload, low CO, or cardiogenic shock.[2,14,45,49] Further, dose reduction or BB withdrawal may be necessary in patients with symptomatic hypotension persisting after withdrawing other antihypertensive drugs.[50]

Bisoprolol in HF with Reduced Ejection Fraction

Since overactivation of sympathetic and RAAS systems is involved in the pathophysiology of HFrEF, pharmacological agents antagonizing the chain of events stimulated by this neurohormonal overactivation are known to reduce morbidity and mortality in HFrEF.[45,51]

Evidence-based BBs reduce mortality and morbidity and improve symptoms in

Current evidence highlights the efficacy and safety of BB in CHF as follows[38]:

Bisoprolol > carvedilol = metoprolol succinate = nebivolol > metoprolol tartrate

Where ">": Prior to; "=": equal to

patients with HFrEF when given with an ACEi and diuretic.[28–30,45,52,53] Bisoprolol is one of the guideline-recommended evidence-based BBs of choice in HFrEF.[11–14] Literary evidence on the efficacy and safety of bisoprolol in HFrEF is represented in Table 3.

Though there is no strong evidence on using an ARNi/ACEi/ARB or evidence-based BB (such as bisoprolol) as initiation of therapy, evidence-based BBs are better suited for patients who have less fluid overload and have an adequate resting HR.[14]

Table 3: Clinical evidence of bisoprolol

Trial	*N/Bisoprolol vs comparator*	*Inclusion criteria*	*Mean treatment follow-up*	*Primary endpoint results*	*Other results*	*Adverse effects*
CIBIS-II; placebo controlled RCT[43]	*N* = 2647; bisoprolol (*n* =1327 vs placebo (*n* =1320) Bisoprolol started at 1.25 mg daily and progressively increased to 10 mg daily	HFrEF (LVEF <35%) NYHA III or IV HF from ischemic to nonischemic cardiomyopathies Patients were already on ACEi or diuretics	1.3 years	Significant reduction in all-cause mortality by 34% (12% vs 17%) ($p < 0.001$)	Significant reduction in combined CV mortality or CV hospitalization rate by 21% ($p < 0.001$) Significantly lower hospital admission for worsening HF: 18 vs 12% ($p = 0{\cdot}0001$) Significant reduction in sudden death (by 44%) and pump failure deaths (by 26%)	AE other than mortality not evaluated Significant reduction in mortality
CIBIS III[44]	*N* = 1010; bisoprolol (target dose 10 mg QD; *n* = 505) or enalapril (target dose 10 mg BID; *n* = 505) for 6 months, followed by their combination for 6–24 months	Mild-to-moderate CHF HFrEF (LVEF <35%), not receiving ACEi or BB or ARB	1–2.5 years	PE of all-cause mortality or hospitalization: Bisoprolol-first treatment was noninferior to enalapril-first treatment Bisoprolol first vs enalapril first Intention-to-treat sample: 178 vs 186 PE (absolute difference:1.6%, HR 0.94). Per-protocol sample: 163 vs 165 PE (absolute difference:0.7%, HR 0.97)	Death: 65 vs 73 pts (HR 0.88) Hospitalizations: 151 vs 157 (HR 0.95) Worsening of CHF requiring hospitalization: 63 vs 51 ($p = 0.23$)	Early introduction of the second drug: 7.7 vs 7.3% ($p = 0.81$) Permanent discontinuation during monotherapy: 6.9 vs 9.7% Combined therapy phase: 4.2% permanently discontinued bisoprolol vs 10.4% discontinued enalapril
Tenacity real-world study[42]	*N* = 400; bisoprolol 1.25, 2.5, 5, or 10 mg at the discretion of physician	Post-ACS Asians patients LVD with HFmrEF and HFrEF (LVEF <50%)	1 year	Significant LVEF improvement (41.45 vs 48.73%) and HR reduction (85.06 vs 76.73 bpm) at ($p = 0.0001$)	Significant reduction in ST segment deviation at J point	No adverse effect on lipid and HbA1C
BISCOR observational study[24]	*N* = 334; bisoprolol started at 1.25 mg/day; weekly increments to 5 mg/day followed by increments every 4 weeks to a targeted doses of 10 mg/day	Chronic stable HF NYHA class II–IV outpatient setting	9 months	Maximum targeted dose achieved in 63%; mean dose at the end of follow-up was 8.5 mg	Significant improvement in functional status, quality of life and ejection fraction	Only four patients had SAE

ACS, acute coronary syndrome; CIBIS, Cardiac Insufficiency Bisoprolol Study; CHF, chronic heart failure; CV, cardiovascular; HbA1c, glycosylated hemoglobin; HF, heart failure; HFmrHF, heart failure with mildly reduced ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PE, primary endpoint; RCT, randomized controlled trial; SAE, serious adverse events

Bisoprolol in HF with Mildly Reduced Ejection Fraction

There is no specific study evaluating β-blockade in HFmrEF. However, many patients with HFmrEF may already be on an evidence-based BB due to an underlying CV condition such as angina and AF.[11]

However, an individual patient data meta-analysis involving 11 trials suggested that evidence-based BB, including bisoprolol, reported similar reductions in CV and all-cause mortality in patients with sinus rhythm HFrEF and HFmrEF.[54]

Further, a recent exploration of results of two prospective observation studies reported lower adjusted all-cause mortality risk in HFmrEF and HFrEF (but not in HFpEF) for patients who received the highest doses of guideline-recommended BBs or ARNi/ACEi/ARB.[55] In this context, each mg bisoprolol equivalent correlated with significant incremental mortality risk reduction in patients with HFmrEF (p = 0.047).[55]

Hence, an evidence-based BB, including bisoprolol, has been considered in HFmrEF by the European guideline to reduce the risk of hospitalizations and death.[11,56]

Bisoprolol in HF with Preserved Ejection Fraction

Historically, there has been no evidence of BB translating into a recommendation for their use in HFpEF, except in specific patient populations.[57,58] A vast majority of patients with HFpEF are already on an evidence-based BB (such as bisoprolol) due to background CV diseases such as CAD, AF, and hypertension.[11] The PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) study in patients with HFpEF reported that 80% of patients were receiving a background BB therapy at baseline.[59]

The RATE-AF (Rate Control Therapy Evaluation in Permanent Atrial Fibrillation) trial highlighted that, at 6 months, bisoprolol provided similar HR control and quality of life (QoL) as digoxin in elderly patients with HFpEF and AF, at the expense of a higher rate of dizziness lethargy, and hypotension with bisoprolol at 12 months.[60]

A real-world study including 1,078 patients with HFpEF in sinus rhythm reported that BB use was not associated with 1-year mortality or HF readmission and mortality.[61]

The 2023 American College of Cardiology (ACC) consensus highlighted that BBs may be used in HF patients with prior MI (≤3 years), angina, or AF.[57] At the same time, the guideline cautioned that BBs can possibly cause chronotropic incompetence, and therefore, physicians should carefully monitor exercise tolerance.[57]

Panel Discussion: Literary Evidence for Bisoprolol in HF with Comorbidities

Patients with HF are often receiving ACEi, and/or BB or diuretics because of concomitant hypertension, ischemic heart disease (IHD), AF, CAD, or other conditions.[11,62]

Guideline Recommendations for Beta-blockers/bisoprolol in HF with Comorbidities

Table 4 gives guideline recommendations for bisoprolol in HF with comorbidities.

Heart Failure in Patients with CAD

Medical therapy with evidence-based BB (such as bisoprolol) should be considered in HFpEF for angina relief.[11,58] Evidence-based BB (such as bisoprolol) are the mainstay of therapy in patients with HFrEF and CAD because of their prognostic benefit.[11]

Table 4: Guideline recommendations for β-blockers/bisoprolol in HF with other comorbidities

Guideline	*Type of HF*	*Recommendation*	*Class of recommendation*	*Level of evidence*
European Society of Cardiology (ESC) 2021[11]	HF with arrythmia	"β-blockers* should be considered for short- and long-term rate control in patients with HF and AF"	IIa	B
		"For patients in NYHA class IIII, a β-blocker, usually given orally, is safe and therefore is recommended as first line treatment to control ventricular rate, provided the patient is euvolaemic"	I	NA
	CCS and HFrEF	β-blockers are the mainstay of therapy in patients with HFrEF andCAD because of their prognostic benefit	I	NA
ESC 2023[68]	HFrEF (NYHA class II–IV) with diabetes	One of the evidence based BBs* are recommended to reduce the risk of HF hospitalization and death	I	A
		Intensive treatment with early initiation of one of the GDMTs (which include BBs) with rapid uptitration to target dose before discharge; frequent follow-up visits in the first 6 weeks postdischarge to reduce readmissions or mortality	I	B
Heart Failure Association of the European Society of Cardiology 2021[62]	HF with CAD and angina	Evidence-based BB* may help control symptoms		
	HF with **d**iabetes	Evidence-based BB* have similar benefits in patients with diabetes as those without diabetes		
	HF with COPD/asthma	Evidence-based BB* can be given in COPD		
	HF in patients with erectile dysfunction	Evidence-based BB* may aggravate erectile dysfunction		

*Bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol; AF, atrial fibrillation; BB, β-blocker; CCS, Chronic coronary syndrome; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NA, not available; NYHA, New York Heart Association

The Tenacity real-world study highlighted that bisoprolol given with other GDMTs conferred a significant 1-year improvement in LVEF and New York Heart Association class with a significant reduction in HR (Table 3).[42]

Heart Failure in Patients with Hypertension

Hypertension is the most important underlying cause of HFpEF, and the use of an evidence-based BB (such as bisoprolol) may reduce the incidence of HF in hypertensive patients.[11] However, evidence-based BB (such as bisoprolol) should be used with caution in HFpEF due to its negative chronotropic effects.[57]

Heart Failure and Arrhythmia

Evidence-based BB (e.g., bisoprolol) should be considered for short- and long-term rate control in patients with HFrEF or HFmrEF and AF.[11] These BBs improved LVEF and reduced all-cause and CV mortality in patients with HFrEF and HFmrEF but not in HFpEF.[54,63] However, bisoprolol may be used in patients with HFpEF and AF based on the results of the RATE-AF trial.[58] However, patients should be monitored strictly for adverse effects such as hypotension, dizziness, and drowsiness.

Furthermore, evidence-based BBs (e.g., bisoprolol), in their maximally tolerated dose, are often used as first-line treatment for ventricular rate control in patients with HF and ventricular arrhythmias.[11,49]

Heart Failure in Patients with Aortic Regurgitation (AR)

β-blockers should be cautiously used in patients with HF and AR as BBs prolong diastole and may worsen AR.[11]

Heart Failure in CKD Patients

The beneficial effects of evidence-based BB (e.g., bisoprolol) in reducing mortality and hospitalization for worsening HF are evident in HFrEF patients with moderate to moderately severe renal dysfunction (eGFR 45–59 mL/minute/1.73 m^2 and 30–44 mL/minute/1.73 m^2, respectively).[11,64] However, there is limited evidence of their benefit in severe renal impairment.[11] Therefore, moderate-to-moderately severe renal impairment should not limit the use of bisoprolol in patients with HF.[64]

Heart Failure and Diabetes

In India, approximately 50% of patients with CHF have coexisting type 2 diabetes mellitus (T2DM). HF is more prevalent than MI in patients with type T2DM.[1] All GDMTs recommended for HFrEF have similar efficacy in patients with or without T2DM.[1,11,62] Evidence-based BBs demonstrated a reduction in all-cause mortality in patients with HF and T2DM.[65]

The Tenacity real-world study demonstrated that bisoprolol with other GDMTs was neutral for HbA1c.[42] Bisoprolol does not worsen glycemic parameters in patients with HF and diabetes and can be safely used in this patient population.[39]

β-blockers use in T2DM may cause blunting of hypoglycemia symptoms and precipitate severe hypoglycemia in patients with T2DM.[1,66] However, the treatment benefits of HF far outweigh the risk of hypoglycemia.[67] Nonetheless, careful blood glucose monitoring should be advised for patients with HF and T2DM who are being treated with BBs.

Hence, the 2023 ESC guidelines for the management of CVD in patients with diabetes recommend the use of BB (including bisoprolol) for the management of HFrEF to reduce the risk of HF hospitalizations and mortality.[68] Further, the guideline recommends intensive and early treatment with quick up-titration to the target dose.[68]

Heart Failure in Patients with Asthma

Asthma is a known relative contraindication for the use of BB. However, the Global Initiative for Asthma (GINA) considers the use of cardio-selective BB such as bisoprolol in patients with chronic obstructive pulmonary disease (COPD)/asthma and HF.[62] Patients should be started on low-dose bisoprolol and carefully monitored for signs of airway obstruction (such as wheezing or shortness of breath with prolonged expiration).[11,62]

Pregnancy in Preexisting HF

Only evidence-based BBs such as bisoprolol should be continued, and only milder HF cases should be managed with oral drugs.[11]

Conclusion

Heart failure is a considerable health burden in India. Sympathetic overdrive is a common feature with HF. BB, one of the GDMTs for HF, plays an important and significant role in the management of sympathetic overdrive in HF. Bisoprolol is a superior BB because of its β1 super selectivity. Further, titrating the bisoprolol dose to the maximum tolerated or targeted dose (10 mg/day) helps in achieving the target HR and in cardiovascular remodelling, especially in HFrEF and HFmrEF. The drug's cardiometabolic, pharmacokinetic, and pharmacodynamic-friendly profile confers enormous mortality and morbidity benefits, including reduction in sudden cardiac death, CV mortality, all-cause mortality, and HF hospitalization. Bisoprolol has several advantages over other BBs, especially in Indian patients with HF and other comorbidities. The robust all-cause and CV survival benefits seen with bisoprolol help in improving HF prognosis. It is, therefore, proposed to incorporate bisoprolol in the management of HF in India as per the recommendations of the panel.

Consensus Statements

No.	Consensus statements
1	The 5-year mortality rate in HF in India is 59%; sudden cardiac death occurs in 46% of patients; those receiving GDMT at discharge had better survival
2	Sympathetic overdrive is the forerunner in HF before RAAS and NPS activation
3	Sympathetic overdrive is well documented in patients with HFrEF, HFmrEF, and HFpEF with or without significant comorbidities
4	Sympathetic overdrive is seen in 62.5% of Indians, especially in those with metabolic syndrome
5	Bisoprolol is an unique BB due to its β1 super selectivity
6	Bisoprolol has no adverse effect on lipid and glucose metabolism as compared to other BBs, pharmacokinetically and pharmacodynamically superior to other BBs, is more lyophilic, has higher bioavailability, longer half-life of up to 17 hours in CHF, and no intrinsic sympathomimetic activity
7	Sympathetic overdrive is the main cause of CV remodeling, which results in sudden cardiac death, CVD, all-cause mortality, MACE, HF hospitalization, arrhythmia, and worsening of HF
8	Bisoprolol is unique in the reduction of sudden cardiac death, CV death, all-cause mortality, and HF hospitalization (meta-analysis of CIBIS- I, CIBIS-II)
9	Bisoprolol targets both sympathetic overdrive and RAAS activation involved in cardiac remodeling

Contd....

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No.	*Consensus statements*
10	Bisoprolol reduces cardiac mortality by reversing cardiac (atrial, ventricular, and vascular) and renal remodeling
11	Bisoprolol reverses epinephrine-mediated cell toxicity by increasing the expression of β-arrestin and exerts anti-inflammatory action by reducing CRP
12	Bisoprolol has robust survival benefits at all dose levels in HF. (CIBIS-II)
13	Sudden bisoprolol withdrawal is associated with a significant increase in mortality risk
14	Bisoprolol is superior to other BBs in improving prognosis in HF
15	The morbidity and mortality in HF can be reduced by achieving the target HR and by optimizing elevated epinephrine and renin levels
16	Maximum benefits of bisoprolol are seen at a target HR of around 60–70/minute achieved with a dose titrated from 1.25 to 10 mg per day
17	Bisoprolol efficacy and safety are well established in both hospital and outpatient HF treatment (CIBIS II, CIBIS III, BISCOR study)
18	Bisoprolol provides a higher survival benefit than metoprolol, with a significantly lower hospital readmission rate in CHF as compared to metoprolol
19	Bisoprolol can be effectively and safely used in ADHF with a lower need for dose titration and a better tolerance profile
20	Bisoprolol is an evidence-based GDMT for HFrEF and HFmrEF but has limited evidence of efficacy in right ventricular failure secondary to LV failure
21	Bisoprolol has a compelling indication in HFpEF (as the vast majority of patients are already on bisoprolol for hypertension, CAD, AF, ventricular arrhythmia, previous infarction <3 years, and angina). It should be used with caution in the elderly as it may cause chronotropic incompetence; the drug should be monitored for exercise tolerance (PARAGON HF Study, ACC-2023)
22	Bisoprolol has prognostic benefits in patients with HF with CAD, hypertension, and arrhythmia
23	Bisoprolol confers renovascular remodeling reversal benefits in HF patients with moderately severe renal impairment
24	Bisoprolol is safe in patients with COPD and asthma; it should start at a lower dose and be monitored for signs of airway obstruction
25	Bisoprolol should be used with caution in patients with AR as it prolongs diastole and may worsen AR
26	Overall, bisoprolol is a superior β-1 super selective BB with robust survival benefits and enormous morbidity and mortality reduction in HF hospitalization, MACE, and arrhythmia, and it prevents progression to severe HF

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Conflict of Interest

Dr Onkar Swami, Dr Sanjay Jain, and Dr Priyank Shah are full-time employees of Alembic Pharmaceuticals Limited, which actively markets bisoprolol.

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