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Research Article

Optimizing Long-Term Management of Chronic Heart Failure: An Expert Consensus on the Evolving Role of Ivabradine

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Abstract

Persistent sinus tachycardia contributes to the progression of chronic Heart Failure (HF) and remains an important modifiable therapeutic target despite the widespread use of contemporary quadruple Guideline-Directed Medical Therapy (GDMT). Ivabradine, a selective inhibitor of the sinus node If current, effectively lowers resting Heart Rate (HR) without exerting negative inotropic or hypotensive effects. Evidence from the Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT) and subsequent meta-analyses has demonstrated significant long-term clinical benefits, including an 18% relative reduction in the composite of cardiovascular death or first HF hospitalization and a 26% reduction in HF-related hospitalizations, with greater benefit observed in patients achieving larger reductions in HR. Long-term registry data and extension studies further support the durability of ivabradine therapy, demonstrating sustained HR reductions of 10-25 beats/min, persistent improvement in New York Heart Association (NYHA) functional class and treatment persistence exceeding 80% over three years or longer. The development of a once-daily prolonged-release formulation, which is pharmacokinetically bioequivalent to the conventional twice-daily immediate-release formulation, provides comparable HR-lowering efficacy while reducing pill burden and potentially enhancing long-term adherence. Ivabradine can be safely combined with other components of GDMT, including sacubitril/valsartan, mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 inhibitors, as it has no clinically relevant drug-drug interactions with these therapies. Clinical trials and real-world studies have consistently demonstrated a favorable safety profile, with infrequent reports of luminous visual phenomena, a low incidence of new-onset atrial fibrillation and a minimal risk of reversible bradycardia. The greatest benefit is observed in patients with sinus rhythm and a resting HR >70 beats/min despite receiving maximally tolerated β-blocker therapy or in those who are unable to tolerate β-blockers. Emerging evidence also suggests a potential role for ivabradine in device optimization and selected cases of acute decompensated HF. Despite the growing body of evidence supporting its efficacy and safety, uncertainties remain regarding the optimal long-term positioning of ivabradine in HF management, particularly in routine clinical practice. To address this gap, five focused group discussions involving 60 leading cardiologists across India were conducted to capture expert perspectives on the long-term management of HF and the evolving role of ivabradine. This review integrates current scientific evidence with these expert insights to define the role of once-daily ivabradine as a hemodynamically neutral, heart rate-selective adjunct that provides sustained symptomatic and prognostic benefits, thereby reinforcing its value in the lifelong management of patients with tachycardic heart failure.

Keywords: Ivabradine; Heart Rate Reduction; Once Daily Formulation; Chronic Heart Failure; Long Term Outcomes; Guideline Directed Medical Therapy

Introduction

Resting sinus tachycardia remains one of the most independent contributors to adverse prognosis in chronic Heart Failure (HF). In the placebo arm of the systolic heart failure treatment with the If inhibitor Ivabradine Trial (SHIFT) trial, patients whose baseline Heart Rate (HR) was ≥ 87 beats min^{-1} experienced more than a twofold increase in the composite of cardiovascular death or HF admission compared with those at 70-72 beats min^{-1}; every 5 bpm increment amplified risk by 16% [1]. Contemporary registries echo this signal: five year all cause mortality in the Trivandrum Heart Failure Registry (THFR) reached 59 %, with readmission approaching 49 %, despite increasing use of Guideline Directed Medical Therapy (GDMT) [2]. Taken together, HR ≥ 70 bpm effectively doubles rehospitalization risk and nudges long term mortality toward the 50 % mark even when quadruple GDMT is prescribed.

Ivabradine, a selective If-current inhibitor, lowers HR without compromising blood pressure, inotropy or atrio-ventricular conduction, making it uniquely suited to Asian populations in whom hypotension, small body habitus and β-blocker intolerance limit traditional rate control. The pivotal SHIFT outcome study confirmed that adding ivabradine to standard therapy reduced the composite of Cardiovascular (CV) death or HF hospitalisation by 18 % and cut first HF admissions by 26 %, benefits proportional to the magnitude of HR reduction [3]. The objective of this review is to evaluate the role of long-term ivabradine therapy in chronic Heart Failure (HF), with particular emphasis on emerging Once-Daily (OD) formulations and to provide practical guidance for cardiologists seeking a Heart Rate (HR)-selective adjunct to address the residual heart rate gap.

Pharmacology of Ivabradine: From Twice-Daily to Once-Daily

Immediate-Release (IR) Formulation

The conventional film-coated tablet is rapidly absorbed (Tmax = 1 h) with around 40% absolute bioavailability constrained by CYP3A4 first-pass metabolism; over 70% of the circulating drug is bound to proteins. Ivabradine is metabolized into the equally potent compound S-18982, resulting in an effective terminal half-life of 6-11 hours, necessitating a bi-daily dosage of 5 mg or 7.5 mg for continuous heart rate management. Renal and biliary excretion play almost equal roles and linear kinetics are maintained from 1 mg to 24 mg. The medication is clinically well accepted, with phosphenes and asymptomatic bradycardia (< 5%) identified as the main dose-dependent side effects noted in regulatory documentation [4].

Rationale for a Prolonged Release (PR) Once Daily Formulation

Medication complexity undermines long term adherence in HF. A hydrophilic matrix platform was therefore developed to extend ivabradine dissolution, flatten the concentration-time curve and maintain steady HR suppression for 24 h. Population PK simulations predicted that PR 10 mg and 15 mg once daily deliver an area under the curve bioequivalent to IR 5 mg and 7.5 mg twice daily, but with ≈ 30 % lower peak levels and negligible end of dose trough [5]. The phase 3 PROFICIENT trial demonstrated that once-daily ivabradine Prolonged-Release (PR) was non-inferior to the twice-daily Immediate-Release (IR) formulation in 180 patients with stable Heart Failure with reduced Ejection Fraction (HFrEF). Switching from IR to PR (10/15 mg) maintained resting heart rate (Δ +0.8 bpm ± 1.2) and 24-hour Holter heart rate profiles over 12 weeks, with a comparable safety profile. The simplified once-daily regimen may improve long-term treatment adherence and compliance [6].

Landmark Outcomes: Shift, Beautiful and Key Meta Analyses

The evidence for ivabradine's disease modifying potential rests on two pivotal randomised outcome trials and a series of high quality meta analyses.

SHIFT (Systolic Heart failure treatment with the If inhibitor Ivabradine Trial): SHIFT provides the pivotal evidence that selective HR reduction with ivabradine reduces cardiovascular death and HF hospitalization in symptomatic HFrEF patients with sinus rhythm and elevated resting HR despite guideline-directed therapy.

In 6558 Symptomatic HFrEF patients (mean left ventricular ejection fraction 29 %, sinus rhythm ≥ 70 beats min^{-1}, maximally tolerated β blocker), ivabradine 5-7.5 mg twice daily produced an 18 % relative reduction in the primary composite of

cardiovascular death or first HF hospitalization (hazard ratio 0.82; 95 % CI 0.75-0.90; $p < 0.0001$). Component analysis showed a 26 % fall in HF hospitalization and a 17 % fall in cardiovascular death; benefits were graded, emerging from a baseline HR threshold of ≈ 70 bpm and maximizing in those reduced to < 60 bpm [7].

BEAUTIFUL (Morbidity Mortality Evaluation of the I_f inhibitor Ivabradine in Patients with Coronary Disease and Left Ventricular Dysfunction)

Although neutral for its primary composite, the prespecified subgroup with baseline HR ≥ 70 beats min^{-1} experienced a 36 % reduction in fatal or non fatal myocardial infarction and a 30 % reduction in coronary revascularization, alongside fewer first HF admissions highlighting HR as a modifiable driver of ischemic HF events. BEAUTIFUL identified elevated resting HR as a modifiable determinant of ischemic cardiovascular events and showed that ivabradine benefits patients with HR ≥70 bpm, thereby providing the physiological and clinical rationale for targeting HR in subsequent HF trials such as SHIFT [7].

Meta Analysis Studies

The most recent open access meta analysis (11 RCTs, 1,687 participants) confirmed significant pharmacodynamic and structural gains [8]:

- HR reduction -11.7 beats min^{-1} (95 % CI -12.9 to -10.5)
- LVEF increase +3.0 percentage points (95 % CI +2.1 to +4.0) [12]
- NT proBNP fall -384 pg mL^{-1} (95 % CI -582 to -188)

Mortality and all-causes readmission were directionally favourable but not statistically different from placebo and symptomatic bradycardia was observed in < 3% [12].

Bridging to the Once-Daily Era

FIRST trial: In a multicenter, double blind trial of 360 clinically stable patients with HF and reduced Ejection Fraction (HFrEF), participants were randomized to receive Sustained Release (SR) ivabradine or placebo on top of guideline directed pharmacotherapy. Ivabradine SR was initiated at 5 mg once daily and up-titrated to a maximum of 15 mg once daily. After 32 weeks, ivabradine SR produced a mean resting heart rate reduction of −14 beats min^{-1}, whereas the placebo group showed a mean increase of +2 beats min^{-1}, as documented by serial ECG and 24 hour Holter monitoring. The primary endpoint, Left Ventricular End Systolic Volume Index (LVESVI), improved by 12.5 mL m^{-2} in the ivabradine arm, yielding an adjusted between group difference of −11.7 mL m^{-2} (95 % CI −17.0 to −6.4; $p < 0.0001$). Although a greater proportion of patients in the ivabradine group were in New York Heart Association (NYHA) functional class III/IV at baseline (57.1 % vs 46.5 %), treatment was associated with meaningful gains in functional status and health related quality of life. Adverse events were evenly distributed overall; bradycardia (13.6 % vs 1.1 %) and hypertension (3.9 % vs 0.6 %) were more frequent with ivabradine, whereas worsening HF occurred less often (10.2 % vs 20.1 %; $p = 0.012$). No serious event was judged drug related. Collectively, these findings indicate that once daily SR ivabradine provides effective heart rate control and favorable ventricular remodeling with a tolerable safety profile in patients with HFrEF.

Proficient Study

In this double blind, phase 3, non inferiority trial, 180 adults with stable HFrEF (sinus rhythm ≥ 50 bpm, LVEF ≤ 40 %) who had received ivabradine Immediate Release (IR) 5 or 7.5 mg twice daily for ≥ 1 month were randomized 1:1 either to once daily ivabradine Prolonged Release (PR) 10 or 15 mg or to continue IR therapy. The primary endpoint was the change in resting 12 lead ECG HR after 3 months; non inferiority required the upper bound of the 95 % Confidence Interval (CI) for the between group difference to be < 6.5 beats min^{-1}. Of 169 completers (PR = 84; IR = 85), the least squares mean HR change favoured PR by +0.76 ± 1.19 beats min^{-1} (95 % CI -1.59 to +3.11), satisfying the non inferiority criterion. Twenty four hour Holter metrics (overall, awake, asleep HR) did not differ between groups. Thirty nine treatment emergent adverse events were mostly mild to moderate; serious events occurred in 2 PR and 5 IR patients (one fatality in the IR arm). Bradycardia incidence was comparable. These data show that once daily ivabradine PR maintains HR control as effectively and safely as twice daily IR dosing, offering a simplified regimen that may enhance adherence in chronic heart failure management [10].

Together, SHIFT and BEAUTIFUL establish ivabradine's class leading evidence in patients whose resting HR remains ≥ 70 bpm, while contemporary meta analysis and once daily formulation trials confirm that these benefits persist and are easier to deliver during long term follow up. The PROFICIENT study provides the clinical rationale for adopting the once-daily prolonged-release

formulation by demonstrating non-inferior heart rate control and comparable safety to the twice-daily formulation, with the potential to improve adherence and long-term treatment persistence.

Real-World Durability - Registries and Extension Studies

While Randomized Controlled Trials (RCTs) have established the efficacy of ivabradine in chronic HF, real-world evidence is crucial in assessing whether these benefits persist outside controlled environments and over extended treatment durations. Several registries and extension studies have addressed these questions, demonstrating the long-term value of ivabradine in routine clinical practice.

ETHIC AHF Prospective Registry (Spain)

Early in hospital initiation of ivabradine alongside β blockers in 71 patients with acute HFrEF produced a rapid HR fall that was maintained at one year follow up (baseline 78 ± 9 bpm → 61.8 ± 5.5 bpm; Δ 16 bpm) and translated into a shift from NYHA III/IV to NYHA I/II in 85 % of survivors. Drug persistence was 81 %, with no severe ivabradine related adverse events, demonstrating that once therapeutic HR targets are achieved, they remain stable without compromising β blocker uptitration.

Ivabradine Use in Patients with HFrEF in the Heart Failure Multidisciplinary Program (PIC) (Costa Rica)

In a single centre heart failure clinic, 26 ambulatory HFrEF patients were followed for three years after ivabradine initiation. Mean HR decreased from 89 ± 9 bpm to 62 ± 8 bpm (Δ 27 bpm) and remained < 70 bpm in 77 % of completers. Left ventricular ejection fraction improved from 29 % to 35 % and 10 of 18 evaluable patients gained ≥ 1 NYHA class. Only one discontinuation (3 %) occurred because of asymptomatic bradycardia, underscoring long term tolerability.

Cardiac Transplant Extension Cohort (Germany)

Among 27 stable heart transplant recipients with sinus tachycardia, ivabradine therapy sustained a significant HR reduction over 36 months (91 → 81 bpm; $p < 0.001$) and was associated with regression of indexed left ventricular mass (104 → 93 g m^{-2}). Ninety per cent of patients remained on treatment; no phosphenes or dose limiting bradyarrhythmia were observed, indicating that ivabradine's benefits extend to complex post transplant physiology.

Indian Post Marketing Observational Study

A retrospective cohort of 391 chronic HF out patients treated between 2016 and 2020 showed that ivabradine was rarely limited by bradycardia (6.9 %), achieved guideline HR targets (< 70 bpm) in > 50 % of patients and reached > 85 % refill based adherence at 12 months. Rehospitalization for HF was significantly lower than in matched controls, highlighting real-world effectiveness in a large South Asian population.

Long-Term Post-Marketing Multicenter Study of Once-Daily Ivabradine in Patients with Heart Failure with Reduced Ejection Fraction

Long-term real-world evidence from a multicenter Indian post-marketing observational study involving 500 patients with stable chronic HFrEF who were transitioned from twice-daily to once-daily prolonged-release ivabradine demonstrated sustained heart rate control over 12 months. Baseline mean age was 55.9 ± 11.7 years; 29.8 % were women and all participants were of Asian ethnicity. At enrolment (Visit 1, Day 0), the mean resting Heart Rate (HR) was 76.3 ± 12.2 beats min^{-1}. Patients were followed at three-month intervals to 12 months (Visit 5). Retention was high: 435/500 (87 %) completed the final visit, with 17 voluntary withdrawals and 5 deaths accounting for most attrition.

Primary outcome: Mean resting HR declined by 3.6 ± 14.1 beats min^{-1} over 12 months ($p < 0.0001$), with significant reductions evident as early as three months (5.1 ± 11.8 beats min^{-1}; $p < 0.0001$).

Secondary outcomes: During follow up, cardiovascular death occurred in 4 patients (0.8 %), all cause mortality in 5 (1.0 %) and hospitalisation for worsening HF in 2 (0.4 %). Median times to first cardiovascular death and all cause death were 88 and 80 days, respectively. Concomitant HR lowering therapy remained stable: < 1 % required ivabradine dose adjustment and use of other HR lowering agents fell modestly from 44.2 % to 42.3 %.

Safety: No unexpected adverse drug reactions were reported; the adverse event profile mirrored that observed in pivotal trials.18

Across diverse care settings, including acute-care wards, multidisciplinary clinics, transplant programs and community practice, ivabradine delivers a consistent 10-25 bpm HR reduction that persists for at least three years. Functional class gains follow HR control, remodeling benefits extend to specialized populations and discontinuations for bradycardia remain uncommon (< 3 %). These long term data reinforce guideline recommendations and support ivabradine as a chronic, disease modifying strategy in HFrEF patients who remain tachycardic despite β blockade.

Guideline Positioning of Ivabradine

Ivabradine now occupies a clearly defined role within Guideline-Directed Medical Therapy (GDMT) for HF with reduced Ejection Fraction (HFrEF) (Table 1).

Guideline/Consensus	Recommendation	Eligible Patients	Positioning of Ivabradine	Key Rationale/Comments
ESC Heart Failure Guideline (2023 Focused Update)	Class IIa, Level B	Patients with symptomatic HFrEF in sinus rhythm, resting HR ≥70 beats/min despite maximally tolerated β-blocker therapy or documented β-blocker intolerance	Recommended after optimization of foundational GDMT, including ARNI/ACEI/ARB, β-blockers, Mineralocorticoid Receptor Antagonists (MRAs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors	Reduces cardiovascular mortality and HF hospitalizations through selective HR reduction without negative inotropic or hypotensive effects.
ACC/AHA/HFSA Guideline (2022)	Class IIa, Level B-R	Symptomatic NYHA class II-III, LVEF ≤35%, sinus rhythm, resting HR ≥70 beats/min despite maximally tolerated GDMT	Recommended as an adjunct to optimized GDMT in eligible patients	Based primarily on the SHIFT trial demonstrating reductions in HF hospitalization and cardiovascular death while preserving myocardial contractility and blood pressure.
Indian Expert Consensus (2023)	Expert Consensus Recommendation	Patients with chronic HFrEF	Recommends lifelong continuation once	Supports sustained reverse remodeling,

		receiving long-term ivabradine therapy	target resting HR of 55-60 beats/min is achieved	reduced long-term rehospitalization risk and particular benefit in patients with low systolic blood pressure where β-blocker up-titration is limited.
Heart Failure Association of India (HFAI) Guidelines, 2025	Symptomatic HFrEF with persistent sinus tachycardia	Patients with symptomatic chronic HFrEF (LVEF ≤35%), sinus rhythm and resting HR ≥70 beats/min despite optimized GDMT, including maximally tolerated β-blockers.	Recommended as an adjunct to the four pillars of GDMT (ARNI/ACEI/ARB, β-blocker, MRA and SGLT2 inhibitor) after optimization of foundational therapy to achieve additional heart rate reduction and improve clinical outcomes.	Selective heart rate reduction with ivabradine lowers the risk of heart failure hospitalization and cardiovascular death without adversely affecting blood pressure or myocardial contractility. The guideline emphasizes achieving a resting HR of 50-60 beats/min, particularly in patients with persistent tachycardia, low blood pressure or limited tolerance to β-blockers.
ACC: American College of Cardiology; AHA: American Heart Association; ARNI: Angiotensin Receptor-Neprilysin Inhibitor; ESC: European Society of Cardiology; GDMT: Guideline-Directed Medical Therapy; HF: Heart Failure; HFSA: Heart Failure Society of America; HFrEF: Heart Failure with reduced Ejection Fraction; HR: Heart Rate; LVEF: Left Ventricular Ejection Fraction; MRA: Mineralocorticoid Receptor Antagonist; NYHA: New York Heart Association; SGLT2: Sodium-Glucose Cotransporter-2.				

Table 1: Guideline Recommendations and Clinical Positioning of Ivabradine in Heart Failure with Reduced Ejection Fraction (HFrEF).

The panel highlights particular utility in patients with low systolic blood pressure, where β blocker up-titration is frequently limited. Collectively, contemporary guidelines converge on three clinical imperatives, as shown in Fig. 1.

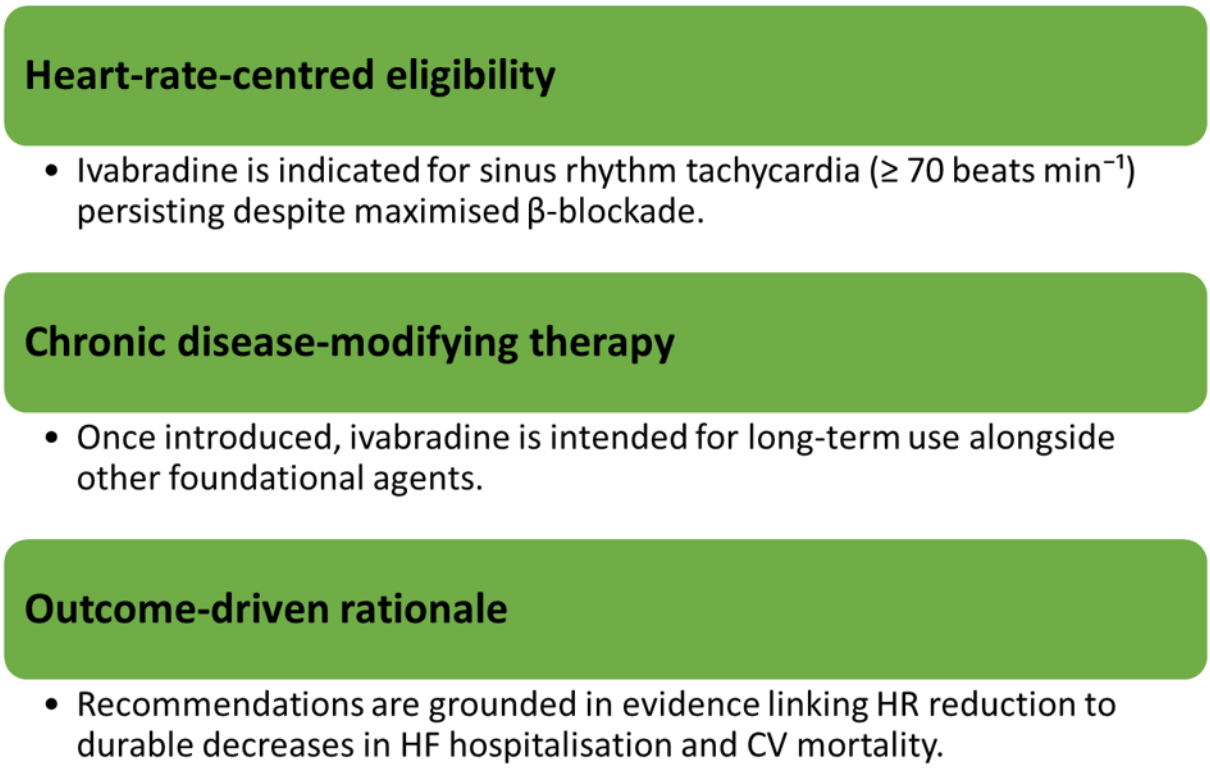

Figure 1: Three fundamental principles supporting the guideline-driven application of ivabradine in heart failure. These aligned statements confirm ivabradine as an integral pillar of modern HFrEF management rather than an optional or acute only add on.

The focus group panels agreed that ivabradine is indicated in chronic HFrEF patients who remain in sinus rhythm with a resting HR > 70 beats min^{-1} despite maximal tolerated β blockade or in whom β blockers are contraindicated. Once initiated, a target resting HR of 55-60 beats min^{-1} is considered acceptable, mirroring the treatment arm of the SHIFT trial, yet values down to 50 beats min^{-1} are permissible if the patient is asymptomatic. Bradycardia requiring discontinuation is uncommon; most panelists escalate to 5 mg twice daily (BD) when HR persists > 90 beats min^{-1} and de-escalate to 2.5 mg BD if HR falls < 50 beats min^{-1}. For pill burden reduction, a switch to a Once Daily (OD) formulation after 4-6 weeks of stability is favor. Overall, the panels concur that ivabradine provides a hemodynamically neutral means to achieve HR targets and facilitate optimization of neuro hormonal therapy in tachycardic HF phenotypes.

Heart Failure Continuum: Stage Specific Heart Rate Targets and Ivabradine Application

The 2022 ACC/AHA/HFSA guideline partitions the natural history of HF into four progressive stages - A (at risk), B (pre HF), C (symptomatic HF) and D (advanced HF), each defined by an incremental burden of structural abnormality, biomarker elevation and clinical manifestations. Within this framework, rising resting sinus HR accompanies neuro hormonal activation and ventricular remodeling, making HR an accessible metric for risk stratification and an actionable target across all stages.

Stage A (at risk myocardium).

Individuals with hypertension, atherosclerotic cardiovascular disease, diabetes, obesity, exposure to cardiotoxic agents or a positive family history of cardiomyopathy are classified as Stage A [22]. Lifestyle modification, optimal blood pressure control, weight management and early initiation of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes reduce incident HF. Consensus statements recommend maintaining a resting HR < 80 beats min^{-1} through risk factor control; specific HR lowering pharmacotherapy, including ivabradine, is not indicated because structural heart disease is absent.

Stage B (pre HF)

Stage B is characterized by asymptomatic left ventricular structural disease or persistent biomarker elevation [e.g., N terminal

pro B type natriuretic peptide (NT proBNP) > 125 pg mL^{-1}, high sensitivity cardiac troponin] without HF symptoms [22]. Echocardiographic findings such as reduced left ventricular ejection fraction (LVEF ≤ 40 %), increased wall thickness or left atrial volume index and elevated pulmonary artery systolic pressure fulfil diagnostic criteria. Patients meeting these criteria experience event free survival curves that approximate those of low risk symptomatic HF (Stage C), underscoring the need for aggressive intervention [24]. Guideline-Directed Medical Therapy (GDMT) with angiotensin converting enzyme inhibitors or angiotensin receptor blockers, β blockers and, when appropriate, implantable cardioverter defibrillators is class I recommended [22]. In individuals with persistent sinus HR ≥ 70 beats min^{-1} despite maximally tolerated β blockade or when β blockade is limited by hypotension, early ivabradine may be considered to attenuate adverse remodelling; a pragmatic HR goal is < 70 beats min^{-1}, extrapolated from post hoc analyses of SHIFT and aligned with ESC and ACC/AHA/HFSA guidance for symptomatic HF [7,19].

Stage C (symptomatic HFrEF; NYHA II-III)

Once clinical symptoms appear, HR reduction becomes a cornerstone of outcome modification. Randomized evidence (SHIFT) demonstrated that achieving a resting HR of 55-60 beats min^{-1} with ivabradine on top of Guideline Directed Medical Therapy (GDMT) reduced cardiovascular death and HF rehospitalization; regulatory approvals and global guidelines therefore assign ivabradine a class IIa recommendation when sinus HR ≥ 70 beats min^{-1} persists after Guideline- Directed Medical Therapy (GDMT) optimization [7,19].

Stage D (advanced or refractory HF)

Patients with persistent NYHA III-IV symptoms despite Guideline Directed Medical Therapy (GDMT), recurrent hospitalisations or dependence on intravenous inotropes constitute Stage D. Small observational cohorts indicate that ivabradine can safely achieve HR targets < 70 beats min^{-1} and facilitate β blocker re introduction in those receiving ambulatory inotropes or awaiting mechanical circulatory support, without compromising hemodynamic [16]. Although evidence quality is lower than for Stage C, HR control remains pathophysiologically relevant and is incorporated into pharmacotherapy algorithms for advanced HF.

In summary, mapping HR thresholds to ACC/AHA stages highlights the potential for ivabradine to complement β blockers from Stage B onward when sinus tachycardia persists, with progressively lower HR targets (Stage B < 70 beats min^{-1}; Stage C-D 55-60 beats min^{-1}) to mitigate remodelling, reduce hospitalisation and improve survival across the HF continuum.

Beyond Chronic HFrEF: Selected Clinical Scenarios in Which Ivabradine Provides Therapeutic Heart Rate Control

Acute Decompensated Heart Failure

Acute Heart Failure (AHF) is a life threatening syndrome that rapidly precipitates pulmonary oedema, systemic congestion and malignant arrhythmias [19]. Early sinus rate reduction decreases myocardial oxygen demand and can facilitate β blocker re initiation once hemodynamics stabilize. A meta analysis of eight prospective studies (n = 448) showed that ivabradine added to standard care reduced HR by a standardized mean difference of -0.73 (95 % CI -0.93 to -0.54) at discharge and improved Left Ventricular Ejection Fraction (LVEF) four months later [20]. The open label ETHIC AHF trial confirmed sustained HR lowering (≈ -15 bpm) and more favorable NT proBNP trajectories one year after in hospital initiation [21]. Formal guideline endorsement is pending, but these data support selective use once blood pressure is adequate and inotrope support has been withdrawn.

Chronic Coronary Syndrome (Stable Angina)

In the BEAUTIFUL trial (10 ,917 patients with Coronary Artery Disease (CAD) and LVEF < 40 %), ivabradine did not alter the primary composite endpoint, yet it significantly reduced admissions for myocardial infarction (hazard ratio 0.64) and coronary revascularization (HR 0.70) in the prespecified subgroup with baseline HR ≥ 70 bpm [11]. The ASSOCIATE trial demonstrated that ivabradine added to β blocker therapy increased exercise duration and reduced angina attacks over four months. Reflecting these data, the 2019 European Society of Cardiology (ESC) guideline for chronic coronary syndromes designates ivabradine as a second line agent when β blockers or rate limiting calcium channel blockers are contraindicated or insufficient (Class IIa, Level B) [23]. An Indian expert consensus recommends its combination with β blockers in patients who have concomitant HFrEF and persistent angina at HR ≥ 70 bpm [21].

Other Uses

The beneficial effects of ivabradine as premedication for coronary computed tomography angiography, HR lowering in Postural

Tachycardia Syndrome (POTS) and inappropriate sinus tachycardia constituted most studies among off-label uses. The promising results have been reported on the efficacy of ivabradine in controlling HR, especially in patients with inappropriate sinus tachycardia or POTS. Owing to the unique mechanism of action, ivabradine has the potential to be used more frequently in future clinical practice [24].

Ivabradine Synergy with Quadruple Guideline Directed Medical Therapy (GDMT) and Device Based Therapy

Pharmacodynamic Complementarity with Foundational Drugs

Ivabradine's selective If channel inhibition produces HR reduction without affecting blood pressure, renal function or electrolyte balance; consequently, it layers smoothly onto the "quadruple Guideline-Directed Medical Therapy (GDMT)" backbone of sacubitril/valsartan (ARNI), β blocker, Mineralocorticoid Receptor Antagonist (MRA) and Sodium-Glucose Cotransporter 2 inhibitor (SGLT 2i). In a multicenter database analysis, the synergistic effect of sacubitril/valsartan and ivabradine was evaluated [25]. Authors concluded that, among patients with HFrEF, simultaneous rather than sequential treatment with sacubitril/valsartan and ivabradine was a better strategy to reduce adverse events and achieve left ventricular reverse remodeling. Ivabradine treatment had a more significant benefit on improving hemodynamic stability [31]. DAPA-HF and EMPEROR-Reduced sub-analyses confirmed that SGLT-2i benefits were independent of baseline HR and were maintained in patients treated with ivabradine, indicating mechanistic complementarity rather than redundancy [26].

Merits: Facilitating Optimal Device Function

Persistent sinus tachycardia can compromise biventricular pacing percentages and ventricular filling in recipients of Cardiac Resynchronization Therapy (CRT) or Implantable Cardioverter Defibrillators (ICDs). Case series and small prospective studies demonstrate that ivabradine lowers intrinsic ventricular rates, raising effective CRT pacing from ≈72 % to > 90 % within two weeks and improving NYHA class without increasing atrial fibrillation burden [27]. In Left Ventricular Assist-Device (LVAD) cohorts, adjunctive Ivabradine has been associated with enhanced reverse remodeling and improved functional capacity, suggesting a role in device bridged myocardial recovery protocols [28].

Taken together, Ivabradine provides a haemodynamically neutral, HR selective intervention that unites with neuro hormonal blockade, glyco diuretic therapy and advanced devices-supporting its integration as a lifelong pillar alongside quadruple Guideline-Directed Medical Therapy (GDMT) and hardware based strategies in chronic HFrEF management.

Discussion

The methodology for developing this consensus statement involved a multidisciplinary panel of cardiologists from across India who convened to discuss the long term management of heart failure and the role of ivabradine. Indian experience underscores why the "HR gap" is particularly consequential in Asia. Consecutive registry work from Trivandrum found a mean presentation age of 61 years, fully a decade younger than Western cohorts and a one year mortality of 29% [29]. Long term follow up of the same cohort showed 59 % mortality at five years despite care in tertiary centres [2]. National data collected across 53 hospitals (NHFR; n = 10 851) corroborate the youthful, low blood pressure phenotype: mean age 59.9 ± 13.5 years, with 35 % of patients still tachycardic at > 100 beats min^{-1} on admission and fewer than half receiving full triple drug Guideline Directed Medical Therapy (GDMT). Across 11 Asian countries in the ASIAN HF registry, median resting HR remained 79 ± 16 beats min^{-1} while average systolic pressure hovered at 121 ± 21 mmHg, values that often pre empt further β blocker up titration [31].

Indian registry analyses further highlight sub optimal implementation of evidence based care: despite proven survival gains with quadruple Guideline- Directed Medical Therapy (GDMT), fewer than 50 % of patients are discharged on even triple therapy and guideline recommended diagnostic work up (echocardiography plus natriuretic peptides) is inconsistently applied—underscoring a persistent treatment gap in a cohort that is both younger and more comorbidity laden than Western counterparts [2,5,29]. Additional barriers highlighted by the Indian experts included limited drug availability in public formularies, diagnostic delays in rural settings, where breathless patients may be mislabeled as asthma or COPD and fragmented follow up that hampers medication titration. Dedicated HF clinics, nurse led programs, single pill combinations, aggressive correction of iron and vitamin D deficiency and selective addition of ivabradine for tachycardic, low blood pressure phenotypes have been proposed to narrow this treatment gap.

Summary and Conclusion

Ivabradine complements modern quadruple Guideline-Directed Medical Therapy (GDMT) by selectively reducing sinus tachycardia without compromising blood pressure or renal function. Evidence from randomized trials and real-world studies indicates that the Once-Daily (OD) formulation provides sustained heart rate control with efficacy and safety comparable to the twice-daily formulation while reducing pill burden. Consequently, OD ivabradine offers a convenient, well-tolerated and evidence-based option that may enhance long-term adherence and improve clinical outcomes in appropriately selected patients with HFrEF.

Conflict of Interest

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the preview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was obtained from all participants included in the study.

Authors' Contributions

All authors contributed equally to this paper.

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