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Ivabradine in Heart Failure with Reduced Ejection Fraction (HFrEF): A Narrative Review of Clinical Outcomes

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ABSTRACT

Background: Therapy for heart failure with reduced ejection fraction (HFrEF) patients is complex, involving several combinations of treatments, but there are still some problems, such as rehospitalization, reduced ejection fraction values, increased heart rate, and decreased quality of life. Ivabradine, a selective heart rate-lowering agent, offers adjunctive therapeutic benefits.

Objective: This study aims to determine the characteristics of HFrEF patients who received additional therapy with ivabradine and to determine how ivabradine affects their clinical outcomes.

Methods: This narrative review searched articles on PubMed, Cochrane Library, Google Scholar, and ScienceDirect. The research was limited to randomized controlled trial articles, observational studies, and cohorts with international and national English and/or Indonesian articles published in the last 10 years.

Results: Twenty-eight studies (n=36,765) met the problem formulation and inclusion criteria were analyzed. Patients receiving ivabradine were predominantly male (74.9%), aged 56-65 years (81.9%), and had a history of smoking. Most patients had heart rate ≥70 bpm (75.4%), LVEF ≤30% (55.3%), BMI ≥28 kg/m² (87.1%), and NYHA class II-III (85.5%). The addition of ivabradine to the clinical outcome of HFrEF patients reduces heart rate (15.7 bpm), blood pressure (SBP: -4.4 mmHg; DBP: -0.9 mmHg), rehospitalization, and mortality, while improving LVEF and stroke volume, and quality of life. Adverse effects included manageable bradycardia and transient visual disturbances.

Conclusion: Ivabradine effectively improves clinical outcomes in HFrEF patients as adjunct therapy, with significant benefits in cardiac function, symptom control, and prognosis.

Keywords: Characteristics; Clinical Outcome; Effectiveness; HFrEF; Ivabradine

INTRODUCTION

Heart failure represents a major global health threat[1], significantly impacting public health and quality of life. It is a pathological condition characterized by structural or functional cardiac abnormalities resulting in inadequate blood and oxygen distribution throughout the body[2]. Heart failure is the only cardiovascular disease with a continuously increasing incidence, evidenced by rising patient numbers, recurrent hospitalizations, and increased disability and mortality rates[3]. According to data from the Global Burden of Disease (GBD) and the Institute for Health Metrics and Evaluation (IHME) for 2014–2019, heart disease remains Indonesia's leading cause of mortality[4]. Additionally, the National Basic Health Research (Riskesdas) reported a threefold increase in heart disease prevalence from 0.5% (2013) to 1.5% (2018), with an estimated incidence of 15 per 1,000 individuals annually[5,6].

Congestive heart failure (CHF) is a condition in which the heart fails to pump blood effectively, resulting in inadequate oxygen delivery to meet the body's metabolic demands[7]. CHF is a complex disorder that encompasses multiple etiologies and comorbidities[8]. According to data from the Global Health Data Exchange (GHDx) in 2020, the global prevalence of CHF reached 64.34 million cases. In Indonesia, CHF is the second leading cause of mortality after stroke[9]. CHF can be classified into two primary pathophysiological mechanisms: systolic dysfunction and diastolic dysfunction. Systolic dysfunction is primarily characterized by reduced ejection fraction.

Management of heart failure with reduced ejection fraction (HFrEF) is inherently complex, encompassing pharmacological therapy, surgical interventions, and implantable devices. Several pharmacological agents are recommended for the treatment of HFrEF, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), and β-blockers[10]. However, challenges remain, including recurrent hospitalizations, progressive ejection fraction decline, elevated heart rate, and diminished quality of life, all contributing to high morbidity and mortality in HFrEF patients. Therefore, additional therapeutic interventions are required[11]. Ivabradine, a selective heart rate-lowering agent, represents one adjunctive therapy indicated for HFrEF management[12]. Ivabradine belongs to hyperpolarization-activated cyclic nucleotide-gated (HCN) channel inhibitors[13], exerting its pharmacological effect by selectively inhibiting the I*f* current in the sinoatrial node[14]. This study aims to characterize HFrEF patients receiving adjunctive ivabradine therapy and to evaluate its impact on clinical outcomes based on available clinical evidence.

METHODS

This study employed a narrative review design based on theoretical frameworks and comparative data analysis from previously published research articles within a specified timeframe. This study employed narrative review methodology. All data were secondary, derived from published articles.

Search strategy

A systematic literature was conducted across four electronic databases: PubMed, Cochrane Library, Google Scholar, and ScienceDirect. The search strategy employed specific keywords combined with Boolean operators. Boolean operators (AND, OR) were applied to identify prospective studies, including randomized controlled trials (RCTs), observational studies, and cohort studies published between 2013 and 2023. The search was restricted to articles published in English or Indonesian. The specific keywords utilized in this study were "Effectiveness" AND "Characteristics," "Quality of life," AND "Systolic heart failure" OR "Heart failure with reduced ejection fraction" AND "Ivabradine**."**

Eligibility criteria

This review included studies published between 2013 and 2023 investigating ivabradine effectiveness in patients with HFrEF. Eligible articles included randomized controlled trials (RCTs), cohort studies, and observational studies published in English or Indonesian. Indonesian journals required SINTA 1–4 accreditation, while international journals required Scopus indexing (Q1–Q4). These criteria ensured comprehensive synthesis of high-quality evidence regarding ivabradine efficacy in HFrEF management.

Study Quality Assessment

Study quality was assessed using two complementary approaches: SJR (Scimago Journal Rank) metric for journal quality evaluation and the Joanna Briggs Institute (JBI) Critical Appraisal Tools for methodological rigor assessment.

Data extraction

Data were extracted manually and systematically organized using Microsoft Word and Excel.

Data analysis

Study quality was evaluated using the SCImago Journal Rank (SJR) for journal credibility assessment and the Joanna Briggs Institute (JBI) Critical Appraisal Tools for methodological quality evaluation. The SJR indicator was assessed journal prestige based on quartile ranking (Q1–Q4). JBI Critical Appraisal Tools, tailored to specific study designs (experimental and observational), were used to evaluate methodological rigor. JBI checklists consist of several questions with response options: ‘yes’, ‘no’, ‘unclear’, or ‘not applicable’. Each ‘yes’ response was assigned one point; all other responses received zero points. Studies achieving ≥50% of the total possible score were considered to have acceptable methodological quality according to JBI standards.

RESULTS AND DISCUSSION

Overview of the Included Studies

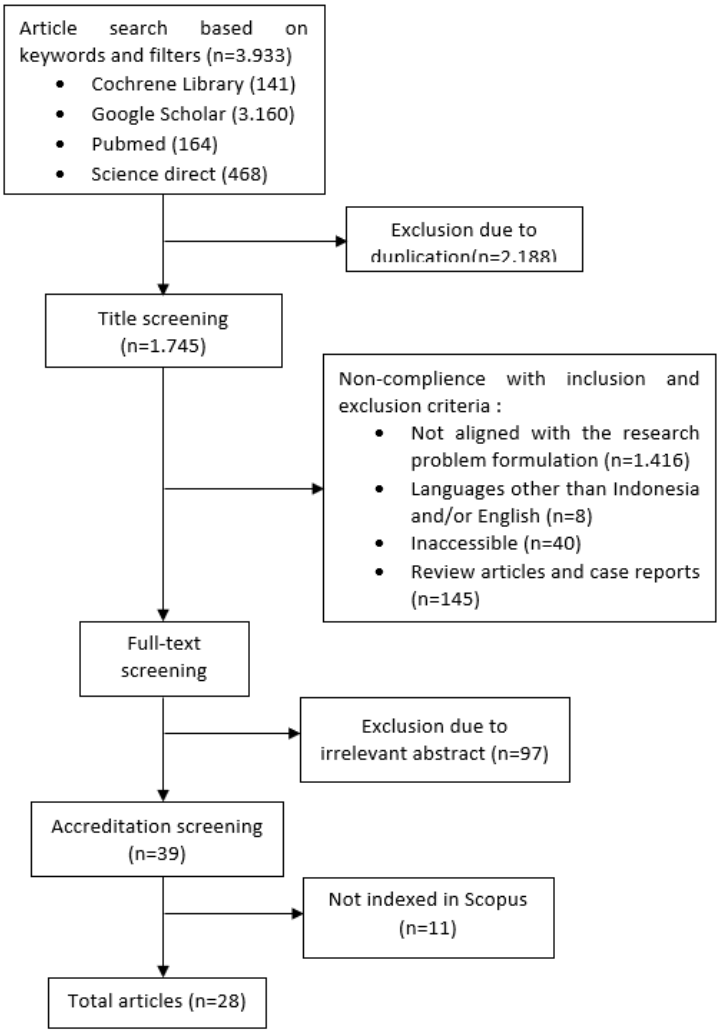

Figure 1. Literature Analysis Framework

Figure 1 presents the PRISMA flowchart for the study selection process. Table I summarizes the characteristics of the 28 included studies.

Sociodemographic Characteristic

Table II summarizes the sociodemographic characteristics of 36,735 HFrEF patients receiving adjunctive ivabadrine therapy across 28 studies**.** Analyzed factors included age, sex, smoking status, baseline heart rate (HR), baseline left ventricular ejection fraction (LVEF), body mass index (BMI), and New York Heart Association (NYHA) functional class.

Age is a non-modifiable risk factor for heart failure. The mean age of HFrEF patients in the reviewed studies was 61.1 years (range: 36–65 years and >65 years)**.** The majority (81.9%) of patients receiving ivabradine were aged 56–65 years. This age-related predominance is critical, as advancing age is associated with progressive decline in physiological and functional cardiac reserve, contributing to increased mortality and morbidity[43].

Males comprised the majority of patients (74.9%, n=27,519 patients), while females represented 25.1% (n=9,217)**.** This male predominance in HFrEF aligns with known sex-related differences in heart failure etiology and pathophysiology. Men more frequently develop ischemic heart disease, a leading cause of HFrEF, whereas wome n more commonly present with hypertension and diabetes mellitus as primary risk factors**.**

Table 1. Characteristics of Individual Studies

No	Authors, Years	Title	Study Setting	Methods	Sample (patient)	Dose	Primary Outcomes	JBI Score
1.	**Komajda M et al (2019)**[15]	Beneficial effects of ivabradine in patients with heart failure, low ejection fraction, and heart rate above 77 b.p.m.	SHIFT study was performed at 37 countries.	● RCT (randomized) ● SHIFT trial ● KCCQ (the Kansas city cardiomyopathy questionnaire)	674	● 5mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Mortality & Hospitalization (↓) significant	100%
2.	**Bocchi et al (2015)**[16]	Effect of Combining Ivabradine and β-Blockers: Focus on the Use of Carvedilol in the SHIFT Population	SHIFT study was performed at 37 countries.	● RCT (randomized) ● SHIFT trial	2.596	● 5mg/ 2x a day ● 7.5 mg/ 2x a day	● Resting HR (↓) significant ● Mortality & Hospitalization (↓) significant	100%
3.	**Erdem et al (2017)**[17]	The Effects of Ivabradine on Left Ventricular Synchronization and Tei Index in Patients with .Systolic Heart Failure	Cardiology Clinic of Abant Izzet Baysal University Hospital, Turkey	● Observational study, in cardiology clinic, Abant Izzet Baysal university hospital	40	● 5mg/ 2x a day ● 7.5mg/ 2x a day ● 2.5mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Mortality & Hospitalization (↓) ● significant ● SBP (↓) slightly significant ● DBP (↓) slightly significant	100%
4.	**Michael, Jeffrey et al (2015)**[18]	Twenty-four-hour heart rate lowering with ivabradine in chronic heart failure: insights from the SHIFT Holter substudy	SHIFT Holer substudy was performed at 82 centres in 21 countries	● RCT (randomized) ● SHIFT trial	602	● 5mg/ 2x a day ● 7.5mg/ 2x a day ● 2.5mg/ 2x a day	● Resting HR (↓) significant ● Mortality & Hospitalization (↓) significant	100%
5.	**Reil et al (2013)**[19]	Selective heart rate reduction with ivabradine unloads the left ventricle in heart failure patients	The SHIFT echocardiography substudy was performed at 89 centers in 21 countries	● RCT (randomized) ● SHIFT trial	275	● 5mg/ 2x a day ● 7.5mg/ 2x a day ● 2.5mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significan ● SV (*stroke volume*) (↑) significant	100%
6.	**Hamill et al (2015)**[20]	Repeated Heart Rate Measurement and Cardiovascular Outcomes in Left Ventricular Systolic Dysfunction	BEAUTIFUL trial was performed at 781 centres in 33 countries.	● RCT (randomized) ● SHIFT trial ● BEAUTIFUL trial	8.699 SHIFT 5.438 BEU	● 5 mg/ 2x a day	● Resting HR (↓) significant in three different HR	100%
7.	**Çavuşoğlu et al (2021)**[21]	Resting heart rate and real-life treatment modalities in outpatients with left ventricular systolic dysfunction study: A multicenter, prospective, observational, and	16 participating centers including academic centers and community hospitals in various geographical areas in Turkey	● Observational study ● The REALITY study ● KCCQ (Kansas city cardiomyopathy questionnaire)	1.054	● 5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Quality of Life (↑) on the KCCQ score	100%

No	Authors, Years	Title	Study Setting	Methods	Sample (patient)	Dose	Primary Outcomes	JBI Score
8.	**Khaled M et al (2019)**[22]	Safety and efficacy of off-label use of ivabradine in patients with acute heart failure	Ain Shams University (Cairo, Egypt)	● RCT (randomized ● MLWHFQ (Minnesota living with heart failure questionnaire)	40	● 5 mg/ 2x a day	● Resting HR (↓) significant ● Mortality (↓) signifikan	92.31%
9.	**D. Zachariahet al (2017)**[23]	Quality of life improvement in older patients with heart failure initiated on ivabradine: Results from the UK multi-centre LIVE:LIFE prospective cohort study	44 centres across England, Wales, Scotland and Northern Ireland	● Cohort study ● LIVE:LIFE study ● MLWHFQ ● (Minnesota living with heart failure questionnaire)	1.056	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● Resting HR (↓) significant ● Quality of Life (↑) on MLWHF score ● Mortality (↓) significant	100%
10.	**Yuri M et al (2017)**[24]	Optimization of heart rate lowering therapy in hospitalized patients with heart failure: Insights from the Optimize Heart Failure Care Program	International multicenter Optimize Heart Failure Care program in Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Russia, Ukraine, and Uzbekistan	● Observational study ● MLWHFQ ● (minnesota living with heart failure questionnaire)	370	● dxc5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Quality of Life (↑) on MLWHFQ score ● Mortality & Hospitalization (↓) significant	100%
11.	**Riccioni et al (2013)**[25]	Ivabradine Improves Quality of Life in Subjects with Chronic Heart Failure Compared to Treatment with β-Blockers: Results of a Multicentric Observational APULIA Study	Cardiology and Internal Medicine Units within the region of, Apulia, Italy	● Observational study ● APULIA study (ivabradine improves quality of life in subjects with chronic heartfailure compared to treatment with β-blockers)	221	● 5 mg/ 2x a day	● Resting HR (↓) significant ● Quality of Life (↑) with APULIA ● Mortality & Hospitalization (↓) significant	100%
12.	**Christian Zugck et al (2014)**[26]	Ivabradine Treatment in a Chronic Heart Failure Patient Cohort: Symptom Reduction and Improvement in Quality of Life in Clinical Practice	694 centers in Germany	● Cohort study ● Intensify Study	1.956	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Quality of Life (↑)	100%
13.	**Liu YX et al (2022)**[27]	Initiating ivabradine during hospitalization in patients with acute heart failure: A real-world experience in China	Peking Union Medical College Hospital, China	● Cohort study	126	● 5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● SBP dan DBP (↑) significant ● Mortality & Hospitalization (↓) significant	100%

No	Authors, Years	Title	Study Setting	Methods	Sample (patient)	Dose	Primary Outcomes	JBI Score
14.	**Hiroyuki T et al (2015)**[28]	Heart Rate Control With If Inhibitor, Ivabradine, in Japanese Patients With Chronic Heart Failure	73 institutions in Japan	● RCT (randomized) ● SHIFT trial	126	● 5 mg/ 2x a day ● 2.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant	100%
15.	**Ilonka R et al (2016)**[29]	Impact of Ivabradine on Inflammatory Markers in Chronic Heart Failure	Department of Cardiology of the University Hospital Jena, Germany	● Cohort study	50	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Quality of Life (↑) significant ● DBP (↓) significant	100%
16.	**Hiroyuki T et al (2019)**[30]	Efficacy and Safety of Ivabradine in Japanese Patients With Chronic Heart Failure	Japan	● RCT (randomized) ● Japanese SHIFT trial	254	● 2.5 mg/ 2x a day ● 5 mg/ 2x a day ● 7.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Quality of Life (↑) significant ● Mortality & Hospitalization (↓) ● significant	100%
17.	**Ajit Mullasari (2020)**[31]	Efficacy and Safety of Ivabradine Once-Daily Prolonged-Release versus Twice-Daily Immediate Release Formulation in Patients with Stable Chronic Heart Failure with Systolic Dysfunction: A Randomized, Double-Blind, Phase 3 Non-Inferiority (PROFICIENT) Study	Study setting unspecified	● RCT (randomized ● PROFICIENT study	169	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day	● Resting HR (↓) significant	100%
18.	**Luigi T et al (2013)**[32]	Efficacy and safety of ivabradine in chronic heart failure across the age spectrum: insights from the SHIFT study	SHIFT study involves 37 countries	● RCT (randomized) ● SHIFT trial	6.505	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● Resting HR (↓) significant ● Bradycardia ● Mortality & Hospitalization (↓) ● Significant	92,31%
19.	**Francisco J et al (2016)**[33]	Effect of early treatment with ivabradine combined with beta- blockers versus beta-blockers alone in patients hospitalised with heart failure and reduced left ventricular ejection fraction (ETHIC-AHF): A randomised study	Hospital (hospital name unspecified in the study)	● RCT (randomized) ● ETHIC-AHF trial	71	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Mortality and Hospitalization (↓) ● significant ● Bradycardia ● Vision impairment	76,92%

No	Authors, Years	Title	Study Setting	Methods	Sample (patient)	Dose	Primary Outcomes	JBI Score
20.	**Karl S et al (2012)**[34]	Effects on Outcomes of Heart Rate Reduction by Ivabradine in Patients With Congestive Heart Failure: Is There an Influence of Beta-Blocker Dose? Findings From the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine Trial) Study	SHIFT study involves 37 countries	● RCT (randomized) ● SHIFT trial	6.39 8	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● Resting HR (↓) significant	100%
21.	**Douglas H et al (2012)**[35]	Characterizing Patients with Chronic Heart Failure in Community Care After Hospitalization: A Potential Role for Ivabradine	*Tayside Heart Failure Nurse Liaison Service (THFNLS), Scotland*	● Restrospective clinical	166	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● Resting HR (↓) significant	100%
22.	**Riccardo C et al (2012)**[36]	Clinical Efficacy of Ivabradine in Patients With Inappropriate Sinus Tachycardia A Prospective, Randomized, Placebo-Controlled, Double-Blind, Crossover Evaluation	Not stated	● RCT (randomized)	11	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● Resting HR (↓) significant ● Quality of Life (↑) significant	100%
23.	**Jeffrey S. B et al (2012)**[37]	Effect of ivabradine on recurrent hospitalization for worsening heart failure in patients with chronic systolic heart failure: the SHIFT Study	SHIFT study involves 37 countries	● RCT (randomized) ● SHIFT trial	1.186	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● Resting HR (↓) significant ● Hospitalization (↓) significant	100%
24.	**Riet D et al (2014)**[39]	Prescribing Patterns to Optimize Heart Rate Analysis of 1,000 Consecutive Outpatient Appointments to a Single Heart Failure Clinic Over a 6-Month Period	*HF clinic, UK*	● Observational study	824	● 5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR(↓) significant	100%
25.	**Bagriy et al (2015)**[40]	Addition of Ivabradine to b-Blocker Improves Exercise Capacity in Systolic Heart Failure Patients in a Prospective, Open-Label Study	*Cardiology Department of Donetsk Medical University, Ukraine*	● Non RCT (randomized)	69	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● SBP (↓) significant	100%
26.	**Karim Hamed et al (2015)**[41]	Effect of Ivabradine on recurrent hospitalization in patients with chronic systolic heart failure JBI 100%	SHIFT study involves 37 countries	● RCT (randomized)	50	● 5 mg/ 2x a day ● 7.5 mg/ 2x a day ● 2.5 mg/ 2x a day	● LVEF (↑) significant ● Resting HR (↓) significant ● Hospitalization (↓) significant	100%

Table II. Sociodemographics Characteristics of HFrEF Patients Receiving Ivabadrine Therapy

Patient Charachteristic	Number		Percentage
Age (years)	36-45 years	82	0.2
	46-55 years	229	0.6
	56-65 years	30,101	81.9
	≥65 years	6323	17.2
Sex	Male	27,519	74.9
	Female	9,217	25.1
HR (bpm)	≤70 *bpm*	179	0.5
	≥70 *bpm*	27,707	75.4
	≥80 *bpm*	8,759	23.8
	≥90 *bpm*	90	0.2
LVEF (%)	≤30%	20,321	55.3
	≥30%	16,016	43.6
	≥40%	110	0.3
	Unknown	288	0.8
BMI (kg/m^2)	≤28 kg/m^2	632	1.7
	≥28 kg/m^2	32,001	87.1
	Unknown	4,102	11.2
NYHA Class	I	1,370	3.7
	II	17,756	48.3
	III	13,675	37.2
	IV	3,609	9.8
Smoking	Yes	4,975	14
	No	253	0.7
	Unknown	29,851	85

Additionally, women with heart failure typically exhibit increased left ventricular stiffness with relatively preserved ejection fraction, making them more likely to be diagnosed with heart failure with preserved ejection fraction (HFpEF) rather than HFrEF[44].

One of the primary contributors to the higher incidence of HFrEF in men **is** smoking behavior. Smoking status was documented in 14.7% of patients: 14% (n=4,975) were active smokers, 0.7% (n=253) were non-smokers, and 85% (n=29,851) had unknown status. The high proportion of unknown data limits interpretation; however, among those with documented smoking history, the prevalence was substantial. Smoking represents well-established cardiovascular risk factor for and may partially explain the male predominance in HFrEF, as smoking rates are typically higher among men[45]. In patients with heart failure, particularly those with HFrEF**,** smoking is correlated with clinical outcomes, including increased hospitalization rates, elevated blood pressure, increased heart rate, and impaired systolic function, all contributing to disease progression[46]. Additionally, smoking can impair systolic function, further exacerbating the risk of HFrEF development**.**

Another aggravating factor in HFrEF patients receiving ivabradine therapy is obesity**.** The majority of patients (87.1%, n=32,001) had a BMI ≥28 kg/m², while 1.7% (n=632) had BMI ≤28 kg/m², and 11.2% (n=4,102) had unknown BMI. This high prevalence of elevated BMI is clinically significant, as obesity imposes substantial cardiac workload and promotes adverse cardiovascular remodeling. Excess body weight contributes to left ventricular hypertrophy, increase cardiac oxygen demand, thereby exacerbating HFrEF progression**[47]**.

Table III. Prevalence of Comorbidities in HFrEF Patients Receiving Ivabradine

Patient Comorbidity	Number	Percentage	References
Hypertension	23.109	62,9	Erdem et al (2017)[17] Çavuşoğlu et al (2021)[21] Khaled M et al (2019)[22] Riccioni et al (2013)[25] Christian Zugck et al (2014)[26] Liu YX et al (2022)[27] Hiroyuki T et al (2015)[28] Ilonka R et al (2016)[29] D. Zachariahet al (2017)[23] Hiroyuki T et al (2019)[30] Ajit Mullasari (2020)[31] Riccardo C et al (2012)[36] Riet D et al (2014)[39]
Myocardial Infarction (MI)	19.154	52,1	Reil et al (2013)[19] Çavuşoğlu et al (2021)[21] Hiroyuki T et al (2015)[28] D. Zachariahet al (2017)[23] Hiroyuki T et al (2019)[30]
Ischemia	16.763	45,6	Khaled M et al (2019)[22] Christian Zugck et al (2014)[26] Hiroyuki T et al (2015)[28] Ilonka R et al (2016)[29] D. Zachariahet al (2017)[23] Hiroyuki T et al (2019)[30] Ajit Mullasari (2020)[31] Douglas H et al (2012)[35] Riet D et al (2014)[39]
Diabetes Mellitus (DM)	11.694	31,8	Erdem et al (2017)[17] Reil et al (2013)[19] Çavuşoğlu et al (2021)[21] Khaled M et al (2019)[22] Riccioni et al (2013)[25] Christian Zugck et al (2014)[26] Liu YX et al (2022)[27] Hiroyuki T et al (2015)[28] Ilonka R et al (2016)[29] D. Zachariahet al (2017)[23] Hiroyuki T et al (2019)[30] Ajit Mullasari (2020)[31] Douglas H et al (2012)[35] Riccardo C et al (2012)[36]
Stroke	3.407	9,3	Çavuşoğlu et al (2021)[21] D. Zachariahet al (2017)[23] Hiroyuki T et al (2019)[30]
Atrial Fibrillatiion (AF)	1.842	5	Çavuşoğlu et al (2021)[21] Christian Zugck et al (2014)[26] Liu YX et al (2022)[27] Hiroyuki T et al (2015)[28] Ilonka R et al (2016)[29] Ajit Mullasari (2020)[31] Hiroyuki T et al (2019)[30] Douglas H et al (2012)[35] Riet D et al (2014)[39]

Baseline resting heart rate (HR) averaged 80 bpm across the reviewed studies, with patients categorized into four ranges: ≤70 bpm (0.5%, n=179), ≥70 bpm (75.4%, n=27,707), ≥80 bpm (23.8%, n=8,759), and ≥90 bpm (0.2%, n=90). The predominance of patients with HR ≥70 bpm reflects appropriate patient selection for ivabradine therapy, as this stage is specifically indicated for HFrEF patients with elevated heart rates despite optimal beta-blocker therapy[13]. These baseline HR distributions align with guideline recommendations and the SHIFT trial criteria, in which ivabradine demonstrated efficacy in reducing heart rate to approximately 60 bpm within 28 days in patients with baseline heart rate of ≥75 bpm[48]. The target resting heart rate for adjunctive therapy with ivabradine is 60 bpm[13]. Therefore, ivabradine is not recommended for patients with a resting heart rate of ≤60 bpm[13].

Baseline left ventricular ejection fraction (LVEF) was ≤30% in 55.3% of patients (n=20,321), 30-40% in 43,6% (n=16,016), ≥40% in 0.3% (n=110), with 0.8% (n=288) having unknown LVEF. This distribution demonstrates that majority of patients had severily reduced ejection factions, consistent with guideline criteria for HFrEF diagnosis and ivabradine indication. The predominance of patients with LVEF ≤30% is clinically appropriate, as this populations experiences the greatest symptomatic burden and has been shown to derive significant benefit from ivabradine therapy, including improvements in LVEF, reduced hospitalizations, and mortality reduction[49].

The functional status of heart failure patients is classified according to the NYHA functional classification[50]. NYHA functional class distribution was: Class I (3.7%, n=1,370), Class II (48.3%, n=17,756), Class III (37.2%, n=13,675), and Class IV (9.8%, n=3,609). The majority of patients (85.5%) were classified as NYHA Class II-III,

indicating moderate functional impairment. Previous studies have demonstrated a correlation between reduced LVEF and NYHA functional class. As the NYHA functional class increases in severity, LVEF tends to decline further.

Comorbidities in the Study Population

The worsening of NYHA functional class is associated with an increased risk of mortality, hospitalization, and changes in risk status depending on whether the patient's condition improves or deteriorates[51]. In addition to sociodemographic characteristics, comorbidities represent a significant risk factor that exacerbates disease progression in HFrEF patients.

Comorbidity data were available for multiple studies and are summarized in Table III. The most prevalent comorbidities among HFrEF patients receiving ivabradine therapy were hypertension (62.9%, n=23,109), followed by myocardial infarction (52.1%, n=19,154) and ischemia (45.6%, n=16,763).

The high prevalence of hypertension aligns with its established role as a risk factor for HFrEF development. Chronic hypertension increases cardiac afterload, leading to left ventricular hypertrophy, diastolic dysfunction, and eventually systolic impairment[52]. The Framingham Heart Study demonstrated that heart failure and hypertension are closely correlated as triggers for systolic or diastolic dysfunction of the left ventricle, with 68% of HFrEF cases being associated with a history of hypertension[52]. Persistent hypertension increases the workload of the heart, leading to myocardial hypertrophy. Over time, prolonged hypertension causes cardiac enlargement and weakening. If elevated arterial pressure persists, it results in progressive deterioration of cardiac function, ultimately leading to a decline in cardiac output[43].

Systolic heart failure leads to an increase in left ventricular end-diastolic pressure, which in turn raises left atrial pressure, serving as a triggering factor for atrial fibrillation. In this review, the prevalence of atrial fibrillation among HFrEF patients receiving adjunctive ivabradine therapy was 5%, affecting 1,842 patients. Atrial fibrillation is the most common cause of tachycardia-induced cardiomyopathy. Among HFrEF patients, atrial fibrillation is a leading cause of all-cause mortality and heart failure-related hospitalizations[53]. Uncontrolled atrial fibrillation can result in ventricular remodeling, ultimately manifesting as heart failure[54]. If left untreated, atrial fibrillation can induce ventricular dysfunction through tachycardia-induced cardiomyopathy, exacerbating heart failure progression due to impaired atrial contraction during ventricular filling[3,1]. HFrEF patients are highly susceptible to hemodynamic changes, and atrial fibrillation significantly contributes to hemodynamic instability. Furthermore, atrial fibrillation is associated with increased mortality in patients with ischemic cardiomyopathy.

Ivabradine Dosage Regimen

Ivabradine dosing regiments across the reviewed studies were consistent with clinical guideline recommendations, as summarized in Table IV.

Table 4. Ivabradine Dosing Regimens in Reviewed Studies

Dosage	References
2.5 mg/ twice a day	17, 18, 19, 23, 26, 28, 30, 34, 35, 36, 37, 41, 42
5 mg/ twice a day	15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42
7.5 mg/ twice a day	16, 17, 18, 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 40, 41, 42

The standard initial dose of ivabradine in HFrEF is 5 mg twice daily, consistent across all reviewed studies. Dose adjustments are guided by resting heart rate monitoring[55].

After two weeks of treatment, doses may be titrated increased based on HR response. For patients maintaining HR ≥60 bpm, the dose may be increased to the maximum of 7.5 mg twice daily. Conversely, for patient with ≤50 bpm or experiencing bradycardia-related symptoms (dizziness, fatigue, hypotension), the dose may be reduced to 2.5 mg twice daily. If the patient's HR remains between 50 and 60 bpm consistently, the ivabradine dose may be maintained at the initial dose of 5 mg twice daily[55]. Treatment discontinuation is recommended if the patient maintains a resting HR of ≤50 bpm or if symptomatic bradycardia persists[61]. While all reviewed studies adhered to guideline-recommended dosing protocols detailed information regarding individual dose adjustments and treatment duration for specific patients was not reported in the research.

Clinical Outcomes of Ivabradine in HFrEF

Clinical outcomes assessed across the reviewed studies included resting heart rate, left ventricular ejection fraction, systolic and diastolic blood pressure (SBP/DBP), mortality, hospitalization, stroke volume, and quality of life. Results are summarized in Table V.

Table 5. Summary of Clinical Outcomes with Ivabradine Therapy in HFrEF

Clinical Outcome Parameters	Conclusion	References
LVEF (%)	(↑) Significant	15, 17, 19, 24, 26, 28, 29, 30, 33, 39, 40, 41
Stroke Volume	(↑) Significant	19
Resting HR (bpm)	(↓) Significant	16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 39, 40, 41, 42
	Not Significant	18
Systolic Blood Pressure (SBP)	(↓) Significant	17, 27, 40, 42
Diastolic Blood Pressure (DBP)	(↓) Significant	17, 27, 29, 30
Mortality HFrEF	(↓) Significant	15, 16, 17, 18, 22, 23, 24, 25, 27, 30, 32, 33, 38
Hospitalization	(↓) Significant	15, 16, 17, 18, 24, 25, 27, 30, 32, 33, 37, 38, 41, 35

Twelve studies (15, 17, 19, 24, 26, 28, 29, 30, 33, 39, 40, 41) reported significant improvements in LVEF with ivabradine therapy. A commonly observed clinical parameter in patients with HFrEF is a decrease in LVEF[56]. Mean baseline LVEF was 29.4% (range: 20-45%), increasing to 34.7% post-treatment. This improvement aligns with the primary objective of adding ivabradine in HFrEF management, which is to enhance LVEF, particularly in patients with an LVEF of ≤30%. A decline in LVEF in HFrEF patients is associated with a reduction in quality of life, as lower LVEF exacerbates the severity of cardiac dysfunction. A decreased LVEF can lead to hypoxia or inadequate oxygen supply to the body[57]. Additionally, LVEF in HFrEF patients is directly correlated with reductions in stroke volume and cardiac output. In a healthy individual, stroke volume typically ranges between 60–100 mL per heartbeat.

The addition of ivabradine in the treatment of HFrEF has demonstrated a significant reduction in resting heart rate, with a statistical range of $P < 0.001$ to 0.005. Across all reviewed articles, heart rate decreased from 81.05 bpm to 65.2 bpm, with an overall change of 15.7 bpm, observed over varying study durations.

The substantial HR reduction achieved with ivabradine is mechanistically consistent with its selective inhibition of the funny current (If) in the sinoatrial node, which prolongs diastolic depolarization without affecting myocardial contractility or vascular tone[58].

Four studies (17, 27, 40, 42) reported significant SBP reduction from 127.9 mmHg to 123.5 mmHg (mean reduction: 4.4 mmHg), while four studies (17, 27, 29, 30) showed DBP reduction from 78.8 mmHg to 77.9 mmHg (mean reduction: 0.9 mmHg). Achieving SBP to <130 mmHg in HFrEF patients has been associated with a 38% risk reduction compared to SBP <140 mmHg targets[59], suggesting that the observed blood pressure changes may contribute to improved outcomes.

Overall, the review of the analyzed articles indicates that the use of ivabradine in patients with HFrEF demonstrates a significant reduction in both mortality and rehospitalization[37]. These outcomes are associated with a decrease in resting heart rate, an increase in LVEF, symptom improvement, and better functional classification according to the NYHA, as well as reduced mortality and rehospitalization endpoint scores due to worsening heart failure. The use of ivabradine in HFrEF patients has been shown to be beneficial in reducing recurrent hospitalizations due to worsening symptoms, though the extent of benefit varies depending on the duration of treatment. However, the reviewed articles indicate that the difference in mortality specifically due to HFrEF is not highly significant[60].

Quality of Life in HFrEF Patients Receiving Ivabradine

The improvement in quality of life among patients with HFrEF is associated with a reduction in resting heart rate, an increase in LVEF, and a decrease in mortality and rehospitalization endpoints. The method used to assess quality of life improvement in HFrEF patients was questionnaire-based evaluation. The results reflecting quality of life improvements in patients can be observed in Table VI.

Table VI. Quality of Life Parameters

Quality of Life	Conclusion	References
	(↑) Significant	21, 23, 24, 25, 26, 29, 30, 36

The questionnaires used in the reviewed articles are KCCQ (Kansas City Cardiomyopathy Questionnaire), MLWHFQ (Minnesota Living with Heart Failure Questionnaire), and SF-36 (Short Form-36). These three methods are questionnaires utilized for patients with heart failure. The difference between these three methods is that in KCCQ, there are 15 questions related to physical limitations, symptom frequency, symptom severity, symptom stability, self-efficacy, social limitations, and quality of life[61]. Overall, the addition of ivabradine in HFrEF therapy has shown positive results, indicated by a reduction in resting HR from ≥70 bpm to ≥60 bpm, an increase in LVEF from ≤35-40% to ≥40-50%, and an improvement in NYHA functional class, which correlates with an enhanced quality of life in patients with HFrEF. There was an increase in the total KCCQ score in one of the reviewed articles by 43.2% with a treatment duration of 12 months compared to the placebo group[48,62]. In the MLWHFQ method, one article demonstrated a significant improvement in the clinical summary score from 49.9 to 29.5 over one year in the β-blocker plus ivabradine group ($p= 0.0001$)[50].

Lastly, in the SF-36 method, ivabradine therapy as associated with a significant improvement was observed across all dimensions of QoL (physical health, emotional health, and social activities) over 6 months compared to β-blocker monotherapy ($p <0.05$)[53].

Adverse Effect of Ivabradine Therapy

Adverse effects were reported in 13 studies (Table VII). The most common was bradycardia (symptomatic and asymptomatic), reported in 12 studies (16, 17, 18, 23, 26, 27, 28, 30, 32, 33, 41, 42). Visual disturbances (phospones) were reported in three studies (23, 26, 33).

Table VII. Adverse Effect of Ivabradine

Adverse Effect	References
Bradycardia	16, 17, 18, 23, 26, 27, 28, 30, 32, 33, 41, 42
Visual Impairment	23, 26, 33

The most commonly occurring adverse effect in patients receiving ivabradine is bradycardia. Ivabradine can induce bradycardia as it is a heart rate-lowering agent that exerts its effect by blocking the pacemaker current in the sinoatrial (SA) node, leading to prolongation of diastolic depolarization and a subsequent reduction in heart rate (HR). Therefore, the use of ivabradine must be accompanied by regular HR monitoring in patients to prevent the occurrence of bradycardia. Overall, the adverse effects identified in the reviewed articles include symptomatic and asymptomatic bradycardia. The distinction between the two lies in the presence of clinical manifestations: symptomatic bradycardia is characterized by symptoms such as dyspnea, chest pain, dizziness, and decreased consciousness, whereas asymptomatic bradycardia occurs without any noticeable symptoms[63].

Visual disturbances (phospones) occur due to ivabradine's inhibition of I_h channels in the retina[64]. These luminous phenomena are typically transient, occurring during the first weeks of treatment and resolving spontaneously. In clinical trials, visual symptoms rarely led to treatment discontinuation.

LIMITATION OF STUDY

The limitation of this study is that several full-text articles were not freely accessible. Additionally, the article selection process was conducted manually, which required a relatively long duration. For future research, the use of applications such as Mendeley Desktop could streamline the article selection process, thereby reducing the study duration and facilitating researchers in selecting relevant articles.

CONCLUSION

Based on the findings of this literature review, it can be concluded that the characteristics of HFrEF patients receiving adjunct ivabradine therapy are predominantly individuals aged 56–65 years, with the majority being

male and having a history of smoking. The majority of HFrEF patients had a heart rate (HR) ≥70 bpm, left ventricular ejection fraction (LVEF) ≤30%, body mass index (BMI) ≥28 kg/m², and were classified as NYHA class II–III. Most patients had comorbidities such as hypertension, diabetes mellitus, myocardial infarction, ischemia, atrial fibrillation, and stroke. The addition of ivabradine to the treatment regimen of HFrEF patients demonstrated significant benefits in reducing HR, systolic blood pressure (SBP), and diastolic blood pressure (DBP), as well as in lowering rehospitalization rates and mortality. Furthermore, ivabradine therapy significantly improved LVEF and stroke volume.

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STATEMENT OF ETHICS

This article was written in accordance with the code of ethics and was not published or under review in another journal.

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