JOURNAL OF MARKET ACCESS & HEALTH POLICY
2023, VOL. 11, 2262073
https://doi.org/10.1080/20016689.2023.2262073

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ORIGINAL RESEARCH ARTICLE

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Ivabradine in patients with heart failure: a systematic literature review

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ABSTRACT

Background: Heart failure is a chronic disease linked with significant morbidity and mortality, and uncontrolled resting heart rate is a risk factor for adverse outcomes. This systematic literature review aimed to assess the efficacy, safety, and patient-reported outcomes (PROs) of ivabradine in patients with heart failure (HF) with reduced ejection fraction (HFrEF) in randomized controlled trials (RCTs) and observational studies.

Methods: We searched electronic databases from their inception to July 2021 to include studies that reported on efficacy, safety, or PROs of ivabradine in patients with HFrEF.

Results: Of 1947 records screened, 51 RCTs and 6 observational studies were identified. Ivabradine on top of background therapy demonstrated a significant reduction in composite outcomes including hospitalization for HF or cardiovascular death. In addition, observational studies suggested that ivabradine was associated with a significant reduction in mortality. Across all studies, ivabradine use on top of background therapy was associated with greater reductions in heart rate, improved EF, and improved health-related quality of life (QoL) and comparable risk of total adverse events compared to those treated with background therapy alone.

Conclusions: Ivabradine on top of background therapy is beneficial for heart rate, hospitalization risk for HF, mortality, EF, and patients' QoL. Moreover, these benefits were achieved with no significant increase in the overall risk of total adverse events.

ARTICLE HISTORY
Received 6 July 2023
Revised 13 September 2023
Accepted 15 September 2023

KEYWORDS
Heart failure; ivabradine; systematic review; quality of life; patient-reported outcomes

Introduction

Heart failure (HF) is a debilitating and often fatal condition affecting an estimated 64 million people. Despite advancements in treatments and improved prognosis in the past decades, the mortality associated with HF remains high [1]. Up to 50% of the patients with HF with reduced ejection fraction (HFrEF) have ejection fraction ≤40% measured by echocardiography. However, the prevalence of HFrEF has stabilized and is actually declining in developed countries [2]. Recommended pharmacologic treatment of HFrEF includes angiotensin-converting enzyme inhibitors (ACEIs), mineralocorticoid receptor antagonists (MRAs), sodium-glucose cotransporter-2 inhibitors (SGLT2i) such as dapagliflozin or empagliflozin, and beta-blockers unless contraindicated or not tolerated [2–5]. In patients with HF, elevated resting heart rates have been established as a strong predictor of cardiovascular (CV) mortality and morbidity. Thus, reducing resting heart rate is a crucial target in the treatment of HF [6,7]. Ivabradine was approved by the European Medicines Agency (EMA) in 2005 [8]. Ivabradine lowers the heart rate by prolonging the diastolic depolarization, which reduces the stress on the heart, thereby slowing the progression of HF and improving symptoms [9]. Ivabradine is recommended for patients with HFrEF who are receiving guideline-directed medical therapy including a beta-blocker at the maximum tolerated dose, and with elevated resting heart rate ≥70 bpm, to reduce HF hospitalizations and CV deaths. The EMA approved ivabradine for the treatment of chronic HF in adult patients in sinus rhythm with a heart rate ≥75 bpm and New York Heart Association (NYHA) class II to IV with systolic dysfunction, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated [2,10,11]. Therefore, this systematic literature review (SLR) focuses on patients with HFrEF. Traditionally, data from randomized controlled trials (RCTs) have been considered a gold standard in the evaluation process

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/20016689.2023.2262073.

of new health technologies. However, there has been a noticeable surge in the importance placed on real-world evidence (RWE) derived from observational studies for evaluating healthcare practices.

The aim of this SLR was to collect data from RCTs and observational studies to get an updated assessment of ivabradine's efficacy and safety in patients with HFrEF. Considering the higher external validity of the observational studies, we also collected studies of ivabradine, which assess its effectiveness and safety in routine clinical practice, since its approval.

Methods

This SLR adhered to the Cochrane Handbook for Systematic Review of Interventions [12], as well as the Centre for Reviews and Dissemination guidelines [13]. The data were collected from the Embase, MEDLINE, Cochrane CENTRAL, and ClinicalTrials.gov databases from their inclusion until July 2021, as well as by manually searching selected conference websites for abstracts from 2019 to 2021 (Supplementary content 1). The search was based on keywords and medical subject headings related to heart failure, ivabradine, and RCTs and observational studies. The complete search strategy can be found in Supplementary Table S1 and RCT, randomized controlled trial

The inclusion criteria for this study were determined based on the Population, Intervention, Comparators, Outcomes, and Study design (PICOS) framework, as described in Table 1. For inclusion, studies comparing ivabradine (including the branded product Procoralan®) with either active comparators or placebo were considered. The included studies needed to report ≥1 of the

Table 1. Inclusion criteria.

PICOS	Inclusion
Population	Adult patients with HF[a]
Intervention	Ivabradine
Comparators	Active or non-active comparators including potentially Procoralan® generic

Outcomes	• Efficacy (including composite outcomes):
	  • Hospitalization for worsening of HF
	  • All-causehospitalization
	  • CV hospitalization
	  • Percentage of patients according to the NYHA class
	  • Change in NYHA (% of patients with change/improvement, mean change)
	  • Death from HF
	  • CV death
	  • All-cause death
	  • Reduction in heart rate
	  • Change in resting heart rate
	  • Blood pressure
	  • Change in LVEF
	  • Change in NT-proBNP
	  • 6-minute walk test
	  • Echocardiographic parameters (LVEDVI, LVESVI, LVESV, and LVEDV)
	  • Oxygen consumption [peak oxygen consumption (VO2), maximal oxygen consumption (VO2 max), double product]
	  • Minute ventilation/carbon dioxide production (VE/VCO2)
	• Safety:
	  • Total AEs
	  • Total SAEs
	  • Cardiac disorders (bradycardia, atrial fibrillation)
	  • Luminous phenomena (phosphenes)
	• Health resource use
	• Patient-reported outcomes

Study design	• RCTs • Comparative observational studies

AE, adverse event; HF, heart failure; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume index; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RCT, randomized controlled trial; SAE, serious adverse event; VE/VCO2, minute ventilation/carbon dioxide production; VO2, peak oxygen consumption.

[a]During the study selection, studies analyzing patients with heart failure (HF) regardless of left ventricular ejection fraction (LVEF) were included, but after full-text review, only those that reported data for patients with HF with reduced ejection fraction were included. The subgroups of patients of interest were as follows: New York Heart Association class, patients with heart rate ≥ 70 or 75 or 77 bpm, patients in whom β-blocker therapy is contraindicated or not tolerated, angina, renal dysfunction, chronic obstructive pulmonary disease/asthma, diabetes, elderly (over 65 years and others; cut-off above 65 years), blood pressure level (all subgroups stratified for blood pressure), vulnerable patients, sex (male/female), duration of HF (≥4 weeks to <1.5 years; 1.5 years to <4 years; ≥4 years), patients with Chagas heart disease, patients with left bundle branch block, mineralocorticoid receptor antagonist usage at baseline (yes/no), angiotensin converting enzyme or angiotensin receptor-neprilysin inhibitor (renin-angiotensin system inhibitor) usage at baseline (yes/no), β-blocker usage at baseline (yes/no), digoxin usage at baseline (yes/no), cardiac resynchronization therapy (yes/no), implantable cardioverter defibrillator (yes/no), N-terminal pro-B-type natriuretic peptide, etiology of HF (ischemic/non-ischemic), LVEF (<35%/≥35%, <40%/≥40%, <50%/≥50%), hypertension (yes/no), class of (overall summary score) Kansas City Cardiomyopathy Questionnaire, B-type natriuretic peptide, Asian patients, subgroups defined by left ventricular diastolic dysfunction classification (grade I, II, and III), data for therapy intensification.

efficacy/effectiveness outcomes (Table 1), safety outcomes, or patient-reported outcomes including health-related quality of life (HRQoL). No language or geographic restrictions were applied. We excluded dose-ranging studies, literature reviews, editorials, letters, opinion articles, preclinical studies, and general discussion articles.

We predefined subgroups of interest: subgroups according to the NYHA class, heart rate (≥70 or 75 or 77 bpm), angina, renal dysfunction, diabetes, elderly patients (aged ≥65 years and <65 years), blood pressure, sex, duration of HF, N-terminal pro-B-type natriuretic peptide (NT-proBNP), etiology of HF (ischemic/nonischemic), left ventricular ejection fraction (LVEF) (<35% or ≥35%, <40% or ≥40%, <50% or ≥50%), hypertension (yes/no), B-type natriuretic peptide (BNP), Asian patients, and subgroups defined by left ventricular (LV) diastolic dysfunction classification (grade 1, 2, or 3). During the study selection, we included all RCTs and comparative observational studies of patients with HF, regardless of LVEF. During the full-text review stage, only studies restricted to patients with HFrEF and studies that reported data for subgroups of patients with HFrEF were selected.

Two independent reviewers screened the abstracts and full-text publications (HB and FK) to select relevant articles based on the inclusion criteria, and a third reviewer (EO) resolved any discrepancies that arose. Afterward, papers reporting results from the same studies were grouped together. A reviewer (FK) extracted data from studies that met the PICOS criteria using extraction templates created in Microsoft Excel, and another reviewer (EO) validated the accuracy of the extracted data. These data included publication details, study design, baseline characteristics, results, and data necessary for the quality assessment. The trial results were extracted at the maximum follow-up time for all outcomes.

One reviewer assessed the quality of RCTs and observational studies using the Cochrane Risk-of-Bias tool (RoB2) [14,15] and the Newcastle-Ottawa Scale (NOS) [16], respectively. Another reviewer validated the accuracy of assessment, and discrepancies were resolved via discussion. RoB2 addresses five specific domains: the bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. The judgments in each domain lead to an overall risk of bias judgement [14,15]. The NOS assesses the appropriateness of three domains: selection of study groups, comparability of groups, and ascertainment of exposure and outcomes for case-control and cohort studies. A star system, ranging from 0 to 9 stars, is used to rate the study quality [16].

After conducting the SLR, the feasibility of conducting a meta-analysis comparing ivabradine on top of background therapy versus background therapy alone was assessed. Meta-analysis can only be performed when the underlying clinical questions of the studies being considered for inclusion are similar enough for pooling to be meaningful. However, because of the low number of studies reporting complete numeric results for each specific endpoint and the non-negligible clinical heterogeneity identified, a meta-analysis was not performed.

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1) illustrates the scheme for the study selection. The literature search resulted in 1911 studies focusing on patients with HF. This included 33 RCTs (61 publications) and 8 comparative observational studies. After full-text review and application of inclusion criteria, 24 RCTs (51 publications) and 6 observational studies focusing on patients with HFrEF were included in the SLR. Table 2 presents the characteristics of the included studies and patients.

Among the included RCTs, the sample size ranged from 21 to 6505 patients in the SHIFT trial [35,41]. In the pooled analysis for SHIFT and BEAUTIFUL, 11897 patients were studied. Most studies included patients with heart rate ≥70 bpm [18,21,22,27,30,34,37,41,48], ≥75 bpm [19,23,24,28,38,40], or ≥80 bpm [20], except Potapenko et al. (2011) [29], in which patients with heart rate ≥60 bpm were included. The majority of the included studies analyzed patients with baseline LVEF ≤40% [17,20,22,26,28,29,32–34,49] or ≤35% [19,21,23,27,30,35,37,40]. The mean age of patients ranged from 42 years to 74 years [20,50].

Six trials compared ivabradine with placebo on top of background therapy [17,20,23,34–36], and 16 trials evaluated ivabradine on top of background therapy [18,19,21,22,24,26–29,31–33,37,38,41,49], including various beta-blockers, ARBs, ACEIs, and MRAs, either with or without placebo. One study compared ivabradine and pyridostigmine [41], and one trial compared ivabradine alone and placebo [39]. The studies that compared ivabradine with placebo on top of background therapy listed mainly different types of beta-blockers [18,19,22,24,28,33,38,49,51–53]. The SHIFT trial publications presented about 40% of included papers [7,11,35,36,48,55–65]. Among the included observational studies, four studies were designed as prospective cohort studies [43,46,47], one was a retrospective database analysis [45], and one was a combination of database analysis and registry from Taiwan [44]. All the included observational studies initiated ivabradine as

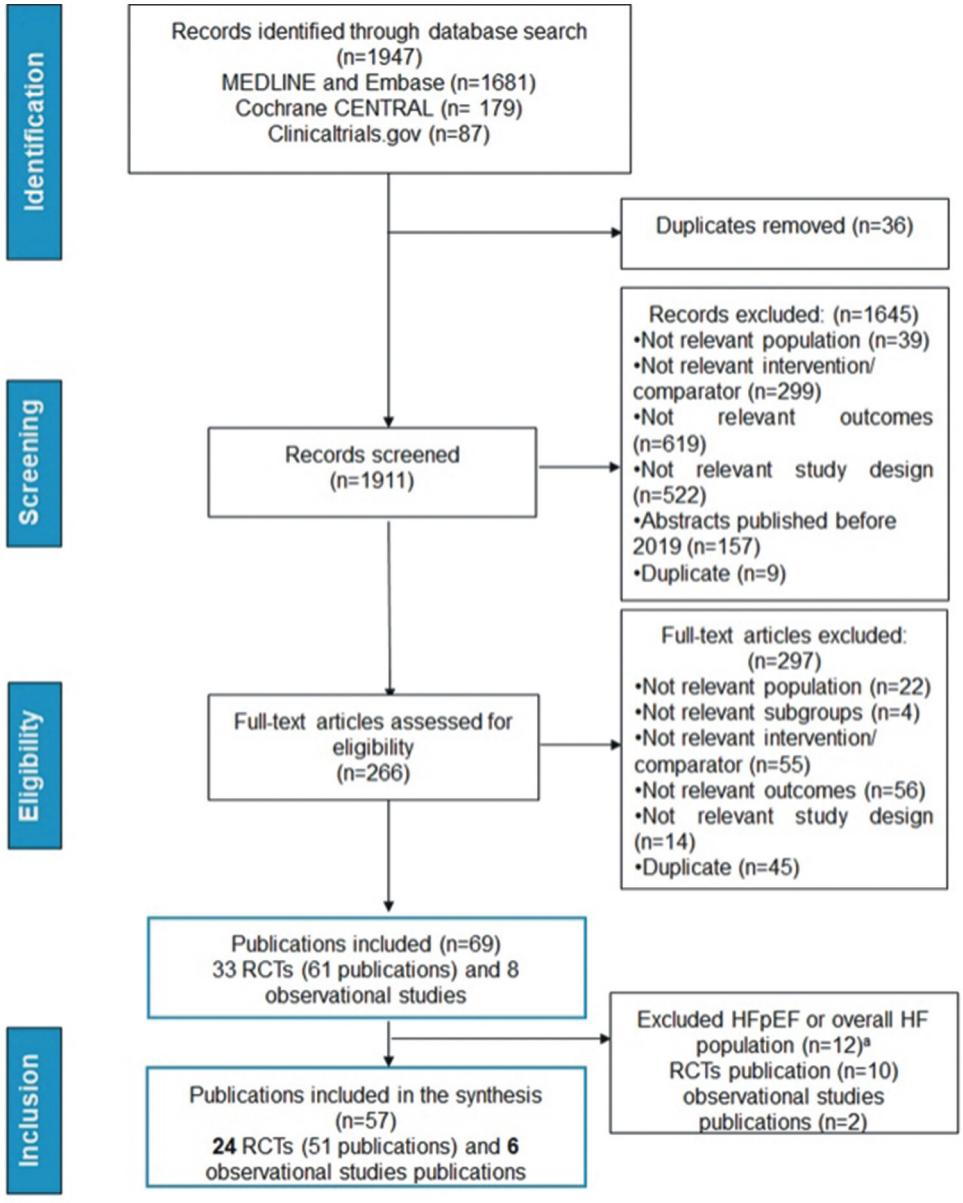

Figure 1. The preferred reporting items for systematic reviews and meta-analyses chart.

an add-on treatment to the current background therapy at discharge. The sample size ranged from 65 to 2364 patients [42,43]. The population of interest in the studies comprised mainly patients with a heart rate of ≥70 bpm, except in one study that included patients with a heart rate of ≥60 bpm [46]. The definition of reduced ejection fraction varied between studies and ranged from ≤40% to <50% [42,45,47].

The overall risk of bias in the RCTs was assessed as high (Error! Reference source not found.) (Figure 2). Most studies were rated as low risk in terms of missing outcomes data (83%), measurements of the outcomes (83%), and selection of the reported results (74%). The randomization process and the deviations from intended interventions presented some concerns (57%) related to missing information or being unable to conceal allocation to intervention or usual care arms after randomization from research team and patients. In general, the risk of bias varied from low to high across some aspects of the included studies, with insufficient detail provided to inform judgment in several cases (Suplementary Table S3). However, almost all included observational studies were of good quality, with a total score of 8 stars on the NOS. One study received a score

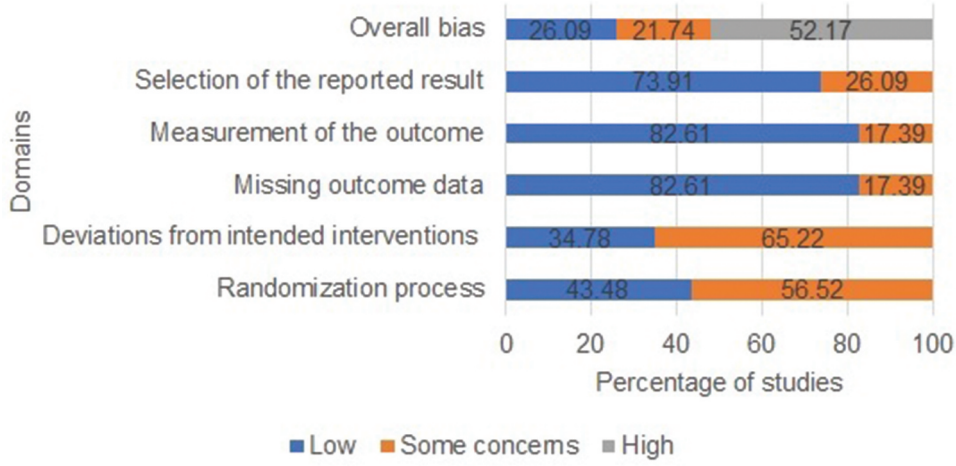

Figure 2. Assessment of bias in randomized controlled trials.

of 7 stars because of a not relevant assessment of the outcome, and another received a score of 6 stars because of a not relevant assessment of the outcome and a short follow-up period of 1 month (Supplementary Table S4).

Randomized controlled trials

Most results came from either a large pivotal RCT that evaluated the effects of ivabradine on CV outcomes in patients with HFrEF (SHIFT trial) [7,11,35,36,48,54–65] or a pooled analysis of individual trial data from the SHIFT and BEAUTIFUL trials, which included patients with LV dysfunction and heart rate ≥70 bpm [36]. Publications were excluded if they presented results for the overall population in the BEAUTIFUL study because it included patients with both symptomatic and asymptomatic HF and coronary artery disease.

Composite outcomes

In the SHIFT trial, treatment with ivabradine on top of background therapy compared with background therapy alone significantly reduced the risk of composite outcome, defined as CV death or hospitalization for worsening HF at a median follow-up of 22.9 months (hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.75–0.90; $p < 0.0001$) [11]. This reduction was primarily driven by a reduction in hospitalizations for worsening HF [35,36,56]. Similar findings were noted in the pooled analysis of the SHIFT and BEAUTIFUL trials (HR, 0.87; 95% CI, 0.8–0.94; $p < 0.001$) [36]. The positive effects of ivabradine on the considered primary composite outcome were seen consistently across various patient subgroups except those defined according to baseline heart rate [35]. Significant improvement was observed in the subgroup with a median baseline heart rate >77 bpm (HR, 0.75; 95% CI, 0.67; 0.85; $p < 0.0001$) [54].

The effect of ivabradine on the considered composite outcome was also evaluated in the J-SHIFT study, which involved Japanese patients with HFrEF, ejection fraction ≤35%, and resting heart rate ≥75 bpm. The J-SHIFT study demonstrated that ivabradine improved the primary composite endpoint of CV death or hospital admission for worsening HF in the ivabradine group compared with the placebo group after 52 weeks of treatment (20.5% vs 29.1%; $p = 0.1179$; HR, 0.67; 95% CI, 0.4–1.11) [40].

Furthermore, the SHIFT trials found that ivabradine was associated with a significantly lower rate of CV death, hospitalization for worsening of HF, and hospitalization for non-fatal myocardial infarction (HR, 0.82; 95% CI, 0.74–0.89) up to 42 months of follow-up [35,36].

Cardiovascular death and all cause-death

The included studies did not show a significant reduction in CV or all-cause deaths [29,35,36,40,56,59,66]. However, a SHIFT trial analysis revealed that the beneficial effect of ivabradine was greater in patients with heart rate ≥75 bpm. This result was not only linked to a reduction in HF hospitalizations and deaths from HF but also to a significant reduction in CV and all-cause deaths, which was not observed in patients with baseline heart rate <75 bpm [11].

Heart rates at follow-up

The included studies showed that the reduction in heart rate was greater in patients with HFrEF who received ivabradine on top of background therapy group compared with those who only received

Table 2. Overview of included studies.

Study name or author year	Study design	Population	Sample size	EF, %	Heart rate	NYHA	Intervention/ comparator	Mean age (SD)	Male, %
RCT									
Abdel-Salam, 2015 [17]	RCT, DB	Patients with idiopathic DCM	43	≤40	≥70 bpm	2–4	Ivabradine + BT	49.1 (15.7)	50
							Placebo + BT	52.3 (13.5)	56.5
Abdullaev, 2020 [18]	RCT	CHF with a low EF of the left ventricle	140	Low	≥70 bpm	2–3	Ivabradine + BT	66.3 (8.4)	85
							Nebivolol +BT	64.8 (9.2)	87
CARVIVA-HF [19]	RCT, OL	Patients with chronic HF	121	≤35	≥75 bpm	2–3	Ivabradine	67.2 (9.5)	68.3
							Ivabradine + Carvedilol	66.7 (10.1)	66.7
							Carvedilol	66.5 (9.2)	68.4
CONSTATHE-DHF [20]	RCT, DB	Patients with ADHF in sinus rhythm	26	≤40	≥80 bpm	2–4	Ivabradine + BT	37 (11)	46
							Placebo + BT	47 (17)	62
Cavusoglu, 2015 [21]	RCT	Patients hospitalized with acute decompensated HF	58	≤40	≥70 bpm	2–4	Ivabradine + Dobutamine + BT	64 (8.4)	65
							Dobutamine + BT	67 (12)	72
ETHIC-AHF [22]	RCT, OL	Patients hospitalized with HF and HFrEF	71	≤40	≥70 bpm	3–4	Ivabradine + BB	66.2 (15.4)	71.9
							BB	67.7 (12.3)	68.6
J-SHIFT [23]	RCT, DB	Patients with stable symptomatic chronic HF	254	≤35	≥75 bpm	2–5	Ivabradine + BT	61.2 (13.3)	84.3
							Placebo + BT	60.1 (13.7)	80.3
Kanorskiĭ, 2011 [24]	RCT, SB	Patients with CHF FC III and IHD and/ or stage III hypertension (HT) who had been prescribed complex therapy (quinapril, torasemide, spironolactone)	100	≤50	≥75 bpm	3	Ivabradine + BT (not BB)	59.4 (2.3)	45.45
							Metoprolol succinate (BB)	62.9 (2.8)	53.6
Babushkina 2020 [25]	RCT	Patients with stable angina of II and III FC with CHF I-III FC and type I diastolic dysfunction of the left ventricle	73	≤40	≥70 bpm	1–3	Ivabradine + BT	NR	NR
							Bisoprolol +BT		
							Bisoprolol + Ivabradine +BT		
Mansour, 2011 [26]	RCT, DB	Idiopathic DCM	53	≤40	≥70 bpm	2–4	Ivabradine + BT	47 (13)	60
							BT	52 (13)	61
Ordu, 2015 [27]	RCT, DB	Patients with CHF, on optimized medical therapy according to the European Society of Cardiology guidelines	98	≤35	≥70 bpm	2–3	Ivabradine + BT	65.24 (8.7)	33
							BT	66.38 (11.57)	35
Othman, 2019 [28]	RCT	Patients with acute HF	40	≤40	≥75 bpm	3–4	Ivabradine + BT (BB)	60.35 (11.08)	70
							BB	60.85 (11.41)	80
Potapenko, 2011 [29]	RCT, OL	Patients after myocardial infarction with systolic chronic cardiac failure	49	≤40	≥60	2–3	Ivabradine + BT	NR	78.2
							BT	NR	84.6
PRIME-HF [30,31]	RCT, OL	Patients hospitalized for acute HF but stabilized and preparing for discharge	104	≤35	≥70 bpm	NR	Ivabradine + BT (+max dose of BB)	56.5 (14.8)	55.8
							BT, mainly BB	58.5 (12)	73.1
Raja, 2018 [32]	RCT	Symptomatic HF secondary to idiopathic DCM	125	≤40	≥70 bpm	2–4	Ivabradine + BT	48.9 (16)	55
							BT	45.5 (13.8)	59
Sallam, 2016 [33]	RCT	Ischemic CHF	100	≤40	≥70 bpm	3–4	Ivabradine + Carvedilol + BT	62 5 (9.2)	66
							Carvedilol +BT	65 (10)	74
Sarullo, 2010 [34]	RCT, SB	Patients with ischemic CHF in stable condition	60	≤40	≥70 bpm	2–3	Ivabradine + BT	52.1 (6.1)	76
							Placebo + BT	52.9 (4.9)	74
SHIFT [35]	RCT, DB	Moderate to severe chronic HFrEF	6,505	≤35	≥70 bpm	2–4	Ivabradine + BT	60.7 (11.2)	76
							Placebo + BT	60.1 (11.5)	77
SHIFT + BEAUTIFUL [36]	RCT, DB	Moderate to severe chronic HFrEF	11897	≤35	≥77 bpm	2–4	Ivabradine + BT	62.6 (10.3)	79
							Placebo + BT	62 (10.5)	79

(*Continued*)

Table 2. (Continued).

Study name or author year	Study design	Population	Sample size	EF, %	Heart rate	NYHA	Intervention/ comparator	Mean age (SD)	Male, %
Sisakian, 2016 [37]	RCT, OL	HFrEF and severely impaired diastolic function	54	≤35	≥70 bpm	2–4	Ivabradine + BT	58.(12.2)	81.48
							BT	61.4 (9.67)	81.48
Tregubov, 2015 [38]	RCT	Patients with hypertensive disease and/or ischemic heart disease and CHF	100	≤55	≥75 bpm	3	Ivabradine + BT	57.1 (21.4)	53.57
							Metoprolol + BT	57.1 (21.7)	45.45
TREPPE [39]	RCT, DB	Patients with stable CHF and pacemakers or defibrillators	40	≤45	NR	1–3	Ivabradine	74 (9)	76.9
							Placebo	74 (9)	76.9
Tsutsui, 2019 [40]	RCT, DB	Japanese patients with HF	126	≤35	≥75 bpm	>2	Ivabradine 5 mg + BT	60 (13.9)	88.1
							Ivabradine 2.5 mg + BT	57.7 (13)	88.1
							Placebo + BT	59.4 (12.7)	81
Villacorta, 2019 [41]	RCT, DB	Patients with CHF	21	≤50	≥70 bpm	3–4	Ivabradine	56.2 (13.7)	90
							Pyridostigmine	62.6 (12.1)	18
Observational studies									
Chang, 2019 [42][a]	Prospective, cohort study	Patients with CRT and HFrEF	65	<40	≥70 bpm	NR	Ivabradine + BT	NR	NR
							BT	NR	NR
Guzman, 2018 [43]	Prospective, cohort study	Patients with HFrEF in sinus rhythm	2364	NR	≥70 bpm	1–4	Ivabradine + BT	70.8 (7.4)	56.6
							Digoxin + BT	70.6 (7.3)	59
							BT	70.7 (7.5)	47.7
Liao, 2021 [44]	Retrospective, cohort, database analysis and registry[b]	Patients with acute HFrEF discharged from hospital	Before propensity score matching: 1630 After propensity score matching: 876	NR	≥70 bpm	3	Ivabradine + BT	60.5 (14.9)	76.7
							BT alone	60.8 (14.4)	76.9
Lopatin, 2018 [45]	Retrospective, database analysis	Patients with sinus rhythm	370	<40	≥70 bpm	3	Ivabradine + BT	62.9 (12.8)	71.3
							BT (BB alone)	60.7 (12.1)	75.9
Prathibha, 2020 [46]	Prospective, database analysis	Patients with HF	156	NR	≥60 bpm	3–4	Ivabradine	57.4 (10.9)	NR
							Ivabradine + BT (metoprolol)	58.3 (9.1)	NR
							Metoprolol	60.8 (7.8)	NR
APULIA [47]	Prospective, cohort study	Patients with CHFrEF	221	<50	≥70 bpm	2–4	Ivabradine + BT (not BB)	63 (5)	49
							BB + BT	64 (4)	49.5

ADHF, acute decompensated heart failure; BB, beta-blockers; bpm, beats per minute; BT, background therapy; CHF, chronic heart failure; CHFrEF, chronic heart failure with reduced ejection fraction; CRT, cardiac resynchronization therapy; DB, double blind; DCM, dilated cardiomyopathy; EF, ejection fraction; FC, functional classification; HF, heart failure, HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; n, number; NR, not reported; NYHA, New York Heart Association; OL, open label; RCT, randomized controlled trial; SB, single blind; SD, standard deviation.

[a]Conference paper.

[b]TSOC-HFrEF registry which contains data on a prospective, multicentre, and observational survey of 1,509 patients with HFrEF recently admitted in 21 hospitals in Taiwan for HF from 2013 to 2014.

background therapy [17,18,28,33,34,38,41,49,51,66]. In the SHIFT trial, heart rate among patients treated with ivabradine decreased by a mean (SD) of 15.4 (10.7) bpm compared with their pretreatment heart rate of 80 bpm after 28 days of treatment. When corrected for changes in the placebo group, the net reduction with ivabradine was 10.9 bpm (95% CI, 10.4–11.4). This reduction was maintained throughout the study, with a heart rate decrease of 9.1 bpm (95% CI, 8.5–9.7) at 12 months and 8.1 bpm (95% CI, 7.5–8.7) at the end of the 23-month study period [35].

The ivabradine group showed a significant reduction in heart rate compared with the placebo group and background therapy group at a median follow-up of 24.5 months and a maximum follow-up of 29.3 months, as reported by Ekman et al. [67]. The mean reduction in heart rate was −10.1 bpm (95% CI, −11 to −9; $p < 0.001$). Significant reductions in heart rate of −11.9 bpm were also reported in J-SHIFT [40] from 6 weeks (SD, 1.1; $p < 0.0001$) to 1 year (SD, 1.4, $p < 0.0001$), in the PRIME-HF trial [30] through 180 days with a mean decrease of −10 bpm (95% CI, −15.7 to −4.3) versus 0.7 bpm (95% CI, −5.4 to 6.7; $p = 0.011$), and in the study by Sisakian et al. [37] at 3 months (−18.9 bpm versus −1.6 bpm; $p < 0.0001$).

Ejection fraction

Across the included studies, ivabradine was associated with an improved ejection fraction [20,21,23,24,26,29,32–34,38,40,41]. A SHIFT echocardiographic substudy showed that ivabradine reversed cardiac remodeling in patients with HF and LV systolic dysfunction. Ivabradine significantly reduced left ventricular end-systolic volume index compared with placebo. This reduction was independent of HF etiology, baseline LVEF, and use of beta-blockers. Furthermore, the results of the SHIFT echocardiographic substudy showed that ivabradine significantly improved LVEF. However, this substudy reported results for a small population ($n = 411$) of patients for whom complete echocardiographic data at baseline and 8 months were available [68]. Similar significant reductions in LV volumes and improvements in LVEF were observed in the J-SHIFT study [40], as well as in ETHIC-AHF [22,32].

In addition, the results showed a significant difference in change from baseline of LVEF in patients with symptomatic HF secondary to idiopathic dilated cardiomyopathy, LVEF < 40%, NYHA classes 2 to 4, and heart rate >70 bpm at 3 and 6 months for ivabradine on top of background therapy versus background therapy alone ($p < 0.001$) [32].

Patient-reported outcomes

Across the included studies, ivabradine demonstrated an improvement in HRQoL [17,19,26,28,30,32–35,41,54,67,69]. For instance, at 12 months in the SHIFT trial, a significantly greater improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score was demonstrated in both the clinical summary score ($p = 0.018$) and the overall summary score ($p < 0.001$). These data came from the SHIFT substudy, which included only 1944 participants (approximately 30% of the SHIFT population). Low HRQoL was associated with an increased rate of CV death or hospitalization for HF. However, heart rate reduction with ivabradine was associated with an improvement in HRQoL [67].

In CARVIVA-HF, when using the visual analog scale and MacNew Quality-of-Life after Myocardial Infarction (QLMI) tool, patients who received both ivabradine and carvedilol had better HRQoL compared with baseline ($p < 0.02$), whereas those who received carvedilol alone showed no changes [19]. After 3 months, the combination of ivabradine and carvedilol was associated with an improvement in the KCCQ clinical summary score [33]. Similar results were reported when comparing ivabradine on top of beta-blockers with beta-blockers alone after 1 month [28], and with background therapy at 3 and 6 months [32].

The comparison of ivabradine on top of background therapy with background therapy alone in the PRIME-HF trial showed no difference in KCCQ and patient global assessment from baseline to 180 days ($p > 0.05$) [30].

Safety

The risk of total adverse events (AEs) was comparable between patients treated with ivabradine on top of the background therapy versus background therapy alone [30,35,40,70]. In the SHIFT trial, serious AEs occurred less frequently in the ivabradine group compared with the placebo group ($p = 0.025$) [35].

Furthermore, all SHIFT publications, except for J-SHIFT, reported comparable rates of total AEs for patients receiving ivabradine on top of the background therapy compared with those receiving placebo on top of the background therapy. However, the J-SHIFT study revealed a significant increase in the incidence of total AEs among Japanese patients with HFrEF who received ivabradine on top of the background therapy compared with those who received placebo on top of the background therapy [35,36,58,60–62,64,65,70].

Observational studies

The findings reported in the included observational studies in the analysis confirmed the results observed in RCTs. The use of ivabradine on top of background therapy was associated with a significant reduction in the risk of composite outcomes, hospitalization for worsening of HF, and all-cause hospitalizations [43–46,71].

Among the six observational studies identified, three reported significant reduction in all-cause deaths [43–45], and two reported significant reduction in CV deaths with ivabradine on top of background therapy compared with background therapy alone (including beta-blockers) [43,44], which was not observed in large phase 3 RCTs [29,35,40,56].

In a study by Liao et al. [44], treatment with ivabradine on top of background therapy was associated with a significantly lower risk of CV death compared with background therapy after 1 year (5.8 vs 12.2 per 100 person-years; $p = 0.003$). In another observational study by Guzman et al. [43], the addition of ivabradine to background therapy was associated with a significant reduction in the risk of CV death compared with digoxin on top of background therapy after a median follow-up of 57.5 months (HR, 0.87; 95% CI, 0.81–0.96).

All four included studies that reported all-cause deaths showed a beneficial effect of ivabradine [42–45]. For instance, in Liao et al. [44], ivabradine on top of background therapy was associated with a significantly lower risk of all-cause deaths compared with background therapy at 1-year follow-up (HR, 0.48; 95% CI, 0.3–0.77). Another study conducted by Chang et al. [42] demonstrated similar results, but they were not significant at 587 days. In the study by Guzman et al. [43], ivabradine was associated with significantly lower rates of all-cause deaths compared with background therapy (without commencing therapy with either ivabradine or digoxin) after a median follow-up of 57.5 months (HR, 0.9; 95% CI, 0.84–0.97). In the study by Lopatin et al. [45], adding ivabradine on top of background therapy reduced the risk of all-cause deaths compared with using beta-blocker alone after 6 months ($p < 0.0001$).

Moreover, ivabradine was found to result in a greater reduction in heart rate compared with standard treatment among patients with HFrEF after 1 year of follow-up ($p = 0.005$) [44]. Additionally, the use of ivabradine was found to significantly improve LVEF in some studies [45,71], whereas these improvements were not significant in others [42,44,72]. Finally, the use of ivabradine on top of the background therapy was associated with a greater improvement in QoL, as assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), compared with beta-blockers alone ($p = 0.0001$) at 12 months [45].

Discussion

The purpose of this systematic review was to gather and summarize data on the efficacy and safety of ivabradine in both experimental settings (RCTs) and real-world settings (observational studies). The primary sources of data for this SLR were a large RCT known as the SHIFT trial [7,11,35,36,48,54–65], which evaluated the effects of ivabradine on CV outcomes in patients with HFrEF, and a pooled analysis of individual trial data from the SHIFT and BEAUTIFUL trials, which included patients with LV dysfunction and heart rate ≥70 bpm [36]. The results of this SLR suggest that ivabradine, when used on the top of background therapy, can effectively reduce the major risks associated with HFrEF. Both RCTs [7,35,36,40] and observational studies [43–46,71] resulted in a significant reduction in composite outcomes, including hospitalization and mortality with the use of ivabradine. This implies that ivabradine has the potential to improve outcomes for patients with HFrEF.

The results from large phase 3 RCTs did not consistently show a significant reduction in CV or all-cause deaths with the use of ivabradine in patients with HFrEF [29,35,36,40,56,59,66]. A SHIFT analysis revealed that patients with a baseline heart rate of 75 bpm or higher may benefit more from ivabradine treatment, which was not associated with a significant reduction in CV and all-cause deaths [11]. On the other hand, observational studies reported significant reductions in these outcomes [43–45]. This discrepancy may be attributed to differences in study design, sample size, or follow-up duration between RCTs and observational studies [43–45]. However, there is limited real-world evidence available [42–46], so additional studies are necessary to confirm these findings.

The findings from RCTs also highlighted the positive impact of ivabradine on heart rate reduction [17,18,28,33,34,38,41,49,51,66], and improvement in LVEF [20,21,23,24,26,29,32–34,38,40,41]. This has been supported by Tardif et al. [68] who found that these positive effects can occur regardless of a patient's baseline LVEF or use of beta-blockers or the ischemic cause of HF. These effects were consistent across the RCTs and observational studies, indicating that ivabradine can have a positive impact on cardiac function in patients with HFrEF [42,44]. However, the improvement in LVEF was not observed in all studies, indicating potential heterogeneity in treatment response [42,44,45,71,72].

The limited assessment of HRQoL in the included studies makes it challenging to draw definitive conclusions. However, the available evidence suggests that ivabradine may lead to improvements in HRQoL, as

reported in the majority of RCTs [19,26,32–34,67] and observational studies [45,47] that assessed the outcome. The largest study, by Ekman et al. [68], found an association between ivabradine-induced reduction in heart rate and improved HRQoL, and a SHIFT trial substudy suggests an inverse correlation between HRQoL and the risk of CV death or hospitalization for HF [45,47,67].

Regarding safety, the majority of studies indicated that ivabradine had a comparable risk of total AEs compared with reference groups [35,36,58,61,62,64,65,70]. However, a Japanese study reported a statistically significant higher risk of total AEs in patients treated with ivabradine ($p = 0.0044$) [23]. Thus, further investigations may be needed to understand the safety profile of ivabradine, especially in different populations.

The subgroup analysis showed that patients with high baseline heart rate or specific age ranges may derive greater benefits from ivabradine. A significant reduction in both HF-related deaths and all-cause deaths was observed only among patients who were aged <53 years or >69 years ($p = 0.008$ for both age ranges at baseline) [63], as well as among patients with a baseline heart rate of at least 80 bpm [7]. This suggests that certain patient characteristics may influence the effectiveness of ivabradine in improving outcomes.

Because of the clinical heterogeneity across the included studies and the low number of studies reporting complete numeric results for each specific endpoint, a meta-analysis was not performed. Regardless of this heterogeneity, the trends between findings of the primary source of information in our SLR (the SHIFT trial publications) and other trials were mostly consistent with each other for the risk reduction of composite outcome (CV death or hospitalization for worsening HF) [29,35,36,40,56,59,66], the risk of CV or all-cause deaths [29,35,36,40,56,59,66], reduction in heart rate [17,18,28,33,34,38,41,49,51,66], or improvement in ejection fraction [22,32].

Our study results align with the findings of other published systematic reviews; however, most of these reviews included only RCTs. Hartmann et al. [73] reported that ivabradine treatment in patients with HFrEF significantly reduced heart rate, with the additional effect on heart rate appearing to be inversely correlated with the dose of a beta-blocker. The study found no significant effect on all-cause deaths, CV deaths, or hospitalization due to HF. A previous SLR by Narayanan et al. [6] compared the outcomes of ivabradine combined with beta-blockers with beta-blockers alone in HFrEF patients, including data from both RCTs and retrospective or prospective observational studies. Despite differences in the types of studies included (six studies; including two observational ones), similar conclusions were drawn. The results revealed that the combined therapy with ivabradine was associated with a significantly lower risk of the composite outcome of CV deaths or hospitalization due to HF. However, no improvement was found in all-cause deaths or CV deaths. A recent SLR and meta-analysis published by Maagaard et al. compared the effect of ivabradine and usual care with usual care (with or without placebo) in patients with HF. Despite the inclusion of 109 RCTs, the analysis heavily relied on the SHIFT and BEAUTIFUL trials, which collectively contributed to over 85% of the overall analysis weight. Authors showed that ivabradine does not affect the risks of all-cause death and CV death in patients with HF (regardless of LVEF). Furthermore, the effect of ivabradine on HRQoL was found to be small and potentially without relevance to patients [74]. A review by Benstoem et al. [75] conducted two meta-analyses on individuals with HFrEF who underwent long-term treatment with ivabradine. The study found evidence indicating that ivabradine did not appear to affect CV mortality or serious AEs. However, because of significant differences in trial design (such as the type of HF, ivabradine dosage, and duration of treatment) and outcome reporting and measurement, the available evidence is uncertain. The investigators could not perform meta-analysis on QoL, but the two studies demonstrated significant improvement in the QoL of patients with HFrEF who underwent long-term treatment (≥6 months) and short-term treatment (<6 months) with ivabradine, using KCCQ and MLHFQ, respectively. However, the certainty of evidence in both studies was low.

This SLR has several strengths. It combined the outcome data from both RCTs and observational studies to provide the latest evidence on the efficacy and safety of ivabradine for the treatment of HFrEF. Additionally, the review followed a strict protocol with clearly defined selection criteria and adhered to the Cochrane guidelines for systematic review reporting. Besides, the comprehensive search strategy, which had no language or geographic restrictions, reduced the risk of reporting bias.

One of the major limitations of this SLR was the heterogeneity of studies in terms of population, sample size, length of follow-up, and intervention (with differences mainly in the background therapy). Furthermore, some studies were published as abstracts only, which limits the availability of data from those studies. Another weakness is that a significant proportion of the observational studies were conducted in the Asian population, which may limit the generalizability of the findings to other populations. Additionally, we

conducted a manual search to cover the new findings that were published after the cut-off date for this review. Only two new RCTs [76,77] and three observational studies [78–80] were relevant for our review criteria. It is worth mentioning that the recently captured clinical trials, FIRST trial (NCT02188082) from China [76] and another trial (NCT04448899) from Egypt [77], have reported consistent results with our SLR findings regarding significant heart rate reduction and the non-beneficial impact in reducing HF hospitalization, all-cause hospitalization, and mortality albeit for a small number of analyzed patients. The new real-world data analyses conducted in Arab (Qatar) [78], Taiwan [79], and China [80] have demonstrated the beneficial effects of ivabradine in controlling heart rate, but without a clear impact on composite outcomes. Lastly, it is important to highlight that the observational studies included in the review demonstrated a satisfactory level of quality, providing a more robust foundation for analysis and interpretation. Conversely, approximately half of the RCTs included in the review were deemed to have a high risk of bias due to inadequate reporting of randomization and allocation processes, which raises concerns about the overall quality of the data.

Conclusions

This SLR confirms beneficial effects of ivabradine in patients with HFrEF in RCTs and observational studies. Ivabradine on top of background therapy was found to be associated with a significant reduction in heart rate, as well as composite risk of mortality and hospitalization for HF. Ivabradine on top of background therapy was also associated with an improvement in LVEF and HRQoL. Long-term observational studies with larger sample sizes comparing ivabradine with other treatments would be needed to further investigate the impact of ivabradine in real life and assist cardiologists in choosing the best treatment strategy for patients with HF.

Acknowledgments

Study selection step was supported by Hamza Ben Salah (HB) from Putnam PHMR, Tunisia, and the medical writing support was provided by Mohammed Alshaikheid and Aparna Sharma from Putnam PHMR, UK.

Disclosure statement

The authors declare that they have a conflict of interest. Briere Jean Baptiste is an employee of Servier, and Zeba M. Khan was a paid consultant for Servier International at the time of the study. Elzbieta Olewinska, Fatma Khrouf, and Mateusz Nikodem are employees of Putnam PHMR, which received funding from Servier to conduct the study. However, this funding did not influence the design, conduct, or reporting of the research presented in this manuscript.

Funding

This was supported by Servier.

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References

[1] Savarese G, Becher PM, Lund LH, et al. Global burden of heart failure: a comprehensive and updated review of epidemiology. Cardiovasc Res. 2023 Feb 12;118 (17):3272–3287. doi: 10.1093/cvr/cvac013
[2] McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021 [2021 Sep 21];42 (36):3599–3726. doi: 10.1093/eurheartj/ehab368
[3] McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019 Nov 21;381 (21):1995–2008. doi: 10.1056/NEJMoa1911303
[4] Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020 Oct 8;383(15):1413–1424. doi: 10.1056/NEJMoa2022190
[5] Ponikowski P, Voors AA, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the heart failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129–2200. doi: 10.1093/eurheartj/ehw128
[6] Anantha Narayanan M, Reddy YN, Baskaran J, et al. Ivabradine in the treatment of systolic heart failure: a systematic review and meta-analysis. World J Cardiol. 2017 Feb 26;9(2):182–190. doi: 10.4330/wjc.v9.i2.182
[7] Böhm M, Swedberg K, Komajda M, et al. Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet. 2010 Sep 11;376 (9744):886–894. doi: 10.1016/S0140-6736(10)61259-7
[8] Les Laboratoires Servier. Procoralan: European Medicines Agency; 2021 [updated Nov 2005;12 April 2023]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/procoralan
[9] Koruth JS, Lala A, Pinney S, et al. The clinical use of ivabradine. J Am Coll Cardiol. 2017 Oct 3;70 (14):1777–1784. doi: 10.1016/j.jacc.2017.08.038

[10] Heidenreich PA, Bozkurt B, Aguilar D, et al. AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American heart Association Joint Committee on clinical practice guidelines. Circulation. 2022 [2022 May 3];145(18):e895–e1032.

[11] Böhm M, Borer J, Ford I, et al. Heart rate at baseline influences the effect of ivabradine on cardiovascular outcomes in chronic heart failure: analysis from the SHIFT study. Clin Res Cardiol. 2013 Jan;102(1):11–22. doi: 10.1007/s00392-012-0467-8

[12] Higgins JT, Chandler J, Cumpston M, et al. editors. Cochrane Handbook for Systematic Reviews of Interventions. 2nd. Chichester (UK): John Wiley & Sons; 2019. doi: 10.1002/9781119536604

[13] CRD. Systematic reviews: cRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York; 2009.

[14] Sterne JS, Page MJ, Elbers RG, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi: 10.1136/bmj.l4898

[15] Julian Higgins DA, Curtin F, Tianjing L, et al. Additional considerations for cross-over trials. Odense, Denmark: Cochrane Bias Methods Group; 2021 [cited 2021]. Available from: https://drive.google.com/file/d/11LFgCuDpWk5-BvBNbHtNzbJv5-qVpTWb

[16] Wells G, Shea B, O'Connell J. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2014.

[17] Abdel-Salam Z, Rayan M, Saleh A, et al. I(f) current inhibitor ivabradine in patients with idiopathic dilated cardiomyopathy: impact on the exercise tolerance and quality of life. Cardiol J. 2015;22(2):227–232. doi: 10.5603/CJ.a2014.0057

[18] Abdullaev A, Mammaev S, Anatova A, et al. The effect of ivabradine as part of standard therapy on vascular endothelial function and cardiac electrical instability in patients with post-infarction cardiosclerosis and heart failure. Russ J Cardiol. 2020 10 02;25(1):52–58. doi: 10.15829/1560-4071-2020-1-3592

[19] Volterrani M, Cice G, Caminiti G, et al. Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with heart failure (the CARVIVA HF trial). Int J Cardiol. 2011 Sep 1;151(2):218–224. doi: 10.1016/j.ijcard.2011.06.098

[20] Lofrano-Alves MS, Issa VS, Biselli B, et al. Control of sinus tachycardia as an additional therapy in patients with decompensated heart failure (CONSTATHE-DHF): a randomized, double-blind, placebo-controlled trial. J Heart Lung Transplant. 2016 Oct;35(10):1260–1264. doi: 10.1016/j.healun.2016.06.005

[21] Cavusoglu Y, Mert U, Nadir A, et al. Ivabradine treatment prevents dobutamine-induced increase in heart rate in patients with acute decompensated heart failure. J Cardiovasc Med (Hagerstown). 2015 Sep;16(9):603–609. doi: 10.2459/JCM.0000000000000033

[22] Hidalgo FJ, Anguita M, Castillo JC, et al. 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. Int J Cardiol. 2016 Aug 15;217:7–11. doi: 10.1016/j.ijcard.2016.04.136

[23] Tsutsui H, Momomura S, Yamashina A, et al. Heart rate control with if inhibitor, ivabradine, in Japanese patients with chronic heart failure: a randomized, double-blind, placebo-controlled phase II study. Circ J. 2016;80(3):668–676. doi: 10.1253/circj.CJ-15-1112

[24] Kanorskiĭ SG, Tregubov VG, Pokrovskiĭ VM. Alternative therapy with ivabradine in patients with functional class III chronic heart failure [in Russian]. Kardiologiia. 2011;51(8):39–44.

[25] Babushkina GV, Shaikhlislamova GI. Ivabradine for treatment of heart failure with preserved ejection fraction [in Russian]. Kardiologiia. 2020;60(10):33–37. doi: 10.18087/cardio.2020.10.n1324

[26] Mansour S, Youssef A, Rayan M, et al. Efficacy of ivabradine in idiopathic dilated cardiomyopathy patients with chronic heart failure. Egypt Heart J. 2011 01 06;63(2):79–85. doi: 10.1016/j.ehj.2011.09.001

[27] Ordu S, Yildiz BS, Alihanoglu YI, et al. Effects of ivabradine therapy on heart failure biomarkers. Cardiol J. 2015;22(5):501–509. doi: 10.5603/CJ.a2015.0012

[28] Othman KMS, Mostafa MAR, Yosef AE, et al. Safety and efficacy of off-label use of ivabradine in patients with acute heart failure. J Saudi Heart Assoc. 2019 Oct;31(4):179–187. doi: 10.1016/j.jsha.2019.05.006

[29] Potapenko AV, Abdulazizov O, Diachuk LI, et al. Efficacy of ivabradin in combined treatment of patients with postinfarction systolic chronic cardiac failure [in Russian]. Ter Arkh. 2011;83(12):19–26.

[30] Mentz RJ, DeVore AD, Tasissa G, et al. PredischaRge initiation of ivabradine in the ManagEment of heart failure: results of the PRIME-HF trial. Am Heart J. 2020 May;223:98–105.

[31] NCT. Predischarge initiation of ivabradine in the management of heart failure (PRIME-HF). NCT02827500: Clinicaltrials.gov; 2018 [12 April 2023]. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01584213/full

[32] Raja DC, Kapoor A, Sinha A, et al. Heart rate manipulation in dilated cardiomyopathy: assessing the role of Ivabradine. Indian Heart J. 2018 Mar-Apr;70(2):246–251. doi: 10.1016/j.ihj.2017.08.009

[33] Sallam M, Al-Saadi T, Alshekaili L, et al. Impact of ivabradine on health-related quality of life of patients with ischaemic chronic heart failure. Curr Vasc Pharmacol. 2016;14(5):481–486. doi: 10.2174/1570161114666160505143003

[34] Sarullo FM, Fazio G, Puccio D, et al. Impact of ''off-label'' use of ivabradine on exercise capacity, gas exchange, functional class, quality of life, and neurohormonal modulation in patients with ischemic chronic heart failure. J Cardiovasc Pharmacol Ther. 2010 Dec;15(4):349–355. doi: 10.1177/1074248410370326

[35] Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010 Sep 11;376(9744):875–885. doi: 10.1016/S0140-6736(10)61198-1

[36] Fox K, Komajda M, Ford I, et al. Effect of ivabradine in patients with left-ventricular systolic dysfunction: a pooled analysis of individual patient data from the BEAUTIFUL and SHIFT trials. Eur Heart J. 2013 Aug;34(29):2263–2270. doi: 10.1093/eurheartj/eht101

[37] Sisakian H, Sargsyan T, Khachatryan A. Effect of selective heart rate reduction through sinus node I(f) current

inhibition on severely impaired left ventricular diastolic dysfunction in patients with chronic heart failure. Acta Cardiol. 2016 Jun;71(3):317–322. doi: 10.1080/AC.71.3.3152092

[38] Tregubov VG, Kanorsky SG, Pokrovsky VM. Evaluation of the regulatory-adaptive status for prognostication in systolic chronic heart failure [in Russian]. Klin Med (Mosk). 2015;93(11):22–28.

[39] Jamil HA, Gierula J, Paton MF, et al. Chronotropic incompetence does not limit exercise capacity in chronic heart failure. J Am Coll Cardiol. 2016 Apr 26;67(16):1885–1896. doi: 10.1016/j.jacc.2016.02.042

[40] Tsutsui H, Momomura SI, Yamashina A, et al. Efficacy and safety of ivabradine in Japanese patients with chronic heart failure: J-SHIFT study. Circ J. 2019 Sep 25;83(10):2049–2060. doi: 10.1253/circj.CJ-19-0227

[41] Villacorta AS, Villacorta H, Caldas JA, et al. Effects of heart rate reduction with either pyridostigmine or ivabradine in patients with heart failure: a randomized, double-blind study. J Cardiovasc Pharmacol Ther. 2019 Mar;24(2):139–145. doi: 10.1177/1074248418799364

[42] Chang HF, Feng AN, Huang KC et al. Effects of ivabradine on patients with depressed left ventricular ejection fraction after cardiac resynchronization therapy. European Journal of Heart Failure. Conference: Heart Failure 2019 and the World Congress on Acute Heart Failure; Athens Greece: Cardiology ESo, ed. Athens, Greece: European Society of Cardiology: ESC Heart Failure; 2019. p. 408.

[43] Guzman M, Gomez R, Romero SP, et al. Prognosis of heart failure treated with digoxin or with ivabradine: a cohort study in the community. Int J Clin Pract. 2018 Nov;72(11):e13217. doi: 10.1111/ijcp.13217

[44] Liao CT, Huang JL, Liang HW, et al. The association between ivabradine and adverse cardiovascular events in acute decompensated HFrEF patients. ESC Heart Fail. 2021 Oct;8(5):4199–4210. doi: 10.1002/ehf2.13536

[45] Lopatin YM, Cowie MR, Grebennikova AA, et al. Optimization of heart rate lowering therapy in hospitalized patients with heart failure: insights from the optimize heart failure care program. Int J Cardiol. 2018 Jun 1;260:113–117. doi: 10.1016/j.ijcard.2017.12.093

[46] Prathibha V, Mukundan C, Bhagyalekshmi N. Ivabradine alone and in combination with metoprolol reduces the incidence of major adverse cardiac events in patients with heart failure: a prospective study. Natl J Physiol Pharm Pharmacol. 2020;10(5):423–430.

[47] Riccioni G, Masciocco L, Benvenuto A, et al. Ivabradine improves quality of life in subjects with chronic heart failure compared to treatment with β-blockers: results of a multicentric observational APULIA study. Pharmacology. 2013;92(5–6):276–280. doi: 10.1159/000355169

[48] Bocchi EA, Rassi S, Guimarães GV. Safety profile and efficacy of ivabradine in heart failure due to Chagas heart disease: a post hoc analysis of the SHIFT trial. ESC Heart Fail. 2018 Jun;5(3):249–256. doi: 10.1002/ehf2.12240

[49] Babushkina GV, Khairutdinova GI. Assessment of diastolic function of the left ventricle, intima-media thickness and exercise tolerance in chd patients taking bisoprolol and ivabradine. Russ J Cardiol. 2016;131(3):87–91. doi: 10.15829/1560-4071-2016-3-87-91

[50] Zweerink A, van der Lingen ACJ, Handoko ML, et al. Chronotropic incompetence in chronic heart failure. Circ Heart Fail. 2018 Aug;11(8):e004969. doi: 10.1161/CIRCHEARTFAILURE.118.004969

[51] Tatarchenko IP, Pozdniakova NV, Biriuchenko MV, et al. Clinical efficacy of ivabradin and nebivolol addition in combined treatment of ischemic heart disease patients with left ventricular dysfunction [in Russian]. Ter Arkh. 2008;80(9):40–44.

[52] Kanorsky SG, Borisenko YV. Comparative evaluation of β-blockers and if-channel inhibitor in patients with chronic heart failure and preserved left ventricular ejection fraction [in Russian]. Kardiologiia. 2016 Feb;56(2):24–29. doi: 10.18565/cardio.2016.2.24-29

[53] Sen J, Chung E, McGill D. Tolvaptan for heart failure in chronic kidney disease patients: a systematic review and meta-analysis. Heart Lung Circ. 2018 Aug;27(8):928–939. doi: 10.1016/j.hlc.2017.12.013

[54] Bouabdallaoui N, O'Meara E, Bernier V, et al. Beneficial effects of ivabradine in patients with heart failure, low ejection fraction, and heart rate above 77 b.P.m. ESC Heart Fail. 2019 Dec;6(6):1199–1207. doi: 10.1002/ehf2.12513

[55] Böhm M, Komajda M, Borer JS, et al. Duration of chronic heart failure affects outcomes with preserved effects of heart rate reduction with ivabradine: findings from SHIFT. Eur J Heart Fail. 2018 Feb;20(2):373–381. doi: 10.1002/ejhf.1021

[56] Borer JS, Swedberg K, Komajda M, et al. Efficacy profile of ivabradine in patients with heart failure plus angina pectoris. Cardiol. 2017;136(2):138–144. doi: 10.1159/000449243

[57] Hu DY, Huang DJ, Yuan ZY, et al. Efficacy and safety analysis of ivabradine hydrochloride treatment of Chinese patients with chronic heart failure: subgroup analysis of Chinese patients in the SHIFT study [in Chinese]. Zhonghua Xin Xue Guan Bing Za Zhi. 2017 Mar 24;45(3):190–197. doi: 10.3760/cma.j.issn.0253-3758.2017.03.005

[58] Komajda M, Tavazzi L, Francq B, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure and diabetes: an analysis from the SHIFT trial. Eur J Heart Fail. 2015 09 17;17(12):1294–1301. doi: 10.1002/ejhf.347

[59] Rogers JK, Kielhorn A, Borer JS, et al. Effect of ivabradine on numbers needed to treat for the prevention of recurrent hospitalizations in heart failure patients. Curr Med Res Opin. 2015;31(10):1903–1909. doi: 10.1185/03007995.2015.1080155

[60] Komajda M, Böhm M, Borer J, et al. Efficacy and safety of ivabradine in patients with chronic systolic heart failure according to blood pressure level in SHIFT. Eur J Heart Fail. 2014 07 01;16(7):810–816. doi: 10.1002/ejhf.114

[61] Voors AA, van Veldhuisen DJ, Robertson M, et al. The effect of heart rate reduction with ivabradine on renal function in patients with chronic heart failure: an analysis from SHIFT. Eur J Heart Fail. 2014 Apr;16(4):426–434. doi: 10.1002/ejhf.59

[62] Tavazzi L, Swedberg K, Komajda M, et al. Efficacy and safety of ivabradine in chronic heart failure across the age spectrum: insights from the SHIFT study. Eur J Heart Fail. 2013 11 01;15(11):1296–1303. doi: 10.1093/eurjhf/hft102

[63] Reil J-C, Robertson M, Ford I, et al. Impact of left bundle branch block on heart rate and its relationship to treatment with ivabradine in chronic heart failure. Eur J Heart Fail. 2013 05/21; 15;15(9):1044–1052. doi: 10.1093/eurjhf/hft072

[64] Komajda M, Böhm M, Borer J, et al. Influence of background treatment with mineralocorticoid receptor antagonists on ivabradine's effects in patients with chronic heart failure. Eur J Heart Fail. 2013 Jan;15 (1):79–84. doi: 10.1093/eurjhf/hfs127

[65] Tavazzi L, Swedberg K, Komajda M, et al. Clinical profiles and outcomes in patients with chronic heart failure and chronic obstructive pulmonary disease: an efficacy and safety analysis of SHIFT study. Int J Cardiol. 2013 12 01;170(2):182–188. doi: 10.1016/j.ijcard.2013.10.068

[66] Tregubov VG, Kanorskiy SG, Pokrovskiy VM. Regulatory adaptive status in assessment of efficacy of pharmacotherapy and prognostication of complications in functional class III chronic heart failure [in Russian]. Kardiologiia. 2016 Jan;56(1):12–17. doi: 10.18565/cardio.2016.1.12-17

[67] Ekman I, Chassany O, Komajda M, et al. Heart rate reduction with ivabradine and health related quality of life in patients with chronic heart failure: results from the SHIFT study. Eur Heart J. 2011 Oct;32(19):2395–2404. doi: 10.1093/eurheartj/ehr343

[68] Tardif JC, O'Meara E, Komajda M, et al. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. Eur Heart J. 2011 Oct;32 (20):2507–2515. doi: 10.1093/eurheartj/ehr311

[69] Pal N, Sivaswamy N, Mahmod M, et al. Effect of selective heart rate slowing in heart failure with preserved ejection fraction. Circulation. 2015 Nov 3;132(18):1719–1725. doi: 10.1161/CIRCULATIONAHA.115.017119

[70] Borer JS, Böhm M, Ford I, et al. Efficacy and safety of ivabradine in patients with severe chronic systolic heart failure (from the SHIFT study). Am J Cardiol. 2014;113(3):497–503. 2014/02/01/. doi: 10.1016/j.amjcard.2013.10.033

[71] Lee YH, Lin PL, Chiou WR, et al. Combination of ivabradine and sacubitril/valsartan in patients with heart failure and reduced ejection fraction. ESC Heart Fail. 2021 Apr;8 (2):1204–1215. doi: 10.1002/ehf2.13182

[72] Mircheva L. Benefits of early administration of ivabradine in stabilized patients hospitalized due to worsening heart failure: insights from the optimize heart failure care program. Heart failure. Athens: European Society of Cardiology; 2019.

[73] Hartmann C, Bosch NL, de Aragão Miguita L, et al. The effect of ivabradine therapy on heart failure patients with reduced ejection fraction: a systematic review and meta-analysis. Int J Clin Pharm. 2018 Dec;40 (6):1443–1453. doi: 10.1007/s11096-018-0715-8

[74] Maagaard M, Nielsen EE, Sethi NJ, et al. Ivabradine added to usual care in patients with heart failure: a systematic review with meta-analysis and trial sequential analysis. BMJ Evid Based Med. 2022 Aug;27(4):224–234. doi: 10.1136/bmjebm-2021-111724

[75] Benstoem C, Kalvelage C, Breuer T, et al. Ivabradine as adjuvant treatment for chronic heart failure. Cochrane Database Syst Rev. 2020 Nov 4;11(11):Cd013004. doi: 10.1002/14651858.CD013004.pub2

[76] Ye F, Wang X, Wu S, et al. Sustained-release ivabradine hemisulfate in patients with systolic heart failure. J Am Coll Cardiol. 2022 Aug 9;80(6):584–594. doi: 10.1016/j.jacc.2022.05.027

[77] Dogheim GM, Khairat I, Omran GA, et al. Clinical comparative study assessing the effect of ivabradine on neopterin and NT-Pro BNP against standard treatment in chronic heart failure patients. Eur J Clin Pharmacol. 2022 Jun;78(6):943–954. doi: 10.1007/s00228-022-03290-6

[78] Al-Balushi S, Alam MF, Abid AR, et al. The effect of ivabradine on hospitalization of heart failure patients: a retrospective cohort study. Heart Views. 2021 Jul-Sep;22(3):165–173. doi: 10.4103/HEARTVIEWS.HEARTVIEWS_23_20

[79] Lin YS, Jan JY, Chang JJ, et al. Ivabradine in heart failure patients with reduced ejection fraction and history of paroxysmal atrial fibrillation. ESC Heart Fail. 2022 Aug;9 (4):2548–2557. doi: 10.1002/ehf2.13966

[80] Yang TY, Tsai MS, Jan JY, et al. Early administration of ivabradine in patients admitted for acute decompensated heart failure. Front Cardiovasc Med. 2022;9:1036418. doi: 10.3389/fcvm.2022.1036418