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DISSOCIATION BETWEEN HEART RATE REDUCTION AND LEFT VENTRICULAR FILLING PRESSURE IN HEART FAILURE WITH PRESERVED EJECTION FRACTION: A META-ANALYSIS OF IVABRADINE TRIALS

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ДИСОЦИАЦИЯ МЕЖДУ НАМАЛЯВАНЕТО НА СЪРДЕЧНАТА ЧЕСТОТА И НАЛЯГАНЕТО НА ПЪЛНЕНЕ НА ЛЯВАТА КАМЕРА ПРИ СЪРДЕЧНА НЕДОСТАТЪЧНОСТ СЪС ЗАПАЗЕНА ФРАКЦИЯ НА ИЗТЛАСКВАНЕ: МЕТААНАЛИЗ НА ПРОУЧВАНИЯ С ИВАБРАДИН

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Abstract.

Background: Heart rate (HR) reduction is commonly proposed to improve diastolic filling and reduce left ventricular (LV) filling pressure in heart failure with preserved ejection fraction (HFpEF). Ivabradine selectively lowers HR without direct myocardial effects, providing a mechanistic model to examine whether HR reduction alone translates into improved LV filling pressure. This study aims to evaluate whether selective HR reduction with ivabradine improves LV filling pressure and diastolic function in patients with HFpEF. **Methods:** MEDLINE and CENTRAL were systematically searched for randomized controlled trials comparing ivabradine with placebo or standard therapy in HFpEF. Outcomes included diastolic echocardiographic parameters (E/e', e' velocity, and left atrial volume index [LAVI]), resting HR, natriuretic peptides, and peak oxygen consumption (peak VO_2). Pooled mean differences (MDs) with 95% confidence intervals (CIs) were calculated using random-effects models. **Results:** Three RCTs (258 patients) were included. Ivabradine significantly reduced resting HR (MD −12.03 bpm; 95% CI −18.43 to −5.63), yet was associated with a significant increase in E/e' (MD 1.02; 95% CI 0.22 to 1.82). Septal e' modestly increased, while no significant differences were observed for lateral or mean e', LAVI, natriuretic peptides, or peak VO_2. Conclusions: These findings suggest a dissociation between HR reduction and LV filling pressure, underscoring the limited role of isolated chronotropic modulation in the pathophysiology of HFpEF.

Key words: ivabradine; heart failure, preserved ejection fraction; doppler echocardiography; cardiac chronotropy

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Резюме.

Въведение: Към намаляването на сърдечната честота (СЧ) обикновено се пристъпва за подобряване на диастолното пълнене и намаляване на налягането на пълнене на лявата камера (ЛК) при сърдечна недостатъчност със запазена фракция на изтласкване (СНзФИ). Ивабрадин селективно понижава СЧ без директни миокардни ефекти, предоставяйки механистичен модел за изследване дали самото намаляване на СР води до подобрено налягане на пълнене на ЛК. Това проучване има за цел да оцени дали селективното намаляване на сърдечната честота с ивабрадин подобрява налягането на пълнене на ЛК и диастолната функция при пациенти със СНзФИ. **Методи:** MEDLINE и CENTRAL бяха систематично търсени за рандомизирани контролирани проучвания, сравняващи ивабрадин с плацебо или стандартна терапия при СНзФИ. Резултатите включваха диастолни ехокардиографски параметри (E/e', скорост на e' и индекс на обема на лявото предсърдие [LAVI]), СР в покой, натриуретични пептиди и пикова консумация на кислород (пик VO_2). Обединените средни разлики (MD) с 95% доверителни интервали (CI) бяха изчислени с помощта на мо-

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дели със случайни ефекти. **Резултати:** Включени бяха три рандомизирани контролирани проучвания (258 пациенти). Ивабрадин значително намалява сърдечната честота в покой (MD −12.03 bpm; 95% CI −18.43 до −5.63), но е свързан със значително повишаване на E/e' (MD 1.02; 95% CI 0.22–1.82). Септалното e' се увеличава умерено, докато не се наблюдават значителни разлики за латералното или средното e', LAVI, натриуретични пептиди или пиково VO_2. **Заключения:** Тези открития показват дисоциация между намаляването на сърдечната честота и налягането на пълнене на лявата камера, което подчертава ограничената роля на изолираната хронотропна модулация в патофизиологията на СНзФИ.

Ключови думи: ивабрадин, сърдечна недостатъчност със запазена фракция на изтласкване, доплерова ехокардиография, сърдечна хронотропия

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Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure cases and is associated with substantial morbidity and mortality, comparable to heart failure with reduced ejection fraction [1-4]. Central to HFpEF pathophysiology is impaired left ventricular (LV) diastolic function, driven by abnormal relaxation, increased stiffness, and elevated filling pressures, for which disease-modifying therapies remain elusive [5-7]. Contemporary echocardiographic frameworks define HFpEF by the presence of impaired myocardial relaxation (reduced e′ velocity) and increased LV filling pressures, most commonly estimated by an elevated E/e′ ratio, with secondary structural remodeling, such as left atrial enlargement, reflecting a chronic diastolic burden [8-12].

Heart rate (HR) reduction has traditionally been proposed as a therapeutic strategy to improve diastolic filling by prolonging diastolic time, thereby potentially lowering LV filling pressure [6]. However, whether this assumption holds true in HFpEF remains uncertain, particularly given that ventricular stiffness rather than filling duration may be the dominant determinant of diastolic dysfunction in this population [13]. Ivabradine, a selective inhibitor of the sinoatrial If current, reduces HR without direct effects on myocardial contractility or vascular tone, providing a unique mechanistic model to isolate the role of HR in diastolic physiology [14].

Randomized controlled trials evaluating ivabradine in HFpEF have reported inconsistent effects on diastolic parameters and functional capacity, likely due to small sample sizes and heterogeneous study designs [15-17]. More importantly, these studies offer an opportunity to examine a fundamental physiological question: whether isolated HR reduction translates into meaningful changes in LV filling pressure. Therefore, this systematic review and meta-analysis aimed to synthesize randomized evidence to assess the effects of ivabradine on echocardiographic indices of diastolic function and, critically, to determine whether reductions in HR are associated with corresponding changes in LV filling pressure in HFpEF.

Materials and methods

Study design and registration

This systematic review and meta-analysis were planned and carried out following the methodological recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and are reported in accordance with the PRISMA 2020 guidelines [18]. A study protocol was prepared in advance, based on our prior work with necessary modifications to address the current research question, and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420251147491).

Search strategy and eligibility criteria

In accordance with PRISMA 2020 guidelines, we systematically searched MEDLINE and CENTRAL up to September 2025 to identify randomized controlled trials (RCTs) comparing ivabradine with placebo in adults with HFpEF. The search strategy combined terms for “ivabradine,” “HFpEF,” and “randomized controlled trial” and was adapted for each database. Reference lists of included studies and relevant reviews were also screened to ensure comprehensiveness. Eligible trials enrolled adults with HFpEF receiving ivabradine or placebo and reported at least one of the predefined outcomes: E/e′ ratio, mitral annular e’ velocity, or LAVI. Studies focusing exclusively on HFrEF, acute decompensated HF, co-interventions preventing isolation of ivabradine effects, or surrogate outcomes without clinical endpoints were excluded.

Data extraction and risk of bias evaluation

Two reviewers independently performed title and abstract screening, full-text eligibility assessment, data extraction, and risk of bias appraisal. Extracted information included study characteristics, publication year, design, sample size, and details of the intervention and comparator. The risk of bias for each trial was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, which evaluates five domains: (I) randomization process, (II) deviations from intended interventions, (III) missing outcome data, (IV) outcome measurement, and (V) selection of reported results [19]. Discrepancies between reviewers were resolved through discussion until consensus was achieved.

Outcomes

The prespecified primary outcomes were echocardiographic markers of LV diastolic function and structural remodeling, including the E/e′ ratio (with septal, lateral, or averaged e′ velocities where available) and LAVI, selected in accordance with contemporary ASE/EACVI recommendations as noninvasive indices of filling pressure and cumulative diastolic load. Secondary outcomes included resting HR, natriuretic peptides (B-type natriuretic peptide [BNP] or N-terminal pro-B-type natriuretic peptide [NT-proBNP]), and exercise capacity assessed by peak VO_2, reflecting pharmacodynamic HR reduction, systolic performance, and global functional capacity, respectively.

Statistical analysis

Data were summarized descriptively in tables and supplemented with a narrative synthesis. Quantitative analyses were performed using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, London, UK) and visualized using MetaAnalysisOnline.com. [20] Pooled mean differences (MDs) with 95% confidence intervals (CIs) were calculated under a random-effects model. The meta-analysis synthesized treatment effects based on the mean change from baseline to post-intervention for each study group, along with the corresponding standard deviation of the change. When the standard deviation of the change was not directly reported, it was derived using the formula:

$$SD_{change} = \sqrt{(SD_{baseline}^2 + SD_{follow\text{-}up}^2 - 2 \times r \times SD_{baseline} \times SD_{follow\text{-}up})}$$

SDbaseline and SDfollow-up denote the standard deviations at baseline and post-intervention, respectively, and r represents the assumed correlation between paired measurements. In the absence of reported correlation coefficients, a conservative value of r = 0.5 was applied. When continuous outcomes were reported as medians with interquartile ranges, the sample mean was estimated using the method proposed by Luo et al. (2018), while the corresponding standard deviation was derived according to the approach described by Wan et al. (2014) [21, 22]. These transformations assume approximate normality and were applied to enable inclusion of nonparametrically reported data in the meta-analysis.

Between-study heterogeneity was assessed using the Cochrane χ^2 test ($p < 0.10$ indicating significance) and quantified with the I2 statistic, interpreted as low (< 50%), moderate (50-74%), or high (≥ 75%). All statistical tests were two-sided, with $p < 0.05$ considered statistically significant. Funnel plot analysis to evaluate publication bias was pre-specified, conducted only if the number of included studies allowed (≥ 10). Subgroup analyses were conducted when at least two studies were available per subgroup, based on baseline HR, treatment duration, or other relevant patient characteristics, with interaction tests considered significant at $p < 0.05$. The certainty of evidence for pooled outcomes was independently evaluated by two reviewers using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework [23].

Results

Search result

The study selection process is summarized in the PRISMA flow diagram (Fig. 1). A total of 104 records were retrieved from the database search (PubMed/MEDLINE = 74; Cochrane/CENTRAL = 30). After removing seven duplicates, 97 unique records underwent title and abstract screening, resulting in 93 exclusions. Full-text assessment was performed on four articles, of which one was excluded due to an ineligible study design (single-arm cohort). Ultimately, three studies met the inclusion criteria and were included in the review. Reference list screening identified one additional record, which was excluded after full-text evaluation.

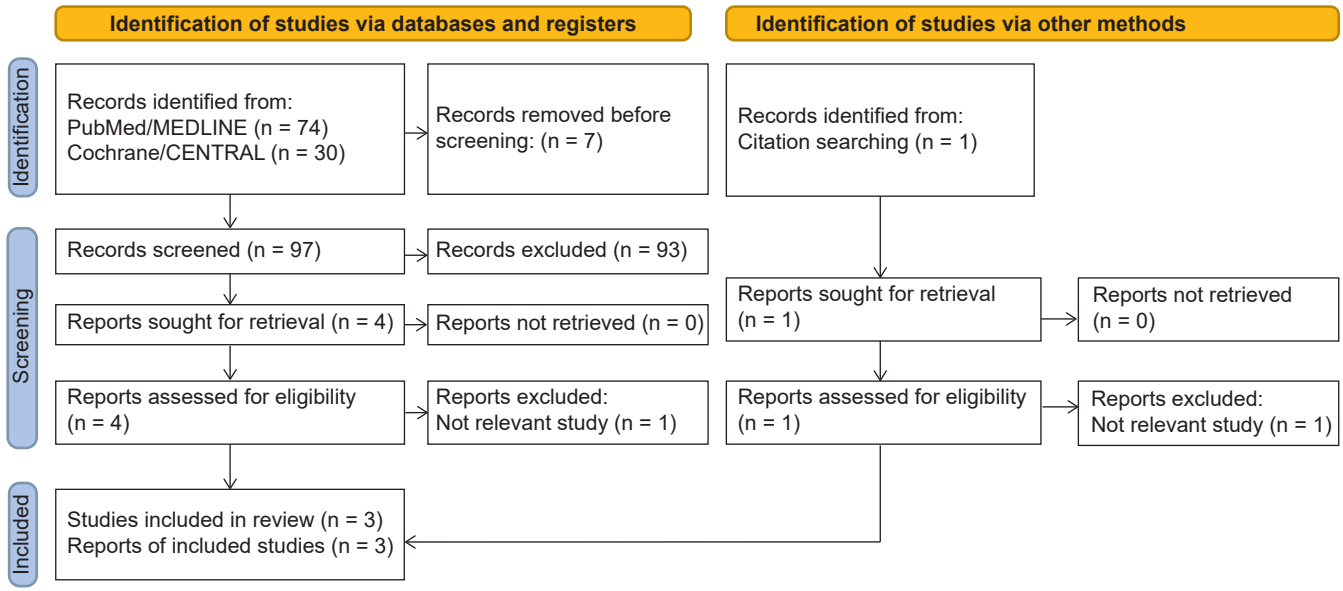

Fig. 1. PRISMA 2020 flow diagram for the identification and screening process

Study characteristics

Study characteristics are summarized in Table 1. Three RCTs (258 patients) with HFpEF were analyzed, comprising two parallel placebo-controlled trials and one crossover study [15, 24, 25]. Ivabradine was administered at 5-7.5 mg twice daily with HR-guided dose adjustment. Across studies, participants were symptomatic HFpEF patients in sinus rhythm with LVEF ≥ 50%, objective evidence of echocardiographic diastolic dysfunction, and impaired exercise capacity assessed by peak VO_2 or 6-minute walk distance. Inclusion criteria varied modestly, with some trials requiring elevated resting HR or natriuretic peptides, while others emphasized post-exercise or resting diastolic abnormalities. Treatment duration varied from seven days to eight months. All studies used standardized transthoracic echocardiography with Doppler and tissue Doppler imaging, consistently reporting E/e′ and e′ velocities, with LVEF assessed by Simpson biplane where specified.

Baseline characteristics of the included populations are summarized in Table 2. Across trials, patients were predominantly older adults (mean age approximately 66-75 years), with a high proportion of women (62-87%) and a high prevalence of overweight or obesity (mean BMI 29-31 kg/m²), consistent with typical HFpEF cohorts. Baseline resting HR ranged from the low 70s to mid-70s bpm, and blood pressure values were generally well controlled and balanced between treatment groups. All studies enrolled patients with preserved systolic function (mean LVEF 60-69%) and evidence of diastolic dysfunction, reflected by mildly to moderately elevated E/e′ ratios and enlarged LAVI, although the severity of abnormalities varied between trials. Importantly, baseline demographic, hemodynamic, and echocardiographic parameters were largely comparable between ivabradine and placebo arms within each study, supporting internal validity and enabling pooled assessment of treatment effects on diastolic function, cardiac structure, and HR-dependent outcomes.

Table 1. Trial characteristics of the included studies

Publication (registry)	Trial design	Intervention	Population	Total (n)	Echocardiographic modality
Kosmala et al., 2013 (ACTRN12610001087044)	Multicenter, randomized, double-blind, placebo-controlled trial.	Ivabradine 5 mg twice daily for 7 days (may be lowered to 2.5 mg if RHR < 50 bpm).	Symptomatic HFpEF patients (18-80 years), LVEF ≥ 50%, echocardiographic diastolic dysfunction, reduced exercise capacity (peak VO_2 < 80% of age- and sex-predicted), and elevated post-exercise E/e' (> 13).	61	Standardized TTE with Doppler and tissue Doppler imaging; LVEF by Simpson biplane; diastolic indices (septal/lateral e', mean e', E/e'); measurements averaged over three cardiac cycles.
Pal et al., 2015 (NCT02354573)	Multicenter, randomized, double-blind, crossover trial.	Ivabradine 7.5 mg twice daily for 2 weeks (crossed over after 2 weeks of a washout period)	Symptomatic HFpEF patients aged ≥ 60 years, LVEF ≥ 50%, nondilated LV with structural heart disease or echocardiographic diastolic dysfunction (E/A, e', E/e'), and reduced exercise capacity (peak VO_2 < 80% of age- and sex-predicted).	44	Resting standardized TTE with Doppler and tissue Doppler imaging; diastolic indices including E, A, DT, septal and lateral e' (mean e'), and E/e'; measurements averaged over three consecutive cardiac cycles.
Komajda et al., 2017 (EudraCT No. 2012 002742 20)	Multicenter, randomized, double-blind, placebo-controlled trial.	Ivabradine 5 mg twice daily as the starting dose, titrated to 7.5 mg (may be adjusted up or down by 2.5 mg to optimize HR reduction).	Symptomatic HFpEF patients (≥ 50 years), sinus rhythm with RHR ≥ 70 bpm, NYHA class II–III, LVEF ≥ 50%, elevated natriuretic peptides, echocardiographic diastolic dysfunction (E/e' > 13, or reduced septal/lateral e', or LAVI > 34 mL/m²), and reduced exercise capacity (6MWT ≤ 450 m).	153	Standardized TTE with Doppler and tissue Doppler imaging; centralized acquisition with blinded core laboratory analysis; diastolic assessment focused on E/e'.

Abbreviations: 6MWT (6-minute walk test); A (late diastolic mitral inflow velocity); BNP (B-type natriuretic peptide); bpm (beats per minute); DT (deceleration time); E (early diastolic mitral inflow velocity); e' (early diastolic mitral annular velocity); E/e' (ratio of early diastolic mitral inflow velocity to mean septal and lateral e'); HFpEF (heart failure with preserved ejection fraction); HR (heart rate); LAVI (left atrial volume index); LVMI (left ventricular mass index); LVEF (left ventricular ejection fraction); NT-proBNP (N-terminal pro–B-type natriuretic peptide); NYHA (New York Heart Association); RHR (resting heart rate); TTE (transthoracic echocardiography); VO_2 peak (peak oxygen consumption).

Table 2. Baseline characteristics and results of the included studies

Publication	Baseline characteristics				Results (hemodynamic & cardiac status)
	Demographic profile	Comorbidity profile	Medication profile	Hemodynamic & cardiac status	
Kosmala et al., 2013	Age (years, mean ± SD): IVA: 66.5 ± 8.5 PLA: 68.0 ± 8.7 Gender (women, %): IVA: 77 PLA: 87 BMI (kg/m^2, mean ± SD): IVA: 30.3 ± 4.0 PLA: 29.1 ± 4.4	Hypertension (%): IVA: 90 PLA: 77 DM (%): IVA: 40 PLA: 32 CAD (%): IVA: N/A PLA: N/A	ACEi and/or ARBs (%): IVA: 97 PLA: 97 β-blockers (%): IVA: 57 PLA: 52 CCB (%): IVA: 37 PLA: 39 Thiazide diuretics (%): IVA: 43 PLA: 35 Loop diuretics (%): IVA: 33 PLA: 32 OHA (%): IVA: 40 PLA: 29	RHR (bpm, mean ± SD): IVA: 72 ± 7 PLA: 70 ± 6 SBP (mmHg, mean ± SD): IVA: 130 ± 18 PLA: 133 ± 17 DBP (mmHg, mean ± SD): IVA: 75 ± 8 PLA: 76 ± 7 LVEF (%, mean ± SD): IVA: 67 ± 7 PLA: 69 ± 6 E/e' (mean ± SD): IVA: 13.5 ± 3.2 PLA: 14.3 ± 3.1 LAVI (%, mean ± SD): IVA: 37.2 ± 9.0 PLA: 36.3 ± 9.3 LVMI (%, mean ± SD): IVA: 115 ± 33 PLA: 113 ± 32	RHR (bpm, mean ± SD): IVA: 62 ± 8 PLA: 70 ± 7 SBP (mmHg, mean ± SD): IVA: 130 ± 15 PLA: 132 ± 15 DBP (mmHg, mean ± SD): IVA: 74 ± 8 PLA: 76 ± 7 LVEF (%, mean ± SD): IVA: 68 ± 6 PLA: 68 ± 5 E/e' (mean ± SD): IVA: 14.2 ± 3.0 PLA: 14.3 ± 3.3 LAVI (%, mean ± SD): IVA: 34.9 ± 8.7 PLA: 35.5 ± 8.6 LVMI (%, mean ± SD): IVA: 118 ± 36 PLA: 115 ± 35
Pal et al., 2015	Age (years, mean ± SD): 74.6 ± 5.9 Gender (women, %): 65 BMI (kg/m^2, mean ± SD): 29.9 ± 6.2	Hypertension (%): 50 DM (%): 10 CAD (%): N/A	ACEi and/or ARBs (%): 59 β-blockers (%): 14 CCB (%): 5	RHR (bpm, mean ± SD): 75 ± 12 SBP (mmHg, mean ± SD): 148 ± 19 DBP (mmHg, mean ± SD): 83 ± 6 LVEF (%, mean ± SD):	RHR (bpm, mean ± SD): IVA: 57 ± 9 PLA: 77 ± 13 SBP (mmHg, mean ± SD): IVA: 149 ± 28 PLA: 142 ± 25 DBP (mmHg, mean ± SD): IVA: 76 ± 10 PLA: 79 ± 12 LVEF (%, mean ± SD): IVA: 66.6 ± 4.5 PLA: 64.4 ± 8 E/e' (mean ± SD): IVA: 10.7 ± 2.4 PLA: 10.4 ± 2.5 LAVI (%, mean ± SD): IVA: 31.3 ± 12.2 PLA: 27.0 ± 10.7 LVMI (%, mean ± SD): IVA: 102.0 ± 22.5 PLA: 109.0 ± 29.1
Komajda et al., 2017	Age (years, mean ± SD): IVA: 72 ± 9.0 PLA: 73 ± 9.1 Gender (women, %): IVA: 62.1 PLA: 67.9 BMI (kg/m^2, mean ± SD): IVA: 30.6 ± 6.9 PLA: 29.5 ± 4.5	Hypertension (%): IVA: 93.7 PLA: 86.9 DM (%): IVA: 43.2 PLA: 44.1 CAD (%): IVA: 50.5 PLA: 56	ACEi and/or ARBs (%): IVA: 88.4 PLA: 85.7 β-blockers (%): IVA: 74.7 PLA: 73.8 CCB (%): IVA: 37.9 PLA: 35.7 Non-MRA diuretics (%): IVA: 58.9 PLA: 70.2 MRA diuretics (%): IVA: 31.6 PLA: 26.2 OHA (%): IVA: N/A PLA: N/A	RHR (bpm, mean ± SD): IVA: 75 ± 5 PLA: 75 ± 6 SBP (mmHg, mean ± SD): IVA: 132 ± 14 PLA: 132 ± 19 DBP (mmHg, mean ± SD): IVA: 76 ± 11 PLA: 78 ± 11 LVEF (%, mean ± SD): IVA: 60 ± 9 PLA: 61 ± 9 E/e' (mean ± SD): IVA: 12.8 ± 4.9 PLA: 13.0 ± 4.4 LAVI (%, mean ± SD): IVA: 41.6 ± 11.0 PLA: 40.0 ± 13.4 LVMI (%, mean ± SD): IVA: 104.2 ± 39.1 PLA: 111.5 ± 39	RHR (bpm, mean ± SD*): IVA: -12.2 ± 9.1 PLA: -4.0 ± 10.9 SBP (mmHg): N/A DBP (mmHg): N/A LVEF (%): N/A E/e' (mean ± SD*): IVA: 1.0 ± 2.9 PLA: -0.46 ± 2.7 LAVI (%, mean ± SD*): IVA: 2.4 ± 12.1 PLA: -1.6 ± 8.8 LVMI (%, mean ± SD*): IVA: 0.59 ± 25.1 PLA: -2.5 ± 25.4

Abbreviations: ACEi (angiotensin-converting enzyme inhibitor); ARBs (angiotensin II receptor blockers); BMI (body mass index); bpm (beats per minute); CCB (calcium channel blocker); DBP (diastolic blood pressure); E/e' (ratio of early diastolic mitral inflow velocity to early diastolic mitral annular velocity); HFpEF (heart failure with preserved ejection fraction); IVA (ivabradine); LAVI (left atrial volume index); LVEF (left ventricular ejection fraction); LVMI (left ventricular mass index); MRA (mineralocorticoid receptor antagonist); N/A (not available); OHA (oral hypoglycemic agent); PLA (placebo); RHR (resting heart rate); SBP (systolic blood pressure); SD (standard deviation).
*Expressed as change from baseline.

Risk of bias assessment.

Risk of bias was assessed using the RoB 2.0 (Fig. 2). Overall, all three included RCTs were judged to have "some concerns" regarding risk of bias. Individual domain assessments indicated generally low risk for the randomization process and outcome measurement in most studies, while some concerns were noted for deviations from intended interventions, missing outcome data, and selective reporting in certain trials. Although no study was rated as high risk in any domain, the presence of some concerns highlights potential limitations in trial conduct that should be considered when interpreting the pooled findings.

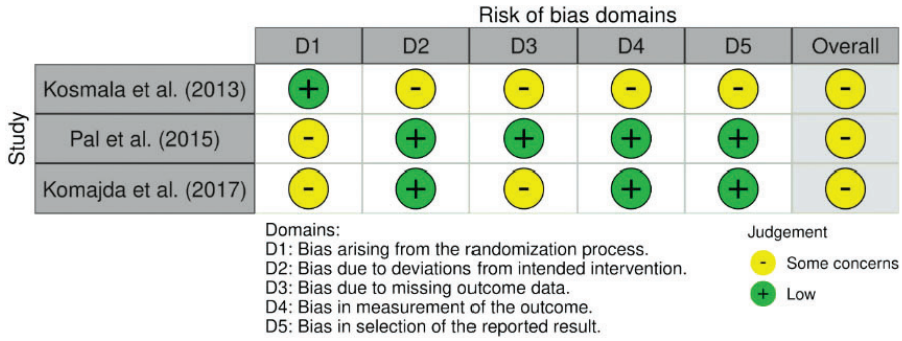

Fig. 2. Risk of bias (RoB 2.0) assessment

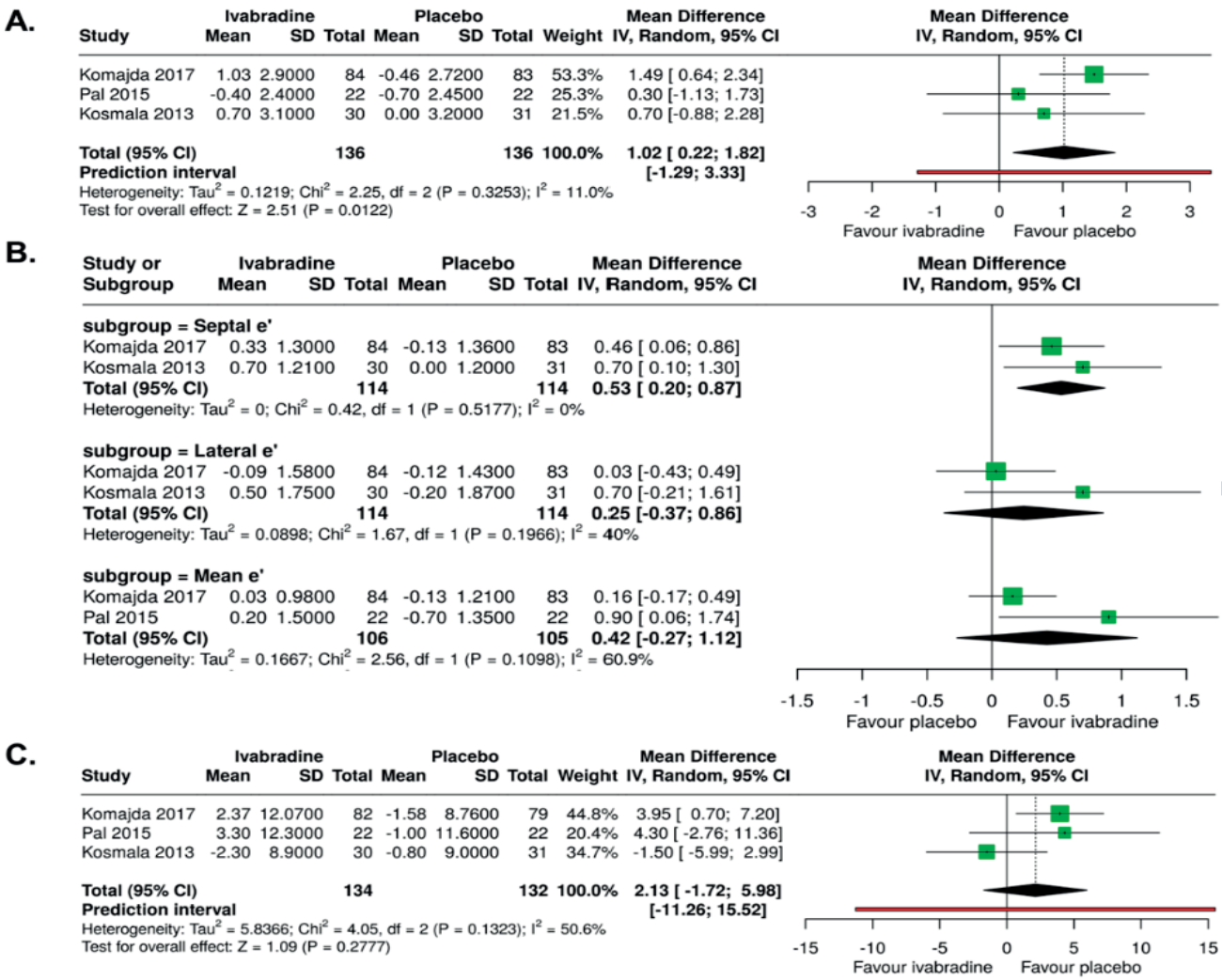

Fig. 3. Forest plot of echocardiographic diastolic function outcomes. **(A)** E/e', **(B)** septal, lateral, and mean e', and **(C)** LAVI. CI (confidence interval), IV (inverse variance), SD (standard deviation)

Echocardiographic indices of left ventricular filling pressure

Three RCTs comprising 258 participants evaluated the effect of ivabradine on echocardiographic indices of diastolic function. Meta-analysis demonstrated a modest but statistically significant increase in E/e′ in the ivabradine group compared with placebo (MD 1.02; 95% CI 0.22 to 1.82) (Fig. 3). Septal e′ velocity was also significantly higher with ivabradine (MD 0.53 cm/s; 95% CI 0.20 to 0.87), whereas changes in lateral e′ (MD 0.25 cm/s; 95% CI −0.37 to 0.86) and mean e′ (MD 0.42 cm/s; 95% CI −0.27 to 1.12) were not statistically significant. No significant between-group differences were observed in LAVI (MD 2.13 mL/m²; 95% CI −1.72 to 5.98). According to GRADE assessment, the certainty of evidence for E/e′ was moderate, downgraded due to indirectness (surrogate for LV filling pressure), and for LAVI was low, downgraded due to additional imprecision (Table 3).

Table 3. Summary of findings – Efficacy of ivabradine compared to placebo for HFpEF

Outcomes	No. of participants (studies)	Mean difference (95% CI)	Certainty of the evidence (GRADE)	Importance	Comments
Left ventricular filling pressure – hemodynamic domain (assessed by E/e' ratio)	258 (3 RCTs)	1.02 (0.22 to 1.82)	⊕⊕⊕◯ Moderate[a,b]	IMPORTANT	E/e' is a core echocardiographic index recommended by ASE/BSE/EACVI guidelines for the noninvasive estimation of instantaneous LV filling pressure and is central to the diagnostic and evaluative framework of diastolic dysfunction in HFpEF.
Left ventricular filling pressure – structural domain (assessed by LAVI [mL/m²])	258 (3 RCTs)	2.13 (-1.72 to 5.98)	⊕⊕◯◯ Low[a,b,c]	IMPORTANT	LAVI reflects cumulative exposure to elevated filling pressures rather than acute diastolic function and is therefore less sensitive to short-term interventions. Its role is complementary within a multiparametric assessment and should not be interpreted as a stand-alone marker of diastolic dysfunction.
Resting heart rate (beats per minute)	258 (3 RCTs)	-12.03 (-18.43 to -5.63)	⊕⊕⊕◯ Moderate[b,d]	IMPORTANT	Heart rate reduction confirms target engagement of ivabradine, but does not in itself equate to improvement in diastolic function or clinical status. In HFpEF, heart rate lowering may interact variably with myocardial relaxation and filling dynamics, underscoring the need to interpret this outcome alongside echocardiographic indices.

Abbreviations: ASE (American Society of Echocardiography); BSE (British Society of Echocardiography); CI (confidence interval); EACVI (European Association of Cardiovascular Imaging); E/e' (ratio of early mitral inflow velocity to early diastolic mitral annular velocity); GRADE (Grading of Recommendations Assessment, Development and Evaluation); HFpEF (heart failure with preserved ejection fraction); LAVI (left atrial volume index); LV (left ventricular); MD (mean difference); RCT (randomized controlled trial); RHR (resting heart rate).

[a]Downgraded by one level for indirectness as outcomes were based on echocardiographic surrogate markers (E/e' ratio and LAVI) rather than direct invasive measurements of left ventricular filling pressure or patient-important clinical outcomes.

[b]Publication bias could not be assessed (k < 10, funnel plot/Egger test not applicable).

[c]Downgraded by one level for imprecision as the confidence intervals included the line of no effect.

[d]Downgraded by one level for inconsistency due to high heterogeneity (≥75%).

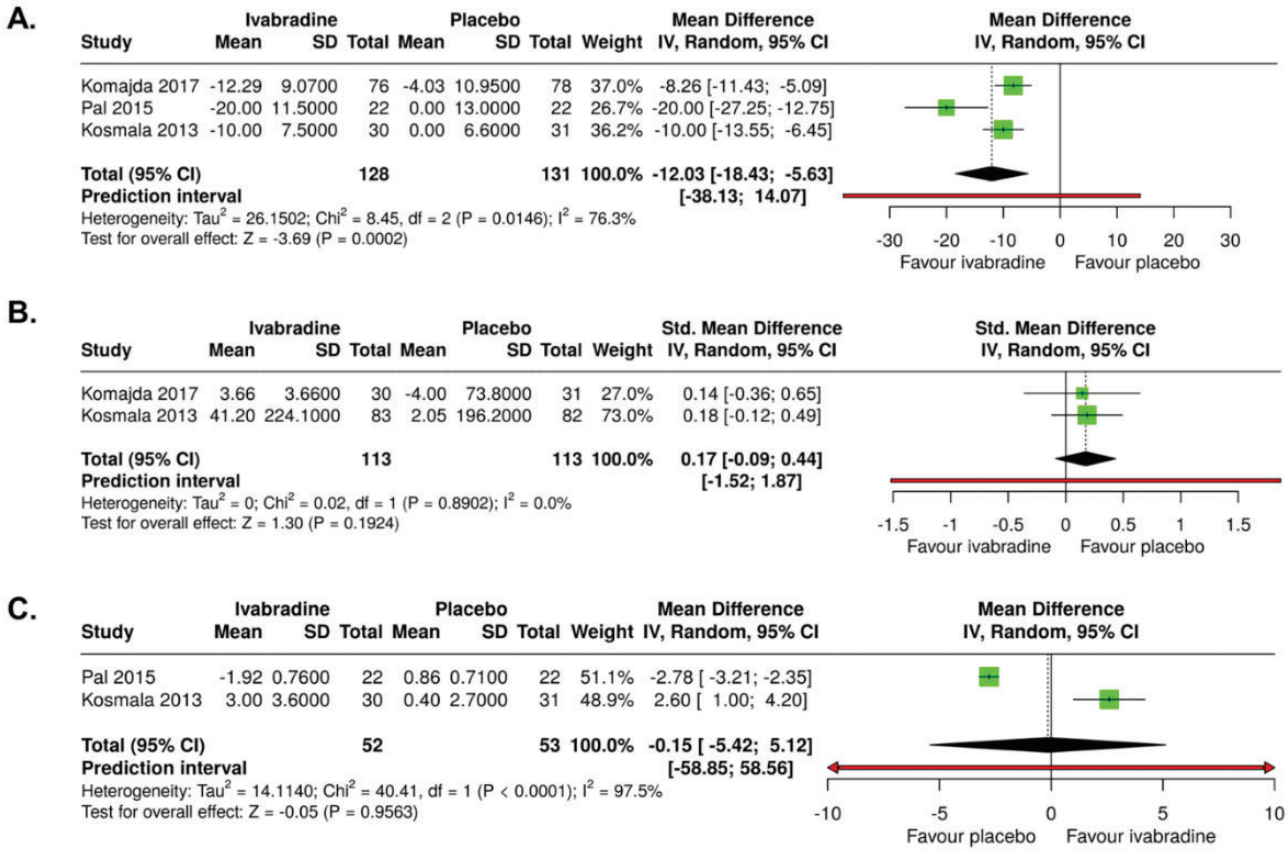

Fig. 4. Forest plot of secondary outcomes. **(A)** resting heart rate, **(B)** natriuretic peptides, and **(C)** peak VO_2

Hemodynamic and functional outcomes

Ivabradine significantly reduced resting HR compared with placebo (MD −12.03 bpm; 95% CI −18.43 to −5.63) (Figure 4). The certainty of evidence was graded as moderate, downgraded by one level due to a high heterogeneity (I2 = 76.3%) (Table 3). Subgroup analysis to explain heterogeneity cannot be conducted due to limited studies (k = 2). In contrast, no significant between-group differences were observed in natriuretic peptide levels, pooled as BNP or NT-proBNP (SMD 0.17; 95% CI −0.09 to 0.44), or in peak VO_2 (MD −0.15 mL/kg/min; 95% CI −5.42 to 5.12).

Discussion

Despite extensive research, no therapy has consistently demonstrated mortality benefits in patients with HFpEF. Elevated HR has been associated with adverse outcomes, prompting interest in HR-lowering strategies. β-blockers, however, have yielded unfavorable results in HFpEF, likely due to their negative inotropic effects [26]. Ivabradine, by selectively inhibiting the sinoatrial If current, reduces HR without affecting myocardial contractility, theoretically prolonging diastolic filling and improving ventricular performance [27]. Resting tachycardia may impair LV function and has been linked to worse prognosis in cardiovascular disease, including heart failure.

Meta-analytic data from three RCTs encompassing 258 patients indicate that ivabradine achieved a robust and consistent reduction in resting HR, confirming effective target engagement through selective If-channel inhibition [15, 24, 25]. Despite this physiological effect, no improvement was observed in key structural or functional outcomes, including LAVI, natriuretic peptide levels, or exercise capacity. Notably, ivabradine was associated with a modest but statistically significant increase in E/e′, one of the core echocardiographic surrogates of LV filling pressure recommended by ASE/BSE/EACVI guidelines. This finding challenges the traditional assumption that HR reduction uniformly alleviates diastolic burden in HFpEF and suggests a more complex and potentially maladaptive hemodynamic response [6,7,28,29]. Consequently, selective HR reduction alone may be insufficient to modify functional capacity or cardiac mechanics in this complex syndrome.

Several pathophysiological mechanisms may explain the paradoxical increase in E/e′ despite effective HR lowering. In HFpEF, stroke volume augmentation is limited by ventricular stiffness, rendering cardiac output more dependent on HR, particularly during rest and low-level activity [13]. Excessive slowing of the HR may

therefore reduce forward flow and impair early diastolic suction, leading to higher transmitral filling pressures [30, 31]. Furthermore, prolongation of diastole does not necessarily improve relaxation when calcium reuptake and myocardial untwisting are intrinsically delayed, as is typical in HFpEF [32]. Under these conditions, reduced HR may unmask or exacerbate filling pressure abnormalities rather than ameliorate them. Emerging evidence further suggests that the relationship between HR and cardiac filling pressures in HFpEF is non-linear rather than unidirectional. In a recent pacing study, moderate increases in HR were associated with significant reductions in left-heart filling pressure, whereas higher pacing rates led to a subsequent increase, indicating a U-shaped relationship [33].

Importantly, interpretation of E/e′ would ideally be complemented by absolute transmitral Doppler E wave velocity, which was not consistently reported across the included trials and therefore could not be pooled in the present analysis. However, in the EDIFY trial, ivabradine treatment was associated with a greater increase in E-wave velocity than placebo (between-group difference: 12.3 cm/s). While this finding does not directly establish improved diastolic function, it offers a limited mechanistic context for interpreting our results. It is therefore plausible that the observed increase in E/e′ reflects, at least in part, a disproportionate rise in transmitral E velocity, potentially related to prolonged diastolic filling time or altered loading conditions following HR reduction. This limitation should still be acknowledged, as incomplete reporting of E velocity across studies precludes definitive conclusions, and changes in E velocity may substantially influence the E/e′ ratio.

Interestingly, ivabradine was associated with a significant increase in septal e′ velocity, suggesting improved myocardial relaxation at the tissue level [34]. However, this did not translate into lower E/e′ or reduced LAVI, suggesting dissociation between local relaxation indices and global filling pressures. The e′ reflects early diastolic myocardial velocity but does not fully capture chamber stiffness, atrial contribution, or ventricular-vascular coupling [35]. Thus, modest improvements in relaxation velocity may be insufficient to offset elevated left ventricular end-diastolic pressure, particularly in a stiff, noncompliant ventricle [13, 34]. This dissociation reinforces the concept that HFpEF is not a simple disorder of delayed relaxation but a multifactorial syndrome in which improvements in one diastolic component may not yield net hemodynamic benefit [28, 32].

The absence of a significant effect on LAVI further supports this interpretation. LAVI represents cumulative exposure to chronically elevated filling pressures and structural atrial remodeling, rather than acute changes in diastolic mechanics [12]. Its evaluation was therefore clinically and conceptually justified, as LAVI serves as an integrative marker of chronic diastolic burden and is a core component of multiparametric diastolic assessment in HFpEF [11]. The lack of LAVI reduction may be attributed to the trials' follow-up period, which ranged from very short-term (seven days) to intermediate duration (up to eight months). Structural reverse remodeling of the left atrium likely requires sustained unloading and comprehensive modulation of filling pressures, which isolated HR reduction alone may be unable to achieve [36]. In HFpEF, left atrial enlargement reflects longstanding ventricular-atrial uncoupling and increased chamber stiffness; thus, the neutral effect of ivabradine on LAVI is mechanistically informative and aligns with its role as a selective chronotropic agent rather than a modifier of structural remodeling [7, 26]. This further supports the notion that isolated chronotropic modulation is insufficient to induce reverse structural remodeling in HFpEF.

The neutral effects of ivabradine on natriuretic peptide levels and peak VO_2 further support this mechanistic interpretation. Natriuretic peptides reflect myocardial wall stress and integrated intracardiac filling pressures over time rather than isolated changes in HR or tissue-level relaxation [37]. In the present analysis, the absence of a reduction in BNP or NT-proBNP is consistent with the observed lack of improvement in E/e′ and LAVI, indicating that HR reduction did not meaningfully unload the left ventricle or reduce atrial pressure burden [38]. Similarly, peak VO_2 is determined by the integrated cardiovascular response to exercise, including chronotropic reserve, stroke volume augmentation, and peripheral oxygen extraction [39]. In HFpEF, where stroke volume reserve is constrained by ventricular stiffness, excessive HR slowing may blunt cardiac output during exertion, offsetting any modest improvements in myocardial relaxation [39,40]. Consequently, the neutral effect on exercise capacity aligns with the dissociation observed between improved e′ velocity and unchanged or worsened global filling pressures, reinforcing the concept that isolated chronotropic modulation is insufficient to improve functional performance in HFpEF.

This study addresses an important clinical question using a PRISMA-adherent synthesis of randomized controlled trials with GRADE-based certainty assessment. However, the synthesis relied on change-score analyses that required imputation of standard deviations using an assumed within-subject correlation ($r = 0.5$) and transformation of nonparametric data, which may introduce uncertainty into pooled estimates. The small number of included trials precluded robust exploration of heterogeneity, sensitivity analyses, or assessment of publication bias. In addition, the reliance on echocardiographic surrogate markers rather than patient-im-

portant outcomes, as none of the studies report the cardiac catheterization method of LV filling pressure measurement, introduces indirectness and may limit the certainty of the evidence. Furthermore, incomplete reporting of key diastolic parameters, particularly transmitral Doppler E wave velocity, limited a more comprehensive interpretation of changes in E/e′, as E velocity was not consistently available across studies and could not be pooled or correlated with HR. Consequently, substantial clinical and methodological heterogeneity may limit the interpretability and generalizability of the quantitative findings.

Several important knowledge gaps remain. Future studies should prioritize invasive or exercise-based assessment of filling pressures, as resting echocardiographic indices may not fully capture the dynamic hemodynamic consequences of HR modulation. Additionally, phenotype-driven trials distinguishing patients with true tachycardia-dependent filling abnormalities from those with fixed ventricular stiffness are needed to identify subgroups that may benefit from chronotropic interventions.

From a clinical perspective, our findings align with and reinforce current guideline recommendations from the American Heart Association (AHA), which emphasize a multifaceted approach to HFpEF management rather than targeting a single physiological parameter such as HR. Contemporary recommendations prioritize blood pressure control, use of sodium-glucose cotransporter-2 inhibitors (SGLT2i), and management of comorbidities, including atrial fibrillation, while selected use of mineralocorticoid receptor antagonists (MRAs), angiotensin receptor blockers (ARBs), and angiotensin receptor-neprilysin inhibitors (ARNIs) may reduce hospitalizations in specific subgroups [41]. In this context, our results provide mechanistic support for these recommendations, suggesting that isolated HR reduction does not translate into meaningful improvement in surrogate markers of filling pressure and therefore should not be assumed to confer clinical benefit. This may explain why contemporary guidelines do not endorse HR reduction as a primary therapeutic target in HFpEF.

Nevertheless, it remains plausible that selected patient subgroups may derive benefit from HR reduction. Patients with elevated resting HR, shortened diastolic filling time, or evidence of tachycardia-mediated impairment of ventricular filling may represent a phenotype in which chronotropic modulation is more relevant. Conversely, in patients with advanced ventricular stiffness and impaired relaxation independent of HR, further slowing may be neutral or even detrimental by increasing filling pressures. These considerations highlight the need for more refined phenotyping strategies in HFpEF, integrating HR dynamics, diastolic reserve, and loading conditions.

Until such data are available, the present evidence cautions against assuming that HR lowering per se is a surrogate for diastolic improvement in HFpEF. In this context, ivabradine serves not merely as a therapeutic agent but as a mechanistic probe, enabling isolation of HR effects and revealing the limited role of chronotropic modulation in HFpEF pathophysiology.

Conclusion

In conclusion, ivabradine consistently reduced resting HR in patients with HFpEF but was not associated with improvement in echocardiographic markers of diastolic burden. These findings support the presence of a dissociation between HR reduction and left ventricular filling pressure, indicating that HR lowering alone may not reliably translate into favorable changes in LV filling pressure or functional performance in HFpEF. Accordingly, consistent with contemporary guideline frameworks, the role of isolated chronotropic modulation in HFpEF appears limited and should be considered within a comprehensive, phenotype-based approach rather than as a stand-alone therapeutic strategy.

Ethics: *This study was a secondary analysis based on the currently existing dataset and did not directly involve human participants or experimental animals. Therefore, the ethics approval was not required in this paper.*

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