Ivabradine Improves Cardiac Function and Increases Exercise Capacity in Patients with Chronic Heart Failure
A Systematic Review and Meta-Analysis

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Summary
To systematically review and conduct a meta-analysis of the ivabradine-induced improvement in cardiopulmonary function, exercise capacity, and primary composite endpoints in patients with chronic heart failure (CHF).

This study was a systematic review and meta-analysis. Databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials and European Union Clinical Trials, were searched for randomized placebo-controlled trials. The efficacy and safety of ivabradine treatment in patients with CHF were assessed and compared to those of the standard anti-heart failure treatment. Review Manager 5.3 software was used to analyze the relative risk (RR) for dichotomous data and the mean difference (MD) for continuous data.

In total, 22 studies with 24,562 patients were included. Cardiopulmonary function analysis showed that treatment with added ivabradine reduced the heart rate (MD = −17.30, 95% CI: 19.52−15.08, P < 0.00001), significantly increased the left ventricular ejection fraction (LVEF) (MD = 3.90, 95% CI: 0.40−7.40, P < 0.0001), and led to a better New York Heart Association (NYHA) classification. Ivabradine significantly reduced the minute ventilation/carbon dioxide production (VE/VCO₂) (MD = −2.68, 95% CI: −4.81−−0.55, P = 0.01) and improved the peak VO₂ (MD = 2.80, 95% CI: 1.05−4.55, P = 0.002) and the exercise capacity, including the exercise duration with a submaximal load (MD = 7.82, 95% CI: −2.57−−18.21, P < 0.00001) and the 6-minute walk distance. The RR of cardiovascular death or worsening heart failure was significantly decreased (RR = 0.93, 95% CI: 0.87−−0.98, P = 0.01) in the patients treated with ivabradine. Additionally, the RRs of heart failure and hospitalization also decreased (RR = 0.91, 95% CI: 0.85−0.97, P = 0.006; RR = 0.86, 95% CI: 0.79−0.93, P = 0.0002). Safety analysis showed no significant difference in the RR of severe adverse events between the ivabradine group and the standard anti-heart failure treatment group (P = 0.40). However, ivabradine significantly increased the RR of visual symptoms in CHF patients (RR = 3.82, 95% CI: 1.80−8.13, P = 0.0005).

Existing evidence showed that adding ivabradine treatment significantly improved the cardiopulmonary function and increased the exercise capacity of patients with CHF. Adding ivabradine to the standard anti-heart failure treatment reduced the mortality and hospitalization risk and improved the quality of life. Finally, ivabradine significantly increased the RR of visual symptoms in CHF patients.

This is the first systematic review and meta-analysis to focus on the efficacy of ivabradine, which improved the cardiac function and increased the exercise capacity in patients with chronic heart failure (CHF). Therefore, this study will help evaluate the quality of life after adding ivabradine to the treatment of patients with CHF, even though there are differences in the standard for resting heart rate, left ventricular ejection fraction (LVEF), and New York Heart Association (NYHA) class in the included studies. This hybrid effect might be smaller when analyzed separately but might have a higher heterogeneity when analyzed in multiple studies.

Key words: Heart rate, Left ventricular ejection fraction, Lung function, Peak VO₂
Chronic heart failure (CHF) has become a global epidemic in the 21st century with considerable effects on a patient’s quality of life and a tremendous burden to healthcare systems. With the increase in the elderly population, the prevalence of heart failure has increased significantly and is significantly higher in women than men. Furthermore, 75% of heart failures occur in the elderly. The guidelines of the American College of Cardiology (ACC), the American Heart Association (AHA), and the Heart Failure Society of America (HFSA) describe the standard anti-heart failure therapy, which includes renin-angiotensin-aldosterone (RAAS) antagonists, beta (β)-blockers, calcium antagonists, and diuretics. Although the existing drug therapy and implantable treatment can slow the development of heart failure and improve heart function, the prognosis of the end-stage disease, especially CHF, is poor.

Elevated heart rate (HR) is an independent risk factor for poor cardiovascular outcomes of CHF. The latest evidence showed that HR is closely related to the clinical consequences in patients with CHF and left ventricular dysfunction. The clinical benefit for CHF patients is closely associated with the degree of HR reduction. β-blockers can effectively decrease the HR, increase the left ventricular ejection fraction (LVEF), and reduce the mortality and length of hospitalization of CHF patients. However, these clinical benefits cannot improve the exercise ability or quality of life of patients. Moreover, a large number of patients have a high HR after being treated with the maximum dose of β-blocker. Although β-blockers are regarded as the first-line treatment, the negative inotropic effect is not beneficial to patients; in addition, the complications and side effects, such as bronchial asthma, hypotension, severe bradycardia, and atrioventricular block, limit the application of β-blockers.

Ivabradine is a new HR-lowering medication that specifically inhibits the ion channels in the sinus node. Ivabradine selectively lowers the HR without affecting cardiac conductivity and repolarization, improves left ventricular diastolic filling, reduces myocardial oxygen consumption, and increases the time of coronary perfusion. Some studies also confirmed that ivabradine could improve exercise tolerance, extend the total exercise duration, and lower the seizure frequency of angina pectoris, as observed during a 3-month follow-up of chronic stable angina. The result of a recent multicenter clinical randomized controlled trial (RCT), Systolic Heart failure Treatment with the If inhibitor ivabradine Trial (SHIFT), showed that the hazard ratio (HR) for the primary cardiovascular composite endpoint decreased significantly in the ivabradine group (793 patients; 24%) [HR = 0.82, 95% confidence interval (CI): 0.75-0.90, P < 0.0001] compared to that in the control group (937 patients; 29%). In this case, the selectivity of the ion channel inhibitor ivabradine provides new hope for CHF patients.

Interestingly, ivabradine did not alter the primary composite endpoint (cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new onset or worsening heart failure) in patients with long-term systolic heart failure (HR = 1.00, 95% CI: 0.91-1.1, P = 0.94) (HR = 0.91, 95% CI: 0.81-1.04, P = 0.17), and no significant difference (P = 0.70) was observed with respect to serious adverse events between the 1233 patients of the ivabradine treatment group (22.5%) and the 1239 patients of the control group (22.8%) in the multicenter clinical RCT morbidity-mortality Evaluation of the If inhibitor ivabradine in patients with coronary disease and left ventricular dysfunction (BEAUTIFUL) study.

However, the European Society of Cardiology and the ACC/AHA/HFSA updated the guidelines for CHF on the same day in 2016. The guideline gives a class IIa recommendation for the ivabradine treatment of symptomatic heart failure (New York Heart Association (NYHA) classification grade II-III) with a stable, chronic decrease in the ejection fraction (LVEF ≤ 35%) to reduce the number of heart failure patients; if the maximum tolerated dose of β-blockers has been used to treat a sinus rhythm with HR ≥ 70 beats per minute (bpm), ivabradine treatment could reduce the rate of hospitalization in cases of heart failure. The currently known results of clinical trials are different and lack an evaluation of the quality of life after adding ivabradine to treat patients with CHF. Therefore, we performed a systematic review and meta-analysis of the addition of ivabradine to standard anti-heart failure therapy for CHF patients regarding the cardiopulmonary function, exercise ability, primary composite endpoint, and side effects.

Methods

Search strategy: Electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Clinical Trials and European Union Clinical Trials, were searched from inception until August 2017 for all clinical RCTs. The search terms included “ivabradine”, “S-16257-2”, “S 16257”, “chronic heart failure”, “CHF”, and “RCTs”.

Selection criteria: Drs. Hui Pei and Zhuo Zhao reviewed the titles or abstracts and subsequently the full text of all retrieved results. We selected the studies that fulfilled the following inclusion criteria: (1) The study was an RCT and published in English; (2) The research groups constituted CHF patients whose ejection fraction was decreased or preserved; and (3) The study assessed the effect and safety of treatment with added ivabradine (5-7.5 mg b.i.d.) or placebo in CHF patients with standard anti-heart failure therapy, including angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARBs), β-blockers, calcium antagonists and diuretics.

Data extraction: Following the guidelines of the Cochrane Handbook for Systematic Reviews, data were independently extracted from each study by two reviewers according to the selection criteria. The following information was extracted from the studies: name of the first author, publication year, study type, patient population, drug and dosage intervention, and duration of follow-up (Table I). The drugs from each study were added to the table. Table II shows the baseline demographic (age, sex ratio, and body mass index (BMI)) and other [HR, LVEF, systolic blood pressure (SBP), diastolic blood pressure (DBP), and NYHA] characteristics of the study population based on each trial included in the analysis.
### Table I. Basic Characteristics of the Study

| Study          | Year | Patients                                                                 | Agents used                                                                 | Ivabradine Dose | Follow-up duration |
|---------------|------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------|-------------------|
| Komajda M     | 2017 | CHF patients in NYHA classes II and III, in sinus rhythm, with HR ≥ 70 bpm, NT-proBNP ≥ 220 pg/mL (BNP ≥ 80 pg/mL) and LVEF ≥ 45%. | ACEI and/or ARBs: 88.4%, Beta-blockers: 74.7%, Diuretic (excluding MRAs): 31.6%, Diuretic: 58.9%, CCB: 37.9% | 7.5-10 mg b.i.d. | 8-month |
| Sisakian H    | 2016 | Patients in NYHA classes II and III with moderate to severe CHF and pseudonormal/restrictive type of diastolic dysfunction with LVEF ≤ 40% and resting HR ≥ 70 beats per minute (bpm) in sinus rhythm | MRAs: 96.3%, ACEI and/or ARBs: 85.2%, Beta-blockers: 81.5%, Diuretic: 77.8%, Digitalis: 25.9% | 2.5-7.5 mg b.i.d. | 3-month |
| Tsutsui H     | 2016 | Japanese patients resting HR ≥ 75 bpm in sinus rhythm, CHF of NYHA class II or higher, LVEF ≤ 35%, and under optimal, stable treatment according to the Japanese Guideline for Treatment of Chronic Heart Failure (JCS 2010). | Beta-blockers: 92.9%, ACEI and/or ARBs: 70.2%, Diuretic: 84.5%, MRAs: 54.8%, Digitalis: 9.5% | 2.5-7.5 mg b.i.d. | 2-month |
| Abdel-Salam Z | 2015 | Patients with dilated cardiomyopathy of no apparent cause, LVEF < 40%, NYHA class ≥ II, sinus HR ≥ 70 bpm, and symptomatic for at least 4 weeks. | Beta-blockers: 100%, ACEI: 100%, MRAs: 100%, Beta-blockers: 99%, ACEI: 100%, MRAs: 100% | 2.5-7.5 mg b.i.d. | 3-month |
| Kosmala W     | 2013 | CHF patients with diastolic dysfunction and heart failure with preserved ejection fraction (HFrEF), exercise capacity < 80%, E/e > 13 after exercise, and NYHA class II or III. | ACEI and/or ARBs: 97%, Beta-blockers: 57%, Diuretic: 76%, CCB: 37%, Hypoglycemic: 40% | 5 mg b.i.d. | 7-day |
| Volterrani M  | 2011 | HF at least 12 months prior to selection, NYHA functional class II to III, and clinically stable for 3 weeks. Patients were either not receiving β-blockers or were receiving beta-blockers but in combination with a suboptimal dose of ACEI. | ACEI: 93%, Diuretic (excluding MRAs): 83%, Beta-blockers: 55%, MRAs: 45%, Cardiac glycosides: 36%, ARBs: 7% | 5 mg b.i.d. | 3-month |
| Mansour S     | 2011 | CHF patients with NYHA class III or IV and LVEF < 40%, HR > 70 bpm in sinus rhythm at rest, as measured on a 12-lead ECG performed after at least a 5-minute rest. | ACEI (% of target): 66.1 ± 23.7%, Carvedilol (mg/day): 18.0 ± 13.6 | 5-7.5 mg b.i.d. | 3-month |
| Sarullo FM    | 2010 | Patients with documented clinical signs and symptoms of heart failure, LVEF ≤ 40%, NYHA classes II to III, and sinus rhythm with a resting HR > 70 bpm were eligible to participate. | Diuretic: 100%, ACEI: 83.3%, Beta-blockers: 56.6%, Nitrites: 46.6%, Amiodarone: 23.3% | 5 mg b.i.d. | 3-month |

**Types of outcome measures:**

**Assessment index of the therapeutic effect** Cardiopulmonary function evaluation index: The effect of adding ivabradine to the standard anti-heart failure therapy on the HR, LVEF, peak early diastolic mitral flow velocity/late diastolic mitral flow velocity (E/A), peak early diastolic mitral flow velocity/peak early diastolic mitral annular velocity (E/Em), minute ventilation/carbon dioxide production (VE/VCO2), peak oxygen consumption (peak VO2), and NYHA class. The exercise capability evaluation index
CHF indicates chronic heart failure; NYHA, New York Heart Association; and N/A, not applicable. Data are the median (IQR, interquartile range) or mean ± SD.

Table I. Basic Characteristics of the Study (continued)

| Study   | Year | Patients | Agents used | Ixabradine Dose | Follow-up duration |
|---------|------|----------|-------------|-----------------|-------------------|
| Swedberg K | 2010 | CHF patients with resting HR > 70 bpm in sinus rhythm, as measured on 12-lead ECG after at least a 5-minute rest, with stable symptomatic CHF of 4 or more weeks’ duration, a previous admission to a hospital for worsening heart failure within the previous 12 months, and LVEF < 35%. | Beta-blockers: 89%, Diuretic (excluding MRA): 84%, ACEI: 79%, Antialdosterone: 61%, Cardiac glycosides: 22%, ARBs: 14% | 2.5-7.5 mg b.i.d. | 32-month |
| Fox K  | 2008 | Patients with CAD, LVEF < 40% and an end-diastolic short-axis internal dimension of greater than 56 mm by ECG, resting HR > 60 bpm in sinus rhythm, heart failure for at least 3 months and appropriate conventional cardiovascular medication for at least 1 month. | ACEI and/or ARBs: 89%, Beta-blockers: 83%, Diuretic (excluding MRAs): 63%, Antialdosterone: 29%, | 5-7.5 mg b.i.d. | 24-month |

Table II. Baseline Characteristics of the Ixabradine Group and the Standard Anti-Heart Failure Treatment Group

| Study   | Year | Number of participants | Age (year) | BMI (kg/m²) | Males, n | HR, bpm | LVEF, % | SBP, mmHg | DBP, mmHg | NYHA class/I/II/III/IV |
|---------|------|------------------------|------------|-------------|----------|---------|---------|-----------|-----------|------------------------|
| Komajda M | 2017 | 95 | (66.0-78.0) | 29.6 (26.4-35.6) | 36 | 75 (72-78) | 60 (54-66) | 132 (123-142) | 76 (69-84) | 0/76/19/0 |
| 84 | 73.0 (67.0-79.0) | 28.8 (26.8-32.8) | 27 | 74 (71-79) | 61 (55-67) | 133 (120-145) | 80 (70-85) | 0/69/15/0 |
| Siskian H | 2016 | 27 | 58.2 ± 12.2 | N/A | 22 | 81.3 ± 7.9 | 30.6 ± 6.66 | 120.2 ± 15.9 | 76.2 ± 10.98 | 0/6/21/0 |
| 27 | 61.4 ± 9.67 | N/A | 22 | 76.4 ± 4.95 | 30.3 ± 5.76 | 118.3 ± 12.33 | 74.3 ± 7.17 | 0/5/22/0 |
| Tsutsui H | 2016 | 42 | 60.0 ± 13.9 | 24.6 ± 4.6 | 37 | 83.4 ± 8.2 | 28.4 ± 4.9 | 119.5 ± 16.2 | 72.5 ± 12.1 | 0/3/9/0 |
| 42 | 59.4 ± 12.7 | 24.3 ± 4.3 | 34 | 81.5 ± 7.4 | 28.5 ± 4.9 | 113.2 ± 16.9 | 70.3 ± 10.4 | 0/3/8/0 |
| Abdel- Salam Z | 2015 | 20 | 49.1 ± 15.7 | N/A | 10 | 85 ± 12 | 34 ± 4 | 101 ± 17 | 69 ± 12 | 0/6/12/0 |
| 23 | 52.3 ± 13.5 | N/A | 13 | 84 ± 10 | 30 ± 8 | 91 ± 5 | 61 ± 4 | 0/5/14/4 |
| Kosmala W | 2013 | 30 | 66.5 ± 8.5 | 30.3 ± 4.0 | 7 | 72 ± 7 | 67 ± 7 | 130 ± 18 | 75 ± 8 | N/A |
| 31 | 68.0 ± 8.7 | N/A | 4 | 70 ± 6 | 69 ± 6 | 133 ± 17 | 76 ± 7 | N/A |
| Volterrani M | 2011 | 42 | 66.5 ± 9.2 | 26.4 ± 3.0 | 28 | 75.7 ± 12.5 | 28 ± 4.7 | 124.8 ± 12.9 | 71.9 ± 8.6 | 0/21/11/0 |
| 38 | 67.6 ± 10.1 | 26.8 ± 3.2 | 26 | 76.7 ± 12.8 | 26 ± 5.0 | 125.4 ± 15.2 | 74.8 ± 9.1 | 0/21/6/0 |
| Mansour S | 2011 | 30 | 47 ± 13 | N/A | 18 | 96 ± 15 | 32.1 ± 6.1 | 97 ± 15 | N/A | 0/7/22/1 |
| 23 | 52 ± 13 | N/A | 14 | 84 ± 10 | 29.0 ± 7.4 | 91 ± 5 | N/A | 0/3/14/6 |
| Sarullo FM | 2010 | 30 | 52.1 ± 6.1 | N/A | 23 | 75 ± 3 | 30.6 ± 6 | 109 ± 7 | N/A | 0/17/13/0 |
| 30 | 52.9 ± 4.9 | N/A | 22 | 76.7 ± 12.8 | 29.9 ± 6 | 110 ± 9 | N/A | 0/18/12/0 |
| Swedberg K | 2010 | 3241 | 60.7 ± 11.2 | 28.0 ± 5.1 | 2462 | 79.9 ± 9.5 | 29.0 ± 5.1 | 122.0 ± 16.1 | 75.7 ± 9.6 | 0/1585/1605/50 |
| 3261 | 60.1 ± 11.5 | 28.0 ± 5.0 | 2508 | 80.1 ± 9.8 | 29.0 ± 5.2 | 121.4 ± 15.9 | 75.6 ± 9.4 | 0/1584/1618/61 |
| Fox K | 2008 | 5479 | 65.3 ± 8.5 | 28.4 ± 4.4 | 4540 | 71.5 ± 9.8 | 32.4 ± 5.5 | 128.1 ± 15.7 | 77.4 ± 9.3 | 840/3346/1293/0 |
| 5438 | 65.0 ± 8.4 | 28.5 ± 4.4 | 4507 | 71.6 ± 9.9 | 32.3 ± 5.5 | 127.9 ± 15.5 | 77.5 ± 9.2 | 840/3359/1239/0 |

BMI indicates body mass index; HR, heart rate; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; DBP, diastolic blood pressure; NYHA, New York Heart Association; and N/A, not applicable. Data are the median (IQR, interquartile range) or mean ± SD.

Included the exercise duration with a submaximal load and the 6-minute walk distance.

The main long-term evaluation index included the cardiovascular primary composite endpoint events in CHF patients after adding ibabradine to the standard treatment. Treatment safety evaluation index The influence of severe adverse events, cardiac dysfunction, nervous system disorder, and visual disturbance during the treatment and follow-up period in CHF patients after the addition of ibabradine was assessed.

Data synthesis and analysis: Dichotomous data are reported using the relative risk (RR) with the 95% CIs, whereas continuous variables (change from baseline to a predefined follow-up time) are reported using the mean difference (MD) with the 95% CIs. The data were evaluated by a fixed effect model when I² < 50% with a high P-value (P > 0.10). Moreover, the random effects model was used when I² > 50% with a low P-value (P < 0.10).
The Cochrane Community meta-analysis software Review Manager 5.3 (http://community.cochrane.org) was used for the meta-analysis. A two-tailed $P$-value $< 0.05$ was considered statistically significant.

**Patient and public involvement statement:** Patients and the public were not involved.

### Results

**Description of included studies:** Figure 1 illustrates the schematic for the study selection. Initially, 350 studies that fulfilled our inclusion criteria were retrieved. After primary screening by two researchers, 128 studies met the inclusion criteria. Finally, a total of 22 studies, 12 studies$^{13-25}$ with 6526 systematically reviewed patients and 10 studies$^{25,26-34}$ with 18,036 patients, were subjected to metanalysis. The characteristics of the component trials and study patients are shown in Tables I, II, respectively. Supplemental Figures 1, 2 show the risk of bias while evaluating the overall quality of the articles by Review Manager 5.3.

**Improved cardiopulmonary function:**

**Decreased HR** Treatment with the addition of ivabradine effectively reduced the HR compared to that in the placebo group (MD = $-17.30$, 95% CI: 19.52–$-15.08$) (Figure 2A). The high heterogeneity might be attributed to the different follow-up times, ejection fractions, and basic HRs during the study period. Related studies found that a decreased HR is associated with the drug dose. The HR of the 5 mg group was significantly lower than that of the 2.5 mg group (13.6 ± 7.8 bpm versus 9.3 ± 9.6 bpm, $P < 0.0001$).$^{21}$ The study by Tarlovskaya, *et al.*$^{19}$ demonstrated that the HR of the ivabradine treatment group was reduced significantly compared to that of the placebo group (81.6 ± 9.0 to 67.7 ± 12.4 bpm versus 81.3 ± 7 to 77 ± 10.0 bpm). Furthermore, Hady, *et al.*$^{15}$ provided stronger evidence that treatment with added ivabradine decreased the HR effect irrespective of the resting HR or peak exercising HR ($P < 0.017$, $P < 0.0245$). Moreover, the study by Hristova, *et al.*$^{19}$ showed that treatment with added ivabradine increased the reduction in heart rate variability (HRV) in patients with heart failure with reduced ejection fraction (HF/EF) (Figure 1).

**Increase left ventricular ejection fraction** Treatment with added ivabradine significantly increased the LVEF in patients with CHF compared to that in the placebo group (MD = 3.90, 95% CI: 0.40–7.40, $P < 0.0001$) (Figure 2B). The studies by Chumburidze, *et al.*$^{16}$ and Mircheva, *et al.*$^{19}$ also showed that ivabradine more significantly improved LVEF than the placebo. Moreover, the analysis of E/A and E/Em showed that the reason for the high heterogeneity might be related to the different follow-up times of the eligible studies. However, the treatment with high-dose ivabradine decreased E/A and E/Em in patients with CHF (Figure 2C, D). The study by Sisakian, *et al.* showed that the time of deceleration time (DT) in the treatment group was also prolonged significantly and that the left atrial volume index (LAVI) obviously decreased. These changes might improve the blood flow dynamics and increase the ventricular filling in patients with CHF.$^{21}$ Treatment with added ivabradine improved the LVEF in a dose-dependent manner. The LVEF of the placebo group increased 2.5 ± 6.0%, the LVEF of the 2.5 mg ivabradine treatment group increased 5.4 ± 7.0%, and the LVEF of the 2.5 mg ivabradine treatment group increased 6.4 ± 9.9% with statistically significant differences between the placebo group and the ivabradine groups ($P = 0.0472$ and $P = 0.0359$, respectively).$^{26}$ Moreover, the study by Hady, *et al.*$^{15}$ found that the treatment with added ivabradine had no significant impact on the left ventricular structure.

**Decreased NYHA score** The study by Abdel-Salam showed that the treatment with ivabradine did not change the NYHA classification.$^{20}$ Tsutui, *et al.* also found that the NYHA classification was not changed by treatment with either 2.5 mg or 5 mg ivabradine.$^{20}$ However, the NYHA classification was significantly improved by treatment with high-dose ivabradine in a large-scale study with an extended follow-up duration. NYHA improved for 874 patients in the ivabradine group (28%) but only for 776 patients in the placebo group (24%) ($P = 0.001$). The NYHA-classified estimations of the ivabradine group included 2118 patients (72%) who showed improvement in the physicians’ report; this improvement was significantly different from that in the placebo group, in which 1772 patients (57%) showed improvement ($P = 0.0011$).$^{20}$ Although the improvement was small, ivabradine improved the NYHA classification in the SHIFT study. Mircheva, *et al.*$^{19}$ conducted a 6-month follow-up study: 77% of the patients treated with added ivabradine reached grade II, and only 45% of the control group reached grade II ($P = 0.023$). Similarly, Speranza, *et al.*$^{21}$ Bennett, *et al.*$^{25}$ and Zugck, *et al.*$^{26}$ reached the same conclusion that treatment with added ivabradine improved the NYHA classification. However, the study by Volterrani, *et al.* found that compared to the patients who received carvedilol, patients who received ivabradine or a combined treatment had a significantly better NYHA class.$^{23}$ Currently, the results of improving NYHA class using ivabradine are controversial.

**Improved lung function** Peak VO$_2$ assesses the exercise...
ability in patients with CHF and was found to be related to prognosis. 35,36) Compared with the standard anti-heart failure therapy, the added ivabradine treatment led to a significantly lower VE/VCO2 (MD = −2.68, 95% CI: −4.81 to −0.55, P = 0.01) in patients with CHF (Figure 2E).

Furthermore, the analysis of the peak VO2 demonstrated that the high heterogeneity might be associated with the different follow-up times of the included studies. However, the treatment with high-dose ivabradine clearly increased the peak VO2 (MD = 2.80, 95% CI: 1.05-4.55, P = 0.002) (Figure 2F).

**Increased exercise capability.** The analysis of exercise tolerance in patients with CHF showed that the added ivabradine treatment group had significantly higher exercise tolerance than the standard anti-heart failure therapy group (MD = 7.82, 95% CI: −2.57-18.21, P = 0.14) (Figure 2 G).

The studies by Chumburidze, et al., 16) Sen, et al., 18) Mircheva, et al., 20) and Volterrani, et al., 28) showed a more obvious improvement in exercise function, as measured by the exercise duration or 6-minute walk distance, for treatment with ivabradine than for placebo. However, 6-minute walk distance is an independent predictor of hospital readmission in patients with chronic heart failure. 37,38) Similar studies also confirmed that the average time of the ivabradine-treated group increased from 328 seconds to 497 seconds (P < 0.0235). 15) The study by Abdel-Salam 32) showed that the proportion of patients with an exercise tolerance of > 6 minutes walking time was significantly
higher in the ivabradine group ($P < 0.05$).

**Cardiovascular composite endpoint events:** We analyzed the RR of cardiovascular composite endpoint events between the added ivabradine group and the standard anti-heart failure therapy group. However, the result showed that the RRs of all-cause mortality and cardiovascular mortality were not significantly different between the two groups ($P = 0.59$ and $P = 0.79$, respectively; Figure 3A). The RRs of cardiovascular death or worsening heart failure, and heart failure were decreased in the added ivabradine group ($RR = 0.93$, 95% CI: 0.87-0.98, $P = 0.01$), ($RR = 0.91$, 95% CI: 0.85-0.97, $P = 0.006$) (Figure 3A). However, the analysis of the causes of death in patients with heart failure showed that the RR of patients who died from heart failure was significantly decreased by the treatment with added ivabradine compared to that in the standard anti-heart failure therapy group ($RR = 0.82$, 95% CI: 0.69-0.96, $P = 0.02$) (Figure 3A). However, a 3-year follow-up study by Tumasyan, et al. confirmed that the hospitalization rate at 1, 2, and 3 years, were decreased by 31.3%, 27.5%, and 24.5%, respectively, ($P < 0.05$), and the 3-year mortality rate decreased by 14%, 10.5%, and 17.1%, respectively ($P < 0.05$) in the 15 mg ivabradine group compared with those in the standard anti-heart failure therapy group.23 Lopatin, et al.24 also postulated a similar conclusion. Altogether, the above analyses indicated that the treatment with added ivabradine was beneficial for the long-term prognosis of patients with HF and did not induce cardiovascular death. Therefore, we analyzed the RRs of admission to hospital, and the result showed a decrease ($P = 0.0002$) (Figure 3A). The study by Zugck, et al. also found that the proportion of patients hospitalized within 1 year decreased from 23% before treatment to 5% with ivabradine therapy. Hence, the treatment with 5-7.5 mg ivabradine decreased the occurrence of cardiovascular events, especially heart failure relapse and hospitalization.

**Side effects and adverse events:** Treatment with ivabradine did not change the RR of serious adverse events compared to the RR of the standard anti-heart failure therapy group ($RR = 0.97$, 95% CI: 0.90-1.04, $P = 0.40$) (Figure 3B). Thus, we can speculate that the treatment with ivabradine does not affect adverse events. Furthermore, we analyzed adverse events such as cardiac dysfunction and nervous system disorders and found that the RRs were also decreased ($RR = 0.92$, 95% CI: 0.83-1.01, $P = 0.07$), ($RR = 0.81$, 95% CI: 0.65-1.00, $P = 0.06$) (Figure 3B). Notably, the RR of visual symptoms in the ivabradine group was significantly higher than that of the standard anti-heart failure therapy group ($RR = 3.82$, 95% CI: 1.80-8.13, $P = 0.0005$) (Figure 3B). Herein, we did not evaluate the possibility of ivabradine-mediated bradycardia adverse events. The included studies did not demonstrate a significant effect on blood pressure upon treatment with the addition of 5-7.5 mg ivabradine. The study by Sen, et al. showed that treatment with ivabradine significantly reduced the stroke rate (1.9% versus 5.4%, $P < 0.004$). However, the study by Chumburidze, et al. found that the adverse cardiovascular events were not increased significantly in the ivabradine treatment group. Moreover, adverse drug reactions were noted in 26 patients (3%) receiving long-term treatment with ivabradine (> 12 months), whereas the results in 767 CHF patients supported the relative safety of ivabradine.25

**Discussion**

Heart rate (HR) is a potentially modifiable cardiovascular risk factor for CHF patients.26 The clinical benefit is associated with the degree of reduction in HR.27 Compared to patients with HR < 70 bpm, patients with HR > 70 bpm showed an increased risk of cardiovascular death (34%), and the admission rate for heart disease increased 53% in the patients with coronary artery disease (CAS) and left ventricular dysfunction.28

The If current is the current to the heart during the cardiac action potential, and the inflow ion is mainly Na+, which is the main pacing current of the sinus node. Ivabradine specifically blocks the If channel and inhibits the If current in a dose-dependent manner, thereby extending the phase 4 depolarization interval and slowing the heart rate during rest or exercise. Compared with traditional heart rate slowing drugs such as beta blockers, ivabradine only specifically acts on the sinoatrial node, has no significant effect on atrial, atrioventricular or ventricular conduction time, and showed no significant effect on myocardial contractility or ventricular repolarization. The study by Volterrani, et al. shows that using carvedilol alone, ivabradine alone, or the combination of ivabradine with carvedilol could enhance the exercise tolerance and quality of life in patients with CHF.29 The study by Abdel-Salam confirmed that the ratio of total exercise duration > 6 minutes was increased in the ivabradine-treated group.30 Moreover, the studies of Mansour, et al.31 and Sarullo, et al.32 confirmed that the exercise endurance time of patients was extended to 2.5 minutes and 13.1 minutes, respectively, in the ivabradine treatment group versus the standard anti-heart failure therapy group. The effect of enhancing patient exercise tolerance might be associated with the different pharmacological effects of ivabradine and β-blockers.45,46 Unlike β-blockers, ivabradine preserved the exercise-induced vasodilatation and increased the blood flow volume,33 coronary blood flow, and LVEF simultaneously.

The study by Abdel-Salam on the effect of HR showed that the resting HR was negatively correlated with the total exercise duration ($r = −0.377$, $P = 0.024$) and positively correlated with the Minnesota questionnaire score ($r = 0.316$, $P = 0.047$).33 The SHIFT study showed that treatment with ivabradine exerted a protective effect of a reduced HR, with adequate event-free survival in those with an HR of 60 bpm.40 Moreover, short-term treatment with 5-7.5 mg ivabradine also improved the exercise capacity in patients with HFpEF.37 This finding was consistent with the increase in left ventricular filling pressure and the decrease in E/e during exercise. Also, ivabradine specifically reduced HR and led to increased coronary flow reserve and myocardial perfusion by increasing the diastolic pressure, which decreased the myocardial oxygen demand and improved the oxygen supply. Therefore, treatment with ivabradine reduced the HR at rest and during exercise and improved the LVEF and left
ventricular dysfunction (LVD), thus increasing the exercise capacity in CHF patients.

Patients with heart failure are characterized by symptoms of dyspnea and exercise intolerance, both of which directly reduces the quality of life of the population. If channel inhibitors reduce heart rate and have no negative inotropic effects. A high heart rate during exercise may be particularly detrimental by shortening diastolic filling time and promoting LV increase. Ivabradine reduces the LV filling period by lowering the heart rate, which can reduce

Figure 3. A: Cardiovascular composite endpoint event; B: Side effects and adverse events.
the elevated filling pressure and the resulting breathing difficulties. The study showed that treatment with ivabradine could safely and efficiently improve the exercise capacity and quality of life in patients with CHF. The studies by Abdel-Salam, Mansour, et al., and Sarullo, et al., confirmed that the Minnesota score of patients increased by 4 (P < 0.05), 2.6 (P < 0.023), and 6 (P < 0.001), respectively, in the ivabradine group versus the placebo group. The study on the quality of life of CHF patients showed that ivabradine reduced the HR by 10.1 bpm (P < 0.001) and improved the Kansas City Cardiomyopathy Questionnaire (KCCQ) results by 1.8 for the clinical summary score (CSS) and by 2.4 for the overall summary score (OSS) (P < 0.02 and P < 0.01, respectively); these changes were associated with the changes in HR for both CSS (P < 0.001) and OSS (P < 0.001). In the ivabradine treatment group, the health-related quality of life at follow-up was better preserved. The studies by Tumasyan, et al., Mircheva, et al., and Speranza, et al., confirmed that compared to the standard anti-heart failure treatment, ivabradine decreased the levels of brain natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) at rest and improved the rate of heart failure and quality of life in patients with CHF.

Ivabradine also interacts with the Ih current in the retina. The Ih current is similar to the heart’s current, which is involved in the regulation of the transient resolution of the visual system by reducing the response of the retina to bright light stimuli. Under induced conditions (such as rapid changes in light intensity), partial inhibition of the Ih current by ivabradine leads to occasional illusion of light in the patient, manifesting as a transient increase in brightness in a localized area of the field of view. The side effects of this visual impairment are easily overlooked in previous meta-analyses and clinical studies.

According to the guideline, for symptomatic heart failure patients (NYHA grade II-III) with a stable, chronic decrease in ejection fraction (LVEF ≤ 35%) who have received the maximum tolerated dose of β-blockers to treat a sinus rhythm with HR ≥ 70 bpm, ivabradine treatment could reduce the rate of hospitalization due to heart failure. Our study also found that ivabradine is suitable for patients with heart failure who are still at high HR after application of β-blockers (ideal heart rate is 55-60 bpm at rest), regardless of whether the ejection fraction is preserved or not. Lakobishvili, et al. conducted an observational study of 550 patients and found that approximately only a quarter of the patients were apparently suitable for consideration for ivabradine treatment. After a 12-month follow-up, 76.1% of the patients using ivabradine combined with β-blockers received at least half of the target dose of β-blockers compared to the 65.5% who received this dose in the only β-blockers group (P < 0.05). Another study proved that a proportion of patients with heart failure and SHIFT-like characteristics may potentially benefit from ivabradine treatment. Thus, a substantial improvement in β-blocker therapy can be achieved by initiating treatment with ivabradine. Furthermore, CHF patients treated with the maximum dose of β-blocker may potentially benefit from the treatment with ivabradine. It is noteworthy that, in most studies, especially in the SHIFT study and the BEAUTIFUL study, ivabradine efficacy was obtained in patients who had received standard anti-heart failure treatment, and the use rate and dosage of the beta blocker were far superior to the real world.

Conclusions

Unlike the results of a previous meta-analysis and systematic review, ivabradine did not reduce the risk of death and hospitalization for heart failure, and no difference was found in safety between ivabradine and placebo. Our current results are positive and optimistic. Presently, the evidence shows that adding ivabradine led to significant improvements in cardiopulmonary function, such as reduced heart rate, increased LVEF, reduced VE/VCO₂, improved peak VO₂, and increased exercise capacity in patients with CHF. Moreover, using ivabradine with the standard anti-heart failure treatment reduced the mortality and hospitalization and improved the quality of life. In addition, ivabradine significantly increased the RR of visual symptoms, thereby rendering ivabradine relatively safe in patients with CHF.

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Disclosures

Conflicts of interest: None.
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**Supplemental Files**

Supplementary Figures 1, 2
Please see supplemental files;
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