Original Article

Effectiveness and safety of ivabradine in the treatment of acute myocardial infarction: a systematic review and meta-analysis

Bo Wang[1#], Xiaoxia Zhang[2#], Jun Chen[3], Shixiong Chen[4], Qinghua Chen[4], Senyan Yang[5], Qiugui Wang[2]

[1]Department of Emergency, Hainan General Hospital (Hainan Affiliated Hospital of Hainan Medical University), Haikou, China; [2]Department of Internal Medicine, Danzhou People's Hospital, Danzhou, China; [3]Department of Intensive Care Unit, Danzhou People's Hospital, Danzhou, China; [4]Department of Internal Medicine-Cardiovascular, Danzhou People's Hospital, Danzhou, China; [5]Department of Cardiothoracic Oncology Surgery, Danzhou People's Hospital, Danzhou, China

Contributions: (I) Conception and design: B Wang, X Zhang, Q Wang; (II) Administrative support: B Wang, Q Wang; (III) Provision of study materials or patients: J Chen, S Chen, Q Chen, S Yang; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: B Wang, X Zhang, S Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Qiugui Wang. Department of Internal Medicine, Danzhou People's Hospital, 21-1 Nada Town Datong Road, Danzhou 571700, China. Email: wangqiugui8853@163.com.

Background: Cardiovascular diseases have become a prominent threat to public health and quality of life. In recent years, some studies have reported that ivabradine can improve the cardiac function and prognosis of patients with acute myocardial infarction (AMI).

Methods: We searched China National Knowledge Infrastructure (CNKI), Wanfang database, Chinese Biomedical Literature (CBM), Chongqing Weipu Chinese Sci-tech Journal Database (VIP), PubMed, Cochrane Library, and EMBASE for randomized controlled trials (RCTs) of ivabradine in the treatment of AMI from January 1980 until December 2020. Each RCT was systematically reviewed.

Results: A total of 7 RCTs with 658 patients were included. Compared with the control group, the heart rate [mean deviation (MD) =−9.20, 95% confidence interval (CI): −13.03 to −5.38, P<0.00001] and brain natriuretic peptide (BNP) (MD =−112.73, 95% CI: −186.12 to −39.35, P=0.003) of patients who received ivabradine combined with conventional standard treatment were significantly lower and left ventricular ejection fraction (LVEF) (MD =3.17, 95% CI: 2.12 to 4.23, P<0.00001) was significantly better. The difference in adverse events was not statistically significant [odds ratio (OR) =2.45, 95% CI: 0.92 to 6.55, P=0.07].

Discussion: Ivabradine combined with β-blockers can reduce the resting heart rate and improve heart function in patients with AMI while not increasing adverse events. However, due to limitations in the number and quality of studies included, our conclusions need to be further confirmed by analyzing more studies.

Keywords: Ivabradine; myocardial infarction; meta-analysis

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Introduction

Cardiovascular diseases have become a prominent threat to public health and quality of life. As one of the most serious cardiovascular diseases, acute myocardial infarction (AMI) changes rapidly, comes with serious complications, and is characterized by high mortality (1). Therefore, controlling the heart rate has garnered increasing attention in the clinical treatment of AMI (2,3). In standard treatment, β-blockers are the most widely used drugs to control heart rate, they can block the heart's beta receptors and lower

the heart rate, thus improving the prognosis of patients with AMI (4,5). Beside β-blockers, ivabradine can decrease the heart rate by prevention of upregulation of IF current, downregulating the sinoatrial node rhythm, and controlling the interval between the continuous cardiac action potential duration (6). In recent years, both local and international studies have reported that ivabradine can improve the cardiac function and prognosis of patients with AMI, however the research has been limited by small sample sizes of single-center studies, and inconsistent treatment courses, follow-up time, and results. Therefore, we aimed to evaluate the efficacy and safety of ivabradine in the treatment of AMI in this meta-analysis by systematically reviewing relevant local and international clinical studies of recent years, providing evidence for guiding the treatment of AMI. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-21-563).

Methods

Criteria for inclusion and exclusion

Study type

We included randomized controlled trials (RCTs) published in China and internationally. Studies were restricted to those published in Chinese and English.

Participants

The diagnosis of AMI in all participants met the 2007 Chinese Medical Association Cardiovascular Branch (7) and the 2007 American Heart Association/American College of Cardiology (8) diagnostic criteria, regardless of age and gender.

Intervention

The experimental group was treated with ivabradine combined with the standard regime, and the control group was treated with the standard regime, with no restrictions on the dose and course of treatment.

Outcome measures

(I) Heart rate; (II) left ventricular ejection fraction (LVEF); (III) pro-brain natriuretic peptide (NT-proBNP); (IV) occurrence of adverse reactions.

Exclusion criteria

(I) Non-RCT studies; (II) studies published in neither Chinese nor English languages; (III) duplicate studies, experience summaries, case reports, reviews, studies with incomplete information, animal experiments, meeting minutes; (IV) studies with fewer than 15 cases; (V) the loss rate of the subjects was >20%.

Search strategy

The databases searched included: (I) China National Knowledge Internet (CNKI); (II) Wanfang database; (III) Chinese Biomedical Database (CBM); (IV) Chongqing Weipu Chinese Sci-tech Journal Database (VIP); (V) PubMed; (VI) the Cochrane Library; (VII) Embase. Chinese search terms used were "acute myocardial infarction", "ivabradine", and so on. English search terms used were "acute myocardial infarction", "cardiovascular stroke", "heart attack", "myocardial infarct", and "ivabradine".

Data extraction and quality assessment

The Cochrane risk of bias assessment tool (9) was used to evaluate the quality of RCT. Items which we evaluated included: random allocation method, concealment of allocation, blinding method, integrity of resulting data, selective report research results, and other sources of bias.

Data extraction

General information (researchers, year of publication, countries, age of cases, sample size), intervention measures for experimental and control group, outcome indicators [heart rate, LVEF, brain natriuretic peptide (BNP) precursor, adverse events], and so on, was extracted independently by two of the investigators. Any disagreement was resolved through discussion with a third investigator. When relevant data was missing or unclear, we attempted to contact the original author for complete data, and studies without data available were excluded.

Statistical method

The statistical software RevMan version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen) was used for data analysis. Odds ratio (OR) and 95% confidence interval (CI) were used as the effect value of the count data, and the mean difference (MD) and 95% CI were used as the effect value of the measurement data. Firstly, a Q test was conducted: (I) when P>0.10 and

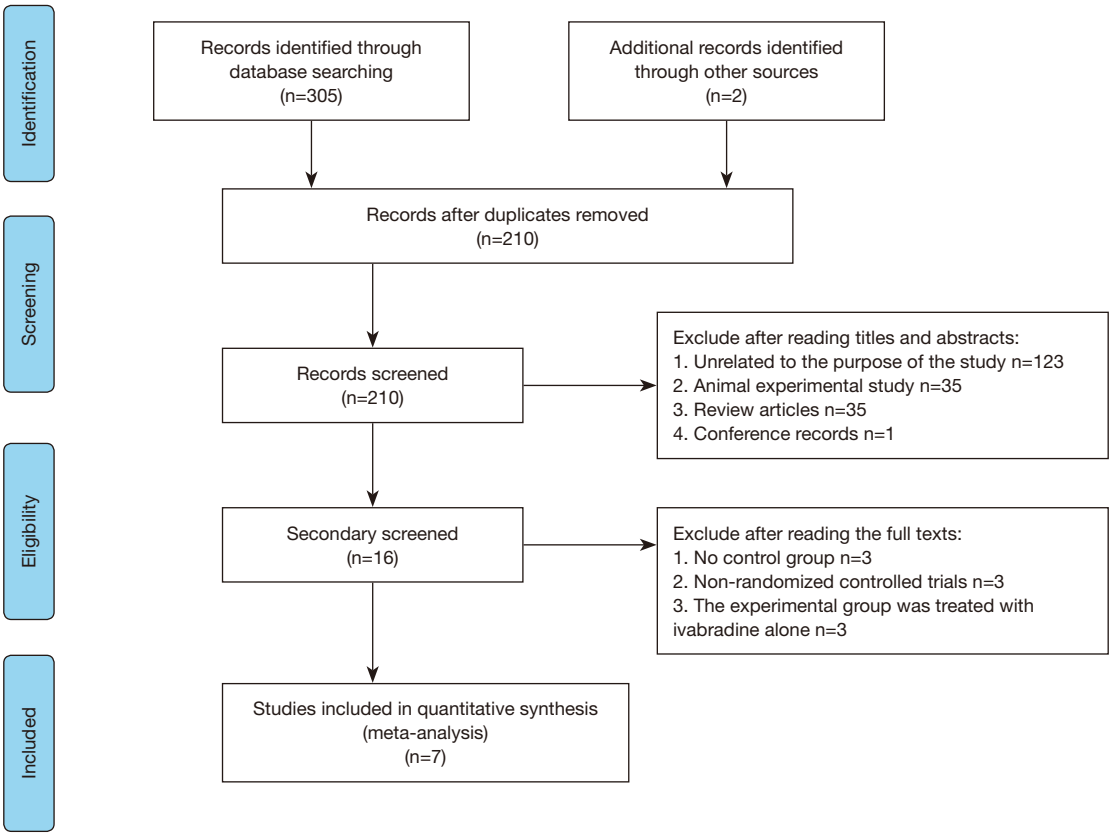

Figure 1 Study selection.

$I^2 \leq 50\%$, there was no significant statistical heterogeneity; the data was thereby analyzed with a fixed effect model in RevMan 5.3; (II) when $P \leq 0.10$ and $I^2 > 50\%$, there was a significant statistical heterogeneity; the data was thereby analyzed with a random effects model in RevMan 5.3; (III) when $P < 0.05$, there was a statistical difference.

Results

Characteristics of articles

A total of 307 articles were identified from manual and bibliography searches through the databases. After removal of 97 duplicates in our primary search, 123 irrelevant articles, 35 experimental animal studies, 35 reviews, and 1 meeting minutes were excluded by screening for title and abstract. The remaining 16 articles were re-screened by full-text screening. There were 3 articles without a control group, 3 non-RCTs, and 3 articles with an experimental group treated with ivabradine alone. After the step-by-step screening (*Figure 1*), 7 articles (*Table 1*) (10-16) were eventually included. The baseline comparability was "comparable".

Evaluation of the methodological quality of the studies

All studies (10-16) were RCTs; 1 study (10) applied the computer stochastic method; 6 studies (11-16) reported the random number table method for grouping; 1 study (10) used allocation concealment methods; 1 study (10) mentioned that the investigator and the subjects were blinded; all studies (10-16) contained complete outcome data; all studies (10-16) did not selectively report the results; all studies (10-16) did not mention other sources of bias (*Figures 2,3*).

Meta-analysis results

Heart rate

A total of 6 studies (10-15) (499 patients) reported improved heart rate with ivabradine combined with standard treatment of AMI and statistical heterogeneity

Table 1 General information of included studies

Authors (publication year)	Country	Cases		Age ($\bar{x}$±s), years		Intervention		Follow-up time	Outcomes
		Experimental group (male/female)	Control group (male/female)	Experimental group	Control group	Experimental group	Control group		
Francesco Barillà 2016, (10)	Switzerland	30 (21/9)	28 (18/10)	56.3±9.7	54.4±10.4	Ivabradine + standard therapy	Standard treatment	4 months	(I), (IIII)
Jiadong Fu 2020, (11)	China	34 (28/6)	34 (27/7)	63.62±4.37	63.50±4.31	Ivabradine + standard therapy	Standard treatment	Not described	(I), (IV)
Jing Liu 2020, (12)	China	56 (33/23)	56 (36/20)	63.7±9.7	63.2±11.7	Ivabradine + standard therapy	Standard treatment	6 months	(I), (II), (IV)
Wenying Zhang 2020, (13)	China	32 (31/1)	34 (33/1)	51.28±9.42	51.50±9.55	Ivabradine + standard therapy	Standard treatment	90 days	(I), (II), (IV)
Zhen Yang 2019, (14)	China	67 (45/22)	68 (46/22)	66.31±8.53	65.18±8.37	Ivabradine + standard therapy	Standard treatment	2 weeks	(I), (II), (III)
Chenchen Shen 2019, (15)	China	25 (15/10)	25 (13/12)	53.2 [44–67]	51.7 [45–63]	Ivabradine + standard therapy	Standard treatment	Not described	(I), (III)
Shengda Hu 2018, (16)	China	85 (82/3)	84 (81/3)	63.9±17.2	62.1±16.7	Ivabradine + standard therapy	Standard treatment	Not described	(II), (IV)

(I) Heart rate; (II) left ventricular ejection fraction (LVEF); (III) brain natriuretic peptide precursor (NT-proBNP); (IV) the occurrence of adverse reactions.

was observed (P<0.00001, I^2=88%). The random effects model combined with effect size was used for analysis. As a result, ivabradine combined with standard treatment could significantly reduce heart rate (MD =–9.20, 95% CI: –13.03 to –5.38, P<0.00001) (*Figure 4*). As for sensitivity analysis, no directional changes were observed after the removal of individual studies, suggesting that the results of this study were basically stable (*Table 2*).

Left ventricular ejection fraction (LVEF)

A total of 4 studies (12,13,15,16) (482 participants) reported improved LVEF with ivabradine combined with standard treatment of AMI and no statistical heterogeneity was observed (P=0.39, I^2=1%). The fixed-effect model combined with effect size was used for analysis. As a result, ivabradine combined with conventional standard treatment could significantly improve LVEF (MD =3.17, 95% CI: 2.12 to 4.23, P<0.00001). The difference between the two groups was statistically significant (*Figure 5*).

NT-proBNP

A total of 3 studies (10,14,15) (243 participants) reported improved BNP with administration of ivabradine combined with conventional standard treatment of AMI and no statistical heterogeneity was observed (P=0.61, I^2=0%). The fixed-effect model combined with effect size was used for analysis. As a result, ivabradine combined with conventional standard treatment could significantly reduce

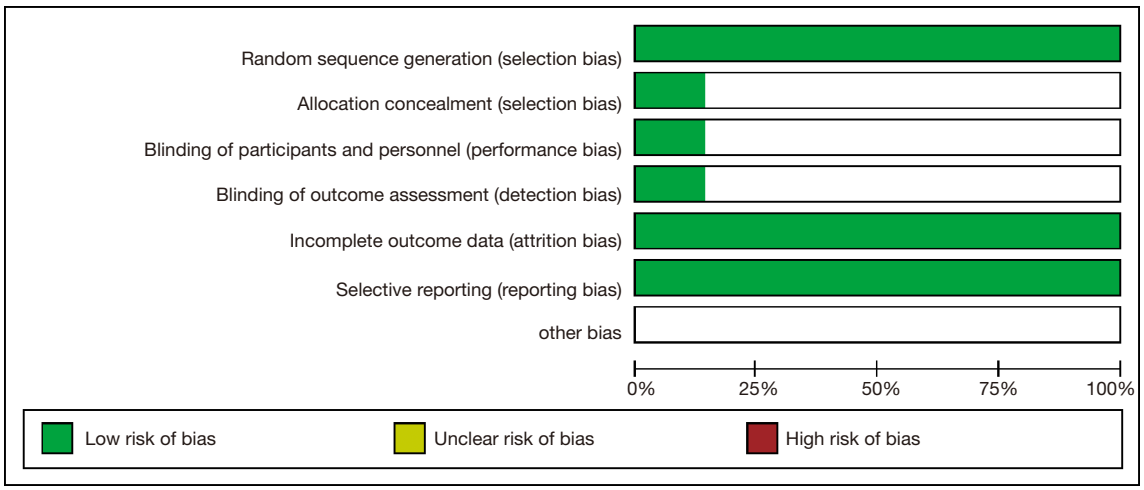

Figure 2 Bar chart of bias risk.

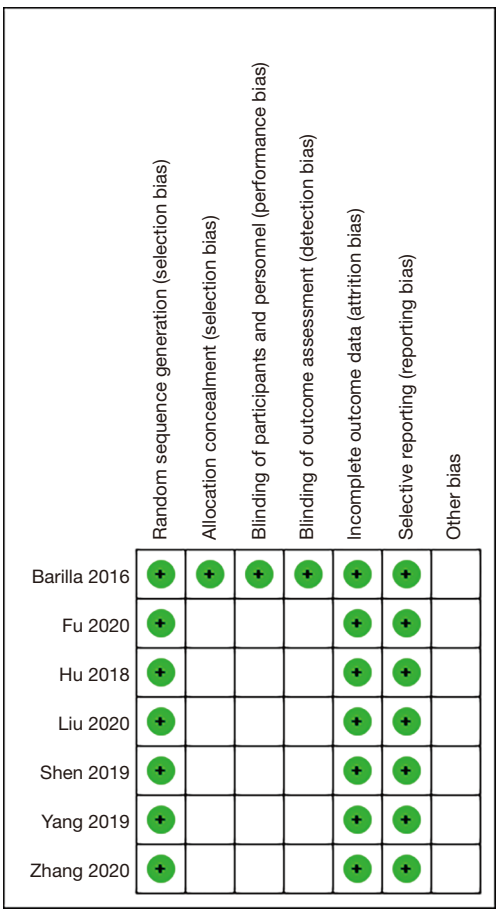

Figure 3 Bias risk chart.

BNP (MD =–112.73, 95% CI: –186.12 to –39.35, P=0.003). The difference between the two groups was statistically significant (*Figure 6*).

Adverse reactions

A total of 4 studies (11,12,13,16) (407 participants) reported adverse events resulting from administration of ivabradine combined with conventional standard treatment of AMI and no statistical heterogeneity was observed (P=0.91, I^2=0%). The fixed-effect model combined with effect size was used for analysis. As a result, there was no statistically significant difference of adverse events between the two groups (OR =2.45, 95% CI: 0.92 to 6.55, P=0.07) (*Figure 7*).

Discussion

With the development of society, environmental and human lifestyle changes, the incidence of AMI has increased over recent years, even affecting younger generations and becoming one of the critical causes of death and disability (17). As an independent risk factor of cardiovascular diseases, the increase of resting heart rate is positively associated with the mortality of cardiovascular events from AMI (18,19), which leads to the increase of myocardial oxygen consumption amount, the decrease in coronary artery perfusion, causes myocardial ischemia, an increase in the number of necrotic myocardial cells and the reduction of myocardial compliance, which could

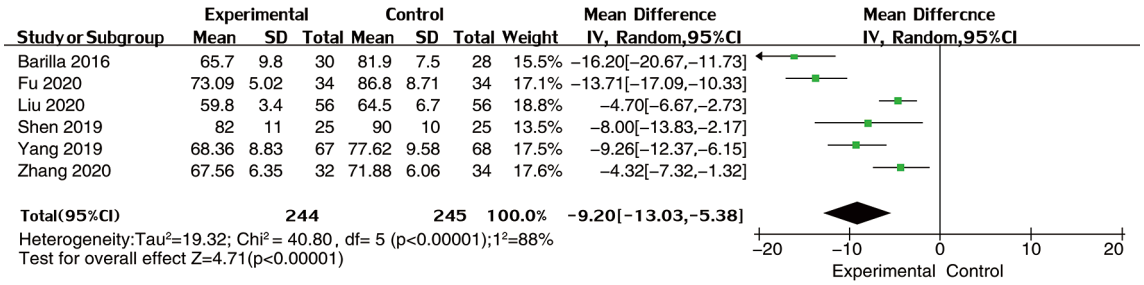

Figure 4 Forest plot of meta-analysis of heart rate in two groups.

Table 2 Results of sensitivity analysis

Excluded studies	Number of cases after exclusion of studies	Heterogeneity		Combined model	MD (95% CI)	P value
		P value	I^2 (%)			
Francesco Barillà 2016	431	<0.0001	84	Random effect	−7.88 (−11.44, −4.33)	<0.0001
Jiadong Fu 2020	421	<0.0001	85	Random effect	−8.22 (−12.03, −4.42)	<0.0001
Jing Liu 2020	377	<0.0001	85	Random effect	−10.25 (−14.54, −5.95)	<0.0001
Wenying Zhang 2020	423	<0.00001	89	Random effect	−10.27 (−14.75, −5.78)	<0.00001
Zhen Yang 2019	354	<0.00001	90	Random effect	−9.24 (−13.95, −4.52)	<0.00001
Chenchen Shen 2019	439	<0.00001	90	Random effect	−9.41 (−13.72, −5.11)	<0.00001

MD, mean difference; CI, confidence interval.

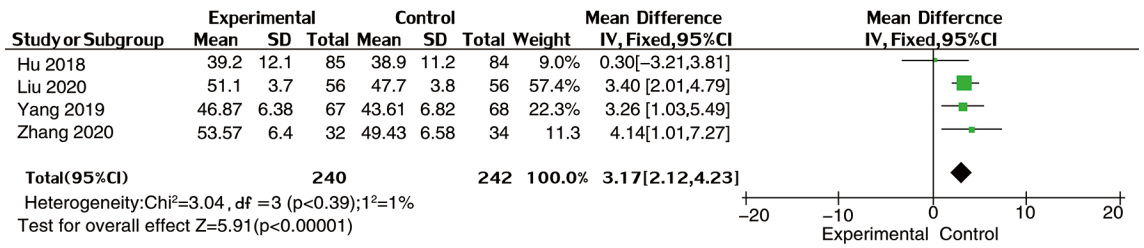

Figure 5 Forest plot of meta-analysis of LVEF in two groups. LVEF, left ventricular ejection fraction.

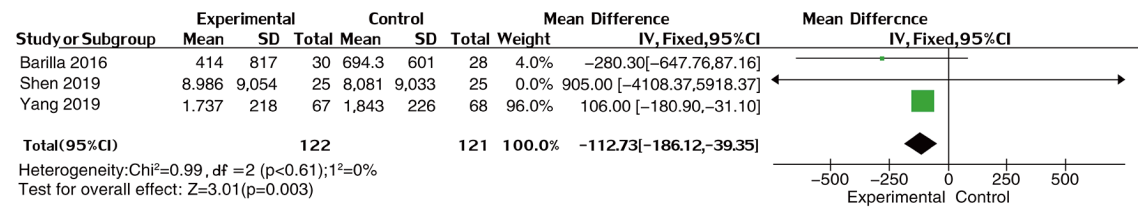

Figure 6 Forest plot of meta-analysis of NT-proBNP in two groups. NT-proBNP, N-terminal pro-brain natriuretic peptide.

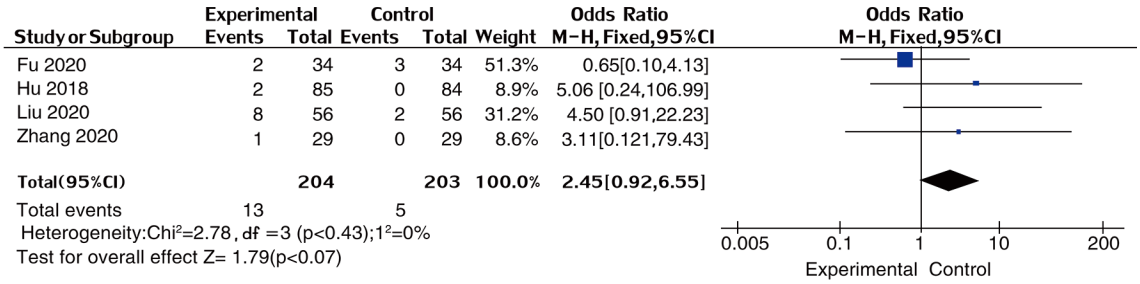

Figure 7 Forest plot of meta-analysis of adverse reactions in two groups.

further cause the heart myocardial remodeling and cardiac function failure (20). Therefore, active clinical control of the resting heart rate has become one of the most important methods for treating AMI (21). Although β-blockers are clinically used to slow down the heart rate, effects such as negative conduction, negative muscle strength, and lower blood pressure, and side effects and contraindications all require consideration with the clinical application of these drugs (22), which limits its clinical application. Ivabradine, a pacemaker I_f current inhibitor, can specifically reduce the rhythm of sinus nodules and slow the heart rate with no additional effects such as negative muscle strength and blood pressure reduction (23,24). Besides, other drugs, such as beta-blockers, are slower to control heart rate, because the dosage of them need to increase step by step, while ivabradine can more quickly and efficiently control the heart rate without worsening cardiac function (25). The advent of ivabradine has brought a new hope to patients with AMI.

A total of 7 RCTs and 658 participants were included in this meta-analysis. Compared with the control group, the heart rate (MD =−9.20, 95% CI: −13.03 to −5.38, P<0.00001) and BNP (MD =−112.73, 95% CI: −186.12 to −39.35, P=0.003) of the ivabradine combined with conventional standard treatment group were significantly lower and LVEF (MD =3.17, 95% CI: 2.12 to 4.23, P<0.00001) was significantly improved. There was no statistically significant difference in adverse events (OR =2.45, 95% CI: 0.92 to 6.55, P=0.07). In fact, the safety of ivabradine has been proven in a number of studies and clinical trials. The most common side effects were sinus bradycardia and transitory visual symptoms.

The mechanisms of ivabradine reducing the resting heart rate and improving cardiac function in patients with AMI are as follows: (I) ivabradine can bind to the sinus node I_f channel to inhibit the I_f current, reduce the sinus node autonomy, and slow down the heart rate (26,27); (II) slowing down the heart rate can prolong the diastolic period, increase myocardial oxygen supply and coronary perfusion, increase cardiac output, and improve cardiac function; (III) heart rate is positively correlated with ventricular volume and heart rate reduction can reduce ventricular volume load, reduce myocardial work and oxygen consumption, and improve exercise tolerance (28,29). Formed by the degradation of BNP precursor secreted by ventricular myocytes, NT-proBNP is negatively correlated with LVEF and reflects the changes of cardiac function in patients with AMI (30), which can be reduced by ivabradine via improved cardiac function. As reported, heart rate reduction with ivabradine improved outcomes independently of HF duration (31). Reducing HR with ivabradine reduced the rate of cardiovascular death and hospitalization for worsening heart failure in left-ventricular systolic dysfunction but among patients who had stable coronary artery disease without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve 3-month survival rate (32,33).

There were some limitations to this meta-analysis: (I) some studies were without specific randomization methods, allocation concealment, blinding, and so on, and some studies did not mention the reasons for loss to follow-up and withdrawal despite the large sample size included; (II) there might have been a language bias since only English studies were included; (III) the small sample size of a single RCT may have been insufficient to test; only small number of studies were associated with each outcome index; it was not possible to carry out subgroup analysis to evaluate each outcome index; an explanation of heterogeneity was lacking; (IV) the follow-up times were different and not recorded in different studies, and the follow-up time of some studies was too brief. The factors above may affect the accuracy of conclusions of this meta-analysis. More high quality double-

blind randomized studies are needed to unify the duration of follow-up and the duration of medication to solve the above problems.

To conclude, ivabradine combined with β-blockers can reduce the resting heart rate and improve heart function in patients with AMI, and the combination is safe and reliable. Our conclusions require further confirmation through analysis of more high-quality studies and more high quality double-blind randomized studies need to be carried out.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/apm-21-563

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-21-563). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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