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Original Research

Efficacy and Safety of Ivabradine in Arrhythmias: A Systematic Review

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Abstract

Background: Treating arrhythmia adequately is crucial to prevent cardiac morbidity and mortality. Previous studies report that ivabradine may increase the risk of atrial fibrillation; however, emerging evidence shows that the drug may have beneficial effect in treatment of arrhythmia. **Purpose:** The present research explored the clinical evidence regarding the clinical efficacy and safety of ivabradine to treat arrhythmias. **Method:** A comprehensive literature search was conducted using MEDLINE, EMBASE, Scopus, Google Scholar and Web of Science databases. Full text articles that report on the use of ivabradine in human subjects with arrhythmia are included. Studies not written in English language and those not published in the period between 2016 and May 2021 were excluded. **Results and discussion:** Eight articles were included in the current review after screening a total of 1100 articles. The studies depicted that ivabradine is effective in improving ventricular rate, heart rate, and sinus rhythm in atrial fibrillation and has limited or no side effects. In addition, the findings indicate that combining ivabradine with other medications is more effective for improving the ventricular rate and maintain sinus rhythm than when used alone. **Conclusion:** Ivabradine alone or in combination with other medications can therefore be used as a potential treatment for arrhythmias.

Keywords: ivabradine; arrhythmia; atrial fibrillation; ventricular rate; sinus rhythm

INTRODUCTION

Arrhythmia is associated with adverse cardiac outcomes. A total of 30-50% of New York Heart Association Patients, who had arrhythmia succumbed to cardiac mortality.[1,2] Atrial fibrillation (AF), a type of arrhythmia, is related to high mortalities, hospitalization rates, and high treatment costs.[3] In addition, if a patient has heart failure (HF) and develops ventricular arrhythmia (VA), they become at risk of pump failure death, premature mortality, and hemodynamic decomposition.[4]

Most anti-arrhythmic medications were reported to work through heart rate control mechanisms.[5] Examples of traditional antiarrhythmic drugs include digoxin, beta-blockers, Calcium Channel Blockers, etc. Beta blockers are not safe in patients with unstable cardiovascular diseases[6] while digoxin may not reduce hospitalization rate and mortality.[7] Therefore, it is vital to find an alternative medication, which are more effective and have less adverse effects when treating arrhythmia. Ivabradine by inhibiting HCN, selectively blocks the I*f* current in the sinus node. Through this mechanism the drug reduces heart rate without appreciable effects on blood pressure. Ivabradine is licensed for use as an antianginal medication and heart rate-lowering agent in selected patients with heart failure.[8] Beneficial effect of ivabradine to improve quality of life, reduce mortality and to significantly lower heart rate was reported in the SHIFT study[9] and the BEAUTIFUL holter study.[10] Ivabradine may cause sinus bradycardia and transitory visual symptoms, AF, high or low blood pressure. Hence it is contraindicated in patients with acute MI, blood pressure below 90/50 mmHg, sick sinus syndrome, unstable angina and in pregnant patients that have a HR below 70bpm.[13] Additionally, Ivabaradine may be unsafe if it is combined with hazardous HR control drugs such as verapamil or diltiazem.[13]

The link between Ivabradine and arrhythmia is ambiguous. While some studies showed ivabradine may be beneficial in the treatment of arrhythmia others reported the drug may increases the risk of atrial fibrillation.[5,11,13] Therefore, this systematic review is conducted to assess the evidence on safety and efficacy of Ivabradine use in arrhythmia treatment and to compare its efficacy with other HR controlling agents used in the treatment of arrhythmia.

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METHODOLOGY

A Preferred Reporting Item for Systematic Review and Meta-analyses (PRISMA) guideline was followed for the conduct of this systematic review.[14]

Search strategy

A literature search process was performed to obtain the relevant studies for review. Five reputable electronic databases were utilised to locate the articles, and they included MEDLINE, Scopus, EMBASE, Google Scholar, and the Web of Science. The keywords used for the search were (Ivabradine)

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OR (HCN channel inhibitor) AND (randomised controlled trials) OR (RCTs) AND (arrhythmia) OR (atrial fibrillation) OR (Atrial flutter) OR (paroxysmal supraventricular tachycardia) OR (ventricular arrhythmias) OR (ventricular fibrillation) OR (ventricular tachycardia) OR (inappropriate sinus tachycardia) AND (high blood pressure) OR (hypertension) AND (luminous phenomena).

Selection of eligible studies

The following inclusion criteria was used for identification and selection of eligible studies:

Study's design: Randomised controlled trial

Study's population: human subjects with arrhythmia treated with ivabradine

Study's objective: To compare the effect of Ivabradine with any other active treatment or placebo on arrhythmias.

Publication type: The full text article published in English between the period of 2016 to 30th, May 2021.

The following criteria were used for exclusion of studies:

The study's design: not a randomised controlled trial, that is, non-original studies like reviews, meta-analysis, and those investigating outcomes other than heart rate reduction with Ivabradine.

The study's population: not involving human subjects.

The study's objective: not to compare the effect of Ivabradine with any other active treatment or placebo on arrhythmias.

Publication type: Articles whose full text could not be obtained by the researchers.

Quality assessment

Based on quality assessment, eligible studies obtained from the databases were evaluated using the Cochrane risk of bias tool.[16] Thus, Cochrane risk of bias assessment for RCTs was used based on the seven domains of generation of sequence and allocation concealment, blinding of study participants, incomplete data outcomes, selective reporting of research findings, and the auxiliary part. Each domain in the Cochrane tool was scored as low, high, or unclear risk of bias or quality (Tables 1A to 1E).[16]

Data extraction and synthesis

Data extracted entailed evaluation of study population, intervention, comparison and outcome measures. The dose and duration of Ivabradine used, the adverse events related to drug use, and the primary outcomes, including changes in heart rate were assessed. Descriptive information, such as the authors' names, study design, characteristics of study population, data analysis method, and the intervention under study were also extracted. Data synthesis focuses on summarising the information presented in the articles that met inclusion criteria.[15] In this review, the main points were summarized through narrative synthesis and tables. Based on this narrative analysis, information from the existing literature was used to explain the clinical efficacy and effectiveness of treating arrhythmias with ivabradine.

RESULTS

A total of 1100 articles were found from the selected databases. Out of these articles, 8 published studies were eligible for review based on the selection criteria used as shown in the PRISMA flow diagram presented in Figure 1. The quality assessment of the included studies using the Cochrane risk of bias assessment tool is presented in Tables 1A to 1E while the characteristics of all the studies included for review and their findings are presented in Table 2.

Clinical efficacy and safety of ivabradine on ventricular rate

In an RCT of 32 adult patients with non- paroxysmal atrial fibrillation, patients were assigned to treatment groups of 5 mgs of ivabradine twice a day for one month and placebo group. The outcome measures on ventricular rates were assessed in 24 hours.[11] The study's findings showed a significant reduction

Table 1A. Summary table of eligible studies included for review

Author/Year	Design	Sample Size	Treatment group	Comparator	Duration of treatment	Main efficacy outcome	Findings
Wongcharoen et al. [11]	RCT	32 adult patients	Ivabradine, 5 mg twice a day (treatment group, n = 21)	placebo (n = 11)	1 month/4 weeks	Ventricular rate	Decreased ventricular rate following administration of 5 mg of Ivabradine (6.0 ± 10.9 beats/min to 79.2 ± 9.6 beats/ min(p<0.001) No significant changes observed in placebo group (84.3 ± 11.2 vs.82.9 ± 9.9 beats/min, p = 0.469)
Fischer-Rasok at et al. [19]	RCT	24 patients with CAD and normal LV ejection fraction on chronic beta-blocker therapy	Beta-blocker (metoprolol, bisoprolol, carvedilol, and nebivolol and Ivabradine (average daily dosage 13.0±2.6 mg)	Placebo received Beta-blockers	Six weeks	Left ventricular filling pressures and stroke volume	Ivabradine therapy reduced left ventricular pressure in patients with a high left ventricular filling index (10.7±2.9 vs 8.9±1.7; p<0.01) No significant change observed in patients with low left ventricular filling index (6.4±0.7 vs 6.5±1.1; p=ns)

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Table 1B. Summary table of eligible studies included for review

Author/Year	Design	Sample Size	Treatment group	Comparator	Duration of treatment	Main efficacy outcome	Findings
Lee *et al.* [20]	RCT	24 healthy volunteers	Ivabradine in the first treatment visit	placebo at the second treatment visit Ivabradine-placebo arm	28 days	Heart rates and analgesic effects	slower heart rate (difference of 10.10 beats/min, P-value <0.0001
Abdel-Salam Za *et al.* [21]	RCT	740 patients scheduled to undergo CABG Group 1, *n*=212 Group 2, *n*= 288) Group 3, *n*=240	**Group 1=** Ivabradine given perioperatively (48 hours preoperatively, then one week postoperatively **Group 2=** bisoprolol given preoperatively 5 mg bid **Group 3**= Ivabradine as before+bisoprolol 5 mg once daily	**Group 1=** Ivabradine given perioperatively (48 hours preoperatively, then one week postoperatively **Group 2=** bisoprolol given preoperatively 5 mg bid **Group 3**= Ivabradine as before+bisopro lol 5 mg once daily	30 days	Incidences of postoperative atrial fibrillation,	Significant reduction in the incidences of atrial fibrillation in group 3 (combined Ivabradine and bisoprolol) (P<0.001) than in group 1 and group 2 with 5.5%), and 12.2%, respectively
Fontenla *et al.* [23]	RCT	232 patients with uncontrolled d permanent atrial fibrillation	Ivabradine group (starting dose of 2.5mg/12h with the possibility of raising the dose to 5mg/12h)	Digoxin group (0.25mg/24 h dose)	Three months by 24-hour Holter monitoring	Reduction in daytime heart rate measured	Ivabradine is hypothesized to be effective in reducing heart rate in atrial fibrillation

Table 1C. Summary table of eligible studies included for review

Author/Year	Design	Sample Size	Treatment group	Comparator	Duration of treatment	Main efficacy outcome	Findings
Arvind *et al.* [24]	RCT	94 children aged ≤18 years Group 1, *n*=48 Group 2, *n*=46	Ivabradine group	Amiodarone group	Four weeks	Postoperative junctional ectopic tachycardia	Ivabradine is not more effective than amiodarone in converting postoperative junctional ectopic tachycardia to sinus rhythm. [P=0.36]
Komajda *et al.* [25]	RCT	179 patients Group 1, *n*=95 Group 2, *n*=84	Ivabradine group (7.5 mg)	Placebo group	241days	Heart rate and cardiac function	Ivabradine did not reduce heart rate and cardiac function [P=ns]. Thus, Ivabradine should not be used as a potential medication for heart failure patients.
Chobanyan-Jü rgens *et al.* [36]	RCT	Nineteen healthy normotensive men aged between 18–40 years, body	Ivabradine (7.5mg),	Metoprolol (95mg) and Placebo	Not stated	HCN4 inhibition with the administration of Ivabradine on atrial arrhythmias.	No differences in atrial events observed in the three treatments Ivabradine did not protect from atrial arrhythmias under
Tsutsui *et al* [41]	RCT	254 Japanese patients (127 ivabradine group and 127 placebo group) aged 20 years and over with stable symptomatic chronic heart failure and had received optimal treatment for heart failure	Ivabradine started at 2.5 mg twice daily and later adjusted at each visit in a range of 2.5–7.5 mg	Placebo received 2.5 mg of ivabradine twice daily	Follow up of 561 days for ivabradine and 549 days for placebo group	Reduction in cardiovascular death or hospital admission for worsening heart failure Heart failure deaths Reduction in myocardial infarction.	There was a significant reduction in heart failure in ivabradine group (5.2 vs. 6.1 beats/min, p<0.0001) No symptomatic bradycardia reported

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Table 1D. Summary table of eligible studies included for review

Author/Year	Design	Sample Size	Treatment group	Comparator	Duration of treatment	Main efficacy outcome	Findings
Nguyen *et al.* [44]	RCT	Nineteen patients with left ventricular ejection fraction below 40% presenting sinus tachycardia with at least 100 bpm	Intravenous Ivabradine	Placebo group	48 hours	Reduction in heart rate Changes in tissue perfusion, systolic, diastolic, and mean blood pressure, left ventricular stroke work index Changes in right atrial pressure and pulmonary capillary wedge pressure	Ivabradine decreased heart rate (from 112 to 86 bpm, P <0.001) Ivabradine increases cardiac index (P = 0.02), stroke volume (P <0.001), and systolic blood pressure
Mert *et al.* [45]	RCT	Seventy-three patients aged 18 years and over, hospitalized with decompensated heart failure	Ivabradine (twice a day in doses of 7.5 mg orally)	Control group (did not receive ivabradine)	Not stated	Dobutamine-induced ventricular arrhythmias Ventricular premature contractions	Ivabradine showed no statistically significant effect on dobutamine-ventricular arrhythmias, especially in patients with decompensated heart failure syndromes However, there was significant reduction in ventricular premature contractions after oral administration of ivabradine

Table 1E. Summary table of eligible studies included for review

Author/Year	Design	Sample Size	Treatment group	Comparator	Duration of treatment	Main efficacy outcome	Findings
Hidalgo *et al.* [46]	RCT	Seventy-one patients aged 18 years and older with Left ventricular EF less than 40% and heart rate above 70 bpm and have not been under ivabradine treatment	Ivabradine group (5 mg/12 hours of ivabradine was added after beta-blockers)	Control group	4 months	Heart rate Left ventricular ejection fraction	Significant reduction in heart rate at 28 days (from 70.3 ± 9.3 to 64.3 ± 7.5 bpm, p= 0.01) No severe side effects attributable to the early administration of ivabradine
Agrawal *et al.* [47]	RCT	Nnety-seven patients aged between 18 and 70 years with mild, moderate or severe mitral stenosis	Ivabradine group (50 patients)	Metoprolol group (47 patients)	6 weeks	Heart rate Right ventricular systolic pressure	Both ivabradine and metoprolol were effective in controlling exertional symptoms However, ivabradine is more effective than metoprolol in reducing heart rate (from 186±8.15 to 147.12±6.59 p<0.001) than metoprolol (from 184.36±10.86 152.17±6.76 p<0.001)
Rajesh *et al.* [48]	RCT	Eighty-two patients with moderate mitral stenosis in sinus rhythm	Ivabradine of 5 mg twice daily) or atenolol 50 mg daily	Control group	6 weeks	Sinus rhythm heart rate control	Ivabradine group showed a significant improvement in sinus rhythm and heart rate control (298.57 ± 99.05 s vs. 349.12 ± 103.53 s; p = 0.0001) Significant improvement in atenolol group was observed (290.90 ± 92.42 s vs. 339.90 ± 99.84 p = 0.0001) Ivabradine or atenolol can be used as the best treatment for heart rate control in people with mitral stenosis in sinus rhythm. However, ivabradine is not more effective than atenolol for sinus rhythm

Abbreviations: bid: twice daily; bpm: beats per minute; CAD: Coronary artery disease; CABG: coronary artery bypass graft; HCN; Hyperpolarization-activated cyclic nucleotide OD: one daily; LV: left ventricular function; IV: Intravenous; RCT: randomised controlled trial

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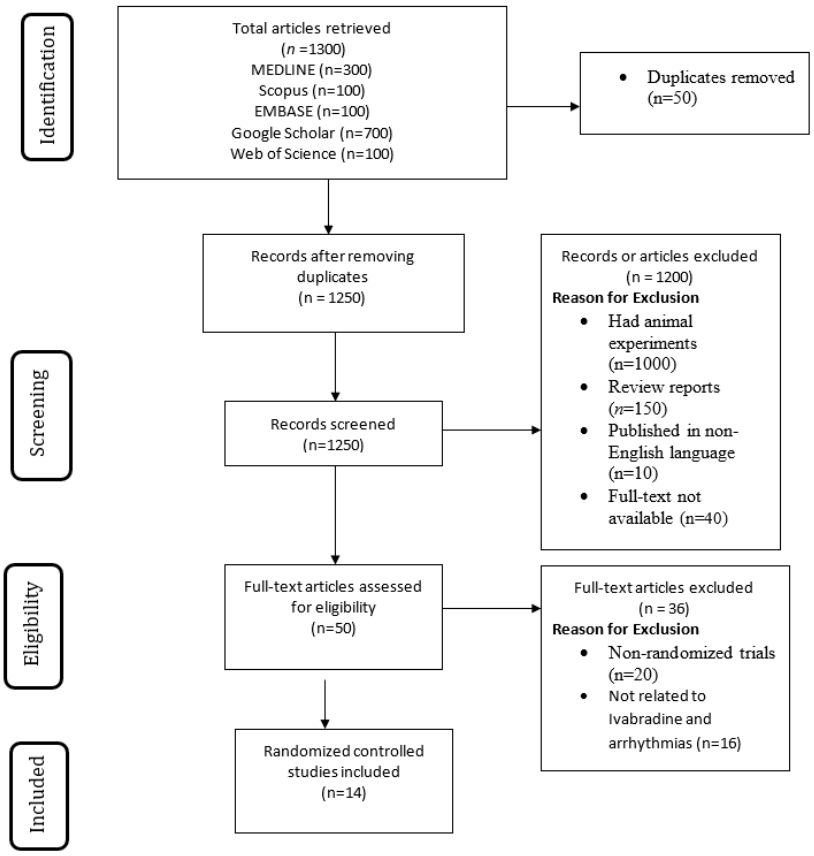

Figure 1. Flow diagram representing study selection for systematic review

Table 2. Quality assessment of included studies using Cochrane risk of bias tool

SN	Authors	Random Sequence Generation	Allocation Concealment	Blinding of Participants	Blinding of Outcome Assessment	Incomplete Data Outcomes	Selective Reporting of Results	Other Bias
1	Wongcharoen et al. [11]	Low risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
2	Fischer-Rasokat et al. [19]	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
3	Lee et al. [20]	Low risk of bias	High risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
4	Abdel-Salam et al. [21]	High risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
5	Fontenla et al. [23]	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
6	Arvind et al. [24]	Low risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
7	Komajda et al. [25]	Low risk of bias	Low risk of Bias	Low risk of Bias	Unclear risk of bias	High risk of bias	Low risk of bias	Low risk of bias
8	Chobanyan-Jürgens et al. [26]	Low risk of bias	Unclear risk of bias	Low risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
9	Tsutsui et al [41]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
10	Nguyen et al. [44]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
11	Mert et al. [45]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

12	Hidalgo et al. [46]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
13	Agrawal et al. [47]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias
14	Rajesh et al. [48]	Low risk of bias	Low risk of bias	Unclear risk of bias	Unclear risk of bias	Low risk of bias	Low risk of bias	Low risk of bias

in the mean ventricular rate from 86.0 ± 10.9 beats/min to 79.2 ± 9.6 beats/min (p<0.001).[11] There were no significant changes observed in the placebo group 84.3 ± 11.2 vs 82.9 ± 9.9 beats/min, p = 0.469).[11] Based on the safety of ivabradine, the study revealed no adverse side effects associated with the medication in both groups. The statistically significant differences were observed between the two groups (p = 0.024) showed that ivabradine is an effective and safe medication that can be used to treat atrial fibrillation for improved ventricular rate.[11]

Another RCT of 24 patients with normal left ventricular ejection fraction and CAD and undergoing or have undergone chronic beta-blocker therapy found a significant decrease in the ventricular filling pressure among patients with high left ventricular index after administration of ivabradine for six weeks (10.7±2.9 vs 8.9±1.7; p<0.01) compared to no significant differences among those with lower left ventricular index (6.4±0.7 vs 6.5±1.1; p=ns).[19] Also, there was an increased oxygen uptake and reduced NT-proBNP serum levels after exercise (190±256 vs 136±162 pg/ml; p<0.05) among patients with high left ventricular index.[19]

A clinical trial of 55 health volunteers that received a single oral dose of 15 mg Ivabradine, taken as two tablets, with each drug consisting of 7.5 mg showed no significant effects observed between the treatment and the placebo groups, but a slower heart rate (10.10 beats/min, P-value <0.0001]) after administration of ivabradine during the second trial.[20] The study showed that ivabradine administration within one hour before applying topical capsaicin is effective and safe to improve ventricular rate.

Another RCT of 740 patients undergoing coronary artery bypass graft assigned to Ivabradine (5 mg of the drug for 2 hours followed by 7.5 mg), bisoprolol (5 mg), and a combination of Ivabradine and bisoprolol showed lower atrial fibrillation with a significant reduction in patients with combined ivabradine and bisoprolol (4.2% reduction, p<0.001) that Ivabradine alone (15.5%) and bisoprolol alone (12.2% reduction).[21]

A different RCT of 232 patients with uncontrolled atrial fibrillation despite using beta-blockers and calcium channel blockers presented similar findings that combining ivabradine (5 mg after every 12 hours) with Digoxin (0.15 mg after 24 hours) is more effective and safer in reducing atrial fibrillation than when used as a single drug.[23]

Clinical efficacy and safety of ivabradine on maintaining sinus rhythm

Three RCTs presented similar results that ivabradine is effective and safe in reducing sinus rhythm.[24-26] One of the studies that involved 19 health individuals showed no significant differences in atrial events on the use of cardiac pacemaker channel (HCN4) inhibition of ivabradine and metoprolol.[26] However, after tilting back, there was a significant improvement in atrial events in the ivabradine group than those in metoprolol and placebo treatment, which showed that HCN4 inhibition, including Ivabradine may have pro-arrhythmic activity.[26]

DISCUSSION

Most reviewed studies supported the clinical efficacy and safety of ivabradine as the drug has limited or no possible adverse side effects, therefore ivabradine can be used as a potential therapeutic drug to improve ventricular rate and sinus rhythm in patients with arrhythmias.[11,19,20,23,26] A single oral dose of 7.5 mg ivabradine administrated as two tablets is recommended to slow down heart rate in people with arrhythmias.[1,5,6,20] The effectiveness and safety of ivabradine is shown by improved ventricular filling pressure and diastolic pressure. The drug increases oxygen uptake and improves stroke volume.[19] A single dose of 15 mg ivabradine taken twice per day for not less than four weeks but with a maximum of 5 weeks lowers heart rate.[23]

Further, combining ivabradine with other medications, such as bisoprolol, ranolazine, Nadolol, and digoxin are more effective in reducing ventricular pressure than when used alone.[21,22,24] Despite the effectiveness of using ivabradine alone, combination with other drugs is more effective and safer to achieve better clinical outcomes. However, there were no significant changes reported in some studies on the use of ivabradine to improve ventricular rate.[19,20] The contradicting findings could be attributed to the sample used and varying dose of ivabradine used in the studies. However, the efficacy and safety of ivabradine to treat arrhythmias is supported by most studies. Thus, ivabradine alone or in combination with other appropriate medications may be recommended.

Moreover, ivabradine improves heart rate and maintenance of sinus rhythm. The medication slows down the heart rate by improving sinus rhythm in patients with atrial fibrillation.[23-26] Ivabradine has no side effects and is safely administrated intravenously or through oral dose to reduce atrial fibrillation, which confirms the therapeutic properties of Ivabradine for arrhythmias.[22] The findings from the reviewed studies, therefore, showed the possibility that patients with arrhythmias are more likely to achieve improved clinical outcomes after administering the recommended dose of ivabradine medication with limited or no adverse side effects. The findings showed the potential to reduce the risk of hospitalisation and mortality of patients with arrhythmias and related heart or cardiac diseases.

This systematic review gives insights on role of ivabradine on treating arrhythmias. However, it is having some limitations.

Firstly, the use of RCTs alone might have limited the ability for more in-depth explanations of the drugs clinical efficacy and safety of ivabradine in arrhythmias. This systematic review also included only full text articles which are published between 2016 and 2021, which might have affected the quality of results. Some of the studies have small sample size which may limit the ability to make meaningful conclusions on the outcomes.

CONCLUSION

In this systematic review the evidence on clinical efficacy and safety of ivabradine in treating arrhythmias is evaluated. The findings indicate that ivabradine has a potential to treat arrythmias such as atrial fibrillation and ventricular tachycardia. The studies showed that ivabradine improves ventricular rate, heart rates, and sinus rhythm in patients with atrial fibrillation. Ivabradine when used alone or in combination with other drugs that lower HR has been shown to have limited or no adverse side effects. With more emerging data from ongoing clinical trials and expanded of label use of the drug, more indications for the drug are likely to evolve. Ivabradine has a potential to improve clinical outcomes and to enhance the quality of patient's life in patients with arrhythmia.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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