Meta-analysis of the efficacy and safety of nifekalant in the conversion of atrial fibrillation

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Abstract. Atrial fibrillation (AF) is the most common type of supraventricular tachyarrhythmia. Nifekalant is a new class III antiarrhythmic drug approved for the treatment of ventricular tachyarrhythmias, but its effectiveness in converting AF to sinus rhythm remains unclear. The present analysis aimed to investigate the effect of nifekalant in the conversion of AF. PubMed, Cochrane Library and China National Knowledge Infrastructure databases were systematically used to search relevant studies published between 1999 (data at which the drug was first approved for marketing in Japan) and 2022. Randomized clinical trials, prospective studies and retrospective studies on the use of nifekalant for AF were screened. The study metrics included the success rate of the conversion of AF, the mean time to conversion, the success rate of 12 months after a single AF catheter ablation procedure and the incidence of adverse events. The eligible studies screened included six randomized clinical trials, three prospective studies and three retrospective studies, totalling 12 studies with 1,162 patients. The risk ratio (RR) for successful conversion in the nifekalant and control groups was 1.95 [95% confidence interval (CI), 1.23-3.08; P=0.005] and the mean difference for the mean time to conversion was -1.73 [95% CI, -2.69-(-0.77); P=0.0004]. Statistically significant differences were observed between nifekalant and control groups. Subgroup analysis revealed a statistically significant difference in the success rate of conversion following catheter ablation in the nifekalant group compared with the amiodarone group and the RR value was 1.95 (95% CI, 1.37-2.77; P=0.0002). Statistically significant difference was observed compared with the electrical cardioversion group and the RR value was 0.90 (95% CI, 0.84-0.98; P=0.01). However, the combined RR values for the two groups were 1.18 (95% CI, 0.85-1.65; P<0.0002). The RR value for adverse events was 0.85 (95% CI, 0.51-1.43; P=0.55), with no statistically significant differences between nifekalant and control groups. In conclusion, the results demonstrated that the success rate and time to conversion in the nifekalant group were improved compared with those in the control group, particularly after catheter ablation, and the conversion effect with nifekalant was significantly improved compared with that in the control group.

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Abbreviations: AF, atrial fibrillation; MD, mean difference; RR, risk ratio; CI, confidence interval; SR, sinus rhythm

Key words: nifekalant, amiodarone, radiofrequency ablation, atrial fibrillation

Introduction

Atrial fibrillation (AF) is one of the most common types of tachyarrhythmia and its prevalence increases with age (1,2). AF is characterized by high morbidity, disability and mortality. AF predicts prolonged hospitalization and increases long-term mortality and major adverse cardiovascular events in patients with acute myocardial infarction (3). Therefore, interventions for AF, either early and timely diversion therapy or anticoagulation for persistent AF, are necessary. According to epidemiological surveys, the number of patients with AF in the United States is expected to reach 7 million by 2050 (4).

Currently, the two main modalities for the treatment of AF are antiarrhythmic drugs and radiofrequency ablation (5). Radiofrequency ablation is increasingly used to treat drug-refractory symptomatic paroxysmal or persistent AF, as it significantly improves postoperative survival in patients with paroxysmal AF compared with antiarrhythmic drugs. However, during actual radiofrequency ablation, antiarrhythmic drugs or Electrical cardioversion are usually selected to improve the success rate of AF conversion (6). In addition, the mechanism of early recurrence of AF, especially following AF ablation, differs from that of conventional atrial arrhythmias and the efficacy of conventional drugs for early AF recurrence needs to be evaluated (7).

The antiarrhythmic drugs now recommended for cardioversion in AF by the European Resuscitation Council guidelines and the International Consensus on Cardiopulmonary Resuscitation are propafenone, amiodarone and lidocaine (8). However, all drugs have certain drawbacks. For example, propafenone is only efficient for AF within the first 48-72 h, while amiodarone takes longer to convert the abnormal heartbeat to sinus rhythm (SR) than propafenone and is prone to adverse effects, even malignant arrhythmias (9).

Nifekalant is a class III antiarrhythmic drug approved by the European Resuscitation Council guidelines and the International Consensus on Cardiopulmonary Resuscitation for the treatment of ventricular arrhythmias (10,11). It suppresses atrial or ventricular tachycardia by inhibiting potassium channels and prolonging effective atrial inactivity. Available studies indicate that nifekalant can inhibit cardiac potassium current rectification in patients with delayed heartbeats by prolonging effective cardiac inactivity, which not only helps localize areas for radiofrequency ablation, but may also improve the success of cardiac resuscitation (12,13).

To the best of our knowledge, there is no meta-analysis on PubMed on the efficacy of nifekalant for the treatment of AF. Given the superiority of nifekalant in the treatment of AF, this drug not only compensates for some of the disadvantages of classical drugs, such as propafenone and amiodarone, but also improves the patient's experience of treatment (14). In addition, to the best of our knowledge, there are limited data on the pharmacological conversion of AF by intravenous nifekalant administration during radiofrequency ablation (15). The present study aimed to review the available evidence and assess the efficacy and safety of nifekalant in the conversion of AF by performing statistical analysis on conversion indicators.

Materials and methods

Search strategy. PubMed (pubmed.ncbi.nlm.nih.gov/), Cochrane Library (cochranelibrary.com/) and China National Knowledge Infrastructure (kns.cnki.net) data published between 1999 and 2022 were searched, based on the recommendations of The Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, to select single studies receiving nifekalant for AF reversal (16). The search keyword was 'nifekalant'. Two independent researchers (KL and PL) searched and reviewed the titles, abstracts and full text to identify them for inclusion.

Data selection inclusion criteria. The published studies included in the present study had to be randomized controlled trials, retrospective or prospective studies with patients that received nifekalant alone. The control group is defined as treated with either lidocaine or amiodarone. The inclusion criteria were as follows: i) Paroxysmal AF for ≤48 h or persistent AF for ≥7 days; ii) discontinuation of other antiarrhythmic drugs after >5 half-lives before radiofrequency ablation; and iii) no other antiarrhythmic drugs applied during radiofrequency ablation. The study outcomes included the success rate of conversion, the success rate of conversion following radiofrequency ablation, the mean time to conversion and the incidence of adverse events. The study endpoint was the conversion of AF to SR and the secondary efficacy endpoint was the termination of AF. Adverse events included bradycardia, ventricular arrhythmias, hypotension or gastrointestinal adverse reactions. Reviews, case reports, animal studies, editorials, studies with unclear study types and studies with insufficient data were excluded.

Data extraction and quality assessment. The following data were collected from eligible studies screened by both authors: i) The first author; ii) year of publication; iii) description; iv) sample size; v) follow-up time; vi) clinical characteristics; and vii) outcomes. The Cochrane risk-of-bias tool was used to assess the quality of the included studies by both authors. Any disagreements between the two authors were discussed and solutions were found, or a third researcher (SW) was consulted. Publication bias checks were analysed using Stata 16 software (StataCorp LP).

Statistical analysis. The present meta-analysis followed the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions and study endpoint parameters (including success rate of conversion, success rate of conversion following radiofrequency ablation, mean time to conversion and incidence of adverse events) were collected to assess the treatment effects (17). Statistical data analysis was performed using RevMan 5.4 (The Cochrane Collaboration) and Stata 16 (StataCorp LP). Once these data had been extracted, the risk ratio (RR), mean difference (MD) and 95% confidence interval (CI) were calculated using the two software packages aforementioned. $P<0.05$ was considered to indicate a statistically significant difference. Egger's test was used to verify the presence of publication bias. Heterogeneity was assessed using the I^2 statistic and Cochrane's Q test. I^2 statistics of 0, <25, 25-49 and >50% were considered to indicate no, low, moderate and high heterogeneity, respectively. To ensure the accuracy and stability of the results, a random effects model was selected directly for statistical analysis when there was moderate or high heterogeneity in the study.

Results

Results of the article search. A preliminary search of PubMed (160 articles), the Cochrane Library (two articles) and China National Knowledge Infrastructure (255 articles) yielded a total of 417 articles. After reading the titles and abstracts and excluding duplicate publications, a total of 368 articles were excluded, and 49 articles were selected and further screened by full-text reading. A total of 37 of these were further excluded for various reasons, such as insufficient data and inappropriate controls. Finally, 405 articles were excluded and 12 research studies met all the inclusion criteria (10,18-28). A flow chart of the study selection process is shown in Fig. 1A. A total of 12 studies including 1,162 patients were considered by the present meta-analysis. All included studies were published between 1999 and 2022. Table I summarizes the information on the main baseline characteristics of patients and the doses used for nifekalant and the controls.

Methodological quality assessment of the included studies. All included studies were of medium to high quality (Fig. 1B and C). Bias analysis was performed with P=0.864, demonstrating the lack of significant publication bias in the included studies (Fig. 1D and Table II).

Effect of nifekalant on diversion success rates. A total of 12 studies were screened for analysis, nine of which reported the success rate of nifekalant on AF reversal (Fig. 2A). Some degree of heterogeneity was present as ascertained through the heterogeneity test with $I^2>50$. A random effects model was selected for the analysis and the RR value was 1.95 (95% CI, 1.23-3.08; P=0.005), which was statistically significant and therefore demonstrated a success rate of conversion of AF to SR with nifekalant higher than that achieved with the control treatment modalities (amiodarone or lidocaine).

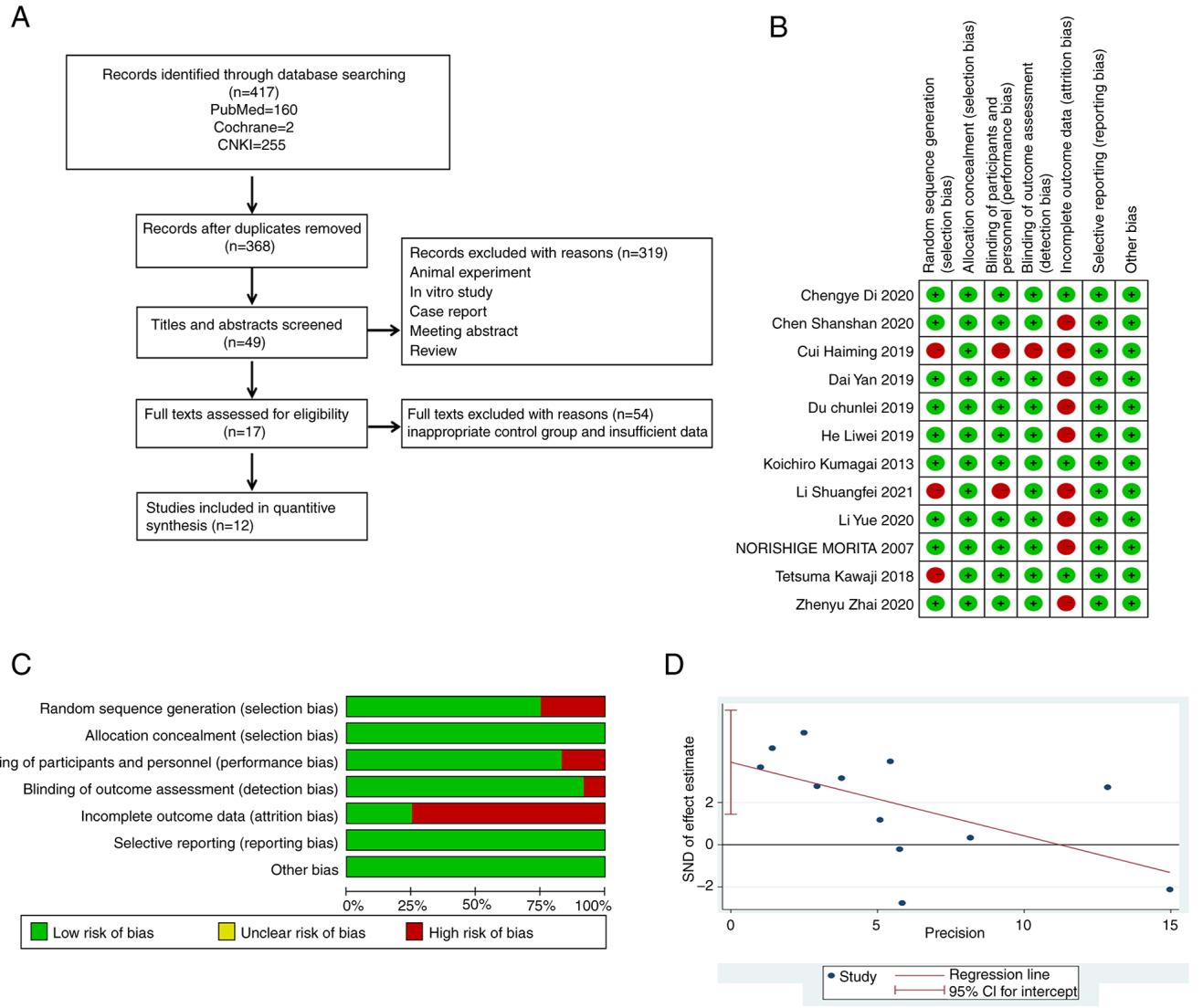

Figure 1. Article screening steps and quality analysis. (A) Article screening flow chart. (B and C) Analysis of the quality of the literature showed that the majority were articles of medium to high quality. (D) Article bias analysis resulted in P=0.864, indicating no publication bias. CI, confidence interval; CNKI, China National Knowledge Infrastructure()SND is defined as the sample mean divided by its standard error.

Effect of nifekalant on time to reversal. Out of the 12 screened studies, seven reported indicators related to time to conversion. Some heterogeneity was present as indicated by the heterogeneity test with I^2>50. A random effects model was selected for analysis, and the MD was -1.73 [95% CI, -2.69-(-0.77), P=0.0004], which was statistically significant, thus demonstrating that nifekalant had less time to conversion than the control group (Fig. 2B). The RR value was 0.090 (95% CI, 0.84-0.98; P=0.01) compared with the electro-recovery group, which was statistically different and demonstrated that the success rate of electro-recovery was higher than that of nifekalant (Fig. 2C).

Effect of nifekalant on the success rate of AF conversion after catheter ablation. A total of six studies reported the success rate of AF conversion following catheter ablation (18,19,22,23,25,27). A subgroup analysis was performed due to a heterogeneity test score of I^2>50, and the control group was divided into amiodarone and electrical resuscitation groups. Compared with the amiodarone group, I^2 was <50 and the RR value was 1.95 (95% CI, 1.37-2.77; P=0.0002), which was statistically significant, indicating that the success rate of conversion was higher in the nifekalant compared with the control group. There was no statistical difference with I^2>50 and an RR value of 0.85 (95% CI, 0.71-1.03; P=0.09), in the nifekalant compared with the electrical resuscitation group (Fig. 3A). AF recurrence rates after 12 months of follow-up were reported in three studies, with an RR value of 1.04 (95% CI, 0.82-1.32; P=0.73) and no statistically significant difference, demonstrating that nifekalant did not affect AF recurrence differently from the control group (Fig. 3B).

Incidence of adverse events with nifekalant. A total of eight studies reported the incidence of adverse events with nifekalant with a heterogeneity of I^2<50 and an RR value of 0.85 (95% CI, 0.51-1.43; P>0.05) with no statistical difference, demonstrating no difference in the incidence of adverse events between nifekalant and the control group (Fig. 3C).

Table I. Characteristics of patients.

First author/s, year	Description (nifekalant/control)	Follow-up duration	Atrial fibrillation duration (nifekalant/control)	Number of patients (nifekalant/control)	Sex (male/female)	Age (nifekalant/control), years	(Refs.)
Di *et al*, 2020	0.3 mg/kg intravenous injection/amiodarone was infused at 150 mg intravenously, and then continuously pumped in at 1	12 months	0.40±9.25/0.40±10.70 months	60/42	65/37	68.6±9.6/67.1±9.1	(18)
Kumagai and Toyama, 2013	0.3 mg/kg intravenous injection/the control was unknown	12 months	310±34.00/30.00±32.00 months	50/50	89/11	56.0±10.0/57.0±11.0	(19)
Morita *et al*, 2007	0.3 mg/kg intravenous injection/the control was unknown	NA	17.00±41.50/21.40±44.50 h	15/16	25/6	67.9±12.5/67.9±9.7	(20)
Kawaji *et al*, 2018	0.3 mg/kg intravenous injection/the control was unknown	12 months	NA	79/78	121/36	65.9±10.2/65.4±7.6	(10)
Zhai *et al*, 2021	0.3 mg/kg intravenous injection/the method of placebo used was unknown	NA	Data not available	110/110	142/78	55.0-68.0/58.0-67.0	(21)
Chen *et al*, 2020	0.3 mg/kg intravenous injection/amiodarone was infused at 150 mg intravenously, and then continuously pumped in at 1 mg/min	NA	6.60±0.50/6.10±0.80 months	45/37	43/39	61.0±11.0/63.0±9.0	(22)
He *et al*, 2019	0.3 mg/kg intravenous injection/electrical cardioversion	NA	NA	41/60	56/45	60.7±12.1/58.2±17.6	(23)
Cui *et al*, 2019	0.3 mg/kg intravenous injection/electrical cardioversion	NA	25.10±14.40/22.00±14 months	23/15	27/11	66.7±8.6/66.2±7.1	(24)
Li *et al*, 2021	0.3 mg/kg intravenous injection/amiodarone was infused at 150 mg intravenously, and then continuously pumped in at 1 mg/min	NA	22.30±2.30/21.50±2.20 months	37/34	35/36	57.9±2.0/59.6±2.1	(25)
Du *et al*, 2019	0.3 mg/kg intravenous injection/amiodarone was infused at 150 mg intravenously, and then continuously pumped in at 1 mg/min	NA	<48.00 h	52/54	88/18	68.0±10.0/67.0±10.0	(26)
Li *et al*, 2020	0.3 mg/kg intravenous injection/amiodarone was infused at 150 mg intravenously, and then continuously pumped in at 1 mg/min	NA	NA	47/47	51/43	61.64±2.35/62.03±3.21	(27)
Dai *et al*, 2019	0.3 mg/kg intravenous injection/amiodarone was infused at 150 mg intravenously, and then continuously pumped in at 1 mg/min	NA	<48.00 h	30/30	40/20	61.33±11.76/62.10±10.64	(28)

NA, not applicable.

Table II. Egger test for 12 studies.

Type of measurement	Coefficient	Standard error	t-value	P-value >|t|	95% CI
Standardized effect	1.252067	1.427434	0.88	0.401	-1.92845-4.43258
Slope bias	0.3900094	2.221697	0.18	0.864	-4.56024-5.34026

Root mean squared error=2.836. Test of null hypothesis (no small-study effects), P=0.864. CI, confidence interval.

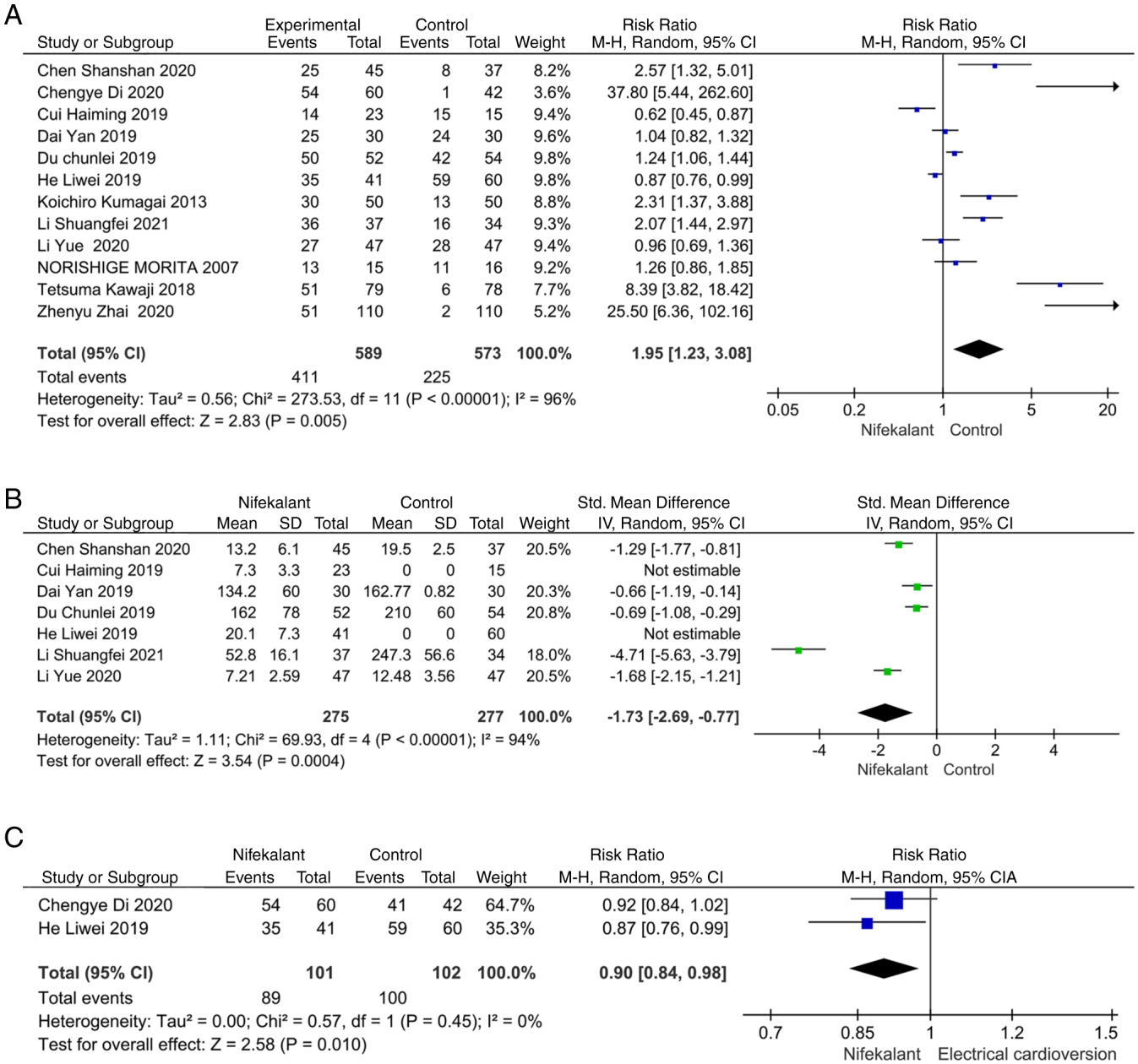

Figure 2. Nifekalant has a high success rate in reversing atrial fibrillation. (A) Nifekalant conversion success rate was higher than that in the control group. (IV is inverse-variance and M-H is Mantel-Haenszel). (B) Nifekalant took less time to convert than the control group. (C) Nifekalant convert is less successful than in the Electrical cardioversion group. CI, confidence interval.

Discussion

AF is one of the most common types of tachyarrhythmia, whose incidence increases significantly with age, causing high morbidity, disability and mortality rates (8,29). In addition, cardiac emergencies, such as acute myocardial infarction, can induce new-onset AF, which in severe cases can lead to heart failure and induce severe

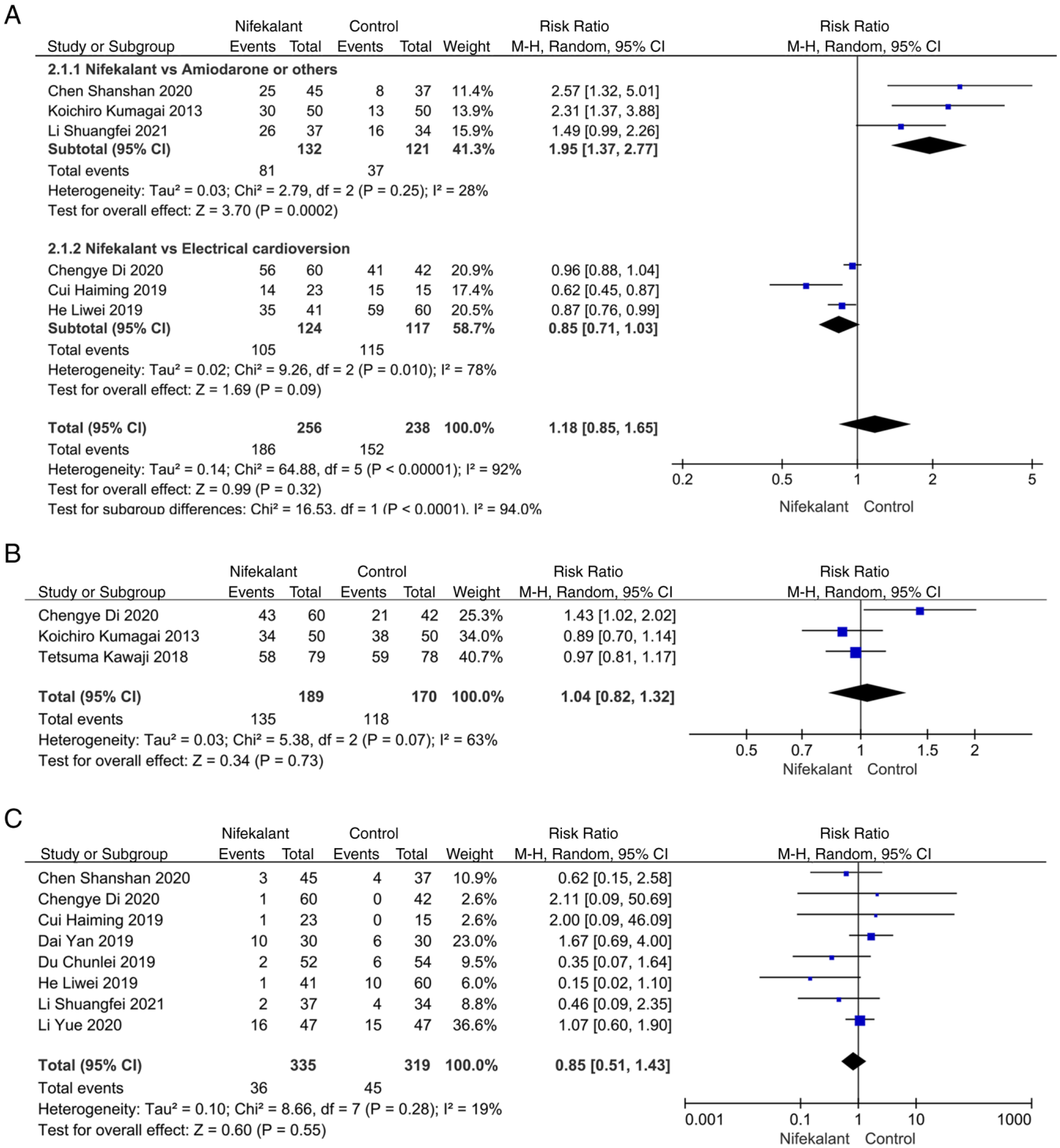

Figure 3. Analysis of nifekalant diversion indicators. (A) Nifekalant improved the success rate of conversion in radiofrequency ablation. (B) At 12 months of follow-up, there was no difference in the recurrence rate of atrial fibrillation in the nifekalant group compared with the control group. (C) There was no difference in the incidence of adverse events in the nifekalant group compared with the control group. CI, confidence interval; IV, inverse-variance; M-H, Mantel-Haenszel.

hemodynamic dysfunction (30). Therefore, early paroxysmal AF should be reversed as early as possible. Patients with persistent AF should receive regular anticoagulation treatment and, if necessary, interventional therapy may be provided (31,32).

Pharmacological conversion is the most traditional and classical treatment for patients with AF for restoring the SR of the heart (33). However, each of the traditional antiarrhythmic drugs have their advantages and disadvantages. Propafenone, although recommended as a class I drug, is <50% effective and is contraindicated in patients with left ventricular systolic dysfunction and ischemic heart disease due to its negative ionic nature (34,35). Amiodarone is recommended as a class III drug, but studies have shown that it is ineffective in AF reversal and is prone to causing adverse events (36). Ibutilide, while it exhibits improved

efficacy over the first two, is prone to QT prolongation and may induce torsional angles and even ventricular arrhythmias (37).

Catheter radiofrequency ablation is an alternative and an important treatment for AF and is more effective than antiarrhythmic drugs. However, due to the specific pathophysiological mechanism of AF, atrial arrhythmias still recur in 25-50% of patients following ablation, of which 21-38% are early recurrences (38). Some patients still have persistent AF following radiofrequency ablation, and although the traditional drug amiodarone and electrical resuscitation can be used to revert sinus rhythm, the time required for reversion and the need for complex electric shock operations are increasingly unable to meet the treatment needs of patients (3,39).

The current high recurrence rate is the main reason catheter radiofrequency ablation is not widely available (40,41). The primary treatment options are electrical cardioversion, intravenous pharmacological cardioversion and oral pharmacological rhythm control. Although electrical resuscitation can be rapid and effective, it requires intravenous anaesthesia and may cause skin burns and myocardial damage, and in some cases may even induce acute pulmonary oedema (42). There is also no consensus on the choice of antiarrhythmic drugs (18).

Nifekalant is a new class III antiarrhythmic drug that was approved in 1999 for the treatment of ventricular tachyarrhythmias. Nifekalant is a single-channel blocker that does not block sodium and calcium channels and has no significant effect on myocardial cell conduction velocity or myocardial contractility. Therefore, the incidence of adverse events, such as bradycardia and hypotension, is low and the efficiency of conversion is high; however, the effectiveness of nifekalant in the treatment of postoperative AF recurrence has not been established (43).

In the present study, patient information from 12 studies was comprehensively evaluated to demonstrate the superiority of nifekalant in AF conversion. The present meta-analysis showed that nifekalant had a higher success rate of conversion compared with conventional drugs in the control group, particularly during radiofrequency ablation and in the treatment of postoperative recurrence. In the 12-month follow-up study, no difference was identified between the nifekalant group and the control group. However, further studies are required, since only three studies were included, and the sample was small. During conversion, the incidence of adverse events in the nifekalant group did not differ from the control group, and although it has been reported that nifekalant may cause prolongation of the QT interval or tip-twisting ventricular tachycardia, no significant tendency was found in the present study (44).

Several limitations should be noted in the present meta-analysis. Firstly, there were few post-reversal follow-up studies and the overall sample size was small, with most of the included studies being in the Chinese region; further clinical trial study centres are therefore needed to perform validation of the effects of nifekalant on reversal. Secondly, some of the studies included in the present analysis were retrospective or prospective studies with insufficient research evidence. In addition, although there was no significant variability in the basic information of the patients included in the current study, the underlying disease of the patients included and whether the patients were using other medications was not detailed in the literature, and therefore there may be a potential confounding effect; this may have also been a cause of the large heterogeneity. In addition, there were differences in the treatment modalities of the controls included in the present study, and although the majority of the control group was treated with amiodarone, there was also a proportion of treatments, such as electrical cardioversion and lidocaine, which may also have contributed to the heterogeneity of the analysis. The molecular mechanism of nifekalant in AF reversal is not fully understood; therefore, further studies of nifekalant in AF regression are required.

In conclusion, patients with AF in the nifekalant group had a better success rate of conversion and time consumed for conversion than the control group. In particular, the success rate of cardiac SR conversion with the aid of nifekalant was significantly better than that in the control group during catheter ablation, and there was no difference in the incidence of adverse events between the two groups. In addition, the results of the 12-month follow-up showed that the incidence of AF recurrence was not associated with choice of drug.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

PL, KL and SW designed the study, searched databases, extracted and assessed the literature and drafted the manuscript. PL, LW and ML statistically analyzed the data. KW and LW confirm the authenticity of all the raw data. PL and GS conceived and designed the present study, provided general supervision and finalized the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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