

Beta-Blocker Landiolol Hydrochloride in Preventing Atrial Fibrillation Following Cardiothoracic Surgery: A Systematic Review and Meta-Analysis

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Objective: The purpose of this article was to assess the benefit of perioperative administration of the intravenous beta-blocker landiolol hydrochloride in preventing atrial fibrillation (AF) after cardiothoracic surgery.

Methods: We performed a systematic search in PubMed, Web of Science, CNKI, and OVID to identify randomized controlled trials (RCTs) and cohorts up to January 2021. Data regarding postoperative atrial fibrillation (POAF) and safety outcomes were extracted. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined using the Mantel-Haenszel method. Meanwhile, subgroup analyses were conducted according to surgery type including lung cancer surgery, esophageal cancer surgery, and cardiac surgery.

Results: Seventeen eligible articles involving 1349 patients within 13 RCTs and four cohorts were included in our meta-analysis. Compared with control group, landiolol administration was associated with a significant reduction of the occurrence of AF after cardiothoracic surgery (OR = 0.32, 95% CI 0.23–0.43, P < 0.00001). In addition, the results demonstrated that perioperative administration of landiolol hydrochloride minimized the occurrence of postoperative complications (OR = 0.48, 95% CI 0.33–0.70, P = 0.0002). Funnel plots indicated no obvious publication bias.

Conclusions: Considering this analysis, landiolol was effective in the prevention of AF after cardiothoracic surgery and did not increase the risk of major postoperative complications.

Keywords: landiolol, atrial fibrillation, cardiothoracic surgery, postoperative complications

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Introduction

The incidence of atrial fibrillation (AF) ranges from 8% to 42%.^{1,2} AF is one of the most common forms of arrhythmia^{3,4} with a high occurrence rate, and low rate of successful treatment, following cardiothoracic surgery. Despite AF being a transient symptom in most cases, it can lead to occasional serious outcomes, such as thromboembolic events and hemodynamic deterioration, which can result in death.⁵ Postoperative atrial fibrillation (POAF) may also result in extended hospital stays and endanger public health and well-being.^{1,6,7} Therefore, to prevent the occurrence of POAF has been a universal concern.

The main therapy for POAF is antiarrhythmic medications, including digoxin,⁸⁾ calcium channel blockers,^{9,10)} and β -blockers.^{11,12)} Although calcium channel antagonists are effective against AF, they are often associated with adverse side effects like bradycardia.¹³⁾ β -blockers were also reported to successfully prevented POAF after cardiac surgery through anti-ischemic, anti-inflammatory, and sympatholytic effects,¹⁴⁾ but they often cause hypotension due to their cardio-depressant effect.^{13,15,16)} Currently, esmolol, a β -blocker, is the most commonly used drug to prevent AF in patients undergoing cardiovascular surgery. However, its effect was unknown in pulmonary surgery and esophageal surgery. Landiolol, a newly developed drug, is a new compound obtained based on the chemical structure of esmolol and is reported to be able to successfully prevent the occurrence of POAF successfully.¹⁷⁾ Landiolol is an ultrashort acting β -adrenoceptor antagonist with a high selection of β_1 -blocker¹⁸⁾ and has a weaker negative inotropic effect among intravenous β_1 -blockers,¹⁹⁾ and many researchers showed that its blood concentration half-life was 4 min in humans with intravenous administration.²⁰⁾ Therefore, landiolol may avoid postoperative hypotension.²¹⁾ The acting mechanism of landiolol is β -blockers first selectively interact with beta adrenergic receptors and thereby antagonize the excitatory effects of neurotransmitters and catecholamines on beta receptors. Regarding the selectivity of β_1 -blockers, landiolol hydrochloride has a much higher cardio-selectivity ($\beta_1/\beta_2 = 255$) than esmolol hydrochloride ($\beta_1/\beta_2 = 33$); therefore, it might have a few effects on the respiratory system.^{22,23)} However, landiolol's efficacy in patients undergoing cardiothoracic surgery including lung cancer surgery, esophageal cancer surgery, and cardiac surgery has yet to be confirmed.

Previous research has focused on the efficacy of landiolol in preventing POAF; however, no convinced consensus has been reached for small sample, limited outcomes, and inevitable heterogeneity. Therefore, a comprehensive systematic review and meta-analysis is required to provide more accurate evidence with enlarged sample sizes. This systematic review and meta-analysis aims to identify the effects of landiolol on preventing POAF following cardiothoracic surgery and occurrence of AF, complications, length of hospital stay, and mortality compared with placebo.

Materials and Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis.²⁴⁾

Literature research

We performed a systematic search in widely acknowledged authenticated databases including PubMed, CNKI, Web of Science, and OVID using the following terms: “landiolol” OR “ONO 1101” OR “ONO 11-01” OR “landiolol hydrochloride” OR “onoact”. All available studies were published up to January 2021. The language was restricted to English. Any discordance was resolved by discussion and consensus.

Inclusion criteria and exclusion criteria

Studies were carefully selected according to the criteria as follows: a) the designs had to be the randomized controlled trials (RCTs) or cohort studies; b) studies had to be relevant with cardiac surgery, lung cancer surgery or esophagus cancer surgery; c) the full text had to be accessible; d) published English studies; and e) the articles reported outcomes including the occurrence of AF, complications, length of hospital stay, and mortality rates.

The exclusion criteria were as follows: a) review, case report, single sample experiments, comments and editorials; b) studies with no human subjects; and c) published studies in which data could not be extracted or those having wrong data.

Data extraction and quality assessments

The parameters that indicate the efficacy and safety of landiolol in preventing AF were extracted by two experienced investigators independently with a standard extraction table. The information of the essays was extracted from basic information such as the title, first author's name, publication year, nationality, department, ethnicity, study design, age and gender of the samples (in both the landiolol group and the control group), enrolled year, and comparison of correlated outcomes (primary outcomes like the occurrence of AF and secondary outcomes such as complications, length of hospital stay, and mortality rates).

The Cochrane risk-of-bias tool was applied to assess the quality of the included studies. We carefully read each included article based on the evaluation tools and evaluated the quality of each article subjectively by selecting a value of “high”, “low”, or “unclear” risk of

bias to the following categories: a) random sequence generation, b) allocation concealment, c) blinding of participants and personnel, d) blinding of outcome assessment, e) incomplete outcome data, f) selective reporting, and g) other bias. If discrepancies were met, we resolved them via consensus.

Statistical analysis

Data analysis was performed on Review Manager 5.3. We applied I^2 tests to assess heterogeneity for each overall analysis, and when P-value was >0.10 and $I^2 <50\%$, it suggested acceptable heterogeneity. If heterogeneity existed, the random-effects model was used to calculate pooled values. Otherwise, we used the fixed-effect model. We applied odds ratios (ORs) for dichotomous variables and mean differences for continuous variables with their 95% confidence intervals (CIs), and statistical

significances were set as $P <0.05$. When the units of continuous variables were inconsistent, we used a standardized mean difference method. Funnel plots for log OR were created to estimate publication bias and other types of bias. The Begg and Mazumdar rank correlation test was used to test the symmetry of the funnel plots.

Subgroup analysis

Subgroup analyses were conducted according to surgery type, including lung cancer surgery, esophageal cancer surgery, and cardiac surgery.

Results

The literature selection and screening processes are shown in **Fig. 1**. A total of 349 potential relevant articles were searched in PubMed, Embase, CNKI, OVID, and

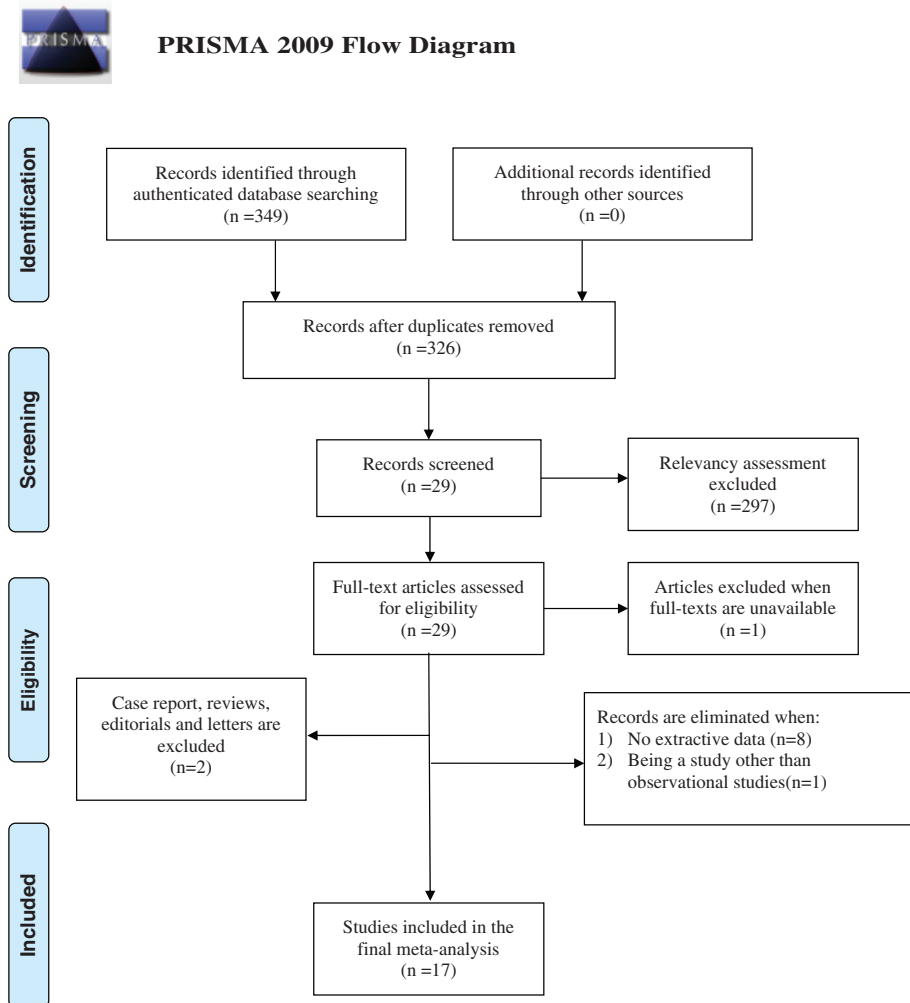


Fig. 1 Flow diagram of search strategy according to PRISMA guidelines (2009). PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

Web of Science in January 2021. After duplicates were removed, 326 articles were left. We then reviewed the titles and abstracts. In all, 297 unrelated articles were excluded. Then, we read the full text of the remaining articles; 17 articles were eligible based on our inclusion and exclusion criteria.

Description of studies

The basic characteristics of the 17 eligible articles are summarized in **Table 1**. In total, 13 RCTs and four cohorts studied were included in this meta-analysis. Ten articles studied the prognosis of landiolol hydrochloride infusion for the prevention of POAF in patients undergoing cardiac surgery,^{15,25–33} four articles focused on the esophageal surgery,^{34–37} and three articles were studies on patients undergoing lung surgery.^{20,38,39} A total of 1349 patients were included, and each study included 15–230 patients ranging in age from 62 to 83. AF that occurs within a week after surgery is defined as POAF. In those 17 included studies, the landiolol was infused with a dosage of 3 or 5 µg/kg/min during general anesthesia in the landiolol group and the placebo was infused in the control group for 24–72 h after the induction of anesthesia. Regarding the data in all 17 articles, the primary outcome was the overall incidence of AF occurring during the first week after surgery.

Quality of studies

Standard quality evaluation of the 17 included studies was assessed by the Cochrane risk-of-bias tool. Three articles were at a relatively higher risk of bias. The details of the quality in each study are shown in **Fig. 2**.

The outcome results

Incidence of AF occurring during the 7 days after cardiothoracic surgery

In total, 17 articles with 1349 patients reported the effectiveness of landiolol hydrochloride in preventing AF after cardiothoracic surgery. The overall incidence of AF was 11% (66/598) in the landiolol group and 25% (188/751) in the control group. Our results showed that landiolol administration was associated with a significant reduction of the occurrence of AF after cardiothoracic surgery (OR = 0.32, 95% CI 0.23–0.43, $P < 0.00001$; **Fig. 3**), especially in esophageal surgery and cardiac surgery patients (OR = 0.38, 95% CI 0.18–0.78, $P = 0.008$ and OR = 0.27, 95% CI 0.18–0.40, $P < 0.00001$,

respectively). The heterogeneity among these 17 studies was low ($I^2 = 0\%$), which indicated a reliable result.

Lung cancer

Three articles reported the effectiveness of landiolol hydrochloride in preventing POAF after lung resection with the initial dose of landiolol as 5 µg/kg/min during general anesthesia. The incidence of AF within the first week after surgery was 7.6% (9/117) in the landiolol group, which was much lower than that in the control group (13.6% [36/264]) (OR = 0.50, 95% CI 0.22–1.12, $P = 0.09$). The forest plot of all the three studies is shown in **Fig. 3**.

Esophageal cancer

The efficacy of landiolol in preventing POAF after esophageal cancer surgery was reported in four articles. Compared with the control group, the incidence of AF in the landiolol group was reduced by 11.5%. The pooled analysis showed that compared with the control group, landiolol could significantly reduce the incidence of AF within the first postoperative week (OR = 0.38, 95% CI 0.18–0.78, $P = 0.008$). The forest plot of all the four studies is shown in **Fig. 3**.

Cardiac surgery

In the analysis of 10 related studies, the occurring of POAF was 13% (45/345) in the landiolol group and 35.5% (124/349) in the control group (OR = 0.27, 95% CI 0.18–0.40, $P < 0.00001$). The forest plot of all the 10 studies is shown in **Fig. 3**. Compared with the control group, the occurrence of POAF in the landiolol group was significantly lower, indicating a potential effectiveness of landiolol in preventing POAF.

Incidence of complications after cardiothoracic surgery

In total, 10 articles with 752 patients reported the effectiveness of landiolol hydrochloride in preventing complications after cardiothoracic surgery. The incidence of complications in the landiolol group was lower than that in the control group by 11% (61/379, 101/373). The result indicated that perioperative administration of landiolol hydrochloride would minimize the occurrence of postoperative complications (OR = 0.48, 95% CI 0.33–0.70, $P = 0.0002$; **Fig. 4**).

There were no obvious differences between the groups regarding blood pressure before and after using landiolol. In both groups after medication, the heart rate was reduced immediately but more predominantly in the

Table 1 Characteristics of included studies

Author, year	Country	No. of patients	M	F	Age (yrs) Control	Age (yrs) Landiolol	Use of CPB	Type of surgery	Initial dose of landiolol	Start of landiolol	Duration of use of landiolol (landiolol group)	Primary outcome	Secondary outcome
Aoyama, 2016 ²⁰⁾	JPN	50	31	19	66.9 ± 8.9	67.4 ± 8.7	NA	VATS: 36 Open: 14	5 µg/kg/min	During general anesthesia	NA	Incidence of AF until 7 POD	Plasma concentration of IL-6, serum Mg, serum Ca, CRP, NT Pro-BNP by blood sampling, three fractions of catecholamines (adrenaline, noradrenaline, and dopamine) NA
Okita, 2008 ³⁹⁾	JPN	301	NA	NA	NA	NA	NA	5 µg/kg/min	Before surgery	Before surgery	NA	Incidence of AF until 2 POD	NA
Nojiri, 2011 ³⁸⁾	JPN	30	19	11	69.5 ± 7.3	72.2 ± 5.7	NA	VATS: 18 Open: 12	10 patients received 5 µg/kg/min; 5 min; 5 min; 10 µg/kg/min	Before surgery	24 h	Incidence of AF until 2 POD	Bradycardia, hypotension, congestive heart failure, myocardial infarction, angina pectoris, pneumonia, acute respiratory failure, respiratory insufficiency requiring tracheostomy, respiratory failure requiring mechanical ventilation, atelectasis with bronchoscopic therapy, home oxygen treatment, thromboembolic events, death
Horikoshi, 2017 ³⁴⁾	JPN	39	33	6	63 ± 8	67 ± 7	NA	Esophagectomy	5 µg/kg/min	Before surgery	20.5 ± 7.5 h	Incidence of AF until 2 POD	Amount of bleeding, infusion volume of crystalloid, blood transfusion volume, urine volume, Hb after surgery, length of hospital stay
Ojima, 2017 ³⁵⁾	JPN	100	77	23	69 (45–83)	68 (31–85)	NA	Thoracoscopic oesophagectomy, 99 transthoracic	3 µg/kg/min	After surgery	72 h	Incidence of AF between 1 and 7 POD	Rate of occurrence of AF in the hospital, postoperative complications, hemodynamic performance, changes in inflammatory markers
Yoshida, 2017 ³⁷⁾	JPN	79	67	12	62 (45–82)	64 (48–79)	NA	VATS	5 µg/kg/min	Before surgery	24 h	Incidence of AF until 2 POD	Anastomotic leakage, pneumonia, recurrent nerve palsy, ileus, chylothorax, over 38° of body temperature
Aoki, 2020 ³⁶⁾	JPN	56	42	14	69 (60–71)	68 (62–74)	NA	Esophagectomy	3 µg/kg/min	Before surgery	24 h	Incidence of AF until 4 POD	The proportion of patients whose AF appeared within 24 h, other complications based on the Clavien–Dindo classification, the intensive care unit, hospital stays

Author, year	Country	No. of patients	M	F	Age (yrs) Control	Age (yrs) Landiolol	Use of CPB	Type of surgery	Initial dose of landiolol	Start of landiolol	Duration of use of landiolol (landiolol group)	Primary outcome	Secondary outcome
Sakaguchi, 2012 ³⁰⁾	JPN	60	32	28	68.7 ± 10.0	69.3 ± 8.6	Yes	CABG: 0 Valve: 55 CABG + valve: 4	10 µg/kg/min	After surgery	72 h	Incidence of AF until 2 POD	HR, systemic blood pressure, cardiac index, average pulmonary arterial blood pressure
Fujii, 2012 ²⁵⁾	JPN	70	49	31	68.5	NA	No	Aortic root OPCABS 100%	5 µg/kg/min	After surgery	50 h	Incidence of AF until 7 POD	Hospital mortality, HR, BP, fluid balance
Fujiwara, 2009 ²⁶⁾	JPN	55	38	17	69.2 ± 7.6	69.9 ± 9.1	Yes	CABG	1.5–2.5 µg/kg/min	After CPB	48 h	Incidence of AF	Cardiac index, dose of inotropic agents, intubation time, length of ICU stay, postoperative LVEF
Nagaoka, 2014 ²⁷⁾	JPN	45	37	8	69 ± 6.3	67 ± 8.5	No	CABG	0.5 µg/kg/min	After surgery	38.4 ± 16.8 h	Incidence of AF until 7 POD	HR, SBP obtained from an arterial line, CI, SPA, PCWP, SVI
Nakanishi, 2013 ²⁸⁾	JPN	105	NA	NA	65.7 ± 12.6	67.2 ± 11.5	No	CABG: 55 Valve: 50	1 µg/kg/min	Before surgery	23.9 ± 32 h	Incidence of AF	HR, length of ICU stay, time to extubation, postoperative complications
Ogawa, 2013 ²⁹⁾	JPN	136	105	21	71.6 ± 7.8	69.3 ± 6.3	No	CABG	3–5 µg/kg/min	Before surgery	72 h	Incidence of AF until 7 POD	Postoperative levels of troponin I, CK-MB isoenzyme, and CRP
Sakamoto, 2012 ³¹⁾	JPN	71	48	23	69.3 ± 8.4	70.2 ± 10.6	NA	CABG: 25VR: 25CABG + VR: 9Others: 12	0.5–2 µg/kg/min	After surgery	72 h	Incidence of AF until 3 POD	Hospital mortality, HR, BP, fluid balance
Sezai, 2011 ¹⁵⁾	JPN	140	138	12	66.7 ± 8.9	68.5 ± 4.7	No	CABG	2 µg/kg/min	During surgery	48 h	Incidence of AF until 7 POD	Operative mortality and complications; hemodynamics at the return to the ICU at 12, 24, and 48 h after administration and at 24 hours after discontinuing administration; fluid balance; CK-MB isoenzyme; troponin-I and human heart fatty acid-binding protein; IL-6, IL-8, and hs-CRP; urinary 8-hydroxydeoxyguanosine; total cost of hospital treatment

Author, year	Country	No. of patients	M	F	Age (yrs) Control	Age (yrs) Landiolol	Use of CPB	Type of surgery	Initial dose of landiolol	Start of landiolol	Duration of use of landiolol (landiolol group)	Primary outcome	Secondary outcome
Sezai, 2012 ⁽³²⁾	JPN	68	56	12	68.2 ± 7.5	68.5 ± 9.6	Yes	CABG	5 µg/kg/min	During surgery	72 h	Incidence of AF until 7 POD	Operative mortality and complications, SBP and diastolic BP and HR, CK-MB isoenzyme, troponin-I, and human heart fatty acid-binding protein, hs-CRP, PTX-3, ADMA, and BNP
Sezai, 2015 ⁽³³⁾	JPN	60	50	10	68.3 ± 9.4	64.8 ± 9.6	Yes	CABG; 46 Valve; 12CABG + Valve: 2	2 µg/kg/min	During surgery	48 h	Incidence of AF until 8 POD	Operative mortality and complications, SBP and diastolic BP and HR, CK-MB isoenzyme, troponin-I, and human heart fatty acid-binding protein, hs-CRP, PTX-3, ADMA, and BNP

JPN: Japan; CPB: cardiopulmonary bypass; VATS: video-assisted thoracic surgery; Valve: heart valve surgery; CABG: coronary artery bypass grafting; OPCABS: off pump coronary artery bypass surgery; AF: atrial fibrillation; POD: postoperative day; BP: blood pressure; HR: heart rate; LVEF: left ventricular ejection fraction; M: male; F: female; NA: not applicable; IL-6: interleukin-6; Mg: magnesium; Ca: calcium; CRP: C-reactive protein; NT Pro-BNP: N-terminal pro-brain natriuretic peptide; Hb: hemoglobin; ICU: intensive care unit; SBP: systolic blood pressure; CT: cardiac index; SPA: systolic pulmonary artery pressure; PCWP: pulmonary capillary artery wedge pressure; SVI: stroke volume index; CK-MB: creatine kinase-MB; hs-CRP: high-sensitivity C-reactive protein; PTX-3: pentraxin-3; ADMA: asymmetric dimethylarginine; BNP: brain natriuretic peptide; VR: valve replacement

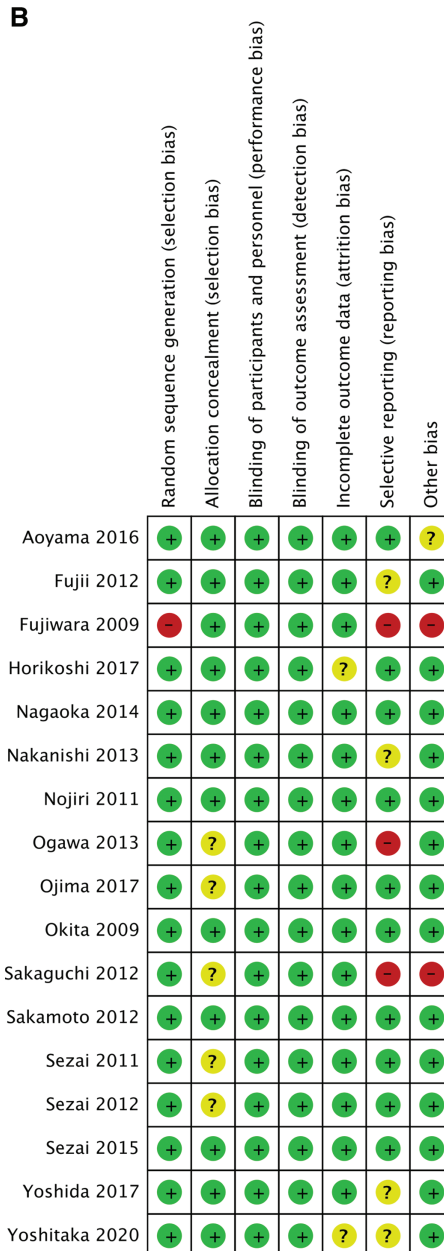
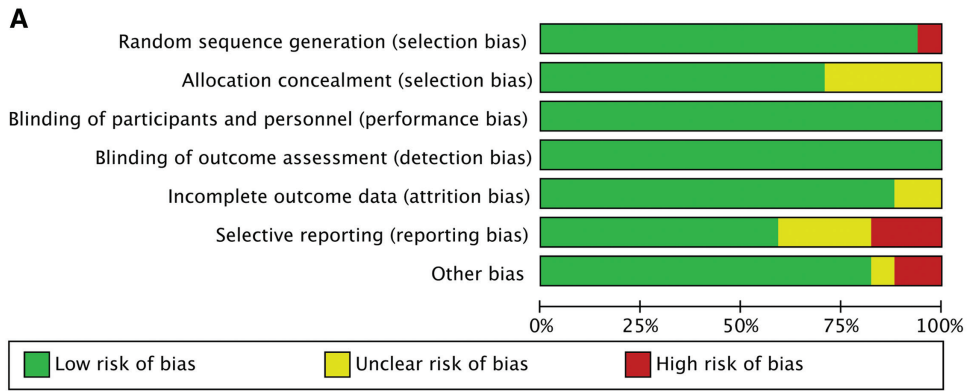


Fig. 2 Risk of bias in the included studies. The Cochrane Collaboration tool was used to assess the risk of bias. The authors' judgments were used to assign the risk of bias for each included study. Green: low risk of bias, red: high risk of bias, and yellow: unclear risk of bias.

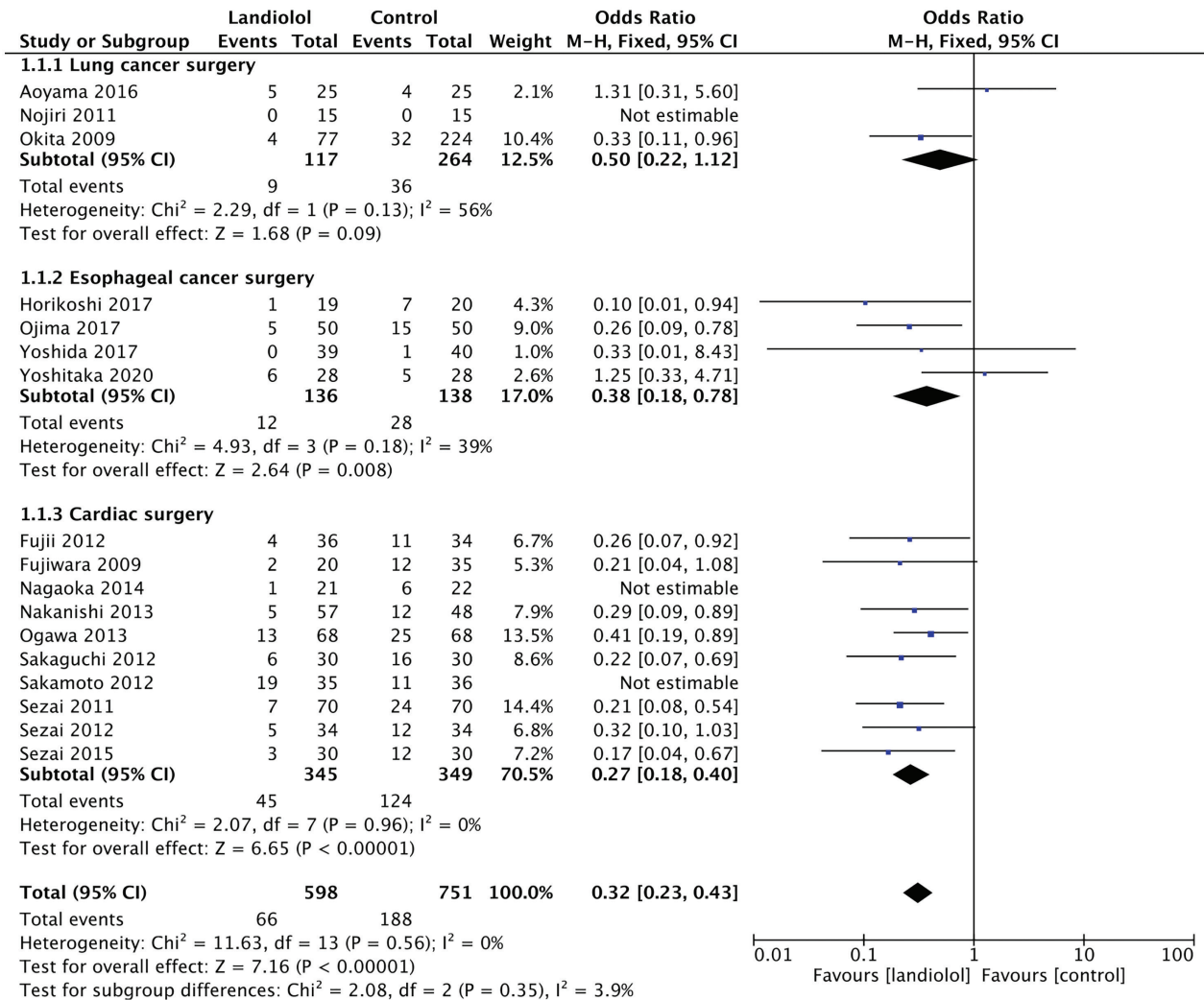


Fig. 3 Forest plot for the incidence of AF occurring during the 7 days after cardiothoracic surgery. AF: atrial fibrillation; CI: confidence interval; M-H: Mantel-Haenszel

landiolol group. In addition, the plasma concentration of interleukin-6 (IL-6) sampled at the end of surgery was significantly lower in the landiolol group.

Hospital stay and mortality

In total, five articles reported the association between perioperative administration of landiolol hydrochloride and length of hospital stay. Results showed that there were no significant differences in length of hospital stay in both group of patients undergoing cardiothoracic surgery (OR = -0.61, 95% CI -1.96-0.73, P = 0.37; **Fig. 5**).

Three articles reported that the perioperative administration of landiolol hydrochloride would reduce the mortality significantly in patients after cardiothoracic surgery (OR = 0.32, 95% CI 0.06-1.63, P = 0.17; **Fig. 6**).

Risk of bias across studies

The funnel plot of our study indicated the absence of obvious publication bias (**Fig. 7**).

Discussion

In our study, we focused on the efficacy and safety of landiolol in the prevention of AF after cardiothoracic surgery. Until now, only a fewer relevant RCTs have focused on the efficacy of landiolol in the prevention of POAF in cardiothoracic surgery, though none had attempted a meta-analysis. We are the first team to give a meta-analysis on this field. According to 17 associated studies, our analysis indicated that landiolol might be effective in the prevention of AF after cardiothoracic surgery without increasing the risk of major postoperative

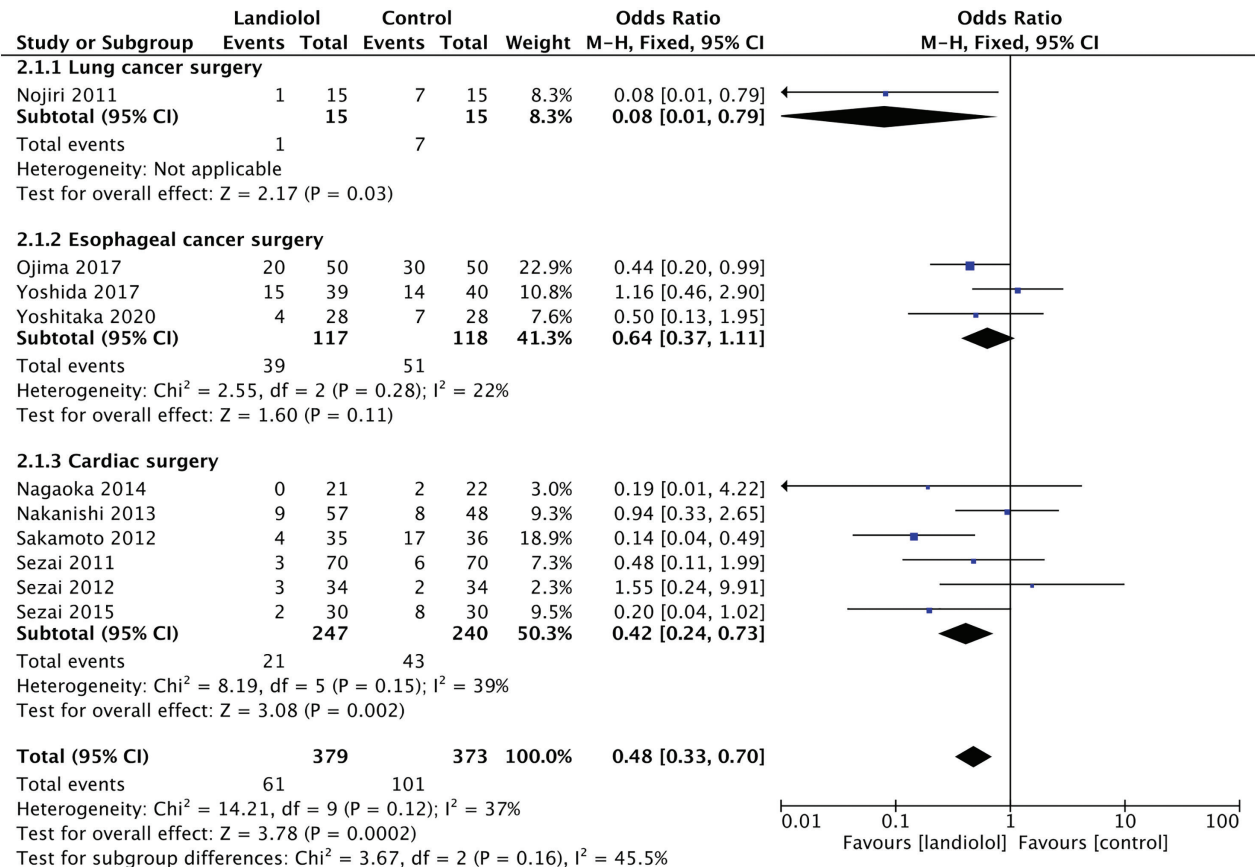


Fig. 4 Forest plot for the incidence of complications after cardiothoracic surgery. CI: confidence interval; M-H: Mantel-Haenszel

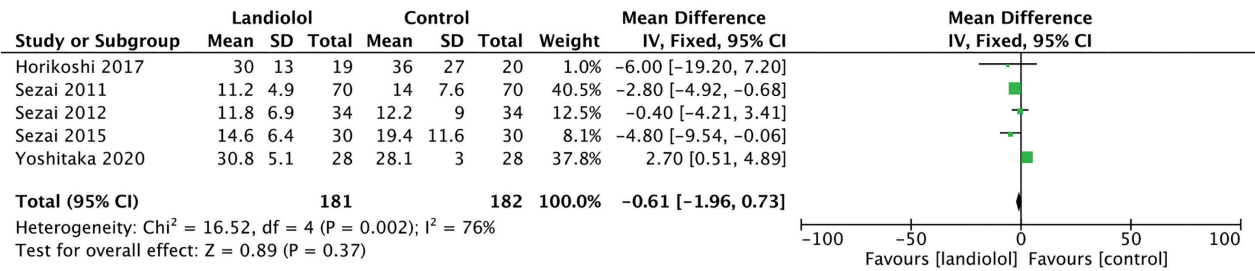


Fig. 5 Forest plot for hospital stay after cardiothoracic surgery. CI: confidence interval; SD: standard deviation

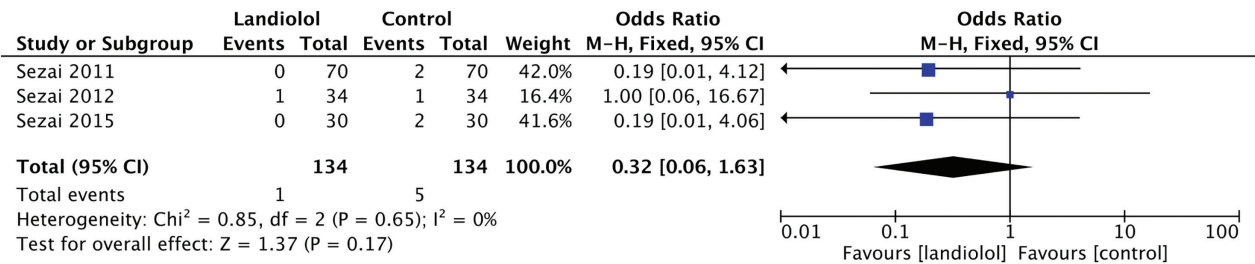


Fig. 6 Forest plot for mortality after cardiothoracic surgery. CI: confidence interval; M-H: Mantel-Haenszel

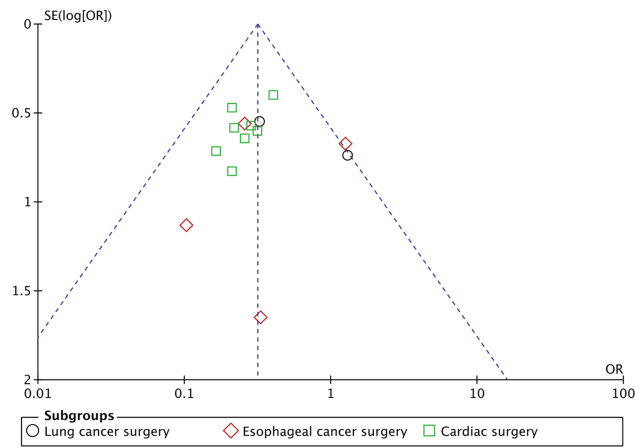


Fig. 7 The funnel plot of ORs of 17 included studies on the x-axis against the standard error of log OR of each study on the y-axis. OR: odds ratio; SE: standard error

complications. Additionally, the plasma concentration of IL-6 sampled at the end of surgery was significantly lower in the landiolol group. Excessive production of IL-6 can damage the cytokine system and promote myocardial injury, and it is also a predictor of subsequent serious clinical complications.^{40,41} This suggests that landiolol can reduce the incidence of AF as well as relevant complications after cardiothoracic surgery.

To our knowledge, AF is one of the most common arrhythmias, and it is reported that multiple factors are associated with the occurring of AF after surgery. For instance elevation in atrial pressure from postoperative impaired ventricular function, tracheal intubation, advanced age, oxidative stress, ischemic damage, sequential combined sympathetic and vagal activation,⁴² right ventricular overload, systemic inflammatory responses,⁴³ smoking pneumonectomy, postoperative acid-base imbalance, electrolyte imbalance, complications (pleural atelectasis, liquid pneumothorax), postoperative analgesia, and so on were all significantly associated with postoperative arrhythmia.⁴⁴ Landiolol may reduce the occurrence of AF after cardiothoracic surgery by attenuating some of these factors.

In Japan, researchers have found that three β -blockers (landiolol, esmolol, and propranolol) are all available for intravenous injection for the treatment of POAF. Landiolol is an ultra-short-acting β_1 -selective blocker with a higher selectivity (β_1/β_2 : landiolol 277, esmolol 20, propranolol 0.6)^{22,45}; besides, landiolol has a shorter plasma half-life (4 min) compared with esmolol and propranolol (esmolol 9 min, propranolol 2 h).⁴⁵ These may suggest that cacoethic respiratory effects will rarely develop with

landiolol, which makes it more suitable for the treatment of POAF after cardiothoracic surgery.

Aoyama et al.'s²⁰ study reported that they couldn't give a conclusion on whether using landiolol could prevent POAF after lung resection. Compared with the other researches that indicated the efficacy and safety of landiolol as the prophylaxis for POAF after lung resection, one definite major disparity was the surgical approach. Other possible disparities were the duration and dosage of landiolol administration. Nojiri et al.'s⁴⁶ study reported that landiolol had a rapid effect with safe administration in patients who developed AF after lung resection. In Aoyama et al.'s study, the duration of landiolol administration was 24 h from the start of the operation during general anesthesia, but in Nojiri et al.'s study, the duration of landiolol administration was 48 h from the same starting point. This may suggest that a longer duration of landiolol administration might affect the efficacy and safety of landiolol in the prevention of AF after surgery.

In the course of our study, we also discovered an interesting phenomenon: smoking might have correlation with the occurrence of POAF. We searched other relevant literature to analyze the relationship between smoking and POAF and found that smokers were more likely to encounter postoperative arrhythmia.⁴⁷ Since smoking results in both the dysfunction of small airways and lung ventilation, it can further induce chronic obstructive pulmonary disease and subsequent cardiovascular lesions. Moreover, certain molecules in tobacco can trigger myocardial anoxia, coronary artery spasms, and variations in blood viscosity, such as nicotine, nitric oxide, and oxynitride. Smoking can also change blood composition, interfering the process of lipid metabolism and enhancing precipitation of cholesterol substances.⁴⁸ Furthermore, it initiates the peroxidation of lipids, accelerating the progress of arterial sclerosis. These are all significant risk factors that could explain the high susceptibility of postoperative arrhythmia among smoking individuals.

In addition, we found that in the all included articles in our study, the surgical procedures of the included patients were not the same. Some patients performed video-assisted thoracic surgery (VATS), while the remaining patients underwent conventional open surgery. In these studies, the authors did not record the details of incidence of POAF in patients who received VATS versus those who underwent conventional open surgery in either the landiolol group or the control group. Many studies believe that the occurrence of POAF is closely related to the surgical approach. If we could study in different surgical methods

the incidence of POAF after cardiothoracic surgery in the landiolol group and the control group, we would get a better understanding of not only the role and efficacy of landiolol in the prevention of POAF but also in which type of surgeries landiolol is more effective.

A previous meta-analysis^{21,49–51}) simply reports the effect of landiolol in preventing POAF after cardiac surgery. The included studies all conclude that landiolol is effective in preventing POAF after cardiac surgery and could be well tolerated. However, their research had certain limitations due to the small number of included articles and single research indicators. In this meta-analysis, we made a subgroup analysis and combined the whole cardiothoracic surgery including cardiac, lung, and esophagus surgery to discover the efficacy of landiolol in the whole of cardiothoracic surgery. These results may prove beneficial to patients undergoing cardiothoracic surgery.

Limitations

There are several limitations to this study. First, we performed a combined meta-analysis of RCTs and cohort studies, which might weaken the strength of the overall results. Then, up to now, there have been few studies about the landiolol in the prevention and treatment of AF after esophageal and lung surgery. Due to the small number of included RCTs, the quality of our research might be affected to a certain extent.

Although our research had limitations, the significance of our research is also important. We have comprehensively analyzed the data of all the published articles, and we used statistical software to analyze the data in a comprehensive way to give more reliable results.

Conclusion

In conclusion, this meta-analysis demonstrated that landiolol effectively prevented the incidence of AF after cardiothoracic surgery without increasing the risk of major postoperative complications. Nevertheless, due to the potential bias and confounding in the included studies, the results should be elucidated cautiously. More high-quality studies comparing landiolol with placebo would be worthwhile.

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Author Contributions

Lunxu Liu: conceptualization, writing – review and editing, and funding acquisition.

Jianqi Hao: conceptualization, writing – original draft, and data curation.

Jian Zhou: methodology.

Wenying Xu: writing – original draft.

Cong Chen: validation.

Jian Zhang: funding acquisition and data curation.

Haoning Peng: software.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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