

Review Article

Efficacy and safety of landiolol for prevention of atrial fibrillation after cardiac surgery: a meta-analysis of randomized controlled trials

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Abstract: Atrial fibrillation (AF) is a quite common complication during the postoperative period after cardiac surgery. Increasing studies have reported that landiolol may be effective in prevention of AF after cardiac surgery. Its efficacy and safety are seldom explored; hence we conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of landiolol in prevention of AF after cardiac surgery. Databases of PubMed, Embase and Cochrane Central Register of Controlled Trials were searched from inception through to December 2014 for RCTs that explored the efficacy and safety of landiolol on the prevention of AF after cardiac surgery. Pooled results were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Nine eligible RCTs involving 807 patients were included in this meta-analysis. Compared with the control group, landiolol was associated with a significant reduction of AF after cardiac surgery (RR=0.41; 95% CI 0.32-0.52; $P<0.001$), and the administration of landiolol seems more effective in patients who underwent coronary artery bypass grafting (CABG) (RR=0.36; 95% CI 0.25-0.52; $P<0.001$). Compared with placebo, no difference was detected in the incidence of major complications (RR=0.77; 95% CI 0.34-1.72; $P=0.52$). Landiolol is effective in prevention of AF after cardiac surgery and without increasing the risk of major complications.

Keywords: Landiolol, atrial fibrillation, cardiac surgery

Introduction

Cardiac surgery has been routinely performed worldwide and more than 5.5 million Americans had coronary artery bypass grafting (CABG) from 1998 to 2005 for example [1]. Atrial fibrillation (AF) is the most common arrhythmic complication after cardiac surgery, and its incidence has been reported differently as 16% to 85% [2-6]. AF after cardiac surgery is associated with increased morbidity and mortality, such as heart failure or stroke, which may also prolongs hospital stay and increases hospitalization costs [7-10]. Therefore preventing management of AF after cardiac surgery should be an important clinical problem and healthcare issue as well. Landiolol, an ultra-short acting β_1 -selective blocker, first launched in Japan, has a serum half-life as short as approximately four minutes, which could be given intravenously and has a weaker negative inotropic effect among intravenous β_1 -blockers [11-14]. The

β_1 -blockers were strongly recommended by the guidelines for AF, and it has been approved that landiolol could be used for treatment of intraoperative and postoperative tachyarrhythmias [15, 16]. Recently, several randomized controlled trials (RCTs) have confirmed that landiolol could prevent AF after several kinds of cardiac surgery, however, due to the small sample size and limited data, few of these trials have been sufficiently powered to determine the usefulness of the treatment in preventing this arrhythmia definitively, we thus conducted a systemic review and meta-analysis of RCTs to evaluate the effectiveness and safety of landiolol on the prevention of AF after cardiac surgery.

Methods

A systematic review of the literature was performed followed methodological recommendations for systematic reviews as given in the

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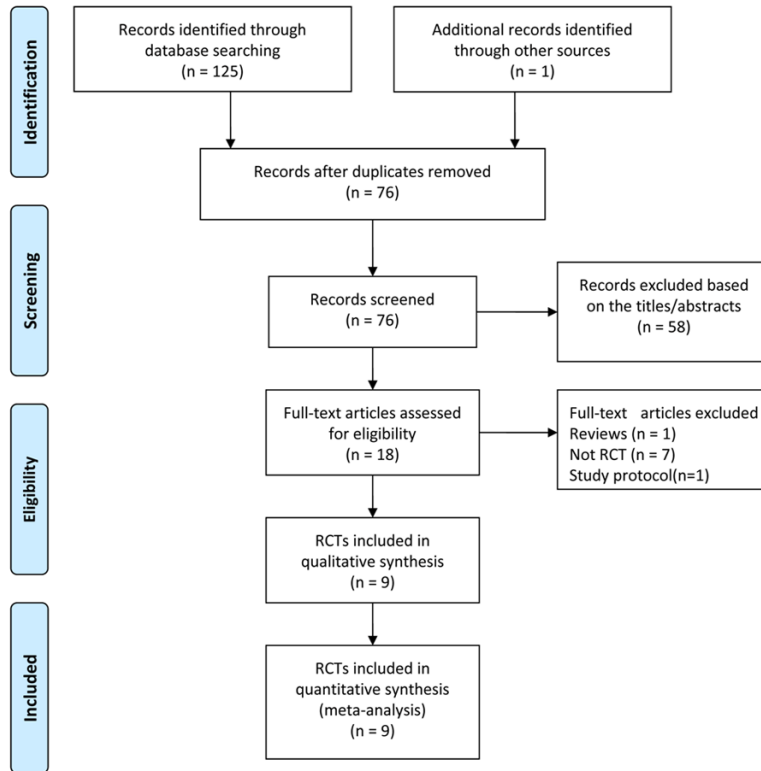


Figure 1. PRISMA flow diagram describing search strategy for the review. RCTs: randomized controlled trials.

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the Cochrane Handbook for Systematic Reviews [17, 18].

Literature search and selection criteria

Two reviewers identified the relevant articles by searching the following data sources respectively: PubMed, Embase and Cochrane Central Register of Controlled Trials (from inception of each database to December 2014). The structured search strategies used the following format of search terms: (landiolol AND 'atrial fibrillation'), and the results were limited to human and no language restrictions were applied. References of included studies and narrative reviews were also considered for additional potential eligible studies.

Prespecified inclusion criteria were as follows: (i) the study design was randomized controlled trials; (ii) The objects underwent any kind of cardiac surgery; (iii) The comparison was between landiolol and placebo or saline or other treatment about the preventive other than treatment effect of AF after cardiac surgery; (iv) the

incidence of AF or major complications was reported.

Two investigators subjectively reviewed each title and abstract. Studies were marked for possible inclusion by either reviewer underwent dual, independent full-text review. Any disagreement was resolved by discussion and consensus.

Data extraction and quality assessment

We used pre-generated structured data extraction forms to gather the following variables from each records: first author, publication year, study area, article type, sample size, patient age and gender, cardiac surgery type, the intervention of landiolol and control groups, the dosage and duration of landiolol used for prevention, the definition of AF, the duration of follow-up and the occurrence of AF or major complications. All data extractions were reviewed for completeness and accuracy by at least 2 investigators. All disputes were resolved by consensus.

The quality of included studies was assessed using the Cochrane Collaboration's tool [17]. Two reviewers independently conducted the risk of bias assessment and assigned 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. Studies with high risk of bias for any one or more key domains were considered of high risk of bias, while trials with low risk of bias for all key domains were considered of low risk of bias. Otherwise they were considered of unclear risk of bias. All discrepancies were resolved via consensus.

Statistical analysis

We assessed the overall efficacy and safety of landiolol on the prevention of AF after cardiac

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Table 1. The main characteristics of studies included in this meta-analysis

Author	Year/area	Patients (L/C)	Age (yr)	Male (%)	Surgery	Treatment group	Control group	Dose & time	Follow-up	Definition of AF	Article type
Sezai et al. [19]	2011/Japan	70/70	67.7	91.4	On-pump CABG	Landiolol	Saline	Administered at the time of central anastomosis during CABG; started at 2 mg/kg/min and discontinued after 48 hours	1 week after surgery	Persistence of arrhythmia for 5 minutes or more or a requirement for treatment because of hemodynamic changes	Full-text
Fujii et al. [20]	2012/Japan	36/34	68.5	68.6	Off-pump CABG	Landiolol and oral carvedilol after extubation	No treatment and oral carvedilol after extubation	Immediately after surgery at 5 µg/kg/min and was continued 0-10 µg/kg/min; it was administered over a mean period of 50 hours	1 week after surgery	Irregular narrow-complex rhythm with absence of a discrete P wave lasting >10 min, or requirement for treatment because of intolerable symptoms or hemodynamic deterioration	Full-text
Ishigaki et al. [21]	2012/Japan	34/15	NA	NA	Catheter ablation	Landiolol	Placebo	Small amount of landiolol (1 µg/kg/min) was continued for 3 days after the CA	3 days after CA	Supraventricular arrhythmia more than 5 min	Abstract
Ishigaki et al. [22]	2012/Japan	31/24	NA	NA	Catheter ablation	Landiolol	Placebo	Small amount of landiolol (1 µg/kg/min) was continued for 3 days after the CA	3 days after CA	As supraventricular arrhythmia more than 5 min	Abstract
Sakaguchi et al. [23]	2012/Japan	30/30	69	53.3	Heart valve surgery	Landiolol	No treatment	Started at a dose of 10 µg/kg/min on admission to the ICU and continued 72 hours; the dose was controlled to keep heart rate >60 beats/min	72 hours after surgery	Persistence of arrhythmia ≥1 min	Full-text
Sezai et al. [24]	2012/Japan	77/34	68.3	81.2	On-pump CABG	Landiolol or landiolol with oral bisoprolol	Saline	Intravenous landiolol perioperatively at 5 mg/kg/min for 3 days, or receiving oral bisoprolol postoperatively together with landiolol	1 week after surgery	If arrhythmia persisted for more than 5 minute sor affected hemodynamics and required treatment	Full-text
Osada et al. [25]	2012/Japan	73/68	NA	NA	All types of open-heart surgery	Landiolol	No treatment and oral carvedilol after extubation	Landiolol hydrochloride 2-3 mg/kg/min was started soon after arrival in the intensive care unit after surgery and was continued for 48 hours	NA	NA	Abstract
Nagaoka et al. [26]	2013/Japan	22/23	65.1	78.7	Off-pump CABG	Landiolol	Diltiazem	0.5 to 2 µg/min/kg to allow evaluation of the efficacy of landiolol at an ultra-low dose	1 week after surgery	Postoperative new-onset atrial fibrillation or atrial flutter requiring treatment or lasting >5 min	Full-text
Ogawa et al. [27]	2013/Japan	68/68	70.5	77.2	Off-pump CABG	Landiolol	No treatment	Started immediately after induction of anesthesia, with adjustment of the dose between 3-5 mg/kg/min to control the heart rate at 60-90 beats/min; administration continued for 2 days after the operation	1 week after surgery	AF that continued for ≥10 min	Full-text

CABG: coronary artery bypass grafting; AF: atrial fibrillation; CA: catheter ablation; NA: not available.

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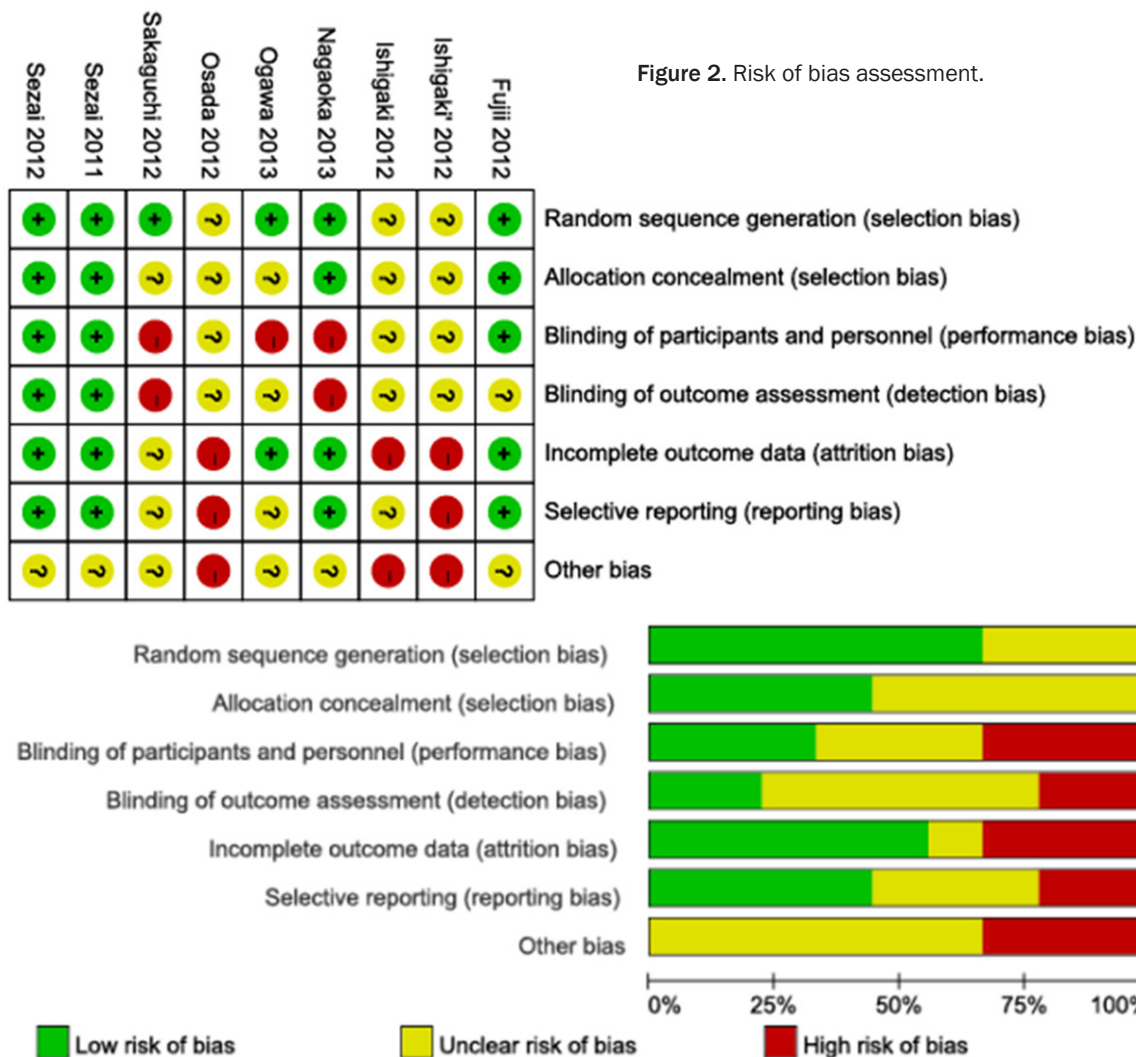


Figure 2. Risk of bias assessment.

surgery based on the data from the nine RCTs. The major analysis was focused on the preventive effect of landiolol, subgroup analysis stratified by the type of cardiac surgery was also performed and we mainly paid attention to CABG studies which were performed mostly. We also analyzed the major complications to explore the safety of landiolol.

The pooled results of dichotomous outcomes were expressed as relative risks (RRs) with 95% confidence intervals (CIs). Weather fixed-effect model or random-effect model was used according to the heterogeneity. The heterogeneity across studies was tested by Q statistic (a significant level of P value <0.1) and the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, moderate, and considerable heterogeneity, respectively). A two-tailed P value <0.05 was considered statisti-

cally significant. Statistical analyses were performed using RevMan 5.3 (The North Cochrane Centre, Copenhagen, Denmark).

Results

Study characteristics and quality

Figure 1 describes the literature search. Overall, the initial electronic search identified 125 potentially eligible articles, and one additional record obtained through other sources. We excluded 50 duplicated records, removed 58 records which were identified as irrelevant by scanning titles and abstracts, the remaining 18 full-text articles were further reviewed. Nine eligible RCTs including 807 participants were included in the meta-analysis [19-27].

Detailed characteristics of nine eligible studies are presented in Table 1. In total, 807 patients

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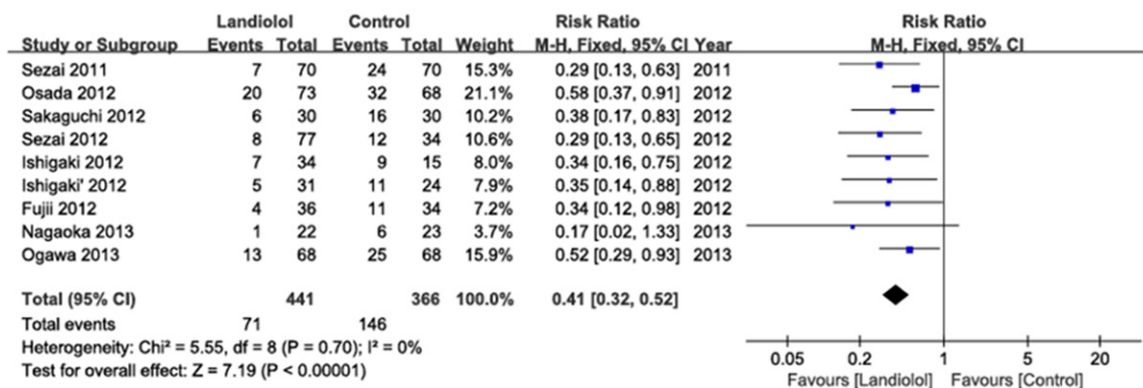


Figure 3. Forest plot comparing the protective effect of landiolol with control group. A Mantel-Haenszel fixed-effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

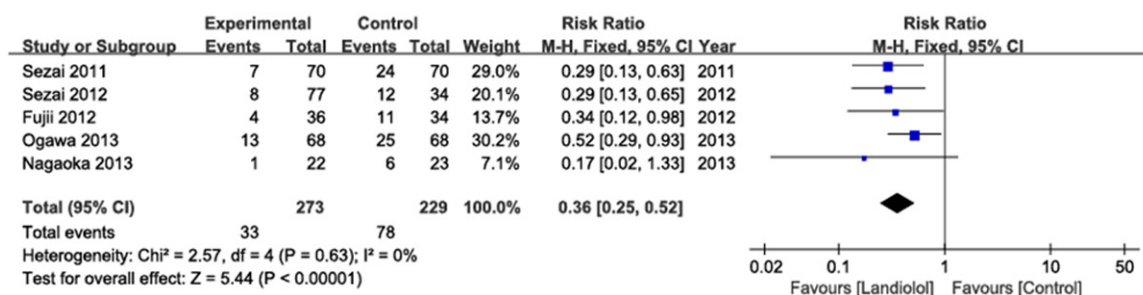


Figure 4. Pooled result of sub-group analysis of the incidence of postoperative atrial fibrillation in RCTs of coronary artery bypass grafting surgery. A Mantel-Haenszel fixed-effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

were included, 441 of these patients were allocated to landiolol group, and the median sample size was 70 (range 45-141) patients. All of these RCTs were conducted in Japan, which mainly on account of landiolol was first launched and approved for clinic usage in Japan. Of the nine included RCTs, five RCTs were performed in patients who underwent CABG, two RCTs conducted catheter ablation, one RCTs received heart valve surgery and one contains all types of open-heart surgery.

The quality of included studies were assessed according to the published Cochrane guidelines, the nine RCTs especially three conference abstracts were at high risk of bias, and the details of risk of bias for each included trial are shown in **Figure 2**.

Efficacy outcomes

The incidence of AF after cardiac surgery were reported in all nine RCTs, the pooled results indicated that, compared with placebo, landio-

lol was associated with a significant reduction of AF after cardiac surgery (RR=0.41; 95% CI 0.32-0.52; $P < 0.001$) (**Figure 3**), and subgroup analysis of the CABG surgery type revealed that the administration of landiolol seems more effectiveness in patients who underwent coronary artery bypass grafting (CABG) (RR=0.36; 95% CI 0.25-0.52; $P < 0.001$) (**Figure 4**).

Safety outcome

We subsequently analyzed the safety of landiolol. Major complications were reported in three RCTs, there was one death in each group, other serious complications happened in landiolol group were low output syndrome, cerebral infarction, asthma, hypotension and mediastinitis in one case each, myocardial infarction (two case), acute renal failure (three case), while mediastinitis, cerebral infarction in one case each, low output syndrome (two case), arrhythmia (two case), heart failure (three case) in the control group. The safety analysis found no difference in the incidence of major compli-

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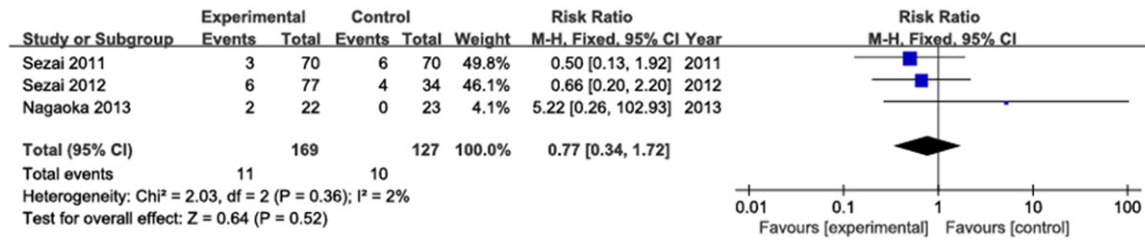


Figure 5. Forest plot comparing the side effects of landiolol group with control group. A Mantel-Haenszel fixed-effects model was used for meta-analysis. Risk ratios are shown with 95% confidence intervals.

cations between landiolol and control groups (RR=0.77; 95% CI 0.34-1.72; P=0.52) (**Figure 5**).

Discussion

To our knowledge, this meta-analysis is a comprehensive review which included RCTs no matter the type of cardiac surgery to assess the preventive effect of landiolol on occurrence of AF after cardiac surgery. The trials included in this analysis are of medium quality, which can not only give power to assess the efficacy and safety of landiolol, but also possess instructional significance and referenced value for the further studies. According to our findings, compared with control group, landiolol could significantly reduce the incidence of AF after cardiac surgery by 59%, and subgroup analysis confirmed more effective in CABG by a reduction of 64%, without increased risk of major complications.

Various factors have been reported to have an association with AF after cardiac surgery such as advanced age, obesity, cardiac dysfunction, chronic obstructive pulmonary disease, sympathetic hypertonia, oxidative stress and inflammation, other possible factors like calcium antagonists still need further exploration [24, 28-32]. The β -blockers have been associated with myocardial protection through anti-ischemic, anti-inflammatory and sympatholytic effects. They are routinely used as a countermeasure and have been proved to inhibit the onset of AF after cardiac surgery, but they often cause hypotension due to their cardiodepressant effect [15, 19, 33-35]. However, landiolol is highly selective with little negative inotropic and hemodynamic effect, and is also easy to vary with haemodynamics due to its extremely short half-life [24, 36]. The anti-inflammatory effect of landiolol was studied in four RCTs [19, 25-27] but Nagaoka et al. failed to identify the

anti-inflammatory effect, and the detailed mechanism of landiolol still need further exploration.

In the nine RCTs included, there is a variety of dosage, timing and duration of landiolol administration. The diversity of interventions not only contributes to the inconformity of the reported outcomes, but also closely in touch with the preventive effect. Considering that AF usually occurs during 1 and 3 days postoperatively, with a highest incidence on the second day after cardiac surgery, thus both intravenous of landiolol in the acute phase and maintenance therapy after intravenous administration are of great importance because some patients developed AF after termination of landiolol [24]. In addition, Sezai et al. found combining landiolol with an oral β -blocker may further reduce the incidence of postoperative AF [25]. Therefore, the dose, duration and combination use of landiolol administration still need further investigations to inhibit AF better.

Data on major complications were only available in three studies. All together, there was no difference between the two groups of the major complication, but the limited data is of small power because the side-effect of landiolol is seldomly reported and its safety remains disputable, more attention should be paid to the complications. Apart from safety, the cost-effectiveness and quality of life should be explored further. Only one study reported hospital cost, although the cost of landiolol for prevention is approximately \$ 400 averagely, it is still significant lower than control group mainly on account of additional drug for treatment of AF and longer hospital stay in control group [19]. Thus it seems prevention of AF is of better cost-effectiveness. Adequate data on these outcomes contribute to a comprehensive evaluation of landiolol.

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Up to now, various pharmacological and non-pharmacological interventions have been developed to focus on the root causes and comorbidities factors and reduce the incidence of AF. Our updated results are in agreement with those presented in these previous reviews [37, 38]. In the nine RCTs we included in our meta-analysis, only Nagaoka et al. compared landiolol with diltiazem rather than saline or placebo or no treatment. Although present trials and limited relevant data indicate that landiolol is efficacious and safe, whether landiolol exhibits better than current first line prophylactic is not known, and compared with placebo maybe inappropriate because the incidence of AF is very high in the placebo group [25]. In the further studies, the efficacy and safety problems related to landiolol should be clarified in comparison with amiodarone and other β -blockers which have been proved to be effective and safety for the majority of patients and recommended in the American College of Cardiology/American Heart Association guideline [39-41].

Several potential limitations of our meta-analysis should be taken into consideration. First, it was primarily limited by the lack of complete availability of relevant outcomes data especially about the side-effects, other diameters like cost and length of hospital stay were rarely reported in the studies. Second, this meta-analysis was limited by the moderate quality of the available studies. Single-blinding within pharmacological trials for safety, selective reporting, incomplete outcome data and unclear risk of other bias, these were all associated with variation in the pooled summary estimates for prevention of post-operative AF. Third, dosing regimens and the follow-up time varied between studies, these discrepancies may partly contribute to the clinical heterogeneity among the included studies, although no or low statistical heterogeneity is found. In addition, more than half of the included studies had a modest sample size, and the exclusion of non-English language studies which we have no access to the full-text, these may lead to bias in effect size.

In conclusion, this meta-analysis of nine RCTs revealed that prophylactic landiolol significantly reduced the incidence of AF after cardiac surgery by 59%, and subgroup analysis confirmed it is more effective in patients who underwent

CABG by a reduction of 64%, without increased risk of major complications. Nevertheless, the results should be elucidated cautiously due to the potential bias and confounding in the included studies. Larger studies compare landiolol with other first line prophylactic would be worthwhile.

Disclosure of conflict of interest

None.

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