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# Administration of Low-Dose Landiolol Prevents Postoperative Atrial Fibrillation After Aortic Valve Replacement

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**Abstract:** *Background*: Postoperative atrial fibrillation (POAF), a common complication of cardiac surgery, increases postoperative mortality, morbidity, and medical costs. POAF after coronary artery bypass grafting is well investigated; however, little is known about POAF after aortic valve replacement (AVR). This study aimed to investigate the efficacy of low-dose landiolol in preventing POAF after AVR. *Methods*: Thirty patients who underwent AVR were randomized into two groups, with or without administration of landiolol (Landiolol, N=15; Control, N=15). In Landiolol, continuous infusion of landiolol (3 μg/kg/min) was maintained for 48 h from admission to the intensive care unit. The occurrence of POAF during seven days after surgery, heart rate, blood pressure, cardiac index, and mixed venous oxygen saturation were compared between the two groups. *Results*: POAF occurred in one and seven patients in Landiolol (6.7%) and Control (46.7%), respectively, with significantly lower incidence in Landiolol than in Control (p=0.0352). The heart rate was significantly lower in Landiolol than in Control. No significant differences were observed in blood pressure, cardiac indices, and mixed venous hemoglobin oxygen between the two groups. *Conclusions*: The administration of low-dose landiolol following AVR significantly decreased the incidence of POAF without hemodynamic deterioration, suggesting that it may safely and effectively prevent POAF in patients undergoing AVR.

**Keywords:** Landiolol, POAF, AVR

## 1. Introduction

Postoperative atrial fibrillation (POAF) is the most frequent complication after cardiac surgery, leading to detrimental complications such as stroke, hemodynamic instability, and congestive heart failure in addition to prolonged hospitalization and increased healthcare costs [1, 2]. Despite improvements in surgical techniques and perioperative management, POAF after cardiac surgery has remained high over the past several decades, with an incidence rate ranging between 17% and 65% [3-7]. The occurrence of POAF after valve replacement surgery (AVR) is higher than that after coronary artery bypass grafting (CABG) [1, 2]. Although POAF is usually temporary, it increases morbidity and mortality; therefore, preventing POAF is crucial in patients undergoing cardiac surgery. Preoperative beta-blocker (BB), amiodarone, angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), statin, corticosteroid, and postoperative atrial pacing can effectively prevent POAF [3, 8, 9]. However, treatment with BB is associated with an increased risk of bradycardia, hypotension, and hemodynamic deterioration, which limits its perioperative use. Landiolol (Ono Pharmaceutical Co, Ltd, Osaka, Japan) is an ultra-short-acting, highly selective beta 1 receptor antagonist that is available in Japan and in some European countries. Landiolol may offer effective prophylaxis against POAF without adverse hemodynamic effects [10]. Low dose

administrarion of landiolol has been reported to prevent POAF following CABG [11-16]. To date, only a limited number of studies have focused on the use of landiolol after heart valve surgery [17, 18] and only one study has investigated its effect at preventing POAF after AVR [18]; however, the study was retrospective.

The present study aimed to evaluate the impact of low-dose landiolol on the occurrence of POAF, hemodynamics in the acute postoperative phase in patients who underwent AVR. To the best of our knowledge, this is the first randomized study on the efficacy of landiolol in preventing POAF, focusing on AVR.

# 2. Patients and Methods

### *2.1. Patients and Groups*

Between September 2009 and September 2011, 119 patients underwent AVR for aortic valve stenosis (AS) or aortic valve regurgitation (AR) in Kurume University Hospital. Patients with a history of atrial fibrillation (AF), prior use of antiarrhythmic agents, pacemaker implantation, any degree of atrioventricular block, or uncontrolled heart failure were excluded. Accordingly, 30 patients (15 men and 15 women) with a mean age of 70.0 years (range, 26–90 years) met the inclusion criteria. Written informed consent was obtained from each patient in advance, and the ethical committee of Kurume University approved this randomized controlled trial (registry number; 09009). Thirty patients were randomly assigned to two groups: Landiolol (N=15) and Control (N=15) using the lottery method on the previous day of the surgery. Each patient drew a card which was written Landiolol or Control from the box for grouping. The physicians and medical staff involved in the study were not blinded; however, the patients were blinded.

During surgery, cardiopulmonary bypass was established with cannulation of the ascending aorta and the right atrium. Myocardial protection was achieved with intermittent antegrade blood cardioplegia during aortic cross-clamping. Right atrial and right ventricular temporary pacing leads were placed on the heart.

In Landiolol, after admission to the intensive care unit (ICU), continuous intravenous administration of landiolol was initiated at a dose of 3 μg/kg/min for 48 h. The dosage was not changed during the study period. In Control, landiolol was not administered. When oral drug intake became available, oral bisoprolol (2.5mg per day) was started to all patients in both groups.

Continuous electrocardiographic telemetry was monitored during seven days after the surgery. When the heart rate (HR) was less than 80 beats/min, right atrial pacing worked at the rate of 80 beats/min for 48 h after surgery. POAF was defined as AF lasting for 5 min or more or the need for treatment with antiarrhythmic medication or electrical defibrillation.

### *2.2. Determination of the Effects of Landiolol*

To evaluate the effects of landiolol on hemodynamics, the HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiac index (CI), and mixed venous oxygen saturation ($SvO_2$) were recorded. HR was measured after temporarily discontinuing the pacemaker. HR, SBP, and DBP were recorded 1, 3, 12, 24, 48, 72, 120, and 168 h after admission to the ICU. CI and $SvO_2$ were measured at the time of ICU admission and 1, 3, 6, and 12 h after using a Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA).

### *2.3. Statistical Analysis*

Data are expressed as the mean ± standard deviation. Categorical variables were analyzed using either the chi-square test or Fisher's exact test. Continuous variables were analyzed using Student's *t-test*. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the JMP 15 software package (SAS Institute Inc., Cary, NC, USA).

# 3. Results

### *3.1. Patient Characteristics*

All 30 enrolled patients completed the study. The administration of landiolol was not discontinued in Landiolol because of hemodynamic instability, such as bradycardia or hypotension. The characteristics and operative data of the two groups are shown in Table 1. There were no significant differences in age, sex, body mass index, etiology of the main aortic valve lesion (AS or AR), left ventricular ejection fraction, hypertension, diabetes mellitus, dyslipidemia, preoperative medication including BB, ACEI/ARB, and statins between Landiolol and Control. Additionally, no significant differences were observed in cardiopulmonary bypass time or aortic cross-clamping time between the two groups.

***Table 1.*** *Patient Characteristics.*

| patients | Landiolol (N=15) | Control (N=15) | p Value |
|---|---|---|---|
| Age | 69.3 ± 13.7 | 70.8 ± 13.3 | 0.7588 |
| Gender (male/female) | 9/6 | 6/9 | 0.4661 |
| BMI ($kg/m^2$) | 21.6 ± 3.5 | 21.0 ± 3.5 | 0.6588 |
| Etiology (AS/AR) | 9/6 | 9/6 | 1 |
| LVEF (%) | 63.7 ± 8.1 | 64.4 ± 11.4 | 0.8406 |
| Hypertension | 12 | 11 | 1 |
| Diabetes mellitus | 1 | 2 | 1 |
| Dyslipidemia | 6 | 3 | 0.4270 |
| β-blocker | 4 | 3 | 1 |

| patients | Landiolol (N=15) | Control (N=15) | p Value |
|---|---|---|---|
| ACEI/ARB | 10 | 8 | 0.7104 |
| Statin | 5 | 2 | 0.3898 |
| CPBT (min) | 144.0 ± 29.9 | 136.5 ± 34.0 | 0.5247 |
| ACCT (min) | 110.1 ± 20.3 | 101.3 ± 28.3 | 0.3401 |

Legends: BMI: body mass index, AS: aortic valve stenosis, AR: aortic valve regurgitation,
LVEF: left ventricular ejection fraction,
ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker,
CPBT: cardiopulmonary bypass time, ACCT: aortic cross-clamping time.

### *3.2. Operative Mortality and Complications*

There were no in-hospital mortalities or major complications such as low cardiac output syndrome requiring mechanical circulatory support, respiratory failure requiring mechanical ventilation for more than 24 h or a tracheostomy, stroke, mediastinitis, renal failure requiring new hemodialysis, and multi-organ failure in both groups.

### *3.3. Occurrence of POAF*

POAF occurred in one patient (6.7%) in Landiolol and seven (46.7%) patients in Control. The incidence of POAF was significantly lower (p=0.0352) in Landiolol than in Control. The distribution of the timing of the occurrence of POAF is shown in Figure 1. All cases of POAF occurred within four postoperative days (POD) in both groups. All of these patients did not experience repeated POAF during seven days after the surgery. In Landiolol, one patient experienced POAF on POD 2, which occurred 6 h after the termination of treatment with landiolol.

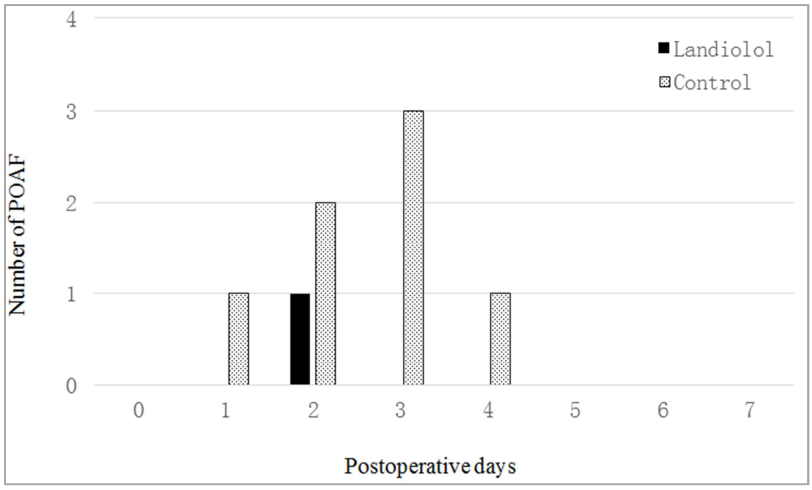


***Figure 1.*** *Timing of POAF. Legends: POAF: postoperative atrial fibrillation.*

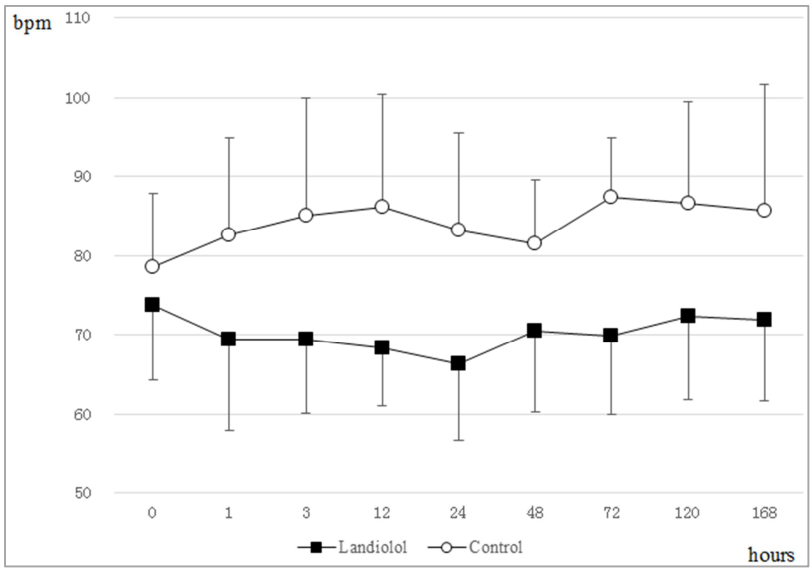


***Figure 2.*** *Heart Rate.*

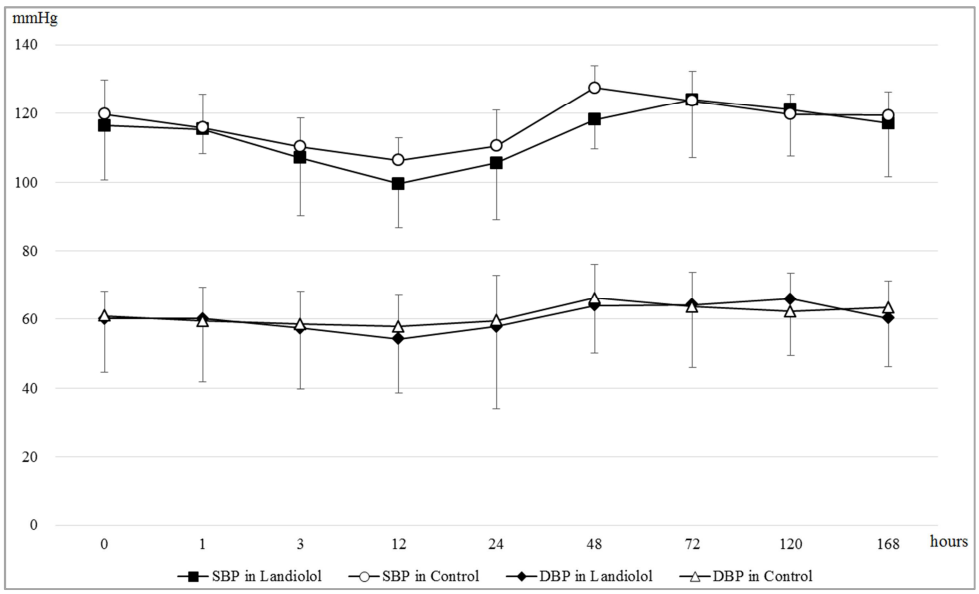


***Figure 3.*** *SBP and DBP. Legends: SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure.*

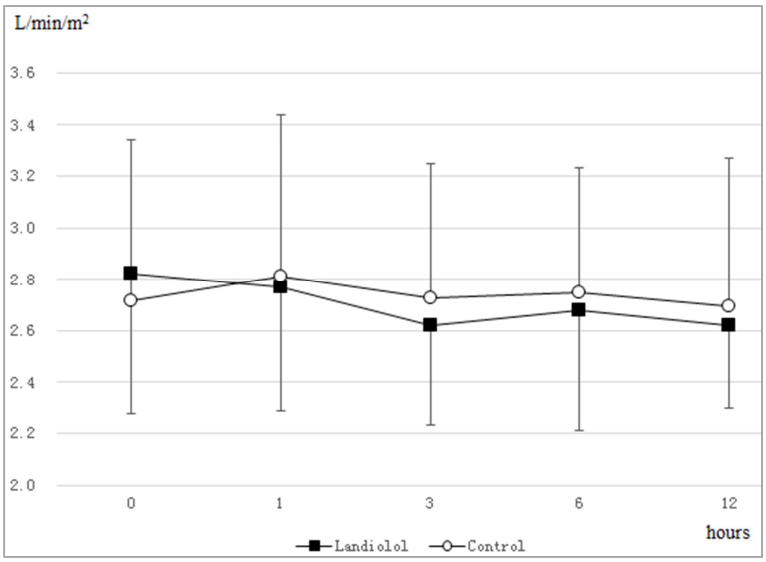


***Figure 4.*** *Cardiac Index.*

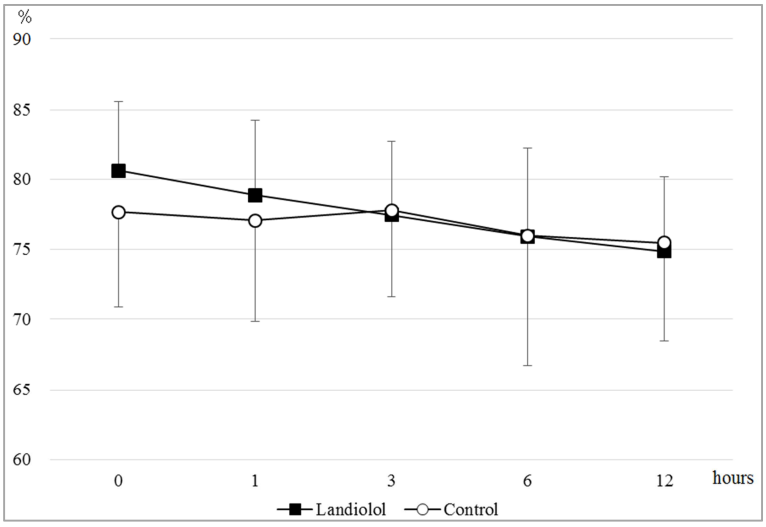


***Figure 5.*** *Mixed Venous Oxygen Saturation.*

### *3.4. Hemodynamics*

Changes in hemodynamics such as HR, SBP, DBP, CI, and $SvO_2$ are shown in Figures 2, 3, 4, and 5, respectively. There was no significant difference in HR at the time of admission to the ICU between the two groups. However, HR was significantly lower in Landiolol than in Control at 1, 3, 12, 24, 48, 72, 120, and 168 h after admission to the ICU. Moreover, no significant differences in SBP, DBP, CI, and $SvO_2$ were observed between the two groups at any point.

## 4. Discussion

The incidence of POAF is approximately 32% after isolated CABG, 42–48% after isolated mitral valve surgery, 49% after isolated AVR, and 60–92% after combined valve and CABG procedures [1]. Filardo et al. reported that patients who experience new-onset POAF following AVR have a 48% higher risk of long-term mortality than those who do not, and they hypothesized that patients with POAF would develop chronic or recurrent AF [19]. Therefore, patients with POAF might experience a higher risk of stroke and congestive heart failure in the long term [18]. Although many studies on POAF after CABG have been reported [6, 7, 11-16], only a few studies have investigated POAF after AVR [18-20]. Moreover, the number of patients with AS has dramatically increased with the aging population; accordingly, the number of AVR has also increased. Consequently, the present study investigated the preventive effect of landiolol on POAF in patients after AVR.

POAF typically occurs within five days postoperatively, with a peak incidence on POD 2 [21]. In our study, POAF occurred from POD 2 to 4 in one patient (6.7%) in Landiolol and seven (46.7%) patients in Control, indicating a significant difference in the occurrence of POAF between the two groups. Notably, POAF occurred six hours after the cessation of landiolol in the patient in Landiolol, indicating that no patient experienced POAF during the administration of landiolol. Moreover, treatment with BB after cardiac surgery is associated with adverse effects, including bradycardia and hypotension. Therefore, to avoid hypotension, landiolol is administered at a low dose. In the present study, we administered 3 μg/kg/min of landiolol to patients and observed no significant differences in SBP, DBP, CI, and $SvO_2$ between treated and untreated patients. Consistent with our results, the continuous administration of 1.5–2.5 μg/kg/min [11] and 2 μg/kg/min [12] landiolol in patients who underwent CABG resulted in a significant decrease in the incidence of POAF without any hemodynamic adverse effects. Overall, our findings indicate that the administration of landiolol significantly decreases the incidence of POAF in the acute postoperative phase after AVR without causing hemodynamic adverse effects.

In a previous study, Kalman et al. [22] measured plasma norepinephrine levels in the right atrium as an indicator of the level of cardiac sympathetic activation in patients who underwent CABG and demonstrated significantly high levels up to 48 h postoperatively in patients with POAF. In their study, the HR increased during the last minute of the onset of POAF. BB stabilize excessive sympathetic activity; therefore, they may act as prophylaxis for POAF. Moreover, landiolol exhibits high beta 1 receptor selectivity and a weaker negative inotropic effect than other intravenous BB, with a blood half-life of only 4 min, which helps control the dose for intravenous administration. Thus, the use of landiolol is simple and easy in cardiac surgery. In our study, significantly lower HR without a significant decline in blood pressure and cardiac output was observed in Landiolol compared to Control. Collectively, these results suggest that landiolol may inhibit sympathetic hyperactivity after AVR and prevent myocardial ischemia by decreasing myocardial oxygen consumption, thereby decreasing the incidence of POAF in the postoperative acute phase. Consistent with our results, Sakamoto et al. [23] emphasized the importance of this mechanism in the treatment of POAF after cardiac surgery. Sezai et al. [12] reported the efficacy of low-dose landiolol in preventing POAF after CABG; they demonstrated that the landiolol group had a significantly lower incidence of POAF than the placebo group and concluded that landiolol alleviated ischemia, exhibited an anti-inflammatory effect, and inhibited sympathetic hypertonia, which may have reduced the occurrence of POAF.

In recent decades, transcatheter aortic valve replacement has emerged as an effective alternative therapy for AS. In the PARTNER 3 trial, early POAF was more frequent following conventional surgical AVR than transcatheter AVR [24]. Therefore, the protective effect of perioperative administration of landiolol against POAF in patients undergoing transcatheter AVR should be investigated in future studies.

In this study, we confirmed the efficacy of transvenous landiolol in managing POAF. Yokota et al. reported that the preoperative oral use of BB is associated with a nearly two-fold decrease in the risk of POAF after AVR [17]. Okamura et al. suggested that the use of transdermal BB is independently associated with a lower rate of POAF in patients after cardiac and/or thoracic aortic surgery [25]. In other words, BB may have a preventive effect on POAF after cardiac surgery irrespective of the route of administration.

The present study had some limitations. First, the patients were randomized into two groups using the lottery method but were not treated in a double-blind manner. Second, the number of patients in each group was small; therefore, the possibility of individual differences in patients cannot be ignored.

## 5. Conclusion

This study demonstrated that the postoperative administration of low-dose landiolol has a preventive effect on the occurrence of POAF without hemodynamic deterioration after AVR. These results suggest that low-dose landiolol is a

useful and safe option to prevent POAF after AVR.

## Abbreviation

POAF: Postoperative Atrial Fibrillation
AVR: Aortic Valve Replacement
CABG: Coronary artery Bypass Grafting
BB: Beta-Blocker
ACEI: Angiotensin-Converting Enzyme Inhibitor
ARB: Angiotensin II Receptor Blocker
AS: Aortic Valve Stenosis
AR: Aortic Valve Regurgitation
AF: Atrial Fibrillation
ICU: Intensive Care Unit
HR: Heart Rate
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure
CI: Cardiac Index
$SvO_2$: Mixed Venous Oxygen Saturation
POD: Postoperative Day

## Declarations

### *Ethical Approval and Consent to Participate*

This study was approved by the ethical committee of Kurume University Hospital (registry number; 09009). All participants provided written informed consents.

### *Conflict Interests*

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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### *Authors' Contributions*

TO wrote the manuscript with the support of RM, ET, and SA. TO and RM collected and analyzed the data. All authors have read and approved the final manuscript.

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