Intravenous landiolol for the prevention of atrial fibrillation after aortic root, ascending aorta, and aortic arch surgery: A propensity score-matched analysis

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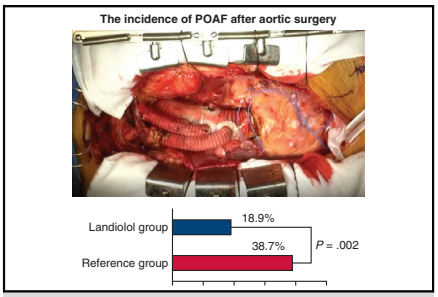
ABSTRACT

Objective: Postoperative atrial fibrillation (POAF) after cardiac surgery is associated with increased mortality. The efficacy of landiolol hydrochloride for POAF prevention after coronary artery bypass grafting procedure and valve surgery has been reported. However, little evidence is available on its role in POAF prevention after aortic root, ascending aorta, and aortic arch surgery. This study aimed to determine the association between intravenous landiolol and the incidence of POAF after these aortic surgeries.

Methods: We included 358 consecutive adult patients without preoperative atrial fibrillation who underwent aortic root, ascending aorta, and aortic arch surgery between January 1, 2011, and December 31, 2018, at our institution. The therapeutic influence of landiolol in preventing POAF was estimated by propensity score-matched analysis (n = 222). The primary end point was the incidence of POAF within 72 hours after surgery. The secondary end points included adverse clinical events such as 30-day mortality and symptomatic cerebral infarction.

Results: The median age of the cohort was 72 years, 68.5% were men, and 46.4% received postoperative oral or transdermal β-blockers. After minimizing differences in patient background by propensity score matching, the incidence of POAF in the landiolol group was significantly lower than that in the reference group (18.9% vs 38.7%; $P = .002$). Landiolol use was associated with reduced incidence of POAF (odds ratio, 0.39; 95% CI, 0.21 to −0.72; $P = .003$). There were no significant differences in secondary end points.

Conclusions: Intravenous landiolol was associated with a lower incidence of POAF after aortic root, ascending aorta, and aortic arch surgery. (JTCVS Open 2022;11:49-58)



Landiolol was associated with a lower incidence of POAF after aortic surgery.

CENTRAL MESSAGE

In a propensity score-matched cohort, intravenous landiolol was related with a lower incidence of postoperative atrial fibrillation after aortic root, ascending aorta, and aortic arch surgery.

PERSPECTIVE STATEMENT

Several trials have shown that intravenous landiolol prevents POAF after cardiac surgeries, but its role after aortic root, ascending aorta, and aortic arch surgery is unclear. We found that landiolol is associated with lower POAF incidence. Physicians or surgeons should consider landiolol as a therapeutic option for POAF prevention after these surgeries.

Video clip is available online.

Atrial fibrillation (AF) is among the most commonly encountered arrhythmias in a variety of clinical settings and a common complication after cardiac surgery.[1] For example, postoperative AF (POAF) occurs in 20% to 30% of patients after coronary artery bypass grafting

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Received for publication Aug 5, 2021; revisions received May 27, 2022; accepted for publication June 9, 2022; available ahead of print July 11, 2022.

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2666-2736

https://doi.org/10.1016/j.xjon.2022.06.010

Abbreviations and Acronyms

AF = atrial fibrillation
CPB = cardiopulmonary bypass
ICU = intensive care unit
IPTW = inverse probability of treatment weighting
POAF = postoperative atrial fibrillation
PS = propensity score
RASI = renin-angiotensin system inhibitor

(CABG),[1,2] in 35% to 50% of patients after valve surgery,[1,3] and in 49% to 52% of the patients after aortic root, ascending aorta, and aortic arch surgery.[4,5] POAF has interested physicians and surgeons for decades, and various studies have been conducted due to its association with adverse clinical events, such as postoperative bleeding, organ failure, longer hospital or intensive care unit (ICU) stay, cerebral infarction, cardiac arrest, high 30-day and 6-month mortality, and even 5- and 10-year mortality.[1,6] Thus, the prevention of POAF is an important clinical challenge. A recent systematic review suggested that beta-blockers such as carvedilol and sotalol, as well as amiodarone, atrial pacing, and antioxidant vitamins lower the risk of POAF[7]; in that review, most studies involved the use of beta-blockers.

Accordingly, intravenous landiolol hydrochloride, an ultra-short-acting β_1-selective blocker, could be considered an option for the prevention of POAF after cardiac or aortic surgery.[8-10] Several observational studies[11-15] and randomized controlled trials[16-23] have reported that landiolol prevents POAF after cardiac surgeries such as CABG and valve surgery. However, little evidence is available regarding its role in POAF prevention after aortic root, ascending aorta, or aortic arch surgeries.

The objective of this single-center retrospective observational study was to investigate the association between intravenous landiolol administration and the incidence of POAF among patients who underwent aortic root, ascending aorta, and aortic arch surgery with or without concomitant CABG or valve surgery. We hypothesized that landiolol administration leads to a lower incidence of POAF than its omission. Any potential therapeutic effects were measured by propensity score (PS)-matched analysis, and the robustness of the result was evaluated by inverse probability of treatment weighting (IPTW).[24]

METHODS

Study Patients

Among the 462 adult patients (aged ≥18 years) who underwent aortic root, ascending aorta, and aortic arch surgery at Hiroshima Citizens Hospital between January 1, 2011, and December 31, 2018, 358 patients without preoperative AF were retrospectively included in the present study (Figure 1). We included patients with or without CABG or any kind of valve surgery. To meet the eligibility criteria shown in Figure 1, 46 patients with a preoperative history of any type of AF were excluded from the study population. Perioperative data shown in Tables 1 through 4 and Figure 1 were retrospectively collected from surgical or patient clinical records. The study protocol complied with the standards outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Hiroshima Citizens Hospital (approval No.: 30-117; December 14, 2018). The requirement for informed consent was waived due to the retrospective nature of the present study. The opt-out option granted patients the right to be excluded from the study.

Perioperative Management

Regarding preoperative beta-blocker use, this was continued until the day of surgery for regular users, and no new doses were started for non-users. Aortic surgery was performed under general anesthesia with intubation. Anesthesia was induced and maintained using intravenous propofol in combination with the inhalation of sevoflurane for sedation, fentanyl or remifentanil for analgesia, and rocuronium for muscle relaxation. For root or ascending aortic replacement, after median sternotomy and systemic heparization (300 U/kg), the ascending aorta was cannulated for systemic perfusion, whereas the right atrium, or the superior and inferior venae cavae were cannulated for venous drainage to establish cardiopulmonary bypass (CPB). Following crossclamping at the ascending aorta, cardiac arrest was obtained by antegrade infusion of cardioplegic solution using St Thomas solution No. 2 (Miotecter; Fuso Pharmaceutical Industries, Ltd) into the coronary circulation at 15 mL/kg, with additional infusion of 7.5 mL/kg every 30 minutes thereafter for maintaining the status. Retrograde infusion of the cardioplegic solution was combined when concomitant coronary dissection or moderate to severe aortic regurgitation was present. Aortic graft replacement was performed under cardiac arrest and CPB support. The body temperature during CPB was set around 32 to 34 °C.

Regarding aortic arch replacement, we used the anterograde selective cerebral perfusion method for all patients. Details of the procedure have previously been reported from our institution[25] and can be summarized as follows. The brachiocephalic artery and the femoral artery were used for systemic perfusion, and the right atrium or the superior and inferior venae cavae were cannulated for venous drainage to establish CPB. Body temperature control was started at the initiation of CPB, and the target temperature was set at 28 °C, which was achieved within 30 minutes from CPB initiation. In cases where anatomical anastomosis of the aorta was difficult because of anatomical malformation or severe aortic diseases, a lower body temperature (moderate hypothermia was defined as body temperature >20 to ≤28 °C) was considered to maintain brain and renal function. After crossclamping and antegrade crystalloid cardioplegia infusion as stated above, the artificial graft was anastomosed to the proximal aortic stump. After cooling to the target temperature and performing a proximal graft anastomosis, systemic circulation was arrested and the diseased aorta was resected. Subsequently, anterograde selective cerebral perfusion was instituted. During open distal anastomosis, blood perfusion to the lower body was paused. After completion of the distal anastomosis, lower body circulation was restarted and the body temperature was restored to normal during the left subclavian, left cervical, and innominate arteries reconstruction. After the aortic surgery, all patients were transferred to the ICU.

During the study period, landiolol was administered to prevent new-onset AF in approximately 4 out of 7 patients, and the decision of administration was based on the discretion of the attending anesthesiologist and/or cardiac surgeon (Figure 1). Intravenous landiolol was started at the time of withdrawal from CPB in the operating theater or within 3 hours after admission to the ICU. More specifically, it was started using a syringe pump when weaning from the CPB if the mean blood pressure was maintained above 70 mm Hg. If there were signs of conduction abnormality, administration was not performed. In contrast, if the heart rate was simply low and <60 bpm with hemodynamic stability, administration was started with backup pacing. When blood pressure could not be maintained above

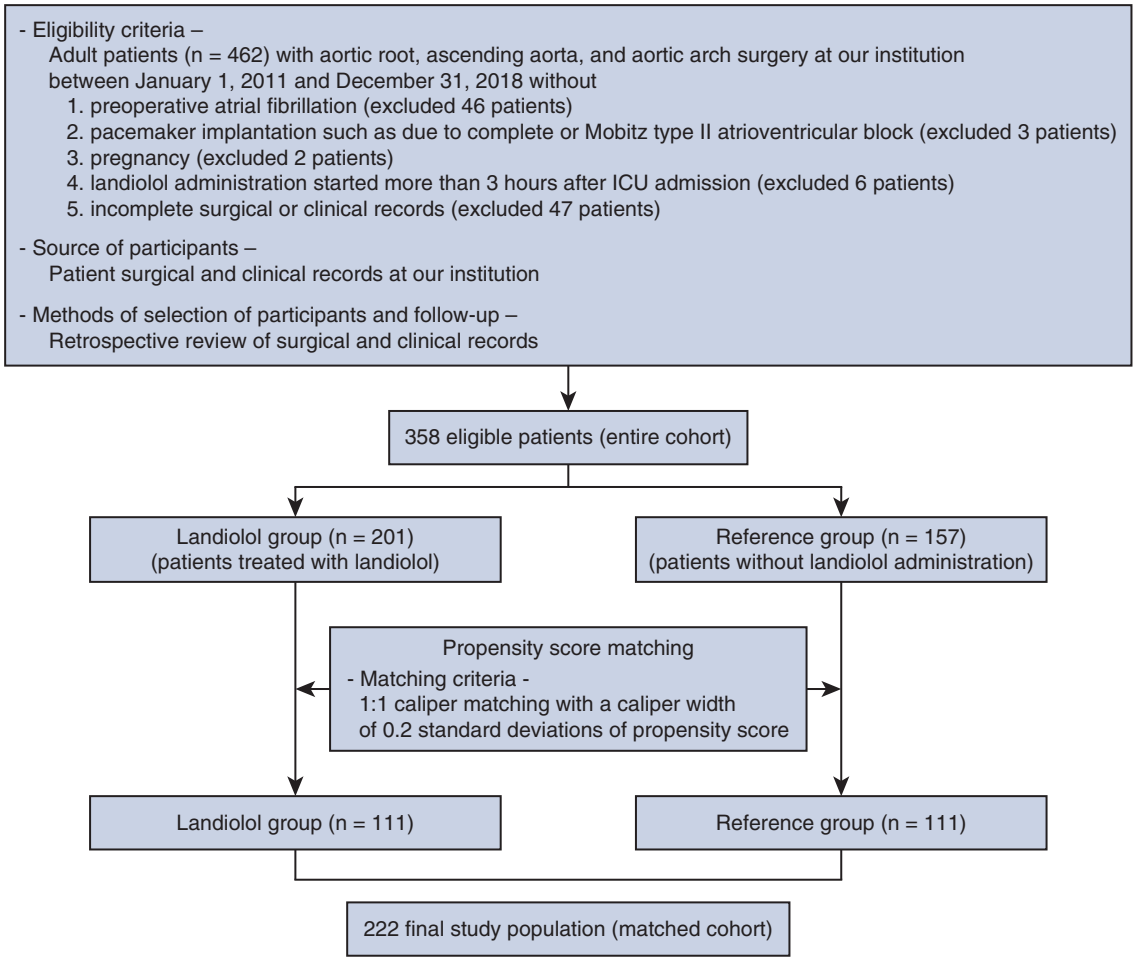

FIGURE 1. Eligibility criteria and selection flow diagram of the study population. *ICU*, Intensive care unit.

70 mm Hg after weaning from CPB, landiolol administration was continued in combination with fluid loading and/or inotropic agents. Landiolol was initiated or titrated at an infusion rate of 0.25 to 5.0 μg/kg/min. Landiolol infusion was discontinued if prolonged hemodynamic instability (bradycardia or hypotension) ensued or whenever an oral or transdermal beta-blocker was administered. The initiation of postoperative oral or transdermal beta-blockers was also at the discretion of the attending anesthesiologist and/or cardiac surgeon. However, there was a conflict that oral or transdermal beta-blocker use for the prevention of POAF was not covered by medical insurance in Japan during the study period. Patients usually received 2.5 to 5.0 mg carvedilol or 1.25 to 2.5 mg bisoprolol after extubation. If patients were not able to take the medication orally, a transdermal 4.0-mg bisoprolol patch was considered.

End Points

The primary end point was set as the incidence of new-onset POAF. We defined AF as an irregular narrow complex rhythm with absent P waves lasting more than 1 minute on continuous electrocardiogram monitoring. New-onset AF was defined as AF that occurred within 72 hours postoperatively, based on previous reports that the peak incidence of new-onset AF falls between 48 and 72 hours.[18,26,27] Patients were continuously monitored in the ICU and wards using 3-lead electrocardiograms until hospital discharge.

Secondary end points included 30-day mortality, 30-day symptomatic cerebral infarction, 30-day readmission for arrhythmia after discharge, AF at discharge, length of hospital stay, length of ICU stay, length of mechanical ventilation, need for pacemaker support (using pacemaker for stability of hemodynamics), and mean blood pressure and heart rate during the first 72 hours of ICU admission. The mean blood pressure and heart rate were determined by extracting each of the 72-hour postoperative measurements maintained in the electronic medical record of the postoperative ICU.

Statistical Analysis and PS Matching

Continuous variables are summarized using the median with first and third quartiles, and categorical variables using frequency with percentages. The study population was first divided into two groups according to landiolol use (landiolol vs reference groups). To estimate the influence of landiolol on the incidence of POAF, logistic regression analyses with 95% CI were performed on a PS-matched population by parity. IPTW was used to evaluate the robustness of the result. PS-matching was performed using the caliper matching method, as previously reported, with a caliper width of 0.2 SD.[28] Explanatory variables for calculating PS and weights of IPTW were selected clinically based on previous reports and included the following: age, sex, body mass index, past medical history (ie, hypertension, dyslipidemia, diabetes mellitus, and smoking), preoperative medication (ie, renin-

TABLE 1. Baseline characteristics of the total study population and propensity score-matched cohort

Parameter	Total study population (n = 358)				Matched cohort (n = 222)			
	Total (n = 358)	Landiolol (n = 201)	Reference (n = 157)	SMD	Total (n = 222)	Landiolol (n = 111)	Reference (n = 111)	SMD
Operation								
Isolated aortic surgery	239 (66.8)	152 (75.6)	87 (55.4)	0.435	144 (64.9)	72 (64.9)	72 (64.9)	0.000
With CABG	30 (8.4)	15 (7.5)	15 (9.6)	0.075	19 (8.6)	9 (8.1)	10 (9.0)	0.032
With valve surgery	88 (24.6)	34 (16.9)	54 (34.4)	0.408	59 (26.6)	30 (27.0)	29 (26.1)	0.020
With CABG and valve surgery	1 (0.3)	0 (0.0)	1 (0.6)	0.113	0 (0.0)	0 (0.0)	0 (0.0)	–
Age (y)	71 (64-76)	71 (64-75)	73 (65-78)	0.255	72 (65-77)	72 (67-77)	72 (65-78)	0.008
Male	252 (70.4)	148 (73.6)	104 (66.2)	0.162	152 (68.5)	73 (65.8)	79 (71.2)	0.117
Body mass index	23.8 (21.6-25.8)	23.8 (21.7-25.5)	23.9 (21.5-26.4)	0.133	24.2 (21.9-26.1)	24.3 (22.1-26.0)	24.1 (21.8-26.8)	0.036
Past history								
Hypertension	280 (78.2)	155 (77.1)	125 (79.6)	0.061	175 (78.8)	84 (75.7)	91 (82.0)	0.155
Dyslipidemia	147 (41.1)	84 (41.8)	63 (40.1)	0.034	87 (39.2)	44 (39.6)	43 (38.7)	0.018
Diabetes mellitus	63 (17.6)	44 (21.9)	19 (12.1)	0.263	30 (13.5)	13 (11.7)	17 (15.3)	0.106
Smokers	159 (44.4)	90 (44.8)	69 (43.9)	0.017	108 (48.7)	54 (48.6)	54 (48.6)	0.000
Preoperative medication								
RASI	173 (48.3)	88 (43.8)	85 (54.1)	0.208	116 (52.3)	57 (51.4)	59 (53.2)	0.036
Beta-blocker	113 (31.6)	54 (26.9)	59 (37.6)	0.231	73 (32.9)	34 (30.6)	39 (35.1)	0.096
Dose (mg)*	7.5 (5.0-10.0)	5.0 (5.0-10.0)	10.0 (5.0-10.0)	0.087	6.3 (5.0-10.0)	7.5 (5.0-10.0)	6.3 (4.4-10.0)	0.056
Statin	104 (29.1)	60 (29.9)	44 (28.0)	0.040	63 (28.4)	34 (30.6)	29 (26.1)	0.100
Laboratory data								
Preoperative e-GFR (mL/min/1.73 m^2)	59 (49-72)	59 (49-73)	59 (49-68)	0.171	58 (47-70)	58 (49-71)	59 (47-69)	0.033
Echocardiography								
LAD (mm)	38 (33-42)	37 (34-41)	38 (33-42)	0.089	38 (33-42)	37 (34-42)	38 (33-43)	0.092
LVEF (%)	66 (62-70)	66 (63-70)	67 (62-71)	0.056	67 (63-71)	67 (63-71)	67 (63-71)	0.018
Intraoperative factor								
Emergency	77 (21.5)	43 (21.4)	34 (21.7)	0.006	43 (19.4)	23 (20.7)	20 (18.0)	0.068
Duration of CPB time (min)	181 (152-221)	175 (150-207)	194 (159-238)	0.348	183 (157-220)	182 (159-212)	186 (155-231)	0.107
Operation including aortic arch	303 (84.6)	180 (89.6)	123 (78.3)	0.309	192 (86.5)	97 (87.4)	95 (85.6)	0.053
Moderate hypothermia (min)	46 (0-68)	47 (0-68)	43 (0-68)	0.002	48 (3-68)	46 (4-68)	49 (3-69)	0.054
Inotropic agents use†	240 (67.0)	130 (64.7)	110 (70.1)	0.115	149 (67.1)	76 (68.5)	73 (65.8)	0.058
Postoperative medication								
Beta-blocker	186 (52.0)	126 (62.7)	60 (38.2)	0.505	103 (46.4)	54 (48.6)	49 (44.1)	0.090
Dose (mg)*	5.0 (2.5-10.0)	5.0 (2.5-10.0)	5.0 (2.5-10.0)	0.228	5.0 (2.5-10.0)	5.0 (2.5-10.0)	5.0 (2.5-10.0)	0.089
Transdermal	40 (11.2)	27 (13.4)	13 (8.3)	0.166	23 (10.4)	11 (9.9)	12 (10.8)	0.030
Inotropic agent use†	155 (43.3)	75 (37.3)	80 (51.0)	0.277	102 (46.0)	52 (46.8)	50 (45.0)	0.036
Postoperative potassium‡ (mM)	3.6 (3.3-3.9)	3.5 (3.3-3.9)	3.7 (3.4-4.1)	0.323	3.6 (3.4-4.0)	3.6 (3.4-3.9)	3.6 (3.3-4.0)	0.063

Continuous variables are presented as median (first quartile-third quartile) and categorical variables are presented as n (%). *SMD*, Standardized mean difference; *CABG*, coronary artery bypass grafting; *RASI*, renin-angiotensin system inhibitor; *e-GFR*, estimated glomerular filtration rate; *LAD*, left atrial diameter; *LVEF*, left ventricular ejection fraction; *CPB*, cardiopulmonary bypass. *The dose of beta-blocker is presented in terms of carvedilol. For oral drugs, the carvedilol dose was 4 times the bisoprolol dose, and for transdermal drugs, the carvedilol dose was 2.5 times the bisoprolol dose. †Inotropic agents included dopamine, dobutamine, noradrenaline, milrinone, and adrenaline. Moderate hypothermia was defined as a body temperature >20 to ≤28 °C. ‡The minimum value within 72 hours after operation.

angiotensin system inhibitor [RASI], beta-blocker, and statin), postoperative use of oral or transdermal beta-blocker within 72 hours after surgery, laboratory data (ie, preoperative estimated glomerular filtration rate), preoperative echocardiography (ie, left ventricular ejection fraction and left atrial diameter), and peri-operative indices (ie, presence or absence of concomitant CABG or valve surgery, emergency operation, duration of hypothermia and CPB time, intraoperative inotropic agent use, and postoperative use within 24 hours after ICU admission, and minimum potassium

TABLE 2. Timing, administration dose, and the total amount of prophylactic landiolol used

Variable	Total study population (n = 201)	Matched cohort (n = 111)
Landiolol initiation at		
Operation room	192 (95.5)	106 (95.5)
Within 3 h after ICU admission	9 (4.5)	5 (4.5)
Landiolol dose rate at		
Operation room (μg/kg/min)	1.0 (0.5-1.0)	1.0 (0.5-1.0)
ICU (μg/kg/min)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Total dose (mg)	169.6 (94.3-266.1)	169.6 (90.5-263.7)
Total duration (h)	48.3 (34.6-71.3)	51 (30.3-73.5)

Continuous variables are presented as median (first quartile-third quartile) and categorical variables are presented as n (%). *ICU*, Intensive care unit.

level within 72 hours after ICU admission). Pre- or postmatching balance in patient backgrounds between groups were evaluated using the standardized mean difference (SMD), and an SMD <0.1 was defined as well balanced. Differences in each end point between groups were evaluated using the Wilcoxon rank sum test in the nonmatched cohort or Wilcoxon signed rank test considering parity in the PS-matched cohort for continuous variables. The Pearson χ^2 test in the nonmatched cohort and McNemar χ^2 test considering parity in the PS-matched cohort were employed to evaluate differences in categorical variables, with Fisher exact test used when the expected values in any of the cells of a contingency table were below 5. Ad-hoc subgroup analysis was also performed among 4 different treatment groups: landiolol plus postoperative oral or transdermal beta-blocker, landiolol alone, postoperative oral or transdermal beta-blocker alone, and neither of these agents. The differential effects of landiolol and oral/transdermal beta-blockers were tested with the interaction *P* value, and multiple pairwise comparisons performed. The pairwise comparisons were not adjusted for multiplicity. There were no missing data in the study population, including the PS-matched cohort. All analyses were performed using Microsoft R Open, version 3.5.1 (Microsoft Corporation).

RESULTS

Figure 1 shows the eligibility criteria of the total study population. We included 358 eligible patients, of whom 201 received prophylactic landiolol for the prevention of POAF and 157 patients who did not. There were no patients with advanced atrioventricular block or sick sinus syndrome. Finally, 222 patients were matched, with 111 patients in each group (Figure 1). Table 1 shows the characteristics of the total study population and of the PS-matched cohort.

Differences in background characteristics were minimized and almost well-balanced after PS-matching with

TABLE 3. Incidence of primary and secondary end points in the total study population and propensity score-matched cohort

	Total study population (n = 358)				Matched cohort (n = 222)			
Parameter	Total (n = 358)	Landiolol (n = 201)	Reference (n = 157)	*P* value	Total (n = 222)	Landiolol (n = 111)	Reference (n = 111)	*P* value
Primary end point								
POAF	95 (26.5)	36 (17.9)	59 (37.6)	<.001	64 (28.8)	21 (18.9)	43 (38.7)	.002
Burden	n = 95	n = 36	n = 59		n = 64	n = 21	n = 43	
Duration (min)	377 (177-971)	467 (208-1238)	285 (128-758)	.199	446 (173-1433)	720 (235-1536)	377 (136-1096)	.293
Electrical cardioversion	63 (66.3)	27 (75.0)	36 (61.0)	.162	41 (64.1)	15 (71.4)	26 (60.5)	.391
Pharmacological cardioversion	43 (45.3)	20 (55.6)	23 (39.0)	.115	28 (43.8)	10 (47.6)	18 (41.9)	.663
Secondary end points								
30-d mortality	4 (1.1)	0 (0.0)	4 (2.5)	.023*	3 (1.4)	0 (0.0)	3 (2.7)	.247*
30-d symptomatic cerebral infarction	27 (7.5)	10 (5.0)	17 (10.8)	.037	20 (9.0)	9 (8.1)	11 (9.9)	.655
30-d hospital readmission for arrhythmia after discharge	1 (2.2)	1 (2.5)	0 (0.0)	.999*	0 (0.0)	0 (0.0)	0 (0.0)	-
AF at discharge	8 (2.2)	1 (0.5)	7 (4.5)	.024*	6 (2.7)	1 (0.9)	5 (4.5)	.212*
Length of hospital stay (d)	31 (25-41)	30 (26-39)	32 (24-43)	.910	32 (26-43)	31 (26-43)	32 (24-43)	.620
Length of ICU stay (d)	5 (3-7)	4 (3-6)	5 (4-7)	.013	5 (4-7)	5 (4-7)	5 (4-7)	.646
Length of mechanical ventilation (h)	14.7 (8.5-23.2)	14.7 (8.1-23.6)	14.6 (9.6-21.5)	.517	15.3 (10.3-25.8)	15.6 (10.0-30.0)	14.9 (11.3-21.3)	.943
Needs for PM support	148 (41.3)	68 (33.8)	80 (51.0)	.001	97 (43.7)	46 (41.4)	51 (45.9)	.492
Mean BP over 72 h (mm Hg)	78 (74-82)	78 (74-82)	79 (74-83)	.159	78 (74-83)	78 (74-83)	79 (74-83)	.449
Mean HR over 72 h (bpm)	80 (74-84)	80 (74-84)	79 (75-84)	.755	80 (74-83)	80 (74-83)	79 (74-83)	.797

Continuous variables are presented as median (first quartile-third quartile) and categorical variables are presented as n (%). *POAF*, Postoperative atrial fibrillation; *AF*, atrial fibrillation; *ICU*, intensive care unit; *PM*, pacemaker; *BP*, blood pressure; *HR*, heart rate. *Fisher exact test.

TABLE 4. Association between landiolol treatment and incidence of postoperative atrial fibrillation in the propensity score (PS)-matched cohort and in subgroups

Variable	Odds ratio (95% CI)	*P* value
PS-matched cohort (n = 222)	0.39 (0.21-0.72)	.003
Subgroup analysis		
Landiolol plus postoperative beta-blocker (n = 54)	0.26 (0.10-0.63)	.004
Landiolol alone (n = 57)	0.45 (0.20-0.98)	.049
Postoperative beta-blocker alone (n = 48)	0.91 (0.42-1.97)	.815
Neither agent (n = 63)	1.0*	–
P value for interaction		.001

*Reference category.

an SMD <0.1 (Table 1 and Figure 2). The distributions of PS were also well balanced with a median PS of 0.54 (interquartile range, 0.39-0.64) in the landiolol group versus 0.53 (0.39-0.64) in the reference group (Figure 2). Nevertheless, there were slight differences in sex, prevalence of hypertension, diabetes mellitus, statin use, and duration of CPB time (Table 1). In the PS-matched cohort, the median age was 72 years (interquartile range [IQR], 65-77 years). Moreover, 152 (68.5%) patients were men, 175 (78.8%) had hypertension, 116 (52.3%) took RASI preoperatively, 73 (32.9%) took preoperative beta-blockers, and 103 (46.4%) received postoperative oral or transdermal beta-blockers. The median preoperative left ventricular ejection fraction was 67% (interquartile range, 63%-71%), and 43 (19.4%) patients underwent emergency surgery. Regarding hypothermia, 170 (76.6%) patients experienced moderate hypothermia (defined as a body temperature >20 to ≤28 °C) for median of 48 minutes (IQR, 3-68 minutes).

Table 2 shows the timing, administration dose, and the total amount of prophylactic landiolol administration. Landiolol was started at the operation room in 106 (95.5%) patients, whereas the remaining 5 (4.5%) patients received landiolol within 3 hours after ICU admission. The median dose rate was 1.0 μg/kg/min and the total amount of prophylactic landiolol administered was 169.6 mg (IQR, 90.5-263.7 mg).

The incidence of primary and secondary end points is presented in Figure 3 and Table 3. The absolute frequency and incidence of POAF after aortic root, ascending aorta, and aortic arch surgery in the PS-matched cohort was 64 patients (28.8%) overall, with that of the landiolol group being significantly lower than that of the reference group (21 [18.9%] vs 43 [38.7%]; $P = .002$) (Figure 3 and Table 3). Landiolol use was associated with a reduction in POAF incidence (odds ratio [OR], 0.39; 95% CI, 0.21-0.72; $P = .003$ by PS-matched analysis) (Table 4). A similar result was obtained by IPTW (OR, 0.39; 95% CI, 0.22-0.70; $P = .002$). Subgroup analysis suggested that the combination of landiolol with a postoperative beta-blocker provided an additional benefit (*P* value for interaction = .001) (Figure 3 and Table 4). Regarding the duration of POAF and cardioversion rate, there were no statistical differences between groups (Table 3). One patient in the landiolol group (n = 201) developed POAF after the completion of preventive landiolol administration, and landiolol was restarted for POAF cessation and heart rate control. In contrast, 20 patients in the reference group (n = 157) underwent pharmacologic cardioversion or heart rate control using landiolol for managing POAF; however, these patients were also treated as the reference group according to the definition of the

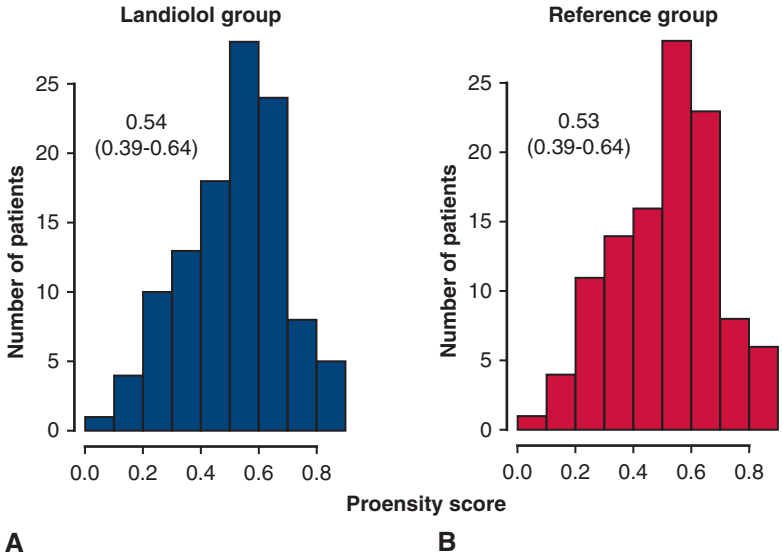

FIGURE 2. Histogram of propensity scores in landiolol (A) and reference (B) group.

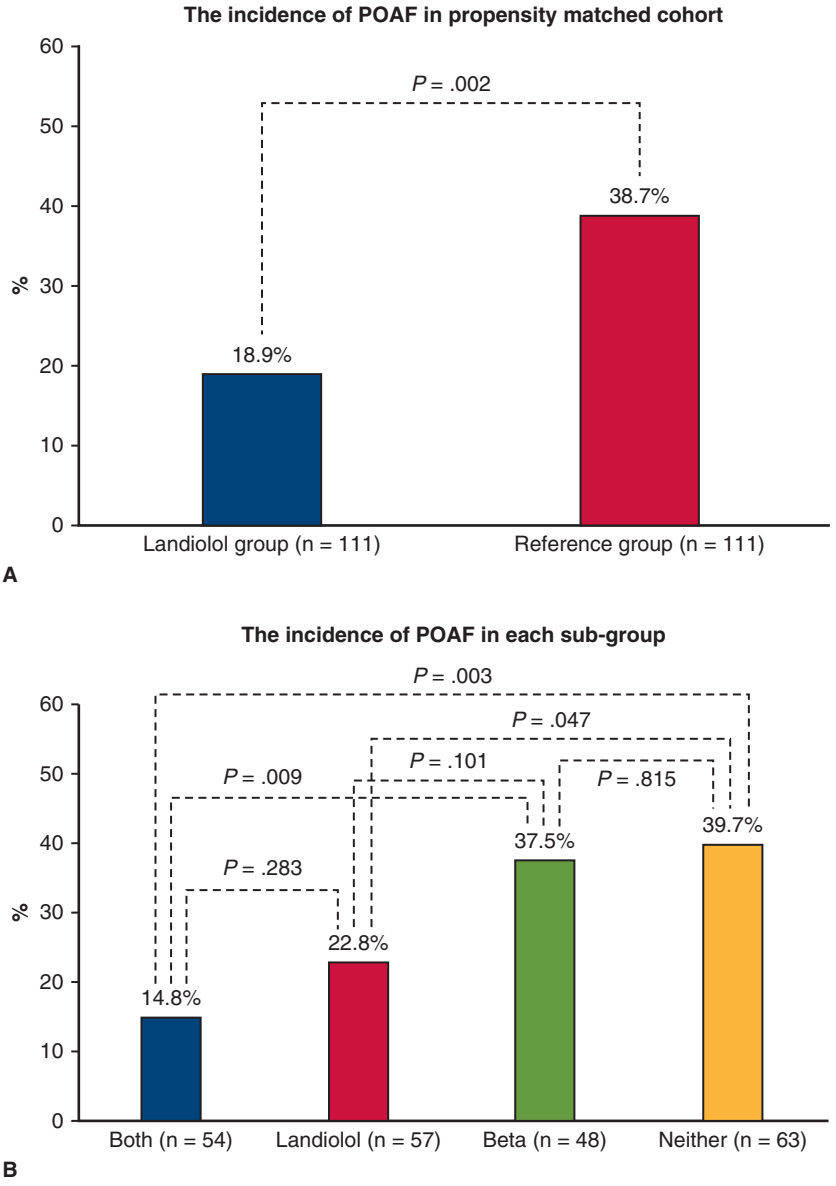

FIGURE 3. The incidence of postoperative atrial fibrillation (*POAF*) in the propensity-matched cohort (A) and each subgroup (B). Both (n = 54) included patients who received both landiolol and postoperative oral or transdermal beta-blockers. Landiolol (n = 57) included patients who received landiolol administration. Beta (n = 48) included patients who received postoperative oral or transdermal beta-blockers. Neither (n = 63) included patients who did not receive neither landiolol nor postoperative beta-blockers.

landiolol group as patients who received landiolol at the operation room or within 3 hours after ICU admission (Figure 1).

Regarding the secondary end points in the PS-matched cohort, there were no significant differences in the 30-day mortality between the landiolol and reference groups (0 [0.0%] vs 3 [2.7%]; $P = .247$), 30-day symptomatic cerebral infarction (9 [8.1%] vs 11 [9.9%]; $P = .655$), 30-day readmission for arrhythmia after discharge (no events in both groups), length of hospital stay (31 days [IQR, 26-43 days] vs 32 days [IQR, 24-43 days]; $P = .620$), length of ICU stay (5 days [IQR, 4-7 days] vs 5 days [IQR,4-7 days]; $P = .646$), length of mechanical ventilation (15.6 hours [IQR, 10.0-30.0 hours] vs 14.9 hours [IQR, 11.3-21.3 hours]; $P = .943$), need for pacemaker support (46 patients [41.4%] vs 51 patients [45.9%]; $P = .492$), mean blood pressure (78 mm Hg [IQR, 74-83 mm Hg] vs 79 mm Hg [IQR, 74-83 mm Hg]; $P = .449$) and mean heart rate (80 bpm [IQR, 74-83 bpm] vs 79 bpm [74-83 bpm]; $P = .797$). In addition, there was no early death within 72 hours after surgery

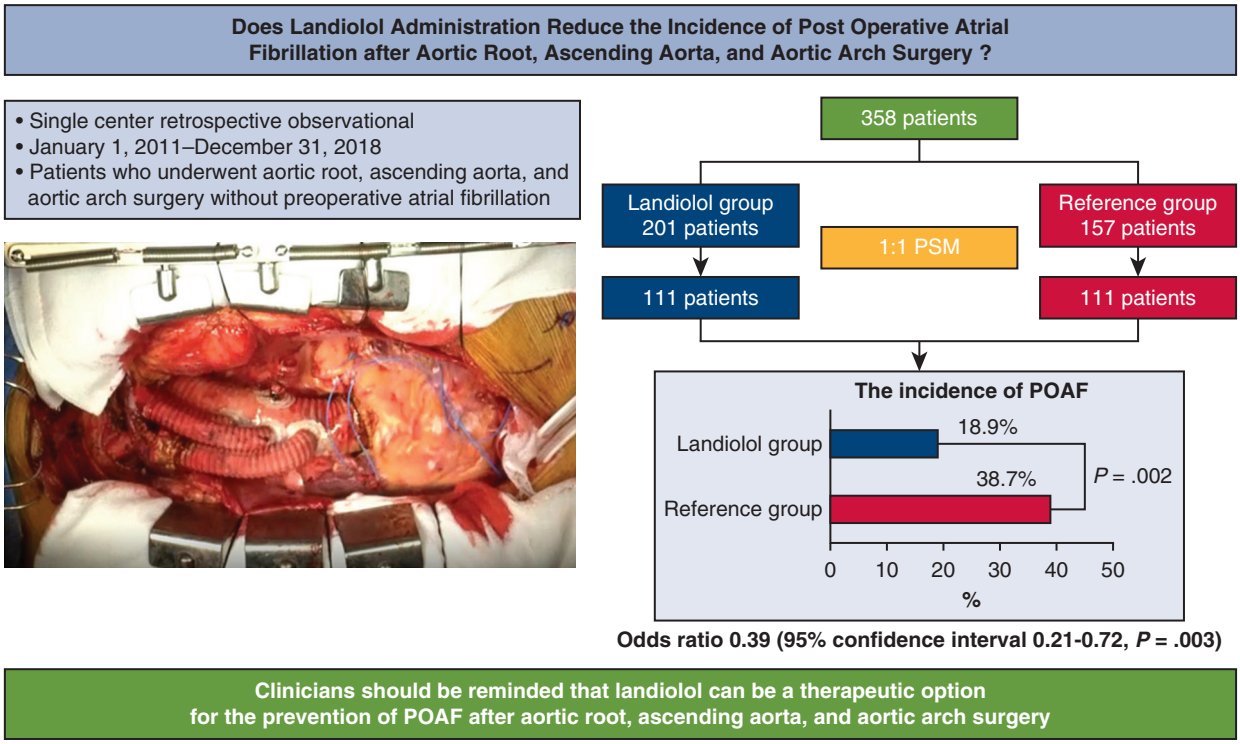

FIGURE 4. Our main finding was that intravenous landiolol administration is associated with a lower incidence of postoperative atrial fibrillation (*POAF*) after aortic root, ascending aorta, and aortic arch surgery in a propensity score (*PS*)-matched cohort.

during the study period, and we did not need to consider this competing risk in the analysis.

DISCUSSION

Our main finding was that intravenous landiolol is associated with a lower incidence of POAF after aortic root, ascending aorta, and aortic arch surgery in a PS-matched cohort (Figure 4 and Video 1). The OR of developing POAF was 0.39 (95% CI, 0.21-0.72; $P = .003$) with landiolol use. The robustness of the result was confirmed by IPTW analysis. There were no significant differences in secondary end points such as the 30-day mortality and symptomatic cerebral infarction. Because little is known regarding the association between landiolol and POAF incidence after aortic root, ascending aorta, and aortic arch surgery, our results bridge this gap of evidence in the literature. Our findings could contribute to the appropriate management of POAF after aortic root, ascending aorta, and aortic arch surgery.

Preventive Effects on POAF

In the present study, we demonstrated that intravenous landiolol was associated with a lower incidence of POAF, with an OR of 0.39. Aortic root, ascending aorta, and aortic arch surgery is among the most invasive isolated operations in the field of cardiovascular surgery, with historically the highest incidence of POAF (49%-52%) when compared with that of CABG and valve surgery.[4,5] POAF is caused by multiple factors such as inflammation, oxidative stress, operative trauma, changes in atrial pressure, sympathetic stimulation, and hypothermia.[29,30] Among the above therapeutic targets, inhibition of sympathetic stimulation using beta-blockers is one of the most widely adopted option for the management of POAF due to the efficacy and safety

VIDEO 1. We retrospectively divided 358 eligible patients into 2 groups and estimated the therapeutic influence of landiolol on the prevention of postoperative atrial fibrillation (POAF) by propensity matched analysis. The landiolol was associated with a lower incidence of POAF than that of reference group. This study showed that landiolol can be a therapeutic option for the prevention of POAF after aortic root, ascending aorta, and aortic arch surgery. Video available at: https://www.jtcvs.org/article/S2666-2736(22)00281-9/fulltext.

of these agents.[31,32] The high β_1-to-β_2 selectivity ratio of landiolol hydrochloride (250:1) might explain its favorable influence. Several systematic reviews and meta-analyses have suggested that landiolol is effective for POAF prevention after CABG and valve surgery, with most conclusions obtained from patients subjected to CABG.[33-35] Our data on aortic root, ascending aorta, and aortic arch surgery provide complementary information in this field. The >50% reduction in the relative risk for POAF would also be useful information for clinicians.

Utility of Landiolol

There were no significant differences in secondary end points such as mean blood pressure, heart rate, and the need for pacemaker support between the landiolol group and the reference group. The European Association for Cardio-Thoracic Surgery guidelines on perioperative medication in adult cardiac surgery list perioperative oral beta-blockers as a class 2a recommendation for the prevention of POAF.[31] It is also common consensus that oral beta-blockers should be reinstituted at the earliest after surgery to reduce the incidence of POAF, as indicated in the American College of Cardiology Foundation and American Heart Association guidelines.[32] From these viewpoints, among the advantages of landiolol is its capability to be administered intravenously, rendering it easy to achieve target drug concentrations without any time delay. Moreover, it is known that gastrointestinal edema associated with CPB can interfere with effective absorption of oral beta-blockers and delay the achievement of target drug concentrations. The short half-life of landiolol with minimal negative inotropic effects can also be an advantage because these properties lead to good controllability of the hemodynamic status in postoperative clinical settings.

Clinical Implications

In the present study, we demonstrated that landiolol was associated with a lower incidence of POAF with no statistical differences in adverse clinical events. Although observational data were utilized in our study, attempts have been made to eliminate the influence of confounding factors by estimating the therapeutic effects of landiolol in preventing POAF using PS-matched analyses. The robustness of the result was confirmed by IPTW. As a result, the relative risk was found to be less than half. Thus, the clinical implication of the present study is quite simple. Physicians or surgeons should consider landiolol as a therapeutic option for the prevention of POAF after aortic root, ascending aorta, and aortic arch surgery. Because few reports have investigated the efficacy and safety of landiolol for the prevention of POAF after such surgery, we hope that the present study contributes to efforts in minimizing POAF and achieving better prognosis in clinical settings.

Study Limitations

Several limitations of the present study should be considered when interpreting the results. First, because this was a single-center retrospective observational study, the therapeutic effects of landiolol for the prevention of POAF could not be determined despite the attempts made to eliminate the influence of confounding factors by performing PS-matched or IPTW analyses. Especially, it is unclear how our hypothermia protocol influences the generalizability of the study results given the association between hypothermia and arrhythmic events such as POAF.[30] Second, several patient background characteristics could not be well balanced; thus, we evaluated the robustness of the results using IPTW. Third, the prescription rate of postoperative oral or transdermal beta-blockers was quite low partly because their use for the prevention of POAF was not covered by medical insurance in Japan during the study period. Fourth, the small sample sizes in the subgroup analysis may limit meaningful conclusions. Fifth, differences in hard end points such as the 30-day mortality and cerebral infarction were statistically underpowered because of the low incidence of these events and the small study population. The sample size was too small to address the more serious consequences of POAF in this study and we need more investigations or meta-analysis. Hence, further evaluations by larger cohort studies or randomized trials are warranted.

CONCLUSIONS

Intravenous landiolol administration was associated with a lower incidence of POAF in a PS-matched cohort after aortic root, ascending aorta, and aortic arch surgery.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

The authors thank the Japan Society of Clinical Research for their dedicated support.

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Key Words: atrial fibrillation, landiolol hydrochloride, beta-blocker, aortic surgery