

# Evaluating the Therapeutic Efficacy and Safety of Landiolol Hydrochloride for Management of Arrhythmia in Critical Settings: Review of the Literature

This article was published in the following Dove Press journal:  
*Vascular Health and Risk Management*

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**Background:** Landiolol hydrochloride, a highly cardio-selective beta-1 blocker with an ultra-short-acting half-life of 4 minutes, was originally approved by Japan for treatment of intraoperative tachyarrhythmias. This review aims to provide an integrated overview of the current state of knowledge of landiolol hydrochloride in the management of arrhythmia in critical settings.

**Methods:** We searched MEDLINE, EMBASE, and the Cochrane Library to retrieve relevant articles with a total of 65 records identified.

**Results:** The high  $\beta_1$  selectivity ( $\beta_1/\beta_2$  ratio of 255:1) of landiolol causes a more rapid heart rate (HR) decrease compared to esmolol while avoiding decreases in mean arterial blood pressure. Recently, it has been found useful in left ventricular dysfunction patients and fatal arrhythmia requiring emergency treatment. Recent random clinical trials (RCT) have revealed therapeutic and prophylactic effects on arrhythmia, and very low-dose landiolol might be effective for preventing postoperative atrial fibrillation (POAF) and sinus tachycardia. Likewise, landiolol is an optimal choice for perioperative tachycardia treatment during cardiac surgery. The high  $\beta_1$  selectivity of landiolol is useful in heart failure patients as a first-line therapy for tachycardia and arrhythmia as it avoids the typical depression of cardiac function seen in other  $\beta$ -blockers. Application in cardiac injury after percutaneous coronary intervention (PCI), protection for vital organs (lung, kidney, etc.) during sepsis, and stabilizing hemodynamics in pediatric patients are becoming the new frontier of landiolol use.

**Conclusion:** Landiolol is useful as a first-line therapy for the prevention of POAF after cardiac/non-cardiac surgery, fatal arrhythmias in heart failure patients and during PCI. Moreover, the potential therapeutic effect of landiolol for sepsis in pediatric patients is currently being explored. As positive RCT results continue to be published, new clinical uses and further clinical studies in various settings by cardiologists, intensivists and pediatric cardiologists are being conducted.

**Keywords:** landiolol,  $\beta$ -blocker, management of arrhythmia

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## Introduction

The contribution of  $\beta$ -blockers in preventing refractory and urgent fatal arrhythmia and tachycardia is well known in chronic phase. Landiolol hydrochloride, a highly cardio-selective beta-1 blocker with an ultra-short-acting half-life of 4 minutes,<sup>1</sup> is widely used in Japan under the brand name Onoact<sup>®</sup>. Recently, European Union

health authorities have approved usage under the name Rapibloc<sup>®</sup>.<sup>2,3</sup> Landiolol was originally approved by Japan for treatment of intraoperative tachyarrhythmias<sup>4</sup> and was later approved for tachycardia atrial fibrillation (AF) and atrial flutter (AFL) during left ventricular (LV) dysfunction in November 2013.<sup>5</sup> More recently, landiolol expanded its utility into usage for fatal arrhythmia requiring emergency treatment in 2019<sup>6</sup> and is fast becoming a reliable therapeutic choice for management of arrhythmia in acute phase. The aim of this review is to provide an integrated overview of the current state of knowledge of landiolol hydrochloride and the management of arrhythmia in critical settings.

## Review Process

We searched MEDLINE (via PubMed), EMBASE, and the Cochrane Library to retrieve relevant articles for the literature review and relevant data. We used the search term “landiolol” for articles published before January 2020 with no language limitations. We explored observational studies and randomized clinical trials (RCTs) exploring the following topics: 1) pharmacokinetics and pharmacodynamics, 2) the role of prophylactic landiolol in non-cardiac surgeries, 3) the role of prophylactic landiolol in percutaneous coronary intervention, 4) the role of prophylactic landiolol in heart failure patients, 5) the role of prophylactic landiolol in sepsis-induced fatal arrhythmia, 6) and the role of prophylactic landiolol in pediatric patients.

A total of 951 records were identified in all searches (MEDLINE: 342, EMBASE: 602, the Cochrane Library: 2, manual search: 5). After excluding duplicate studies (n=326), we screened 625 studies. A further 560 were excluded for the following reasons: 157 were some other publication type; 403 studies were not relevant to the topic or had small sample numbers not rigorous enough for significant conclusions. A total of 65 records were thus eligible for final reviewing. The identified core studies are in [Supplementary File 1](#).

## Pharmacokinetics and Pharmacodynamics

Landiolol hydrochloride has a  $\beta_1/\beta_2$  ratio of 255,<sup>7</sup> and, compared to propranolol, its  $\beta_1$ -selectivity is 74–380 times greater while it has a 33–263 times greater  $\beta_1$  affinity than esmolol.<sup>8</sup> This high  $\beta_1$ -selectivity results in a more potent negative chronotropic effect and a less potent hypotensive effect.<sup>7</sup> Work in rabbit animal models revealed

a more rapid HR decrease with landiolol than with esmolol while the decrease in mean arterial blood pressure (MAP) seen with esmolol was not observed with landiolol.<sup>9</sup> Similar results were obtained in isolated rabbit<sup>10</sup> and guinea pig hearts.<sup>11</sup>

Landiolol metabolism is mainly in the liver (approximately half) and plasma and is predominantly catalyzed by liver carboxylesterase and plasma pseudocholinesterase.<sup>12</sup> In hepatically impaired patients, maximum concentration (C<sub>max</sub>) and area under the concentration (AUC)–time curve values were 42% and 44% higher, respectively, but half-life did not differ compared with healthy patients and no drug-related adverse events were observed.<sup>13</sup> A standardized method for detecting pharmacokinetics in plasma with liquid chromatography–tandem mass spectrometry (LC MS-MS) in humans<sup>14</sup> has yielded pharmacokinetics and pharmacodynamics for Japanese,<sup>1</sup> Chinese<sup>15</sup> and Caucasian healthy<sup>16</sup> and acute-phase AF/AFL populations.<sup>17</sup> Table 1 summarizes pharmacokinetics by population.

## Role of Prophylactic Landiolol in Non-Cardiac Surgeries

Several observational studies have reported on landiolol for management of postoperative atrial fibrillation (POAF). In esophageal cancer patients, POAF is a common complication after esophagectomy<sup>18</sup> and is associated with longer hospital stays, complications,<sup>19</sup> and mortality.<sup>20</sup> Three RCTs of landiolol for POAF have been completed. Yoshida et al conducted a 79-patient study where landiolol was administered at 5  $\mu\text{g}/\text{kg}/\text{min}$  for 24 h after induction of anesthesia, then compared the AF incidents with a control group.<sup>21</sup> POAF occurred in one control patient, leading to the conclusion that prophylactic 24h low-dose landiolol was not superior to non-treatment. Ojima et al also administered landiolol at 3  $\mu\text{g}/\text{kg}/\text{min}$  from post-operative day (POD) 1 for 72h and, when compared to a placebo group of 100 patients, use of landiolol significantly reduced the incidence of POAF within the first postoperative week (incidence: landiolol: 30% vs placebo: 10%,  $p=0.012$ ) and the overall incidence of postoperative complications (incidence: landiolol: 40% vs placebo: 60%,  $p=0.046$ ).<sup>22</sup> Horikoshi et al administered landiolol at 5  $\mu\text{g}/\text{kg}/\text{min}$  from the induction of anesthesia until the morning of POD 1 and use of landiolol significantly reduced the incidence of POAF (incidence: landiolol: 5.3% vs placebo: 35%,  $p<0.05$ ) and also sinus tachycardia (incidence: landiolol: 0% vs placebo: 25%,  $p<0.05$ ).<sup>23</sup> Moreover, they evaluated post-operative inflammation cytokines (IL-1 $\beta$ , IL-6, IL-8, IL-10,

Table 1 Pharmacokinetics by Population

Study	M. Wang, Drug Res (Stuttg), 2014 <sup>15</sup>			M Nakashima, J. Clin. Therap. Med, 2000 <sup>1</sup>			Krumpal G, J. Cardiovasc. Pharmacol, 2016 <sup>16</sup>		
Population	Healthy Chinese			Healthy Japanese			Healthy Caucasians		
Dosage	L(low): 0.125mg/kg/min (1min) load-ing→0.02mg/kg/min (20min) continuous.	H(high): 0.25mg/kg/min (1min) loading→0.04mg/kg/min (20min) continuous		0.04mg/kg/ min (60min) continuous	0.25mg/kg/min (1min) loading→0.04mg/kg/ min (60min) continuous		0.01mg/kg/ min (120min) continuous	0.02mg/kg/ min (120min) continuous	0.04mg/kg/ min (20h) continuous
Participated number	10	10		5	5		12	12	12
Age	24 ± 3	22 ± 2		26 ± 2	-		34.3 ± 9.5	34.3 ± 9.5	34.3 ± 9.5
Female (%)	50	50		-	-		41.7	41.7	41.7
C max (ng/mL)	400 ± 110	731 ± 246		-	2008 ± 798		230 ± 46	520 ± 93	980 ± 147
C 21 min (ng/mL)	327 ± 109	508 ± 141		-	-		-	-	-
C 60 min (ng/mL)	-	-		1008 ± 303	-		-	-	-
C 61 min (ng/mL)	-	-		-	1237 ± 329		-	-	-
T max (min)	10.1 ± 6.5	6.2 ± 5.7		-	2		-	-	-
t 1/2 (min)	4.7 ± 1.6	6.5 ± 1.7		3.96 ± 0.46	3.47 ± 0.44		-	-	4.52 ± 0.99
T 80% (min)	-	-		-	-		30 (20, 60)	10 (6, 12)	6 (6, 8)
AUC 0-81 min (µg/mL · min)	8.28 ± 1.12	14.49 ± 3.28		-	-		-	-	-
AUC 0-∞ (µg/mL · min)	8.30 ± 1.13	14.50 ± 3.28		59.34 ± 12.49	82.43 ± 23.52		-	-	153 ± 29
CL (mL/min/kg)	-	-		41.8 ± 8.3	-		58 ± 13	47 ± 8	52 ± 7
CL/F (mL/min/kg)	64 ± 9	76 ± 16		-	-		-	-	-
Vd (L/kg)	-	-		0.242 ± 0.067	-		-	-	-
Vd/F (L/kg)	0.425 ± 0.114	0.694 ± 0.171		-	-		-	-	-

**Abbreviations:** AUC0-t, area under the blood concentration-time curve from initiation until end of respective dose level; AUC0-∞, AUC from 0 hr to infinity; C 21min; C 60 min; C 61 min, the concentration at completion of continuous infusion at that time; T max; time point of maximum blood concentration; CL, total clearance; CL/F, CL by bioavailability; T 1/2, the elimination half-life; T80%, time until 80% of T max; VD, volume of distribution; VD/F:VD divided by bioavailability.

and TNF- $\alpha$ ) and use of landiolol significantly suppressed IL-6 elevation but not other cytokines.

From these RCT results, one study found no superiority for prophylactic usage, but this study suffered from low statistical power and other studies showed significance in preventing POAF. Therefore, very low-dose landiolol might be effective for preventing POAF and sinus tachycardia in addition to suppressing IL-6 elevation after surgery.

## Role of Prophylactic Landiolol in Cardiac Surgeries

There are several observational studies that have used landiolol to manage perioperative arrhythmia and reported prophylactic effects against POAF,<sup>24–30</sup> treatment of POAF,<sup>31</sup> treatment of supraventricular tachycardia (SVT),<sup>32</sup> different treatment effects between AF and AFL/atrial tachycardia (AT),<sup>33</sup> safe decreases in HR and improvement of hemodynamics in patients receiving catecholamine.<sup>34</sup>

RCTs have already been conducted to study the effect of landiolol on prevention of POAF after cardiac surgery (Table 2). For off-pump CABG, Nagaoka et al dosed 0.5 to 2  $\mu\text{g}/\text{min}/\text{kg}$  until PO drug start and compared the POAF incidence with the use of diltiazem (0.5 to 2  $\mu\text{g}/\text{min}/\text{kg}$  until PO drug start), finding that landiolol significantly reduced the incidence of POAF (landiolol: 4.8% vs diltiazem: 27%,  $p<0.05$ ).<sup>35</sup> Fujii et al also reported a prophylactic effect of landiolol for POAF until PO  $\beta$ -blocker (carvedilol) start (landiolol: 11.1% vs placebo: 32.3%,  $p<0.05$ ).<sup>36</sup> Ogawa et al reported both on the prophylactic effect of landiolol for POAF (landiolol: 19% vs placebo: 37%,  $p<0.05$ ) and for tachycardia (landiolol: 13% vs placebo: 32%,  $p<0.05$ ) without increasing bradycardia (landiolol: 15% vs placebo: 13%,  $p=0.99$ ).<sup>37</sup>

For coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB), the PASCAL Trial conducted by Sezai et al showed a significant prophylactic effect of landiolol for preventing POAF compared with placebo (landiolol: 10% vs placebo: 34.3%,  $p<0.05$ ).<sup>38</sup> The same group also conducted an RCT named the BABYLON Trial for CABG on CPB patients with three groups (Group L: landiolol 5mg/kg/min for 3 days, Group LB: landiolol 5mg/kg/min for 3 days, then bisoprolol 2.5mg/day PO for 2 days, Group C: placebo) that compared POAF incidence.<sup>39</sup> Using both landiolol and bisoprolol significantly reduced the incidence of POAF compared with placebo. (Group L: 14.7% vs Group LB: 9.1% vs Group C: 34.3%,  $p<0.05$  compared with Group LB and Group C).

For valve surgery, Sakaguchi et al conducted an RCT<sup>40</sup> using landiolol 40 $\mu\text{g}/\text{kg}/\text{min}$  for 72h and saw significant reductions in POAF incidence compared with placebo. (landiolol: 20% vs control: 53.3%,  $p<0.05$ )<sup>40</sup> Sezai et al conducted a RCT trial named the PLATON Trial for evaluating the prophylactic effect of landiolol in cardiac surgery under CPB in LV dysfunction [Ejection fraction (EF)  $>35\%$ ] patients.<sup>41</sup> The use of landiolol 2 $\mu\text{g}/\text{kg}/\text{min}$  for at least 2 days significantly reduced the incidence of POAF compared with no landiolol use (landiolol: 10% vs placebo: 40%,  $p<0.05$ ) without significant decreases in HR and blood pressure.

Landiolol not only prevents POAF may be useful for treatment of POAF as well. Sakamoto et al conducted an RCT using landiolol at 0.5–40 $\mu\text{g}/\text{kg}/\text{min}$  for treatment of POAF in CABG and valve surgery and observed significant reductions of POAF recurrence compared with diltiazem (landiolol: 11.5% vs diltiazem: 27.2%).<sup>42</sup>

Recent meta-analysis of landiolol with regard to prophylactic effect against POAF after cardiac surgery reported significant reductions in the risk of onset POAF [overall cardiac surgery: odds ratio (OR): 0.27; 95% confidence interval (CI): 0.18–0.42, cardiac surgery on CPB: OR: 0.23; 95% CI: 0.13–0.40, off-pump CABG: OR: 0.36; 95% CI: 0.19–0.70] but not mortality and complication risk (mortality: OR: 0.45; 95% CI: 0.07–2.74, complication: OR: 0.45; 95% CI: 0.16–1.23).<sup>43</sup> From these diverse RCT and meta-analysis results, very low-dose landiolol might be effective for preventing POAF but has not been observed to change the risk of mortality and complications.

## Role of Prophylactic Landiolol in Percutaneous Coronary Intervention

There is limited and conflicting knowledge about the effect of landiolol during percutaneous coronary intervention (PCI). An observational study reported that landiolol use just before reperfusion at 3  $\mu\text{g}/\text{kg}/\text{min}$  was an independent predictor of an ST-segment resolution (STR)<sup>44</sup> and prevented Killip class grade progression<sup>44</sup> but one study reported associated hypotension<sup>44</sup> while another reported no serious complications.<sup>45</sup> Hanada et al conducted an RCT that used landiolol during PCI at 3  $\mu\text{g}/\text{kg}/\text{min}$  without loading and continued for 24 h just after PCI.<sup>46</sup> Landiolol use significantly reversed LVEF from acute phase to chronic phase (LVEF: landiolol: 49.1% to 52.0,  $p=0.01$ , control 50.2% to 50.2%,  $p=0.99$ ) but did not significantly alter the incidence of arrhythmias in the first 24 h after PCI (Sustained ventricular tachycardia (VT)/Ventricular fibrillation (VF): landiolol: 0%

**Table 2** Therapeutic and Prophylactic Effects of Landiolol During Cardiac Operation in Randomized Control Trials

Author	Year	Study Name	Type of Surgery	Landiolol Dose	Compare Drug	Participants	POAF	Adverse Effects
Treatment of POAF								
Sakamoto et al <sup>42</sup>	2012	JL-KNIGHT Study	CABG, valve replacement	0.5–40 µg/kg/min	DIL: bolus dose of 0.25 mg/kg over 2 min, 3–15 mg/h	LAN:35 DIL:36	Incidence: LAN:11.5% vs DIL:27.2%, Conversion to sinus rhythm (<8h): LAN:54.3% vs DIL:30.6%, HR controlled, but not converted (<8): LAN:62.9% vs DIL:50%	Hypotension: LAN:11.4% vs DIL:30.6%*, Bradycardia: LAN:0% vs DIL:11.1%*, ICU stay (days): LAN:3.9 vs DIL:3.4. Bradycardia: LAN:0% vs DIL:11.1%* * ICU stay (days): LAN:3.9 vs DIL:3.4.
Prevention of POAF in CABG on CPB								
Sezai A et al <sup>38</sup>	2011	PASCAL Trial	CABG on pump	Started at 2 µg/kg/min and discontinued after 48 h	Placebo	LAN:70 placebo:70	Incidence: LAN:10% vs Placebo:34.3%*	Mortality:0% vs 2.8%, Complications:4.2% vs 8.5%, Hospital stay (days): 11.2 vs 14.0*
Sezai A et al <sup>39</sup>	2012	BABYLON trial	CABG on pump	Group L: using LAN 5mg/kg/min for 3 days, Group LB:using LAN 5mg/kg/min for 3 days, then BIS 2.5mg/day PO for 2 days	Group C: placebo	Group L:34 Group LB:33 Group C:34	Incidence: Group L:14.7% vs Group LB:9.1%* vs Group C:34.3%	Mortality:Group L:2.9% vs Group LB:0% vs Group C:0%, Complications:Group L:5.8% vs Group LB:9% vs Group C:8.8%, Hospital stay (days): Group L:11.8 vs Group LB:11 vs Group C:12
Prevention of POAF in Off-Pump CABG								
Fujii et al <sup>36</sup>	2012		CABG off pump	5 (range 0–10) µg/kg/min untill PO drug start then CAR 2.5–5mg/day PO continued postoperatively	Placebo untill PO drug start then CAR 2.5–5mg/day PO continued postoperatively	LAN:36 placebo:34	Incidence: LAN:11.1% vs Placebo:32.3%*	-
Ogawa S et al <sup>37</sup>	2012		CABG off pump	3–5 µg/kg/min for 2 days	Not using LAN	LAN:68 control:68	Incidence: LAN:19% vs Control:37%*	Tachycardia:LAN:13% vs Control:32%*, Bradycardia:LAN:15% vs Control:13%,
Nagaoka et al <sup>35</sup>	2014		CABG off pump	0.5 to 2 µg/min/kg untill PO drug start	DIL:0.5 to 2 µg/min/kg untill PO drug start	LAN:21 DIL:22	Incidence: LAN:4.8% vs DIL:27%*	-
Prevention of POAF on Valve Surgery								
Sakaguchi M et al <sup>40</sup>	2012		Valve Surgery	10 µg/kg/min for 72h	Not using LAN	LAN:30 control:30	Incidence: LAN:20% vs Control:53.3%*	-
Prevention of POAF on Cardiac Surgery with LV Dysfunction								

(Continued)

Table 2 (Continued).

Author	Year	Study Name	Type of Surgery	Landirolol Dose	Compare Drug	Participants	POAF	Adverse Effects
Sezai A et al <sup>41</sup>	2015	PLATON trial	Cardiac surgery under CPB and had LV dysfunction (EF >35%)	2µg/kg/min at least 2 days	Not using LAN	LAN:30 control:30	Incidence: LAN:10% vs Control:40%*	In-hospital death: LAN:0% vs Control:6.6%, Complications: LAN:3.3% vs Control:13.3%, ICU stay (days): LAN:4.1 vs Control:4.3, Hospital stay (days): 14.6 vs 19.4*

Note: \*p<0.05, if the ones with no \* are not statistically significant.

Abbreviations: BIS, bisoprolol; CABG, coronary artery bypass grafting; CAR, carvedilol; CPB, cardiopulmonary bypass; DIL, diltiazem; LAN, landiolol; PO, oral administration; ICU, Intensive care unit.

vs control: 0%, unsustained VT: landiolol:34% vs control: 22%, newly developed AF: landiolol: 2% vs control: 2%). One patient in the landiolol group showed bradycardia at a rate of 50 beats/min at 12 h after administration, recovering approximately 10 min after discontinuation of the drug. Park et al also conducted an RCT using landiolol during PCI but administered it over 1 min in an intracoronary fashion (0.06 mg/kg) via an Over-the-Wire balloon catheter before and after balloon inflation.<sup>47</sup> They then intravenously administered landiolol (0.02 mg/kg/min) after the last stent deployment and continued for 6 h after PCI. This preserved the LV wall motion score index (LV wall motion score index change from pre-PCI: landiolol:0.00 vs control: -0.01, p<0.05) and decreased cardiac troponin-I (cTnI) to  $\leq$ 0.12 ng/mL after PCI (incidence of cTnI  $\geq$  0.12 ng/mL: landiolol: 41% vs control: 70%, p=0.016). As cTnI  $\geq$  0.12 ng/mL is considered as MI status in elective PCI,<sup>48</sup> landiolol can thus reduce the incidence of PCI-related MI.

From these results, observational studies and RCTs (Table 3) using continuous landiolol for 24 h just after PCI via intracoronary administration before and after balloon inflation potentially protect against arrhythmia and cardiac injury after PCI.

## Role of Prophylactic Landiolol in Heart Failure Patients

Risks and benefits of using  $\beta$ -blockers for heart failure (HF) patients must be carefully weighed. Several observational studies and RCTs using landiolol for HF patients with regard to infusion-to-oral beta-blocker (BB) therapy commencement have shown HR reduction without

markedly decreasing blood pressure<sup>49,50</sup> compared to diltiazem.<sup>51</sup>

Additionally, combination-therapy, lower-dose landiolol with milrinone has a potentially beneficial effect for acute decompensated heart failure (ADHF) patients. Kobayashi et al conducted a study for ADHF (both depressed LV function [EF $\leq$ 0.35] and HR >90 bpm with sinus rhythm, not receiving i.v. inotropes, and the absence of specific devices) in tachycardia patients and revealed that lower-dose landiolol (1.5µg/kg/min) with milrinone (0.25–0.5µg/kg/min) increased hemodynamic parameters, including pulmonary capillary wedge pressure (PCWP), stroke volume index (SVI), and oxygen saturation of mixed venous blood (SvO<sub>2</sub>).<sup>52</sup> This effect disappeared at higher doses of landiolol ( $\geq$ 3.0µg/kg/min).<sup>52</sup> Kobayashi et al also conducted animal experiments using a canine heart failure model to determine the mechanism of this combination therapy. They administered various doses (0 nM to 1000 nM) of landiolol then measured cardiomyocyte cell shortening (CS) and intracellular Ca<sup>2+</sup> transients (CaT). Ca<sup>2+</sup> spikes were measured and the presence or absence of milrinone and heart failure were correlated (three factors; 8 patterns in total). They observed that simultaneous administration of both landiolol and milrinone to failing cardiomyocytes did not decrease cardiomyocyte function but significantly decreased the frequency of diastolic Ca<sup>2+</sup> spikes (CaSF) with further increases in sarcoplasmic reticulum Ca<sup>2+</sup> concentration while peak CaT and CS improved compared with administration of milrinone alone.<sup>53</sup> Moreover, landiolol had no effect on levels of phosphorylated PLB (Ser16 and Thr17) but suppressed the hyperphosphorylation of RyR2.



**Table 3** Therapeutic Effect of Landiolol During Percutaneous Coronary Intervention in Randomized Control Trials

Author	Year	Landiolol Dose	Compare Drug	Timing of Dosage	Participants	Excluded	LV Function	Biomarkers in Acute Myocardial Injury	Arrhythmias	Adverse Effects
Hanada K <sup>46</sup>	2012	3 µg/kg/min without loading and continued for 24 h.	Non LAN	Just after PCI	LAN: 47 Control: 49	Those with Killip class 3 or 4, bradycardia <50 beats/min, hypotension with systolic BP <90 mmHg, bronchospasm, or second- or third-degree atrioventricular block.	LVEF acute phase to chronic phase: LAN 49.1% to 52.0 (p=0.01), Control 50.2% to 50.2%, p=0.99).	-	Arrhythmias in first 24 h, Sustained VT/Vf: LAN:0% vs Control:0%, Unstained VT: LAN:34% vs Control:22%, Newly developed AF: LAN:2% vs Control:2%	One patient in the landiolol group showed bradycardia at a rate of 50 beats/min at 12 h after administration, which recovered approximately 10 min after discontinuation of the drug.
Park H <sup>47</sup>	2013	Intracoronary administration of landiolol (0.06 mg/kg)	Intracoronary administration of the same volume (5 mL) of saline	1 min via Over-the-Wire balloon catheter before and after balloon inflation. Intravenous administration of landiolol (0.02 mg/kg/min) or saline was started after the last stent deployment and continued for 6 h after PCI.	LAN: 35 Control: 35	Elevation of cardiac enzymes, NYHA ≧ III or Killip class ≧ III or an LV ejection fraction below 30%, BP below 100 mm Hg or a HR below 50 bpm without anti-hypertensive drugs or antiarrhythmic drugs, respectively, heart block or CKD ≧ stage IV.	LV wall motion score index: Change from pre-PCI: LAN:0.00 vs Control: -0.01*	cTnl (ng/mL): LAN: 0.57 vs Control: 1.27, cTnl ≧ 0.05 ng/mL: LAN: 56% vs Control: 79%*, cTnl ≧ 0.12 ng/mL: LAN: 41% vs Control: 70%*, CK-MB (ng/mL): LAN: 3.17 vs Control: 7.09	-	-

**Note:** \*p<0.05, if the ones with no \* are not statistically significant.

**Abbreviations:** BP, blood pressure; cTnl, cardiac troponin-I; CKD, chronic kidney disease; HR, heart rate; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; LAN, landiolol; LV, left ventricular; LVEF, left ventricular ejection fraction; Vf, ventricular fibrillation; VT, ventricular tachycardia.

From these results, they concluded that improved function in failing cardiomyocytes was via inhibition of the phosphorylation of ryanodine receptor 2 (RyR2) and subsequent diastolic Ca<sup>2+</sup>-leakage.<sup>53</sup>

An RCT conducted by Nagai et al named the J-Land Study dosed 1–10 µg/min/kg of landiolol for patients with AF/AFL (over HR ≥120 beats/min), with low EF (LVEF: 25–50%) and compared the achievement rate of the primary end point (both HR <110 beats/min and ≥20% decrease from baseline at 2 h after administration) with digoxin.<sup>54</sup> The landiolol group achieved a significantly higher rate of reaching the primary endpoint (Achievement rate of primary endpoint: landiolol: 48% vs digoxin: 13.9%, *p*<0.0001) with an average landiolol dosage of 6.7±3.2 µg/kg/min. Wada et al<sup>55</sup> also conducted an observational study for LV dysfunction patients using the same primary endpoint and reported 74% of patients were responsive for AF/AFL and 58% of patients were responsive for VTs.<sup>55</sup>

From the safety aspect of dosing landiolol in HD patients, several studies have reported adverse events. One observational study<sup>56</sup> used landiolol at an infusion rate of 1 g/kg/min for 52 HF patients and 3 patients experienced transient asymptomatic hypotension requiring cessation (average dose of landiolol: 10.8±9.4L g/kg/min) while another reported that hypotension after landiolol treatment occurred in about 10% of patients with AF, AFL, or AT ventricular response 120 bpm refractory 12 VTs.<sup>55</sup> In the J-Land Study, the prevalence of adverse events over the total observational time was not significantly different between landiolol and digoxin groups (adverse events over total observational time: landiolol: 32.3%, digoxin: 32.7%, *p*=0.95), but the landiolol group experienced a significantly higher prevalence of adverse events over a 2-h treatment period (adverse events over a 2-h treatment period: landiolol: 8.6%, digoxin: 1.9%, *p*=0.029).<sup>54</sup> These events included 2 serious adverse events (congestive heart failure and embolic stroke). In 3 digoxin group patients, sinus arrest, diabetes insipidus, and pneumonia occurred while 3 landiolol group patients experienced embolic stroke, hypotension, and asthma. All of these patients had to discontinue therapy because of these serious adverse events. However, another conflicting study reported no adverse events observed during the study period.<sup>50</sup>

From these results of observational studies and RCT, landiolol is useful as a first-line therapy in HF patients but

careful observation is needed to maintain hemodynamic status.

## Role of Prophylactic Landiolol in Sepsis-Induced Fatal Arrhythmia

Sepsis is a severe critical status and inflammatory immune reaction that causes multiple organ dysfunction syndrome (MODS). Sepsis-related cardiac dysfunction is a fatal consequence of sepsis first described in 1981<sup>57</sup> and can be diagnosed in up to 60% of patients with septic shock.<sup>58</sup> There are several mechanisms that transduce this cardiac dysfunction, including downregulation of β-adrenergic receptors,<sup>59–61</sup> and use of β-1 agonists (eg, dobutamine) was reported to be ineffective in sepsis<sup>62</sup> due to failing systemic oxygen delivery<sup>63</sup> while catecholamine vasopressor therapy would increase cardiac adverse events.<sup>64</sup> In addition, tachycardia was associated with a poor outcome in sepsis patients. Therefore, preserving heart load and HR has been considered as a potential treatment for sepsis, as evidenced by use of β-adrenergic blocker esmolol that was reported to significantly decrease mortality in patients with septic shock in a recent RCT<sup>65</sup> (esmolol: 49.4% vs control: 80%, *p*<0.001).

Esmolol is already reported to have a therapeutic effect against sepsis in animal models<sup>66–68</sup> and landiolol treatment has shown significant decreases in serum TNF-α and IL-6 with increased cardiac function in a lipopolysaccharide (LPS)-induced rat model.<sup>69,70</sup> Seki et al evaluated the cardioprotection of landiolol in an LPS-induced, systemically inflamed rat model. Continuous landiolol administration significantly reduced cardiac tumor necrosis factor-α (TNF-α) levels and the percentage of fractional shortening in the murine hearts was significantly increased. Endothelin-1 (ET-1), a potent vasoconstrictor implicated in pathogenesis of sepsis, was normalized by landiolol treatment and the authors concluded that landiolol has a cardioprotective effect possibly modulated by cardiac vasoactive peptides such as ET.<sup>68</sup> Hagiwara et al also used LPS-induced, systemically inflamed rats to evaluate cardioprotective effects of landiolol and found it to both normalize cardiac function and significantly reduce serum levels of High-mobility group box 1 (HMGB-1), an inflammatory mediator critical to the development of sepsis. Surprisingly, it was reported that landiolol ameliorates not only heart but also kidney<sup>71,72</sup> and lung<sup>73</sup> damage in animal sepsis models. However, Kurita et al revealed that landiolol administration causes reductions in cerebral tissue oxygenation<sup>74</sup> in an LPS-induced,



systemically inflamed swine model by measuring hemodynamics, blood variables, and cerebral tissue oxygenation index (TOI) by near-infrared spectroscopy. They revealed that landiolol reduces LPS-induced tachycardia but induces thermodynamic depression depending on the endotoxemia stage. This reduction was especially seen when SV did not increase in response to the decrease in HR. Interestingly, sex-mediated responses were observed in an animal study by Mathieu et al where landiolol was tested in a cecal ligation and puncture (CLP) sepsis model in both male and female rats.<sup>75</sup> Landiolol increased SVI compared with non-treated sepsis rats in males but not females. This sex-mediated response for  $\beta$ -blockers after high-risk vascular surgery has already been clinically reported.<sup>76</sup>

Clinically, several case reports reported successful management of tachycardiac atrial fibrillation in sepsis patients with landiolol.<sup>77,78</sup> An on-going RCT is currently using landiolol for sepsis patients has set the primary endpoint as HR response (HR = 80–94 bpm) and maintenance without increases in vasopressor requirement was observed during the first 24 h after administration.<sup>79</sup>

From these results of animal studies and clinical reports, use of landiolol for sepsis reveals the therapeutic

effect of rate control during sepsis and a subsequent beneficial effect for other vital organs.

## Role of Prophylactic Landiolol in Pediatric Patients

There is a new appreciation for the need of landiolol in pediatric patients. In adult patients, both esmolol and landiolol are used for tachycardia rate control because of high  $\beta_1$ : $\beta_2$  selectivity ratios. Due to the low hemodynamic stability of pediatric patients, esmolol has been shown to control hypertension effectively in children after cardiac surgery.<sup>80,81</sup> From this fact, it may be inferred that the higher  $\beta_1$ : $\beta_2$  selectivity of landiolol over esmolol would render it the superior choice for tachycardia treatment in pediatric patients.

Several case reports have reported the usefulness of landiolol for preventing idiopathic ventricular tachycardia in neonates<sup>82</sup> as well as supraventricular tachycardia caused by viral myocarditis.<sup>83</sup> Miyake et al evaluated the efficacy and safety of landiolol for tachyarrhythmia in patients undergoing the Fontan procedure (total cavopulmonary connection; TCPC).<sup>84</sup> The average initial dose of landiolol was  $4.7 \pm 2.3$   $\mu\text{g}/\text{kg}/\text{min}$ , without a loading dose, and this significantly

**Table 4** Ongoing Randomized Control Trials in New Therapeutic Area

Author	Year	Study Name	Age	Disease of Eligible Patients	Landiolol Dose	Compare Drug	Sample Size	Primary Endpoint	Secondary Endpoint
Sepsis Unger M et al <sup>79</sup>	2018-	LANDI-SEP study	Aged $\geq$ 18 years	Septic shock and tachycardia (HR $\geq$ 95 bpm) despite a hemodynamic optimization period of 24– 36 h.	1–40 $\mu\text{g}/\text{kg}/$ min at intervals of at least 20 min to obtain and maintain a HR of 80–94 bpm.	Standard care	200	HR response (HR =80–94 bpm) and maintenance thereof without increase in vasopressor requirements during the first 24h.	ICU and 28-day mortality, ICU and hospital stay duration, SOFA score, and inotrope and vasopressor support requirements.
Pediatric Patients with Heart Failure									
Sumitomo N et al <sup>87</sup>	2015–2021	HEARTFUL study	Aged $\cong$ 3 months and <15 years	Have tachyarrhythmia (AF, AFL, SVT) as well as heart failure.	1–10 $\mu\text{g}/\text{kg}/$ min	Not written	25	$\cong$ 20% reduction from baseline heart rate or return to normal sinus rhythm within 2 h after starting intravenous administration.	HR, return to normal sinus rhythm, percentage of patients with 20% reduction in heart rate or return to normal sinus rhythm, and return to the resting HR before the arrhythmia attack.

**Abbreviations:** AF, atrial fibrillation; AFL, atrial flutter; HR, heart rate; ICU, Intensive care unit; SOFA, sequential organ failure assessment; SVT, supraventricular tachycardia.

reduced HR without significant blood pressure decreases. Tokunaga et al also evaluated the efficacy and safety of landiolol in the management of tachyarrhythmias after pediatric cardiac surgery. An average loading dose of  $11.3 \pm 4.0 \mu\text{g/kg/min}$  and maintenance doses of  $6.8 \pm 0.9 \mu\text{g/kg/min}$  were sufficient to achieve rate control without significant blood pressure decreases.<sup>85</sup> Moreover, 70% of these cases experienced sinus rhythm conversion from tachyarrhythmias within an average of  $2.3 \pm 0.5$  hours. They recommended low starting doses (3–5  $\mu\text{g/kg/min}$ ) for pediatric patients in place of recommended dosing (40  $\mu\text{g/kg/min}$  for loading dose, 10  $\mu\text{g/kg/min}$  for maintenance dose). Yoneyama et al reported efficacy of landiolol for managing junctional ectopic tachycardia (JET) in pediatric patients who underwent open-heart surgery. The average loading dose of  $8.5 \pm 3.6 \mu\text{g/kg/min}$  and maintenance doses of  $7.9 \pm 0.6 \mu\text{g/kg/min}$  achieved rate control without significant blood pressure decreases.<sup>86</sup> Approximately 80% patients were converted to regular sinus rhythm within 24 hours after starting administration of landiolol and 90% patients had atrioventricular sequential pacing to maintain appropriate heart rate under landiolol suppression of the junctional heart rate.

There is one RCT conducted by Sumitomo et al named the HEARTFUL study in which landiolol was administered to prevent tachyarrhythmia in a dose starting from 1  $\mu\text{g/kg/min}$  to achieve a 20% reduction of HR in patients aged from 3 months to 15 years old patients with heart failure<sup>87</sup> (Table 4).

Reports of landiolol usage in pediatric patients are scarce, but initial researches into the therapeutic effect of landiolol for tachyarrhythmia in pediatric patients are promising and further studies are required.

## Conclusion

Landiolol, by virtue of its high  $\beta_1$  selectivity, can treat arrhythmia without decreasing heart contraction and is useful as a first-line therapy for the prevention of POAF after cardiac/non-cardiac surgery, fatal arrhythmias in heart failure patients and during PCI. Moreover, the potential therapeutic effect of landiolol for sepsis and pediatric patients is currently being explored. Recent, positive RCT results will thus continue to inspire cardiologists, intensivists and pediatric cardiologists to find new uses for and conduct studies with this drug.

## Abbreviations

ADHF, acute decompensated heart failure; AFL, atrial flutter; AF, atrial fibrillation; AT, atrial tachycardia; AUC, area

under the concentration; CaSF, the frequency of diastolic Ca<sup>2+</sup> + sparks; CaT, intracellular Ca<sup>2+</sup>-transients; cTnI, cardiac troponin-I; CS, cardiomyocyte cell shortening; CPB, cardiopulmonary bypass; CI, confidence interval; CABG, coronary artery bypass grafting; EF, ejection fraction; HR, heart rate; HF, heart failure; LV, left ventricular; C<sub>max</sub>, maximum concentration; MAP, mean arterial blood pressure; MODS, multi-organ dysfunction syndrome; OR, odds ratio; SvO<sub>2</sub>, oxygen saturation of mixed venous blood; PCI, percutaneous coronary intervention; POAF, postoperative atrial fibrillation; POD, post-operative day; PCWP, pulmonary capillary wedge pressure; RCT, random clinical trial; RyR2, ryanodine receptor 2; SVI, stroke volume index; SVT, supraventricular tachycardia; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; VT, ventricular tachycardia; VF, ventricular fibrillation.

## Funding

This work was performed at Tsukuba University Hospital, Ibaraki, Japan. No financial support was received to conduct or publish this study.

## Disclosure

The authors report no conflicts of interest in this work.

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