



Original article

A prospective observational survey on landiolol in atrial fibrillation/atrial flutter patients with chronic heart failure – AF-CHF landiolol survey



Takeshi Yamashita (MD, PhD, FJCC)^{a,*}, Yukiko Nakasu (BSc)^b, Hiroto Mizutani (MSc)^b, Kenji Sumitani (BSc)^b

^a The Cardiovascular Institute, Tokyo, Japan

^b Pharmacovigilance Division, Ono Pharmaceutical Co., Ltd., Osaka, Japan

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ABSTRACT

Background: Atrial fibrillation and atrial flutter occur commonly in patients with heart failure. Ultrashort-acting β -blockers, including landiolol, can rapidly control heart rate. As part of postmarketing surveillance for landiolol in Japan, a real-world drug-use survey (AF-CHF landiolol survey) was established for the treatment of atrial fibrillation and atrial flutter in patients with heart failure. We report the safety and effectiveness of landiolol from this survey, focusing on adverse events/adverse drug reactions.

Methods: Consecutive patients with cardiac dysfunction who received landiolol (continuous intravenous infusion, starting at 1 $\mu\text{g}/\text{kg}/\text{min}$) for atrial fibrillation or atrial flutter in routine clinical practice in Japan were enrolled between June 2014 and May 2016. Safety variables included adverse events and adverse drug reactions (number of patients and events, incidence rate, types, seriousness). Effectiveness variables included the proportion of patients with a $\geq 20\%$ decrease in heart rate.

Results: Data were available for 1121 patients (safety analysis set); 888 patients were evaluable for effectiveness parameters. Mean (\pm standard deviation) patient age was 72.5 ± 13.5 years, 57.2% were male. Most patients (84.2%) received landiolol for atrial fibrillation. Overall, 174 adverse events occurred in 140 patients (12.5%), including 105 serious adverse events. The most common type of adverse events was cardiac (60 events). Seventy-five events in 63 patients were categorized as adverse drug reactions (5.6% of patients). Mean heart rate decreased substantially after treatment with landiolol, by $\geq 20\%$ in 77.5% of patients.

Conclusions: In a real-world setting in Japan, landiolol for the treatment of atrial fibrillation or atrial flutter with heart failure was acceptable without new safety concerns, and most patients achieved effective heart rate control during their arrhythmias.

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Introduction

Atrial fibrillation and atrial flutter are common in patients with heart failure. Atrial fibrillation affects 10–50% of patients with heart failure [1,2], and is associated with poor outcomes in these patients [3,4]. For the acute control of atrial fibrillation in cardiac dysfunction/heart failure, beta-blockers, amiodarone, and digoxin

are available [5,6], where intravenous ultrashort-acting β -blockers are choices for acute clinical situations [7,8].

Landiolol hydrochloride (hereafter referred to as landiolol) is an ultrashort-acting highly cardioselective β_1 blocker with a rapid onset of action that is used for short-term control of tachyarrhythmias [8,9]. In Japan it was initially approved for the emergency treatment of intraoperative and postoperative atrial fibrillation, atrial flutter, and sinus tachycardia. More recently, in 2013, it was also approved for the treatment of atrial fibrillation and atrial flutter in patients with cardiac dysfunction.

As part of the postmarketing surveillance program for landiolol in Japan, a prospective drug-use survey (AF-CHF landiolol survey)

* Corresponding author at: 3-2-19, Nishiazabu, Minato-ku, Tokyo 106-0031, Japan.

E-mail address: yamt-ky@umin.ac.jp (T. Yamashita).

was established [10]. This survey is monitoring the occurrence of adverse drug reactions (and other adverse events) associated with landiolol for the treatment of atrial fibrillation or atrial flutter in patients with cardiac dysfunction in Japan. Particular attention is paid to events associated with its cardiodepressant activity, and also to the use of concomitant medications and any drug–drug interactions. Data on concomitant medications, drug interactions, and mid- to long-term outcomes will be evaluated at the end of the survey. The results of the current analysis focus on adverse drug reactions and other adverse events during the acute phase of landiolol use.

Methods

This postmarketing surveillance, real-world, prospective, observational survey enrolled consecutive patients with cardiac dysfunction who were treated with landiolol for atrial fibrillation or atrial flutter in a routine clinical practice setting. Enrolment was during a 2-year period with the full survey lasting 3 years. Patients were treated at 209 medical institutions throughout Japan by physicians experienced in the treatment of heart failure. The study was performed in compliance with Good Postmarketing Study Practice according to the Japanese Pharmaceutical Affairs Act. Patients' informed consent was not required for this survey; information about direct patient identifiers was not collected.

Landiolol hydrochloride was planned to be administered as a continuous intravenous infusion, starting at a rate of 1 $\mu\text{g}/\text{kg}/\text{min}$. Thereafter, the dose was planned to be adjusted between 1 and 10 $\mu\text{g}/\text{kg}/\text{min}$ as appropriate, depending on heart rate and blood pressure.

Data were collected using the ADDIN electronic data capture system (ASKLEP Inc., Tokyo, Japan). Two electronic survey forms were used. The current analysis, based on the first survey form, includes data captured during the period from the day before the start of landiolol treatment to 7 days after its discontinuation. The

second form captured data for the period from the end day of the first form to 180 days after the start of treatment (mid- to long-term outcomes).

Data collected between the day before the start of landiolol treatment and 7 days after its discontinuation included the following: baseline patient characteristics and cardiac function tests; duration and rates of landiolol administration; clinical course through to 7 days after discontinuation, including heart rate and blood pressure (before treatment and immediately, 30 min, and 7 days after its discontinuation); concomitant medications/therapies (through to 7 days after discontinuation of landiolol); adverse events (from start of landiolol to 48 h after its discontinuation). Adverse events were coded using MedDRA/J version 20.1.

Summary statistics were used for data analysis. Safety variables included adverse drug reactions and adverse events (number of patients and events, incidence rate, types, seriousness). Effectiveness variables included the proportion of patients whose heart rate decreased by $\geq 20\%$, increased by $\geq 10\%$, or was not changed (heart rate change -20% – 10%). Variables were analyzed according to the type of tachyarrhythmia (atrial fibrillation or atrial flutter) as well as for the effectiveness analysis set. Analyses were conducted using SAS software.

An analysis population of 500 was planned, as this number would enable a comparison with data from a Japanese clinical trial and postmarketing surveillance based on the interval estimates of population proportions and what can be accrued in real-world settings. The results of a Japanese clinical trial in patients with a tachyarrhythmia and cardiac dysfunction [11], and postmarketing surveillance [12,13], suggested that if adverse drug reactions occurred in 4%, 6%, or 8% of 500 patients, the frequency of adverse drug reactions in the population can be estimated to be in the ranges of 2.3–5.7%, 3.9–8.1%, or 5.6–10.4% (95% confidence interval), respectively. To allow for potential dropouts during the survey and patients excluded from the analysis, a sample size of 800 patients was chosen.

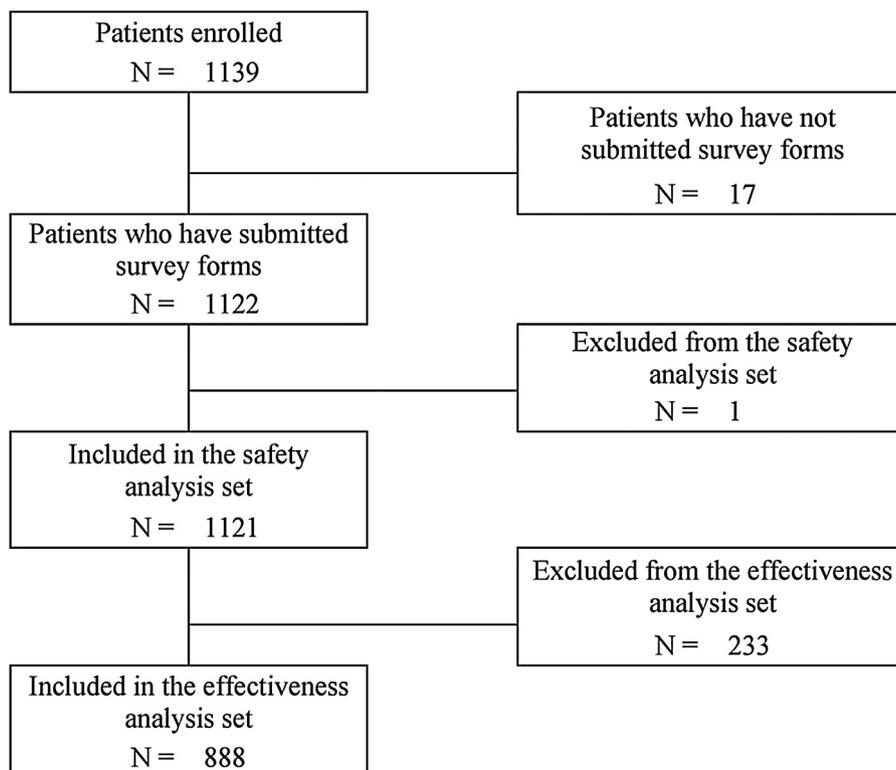


Fig. 1. Population distribution.

Table 1
Patients' characteristics at baseline.

Parameter	Category	Number of patients (%) ^a
Total number of patients (safety analysis set)		1121
Age (mean ± SD), years		72.5 ± 13.5
Male/female		641 (57.2)/480 (42.8)
Reason for use of landiolol	Atrial fibrillation	944 (84.2)
	Atrial flutter	73 (6.5)
	Atrial fibrillation + atrial flutter	31 (2.8)
	Other	73 (6.5)
History of cardiac and other diseases ^b		1083 (96.6)
	Heart disease	939 (83.8)
	Diabetes mellitus	281 (25.1)
	Stroke (including TIA)	148 (13.2)
	Renal disease	240 (21.4)
New York Heart Association functional class	Normal	13 (1.2)
	I	73 (6.5)
	II	153 (13.6)
	III	411 (36.7)
	IV	388 (34.6)
Left ventricular fraction on echocardiography (%) [N=938]	Unknown	83 (7.4)
	Mean ± SD	40.7 ± 15.9
	Median (min – max)	40.0 (7.0 – 85.0)
	<40	454 (48.3)
	≥40 to <50	206 (21.9)
≥50	278 (29.6)	

max, maximum; min, minimum; SD, standard deviation; TIA, transient ischemic attack.
^a Unless indicated otherwise.
^b Other patients were confirmed as not having the disease or had unknown status.

Results

A total of 1139 patients were enrolled between June 2014 and May 2016, with survey forms submitted by 1122 patients; data were available for 1121 patients (safety analysis set), with 888 patients being included in the effectiveness analysis set (Fig. 1). A total of 233 patients were excluded from the effectiveness analysis because no data were available for the assessment of heart rate ($n = 175$) or because they were treated with off-label use ($n = 71$); 13 patients met both reasons for exclusion.

Patients' baseline characteristics are summarized in Table 1. The mean (\pm standard deviation) age of patients was 72.5 ± 13.5 years and just over half were male (57.2%). Most patients (84.2%) were given landiolol for atrial fibrillation, with 6.5% receiving it for atrial flutter and 2.8% for both conditions. Most patients (83.8%) had been diagnosed with at least one concurrent cardiac disease, most commonly chronic cardiac failure (61.1%). Overall, 71.3% of patients had New York Heart Association (NYHA) functional class III or IV, and 76.6% had a left ventricular ejection fraction (LVEF) of $\leq 50\%$.

Landiolol treatment profiles are summarized in Table 2. The median (minimum–maximum) heart rate before starting landiolol treatment was 140.0 (48–260) beats per minute (bpm). Landiolol infusion was administered for a mean of 80.9 ± 100.9 h. The infusion was started at a rate of $1 \mu\text{g}/\text{kg}/\text{min}$ in most patients (62.7%). The highest infusion rate administered during treatment ranged from 0.1 to $25.0 \mu\text{g}/\text{kg}/\text{min}$ (median 3.0).

Reasons for discontinuation of landiolol were: responses to treatment (83.1%), insufficient effectiveness (8.2%), adverse event (5.0%), and 'others' (5.6%). Of 30 patients who reinitiated landiolol within 7 days of discontinuation, 26 patients (86.7%) showed tachycardia with atrial fibrillation.

Table 2
Landiolol usage.

Parameter	Category	Number of patients (%) ^a
Total number of patients (safety analysis set)		1121
Duration of use (h) [N=981]	Mean ± SD	80.9 ± 100.9
	Median (min – max)	49.0 (0.2 – 1082.0)
	<1	11 (1.0)
	≥1 to <2	9 (0.8)
	≥2 to <3	16 (1.4)
	≥3 to <6	24 (2.1)
	≥6 to <12	68 (6.1)
	≥12 to <24	147 (13.1)
	≥24	706 (63.0)
	Unknown	140 (12.5)
Starting infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	Mean ± SD	1.5 ± 1.7
	Median (min – max)	1.0 (0.05 – 25.0)
	<1	89 (7.9)
	1	703 (62.7)
>1	329 (29.3)	
Heart rate before treatment (beats per minute) [N=1110]	Mean ± SD	136.3 ± 25.2
	Median (min – max)	140.0 (48 – 260)
	<60	3 (0.3)
	≥60 to <80	28 (2.5)
	≥80 to <100	46 (4.1)
	≥100 to <120	127 (11.3)
	≥120 to <140	350 (31.2)
	≥140	556 (49.6)
	Unknown	11 (1.0)
	Lowest infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	Mean ± SD
Median (min – max)		1.0 (0.0 – 25.0)
<1		162 (14.5)
1		714 (63.7)
>1	245 (21.9)	
Highest infusion rate ($\mu\text{g}/\text{kg}/\text{min}$)	Mean ± SD	4.1 ± 3.3
	Median (min – max)	3.0 (0.1 – 25.0)
	≤2	427 (38.1)
	>2 to ≤4	301 (26.9)
	>4 to ≤6	182 (16.2)
	>6 to ≤8	83 (7.4)
	>8 to ≤10	92 (8.2)
	>10	36 (3.2)

max, maximum; min, minimum; SD, standard deviation.
^a Unless indicated otherwise.

Safety

A total of 174 adverse events occurred in 140 of the 1121 patients (12.5%) (Table 3), including 105 serious adverse events. The most common types of adverse events (by classification and event) were cardiac disorders (60 events in 57 patients), as were the most common serious adverse events (47 events in 46 patients). The most common adverse event was hypotension (37 events), followed by aggravation of cardiac failure (21 events), pneumonia (11 events), bradycardia (8 events), and ventricular tachycardia (6 events).

A total of 75 events in 63 patients were categorized as adverse drug reactions by attending physicians (5.6% of patients) (Table 4). Most adverse drug reactions were classified as vascular disorders (2.8% of patients) or cardiac disorders (2.4%). The most common adverse drug reactions were hypotension (30 events), aggravation of cardiac failure (11 events), and bradycardia (7 events). Thirty-five adverse drug reactions were considered serious, with the most common being aggravation of cardiac failure (11 events), hypotension (7 events), and bradycardia (3 events).

The incidence of adverse drug reactions was 6.7% (6/89 patients) among those in whom the initial landiolol infusion rate was $<1 \mu\text{g}/\text{kg}/\text{min}$, 6.4% (45/703) in those in whom the rate was

Table 3

Adverse events recorded with landiolol (N=1121).

Classification	No. of patients (%)	Event	No. of events (%)	Seriousness (no. of events [%])			
				Serious	Non-serious		
ALL	140 (12.5)		174	105 (9.4)	69 (6.2)		
Infections and infestations	19 (1.7)	Gastrointestinal clostridial	1 (0.1)	0	1 (0.1)		
		Meningitis bacterial	1 (0.1)	1 (0.1)	0		
		Pneumonia	11 (1.0)	11 (1.0)	0		
		Pneumonia pseudomonal	1 (0.1)	1 (0.1)	0		
		Pyelonephritis	1 (0.1)	1 (0.1)	0		
		Sepsis	4 (0.4)	4 (0.4)	0		
		<i>Pneumocystis jirovecii</i> pneumonia	1 (0.1)	1 (0.1)	0		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.1)	Malignant neoplasm of renal pelvis	1 (0.1)	1 (0.1)	0		
Blood and lymphatic system disorders	2 (0.2)	Anemia	1 (0.1)	1 (0.1)	0		
		Disseminated intravascular coagulation	1 (0.1)	1 (0.1)	0		
Endocrine disorders	1 (0.1)	Thyrototoxic crisis	1 (0.1)	1 (0.1)	0		
Metabolism and nutrition disorders	7 (0.6)	Hypoglycemia	1 (0.1)	1 (0.1)	0		
		Hypokalemia	5 (0.4)	0	5 (0.4)		
		Decreased appetite	1 (0.1)	1 (0.1)	0		
Psychiatric disorders	1 (0.1)	Delirium	1 (0.1)	0	1 (0.1)		
Nervous system disorders	3 (0.3)	Cerebral infarction	3 (0.3)	3 (0.3)	0		
Cardiac disorders	57 (5.1)	Acute myocardial infarction	1 (0.1)	1 (0.1)	0		
		Aggravation of cardiac failure	21 (1.9)	21 (1.9)	0		
		Aortic valve stenosis	1 (0.1)	1 (0.1)	0		
		Atrial fibrillation	2 (0.2)	1 (0.1)	1 (0.1)		
		Atrial flutter	1 (0.1)	1 (0.1)	0		
		Bradycardia	8 (0.7)	4 (0.4)	4 (0.4)		
		Bundle branch block left	1 (0.1)	0	1 (0.1)		
		Bundle branch block right	1 (0.1)	0	1 (0.1)		
		Cardiac arrest	1 (0.1)	1 (0.1)	0		
		Cardio-respiratory arrest	3 (0.3)	3 (0.3)	0		
		Cardiogenic shock	3 (0.3)	3 (0.3)	0		
		Left ventricular failure	1 (0.1)	1 (0.1)	0		
		Low cardiac output syndrome	1 (0.1)	1 (0.1)	0		
		Myocardial infarction	4 (0.4)	2 (0.2)	2 (0.2)		
		Myocardial ischemia	1 (0.1)	1 (0.1)	0		
		Sinus arrest	1 (0.1)	0	1 (0.1)		
		Ventricular extrasystoles	1 (0.1)	0	1 (0.1)		
		Ventricular fibrillation	1 (0.1)	1 (0.1)	0		
		Ventricular tachycardia	6 (0.5)	4 (0.4)	2 (0.2)		
		Vascular disorders	39 (3.5)	Ischemic cardiomyopathy	1 (0.1)	1 (0.1)	0
Aortic aneurysm	1 (0.1)			1 (0.1)	0		
Hypotension	37 (3.3)			11 (1.0)	26 (2.3)		
Respiratory, thoracic, and mediastinal disorders	8 (0.7)	Shock	1 (0.1)	1 (0.1)	0		
		Dyspnea	1 (0.1)	0	1 (0.1)		
		Epistaxis	1 (0.1)	0	1 (0.1)		
		Interstitial lung disease	1 (0.1)	1 (0.1)	0		
		Pleural effusion	1 (0.1)	0	1 (0.1)		
		Pneumonia aspiration	3 (0.3)	3 (0.3)	0		
		Respiratory failure	2 (0.2)	2 (0.2)	0		
		Gastrointestinal disorders	5 (0.4)	Abdominal distension	1 (0.1)	0	1 (0.1)
				Constipation	1 (0.1)	0	1 (0.1)
				Diarrhea	2 (0.2)	2 (0.2)	0
Dry mouth	1 (0.1)			0	1 (0.1)		
Nausea	1 (0.1)			0	1 (0.1)		
Hepatobiliary disorders	2 (0.2)	Hepatic function abnormal	1 (0.1)	0	1 (0.1)		
		Liver disorder	1 (0.1)	0	1 (0.1)		
Skin and subcutaneous tissue disorders	3 (0.3)	Purpura	1 (0.1)	0	1 (0.1)		
		Rash generalized	1 (0.1)	0	1 (0.1)		
		Rash pruritic	1 (0.1)	0	1 (0.1)		
Musculoskeletal and connective tissue disorders	1 (0.1)	Back pain	1 (0.1)	0	1 (0.1)		
Renal and urinary disorders	2 (0.2)	Renal failure	1 (0.1)	1 (0.1)	0		
		Renal infarct	1 (0.1)	1 (0.1)	0		
General disorders and administration site conditions	6 (0.5)	Chest discomfort	2 (0.2)	1 (0.1)	1 (0.1)		
		Pyrexia	1 (0.1)	0	1 (0.1)		
		Multiple organ dysfunction syndrome	3 (0.3)	3 (0.3)	0		
Laboratory abnormalities	9 (0.8)	Blood glucose increased	1 (0.1)	0	1 (0.1)		
		Blood pressure increased	1 (0.1)	1 (0.1)	0		
		Blood uric acid increased	1 (0.1)	1 (0.1)	0		
		Gamma-glutamyltransferase increased	1 (0.1)	0	1 (0.1)		
		White blood cell count increased	1 (0.1)	0	1 (0.1)		
		Blood alkaline phosphatase increased	1 (0.1)	0	1 (0.1)		
		Urine output decreased	2 (0.2)	1 (0.1)	1 (0.1)		
		Hepatic enzyme increased	1 (0.1)	0	1 (0.1)		
		Electrocardiogram change	1 (0.1)	0	1 (0.1)		
		Injury, poisoning, and procedural complications	1 (0.1)	Wound complication	1 (0.1)	0	1 (0.1)

Table 4
Adverse drug reactions reported with landiolol (N = 1121).

Classification	No. of patients (%)	Event	No. of events (%)	Seriousness (no. of events [%])	
				Serious	Non-serious
ALL	63 (5.6)		75	35 (3.1)	40 (3.6)
Infections and infestations	2 (0.2)	Pneumonia	2 (0.2)	2 (0.2)	0
Metabolism and nutrition disorders	3 (0.3)	Hypoglycemia	1 (0.1)	1 (0.1)	0
		Hypokalemia	1 (0.1)	0	1 (0.1)
		Decreased appetite	1 (0.1)	1 (0.1)	0
Cardiac disorders	27 (2.4)	Aggravation of cardiac failure	11 (1.0)	11 (1.0)	0
		Bradycardia	7 (0.6)	3 (0.3)	4 (0.4)
		Cardiorespiratory arrest	2 (0.2)	2 (0.2)	0
		Cardiogenic shock	2 (0.2)	2 (0.2)	0
		Low cardiac output syndrome	1 (0.1)	1 (0.1)	0
		Myocardial infarction	1 (0.1)	0	1 (0.1)
		Sinus arrest	1 (0.1)	0	1 (0.1)
		Ventricular extrasystoles	1 (0.1)	0	1 (0.1)
		Ventricular tachycardia	2 (0.2)	1 (0.1)	1 (0.1)
Vascular disorders	31 (2.8)	Hypotension	30 (2.7)	7 (0.6)	23 (2.1)
		Shock	1 (0.1)	1 (0.1)	0
Respiratory, thoracic, and mediastinal disorders	3 (0.3)	Dyspnea	1 (0.1)	0	1 (0.1)
		Pleural effusion	1 (0.1)	0	1 (0.1)
		Respiratory failure	1 (0.1)	1 (0.1)	0
Gastrointestinal disorders	1 (0.1)	Diarrhea	1 (0.1)	1 (0.1)	0
Hepatobiliary disorders	2 (0.2)	Hepatic function abnormal	1 (0.1)	0	1 (0.1)
		Liver disorder	1 (0.1)	0	1 (0.1)
Laboratory abnormalities	4 (0.4)	Blood uric acid increased	1 (0.1)	1 (0.1)	0
		Gamma-glutamyltransferase increased	1 (0.1)	0	1 (0.1)
		Blood alkaline phosphatase increased	1 (0.1)	0	1 (0.1)
		Hepatic enzyme increased	1 (0.1)	0	1 (0.1)
		Electrocardiogram change	1 (0.1)	0	1 (0.1)

1 $\mu\text{g}/\text{kg}/\text{min}$, and 3.7% (12/329) among those who received an initial rate of $>1 \mu\text{g}/\text{kg}/\text{min}$.

Mean blood pressure decreased slightly after landiolol treatment (Fig. 2a) without significant differences between the types of tachyarrhythmias (Fig. 2b) in patients with blood pressure data available.

Effectiveness

Among 545 patients with complete heart rate data, mean heart rate decreased substantially after treatment with landiolol (Fig. 3a). The reduction was similar between the subgroups with atrial fibrillation and atrial flutter (Fig. 3b).

Based on the percent change in heart rate from immediately before landiolol to immediately after discontinuation of landiolol, tachycardia was categorized as “improved” ($\geq 20\%$ reduction in heart rate) in 77.5% of patients and “worsened” ($\geq 10\%$ increase in heart rate) in 1.1%, with 21.4% categorized as “unchanged”. Among 432 (48.6%) patients admitted to ICU/CCU, tachycardia was “improved,” “unchanged,” or “worsened” in 75.2%, 23.6%, and 1.2% of patients, respectively.

Of the 888 patients in the effectiveness analysis set, 299 patients (33.7%) showed recovery of sinus rhythm within 7 days after discontinuation of the drug; the median time to first return to sinus rhythm was 14 h (range 0.1–451.2 h).

Discussion

This postmarketing surveillance of landiolol for the treatment of atrial fibrillation/atrial flutter in patients with heart failure in a real-world setting in Japan found no new safety concerns and indicated that the drug provided effective control of tachyarrhythmias in most of the patients.

Landiolol is an ultrashort-acting β_1 -blocker that is effective in the treatment of perioperative tachyarrhythmias and the

prevention of atrial fibrillation after cardiac surgery [8,9,14–16]. It has also been reported to be effective for treating tachyarrhythmias in patients with heart failure [11]. The prospective, multicenter, randomized, single-blind J-LAND trial showed that landiolol was more effective than digoxin in controlling heart rate in patients with left ventricular dysfunction (NYHA class III–IV and LVEF 25–50%) who had atrial fibrillation or atrial flutter (with a heart rate of ≥ 120 bpm) [11]. Successful heart rate control (defined as $\geq 20\%$ reduction, with heart rate <110 bpm after 2 h) was achieved in 48.0% of patients treated with landiolol compared with 13.9% of digoxin recipients. Based on the results of this trial, landiolol was approved in Japan for the treatment of tachyarrhythmias (atrial fibrillation/atrial flutter) in patients with cardiac dysfunction, and is included in the latest Japanese Circulation Society guidelines as one of the recommended agents for rate control of atrial fibrillation in patients with heart failure [5].

Supportive data for the use of landiolol to control heart rate in patients with heart failure come from small noncomparative and/or retrospective studies. In prospective noncomparative trials, landiolol used as an adjunct to other therapy (diuretics, vasodilators, inotropes) was effective in reducing the heart rate in patients with acute decompensated heart failure with atrial fibrillation [17], tachycardia [18], and supraventricular tachyarrhythmias [19]. Retrospective studies found that landiolol was more effective than diltiazem in reducing heart rate in patients with heart failure and supraventricular tachycardias, facilitating an earlier switch to oral β -blockers [20], and was also effective for refractory ventricular tachyarrhythmias in patients with heart failure [21]. J-LAND remains the only prospective controlled study evaluating landiolol for treating tachyarrhythmias in patients with heart failure. Additional information on the safety and effectiveness of landiolol in this indication is needed, including data from routine clinical practice. Consequently, the present study, an observational postmarketing surveillance, was established in Japan.

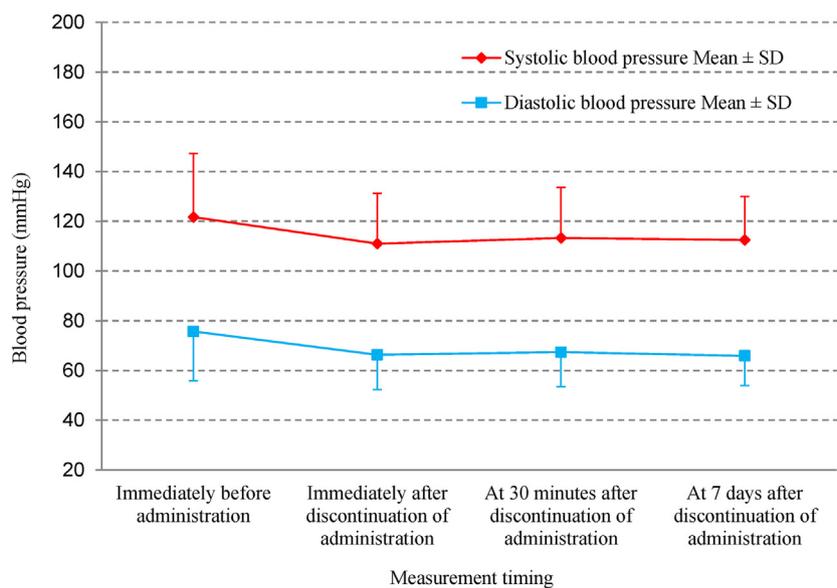
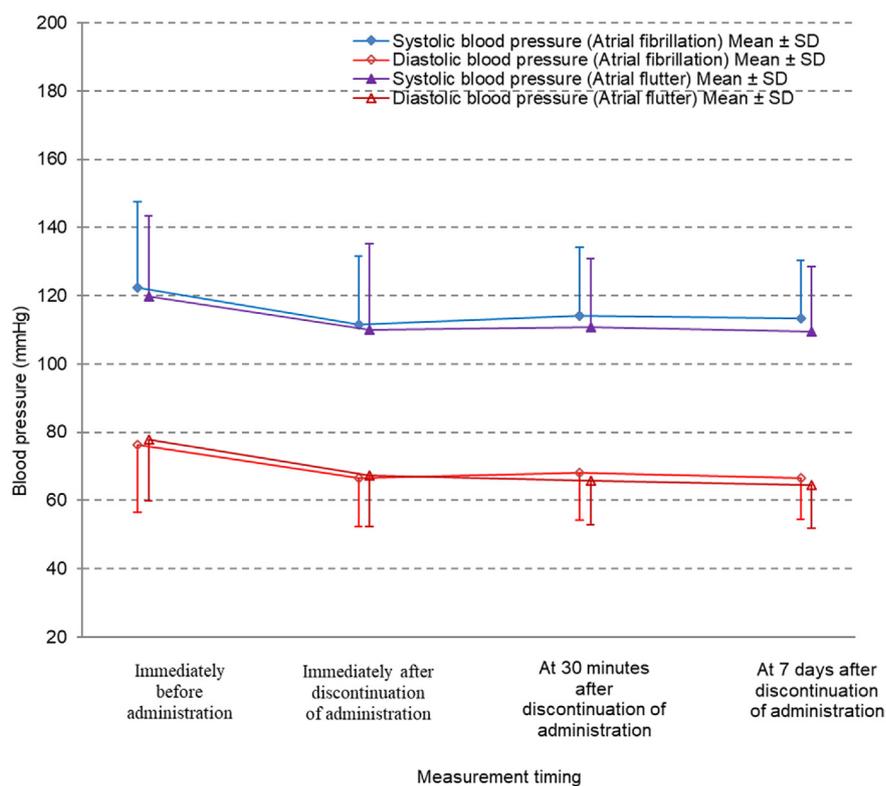
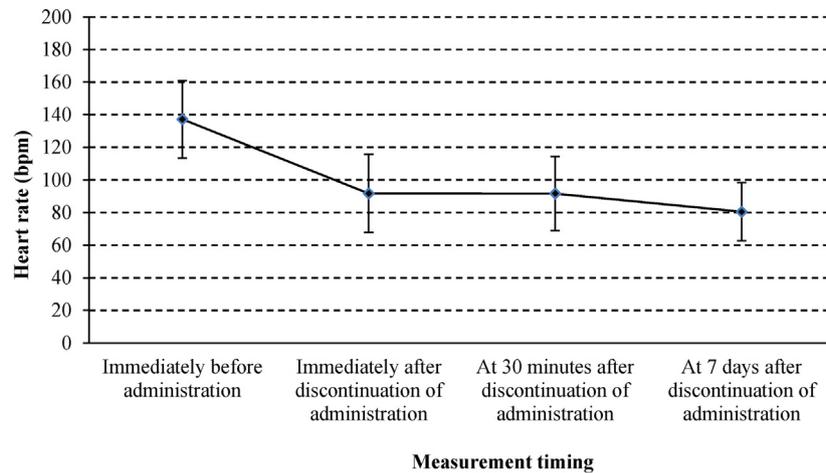
a Overall study population (Systolic BP, N=450; Diastolic BP, N=447)**b Subgroups with atrial fibrillation (Systolic BP, N=397; Diastolic BP, N=395) or atrial flutter (Systolic BP, N=33; Diastolic BP, N=32)**

Fig. 2. Blood pressure over time (from immediately before landiolol treatment to 7 days after discontinuation of treatment) among patients with complete blood pressure data sets. (a) Overall study population (systolic blood pressure, $N = 450$; diastolic blood pressure, $N = 447$). (b) Subgroups with atrial fibrillation (systolic blood pressure, $N = 397$; diastolic blood pressure, $N = 395$) or atrial flutter (systolic blood pressure, $N = 33$; diastolic blood pressure, $N = 32$).

a Overall study population (N=545)



b Subgroups with atrial fibrillation (N=475) or atrial flutter (N=45)

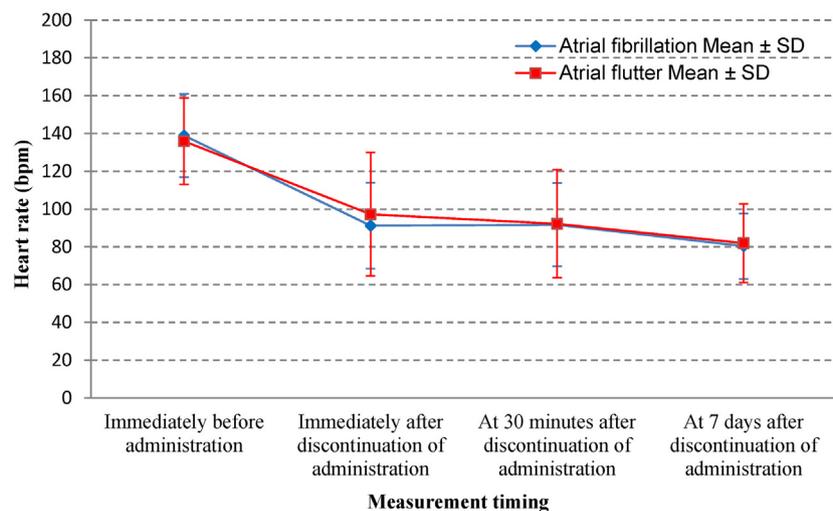


Fig. 3. Heart rate over time (from immediately before landiolol treatment to 7 days after discontinuation of treatment) among patients with complete heart rate data sets. (a) Overall study population ($N = 545$). (b) Subgroups with atrial fibrillation ($N = 475$) or atrial flutter ($N = 45$).

The current report focuses on an analysis of safety and effectiveness. An improvement in tachycardia (defined as $\geq 20\%$ reduction in heart rate immediately after discontinuation of landiolol) was observed in approximately 80% of the patients treated with landiolol in this real-world survey. This compares favorably with the 48% success rate reported in the J-LAND clinical trial, which enrolled a specifically defined patient population and used a slightly different definition of success ($\geq 20\%$ reduction plus heart rate < 110 bpm after 2 h) [11].

The main objective of this postmarketing survey was to evaluate the safety of landiolol. It is known that landiolol is generally well tolerated, although most data come from its use in the perioperative setting [8,9,22]. Hypotension and bradycardia are the most common adverse events reported with landiolol [8,9,22].

In the current survey, adverse events occurred in 12.5% of patients, which is consistent with the rate reported during the 2-h treatment period in the J-LAND trial (8.6%) [11]. Events were categorized as adverse drug reactions in 5.6% of patients. The most common adverse events in the current survey were decreased

blood pressure, cardiac failure, pneumonia, and bradycardia. Decreased blood pressure was reported as an adverse event in 2.8% of patients and hypotension in 0.5% of patients (2.1% and 0.5%, respectively, as adverse drug reactions). These data are consistent with postmarketing treatment outcome studies/surveys of landiolol used in the perioperative setting ($n = 1257$), in which the incidence of hypotension was 0.8% [22]. In J-LAND, the incidence of hypotension was 7.5%, which was consistent with the pooled rate for controlled trials in the perioperative setting (8.5%) [22].

Bradycardia was reported as an adverse event in 0.7% of patients in the current analysis, all but one of which were considered adverse drug reactions. This is consistent with postmarketing surveillance studies in the perioperative setting, in which the incidence of bradycardia was 0.7% [22]. In controlled trials in the perioperative setting the pooled incidence of bradycardia was 2.1% [22]. Bradycardia was not reported in J-LAND [23]. Overall, the safety results from the current postmarketing survey are consistent with those from previous studies.

The current analysis focuses on the adverse event/adverse drug reaction profile of landiolol when used to treat tachyarrhythmias in

patients with heart failure. Further analysis of this study will also evaluate data on concomitant medications and drug–drug interactions, switches to oral β -blockers after discontinuation of landiolol therapy, and mid- to long-term outcomes during the 180 days after starting landiolol (including deaths or readmissions due to heart failure) [10]. This may provide additional data to guide the use of landiolol in this patient population.

The study has some significant limitations which are inherent based on the study design of postmarketing surveys. Firstly, the study was observational with no control group. Secondly, we could not control and capture all items to be assessed in the study, because the survey was conducted in real-life clinical settings with decisions made at the discretion of individual physicians depending on patient circumstances. These limitations should be considered when interpreting the present results.

In conclusion, based on an analysis of a postmarketing surveillance survey in a routine clinical practice setting, no new safety concerns were identified with respect to the use of landiolol for the treatment of atrial fibrillation or atrial flutter in patients with heart failure, and effective control of these tachyarrhythmias was achieved in most of the patients.

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Conflicts of interest

Takeshi Yamashita reports personal fees from Ono Pharmaceutical Co., Ltd., grants and personal fees from Daiichi Sankyo, grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Bayer, personal fees from Nippon Boehringer, and personal fees from Toa Eiyo, outside the submitted work; Yukiko Nakasu, Hiroto Mizutani, and Kenji Sumitani are employees of Ono Pharmaceutical Co., Ltd.

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