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ORIGINAL ARTICLE
Heart Failure

Mid-Term Prognosis After Landiolol Treatment in Atrial Fibrillation/Atrial Flutter Patients With Chronic Heart Failure

— A Prospective Observational Survey (AF-CHF Landiolol Survey) —

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Background: The aim of the prospective post-marketing AF-CHF Landiolol Survey was to evaluate the safety and effectiveness of landiolol for the treatment of atrial fibrillation or atrial flutter in patients with cardiac dysfunction in clinical practice in Japan. This analysis reports mid-term prognoses with a focus on switching from landiolol to oral β-blockers.

Methods and Results: The AF-CHF Landiolol Survey took place between June 2014 and May 2016 and involved 1,121 patients with cardiac dysfunction and atrial fibrillation/atrial flutter. Data collected about switching from landiolol to oral β-blockers were analyzed in relation to all-cause mortality within 180 days after landiolol initiation. Among 1,002 patients with available follow-up data, the 6-month all-cause mortality rate was 14. 6% (n=146 patients), of whom 39.7% had died from heart failure (HF). Kaplan-Meier survival curves showed significantly longer survival in patients who had switched to oral β-blockers vs. those who had not, with hazard ratios of 0.39 (95% confidence interval [CI] 0.28–0.55) for all-cause mortality and 0.40 (95% CI: 0.23–0.70) for death from HF. Only male sex and advanced age were independently associated with all-cause mortality and death from HF.

Conclusions: This large-scale routine practice survey of landiolol in HF patients with atrial fibrillation/flutter showed high mid-term all-cause mortality. Switching from landiolol to oral β-blockers was apparently, although not independently, associated with lower all-cause mortality and death from HF.

Key Words: Atrial fibrillation; Beta-blockers; Heart failure; Landiolol; Mortality

Heart failure (HF) is frequently complicated by atrial fibrillation,[1–5] which can reduce cardiac output by approximately 20%, further worsening hemodynamics[1] and resulting in poorer survival outcomes.[4,6,7] To avoid this vicious cycle, the onset of atrial fibrillation or atrial flutter in HF requires emergency management.

Pharmacotherapies for atrial fibrillation/atrial flutter include a wide range of drugs. However, options are limited in patients with HF. Because calcium channel blockers and β-blockers exert a negative inotropic effect, digoxin has historically been recommended for heart rate control in patients with atrial fibrillation and cardiac dysfunction.[8–10] Although β-blockers starting at low doses may be recommended for HF with reduced ejection fraction, the use of oral β-blockers to treat atrial fibrillation in patients with HF is considered contentious. In particular, in the acute phase of HF, administering oral β-blockers at a dose sufficient to control heart rate in atrial fibrillation is difficult.

Landiolol hydrochloride (hereafter landiolol) is a short-acting selective β_1-adrenoceptor antagonist developed to control heart rate in tachyarrhythmia. Landiolol is administered intravenously and has an ultrashort half-life of approximately 4 min, facilitating simple dose adjustment. The J-Land Study of atrial fibrillation demonstrated significantly superior efficacy of landiolol compared with digoxin for heart rate control at 2 h after initiation in patients with tachyarrhythmias and HF.[9] The 2017 update of the Japanese guideline on the diagnosis and treatment of acute and chronic HF recommends landiolol as an option to treat atrial fibrillation complicating HF (Class IIa, evidence Level B) and for acute HF (Class I, evidence Level C).[11] However, data on mid- to long-term outcomes of these patients are lacking. In the J-Land Study, although switching patients from landiolol to an oral β-blocker during follow-up was common, mid- and long-term outcomes could not be analyzed because of limited patient numbers.[9]

As society in Japan continues to age, the number of patients with HF and tachyarrhythmias is expected to

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Table 1. Baseline Demographic and Clinical Characteristics According to Whether Patients Had or Had Not Switched to Oral β-Blockers After Receiving Intravenous Landiolol (All Patients, n=1,121)

	No. patients (%)	Switch to oral β-blockers		P value[D]
		Yes[A]	No[B]	
All patients (n=1,121)		589 (52.5[C])	532 (47.5[C])	
Sex				0.81
Male	641 (57.2)	339 (57.6)	302 (56.8)	
Female	480 (42.8)	250 (42.4)	230 (43.2)	
Age (years; n=1,121; mean ± SD, 72.5±13.5 years; median 75 years [min-max: 0–100 years])				0.16
<65	267 (23.8)	154 (26.1)	113 (21.2)	
65 to <75	293 (26.1)	149 (25.3)	144 (27.1)	
≥75	561 (50.0)	286 (48.6)	275 (51.7)	
Tachyarrhythmia				0.006[#]
Atrial fibrillation	944 (84.2)	511 (86.8)	433 (81.4)	
Atrial flutter	73 (6.5)	40 (6.8)	33 (6.2)	
Atrial fibrillation and flutter	31 (2.8)	13 (2.2)	18 (3.4)	
Others	73 (6.5)	25 (4.2)	48 (9.0)	
LVEF (n=938; mean ± SD, 40.7±15.9%; median 40% [min-max: 7–85%])				
LVEF by equal intervals (%)				<0.001[#]
<25	149 (15.9)	87 (14.8)	62 (11.7)	
25 to 50	570 (60.7)	316 (53.7)	254 (47.7)	
>50	219 (23.3)	91 (15.4)	128 (24.1)	
LVEF by ESC heart failure guidelines (%)				<0.001[#]
<40	454 (48.3)	263 (44.7)	191 (35.9)	
40 to <50	212 (22.6)	113 (19.2)	99 (18.6)	
≥50	272 (29.0)	118 (20.0)	154 (28.9)	
Blood BNP (pg/mL; n=816; mean ± SD, 773.9±899.3 pg/mL; median 551 pg/mL [min-max: 4–9,666 pg/mL])				0.24
<200	148 (18.1)	67 (11.4)	81 (15.2)	
200 to <500	223 (27.3)	125 (21.2)	98 (18.4)	
500 to <1,000	266 (32.6)	141 (23.9)	125 (23.5)	
≥1,000	179 (21.9)	94 (16.0)	85 (16.0)	
Any interruption of landiolol infusion				0.48
No	1,043 (93.0)	551 (93.5)	492 (92.5)	
Yes	78 (7.0)	38 (6.5)	40 (7.5)	
Duration of use of landiolol (h; n=981; mean ± SD 80.9±100.9; median 49 h [min-max: 0.2–1,082 h])				<0.001[#]
<1	11 (1.0)	3 (0.5)	8 (1.5)	
1 to <2	9 (0.8)	3 (0.5)	6 (1.1)	
2 to <3	16 (1.4)	4 (0.7)	12 (2.3)	
3 to <6	24 (2.1)	5 (0.8)	19 (3.6)	
6 to <12	68 (6.1)	25 (4.2)	43 (8.1)	
12 to <24	147 (13.1)	74 (12.6)	73 (13.7)	
24 to <48	201 (17.9)	114 (19.4)	87 (16.4)	
48 to <72	136 (12.1)	84 (14.3)	52 (9.8)	
72 to <96	99 (8.8)	55 (9.3)	44 (8.3)	
96 to <120	64 (5.7)	36 (6.1)	28 (5.3)	
120 to <144	59 (5.3)	36 (6.1)	23 (4.3)	
144 to <168	46 (4.1)	28 (4.8)	18 (3.4)	
≥168	101 (9.0)	52 (8.8)	49 (9.2)	
Unknown	140 (12.5)	70 (11.9)	70 (13.2)	

(**Table 1** continued the next page.)

	No. patients (%)	Switch to oral β-blockers		P value[D]
		Yes[A]	No[B]	
Total landiolol dose (mg; n=918; mean±SD 1,233.4±2,501.2 mg; median 486 mg [min-max: 1–41,184 mg])				<0.001[#]
100	162 (14.5)	62 (10.5)	100 (18.8)	
100 to <500	306 (27.3)	159 (27.0)	147 (27.6)	
500 to <1,000	152 (13.6)	86 (14.6)	66 (12.4)	
1,000 to <1,500	97 (8.7)	50 (8.5)	47 (8.8)	
≥1,500	201 (17.9)	124 (21.1)	77 (14.5)	
Unknown	203 (18.1)	108 (18.3)	95 (17.9)	
Heart rate at start of landiolol (beats/min; n=1,110; mean±SD 136.3±25.2 beats/min; median 140 beats/min [min-max: 48–260 beats/min])				
Heart rate by equal intervals (beats/min)				0.034[#]
<60	3 (0.3)	0 (0.0)	3 (0.6)	
60 to <80	28 (2.5)	13 (2.2)	15 (2.8)	
80 to <100	46 (4.1)	21 (3.6)	25 (4.7)	
100 to <120	127 (11.3)	63 (10.7)	64 (12.0)	
120 to <140	350 (31.2)	170 (28.9)	180 (33.8)	
≥140	556 (49.6)	318 (54.0)	238 (44.7)	
Unknown	11 (1.0)	4 (0.7)	7 (1.3)	
Heart rate by dichotomy (beats/min)				0.003[#]
<140	554 (49.4)	267 (45.3)	287 (53.9)	
≥140	556 (49.6)	318 (54.0)	238 (44.7)	
Unknown	11 (1.0)	4 (0.7)	7 (1.3)	
Heart rate just after landiolol discontinuation (beats/min)				0.094
<140	909 (81.1)	482 (81.8)	427 (80.3)	
≥140	45 (4.0)	18 (3.1)	27 (5.1)	
Unknown	167 (14.9)	89 (15.1)	78 (14.7)	
Heart rate 30 min after landiolol discontinuation (beats/min)				0.40
<140	652 (58.2)	347 (58.9)	305 (57.3)	
≥140	37 (3.3)	17 (2.9)	20 (3.8)	
Unknown	432 (38.5)	225 (38.2)	207 (38.9)	
Heart rate 7 days after landiolol discontinuation (beats/min)				0.057
<80	482 (43.0)	285 (48.4)	197 (37.0)	
80 to <120	430 (38.4)	229 (38.9)	201 (37.8)	
120 to <140	27 (2.4)	10 (1.7)	17 (3.2)	
≥140	5 (0.4)	3 (0.5)	2 (0.4)	
Unknown	177 (15.8)	62 (10.5)	115 (21.6)	
Heat rate reduction just after landiolol discontinuation (%)				0.22
<20	223 (19.9)	109 (18.5)	114 (21.4)	
≥20	723 (64.5)	388 (65.9)	335 (63.0)	
Unknown	175 (15.6)	92 (15.6)	83 (15.6)	
Heat rate reduction 30 min after landiolol discontinuation (%)				0.16
<20	170 (15.2)	82 (13.9)	88 (16.5)	
≥20	517 (46.1)	282 (47.9)	235 (44.2)	
Unknown	434 (38.7)	225 (38.2)	209 (39.3)	
SBP at start of landiolol (mmHg; n=1,087; mean±SD 121.9±26.1 mmHg; median 120 mmHg [min-max: 46–250 mmHg])				<0.001[#]
<120	523 (46.7)	226 (38.4)	297 (55.8)	
≥120	564 (50.3)	347 (58.9)	217 (40.8)	
Unknown	34 (3.0)	16 (2.7)	18 (3.4)	

Unless indicated otherwise, data are expressed as n (%). [#]Statistically significant difference in between-group comparison for patients switched or not switched to an oral β-blocker. [A]Expressed as a percentage of the total number of patients in the 'yes' group (n=589). [B]Expressed as a percentage of the total number of patients in the 'no' group (n=532). [C]Expressed as a percentage of the total number of patients (n=1,121). [D]Fischer's exact test. BNP, B-type natriuretic peptide; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Table 2. Oral β-Blocker Use: Starting Time, Initial Dose, and Time to End of Landiolol Use

β-blocker	Time from start of landiolol to start of oral β-blocker (days)		Initial daily dose of oral β-blocker (mg)		Time from start of oral β-blocker to end of landiolol use (days)	
	No. patients	Mean±SD	No. patients	Mean±SD	No. patients	Mean±SD
Total	589	2.4±3.2	–	–	496	2.0±2.8
Bisoprolol fumarate+bisoprolol	495	2.3±3.1	427	1.66±1.33	427	2.0±2.6
Carvedilol	86	3.2±3.4	86	2.68±1.94	62	2.1±3.9
Atenolol	4	2.3±1.0	4	62.5±25.0	3	1.0±0.0
Metoprolol tartrate	3	1.3±0.6	3	30.0±26.5	3	0.0±0.0
Propranolol hydrochloride	1	1	1	30	1	0

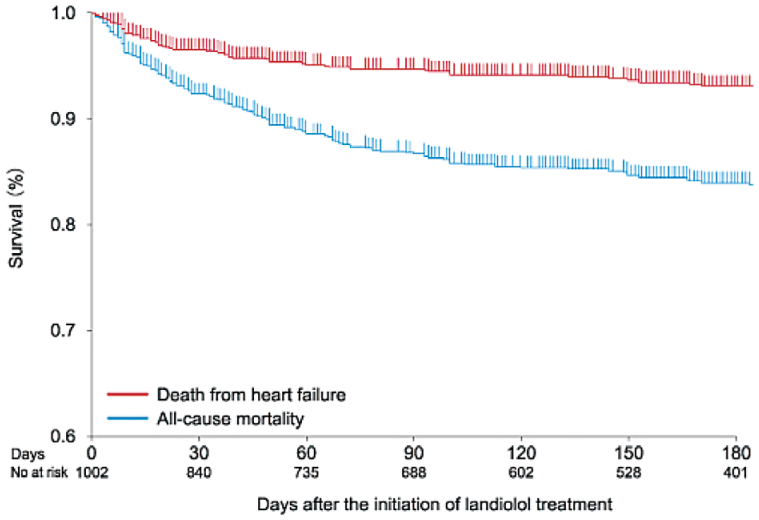

Figure 1. Kaplan-Meier curves for all-cause mortality and death from heart failure.

increase, underlying the need for prolonged follow-up data after the use of landiolol in this clinical setting. The prospective post-marketing Atrial Fibrillation/Atrial Flutter in patients with Chronic Heart Failure (AF-CHF) Landiolol Survey was conducted with the aim of evaluating the safety and effectiveness of landiolol for the treatment of atrial fibrillation or atrial flutter in patients with cardiac dysfunction in clinical practice in Japan.[12] Short-term safety and efficacy results of this study have been reported previously.[13] The present analysis reports the mid-term (6-month) prognosis of patients who had participated in the AF-CHF Landiolol Survey.

Methods

Survey Design

The multicenter prospective observational AF-CHF Landiolol Survey was conducted at 209 medical facilities in Japan and involved physicians experienced in treating HF. The study enrolled consecutive patients with HF who had a tachyarrhythmia (atrial fibrillation or atrial flutter) requiring treatment and were treated with intravenous landiolol. Because the study was conducted in the routine clinical setting, no specific exclusion criteria were applied. Patients were enrolled over a 2-year period, with the full survey lasting 3 years.[12,13]

The survey used the ADDIN electronic data capture (EDC) system provided by ASKLEP (Tokyo, Japan; currently INTAGE Healthcare). Two EDC survey forms were used. The first form collected data from the day before landiolol initiation to 7 days after its discontinuation, including baseline characteristics, details of landiolol administration, the clinical course up to 7 days after discontinuation of landiolol, concomitant medications (up to 7 days after landiolol discontinuation), and adverse events. The second survey form collected data on all-cause mortality and death from HF at 30, 90 and 180 days after the initiation of landiolol treatment.[12,13]

The present analysis reports the mid-term prognosis of participating patients with an emphasis on patients who were switched from landiolol to an oral β-blocker. Parameters evaluated and described were: landiolol dose; oral β-blocker use (drug, dose, and duration) after intravenous landiolol treatment; and patient outcomes (all-cause mortality, death from HF) up to 180 days after the start of landiolol treatment. Potential prognostic factors for patient outcomes were also evaluated.

Ethics

The AF-CHF Landiolol Survey was conducted in compliance with Good Postmarketing Study Practice according to the Japanese *Pharmaceutical Affairs Law*. Because the

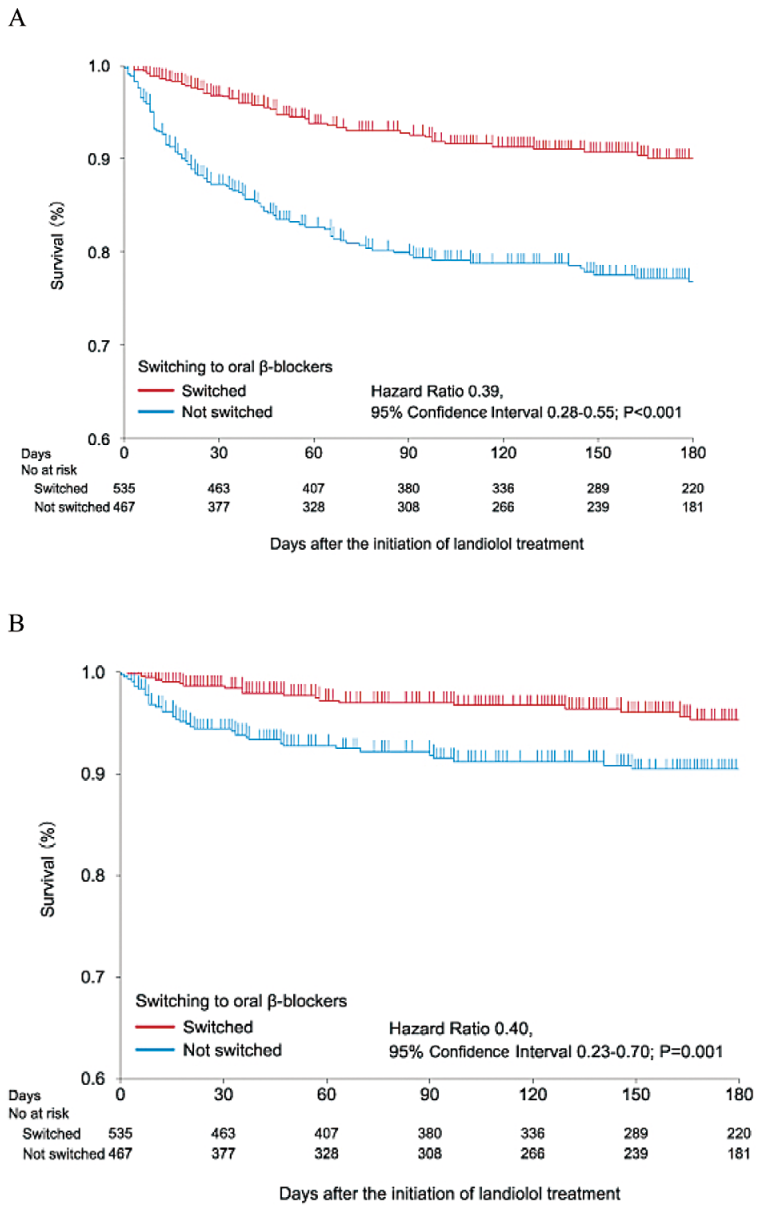

Figure 2. Kaplan-Meier curves for (**A**) all-cause mortality and (**B**) death from heart failure in patients who had or had not switched to oral β-blockers after receiving intravenous landiolol.

survey did not collect any direct personal identifiers for patients, informed consent was not required. Access to the EDC system from each survey site was carefully controlled by the system administrator.

Statistical Analysis

Patient characteristics and treatment are reported using summary statistics: mean±SD for continuous variables and number (n) and frequency (%) for categorical variables. All-cause mortality and death from HF over time were analyzed using Kaplan-Meier survival curves in patients who had or had not switched to oral β-blockers. To explore independent prognostic factors in these patient groups, multivariate analyses were performed using a Cox regression model; hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated. Categorical baseline variables were compared using Fisher's exact test. Statistical significance was set at two-sided $P<0.05$. Analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC, USA).

An analysis population of 500 patients was planned for the AF-CHF Landiolol Survey based on estimates of population proportions and potential patient accrual in a real-world setting in order to enable comparisons with other studies. To allow for dropouts, a sample size of 800 was chosen.

Results

In all, 1,139 patients were enrolled in the AF-CHF Landiolol Survey between June 2014 and May 2016. Survey forms were completed for 1,121 patients who formed the study population. Follow-up data on mid-term outcomes were available for 1,002 patients.

Table 3. Multivariate Cox Regression Analysis of Potential Prognostic Factors for All-Cause Mortality

Explanatory variables	n	No. deaths (%)	Comparison between categories (multivariate)	Multivariate HR for survival (95% CI)
Sex				
Male	566	79 (14.0)		
Female	436	67 (15.4)	Male vs. female	0.76 (0.61–0.93)
Age (years)				
<65	246	28 (11.4)		
65 to <75	265	30 (11.3)	<65 vs. 65 to <75	1.42 (1.07–1.88)
≥75	491	88 (17.9)	<65 vs. ≥75	1.36 (1.05–1.77)
LVEF (%)				
<25	132	21 (15.9)		
25 to <50	460	65 (14.1)	<25 vs. 25 to <50	1.22 (0.91–1.63)
≥50	252	30 (11.9)	<25 vs. ≥50	1.21 (0.86–1.71)
Blood BNP (pg/mL)				
<200	139	15 (10.8)		
200 to <500	203	17 (8.4)	<200 vs. 200 to <500	1.22 (0.90–1.66)
500 to <1,000	236	25 (10.6)	<200 vs. 500 to <1,000	1.25 (0.92–1.71)
≥1,000	159	38 (23.9)	<200 vs. ≥1,000	1.27 (0.91–1.78)
Heart rate before landiolol administration (beats/min)				
<120	184	20 (10.9)		
120 to <140	316	41 (13.0)	<120 vs. 120 to <140	0.87 (0.65–1.17)
≥140	491	83 (16.9)	<120 vs. ≥140	0.95 (0.72–1.26)
Total landiolol dose (mg)				
<100	140	21 (15.0)		
100 to <500	276	36 (13.0)	<100 vs. 100 to <500	1.04 (0.74–1.45)
500 to <1,000	138	26 (18.8)	<100 vs. 500 to <1,000	0.94 (0.64–1.38)
1,000 to <1,500	87	17 (19.5)	<100 vs. 1,000 to <1,500	1.24 (0.82–1.86)
≥1,500	183	20 (10.9)	<100 vs. ≥1,500	1.21 (0.84–1.73)
Any interruption of landiolol infusion				
No	928	126 (13.6)		
Yes	74	20 (27.0)	No vs. yes	1.31 (0.84–2.03)
Switch to oral β-blockers				
No	467	99 (21.2)		
Yes	535	47 (8.8)	No vs. yes	1.17 (0.95–1.44)
Heart rate 7 days after landiolol discontinuation (beats/min)				
<80	439	32 (7.3)		
80 to <120	396	62 (15.7)	<80 vs. 80 to <120	0.92 (0.74–1.13)
120 to <140	25	6 (24.0)	<80 vs. 120 to <140	0.91 (0.45–1.83)
≥140	4	2 (50.0)	<80 vs. ≥140	0.81 (0.19–3.49)
SBP at start of landiolol (mmHg)				
<120	470	96 (20.4)		
≥120	499	46 (9.2)	<120 vs. ≥120	1.07 (0.86–1.32)
Concurrent diseases				
Ischemic	254	56 (22.0)		
Other[A]	748	90 (12.0)	Other vs. ischemic	1.17 (0.92–1.50)

[A]Includes concurrent disease other than ischemic heart disease, no concurrent diseases and unknown. BNP, B-type natriuretic peptide; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Patient Characteristics

Patients' baseline characteristics are summarized in **Table 1**. The mean±SD age of study participants was 72.5±13.5 years, and 57.2% were male. At enrolment, 944 patients (84.2%) had atrial fibrillation, 73 (6.5%) had atrial flutter, and 31 (2.8%) had both. The remaining patients (6.5%) had other atrial arrhythmias (ventricular tachycardia, supraventricular tachycardia, sinus tachycardia, extrasystole etc.). Overall, 87% of patients had atrial fibrillation at enrolment. Mean left ventricular ejection fraction (LVEF) at enrolment was 40.7±15.9% and the mean heart rate before start of landiolol was 136.3±25.2 beats/min.

Overall, 589 patients (52.5%) were switched from landiolol to oral β-blockers (**Table 1**). The distribution of tachyarrhythmia type differed significantly (P=0.006) between patient groups switched or not switched to oral β-blockers.

Table 4. Multivariate Cox Regression Analysis of Potential Prognostic Factors for Death From Heart Failure

Explanatory variable	n	No. deaths (%)	Comparison between categories (multivariate)	Multivariate HR for survival (95% CI)
Sex				
Male	566	34 (6.0)		
Female	436	24 (5.5)	Male vs. female	0.77 (0.63–0.95)
Age (years)				
<65	246	10 (4.1)		
65 to <75	265	13 (4.9)	<65 vs. 65 to <75	1.37 (1.04–1.80)
≥75	491	35 (7.1)	<65 vs. ≥75	1.34 (1.04–1.72)
LVEF (%)				
<25	132	14 (10.6)		
25 to <50	460	25 (5.4)	<25 vs. 25 to <50	1.27 (0.96–1.68)
≥50	252	9 (3.6)	<25 vs. ≥50	1.19 (0.85–1.66)
Blood BNP (pg/mL)				
<200	139	2 (1.4)		
200 to <500	203	10 (4.9)	<200 vs. 200 to <500	1.13 (0.84–1.53)
500 to <1,000	236	11 (4.7)	<200 vs. 500 to <1,000	1.20 (0.88–1.62)
≥1,000	159	18 (11.3)	<200 vs. ≥1,000	1.27 (0.92–1.76)
Heart rate before landiolol administration (beats/min)				
<120	184	13 (7.1)		
120 to <140	316	13 (4.1)	<120 vs. 120 to <140	0.87 (0.65–1.17)
≥140	491	31 (6.3)	<120 vs. ≥140	1.00 (0.77–1.31)
Total landiolol dose (mg)				
<100	140	8 (5.7)		
100 to <500	276	11 (4.0)	<100 vs. 100 to <500	1.07 (0.77–1.47)
500 to <1,000	138	11 (8.0)	<100 vs. 500 to <1,000	0.94 (0.65–1.37)
1,000 to <1,500	87	7 (8.0)	<100 vs. 1,000 to <1,500	1.16 (0.78–1.72)
≥1,500	183	10 (5.5)	<100 vs. ≥1,500	1.14 (0.80–1.60)
Any interruption of landiolol infusion				
No	928	54 (5.8)		
Yes	74	4 (5.4)	No vs. yes	1.36 (0.90–2.07)
Switch to oral β-blockers				
No	467	39 (8.4)		
Yes	535	19 (3.6)	No vs. yes	1.11 (0.91–1.36)
Heart rate 7 days after landiolol discontinuation (beats/min)				
<80	439	12 (2.7)		
80 to <120	396	22 (5.6)	<80 vs. 80 to <120	0.98 (0.81–1.20)
120 to <140	25	4 (16.0)	<80 vs. 120 to <140	1.00 (0.51–1.94)
≥140	4	0 (0.0)	<80 vs. ≥140	0.79 (0.18–3.36)
SBP at start of landiolol use (mmHg)				
<120	470	40 (8.5)		
≥120	499	17 (3.4)	<120 vs. ≥120	1.07 (0.87–1.31)
Concurrent diseases				
Ischemic	254	28 (11.0)		
Other[A]	748	30 (4.0)	Other vs. ischemic	1.19 (0.94–1.51)

[A]Includes concurrent disease other than ischemic heart disease, no concurrent diseases and unknown. BNP, B-type natriuretic peptide; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

The group switched to oral β-blockers showed a significant trend towards a lower LVEF (P<0.001) and was more likely to have a heart rate >140 beats/min (P=0.003) and systolic blood pressure (SBP) >120 mmHg (P<0.001) at the time of landiolol initiation. Significant trends towards a longer duration of landiolol use (P<0.001) and a higher total dose of landiolol (P<0.001) were observed in the group switched to oral β-blockers.

Landiolol Dose

The mean total dose of landiolol administered was 1,233.4±2,501.2 mg, and the median total dose was 486 mg (min-max: 1–41,184 mg).

Switching to Oral β-Blockers

The oral β-blockers administered to patients and other treatment details after switching from intravenous landiolol are

listed in **Table 2**. The most common oral β-blocker used was bisoprolol/bisoprolol fumarate (84.0%), followed by carvedilol (14.6%). The mean initial dose of oral bisoprolol was 1.66±1.33 mg. Oral β-blocker treatment began a mean of 2.4±3.2 days after the initiation of landiolol, and landiolol was discontinued a mean of 2.0±2.8 days after starting the oral β-blocker. Oral β-blocker treatment commenced during landiolol therapy or on the day of the last landiolol infusion in 84.2% of cases (496/589).

Mid-Term Patient Outcomes

Mid-term outcomes were evaluated in 1,002 patients with available follow-up data. Kaplan-Meier curves for time to all-cause mortality and death from HF are shown in **Figure 1**. At 6 months (180 days), the all-cause mortality rate was 14.6%, or 146 deaths, of which 39.7% were deaths from HF. Apart from HF, the most common causes of death were pneumonia (14.4%) and sepsis (13.0%; **Supplementary Table**).

Patients who were switched to oral β-blockers after intravenous landiolol had significantly longer survival compared with non-switchers, with HRs (oral β-blockers vs. no oral β-blockers) of 0.39 (95% CI 0.28–0.55; P<0.001) for all-cause mortality (**Figure 2A**) and 0.40 (95% CI 0.23–0.70; P=0.001) for death from HF (**Figure 2B**).

Prognostic Factors

The results of multivariate Cox regression analyses of potential prognostic factors for all-cause mortality and for death from HF are presented in **Table 3** and **Table 4**, respectively. Male sex and advanced age were the only independent prognostic factors significantly associated with all-cause mortality or death from HF. Other variables, including LVEF, B-type natriuretic peptide (BNP), heart rate at admission, and switching to oral β-blockers, were not significant independent factors for all-cause mortality or death from HF in the study population.

Discussion

This analysis of the AF-CHF Landiolol Survey aimed to describe mid-term patient prognoses and provide information about switching to an oral β-blocker after treatment with intravenous landiolol for tachyarrhythmias in patients with cardiac dysfunction in a real-world setting in Japan. Survival outcome data were analyzed for up to 6 months after the start of landiolol treatment. A major finding of the study was that mid-term all-cause mortality was high (~15% in 6 months), likely reflecting, at least in part, greater disease severity (including a high starting heart rate) in patients with an indication for landiolol treatment. Although switching to oral β-blockers after landiolol was apparently associated with better mid-term prognoses, the association was not significant in multivariate analysis.

A previous report of the AF-CHF Landiolol Survey found that initial treatment with intravenous landiolol was associated with a substantial decrease in the mean heart rate, with 77.5% of patients experiencing a reduction of ≥20%.[13] Because landiolol is administered intravenously, patients who require longer-term treatment must be switched to an oral β-blocker. The present mid-term analysis indicated that slightly more than half the patients had been switched to an oral β-blocker, most commonly bisoprolol/bisoprolol fumarate (84%), although the mean initial dose of 1.66 mg was at the low end of the bisoprolol dose range recommended for long-term rate control in atrial fibrillation (1.25–20 mg daily).[7] The switch to oral β-blockers occurred a mean of 2.4 days after initiation of landiolol, and landiolol was continued for a mean of 2 days after the switch.

Two large observational studies from Japan, namely Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD)[5,14] and Chronic Heart Failure Analysis and Registry in the Tohoku District-2 (CHART-2),[15,16] have previously reported the clinical characteristics and prognoses of patients with HF and atrial fibrillation. However, differences in eligibility criteria, demographic and disease-related characteristics, as well as other study conditions, preclude comparing the findings with the AF-CHF Landiolol Survey population. To date, no Japanese registries for acute HF (acute decompensated heart failure syndromes [ATTEND], West Tokyo Heart Failure [WET-HF], and Registry Focused on Very Early Presentation and Treatment in Emergency Department of Acute Heart Failure [REALITY-AHF]) have published information about heart rate specific to patients with atrial fibrillation. Similarly, overseas registries of acute HF (Acute Decompensated HEart Failure National REgistry [ADHERE], Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure [OPTIMIZE-HF], and EuroHeart Failure Survey II [EHFS II]) have yet to conduct studies that focus solely on patients with atrial fibrillation, and information about heart rate is lacking. The Get With The Guidelines–Heart Failure (GWTG-HF) program in the US reported that the mean heart rate in patients with acute HF who were in atrial fibrillation was 82 beats/min.[17] Because enrollment in the AF-CHF Landiolol Survey was limited to patients with HF and atrial fibrillation who required treatment for tachycardia, a direct comparison between these 2 studies is inappropriate. In the absence of any other reports in this setting, the description of patients with HF and tachycardic atrial fibrillation, as captured by the AF-CHF Landiolol Survey, is a useful addition to the clinical literature.

Survival curve analyses indicated that treatment with an oral β-blocker after intravenous landiolol was significantly associated with a lower risk of all-cause mortality and death from HF, although this association should be interpreted cautiously given that previous studies on this topic have been complex and controversial. Data from randomized clinical trials suggest that β-blockers have no significant effect on mortality reduction in patients with HF and concurrent atrial fibrillation,[18,19] whereas β-blockers are known to be associated with improved survival in patients with reduced LVEF who are in sinus rhythm. The JCARE-CARD and CHART-2 observational studies demonstrated that β-blocker use was associated with improved prognosis for overall study populations with HF.[20,21] Conversely, a subgroup analysis of JCARE-CARD found that β-blockers did not alter the risk of death for HF patients with vs. without atrial fibrillation.[5]

Multivariate analyses identified male sex and advanced age as independent factors for death from HF at 6 months, whereas switching to oral β-blockers, LVEF, BNP, and heart rate at admission had no significant independent prognostic association. A better prognosis for female vs. male patients with HF has long been described.[22,23] CHART-2 reported a lower risk of mortality in women than in men, with an adjusted HR of 0.79 (95% CI 0.64–0.98; P=0.031),[24] similar to that observed in the present analysis. An association between older age and increased

risk of mortality has also been reported for HF patients.[25–27] This was observed in CHART-2,[28] as well as in JCARE-CARD, which reported an adjusted HR for all-cause mortality of 2.15 (95% CI 1.62–2.86) for age ≥80 vs. <80 years.[29] Mid-term findings of the AF-CHF Landiolol Survey appear to be consistent with these reports. In this context, the apparent association between switching to oral β-blockers and improved prognosis may have arisen, at least in part, from confounding with these important patient characteristics. Further studies are required to better understand the long-term management of patients with HF and atrial fibrillation treated with landiolol.

Study Limitations

The AF-CHF Landiolol Survey had some inherent design limitations. The study was observational and did not incorporate a control group. Because the study was conducted in the clinical setting, data were not adjusted for survey items, including potential confounding factors that can have an effect on survival. Not all variables known to affect prognosis in patients with HF and atrial fibrillation (e.g., heart rhythm or LVEF at discharge) were investigated because they were not deemed necessary to include in the survey at the time of protocol development. Finally, because mid-term findings still represent a relatively short follow-up period in the patient population, longer-term results are awaited with interest.

Conclusions

The large-scale survey of HF patients with atrial fibrillation/atrial flutter who were treated with intravenous landiolol showed a relatively high all-cause and HF mortality at mid-term follow-up. Switching from landiolol to oral β-blockers was apparently associated with lower mortality. However, in contrast with male sex and advanced age, switching was not a significant independent factor for mortality in these patients. Future studies are warranted to better understand the relationship between switching to oral β-blockers and mortality.

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IRB Information

The AF-CHF Landiolol Survey was conducted as part of the mandatory actions for approval of landiolol in Japan and complied with the Japanese ministerial ordinance on Good Postmarketing Study Practice.

According to this ordinance, ethics approval of the participating medical institutions and patient consent are not required. This post-marketing survey is registered on the Japan Pharmaceutical Information Center database (JapicCTI-142623).

Data Availability

Deidentified participant data will not be shared. For more information on Ono Pharmaceutical Co. Ltd.'s policy for the disclosure of clinical study data, please see https://www.ono.co.jp/eng/rd/policy.html (accessed December 2, 2020).

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Supplementary Files

Please find supplementary file(s);
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