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ORIGINAL RESEARCH

Impacts of Patient Characteristics on the Effectiveness of Landiolol in AF/AFL Patients Complicated with LV Dysfunction: Subgroup Analysis of the J-Land Study

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ABSTRACT

Introduction: Results from the multicenter trial (J-Land study) of landiolol versus digoxin in atrial fibrillation (AF) and atrial flutter (AFL) patients with left ventricular (LV) dysfunction revealed that landiolol was more effective for controlling rapid HR than digoxin. The subgroup analysis for patient characteristics was conducted to evaluate the impact on the efficacy and safety of landiolol compared with digoxin.

Methods: Two hundred patients with AF/AFL, heart rate (HR) $\geq$ 120 beats/min, and LV ejection fraction (LVEF) 25–50% were randomized to receive either landiolol ($n = 93$) or digoxin ($n = 107$). Successful HR control was defined as $\geq$20% reduction in HR together with

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HR < 110 beats/min at 2 h after starting intravenous administration of landiolol or digoxin. The subgroup analysis for patient characteristics was to evaluate the impact on the effectiveness of landiolol in AF/AFL patients complicated with LV dysfunction.

Results: The efficacy in patients with NYHA class III/NYHA class IV was 52.3%/35.3% in landiolol, and 13.8%/9.1% in digoxin ($p < 0.001$ and $p = 0.172$), lower LVEF (25–35%)/higher LVEF (35–50%) was 45.7%/51.1% in landiolol, and 14.0%/12.7% in digoxin ($p < 0.001$ and $p < 0.001$), CKD stage 1 (90 < eGFR)/CKD stage 2 ($60 \leq$ eGFR < 90)/CKD stage 3 ($30 \leq$ eGFR < 60)/CKD stage 4 ($15 \leq$ eGFR < 30) was 66.7%/59.1%/39.6%/66.7% in landiolol, and 0%/13.8%/17.0%/0% in digoxin ($p = 0.003$, $p < 0.001$, $p = 0.015$ and $p = 0.040$).

Conclusions: This subgroup analysis indicated that landiolol was more useful, regardless of patient characteristics, as compared with digoxin in AF/AFL patients complicated with LV dysfunction. Particularly, in patients with impaired renal function, landiolol should be preferred for the purpose of acute rate control of AF/AFL tachycardia.

Keywords: Landiolol; Digoxin; Rate control; Acute; Japanese; Atrial fibrillation; Atrial flutter; Left ventricular dysfunction; Heart failure; J-Land

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INTRODUCTION

Atrial fibrillation (AF) and atrial flutter (AFL) are common arrhythmias in patients with left ventricular (LV) dysfunction. Over 20% of patients with heart failure exhibit AF [1, 2]. In these patients, AF/AFL are often associated with a rapid ventricular response during the worsening of heart failure [3, 4]. However, a sustained rapid ventricular response may further deteriorate cardiac function [5], accelerating the symptoms of heart failure [6–8]. Intravenous administration of digoxin is considered the standard therapy for controlling the rapid ventricular response in AF/AFL patients with cardiac dysfunction or heart failure [4, 9]. Although digoxin has some beneficial effects for treating heart failure by way of its positive inotropic effects, digoxin may also have a negative chronotropic effect as a result of vagal stimulation. Of note, the negative chronotropic effect develops much more slowly, often taking several hours to reach the maximal effect [9, 10]. Short-acting parenteral β-blockers can act more rapidly than digoxin, and may provide a swift control of heart rate (HR) in these clinical settings. However, there is a concern that β-blockers may depress cardiac function and further deteriorate ventricular dysfunction, accelerating heart failure. Landiolol, an ultra-short-acting β-blocker, is rapidly metabolized to inactive forms in the blood and liver, resulting in a short half-life of approximately 4 min in human blood. In addition, it selectively binds to β1 receptors, with a β1 receptor selectivity (β1/β2) as high as 251 [11]. Based on these properties, landiolol has been reported to be useful for treating several acute disorders, including arrhythmias during heart surgery [12], acute myocardial infarction [13], acute decompensated heart failure [14], and refractory

electrical storm [15]. Ultra-short-acting β-blockers may be useful to control HR with minimal effects on cardiac function. Even though the negative inotropic effect by landiolol is manifested, it is not theoretically and practically sustained by decreasing the dose or stopping administration of these drugs.

This hypothesis was tested in the Japanese Landiolol versus Digoxin study (J-Land study), which investigated the efficacy and safety of intravenous landiolol for achieving rapid control of tachycardia in patients with AF/AFL and LV dysfunction. The results of the J-Land study showed that landiolol was more effective for controlling rapid HR than digoxin in AF/AFL patients with LV dysfunction [16]. To further assess these findings, we analyzed effectiveness in the J-Land study population according to patient characteristics.

METHODS

Study Design and Patients

The design of the J-Land study has been described previously [16]. In brief, the J-Land study was a central registration, prospective, multicenter, single-blind, randomized, parallel-group study that included 200 patients with AF/AFL and LV dysfunction. Average age was 71.6 ± 11.5 years, 106 (53%) were men, New York Heart Association (NYHA) classes were equally distributed between III ($n = 163$, 81.9%) and IV ($n = 36$, 51%), Left ventricular ejection fraction (LVEF) was $36.6 \pm 7.6\%$, and heart rate (HR) was 138.1 ± 15.3 beats/min in average. The use of antiarrhythmic drugs, sympathomimetic drugs, sympatholytic drugs, defibrillator use, catheter ablation, and pacemaker therapy were prohibited from the enrollment until completing all observations at 2 h after starting treatment. However, patients being treated with guideline-directed oral β-blockers (carvedilol or bisoprolol) or oral digitalis preparations for chronic heart failure, chronic AF, and/or chronic AFL could participate in the study under continued treatment without changes in their doses. In the landiolol group, continuous administration of landiolol was intravenously started at a dose of 1 μg/kg/min and titrated to a maximum dose of 10 μg/kg/min according to the patient's condition. Landiolol was administered for ≥2 h and up to 72 h. In the digoxin group, digoxin was intravenously administered at an initial dose of 0.25 mg and could be uptitrated within 72 h according to the patient's condition. The Japanese guideline for the treatment of atrial fibrillation recommends that the maximum dose of digoxin is 0.25 mg within 2 h. For patients treated with oral digitalis, the parenteral digoxin dose could be reduced to 0.125 mg according to the patient's condition to prevent digitalis intoxication. The final observation of this study was performed for up to 48 h after the end of administration of landiolol or for up to 48 h after the final dose in the digoxin group. The investigators for the study are listed in the Appendix [16].

In this study, we analyzed the primary endpoint, in which the percentage of patients with both HR < 110 beats/min and ≥20% decrease from baseline at 2 h after administration. Heart rate was measured by the electrocardiogram over 1 min and was reviewed at the core laboratory in a blinded manner. The safety endpoint was the incidence of adverse events related or unrelated to the study drugs. For this analysis, we divided the landiolol and the digoxin groups by patient characteristics at baseline (Fig. 1).

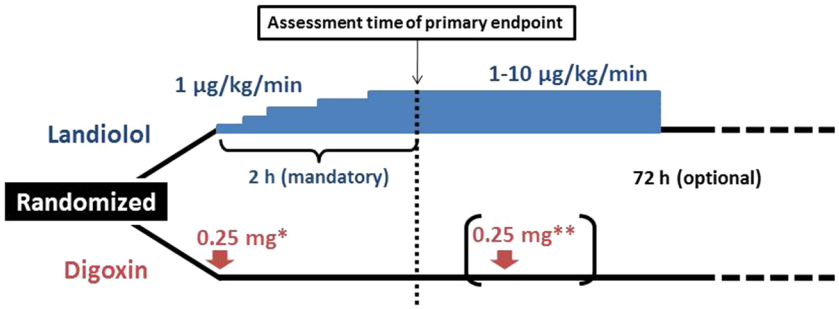

Fig. 1 Study protocol

Statistical Analysis

Data are expressed as the mean ± standard deviation or percentages of patients. Student's t test and χ^2 test were used to compare the means and percentages, respectively, between the two groups. The subgroup analysis for the primary endpoint was conducted by stratifying the J-Land study population by age, sex, NYHA, baseline HR, baseline systolic blood pressure (SBP), LVEF, β-blocker and eGFR using a linear probability model with HR and LVEF measured immediately before starting the study drug as covariates. The subgroup analysis for adverse events was conducted by stratifying the J-Land study population by the above factors using χ^2 test. Values of $p < 0.05$ were considered statistically significant (2-sided). All analyses were performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC, USA).

RESULTS

Patient Disposition and Baseline Characteristics

The disposition of patients in this study is shown in Fig. 2. A total of 214 patients were randomized to either landiolol ($n = 99$) or digoxin ($n = 115$). Of these, 14 patients were not treated (the landiolol group, $n = 6$; the digoxin group, $n = 8$) and 2 patients in the landiolol group did not comply with the protocol. Therefore, 200 patients (the landiolol group, $n = 93$; the digoxin group, $n = 107$) were included in the safety subgroup analysis set. Of these, 18 patients had no data of the primary endpoint (the landiolol group, $n = 9$; the digoxin group, $n = 9$). Therefore, 180 patients were included in the efficacy subgroup analysis set (the landiolol group, $n = 82$; the digoxin group, $n = 98$). The demographics of the study patients are shown in Table 1. There were no differences in the general characteristics of the 2 groups. 141 patients (70.5%) were ≥65 years, and 106 patients (53.0%) were male. The NYHA class was III in 163 patients (81.9%) and IV in 36 patients (18.1%). 115 patients (58.4%) were HR < 140 bpm, and 111 patients (55.8%) were SBP ≥ 120 mmHg. Before starting study treatment, oral β-blockers were used in 41 patients (20.5%). About 60% of patients or more had moderate or severe renal dysfunction (15 ≤ eGFR (mL/min/1.73 m^2) < 60).

Efficacy

The subgroup analysis of the primary endpoint is shown in Table 2. The percentage of patients with both HR < 110 beats/min and ≥20% decrease from baseline to 2 h after administration was determined to examine the influence of HR and LVEF at baseline. Overall,

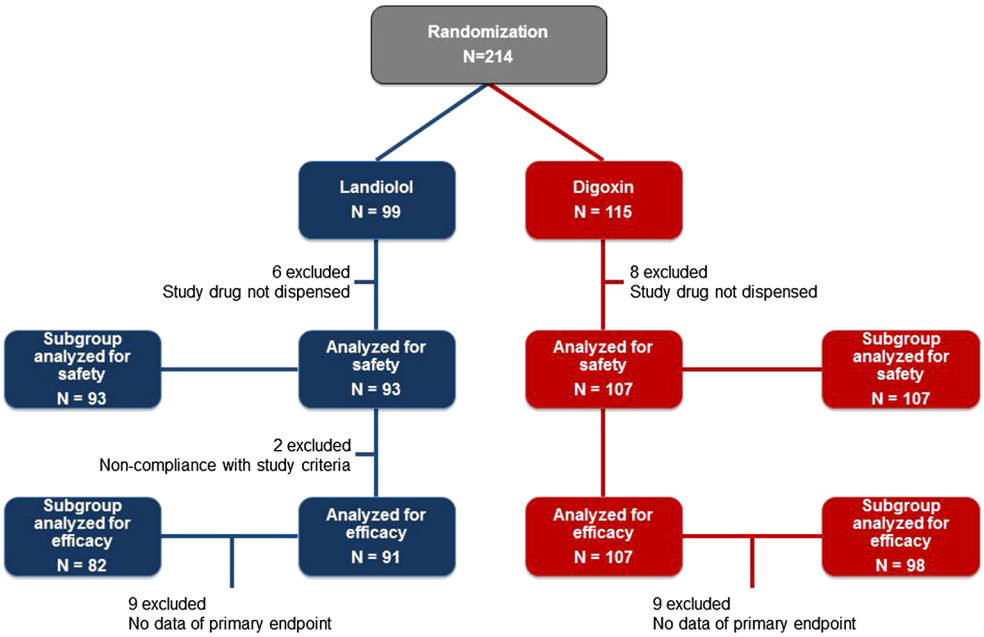

Fig. 2 Patient disposition

48.0% ($n = 40/82$) of patients in the landiolol group and 13.9% ($n = 13/98$) of patients in the digoxin group achieved the primary endpoint, with a between-group difference of 34.1% (95% confidence interval, 22.1–46.2; $p < 0.0001$). There was no impact on the primary endpoint by age, sex, baseline SBP, LVEF, and β-blocker (oral) intake. In patients with NYHA IV, there was no significant difference between the two groups, but the percentage of patients who reached the primary endpoint was numerically higher in the landiolol group [the landiolol group; 35.3% (6/17 patients), and the digoxin group; 9.1% (1/11 patients)]. In patients with renal dysfunction of moderate or more [$15 \leq$ eGFR (mL/min/1.73 m^2) < 60], the landiolol group had also a significantly better outcome as compared to the digoxin group.

Safety

The incidence of the adverse events in the subgroup is shown in Table 3. Adverse events occurred in 30 patients (32.3%) in the landiolol group and in 35 patients (32.7%) in the digoxin group, which was not statistically significant ($p = 0.946$). There was no impact on the incidence of the adverse events in the subgroup by age, sex, NYHA, baseline HR, LVEF, and oral β-blocker intake. In the population with low SBP, the incidence of the adverse events was significantly higher in the digoxin group compared with the landiolol group. Conversely, in the population with high SBP, the incidence of adverse events was significantly higher in the landiolol group compared with the digoxin group. Adverse events associated with heart and renal function are shown in Table 4. In the safety subgroup analysis of SBP, the incidence of adverse events associated with heart and renal function was 12.8% (5/39) in the landiolol group with low SBP, 13.2% (7/53) in the landiolol group with high SBP, 24.5% (12/49) in the digoxin group with low SBP, and 6.9% (4/58) in the digoxin group with high SBP. In the

Table 1 Baseline characteristics

	Total	Landiolol	Digoxin	*p* value
Age (*n*)		93	107	
20 to <65 years	59 (29.5%)	32 (34.4%)	27 (25.2%)	
≥65 years	141 (70.5%)	61 (65.6%)	80 (74.8%)	
Mean ± SD	71.6 ± 11.5	70.5 ± 12.0	72.5 ± 11.0	0.221
Sex (*n*)		93	107	
Male	106 (53.0%)	50 (53.8%)	56 (52.3%)	0.840
Female	94 (47.0%)	43 (46.2%)	51 (47.7%)	
NYHA (*n*)		93	107	
Class III	163 (81.9%)	71 (77.2%)	92 (86.0%)	0.108
Class IV	36 (18.1%)	21 (22.8%)	15 (14.0%)	
Baseline HR (*n*)		90	107	
<140 bpm	115 (58.4%)	55 (61.1%)	60 (56.1%)	
≥140 bpm	82 (41.6%)	35 (38.9%)	47 (43.9%)	
Mean ± SD	138.1 ± 15.3	138.2 ± 15.7	138.0 ± 15.0	0.934
Baseline SBP (*n*)		92	107	
<120 mmHg	88 (44.2%)	39 (42.4%)	49 (45.8%)	
≥120 mmHg	111 (55.8%)	53 (57.6%)	58 (54.2%)	
Mean ± SD	125.7 ± 21.8	124.6 ± 19.8	126.6 + 23.5	0.523
LVEF (*n*)		92	107	
25.0 to <35.0%	90 (45.2%)	41 (44.6%)	49 (45.8%)	
35.0 to 50.0%	109 (54.8%)	51 (55.4%)	58 (54.2%)	
Mean ± SD	36.6 ± 7.6	36.4 ± 7.9	36.7 ± 7.3	0.753
Beta blocker (oral) (*n*)		93	107	
No beta-blockers intake	159 (79.5%)	75 (80.6%)	84 (78.5%)	
Beta-blockers intake	41 (20.5%)	18 (19.4%)	23 (21.5%)	0.708
eGFR (*n*)		92	107	
$90 \leq$ eGFR	18 (9.1%)	8 (8.7%)	10 (9.4%)	
$60 \leq$ eGFR < 90	58 (29.1%)	26 (28.3%)	32 (29.9%)	
$30 \leq$ eGFR < 60	109 (54.8%)	51 (55.4%)	58 (54.2%)	
$15 \leq$ eGFR < 30	14 (7.0%)	7 (7.6%)	7 (6.5%)	
Mean ± SD	57.3 ± 19.7	57.6 ± 19.7	57.0 ± 19.8	0.845

Mean ± SD or number (%), Student's *t* test and χ^2 test

digoxin group with low SBP, the incidence of adverse events associated with heart and renal function was significantly higher as compared to the high SBP group ($p = 0.011$). In addition, in patients with severe renal impairment [$15 \leq$ eGFR (mL/min/1.73 m^2) < 30], the incidence of adverse events was significantly lower in the landiolol group than compared with the digoxin group.

DISCUSSION

Our results showed that in patients with LV dysfunction, who had AF/AFL with HR of 120 bpm or higher, there was a subgroup that the administration of landiolol should be recommended. Our subgroup analysis in patients with severe renal dysfunction demonstrated that the incidence of adverse events was significantly low in the landiolol group compared with the digoxin group, and that swift rate control effect was significantly more prevalent by landiolol than by digoxin.

According to the several registries for chronic heart failure patients, the ratio of patients with renal impairment has been reported approximately to be 30–70% (ADHERE, JCARE-CARD, CHART) [18–20]. It is also reported that long-term prognosis is poor if renal dysfunction is severe [19]. In the treatment of acute heart failure, there have been concerns about nesiritide that may deteriorate renal function

Table 2 Subgroup analysis for primary endpoint

Subgroup	Landiolol	Digoxin	Risk Diferrence [95%CI]	p value
Overall	40/82(48.8%)	13/98(13.3%)	34.1 [22.1 , 46.2]	p<0.001 *
Age				
20 - <65 years	17/27(63.0%)	1/22(4.5%)	56.1 [34.4 , 77.8]	p<0.001 *
>=65 years	23/55(41.8%)	12/76(15.8%)	24.8 [10.2 , 39.5]	p=0.001 *
Sex				
Male	24/44(54.5%)	6/50(12.0%)	38.1 [21.4 , 54.8]	p<0.001 *
Female	16/38(42.1%)	7/48(14.6%)	27.9 [10.1 , 45.7]	p=0.002 *
NYHA class				
Class III	34/65(52.3%)	12/87(13.8%)	38.3 [25.3 , 51.3]	p<0.001 *
Class IV	6/17(35.3%)	1/11(9.1%)	24.3 [-11.3 , 59.9]	p=0.172 N.S.
Baseline HR				
<140 bpm	33/55(60.0%)	10/54(18.5%)	43.1 [26.0 , 60.3]	p<0.001 *
>=140 bpm	7/27(25.9%)	3/44(6.8%)	18.1 [1.4 , 34.9]	p=0.034 *
Baseline SBP				
<120 mmHg	16/35(45.7%)	6/43(14.0%)	31.1 [12.4 , 49.8]	p=0.001 *
>=120 mmHg	24/47(51.1%)	7/55(12.7%)	36.3 [20.1 , 52.4]	p<0.001 *
LVEF				
25.0 - <35.0 %	17/36(47.2%)	4/43(9.3%)	33.1 [14.7 , 51.5]	p<0.001 *
35.0 - 50.0 %	23/46(50.0%)	9/55(16.4%)	31.2 [14.4 , 47.9]	p<0.001 *
Beta blockers (oral)				
No beta-blockers intake	31/64(48.4%)	9/77(11.7%)	34.7 [21.1 , 48.3]	p<0.001 *
Beta-blockers intake	9/18(50.0%)	4/21(19.0%)	31.8 [1.6 , 62.0]	p=0.040 *
eGFR				
90 <= eGFR	4/6(66.7%)	0/9(0.0%)	62.1 [26.1 , 98.2]	p=0.003 *
60 <= eGFR <90	13/22(59.1%)	4/29(13.8%)	49.3 [24.2 , 74.4]	p<0.001 *
30 <= eGFR <60	19/48(39.6%)	9/53(17.0%)	21.0 [4.1 , 37.9]	p=0.015 *
15 <= eGFR <30	4/6(66.7%)	0/7(0.0%)	57.3 [3.2 , 111.5]	p=0.040 *

Number (%), using a linear probability model .
*: p<0.05, N.S.: p≧ 0.05.

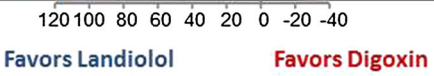

Table 3 Subgroup analysis for adverse events

Subgroup	Landiolol	Digoxin	Risk Diferrence [95%CI]	p value
	30 / 93 (32.3)	35 / 107 (32.7)	-0.5 [-13.5 , 12.6]	p=0.946 N.S.
Age				
20 - <65 years	12 / 32 (37.5)	10 / 27 (37.0)	0.5 [-24.3 , 25.2]	p=0.971 N.S.
>=65 years	18 / 61 (29.5)	25 / 80 (31.3)	-1.7 [-17.0 , 13.6]	p=0.824 N.S.
Sex				
Male	15 / 50 (30.0)	17 / 56 (30.4)	-0.4 [-17.9 , 17.1]	p=0.968 N.S.
Female	15 / 43 (34.9)	18 / 51 (35.3)	-0.4 [-19.8 , 19.0]	p=0.967 N.S.
NYHA class				
Class III	21 / 71 (29.6)	27 / 92 (29.3)	0.2 [-13.9 , 14.3]	p=0.975 N.S.
Class IV	9 / 21 (42.9)	8 / 15 (53.3)	-10.5 [-43.4 , 22.5]	p=0.535 N.S.
Baseline HR				
<140 bpm	14 / 55 (25.5)	22 / 60 (36.7)	-11.2 [-28.0 , 5.6]	p=0.195 N.S.
>=140 bpm	16 / 35 (45.7)	13 / 47 (27.7)	18.1 [-2.8 , 38.9]	p=0.091 N.S.
Baseline SBP				
<120 mmHg	10 / 39 (25.6)	23 / 49 (46.9)	-21.3 [-40.9 , -1.7]	p=0.040 *
>=120 mmHg	20 / 53 (37.7)	12 / 58 (20.7)	17.0 [0.3 , 33.7]	p=0.048 *
LVEF				
25.0 - <35.0 %	15 / 41 (36.6)	19 / 49 (38.8)	-2.2 [-22.3 , 17.9]	p=0.831 N.S.
35.0 - 50.0 %	15 / 51 (29.4)	16 / 58 (27.6)	1.8 [-15.2 , 18.8]	p=0.833 N.S.
Beta blockers (oral)				
No beta-blockers intake	26 / 75 (34.7)	25 / 84 (29.8)	4.9 [-9.6 , 19.5]	p=0.508 N.S.
Beta-blockers intake	4 / 18 (22.2)	10 / 23 (43.5)	-21.3 [-49.2 , 6.7]	p=0.154 N.S.
eGFR				
90 <= eGFR	2 / 8 (25.0)	3 / 10 (30.0)	-5.0 [-46.3 , 36.3]	p=0.814 N.S.
60 <= eGFR <90	8 / 26 (30.8)	9 / 32 (28.1)	2.6 [-21.0 , 26.3]	p=0.826 N.S.
30 <= eGFR <60	18 / 51 (35.3)	17 / 58 (29.3)	6.0 [-11.6 , 23.6]	p=0.504 N.S.
15 <= eGFR <30	2 / 7 (28.6)	6 / 7 (85.7)	-57.1 [-99.5 , -14.8]	p=0.031 *

Number (%), χ^2 test
*: p<0.05, N.S.: p≧0.05.

and worsen short-term prognosis (30 days after) [21, 22]. ASCEND-HF study never proved any significant efficacy over placebo, which resulted in a marked decline in the share of nesiritide [23]. On the other hand, serelaxin, which is currently being developed as a therapeutic agent for acute heart failure, improved the prognosis after 180 days of administration with the fewer adverse events related to renal function [24, 25]. Accordingly, safety for renal function may be indispensable for less adverse impact on the long-term prognosis of acute heart failure patients.

Digoxin is excreted by kidneys and its dose should be decreased in many patients with renal dysfunction [17]. However, landiolol is not metabolized at all by kidneys or neither have adverse effects on renal function. As a result, landiolol can be uptitrated safely to achieve rate control in a shorter period regardless of patients' renal function. In fact, landiolol was faster than digoxin in the rate control during acute phase of AF/AFL among the patients with renal dysfunction. Moreover, our subgroup analysis consistently demonstrated that the incidence of adverse events was lower by the landiolol treatment compared with the digoxin in patients with severe renal dysfunction. Furthermore, in the digoxin group with low SBP, that is considered to have decreased renal

Table 4 Adverse events associated with heart and renal function

Group	Baseline SBP (mmHg)	Subject	Adverse events	Time to events from the administration of the study drug (h)	Severity	Relationship to the study drug	Outcome[a]
Landiolol	<120	L-1	Blood pressure increased	21	Mild	Not related	Recovered
		L-2	Blood pressure decreased	29.2	Mild	Not related	Recovered
		L-3	Serum creatinine increased	62.8	Mild	Not related	Recovered
			Blood pressure systolic decreased	2	Mild	Related	Recovered
			Blood urea nitrogen increased	62.8	Mild	Not related	Recovered
			Brain natriuretic peptide increased	71.9	Moderate	Not related	Recovered
			Dehydration	56.8	Mild	Not related	Recovered
		L-4	Blood pressure decreased	0.9	Moderate	Related	Recovered
		L-5	Palpitations	11	Mild	Not related	Ongoing
			Serum creatinine increased	18	Mild	Not related	Ongoing
	≥120	L-6	Blood pressure decreased	5.6	Moderate	Not related	Recovered
			Blood pressure decreased	33.1	Moderate	Not related	Recovered
		L-7	Hypotension	3.2	Moderate	Related	Recovered
		L-8	Serum potassium decreased	47.8	Mild	Not related	Recovered
			Blood pressure decreased	90.2	Moderate	Not related	Recovered
		L-9	Serum creatinine increased	46.7	Mild	Not related	Recovered
			Blood urea nitrogen increased	46.7	Mild	Not related	Lost to follow-up
			Dehydration	32.8	Mild	Not related	Recovered
		L-10	Tachycardia	17.3	Mild	Not related	Recovered
		L-11	Blood pressure decreased	1	Mild	Related	Recovered
		L-12	Congestive heart failure	14.3	Severe	Not related	Lost to follow-up
			Blood urea nitrogen increased	4.2	Mild	Not related	Lost to follow-up

Table 4 continued

Group	Baseline SBP (mmHg)	Subject	Adverse events	Time to events from the administration of the study drug (h)	Severity	Relationship to the study drug	Outcome[a]
Digoxin	<120	D-1	Serum creatinine increased	4.6	Mild	Not related	Recovered
			Serum potassium increased	44.1	Moderate	Not related	Recovered
			Blood pressure decreased	4.6	Mild	Not related	Recovered
		D-2	Serum potassium decreased	31.6	Mild	Not related	Recovered
		D-3	Blood pressure decreased	21.5	Moderate	Not related	Recovered
			Blood pressure decreased	41.5	Moderate	Not related	Recovered
		D-4	Serum creatinine increased	36	Mild	Not related	Recovered
		D-5	Hypokalemia	39	Mild	Not related	Recovered
		D-6	Serum creatinine increased	46.1	Mild	Not related	Recovered
			Blood urea nitrogen increased	46.1	Mild	Not related	Recovered
		D-7	Tachycardia	21	Mild	Not related	Recovered
		D-8	Blood pressure increased	12.1	Mild	Not related	Recovered
		D-9	Hypokalemia	17.3	Mild	Not related	Recovered
		D-10	Blood pressure decreased	31.2	Mild	Not related	Recovered
		D-11	Sinus arrest	21.5	Mild	Not related	Recovered
		D-12	Blood pressure increased	0.3	Mild	Related	Recovered
	≥120	D-13	Blood pressure decreased	12.6	Moderate	Not related	Recovered
			Blood pressure decreased	27.6	Moderate	Not related	Recovered
		D-14	Tachycardia	6.6	Moderate	Not related	Recovered
			Serum potassium decreased	15.9	Mild	Not related	Recovered
		D-15	Tachycardia	45.1	Mild	Not related	Recovered
		D-16	Dehydration	40.2	Mild	Not related	Recovered

[a] The final observation was performed for up to 48 h after the end of administration of landiolol or for up to 48 h after the final dose in the digoxin group

blood flow, the incidence of adverse events related to heart and renal function has increased. We speculate the delayed excretion of digoxin due to a decrease in renal blood flow has affected the incidence of adverse events. In this regard, for the rate control during acute phase of AF/AFL patients, especially those who are associated with severe renal dysfunction, landiolol should be considered as the first-choice drug.

This study had several limitations. Firstly, the efficacy of landiolol in patients in cardiogenic shock was not examined because patients with SBP < 90 mmHg were excluded. Secondly, the efficacy of landiolol in patients with severe LV dysfunction was not determined because patients with a baseline LVEF < 25 % were excluded. Thirdly, the impact of landiolol on the long-term prognosis should be examined in the future. Lastly, in this study, the efficacy and safety was only compared between landiolol and digoxin. Therefore, it is still unclear whether the effects of landiolol are superior to those of propranolol or esmolol. However, the *t*1/2 of landiolol is shorter than that of propranolol and esmolol [26], and β1-selectivity is higher [27], which make landiolol favorable for use in the acute rate control of AF/AFL tachycardia because of less possibility of serious adverse events.

CONCLUSIONS

This subgroup analysis indicated that landiolol was more useful, regardless of patient characteristics, as compared with digoxin in AF/AFL patients complicated with LV dysfunction. Particularly, in the rate control of AF/AFL tachycardia patients with impaired renal function, landiolol should be preferred over digoxin.

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APPENDIX

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