Urgent Management of Rapid Heart Rate in Patients With Atrial Fibrillation/Flutter and Left Ventricular Dysfunction
– Comparison of the Ultra-Short-Acting β1-Selective Blocker Landiolol With Digoxin (J-Land Study) –

Ryozo Nagai, MD, PhD; Koichiro Kinugawa, MD, PhD; Hiroshi Inoue, MD, PhD; Hirotugu Atarashi, MD, PhD; Yoshihiko Seino, MD, PhD; Takeshi Yamashita, MD, PhD; Wataru Shimizu, MD, PhD; Takeshi Aiba, MD, PhD; Masafumi Kitakaze, MD, PhD; Atsushiro Sakamoto, MD, PhD; Takenori Ikeda, MD, PhD; Yasushi Imai, MD, PhD; Takashi Daimon, PhD; Katsuhiko Fujino, MSc; Tetsuji Nagano, MSc; Tatsuki Okamura, MSc; Masatsugu Hori, MD, PhD; the J-Land Investigators

**Background:** A rapid heart rate (HR) during atrial fibrillation (AF) and atrial flutter (AFL) in left ventricular (LV) dysfunction often impairs cardiac performance. The J-Land study was conducted to compare the efficacy and safety of landiolol, an ultra-short-acting β-blocker, with those of digoxin for swift control of tachycardia in AF/AFL in patients with LV dysfunction.

**Methods and Results:** The 200 patients with AF/AFL, HR ≥120 beats/min, and LV ejection fraction 25–50% were randomized to receive either landiolol (n=93) or digoxin (n=107). Successful HR control was defined as ≥20% reduction in HR together with HR <110 beats/min at 2h after starting intravenous administration of landiolol or digoxin. The dose of landiolol was adjusted in the range of 1–10 μg·kg⁻¹·min⁻¹ according to the patient’s condition. The mean HR at baseline was 138.2±15.7 and 138.0±15.0 beats/min in the landiolol and digoxin groups, respectively. Successful HR control was achieved in 48.0% of patients treated with landiolol and in 13.9% of patients treated with digoxin (P<0.0001). Serious adverse events were reported in 2 and 3 patients in each group, respectively.

**Conclusions:** Landiolol was more effective for controlling rapid HR than digoxin in AF/AFL patients with LV dysfunction, and could be considered as a therapeutic option in this clinical setting.

**Key Words:** Atrial fibrillation; Atrial flutter; β-blocker; Landiolol; Left ventricular dysfunction

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. In these patients, AF/AFL are often associated with a rapid ventricular response during the worsening of heart failure. However, a sustained rapid ventricular response may...
further deteriorate cardiac function,5 accelerating the symptoms of heart failure.6–8

Editorial p ????

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, because of its positive inotropic effects, digoxin may also have a negative chronotropic effect as a result of vagal stimulation that 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 swift control of the heart rate (HR) in these clinical settings. However, there is 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, acute myocardial infarction,13 acute decompensated heart failure,14 and refractory electrical storm.15

Ultra-short-acting β-blockers may be useful to control the HR with minimal effects on cardiac function because the negative inotropic effect is not sustained after decreasing the dose or stopping administration of these drugs. Therefore, the present study was designed to evaluate the efficacy and safety of intravenous landiolol for achieving rapid control of tachycardia in patients with AF/AFL and LV dysfunction.

Methods

Study Design and Patients
This study was designed as a central registration, prospective, multicenter, single-blind, randomized, parallel-group study for examining tachycardia in patients with AF/AFL and LV dysfunction. It was conducted in 95 hospitals in Japan between March 2011 and August 2012. The main inclusion criteria were: male or female inpatients aged ≥20 years; New York Heart Association (NYHA) class III or IV; and AF/AFL with an LV ejection fraction (EF) of 25–50% and a HR ≥120 beats/min. The main exclusion criteria were: necessity for electrical cardioversion; serious valve stenosis; confirmed or suspected hyperthyroidism; implantable cardiac pacemaker and/or implantable defibrillator; necessity for mechanical ventilation; and cardiogenic shock (systolic blood pressure (BP) <90 mmHg). The use of antiarrhythmic drugs, sympathomimetic drugs, sympatholytic drugs, defibrillator use, catheter ablation, and pacemaker therapy were prohibited from administration until completing all observations at 2 h after starting treatment. However, patients being treated with 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.

The enrolled patients gave informed consent before randomization to either treatment. The study protocol was approved by the institutional review boards at all of the participating institutions, and the study was conducted in accordance with the Declaration of Helsinki.

Study Protocol
The study protocol is shown in Figure 1. After enrolment, each patient was randomized to receive landiolol or digoxin using the permuted block method. In the landiolol group, continuous intravenous administration of landiolol was started at a dose of 1 μg·kg⁻¹·min⁻¹ and titrated to a maximum dose of 10 μg·kg⁻¹·min⁻¹ 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. 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 primary efficacy endpoint was the percentage of patients with both a HR <110 beats/min and ≥20% decrease from baseline at 2 h after administration. The secondary endpoints were HR at 0.5, 1, and 2 h, conversion to normal sinus rhythm, and subjective symptoms and objective findings (palpitations,
chest pain, dizziness, dyspnea, and edema) at these times.

The safety endpoint was the incidence of adverse events related or unrelated to the study drugs. Adverse events that resulted in death, were life-threatening, required hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity, and crucial medical events were classified as serious adverse events.

After completing the observations at 2h after starting the administration of landiolol, it was replaced with an oral \( \beta \)-blocker, as deemed necessary, at the investigator’s discretion.

**Statistical Analysis**

Data are expressed as the mean ± standard deviation or percentages of patients. Student’s t-test and \( \chi^2 \) test were used to compare the means and percentages, respectively, between the 2 groups. The primary endpoint was compared between the 2 groups using a linear probability model with HR and LVEF measured immediately before starting the study drug as covariates. The changes in HR and BP after starting the study drugs were compared between the 2 groups using a linear mixed-effects model with adjustment for HR/BP and LVEF before starting the study drug. The following covariance structures were considered: unstructured, compound symmetrical, first-order autoregressive, and Toeplitz. The covariance structure that provided the best fit according to the Akaike information criterion was used in the analysis. Assessment times were treated as categorical factors. Student’s t-test was used to compare outcomes between the 2 groups at each time, while the paired t-test was used to compare values between baseline and each time within each group. Bonferroni correction was used for multiple comparisons, except for the change in BP, which was assessed as a safety parameter. Subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) were analyzed using the Wilcoxon rank sum test for comparisons between the 2 groups and the Wilcoxon signed rank sum test for comparisons within each group. 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 *Figure 2*. A total of 214 patients were randomized to either landiolol (\( n=99 \)) or digoxin (\( n=115 \)). Of these, 14 patients were not treated (landiolol group, \( n=6 \); digoxin group, \( n=8 \)) and 2 patients in the landiolol group did not comply with the protocol. Therefore, 200 patients (landiolol group, \( n=93 \); digoxin group, \( n=107 \)) were included in the safety analysis set and 198 patients were included in the efficacy analysis set (landiolol group, \( n=91 \); digoxin group, \( n=107 \)).

The demographics of the study patients are shown in *Table 1*. There were no differences in the general characteristics of the 2 groups. The mean age was 71.6 ± 11.5 years, and 106 patients (53.0%) were male. The type of atrial tachyarrhythmia at entry was AF in 174 patients (87.0%), AFL in 21 patients (10.5%), and a mixture of AF/AFL in 4 patients (2.0%). The cardiovascular disease was hypertension in 133 patients (66.5%), ischemic heart disease in 30 patients (15.0%), and cardiomyopathy in 13 patients (6.5%). The mean HR was 138.1 ± 15.3 beats/min and the mean LVEF was 36.6 ± 7.6%. The NYHA class was III in 163 patients (81.9%) and IV in 36 patients (18.1%). Before starting study treatment, diuretics were used in 100 patients (50.0%), oral \( \beta \)-blockers were used in 41 patients (20.5%), and nitrate was used in 29 patients (14.5%).

**Effects of Landiolol on AF and AFL**

The changes in HR and BP for 2h after starting the administration of landiolol and digoxin are shown in *Figure 3*. Landiolol and digoxin significantly decreased the HR from baseline for over 30 min after administration. However, the
Diastolic BP was also significantly different between the landiolol and digoxin groups at 30 min (79.7 vs. 85.3 mmHg) and 1 h (76.4 vs. 84.5 mmHg).

The results for the primary endpoint are shown in Figure 4. The percentage of patients with both a 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, 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). AF/AFL was converted to sinus rhythm within 2 h in 2 patients (2.2%) in the landiolol group and in 2 patients (1.9%) in the digoxin group.

The mean dose of landiolol at 2 h was 6.7±3.2 μg · kg⁻¹ · min⁻¹. The percentage of patients who achieved the primary endpoint

| Table 1. Baseline Characteristics of Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction |
|---------------------------------------------------------------|-----------|-----------|-----------|
| Demographic characteristics                                  | Total     | Landiolol | Digoxin   |
| Age (years)                                                  | 71.6±11.5 | 70.5±12.0 | 72.5±11.0 |
| Male, n (%)                                                  | 106 (53.0) | 50 (53.8) | 56 (52.3) |
| Weight (kg)                                                  | 60.5±13.2 | 60.8±13.4 | 60.2±13.1 |
| Baseline arrhythmia, n (%)                                   |           |           |           |
| Atrial fibrillation                                          | 174 (87.0) | 80 (86.0) | 94 (87.9) |
| Atrial flutter                                               | 21 (10.5)  | 8 (8.6)   | 13 (12.1) |
| Atrial fibrillation or flutter                               | 4 (2.0)   | 4 (4.3)   | 0 (0)     |
| Other                                                        | 1 (0.5)   | 1 (1.1)   | 0 (0)     |
| History of heart failure, n (%)                              | 120 (60.0) | 57 (61.3) | 63 (58.9) |
| Baseline CV disease, n (%)                                   |           |           |           |
| Hypertension                                                 | 133 (66.5) | 63 (67.7) | 70 (65.4) |
| Ischemic heart disease                                       | 30 (15.0)  | 12 (12.9) | 18 (16.8) |
| DCM                                                         | 11 (5.5)   | 6 (6.5)   | 5 (4.7)   |
| HCM                                                         | 2 (1.0)    | 2 (2.2)   | 0 (0)     |
| Hemodynamic parameters                                       |           |           |           |
| HR (beats/min)                                               | 138.1±15.3 | 138.2±15.7 | 138.0±15.0 |
| SBP (mmHg)                                                   | 125.7±21.8 | 124.6±19.8 | 126.6±23.5 |
| DBP (mmHg)                                                   | 84.2±19.2  | 81.5±16.5  | 86.5±21.1  |
| LVEF (%)                                                     | 36.6±7.6   | 36.4±7.9   | 36.7±7.3   |
| Creatinine (mg/dl)                                           | 0.98±0.32  | 0.98±0.33  | 0.97±0.32  |
| BNP (pg/ml)                                                  | 661.7±561.0 | 688.0±663.8 | 639.0±456.6 |
| NYHA class, n (%)                                            |           |           |           |
| III                                                          | 163 (81.9) | 71 (77.2) | 92 (86.0) |
| IV                                                           | 36 (18.1)  | 21 (22.8) | 15 (14.0) |
| Treatment before administration, n (%)                       |           |           |           |
| Diuretic                                                     | 100 (50.0) | 48 (51.6) | 52 (48.6) |
| hANP                                                         | 67 (33.5)  | 28 (30.1) | 39 (36.4) |
| β-blocker (oral)                                             | 41 (20.5)  | 18 (19.4) | 23 (21.5) |
| ARB                                                          | 31 (15.5)  | 13 (14.0) | 18 (16.8) |
| Nitrate                                                      | 29 (14.5)  | 11 (11.8) | 18 (16.8) |
| Aldosterone antagonist                                       | 25 (12.5)  | 11 (11.8) | 14 (13.1) |
| ACE inhibitor                                                | 17 (8.5)   | 7 (7.5)   | 10 (9.3)  |
| Digitalis (oral)                                             | 8 (4.0)    | 6 (6.5)   | 2 (1.9)   |

Data are mean±standard deviation, or n (%).

One patient with PSVT who violated the study protocol was enrolled, but the NYHA class was missing.

ACE, angiotensin-converting enzyme; ARB, angiotensin type 1 receptor blocker; BNP, B-type natriuretic peptide; CV, cardiovascular; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; hANP, human atrial natriuretic peptide; HCM, hypertrophic cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PSVT, paroxysmal supraventricular tachycardia; SBP, systolic blood pressure.
Figure 3. Time course of hemodynamic parameters of patients with atrial fibrillation/atrial flutter and left ventricular dysfunction treated with landiolol or digoxin. (A) Changes in mean heart rate (HR) during the study in the efficacy population (landiolol, n=87; digoxin, n=102). (B) Changes in blood pressure (BP) in the safety population (landiolol, n=93; digoxin, n=107). Data are mean±standard deviation. ‡Mixed-effects model used to compare data between the landiolol and digoxin groups (interaction: group×time). †P<0.05 vs. digoxin, *P<0.05 vs. baseline.

Figure 4. Comparison of the primary endpoint with the incidence of serious adverse events (AEs) or AEs resulting in study drug discontinuation. The percentages of patients with the primary endpoint (based on both heart rate <110 beats/min and ≥20% decrease in heart rate from baseline at 2h after administration) were compared using a linear probability model with heart rate and left ventricular ejection fraction at baseline as covariates (landiolol, n=82; digoxin, n=98). Safety data are expressed as the incidence of serious AEs or AEs leading to study drug discontinuation within 2h after administration (landiolol, n=93; digoxin, n=107).
Figure 5. Percentages of patients who achieved the primary endpoint (based on both heart rate <110 beats/min and ≥20% decrease in heart rate from baseline at 2h after administration) according to the dose of landiolol (total n=82). *One patient treated at a dose of 15 μg·kg⁻¹·min⁻¹ violated the protocol. Data are shown as the percentage of patients in each dose. Values in parentheses are the numbers of patients given each dose.

Table 2. Incidence of AEs in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

<table>
<thead>
<tr>
<th></th>
<th>Landiolol (n=93)</th>
<th>Digoxin (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–2 h</td>
<td>Total</td>
</tr>
<tr>
<td>All, n (%)</td>
<td>8 (8.6)</td>
<td>30 (32.2)</td>
</tr>
<tr>
<td>Any serious AE, n (%)</td>
<td>1 (1.1)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>Any AE leading to study drug discontinuation, n (%)</td>
<td>3 (3.2)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>AEs occurring in &gt;3%, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (3.2)</td>
<td>7 (7.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0 (0)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Increased creatinine*</td>
<td>0 (0)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Increased urea*</td>
<td>0 (0)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Data are n (%). “0–2h” included the number of patients with events occurring within 2h after starting treatment. “Total” included the number of patients with events occurring between the start of treatment and the final observation. Only AEs occurring at a frequency of ≥3% are shown.

*Defined as an increase in values from normal to abnormal or worsening of the parameter from baseline; these events were judged by the investigators as an AE based on the clinical significance of the change. AEs, adverse events.

Table 3. Changes in Parameters at the Final Observation in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

<table>
<thead>
<tr>
<th></th>
<th>Landiolol (n=93)</th>
<th>Digoxin (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Final</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>138.2±15.7</td>
<td>98.3±17.6</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>124.6±19.8</td>
<td>113.3±18.4</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>81.5±16.5</td>
<td>72.8±14.3</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>36.4±7.9</td>
<td>43.1±13.1</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.98±0.33</td>
<td>0.99±0.35</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>I</td>
<td>12 (13.6)</td>
<td>12 (11.3)</td>
</tr>
<tr>
<td>II</td>
<td>50 (56.8)</td>
<td>51 (48.1)</td>
</tr>
<tr>
<td>III</td>
<td>71 (77.2)</td>
<td>24 (27.3)</td>
</tr>
<tr>
<td>IV</td>
<td>21 (22.8)</td>
<td>2 (2.3)</td>
</tr>
</tbody>
</table>

The final observation was performed at 48 h after the end of administration of landiolol or at 48 h after the final dose in the digoxin group. Abbreviations as in Table 1.
in the landiolol group at each dose is shown in Figure 5. The effective dose of landiolol ranged from 1 to 10 μg·kg⁻¹·min⁻¹ without dose-dependency.

The changes in subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) during the study treatment are shown in Table S1. Palpitations, dyspnea, and edema improved significantly from baseline to 2h in both groups. However, there were no clinically relevant differences in subjective symptoms or objective findings between the 2 groups. The mean duration of treatment with landiolol was 20.4 ± 20.8 h (range, 0.8 – 72 h), and the mean dose of landiolol throughout the treatment was 6.3 ± 3.5 μg·kg⁻¹·min⁻¹. After the study treatment period, landiolol was replaced bisoprolol in 47 patients (50.5%) and by carvedilol in 27 patients (29.0%), at maintenance doses of 1.8 ± 1.3 mg and 3.2 ± 2.7 mg, respectively.

Safety
The incidence of adverse events is shown in Table 2. 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 = 0.95). During the 2-h treatment period, adverse events occurred in 8 patients (8.6%) in the landiolol group and in 2 patients (1.9%) in the digoxin group, which was statistically significant (P = 0.029). Hypotension was reported as an adverse event in 7 patients (7.5%) in the landiolol group and in 4 patients (3.7%) in the digoxin group, showing no significant difference between the 2 groups (P = 0.24). Vomiting and nausea were reported in 4 patients (4.3%) and 3 patients (3.2%), respectively, in the landiolol group. Vomiting was reported in 1 patient (0.9%) in the digoxin group, but nausea was not reported in this group.

Serious adverse events were reported in 2 patients in the landiolol group (congestive heart failure and embolic stroke in 1 patient each) and in 3 patients in the digoxin group (sinus arrest, diabetis insipidus, and pneumonia in 1 patient each). One patient in the landiolol group developed acute exacerbation of congestive heart failure at 12h after the end of administration of landiolol. Despite the intensive treatments, the patient died at 31h after the end of administration of landiolol. The administration of landiolol was stopped in 3 patients because of an adverse event (embolic stroke, hypotension, and asthma in 1 patient each).

The changes in the hemodynamic parameters, renal function, and symptoms at the final observation are shown in Table 3. The period to the final observation was 66.6 ± 22.5h in the landiolol group and 49.9 ± 11.9h in the digoxin group. None of the laboratory parameters worsened from baseline to the end of the study in either group. The brain natriuretic peptide levels did not increase from baseline in either group (Figure S1).

Discussion
The results of this study show that continuous intravenous administration of landiolol in a dose-escalating manner effectively controlled rapid HR in patients with AF/AFL and LV dysfunction. Landiolol and digoxin were effective in 48.0% and 13.9% of patients, respectively, at 2h after starting treatment, indicating that the ultra-short-acting landiolol is more useful than the slow-acting digoxin. Regarding the safety of these drugs for rapid control of HR, the incidence of hypotension was similar in both groups. During treatment with landiolol, which rapidly reaches steady state and has a half-life of 4min, the risk of hypotension may be low because its dose can be carefully adjusted according to the patient’s condition. Other adverse effects associated with a reduction in HR include gastrointestinal symptoms such as nausea/vomiting caused by blood flow stasis. However, there were no abnormal changes in laboratory data, including serum bilirubin levels.

It has been reported that the control of HR in patients with tachycardic AF/AFL helps to prevent worsening of heart failure and ventricular dysfunction, because it contributes to improvements in circulatory dynamics and subjective symptoms. However, the optimal target HR in the treatment of AF/AFL in patients with LV dysfunction has not been clearly established. In patients with LV dysfunction, a rapid and vigorous decrease in HR might be detrimental if accompanied by a decrease in cardiac output. However, in the RACE II study, which was conducted in patients with persistent AF and normal to moderate LV dysfunction, there were no differences in prognosis, including mortality, incidence of heart failure, and improvements in subjective symptoms, between the levetiracetam control (resting HR < 110 beats/min) and strict control (resting HR < 80 beats/min and HR during moderate exercise < 110 beats/min) groups. In the present study conducted in patients with LV dysfunction and NYHA class III or IV symptoms, the target HR of < 110 beats/min, corresponding to the levetiracetam criterion in the RACE II study, may be reasonable based on the results of earlier studies. In addition, a 20% decrease in HR from baseline has been conventionally used to verify the drug-induced HR reduction in AF. Accordingly, the primary endpoint in this study combined both criteria.

In general, the optimal dose of β-blockers in patients with LV dysfunction should be determined according to the patient’s cardiac function and general condition. It should also be noted that the response to β-blockers in patients with AF varies depending on polymorphisms (e.g., G389R and S49G) in the β1 receptor gene. In fact, the present study showed that the optimal dose varied among the patients with variable response to landiolol. Therefore, the optimal dose of β-blocker for HR control cannot be determined before treatment. The dosage of rate-controlling drugs for treating AF/AFL in patients with LV dysfunction should be highly adjustable, according to the patient’s hemodynamic response. The efficacy and safety results of this study provide support for the ultra-fast-acting and easily adjustable landiolol for swift control of rapid HR in patients with AF/AFL and LV dysfunction. However, in the present study, there were no significant differences between the 2 groups in the subjective symptoms reported within 2h after starting administration. The rapid decrease in HR elicited by landiolol may not necessarily be associated with symptomatic relief in these patients. These findings suggest that it is difficult to evaluate how rapid HR contributes to the hemodynamic status and symptoms of heart failure in patients with AF/AFL.

The guidelines of the American Heart Association and the European Society of Cardiology recommend digitalis and amiodarone for acute rate-control therapy in patients with AF and LV dysfunction. Although amiodarone is classified as a rhythm-control drug, it can also decrease the HR because it blocks K⁺ channels, Ca²⁺ channels, and β receptors. However, because amiodarone has a long half-life, it is difficult to adjust its dose according to the patient’s condition.

In the present study, we observed better control of HR with landiolol than with digoxin. As landiolol was the only intravenous β-blocker used in this study, the efficacy of esmolol, propranolol, and amiodarone in this setting remains unknown. Thus, we cannot confirm whether landiolol is more effective than these drugs. Nevertheless, landiolol may be easier to use
than other drugs for acute rate-control therapy in patients with AF/AFL and LV dysfunction because it is faster-acting and shows greater selectivity for β₁ receptors than esmolol, propranolol or amiodarone. In addition, this study was intended to test the usefulness of landiolol in acute rate-control therapy with up to 5 days of follow-up. Therefore, the medium- and long-term prognosis of these patients after treatment with landiolol should be studied in future.

Conclusions

In the treatment of AF/AFL in patients with LV dysfunction, landiolol rapidly decreased the HR in approximately 50% of the patients, and was more effective for urgent HR control than digoxin, without an increase in the incidence of adverse events. Landiolol is an ultra-short-acting, highly cardioselective intravenous β-blocker that could be a promising drug for controlling rapid HR in patients with AF/AFL and LV dysfunction.

Acknowledgments

The authors thank all of the investigators and site staff who participated in this clinical trial.

Disclosures


References


Appendix

Investigators and Study Sites

Toshihiro Takeuchi, Asakihaka Medical University Hospital; Shigekinakino, Otaru Kyokai Hospital; Minoru Sato, Hokkaido Medical Center; Hiratsuka Murakami, Torii Hospital; Kenji Ma, Kumamoto University Graduate School of Medicine; Tetsuya Yagi, Sendai City Hospital; Tsuyoishinozaki, Sendai Medical Center; Koji Fukuda, Tohoku University Graduate School of Medicine; Kaname Takizawa, Sendai Kousei Hospital; Tetsu Watanabe, Yamagata University Hospital; Shiuchi Taguchi, Mito Medical Center; Shoji Suzuki, Kasumigaura Medical Center; Kazutaka Aomma, Tsukuba University Hospital; Daikube Ake, Ibaraki Prefectural Central Hospital; Shoichi Take, Maebashi Red Cross Hospital; Shigeto Naito, Gunma Prefectural Cardiovascular Center; Shu Kasama, Cardiovascular Hospital of Central Japan (Kitakanto Cardiovascular Hospital); Shin-ichi Momomura, Saitama Medical Center, Ichi-Medical University; Kazuo Matsumoto, Saitama Medical University International Medical Center; Masayuki Inagaki, Funabashi Municipal Medical Center; Atsushi Hirayama, New Tokyo Hospital; Takamori Ikeda, Toho University Omori Medical Center; Seiji Fukumizu, Tokyo

NAGAI R et al.
Supplementary Files

Table S1. Subjective Symptoms and Objective Findings in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

Figure S1. Distribution of levels of B-type natriuretic peptide (BNP). Please find supplementary file(s): http://dx.doi.org/10.1253/circj.CJ-12-1618