Differential Effectiveness of Landiolol Between Atrial Fibrillation and Atrial Flutter/Atrial Tachycardia Patients With Left Ventricular Dysfunction

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Background: Landiolol, an ultra-short acting β1-selective blocker, is more effective for controlling the heart rate (HR) than digoxin in patients with atrial tachyarrhythmias and left ventricular (LV) dysfunction. The impact of the type of atrial tachyarrhythmias on the effectiveness of landiolol is uncertain. We evaluated the efficacy and safety of landiolol on tachycardiac atrial fibrillation (AF) and tachycardiac atrial flutter/atrial tachycardia (AFl/AT) in patients with reduced LV function.

Methods and Results: Seventy-seven patients treated with landiolol were retrospectively analyzed. There were no significant differences in the baseline characteristics between the AF group (n=65) and AFl/AT group (n=12). Despite a higher dosage, the %change in HR from baseline to 12 and 24 h was only −10.2±12.7% and −16.1±19.4% in the AFl/AT group, while it was −28.3±13.2% and −31.3±11.3% in the AF group (P<0.02), respectively. The prevalence of the responders to landiolol treatment was much greater in the AF group than in the AFl/AT group (P<0.001). Alternative treatments such as i.v. amiodarone and electrical cardioversion were required in 83% of the AFl/AT patients.

Conclusions: Landiolol was ineffective in the majority of AFl/AT patients. An alternative management to prevent any worsening of heart failure might be considered in those patients.

Key Words: Atrial fibrillation; Atrial flutter/atrial tachycardia; Heart failure; Landiolol; Left ventricular dysfunction

Atrial tachyarrhythmias such as atrial fibrillation (AF), atrial flutter (AFl), and atrial tachycardia (AT) often coexist in patients with reduced left ventricular (LV) function and heart failure (HF). A persistent rapid ventricular response during AF might cause a worsening of the HF. Therefore, it is important to control the heart rate (HR) of atrial tachyarrhythmias within an optimal range. I.v. digoxin or amiodarone has been recommended as the standard pharmacological therapy for atrial tachyarrhythmias in patients with reduced LV function. The effect of digoxin for controlling HR, however, is limited especially in patients with excessive sympathetic nervous activity due to congestive HF. In addition, i.v. non-dihydropyridine calcium blockers (i.e., diltiazem and verapamil) for HR control should be avoided, especially in patients with reduced LV function, because of their negative inotropic effect. Recently, the J-Land study showed that landiolol, an ultra-short acting β1-selective blocker, was more effective for controlling rapid HR than digoxin in patients with AF/AFl and reduced LV systolic function. The J-Land study included both AF and AFl, the mechanism of which differed, and the impact of the type of atrial tachyarrhythmia on the effectiveness of landiolol was uncertain. In addition, the majority of those patients treated with landiolol were admitted to the intensive care unit or cardiac care unit, where continuous invasive arterial blood pressure monitoring and mechanical ventilation were available. The purpose of the present study was to evaluate the efficacy and safety of landiolol treatment for tachycardiac AF and tachycardiac AFl/AT patients with LV dysfunction in a general cardiovascular ward.

Subjects
Seventy-seven consecutive patients with acute decompen-sated HF (ADHF) who were treated with landiolol for atrial tachyarrhythmia on the general ward of the Department of Cardiology at Nippon Medical School Hospital were retrospectively analyzed between November 2013 and March 2016. In this study, the patients were divided into 2 groups according to the mechanisms of the atrial tachyarrhythmia at the time of admission (Figure 1).

The main inclusion criteria were ADHF (New York...
Heart Association [NYHA] class III or IV and LV ejection fraction [EF] <50%) and HR ≥120 beats/min with an atrial tachyarrhythmia (AF/AFI/AT). The exclusion criteria were as follows: age <20 years, perioperative period, necessity for mechanical circulatory support devices such as an intra-aortic balloon pump (IABP) or percutaneous cardiopulmonary support system, mechanical ventilation by tracheal intubation, and cardiac shock (systolic blood pressure [SBP] <80mmHg).

**Study Protocol**

All patients were admitted to the general ward of the Department of Cardiology for HF, and were treated with oxygen inhalation, vasodilators, diuretics, and/or i.v. low dose inotropic agents with dobutamine. The HR was continuously measured on ECG, and non-invasive blood pressure was measured every 10–15min for the first 1h after landiolol initiation, followed by measurement every 1–3h. Continuous i.v. landiolol was initiated from 1µg/kg/min and titrated by 1-γ increments to a maximum dose of 10γ according to the patient’s condition. Once the target heart rate (HR) was reached, the dose was not increased. BP, blood pressure; ECG, electrocardiogram; SpO2, saturation of percutaneous oxygen.

**Figure 1.** Study design. ADHF, acute decompensated heart failure; AF, atrial fibrillation; AFI, atrial flutter; AT, atrial tachycardia; HR, heart rate; IABP, intra-aortic balloon pump; LV, left ventricular; NYHA, New York Heart Association; PCPS, percutaneous cardiopulmonary support system.

**Figure 2.** Study protocol. (A) Treatment regimen after landiolol in patients with atrial tachyarrhythmia. The timing of switch to oral β-blockers or an alternative therapy was left to the physician. (B) Example of the titration of landiolol. We started at 1µg/kg/min (γ) and titrated by 1-γ increments to a maximum dose of 10γ according to the patient’s condition. When the target heart rate (HR) was reached, the dose was not increased. BP, blood pressure; ECG, electrocardiogram; SpO₂, saturation of percutaneous oxygen.
Effectiveness of Landiolol in AF and AFl/AT

Table 1. Baseline Patient Characteristics

| Baseline characteristics and hemodynamic parameters | Total (n=77) | AF (n=65) | AFl/AT (n=12) | P-value |
|-----------------------------------------------------|-------------|-----------|---------------|---------|
| Age (years)                                         | 72.4±12.6   | 73.1±12.6 | 68.7±14.0     | 0.288   |
| Male                                                | 54 (70.1)   | 45 (69.2) | 9 (75.0)      | 1.000   |
| Weight (kg)                                         | 58.0±14.6   | 57.4±14.9 | 61.7±12.6     | 0.354   |
| Heart rate (beats/min)                              | 143.1±15.2  | 142.0±15.7| 149.2±10.8    | 0.137   |
| SBP (mmHg)                                          | 120.2±20.9  | 120.3±21.3| 119.8±19.2    | 0.931   |
| DBP (mmHg)                                          | 73.4±15.6   | 72.8±16.3 | 76.8±6.7      | 0.420   |
| LAD (mm)                                            | 47.1±10.0   | 47.4±10.2 | 45.5±8.4      | 0.550   |
| LVDD (mm)                                           | 52.9±10.0   | 53.8±10.0 | 48.3±8.9      | 0.077   |
| LVDs (mm)                                           | 41.5±11.5   | 42.4±11.2 | 36.2±12.7     | 0.139   |
| LVEF (%)                                            | 33.1±13.7   | 34.3±13.0 | 26.8±15.9     | 0.083   |
| BNP (pg/mL)                                         | 807.0±883.2 | 868.5±940.0| 473.9±324.2  | 0.156   |
| Creatinine (mg/dL)                                  | 1.2±0.8     | 1.3±0.9   | 0.9±0.2       | 0.145   |

Baseline arrhythmia

| AF                                    | 65 (84.4) | 65 (100)   | 0 (0.0)     |
| Paroxysmal AF                         | 28 (36.4) | 28 (43.1)  | 0 (0.0)     |
| Persistent AF                         | 37 (48.1) | 37 (56.9)  | 0 (0.0)     |
| AFl                                    | 5 (6.5)   | 0 (0.0)    | 5 (41.7)    |
| AT                                    | 7 (9.1)   | 0 (0.0)    | 7 (55.6)    |
| First arrhythmia episode              | 36 (46.8) | 31 (47.7)  | 5 (41.7)    | 0.762   |

Baseline cardiovascular disease

| IHD                                   | 16 (20.8) | 15 (23.1)  | 1 (8.3)     | 0.441   |
| Valvular disease                      | 25 (32.4) | 23 (35.4)  | 2 (16.7)    | 0.317   |
| DCM                                   | 6 (7.8)   | 6 (9.2)    | 0 (0.0)     | 0.582   |
| HCM                                   | 2 (2.6)   | 2 (3.1)    | 0 (0.0)     | 1.000   |
| TIC                                   | 26 (33.8) | 17 (26.2)  | 9 (75.0)    | 0.002   |
| HHD                                   | 1 (1.3)   | 1 (1.5)    | 0 (0.0)     | 1.000   |
| Other                                 | 1 (1.3)   | 1 (1.5)    | 0 (0.0)     | 1.000   |

Treatment before admission

| Diuretic (oral)                       | 30 (39.0) | 29 (44.6)  | 1 (8.3)     | 0.023   |
| β-blocker (oral)                      | 34 (44.2) | 31 (47.7)  | 3 (25.0)    | 0.209   |
| ACEI/ARB                              | 34 (44.2) | 32 (49.2)  | 2 (16.7)    | 0.056   |
| Digitalis (oral)                      | 2 (2.6)   | 2 (3.1)    | 0 (0.0)     | 1.000   |

Endpoints

The primary endpoint of this study was the prevalence of patients with response to landiolol. Response was defined as decrease of HR <110 beats/min ≤24 h after the start of landiolol, and treatment could be switched to oral medication without any alternative management. The secondary endpoints were HR at 12 and 24 h after the initiation of landiolol, maximum dose and mean dose at each time point, dosing period of landiolol, and percentage of patients with both HR <110 beats/min and ≥20% decrease in HR from baseline 2 h after landiolol treatment, which was defined as the primary endpoint of the J-Land Study. Any adverse events of landiolol treatment, such as bradycardia, hypotension, or other serious events were recorded.

Statistical Analysis

Data are expressed as mean±SD or percentage of patients. Comparison between the 2 groups was performed using Student’s t-test for continuous variables and chi-squared or Fisher’s test for categorical variables. For time-dependent comparisons, a linear mixed-effects model was used. Bonferroni correction was used for multiple comparisons. Single-variable analysis was conducted first, followed by multivariable analysis adjusted for variables with single-variable P<0.10. Adjusted odds ratios (OR) and 95% CI were examined on binary logistic regression to determine the multiple predictors of non-response to landiolol. All tests were 2-sided and P<0.05 was considered statistically significant. All statistical analysis was conducted using IBM SPSS Statistics version 21 for Windows.

Results

Patient Characteristics

The baseline characteristics of the 77 patients are listed in Table 1. There were 65 patients in the AF group and 12 in the AFl/AT group. Paroxysmal AF was seen in 28 patients and persistent AF in 37. Five of the 12 patients in the AFl/
effects of LVEF were 34.3±13.0% and 26.8±15.9%, respectively, for the AF and AFl/AT groups (P=0.083). LV end-diastolic diameter tended to be greater in the AF than the AFl/AT group (53.8±10.0 mm vs. 48.3±8.9 mm, P=0.077). There were no significant differences in the baseline characteristics or hemodynamic parameters between the 2 groups.

Baseline underlying cardiovascular disease and baseline treatment before admission are also listed in Table 1. The cardiovascular diseases were ischemic heart disease in 16 patients (20.8%), valvular disease in 25 (32.4%), dilated and hypertrophic cardiomyopathy in 8 (10.4%), and tachycardia-induced cardiomyopathy (TIC) in 26 (33.8%). The diagnosis of TIC was made after demonstrating recovery of LV function after controlling the tachyarrhythmia in the absence of any other identifiable etiologies such as myocardial ischemia. There were significantly more patients with TIC in the AFl/AT group than in the AF group (P=0.002).

Before being hospitalized, the number of patients who had taken oral diuretics, oral β-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin type 2 receptor blockers (ARB), and oral digitalis are also listed in Table 1. Although oral β-blockers had been used in both groups, diuretics and ACEI/ARB were more frequently used in the AF group because of a baseline cardiovascular disease.

Effects of Landiolol

The time course of HR during landiolol treatment is shown in Figure 3. Compared with the AFl/AT group, landiolol was significantly more effective for the AF group to control rapid HR. On multivariate linear mixed effect modeling, landiolol significantly decreased HR in the AF group at 2, 12, and 24 h (vs. baseline, P<0.05). The magnitude of the reduction in HR was significantly greater in the AF group than in the AFl/AT group (mixed-effects model: interaction [group×time], P<0.0001). Despite a significantly higher dosage at each time point, HR at 2, 12, and 24 h was significantly higher in the AFl/AT group than the AF group (Figure 3).

As shown in Table 2, the percent decrease in HR from baseline to 12 h was −10.2±12.7% in the AFl/AT group and −28.3±13.2% in the AF group (P<0.001). The maximum dose was significantly higher in the AFl/AT group than the
Effectiveness of Landiolol in AF and AFl/AT

### Table 2. Landiolol Treatment Results

|                  | AF (n=65) | AFl/AT (n=12) | P-value |
|------------------|-----------|----------------|---------|
| **Primary endpoints** |           |                |         |
| Responder to landiolol treatment | 47 (72.3) | 2 (16.7) | <0.001 |
| Alternative treatment | 16 (24.6) | 10 (83.3) | <0.001 |
| I. v. amiodarone | 6         | 5              |         |
| Electrical cardioversion | 10       | 4             |         |
| I. v. diltiazem | 2         | 1              |         |
| **Secondary endpoints** |           |                |         |
| HR at 12h after treatment (beats/min) | 100.3±16.7 | 131.9±17.3 | <0.001 |
| %HR change at 12h vs. baseline | −28.3±13.2 | −10.2±12.7 | <0.001 |
| HR at 24h after treatment (beats/min) | 96.6±12.9 | 124.0±23.0 | <0.001 |
| %HR change at 24h vs. baseline | −31.3±11.3 | −16.1±19.4 | 0.018  |
| Maximum dose (μg/kg/min) | 3.6±2.4 | 8.5±3.0 | <0.001 |
| Dosing period (days) | 2.5±2.2 | 1.2±1.3 | 0.100  |
| HR at 2h after treatment (beats/min) | 114.9±17.4 | 139.2±16.8 | <0.001 |
| %HR change at 2h vs. baseline | −19.0±10.6 | −6.5±11.1 | <0.001 |
| Achieved J-Land primary endpoint* | 23 (35.4) | 1 (8.3) | 0.091  |
| **Concomitant treatment after admission** |           |                |         |
| Loop diuretics | 26 (40.0) | 4 (33.3) | 0.756  |
| Vasodilator | 20 (30.1) | 5 (41.7) | 0.757  |
| Low dose inotropes | 12 (18.5) | 0 (0.0) | 0.195  |
| I. v. digoxin | 24 (36.9) | 5 (41.7) | 0.756  |
| Non-invasive PPV | 7 (10.8) | 1 (8.3) | 1.000  |

Data given as mean±SD or n (%). *HR <110 beats/min and a ≥20% decrease in HR from baseline at 2h after landiolol treatment. HR, heart rate; PPV, positive pressure ventilation. Other abbreviations as in Table 1.

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**Figure 4.** Flowchart of treatment. Response to landiolol treatment was defined as decrease of heart rate <110beats/min in the 24h after the start of landiolol, and switch to oral medication without any alternative management. The timing to switch to oral therapy or alternative therapy was left to the physician. AF, atrial fibrillation; AFl/AT, atrial flutter/atrial tachycardia; AMD, i.v. amiodarone; DC, direct current cardioversion.
OKA E et al.

Also shown in Figure 4. More than half of the patients in the AF/AT group abandoned landiolol in ≤24 h and required alternative treatment. The condition of the non-responders then improved. Electrical cardioversion was performed after the absence of any left atrial appendage thrombi was confirmed on transesophageal echocardiography and the appropriate anticoagulation therapy had been continued.

We also performed further statistical analysis by dividing the study subjects into 2 groups according to the effectiveness of landiolol (Table 3). Baseline characteristics and cardiovascular disease did not differ between the responder group (n=49) and non-responder group (n=28). There were significantly many more patients with persistent AF in the responder group than in the non-responder group (P=0.004). In contrast, most of the patients with AF/AT belonged to the non-responder group (P=0.0004) and developed TIC. The proportion of patients who were hospitalized with first-episode arrhythmia was 38.8% in the responder group and 60.7% in the non-responder group, showing that there was no significant difference between the 2 groups (P=0.096). As shown in Table 4, on logistics regression analysis AF/AT was an independent predictor of non-response to landiolol treatment (OR, 14.827; 95% CI: 2.498–88.011; P=0.003).

Overall, 2 patients in the AF group died of infection during hospitalization. Only 3 patients (2 in the AF group),

Table 3. Baseline Patient Characteristics vs. Landiolol Effectiveness

| Baseline characteristics and hemodynamic parameters | Total (n=77) | Responder (n=49) | Non-responder (n=28) | P-value |
|-----------------------------------------------------|-------------|-----------------|----------------------|--------|
| Age (years)                                         | 72.4±12.6   | 73.2±12.2       | 71.0±13.3            | 0.464  |
| Male                                                | 54 (70.1)   | 33 (67.3)       | 21 (75.0)            | 0.607  |
| Weight (kg)                                         | 58.0±14.6   | 57.7±14.6       | 58.6±14.8            | 0.807  |
| Heart rate (beats/min)                              | 143.1±15.2  | 142.6±16.7      | 144.1±12.6           | 0.677  |
| SBP (mmHg)                                          | 120.2±20.9  | 121.9±22.7      | 117.3±16.9           | 0.359  |
| DBP (mmHg)                                          | 73.4±15.6   | 74.3±16.5       | 71.8±14.1            | 0.508  |
| LAD (mm)                                            | 47.1±10.0   | 47.6±10.9       | 46.3±8.2             | 0.578  |
| LVDD (mm)                                           | 52.9±10.0   | 52.3±9.3        | 54.0±11.2            | 0.481  |
| LVDS (mm)                                           | 41.5±11.5   | 40.2±10.7       | 45.4±12.3            | 0.200  |
| LVEF (%)                                            | 33.1±13.7   | 35.3±13.4       | 29.3±13.5            | 0.060  |
| BNP (pg/mL)                                         | 807.0±883.2 | 717.3±694.1     | 963.9±1,139.8        | 0.241  |
| Creatinine (mg/dL)                                  | 1.2±0.8     | 1.3±0.7         | 1.2±1.0              | 0.875  |

Baseline arrhythmia

| Paroxysmal AF                                       | 28 (36.4)   | 17 (34.7)       | 11 (39.3)            | 0.806  |
| Persistent AF                                       | 37 (48.1)   | 30 (61.2)       | 7 (25.0)             | 0.004  |
| AF/AT                                               | 12 (15.6)   | 2 (4.1)         | 10 (35.7)            | <0.001 |
| First arrhythmia episode                            | 36 (46.8)   | 19 (38.8)       | 17 (60.7)            | 0.096  |

Baseline cardiovascular disease

| IHD                                                  | 16 (20.8)   | 10 (20.4)       | 6 (21.4)             | 1.000  |
| Valvular disease                                     | 25 (32.4)   | 19 (38.8)       | 6 (21.4)             | 0.137  |
| DCM/HCM                                             | 8 (10.3)    | 5 (10.2)        | 3 (10.7)             | 1.000  |
| TIC                                                  | 26 (33.8)   | 13 (26.5)       | 13 (46.4)            | 0.086  |
| HHD                                                  | 1 (1.3)     | 1 (2.0)         | 0 (0.0)              | 1.000  |
| Other                                                | 1 (1.3)     | 1 (2.0)         | 0 (0.0)              | 1.000  |

Treatment before admission

| Diuretic (oral)                                      | 30 (39.0)   | 21 (42.9)       | 9 (32.1)             | 0.467  |
| β-blocker (oral)                                     | 34 (44.2)   | 23 (46.9)       | 11 (39.3)            | 0.635  |
| ACEI/ARB                                             | 34 (44.2)   | 23 (46.9)       | 11 (39.3)            | 0.635  |
| Digitalis (oral)                                     | 2 (2.6)     | 2 (4.1)         | 0 (0.0)              | 1.000  |

Data given as mean±SD or n (%). Abbreviations as in Table 1.

| OR | 95% CI | P-value |
|----|--------|---------|
| LVEF (%) | 0.979 | 0.938–1.023 | 0.344 |
| AF/AT | 14.827 | 2.498–88.011 | 0.003 |
| First arrhythmia episode | 3.021 | 0.941–9.704 | 0.063 |
| TIC | 1.099 | 0.336–3.597 | 0.876 |

Table 4. Predictors of Non-Response to Landiolol

LVEF, left ventricular ejection fraction. Other abbreviations as in Table 1.

AF group (8.5±3.0 vs. 3.6±2.4 μg/kg/min, P<0.001). The dosing period was 1.2±1.3 days in the AF/AT group and 2.5±2.2 days in the AF group (P=0.100).

The primary endpoint is shown in Table 2 and Figure 4. The prevalence of response to landiolol treatment was much greater in the AF group than the AF/AT group (72.3% vs. 16.7%, P=0.0004). To prevent any exacerbation in HF, the percentage of non-responders receiving alternative treatment was overwhelmingly higher in the AF/AT group (P=0.0008). Ten of the 12 patients in the AF/AT group required alternative management: i.e. amiodarone in 5 patients, electrical cardioversion in 4, and i.v. diltiazem in 1 (Table 2). The timing of switching to other treatment is also shown in Figure 4. More than half of the patients in the AF/AT group abandoned landiolol in ≤24 h and required alternative treatment. The condition of the non-responders then improved. Electrical cardioversion was performed after the absence of any left atrial appendage thrombi was confirmed on transesophageal echocardiography and the appropriate anticoagulation therapy had been continued.

We also performed further statistical analysis by dividing the study subjects into 2 groups according to the effectiveness of landiolol (Table 3). Baseline characteristics and cardiovascular disease did not differ between the responder group (n=49) and non-responder group (n=28). There were significantly many more patients with persistent AF in the responder group than in the non-responder group (P=0.004). In contrast, most of the patients with AF/AT belonged to the non-responder group (P=0.0004) and developed TIC. The proportion of patients who were hospitalized with first-episode arrhythmia was 38.8% in the responder group and 60.7% in the non-responder group, showing that there was no significant difference between the 2 groups (P=0.096). As shown in Table 4, on logistics regression analysis AF/AT was an independent predictor of non-response to landiolol treatment (OR, 14.827; 95% CI: 2.498–88.011; P=0.003).

Overall, 2 patients in the AF group died of infection during hospitalization. Only 3 patients (2 in the AF group),
treated with landiolol on the general ward, needed intensive treatment in the cardiac care unit for septic shock and low output syndrome.

On comparison of HR at 2 h after initiation of landiolol, those in the AF group also had a lower HR than those in the AFl/AT group (114.9±17.4 vs. 139.2±16.8 beats/min, P<0.001). Mean HR, however, did not reach the target HR, and the proportion of patients who achieved the J-Land study primary endpoint did not differ between the 2 groups.

There was also no significant difference in the concomitant treatment, including digoxin, after admission (Table 2). I.v. digoxin was used in 24 patients in the AF group and in 5 in the AFl/AT group (P=0.756). It was difficult for 3 patients in the AFl/AT group to continue landiolol due to hypotension, as well as due to uncontrolled HR. In contrast, although the rapid HR was able to be controlled, landiolol was discontinued in 6 patients in the AF group because of hypotension and in 1 because of bradycardia. SBP <80 mmHg and HR <50 beats/min were recorded as hypotension and bradycardia, respectively. No other adverse events, such as drug-induced renal dysfunction, bronchial asthma, or gastrointestinal symptoms (e.g., constipation and nausea/vomiting) were observed in either group.

Discussion

In the present study HR was effectively reduced by approximately 30%, 12 h after landiolol treatment in the AF group, whereas it was reduced by only approximately 10% in those with AFl/AT. The majority of the patients with tachyarrhythmic AF with reduced LV function could be treated with landiolol without requiring intensive care such as mechanical ventilation and IABP. In contrast, in the majority of patients in the AFl/AT group (approximately 83%), alternative treatment instead of landiolol was required to control HR and HF.

Mechanisms of HR Reduction by Landiolol in Atrial Tachyarrhythmias

The mechanism of AV nodal conduction velocity slowing, leading to a prolongation of the RR interval during atrial tachyarrhythmias, was associated with an increased AV nodal effective refractory period (ERP) and concealed conduction in the AV node. The effect of \( \beta \)-blockers on the AV node is mainly associated with ERP prolongation rather than concealed conduction. 7 A medium dose of diltiazem, however, increases the ERP of the AVN and the degree of concealed conduction in the AV node, and enhances the irregularity of the ventricular response during AF. 8,9 Therefore, it is suggested that the effect of landiolol on controlling HR was mainly due to the prolongation of the ERP of the AV node.

Differential Effectiveness of Landiolol

Although the clinical interrelationship between AF and AFl has been reported, 10 the mechanisms of AF and AFl differ. AF can be maintained by multiple circuit reentry and/or rapid focal ectopic firing, whereas AFl can be sustained by a single macro-reentrant circuit in the atria.

\( \beta \)-blockers have a negative dromotropic effect on the AV node and lead to a prolongation of the AV nodal conduction time. In patients with AF, rapid fibrillatory excitation 400–500 beats/min in the atria can conduct to the AV node. The \( \beta \)-blockers more or less decrease the AV node conductivity, leading to a reduction in HR during AF, leading to increased cardiac output. In contrast, it was hard to control HR in the patients with AFl/AT if landiolol did not reduce the AV conduction ratio (i.e., from 2:1 AV conduction to 3:1 AV conduction). There is no intermediate effect of controlling HR in AFl/AT, which differs from AF. The effect of landiolol, without changing HR, might lead to a decompensation of the HF by its negative inotropic effect.

Long-Term Effect of Landiolol for Controlling HR

In the present study, landiolol effectively reduced HR in the patients with AF by 28.3% and 31.3% at 12 and 24 h after drug treatment, respectively. The treatment interval with landiolol in the AF group and AFl/AT group was 2.5±2.2 and 1.2±1.3 days, respectively. Of the total group, adverse events occurred in 10 patients (13.0%). The incidence of adverse events in this study was much lower than in the J-Land study. There were no fatal complications due to landiolol, because it has a very short half-life of only 4 min.

There was no venous phlebitis associated with long-term landiolol via a peripheral vein. Also, i.v. amiodarone, in patients with LV dysfunction or signs of congestive HF, was recommended as an option when the ventricular rate remained high despite treatment with the smallest-dose \( \beta \)-blockers. 11 The long-term infusion of i.v. amiodarone should be given by central venous access for the prevention of venous phlebitis. 12,13 Therefore, i.v. landiolol might be a safe therapeutic option in patients with tachycardiac AF and LV dysfunction. Taking the medical economic burden into account, however, it is also important to make an effect judgment in a few days using an appropriate dosage of landiolol.

Alternative Therapy in Landiolol Refractoriness

It is reported that AF begets HF, and HF also begets AF. 14 Higher admission HR is independently associated with worse outcomes, 15 and the cardiac output also begins to decrease at HR >120 beats/min. 12 Persistent uncontrolled rapid HR has the potential to worsen HF. HR reduction from the acute phase to discharge on \( \beta \)-blocker treatment is a stronger predictor of the clinical outcome of future cardiac events in patients with ADHF. 16 Therefore in the patients with AF who are not responsive to landiolol in 24 h, an alternative treatment should be considered. In addition, in the patients with tachycardiac AFl/AT, prompt alternative treatment might be considered in cases of landiolol refractoriness.

According to the ESC guidelines, i.v. amiodarone is also recommended for controlling HR in patients with HF and rapid AF, 11 but it is difficult to adjust the dose of amiodarone according to patient condition. We should pay attention to not only the acute adverse effects, such as hypotension, bradycardia, and QT prolongation, but also to the amiodarone-induced side-effects such as pulmonary fibrosis. There is individual variability in the action time after amiodarone treatment because it is a lipophilic drug. In a meta-analysis, the conversion rate to sinus rhythm for i.v. amiodarone was approximately 17% at 1–2 h, 56% at 6–8 h, and 82% at 24 h. 17 Therefore, even if we intend to use i.v. amiodarone for the purpose of controlling a rapid HR during the acute phase, the probability of cardioversion of AF/AFl is relatively high. Thromboembolisms must be taken more seriously into consideration.

In most cases of abandonment of landiolol and switch to i.v. amiodarone, HR could be controlled without any
adverse events. In more than half of the patients with amiodarone in both groups, amiodarone resulted in the restoration of sinus rhythm.

Because the majority of the patients in the AFI/AT group developed TIC, it is important to control acute HR more strictly. AFI, however, may not be well controlled by pharmacological therapies (digoxin, calcium channel blockers, and β-blockers) in some cases of not only reduced EF but also preserved EF, and it is sometimes necessary to use cardioversion to sinus rhythm. Potassium-channel blockers and pure class III anti-arrhythmic drugs are effective for the acute conversion of AFI. Nifekalant is effective for conversion of AFI, with a potent effect even in patients with structural heart disease. These anti-arrhythmic drugs, however, have a risk of QT prolongation and subsequent torsade de pointes. Linear catheter ablation of the inferior vena cava-tricuspid isthmus (CTI) is also recommended by the ACC/AHA/ESC guidelines as a class I indication treatment for the long-term management of AFI, and has become the standard treatment for typical AFI. In approximately 95% of cases successful bilateral CTI block can be achieved without requiring much time for the procedure. We performed catheter ablation for typical AFI in 2 patients with recurrent AFI after electrical cardioversion as a quasi-emergency. Although HR adjustment is often difficult with AFI, catheter ablation of typical AFI is considered an effective treatment.

Study Limitations
This study was a retrospective and single-center study with a small population. The present study did not include any patients with severely hemodynamic compromise requiring intensive care management. The effect of lindiolol in such patients still remains uncertain. Further multicenter studies with a large number of patients are needed to confirm those findings.

Conclusions
Lindiolol was less effective for controlling rapid HR in patients with AFI/AT and LV dysfunction than in those with AF. Alternative management to prevent the worsening of HF should be considered in patients refractory to lindiolol.

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Disclosures
The authors declare no conflicts of interest.

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