Comparison of Landiolol and Digoxin as an Intravenous Drug for Controlling the Heart Rate in Patients with Atrial Fibrillation and Severely Depressed Left Ventricular Function

Masaya Shinohara, MD, Ryou Wada, MD, Kensuke Yano, MD, Katsuya Akitsu, MD, Hideki Koike, MD, Toshio Kinoshita, MD, Takeya Suzuki, MD, Tadashi Fujino, MD and Takanori Ikeda, MD

Summary
Clinical experience with landiolol use in patients with atrial fibrillation (AF) and a severely depressed left ventricular (LV) function is limited. We compared the efficacy and safety of landiolol with that of digoxin as an intravenous drug in controlling the heart rate (HR) during AF associated with a very low LV ejection fraction (LVEF).

We retrospectively analyzed 53 patients treated with landiolol (n = 34) or digoxin (n = 19) for AF tachycardias with an LVEF ≤ 25. The landiolol dose was adjusted between 0.5 and 10 μg/kg/minute according to the patient’s condition. The response to treatment was defined as a decrease in the HR of ≤ 110/minute, and that decreased by ≥ 20% from baseline.

There were no significant differences between the two groups regarding the clinical characteristics. The responder rate to landiolol at 24 hours was significantly higher than that to digoxin (71.0% versus 41.2%; odds ratio: 4.65, 95% confidence interval: 1.47-31.0, P = 0.048). The percent decrease in the HR from baseline at 1, 2, 12, and 24 hours was greater in the landiolol group than in the digoxin group (P < 0.01, P = 0.071, P = 0.036, and P = 0.016, respectively). The systolic blood pressure (SBP) from baseline within 24 hours after administering landiolol was significantly reduced, whereas digoxin did not decrease the SBP over time. Hypotension (< 80 mmHg) occurred in two patients in the landiolol group and 0 in the digoxin group (P = 0.53).

Landiolol could be more effective in controlling the AF HR than digoxin even in patients with severely depressed LV function. However, careful hemodynamic monitoring is necessary when administering landiolol.

Key words: Selective β1 blocker, Heart failure, Left ventricular dysfunction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. There has been an increase in the prevalence rate of AF, and heart failure (HF) associated with AF has also been increasing. This could especially be fatal in patients with AF and a severely depressed left ventricular (LV) function. Therefore, the necessity to decrease the heart rate (HR) in the acute setting of HF has been demonstrated. The intravenous administration of digoxin is considered to be a reasonable therapy for controlling a rapid HR during AF because of its parasympathomimetic activity. Even in patients with cardiac dysfunction and/or HF, digoxin has some beneficial effects by way of its positive inotropic effect. Recently, for controlling the HR, patients with AF and HF also have received a continuous administration of the ultra-short-acting β blocker landiolol. There is a concern that β blockers may depress the cardiac function because of their negative inotropic effect. In this situation, the J-Land study conducted in Japan revealed that landiolol is more effective for controlling the HR than digoxin without increasing adverse events (AEs) in patients with AF and depressed LV function (LV ejection fraction [LVEF] of 25%-50%). However, clinical practice reports of landiolol use in those with a much lower LVEF (≤ 25%) have so far been very limited. Therefore, we compared the efficacy and safety of landiolol with those of digoxin as an intravenous drug to control the HR in patients with AF and an LVEF of ≤ 25%.

Methods

Subjects: A total of 53 consecutive patients who were
treated with landiolol or digoxin for AF tachycardias due to acute HF and admitted to our hospital from October 2015 to April 2019 were retrospectively analyzed. The main inclusion criteria were HF (New York Heart Association class III or IV and an LVEF of ≤ 25%) and an HR of ≥ 120 beats/minute with AF tachycardias. Echocardiography was conducted on admission in all patients. The LVEF was calculated using the modified Simpson’s formula by two readers. The exclusion criteria were as follows: HF requiring a mechanical circulatory support device and/or mechanical ventilation by tracheal intubation and cardiac shocks (systolic blood pressure [SBP] < 80 mmHg). A comparison was conducted between the landiolol group treated with landiolol (n = 34) and digoxin group treated with digoxin (n = 19).

**Study protocol:** All patients were admitted into the care unit of our hospital for acute HF. The attending physician determined the treatment strategy including the choice of drugs. Patients using oral β blockers before hospitalization continued taking them or at a reduced dose. In the landiolol group, landiolol was administered continuously at an initial dosage of 0.5 μg/kg/minute and titrated to a maximum dose of 10 μg/kg/minute according to the patient’s condition. Landiolol was administered for ≥ 2 hours and up to 24 hours. In the digoxin group, digoxin was intravenously administered at an initial dose of 0.25 mg and could be up-titrated within 24 hours according to the patient’s condition. Continuous electrocardiogram monitoring was used during the landiolol and digoxin therapy. We managed our HF patients with AF tachycardia by setting the target HR of ≤ 110 beats/minute based on previous reports. If the HR control was not achieved within 2 hours, the patients were allowed to have an alternative treatment added including electrical cardioversion at the attending physician’s discretion. If treatment-related AEs occurred, the landiolol or digoxin dose was reduced or the treatment was discontinued.

**Study endpoints:** In the present study, we investigated the primary efficacy endpoint, in which the prevalence of patients with a response to landiolol or digoxin was determined at 1, 2, 12, and 24 hours after starting the treatment. A response was defined as a decrease in the HR of ≤ 110 beats/minute and that which decreased by ≥ 20% from the baseline HR, which was defined as a responder in the J-Land study. The secondary efficacy endpoint was the HR at 1, 2, 12, and 24 hours, percent change in the HR during those times, and the improvement ratio in the subjective symptoms at 2 and 24 hours after starting the treatment. We excluded patients in whom AF was converted to sinus rhythm at each time point to estimate the HR-reducing effect during AF. We also investigated the changes in the SBP and diastolic BP (DBP) from baseline to within 24 hours. The safety endpoint was evaluated based on the incidence of AEs such as hypotension (defined as an SBP of < 80 mmHg), bradycardia (defined as an HR of < 40 beats/minute), or any other AE requiring the discontinuation of the infusion. AEs that resulted in a significant disability and crucial medical events were classified as serious AEs.

**Ethical considerations:** The Toho University Omori Medical Center Ethical Committee approved the study protocol on December 24, 2019 (approval no.: M19195).

**Statistical analysis:** The statistical analyses were conducted with EZR on R-commander version 1.24 software (Saitama Medical Center, Jichi Medical University, Saitama, Japan). All continuous variables were tested for the normality of the distribution using the Kolmogorov-Smirnov test. Continuous variables with a normal distribution were described as the mean ± standard deviation (SD), continuous variables with a skewed distribution were described as the median (quartile: 25%-75%), and categorical variables were described as the frequency (percentage). Comparisons between groups were analyzed using a Fisher’s exact test, unpaired t-test, or Mann-Whitney test. For time-dependent comparisons of the baseline data and data during the treatment when the efficacy and safety of the treatment were considered, a repeated-measures analysis of variance (ANOVA) was used. A Bonferroni correction was used for multiple comparisons. A multivariate logistic analysis was constructed to identify the predictor of the responders to treatment. This model was adjusted by age, sex, and creatinine clearance (CrCl). In all tests, a p-value of less than 0.05 was considered statistically significant.

**Results**

**Baseline characteristics:** A total of 53 patients (landiolol group, n = 34; digoxin group, n = 19) were enrolled in the present study. Thirty-five patients (66.0%) were male. The mean age was 66.7 ± 16.1 years. The average LVEF was 23.8 ± 3.9%. The HR was 142.3 ± 16.8 beats/minute on average. Before starting the study treatment, diuretics were used in 22 patients (41.5%), oral β blockers in 13 (24.5%), and renin-angiotensin system inhibitors in 13 (41.5%). About 60% or more of the patients had moderate or severe renal dysfunction (CrCl ≤ 50 mL/minute). Eleven patients (20.8%) had ischemic heart disease. Other etiologies of cardiomyopathy were valvular heart disease (one patient), hypertensive heart disease (two patients), and idiopathic dilated cardiomyopathy (five patients). The remaining 33 patients were considered to have tachycardia-induced cardiomyopathy. The baseline clinical characteristics of both groups are shown in Table I. There were no significant differences in the clinical characteristics between groups.

**Efficacy endpoint:** The changes in the HR, SBP, and DBP 24 hours after starting the infusion of landiolol and digoxin are shown in Figures 1-3. The HR from baseline to that at 1 hour onward after the administration of landiolol was significantly reduced, and digoxin significantly decreased the HR from baseline to that at 2 hours onward. The magnitude of the reduction in the HR was significantly greater in the landiolol group than in the digoxin group (repeated-measures ANOVA: interaction [group × time], P = 0.024) (Figure 1). The SBP from baseline to that at 12 hours onward after the administration of landiolol was significantly reduced, whereas digoxin did not decrease the SBP from baseline over time. The magnitude of the reduction in the SBP was significantly greater in the landiolol group than in the digoxin group (repeated-measures ANOVA: interaction [group × time], P < 0.01)
The efficacy endpoints are shown in Table II. The treatment before administration, n (%) of the renin-angiotensin system. Data are expressed as the mean ± SD, median (25%-75%), or number (%). The P values were determined by an *unpaired t-test, **Fisher’s exact test, or ***Mann-Whitney test.

### Table I. Baseline Characteristics

| Demographic characteristics | All patients (n = 53) | Landiolol group (n = 34) | Digoxin group (n = 19) | P value |
|-----------------------------|----------------------|-------------------------|------------------------|---------|
| Male, n (%)                 | 35 (66.0%)           | 21 (62.2%)              | 14 (75.0%)             | 0.55**  |
| Age (years)                 | 66.7 ± 16.1          | 66.1 ± 16.9             | 67.9 ± 14.4            | 0.72*   |
| BMI (kg/m²)                 | 22.8 ± 3.2           | 23.0 ± 3.4              | 22.9 ± 4.8             | 0.91*   |
| Hypertension, n (%)         | 39 (73.6%)           | 24 (70.3%)              | 15 (81.3%)             | 0.50**  |
| Diabetes mellitus, n (%)    | 16 (30.2%)           | 9 (29.7%)               | 7 (31.3%)              | 0.53**  |
| Etiology of cardiomyopathy, n (%) |                      |                        |                        |         |
| Ischemic heart disease      | 11 (20.8%)           | 8 (23.6%)               | 3 (15.8%)              | 0.73*   |
| Valvular disease            | 1 (1.9%)             | 1 (2.9%)                | 0 (0)                  | 0.36*   |
| Hypertensive heart disease  | 2 (3.8%)             | 1 (2.9%)                | 1 (5.3%)               | 1.0*    |
| Dilated cardiomyopathy      | 5 (9.4%)             | 3 (8.8%)                | 2 (10.5%)              | 1.0*    |
| Tachycardia induced cardiomyopathy | 33 (62.3%) | 20 (58.8%)             | 13 (68.4%)             | 1.0*    |
| Others                      | 1 (1.9%)             | 1 (2.9%)                | 0 (0)                  | 1.0*    |
| Hemodynamic parameter       |                      |                        |                        |         |
| Systolic blood pressure (mmHg) | 120.6 ± 27.7        | 122.7 ± 24.9            | 115.9 ± 33.8           | 0.41*   |
| Diastolic blood pressure (mmHg) | 74.34 ± 23.4       | 75.0 ± 23.1             | 73.0 ± 24.8            | 0.78*   |
| Heart rate (beats/minute)   | 142.3 ± 16.8         | 142.9 ± 15.8            | 140.9 ± 19.4           | 0.69*   |
| Laboratory data             |                      |                        |                        |         |
| Creatinine (mg/dL)          | 1.65 ± 2.14          | 1.78 ± 2.31             | 1.53 ± 1.77            | 0.56*   |
| Creatinine Clearance (mg/mL) | 50.3 ± 29.5          | 51.0 ± 30.8             | 48.5 ± 27.0            | 0.82*   |
| BNP (pg/mL)                 | 1118.2 (581.6-1620.5)| 841.5 (466.9-1426.3)    | 1545.0 (696.5-1808.5)  | 0.053***|
| Echocardiography            |                      |                        |                        |         |
| LVEF (%)                    | 23.8 ± 3.9           | 23.6 ± 4.0              | 24.6 ± 3.6             | 0.46*   |
| Treatment before administration, n (%) | 13 (24.5%) | 9 (29.7%)               | 4 (21.1%)              | 1.0**   |
| β-blocker (oral)            | 0 (0)                | 0 (0)                   | 0 (0)                  | 0.56**  |
| Digitalis (oral)            | 22 (41.5%)           | 12 (35.3%)              | 10 (52.6%)             | 0.24**  |
| Diuretic                    | 13 (24.5%)           | 8 (23.6%)               | 5 (26.3%)              | 0.68**  |
| Aldosterone antagonist      | 16 (30.2%)           | 8 (23.6%)               | 8 (42.1%)              | 0.19**  |

BMI indicates body mass index; HR, heart rate; BN, brain natriuretic peptide; LVEF, left ventricular ejection fraction; and RAS-I, inhibitors of the renin-angiotensin system. Data are expressed as the mean ± SD, median (25%-75%), or number (%). The P values were determined by an *unpaired t-test, **Fisher’s exact test, or ***Mann-Whitney test.

The efficacy endpoints are shown in Table II. The rate of a responder at 1 and 2 hours in the landiolol group was the same as that in the digoxin group (11.8% versus 5.3%; odds ratio [OR]: 1.91, 95% confidence interval [CI]: 0.17-101.52, P = 1.0, and 24.2% versus 27.8%; OR: 1.0, 95% CI: 0.24-4.60, P = 1.0, respectively). Conversely, the rate of a responder at 12 and 24 hours in the landiolol group was slightly higher than that in the digoxin group (48.5% versus 27.8%; OR: 2.69, 95% CI: 0.63-13.98, P = 0.21, and 71.0% versus 41.2%; OR: 3.47, 95% CI: 0.82-15.66, P = 0.096, respectively). A multivariate logistic analysis revealed that landiolol treatment was significantly associated with responders at 24 hours (OR: 4.65, 95% CI: 1.47-31.0, P = 0.048). The HR at 24 hours was significantly lower in the landiolol group than in the digoxin group (97.5 ± 17.2 beats/minute versus 111.6 ± 27.1 beats/minute; P = 0.048, respectively). The percent change in the HR from baseline at 1 hour onward was greater in the landiolol group than digoxin group (−12.7

was the same as that in the digoxin group (11.8% versus 5.3%; odds ratio [OR]: 1.91, 95% confidence interval [CI]: 0.17-101.52, P = 1.0, and 24.2% versus 27.8%; OR: 1.0, 95% CI: 0.24-4.60, P = 1.0, respectively). Conversely, the rate of a responder at 12 and 24 hours in the landiolol group was slightly higher than that in the digoxin group (48.5% versus 27.8%; OR: 2.69, 95% CI: 0.63-13.98, P = 0.21, and 71.0% versus 41.2%; OR: 3.47, 95% CI: 0.82-15.66, P = 0.096, respectively). A multivariate logistic analysis revealed that landiolol treatment was significantly associated with responders at 24 hours (OR: 4.65, 95% CI: 1.47-31.0, P = 0.048). The HR at 24 hours was significantly lower in the landiolol group than in the digoxin group (97.5 ± 17.2 beats/minute versus 111.6 ± 27.1 beats/minute; P = 0.048, respectively). The percent change in the HR from baseline at 1 hour onward was greater in the landiolol group than digoxin group (−12.7
0.26 ± 0.06 mg and 0.43 ± 0.13 mg, respectively. There was no significant difference in the concomitant treatment after starting the infusion of landiolol or digoxin within 24 hours (Table III).

Safety endpoint: AEs, all involving hypotension, occurred in two patients in the landiolol group and in zero patients in the digoxin group but was not statistically significant (P = 0.53). Landiolol was discontinued in both patients after hypotension developed. The low BP caused by landiolol recovered immediately after discontinuing it. There were no serious AEs due to landiolol or digoxin. One patient experienced an in-hospital death due to HF after 24 hours in the landiolol group, and the remaining 33 patients were successfully discharged. Conversely, in the digoxin group, all 19 patients were successfully discharged. The rate of a successful discharge did not differ between the two groups (P = 1.0). The average hospitalization also did not show any significant difference between the two groups (23.5 ± 12.6 days versus 25.4 ± 21.9 days, P = 0.65).

Discussion

Main findings: The present study had the following main findings: (1) although landiolol resulted in a significant reduction in the HR from baseline more rapidly than digoxin, the rate of a responder at 2 hours after starting the treatment in the landiolol group was the same as that in the digoxin group. However, landiolol was more effective in reducing the HR than digoxin at 24 hours; (2) the SBP significantly decreased in the landiolol group compared with that in the digoxin group, and a few landiolol-related AEs, such as hypotension, were observed; and (3) careful hemodynamic monitoring is mandatory for the safe use of
landiolol, which resulted in a relatively low achievement rate of responders at 2 hours in the landiolol group.

**Efficacy and safety of landiolol:** It is reported that a rapid HR is both the cause and consequence of worsening HF in patients with AF. Thus, a prompt and appropriate HR control is necessary among patients with HF and depressed LV dysfunction. Landiolol may be useful to control the HR with minimal effects on the cardiac function in these patients as a first-line therapy. However, few studies have analyzed the efficacy and safety of landiolol for patients with AF and severely depressed LV function. Wada, et al. reported that landiolol was not so effective for HR control in patients with AF and severely depressed LV function (LVEF ≤25%). In fact, the rate of responders to landiolol at 2 hours in the present study was much lower than that reported by the J-Land study (24.2% versus 49.6%). The reason is that the mean dose of landiolol at 2 hours was smaller in the present study than in the J-Land study (2.3 ± 1.8 μg/kg/minute versus 6.7 ± 3.2 μg/kg/minute). Previous preclinical evaluations showed that the HR-reducing effect of landiolol for atrial tachyarrhythmias depended on its dose. In the present study, the mean dose of landiolol and rate of responders were very low at 2 hours, but both actually increased at 24 hours (2.3 ± 1.8 μg/kg/minute versus 5.2 ± 2.7 μg/kg/minute; P < 0.01, 24.2% versus 71.0%; P < 0.01, respectively). Consequently, the rate of responders at 24 hours was relatively high. Therefore, we learned from the experience in the present study that it is important that the dose of landiolol be increased more gradually to prevent an acute BP decrease in patients with severely depressed LV function.

**Figure 3.** The time course of the diastolic blood pressure in the patients treated with landiolol and digoxin within 24 hours after starting the treatment. *P < 0.05 versus baseline.

### Table II. Efficacy Endpoints

| Endpoints | Landiolol group (n = 34) | Digoxin group (n = 19) | P value |
|-----------|-------------------------|-----------------------|--------|
| Primary endpoints | | | |
| Responder rate at 1 hour (%) | 4/34 (11.8%) | 1/19 (5.3%) | 1.0* |
| Responder rate at 2 hours (%) | 8/33 (24.2%) | 5/18 (27.8%) | 1.0* |
| Responder rate at 12 hours (%) | 16/33 (48.5%) | 5/18 (27.8%) | 0.21* |
| Responder rate at 24 hours (%) | 22/31 (71.0%) | 7/17 (41.2%) | 0.096* |
| Secondary endpoints | | | |
| HR 1 hour after treatment (beats/minute) | 125.8 ± 23.0 | 134.1 ± 19.2 | 0.22** |
| HR 2 hours after treatment (beats/minute) | 117.3 ± 22.4 | 125.5 ± 20.1 | 0.23** |
| HR 12 hours after treatment (beats/minute) | 106.4 ± 20.9 | 118.5 ± 19.6 | 0.063** |
| HR 24 hours after treatment (beats/minute) | 97.5 ± 17.2 | 111.6 ± 27.1 | 0.048** |
| Percent change in the HR at 1 hour (%) | −12.7 (−19.3 to −5.0) | −1.6 (−9.0 to 1.4) | < 0.01*** |
| Percent change in the HR at 2 hours (%) | −15.5 (−23.1 to −8.6) | −3.3 (−2.2 to 2.1) | 0.071*** |
| Percent change in the HR at 12 hours (%) | −23.7 (−33.3 to −15.2) | −15.4 (−21.8 to −12.4) | 0.036*** |
| Percent change in the HR at 24 hours (%) | −29.8 (−37.8 to −22.7) | −19.1 (−26.2 to −8.4) | 0.016*** |
| Improvement rate of subjective symptoms at 2 hours (%) | 18 (52.9%) | 10 (52.6%) | 0.39* |
| Improvement rate of subjective symptoms at 24 hours (%) | 25 (73.9%) | 15 (73.7%) | 1.0* |

HR indicates heart rate. Data are expressed as the mean ± SD, median (25%-75%), or number (%). The P values were determined by a *Fisher’s exact test, **unpaired t-test, or ***Mann-Whitney test.
occurred in only two patients. The dosage of landiolol was adjusted easily according to the patient’s hemodynamics because of its ultra-short-acting property. In other words, in the patients who are not responsive to landiolol with a gradual up-titration to the maximum tolerated dose, an alternative treatment including electrical cardioversion should be considered.

Comparison of the efficacy of landiolol and digoxin: European and US guidelines state that digoxin may be useful to reduce a rapid ventricular response, but it is only recommended for treatment when other therapeutic options including β blockers cannot be pursued in patients with rapid AF and depressed LV function.17,18 One reason is that β blockers could be preferred over digoxin to treat AF caused by excessive sympathetic nervous activity due to HF in patients with HF.19,20 Indeed, we also observed a better control of the HF with landiolol than with digoxin. However, we need to mention the digoxin dose in the present study. We set the initial dose of digoxin at 0.25 mg to follow the J-Land study.19 However, even if digoxin was administered, some patients with renal dysfunction stopped receiving digoxin or decreased that dosage early before developing digoxin toxicity. In the present study, mean serum creatinine value was 1.53 ± 1.77 mg/dL and mean CrCl was 48.5 ± 27.0 mg/mL for patients receiving digoxin, and approximately 60% or more among them had moderate or severe renal dysfunction (CrCl ≤ 50 mL/minute). We usually tend to avoid the administration of digoxin in patients with renal dysfunction because renal impairment is a well-recognized risk factor for digoxin toxicity.21 The Digitalis in Acute Atrial Fibrillation (DAAF) trial, which examined the effects of intravenously administered digoxin in patients with AF, described the effective dose of digoxin for controlling the HR in detail.22 The mean total dose of digoxin during the study period was less in the present study than in the DAAF trial (0.43 ± 0.13 mg versus 0.88 ± 0.35 mg). However, HF with a significant cardiac output decline can lead to renal dysfunction.22 Actually, the serum creatinine value in the enrolled patients was higher in the present study than in the DAAF trial (1.53 ± 1.77 mg/dl versus 1.08 ± 0.34 mg/dl). Considering that, we might not have administered enough digoxin to reduce the HR for fear of digoxin toxicity. An underdosing of the digoxin dosage might have caused the difference in the therapeutic effects in controlling the HR between landiolol and digoxin. Conversely, the metabolism of landiolol is not affected by the renal function. It may be a big advantage of landiolol over digoxin that landiolol can be administered in an adequate dose regardless of the renal function.

Another notable point in the present study was that the HR reduction was more immediate in the landiolol group than in the digoxin group. However, there were no significant differences between the two groups in the improvement rate of the subjective symptoms within 24 hours after starting the treatment. We could not show that the rapid HR reduction elicited by landiolol compared with that by digoxin contributed to the improvement in the subjective symptoms. Furthermore, in the present study, landiolol could attain better control of the HR than could digoxin; however, it also did not contribute to the improvement in the subjective symptoms. As shown in these results, the HR reduction may not necessarily have been associated with symptomatic relief in these patients. Subjective symptoms are one of the factors for estimating the degree of HF. Unfortunately, we did not estimate the hemodynamic status on the basis of the data acquired from echocardiography or right/left heart catheterization before or after the treatment. Hence, it was difficult to demonstrate that the HR reduction actually contributed to the improvement in the degree of HF based on the hemodynamic status. However, a previous study revealed that the HR reduction contributed to the improvement in the hemodynamic status based on data acquired from right heart catheterization and LV angiography in failing hearts.23 Those findings suggest that it is difficult to evaluate how the relationship of a rapid HR and the hemodynamic status contribute to the subjective symptoms of HF in patients with AF.

Comparison of the safety of landiolol and digoxin: In the present study, two patients in the landiolol group experienced AEs during the follow-up period. Hypotension was reported as an AE in two patients in the landiolol group and in zero patients in the digoxin group. During the use of landiolol, the BP should be carefully monitored in patients with a severely depressed LV function. However, hypotension caused by landiolol recovered after discontinuing it because it has a very short half-life of only 4 minutes.

Limitations: The present study had some potential limitations. First, the present study was a single-center, retrospective, non-randomized, and observational study. The attending physician selected the treatment with landiolol or digoxin. The statistically significant results might not reflect the true effect and should be interpreted carefully. Second, the number of patients was small. Third, the

---

### Table III. Concomitant Treatment with Landiolol Or Digoxin

|                     | Landiolol group (n = 34) | Digoxin group (n = 19) | P value |
|---------------------|--------------------------|------------------------|---------|
| Loop diuretics      | 20 (58.8%)               | 11 (57.8%)             | 0.63*   |
| Carperitide         | 18 (52.9%)               | 7 (36.8%)              | 1.0*    |
| PDE3 inhibitor      | 1 (2.9%)                 | 2 (10.5%)              | 0.20*   |
| Catecholamine       | 3 (8.8%)                 | 4 (21.0%)              | 0.17*   |
| NIPPV               | 1 (2.9%)                 | 1 (5.3%)               | 0.51*   |
| Intubation          | 0 (0)                    | 0 (0)                  | 1.0*    |

PDE3 indicates phosphodiesterase 3, and NIPPV, non-invasive positive pressure ventilation. Data are expressed as the number (%). The P values were determined by a *Fisher’s exact test.
treatment period was short, so we did not evaluate how the significant and rapid decrease in the HR elicited by landiolol contributed to the medium- and long-term prognoses. Future large-scale randomized studies should be conducted.

Conclusions

Landiolol could be more effective in controlling the HR associated with AF than digoxin, even in patients with severely depressed LV function. However, careful hemodynamic monitoring is necessary during the administration of landiolol.

Disclosure

Conflicts of interest: T.I. has received grant support through his institution from Daiichi Sankyo and Bristol-Myers Squibb and honoraria for lectures from Bayer Healthcare, Daiichi Sankyo, Bristol-Myers Squibb, Pfizer, Tanabe-Mitsubishi, and Ono Pharmaceutical. Regarding the present study, all authors declare that there are no potential conflicts of interest.

References

1. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003; 91: 2D-8D.
2. Bui AL, Grau-Sepulveda MV, Hernandez AF, et al. Admission heart rate and in-hospital outcomes in patients hospitalized for heart failure in sinus rhythm and in atrial fibrillation. Am Heart J 2013; 165: 567-74.
3. Clark DM, Plumb VJ, Epstein AE, Kay GN. Hemodynamic effects of an irregular sequence of ventricular cycle lengths during atrial fibrillation. J Am Coll Cardiol 1997; 30: 1039-45.
4. Rawles JM. What is meant by a “controlled” ventricular rate in atrial fibrillation? Br Heart J 1990; 63: 157-61.
5. Hasenfuss G, Holubarsch C, Hermann HP, Ashtheimer K, Pleske B, Just H. Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. Eur Heart J 1994; 15: 164-70.
6. Hess PL, Sheng S, Matsouaka R, et al. Strict versus lenient versus poor rate control among patients with atrial fibrillation and heart failure (from the get with the guidelines - heart failure program). Am J Cardiol 2020; 125: 894-900.
7. Takahama H, Yokoyama H, Kada A, et al. The extent of heart rate reduction during hospitalization using beta-blockers, not the achieved heart rate itself at discharge, predicts the clinical outcome in patients with acute heart failure syndromes. J Cardiol 2013; 61: 58-64.
8. The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Intravenous digoxin in acute atrial fibrillation: Results of a randomized, placebo-controlled multicentre trial in 239 patients: The Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Eur Heart J 1997; 18: 649-54.
9. Gheorghiade M, Adams Jr KF, Colucci WS. Digoxin in the management of cardiovascular disorders. Circulation 2004; 109: 2959-64.
10. Kobayashi S, Susa T, Tanaka T, et al. Low-dose β-blocker in combination with milrinone safely improves cardiac function and eliminates pulsus alternans in patients with acute decompensated heart failure. Circ J 2012; 76: 1646-53.
11. Nitta D, Kinugawa K, Imamura T, et al. An experience of landiolol use for an advanced heart failure patient with severe hypotension. Int Heart J 2015; 56: 564-7.
12. Yamashita T, Nakasui Y, Mizutani H, Sumitani K. A prospective observational survey on landiolol in atrial fibrillation/atrial flutter patients with chronic heart failure-AF-CHF landiolol survey. J Cardiol 2019; 74: 418-25.
13. Nagai R, Kinugawa K, Inoue H, et al. Urgent management of rapid heart rate in patients with atrial fibrillation/flutter and left ventricular dysfunction: comparison of the ultrashort-acting beta 1-selective blocker landiolol with digoxin (J-Land Study). Circ J 2013; 77: 908-16.
14. Van Gelder IC, Groenveld HF, Crijns HJ, et al. RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010; 362: 1363-73.
15. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial fibrillation begets heart failure and vice versa: Temporal associations and differences in preserved versus reduced ejection fraction. Circulation 2016; 133: 484-92.
16. Wada Y, Aiba T, Tsujita Y, et al. Practical applicability of landiolol, an ultra-short-acting β1-selective blocker, for rapid atrial and ventricular tachyarrhythmias with left ventricular dysfunction. J Arrhythm 2016; 32: 82-8.
17. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
18. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the heart failure society of America. Circulation 2017; 136: e137-64.
19. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. J Am Coll Cardiol 1999; 33: 304-10.
20. Eichhorn EJ, Gheorghiade M. Digoxin. Prog Cardiovasc Dis 2002; 44: 251-66.
21. Sae-Lim O, Doungngern T, Jaisue S, et al. Prediction of serum digoxin concentration using estimated glomerular filtration rate in Thai population. Int J Gen Med 2019; 12: 455-63.
22. Tugel C, Bunsal N. Heart failure in patients with kidney disease. Heart 2017; 103: 1848-53.