Journal of Cardiology 73 (2019) 386–393

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Comparison of heart rate reduction effect and safety between bisoprolol transdermal patch and bisoprolol fumarate oral formulation in Japanese patients with persistent/permanent atrial fibrillation (BISONO-AF study)

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ARTICLE INFO

Article history:
Received 12 September 2018
Received in revised form 7 November 2018
Accepted 14 November 2018
Available online 24 December 2018

Keywords:
Atrial fibrillation
Bisoprolol transdermal patch
Heart rate control therapy
Noninferiority clinical trial

ABSTRACT

Background: TY-0201 (TY) is a transdermal patch containing bisoprolol. The objectives of this study were to evaluate the noninferiority of TY to bisoprolol oral formulation (BO) in patients with persistent or permanent atrial fibrillation (AF).
Methods: In this multicenter, double-blind, comparative study, Japanese patients with persistent or permanent AF were randomized to TY 4-mg (n = 55), TY 8-mg (n = 55), BO 2.5-mg (n = 55), or BO 5-mg (n = 55) groups. All patients were administered TY 4 mg or BO 2.5 mg once a day for the first 2 weeks. Patients in the TY 8-mg or BO 5-mg group, in whom dose escalation was required, were administered TY 8 mg or BO 5 mg for a further 2 weeks, and the other patients continued to receive TY 4 mg or BO 2.5 mg. The primary endpoint was a change in 24-h mean heart rate (mHR) from baseline by Holter electrocardiogram, and the noninferiority of the TY 4-mg to the BO 2.5-mg groups and that of the TY 8-mg to the BO 5-mg groups were evaluated.
Results: Adjusted means of changes in 24-h mHR from baseline in the TY 4-mg, TY 8-mg, BO 2.5-mg, and BO 5-mg groups were −12.3, −13.8, −12.7, and −14.3 bpm, respectively. Differences between values for the TY 4-mg and BO 2.5-mg groups and between values for the TY 8-mg and BO 5-mg groups were estimated to be 0.5 (95% CI: −1.9 to 2.9) and 0.5 (−1.9 to 2.9) bpm, respectively, which did not exceed the predefined noninferiority margins. The incidence of adverse events did not differ between the groups.
Conclusions: In Japanese patients with persistent or permanent AF, TY 4 mg and TY 8 mg had heart rate-reducing effects similar to those of BO 2.5 mg and BO 5 mg, respectively.

Introduction

Atrial fibrillation (AF) is one of the most frequently diagnosed arrhythmias, with its prevalence increasing with patient age. Both rhythm control and rate control therapies are effective for AF, and β-blockers are recommended for rate control therapy by US, European, and Japanese guidelines for the management of patients with AF [1–3]. In the J-RHYTHM study [4], the Fushimi AF registration study [5], and the SAKURA AF registration study [6] conducted in Japan, β-blockers were prescribed in >50% of patients who received rate control therapy.

As AF is common in the elderly and they often have difficulty in using oral drugs due to impaired swallowing function from aging or cerebral infarction, we assumed that a transdermal formulation is useful for those patients.

TY-0201 (TY) is a transdermal patch containing β_1-blocker bisoprolol, which is a free base of bisoprolol fumarate available as an oral formulation (BO) that is widely used in chronic heart failure, essential hypertension, angina pectoris, and AF. TY 8 mg was designed to maintain a sustained concentration of bisoprolol in plasma by having a lower peak concentration and a higher

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https://doi.org/10.1016/j.jjcc.2018.11.009

trough concentration than BO 5 mg. The antihypertensive effect of TY 8 mg is noninferior to that of BO 5 mg [7] and is dose-dependent in the range of TY 2–8 mg in patients with essential hypertension [8]. Also, it has been reported that TY 4 mg was effective for treating frequent premature ventricular contractions [9]. Although TY seems to have similar effects as BO in AF, the optimal dose is not clear.

We conducted the multicenter, randomized, double-blind study to evaluate noninferiority of BISO prolol traNsdermal patch to bisoprolol Oral formulation in Japanese patients with persistent/permanent Atrial Fibrillation (BISONO-AF) to compare TY 4 mg to BO 2.5 mg and TY 8 mg to BO 5 mg, respectively.

Methods

Patients

This study enrolled patients who fulfilled the following criteria: outpatients aged between 20 and 80 years with persistent or permanent AF; resting heart rate (HR) at randomization ≥80 bpm on the 12-lead electrocardiogram (ECG); provision of written informed consent. Exclusion criteria of this study included: cardiogenic shock, heart failure (New York Heart Association functional class II–IV), cardiomyopathy, myocarditis, cardiac function deterioration (left ventricular ejection fraction <50%); severe arrhythmia, including atrioventricular block (II–III), sino-atrial block, and sick sinus syndrome; HR controlled by a pacemaker, implantable cardioverter defibrillator, or cardiac resynchronization therapy; patients who had undergone electrical defibrillation or catheter ablation; systolic blood pressure at randomization <110 mmHg; patients who had poor skin condition at the patch application site. Detailed exclusion criteria are mentioned in Supplementary Table 1.

Study design

This multicenter, randomized, double-blind, double-dummy, active-controlled comparative study was conducted at 41 institutions in Japan from February 2015 to April 2016.

Patients were randomly assigned to TY 4-mg, TY 8-mg, BO 2.5-mg, or BO 5-mg groups at a ratio of 1:1:1:1 by a dynamic allocation method adjusted for baseline 24-h mean HR (mHR) by Holter ECG and for history of treatment with β-blockers within 6 months before randomization. During period I, patients were treated with TY 4 mg once daily in the TY 4-mg and TY 8-mg groups, and BO 2.5 mg once daily in the BO 2.5-mg and BO 5-mg groups for 2 weeks. At the end of period I, patients were evaluated for the need to increase dose. Patients fulfilling the dose escalation criteria in the TY 8-mg group or BO 5-mg group were administered TY 8 mg or BO 5 mg, respectively, and patients who did not meet the criteria and patients in the TY 4-mg group or BO 2.5-mg group were administered the same dose as that in period I for 2 additional weeks designated as period II (Fig. 1). Concomitant use of β-blockers, calcium channel blockers (diltiazem and verapamil), antiarrhythmics, and digitalis was prohibited from 13 days before randomization to the end of treatment period.

To evaluate the efficacy, we measured mHR by Holter ECG for 24 h and resting HR by 12-lead ECG. For safety assessment, 12-lead ECG, blood pressure, and clinical laboratory tests were conducted, and adverse events (AEs) were investigated.

The study was approved by the institutional review board at each participating institution before starting the study, and it was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. This study has been registered in the Japan Pharmaceutical Information Center, number JapicCTI-152789.

Dose escalation criteria

At the end of period I, treatment dose was increased in patients with systolic blood pressure ≥110 mmHg and if they met one of the following criteria: (1) the resting HR in 12-lead ECG was ≥80 bpm, or (2) the resting HR in 12-lead ECG was 70–79 bpm and subjective symptoms did not resolve.

Holter ECG

Holter ECG, Cardy 303 pico+ (Suzuken, Nagoya, Japan) was used to measure 24-h ECG profile during daily routine life. Holter ECG data were analyzed using Cardy Analyzer, Ver. 4.75.

Study endpoints

Change in 24-h mHR after 4-week treatment from baseline was the primary endpoint based on which the noninferiority of TY 4 mg to BO 2.5 mg and that of TY 8 mg to BO 5 mg was primarily determined. The measurement of difference in 24-h mHR between the TY 4-mg and TY 8-mg groups was the secondary objective, based on which enhancement in the HR-lowering effect upon escalating the dose of TY from 4 mg to 8 mg was evaluated. The secondary endpoints for efficacy were 24-h mHR, maximum HR, minimum HR and circadian changes in hourly mHR at Week 4, and resting HR and the proportion of patients with resting HR <80 bpm at each observation point. For resting HR at Week 4 [the last observation carried forward (LOCF)], the results after 4 weeks of treatment were used; in case the final measurement was not made, LOCF was used for analysis.

The safety of TY was assessed based on the incidences of AEs and adverse drug reactions. The reported terms for AEs were coded using MedDRA/J version 17.1.

Statistical analysis

Sample size and noninferiority margin

We assumed that HR reduction by placebo, BO 2.5 mg, and BO 5 mg as 0, −12.2, and −15 bpm based on results from previous studies [10–12]. The noninferiority margins of BO 2.5 mg and BO 5 mg were defined to be 6 and 7.5 bpm, respectively, considering 50% difference from the placebo.

Sample size was calculated from each condition for comparing the TY 8-mg and BO 5-mg groups, and that for comparing the TY 4-mg and BO 2.5-mg groups, respectively, and the larger one was selected for this study. Details of the calculation condition are shown below.

Assuming that the standard deviation of a change in HR for the BO 5-mg group was 12 bpm, if the difference between the TY 8-mg and BO 5-mg groups is zero bpm, when the significance level is 2.5% (one-sided) and the power is 80%, the number of patients for confirming the noninferiority was calculated to be at least 42 patients per group. We set it to 47 patients per group, considering drop outs.

Analysis of endpoints

The values are presented as mean ± standard deviation and/or 95% confidence interval (CI) for continuous variables, or as n (%) for categorical variables. The statistical significance level was set to 0.05 (two-sided), unless otherwise noted. When interval estimation was performed, the CI was set to 95%. Efficacy analysis was performed for a full analysis set (FAS) by including all patients who took the study drugs at least once, excluding patients who violated Good Clinical Practice, did not meet eligibility criteria, or did not yield any efficacy data. Sensitivity analysis of the primary endpoint was performed for a per-

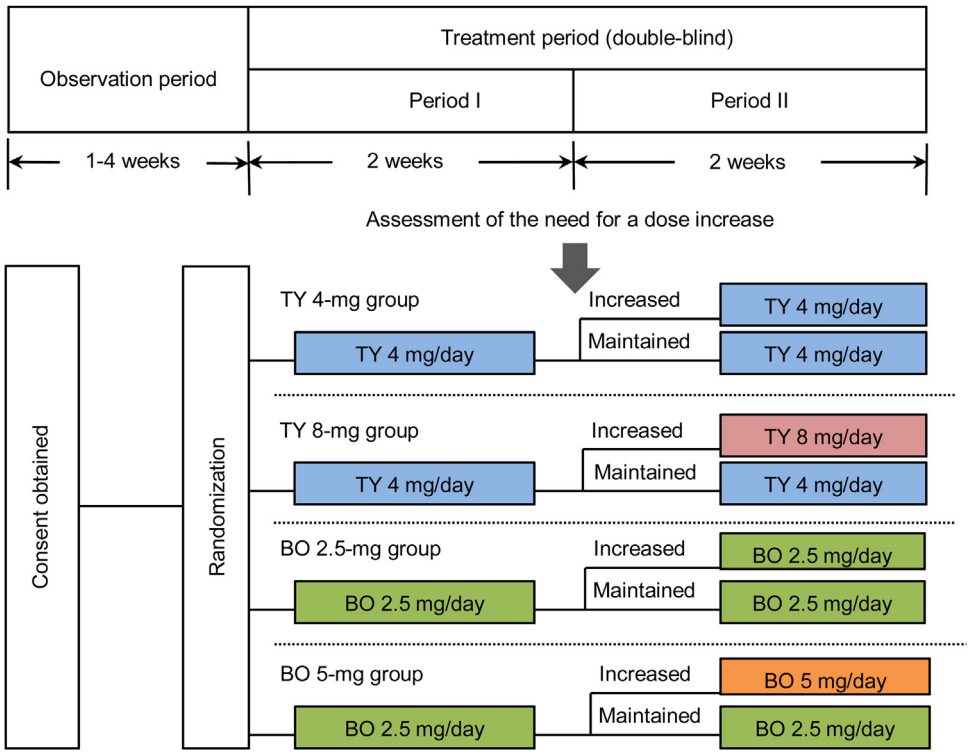


Fig. 1. Study design. TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation.

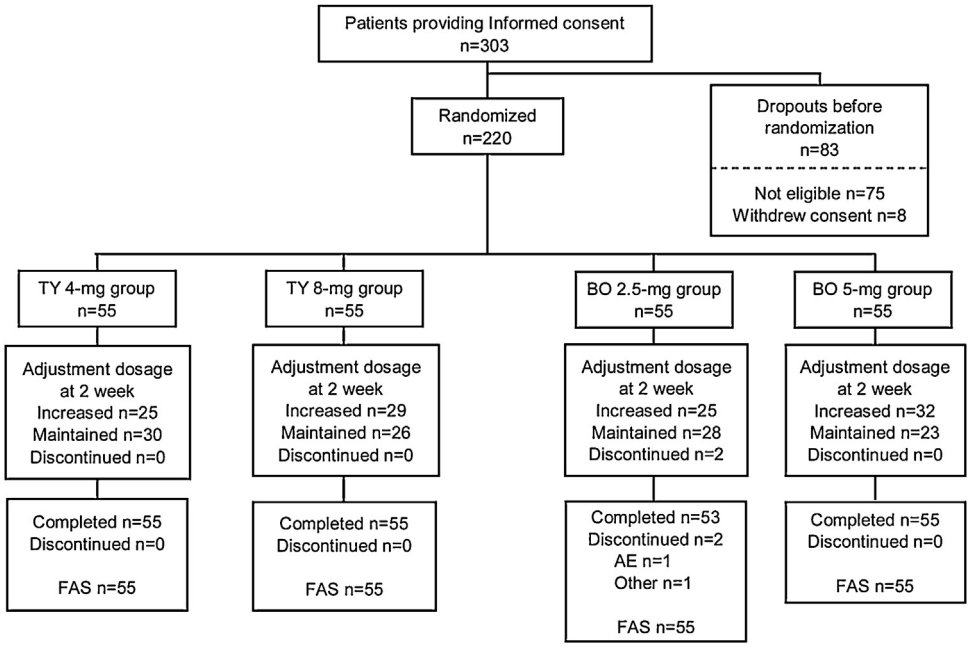


Fig. 2. Patient disposition. TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation; FAS, full analysis set.

protocol set (PPS) by excluding patients from FAS who violated the major protocol. For evaluating the primary endpoint, i.e. a change in 24-h mHR from baseline, analysis of covariance (ANCOVA) was performed using "treatment group," "pretreatment with β-blocker within 6 months before randomization," and "24-h mHR at baseline" as covariates, and the adjusted mean and its 95% CI for each treatment group were calculated. The point estimates and the 95% CIs of the differences between the TY 4-mg and BO 2.5-mg groups, and between the TY 8-mg and BO 5-mg groups were calculated, and noninferiority was evaluated. When the noninferiority of both the TY 4-mg group to BO 2.5-mg group and the TY 8-mg group to BO 5-mg group was confirmed, the noninferiority of TY to BO would be established.

For evaluating the dose escalation effect of TY 8 mg as the secondary objective, ANCOVA was conducted in a similar manner as previously mentioned for the primary objective. The difference between the TY 4-mg and TY 8-mg groups was calculated and the escalation effect was assessed with point estimates.

Table 1
Baseline patient characteristics.

	TY 4-mg group	TY 8-mg group	BO 2.5-mg group	BO 5-mg group	*p*-Value
n	55	55	55	55	
Age (years)	67.9 ± 9.2	70.0 ± 8.5	67.9 ± 8.1	67.7 ± 9.0	0.4823†
≥65	38 (69.1%)	41 (74.5%)	42 (76.4%)	42 (76.4%)	0.8129‡
≥75	15 (27.3%)	20 (36.4%)	13 (23.6%)	11 (20.0%)	0.2593‡
Male	43 (78.2%)	44 (80.0%)	36 (65.5%)	44 (80.0%)	0.2587†
Height (cm)	164.63 ± 9.09	163.88 ± 9.15	163.84 ± 8.20	163.89 ± 7.67	0.9546†
Weight (kg)	68.46 ± 14.35	66.69 ± 13.78	65.44 ± 13.14	67.59 ± 14.09	0.6966†
Body mass index (kg/m^2)	25.07 ±3.74	24.63 ± 3.24	24.20 ± 3.44	25.02 ± 3.97	0.5596†
Holter ECG					
Mean heart rate (bpm)	89.5 ± 14.4	91.6 ± 13.8	89.5 ± 12.3	90.0 ± 10.5	0.7930†
≥100	12 (21.8%)	11 (20.0%)	11 (20.0%)	10 (18.2%)	0.9953‡
Maximum heart rate (bpm)	183.9 ± 26.2	182.0 ± 23.4	177.6 ± 29.1	184.1 ± 24.7	0.5276†
Minimum heart rate (bpm)	48.7 ± 9.1	50.3 ± 9.2	50.7 ± 7.5	50.2 ± 7.3	0.6026†
Mean heart rate on resting 12-lead ECG (bpm)	93.6 ± 13.0	97.9 ± 15.1	91.6 ± 9.1	94.5 ± 10.7	0.0573†
Systolic blood pressure (mmHg)	132.0 ± 14.0	128.4 ± 14.3	131.1 ± 14.6	129.7 ± 11.6	0.5413†
Diastolic blood pressure (mmHg)	80.5 ± 11.3	79.6 ±13.4	81.3 ± 12.5	81.3 ± 12.5	0.8772†
Duration of atrial fibrillation (years)	4.06 ±5.09	5.94 ± 4.95	6.25 ± 5.94	5.43 ± 6.61	0.1939†
Concomitant diseases					
Hypertension	39 (70.9%)	36 (65.5%)	36 (65.5%)	44 (80.0%)	0.2859‡
Dyslipidemia	16 (29.1%)	28 (50.9%)	23 (41.8%)	26 (47.3%)	0.1028‡
Diabetes mellitus	15 (27.3%)	16 (29.1%)	8 (14.5%)	11 (20.0%)	0.2324‡
Hyperuricemia	13 (23.6%)	19 (34.5%)	13 (23.6%)	18 (32.7%)	0.4558‡
Use of a β blocker[a]	12 (21.8%)	11 (20.0%)	11 (20.0%)	12 (21.8%)	1.000‡
Previous AF medication					
None	30 (54.5%)	26 (47.3%)	31 (56.4%)	30 (54.5%)	0.8071‡
Ca channel blocker[b]	5 (9.1%)	6 (10.9%)	4 (7.3%)	3 (5.5%)	0.8432‡
Digoxin	13 (23.6%)	13 (23.6%)	11 (20.0%)	11 (20.0%)	0.9492‡
Antiarrhythmic drug	3 (5.5%)	5 (9.1%)	2 (3.6%)	0 (0.0%)	0.1515‡
eGFR (mL/min/1.73 m^2)					
≥90	4 (7.3%)	2 (3.6%)	3 (5.5%)	3 (5.5%)	0.8975‡
60–89	34 (61.8%)	31 (56.4%)	36 (65.5%)	35 (63.6%)	
30–59	17 (30.9%)	22 (40.0%)	16 (29.1%)	17 (30.9%)	

Values are number of patients (%), or mean ± standard deviation.
AF, atrial fibrillation; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation.
† *p*-Values were calculated using analysis of variance.
‡ *p*-Values were calculated using Fisher's exact test.
[a] Use of a β-blocker within 6 months before randomization.
[b] Ca channel blocker used was diltiazem or verapamil.

The safety analysis was performed on a population consisting of all patients who received the study drugs at least once and had ≥one safety assessment.

All analyses were performed using SAS version 9.3 (SAS Institute Japan Ltd., Tokyo, Japan).

Results

Patient characteristics

A total of 220 patients were considered eligible and were randomized to TY 4-mg, TY 8-mg, BO 2.5-mg, and BO 5-mg groups with 55 patients in each group (Fig. 2). In the BO 2.5-mg group, one patient withdrew due to AE occurrence and another based on the doctor's indication. The number of patients in whom dose escalation was considered necessary at Week 2 in the TY 4-mg, TY 8-mg, BO 2.5-mg, and BO 5-mg groups were 25, 29, 25, and 32, respectively. Holter ECG data at Week 4 were missing for 5 patients due to dropout ($n = 2$) and poor recording ($n = 3$). Baseline characteristics are shown in Table 1. There were no differences among the groups at baseline.

Efficacy

mHR on Holter ECG

At Week 4, the adjusted means of change in 24-h mHR from baseline, which was the primary endpoint, in the TY 4-mg, TY 8-

Table 2
Changes in 24-h mean heart rate at Week 4.

	TY 4-mg group	TY 8-mg group	BO 2.5-mg group	BO 5-mg group
Baseline				
N	55	55	55	55
Mean ± SD	89.5 ± 14.4	91.6 ± 13.8	89.5 ± 12.3	90.0 ± 10.5
At Week 4				
N	55	55	51	54
Mean ± SD	77.8 ± 11.9	77.9 ± 10.9	77.5 ± 11.7	76.0 ± 8.8
Change from baseline				
Mean ± SD	−11.6 ± 6.9	−13.7 ± 8.3	−12.1 ± 6.3	−13.7 ± 7.8
Adjusted means of change from baseline at Week 4 (Estimates (95% CI))	−12.3 (−14.1 to −10.5)	−13.8 (−15.6 to −12.0)	−12.7 (−14.6 to −10.9)	−14.3 (−16.0 to −12.5)

TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation; SD, standard deviation; CI, confidence interval.

Table 3
Differences between the treatment groups versus comparison groups.

Treatment group	Comparison group	Difference (95% CI)[a]	*p*-Value
TY 4-mg group	BO 2.5-mg group	0.5 (−1.9 to 2.9)	0.7059
TY 8-mg group	BO 5-mg group	0.5 (−1.9 to 2.9)	0.6884
TY 8-mg group	TY 4-mg group	−1.5 (−3.8 to 0.9)	0.2174
BO 5-mg group	BO 2.5-mg group	−1.5 (−3.9 to 0.9)	0.2205

TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation.
[a] Difference = treatment group − comparison group.

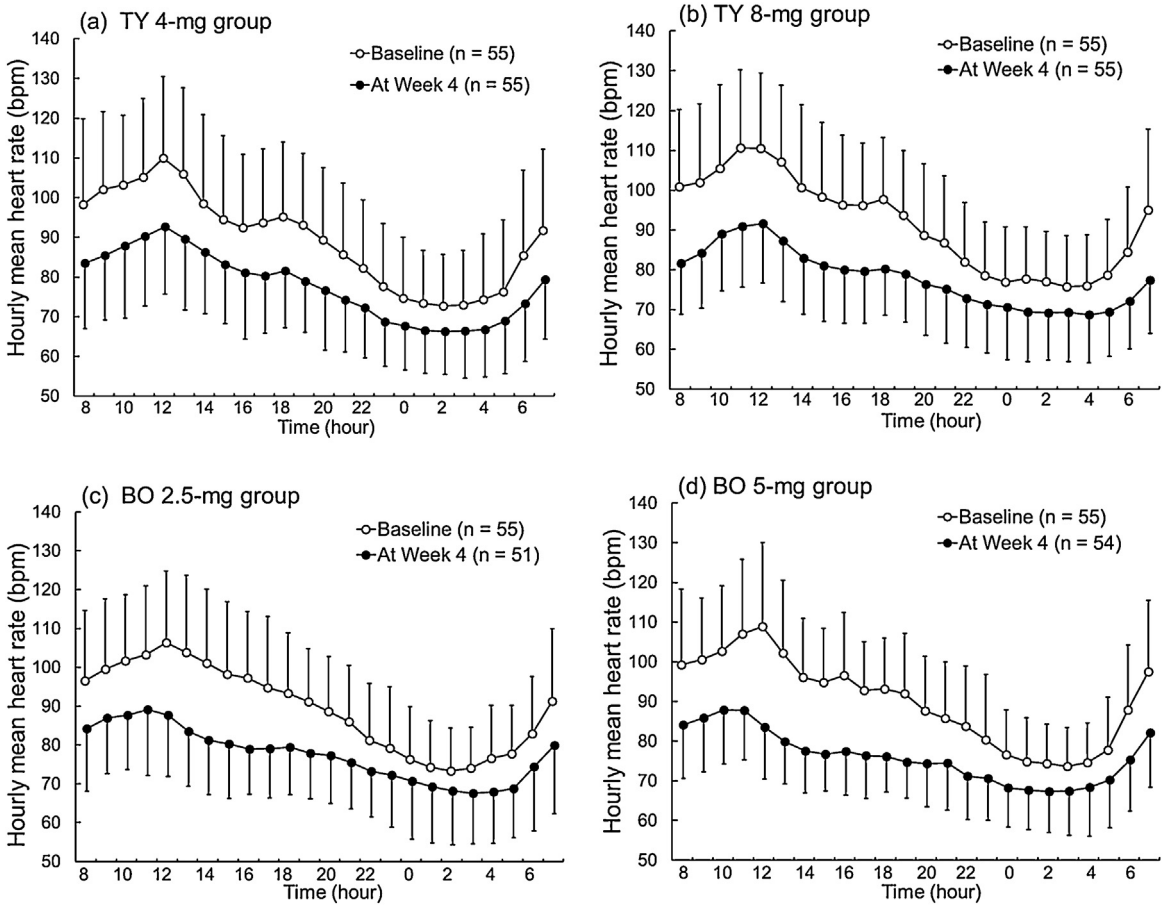


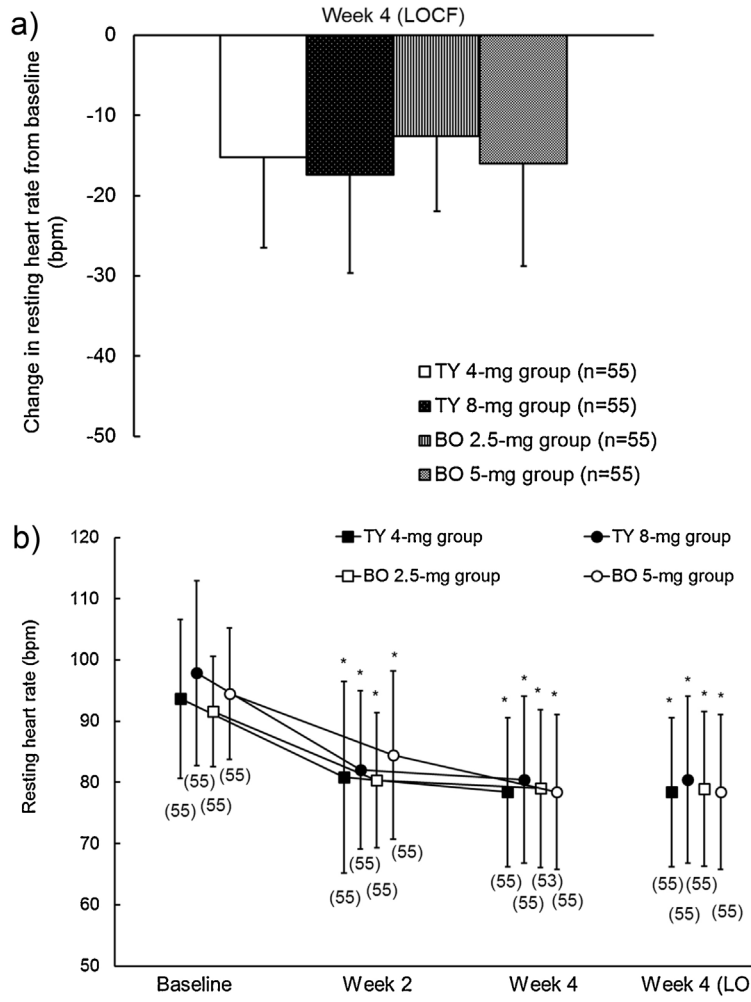
Fig. 3. Changes in the hourly mean heart rate by 24-h Holter electrocardiogram monitoring. Each symbol and bar represents the mean and standard deviation. TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation.

mg, BO 2.5-mg, and BO 5-mg groups showed significant differences (Table 2). The difference between the adjusted means of change in 24-h mHR from baseline in the TY 4-mg and BO 2.5-mg groups was estimated to be 0.5 (−1.9 to 2.9, Table 3), and the upper limit of its 95% CI did not exceed the predefined noninferiority margin (6 bpm). Similarly, the difference between the TY 8-mg and BO 5-mg groups was estimated to be 0.5 (−1.9 to 2.9, Table 3) bpm, and the upper limit of its 95% CI did not exceed the predefined noninferiority margin (7.5 bpm). These indicated that the noninferiority of TY to BO was established. The difference between the adjusted means in change in 24-h mHR from baseline in the TY 8-mg and TY 4-mg groups was estimated as −1.5 (−3.8 to 0.9) bpm; therefore, the reduction in 24-h mHR was greater for the TY 8-mg group than for the TY 4-mg group. The value was similar to the difference between the BO 5-mg group and BO 2.5-mg group. The analysis in PPS showed similar results and the robustness of the results was confirmed.

Regarding circadian changes, hourly mHR in all groups decreased significantly from baseline over 24 h, and the decrease in hourly mHR was greater during the day than during the night (Fig. 3). Changes in maximum and minimum HR were shown in Supplementary Table 2. The number of patients with RR interval ≥3 s at baseline and Week 4 were respectively 6 and 11 patients in the TY 4-mg group, 4 and 10 patients in the TY 8-mg group, 2 and 5 patients in the BO 2.5-mg group, and 3 and 9 patients in the BO 5-mg group.

Resting HR on 12-lead ECG

At Week 4 (LOCF), in all groups, resting HR on 12-lead ECG decreased significantly (Fig. 4), and the proportion of patients who



Group	Baseline	Week 2	Week 4	Week 4 (LOCF)
TY 4-mg group	93.6±13.0	80.9±15.7	78.4±12.2	78.4±12.2
TY 8-mg group	97.9±15.1	82.0±12.9	80.5±13.7	80.5±13.7
BO 2.5-mg group	91.6±9.1	80.3±11.1	79.0±12.9	78.9±12.7
BO 5-mg group	94.5±10.7	84.5±13.8	78.5±12.6	78.5±12.6

Fig. 4. Change in resting heart rate from baseline to endpoint by 12-lead electrocardiogram (a) and over time (b). Values are the mean ± standard deviation (full analysis set using the last observation carried forward method). $^{*}p < 0.001$ (paired *t*-test versus baseline). LOCF, last observation carried forward; TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation.

achieved the target resting HR in the TY 4-mg, TY 8-mg, BO 2.5-mg, and BO 5-mg groups were 56.4%, 54.5%, 60.0%, and 58.2%, respectively. The changes in resting HR and the proportion of patients who achieved target resting HR in the TY 4-mg and TY 8-mg groups were similar to those in the BO 2.5-mg and BO 5-mg groups, respectively.

Safety

Blood pressure

Throughout the treatment period, blood pressure decreased mildly in all groups (Supplementary Fig. 1).

AEs

The incidence of AEs in the two groups of TY was not different between the two groups of BO (Table 4). A serious AE (acute myocardial infarction) occurred in the BO 5-mg group. This was improved with appropriate treatment without discontinuing the study. An AE leading to study discontinuation (cardiac failure) occurred in the BO 2.5-mg group. The symptoms improved by treatment with appropriate medication after discontinuing the study drug. Mild AEs at the patch application site were observed in 3 patients in the two groups of TY.

Discussion

The main findings of the present study were as follows: (1) the 24-h mHR-lowering effects of TY 4 mg and TY 8 mg were noninferior to BO 2.5 mg and BO 5 mg, respectively; (2) the effect of dose escalation from TY 4 mg to TY 8 mg was confirmed by the change in 24-h mHR, which was comparable to the effect of dose increase from BO 2.5 mg to BO 5 mg; (3) the reduction in HR in the TY groups was greater during the day than during the night; (4) All AEs at the application site were mild in the TY groups, and the incidence of other AEs were similar between the TY and BO groups.

Table 4
Adverse events.

	TY 4-mg group ($n=55$)	TY 8-mg group ($n=55$)	BO 2.5-mg group ($n=55$)	BO 5-mg group ($n=55$)
AE	14 (25.5%)	12 (21.8%)	15 (27.3%)	16 (29.1%)
AE related to study drug	6 (10.9%)	5 (9.1%)	5 (9.1%)	3 (5.5%)
Serious AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
AE leading to study discontinuation	0 (0.0%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
AE excluding application site	12 (21.8%)	11 (20.0%)	14 (25.5%)	14 (25.5%)
AE at application site[a]	2 (3.6%)	1 (1.8%)	2 (3.6%)	2 (3.6%)
Application site dermatitis	1 (1.8%)	1 (1.8%)	1 (1.8%)	1 (1.8%)
Application site pruritus	1 (1.8%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Application site exfoliation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.8%)
AE[b]				
Cardiac failure	2 (3.6%)	1 (1.8%)	1 (1.8%)	0 (0.0%)
Nasopharyngitis	1 (1.8%)	1 (1.8%)	2 (3.6%)	4 (7.3%)
Liver function test abnormal	0 (0.0%)	2 (3.6%)	1 (1.8%)	0 (0.0%)
Dermatitis contact	1 (1.8%)	0 (0.0%)	2 (3.6%)	3 (5.5%)

Values are expressed as the number of subjects (%).
TY, transdermal patch containing bisoprolol; BO, bisoprolol oral formulation; AE, adverse event.
[a] In the BO 2.5-mg and BO 5-mg groups, adverse events were caused by TY placebo.
[b] Occurring in ≥2% of patients in any treatment groups.

The dosage regimen for BO in patients with AF in Japan is defined as the starting dose of 2.5 mg, which may be increased to 5 mg if the effect is insufficient. In the present study, the HR-reducing effects in the TY 4-mg and BO 2.5-mg groups, and the effects in the TY 8-mg and BO 5-mg groups showed similar measurements respectively by both Holter ECG and resting 12-lead ECG. We found that the dose of TY was shown to be increased to TY 8 mg if TY 4 mg is the starting dose and the effect is insufficient. In the application of hypertension, the blood pressure-lowering effect of TY 8 mg was similar to that of BO 5 mg [7], and the findings in this study were consistent. Diurnal variation in hourly mHR in the TY groups showed a significant reduction from baseline at all times, as expected from previous studies [10,13], and no induction of bradycardia during the night. It is considered that the HR-lowering effect of TY is maximum in the early morning when the HR is rising or in the condition of high HR due to sympathetic input; therefore, TY is more effective in patients with sympathetic nervous tension.

Beta-blockers are recommended for rate control therapy according to AF guidelines in Japan, the USA, and the EU, for which only oral and intravenous formulations are available; therefore, there are several benefits of using TY, a transdermal formulation. TY can improve drug adherence because both patients and persons concerned can check for the presence or absence of the TY patch through direct visual observation to appropriately monitor drug therapy. As another view point, TY can be used in AF patients with a condition that makes them unsuitable for oral administration as well as ordinary AF patients: impaired swallowing function from aging, and cerebral infarction as a complication of AF. In addition, AF is the most common arrhythmia in the perioperative period, and injections of ultra-short-acting β-blockers are used for its treatment, but oral administration after intravenous administration may be impossible in some cases. Recently, the prevention of perioperative AF has also gained attention, and it has been reported that bisoprolol was significantly less likely to cause perioperative AF in cardiac surgery patients with poor cardiac function than carvedilol [14]. Furthermore, discontinuation of preoperative β-blockers increases the incidence of postoperative AF [15], and TY, which is a dosage form that can be administered perioperatively, may be useful. Thus, TY can provide a new treatment option for various cases as a transdermal patch.

Overall, TY was well tolerated. In using TY in the clinical setting, it is assumed that not only AEs at application site but also those specific for β-blockers such as hypotension, heart failure, and bradycardia will occur. Careful observation is necessary for elderly patients because of the high risk of developing AEs due to decreased physiological function, multidrug therapy, or various complications.

The present study had several limitations. Firstly, in the TY 8-mg or BO 5-mg groups, patients in whom dose escalation was not considered essential continued treatment with TY 4 mg or BO 2.5 mg, respectively. Therefore, the HR-reducing effect was underestimated. Secondly, the treatment period was 4 weeks; therefore, the long-term effect could not be clarified. Thirdly, we did not set a placebo group concerning ethical aspects. Fourthly, we did not evaluate the prognosis or the quality of life; therefore, it is necessary to evaluate them in a large-scale study in the future.

Conclusions

TY 4 mg and TY 8 mg have HR-lowering effects similar to those of BO 2.5 mg and BO 5 mg, respectively, and their effects persisted for 24 h. The enhancement in the HR-lowering effect of TY upon increasing the dose from 4 mg to 8 mg was also observed. Although AEs at the patch application site were observed, TY was tolerable, and AEs excluding the patch application site were similar between the TY and BO groups.

Funding

This research was supported by TOA EIYO Ltd.

Conflict of interests

Takeshi Yamashita and Takanori Ikeda received consultancy fees from TOA EIYO Ltd. Yasuhiko Akita is an employee of TOA EIYO Ltd.

Acknowledgments

We thank Dr Naoki Uchida for his advice on the study and acknowledge the investigators who are listed in Appendix A and the project staff of the sponsor for their support and contribution throughout the study.

Appendix A

List of investigators and study sites for the BISONO-AF study

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Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2018.11.009.

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