Do the Efficacy and Safety of Treatment with Landiolol, an Ultra-short-acting β1-Selective Blocker, Differ in the Urgent Management of Rapid Atrial Fibrillation between Patients Complicated with Cardiac Versus Non-cardiac Disease?

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Purpose : Atrial fibrillation (AF) is highly prevalent in patients with non-cardiac diseases and in patients with cardiac disease. However, only a few studies have evaluated the characteristics of patients with AF complicated with non-cardiac diseases. We aimed to investigate whether the safety and efficacy of landiolol, an ultra-short-acting β1-selective blocker for controlling rapid heart rate (HR), for patients with AF differed between those with cardiac disease and those with non-cardiac diseases.

Materials and Methods : All AF patients with HRs≥120 beats/min who received continuous intravenous landiolol administration were included in this study (n=133). The patients were divided into the cardiac (n=55) and non-cardiac (n=78) disease groups. Successful HR control was defined as an HR<110 beats/min and a≥20 % decrease in HR in 2 hr after landiolol initiation.

Results : Landiolol significantly decreased the HRs of patients with rapid AF in both groups (cardiac : 145±17 to 103±22 beats/min, $P<0.001$; non-cardiac : 145±18 to 114±23 beats/min ; $P<0.001$). The proportion of patients achieving the efficacy endpoint was higher in the cardiac group than in the non-cardiac group (58.2 %, n=32 vs. 35.9 %, n=28 ; $P=0.02$). No intergroup difference was noted in the incidence of adverse events. C-reactive protein levels were independent factors associated with non-effective landiolol responses (odds ratio : OR, 0.958 ; 95 % CI, 0.920－0.997 ; $P=0.04$). A non-effective landiolol response was significantly and independently associated with 30-day mortality (Hazard ratios : HzR, 5.043 ; 95 % CI, 1.516-16.777 ; $P<0.01$).

Conclusions : Landiolol may be a therapeutic option for the acute control of rapid AF in patients with either cardiac or non-cardiac complications, especially in those without marked inflammation. *Shinshu Med J 68 : 31—39, 2020*

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Key words : atrial fibrillation, non-cardiac disease, inflammation, landiolol

I Introduction

Currently, there is increasing evidence of a high incidence of atrial fibrillation (AF) in patients with non-cardiac diseases[1)2)], including cancer[3)], sepsis[4)], chronic obstructive pulmonary disease[5)], obstructive sleep apnea[6)], chronic kidney disease[7)], and critical illnesses[8)]. Although the prevalence of AF in patients with non-cardiac diseases is often underestimated, several studies have reported that AF is commonly observed in patients with non-cardiac diseases and its presence increases the mortality rates associated with such patients[3)-10)].

The guidelines of the American Heart Association and the European Society of Cardiology recommend

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digitalis, amiodarone, and β-blockers for acute rate-control therapy in patients with AF[1)2)]. However, only a few studies regarding AF associated with non-cardiac diseases have been conducted and the treatment of AF in the context of non-cardiac disease complications is mainly based on studies involving patients with cardiac diseases[1)]. Additionally, amiodarone and digitalis have long half-lives ; thus, adjusting the dose according to the patient's condition is difficult in some emergency settings. Landiolol, an ultra-short-acting β1-selective blocker (β1/β2 receptor selectivity is as high as 251) with a half-life of 4 min in human blood, is rapidly metabolized to its inactive form in the blood and liver[11)]. Thus, landiolol decreases heart rate (HR) with less of an effect on blood pressure (BP), and its dosage can be easily adjusted according to the patient's hemodynamic response.

Fewer studies have evaluated the characteristics of patients with AF complicated with non-cardiac disease, compared to those with AF and cardiac disease. Questions remain regarding the differences in the safety and effectiveness of β-blockers for the urgent control of rapid HR in AF patients complicated with cardiac versus non-cardiac diseases. Therefore, we investigated the efficacy and safety of patients treated with intravenous landiolol for the urgent control of rapid HR in AF complicated with cardiac and non-cardiac disease.

Ⅱ Materials and Methods

A Study population

All patients with AF, who were admitted to Shinshu University Hospital between January 2011 and October 2016 and received continuous intravenous landiolol were screened. The exclusion criteria were : age＜20 years, HR＜120 beats/min at the time of landiolol initiation, non-cardiac disease patients with a history of cardiac disease, electrical cardioversion or death within 2 hr of landiolol administration, and inadequate medical records. Patients treated with oral β-blockers before landiolol initiation were included.

The patients were assigned to either the cardiac or non-cardiac group. The cardiac group consisted of patients with primary diagnoses of a cardiac disease upon admission, including ischemic heart disease, infective endocarditis, acute decompensated heart failure, any arrhythmia, and valvular heart disease. The non-cardiac group consisted of patients with primary non-cardiac disease diagnoses upon admission, without a history of cardiac disease. The surgical subgroups included patients with AF determined postoperatively. The non-surgical subgroups included patients diagnosed with AF and treated with landiolol prior to any surgery performed during hospitalization. Patient hemodynamic parameters were assessed using two-dimensional cardiac echocardiography ; non-cardiac disease patients with a left ventricular ejection fraction (LVEF)＜50 % or those with a moderate to severe valvular heart disease were excluded as an echocardiographic abnormality.

B Endpoints

The efficacy endpoint was assessed 2 hr after landiolol administration ; the clinical outcome was classified as "effective" when the patient achieved an HR＜110 beats/min and presented a≥20 % decrease from the baseline HR (HR immediately before landiolol administration), based on a previous investigation[12)]. The safety endpoint was defined as the incidence of adverse events related or unrelated to landiolol administration, leading to its discontinuation. The clinical endpoint was 30-day mortality, defined as all-cause mortality within 30 days after landiolol administration. The protocol was approved by the Ethics Committees at Shinshu University Graduate School of Medicine.

C Statistical Analyses

Statistical analyses were performed using SPSS Ver. 22.0 (SPSS, Chicago, IL, USA). Unless otherwise stated, data are presented as means±standard deviations when normally distributed and as medians with interquartile ranges (25^{th}–75^{th} percentiles) when non-normally distributed. Group differences were evaluated using unpaired 2-tailed Student's *t*-tests for normally distributed data and Mann-Whitney tests for non-normally distributed data. Paired, non-normally distributed data were analyzed using the

Wilcoxon signed-rank test. Categorical variables were evaluated using the chi-squared test or Fisher's exact test. Linear and logistic regression analyses were used to evaluate potential associations between the variables and endpoints. Multivariate logistic regression analysis was performed to identify factors associated with achieving the efficacy endpoint. Multivariate Cox's proportional hazards analysis was performed to determine the factors associated with all-cause 30-day mortality. If variables were missing for>20 % of patients in the univariate analysis, they were excluded from the multivariate analysis. Hazard ratios (HzRs), odds ratios (ORs), and 95 % confidence intervals (CIs) were also determined. *P* values<0.05 were considered statistically significant.

Ⅲ Results

Among the 218 patients who received landiolol during the study period, 85 were excluded for the following reasons: age<20 years (n=6), HR<120 beats/min at the time of landiolol initiation (n=29), electrical cardioversion (n=10) or death (n=1)

Table 1 Baseline characteristics of the patients with atrial fibrillation complicated with cardiac or non-cardiac disease

	Cardiac N=55	**Non-cardiac** N=78	***P*-value**
Demographics			
Age (years)	73 ± 12	73 ± 11	0.68
Male, n (%)	38 (69.1)	53 (67.9)	0.91
Weight (kg)	58.0 ± 14.7	59.4 ± 13.8	0.49
PAF, n (%)	46 (83.6)	57 (73.1)	0.20
History of cardiac disease, n (%)	22 (35.6)	0 (0)	<0.001
Hemodynamic parameters			
HR (beats/min)	145 ± 17	143 ± 18	0.94
SBP (mmHg)	112 ± 27	116 ± 25	0.25
DBP (mmHg)	73 ± 21	71 ± 15	0.95
LVEF (%)	51.4 ± 17.6	66.4 ± 8.6	<0.001
Creatinine (mg/dL)	1.02 [0.81−1.56]	0.92 [0.64−1.53]	0.39
eGFR (mL/min/1.73m^2)	50.6 ± 27.5	59.1 ± 33.8	0.14
CRP (mg/dL)	4.32 [0.88−14.0]	12.55 ± 9.89	0.01
Drugs, n (%)			
Diuretics	37 (67.3)	24 (30.8)	<0.001
Aldosterone antagonist	9 (16.4)	5 (6.4)	0.08
ARBs/ACE-inhibitors	27 (49.1)	13 (16.7)	<0.001
Nitrates	22 (40.0)	8 (10.3)	<0.001
β-blockers	24 (43.6)	17 (21.8)	0.02
Digitalis	12 (21.8)	2 (2.56)	<0.01
Amiodarone	6 (10.9)	1 (1.28)	<0.01
Statins	19 (34.5)	7 (8.9)	<0.001
Inotropes and vasopressors, n (%)			
Dopamine	15 (27.3)	14 (17.9)	0.21
Dobutamine	18 (32.7)	10 (16.3)	<0.01
Noradrenaline	8 (14.5)	11 (14.1)	0.77
AF scores			
CHA2DS2-VASc	3.8 ± 1.6	3.3 ± 1.8	0.11

Data are presented as means ± SD or medians and interquartile ranges [25th−75th percentiles]. PAF, paroxysmal atrial fibrillation; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; ARBs, angiotensin II receptor blockers; ACE, angiotensin-converting enzyme

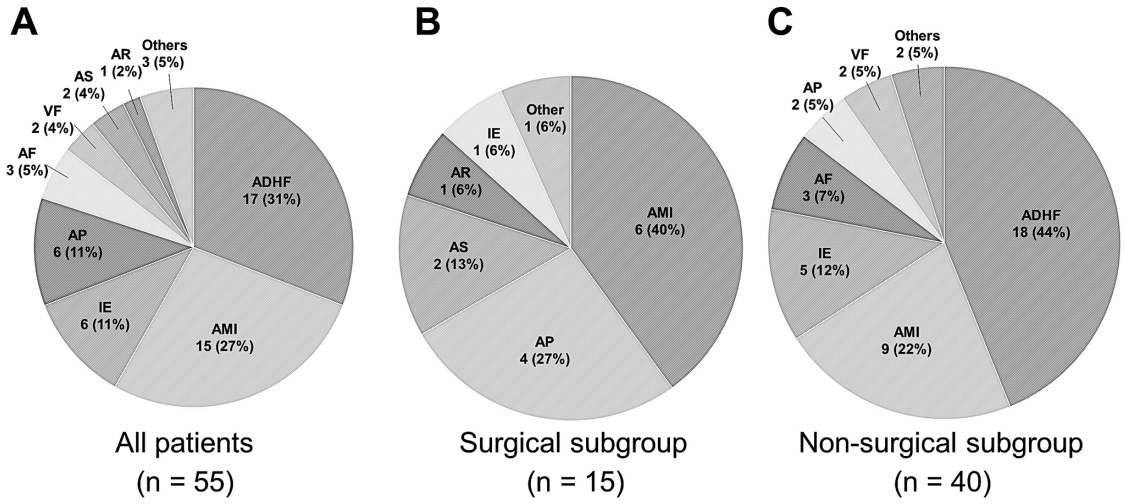

Fig. 1 Primary diagnosis at admission for patients with atrial fibrillation (AF) complicated with cardiac diseases is shown for (A) all patients, (B) surgical patients, and (C) non-surgical patients.
ADHF, acute decompensated heart failure ; AMI, acute myocardial infarction ; IE, infective endocarditis ; AP, angina pectoris ; VF, ventricular fibrillation ; AS, aortic stenosis ; AR, aortic regurgitation.

within 2 hr after landiolol administration, inadequate medical records (n = 2), non-cardiac patients with a history of cardiac disease (n = 23), and an echocardiographic abnormality (n = 14). Thus, 133 patients were included in the analysis.

Table 1 summarizes the baseline characteristics of the patients assigned to the cardiac (n = 55) and non-cardiac (n = 78) disease groups. Compared with the non-cardiac group, the cardiac group demonstrated a significantly greater use of oral β-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), nitrates, digitalis, amiodarone, statins, and intravenous dobutamine. LVEF and C-reactive protein (CRP) levels were significantly higher in the non-cardiac group than in the cardiac group (51.4 ± 17.6 vs. 66.4 ± 8.6 %, $P < 0.001$ and 4.32 [0.88 − 14.0] vs. 12.55 ± 9.89, $P = 0.01$, respectively).

The primary diagnoses on admission for the patients in the cardiac and non-cardiac groups are shown in **Fig. 1, 2**, respectively. In the cardiac group, the most common primary diagnoses were acute decompensated heart failure (31 %) and acute myocardial infarction (27 %) ; other diagnoses included infective endocarditis, angina pectoris, arrhythmias, and valvular heart disease (**Fig. 1A**). A similar tendency was observed in the surgical (n = 15) and non-surgical (n = 40) subgroups (**Fig. 1B, C**, respectively). In the non-cardiac group, aortic dissection (27 %) was the most common primary diagnosis, followed by cancer (23 %), infectious disease (17 %), cerebrovascular disease (11 %), and trauma (5 %) ; other diagnoses included pulmonary disease, gastrointestinal disease, endocrine disease, acute renal failure, orthopedic disease, and leukemia (**Fig. 2A**). Infectious disease, cancer and cerebrovascular diseases were common in both the surgical and non-surgical subgroups (**Fig. 2B, C**, respectively).

The proportion of patients achieving the efficacy endpoint are shown in **Fig. 3**. Overall, landiolol administration significantly decreased HRs 2 hr after administration as 45.1 % (n = 60) of patients achieved the efficacy endpoint. The proportion of patients achieving the primary efficacy endpoint was higher in the cardiac (58.2 %, n = 32) than in the non-cardiac group (35.9 %, n = 28, $P = 0.02$; **Fig. 3A**). Although no difference was noted in the proportion of surgical patients achieving the efficacy endpoint between the cardiac and non-cardiac groups (60.0 % , n = 9 vs. 42.9 % , n = 21, $P = 0.24$; **Fig. 3B**), the proportion of non-surgical patients achieving the efficacy endpoint was significantly higher in the cardiac group than in the non-cardiac group (57.5 %, n = 23 vs. 24.1 %, n = 7, $P = 0.02$; **Fig. 3C**).

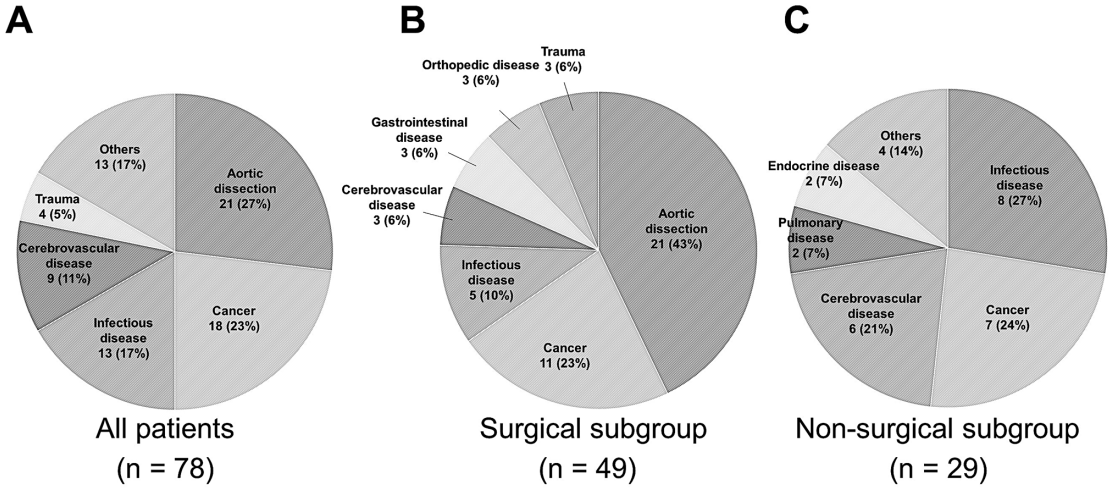

Fig. 2 Primary diagnosis at admission for patients with atrial fibrillation complicated with non-cardiac diseases is shown for (A) all patients, (B) surgical patients, and (C) non-surgical patients.

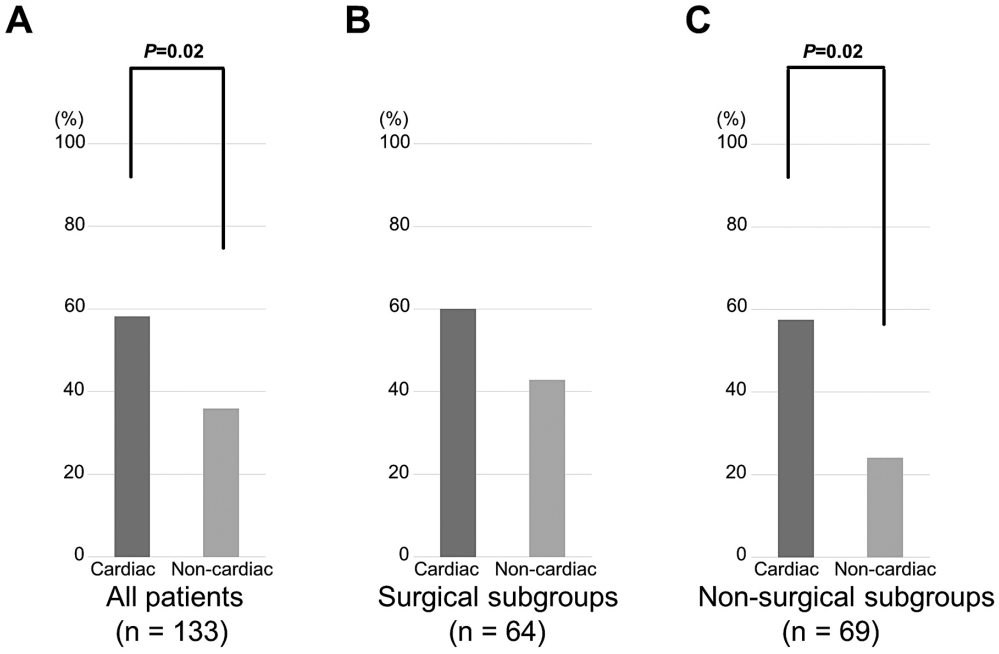

Fig. 3 Effects of landiolol in controlling rapid heart rate in patients with atrial fibrillation (AF). The proportion of (A) all patients, (B) surgical patients, and (C) non-surgical patients who achieved the efficacy endpoint (based on both a heart rate＜110 beats/min and a≥20 % decrease in HR from baseline at 2 hr after the intravenous administration of landiolol).

The baseline and post-treatment changes in HR and BP 2 hr after landiolol administration are shown in **Table 2**. There was no difference in HR between the cardiac and non-cardiac group at baseline (P = 0.94), but landiolol significantly decreased the HRs of the patients, from the baseline value 2 hr after its administration in both the cardiac and non-cardiac groups. The HR reduction was significantly greater in the cardiac group than in the non-cardiac group (27.2 ± 16.8 % vs. 20.9 ± 12.4 %, P = 0.03). However, among the surgical patients, no difference in HR reduction was noted between the two groups, whereas among the non-surgical patients, the HR reduction was significantly greater in the cardiac group than in the non-cardiac group. There was no significant change in BP after administration of

Table 2 Pre-and post-treatment hemodynamic parameters associated with landiolol administration

	Cardiac group		Non-cardiac group		*P*-value
	Pre	Post	Pre	Post	
HR (beats/min)					
Overall	145 ± 17	103 ± 22[a]	145 ± 18	114 ± 23[a]	
% reduction	27.2 ± 16.8		20.9 ± 12.4		0.03
Surgical subgroup	148 ± 18	104 ± 22[a]	142 ± 16	108 ± 18[a]	
% reduction	29.1 ± 15.8		23.2 ± 11.8		0.38
Non-surgical subgroup	141 ± 16	102 ± 23[a]	149 ± 20	123 ± 22[a]	
% reduction	26.7 ± 17.2[b]		17.1 ± 12.6		0.01
SBP (mmHg)	112 ± 27	113 ± 24	116 ± 25	111 ± 18	
% reduction	−4.48 ± 25.1		0.80 ± 24.2		0.26
DBP (mmHg)	73 ± 21	67 ± 14	72 ± 16	68 ± 15	
% reduction	1.34 ± 28.9		1.50 ± 22.6		0.98
Restoration of sinus rhythm, n (%)	15 (27.3)		12 (15.4)		0.10
Landiolol administration					
Maximum dose (μg/kg/min)	3.60 [0.40−11.3]		3.00 [1.66−4.70]		0.65
Administration time (h)	37 [9.5−113]		47 [21−107]		0.65

Data are presented as means ± SD or medians and interquartile ranges [25th−75th percentiles]. "[a]" indicates that landiolol significantly decreased HR from baseline, 4 h after administration in both the cardiac and non-cardiac groups ($P<0.001$); "[b]" indicates that the HR reduction was significantly greater in the cardiac group than in the non-cardiac group ($P=0.01$); HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3 Adverse events in patients with atrial fibrillation treated with landiolol

Age (y)	Sex	Diagnosis	Adverse event	Landiolol dose at event (μg/kg/min)
53	Male	Dilated cardiomyopathy	Oliguria	1.13
83	Male	Acute myocardial infraction	Dyspnea	9.02
78	Male	Angina pectoris	Hypotension	2.20
65	Female	Acute aortic dissection	Hypotension	2.50
88	Male	Acute renal failure	Sinus arrest	4.46

landiolol.

Five adverse events were observed in patients treated with landiolol and no intergroup differences were noted (**Table 3**).

Univariate and multivariate analyses for independent factors associated with achieving the efficacy endpoint, including significant variables between the cardiac and non-cardiac groups, are shown in **Table 4**. The multivariate logistic regression analysis showed that cardiac disease and postoperative AF were independent factors associated with achieving the efficacy endpoint (OR, 2.877; 95 % CI, 1.216-6.807; $P=0.02$ and OR, 2.753; 95 % CI, 1.239-6.118; $P=0.01$, respectively). In contrast, the CRP level (per 1 mg/dL increase) was an independent factor associated with a non-effective landiolol response (OR, 0.958; 95 % CI, 0.920-0.997; $P=0.04$).

Univariate and multivariate Cox's proportional hazards analyses for an association between a non-effective landiolol response and 30-day mortality are shown in **Table 5**. Using variables associated with efficacy endpoint achievement, we made several models and evaluated the association between a non-effective landiolol response and all-cause 30-day mortality. Potential associations between these variables and non-effective landiolol responses were evaluated using linear and logistic regression analyses; no significant associations were found. The univariate Cox's proportional hazards analysis revealed that the risk of mortality increased by 453 %

Table 4 Univariate and multivariate analysis of factors associated with achieving the efficacy endpoint

	Univariate analysis		Multivariate analysis	
Variables	**OR (95 % CI)**	***P* value**	**OR (95 % CI)**	***P* value**
Age	1.009 (0.979－1.039)	0.57		
Male	1.215 (0.605－2.440)	0.58		
Cardiac disease	2.056 (1.025－4.122)	0.04	2.877 (1.216－6.807)	0.02
Postoperative AF	1.546 (0.801－2.983)	0.19	2.753 (1.239－6.118)	0.01
Oral β-blockers	2.241 (1.070－4.694)	0.03	1.763 (0.797－3.898)	0.16
CRP (per 1 mg/dL increase)	0.964 (0.930－0.998)	0.04	0.958 (0.920－0.997)	0.04
Dopamine	1.086 (0.487－2.423)	0.84		
Dobutamine	1.468 (0.660－3.264)	0.35		
Noradrenaline	1.033 (0.406－2.626)	0.95		
Digitalis	0.545 (0.179－1.660)	0.29		
LVEF	0.998 (0.976－1.021)	0.85		

OR, odds ratio ; CI, confidence interval ; AF, atrial fibrillation ; CRP, C-reactive protein ; LVEF, left ventricular ejection fraction

Table 5 Multivariate Cox regression analyses of association between a non-effective landiolol response and the 30-day mortality

	Non-effective landiolol response	
Endpoint : 30-day mortality	**Hazard ratio (95 % CI)**	***P*-value**
Model 1		
Univariate	5.530 (1.723－17.751)	＜0.01
Model 2		
Adjusted for age and sex	5.956 (1.834－19.347)	＜0.01
Model 3		
Adjusted for age, sex, and CRP levels	5.504 (1.665－18.200)	＜0.01
Model 4		
Adjusted for age, sex, and non-cardiac disease	5.293 (1.613－17.369)	＜0.01
Model 5		
Adjusted for age, sex, CRP levels, and non-cardiac disease	5.043 (1.516－16.777)	＜0.01

CI, confidence interval ; CRP, C-reactive protein

(HzR, 5.530 ; 95 % CI, 1.723-17.751 ; $P<0.01$) in the presence of non-effective landiolol responses. Even after adjusting for age, sex, CRP levels and non-cardiac disease, a non-effective landiolol response was significantly and independently associated with 30-day mortality (HzR, 5.043 ; 95 % CI, 1.516-16.777 ; $P<0.01$)

Ⅳ Discussion

Although treatment guidelines recommend digitalis, amiodarone, and β-blockers for acute rate-control therapy in patients with AF[1)2)], the treatment of AF in patients with non-cardiac disease has been mainly based on studies involving cardiac disease ; there are few reports regarding AF complicated with non-cardiac disease[1)]. In the present study, AF was observed among a more diverse range of diseases than was previously reported, especially among non-cardiac patients. Additionally, our results showed that landiolol was more effective for acute control of rapid HR in patients with AF and cardiac disease than in patients with AF and non-cardiac disease ; however, landiolol significantly decreased the rapid HR of AF in both cardiac and non-cardiac patients and was similarly safe in both groups.

The presence of non-cardiac disease and a high

CRP level were independent factors associated with a non-effective landiolol response in this study. Although several factors appear to contribute to the concomitant presence of AF[12)-14)], inflammation is a common denominator among these conditions and may be one of the most important factors[15)], especially in patients with non-cardiac disease[10)]. Moreover, our results suggest that inflammation is associated with landiolol responses in patients with AF. Expectedly, greater use of digitalis, amiodarone, ACE inhibitors to lower systolic BP, ARBs, dopamine or dobutamine was found in the cardiac group; however, these medication differences were not independent factors associated with effective landiolol responses in the present study. A high CRP level was an independent factor associated with non-effective landiolol responses, suggesting that inflammation contributes to the observed reduced efficacy of landiolol in both the cardiac and non-cardiac groups. Since the mechanisms of postoperative AF differ from those of non-postoperative AF, we investigated the separate groups of patients. Postoperative AF was an independent factor associated with an effective landiolol response in this study.

Although several reports suggest that the presence of AF has a negative impact on mortality[3)-10)], previous clinical studies, to our knowledge, have not attempted to identify the predictive value of β-blocker responses as a clinical outcome in patients with rapid AF accompanied by non-cardiac disease. Non-effective landiolol response was an independent and significant factor associated with all-cause 30-day mortality in our study, even after adjusting for age, sex, CRP level, and non-cardiac disease.

This study has several limitations. First, it was a retrospective study and dose standardization was not possible because of the heterogeneous usage of landiolol. Therefore, we could not evaluate the effect of inadequate dose adjustment on the non-effective responses. Second, because various diseases were examined, especially among patients with non-cardiac disease, the ability to affirm similarities in baseline characteristics, medical therapy, and long-term clinical outcomes was limited. Third, some patients in the non-cardiac group might have latent cardiac disease. However, one of the aims of this study was to clarify the characteristics of rapid AF complicated with non-cardiac disease versus cardiac disease in a real-world setting. Further prospective studies involving a larger number of patients are needed to confirm our results.

V Conclusions

Landiolol was more effective for acute control of rapid HR in patients with AF and cardiac disease than in those with AF and non-cardiac disease; however, landiolol significantly decreased the rapid HR associated with AF in both groups of patients. The safety of landiolol was similarly high in both groups and no between-group clinical outcome differences were noted. Landiolol may be considered as a therapeutic option for the acute control of rapid AF complicated with either cardiac or non-cardiac diseases, especially in patients without high systemic inflammation.

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