

**Acute hemodynamic effects of landiolol, an ultra-short-acting beta-blocker,  
in patients with acute coronary syndrome: Preliminary study**

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**Short title:** Landiolol in Acute Coronary Syndrome

Conflict of interest: No conflicts of interest are declared by any author  
regarding this manuscript.

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## Summary

**Objectives:** We aimed to evaluate acute hemodynamic effects and safety of landiolol in patients with acute coronary syndrome (ACS) treated with percutaneous coronary intervention (PCI).

**Background:** Beta-blockers have been proven to be effective for the treatment of ischemic heart disease in both the acute and chronic phases. Landiolol, an ultra-short-acting and highly cardioselective beta-1 blocker, has become available in Japan. In the clinical setting, the hemodynamic response to landiolol administration remains unclear in patients presenting with ACS.

**Methods:** From August 2007 to April 2008, landiolol was administered intravenously immediately before reperfusion procedure in 22 consecutive ACS patients (mean age,  $63 \pm 9$  years; 15 men) with a heart rate (HR) of  $\geq 70$  beats/min. The initial intravenous administration dose of landiolol was 20  $\mu\text{g}/\text{kg}/\text{min}$  in all patients. The maintenance dose was titrated with the aim of reducing HR by 15%. Acute hemodynamic data including HR and systolic and diastolic blood pressure were serially evaluated.

**Results:** HR dropped significantly (from  $87 \pm 11$  to  $72 \pm 8$  beats/min,  $P < 0.001$ )

20 minutes after landiolol initiation. However, systolic and diastolic pressure remained unchanged during administration of landiolol. Although landiolol was discontinued in 2 patients because of sinus bradycardia, no serious complications such as advanced degree atrioventricular block, requiring temporary cardiac pacing, severe hypotension, cardiogenic shock, or deterioration of heart failure were observed in the patients receiving landiolol.

**Conclusions:** Landiolol was safe and effective in reducing oxygen demand of the ischemic heart by reducing only HR without lowering blood pressure in patients with ACS undergoing PCI.

**Key Words:** landiolol; beta-blocker; acute coronary syndrome; acute hemodynamic response

## INTRODUCTION

Beta-blockers can reduce oxygen consumption in ischemic myocardium [1], and they have been proven to be effective for the management of ischemic heart disease in both the acute and chronic phases [2-6]. However, intravenous propranolol, not usually given as a continuous infusion, has limited safety because it lacks cardioselectivity, and its effects continue long after treatment has stopped. Landiolol hydrochloride (ONOACT™; Ono Pharmaceutical, Osaka, Japan) is an ultra-short-acting, selective beta-1 blocker that is now commercially available in Japan. This agent has an extremely short elimination half-time of 4 minutes [7] and might allow easy titration during the acute phase of acute coronary syndrome (ACS). Previous studies reported the effectiveness and safety of landiolol administration in patients who developed tachyarrhythmia in the perioperative phase [8-14]. However, cardioprotective effects of landiolol against myocardial ischemic injury have not been investigated. In the setting of ACS including myocardial infarction, the hemodynamic response to landiolol administration remains unclear. In this preliminary study, we aimed to evaluate the acute hemodynamic effects and safety of landiolol in patients

with ACS undergoing percutaneous coronary intervention (PCI).

## **METHODS**

### **Study Population**

We conducted a preliminary study of investigating the acute hemodynamic effects of landiolol in patients with ACS. From August 2007 to April 2008, a total of 97 patients with ACS were treated with PCI at our institution. Among them, eligible subjects included 22 consecutive patients with a heart rate of  $\geq 70$  beats/min (mean age,  $62 \pm 9$  years; 15 men) who were administered landiolol intravenously. ACS was defined as prolonged chest pain ( $\geq 10$ min) with ST segment elevation or depression ( $\geq 0.05$ mV) in 2 or more contiguous leads on the electrocardiogram and significant coronary artery stenosis or occlusion on the coronary angiogram. Exclusion criteria included development of cardiogenic shock, bradycardia, atrioventricular block, heart failure of Killip class III or IV, hypotension, and a history of bronchial asthma. Patients who previously had been on oral beta-blockers were also excluded. The study was approved by the ethics committees of our institute.

## **Interventional Procedure**

Prior to the interventional procedure, unfractionated heparin was administered to maintain an activated clotting time of  $\geq 300$  seconds.

Experienced interventional cardiologists performed PCI through the femoral or radial approach with 6 French catheters. Dual antiplatelet agents were prescribed to the patients undergoing coronary artery stenting, i.e. aspirin 200 mg daily and clopidogrel 75 mg daily, following a 300 mg loading dose of clopidogrel. A glycoprotein IIb/IIIa receptor antagonist was not available in Japan at the time of the study. The contrast agent used was iopamidol 370 mg I/ml (Schering AG, Berlin, Germany). Written informed consent was obtained from all patients before undergoing PCI.

## **Treatment with Landiolol**

Landiolol was initiated immediately before the reperfusion procedure. The endpoint of treatment was a 15% reduction in heart rate. Drug administration consisted of initial titration followed by maintenance infusion. The initial intravenous administration dose of landiolol was determined to be 20  $\mu\text{g}/\text{kg}/\text{min}$  for 5 minutes in all patients on the basis of our institution's protocol. At the end of 5 minutes, the patient's vital signs were recorded, and

if they had not met the study endpoint, landiolol was increased by 5 to 10  $\mu\text{g}/\text{kg}/\text{min}$  every 1 minute. If the patient achieved a 15% reduction in heart rate, a maintenance dose of landiolol was titrated. If the decrease in heart rate was inadequate during this period, the landiolol dose could be increased up to a maximum of 40  $\mu\text{g}/\text{kg}/\text{min}$ . The maintenance dose could also be adjusted downward if necessary. After completion of the PCI, landiolol was discontinued and followed by oral beta-blocker treatment.

### **Hemodynamic Evaluation**

Hemodynamic data, including heart rate and systolic and diastolic blood pressure, were recorded at baseline and 1, 2, 5, 10, and 20 minutes after initiation of landiolol. Heart rate was serially recorded by electrocardiographic heart rate monitor and arterial blood pressure was measured invasively through the arterial catheter. Hemodynamic effects were assessed up to 20 minutes after landiolol initiation because of its very short 4-minute half-life in blood.

### **Blood Sampling and Left Ventricular Function**

We drew blood samples to measure serum concentration of creatine phosphokinase (CPK) and the MB isoenzyme of CPK (CPK-MB) before the



procedure and at 6, 12, and 24 hours after PCI. Left ventricular function was assessed by transthoracic echocardiogram at 5 days after PCI.

### **Statistical Analysis**

Continuous variables are expressed as means  $\pm$  SD. The Student *t*-test was used to assess the differences between continuous variables. Categorical variables are reported as observed number of patients (percentages) and were analyzed by either chi-square or Fisher exact test, as appropriate. A repeated measure ANOVA was performed to examine the differences in the time course changes in variables, and post hoc analysis was employed with the Scheffe's test. Pearson's correlation coefficient was used to assess the relation between continuous variables. A two-sided *P* value of  $<0.05$  was considered significant throughout the analysis. Data were analyzed with SPSS Statistics 19.0 for Windows (IBM SPSS Statistics Inc., Chicago, IL, USA).

## **RESULTS**

### **Patient Characteristics**

Baseline patient characteristics are shown in Table 1. Landiolol was

administered intravenously in 13 patients presenting with acute myocardial infarction and 9 patients with unstable angina. The left anterior descending artery was involved most frequently.

### **Hemodynamic Data**

Hemodynamic data at baseline are shown in Table 2. Figure 1.A shows a statistically significant reduction in heart rate after initiation of landiolol, from  $87 \pm 11$  beats/min at baseline to  $72 \pm 8$  beats/min after 20 minutes [ $F(5,170) = 25.8, P < 0.001$ ]. The average decrease in heart rate was 15 beats/min at 20 minutes after administration of landiolol. The reduction in heart rate correlated with baseline heart rate ( $r = 0.687, P < 0.001$ , Figure 2). In contrast, as shown in Figure 1.B, both systolic and diastolic blood pressure remained unchanged during landiolol infusion [ $F(5,170) = 1.75, P = 0.13$ , and  $F(5,170) = 0.84, P = 0.53$ , for systolic and diastolic blood pressure, respectively].

### **Titration of Landiolol**

The initial intravenously administered dose of landiolol was 20  $\mu\text{g}/\text{kg}/\text{min}$  in all patients. This same dose was maintained in 13 (59%) patients. According to the change in heart rate, the maintenance dose was

decreased to 10 µg/kg/min in 7 (32%) patients, whereas 2 (9%) patients required a higher dose. The mean dose of landiolol was  $17.8 \pm 6.0$  µg/kg/min when the appropriate heart rate was obtained. The mean duration of landiolol administration was  $44 \pm 14$  minutes (median, 45 minutes; interquartile range, 38-52 minutes), and 21 (95%) patients received subsequent oral beta-blocker treatment: 11 patients were on carvedilol, 7 patients on metoprolol, and 3 patients on bisoprolol. A representative case of landiolol administration is shown in Figure 3.

### **Adverse Effects**

Landiolol was discontinued prematurely in 2 patients with AMI because of a bradycardic response, which recovered immediately without inserting temporary cardiac pacing. The culprit arteries were the right coronary artery in 1 patient and the left circumflex in the other. In the latter, the left circumflex was the dominant coronary artery with hypoplastic right coronary artery. However, no serious adverse effects such as an advanced degree of atrioventricular block, requiring temporary cardiac pacing, severe hypotension, cardiogenic shock, or deterioration of heart failure were observed. None of the patients who were administered landiolol

intravenously died during hospitalization.

## **DISCUSSION**

The main findings of this study were that landiolol could decrease heart rate rapidly without lowering blood pressure in patients presenting with ACS, and a positive correlation between baseline heart rate and the reduction in heart rate was observed. In addition, landiolol could be used safely without hemodynamic complications approximately in 90% of the selected ACS patients.

Landiolol hydrochloride, which has a pharmacological resemblance to esmolol, is now commercially available in Japan as an ultra-short-acting agent with high beta-1 receptor selectivity. Landiolol has much higher cardioselectivity than that of esmolol (ratio of beta-1/beta-2 selectivity: landiolol, 255; esmolol, 33) and is also shorter acting than esmolol (elimination half-time: landiolol, 4 minutes; esmolol, 9 minutes) [7, 15]. In animal experiments, landiolol had less effect on blood pressure than did esmolol [16]. This favorable property allows easy titration and results in fewer side-effects than with other long-acting beta-1 blockers and is

considered to be a suitable hemodynamic response for ischemic myocardium in the acute phase.

Hemodynamic responses to landiolol administration in patients with ACS have not been investigated in the clinical setting, and the effectiveness and safety of landiolol remain unclear. To our knowledge, this is the first report to investigate the acute hemodynamic effects of landiolol in patients with ACS. The present study showed that landiolol rapidly attenuated the heart rate without lowering the blood pressure. The average of decrease in heart rate was 15 beats/min after 20-minute administration of landiolol, and a positive correlation between baseline and the reduction in heart rate was observed. Previous studies showed a consistent hemodynamic response with landiolol, and the safety and effectiveness of this agent have been shown in patients with tachyarrhythmia in the perioperative setting and in the intensive care unit [8-10, 13, 17]. We propose that landiolol administration would be taken into consideration to the ACS patients concomitant with high heart rate, in whom an attenuation of heart rate by using landiolol might allow decreasing oxygen consumption. The temporary cardiac pacing would not be essential when using landiolol because of its short elimination half

time. However, the AMI patient involving right coronary artery might be inserted temporary cardiac pacing prior to landiolol administration because of a possibility of bradycardiac response. In this study, 4 patients with Killip class of II were administered landiolol safely without deterioration of heart failure, however, the patients with Killip class of III and IV were excluded from this study.

The regimen recommended on the landiolol package insert in Japan is a loading dose of 125  $\mu\text{g}/\text{kg}/\text{min}$ , followed by a maintenance dose of 10-40  $\mu\text{g}/\text{kg}/\text{min}$ . In all patients in the present study, we initiated landiolol at dose of 20  $\mu\text{g}/\text{kg}/\text{min}$  without first infusing a loading dose. The ultra-short-acting and 4-minute elimination half time of landiolol allow easy and rapid titration of the maintenance dose. However, several reports indicated that a low dose of  $\leq 5$   $\mu\text{g}/\text{kg}/\text{min}$  was effective for suppression of tachyarrhythmia or adjustment of heart rate [13, 14, 18]. In the real-world clinical setting, the optimal dose of landiolol for cardioprotection remains to be undetermined, and investigation is continuing.

Several recent basic experiments showed that landiolol has cardioprotective effects against ischemia-reperfusion injury [19-21]. Landiolol

is speculated to have similar cardioprotective effects against myocardial ischemic injury in the human heart. Recently, the PASCAL trial for coronary artery bypass grafting had shown that landiolol decreased levels of postoperative cardiac enzymes including CPK-MB and troponin-I, as well as development of postoperative atrial fibrillation [18]. Because our study was of a single-arm observational design, further investigation will be required to determine whether landiolol has an effect on salvaging ischemic myocardium and improving prognosis in patients with ACS treated by PCI.

## **LIMITATIONS**

The present study has several limitations. First, this study was of a single-arm observational design and was performed at a single center, and the sample size was small. Second, other hemodynamic parameters such as cardiac output, pulmonary artery pressure, and pulmonary capillary wedge pressure were not assessed because a pulmonary artery catheter was not inserted. Third, this study was limited to short-term hemodynamic response, and thus, there were no long-term data on whether prognostic benefit was obtained.

## **CONCLUSIONS**

Landiolol was safe and effective in rapidly reducing heart rate by reducing only heart rate without lowering the blood pressure in patients with ACS undergoing PCI. These effects of landiolol are considered to be a favorable hemodynamic response in patients with ischemic myocardium in the acute phase.



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## Figure legend

Fig.1.A: A repeated measure ANOVA showed a significant attenuation in serial change of heart rate after administration of landiolol [ $F(5,170) = 25.8$ ,  $P < 0.001$ ]. Graph data are presented as mean  $\pm$  SD. Asterisk (\*) indicates significant difference in heart rate ( $P < 0.001$ ) between baseline and each time point as determined by repeated ANOVA followed by Scheffe's post hoc test.

Fig.1.B: Serial changes in systolic and diastolic blood pressure were shown. There were no significant differences in serial change of either systolic or diastolic blood pressure as determined by repeated measure ANOVA. Graph data are presented as mean  $\pm$  SD. Black diamond indicates systolic blood pressure, and white triangle does diastolic blood pressure. SBP, systolic blood pressure; DBP, diastolic blood pressure.

Fig.2: Reduction in heart rate correlated significantly with baseline heart rate.

Fig.3: A representative case is shown of a 66-year-old woman who presented

to the emergency room complaining of chest discomfort. An electrocardiogram showed ST-segment depression (A, left panel), suggesting unstable angina, and the patient was referred to the cath lab. Coronary angiogram showed significant stenosis in the left anterior descending artery (B, left panel). Intravenous administration of landiolol at a dose of 20  $\mu\text{g}/\text{kg}/\text{min}$  was initiated, resulting in immediate improvement of myocardial ischemia (A, right panel and C). Subsequently, a Taxus-Liberte™ stent was successfully implanted in the left anterior descending artery (B, right panel).

Figure 1.A

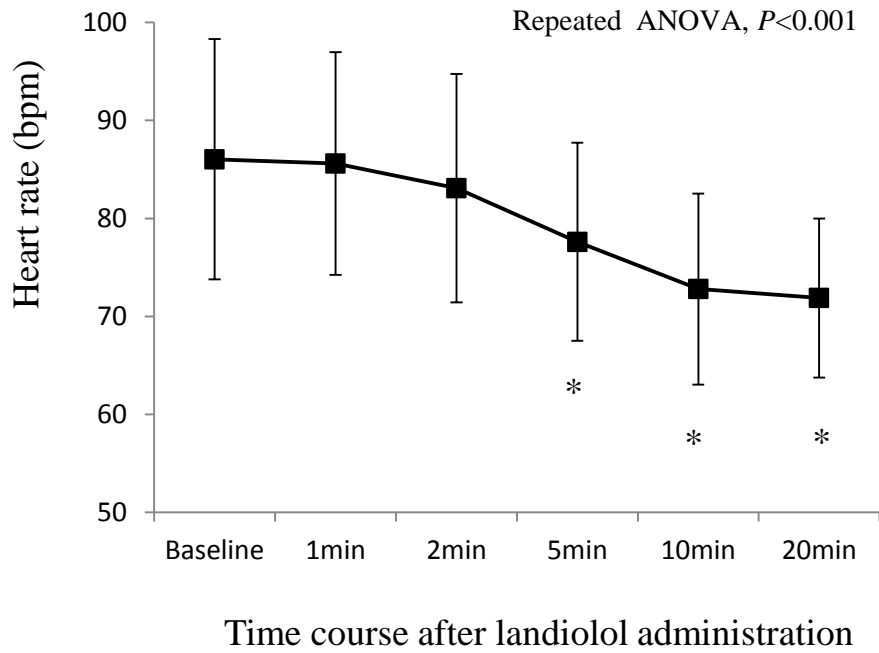


Figure 1.B

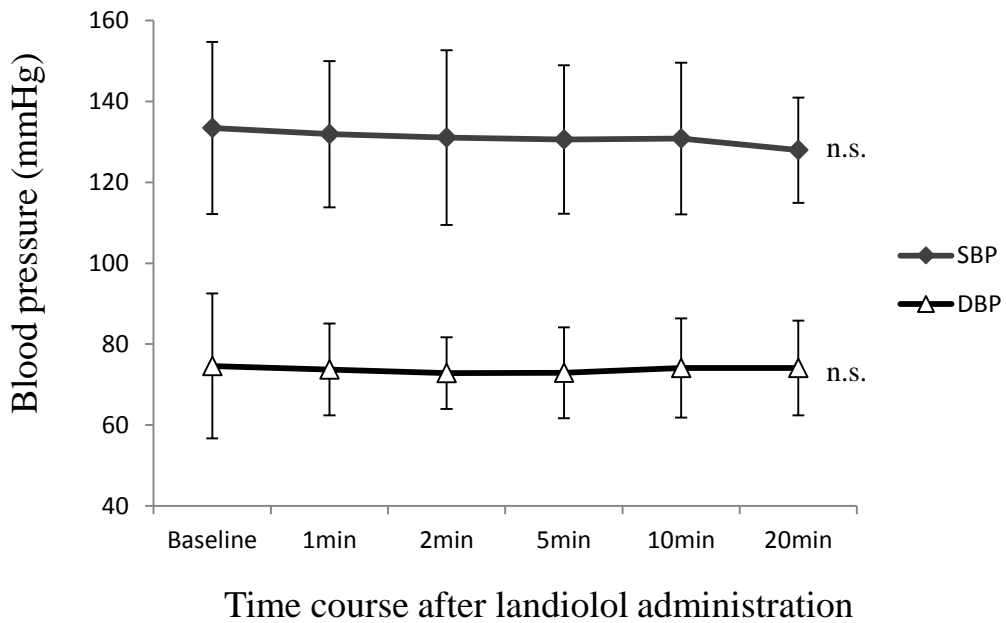




Figure 2

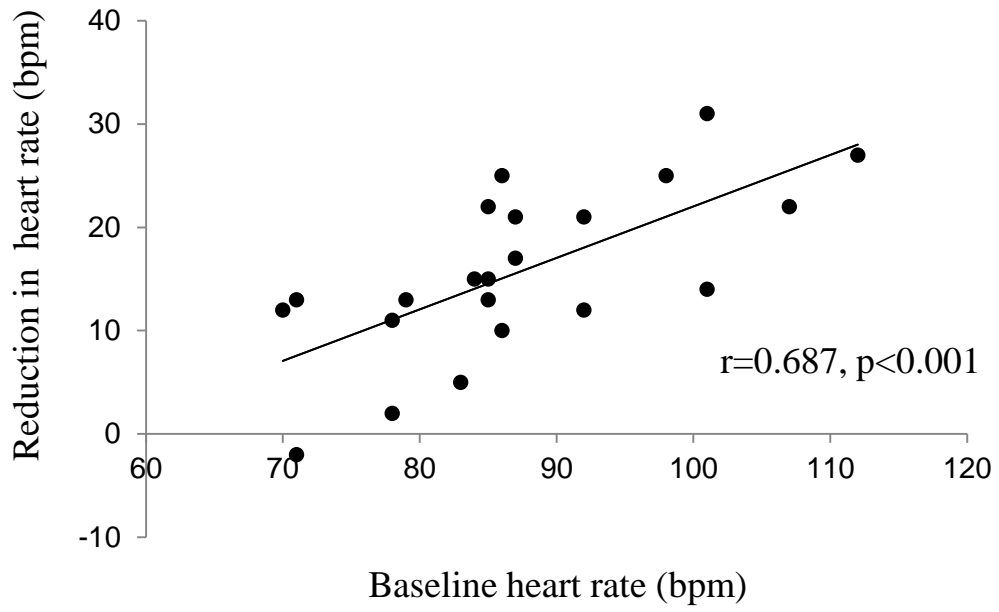
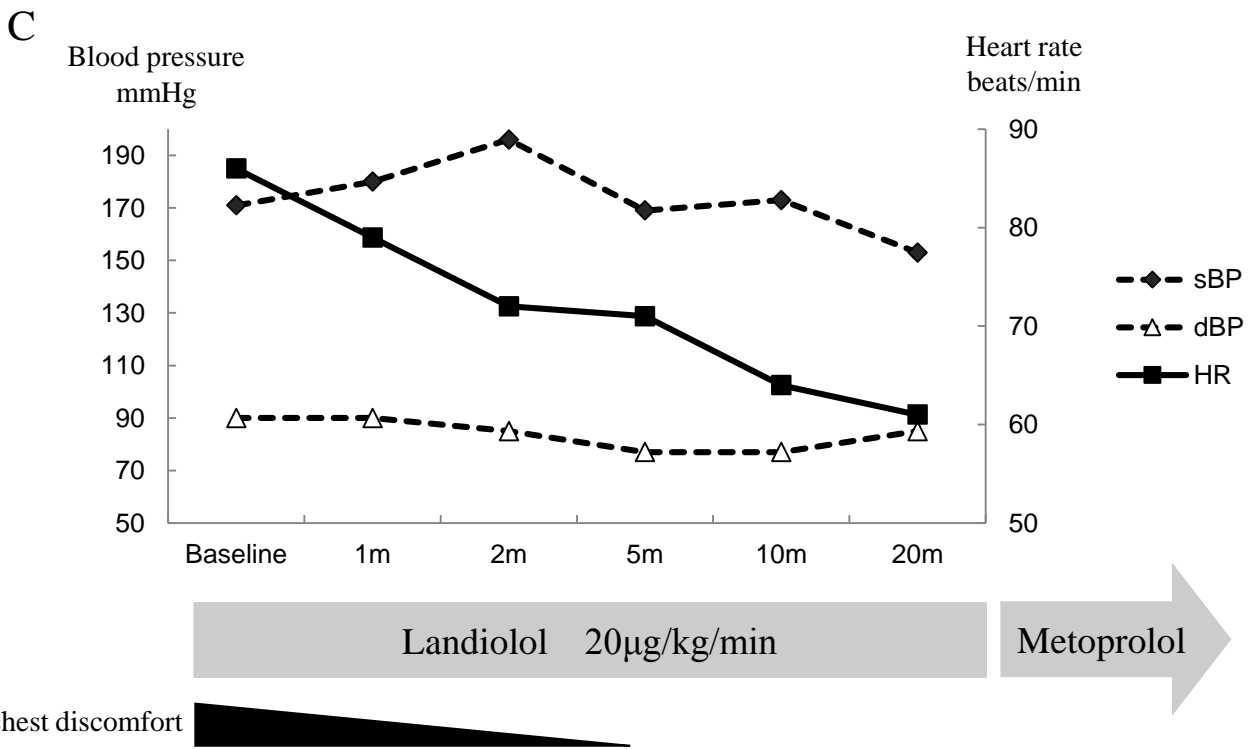
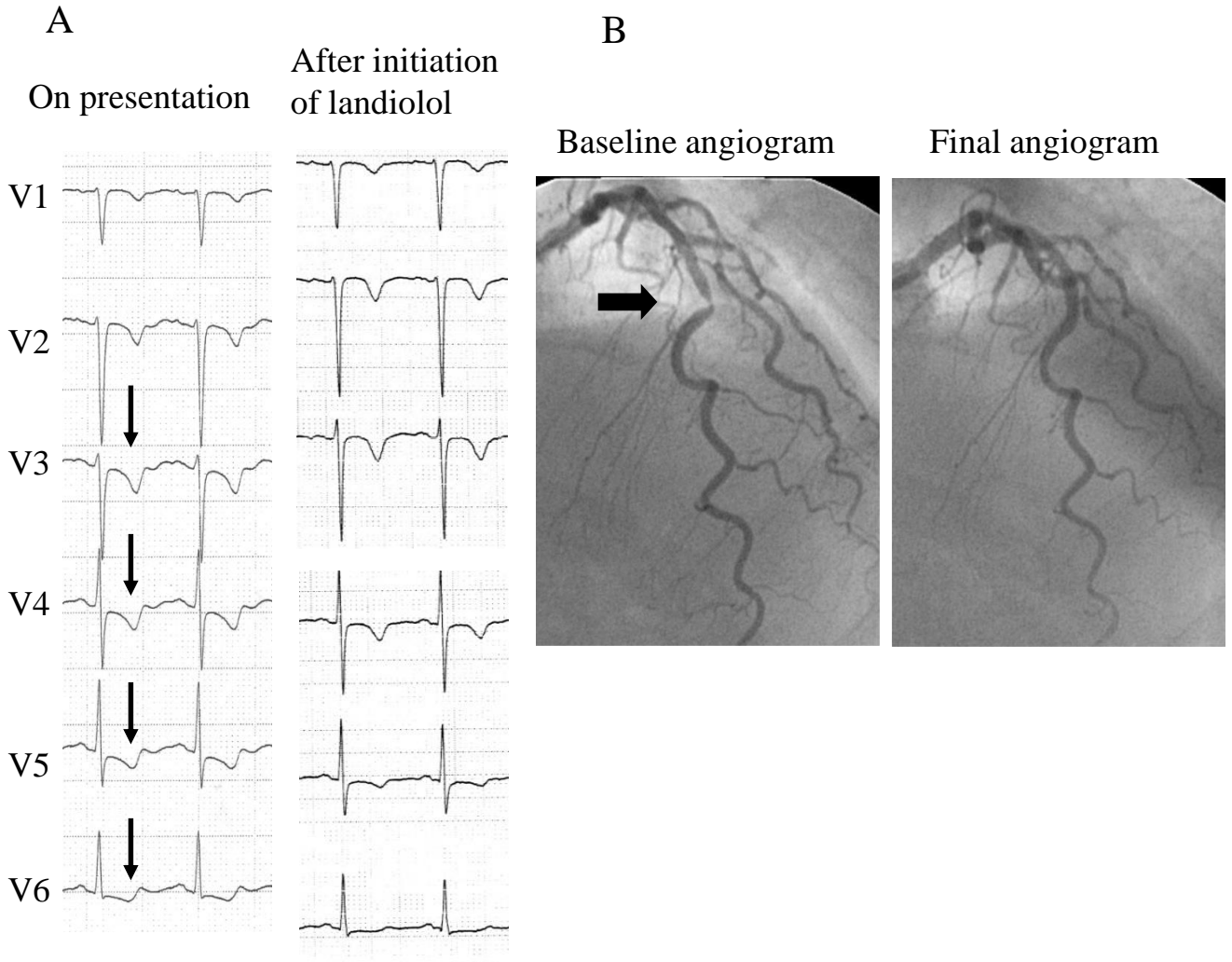


Figure 3



**Table 1. Baseline Patient Characteristics**

Characteristics	N = 22
Age (years)	63 ± 9
Male sex, n (%)	15 (68%)
Risk factors, n (%)	
Hypertension	16 (73%)
Dyslipidemia	11 (50%)
Diabetes	9 (41%)
Smoking	13 (59%)
Killip class, n (I/II/III/IV)	18/4/0/0
ECG on presentation, n (%)	
Sinus rhythm	22 (96%)
Ventricular arrhythmia	1 (4%)
Diagnosis at presentation, n (%)	
Acute myocardial infarction	13 (59%)
Unstable angina	9 (41%)
Culprit artery, n (%)	
Left anterior descending	16 (73%)
Left circumflex	5 (23%)
Right coronary	1 (4%)
Time from symptom onset to reperfusion, (min)	367 ± 301

Data are presented as absolute value (percentage) or mean ± SD.  
ECG, electrocardiogram.

**Table 2. Hemodynamic and Cardiac Enzyme Data**

Characteristics	
Hemodynamic data at baseline	
Systolic blood pressure (mmHg)	133 ± 22
Diastolic blood pressure (mmHg)	76 ± 18
Heart rate (beats/min)	87 ± 11
Cardiac enzymes, AMI only	
Peak CPK, U/L	2900 ± 2234
Peak CPK-MB, U/L	301 ± 236
LVEF	
All patients, %	55 ± 10
AMI patients, %	49 ± 7

Data are presented as mean ± SD. AMI, acute myocardial infarction; CPK, creatine phosphokinase; LVEF, left ventricular ejection fraction.