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Original Article

Efficacy and Safety of Early Intravenous Landiolol on Myocardial Salvage in Patients with ST-segment Elevation Myocardial Infarction before Primary Percutaneous Coronary Intervention: A Randomized Study

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Early treatment with an oral β-blocker is recommended in patients with a ST-segment–elevation myocardial infarction (STEMI). In this multicenter study, we evaluated the effects of a continuous administration of landiolol, an ultrashort-acting β-blocker, before primary percutaneous coronary intervention (PCI) on myocardial salvage and its safety in STEMI patients. A total of 47 Japanese patients with anterior or lateral STEMI undergoing a primary PCI within 12 h of symptom onset were randomized to receive intravenous landiolol (started at 3 μg/min/kg dose and continued to a total of 50 mg; n = 23) or not (control; n = 24). Patients with Killip class III or more were excluded. The primary outcome was the myocardial salvage index on cardiac magnetic resonance imaging (MRI) performed 5-7 days after the PCI. Cardiac MRI was performed in 35 patients (74%). The myocardial salvage index in the landiolol group was significantly greater than that in the control group (44.4 ± 14.6% vs. 31.7 ± 18.9%, respectively; $p = 0.04$). There were no significant differences in adverse events at 24 h between the landiolol and control groups. A continuous administration of landiolol before a primary PCI may increase the degree of myocardial salvage without additional hemodynamic adverse effects within the first 24 h after STEMI.

Key words: myocardial infarction, landiolol, magnetic resonance imaging, STEMI, PCI

Primary percutaneous coronary intervention (PCI) is the best therapeutic strategy for ST-segment–elevation myocardial infarction (STEMI), but patients who have experienced a STEMI remain at high risk of recurrent cardiovascular events such as congestive heart failure, arrhythmia, and sudden death [1,2]. One of the major predictors of mortality and morbidity in this patient population is the extent of myocardial necrosis [3]. Novel therapies that are able to reduce the infarct size are thus desired.

The efficacy of β-blockers for reducing infarct size is well established [4], and current guidelines recommend the early initiation of treatment with β-blockers in STEMI patients [2]. With respect to the benefit of intravenous β-blockers before reperfusion, the METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) trial demonstrated that intravenous metoprolol before PCI reduced the infarct size as observed by cardiac magnetic

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resonance imaging (MRI) [5]. However, the EARLY-BAMI (Early Beta-blocker Administration before reperfusion primary PCI in patients with ST-elevation Myocardial Infarction) trial showed no effect of intravenous metoprolol before primary PCI on the infarct size [6]. The benefit of intravenous β-blockers before primary PCI in STEMI patients thus remains controversial. In addition, because of the negative inotropic and chronotropic effects of β-blockers, there are concerns over the risk of cardiogenic shock or heart failure with the use of β-blockers in the very-acute phase of a STEMI.

The intravenous β-blocker landiolol is ultrashort-acting, with a very short half-life of approximately 4 min. Landiolol has a high β1/β2 selectivity ratio of approximately 255, and a less negative inotropic effect compared to the β-blocker esmolol. Landiolol provides a response at 0-2 min after administration [7, 8]. Kiyokuni *et al*. reported that an early infusion of landiolol during primary PCI was associated with a higher grade of ST-segment resolution and a lower incidence of adverse events in the acute phase of STEMI compared to no treatment with landiolol [9]. However, the benefit of intravenous landiolol on infarct size before PCI in STEMI has not been established. We conducted the present study to evaluate the effects of a continuous administration of landiolol before primary PCI on myocardial salvage revealed by MRI, and its safety, in patients with STEMI in an investigation with a prospective, multicenter, randomized design.

Patients and Methods

Study design. The effect of pre-landiolol treatment on ischemic reperfusion injury in acute myocardial infarction (PROTECTION) trial was a multicenter, prospective, open-label, randomized controlled trial. The primary focus of that trial was to determine whether STEMI patients receiving early intravenous landiolol before reperfusion would have a reduced infarct size compared with control subjects. All patients received oral metoprolol within 24 h after reperfusion, as recommended by current clinical guidelines [2]. The present study was approved by the Okayama University Graduate School of Medicine, Density and Pharmaceutical Sciences, and the Okayama University Hospital Ethics Committee (m07012), as well as the ethics committee of each hospital. This trial was conducted in compliance with the Declaration of Helsinki. This trial was registered in the UMIN Clinical Trials Registry (UMIN-CTR, UMIN000012578). All participants gave written informed consent to participate in the trial and to have their data published.

Patients. Patients eligible for enrollment were ≥ 20 years old and were referred to undergo a primary PCI for a myocardial infarction with ST-segment elevation ≥ 0.2 mV in two or more contiguous precordial leads (one of which should be V2, V3, V4, V5 or V6). A STEMI was diagnosed when the patient was admitted with chest pain that lasted for 30 min, with an ST-segment elevation of ≥ 0.2 mV in at least 2 contiguous leads, and an elevation of creatine kinase (CK) or its MB isozyme to at least twice the normal levels. The exclusion criteria were Killip class III to IV, an estimated time of symptom onset to reperfusion of > 24 h, systolic blood pressure persistently < 120 mmHg, PR interval > 240 ms, heart rate < 60/min, left ventricular (LV) ejection fraction < 30%, history of coronary artery bypass surgery, prior myocardial infarction or hemodialysis, active treatment with any β-blocker, and the implantation of a pacemaker or a cardioverter defibrillator. All of the patients were Japanese.

Interventions and study procedures. Patients fulfilling all criteria who provided written informed consent to participate in this study were enrolled and subsequently randomized (1 : 1) to receive continuous intravenous landiolol or not (control). In the landiolol group, an intravenous infusion of landiolol (Ono Pharmaceutical Co., Osaka, Japan; 3 μg/kg/min) was started just after randomization before PCI [9]. This dose was continued during and after the PCI procedure until a total dose of 50 mg was reached. An unscheduled discontinuation of landiolol was left to the physician's discretion. Randomization was performed using a computer-generated random sequence web response system. Patients were stratified by age (< 60 years, ≥ 60 years), sex, and infarct-related artery (left anterior descending coronary artery vs. other artery). A cardiac MRI examination was scheduled 5-7 days after infarction for each patient.

Outcomes. The primary outcome of this study was the myocardial salvage index on MRI. The prespecified major secondary outcomes were the infarct size quantified by MRI and the infarct size estimated by the peak CK and CK-MB values. The major safety secondary outcome was the incidence of major adverse

cardiac events, defined as a composite of death, malignant ventricular arrhythmia, cardiogenic shock, and atrioventricular block within 24 h after PCI.

PCI procedure. Before undergoing a PCI, all patients received 200 mg aspirin and 300 mg clopidogrel. Each PCI was performed with conventional techniques by the femoral or radial approach. Intravenous heparin (10,000 IU) was administered after arterial access was obtained, to achieve an activated clotting time > 200 sec. Intravenous heparin was continued for 48 h after an angioplasty followed by stent deployment. The postprocedural antithrombotic therapy consisted of 100 mg aspirin daily and 75 mg clopidogrel daily. No patients received glycoprotein inhibitors during the study period.

After their PCI, the patients received optimal medical therapy such as dual antiplatelet agents and statins, based on published guidelines [10]. A successful PCI was defined based on the definition of angiographic and procedural success in the guidelines for PCI [11]. Once the planned intravenous landiolol infusion was completed, all patients received oral metoprolol within 24 h, as recommended by current clinical guidelines [2].

MRI acquisition. The myocardial salvage index value and the infarct size were determined with the use of cardiovascular MRI at 5-7 days after the patients' acute myocardial infarction. The MRI studies were performed using a 3.0 T scanner (MAGNETOM Verio, Siemens, Erlangen, Germany). Short-axis slices covering the whole ventricle using a T2-weighted turbo inversion recovery magnitude sequence (repetition time, 2 × R-R interval [2 heartbeats]; echo time, 67 msec; inversion time, 150 msec, flip angle 180°; voxel size 1.4 × 1.4 × 8.0 mm) were obtained using a body coil. Late enhancement images covering the whole ventricle were acquired approximately 10 min after an intravenous administration of 0.2 mmol/kg body weight of gadoterate meglumine (Magnescope; Guerbert Japan, Tokyo; Fuji Pharma, Tokyo). A phase-sensitive inversion recovery sequence (repetition time, 2 × R-R interval [2 heartbeats]; echo time, 1.48 msec; flip angle, 40°; voxel size, 1.9 × 1.4 × 8.0 mm) was used for image acquisition.

MRI analysis. All MRI analyses were performed independently by the core laboratory at Okayama University. Data were quantified with dedicated software (QMass MR 7.5; Medis, Leiden, Netherlands) (Fig. 1). The following information was obtained in all MRI studies: the LV mass, the myocardium at risk, and the infarcted myocardium. The infarcted myocardium (grams of LV tissue) was defined by the extent of abnormal delayed enhancement, and the myocardium at risk (grams of LV tissue) was defined by the extent of edema (high signal intensity on T2-weighted short T1 inversion-recovery images) [12]. The myocardial salvage index was defined as the difference between the value of the myocardium at risk and that of the infarcted myocardium normalized to the myocardium at risk.

Statistical analyses. Based on previous studies, we estimated that the relative reduction in the myocardial salvage index in the landiolol group would be 13% lower than that in the control group [5, 13]. The standard deviation of the myocardial salvage index was estimated as 0.22. A minimum of 92 patients (46 patients per group) was required to provide 80% power with a two-sided α-level of 0.05 by Student's *t*-test between the 2 groups.

Continuous variables are expressed as the mean ± standard deviation or the median (interquartile range). Dichotomous variables are expressed as the number (proportion). Differences in continuous variables between the 2 groups were analyzed by the paired Student's *t*-test or Mann-Whitney *U*-test, as appropriate. Categorical data were compared by Fisher's test. The MRI data, peak CK, and peak CK-MB values were analyzed by an analysis of covariance (ANCOVA) without and with adjustment for the three stratification variables (age, sex, and infarct-related artery) and current or former smoking. Differences in the interobserver reproducibility were compared using a Bland-Altman plot. The limits of agreement were defined as the mean difference ± twofold standard deviation (SD) of the difference, and are expressed as the mean difference (± limit of agreement). All reported *p*-values were two-sided, and *p*-values < 0.05 were considered significant. The statistical analyses were performed using statistical software (SPSS software ver. 24; IBM Co., Armonk, NY, USA).

Results

Study population. Between July 2013 and April 2016, 47 patients were randomized to receive an intravenous landiolol infusion (n = 23) or intravenous saline infusion (n = 24, control subjects) (Fig. 2). After ran-

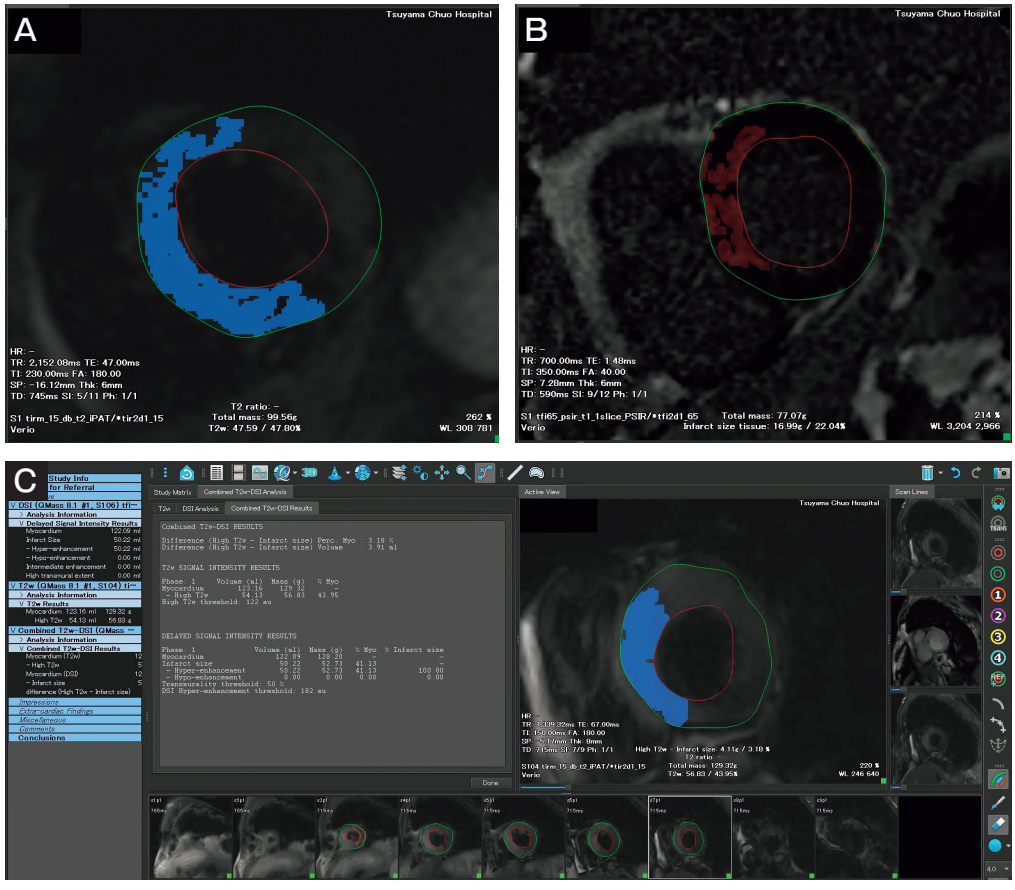

Fig. 1 Magnetic resonance imaging (MRI) analysis of the area at risk and infarcted myocardium. MRI short-axis images obtained at the same left ventricular level in a patient in the PROTECTION trial. The MRI was performed at 7 days post-ST segment elevation myocardial infarction (STEMI). **A**, The area of delayed enhancement (infarcted area, *red area* in the anterior interventricular septum); **B**, The area at risk at the same level of the left ventricle (*blue area* in the interventricular septum); **C**, Corresponds to panel A after the automatic quantification of the area at risk. Quantification of the infarct was also performed. The area of necrosis was smaller than the area at risk.

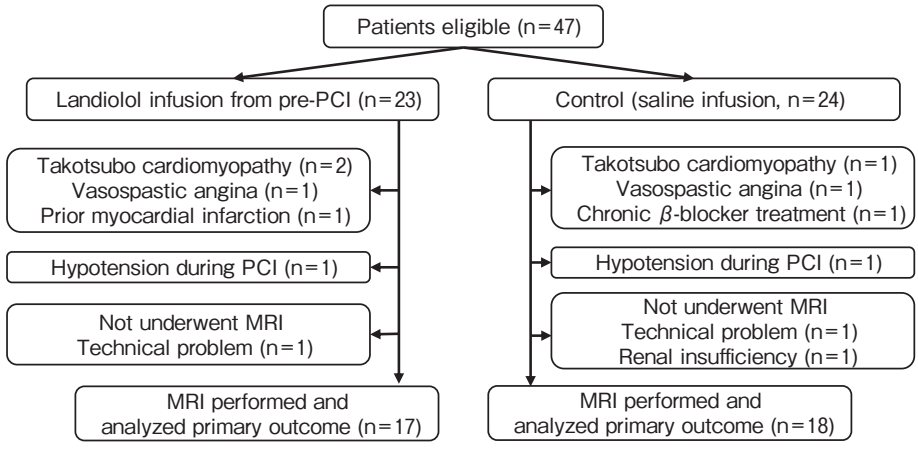

Fig. 2 The CONSORT flow diagram of this study. MRI, –; , magnetic resonance imaging; PCI, percutaneous coronary intervention.

domization, 7 patients (14%) were not scheduled for MRI, based on our study's exclusion criteria. Of the patients scheduled for MRI, 3 (6%) patients did not undergo MRI because of renal insufficiency (n = 1) or technical problems with the magnet (n = 2). Thus, 35 patients (17 receiving intravenous landiolol and 18 controls) had MRI data available for the primary outcome. Of the patients who underwent MRI, there were no significant differences in any of the baseline characteristics (Table 1).

Outcomes. The interobserver reproducibly of the myocardial salvage index on MRI was assessed by a correlation analysis and Bland-Altman plot. The correlation coefficient between observers was 0.88 ($p < 0.01$). The interobserver variability was low, with a mean bias of 1.3% (95% limits of agreement, −3.8% to 6.3%). The MRI data are presented in Table 2 and Fig. 3.

There were no significant differences in the unadjusted or adjusted absolute weights of the LV mass, myocardium at risk, and infarcted myocardium between the landiolol and control groups (Table 2, Fig. 3A, B). There were also no significant differences in the unadjusted or adjusted proportions of infarcted myocardium in LV between the groups (Table 2). However, the unadjusted and adjusted myocardial salvage index values in the landiolol group were significantly greater than those in the control group (Table 2, Fig. 3C). The adjusted mean peak CK values in the landiolol and control groups were 3,102 IU/L and 3,140 IU/L, respectively (adjusted difference, −37 IU/L; 95% confidence interval [95%CI], −1,651 to 1,576IU/L; $p = 0.96$). The adjusted mean peak CK-MB values were 324 IU/L and 363 IU/L in the landiolol and control groups, respectively (adjusted difference, −39 IU/L; 95%CI, −228 to 150 IU/L; $p = 0.68$) (Fig. 3D).

The median length of time from the patient's arrival at the emergency room to the start of landiolol infusion did not differ significantly between the landiolol and control groups (31 min [26-62 min] and 35 min [26-68 min], respectively; $p = 0.85$). The total infusion time of landiolol also did not differ significantly between the landiolol and control groups (254 ± 42 min and 275 ± 58 min, $p = 0.23$). There was no significant association of the myocardial salvage index with the length of time from the arrival at the emergency room to the start of landiolol infusion or with the total infusion time of landiolol ($p = 0.55$ and $p = 0.81$, respectively).

Safety data. The systolic blood pressure at the

Table 1 Baseline characteristics of the patients

	All Patients (n = 47)		Patients undergoing MRI (n = 35)		
	Landiolol (n = 23)	Control (n = 24)	Landiolol (n = 17)	Control (n = 18)	*P* value*
Age, years	64 ± 11	67 ± 13	61 ± 11.8	68 ± 11.5	0.07
Male	21 (91)	21 (87)	16 (94)	16 (89)	0.58
Body mass index, kg/m^2	23.6 ± 2.8	23.9 ± 3.4	24.1 ± 2.9	23.3 ± 3.3	0.48
Hypertension	15 (65)	15 (62)	10 (59)	11 (61)	0.89
Dyslipidemia	9 (3)	8 (33)	5 (29)	6 (33)	0.80
Diabetes mellitus	7 (30)	6 (25)	7 (41)	4 (22)	0.22
Current smoker	16 (69)	9 (37)	15 (88)	11 (61)	0.06
Ischemia duration, min**	219 ± 101	273 ± 140	233 ± 104	242 ± 108	0.81
Killip class I at recruitment	23 (100)	24 (100)	17 (100)	18 (100)	1.00
Infarct artery lesion, LAD/LCX	21/0	21/1	17/0	17/1	0.32
TIMI grade 0–1 flow before PCI	21 (91.3)	22 (91.7)	17 (100)	18 (100)	1.00
Successful PCI	21 (100)	22 (100)	17 (100)	18 (100)	1.00
SBP at the recruitment, mmHg	142 ± 18	144 ± 19	142 ± 18	145 ± 18	0.63
HR at the recruitment, bpm	85 ± 14	81 ± 13	84 ± 11	77 ± 12	0.07
SBP at the starting PC, mmHg	162 ± 21	165 ± 32	162 ± 21	167 ± 26	0.54
HR at the starting PCI, bpm	83 ± 14	85 ± 14	85 ± 13	85 ± 14	0.92

*Comparison between patients undergoing magnetic resonance imaging (MRI). **Mean ischemia duration from symptom onset to reperfusion. DBP, diastolic blood pressure; HR, heart rate; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.

Table 2 Magnetic resonance imaging data

	Patients Undergoing magnetic resonance imaging (n = 35)					
	Landiolol (n = 17)	Control (n = 18)	Unadjusted		Adjusted*	
	Mean (SD)	Mean (SD)	Difference (95% CI)	*P* value	Difference (95% CI)	*P* value
LV mass, g	119.6 ± 21.7	116.2 ± 22.9	3.45 (−11.9 to 18.9)	0.65	2.9 (−13.6 to 19.6)	0.72
Myocardium at risk, g	49.6 ± 16.9	39.5 ± 20.4	10.1 (−2.8 to 23.1)	0.12	9.0 (−5.1 to 23.1)	0.20
Infarcted myocardium, g	24.7 ± 10.3	26.8 ± 19.4	−2.1(−112.9 to 8.7)	0.69	−3.8 (−15.9 to 8.3)	0.50
Infarcted myocardium, % LV	20.8 ± 8.87	22.4 ± 12.7	−1.7 (−9.3 to 5.9)	0.66	−2.4 (−10.9 to −6.3)	0.58
Myocardial salvage index, %	44.4 ± 14.6	31.7 ± 18.9	12.7 (0.9 to 24.4)	0.04	13.8 (0.6 to 27.2)	0.04

*Adjusted by age, sex, infarct-related artery, and current smokers.
Myocardial salvage index was defined as the difference between the weight of myocardium at risk and the weight of infarcted myocardium normalized to the weight of myocardium at risk. CI, confidence interval; SD, standard deviation; LV, left ventricular.

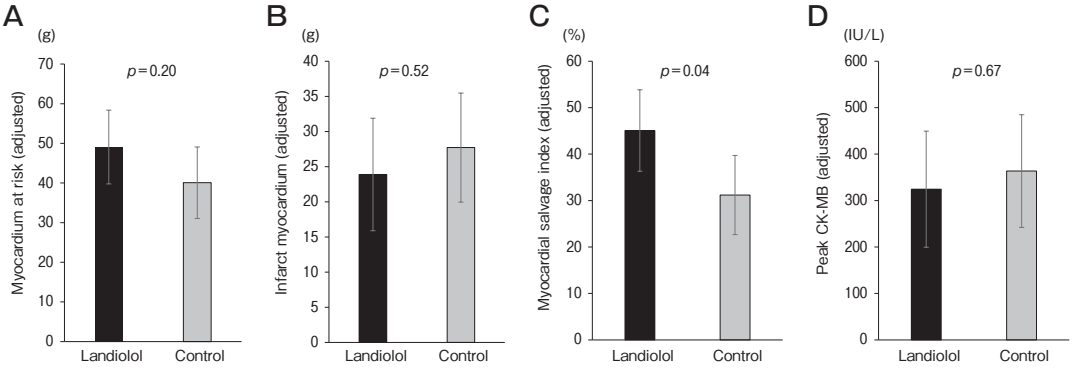

Fig. 3 The effect of the intravenous landiolol administration on infarct size was evaluated by MRI at 5–7 days after infarction. **A**, Myocardium at risk; **B**, Infarct size; **C**, Salvage index. Bars: mean ± 95%CI.

start of the PCI was significantly higher than that at recruitment in both the landiolol group and the control group ($p < 0.01$, for both). However, there were no significant differences between heart rate at the start of the PCI and heart rate at recruitment in either the landiolol group or control group ($p = 0.87$, $p = 0.14$, respectively) (Table 1). The prespecified safety endpoint was the incidence of major adverse cardiac events within 24 h after PCI in all patients (the entire study population). There were 2 events (8.7%) in the landiolol group (one hypotension, one non-sustained ventricular tachycardia associated with reperfusion) and 2 events (8.3%) in the control group (one hypotension, one non-sustained ventricular tachycardia associated with reperfusion). The uses of a continuous landiolol infusion from pre-reperfusion did not increase the incidence of major adverse cardiac events.

Discussion

The key finding of the present study was that the continuous administration of landiolol before the primary PCI in patients with an anterior or lateral STEMI increased the degree of myocardial salvage on MRI within the first 24 h after STEMI, with no additional hemodynamic adverse effects. Despite the findings from several investigations [5, 9, 14, 15], the effects of intravenous metoprolol or a continuous administration of landiolol or esmolol on the infarct size before PCI in STEMI patients remain unclear.

In the present study, there was a significant difference in the primary outcome, *i.e.*, the myocardial salvage index, but not in the infarct myocardium, on MRI. This discrepancy may be explained by the greater myocardium at risk and smaller infarcted myocardium in the landiolol group compared to the control group,

because the myocardial salvage index is calculated as (myocardium at risk − infarct myocardium) / myocardium at risk. Our study included patients with anterior or lateral STEMI, and the adjustment of the myocardium at risk between the 2 groups was difficult before the PCI due to the limited time and limited number of measures for the estimation of infarct size. In the METOCARD-CNIC and EARLY-BAMI trials [5, 14], the myocardium at risk was similar between the metoprolol and control groups. The number of patients undergoing MRI in the present study was small. Thus, despite our finding of a significant difference in the myocardial salvage index, the interpretation of the increased myocardial salvage index should be considered with caution.

We found no additional hemodynamic adverse effects within the first 24 h after STEMI at the dose of 3 μg/kg/min of landiolol. We adopted this dose based on a previous study of STEMI patients [16], which contrasts with the 1 μg/kg/min of landiolol used in another study of patients with LV dysfunction and atrial fibrillation [17]. In the present study, the systolic blood pressure and heart rate did not decrease after the continuous administration of landiolol, and there were no significant differences in the incidence of hypotension during PCI between the landiolol and control groups. Although one patient in each group had to stop taking landiolol during the primary PCI because of hypotension, the vital signs of those patients recovered within a few minutes after the discontinuation of the agent. Because our study included patients in Killip class I, the benefits of β-blockers before reperfusion in patents with hemodynamic instability remain unknown. Although the short half-life of landiolol may have some advantage in avoiding adverse events, further studies are required to confirm the optimal dose of landiolol for STEMI patients.

This study evaluated the effect of landiolol on the myocardial salvage index, but not on the LV ejection fraction. The current guidelines recommend risk stratification in all patients hospitalized for STEMI. As a part of the risk assessment, the resting LV ejection fraction should always be measured before discharge, because it is one of the strongest prognostic predictors. Data regarding the patients' LV function on MRI were not available in our study. However, Hanada *et al.* demonstrated that a continuous administration of landiolol just after PCI in STEMI patients improved the LV ejection fraction assessed at 6 months of recovery [16]. The quantification of salvaged myocardium on MRI has also been proposed as a measure of risk assessment after STEMI. A recent meta-analysis demonstrated that the myocardial salvage index measured by T2-weighted and T1-weighted late gadolinium enhancement MRI provides prognostic information about the risk of major cardiac events [18]. Thus, the myocardial salvage index may be a useful measure after STEMI.

Although some beneficial mechanisms of early intravenous β-blockers have been reported, the exact mechanisms of action remain unclear. A STEMI results in a substantial and sustained release of catecholamines. β-blockers reduce the heart rate and cardiac contractility and thus decrease the myocardial oxygen consumption of the ischemic myocardium [19]. Landiolol can also exert direct anti-inflammatory actions, antioxidant effects, and stabilization of the calcium handling of cardiomyocytes [20–23]. These effects may attenuate ischemia–reperfusion injury.

The present study has some limitations. It was a prospective, randomized, open, blinded end-point (PROBE) trial, although the evaluators of all outcomes were blinded to the patients' treatment allocation. We cannot completely rule out the influence of this design on the results. Second, the predefined sample size of 92 was not achieved. The study was designed to continue for almost 2 years, with an enrollment period from July 2013. However, our study population did not reach the number required for sufficient statistical power during the prespecified enrollment period. We therefore extended the enrollment period to 3 years until April 2016. Unfortunately, the study included only 35 patients undergoing MRI, and we were unable to continue the enrollment of new patients because of a shortage of funds. Thus, the number of patients analyzed in this study was small. Further research is needed to obtain robust evidence of the effect of landiolol on myocardial salvage after STEMI. In addition, the study population was comprised of only Japanese patients. The results may not be applicable to other ethnic groups.

In conclusion, in patients who have experienced an anterior or lateral STEMI, a continuous administration of landiolol before primary PCI may increase the degree of myocardial salvage without additional significant hemodynamic adverse effects. Further evidence is needed to determine the precise effects of landiolol on

the reduction of infarct size and longer-term prognosis in a larger clinical trial.

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