To the Editor: Current treatment guidelines for patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) recommend dual antiplatelet therapy, a combination of aspirin and a P2Y12 inhibitor (i.e., clopidogrel, prasugrel, and ticagrelor) for a minimum of 12 months. Ticagrelor, an oral reversibly binding platelet P2Y12 receptor inhibitor, generates a greater and more consistent inhibitory effect with rapid onset of action as compared to clopidogrel.\(^1\) In addition, \textit{in vitro} and animal experiments\(^2\) demonstrated that ticagrelor might increase the concentration of extracellular adenosine by inhibiting its uptake via red blood cells. Ticagrelor induces an increase in the level of adenosine that produces a series of adenosine-mediated biological effects, such as inhibition of platelet aggregation, relaxation of blood vessels, and protection of heart muscle. The PLATO study\(^3\) showed that ticagrelor reduced the rate of death based on vascular vessels, myocardial infarction (MI), and stroke, without increasing the risk of fatal bleeding in patients with ACS as compared to clopidogrel. A European study\(^4\) found that ticagrelor reduces the risk of mortality, MI, and stroke as compared to clopidogrel in patients with ACS, albeit without increasing the risk of bleeding. These large-scale studies\(^3,4\) selected patients who were primarily Caucasian. However, a Korean study\(^5\) found that clopidogrel neither reduced the ischemic events nor increased the incidence of bleeding complications as compared to ticagrelor in the East Asian patients with ST-segment-elevated MI (STEMI) and successful revascularization. Does ticagrelor reduce the mortality in patients with STEMI as compared to clopidogrel in the real East Asian world?

Herein, we analyzed 460 patients with STEMI undergoing primary PCI (PPCI) in a retrospective study conducted from November 2016 to November 2017 at our hospital. These patients were required to fulfill the following criteria for inclusion in the analysis: typical symptoms plus either persistent ST elevation of $\geq 1$ mV for $\geq 20$ min (not known to be preexisting or resulting from a co-existing disorder) in $\geq 2$ contiguous leads or new or presumed new left bundle-branch block. Furthermore, invasive management with PPCI had to be performed within the initial 12 h postadmission. According to the different antiplatelet therapeutic strategies received before PPCI, the patients were divided into three groups: low-load clopidogrel-treated group, high-load clopidogrel-treated group, and ticagrelor-treated group. Ticagrelor-treated 153 patients received a 180 mg loading dose followed by a maintenance dose of 90 mg two times per day. Low-load clopidogrel-treated 169 patients received a 300 mg loading dose, followed by 75 mg one time per day. High-load clopidogrel-treated 138 patients received a 600 mg loading dose, followed by 75 mg one time per day. All patients received a daily dose of acetylsalicylic acid one time unless intolerance was detected. In the case of patients who did not receive acetylsalicylic acid previously a loading dose of up to 300 mg was preferred. The recommended maintenance dose was 100 mg/d. The administration of intravenous glycoprotein IIb/IIIa inhibitors was allowed at the discretion of the operator. Detailed demographic, clinical, and angiographic data were collected for each patient. In addition, immediate and in-hospital events were recorded. Routine angiographic follow-up was not performed unless clinically indicated. The primary endpoint was cardiovascular death in the hospital, and the secondary endpoints included cardiovascular death, MI, stroke, or heart failure in the hospital. The angiographic no-reflow\(^6\) was diagnosed with a significant decrease in the coronary flow (thrombolysis in MI [TIMI] Grade $<3$ flow) without mechanical obstruction in the final cine-angiograms obtained at the completion of the PCI procedure (no-reflow group). Patients with restored coronary flow (TIMI Grade 3 flow) at the completion of PCI were included in the reflow group.

Of the 460 patients included in the final study group, angiographic no-reflow was observed in 73 patients (15.87%). Nonetheless, no significant differences were observed among the three groups of patients with respect to baseline clinical characteristics and heart function. The angiographic and procedural characteristics are presented in Table 1. Compared to the patients in the ticagrelor-treated...
group, those in the low-load clopidogrel-treated group were likely to show a no-reflow phenomenon (21.3% vs. 11.8%, P = 0.022). Although no significant difference was observed in the clopidogrel-treated groups with respect to the no-reflow phenomenon, patients with low-load clopidogrel-treatment presented a tendency to no-reflow (21.3% vs. 13.8%, P = 0.087). However, no significant difference was noted between the high-load clopidogrel-treated group and ticagrelor-treated group with respect to the no-reflow phenomenon. Interestingly, the angiographic appearance of pre-PPCI TIMI grade, target vessels, multivessel lesions, usage of thrombosis aspiration, and usage of anti-glycoprotein IIb/IIIa pharmacotherapy did not differ. The in-hospital adverse clinical events are listed in Table 2. Furthermore, the in-hospital mortality rate was higher in patients in the low-load clopidogrel-treated group as compared to those in the ticagrelor-treated group (4.2% vs. 0.65%, P = 0.034). In addition, the in-hospital mortality rate tended not to be significantly higher in patients in the low-load clopidogrel-treated group than those in the high-load clopidogrel-treated group (4.2% vs. 0.72%, P = 0.077). Furthermore, no significant difference was observed among the three groups of patients concerning the hospitalization period, occurrence of new-onset atrial fibrillation, recurrent MI, Killip Class III/IV, stroke, and target vessel revascularization. Multivariate Logistic regression analysis was used to adjust for risk factors, and no-reflow was found to be an independent predictor of patients with STEMI undergoing PPCI in-hospital mortality (hazard ratio: 12.562, 95% confidence interval: 2.975–53.035, P = 0.001). Spearman’s correlation coefficient analysis described a close correlation between the no-reflow phenomenon and antiplatelet treatment strategy (r = −0.104, P = 0.018).

In STEMI, improvement in PPCI reperfusion strategies contributed to improved mortality. A total of 13–15% of STEMI patients

### Table 1: Angiographic characteristics and procedural factors of the 460 patients with STEMI undergoing PPCI

| Variables | Low-load clopidogrel-treated group (n = 169) | High-load clopidogrel-treated group (n = 138) | Ticagrelor-treated group (n = 153) | P |
|-----------|---------------------------------------------|---------------------------------------------|------------------------------------|----|
| Pre-PPCI TIMI grade | 0 121 (71.6) 98 (71.0) 96 (62.7) | 1 5 (3.0) 4 (2.9) 13 (8.5) | 2 23 (13.6) 24 (17.4) 23 (15.0) | 3 20 (118) 12 (8.7) 21 (13.7) |
| Target vessel | LM 1 (0.6) 3 (2.2) 2 (1.3) | LAD 69 (40.8) 72 (52.2) 73 (47.7) | LCX 22 (13.0) 14 (10.1) 14 (9.2) | RCA 77 (45.6) 49 (35.5) 64 (41.8) |
| Multivessel lesions | 67 (39.6) 48 (34.8) 60 (39.2) | Thrombosis aspiration 118 (69.8)* 94 (68.1) 89 (58.2)* 0.753 | Anti-GP IIb/IIa 21 (12.4) 14 (10.1) 16 (10.5) | 0.769 |
| Infarct site | Anterior MI 57 (33.7) 68 (49.3) 67 (43.8) | Inferior MI 53 (31.4) 47 (34.1) 46 (30.1) | Inferior + right ventricle 4 (2.4) 5 (3.6) 5 (3.3) | Inferior + right ventricle + posterior 20 (11.8) 4 (2.9) 11 (7.2) |
| | Inferior + posterior 17 (10.1) 7 (5.1) 9 (5.9) | Wide anterior MI 20 (11.8) 7 (5.1) 15 (9.8) | Values were shown as n (%). *P = 0.034. STEMI: ST-segment-elevated myocardial infarction; PPCI: Primary percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction; LM: Left main; LCX: Left circumflex; LAD: Left anterior descending; RCA: Right coronary artery; GP: Glycoprotein; MI: Myocardial infarction. |

### Table 2: In-hospital clinical outcomes of the 460 patients with STEMI undergoing primary PCI

| Variables | Low-load clopidogrel-treated group (n = 169) | High-load clopidogrel-treated group (n = 138) | Ticagrelor-treated group (n = 153) | P |
|-----------|---------------------------------------------|---------------------------------------------|-----------------------------------|----|
| Hospitalization period | 6.2 ± 2.7 | 6.1 ± 2.4 | 6.3 ± 3.2 | 0.783 |
| No-reflow | 36 (21.3)* | 19 (13.8)* | 18 (11.8)* | 0.047 |
| New-onset atrial fibrillation | 14 (8.3) | 13 (9.4) | 10 (6.5) | 0.644 |
| Death | 7 (4.1)* | 1 (0.7)* | 1 (0.7)* | 0.034 |
| MACCE | 21 (12.4) | 16 (11.6) | 14 (9.2) | 0.609 |
| Recurrent MI | 2 (1.2) | 0 | 1 (0.7) | |
| Killip class III/IV | 12 (7.1) | 10 (7.2) | 8 (5.2) | |
| Stroke | 2 (1.2) | 0 | 0 | |
| TVR | 5 (3.0) | 6 (4.3) | 5 (3.3) | |
| Values were shown as mean ± SD, or n (%). *P = 0.087, †P = 0.022, ‡P = 0.061, §P = 0.043. TVR: Target vessel revascularization; SD: Standard deviation; MACCE: Major adverse cardiovascular and cerebrovascular event; STEMI: ST-segment-elevated myocardial infarction; PCI: Percutaneous coronary intervention. |
undergoing PPCI presented an angiographic no-reflow phenomenon that predicts a 30-day and 6-month mortality and reduced left ventricular function.[7] The no-reflow phenomenon is independently associated with mortality, adverse ventricular remodeling, and patient prognosis.[6,7] The current study reported an angiographic no-reflow phenomenon in 15.87% of STEMI patients undergoing PPCI. This study also found that angiographic no-reflow was an independent predictor of in-hospital mortality in STEMI patients undergoing PPCI. A meta-analysis[8] of patients with ACS found that adenosine can reduce the occurrence of no-reflow after PCI, as well as reduce the myocardial infarct size. The adenosine production by biomaterial-supported mesenchymal stromal cells exerted a powerful anti-inflammatory effect that is critical for recovery following myocardial ischemia/reperfusion injury.[9] Thus, adenosine can be designated as a potential treatment of no-reflow.[6,9]

In an in vitro experiment,[3] ticagrelor was shown to increase the concentration of extracellular adenosine by inhibiting its uptake by red blood cells. In a population comprising of the healthy population,[10] ticagrelor enhanced the adenosine-induced coronary blood flow velocity via the inhibition of adenosine uptake by erythrocytes and other cells. Adenosine produces a series of adenosine-mediated biological effects such as platelet inhibition, vasodilation, and protection of myocardium. In experimental studies, ticagrelor has been shown to increase the adenosine-induced physiological response by shifting the dose–response curve for the adenosine-induced coronary blood flow velocity to the left.[11] Ticagrelor increases the adenosine plasma concentration in ACS patients as compared to clopidogrel by inhibiting the adenosine uptake by red blood cells.[11] These results suggested that the pleiotropic properties of ticagrelor could be mediated at least partially by increased adenosine plasma concentration. In an experiment of rat ischemia/reperfusion,[13] ticagrelor but not clopidogrel administered just before reperfusion protected against reperfusion injury. This acute treatment or administration of chronic ticagrelor for 4 weeks or their combination improved heart function, whereas clopidogrel did not exert any effect despite achieving a similar degree of platelet inhibition.

The current study found that in the East Asian population, the proportion of patients with the no-reflow phenomenon in the ticagrelor-treated group was significantly lower than those in the low-load clopidogrel-treated group. This result might lead to a significantly lower in-hospital mortality in the ticagrelor-treated group than in the low-load clopidogrel-treated group. In addition, Spearman’s correlation coefficient analysis exhibited a close correlation between the no-reflow phenomenon and antplatelet treatment strategy. However, this phenomenon was not observed in the high-load clopidogrel-treated group. Thus, it can be speculated that ticagrelor may reduce the incidence of no-reflow by mediating the effects of increasing endogenous adenosine, thereby reducing the in-hospital mortality.

Nevertheless, the present study has some limitations. This retrospective study did not detect plasma adenosine concentrations in patients. Whether ticagrelor can reduce the incidence of no-reflow by increasing the effect of endogenous adenosine and reduce the in-hospital mortality necessitates further confirmation by prospective studies.

Declaration of patient consent
We obtained all appropriate patient consent forms for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and efforts will be made to conceal their identity; however, the anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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