Impact of preprocedural coronary flow grade on duration of dual antiplatelet therapy in acute myocardial infarction

Yong Hoon Kim1,3, Ae-Young Her1,3, Byeong-Keuk Kim2, Sung-Jin Hong2, Chul-Min Ahn2, Jung-Sun Kim2, Young-Guk Ko2, Donghoon Choi2, Myeong-Ki Hong2 & Yangsoo Jang2

We investigated the impact of pre-percutaneous coronary intervention (pre-PCI) thrombolysis in myocardial infarction (TIMI) flow grade (pre-TIMI) on 3-month (3-mo) and 12-mo of dual antiplatelet therapy (DAPT) in patients with acute myocardial infarction (AMI). This was a post hoc analysis of the TICO trial. A total of 2083 patients with AMI (pre-TIMI 0/1: n = 1143; pre-TIMI 2/3: n = 940) were evaluated. The primary outcome was the occurrence of net adverse clinical events (NACE), defined as a composite of TIMI major bleeding and major adverse cardiac and cerebrovascular events (MACCE) within 12-mo following PCI. The secondary outcomes were the occurrence of the individual components of TIMI bleedings and MACCE. In the pre-TIMI 0/1 group, the primary and secondary outcomes were not significantly different between the 3-mo and 12-mo DAPT groups. However, in the pre-TIMI 2/3 group, the occurrences of TIMI minor (adjusted hazard ratio [aHR]: 0.294; p = 0.016) and major or minor bleeding (aHR: 0.483; p = 0.014) on intention-to-treat analysis were significantly higher in the 12-mo than in the 3-mo DAPT group. The occurrence of MACCE was similar between the two groups. A higher bleeding tendency in 12-mo DAPT compared with 3-mo DAPT was more obvious in the pre-TIMI 2/3 group than in the pre-TIMI 0/1 group.

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Current guidelines1,2 recommend 12-month (12-mo) dual antiplatelet therapy (DAPT) consisting of aspirin with a P2Y12 inhibitor after percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI). However, more recent reports3,4 have shown that 3-month (3-mo) duration of DAPT could reduce hemorrhagic risk without increasing the risk of ischemic events. Platelets play a key role in the development of acute coronary syndrome5, and platelet activation and plugging are of significant importance in the development of impaired pre-PCI flow because platelet-mediated release of vasoactive mediators increases platelet-rich thrombi formation5,6. Under the circumstance where blood supply is completely absent, available oxygen in the ischemic zone of the myocardium disappears within seconds. Hence, after a certain duration of complete ischemia, there is no treatment modality that can salvage ischemic myocardium7. However, cardiomyocytes that are exposed to low residual oxygen levels may be able to maintain sufficient adenosine triphosphate to survive for an extended period, even if the amount of adenosine triphosphate is insufficient to allow their contraction8. Hence, we might think that patients with pre-PCI thrombolysis in myocardial infarction (pre-PCI TIMI) flow grade 0/1 (pre-TIMI 0/1) or pre-TIMI 2/38 are in a meaningful different situation. Compared to patients with pre-TIMI 0/1, those with pre-TIMI 2/3 have a lower incidence of cardiogenic shock and improved early and late left ventricular ejection fraction (LVEF) through preservation of flow to the infarct zone, with consequent preservation of myocardial viability5,8,9. However, comparative clinical outcomes between short-term and standard 12-mo DAPT according to pre-TIMI in patients with AMI has not been reported. Therefore, the authors thought that the reevaluation of safety and efficacy of 3-mo and 12-mo DAPT according to the different pre-TIMI in patients with AMI could provide beneficial information to treat those patients. In this post hoc analysis of the TICO trial (Ticagrelor...
Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome), we compared 1-year clinical outcomes between these 2 different antiplatelet strategies in patients with AMI, after new-generation drug-eluting stent (DES) implantation.

Results
Baseline characteristics. Detailed information on antiplatelet therapy during the study period, causes of non-adherence to the allocated treatment, and medications during the study period are shown in Supplementary materials 1, 2, and 3. Table 1 shows the baseline characteristics of the study population. In both patients with pre-TIMI 0/1 and 2/3, the mean age, the number of males, and the mean value of LVEF were similar between the 3-mo and 12-mo DAPT groups. In patients with pre-PCI TIMI 0/1, the number of patients with a history of prior MI, the mean value of estimated glomerular filtration rate (eGFR), and the prescription rate of angiotensin receptor blockers (ARB) and calcium channel blockers (CCB) were significantly higher in the 3-mo DAPT group than in the 12-mo DAPT group. In contrast, the mean value of serum creatinine, and the prescription rates of beta-blockers and angiotensin converting enzyme inhibitors (ACEI) were higher in the 12-mo DAPT group. In patients with pre-TIMI 2/3, eGFR was higher in the 3-mo DAPT group, and the prescription rate of ticagrelor and beta-blockers was higher in the 12-mo DAPT group. Supplementary material 4 shows the baseline characteristics according to 3-mo or 12-mo DAPT strategies. Supplementary materials 5 and 6 show the baseline characteristics of the as-treated population.

Clinical outcomes. Clinical outcomes are summarized in Tables 2, 3, and 4, Supplementary materials 7–10, and Figs. 1a–j.

Net adverse clinical events (NACE). Table 2 shows clinical outcomes by Kaplan–Meier analysis and Cox-proportional hazard ratio analysis. In patients in both pre-TIMI 0/1 and 2/3 groups, the occurrence of NACE was not significantly different between the 3-mo and 12-mo DAPT groups (adjusted hazard ratio [aHR]: 0.689; 95% confidence interval [CI]: 0.389–1.220; p = 0.201; and aHR: 0.741; 95% CI: 0.432–1.273; p = 0.278, respectively) (Fig. 1a,b). In patients in both as-treated pre-TIMI 0/1 and 2/3 groups, the occurrence of NACE was not significantly different between 3-mo and 12-mo DAPT groups (Supplementary materials 7 and 8). On 3-mo landmark analyses between the 3-mo and 12-mo groups (Supplementary material 9), although the occurrence of NACE was not significantly different between 3-mo and 12-mo DAPT (aHR: 0.358; 95% CI: 0.128–1.003; p = 0.051) in pre-TIMI 0/1 group, it was significantly higher in the 12-mo DAPT group than in 3-mo DAPT group in the pre-TIMI 2/3 group (aHR: 0.422; 95% CI: 0.184–0.965; p = 0.041).

Thrombolysis in myocardial infarction (TIMI) bleedings. In patients with pre-TIMI 0/1, the occurrence of TIMI major, minor, and major or minor bleedings (Table 2, Fig. 1c,e,g) were not significantly different between the 3-mo and 12-mo DAPT groups. These results were repeated in patients in the as-treated group and on the 3-mo landmark analysis. In patients with pre-TIMI 2/3, although the occurrence of TIMI major bleeding was similar between the 3-mo and 12-mo DAPT groups (Table 2 and Fig. 1d), the occurrence of TIMI minor bleeding (aHR: 0.294; 95% CI: 0.108–0.799; p = 0.016) and TIMI major or minor bleeding (aHR: 0.483; 95% CI: 0.271–0.862; p = 0.014) were significantly higher in the 12-mo DAPT group than in the 3-mo DAPT group (Table 2, Fig. 1f,h). These results were repeated in patients in the as-treated group. However, on 3-mo landmark analyses between the 3-mo and 12-mo groups (Supplementary material 9), the occurrence of TIMI major, minor, and major or minor bleeding in patients in the pre-TIMI 2/3 group was significantly higher in the 12-mo DAPT group than in the 3-mo DAPT group (aHR: 0.100; 95% CI: 0.012–0.796; p = 0.030, aHR: 0.103; 95% CI: 0.013–0.817; p = 0.031, and aHR: 0.109; 95% CI: 0.025–0.467; p = 0.003, respectively).

Major adverse cardiac and cerebrovascular events (MACCE). The occurrence of MACCE was not significantly different between the 3-mo and 12-mo DAPT groups in patients in both pre-TIMI 0/1 (aHR: 0.773; 95% CI: 0.391–1.527; p = 0.458, Table 2, Fig. 1i) and 2/3 groups (aHR: 0.766; 95% CI: 0.362–1.623; p = 0.487, Table 2, Fig. 1i). These results were repeated in patients in the as-treated group and on the 3-mo landmark analysis.

Subgroup analyses. Subgroup analyses for NACE are shown in Figs. 2 and 3. In patients with pre-TIMI 0/1 (Fig. 2) and old age (≥65 years, HR: 0.37; 0.16–0.89; p = 0.026), female (HR: 0.22; 0.06–0.81; p = 0.022), those with single-vessel disease (HR: 0.30; 0.10–0.92; p = 0.035); and in patients in the pre-TIMI 2/3 group (Fig. 3) with single-vessel disease (HR: 0.36; 0.14–0.92; p = 0.033), 3-mo DAPT showed better outcomes over 12-mo DAPT in this study.

Independent predictors for NACE. In Supplementary material 11, after multivariate analysis of patients with pre-TIMI 0/1, age, prior MI, eGFR, and diameter of deployed stents were independent predictors for NACE. In patients with pre-TIMI 2/3, diabetes mellitus was an independent predictor of NACE in this study.

Clinical outcomes between pre-TIMI 0/1 and 2/3 groups according to 3-month or 12-month DAPT strategies. In Table 3, in patients with 3-mo DAPT, the occurrence of NACE, TIMI major, minor, and major or minor bleeding was similar between the pre-TIMI 0/1 group and the pre-TIMI 2/3 group after adjustment. However, in patients with 12-mo DAPT, the occurrence of TIMI major or minor bleeding was sig-
### Variables

|                 | Pre-PCI TIMI 0/1 (n = 1143) | Pre-PCI TIMI 2/3 (n = 940) |
|----------------|-----------------------------|-----------------------------|
| **Total**      |                             |                             |
| Ticagrelor     |                             |                             |
| Tocagrelor-based 12-mo DAPT group (n = 561) | 56.5 ± 10.7 | 54.6 ± 11.4 |
| p              |                             |                             |
| **Total**      |                             |                             |
| Tocagrelor-based 12-mo DAPT group (n = 472) | 57.7 ± 10.8 | 54.7 ± 11.1 |
| p              |                             |                             |
| **Pre-PCI TIMI 0/1 (n = 1143)** |                             |                             |
| Age (years)    | 58.7 ± 10.8                 | 58.5 ± 10.8                 |
| Male, n (%)    | 957 (83.7)                  | 476 (81.8)                  |
| LVEF (%)       | 49.4 ± 10.7                 | 49.9 ± 10.9                 |
| BMI (kg/m²)    | 24.9 ± 3.2                  | 24.9 ± 3.2                  |
| Hypertension, n (%) | 504 (44.1)             | 261 (44.8)                  |
| Diabetes mellitus, n (%) | 247 (21.6)           | 130 (22.3)                  |
| Dyslipidemia, n (%) | 652 (57.0)               | 332 (57.0)                  |
| Prior MI, n (%) | 32 (2.8)                    | 23 (4.0)                    |
| Prior PCI, n (%) | 65 (5.7)                   | 40 (6.9)                    |
| Prior CAGB, n (%) | 5 (0.4)                    | 3 (0.5)                     |
| Prior HE, n (%) | 19 (1.7)                    | 7 (1.2)                     |
| Prior stroke, n (%) | 42 (3.7)                  | 18 (3.1)                    |
| Current smokers, n (%) | 523 (45.8)              | 254 (43.6)                  |
| White blood cell (x 10^9/L) | 10.9 ± 4.0                | 10.8 ± 4.3                  |
| Hemoglobin (g/dL) | 14.6 ± 1.7                 | 14.5 ± 1.7                  |
| Platelet (x 10^9/L) | 245.1 ± 62.6              | 244.8 ± 60.0                |
| Peak CK-MB (mg/dL) | 476.0 ± 950.8             | 476.7 ± 932.7               |
| Peak troponin-I (ng/mL) | 1.01 ± 0.76               | 0.97 ± 0.55                 |
| Serum creatinine (mg/L) | 77.0 ± 22.4               | 78.5 ± 22.6                 |
| eGFR (mL/min/1.73m²) | 74.7 ± 21.7               | 75.4 ± 22.1                 |
| Clinical presentation |                            |                             |
| NSTEMI         | 360 (31.5)                  | 190 (32.6)                  |
| STEMI          | 783 (68.5)                  | 392 (67.4)                  |
| Antithrombotic drug before PCI |                    |                             |
| Unfractionated heparin, n (%) | 810 (70.9)              | 406 (69.8)                  |
| LMWH, n (%)    | 95 (8.3)                    | 47 (8.1)                    |
| Glycoprotein IIb/IIIa inhibitors | 147 (12.9)               | 73 (12.5)                   |
| Antiplatelet drug before PCI |                    |                             |
| Aspirin, n (%) | 1099 (96.2)                 | 561 (96.4)                  |
| Clopidogrel, n (%) | 219 (19.2)                | 123 (21.1)                  |
| Ticagrelor, n (%) | 951 (83.2)                | 480 (82.5)                  |
| Prasugrel, n (%) | 5 (0.4)                    | 2 (0.3)                     |
| Other discharge medications |                    |                             |
| Beta-blockers, n (%) | 821 (71.8)               | 389 (66.8)                  |
| ACE inhibitors, n (%) | 603 (46.0)               | 253 (43.5)                  |
| ARBs, n (%)    | 230 (20.1)                  | 138 (23.7)                  |
| CCBs, n (%)    | 97 (8.5)                    | 66 (11.3)                   |
| Statin, n (%)  | 1134 (98.3)                 | 572 (98.3)                  |
| Angiographic and procedural characteristics |                    |                             |
| Infarct-related artery |                    |                             |
| LM, n (%)      | 9 (0.8)                     | 6 (1.0)                     |
| LAD, n (%)     | 535 (46.8)                  | 273 (46.9)                  |
| LCx, n (%)     | 204 (17.8)                  | 94 (16.2)                   |
| RCA, n (%)     | 395 (34.6)                  | 209 (35.9)                  |
| Primary PCI, n (%) | 666 (58.3)               | 333 (57.2)                  |
| Bifurcation lesion, n (%) | 124 (10.8)              | 54 (9.3)                    |
| Extent of CAD  |                             |                             |
| Single-vessel disease, n (%) | 544 (47.6)               | 276 (47.4)                  |
| Two-vessel disease, n (%) | 353 (30.9)                | 187 (32.1)                  |
| Continued     |                             |                             |
Table 1. Baseline clinical, laboratory, angiographic and procedural characteristics. Values are mean ± SD or n (%). The p values for continuous data obtained from analysis of the unpaired t-test. The p values for categorical data obtained from chi-square test. Pre-PCI pre-percutaneous coronary intervention, TIMI Thrombolysis In Myocardial Infarction, DAPT dual antiplatelet therapy, LVEF left ventricular ejection fraction, BMI body mass index, MI myocardial infarction, PCI percutaneous coronary intervention, CABG coronary artery bypass graft, HF heart failure, CK-MB creatine kinase myocardial band, eGFR estimated glomerular filtration rate, NSTEMI non-ST-elevation MI, LMWH low-molecular weight heparin, ACE angiotensin converting enzyme, ARB angiotensin receptor blocker, CCB calcium channel blocker, LM left main coronary artery, LAD left anterior descending coronary artery, LCx left circumflex coronary artery, RCA right coronary artery, CAD coronary artery disease, PRECISE Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antplatelet Therapy.

| Variables                                  | Pre-PCI TIMI 0/1 (n = 1143) | Pre-PCI TIMI 2/3 (n = 940) |
|--------------------------------------------|-----------------------------|-----------------------------|
|                                            | Total                        | Ticagrelor monotherapy after 3-mo DAPT (n = 582) | Ticagrelor-based 12-mo DAPT group (n = 561) | P | Total                        | Ticagrelor monotherapy after 3-mo DAPT (n = 472) | Ticagrelor-based 12-mo DAPT group (n = 465) | P |
| ≥ Three-vessel, n (%)                      | 246 (21.5)                  | 119 (20.4)                  | 127 (22.6)                  | 0.388 | 234 (24.9)                  | 114 (24.0)                  | 120 (25.8)                  | 0.547 |
| Transfemoral approach, n (%)               | 663 (58.0)                  | 343 (58.9)                  | 320 (57.0)                  | 0.517 | 418 (44.5)                  | 203 (42.7)                  | 215 (46.2)                  | 0.294 |
| Treated lesions per patient                | 1.19 ± 0.45                 | 1.20 ± 0.46                 | 1.19 ± 0.45                 | 0.696 | 1.25 ± 0.51                 | 1.27 ± 0.54                 | 1.24 ± 0.49                 | 0.505 |
| Multi-lesion intervention, n (%)           | 191 (16.7)                  | 100 (17.2)                  | 91 (16.2)                   | 0.692 | 208 (22.1)                  | 107 (22.5)                  | 101 (21.7)                  | 0.814 |
| Multi-vessel intervention, n (%)           | 148 (12.9)                  | 77 (13.2)                   | 71 (12.7)                   | 0.792 | 176 (18.7)                  | 89 (18.7)                   | 87 (18.7)                   | 0.991 |
| Total number of stents per patient         | 1.33 ± 0.63                 | 1.33 ± 0.64                 | 1.33 ± 0.62                 | 0.967 | 1.35 ± 0.66                 | 1.38 ± 0.71                 | 1.32 ± 0.61                 | 0.191 |
| Stent diameter, mean (mm)                  | 3.16 ± 0.43                 | 3.18 ± 0.43                 | 3.14 ± 0.42                 | 0.132 | 3.18 ± 0.45                 | 3.15 ± 0.46                 | 3.21 ± 0.45                 | 0.034 |
| Total stent length per patient (mm)        | 35.1 ± 19.4                 | 34.8 ± 19.6                 | 36.4 ± 19.1                 | 0.617 | 32.7 ± 20.0                 | 33.1 ± 20.6                 | 32.3 ± 19.4                 | 0.549 |
| PRECISE-DAPT score                        | 21.6 ± 19.5                 | 21.3 ± 20.1                 | 21.8 ± 19.0                 | 0.671 | 21.9 ± 19.9                 | 21.8 ± 20.8                 | 22.0 ± 19.0                 | 0.823 |
| ≥ 25, n (%)                                | 244 (21.3)                  | 124 (21.3)                  | 120 (21.4)                  | 0.972 | 232 (24.7)                  | 122 (25.7)                  | 110 (23.7)                  | 0.471 |

Significantly higher in the pre-TIMI 2/3 group than in the pre-TIMI 0/1 group (aHR: 0.514; 95% CI: 0.299–0.884; p = 0.016).

ST-segment elevation versus non-ST-segment elevation myocardial infarction (STEMI vs. NSTEMI). Table 1 shows the comparison of clinical outcomes between STEMI and NSTEMI is summarized in Supplemen-
tary material 12. After adjustment, in patients with both pre-TIMI 0/1 and 2/3, the occurrence of NACE, TIMI bleedings (major, minor, and major or minor), and MACCE were not significantly different between STEMI and NSTEMI. Supplementary material 13 shows univariate analysis for NACE according to the pre-TIMI in comparing STEMI and NSTEMI.

Interaction between pre-TIMI during an index PCI and the duration of DAPT. Table 4 shows the interaction between pre-TIMI during an index PCI (pre-TIMI 0/1 vs. 2/3) and the duration of DAPT (3-mo or 12-mo DAPT). There were no significant interactions between the different pre-PCI TIMI during an index PCI and the duration of DAPT after adjustment.

Discussion
The TIMI flow grade is a traditional method for assessing coronary blood flow11. Previous studies have shown that various pro-thrombotic markers including platelet count, reactivity, and mean platelet volume were associated with patency of the infarct-related artery in patients with STEMI, before primary PCI12,13. Moreover, in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) and HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) Trials, pre-TIMI 3 was an important independent predictor of 1-year survival14. The main findings of this study were as follows: (1) in patients with pre-TIMI 0/1, the occurrence of NACE, TIMI bleedings (major, minor, and major or minor), and MACCE (all-cause death, cardiac death, MI, ST, and stroke) were not significantly different between the 3-mo and 12-mo DAPT groups. (2) In patients with pre-TIMI 2/3, the occurrence of TIMI minor bleeding and major or minor bleeding were significantly higher in the 12-mo DAPT group than in the 3-mo DAPT group. Moreover, on 3-mo landmark analyses between 3-mo and 12-mo, the occurrence of TIMI major bleeding was significantly higher in the 12-mo DAPT group than in the 3-mo DAPT group. However, the occurrence of MACCE was similar between the 3-mo and 12-mo DAPT groups. (3) The occurrence of NACE, TIMI bleeding, and MACCE were not significantly different between STEMI and NSTEMI.

The present data indicate that pre-TIMI 0/1 is present in 54.8% (STEMI, 68.5%, vs. NSTEMI, 31.5%) and pre-TIMI 2/3 is present in 45.2% (STEMI, 31.1%, vs. NSTEMI, 68.9%). The ratio STEMI/NSTEMI is at the complete opposite between the pre-TIMI 0/1 and 2/3 groups. However, these results are comparable with Bailleul et al.
study^{15}. Although the proportions of STEMI and NSTEMI in patients with pre-TIMI 0/1 or 2/3 were different, these proportions were not significantly different between the 3-mo DAPT or 12-mo DAPT groups (Table 1). Especially, in Table 3, STEMI was included in the multivariate analysis as a significant variable with other variables. The occurrence of TIMI major or minor bleeding was significantly in the pre-TIMI 2/3 group than in the pre-TIMI 0/1 group, similar to the results in Table 2. In addition, as shown in Supplementary material 10, in patients with both pre-TIMI 0/1 and 2/3, the occurrence of NACE, TIMI bleeding (major, minor, and major or minor), and MACCE were similar between STEMI and NSTEMI.

A ruptured, eroded, or protruding calcified atherosclerotic plaque could trigger local thrombosis, which is a critical step in the pathogenesis of AMI^{16}. To date, it remains unclear why some plaques lead to STEMI with poor pre-TIMI but others do not^{17}. Compared to pre-TIMI 0/1, which has prolonged ischemia and late reperfusion, can impair endothelial function, and cause myocardial tissue edema, pre-TIMI 2/3 would have shorter ischemic time and less myocardial damage^{17}. In a state of endothelial dysfunction, disruption of the balance between anti-thrombosis and pro-thrombosis can lead to increased platelet aggregation^{18}. More recently, Bauer et al^{19} reported that, after adjustment, definite stent thrombosis (ST) occurred only in patients with pre-TIMI 0/1 in their ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation

Table 2. Clinical outcomes by Kaplan–Meier analysis and Cox-proportional hazard ratio analysis at 1 year. Pre-PCI pre-percutaneous coronary intervention, TIMI Thrombolysis In Myocardial Infarction, DAPT dual antiplatelet therapy, HR hazard ratio, CI confidence interval, NACE net adverse clinical events, MACCE major adverse cardiac and cerebrovascular events, MI myocardial infarction, TVR target vessel revascularization, ST stent thrombosis, eGFR estimated glomerular filtration rate, LVEF left ventricular ejection fraction, STEMI ST-segment elevation myocardial infarction. *Adjusted by age, prior MI, serum creatinine, eGFR, and stent diameter (Supplementary material 15). †Adjusted by age, male, LVEF, hypertension, diabetes mellitus, prior PCI, serum creatinine, and eGFR (Supplementary material 15).
Myocardial Infarction to Open the Coronary Artery) sub-study. Moreover, they showed that prehospital administration of ticagrelor was less effective in patients with pre-TIMI 0/1 than those with pre-TIMI 2/3 (0.3% vs. 1.3%, p < 0.05). Hence, it could be assumed that on treatment with 3-mo or 12-mo DAPT, the major clinical outcomes could be influenced by pre-TIMI. However, the effect of pre-TIMI on bleeding and cardiovascular events after ticagrelor-based 3-mo or 12-mo DAPT in patients with AMI has not been reported. Thus, this paper may be considered as the first report focused on this perspective.

In our study, compared to the patients with pre-TIMI 0/1, the occurrences of TIMI minor bleeding and major or minor bleeding were significantly higher in the 12-mo DAPT group than in the 3-mo DAPT group, in patients with pre-TIMI 2/3. In addition, on 3-mo landmark analyses between 3-mo and 12-mo, the occurrence of NACE and TIMI major, minor, and major and minor bleeding were also higher in the 12-mo DAPT group than in the 3-mo DAPT group. Because of the absence of previous reports, it could be difficult to provide comparative results between our and previous reports. However, based on our results, it could be considered that the beneficial effects of 3-mo DAPT over 12-mo DAPT in reducing bleeding events are mainly determined by pre-TIMI 2/3 rather than by pre-TIMI 0/1. However, in patients with 12-mo DAPT, the mean age, the number

| Outcomes | Cumulative events (%) | Pre-PCI TIMI 0/1 (n = 582) | Pre-PCI TIMI 2/3 (n = 475) | Log rank | HR (95% CI) | p value | HR (95% CI) | p value |
|----------|----------------------|----------------------------|--------------------------|----------|------------|--------|------------|--------|
| NACE     | 20 (3.5)             | 23 (4.9)                  | 0.257                    | 0.708 (0.389–1.289) | 0.259 | 0.729 (0.384–1.384) | 0.333 |
| TIMI bleeding |                      |                           |                         |          |            |        |            |        |
| Major    | 5 (0.9)              | 12 (2.6)                 | 0.033                    | 0.339 (0.120–0.963) | 0.042 | 0.301 (0.090–1.003) | 0.051 |
| Minor    | 10 (1.7)             | 5 (1.1)                  | 0.364                    | 1.635 (0.559–4.784) | 0.369 | 2.129 (0.694–6.533) | 0.187 |
| Major or minor | 15 (2.6)          | 17 (3.6)                 | 0.349                    | 0.719 (0.359–1.439) | 0.351 | 0.773 (0.396–1.622) | 0.496 |
| MACCE    | 15 (2.6)             | 12 (2.6)                 | 0.952                    | 1.024 (0.479–2.187) | 0.952 | 1.151 (0.513–2.580) | 0.733 |
| All-cause death | 7 (1.2)             | 6 (1.3)                  | 0.935                    | 0.956 (0.321–2.844) | 0.935 | 1.261 (0.391–4.066) | 0.698 |
| Cardiac death | 5 (0.9)             | 2 (0.4)                  | 0.382                    | 2.047 (0.397–10.55) | 0.392 | 2.263 (0.423–12.12) | 0.340 |
| Acute MI  | 3 (0.5)              | 2 (0.4)                  | 0.822                    | 1.288 (0.295–7.349) | 0.822 | 2.297 (0.370–14.25) | 0.372 |
| TVR      | 3 (0.5)              | 3 (0.7)                  | 0.802                    | 0.815 (0.165–4.039) | 0.802 | 0.816 (0.132–5.064) | 0.827 |
| ST       | 3 (0.5)              | 2 (0.4)                  | 0.366                    | 1.261 (0.391–4.066) | 0.698 | 1.243 (0.198–7.796) | 0.817 |
| Stroke   |                      |                           |                         |          |            |        |            |        |
| Ischemic | 3 (0.5)              | 1 (0.2)                  | 0.422                    | 2.451 (0.256–23.57) | 0.437 | 2.544 (0.229–28.27) | 0.401 |
| Hemorrhagic | 0                  | 1 (0.2)                  | 0.270                    | –         | –         | –      | –          | –      |

Table 3. Clinical outcomes between pre-PCI TIMI 0/1 and 2/3 groups according to 3-month or 12-month DAPT strategies. Pre-PCI pre-percutaneous coronary intervention, TIMI Thrombolysis In Myocardial Infarction, DAPT dual antiplatelet therapy, HR hazard ratio, CI confidence interval, NACE net adverse clinical events, MACCE major adverse cardiac events, MI myocardial infarction, TVR target vessel revascularization, ST stent thrombosis, LVEF left ventricular ejection fraction, STEMI ST-segment elevation myocardial infarction, LM left main coronary artery, ACE angiotensin converting enzyme, CCB calcium channel blocker. a Adjusted by age, LVEF, diabetes mellitus, white blood cell, hemoglobin, STEMI, LM, and single-vessel disease (Supplementary material 16). b Adjusted by age, male, hypertension, diabetes mellitus, prior MI, prior PCI, hemoglobin, STEMI, beta-blocker, ACE inhibitor, CCB, transfemoral approach, and stent diameter (Supplementary material 16).
of hypertensive and diabetic patients, and patients with prior history of PCI were significantly higher in the pre-TIMI 2/3 group than in the pre-TIMI 0/1 group. In this study, to adjust the diverse variables, multivariate analysis was performed. But, it could be speculated that these baseline characteristics may play an important role in explaining this higher TIMI major or minor bleeding. Despite the possible benefit of DAPT in reducing ischemic events of infarction, it may be considered that no compound can enter an ischemic no-flow area of myocardium, especially if the culprit coronary artery in totally occlude. Hence, in patients with pre-TIMI 0/1, the occurrence of NACE, TIMI bleeding, and MACCE would not be significantly different between the 3-mo or 12-mo DAPT groups. In contrast, patients with pre-TIMI 2/3 treated with 12-mo DAPT showed a higher incidence of bleeding tendency than those with 3-mo DAPT without showing increased incidences of ischemic events. According to the subgroup analysis (Figs. 2 and 3), in both pre-TIMI 0/1 and 2/3, and in patients with single-vessel disease, 3-mo DAPT may be preferred over 12-mo DAPT to reduce NACE in this study.

In the FAST-MI (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial infarction) study, after 2010, there was no further mortality gain was founded in patients with STEMI with reperfusion therapy or in patients with NSTEMI, regardless of performing PCI. Moreover, there are some debates regarding the long-term prognostis between STEMI and NSTEMI, the occurrence of NACE, TIMI bleeding, and MACCE were not significantly different between these two groups both in pre-TIMI 0/1 and 2/3 groups (Supplementary material 12) in our study and our results were consistent with those of Montalescot's findings.

| Outcomes              | Interaction p value (Intention-to-treat) | Interaction p value (As-treated) |
|-----------------------|----------------------------------------|---------------------------------|
|                       | Unadjusted | Adjusteda | Unadjusted | Adjusteda |
| NACE                  |            |           |            |           |
| Major                 | 0.043      | 0.476     | 0.040      | 0.395     |
| Minor                 | 0.011      | 0.329     | 0.014      | 0.400     |
| Major or minor        | 0.394      | 0.714     | 0.291      | 0.730     |
| MACCE                 | 0.473      | 0.836     | 0.396      | 0.716     |
| All-cause death       | 0.512      | 0.505     | 0.583      | 0.909     |
| Cardiac death         | 0.887      | 0.108     | 0.820      | 0.540     |
| Acute MI              | 0.391      | 0.571     | 0.296      | 0.796     |
| TVR                   | 0.695      | 0.529     | 0.353      | 0.663     |
| ST                    | 0.714      | 0.532     | 0.667      | 0.267     |
| Stroke                |            |           |            |           |
| Ischemic              | 0.546      | 0.622     | 0.505      | 0.733     |
| Hemorrhagic           | 0.710      | 0.862     | 0.715      | 0.904     |

Table 4. Interaction between pre-PCI TIMI during an index PCI (pre-PCI TIMI 0/1 vs. 2/3) and the duration of DAPT (3-mo DAPT vs. 12-mo DAPT) for clinical outcomes. *Adjusted for variables that showed differences with p < 0.05 (age, male, LVEF, hypertension, diabetes mellitus, prior MI, prior PCI, serum creatinine, eGFR, STEMI, beta-blocker, CCB, and stent diameter) (Supplementary material 15) between the pre-PCI TIMI 0/1 and pre-PCI 2/3 groups. Pre-PCI pre-percutaneous coronary intervention, TIMI Thrombolysis In Myocardial Infarction, DAPT dual antiplatelet therapy, 3-mo 3-month, 12-mo 12-month, NACE net adverse clinical events, MACCE major adverse cardiac and cerebrovascular events, MI myocardial infarction, TVR target vessel revascularization, ST stent thrombosis, LVEF left ventricular ejection fraction, eGFR estimated glomerular filtration rate, STEMI ST-segment elevation myocardial infarction, CCB calcium channel blocker.
Figure 1. Time-to-event curves for NACE (a and b), TIMI major bleeding (c and d), TIMI minor bleeding (e and f), TIMI major or minor bleeding (g and h), and MACCE (i and j) in pre-PCI TIMI flow grade 0/1 (a, c, e, g, and i) and 2/3 groups (b, d, f, h, and j).
Figure 1. (continued)
In conclusion, our results suggest that the higher bleeding tendency in 12-mo DAPT compared with 3-mo DAPT was more obvious in patients with pre-TIMI 2/3 than in those with pre-TIMI 0/1. However, more studies are warranted to confirm these results.

**Methods**

**Study design.** A total of 3056 participants from the TICO randomized clinical trial (ClinicalTrials.gov Identifier: NCT02494895; First registration: 10/07/2015) were evaluated in this study. The TICO trial was an investigator-initiated, multicenter, randomized, unblinded trial conducted at 38 centers in South Korea. Briefly, after PCI, patients were randomly assigned in a 1:1 ratio to receive ticagrelor monotherapy after 3-mo dual antiplatelet therapy, 12-mo DAPT ticagrelor-based 12-month dual antiplatelet therapy, HR hazard ratio, CI confidence interval, BMI body mass index, eGFR estimated glomerular filtration rate, NSTEMI non-ST segment elevation myocardial infarction, STEMI ST segment elevation myocardial infarction.

In conclusion, our results suggest that the higher bleeding tendency in 12-mo DAPT compared with 3-mo DAPT was more obvious in patients with pre-TIMI 2/3 than in those with pre-TIMI 0/1. However, more studies are warranted to confirm these results.

**Study population.** Key exclusion criteria included increased risk of bleeding due to prior hemorrhagic stroke, traumatic brain injury or brain surgery within the past 6 months, internal bleeding within the past 6 weeks, need of oral anticoagulation therapy, and anemia (hemoglobin ≤ 8 g/dL). The full inclusion and exclusion criteria are listed in Supplementary material 14. Additionally, patients with unstable angina (n = 926, 30.3%)
and those with post-PCI TIMI flow grade < 3 (n = 47, 1.5%) were excluded. During a 12-mo follow-up period, 17 patients in the pre-TIMI 0/1 group (3-mo DAPT, n = 9; 12-mo DAPT, n = 8) and 12 patients in the pre-TIMI 2/3 group (3-mo DAPT, n = 7; 12-mo DAPT, n = 5) were lost to follow-up. Participants who withdrew the consent (pre-TIMI 0/1 group, n = 14 [3-mo DAPT, n = 6; 12-mo DAPT, n = 8]; pre-TIMI 2/3 group, n = 9 [3-mo DAPT, n = 6; 12-mo DAPT, n = 3]) or those who died (pre-TIMI 0/1 group, n = 15 [3-mo DAPT, n = 7; 12-mo DAPT, n = 8]; pre-TIMI 2/3 group, n = 16 [3-mo DAPT, n = 6; 12-mo DAPT, n = 10]) were also excluded. Hence, a total of 2083 AMI patients were finally included. The patients were classified into pre-PCI TIMI flow grade 0/1 (pre-TIMI 0/1, n = 1143, 54.9%) and pre-TIMI 2/3 (n = 940, 45.1%) groups. Thereafter, the pre-TIMI 0/1 group was further divided into the ticagrelor monotherapy after 3-month dual antiplatelet therapy, 3-mo DAPT ticagrelor-based 12-month dual antiplatelet therapy, HR hazard ratio, CI confidence interval, BMI body mass index, eGFR estimated glomerular filtration rate, NSTEMI non-ST segment elevation myocardial infarction, STEMI ST segment elevation myocardial infarction.

**Figure 3.** Subgroup analysis for NACE in pre-TIMI flow grade 2/3 group. NACE net adverse clinical event, Pre-PCI pre-percutaneous coronary intervention, TIMI Thrombolysis In Myocardial Infarction, 3-mo DAPT ticagrelor monotherapy after 3-month dual antiplatelet therapy, 12-mo DAPT ticagrelor-based 12-month dual antiplatelet therapy, HR hazard ratio, CI confidence interval, BMI body mass index, eGFR estimated glomerular filtration rate, NSTEMI non-ST segment elevation myocardial infarction, STEMI ST segment elevation myocardial infarction.

| NACE | P-for-interaction |
|------|------------------|
| 0.300 |                    |
| 0.029 |                    |
| 0.086 |                    |
| 0.355 |                    |
| 0.164 |                    |
| 0.118 |                    |
| 0.089 |                    |
| 0.407 |                    |
| 0.834 |                    |
| 0.173 |                    |
| 0.464 |                    |

PCI procedure and medical treatment. Diagnostic coronary angiography and PCI were performed using standard techniques. If the patient was not taking aspirin or ticagrelor at the time of PCI, a loading dose of aspirin (300 mg) and ticagrelor (180 mg) were administered before PCI. Thereafter, 100 mg of aspirin per day and 90 mg of ticagrelor twice per day were prescribed as daily maintenance therapy. After 3-mo DAPT consisting of aspirin and ticagrelor, aspirin was discontinued in the ticagrelor monotherapy group and continued in the 12-mo DAPT group.
Study endpoints and definitions. The primary outcome was the occurrence of a NACE, defined as a composite of TIMI major bleeding and MACCE within 12 months of index PCI. The second outcome was the occurrence of TIMI major, minor, and major or minor bleeding and the occurrence of individual components of MACCE, defined as all-cause death, cardiac death (CD), myocardial infarction (MI), target vessel revascularization (TVR), ST, and stroke. Major bleeding was defined according to the TIMI criteria: intracranial bleeding, hemorrhage with a hemoglobin decrease of at least 5 g/dL, or fatal bleeding that caused death within 7 days\textsuperscript{4,26}. Definitions of CD, MI, TVR, ST, and stroke have already been published\textsuperscript{4}. In case of NSTEMI, culprit vessel was evaluated by coronary angiographic findings, 12-lead electrocardiogram, two-dimensional echocardiogram, and noninvasive stress test\textsuperscript{27,28}. A successful PCI was defined as a residual stenosis of < 30% and TIMI flow grade 3 for the infarct-related artery after the procedure. All baseline and procedural angiographic images including TIMI flow grade of the enrolled patients were centrally collected, and quantitative and qualitative analyses were independently performed in the central angiographic core laboratory (Cardiovascular Research Institute, Severance Cardiovascular Hospital, Seoul, South Korea). Moreover, the PRECISE-DAPT (Predicting Bleeding Complications in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy) score was assessed using an online calculator (http://www.precisedaptscore.com) with 5 variables (age, creatinine clearance, hemoglobin, white blood cell count, and previous spontaneous bleeding)\textsuperscript{29}. Adverse events were centrally collected, and any document that could lead to unblinding of treatment assignment was obliterated before submission to the clinical event committee. Outcomes were categorized according to predefined criteria by an independent clinical event committee blinded to the treatment assignments and primary results of the trial\textsuperscript{4}.

Statistical analysis. Primary analyses of this study were performed in an intention-to-treat manner. Pre-specified 3-month landmark analyses were performed. Post-hoc analyses were performed for the as-treated population regarding the actual treatments received. Categorical data were reported as numbers and percentages, and they were compared using the chi-square test or Fisher’s exact test, as appropriate. Continuous variables were expressed as mean ± standard deviation, and were compared using the Student's t-test. Various clinical outcomes were estimated using the Kaplan–Meier method, and intergroup differences were compared using the log-rank test. To determine meaningful variables, all variables with \( p < 0.1 \) and known conventional risk factors for poor outcomes in the AMI population were considered potential confounding factors and were included in the univariate analysis (Supplementary materials 15 and 16). Variables with \( p < 0.05 \) were included in the mul-
A role for changes in platelet production in the cause of acute coronary syndromes.

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Author contributions

Y.H.K. and A.-Y.H. researched data and wrote the manuscript. Y.H.K., A.-Y.H., B.-K.K., J.-S.K., M.-K.H., and Y.J. contributed to study design. Y.H.K., A.-Y.H., B.-K.K., S.-J.H., C.-M.A., J.-S.K., Y.-G.K., D.C., M.-K.H., and Y.J. contributed to the collection research data. Y.H.K. and A.-Y.H., B.-K.K., J.-S.K., Y.-G.K., D.C., M.-K.H., and Y.J.,

tivariate analysis model. For all analyses, a two-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 20 (IBM, Armonk, NY, USA).

Data availability

Data is contained with the article or supplementary material.

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contributed to provide intellectual inputs for the discussion. Y.H.K., A.-Y.H., S.-J.H., contributed to data analysis and edited the manuscript. Y.H.K., D.C., M.-K.H., and Y.J. contributed to provide supervisor role during the full processes of manuscript submitting and editing. All authors take full responsibility for this work.

**Competing interests**
The authors declare no competing interests.

**Additional information**

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**Correspondence** and requests for materials should be addressed to Y.H.K.

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