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# Comparison of Clinical Outcomes Between Ticagrelor and Prasugrel in Patients With ST-Segment Elevation Myocardial Infarction

## — Results From the Korea Acute Myocardial Infarction Registry-National Institutes of Health —

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***Background:*** There is little information regarding comparison of ticagrelor and prasugrel in patients with ST-segment elevation myocardial infarction (STEMI). We sought to compare clinical outcomes between ticagrelor and prasugrel in STEMI.

***Methods and Results:*** A total of 1,440 patients with STEMI who underwent successful primary percutaneous coronary intervention were analyzed; the data were obtained from the Korea Acute Myocardial Infarction Registry-National Institutes of Health. Of the patients, 963 received ticagrelor, and 477 received prasugrel. The primary study endpoint was 12-month major adverse cardiac events (MACE), including cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR). MACE occurred in 91 patients (6.3%) over the 1-year follow-up, and there were no differences in the incidence of MACE (hazard ratio [HR] 1.20, 95% confidence interval [CI] 0.76–1.91, P=0.438) between the 2 groups. Analysis by propensity score matching (429 pairs) did not significantly affect the results. The incidence of in-hospital major bleeding events was still comparable between the 2 groups (2.4% vs. 2.5%, odds ratio 0.75, 95% CI 0.30–1.86, P=0.532), and there was no significant difference in the incidence of MACE (5.4% vs. 5.8%, HR 0.98, 95% CI 0.56–1.74, P=0.951) after matching.

***Conclusions:*** Ticagrelor and prasugrel showed similar efficacy and safety profiles for treating STEMI in this Korean multicenter registry.

**Key Words:** Percutaneous coronary intervention; Prasugrel; ST elevation myocardial infarction; Ticagrelor

Dual antiplatelet therapy using aspirin combined with a P2Y12 receptor inhibitor is key to reducing ischemic events in patients undergoing percutaneous coronary intervention (PCI).[1] New P2Y12 receptor inhibitors such as ticagrelor and prasugrel improve clinical outcomes in patients with acute coronary syndrome (ACS) compared with clopidogrel.[2,3] Several studies have directly compared ticagrelor and prasugrel in patients with ACS; however, few studies have compared the clinical outcomes of ticagrelor and prasugrel in patients with ST-segment elevation myocardial infarction (STEMI) who undergo PCI.[4] Only 1 study performed a randomized head-to-head

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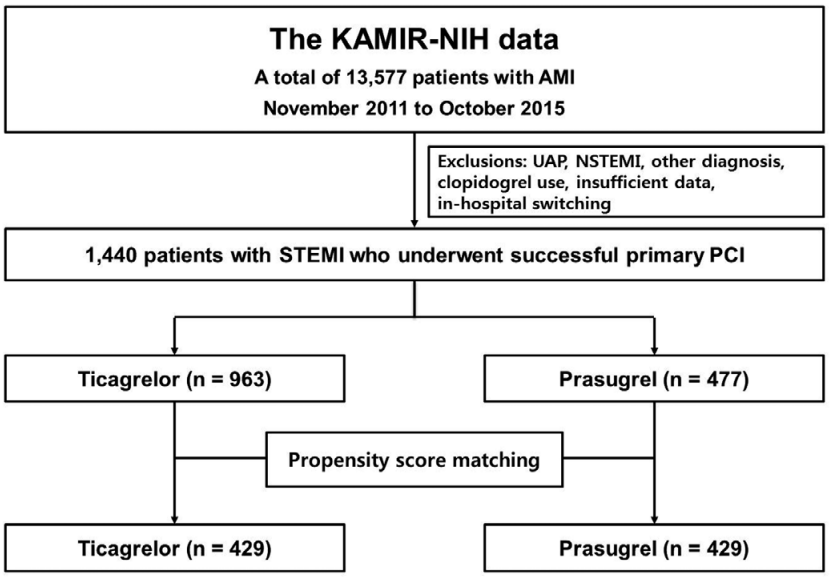


**Figure 1.** Flow chart of study. AMI, acute myocardial infarction; KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institutes of Health; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris.

comparison of the efficacy and safety of ticagrelor and prasugrel, and the results showed no differences in 30-day ischemic and safety outcomes between the 2 groups.[5] Although current guidelines recommend clopidogrel, ticagrelor, and prasugrel as P2Y12 receptor inhibitors with Class I indication for treating STEMI, the efficacy and safety profiles of new P2Y12 receptor inhibitors have differed in East Asian patients with acute MI.[1,6,7] In those studies, potent P2Y12 receptor inhibitors were not found to reduce ischemic events but were associated with increased risk of bleeding complications compared with clopidogrel. Moreover, the safety profiles as well as the clinical effects of these drugs in East Asian STEMI patients have not been well evaluated. In the present study, we compared the efficacy and safety outcomes for ticagrelor and prasugrel in patients with STEMI undergoing primary PCI using data from a large Korean multicenter registry.

## Methods

### Study Design and Patient Population

The Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) is a prospective, multicenter, web-based observational cohort study. Its aim is to develop a prognostic and surveillance index of Korean patients with acute MI from 20 centers in Korea. It has been supported by a grant from the Korea Centers for Disease Control and Prevention since November 2011.[8] A flow chart of the current study is shown in **Figure 1**. Briefly, from among 13,577 patients in the KAMIR-NIH registry we selected 1,440 consecutive patients with STEMI who underwent successful primary PCI. The diagnosis of STEMI was based on the criteria for the 3rd universal definition of MI: ST-segment elevation >2 mm in at least 2 precordial leads, ST-segment elevation >1 mm in at least 2 limb leads, or a new left bundle branch block evident on a 12-lead ECG evaluating the infarct-related arteries, as determined by coronary angiography, with ischemic symptoms and increased levels of cardiac-specific biomarkers (at least 1 value >99th percentile upper reference limit).[9] We excluded patients with a diagnosis other than STEMI (n=7,511), patients receiving clopidogrel (n=4,507), patients who discontinued or switched antiplatelet medications during hospitalization (n=81), and patients with insufficient data about antiplatelet drugs (n=38). The study patients were divided into 2 groups: those receiving ticagrelor (n=963) and those receiving prasugrel (n=477). The study protocols were approved by the ethics committees at each participating center, and all followed the principles of the Declaration of Helsinki. All patients provided written informed consent to participate in the registry. Trained study coordinators at each site collected the data using a standardized format. Standardized definitions of all variables were determined by the Steering Committee Board of KAMIR-NIH.

### Examination, Medical Treatment and PCI Procedure

Laboratory data were obtained on admission, except for lipid profiles, which were obtained after at least 9 h of fasting within 24 h of hospitalization. The baseline left ventricular ejection fraction (LVEF) was measured using 2D echocardiography before or immediately after PCI. The selection of vascular access, use of a glycoprotein IIb/IIIa inhibitor, use of coronary stents, use of thrombus aspiration, and use of intravascular ultrasound were determined at the operators' discretion. Patients who underwent PCI received 300 mg aspirin and 60 mg prasugrel or 180 mg ticagrelor as

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**Table 1. Baseline Clinical Characteristics of Study Population**

| | Crude population | | P value | Propensity-matched population | | P value |
|---|---|---|---|---|---|---|
| | Ticagrelor (n=963) | Prasugrel (n=477) | | Ticagrelor (n=429) | Prasugrel (n=429) | |
| **Demographics** | | | | | | |
| Age (years) | 61.8±12.4 | 55.9±9.7 | <0.001 | 57.2±11.9 | 56.6±9.5 | 0.430 |
| Men, n (%) | 775 (80.5) | 434 (91.0) | <0.001 | 382 (89.0) | 387 (90.2) | 0.576 |
| **Vital signs** | | | | | | |
| Systolic BP (mmHg) | 126.3±31.1 | 122.1±30.9 | 0.017 | 124.2±31.0 | 122.4±30.6 | 0.399 |
| Heart rate (/min) | 75.1±19.7 | 77.2±18.5 | 0.052 | 77.6±20.1 | 76.8±18.1 | 0.557 |
| **Risk factors, n (%)** | | | | | | |
| Current or ex-smoking | 637 (66.1) | 358 (75.1) | 0.001 | 305 (71.1) | 320 (74.6) | 0.250 |
| Hypertension | 429 (44.5) | 182 (38.2) | 0.021 | 170 (39.6) | 164 (38.2) | 0.674 |
| Diabetes mellitus | 215 (22.3) | 108 (22.6) | 0.893 | 95 (22.1) | 95 (22.1) | 1.000 |
| Dyslipidemia | 105 (10.9) | 54 (11.3) | 0.812 | 47 (11.0) | 47 (11.0) | 1.000 |
| Familial history of CAD | 60 (6.2) | 36 (7.5) | 0.346 | 31 (7.2) | 31 (7.2) | 1.000 |
| Prior angina pectoris | 48 (5.0) | 13 (2.7) | 0.045 | 13 (3.0) | 13 (3.0) | 1.000 |
| Prior MI | 52 (5.4) | 14 (2.9) | 0.035 | 15 (3.5) | 14 (3.3) | 0.850 |
| **Killip class ≥3, n (%)** | 100 (10.4) | 52 (10.9) | 0.764 | 48 (11.2) | 46 (10.7) | 0.827 |
| **Laboratory findings** | | | | | | |
| Serum creatinine (mg/dL) | 0.9 [0.8–1.1] | 0.9 [0.7–1.0] | 0.274 | 0.9 [0.8–1.1] | 0.9 [0.7–1.0] | 0.662 |
| Peak troponin-I (mg/dL) | 30 [15.5–81.3] | 25 [8.6–89.4] | 0.658 | 31 [23.0–72.2] | 29 [11.6–84.7] | 0.472 |
| Peak CK-MB (mg/dL) | 145 [51–290] | 143 [48–296] | 0.965 | 155 [57–299] | 144 [48–297] | 0.474 |
| Total cholesterol (mg/dL) | 179 [152–209] | 177 [154–208] | 0.733 | 182 [155–213] | 178 [155–204] | 0.247 |
| Triglycerides (mg/dL) | 111 [72–170] | 110 [76–170] | 0.315 | 129 [79–187] | 114 [74–165] | 0.453 |
| HDL-C (mg/dL) | 41 [35–48] | 38 [33–45] | <0.001 | 40 [34–47] | 39 [34–45] | 0.200 |
| LDL-C (mg/dL) | 116 [89–141] | 115 [91–137] | 0.457 | 117 [91–141] | 115 [95–135] | 0.427 |
| Serum glucose (mg/dL) | 152 [127–196] | 158 [130–216] | 0.042 | 155 [128–202] | 159 [129–213] | 0.690 |
| **LVEF (%)** | 51.5±9.9 | 51.1±9.2 | 0.512 | 50.9±9.9 | 51.3±8.9 | 0.664 |
| **Medications in hospital, n (%)** | | | | | | |
| Statin | 915 (95.0) | 447 (93.7) | 0.303 | 409 (95.3) | 401 (93.5) | 0.235 |
| β-blocker | 820 (85.2) | 422 (88.5) | 0.085 | 382 (89.0) | 377 (87.9) | 0.593 |
| ACEI or ARB | 744 (77.3) | 383 (80.3) | 0.189 | 340 (79.3) | 338 (78.8) | 0.867 |

Values are presented as mean±SD, median [interquartile range] or number (percentage). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; BP, blood pressure; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial band isoenzyme; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; MI, myocardial infarction.

a loading dose prior to PCI. Prasugrel was not prescribed in patients >75 years old, <60 kg in weight, or with prior stroke/transient ischemic attack. Unfractionated heparin (50–70 U/kg) was administered before or during PCI to maintain the activated clotting time at 250–300 s. After PCI, 100–300 mg aspirin and/or 5 or 10 mg prasugrel once daily or 90 mg ticagrelor twice daily were prescribed as a maintenance dose.

## Study Endpoints

The primary study outcome was major adverse cardiac events (MACE), including cardiac death, nonfatal spontaneous MI, and target vessel revascularization (TVR) over the 1-year follow-up (median, 353 days [interquartile range 190–378]). We also analyzed the incidence of all-cause death, cardiac death, MI, TVR, definite stent thrombosis, and in-hospital bleeding events. Nonfatal spontaneous MI was defined as the development of recurrent angina symptoms accompanied by changes on a 12-lead ECG or increased levels of cardiac-specific biomarkers. TVR was defined as any repeat revascularization of any segment of a target vessel. In-hospital bleeding events were Thrombolysis in Myocardial Infarction (TIMI) major and minor bleeding during hospitalization.[10] All study outcomes were registered according to the Academic Research Consortium definitions.[11]

## Statistical Analysis

Continuous variables were compared using the unpaired t-test or Mann-Whitney rank-sum test and are presented as the mean±standard deviation or as the median and interquartile range. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test and are expressed as counts with percentages. Survival curves were constructed using Kaplan-Meier estimates and assessed by log-rank test. We analyzed clinical outcomes using multiple statistical models for head-to-head comparisons using the registry data. We used Cox proportional hazards regression models (with adjustment for covariates) to assess clinical outcomes. Variables with a significant (P<0.100) association with each endpoint in the univariate analyses were included in the multivariate analysis. Following variables were included in the multivariate analysis: age, male, systolic blood pressure, smoking, hypertension, diabetes mellitus,

**Table 2. Angiographic and Procedural Characteristics of Study Population**

| | Crude population | | P value | Propensity-matched population | | P value |
|---|---|---|---|---|---|---|
| | Ticagrelor (n=963) | Prasugrel (n=477) | | Ticagrelor (n=429) | Prasugrel (n=429) | |
| Infarct-related artery, n (%) | | | | | | |
| LAD | 472 (49.1) | 239 (50.1) | 0.710 | 217 (50.6) | 218 (50.8) | 0.946 |
| RCA | 375 (39.0) | 189 (39.6) | 0.815 | 165 (38.5) | 165 (38.5) | 1.000 |
| LCX | 101 (10.5) | 43 (9.0) | 0.377 | 41 (9.6) | 40 (9.3) | 0.907 |
| Left main coronary artery | 14 (1.5) | 6 (1.3) | 0.763 | 6 (1.4) | 6 (1.4) | 1.000 |
| Multivessel disease, n (%) | 480 (49.9) | 184 (38.6) | <0.001 | 179 (41.7) | 167 (38.9) | 0.404 |
| ACC/AHA B2/C lesion, n (%) | 869 (90.3) | 452 (94.8) | 0.004 | 398 (92.8) | 405 (94.4) | 0.329 |
| Pre-PCI TIMI flow grade 0, n (%) | 616 (64.8) | 317 (66.5) | 0.545 | 284 (66.2) | 280 (65.3) | 0.774 |
| Coronary stenting, n (%) | 906 (94.2) | 459 (96.2) | 0.098 | 412 (96.0) | 412 (96.0) | 1.000 |
| Door-to-balloon time (min) | 57 [45–74] | 57 [46–70] | 0.158 | 57 [44–74] | 57 [46–70] | 0.476 |
| Transradial intervention, n (%) | 327 (34.0) | 115 (24.1) | <0.001 | 126 (29.4) | 106 (24.7) | 0.124 |
| Use of GP IIb/IIIa inhibitor, n (%) | 218 (22.6) | 126 (26.4) | 0.114 | 111 (25.9) | 109 (25.4) | 0.876 |
| Use of intravascular ultrasound, n (%) | 220 (22.8) | 66 (13.8) | <0.001 | 74 (17.2) | 65 (15.2) | 0.404 |
| Post-PCI TIMI flow grade 3, n (%) | 932 (96.9) | 461 (96.6) | 0.811 | 416 (97.0) | 417 (97.2) | 0.839 |
| Thrombus aspiration, n (%) | 361 (37.5) | 167 (35.0) | 0.359 | 164 (38.2) | 153 (35.7) | 0.437 |
| Periprocedural shock, n (%) | 88 (9.1) | 58 (12.2) | 0.074 | 43 (10.0) | 51 (11.9) | 0.382 |

Values are presented as median [interquartile range] or number (percentage). ACC, American College of Cardiology; AHA, American Heart Association; GP, glycoprotein; LAD, Left anterior descending artery; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery TIMI, Thrombolysis in Myocardial Infarction.

Killip class 3 or 4, troponin-I, total cholesterol, triglycerides, low-density lipoprotein cholesterol, glucose, statin use, $\beta$-blocker use, culprit left anterior descending artery, culprit left main coronary artery, multivessel disease, coronary stenting, transradial intervention, thrombi aspiration and periprocedural shock. A proportional hazard assumption test using the Schoenfeld residual method showed that the proportional hazard assumption was not violated for any endpoints. We calculated propensity scores for ticagrelor use by logistic regression analysis using the variables shown in **Table 1** and **Table 2**.[12] The C-statistic value for the logistic model was 0.762 according to the receiver-operating characteristic curve, and the Hosmer-Lemeshow goodness-of-fit P-value was 0.350. Finally, we performed 1:1 propensity score matching without replacement by the nearest neighbor method. A caliper width or 0.2 SD was used for matching, and the standardized difference in all variables was within 10%. After propensity score matching, we compared continuous variables using paired t-tests or the Wilcoxon rank-sum test and categorical variables using McNemar's test.

All analyses were 2-tailed, and P<0.05 was considered significant. All statistical analyses were performed using SPSS for Windows (version 21.0; SPSS, Chicago, IL, USA) and R version 2.14.2 (R Foundation for Statistical Computing).

## Results

### Baseline Clinical Characteristics

**Table 1** summarizes the baseline clinical characteristics. The ticagrelor group was comprised of older patients, more females, and patients with higher systolic blood pressure. The ticagrelor group also had higher prevalence of hypertension, prior angina, prior MI; however, current and ex-smokers were more prevalent in the prasugrel group. The 2 groups were comparable in terms of other risk factors for atherosclerosis and prescriptions for evidence-based medications for STEMI. Among the patients receiving prasugrel, only 21 (4.4%) received 5 mg of prasugrel as a maintenance dose during hospitalization. Among the 21 patients who received 5 mg of prasugrel as a maintenance dose, only 4 received 30 mg of prasugrel as a loading dose. The remaining 456 patients in the prasugrel group received 60 mg of prasugrel as a loading dose and 10 mg of prasugrel as a maintenance dose during hospitalization. In the ticagrelor group, 34 patients (3.5%) received 90 mg of ticagrelor as a maintenance dose, and all patients in the ticagrelor group received 180 mg of ticagrelor as a loading dose.

### Angiographic and Procedural Characteristics

The angiographic and procedural features of all patients are presented in **Table 2**. The ticagrelor group was more likely to have multivessel disease at the time of the initial coronary angiography than the prasugrel group. During PCI, the prasugrel group underwent more transfemoral approach treatments and less intravascular ultrasound-guided PCI. American College of Cardiology/American Heart Association B2 or C complex lesion was also seen more often in the prasugrel group. We found no significant between-group differences in door-to-balloon time, distribution of the infarct-related artery, frequency of pre-PCI TIMI flow of 0 or post-PCI TIMI flow of 3, or rate of coronary stenting. Thrombus aspiration and glycoprotein IIb/IIIa inhibitors were used similarly during PCI. There was a greater tendency for periprocedural shock occurrence in the prasugrel group than in the ticagrelor group (9.1% vs. 12.2%, P=0.074). After propensity score matching, 429 matched pairs of patients were obtained, and the differences in baseline, clinical, and procedural characteristics between the groups disappeared (**Tables 1**,**2**).

### Clinical Outcomes

MACE occurred in 91 patients (6.3%) during the 12-month

**Table 3. In-Hospital and 12-Month Clinical Outcomes of Study Population**

| | Crude population | | P value | Propensity-matched population | | P value |
|---|---|---|---|---|---|---|
| | Ticagrelor (n=963) | Prasugrel (n=477) | | Ticagrelor (n=429) | Prasugrel (n=429) | |
| **In-hospital outcomes, n (%)** | | | | | | |
| In-hospital death | 20 (2.1) | 14 (2.9) | 0.313 | 6 (1.4) | 13 (3.0) | 0.104 |
| Definite stent thrombosis | 5 (0.5) | 4 (0.8) | 0.469 | 4 (0.9) | 3 (0.7) | 0.704 |
| TIMI major or minor bleeding | 41 (4.3) | 32 (6.7) | 0.046 | 18 (4.2) | 29 (6.8) | 0.099 |
| TIMI major bleeding | 23 (2.4) | 12 (2.5) | 0.883 | 11 (2.6) | 11 (2.6) | 1.000 |
| **12-month outcomes, n (%)** | | | | | | |
| Major adverse cardiac events* | 65 (6.7) | 26 (5.5) | 0.340 | 23 (5.4) | 25 (5.8) | 0.766 |
| All-cause death | 34 (3.5) | 15 (3.1) | 0.704 | 11 (2.6) | 14 (3.3) | 0.543 |
| Cardiac death | 24 (2.5) | 14 (2.9) | 0.622 | 7 (1.6) | 13 (3.0) | 0.175 |
| Nonfatal MI | 9 (0.9) | 4 (0.8) | 0.856 | 3 (0.7) | 4 (0.9) | 0.704 |
| TVR | 31 (3.2) | 10 (2.1) | 0.228 | 14 (3.3) | 10 (2.3) | 0.408 |
| Definite stent thrombosis | 7 (0.7) | 4 (0.8) | 0.819 | 6 (1.4) | 3 (0.7) | 0.315 |

*Composite of cardiac death, nonfatal MI, and TVR. Values are presented as number (percentage). TVR, target vessel revascularization. Other abbreviations as in Tables 1,2.

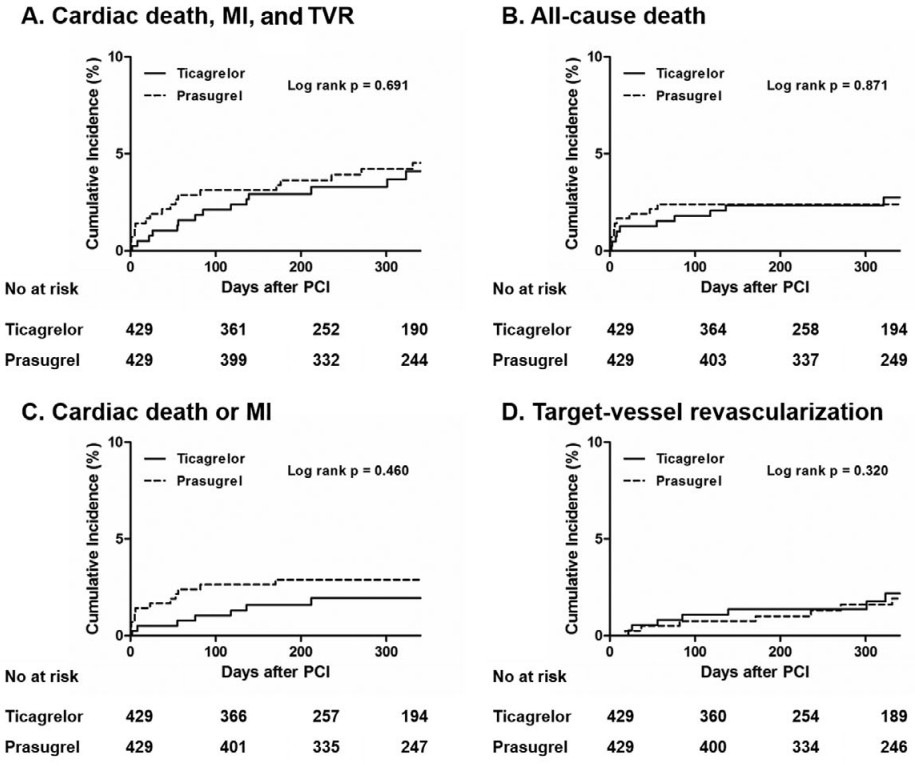


**Figure 2.** Kaplan-Meier curves for (**A**) 12-month major adverse cardiac events, (**B**) all-cause death, (**C**) cardiac death or MI and (**D**) TVR in propensity score-matched population. MI, myocardial infarction; TVR, target vessel revascularization.

follow-up. There were no differences in the crude incidences of MACE, all-cause death, cardiac death, MI, TVR, definite stent thrombosis, in-hospital death, or in-hospital bleeding events between the 2 groups. Analysis by propensity score matching (429 pairs) did not significantly affect the results (**Table 3**), and Kaplan-Meier estimates of ischemic events were similar after propensity score matching (**Figure 2**).

**Table 4** shows the risks of 12-month clinical outcomes for the ticagrelor and prasugrel groups. The risks of MACE were comparable in the ticagrelor and prasugrel groups in the adjusted Cox proportional hazards model (hazard ratio [HR] 1.20, 95% confidence interval [CI] 0.76–1.91, P=0.438) and propensity score-matched model (HR 0.98, 95% CI 0.56–1.74, P=0.951). There were also no significant

**Table 4. Risks of 12-Month Clinical Outcomes Between Ticagrelor and Prasugrel**

| | Unadjusted HR (95% CI) | P value | Adjusted HR (95% CI) | P value | Propensity score-adjusted HR (95% CI)† | P value |
|---|---|---|---|---|---|---|
| Major adverse cardiac events* | 1.36 (0.86–2.15) | 0.183 | 1.20 (0.76–1.91) | 0.438 | 0.98 (0.56–1.74) | 0.951 |
| All-cause death | 1.16 (0.63–2.13) | 0.640 | 0.88 (0.47–1.65) | 0.689 | 0.83 (0.38–1.84) | 0.650 |
| Cardiac death | 0.89 (0.46–1.71) | 0.717 | 0.66 (0.34–1.32) | 0.242 | 0.56 (0.23–1.41) | 0.221 |
| Nonfatal MI | 1.13 (0.34–3.73) | 0.841 | 1.16 (0.34–3.93) | 0.818 | 0.76 (0.17–3.51) | 0.729 |
| TVR | 1.74 (0.85–3.56) | 0.129 | 1.68 (0.81–3.48) | 0.165 | 1.51 (0.66–3.45) | 0.324 |
| Definite stent thrombosis | 0.77 (0.22–2.71) | 0.685 | 0.62 (0.17–2.21) | 0.457 | 1.76 (0.42–7.26) | 0.437 |

*Composite of cardiac death, nonfatal MI, and TVR. †A 429 propensity-matched pair was analyzed in both the ticagrelor and prasugrel groups. HR presented as the risk for study endpoints of ticagrelor compared with prasugrel. CI, confidence interval; HR, hazard ratio. Other abbreviations as in Tables 1,3.

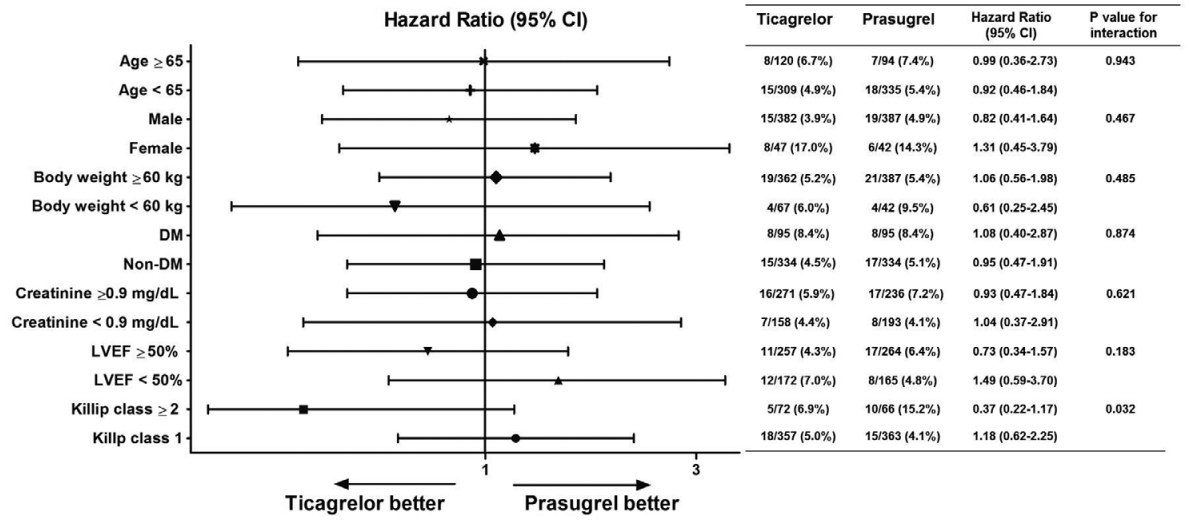


**Figure 3.** Comparative adjusted hazard ratios of major adverse cardiac events in propensity score-matched population for subgroups. CI, confidence interval; DM, diabetes mellitus; LVEF, left ventricular ejection fraction.

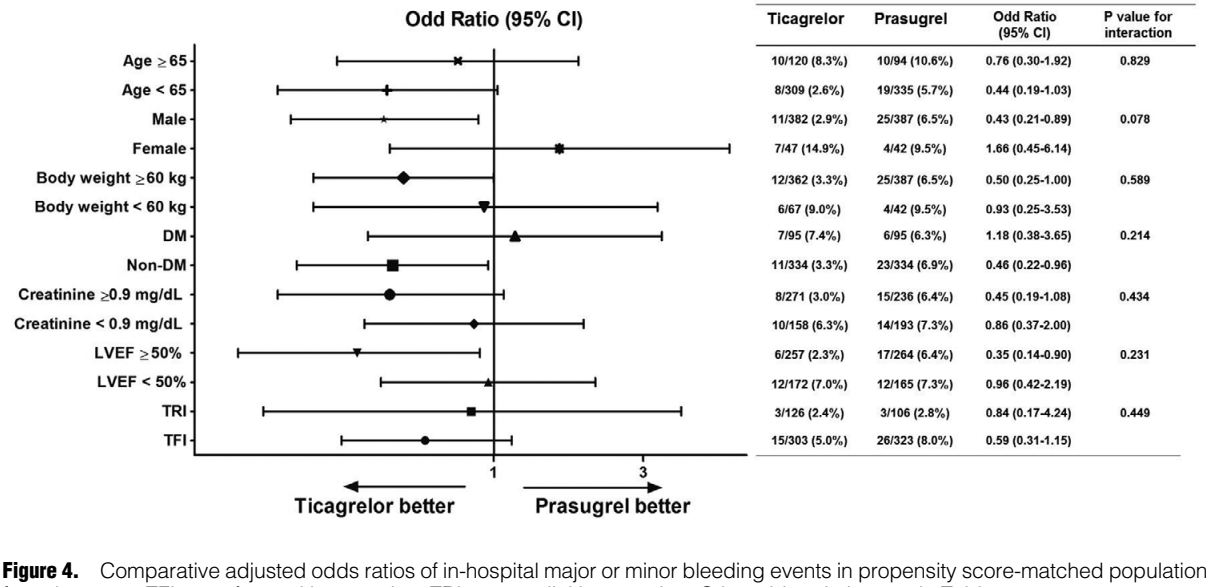


**Figure 4.** Comparative adjusted odds ratios of in-hospital major or minor bleeding events in propensity score-matched population for subgroups. TFI, transfemoral intervention; TRI, transradial intervention. Other abbreviations as in Table 3.

differences in the risks of other secondary endpoints.

### Subgroup Analysis

We analyzed the HRs for MACE (**Figure 3**) and odds ratios for in-hospital TIMI major or minor bleeding events (**Figure 4**) for various subgroups in the propensity-matched population whether the results were consistent. There were no significant differences in MACE rates in any subgroup (**Figure 3**). However, the rate of in-hospital bleeding was lower in the ticagrelor group than in the prasugrel group in males, patients without diabetes, and patients with a preserved LVEF (**Figure 4**). Although there were no significant interactions between the type of P2Y12 receptor inhibitor and in-hospital bleeding events in any subgroup, P2Y12 receptor inhibitor showed significant interaction with Killip class (P for interaction=0.032).

## Discussion

In the current study, we compared the 12-month clinical outcomes after ticagrelor or prasugrel use in patients with STEMI undergoing primary PCI using the KAMIR-NIH registry data. The main findings were as follows: (1) there were no differences in the incidence of MACE, death, MI, TVR, or definite stent thrombosis between the ticagrelor and prasugrel groups; and (2) the incidence of in-hospital TIMI major or minor bleeding events was also comparable between the 2 treatment groups.

Antiplatelet therapy is a major concern for the treatment of ACS, and many studies have proven the efficacy of ticagrelor and prasugrel compared with clopidogrel since their introduction to the market. However, few studies have directly compared ticagrelor and prasugrel in patients with ACS. The results of a recent meta-analysis of 9 studies with 21,360 patients showed that prasugrel was associated with superior 30-day outcomes compared with ticagrelor in ACS patients undergoing PCI.[13] However, only a small portion of the STEMI population was included in that study. The clinical effects of these potent P2Y12 receptor inhibitors have also not been fully evaluated in patients with STEMI. A recent large meta-analysis and European multicenter registry data showed that ticagrelor and prasugrel were more efficacious than clopidogrel in STEMI patients.[14,15] Furthermore, only 1 randomized trial directly compared the long-term clinical outcomes of ticagrelor and prasugrel in patients with STEMI.[5] In that study, the 2 groups undergoing primary PCI did not differ in terms of 30-day ischemic or bleeding events. In the current study, similar results were observed during the 12-month follow-up period despite different baseline characteristics between the 2 groups. We initially hypothesized that ticagrelor is more effective than prasugrel at reducing ischemic events in STEMI based on study results for patients with non-ST-elevation ACS.[16,17] The results of the current study are very interesting, because the pharmacomechanisms of ticagrelor and prasugrel are different; therefore, further large randomized trials are warranted to confirm the study results.

The mechanisms behind the similar efficacy and safety profiles of these new P2Y12 receptor inhibitors are uncertain. Similar antiplatelet effects may be a possible cause. In a single-center randomized study, platelet reactivity did not differ between ticagrelor and prasugrel treatment during the first 24 h of STEMI.[18] A small randomized study in Korea also proved that prasugrel and ticagrelor were similarly effective at inhibiting platelets in Korean patients with STEMI.[19] Unfortunately, platelet function was not fully evaluated in the current study. Among the 1,440 participants in the study, P2Y12 reaction units (PRUs) were evaluated using the VerifyNow assay in only 403 patients (27.9%) during the acute phase of STEMI; mean PRU values were 73.3 in the ticagrelor group (n=250) and 90.9 in the prasugrel group (n=153). Although there was a statistically significant difference between the groups (P=0.023), platelet inhibition by both ticagrelor and prasugrel was sufficient to suppress platelet function. We did not include PRUs in the analysis because the values in our study were too speculative to be used for data interpretation.

In the current study, in-hospital bleeding events occurred more often in the prasugrel group than in the ticagrelor group among males, patients without diabetes, and patients with normal LVEF. This difference might be related to unfavorable baseline characteristics in the prasugrel group. Transfemoral intervention and periprocedural cardiogenic shock were more frequent in the prasugrel group than in the ticagrelor group. However, various statistical methods were used to reduce bias in the current study; therefore, it is possible that prasugrel was associated with increased in-hospital minor bleeding events in STEMI patients with low risk profiles. There were no significant differences in in-hospital major bleeding events between the 2 groups. Furthermore, several studies have reported that the baseline characteristics of East Asian patients differ from those of Western patients, such as body mass index, thrombogenicity, PRUs, and risks of bleeding and ischemia; thus, a low dose of the new P2Y12 receptor inhibitors may be sufficient for East Asian patients.[20,21] Application of larger real-world registries and more randomized trials are needed to explore this issue.

### Study Limitations

First, this study had a nonrandomized, observational design with a small number of patients despite the use of a large multicenter registry, which resulted in differences in baseline clinical and angiographic findings between groups. Although we used multiple statistical methods to supplement the results, other variables not included in our registry might have been associated with the study outcomes. Second, data on dosage reduction during follow-up and patient compliance with P2Y12 receptor inhibitors were unavailable. Switching between P2Y12 receptor inhibitors was also not evaluated in the current study. Third, the incidence of endpoints was lower than in other studies, because our study excluded patients who discontinued or switched antiplatelet agents, and those prescribed clopidogrel. There is a possibility that patients who discontinued or switched antiplatelet drugs had in-hospital bleeding events. Furthermore, patients who were prescribed clopidogrel were older and had more comorbidities than those prescribed ticagrelor or prasugrel in the KAMIR-NIH studies (**Table S1**).[6,7] Therefore, the incidence of clinical outcomes might have been underestimated. Finally, only in-hospital bleeding events were assessed in the registry as safety outcomes. However, a recent randomized trial compared clinical outcomes between ticagrelor and prasugrel in STEMI patients, and showed a similar incidence of 12-month TIMI major bleeding events between the 2 groups.[22]

In conclusion, in Korea ticagrelor was used more in patients with STEMI undergoing primary PCI than prasugrel. However, ticagrelor and prasugrel showed similar

1-year efficacy and safety profiles for the treatment of these high-risk patients in this Korean multicenter registry. The use of prasugrel was associated with increased in-hospital minor bleeding events in STEMI patients with low risk profiles.

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## References

1. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016; **68:** 1082–1115.
2. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–2015.
3. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009; **361:** 1045–1057.
4. Watti H, Dahal K, Zabner HG, Katikaneni P, Modi K, Abdulbaki A. Comparison of prasugrel and ticagrelor in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A meta-analysis of randomized and non-randomized studies. *Int J Cardiol* 2017; **249:** 66–72.
5. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varbarovsky I, Dusek J, et al. Prasugrel versus ticagrelor in patients with acute myocardial infarction treated with primary percutaneous coronary intervention: Multicenter randomized PRAGUE-18 Study. *Circulation* 2016; **134:** 1603–1612.
6. Park KH, Jeong MH, Kim HK, Ahn TH, Seung KB, Oh DJ, et al. Comparison of prasugrel versus clopidogrel in Korean patients with acute myocardial infarction undergoing successful revascularization. *J Cardiol* 2018; **71:** 36–43.
7. Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization: From Korea Acute Myocardial Infarction Registry-National Institutes of Health. *Int J Cardiol* 2016; **215:** 193–200.
8. Kim JH, Chae SC, Oh DJ, Kim HS, Ahn Y, Cho MC, et al. Multicenter cohort study of acute myocardial infarction in Korea: Interim analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. *Circ J* 2016; **80:** 1427–1436.
9. Thysessen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Eur Heart J* 2012; **33:** 2551–2567.
10. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: A consensus report from the Bleeding Academy in Research Consortium. *Circulation* 2011; **123:** 2736–2747.
11. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: A case for standardized definitions. *Circulation* 2007; **115:** 2344–2351.
12. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol* 2006; **163:** 262–270.
13. Watti H, Dahal K, Zabher HG, Katikaneni P, Modi K, Abdulbaki A. Comparison of prasugrel and ticagrelor in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A meta-analysis of randomized and non-randomized studies. *Int J Cardiol* 2017; **249:** 66–72.
14. Danchin N, Lettino M, Zeymer U, Widimsky P, Bardaji A, Barrabes JA, et al. Use, patient selection and outcomes of P2Y12 receptor inhibitor treatment in patients with STEMI based on contemporary European registries. *Eur Heart J Cardiovasc Pharmacother* 2016; **2:** 152–167.
15. Rafique AM, Nayyar P, Wang TY, Mehran R, Baber U, Berger PB, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. *JACC Cardiovasc Interv* 2016; **9:** 1036–1046.
16. Roe MT, Armstrong PW, Fox KA, White HD, Prabhakaran D, Goodman SG, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367:** 1297–1309.
17. Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. *N Engl J Med* 2013; **369:** 999–1010.
18. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Markis G, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment elevation myocardial infarction. *Circ Cardiovasc Interv* 2012; **5:** 797–804.
19. Lee YS, Jin CD, Kim MH, Guo LZ, Cho YR, Park K, et al. Comparison of prasugrel and ticagrelor antiplatelet effects in Korean patients presenting with ST-segment elevation myocardial infarction. *Circ J* 2015; **79:** 1248–1254.
20. Jeong YH. "East Asian paradox": Challenge for the current antiplatelet strategy of "one-guideline-fits-all races" in acute coronary syndrome. *Curr Cardiol Rep* 2014; **16:** 485.
21. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: The PRAFIT-ACS study. *Circ J* 2014; **78:** 1684–1692.
22. Motovska Z, Hlinomaz O, Kala P, Hromadka M, Knot J, Varvarovsky I, et al. 1-Year outcomes of patients undergoing primary angioplasty for myocardial infarction treated with prasugrel versus ticagrelor. *J Am Coll Cardiol* 2018; **71:** 371–381.

## Supplementary Files

**Supplementary File 1**

**Table S1.** Baseline clinical characteristics among ticagrelor, prasugrel and clopidogrel

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-18-0112