Comparison of Clinical Outcomes of Acute Myocardial Infarction Between Prasugrel and Clopidogrel

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Summary
The rapid introduction of dual antiplatelet therapy (DAPT) is important for patients with acute myocardial infarction (AMI). The risks and benefits of reduced-dose prasugrel (20 mg loading and 3.75 mg maintenance) over clopidogrel have not been fully discussed. The purpose of this study was to compare the 90-days clinical outcomes of AMI between prasugrel-based DAPT and clopidogrel-based DAPT. We included 534 AMI patients and divided them into the clopidogrel group (n = 330) and the prasugrel group (n = 204). The primary endpoint was the total ischemic events and total bleeding events. In all, 52 ischemic events and 35 bleeding events were observed during the study period. The total ischemic events were similar between the clopidogrel and the prasugrel groups (P = 0.385). The total bleeding events were similar between the clopidogrel and the prasugrel groups (P = 0.125). The multivariate Cox hazard analysis showed that prasugrel was not associated with the total ischemic events (hazard ratio (HR) 0.955, 95% confidence interval (CI) 0.499-1.829, P = 0.890) and was not associated with the total bleeding events after controlling confounding factors (HR 0.972, 95% CI 0.528-1.790, P = 0.927). In conclusion, as compared to clopidogrel, the reduced dose of prasugrel was not associated with the excess risk of bleeding or the excess risk of ischemic events. Our real-world data support the current regimen of prasugrel for AMI patients who underwent primary percutaneous coronary intervention.

Key words: Dual antiplatelet therapy, Ischemic event, Bleeding

The clinical outcomes of acute myocardial infarction (AMI) have been greatly improved by primary percutaneous coronary intervention (PCI). Dual antiplatelet therapy (DAPT), which is typically composed of aspirin and P2Y12 inhibitors such as clopidogrel or prasugrel, has been important for successful primary PCI, especially since the beginning of clopidogrel loading. As compared to clopidogrel (loading 300 mg and maintenance 75 mg), prasugrel (loading 60 mg and maintenance 10 mg) had a more potent antiplatelet effect, which was confirmed by randomized control trials in Western countries. However, the bleeding risk was greater in prasugrel than in clopidogrel in those trials.

The dose of prasugrel was adjusted (loading 20 mg and maintenance 3.75 mg) for East Asian individuals in Japan, because the bleeding risk was considered to be greater in East Asian individuals than in White individuals. A randomized trial showed that prasugrel (20 mg/3.75 mg) was associated with a low incidence of ischemic events and a low risk of clinically serious bleeding up to 24 weeks in Japanese patients. However, the risks and benefits of prasugrel over clopidogrel have not been fully discussed in real clinical practices. The purpose of this study was to compare the 90-days clinical outcomes of AMI between prasugrel-based DAPT and clopidogrel-based DAPT.

Methods

Study design: We reviewed consecutive AMI patients who underwent primary PCI at our medical center from January 2015 to December 2017. The exclusion criteria were the following: 1) DAPT was not continued for some reasons such as coronary artery bypass surgery, vasospastic angina, or no stent implantation, 2) DAPT was composed of aspirin and ticlopidine, 3) warfarin or direct oral anticoagulant (DOAC) was prescribed together with DAPT, and 4) final PCI procedure without drug-eluting stent implantation. The study patients were divided into the clopidogrel group, in which DAPT was composed of aspirin and ticlopidine, and the prasugrel group, in which DAPT was composed of aspirin and prasugrel. Clinical characteristics and outcomes were compared between the two groups. The primary endpoint for this study was the total ischemic events and total bleeding events. The total ischemic events were defined as the composite of cardiac events.
death, nonfatal AMI, cerebral infarction, and ischemia-driven target vessel revascularization. The total bleeding events were defined as global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries (GUSTO) moderate/severe bleeding.60) The day of admission was defined as the index day, and the patients were followed up until the primary endpoint or 90 days. This study was approved by the institutional review board, and written informed consent was waived because of the retrospective study design.

**Definitions:** The diagnosis of AMI required the following criteria: symptoms consistent with AMI; elevated cardiac enzymes including troponin T, troponin I, and/or creatinine kinase (at least a twofold increase from the normal upper limit), and ST-segment elevation or depression in electrocardiograms compatible with AMI.7) Diagnostic ST elevation was defined as new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mV), and the AMI patients with ST elevation were diagnosed as ST elevation myocardial infarction (STEMI).8) Hypertension was defined as a medical treatment for hypertension and/or a history of hypertension before admission.9) Dyslipidemia was defined as total cholesterol levels > 220 mg/dL or low-density lipoprotein cholesterol levels > 140 mg/dL or medical treatment for dyslipidemia or a history of dyslipidemia.10) Diabetes mellitus was defined as a hemoglobin A1c level (as NGSP value) > 6.5% or a medical treatment for diabetes mellitus or a history of diabetes mellitus.11) Significant coronary artery stenosis was defined as at least a 75% reduction in the internal diameter. Initial and final thrombosis in myocardial infarction (TIMI) flow grades were recorded.12) The Predicting Bleeding Complication in Patients Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score was also calculated to evaluate the bleeding risk according to the literature.13) All strokes in the clopidogrel group (2.9%) (< 0.001). The PRECISE-DAPT score was significantly higher in the clopidogrel group (30 ± 14) than in the prasugrel group (24.7 ± 3.9) (P < 0.001). The prevalence of hemodialysis was significantly higher in the clopidogrel group (11.5%) than in the prasugrel group (2.9%) (P < 0.001). The PRECISE-DAPT score was significantly higher in the clopidogrel group (30 ± 14) than in the prasugrel group (21 ± 12) (P < 0.001). Table II shows the comparison of lesion and procedural characteristics between the two groups. Infarct-related artery and number of narrowed coronary arteries were not different between the two groups. The prevalence of transfemoral PCI was significantly greater in the clopidogrel group (48.2%) than in the prasugrel group (23.0%) (P < 0.001).

**Results**

In all, 751 AMI patients were admitted to our hospital during the study period. Among them, 217 patients were excluded from the analysis. The final study population consisted of 534 AMI patients, and they were divided into the clopidogrel group (n = 330) and the prasugrel group (n = 204) (Figure 1). Table I shows the comparison of the clinical characteristics between the two groups. The mean age was significantly older in the clopidogrel group (72.8 ± 11.9 years) than in the prasugrel group (63.9 ± 13.6 years) (P < 0.001). The prevalence of female sex was significantly greater in the clopidogrel group (30.0%) than in the prasugrel group (18.1%) (P = 0.002). Body mass index was significantly lower in the clopidogrel group (23.5 ± 3.5) than in the prasugrel group (24.7 ± 3.9) (P < 0.001). The prevalence of hemodialysis was significantly higher in the clopidogrel group (11.5%) than in the prasugrel group (2.9%) (P < 0.001). All analyses were performed with IBM SPSS statistics version 25 (Chicago, IL, USA).

**Statistical analysis:** Data were expressed as mean ± standard deviation (SD) for continuous variables and percentage for categorical variables. Normally distributed continuous variables were compared using the unpaired Student’s t-test. Other continuous variables were compared using the Mann-Whitney U-test. Categorical variables were presented as numbers and compared with Fisher’s exact test. Kaplan-Meier survival curves were constructed to investigate the total ischemic events-free survival and the bleeding events-free survival. We also performed multivariate Cox hazard analysis to investigate the association between prasugrel and the total ischemic/bleeding events after controlling confounding factors. In this model, the total ischemic events or total bleeding events were used as a dependent variable, and prasugrel was used as an independent variable. Confounding factors were selected from variables that had a significant difference (P < 0.05) between the clopidogrel and prasugrel groups in univariate comparisons. However, we did not include variables with substantial missing values, and the maximum number of independent variables was set as (number of total ischemic events)/10 or (number of total bleeding events)/10.15) Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were also calculated. A P value < 0.05 was considered to be statistically significant. Propensity score matching was applied to compare the incidence of clinical outcome between the matched clopidogrel group and the matched prasugrel group. First, a logistic regression analysis was performed to calculate the propensity score using the full database. In this model, the prasugrel group was set as a dependent variable, whereas parameters that had a significant difference between the clopidogrel group and the prasugrel group in univariate analysis were set as independent variables. Parameters with missing values were not included as independent variables. For matching, the match tolerance was set as a width of 0.25 multiplied by the SD of the propensity score distribution.16,17) All analyses were performed with IBM SPSS statistics version 25 (Chicago, IL, USA).
To calculate the propensity score, we selected the following parameters as independent variables: age, sex, height, STEMI (or NSTEMI), hypertension, malignancy, prior AMI, prior PCI, prior stroke, serum creatinine, creatine kinase, left main trunk stenosis, chronic total occlusion, and trans-femoral coronary intervention. After applying the propensity score matching, a matched clopidogrel group \((n = 140)\) and a matched prasugrel group \((n = 140)\) were generated for further analysis. The comparison of clinical characteristics between the two matched groups is shown in Supplemental Table I. Clinical characteristics were comparable between the two groups except for calcium-channel blocker before admission, β-blocker and diuretics at discharge, and brain natriuretic peptide on admission. The comparison of lesion and procedural characteristics between the two matched groups is shown in Supplemental Table II. Lesion and procedural characteristics were comparable between the two groups except for approach site. The comparison of clinical outcomes between the two matched groups is shown in Supplemental Table III, and Kaplan-Meier curves were constructed to compare the clinical outcomes between the two matched groups (Supplemental Figure). The total ischemic events-free survival was similar between the two matched groups \((P = 0.421)\), and the total bleeding events-free survival was significantly better in the prasugrel group than in the clopidogrel group \((P = 0.007)\).

**Discussion**

In this retrospective study, we included 534 AMI patients who underwent PCI and divided them into the clopidogrel group \((n = 330)\) and the prasugrel group \((n = 204)\). Regarding the efficacy of antiplatelet therapy, the total ischemic events were not different between the clopidogrel group and the prasugrel group. Regarding the safety of antiplatelet therapy, the total bleeding events were not different between the clopidogrel group and the prasugrel group.
and the clopidogrel group after controlling confounding factors. The multivariate Cox hazard models showed that the total ischemic events and the total bleeding events were not different between the prasugrel group and the clopidogrel group after controlling confounding factors. However, in the propensity score matching analysis, the total bleeding events were significantly less in the prasugrel group than in the clopidogrel group. Our results support the fact that the current regimen of prasugrel adjusted for the Asian population would not increase the risk of bleeding as compared to clopidogrel.
As our retrospective observation study could not investigate, whereas acute and mid-term outcomes were not available.22) Yasuda et al. reported the lower risk of bleeding following reduced-dose prasugrel as compared to that following clopidogrel.23) Although their results were drawn from the large multicenter registry in Japan (J-PCI registry), only in-hospital outcomes were investigated, whereas acute and mid-term outcomes were not available.22) The JAMIR study is a multicenter, nationwide, prospective registry enrolling 3069 patients with 12-months follow-up.24) Our results of the propensity score matching analysis were similar to those of the JAMIR study. However, the incidence of ischemic and bleeding events was greater in the present study than in the JAMIR study, partly because our study included patients with no return of spontaneous circulation on admission after out-of-hospital cardiopulmonary arrest.

The clinical implications of the present study should

| Table II. Comparison of Lesion and Procedural Characteristics between the Clopidogrel Group and the Prasugrel Group |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Infarct related artery, n (%) | Infarct related artery, n (%) |
| Left main trunk and left anterior descending artery | 287 (53.7) | 169 (51.2) | 118 (57.8) |
| Left circumflex artery | 71 (13.3) | 49 (14.8) | 22 (10.8) |
| Right circumflex artery | 170 (31.8) | 108 (32.7) | 62 (30.4) |
| Graft and not determined | 6 (1.1) | 4 (1.2) | 2 (1.0) |
| Number of narrow coronary arteries, n (%) | 0.117 | 0.412 |
| 1 vessel disease | 224 (41.9) | 128 (38.8) | 96 (47.1) |
| 2 vessel disease | 179 (33.5) | 113 (34.2) | 66 (32.4) |
| 3 vessel disease | 131 (24.5) | 89 (27.0) | 42 (20.6) |
| Left main trunk stenosis > 50%, n (%) | 54 (10.1) | 42 (12.7) | 12 (5.9) |
| Chronic total occlusion, n (%) | 62 (11.6) | 48 (14.6) | 14 (6.9) |
| Initial TIMI flow grade, n (%) | 0 | 1 | 3 | < 0.001 |
| 0 | 213 (39.9) | 108 (32.7) | 105 (51.5) |
| 1 | 60 (11.2) | 37 (11.2) | 23 (12.0) |
| 2 | 85 (15.9) | 57 (17.3) | 30 (15.3) |
| 3 | 176 (33.0) | 128 (38.8) | 51 (22.7) |
| Final TIMI flow grade, n (%) | 0.227 | < 0.001 |
| 0 | 4 (0.7) | 2 (0.6) | 2 (1.0) |
| 1 | 3 (0.6) | 3 (0.9) | 0 (0) |
| 2 | 16 (3.0) | 7 (2.1) | 9 (4.4) |
| 3 | 511 (95.7) | 318 (96.4) | 193 (94.6) |
| Approach site, n (%) | < 0.001 | < 0.001 |
| Trans-radial coronary intervention | 305 (57.1) | 153 (46.4) | 152 (74.5) |
| Trans-brachial coronary intervention | 23 (5.5) | 18 (5.5) | 6 (2.5) |
| Trans-femoral coronary intervention | 206 (38.6) | 159 (48.2) | 47 (23.0) |
| Guiding size, n (%) | 0.001 | 0.001 |
| n = 528 | n = 327 | n = 201 |
| 6 Fr | 333 (63.1) | 186 (57.2) | 146 (72.6) |
| 7 Fr | 190 (36.0) | 135 (41.3) | 55 (27.4) |
| 8 Fr | 5 (0.9) | 5 (1.5) | 0 (0) |

Categorical variables were compared using Fisher’s exact test. Normally distributed continuous variables were compared using the unpaired Student’s t-test. Non-normally distributed continuous variables were compared using the Mann–Whitney U-test. TIMI indicates thrombolysis in myocardial infarction.

We should discuss why the incidence of ischemic events was not different between the two groups. First, the possible explanation was that the current regimen of prasugrel (20 mg loading and 3.75 mg maintenance) was not sufficient to prove the superiority of efficacy over clopidogrel, because the current regimen of prasugrel was more conservative as compared to the regimen of the Western dose (60 mg loading and 10 mg maintenance). However, the overall incidences of ischemic events were relatively low in both the clopidogrel and prasugrel groups as compared to those in Western countries.20) Thus, the clopidogrel group as well as the prasugrel group might sufficiently suppress the incidence of ischemic events, which supports the fact that the current reduced dose of prasugrel was appropriate for the Japanese population. Second, the nonsignificant difference between the two groups might be caused by beta error due to the small sample size.21) As our retrospective observation study could not perform sample size calculation, our study population might be too small to find the difference of ischemic events between the two groups.

Moreover, we should discuss why the incidence of bleeding events was not different between the two groups in the unadjusted comparison and the multivariable Cox hazard model, but the incidence of bleeding was significantly less in the prasugrel group than in the clopidogrel group after propensity score matching. A randomized trial in White individuals showed that prasugrel had higher bleeding risk than clopidogrel.20) Although the dose of prasugrel was adjusted for East Asian individuals in Japan, the safety of prasugrel in the adjusted dose was not widely recognized in Japan. Akita et al. reported the greater risk of bleeding following reduced-dose prasugrel as compared to that following clopidogrel.23) Although their results were drawn from the large multicenter registry in Japan (J-PCI registry), only in-hospital outcomes were investigated, whereas acute and mid-term outcomes were not available.22) Our results of the propensity score matching analysis were similar to those of the JAMIR study. However, the incidence of ischemic and bleeding events was greater in the present study than in the JAMIR study, partly because our study included patients with no return of spontaneous circulation on admission after out-of-hospital cardiopulmonary arrest.
Table III. Comparison of 90-Day Clinical Outcomes between the Clopidogrel Group and the Prasugrel Group

|                                        | All patients n = 534 | Clopidogrel n = 330 | Prasugrel n = 204 | P value |
|----------------------------------------|----------------------|---------------------|-------------------|---------|
| Total ischemic event                   | 52 (9.7)             | 35 (10.6)           | 17 (8.3)          | 0.454   |
| Cardiac death                          | 25 (4.7)             | 17 (5.2)            | 8 (3.9)           | 0.674   |
| Nonfatal AMI                           | 11 (2.1)             | 8 (2.4)             | 3 (1.5)           | 0.544   |
| Cerebral infarction                    | 13 (2.4)             | 11 (2.1)            | 2 (1.0)           | 0.145   |
| Ischemia-driven TVR                    | 16 (3.0)             | 8 (2.4)             | 8 (3.9)           | 0.434   |
| Total bleeding event                   | 64 (12.0)            | 45 (13.6)           | 19 (9.3)          | 0.093   |
| Moderate GUSTO bleeding classification | 57 (10.7)            | 42 (12.7)           | 15 (7.4)          | 0.346   |
| **Bleeding site**                      |                      |                     |                   |         |
| Neck                                   | 1 (0.2)              | 1 (0.3)             | 0 (0)             |         |
| Chest                                  | 1 (0.2)              | 0 (0)               | 1 (0.5)           |         |
| Upper extremity                        | 3 (0.6)              | 3 (0.9)             | 0 (0)             |         |
| Pelvis                                 | 4 (0.7)              | 3 (0.9)             | 1 (0.5)           |         |
| Lower extremity                        | 14 (2.6)             | 11 (3.3)            | 3 (1.5)           |         |
| Unspecified but required blood transfusion due to surgery | 5 (0.9) | 3 (0.9) | 2 (1.0) |         |
| Unspecified                            | 29 (5.4)             | 21 (6.4)            | 8 (3.9)           |         |
| Severe GUSTO bleeding classification   | 7 (1.4)              | 3 (0.9)             | 4 (2.0)           | 0.259   |
| **Bleeding site**                      |                      |                     |                   |         |
| Cerebral hemorrhage                    | 1 (0.2)              | 1 (0.3)             | 0 (0)             |         |
| Abdominal pelvis                       | 2 (0.4)              | 0 (0)               | 2 (1.0)           |         |
| Pericardial effusion                   | 4 (0.8)              | 2 (0.6)             | 2 (1.0)           |         |

Categorical variables were compared using Fisher’s exact test. AMI indicates acute myocardial infarction; TVR, target vessel revascularization; GUSTO, global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries.

Figure 2. Kaplan–Meier survival curves of clinical events between the clopidogrel group and the prasugrel group. **A**: Comparison of total ischemic events. **B**: Comparison of total bleeding events. Log-rank test. AMI indicates acute myocardial infarction; and TVR, target vessel revascularization.

be noted. Recent clinical trials, including the STOPDAPT-2 trial, support the short duration of DAPT. The Japanese Circulation Society conducted a focused update on antithrombotic therapy in patients with coronary artery disease, which recommends 1-3 months DAPT for patients with high bleeding risk. If patients do not have high bleeding risk, 3-12 months DAPT is recommended for patients with high thrombotic risk, and 1-3 months DAPT is recommended for patients with low thrombotic risk. Therefore, 3 months DAPT is suitable for all types of patients unless patients have oral antithrombotic therapy. Because our study set the follow-up period as 90 days, our study results would be easily applicable to the contemporary clinical practice.

**Study limitations:** The present study has the following limitations. Because this study was a single-center retrospective observational study, there was a risk of selection bias. As the choice of drugs (prasugrel or clopidogrel) was not randomly assigned to patients, there should be a substantial selection bias regarding the selection of such drugs. It is well known that CYP2C19 polymorphisms are frequent in the Japanese. The antiplatelet effects of clopidogrel might be affected by CYP2C19 polymorphisms, which were not checked in our daily clinical practice. Although we performed multivariate Cox hazard analysis to control confounding factors, we could not adjust potential confounding factors. Because we excluded patients who had warfarin or DOAC, we could not examine the efficacy and safety regarding triple antithrombotic therapy. As our institution was a tertiary university hospi-
tal, patients were referred to their primary care physicians at discharge. We wrote a letter for primary care physicians including the recommended duration of DAPT, which was at least 90 days (3 months) during the study period. Although we expected that all patients had DAPT until 90 days, we could not confirm whether DAPT was continued in each patient as recommended. Moreover, there is a possibility that the regimen of DAPT was changed after the hospital discharge.

Conclusion

As compared to clopidogrel, the reduced dose of prasugrel was not associated with the excess risk of bleeding or the excess risk of ischemic events. Our real-world data support the current regimen of prasugrel for patients with AMI.

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Disclosure

Conflicts of interest: Dr. Sakakura has received speaking honoraria from Abbott Vascular, Boston Scientific, Medtronic Cardiovascular, Terumo, OrbusNeich, Japan Lifeline, Kaneka, Daiichi-Sankyo, Sanofi, and NIPRO; he has served as a proctor for Rotablator for Boston Scientific and as a consultant for Abbott Vascular and Boston Scientific. Dr. Taniguchi has received speaking honoraria from Daiichi-Sankyo and Sanofi. Dr. Yamamoto has received speaking honoraria from Daiichi-Sankyo. Prof. Fujita has served as a consultant for Merogen Group Holdings, Inc. and has received speaking honoraria from Daiichi-Sankyo and Sanofi. The other authors declare no conflict of interest.

References

1. Dégano IR, Salomaa V, Veronesi G, et al. Twenty-five-year trends in myocardial infarction attack and mortality rates, and case-fatality, in six European populations. Heart 2015; 101: 1413-21.
2. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. JAMA 2005; 294: 1224-32.
3. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357: 2001-15.
4. Levine GN, Jeong YH, Goto S, et al. Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. Nat Rev Cardiol 2014; 11: 597-606.
5. Saito S, Ishikita T, Kimura T, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: the PRASFIT-ACS study. Circ J 2014; 78: 1684-92.
6. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123: 2736-47.
7. Watanabe Y, Sakakura K, Taniguchi Y, et al. Determinants of slow flow in percutaneous coronary intervention to the culprit lesion of non-ST elevation myocardial infarction. J Heart J 2018; 59: 1237-45.
8. Tsuki T, Sakakura K, Taniguchi Y, et al. Determinants of short and long door-to-balloon time in current primary percutaneous coronary interventions. Heart Vessels 2018; 33: 498-506.
9. Noguchi M, Sakakura K, Akashi N, et al. The comparison of clinical outcomes between inferior ST-elevation myocardial infarction with right ventricular infarction versus without right ventricular infarction. Int Heart J 2019; 60: 560-8.
10. Sawano S, Sakakura K, Yamamoto K, et al. Further validation of a novel acute myocardial infarction risk stratification (nARS) system for patients with acute myocardial infarction. Int J Heart J 2020; 61: 463-9.
11. Yamamoto K, Sakakura K, Akashi N, et al. Clinical outcomes after acute myocardial infarction according to a novel stratification system linked to a rehabilitation program. J Cardiol 2018; 72: 227-33.
12. Helal AM, Shaheen SM, Elhammady WA, Ahmed MI, Abdel-Hakim AS, Allam LE. Primary PCI versus pharmacoinvasive strategy for ST elevation myocardial infarction. Int J Cardiol Heart Vasc 2018; 21: 87-93.

Table IV. Multivariate Cox Hazard Models to Predict Total Ischemic Events and Total Bleeding Events

| Model 1. Dependent variable: total ischemic events | Hazard ratio | 95% confidence interval | P value |
|---------------------------------------------------|--------------|------------------------|---------|
| Prasugrel (versus clopidogrel)                     | 0.955        | 0.499–1.829            | 0.890   |
| Age (1 year incremental)                          | 1.010        | 0.985–1.036            | 0.437   |
| Current smoker                                    | 1.081        | 0.557–2.096            | 0.819   |
| Serum creatinine                                  | 1.105        | 1.004–1.217            | 0.041   |
| Prior PCI                                         | 1.112        | 0.512–2.412            | 0.789   |

| Model 2. Dependent variable: total bleeding events | Hazard ratio | 95% confidence interval | P value |
|---------------------------------------------------|--------------|------------------------|---------|
| Prasugrel (versus clopidogrel)                     | 0.972        | 0.528–1.790            | 0.927   |
| Age (1 year incremental)                          | 1.047        | 1.020–1.074            | 0.001   |
| Current smoker                                    | 1.548        | 0.858–2.794            | 0.147   |
| Serum creatinine                                  | 1.093        | 0.998–1.197            | 0.055   |
| Prior PCI                                         | 0.806        | 0.379–1.714            | 0.575   |
| Trans-femoral coronary intervention               | 1.480        | 0.864–2.535            | 0.153   |

All variables are adjusted in one step. PCI indicates percutaneous coronary intervention.
13. Costa F, van Klaveren D, James S, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017; 389: 1025-34.

14. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 1993; 24: 35-41.

15. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49: 1373-9.

16. Cavender MA, Norhammar A, Birkeland KI, et al. SGLT-2i nhibitors and cardiovascular risk: an analysis of CVD-REAL. J Am Coll Cardiol 2018; 71: 2497-506.

17. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci 2010; 25: 1-21.

18. Kang J, Park KW, Palmerini T, et al. Racial differences in ischaemia/bleeding risk trade-off during anti-platelet therapy: individual patient level landmark meta-analysis from seven RCTs. Thromb Haemost 2019; 119: 149-62.

19. Jenny JY. [Beta risk: an unrecognized risk of statistical error]. Rev Chir Orthop Réparatrice Appar Mot 2001; 87: 170-2.

20. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (Triton-TIMI 38): double-blind, randomised controlled trial. Lancet 2009; 373: 723-31.

21. Akita K, Inohara T, Yamaji K, et al. Impact of reduced-dose prasugrel vs. standard-dose clopidogrel on in-hospital outcomes of percutaneous coronary intervention in 62,737 patients with acute coronary syndromes: a nationwide registry study in Japan. Eur Heart J Cardiovasc Pharmacother 2020; 6: 231-8.

22. Yasuda S, Honda S, Takegami M, et al. Contemporary antiplatelet therapy and clinical outcomes of Japanese patients with acute myocardial infarction-Results from the prospective Japan acute myocardial infarction Registry (JAMIR). Circ J 2019; 83: 1633-43.

23. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. JAMA 2019; 321: 2414-27.

24. Nakamura M, Kimura K, Kimura T, et al. JCS 2020 guideline focused update on antithrombotic therapy in patients with coronary artery disease. Circ J 2020; 84: 831-65.

25. Jinnai T, Horiuchi H, Makiyama T, et al. Impact of CYP2C19 polymorphisms on the antiplatelet effect of clopidogrel in an actual clinical setting in Japan. Circ J 2009; 73: 1498-503.

Supplemental Files

Supplemental Tables I-III
Supplemental Figure
Please see supplemental files; https://doi.org/10.1536/ihj.20-357