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Retrospective observational analysis of prasugrel dosage after percutaneous coronary intervention using the Clinical Deep Data Accumulation System database

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Abstract: Prasugrel reduces the recurrence of atherosclerotic cardiovascular disease and restenosis after percutaneous coronary intervention (PCI). However, its actual dosage in Japan has not been well studied. This study aimed to compare different prasugrel doses after PCI using retrospective data from the Clinical Deep Data Accumulation System (CLIDAS) database. A retrospective observational study was conducted using the CLIDAS-PCI database with a 2-year follow-up after PCI. There were 2,869 and 52 patients in the 3.75- and 2.5 mg groups, respectively. The 2.5 mg group was comprised of significantly more female, older, shorter, and lower-body-weight patients and included more patients with a history of coronary artery bypass grafting, stroke, peripheral arterial disease, or active malignancy than the 3.75 mg group. Concomitant medications included antiplatelets, anticoagulants, and statins. Laboratory data showed substantially lower hemoglobin and platelet counts in the 2.5 mg group. Most patients weighed < 50 kg; however, fewer had an estimated glomerular filtration rate < 30 mL/min/1.73 m². Major adverse cardio- and cerebrovascular events were similar between groups. The 2.5 mg group had more non-fatal strokes and major bleeding associated with antithrombotic therapy. In Japan, prasugrel 2.5 mg should be considered to reduce major bleeding in patients with low body weight, older adults, women, those receiving concomitant antithrombotic therapy, and those with low platelet counts.

***Keywords*:** prasugrel, major adverse cardiovascular and cerebrovascular events (MACCE), Clinical Deep Data Accumulation System (CLIDAS), percutaneous coronary intervention (PCI)

1. Introduction

Prasugrel is a third-generation thienopyridine antiplatelet drug that rapidly and potently inhibits platelet aggregation. Unlike clopidogrel, its action is not affected by CYP2C19 genetic polymorphisms. In the TRITON-TIMI 38 study of percutaneous coronary intervention (PCI) of acute coronary syndrome (ACS), prasugrel (60 mg loading dose [LD]/10 mg maintenance dose [MD]) resulted in considerably fewer ischemic cardiovascular events than clopidogrel but was associated with increased major bleeding not related to coronary artery bypass grafting (CABG). The risk of bleeding was particularly high in patients aged > 75 years, those with body weight < 60 kg, and those with a history of stroke or transient ischemic attack (TIA) (*1*). The PRASIFIT-ACS study of emergent PCI in ACS (*2*) and the PRASIFIT-Elective study of scheduled PCI in patients with stable angina and old myocardial infarction (chronic coronary syndrome [CCS]) (*3*) showed that 3.75 mg of prasugrel was associated with significantly fewer ischemic cardiovascular accidents than the standard dose of clopidogrel, with similar bleeding risk. Prasugrel (20 mg LD/3.75 mg MD) has therefore been approved and widely used in Japan. According to the drug information, there were no differences in the pharmacokinetics of active metabolites in patients with moderate renal dysfunction (creatinine clearance 30–50 mL/min/1.73 m^2), moderate hepatic dysfunction (Child–Pugh class B), or in older patients (≥ 75 years) compared to healthy or non-older individuals. Antiplatelet therapy is especially important for patients at high bleeding risk (*4*). Since May 2014, a 2.5 mg MD of prasugrel has been available in Japan. The safety and efficacy of prasugrel (2.5 mg) in older and/or low-body-weight Japanese patients with ischemic stroke have been reported (*5*). A Japanese Phase II study in patients ≥ 75 years and/or ≤ 50 kg undergoing elective PCI demonstrated that prasugrel 20 mg LD/2.5 mg MD inhibits platelet function in a manner comparable to clopidogrel (*6*). The real use of prasugrel 2.5mg MD after PCI has not been reported. Therefore, in this study, we conducted a retrospective observational study using the Clinical Deep Data Accumulation System (CLIDAS) database, which follows post-PCI patients, to examine prasugrel use, selection background, cardiovascular events, and major bleeding in real-world clinical practice in Japan.

2. Patients and Methods

2.1. CLIDAS

Seven hospitals (six university hospitals and the National Cerebral and Cardiovascular Center Hospital in Japan) participated in the CLIDAS project. Standardized Structured Medical Information eXchange version 2 (SS-MIX2) standard storage was used to collect essential patient information, prescriptions, and laboratory data from electronic medical records, while SS-MIX2 extended storage was used to capture physiological test results, cardiac catheterization reports, and cardiac catheter intervention reports (*7*).

CLIDAS was developed as part of the Japan Ischemic Heart Disease Multimodal Prospective Data Acquisition for Precision Treatment Project, launched in 2015, which aimed to establish a hospital information system (HIS)-based procedure for electronically capturing medical records and other clinical data in standardized formats for clinical studies (*8*). Data from the HIS, picture archiving and communication system, and physiology server were linked to a multipurpose clinical data repository system (MCDRS) through the SS-MIX2 standard and extended storage. After anonymization, each facility's output data were sent through the MCDRS server to the CLIDAS server. Data managers and researchers at each facility collected patients' background information and follow-up data. Finally, the data stored on the CLIDAS server were analyzed (*9-13*).

2.2. Study design and clinical outcomes

This retrospective multicenter observational study included patients with coronary artery disease who underwent PCI at seven hospitals between May 2014 and December 2023 (*14*). Patients aged < 20 years, those without a prasugrel prescription within 14 days after PCI, and those with no event data after PCI were excluded. The final study population was divided into two groups based on the prasugrel dose. This study was approved by the Institutional Review Board for Clinical Research of the National Center for Global Health and Medicine (NCGM-S-004832-00) and conducted according to the ethical principles of the Declaration of Helsinki. The retrospective design waived the requirement for written informed consent.

The primary outcome was the incidence of major adverse cardiac and cerebrovascular events (MACCE) during the 2-year follow-up, defined as cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or coronary artery revascularization. Secondary outcomes included individual MACCE components and major bleeding. Major bleeding was defined as the need for transfusion of > 2 units of blood or a fall in hemoglobin level of ≥ 2.0 g/dL. Prasugrel dose was also considered a secondary outcome to evaluate the association between patient characteristics and dose selection.

2.3. Definitions

All baseline laboratory data were defined as the most recent values obtained within 14 days before

the index PCI. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or medical treatment for hypertension at the index PCI. Diabetes was defined as glycated hemoglobin ≥ 6.5%, casual blood glucose ≥ 200 mg/dL, fasting blood glucose ≥ 126 mg/dL, or medical treatment for diabetes at the index PCI. Dyslipidemia was defined as medical treatment for dyslipidemia at the index PCI or a recorded diagnosis of dyslipidemia in the electronic medical records. Current and past smokers were included in the smoking category. The estimated glomerular filtration rate (eGFR) was calculated from the serum creatinine (Cr) concentration, age, weight, and sex using the following formula (*15*):

$$\mathrm{eGFR(ml/min/1.73m^2)} = \begin{cases} 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{age}^{-0.287} \text{ (in men)} \\ 194 \times \mathrm{Cr}^{-1.094} \times \mathrm{age}^{-0.287} \times 0.739 \text{ (in women)} \end{cases}$$

Medication status was assessed by counting the number of prescriptions within 14 days prior to the index PCI. Each patient's prasugrel dose was determined as the dose administered for the greatest cumulative duration between the index PCI and the earliest occurrence of any event of interest.

2.4. Statistical analysis

Continuous variables are summarized as means ± standard deviations, and categorical variables as frequencies and percentages. Differences between dose groups were examined using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables, including the number of events for primary and secondary outcomes.

To explore factors associated with dose selection, logistic regression models were fitted with baseline characteristics as explanatory variables. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and *p*-values are reported.

For analyses of MACCE and major bleeding events, survival curves were estimated using the Kaplan–Meier method, and comparisons between dose groups were performed using log-rank tests. Cox proportional hazards models were used to evaluate relative risks between dose groups, providing hazard ratios (HRs) with 95% CIs and *p*-values. Cox models included dose groups and clinically important confounders as covariates.

Missing data were not imputed, and all analyses were conducted using a complete case approach. Statistical significance was defined as a two-sided p-value < 0.05. No adjustments for multiple testing were made due to the exploratory nature of the analyses. All statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Study population

The CLIDAS database included 8,188 consecutive patients who underwent PCI between May 2014 and December 2023 (Figure 1). Patients aged < 20 years (n = 2), those without a prasugrel prescription within 14 days after PCI (n = 4,830), and those without event data after PCI (n = 50) were excluded. Of the remaining patients prescribed prasugrel (n = 3,306), those with an unconfirmed prasugrel dose from the time of PCI to the

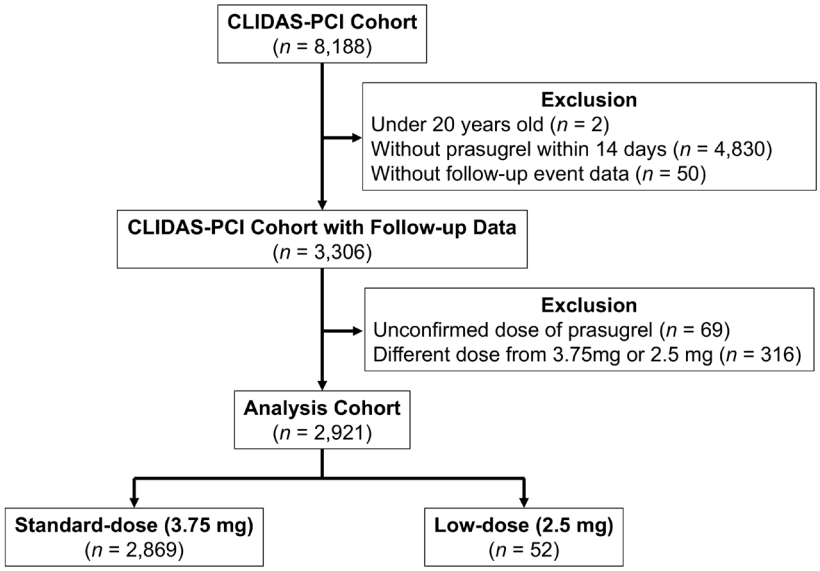

Figure 1. Flowchart of patient enrollment. Among the 8,188 patients in the CLIDAS-PCI cohort, 2,921 were included in this study. The 3.75 and 2.5 mg groups had 2,869 and 52 patients, respectively. *Abbreviations*: PCI, percutaneous coronary intervention; CLIDAS, Clinical Deep Data Accumulation System.

event (n = 69) or with doses different from 3.75 or 2.5 mg (n = 316) were excluded. The final study population included 2,921 patients, analyzed as the 3.75 (n = 2,869) and 2.5 mg groups (n = 52).

3.2. Baseline characteristics

Baseline characteristics of the two groups are presented in Table 1. The 2.5 mg group had a higher proportion of women (44.2% *vs.* 19.1%, $p < 0.001$), older age at PCI (78.3 ± 8.2 *vs.* 67.8 ± 11.3 years, $p < 0.001$), shorter height (157.6 ± 8.7 cm *vs.* 162.9 ± 9.0 cm, $p < 0.001$), lower weight (55.4 ± 11.0 kg *vs.* 65.0 ± 13.3 kg, $p < 0.001$) and lower body mass index (BMI) (22.1 ± 3.1 *vs.* 24.4 ± 3.9, $p < 0.001$) than the 3.75 mg group. Compared to the 3.75 mg group, the 2.5 mg group had fewer smokers (46.2% *vs.* 63.6%, $p = 0.008$), and more patients with a medical history of CABG surgery (9.6% *vs.* 3.1%, $p = 0.024$), stroke (13.5% *vs.* 6.0%, $p = 0.039$), peripheral artery disease (9.6% *vs.* 3.3%, $p = 0.036$), and active malignancy (19.2% *vs.* 10.2%, $p = 0.006$). Patients in the 2.5 mg group had higher rates of antiplatelet therapy (84.6% *vs.* 60.1%, $p < 0.001$), anticoagulants (26.9% *vs.* 3.9%, $p < 0.001$), and statins (30.8% *vs.* 19.1%, $p = 0.049$) than those in the 3.75 mg group. Laboratory data showed lower hemoglobin

Table 1. Baseline characteristics and cardiovascular events in the 3.75 and 2.5 mg groups

Variables	Total (n = 2,921)	3.75 mg (n = 2,869)	2.5 mg (n = 52)	p-value
Characteristics				
Female	571 (19.5%)	548 (19.1%)	23 (44.2%)	< 0.001
Age, years	68.0 ± 11.3	67.8 ± 11.3	78.3 ± 8.2	< 0.001
Height, cm	162.8 ± 9.0	162.9 ± 9.0	157.6 ± 8.7	< 0.001
Weight, kg	64.8 ± 13.3	65.0 ± 13.3	55.4 ± 11.0	< 0.001
BMI, kg/m^2	24.3 ± 3.9	24.4 ± 3.9	22.1 ± 3.1	< 0.001
Smoking	1,849 (63.3%)	1,825 (63.6%)	24 (46.2%)	0.008
Weight ≤ 50 kg	339 (11.6%)	320 (11.2%)	19 (36.5%)	< 0.001
Past medical history				
PCI	350 (12.0%)	341 (11.9%)	9 (17.3%)	0.278
CABG	93 (3.2%)	88 (3.1%)	5 (9.6%)	0.024
Myocaridal infarction	445 (15.2%)	439 (15.3%)	6 (11.5%)	0.562
Heart failure	135 (4.6%)	130 (4.5%)	5 (9.6%)	0.091
Stroke	180 (6.2%)	173 (6.0%)	7 (13.5%)	0.039
Complications				
Diabetes mellitus	1,184 (40.5%)	1,162 (40.5%)	22 (42.3%)	0.887
Dyslipidemia	2,268 (77.6%)	2,232 (77.8%)	36 (69.2%)	0.126
Hypertension	2,299 (78.7%)	2,257 (78.7%)	42 (80.8%)	0.865
Peripheral arterial disease	99 (3.4%)	94 (3.3%)	5 (9.6%)	0.036
Atrial fibrillation	86 (2.9%)	83 (2.9%)	3 (5.8%)	0.198
Hemodialysis	133 (4.6%)	132 (4.6%)	1 (1.9%)	0.731
Active maligancy	304 (10.4%)	294 (10.2%)	10 (19.2%)	0.006
Medications				
Antiplatelet	1,767 (60.5%)	1,723 (60.1%)	44 (84.6%)	< 0.001
Anticoagulant	126 (4.3%)	112 (3.9%)	14 (26.9%)	< 0.001
Statin	565 (19.3%)	549 (19.1%)	16 (30.8%)	0.049
Antihypertensive drug	969 (33.2%)	958 (33.4%)	11 (21.2%)	0.074
Laboratory variables				
eGFR, mL/min/1.73 m^2	63.7 ± 24.8	63.8 ± 24.9	62.6 ± 18.5	0.655
Hemoglobin, g/dL	13.0 ± 1.9	13.0 ± 1.9	11.9 ± 1.7	< 0.001
Platelet, 10^3/μL	111.5 ± 103.6	112.9 ± 103.8	35.8 ± 54.5	< 0.001
Creatinin, mg/dL	1.3 ± 1.7	1.3 ± 1.8	1.0 ± 0.8	0.002
eGFR ≤ 30 mL/min/1.73 m^2	244 (8.4%)	242 (8.4%)	2 (3.8%)	0.006
PCI				
ACS	1,438 (49.2%)	1,419 (49.5%)	19 (36.5%)	0.070
CCS	1,482 (50.7%)	1,449 (50.5%)	33 (63.5%)	
Cardiovascular events				
MACCE	865 (29.6%)	853 (29.7%)	12 (23.1%)	0.359
Non-fatal myocardial infarction	65 (2.2%)	65 (2.3%)	0 (0.0%)	0.630
Non-fatal stroke	36 (1.2%)	33 (1.2%)	3 (5.8%)	0.025
Cardiovascular death	57 (2.0%)	57 (2.0%)	0 (0.0%)	0.625
Coronary revasculization	727 (24.9%)	718 (25.0%)	9 (17.3%)	0.257
Major bleeding	45 (1.5%)	41 (1.4%)	4 (7.7%)	0.008

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

(11.9 ± 1.7 g/dL *vs.* 13.0 ± 1.9 g/dL, $p < 0.001$), platelet count (35.8 ± 54.5 × 10^3/μL *vs.* 112.9 ± 103.8 × 10^3/μL, $p < 0.001$), and creatinine (1.0 ± 0.8 mg/dL *vs.* 1.3 ± 1.8 mg/dL, $p = 0.002$) in the 2.5 mg group. More patients in the 2.5 mg group weighed < 50 kg (36.5% *vs.* 11.2%, $p < 0.001$), and fewer had an eGFR ≤ 30 ml/min/1.73 m^2 (3.8% *vs.* 8.4%, $p = 0.006$) than the 3.75 mg group.

3.3. MACCE and major bleeding

No significant difference was observed between the two groups in the incidence of MACCE (23.1% *vs.* 29.7%, $p = 0.359$) or coronary revascularization procedures (17.3% *vs.* 25.0%, $p = 0.257$). The 2.5 mg group had higher rates of nonfatal stroke (5.8% *vs.* 1.2%, $p = 0.025$) and major bleeding (7.7% *vs.* 1.4%, $p = 0.008$) than the 3.75 mg group (Table 1).

Kaplan–Meier curves for MACCE and major bleeding are shown in Figures 2A and B. In the 2.5 mg group, MACCE showed a non-significant downward trend at 1 year, whereas major bleeding occurred significantly more frequently than in the 3.75 mg group.

3.4. Sub-analysis by ACS or CCS

In the ACS group (n = 1,438), only 0.97% (n = 19) received prasugrel (2.5 mg), the majority of whom were women (n = 14, 73.7%) (Table 2). History of stroke (21.1% *vs.* 4.7%, $p = 0.012$), anticoagulant use (31.6% *vs.* 2.4%, $p < 0.001$), and major bleeding (10.5% *vs.* 1.5%, $p = 0.035$) were more common, while hemoglobin levels were lower (11.7 ± 1.9 g/dL *vs.* 13.3 ± 1.9 g/dL, $p = 0.002$) in the 2.5 mg group. MACCE tended to be lower in the 2.5 mg group (10.5% *vs.* 30.5%, $p = 0.077$).

In scheduled PCI (CCS), the 2.5 mg group had more patients with active malignancy (24.2% *vs.* 13.3%, $p = 0.024$), higher anticoagulant use (21.2% *vs.* 4.9%, $p = 0.001$), and lower platelet counts (21.3 ± 6.9 x 10^3/μL *vs.* 126.5 ± 100.2 × 10^3/μL, $p < 0.001$) than the 3.75 mg group. The 2.5 mg group showed a lower tendency for MACCE, while the incidence of major bleeding was similar between groups (Table 2).

3.5. Sub-analysis by body weight

The package insert for prasugrel states that a 2.5 mg dose may be considered for patients weighing ≤ 50 kg. Therefore, patients were divided into two groups: Weight ≤ 50 kg and Weight > 50 kg (Table 3). In the Weight ≤ 50 kg group (n = 339), only 5.6% (n = 19) were prescribed prasugrel (2.5 mg). Compared to the 3.75 mg group (n = 320), patients receiving 2.5 mg prasugrel had a higher proportion of women (89.5% *vs.* 65.6%, $p = 0.042$), older age at PCI (80.0 ± 7.2 years *vs.* 75.1 ± 9.8 years, $p = 0.01$), higher prevalence of active malignancy (26.3% *vs.* 13.1%, $p = 0.007$), more frequent use of antiplatelet agents (89.5% *vs.* 59.4%, $p = 0.008$) and anticoagulants (21.1% *vs.* 5.3%, $p = 0.023$), lower platelet counts (55.5 ± 77.2 x 10^3/μL *vs.* 119.5 ± 108.9 × 10^3/μL, $p < 0.001$), and a higher proportion experiencing major bleeding (15.8% *vs.* 2.2%, $p = 0.014$). The MACCE rate was not significantly different (15.8% *vs.* 23.1%, $p = 0.582$).

In the Weight > 50 kg group (n = 2,348), the 2.5 mg group (n = 33) had higher age (77.4 ± 8.7 years *vs.* 66.6 ± 11.1 years, $p < 0.001$), shorter height (161.7 ± 6.9 cm *vs.* 164.6 ± 7.9 cm, $p = 0.025$), lower BMI (23.8 ± 2.2 *vs.* 25.0 ± 3.6, $p = 0.004$), and higher prevalence of prior CABG (15.2% *vs.* 3.1%, $p = 0.004$) and prior stroke (15.2% *vs.* 5.4%, $p = 0.033$) than the 3.75 mg group (n = 2,315). The 2.5 mg group also had higher

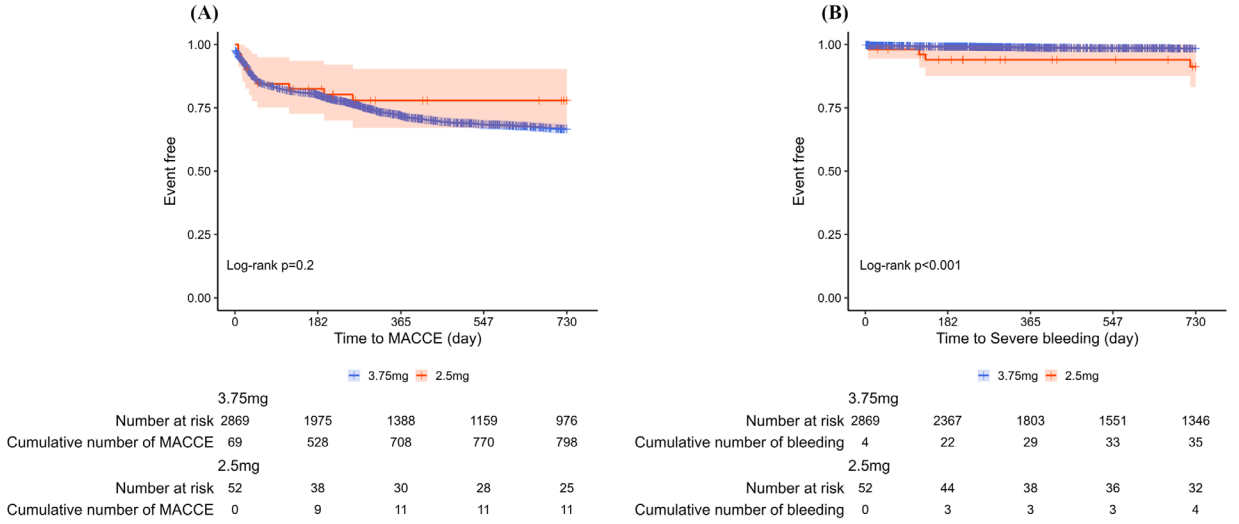

Figure 2. Kaplan–Meier curves of (A) MACCE and (B) major bleeding. *Abbreviations*: MACCE, major adverse cardiovascular and cerebrovascular events (MACCE).

Table 2. Sub-analysis by ACS or CCS

Variables	ACS (n = 1,438)			CCS (n = 1,482)		
	3.75 mg (n = 1,419)	2.5 mg (n = 19)	p-value	3.75 mg (n = 1,449)	2.5 mg (n = 33)	p-value
Characteristics						
Female	277 (19.5%)	14 (73.7%)	< 0.001	271 (18.7%)	9 (27.3%)	0.381
Age, years	66.7 ± 12.0	77.5 ± 6.7	< 0.001	68.9 ± 10.5	78.8 ± 9.1	< 0.001
Height, cm	163.3 ± 8.8	153.3 ± 8.1	< 0.001	162.6 ± 9.2	160.2 ± 8.2	0.105
Weight, kg	65.4 ± 13.4	49.5 ± 10.1	< 0.001	64.5 ± 13.1	58.8 ± 10.1	0.003
BMI, kg/m^2	24.4 ± 4.0	21.0 ± 3.6	< 0.001	24.3 ± 3.9	22.8 ± 2.7	0.003
Weight ≤ 50 kg	153 (10.8%)	10 (52.6%)	< 0.001	167 (11.5%)	9 (27.3%)	0.031
Smoking	940 (66.2%)	9 (47.4%)	0.083	885 (61.1%)	15 (45.5%)	0.069
Past medical history						
PCI	124 (8.7%)	4 (21.1%)	0.083	216 (14.9%)	5 (15.2%)	> 0.999
CABG	30 (2.1%)	2 (10.5%)	0.065	58 (4.0%)	3 (9.1%)	0.153
Myocaridal infarction	206 (14.5%)	2 (10.5%)	> 0.999	232 (16.0%)	4 (12.1%)	0.810
Heart failure	36 (2.5%)	2 (10.5%)	0.088	94 (6.5%)	3 (9.1%)	0.475
Stroke	66 (4.7%)	4 (21.1%)	0.012	107 (7.4%)	3 (9.1%)	0.732
Complications						
Diabetes mellitus	511 (36.0%)	7 (36.8%)	> 0.999	650 (44.9%)	15 (45.5%)	> 0.999
Dyslipidemia	1,141 (80.4%)	11 (57.9%)	0.018	1,090 (75.2%)	25 (75.8%)	> 0.999
Hypertension	1,146 (80.8%)	15 (78.9%)	0.767	1,110 (76.6%)	27 (81.8%)	0.676
Peripheral arterial disease	29 (2.0%)	1 (5.3%)	0.343	65 (4.5%)	4 (12.1%)	0.077
Atrial fibrillation	27 (1.9%)	0 (0.0%)	> 0.999	56 (3.9%)	3 (9.1%)	0.142
Hemodialysis	45 (3.2%)	1 (5.3%)	0.465	87 (6.0%)	0 (0.0%)	0.257
Active maligancy	101 (7.1%)	2 (10.5%)	0.146	193 (13.3%)	8 (24.2%)	0.024
Medications						
Antiplatelet	651(45.9%)	11 (57.9%)	0.357	787 (54.3%)	23 (69.7%)	0.110
Anticoagulants	34 (2.4%)	6 (31.6%)	< 0.001	71 (4.9%)	7 (21.2%)	0.001
Statin	226 (15.9%)	4 (21.1%)	0.528	262 (18.1%)	8 (24.2%)	0.362
Antihypertensive drug	368 (25.9%)	3 (15.8%)	0.432	437 (30.2%)	4 (12.1%)	0.032
Laboratory variables						
eGFR, mL/min/1.73 m^2	66.1 ± 25.7	59.1 ± 21.8	0.182	61.4 ± 23.8	64.6 ± 16.3	0.277
Hemoglobin, g/dL	13.3 ± 1.9	11.7 ± 1.9	0.002	13.0 ± 1.8	12.4 ± 1.6	0.041
Platelet, 10^3/μL	100.4 ± 107.0	63.1 ± 88.8	0.086	126.5 ± 100.2	21.3 ± 6.9	< 0.001
Creatinin, mg/dL	1.2 ± 1.5	1.1 ± 1.3	0.661	1.4 ± 1.9	0.9 ± 0.3	< 0.001
eGFR ≤ 30 mL/min/1.73 m^2	117 (8.2%)	1 (5.3%)	> 0.999	125 (8.6%)	1 (3.0%)	0.363
Cardiovascular events						
MACCE	433 (30.5%)	2 (10.5%)	0.077	419 (28.9%)	10 (30.3%)	0.848
Non-fatal myocardial infarction	59 (4.2%)	0 (0.0%)	> 0.999	6 (0.4%)	0 (0.0%)	> 0.999
Non-fatal stroke	20 (1.4%)	1 (5.3%)	0.245	13 (0.9%)	2 (6.1%)	0.042
Cardiovascular death	35 (2.5%)	0 (0.0%)	> 0.999	22 (1.5%)	0 (0.0%)	> 0.999
Coronary revasculization	334 (23.5%)	1 (5.3%)	0.096	383 (26.4%)	8 (24.2%)	> 0.999
Major bleeding	21 (1.5%)	2 (10.5%)	0.035	20 (1.4%)	2 (6.1%)	0.084

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

rates of antiplatelet therapy (81.8% *vs.* 58.7%, p = 0.007), anticoagulant therapy (30.3% *vs.* 3.3%, p < 0.001), and statin use (33.3% *vs.* 17.8%, p = 0.036), but the incidence of MACCE was similar between the groups (27.3% *vs.* 31.4%, p = 0.708).

3.6. Sub-analysis by Renal Function (eGFR)

Although renal function is not known to affect prasugrel metabolism, patients were classified based on eGFR into a severe renal impairment group (eGFR ≤ 30 ml/min/1.73 m^2, n = 244) and an eGFR > 30 ml/min/1.73 m^2 group (n = 2,329). In the eGFR ≤ 30 ml/min/1.73 m^2 group, only two patients received 2.5 mg prasugrel; therefore, statistical analysis was not possible (Table 4). In the eGFR > 30 ml/min/1.73 m^2 group, results were consistent with the overall patient analysis: nonfatal stroke (5.0% *vs.* 1.0%, p = 0.018) and major bleeding (6.0% *vs.* 1.3%, p = 0.033) were higher in the 2.5 mg group than in the 3.75 mg group.

3.7. Sub-analysis by sex

Sex is an important factor for cardiovascular disease; therefore, a sex-specific sub-analysis was performed (Table 5). In the male group (n = 2,180), the 2.5 mg group (n = 29) had higher age (76.3 ± 8.6 years *vs.* 66.6 ± 11.2 years, p < 0.001), shorter height (163.7 ± 4.6 cm *vs.*

Table 3. Sub-analysis by body weight

Variables	Weight > 50 kg (n = 2,348)			Weight ≤ 50 kg (n = 339)		
	3.75 mg (n = 2,315)	2.5 mg (n = 33)	p-value	3.75 mg (n = 320)	2.5 mg (n = 19)	p-value
Characteristics						
Female	326 (14.1%)	6 (18.2%)	0.454	210 (65.6%)	17 (89.5%)	0.042
Age, years	66.6 ± 11.1	77.4 ± 8.7	< 0.001	75.1 ± 9.8	80.0 ± 7.2	0.010
Height, cm	164.6 ± 7.9	161.7 ± 6.9	0.025	151.5 ± 7.7	150.5 ± 7.0	0.574
BMI, kg/m^2	25.0 ± 3.6	23.8 ± 2.2	0.004	19.6 ± 2.3	19.2 ± 2.4	0.571
Smoking	1,568 (67.7%)	18 (54.5%)	0.089	113 (35.3%)	6 (31.6%)	0.809
Past medical history						
PCI	272 (11.7%)	8 (24.2%)	0.051	38 (11.9%)	1 (5.3%)	0.710
CABG	72 (3.1%)	5 (15.2%)	0.004	10 (3.1%)	0 (0.0%)	> 0.999
Myocaridal infarction	329 (14.2%)	5 (15.2%)	0.804	53 (16.6%)	1 (5.3%)	0.331
Heart failure	98 (4.2%)	3 (9.1%)	0.169	24 (7.5%)	2 (10.5%)	0.650
Stroke	125 (5.4%)	5 (15.2%)	0.033	21 (6.6%)	2 (10.5%)	0.381
Complications						
Diabetes mellitus	960 (41.5%)	16 (48.5%)	0.481	115 (35.9%)	6 (31.6%)	0.808
Dyslipidemia	1,838 (79.4%)	26 (78.8%)	0.828	229 (71.6%)	10 (52.6%)	0.072
Hypertension	1,829 (79.0%)	27 (81.8%)	> 0.999	2,490 (77.8%)	15 (78.9%)	> 0.999
Peripheral arterial disease	66 (2.9%)	3 (9.1%)	0.082	16 (5.0%)	2 (10.5%)	0.283
Atrial fibrillation	71 (3.1%)	2 (6.1%)	0.276	6 (1.9%)	1 (5.3%)	0.337
Hemodialysis	94 (4.1%)	0 (0.0%)	0.642	23 (7.2%)	1 (5.3%)	> 0.999
Active maligancy	220 (9.5%)	5 (15.2%)	0.245	42 (13.1%)	5 (26.3%)	0.007
Medications						
Antiplatelet	1,359 (58.7%)	27 (81.8%)	0.007	190 (59.4%)	17 (89.5%)	0.008
Anticoagulant	77 (3.3%)	10 (30.3%)	< 0.001	17 (5.3%)	4 (21.1%)	0.023
Statin	413 (17.8%)	11 (33.3%)	0.036	50 (15.6%)	5 (26.3%)	0.209
Antihypertensive drug	765 (33.0%)	6 (18.2%)	0.092	93 (29.1%)	5 (26.3%)	> 0.999
Laboratory variables						
eGFR, mL/min/1.73 m^2	64.4 ± 24.7	61.1 ± 15.0	0.221	58.6 ± 25.8	65.2 ± 23.7	0.261
Hemoglobin, g/dL	13.3 ± 1.8	12.4 ± 1.7	0.006	11.5 ± 1.6	11.2 ± 1.3	0.337
Platelet, 10^3/μL	108.5 ± 102.6	24.4 ± 31.8	< 0.001	119.5 ± 108.9	55.5 ± 77.2	0.002
Creatinin, mg/dL	1.3 ± 1.7	0.9 ± 0.3	< 0.001	1.3 ± 1.6	1.0 ± 1.3	0.336
eGFR ≤ 30 mL/min/1.73 m^2	195 (8.4%)	1 (3.0%)	0.327	44 (13.8%)	1 (5.3%)	0.581
PCI						
ACS	1,175 (50.8%)	9 (27.3%)	0.008	153 (47.8%)	10 (52.6%)	0.814
CCS	1,139 (49.2%)	24 (72.7%)		167 (52.2%)	9 (47.4%)	
Cardiovascular events						
MACCE	727 (31.4%)	9 (27.3%)	0.708	74 (23.1%)	3 (15.8%)	0.582
Non-fatal myocardial infarction	54 (2.3%)	0 (0.0%)	> 0.999	4 (1.3%)	0 (0.0%)	> 0.999
Non-fatal stroke	26 (1.1%)	2 (6.1%)	0.058	5 (1.6%)	1 (5.3%)	0.294
Cardiovascular death	42 (1.8%)	0 (0.0%)	> 0.999	11 (3.4%)	0 (0.0%)	> 0.999
Coronary revasculization	623 (26.9%)	7 (21.2%)	0.556	55 (17.2%)	2 (10.5%)	0.751
Major bleeding	31 (1.3%)	1 (3.0%)	0.366	7 (2.2%)	3 (15.8%)	0.014

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

166.0 ± 6.7 cm, $p = 0.011$), lower body weight (62.7 ± 7.4 kg *vs.* 67.7 ± 12.9 kg, $p = 0.001$), and lower BMI (23.4 ± 2.6 *vs.* 24.5 ± 4.0, $p = 0.032$) than the 3.75 mg group (n = 2,151). However, the proportion of patients weighing ≤ 50 kg was similar in both groups (6.9% *vs.* 5.2%, $p = 0.826$). The 2.5 mg group had a higher prevalence of peripheral arterial disease (13.8% *vs.* 3.0%, $p = 0.014$), antiplatelet therapy (82.8% *vs.* 59.6%, $p = 0.012$), and anticoagulant therapy (34.5% *vs.* 3.4%, $p < 0.001$). Laboratory data showed lower hemoglobin (12.7 ± 1.5 g/dL *vs.* 13.4 ± 1.8 g/dL, $p = 0.021$), platelet count (19.9 ± 6.2 × 10^3/μL *vs.* 104.6 ± 102.0 × 10^3/μL, $p < 0.001$), and creatinine (0.9 ± 0.3 mg/dL *vs.* 1.4 ± 1.8 mg/dL, $p < 0.001$). MACCE (27.6% *vs.* 29.9%, $p > 0.999$) and major bleeding (3.4% *vs.* 1.5%, $p = 0.359$) were similar.

In the female cohort (n = 571), the 2.5 mg group (n = 23) had higher age at PCI (81.0 ± 7.1 *vs.* 72.0 ± 10.6, $p < 0.001$), lower body weight (46.2 ± 7.2 kg *vs.* 54.6 ± 12.3 kg, $p < 0.001$), lower BMI (20.5 ± 3.1 *vs.* 23.9 ± 4.7, $p < 0.001$), higher prevalence of active malignancy (17.4% *vs.* 7.5%, $p = 0.014$), and more frequent antiplatelet (87.0% *vs.* 59.1%, $p = 0.008$) and anticoagulant therapy (17.4% *vs.* 4.4%, $p = 0.022$), than the 3.75 mg group (n = 548). Laboratory data showed lower hemoglobin (11.0 ± 1.5 g/dL *vs.* 11.8 ± 1.5 g/dL, $p = 0.019$) and platelet counts (55.8 ± 77.9 × 10^3/μL *vs.*

Table 4. Sub-analysis by renal function (eGFR)

Variables	eGFR > 30 mL/min/1.73 m^2 (n = 2,371)			eGFR ≤ 30 mL/min/1.73 m^2 (n = 244)		
	3.75 mg (n = 2,329)	2.5 mg (n = 50)	p-value	3.75 mg (n = 242)	2.5 mg (n = 2)	p-value
Characteristics						
Female	455 (19.5%)	22 (44.0%)	< 0.001	65 (26.9%)	1 (50.0%)	0.469
Age, years	67.4 ± 11.3	78.2 ± 8.3	< 0.001	70.2 ± 10.5	82.5 ± 6.4	0.216
Height, cm	163.2 ± 9.0	157.8 ± 8.9	< 0.001	161.0 ± 9.1	154.5 ± 0.7	< 0.001
Weight, kg	65.3 ± 13.2	55.4 ± 11.1	< 0.001	62.3 ± 13.7	54.3 ± 8.1	0.392
BMI, kg/m^2	24.4 ± 3.9	22.1 ± 3.2	< 0.001	23.9 ± 4.5	22.8 ± 3.6	0.731
Smoking	1,502 (64.5%)	24 (48.0%)	0.016	144 (59.5%)	0 (0.0%)	0.159
Weight ≤ 50 kg	262 (11.2%)	18 (36.0%)	< 0.001	44 (18.2%)	1 (50.0%)	0.355
Past medical history						
PCI	271 (11.6%)	9 (18.0%)	0.181	35 (14.5%)	0 (0.0%)	> 0.999
CABG	63 (2.7%)	5 (10.0%)	0.013	17 (7.0%)	0 (0.0%)	> 0.999
Myocaridal infarction	378 (16.2%)	6 (12.0%)	0.560	27 (11.2%)	0 (0.0%)	> 0.999
Heart failure	85 (3.6%)	4 (8.0%)	0.116	37 (15.3%)	1 (50.0%)	0.289
Stroke	117 (5.0%)	7 (14.0%)	0.014	31 (12.8%)	0 (0.0%)	> 0.999
Complications						
Diabetes mellitus	918 (39.4%)	22 (44.0%)	0.562	120 (49.6%)	0 (0.0%)	0.498
Dyslipidemia	1,864 (80.0%)	34 (68.0%)	0.046	161 (66.5%)	2 (100.0%)	> 0.999
Hypertension	1,856 (79.7%)	40 (80.0%)	> 0.999	207 (85.5%)	2 (100.0%)	> 0.999
Peripheral arterial disease	60 (2.6%)	5 (10.0%)	0.014	21 (8.7%)	0 (0.0%)	> 0.999
Atrial fibrillation	54 (2.3%)	2 (4.0%)	0.332	10 (4.1%)	1 (50.0%)	0.089
Hemodialysis	10 (0.4%)	0 (0.0%)	> 0.999	97 (40.1%)	1 (50.0%)	> 0.999
Active maligancy	216 (9.3%)	9 (18.0%)	0.007	282 (11.6%)	1 (50.0%)	0.233
Medications						
Antiplatelet	1,443 (62.0%)	42 (84.0%)	0.001	157 (64.9%)	2 (100.0%)	0.544
Anticoagulant	84 (3.6%)	13 (26.0%)	< 0.001	13 (5.4%)	1 (50.0%)	0.112
Statin	437 (18.8%)	15 (30.0%)	0.066	48 (19.8%)	1 (50.0%)	0.362
Antihypertensive drug	802 (34.4%)	11 (22.0%)	0.071	98 (40.5%)	0 (0.0%)	0.517
Laboratory variables						
Hemoglobin, g/dL	13.3 ± 1.7	11.9 ± 1.7	< 0.001	10.9 ± 1.7	12.7 ± 2.4	0.484
Platelet, 10^3/μL	108.0 ± 103.6	36.6 ± 55.4	< 0.001	103.6 ± 98.5	15.5 ± 1.8	< 0.001
Creatinin, mg/dL	0.9 ± 0.2	0.8 ± 0.2	0.201	5.6 ± 3.2	4.2 ± 3.2	0.643
PCI						
ACS	1,186 (50.9%)	18 (36.0%)	0.045	117 (48.3%)	1 (50.0%)	> 0.999
CCS	1,142 (49.0%)	32 (64.0%)		125 (51.7%)	1 (50.0%)	
Cardiovascular events						
MACCE	649 (27.9%)	12 (24.0%)	0.634	95 (39.3%)	0 (0.0%)	0.523
Non-fatal myocardial infarction	49 (2.1%)	0 (0.0%)	0.625	7 (2.9%)	0 (0.0%)	> 0.999
Non-fatal stroke	24 (1.0%)	3 (6.0%)	0.018	4 (1.7%)	0 (0.0%)	> 0.999
Cardiovascular death	33 (1.4%)	0 (0.0%)	> 0.999	17 (7.0%)	0 (0.0%)	> 0.999
Coronary revasculization	557 (23.9%)	9 (18.0%)	0.403	71 (29.3%)	0 (0.0%)	> 0.999
Major bleeding	31 (1.3%)	3 (6.0%)	0.033	6 (2.5%)	1 (50.0%)	0.057

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

119.5 ± 106.5 × 10^3/μL, p < 0.001). Women in the 2.5 mg group had higher rates of non-fatal stroke (8.7% *vs.* 1.3%, p = 0.047) and major bleeding (13.0% *vs.* 1.3%, p = 0.006) than those in the 3.75 mg group.

3.8. Sub-analysis by antithrombotic drugs

Patients receiving prasugrel were analyzed based on concomitant use of other antithrombotic drugs, as these agents (antiplatelet drugs and/or anticoagulants) are associated with MACCE and bleeding (Table 6). Among patients on antithrombotic therapy in addition to prasugrel (n = 1,485), the 2.5 mg group (n = 37) had a lower rate of antiplatelet agent use (91.9% *vs.* 99.3%, p = 0.003) and a higher rate of anticoagulant use (35.1% *vs.* 7.3%, p < 0.001) than the 3.75 mg group (n = 1,448). Triple therapy was administered in 95 and 10 patients in the 3.75 mg (6.6%) and 2.5 mg (27.0%) groups, respectively. With antithrombotic therapy, the incidence of MACCE (29.7% *vs.* 26.7%, p = 0.708) and coronary revascularization (24.3% *vs.* 23.1%, p = 0.845) was comparable between groups. However, the 2.5 mg group had higher rates of major bleeding than the 3.75 mg group (10.8% *vs.* 1.5%, p = 0.003).

In prasugrel monotherapy, the 2.5 mg group had significantly fewer MACCE events (6.7% *vs.* 32.8%,

Table 5. Sub-analysis by sex

Variables	Male (n = 2,180)			Female (n = 571)		
	3.75 mg (n = 2,151)	2.5 mg (n = 29)	p-value	3.75 mg (n = 548)	2.5 mg (n = 23)	p-value
Characteristics						
Age, years	66.6 ± 11.2	76.3 ± 8.6	< 0.001	72.0 ± 10.6	81.0 ± 7.1	< 0.001
Height, cm	166.0 ± 6.7	163.7 ± 4.6	0.011	150.8 ± 6.4	150.0 ± 6.4	0.567
Weight, kg	67.7 ± 12.9	62.7 ± 7.4	0.001	54.6 ± 12.3	46.2 ± 7.2	< 0.001
BMI, kg/m^2	24.5 ± 4.0	23.4 ± 2.6	0.032	23.9 ± 4.7	20.5 ± 3.1	< 0.001
Smoking	1,603 (74.5%)	19 (65.5%)	0.196	123 (22.4%)	5 (21.7%)	> 0.999
Weight ≤ 50 kg	112 (5.2%)	2 (6.9%)	0.826	210 (38.3%)	17 (73.9%)	0.004
Past medical history						
PCI	255 (11.9%)	7 (24.1%)	0.075	55 (10.0%)	2 (8.7%)	> 0.999
CABG	69 (3.2%)	3 (10.3%)	0.069	14 (2.6%)	2 (8.7%)	0.133
Myocaridal infarction	350 (16.3%)	5 (17.2%)	0.804	61 (11.1%)	1 (4.3%)	0.497
Heart failure	89 (4.1%)	3 (10.3%)	0.122	36 (6.6%)	2 (8.7%)	0.661
Stroke	1,161 (5.4%)	4 (13.8%)	0.073	34 (6.2%)	3 (13.0%)	0.183
Complications						
Diabetes mellitus	873 (40.6%)	12 (41.4%)	> 0.999	221 (40.3%)	10 (43.5%)	0.831
Dyslipidemia	1,700 (79.0%)	22 (75.9%)	0.642	427 (77.9%)	14 (60.9%)	0.067
Hypertension	1,695 (78.8%)	22 (75.9%)	0.645	445 (81.2%)	20 (87.0%)	0.781
Peripheral arterial disease	64 (3.0%)	4 (13.8%)	0.014	18 (3.3%)	1 (4.3%)	0.568
Atrial fibrillation	69 (3.2%)	2 (6.9%)	0.245	9 (1.6%)	1 (4.3%)	0.341
Hemodialysis	92 (4.3%)	0 (0.0%)	0.633	25 (4.6%)	1 (4.3%)	> 0.999
Active maligancy	225 (10.5%)	6 (20.7%)	0.078	41 (7.5%)	4 (17.4%)	0.012
Medications						
Antiplatelet	1,281 (59.6%)	24 (82.8%)	0.012	324 (59.1%)	20 (87.0%)	0.008
Anticoagulant	74 (3.4%)	10 (34.5%)	< 0.001	24 (4.4%)	4 (17.4%)	0.022
Statin	389 (18.1%)	9 (31.0%)	0.088	96 (17.5%)	7 (30.4%)	0.160
Antihypertensive drug	715 (33.2%)	4 (13.8%)	0.028	186 (33.9%)	7 (30.4%)	0.825
Laboratory variables						
Hemoglobin, g/dL	13.4 ± 1.8	12.7 ± 1.5	0.021	11.8 ± 1.5	11.0 ± 1.5	0.019
Platelet, 10^3/μL	104.6 ± 102.0	19.9 ± 6.2	< 0.001	119.5 ± 106.5	55.8 ± 77.9	< 0.001
Creatinin, mg/dL	1.4 ± 1.8	0.9 ± 0.3	< 0.001	1.1 ± 1.4	1.0 ± 1.2	0.541
eGFR, mL/min/1.73 m^2	64.6 ± 24.7	63.6 ± 15.5	0.731	60.4 ± 25.2	61.3 ± 22.1	0.842
eGFR ≤ 30 mL/min/1.73 m^2	177 (8.2%)	1 (3.4%)	0.448	65 (11.9%)	1 (4.3%)	0.373
PCI						
ACS	1,089 (50.6%)	5 (17.2%)	< 0.001	277 (50.5%)	14 (60.9%)	0.397
CCS	1,061 (49.3%)	24 (82.8%)		271 (49.5%)	9 (39.1%)	
Cardiovascular events						
MACCE	644 (29.9%)	8 (27.6%)	> 0.999	161 (29.4%)	4 (17.4%)	0.249
Non-fatal myocardial infarction	46 (2.1%)	0 (0.0%)	> 0.999	12 (2.2%)	0 (0.0%)	> 0.999
Non-fatal stroke	24 (1.1%)	1 (3.4%)	0.286	7 (1.3%)	2 (8.7%)	0.047
Cardiovascular death	41 (1.9%)	0 (0.0%)	> 0.999	12 (2.2%)	0 (0.0%)	> 0.999
Coronary revasculization	548 (25.5%)	7 (24.1%)	> 0.999	134 (24.5%)	2 (8.7%)	0.130
Major bleeding	32 (1.5%)	1 (3.4%)	0.359	7 (1.3%)	3 (13.0%)	0.006

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

p = 0.048) and coronary revascularization procedures (0.0% *vs.* 27.0%, p = 0.016) than the 3.75 mg group. No major bleeding was observed with 2.5 mg prasugrel monotherapy. Among patients receiving prasugrel 2.5 mg plus concomitant antithrombotic therapy, serious bleeding occurred in four patients: two received antiplatelet therapy, one received anticoagulant therapy, and one received both (triple therapy).

3.9. Factors associated with prasugrel 2.5 mg

Factors associated with prasugrel 2.5 mg were analyzed using univariate logistic regression (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=117*). Associated factors included female sex (OR = 3.115, 95% CI = 1.770–5.405, p < 0.001), older age at PCI (OR = 1.122, 95% CI = 1.085–1.163, p < 0.001), short height (OR = 1.060, 95% CI = 1.031–1.091, p < 0.001), low body weight (OR = 1.067, 95% CI = 1.042–1.094, p < 0.001), low BMI (OR = 1.192, 95% CI = 1.099–1.294, p < 0.001), non-smoking (OR = 0.468, 95% CI = 0.268–0.812, p = 0.007), prior CABG surgery (OR = 3.341, 95% CI = 1.138–7.859, p = 0.012), history of stroke (OR = 2.409,

Table 6. Sub-analysis by antithrombotic drugs

Variables	Antithrombotic drugs (n = 1,485)			Prasugrel only (n = 1,436)		
	3.75 mg (n = 1,448)	2.5 mg (n = 37)	p-value	3.75 mg (n = 1,421)	2.5 mg (n = 15)	p-value
Characteristics						
Female	276 (19.1%)	15 (40.5%)	0.003	272 (19.1%)	8 (53.3%)	0.008
Age, years	68.7 ± 11.0	78.2 ± 6.9	< 0.001	66.9 ± 10.6	78.7 ± 7.1	0.001
Height, cm	162.5 ± 9.0	158.3 ± 9.0	0.008	163.4 ± 9.1	156.0 ± 8.2	0.567
Weight, kg	64.3 ± 12.6	56.4 ± 10.1	< 0.001	65.7 ± 13.8	52.9 ± 13.0	0.002
BMI, kg/m^2	24.2 ± 3.7	22.4 ± 3.0	< 0.001	24.5 ± 4.1	21.4 ± 3.5	0.004
Smoking	942 (65.1%)	17 (45.9%)	0.022	883 (62.1%)	7 (46.7%)	0.185
Weight ≤ 50 kg	163 (12.6%)	12 (32.4%)	0.002	157 (11.7%)	7 (46.7%)	< 0.001
Past medical history						
PCI	219 (15.1%)	6 (16.2%)	0.835	122 (8.6%)	3 (20.0%)	0.273
CABG	55 (3.8%)	5 (13.5%)	0.039	33 (2.3%)	0 (0.0%)	> 0.999
Myocaridal infarction	258 (17.8%)	3 (8.1%)	0.283	181 (12.7%)	3 (20.0%)	0.513
Heart failure	93 (6.4%)	4 (10.8%)	0.333	37 (2.6%)	1 (6.7%)	0.427
Stroke	109 (7.5%)	5 (13.5%)	0.239	64 (4.5%)	2 (13.3%)	0.276
Complications						
Diabetes mellitus	588 (40.6%)	16 (43.2%)	0.898	574 (40.4%)	6 (40.0%)	> 0.999
Dyslipidemia	1,114 (76.9%)	25 (67.6%)	0.268	1,118 (78.7%)	11 (73.3%)	0.602
Hypertension	1,190 (82.2%)	32 (86.5%)	0.680	1,067 (75.1%)	10 (66.7%)	0.482
Peripheral arterial disease	59 (4.1%)	4 (10.8%)	0.036	35 (2.5%)	1 (6.7%)	0.392
Atrial fibrillation	39 (2.7%)	3 (8.1%)	0.084	44 (3.1%)	0 (0.0%)	> 0.999
Hemodialysis	61 (4.2%)	1 (2.7%)	> 0.999	71 (5.0%)	0 (0.0%)	> 0.999
Active maligancy	199 (13.7%)	8 (21.6%)	0.222	95 (6.7%)	2 (13.3%)	0.017
Medications						
Antiplatelet	1,438 (99.3%)	34 (91.9%)	0.003	0 (0.0%)	0 (0.0%)	> 0.999
Anticoagulants	105 (7.3%)	13 (35.1%)	< 0.001	0 (0.0%)	0 (0.0%)	> 0.999
Statin	401 (27.7%)	9 (24.3%)	0.714	87 (6.1%)	3 (20.0%)	0.063
Antihypertensive drug	637 (44.0%)	6 (16.2%)	< 0.001	168 (11.8%)	1 (6.7%)	> 0.999
Laboratory variables						
eGFR, mL/min/1.73 m^2	62.4 (24.9)	58.5 (18.4)	0.226	65.3 (24.8)	72.6 (15.0)	0.081
Hemoglobin, g/dL	13.0 (1.8)	12.0 (1.6)	< 0.001	13.2 (1.9)	12.5 (1.9)	0.165
Platelet, 10^3/μL	100.6 (100.9)	21.7 (8.2)	< 0.001	128.0 (106.3)	73.3 (97.7)	0.049
Creatinin, mg/dL	1.4 (1.8)	1.1 (1.0)	0.050	1.3 (1.7)	0.7 (0.2)	< 0.001
eGFR ≤ 30 mL/min/1.73 m^2	136 (10.2%)	2 (5.4%)	0.576	106 (8.5%)	0 (0.0%)	0.630
PCI						
ACS	655 (45.2%)	12 (32.4%)	0.134	764 (53.8%)	7 (46.7%)	0.612
CCS	793 (54.8%)	25 (67.6%)		656 (46.2%)	8 (53.3%)	
Cardiovascular events						
MACCE	387 (26.7%)	11 (29.7%)	0.708	466 (32.8%)	1 (6.7%)	0.048
Non-fatal myocardial infarction	18 (1.2%)	0 (0.0%)	> 0.999	47 (3.3%)	0 (0.0%)	> 0.999
Non-fatal stroke	15 (1.0%)	2 (5.4%)	0.065	18 (1.3%)	1 (6.7%)	0.182
Cardiovascular death	33 (2.3%)	0 (0.0%)	> 0.999	24 (1.7%)	0 (0.0%)	> 0.999
Coronary revasculization	335 (23.1%)	9 (24.3%)	0.845	383 (27.0%)	0 (0.0%)	0.016
Major bleeding	21 (1.5%)	4 (10.8%)	0.003	20 (1.4%)	0 (0.0%)	> 0.999

Abbreviations: BMI, body mass index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; ACS, acute coronary syndrome; CCS, chronic coronary syndrome; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization). *P* values were calculated using Fisher's exact test for categorical variables.

95% CI = 0.980–5.088, p = 0.034), peripheral artery disease (OR = 2.971, 95% CI = 1.013–6.975, p = 0.024), active malignancy (OR = 2.196, 95% CI = 1.027–4.275, p = 0.029), antiplatelet use (OR = 3.658, 95% CI = 1.814–8.416, p < 0.001), anticoagulant use (OR = 9.069, 95% CI = 4.630–16.855, p < 0.001), statins use (OR = 1.878, 95% CI = 1.008–4.275, p = 0.038), low hemoglobin (OR = 1.350, 95% CI = 1.171–1.553, p < 0.001) and low platelet count (OR = 1.013, 95% CI = 1.008–3.350, p < 0.001). No association was observed with eGFR (OR = 0.998, 95% CI = 0.987–1.009, p = 0.735).

Multivariate logistic regression analysis (Table 7) identified the following factors independently associated with prasugrel 2.5 mg: female sex (OR = 2.967, 95% CI = 1.126–7.874, p < 0.001), older age at PCI (OR = 1.121, 95% CI = 1.073–1.175, p < 0.001), anticoagulant therapy (OR = 10.580, 95% CI = 4.632–23.748, p < 0.001), statin use (OR = 2.152, 95% CI = 1.057–4.269, p = 0.030), absence of antihypertensive drugs (OR = 3.831, 95% CI = 1.815–8.772, p < 0.001), and thrombocytopenia (OR = 1.014, 95% CI = 1.009–1.022, p < 0.001).

Table 7. Analysis of factors associated with 2.5 mg of prasugrel by multivariate logistic regression models

Variables	Multivariate logistic regression analysis		
	OR	95% CI	*p*-value
Characteristic			
Female	2.966	1.125–7.886	0.028
Age, years	1.121	1.073–1.175	< 0.001
Height, cm	0.946	0.793–1.157	0.569
Weight, kg	1.115	0.845–1.412	0.414
BMI, kg/m^2	0.708	0.388–1.398	0.299
Complications			
Atrial fibrillation	0.721	0.133–2.921	0.672
Medications			
Antiplatelet	2.122	0.971–5.195	0.075
Anticoagulant	10.580	4.632–23.748	< 0.001
Statin	2.152	1.057–4.269	0.030
Antihypertensive drug	0.261	0.114–0.551	< 0.001
Laboratory variables			
eGFR, mL/min/1.73 m^2	1.012	0.992–1.029	0.191
Hemoglobin, g/dL	0.953	0.770–1.180	0.656
Platelet, 10^3/μL	0.986	0.978–0.991	< 0.001
Creatinin, mg/dL	0.848	0.406–1.237	0.526

Abbreviations: OR, odds ratio; CI, confidence interval. BMI, body mass index; eGFR, estimated glomerular filtration rate.

3.10. Factors associated with MACCE and major bleeding

Multivariate Cox proportional hazard models for MACCE and major bleeding are presented in Table 8. MACCE risk decreased with anticoagulant (HR = 0.447, 95% CI = 0.244–0.819, p = 0.009), antihypertensive use (HR = 0.814, 95% CI = 0.673–0.984, p = 0.033), and higher eGFR (HR = 0.995, 95% CI = 0.990–1.000, p = 0.042), but increased with higher platelet count (HR = 1.002, 95% CI = 1.001–1.002, p < 0.001). Low platelet counts were associated with a higher risk of major bleeding (HR = 1.007, 95% CI = 1.002–1.012, p = 0.010).

4. Discussion

For patients with ACS undergoing PCI, guidelines from Europe and the United States recommend the more potent prasugrel or ticagrelor, rather than clopidogrel, as the P2Y12 receptor inhibitor of choice for dual antiplatelet therapy (DAPT) combinations (*16,17*). Modulation of antiplatelet therapy is important because bleeding is a critical issue (*18*). The STOPDAPT-2 ACS study demonstrated that 1-month DAPT was more effective than 12-month DAPT (*19*). The 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guidelines for the management of ACS recommend 5 mg of prasugrel daily as the MD for non-ST-segment elevation ACS or ST-segment elevation myocardial infarction in patients with body weight < 50 kg or age > 75 years (*17*).

Prasugrel 20 mg LD/3.75 mg MD was associated with increased bleeding risk compared with clopidogrel in patients with ACS undergoing PCI in Japan (*20,21*). Conversely, prasugrel 15 mg LD/3.75 mg MD was well tolerated and achieved a more rapid, larger, and consistent antiplatelet effect than clopidogrel in Japanese patients with coronary artery disease undergoing PCI, while prasugrel 10 mg LD/2.5 mg MD showed almost the same inhibition of platelet aggregation as the standard clopidogrel dose (*22*).

In this study, patients weighing ≤ 50 kg accounted for 11.6%, yet only 1.8% received prasugrel 2.5 mg after PCI (Table 1). Most physicians considered 3.75 mg of prasugrel safe and did not feel the need for dose reduction.

The 2.5 mg group included more women than the 3.75 mg group, which may be associated with older age, shorter height, lower body weight, lower BMI, and nonsmoking status. The higher rates of CABG, stroke, and peripheral arterial disease in the 2.5 mg group indicated progression of atherosclerosis. Frequent use of antiplatelets, anticoagulants, and statins also reflected higher cardiovascular risk. Low hemoglobin and platelet counts may have influenced the choice of the 2.5 mg dose.

Prasugrel 2.5 mg did not increase MACCE compared to the 3.75 mg group, which may support its selection (Table 1). However, nonfatal strokes were significantly more common in the 2.5 mg group, suggesting that 3.75 mg may be more appropriate for patients with a history of stroke or TIA. In the 2.5 mg group, major bleeding occurred only with concomitant antithrombotic drugs, indicating that such combinations should be avoided if possible. No major bleeding occurred in the 2.5 mg prasugrel monotherapy group (Table 6).

According to Kaplan–Meier analysis, MACCE occurred within 1 year in the 2.5 mg group, whereas it increased steadily in the 3.75 mg group (Figure 2), suggesting that dose reduction may be appropriate after

Table 8. Analysis of factors associated with MACCE and major bleeding by multivariate logistic regression models

Variables	MACCE			Major bleeding		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Dose						
2.5 mg	0.906	0.492–1.670	0.752	2.246	0.664–7.593	0.193
Characteristic						
Female	1.015	0.773–1.331	0.916	1.107	0.347–3.534	0.863
Age, years	1.004	0.996–1.013	0.328	0.991	0.951–1.032	0.657
Height, cm	1.026	0.975–1.078	0.324	0.988	0.800–1.221	0.910
Weight, kg	0.973	0.917–1.034	0.381	1.027	0.773–1.365	0.855
BMI, kg/m^2	1.087	0.926–1.274	0.307	0.805	0.381–1.699	0.569
Complication						
Atrial fibrillation	1.560	0.994–2.448	0.053	0.708	0.086–5.808	0.748
Medications						
Antiplatelet	1.011	0.857–1.191	0.900	1.090	0.520–2.285	0.820
Anticoagulant	0.447	0.244–0.819	0.009	2.275	0.672–7.707	0.187
Statin	0.845	0.668–1.069	0.160	1.348	0.558–3.253	0.507
Antihypertensive drug	0.814	0.673–0.984	0.033	0.437	0.170–1.122	0.085
Laboratory variables						
eGFR, mL/min/1.73 m^2	0.995	0.990–1.000	0.042	0.990	0.967–1.012	0.365
Hemoglobin, g/dL	1.005	0.956–1.058	0.834	0.931	0.741–1.170	0.539
Platelet, 10^3/μL	1.002	1.001–1.002	< 0.001	0.993	0.988–0.998	0.010
Creatinin, mg/dL	0.986	0.928–1.046	0.633	0.884	0.633–1.235	0.469

Abbreviations: HR, hazard ratio; CI, confidence interval. BMI, body mass index; eGFR, estimated glomerular filtration rate; MACCE: major adverse cardiac and cerebrovascular events (a combination of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization).

1 year. Most major bleeding events occurred within 6 months, highlighting the need for close monitoring during this period.

MACCE occurs more frequently in ACS than in CCS in Japan (*2,3*). Prasugrel 2.5 mg was administered in only 0.97% and 2.22% of patients with ACS and CCS, respectively. MACCE did not increase in the 2.5 mg group compared to the 3.75 mg group in either ACS or CCS (Table 2). Use of 2.5 mg prasugrel was associated with a significant increase in major bleeding in ACS but was non-significant in CCS.

Although the prasugrel package insert states that 2.5 mg may be considered for patients weighing ≤ 50 kg, in actual clinical practice, only 5.6% of patients in the group received a 2.5 mg dose (Table 3), most being female. The incidence of major bleeding was high (15.8%), requiring caution even with the reduced dose.

In patients with eGFR ≤ 30 ml/min/1.73 m^2, only 0.82% received prasugrel 2.5 mg, lower than the 1.8% in the overall population, indicating that dose reduction based on renal function is rarely implemented in Japan (Table 4). Only two patients with severe renal impairment were in the 2.5 mg group, precluding statistical analysis.

The background characteristics of men and women were similar, but among women, the 2.5 mg group had more non-fatal strokes and major bleeding than the 3.75 mg group (Table 5).

Univariate and multivariate logistic regression and Cox hazard model analyses (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=117*, and Table 7) identified multiple factors associated with the 2.5 mg dose. Female sex and older age were consistent with previous reports (*23*). Anticoagulant or statin use, absence of antihypertensive therapy, and thrombocytopenia were also important factors.

Multivariate Cox proportional hazards analysis showed that MACCE decreased with anticoagulant or antihypertensive use and higher eGFR, but increased with higher platelet counts (Table 8). Prasugrel dose did not affect MACCE, and only platelet count was a significant factor for major bleeding.

This study had some limitations. First, it was a retrospective observational study, and dose selection bias may have occurred. Understanding the use of prasugrel 2.5 mg in East Asia is important due to reported bleeding tendencies. Second, the small number of patients in the 2.5 mg group limited statistical power in some sub-analyses. Nevertheless, MACCE and major bleeding rates were detected, and logistic regression analyses identified several factors associated with prasugrel dose selection. Third, the study population was limited to Japanese patients, and the standard prasugrel dose in Japan was lower than that in other countries. Therefore, these results cannot be directly applied to other ethnicities; however, they demonstrate the potential use of prasugrel 2.5 mg in selected patients.

5. Conclusions

In summary, since MACCE did not increase in the 2.5 mg group compared with the 3.75 mg group, prasugrel

2.5 mg may be considered to reduce major bleeding in patients with low body weight, older patients, women, patients receiving concomitant anticoagulants, or those with low platelet counts.

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