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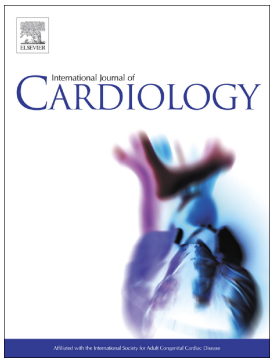

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Clinical outcomes of adjusted-dose versus standard-dose prasugrel in East Asian patients with acute myocardial infarction

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Conflict of Interest

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Keywords:

prasugrel, East Asians, acute myocardial infarction, bleeding event, antiplatelet therapy

ABSTRACT

Background: The comparative efficacy and safety of adjusted- and standard-dose prasugrel in East Asian patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) remain unclear. This study aimed to comparatively assess the ischaemic and bleeding outcomes of adjusted-dose (maintenance dose: 3.75 mg) and standard-dose (maintenance dose: 10 mg) prasugrel in East Asian patients with AMI undergoing PCI.

Methods: From a combined dataset sourced from nationwide AMI registries in Japan and South Korea (n=17118), patients treated with either adjusted- or standard-dose prasugrel were identified. Patients who did not undergo emergent PCI, those on oral anticoagulants, and those meeting the criteria of contraindication of prasugrel in South Korea (age ≥75 years, body weight <60 kg, or history of stroke) were excluded. Major adverse cardiovascular events (MACE) and Thrombolysis in Myocardial Infarction (TIMI) major bleeding events were compared between the adjusted-dose (n=1160) and standard-dose (n=1086) prasugrel groups.

Results: Within the propensity-matched cohort (n=702 in each group), no significant difference was observed in the in-hospital MACE between the adjusted- and standard-dose prasugrel groups (1.85% vs. 2.71%, odds ratio [OR] 0.68, 95% confidence interval [CI] 0.33-1.38, p=0.286). However, the incidence of in-hospital major bleeding was significantly lower in the adjusted-dose prasugrel group than in the standard-dose group (0.43% vs. 1.71%, OR 0.25, 95% CI 0.07-0.88, p=0.031). The cumulative 12-month incidence of MACE was equivalent in both groups (4.70% vs. 4.70%, OR 1.00, 95% CI 0.61-1.64, p=1.000).

Conclusions: Among East Asian patients with AMI undergoing PCI, those administered adjusted-dose prasugrel exhibited a lower risk of in-hospital bleeding events than those administered standard-dose prasugrel, while maintaining a comparable 1-year incidence of

MACE.

1. Introduction

Antiplatelet therapy is an established treatment for patients with acute myocardial infarction (AMI). Prasugrel is known for its faster, more potent, and consistent $P2Y_{12}$ inhibition in comparison with clopidogrel; furthermore, its use (loading dose [LD]/maintenance dose [MD]: 60/10 mg) led to reduced ischaemic events in patients with acute coronary syndrome (ACS) in the TRITON TIMI 38 trial [1]. Although prasugrel led to a significant increase in bleeding events in that trial, its superior efficacy outweighed the elevated bleeding risk in the entire cohort. Consequently, current US and European guidelines prefer prasugrel over clopidogrel for patients with ACS [2,3]. However, the TRITON-TIMI trial's East Asian subgroup accounted for <1% of the enrolled patients. Thus, extrapolating the trial's findings directly to East Asian individuals may not be appropriate because their physiology, genetic makeup, and medical environment are distinct from those of other ethnic groups.

Studies have identified the 'East Asian paradox', i.e. when treated with antithrombotic therapy, East Asians face a higher risk of bleeding events but a lower risk of ischaemic events than Western populations [4,5]. Additionally, pharmacodynamic studies in healthy volunteers have demonstrated that standard-dose prasugrel achieves more consistent platelet inhibition in East Asian individuals than in Caucasian individuals [6]. This suggests that a lower dose of prasugrel may be more suitable for East Asian populations.

To address concerns about bleeding risks, Japan approved an adjusted dose of prasugrel (LD/MD: 20/3.75mg) based on pharmacokinetic studies and randomised clinical trials demonstrating its numerically better efficacy and similar safety compared to clopidogrel for Japanese patients with ACS or those undergoing elective percutaneous coronary intervention [7,8]. Conversely, South Korea and other East Asian countries have predominantly used the standard dose of prasugrel (LD/MD: 60/10mg). The varied dosages of prasugrel among East Asian individuals may yield different outcomes; however, currently

available data are insufficient. Therefore, this study aimed to investigate the ischaemic and bleeding outcomes of adjusted and standard doses of prasugrel in East Asian patients with AMI using large-scale prospective registry data from both Japan and South Korea.

2. Methods

2.1. Study population

This study used a combined dataset sourced from nationwide registries in Japan and South Korea. The Japan Acute Myocardial Infarction Registry (JAMIR) is a prospective multicentre registry that consecutively enrolled patients with AMI from 50 hospitals in Japan between December 2015 and May 2017 (n=3411) [9,10]. The Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) is another multicentre prospective registry that consecutively enrolled patients with AMI from 20 tertiary university hospitals in Korea between November 2011 and December 2015 (n=13707) [11]. Informed consent was obtained from all participating patients in KAMIR-NIH. Because of the observational nature of the JAMIR registry, explicit consent was not sought. However, a summary of the protocol was made available on the registry website, providing patients with a clear notice of their right to refuse enrolment. The ethics committee at each participating centre in both JAMIR and KAMIR-NIH approved the protocol for the current study (M27-019-13). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

2.2. Study endpoints

Major adverse cardiovascular event (MACE) was the primary endpoint of this study; these are defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal ischaemic stroke. The major safety endpoint focused on major bleeding events,

determined on the basis of the Thrombolysis in Myocardial Infarction (TIMI) criteria [12]. The MACE was assessed during hospitalisation and at 12 months. TIMI major bleeding was assessed during hospitalisation.

The secondary endpoints included all-cause mortality, cardiovascular death, myocardial infarction, ischaemic stroke, and stent thrombosis. Myocardial infarction was characterized by the occurrence of cardiogenic chest pain alongside changes on 12-lead electrocardiography and an elevation in cardiac marker levels (specifically, cardiac troponin) above the upper limit of normal. Periprocedural myocardial infarction was not considered as a myocardial infarction event. Ischemic stroke was defined as the presence of acute neurological symptoms or findings consistent with stroke, confirmed through imaging (magnetic resonance imaging or computed tomography). Stent thrombosis was defined as definite or probable based on the Academic Research Consortium definition [13].

2.3. Statistical analysis

Baseline continuous variables are expressed as means ± standard deviations and categorical variables are presented as percentages. The descriptive data are analysed excluding patients with missing data. For comparative analyses of continuous variables, the t-test and Mann–Whitney U test were performed; for dichotomous variables, the χ^2 test was performed. Notably, the TRITON TIMI 38 trial identified the following subgroups as being at high risk for bleeding events when treated with prasugrel: individuals aged ≥75 years, those with a history of cerebrovascular disease, and those with a body weight <60 kg. In South Korea, prasugrel is contraindicated in these high-risk subgroups because of the observed lack of benefit or potential for worse outcomes. Conversely, in Japan, prasugrel is cautiously

prescribed to such patients. To mitigate the selection bias resulting from the differing contraindications to prasugrel between Japan and South Korea, patients contraindicated for prasugrel in South Korea were excluded from the analysis.

Univariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs), comparing the adjusted- and standard-dose prasugrel groups. Propensity scores were estimated using a logistic regression model involving several covariates including age, sex, presence of ST-segment elevation, Killip class upon admission, estimated glomerular filtration ratio, puncture site for the procedure, and culprit lesions in the left anterior descending artery. Propensity score matching (nearest neighbour, 1:1) with a maximum calliper of 2% was conducted to achieve balance in the measured covariates. Subsequently, in the matched population, the ORs for endpoint comparison between adjusted- and standard-dose prasugrel groups were estimated using conditional logistic regression analysis without additional adjustments owing to balanced covariates. The significance level throughout the study was set at $p<0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Baseline patient characteristics

The patient selection and inclusion flowchart is shown in **Supplemental Fig. 1**. In the JAMIR cohort, 2648 patients received adjusted-dose prasugrel (3.75 mg as MD) during hospitalisation. In the KAMIR-NIH cohort, 1,329 patients were treated with standard-dose prasugrel (10 mg, MD). Patients contraindicated for prasugrel in South Korea were excluded; these comprised patients aged ≥75 years, those with a history of cerebrovascular disease, and those with a body weight of <60 kg. Additionally, patients on oral anticoagulants and those not subjected to emergent percutaneous coronary intervention

(coronary intervention within 24 hours of onset) were excluded. Finally, 2246 patients were included in the analysis. Among these, 1160 received adjusted-dose prasugrel, whereas 1086 received standard-dose prasugrel.

The characteristics of both groups are summarised in **Table 1**. Patients treated with adjusted-dose prasugrel were notably older; furthermore, this group had higher proportions of patients with ST-segment elevation; those with a history of hypertension, radial artery puncture, or left anterior descending artery culprit lesion; and those with more frequent use of drug-eluting stents. However, beta-blocker use was less frequent in the adjusted-dose prasugrel group than in the standard-dose group.

Following propensity score matching, 702 pairs were established for comparisons between the adjusted-dose and standard-dose prasugrel groups. No significant differences in the baseline variables were observed between the propensity-matched groups; the exception was the utilisation rate of beta-blockers, which was lower in the adjusted-dose group (**Table 1**).

3.2. In-hospital outcomes

Table 2 shows the in-hospital outcomes of the unmatched and propensity-matched populations. In the unmatched population, the incidence of MACE did not differ significantly between the adjusted- and standard-dose groups (1.98% vs. 3.13%, OR: 0.63, 95% CI: 0.37–1.07, p=0.087). However, the incidence of major bleeding was notably lower in the adjusted-dose group than in the standard-dose group (0.26% vs. 2.03%, OR: 0.13, 95% CI: 0.04–0.42. p<0.001). No significant differences were observed between the groups in terms of the secondary endpoints.

A similar pattern was observed in the propensity-matched population, with no significant differences in the incidence of MACE between the adjusted- and standard-dose

groups (1.85% vs. 2.71%, OR: 0.68, 95% CI: 0.34–1.39. p=0.286; **Fig. 1**). The incidence of major bleeding remained significantly lower in the adjusted-dose group than in the standard-dose group (0.43% vs. 1.71%, OR: 0.25, 95% CI: 0.07–0.89. p=0.031). No significant differences in the secondary endpoints were noted between the groups.

3.3. Twelve-month outcomes

In the unmatched population, the proportion of patients receiving dual antiplatelet therapy (DAPT) was significantly higher in the adjusted-dose prasugrel group compared to the standard-dose prasugrel group at 6 months (88.0% vs. 83.7%, p=0.003). However, it was significantly lower than the standard-dose prasugrel group at 12 months (46.9% vs. 51.6%, p=0.026). Following propensity score matching, no significant differences were observed in the proportion of patients on DAPT between the adjusted-dose prasugrel group and the standard-dose prasugrel group at 6 months (86.0% vs. 83.6%, p=0.206) and at 12 months (47.4% vs. 51.1%, p=0.165).

Table 2 presents the 12-month outcomes of both the unmatched and propensity-matched populations. In the propensity-matched population, the cumulative incidence of MACE at 12 months was equivalent between the adjusted- and standard-dose prasugrel groups (4.70% vs. 4.70%, OR: 1.00, 95% CI: 0.60–1.66. p=1.000). Furthermore, no significant differences were observed in the incidence of all-cause death, cardiovascular death, myocardial infarction, ischaemic stroke, or stent thrombosis between the groups (**Fig. 2**). Similar findings were observed for the 12-month MACE and secondary outcomes in the unmatched population.

3.4. Subgroup analysis

To investigate the potential variations in the clinical outcomes between the adjusted- and

standard-dose prasugrel groups under specific conditions, we conducted subgroup analyses of the entire study population. However, no significant differences in the 12-month MACE were noted between the adjusted and standard-dose prasugrel groups in any subgroup analysis (**Supplemental Fig. 2**). Furthermore, compared with the standard-dose prasugrel group, the adjusted-dose prasugrel group consistently exhibited a trend towards fewer bleeding events across various subgroups (**Supplemental Fig. 3**).

4. Discussion

This analysis, based on AMI registry data from Japan and South Korea, revealed the following key findings: 1) in the in-hospital phase, no significant difference was observed in MACE between the adjusted- and standard-dose prasugrel groups; 2) compared with standard-dose prasugrel usage, adjusted-dose prasugrel usage was associated with a significantly lower incidence of major in-hospital bleeding events; 3) at 12 months, the incidence of MACE was comparable between the adjusted- and standard-dose prasugrel groups; and 4) subgroup analyses indicated comparable 12-month MACE and a consistent trend of fewer in-hospital bleeding events with adjusted-dose prasugrel than with standard-dose prasugrel.

4.1. Balancing efficacy and safety of potent $P2Y_{12}$ inhibitors in East Asian patients with ACS

Previous randomised trials involving Western populations have established the effectiveness of potent $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, in managing ACS [1,14]. However, emerging evidence challenges the efficacy and safety of standard-dose potent $P2Y_{12}$ inhibitors in East Asian populations. The PHILO trial, which enrolled 801 patients with ACS from Japan, Taiwan, and South Korea, found that compared with clopidogrel,

standard-dose ticagrelor was associated with a higher incidence of major bleeding events (6.8% vs. 10.3%) and potentially higher rates of ischaemic events (6.3% vs. 9.0%) [15]. Additionally, the Ticagrelor Versus Clopidogrel in Asia/Korean Patients with ACS Intended for Invasive Management (TICAKOREA) trial, involving 800 Korean patients with ACS intended for invasive management, revealed that compared with clopidogrel, ticagrelor was associated with a higher incidence of major bleeding events (4.1% vs. 7.5%, p=0.04) and a numerically higher incidence of ischaemic events (5.8% vs. 9.2%, p=0.07) [16]. Furthermore, an observational study from KAMIR showed a significantly increased risk of bleeding events with standard-dose prasugrel as compared to that with clopidogrel, without a significant difference in the ischaemic events [17]. In our present study with propensity score matching, standard-dose prasugrel was not associated with a decreased incidence of MACE when compared to adjusted-dose prasugrel but was notably associated with an increased risk of bleeding events. These cumulative findings indicate that standard-dose potent $P2Y_{12}$ inhibitors may not achieve an optimal balance between reducing ischaemic events and limiting the bleeding risk in East Asian patients with AMI [18].

4.2. Potential impact of ethnic variances on prasugrel treatment efficacy

Several factors may account for the different results observed regarding the effectiveness of standard-dose prasugrel in East Asian and non-East Asian populations. First, East Asian individuals exhibit a potentially heightened response to standard-dose prasugrel compared to their non-East Asian counterparts. Pharmacological studies have demonstrated that East Asian individuals display greater platelet inhibition under prasugrel treatment, surpassing Caucasian individuals; East Asian individuals administered a prasugrel dosage of 5 mg/day exhibited platelet inhibition levels mirroring those of Caucasian individuals administered a prasugrel dosage of 10 mg/day [6]. Second, the increased propensity for bleeding events

among East Asian populations could contribute to the higher incidence of major bleeding events associated with standard-dose prasugrel treatment. Studies evaluating the relationship between bleeding events and platelet function have revealed that East Asians are more susceptible to bleeding events than Western individuals exhibiting similar platelet reactivity [19]. Analyses in patients with atrial fibrillation have shown that Asian patients are at a higher risk of intracranial haemorrhage than Caucasian patients, despite having similar international normalised ratios [20]. Finally, potential differences in inherent thrombogenicity between East Asians and other ethnic groups might also play a role. A previous study has unveiled substantial variations in the coagulation, fibrinolysis, and inflammation profiles between East Asian and other ethnic groups [21]. The lower thrombogenicity observed in East Asians might have contributed to the lack of a significant reduction in the ischaemic events in the standard-dose prasugrel group when compared to that in the adjusted-dose prasugrel group. Understanding and addressing these ethnic differences are crucial for tailoring effective prasugrel treatments across diverse populations.

4.3. Adjusted-dose prasugrel safety and efficacy in East Asian populations

Previous studies have proposed the adequacy of reduced-dose prasugrel in East Asian individuals. Pharmacodynamic studies assessing the inhibition of platelet aggregation revealed that prasugrel administered at an LD of 15 mg and an MD of 3.75 mg exerted a more rapid, higher, and consistent antiplatelet effect than clopidogrel [22]. The PRASFIT-ACS trial was a randomised study comparing adjusted-dose prasugrel (20 mg LD and 3.75 mg daily MD) and clopidogrel in 1363 patients with ACS in Japan. It demonstrated that compared with the clopidogrel group, the adjusted-dose prasugrel group exhibited a trend towards lower 6-month MACE (11.8% vs. 9.4%; hazard ratio [HR]: 0.74, 95% CI: 0.52–1.06), without significant differences in the major bleeding events (2.2% vs. 1.9%; HR:

0.82, 95% CI: 0.39–1.73) [7]. In the PRASFIT-ACS trial, it was also observed that the presence of reduced-function cytochrome P450 2C19 genotypes, defined as intermediate or poor metabolisers, constituted more than 50% of the phenotype in Japanese patients with AMI. However, these genotypes did not significantly affect the efficacy and safety of adjusted-dose prasugrel when compared to that of extensive metabolisers [23]. In our current study, the adjusted-dose prasugrel group showed a significantly lower incidence of in-hospital bleeding than the standard-dose prasugrel group, while both groups showed similar results in terms of ischaemic events. These findings further confirm the efficacy and safety of adjusted-dose prasugrel, specifically in East Asian populations.

4.4. Limitations

This study, based on non-randomised observational registry data, has several limitations. The utilization of adjusted dose prasugrel was limited to Japan and was not adopted in South Korea, resulting in significant disparities in the rates of prasugrel usage for acute myocardial infarction (AMI) between the two countries (Japan vs. South Korea: approximately 81% vs. 12%). Although propensity-matched analysis was employed to mitigate potential confounding factors, it could not fully account for unmeasured confounders or potential selection biases. Moreover, the lack of comprehensive post-discharge data restricted the assessment of bleeding events after hospitalisation. In addition, the study's sample size was relatively small, potentially affecting the statistical power to conclusively validate the clinical events (i.e. each component of MACE) and influencing the robustness of the findings. In this study, information regarding the history of peripheral artery disease and door to procedure time, which are potentially related to ischemic and bleeding events, was not available. Finally, the study exclusively included patients without contraindications for prasugrel in South Korea, omitting individuals considered to be at a higher risk for bleeding

due to factors such as older age, lower body weight, or a history of stroke. Consequently, the generalisability of the findings, particularly in patients with a higher bleeding risk, remains uncertain.

These limitations underscore the importance of larger randomised studies encompassing diverse populations and varying dosing regimens. Such studies are crucial for a more comprehensive understanding of the safety and efficacy of prasugrel in East Asian patients with AMI, particularly those at a higher risk of bleeding. Improved data collection, including post-discharge follow-ups, would enhance our understanding of long-term effects and outcomes. Additionally, these findings highlight the need for future research aimed at addressing and refining regional clinical guidelines in East Asia.

5. Conclusions

In conclusion, in East Asian patients with AMI undergoing percutaneous coronary intervention, those administered adjusted-dose prasugrel exhibited a notably reduced risk of major in-hospital bleeding events while maintaining a comparable risk for MACE at 1 year. This finding suggests that a reduced dose of prasugrel could potentially provide a more favourable balance between reducing ischaemic events and minimising the bleeding risk in East Asian patients with AMI.

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Data Availability Statement

The deidentified participant data will not be shared.

Author Contributions

Satoshi Honda: Conceptualization, Data curation, Methodology, Project administration, Visualization, Writing-original draft, Writing- review and editing. Sangyeub Lee: Data curation, Methodology, Project administration, Writing- review and editing. Kyung Hoon Cho: Data curation, Methodology, Project administration, Writing- review and editing., Misa Takegami: Methodology, Formal analysis. Kensaku Nishihira: Data curation, Methodology, Project administration, Writing- review and editing. Sunao Kojima: Methodology, Writing- review and editing. Yasuhide Asaumi: Data curation, Writing- review and editing. Mike Saji: Data curation, Writing- review and editing. Jun Yamashita: Data curation, Writing- review and editing. Kiyoshi Hibi: Data curation, Writing- review and editing. Jun Takahashi: Data curation, Writing- review and editing. Yasuhiko Sakata: Supervision, Writing- review and editing. Morimasa Takayama: Supervision, Writing- review and editing. Tetsuya Sumiyoshi: Supervision, Writing- review and editing. Hisao Ogawa: Supervision, Writing- review and editing. Kazuo Kimura: Supervision, Writing- review and editing. Doo Sun Sim: Data curation, Writing- review and editing. Hyun Kuk Kim: Data curation, Writing- review and editing. Weon Kim: Data curation, Writing- review and editing. Youngkeun Ahn: Supervision, Writing- review and editing. Myung Ho Jeong: Conceptualization, Project administration, Supervision, Writing- review and editing. Satoshi Yasuda: Conceptualization, Project administration, Supervision, Writing- review and editing.

Conflict of interest

Dr. Yasuda reports remuneration for lectures from Takeda, Daiichi Sankyo, and Bristol-Myers Squibb and trust research/joint research funds from Takeda and Daiichi

Sankyo; Dr. Takayama reports lecture fees from Daiichi Sankyo; and Dr. Ogawa reports lecture fees and research grants from Abbot Medical Japan, Bayer, Daiichi Sankyo, Eisai, Kowa, Takeda Pharmaceutical, and Teijin. Other authors have no conflict of interest.

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Figure Legends

Fig. 1. In-hospital outcomes: adjusted-dose (blue bar) vs. standard-dose (orange bar) prasugrel groups. MACE = major adverse cardiovascular events.

Fig. 2. Twelve-month outcomes: adjusted-dose (blue bar) vs. standard-dose (orange bar) prasugrel groups. CV = cardiovascular; MACE = major adverse cardiovascular events.

Tables

Table 1. Patient characteristics.

	Unmatched population			Matched population		
	Adjusted dose	Standard dose		Adjusted dose	Standard dose	
	n=1160	n=1086	p value	n=702	n=702	p value
Age (years)	59.0±9.9	55.0±9.1	<0.001	57.4±9.4	57.2±8.8	0.436
Female	75 (6.5)	69 (6.4)	0.914	42 (6.0)	41 (5.8)	0.910
Body weight (kg)	73.2±10.6	73.6±9.5	0.430	73.7±10.7	73.0±9.0	0.220
STEMI	957 (82.5)	661 (60.9)	<0.001	510 (72.7)	488 (69.5)	0.196
Killip class			0.154			0.788
I	981 (84.6)	947 (87.2)		585 (83.3)	593 (84.5)	
II or III	106 (9.1)	88 (8.1)		68 (9.7)	66 (9.4)	
IV	73 (6.3)	51 (4.7)		49 (7.0)	43 (6.1)	
Hypertension*	815 (70.3)	441 (65.0)	0.020	492 (70.1)	304 (67.1)	0.286
Diabetes*	408 (35.2)	249 (36.7)	0.503	238 (33.9)	177 (39.1)	0.074
Previous myocardial infarction*	73 (6.3)	69 (10.2)	0.003	50 (7.1)	42 (9.3)	0.188
Previous stroke	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Current smoking	646 (55.7)	631 (58.1)	0.249	398 (56.7)	397 (56.6)	0.957
eGFR (mL/min/1.73 m^2)*	72.0±21.6	72.4±22.7	0.678	72.5±21.5	72.1±23.6	0.717
Haemoglobin (g/dL)*	14.9±1.8	14.9±1.6	0.521	14.8±1.9	14.9±1.5	0.644
LVEF (%)*	53.4±11.3	53.2±9.8	0.595	53.0±11.6	52.7±9.6	0.599
Culprit lesion						
Left main coronary artery	14 (1.2)	20 (1.8)	0.218	10 (1.4)	11 (1.6)	0.826
Left anterior descending artery	583 (49.7)	593 (45.4)	0.039	352 (50.1)	334 (47.6)	0.337
Left circumflex artery	171 (14.7)	180 (16.6)	0.232	111 (15.8)	113 (16.1)	0.884
Right coronary artery	423 (36.5)	365 (33.6)	0.156	245 (34.9)	244 (34.8)	0.955
Radial artery puncture*	792 (65.8)	411 (34.2)	<0.001	363 (51.7)	341 (48.6)	0.478
Number of diseased vessels	1.5±0.7	1.5±0.8	0.189	1.5±0.7	1.5±0.7	0.287
Stent use	1104 (95.2)	1001 (92.2)	0.003	663 (94.4)	662 (94.3)	0.908
DES use	1086 (93.6)	979 (90.2)	0.003	649 (92.5)	646 (92.0)	0.765

Medication during hospitalisation						
Aspirin	1158 (99.8)	1084 (99.8)	1.000	701 (99.9)	701 (99.9)	1.000
ACE inhibitors or ARB	950 (81.9)	879 (80.9)	0.560	570 (81.2)	576 (82.1)	0.680
Beta-blockers	805 (69.4)	949 (87.4)	<0.001	501 (71.4)	619 (88.2)	<0.001
Statins	1110 (95.7)	1021 (94.0)	0.072	672 (95.7)	662 (94.3)	0.220
Oral anticoagulants	0 (0)	0 (0)	-	0 (0)	0 (0)	-

Data are given as mean ± standard deviation or number (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; DES = drug-eluting stent; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; STEMI = ST-elevation myocardial infarction

*Missing data were excluded from the descriptive analysis (unmatched population: hypertension, n=408; diabetes, n=408; previous myocardial infarction, n=408; eGFR, n=2, Hemoglobin, n=4, LVEF, n=251) (matched population: previous myocardial infarction, n=249, diabetes, n=249, hypertension, n=249, LVEF, n=145)

Table 2. Clinical outcomes.

	Entire population				Matched population			
	Adjusted dose n=1160	Standard dose n=1086	Odds ratio (95% CI)	p value	Adjusted dose n=702	Standard dose n=702	Odds ratio (95% CI)	p value
In-hospital event								
MACE	1.98	3.13	0.63 (0.37 - 1.07)	0.087	1.85	2.71	0.68 (0.33 - 1.38)	0.286
TIMI major bleeding	0.26	2.03	0.13 (0.04 - 0.42)	<0.001	0.43	1.71	0.25 (0.07 - 0.88)	0.031
All-cause death	1.90	1.38	1.38 (0.71 - 2.68)	0.340	2.28	1.42	1.61 (0.73 - 3.58)	0.239
Cardiovascular death	1.38	1.20	1.15 (0.55 - 2.41)	0.702	1.42	1.14	1.25 (0.49 - 3.20)	0.636
Myocardial infarction	0.52	0.83	0.62 (0.22 - 1.75)	0.370	0.43	0.85	0.50 (0.12 - 2.00)	0.325
Cerebral infarction	0.17	0.37	0.47 (0.09 - 2.56)	0.380	0.14	0.28	0.50 (0.05 - 5.52)	0.571
Stent thrombosis	0.26	0.83	0.31 (0.08 - 1.15)	0.080	0.14	0.43	0.17 (0.02 - 1.38)	0.096
12-month outcomes								
MACE	3.97	5.62	0.69 (0.47 - 1.03)	0.068	4.70	4.70	1.00 (0.61 - 1.64)	1.000
All-cause death	2.84	2.39	1.19 (0.71 - 2.01)	0.505	3.56	2.28	1.58 (0.84 - 2.99)	0.157
Cardiovascular death	1.64	1.84	0.89 (0.47 - 1.67)	0.712	1.85	1.42	1.31 (0.57 - 3.00)	0.529
Myocardial infarction	2.24	2.58	0.87 (0.51 - 1.49)	0.603	2.85	2.28	1.26 (0.65 - 2.45)	0.500
Cerebral infarction	0.34	0.46	0.75 (0.20 - 2.79)	0.666	0.43	0.43	1.00 (0.20 - 4.97)	1.000
Stent thrombosis	0.43	1.10	0.39 (0.14 - 1.10)	0.076	0.43	1.14	0.37 (0.10 - 1.41)	0.146

MACE = major adverse cardiovascular event; TIMI = Thrombolysis in Myocardial Infarction.

graphic

Highlights

- In this analysis from nationwide registry, we aimed to assess the ischaemic and bleeding outcomes of adjusted-dose (maintenance dose: 3.75 mg) and standard-dose (maintenance dose: 10 mg) prasugrel in East Asian patients with acute myocardial infarction.
- Adjusted-dose prasugrel (3.75mg/day) showed a lower incidence of in-hospital major bleeding events than standard-dose prasugrel (10mg/day).
- Incidence of major adverse cardiovascular events at 1 year was comparable between adjusted-dose prasugrel and standard-dose prasugrel.
- A reduced dose of prasugrel may provide a more favourable ischemic/bleeding risk balance in East Asian patients with acute myocardial infarction.

Comparison of Adjusted- and Standard-Dose Prasugrel in East Asian Patients with Acute Myocardial Infarction

Data from the Japan AMI registry and Korea AMI registry

Patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) **(N = 2,246)**

Adjusted-dose prasugrel (n = 1,160) 3.75 mg prasugrel as maintenance dose

Standard-dose prasugrel (n = 1,086) 10 mg prasugrel as maintenance dose

Comparison of:

Major adverse cardiovascular events (MACE)

Thrombolysis in myocardial infarction (TIMI) major bleeding events

Propensity-matched cohort (n = 702/group)

Prasugrel dosage / Parameters	Adjusted-dose prasugrel	Standard-dose prasugrel
In-hospital MACE	No significant difference (1.85%)	No significant difference (2.71%)
In-hospital major bleeding	Lower (0.43%)	Higher (1.71%)
Cumulative 12-month incidence of MACE	Equivalent (4.70%)	Equivalent (4.70%)

In East Asian AMI patients undergoing PCI, adjusted-dose prasugrel showed a lower risk of in-hospital bleeding events compared with standard-dose prasugrel, with an equivalent incidence of ischemic events at 12-month

Graphics Abstract

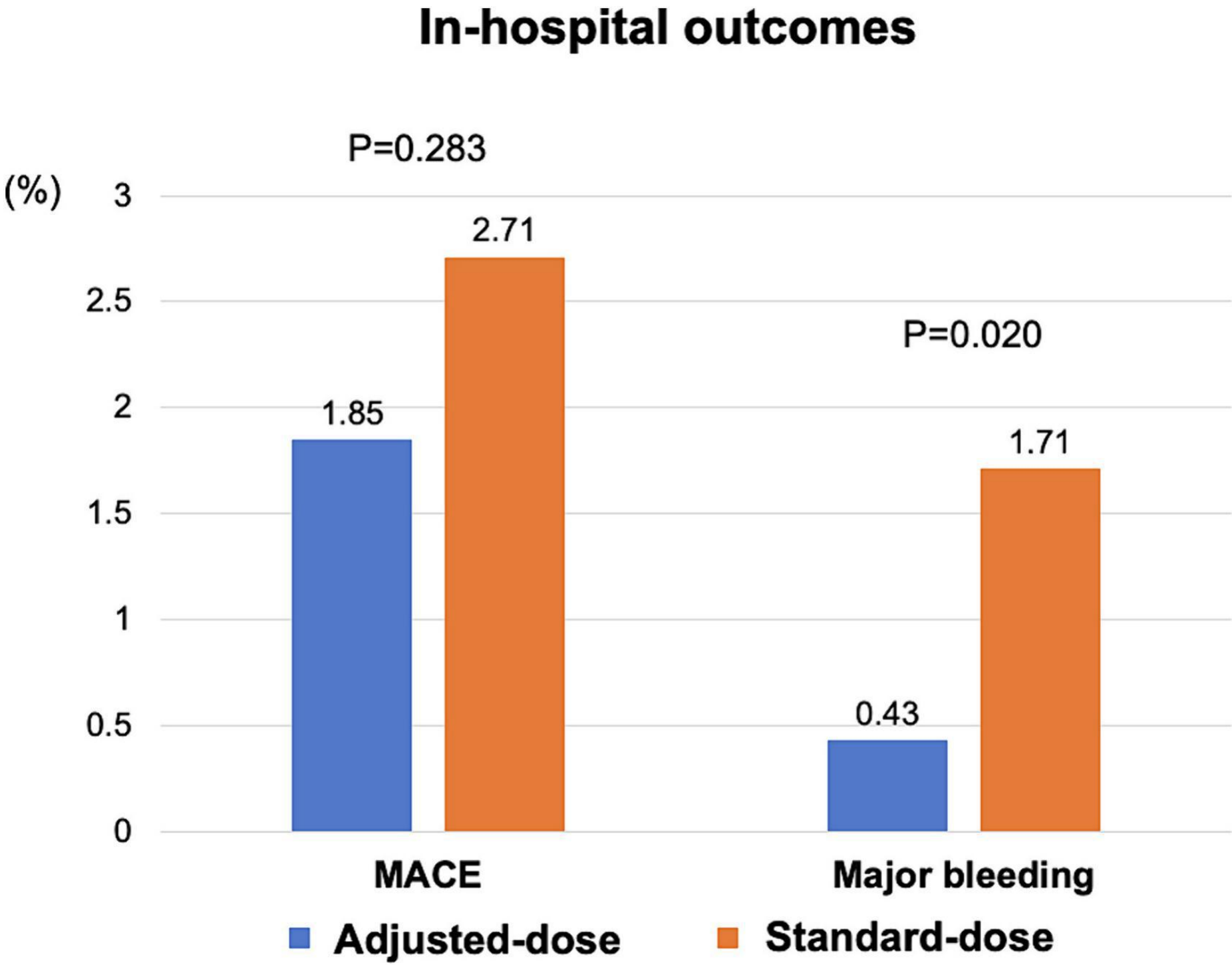
In-hospital outcomes
P=0.283
(%)
3
2.5
2
1.5
1
0.5
0
2.71
1.85
P=0.020
1.71
0.43
MACE
Major bleeding
Adjusted-dose
Standard-dose

Figure 1

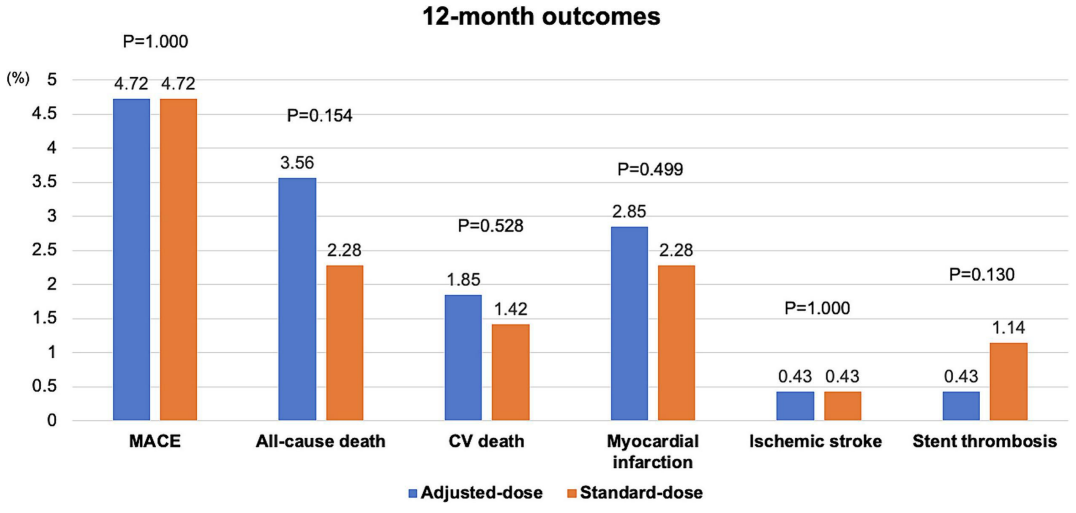
12-month outcomes
(%)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
P=1.000
4.72 4.72
MACE
P=0.154
3.56
2.28
All-cause death
P=0.528
1.85
1.42
CV death
P=0.499
2.85
2.28
Myocardial infarction
P=1.000
0.43 0.43
Ischemic stroke
P=0.130
0.43
1.14
Stent thrombosis
Adjusted-dose
Standard-dose

Figure 2