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Original article

Association of potent P2Y12 blockers with ischemic and bleeding outcomes in non-ST-segment elevation myocardial infarction

Doo Sun Sim (MD, PhD)[a], Myung Ho Jeong (MD, PhD)[a,*], Hyo Soo Kim (MD, PhD)[b], Hyeon Cheol Gwon (MD, PhD)[c], Ki Bae Seung (MD, PhD)[d], Seung Woon Rha (MD, PhD)[e], Shung Chull Chae (MD, PhD)[f], Chong Jin Kim (MD, PhD)[g], Kwang Soo Cha (MD, PhD)[h], Jong Sun Park (MD, PhD)[i], Jung Han Yoon (MD, PhD)[j], Jei Keon Chae (MD, PhD)[k], Seung Jae Joo (MD, PhD)[l], Dong Ju Choi (MD, PhD)[m], Seung Ho Hur (MD, PhD)[n], In Whan Seong (MD, PhD)[o], Myeong Chan Cho (MD, PhD)[p], Doo Il Kim (MD, PhD)[q], Seok Kyu Oh (MD, PhD)[r], Tae Hoon Ahn (MD, PhD)[s], Jin Yong Hwang (MD, PhD)[t] on behalf of the KAMIR-NIH Registry Investigators

[a] *Chonnam National University Hospital, Gwanjgu, Republic of Korea*
[b] *Seoul National University Hospital, Seoul, Republic of Korea*
[c] *Sungkyunkwan University, Seoul Samsung Medical Center, Seoul, Republic of Korea*
[d] *The Catholic University of Korea, Seoul, Republic of Korea*
[e] *Korea University Guro Hospital, Seoul, Republic of Korea*
[f] *Kyungpuk National University Hospital, Daegu, Republic of Korea*
[g] *Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea*
[h] *Pusan National University Hospital, Busan, Republic of Korea*
[i] *Yeungnam University Hospital, Daegu, Republic of Korea*
[j] *Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital, Wonju, Republic of Korea*
[k] *Chunbuk National University Hospital, Jeonju, Republic of Korea*
[l] *Jeju National University Hospital, Jeju, Republic of Korea*
[m] *Seoul National University Bundang Hospital, Seongnam, Republic of Korea*
[n] *Keimyung University Dongsan Medical Center, Daegu, Republic of Korea*
[o] *Chungnam National University Hospital, Daejeon, Republic of Korea*
[p] *Chungbuk National University Hospital, Cheongju, Republic of Korea*
[q] *Inje University Haeundae Paik Hospital, Busan, Republic of Korea*
[r] *Wonkwang University Hospital, Iksan, Republic of Korea*
[s] *Gachon University Gil Medical Center, Incheon, Republic of Korea*
[t] *Kyungsang National University Hospital, Jinju, Republic of Korea*

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ABSTRACT

Background: Potent P2Y12 blockers are preferred in patients with acute non-ST-segment elevation myocardial infarction (NSTEMI) undergoing percutaneous coronary intervention (PCI). However, the risk of bleeding remains a major concern. We assessed the association of potent P2Y12 blockers with ischemic and bleeding outcomes in patients with NSTEMI.

Methods: From the Korea Acute Myocardial Infarction Registry-National Institute of Health database, 4927 patients with NSTEMI receiving drug-eluting stents (DES) were divided into potent P2Y12 blocker (ticagrelor or prasugrel, $n = 901$) and clopidogrel ($n = 3180$) groups. Propensity-matched 12-month ischemic and bleeding events were compared. Patients who received anticoagulants or who discontinued P2Y12 blockers or switched between potent P2Y12 blockers and clopidogrel were excluded.

Results: In the overall population, patients at higher ischemic and bleeding risks more often received clopidogrel. After propensity matching ($n = 901$ in each group), 12-month rates of major adverse cardiac

* Corresponding author at: The Heart Research Center of Chonnam National University Hospital Designated by Korea Ministry of Health, Welfare and Family Affairs, 42, Jebong-ro, Dong-gu, Gwangju, 61469, Republic of Korea.
E-mail address: myungho@chollian.net (M.H. Jeong).

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and cerebrovascular events were lower (7.3% vs. 10.1%, $p = 0.038$), but Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding rates were higher (5.9% vs. 2.2%, $p < 0.001$) with potent P2Y12 blockers. Twelve-month rates of death from any cause, MI, stroke, or TIMI major bleeding were not different. On multivariate analysis, 12-month risk of TIMI major or minor bleeding was higher with B2 or C lesion, potent P2Y12 blocker use, body weight <60 kg, and lower with time to PCI <12 h and radial artery access.

Conclusions: In patients with NSTEMI receiving DES, potent P2Y12 blockers were associated with reduced ischemic but increased bleeding risk with similar net clinical benefits.

Introduction

Patients with acute non-ST-segment elevation acute coronary syndrome (NSTE-ACS) should be treated with dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor blocker. Current guidelines recommend potent P2Y12 blockers such as ticagrelor or prasugrel in preference to clopidogrel in patients with non-ST-segment elevation myocardial infarction (NSTEMI) undergoing invasive management [1,2]. However, the risk of bleeding remains a major concern. Both ticagrelor and prasugrel, compared to clopidogrel, increased non-coronary artery bypass graft surgery (CABG) bleeding [3,4]. Recent observational studies in Korean patients with acute MI showed that the use of potent P2Y12 blockers was associated with higher bleeding risk with similar rates of ischemic events [5–7], suggesting that the bleeding risk needs to be weighed against the ischemic risk, especially in East Asians known to be prone to bleeding [8,9]. In the present study, we sought to evaluate the association of potent P2Y12 blockers with ischemic and bleeding outcomes in patients with NSTEMI undergoing drug-eluting stent (DES) placement using a large-scale, multi-center, nationwide acute MI database in Korea.

Methods

Study population and data collection

The study population was derived from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) database between November 2011 and December 2015. The KAMIR-NIH is a prospective, open, on-line, multi-center data collection registry from 20 tertiary university hospitals capable of PCI in Korea, designed to capture real-world treatment practice and outcome of patients with acute MI [10]. NSTEMI was defined as a rise and/or fall of cardiac biomarker values (troponin I/T or creatine kinase-MB with at least one value above the 99th percentile upper reference limit) without persistent ST-segment elevation and with at least one of the following: symptoms of myocardial ischemia, ischemic changes on the electrocardiogram (ECG) including new horizontal or down-sloping ST-segment depression ≥0.05 mV in two contiguous leads and/or T-wave inversion ≥0.1 mV in two contiguous leads, and imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality [11]. We identified a total of 4927 patients with NSTEMI who underwent PCI with DES. Patients were excluded who received anticoagulants or who discontinued P2Y12 blockers or switched between potent P2Y12 blockers and clopidogrel. Patients were divided into two groups according to the use of P2Y12 receptor blocker in addition to aspirin: potent P2Y12 blockers (ticagrelor or prasugrel, $n = 901$) and clopidogrel ($n = 3180$). The study flow diagram is shown in Fig. 1.

PCI was performed according to the standard guidelines [1,2]. Patients received loading doses of aspirin (300 mg) and P2Y12 blocker (ticagrelor 180 mg, prasugrel 60 mg, or clopidogrel 300–600 mg) before PCI. The selection of vessels treated, devices used, and adjunctive drugs administered to support PCI was left to the discretion of the treating physician. After PCI, patients received maintenance doses of either ticagrelor (90 mg twice daily), prasugrel (10 mg daily), or clopidogrel (75 mg daily) for at least 12 months. Aspirin was given at a dose of 100 mg daily indefinitely. The present study was conducted according to the Declaration of Helsinki. The institutional review board of all participating centers approved the study protocol. The approval number was CNUH-2011-172 of Chonnam National University Hospital. Written informed consent was obtained from all participating patients.

Clinical endpoints and definitions

The primary endpoint of the study was 12-month net adverse clinical events, defined as a composite of death from any cause, MI, stroke, or Thrombolysis in Myocardial Infarction (TIMI) major

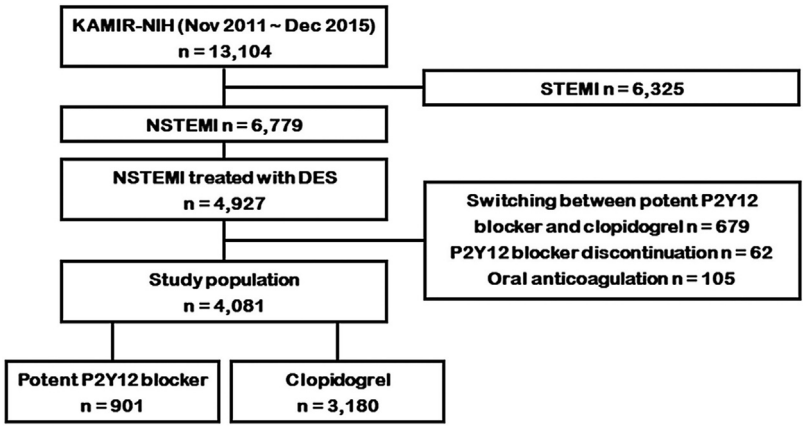

Fig. 1. The study flow diagram of the patients. DES, drug-eluting stents; KAMIR-NIH, Korea Acute Myocardial Infarction Registry-National Institute of Health; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

bleeding. The secondary endpoints were death from any cause, MI, repeat PCI including target-lesion revascularization and target-vessel revascularization, CABG, stent thrombosis, stroke, major adverse cardiac and cerebrovascular events (MACCE: composite of death from any cause, MI, repeat PCI, CABG, and stroke), and TIMI major and/or minor bleeding events. MI was defined as the recurrence of symptoms or the presence of new ischemic ECG changes in association with a rise in cardiac biomarker level above the upper limit of normal in patients whose biomarker level had returned to normal or with a ≥20% increase of the value if the initially elevated value was stable or decreasing [11,12]. Target-lesion revascularization was defined as a repeat PCI in the same coronary segment as the index procedure. Target-vessel revascularization was defined as a repeat PCI of any segment within the entire major coronary vessel proximal and distal to a target lesion, including the target lesion itself. Stroke was defined as focal loss of neurologic function caused by an ischemic or hemorrhagic event, with residual symptoms lasting at least 24 h or leading to death [4]. Stent thrombosis was defined according to the Academic Research Consortium definitions [13]. Bleeding events were classified as major and minor according to TIMI scales [14].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and were compared between two groups with the Student *t* test when normally distributed; they were expressed as median (interquartile range) and were compared with the Mann–Whitney *U* test when the data did not fit a normal distribution. Categorical variables were reported as numbers and percentages and were compared with the chi-square test or Fisher's exact test. Hazard ratios (HR) and their 95% confidence intervals (CI) were calculated for outcome variables using Cox regression analysis. In order to adjust for the bias inherent to the decision of choosing potent P2Y12 blockers versus clopidogrel, propensity scores were used [15,16]. The propensity scores were estimated for the likelihood of receiving potent P2Y12 blockers using a multiple logistic regression model that contained 40 covariates shown in Tables 1 and 2: age, sex, body weight, smoking status, hypertension, diabetes mellitus, dyslipidemia, prior history of MI, angina pectoris, heart failure, stroke, family history of coronary artery disease, typical chest pain at presentation, time from symptom to presentation, systolic blood pressure, diastolic blood pressure, heart rate, Killip class, ST-segment depression, T-wave inversion, left ventricular ejection fraction, white blood cell count, hemoglobin, serum creatinine, time from admission to PCI, radial artery access, infarct-related vessel, American College of Cardiology/American Heart Association (ACC/AHA) lesion type B2 or C, number of diseased vessels, pre-PCI TIMI flow grade, use of second-generation DES, maximum stent diameter, total stent length, number of stents, post-PCI TIMI flow grade, and use of glycoprotein IIb/IIIa inhibitor, aspirin, beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and statin during hospitalization. The c-statistic for the propensity model was 0.72, indicating fair ability to discriminate treatment groups. The Hosmer–Lemeshow goodness-of-fit test *p*-value was 0.88, confirming good calibration and fit of the multivariable model that estimated the propensity score. Matching was performed using a

Table 1
Baseline clinical characteristics between potent P2Y12 blocker and clopidogrel groups before and after propensity score matching.

	All patients					Propensity-matched patients		
	Ticagrelor (*n* = 659)	Prasugrel (*n* = 242)	Potent P2Y12 blocker (*n* = 901)	Clopidogrel (*n* = 3180)	*p*-Value	Potent P2Y12 blocker (*n* = 901)	Clopidogrel (*n* = 901)	*p*-Value
Age (years)	62.4 ± 11.4	56.9 ± 9.1	60.9 ± 11.1	65.7 ± 12.2	<0.001	60.9 ± 11.1	60.8 ± 12.1	0.790
Men	511 (77.5%)	215 (88.8%)	726 (80.6%)	2196 (69.1%)	<0.001	726 (80.6%)	725 (80.5%)	0.953
Body weight (kg)	66.2 ± 11.4	70.9 ± 10.9	67.5 ± 11.4	64.2 ± 11.6	<0.001	67.5 ± 11.4	67.6 ± 11.4	0.801
Smoking	418 (63.4%)	182 (75.2%)	600 (66.6%)	1691 (53.2%)	<0.001	600 (66.6%)	594 (65.9%)	0.765
Hypertension	315 (47.8%)	107 (44.2%)	422 (46.8%)	1756 (55.2%)	<0.001	422 (46.8%)	427 (47.4%)	0.813
Diabetes mellitus	182 (27.6%)	64 (26.4%)	246 (27.3%)	1027 (32.3%)	0.004	246 (27.3%)	236 (26.2%)	0.595
Dyslipidemia	75 (11.4%)	33 (13.6%)	108 (12.0%)	405 (12.7%)	0.549	108 (12.0%)	108 (12.0%)	1.000
Myocardial infarction	25 (3.8%)	11 (4.5%)	36 (4.0%)	226 (7.1%)	0.001	36 (4.0%)	32 (3.6%)	0.621
Angina pectoris	39 (5.9%)	20 (8.3%)	59 (6.5%)	342 (10.8%)	<0.001	59 (6.5%)	57 (6.3%)	0.848
Heart failure	8 (1.2%)	2 (0.8%)	10 (1.1%)	43 (1.4%)	0.571	10 (1.1%)	13 (1.4%)	0.529
Stroke	26 (3.9%)	4 (1.7%)	30 (3.3%)	263 (8.3%)	<0.001	30 (3.3%)	39 (4.3%)	0.269
Family history of CAD	54 (8.2%)	22 (9.1%)	76 (8.4%)	224 (7.0%)	0.158	76 (8.4%)	73 (8.1%)	0.797
Typical chest pain	577 (87.6%)	219 (90.5%)	796 (88.3%)	2627 (82.6%)	<0.001	796 (88.3%)	794 (88.1%)	0.884
Time from symptom to presentation (h)	7.0 (2.3–24.0)	5.4 (2.0–18.6)	6.7 (2.2–21.2)	7.0 (2.6–25.4)	0.036	6.7 (2.2–21.2)	6.9 (2.6–24.0)	0.420
Systolic BP (mmHg)	134.5 ± 25.2	134.7 ± 28.4	134.6 ± 26.0	136.3 ± 27.4	0.087	134.6 ± 26.0	134.3 ± 26.8	0.792
Diastolic BP (mmHg)	81.0 ± 15.7	82.3 ± 17.1	81.5 ± 16.1	81.1 ± 16.3	0.579	81.5 ± 16.1	81.1 ± 16.1	0.625
Heart rate (beats/min)	77.1 ± 16.2	78.9 ± 15.8	77.6 ± 16.1	79.6 ± 17.6	0.001	77.6 ± 18.3	77.4 ± 16.4	0.838
Killip class					<0.001			0.791
I	587 (89.1%)	222 (91.7%)	809 (89.8%)	2576 (81.0%)		809 (89.8%)	804 (89.2%)	
II	30 (4.6%)	7 (2.9%)	37 (4.1%)	293 (9.2%)		37 (4.1%)	43 (4.8%)	
III	33 (5.0%)	12 (5.0%)	45 (5.0%)	248 (7.8%)		45 (5.0%)	41 (4.6%)	
IV	9 (1.4%)	1 (0.4%)	10 (1.1%)	63 (2.0%)		10 (1.1%)	13 (1.4%)	
ST-segment depression	192 (29.1%)	69 (28.5%)	261 (29.0%)	1022 (32.1%)	0.070	261 (29.0%)	264 (29.3%)	0.876
T-wave inversion	173 (26.3%)	66 (27.3%)	239 (26.5%)	889 (28.0%)	0.397	239 (26.5%)	234 (26.0%)	0.789
LVEF (%)	55.1 ± 9.5	56.1 ± 9.2	55.4 ± 9.4	53.6 ± 10.8	<0.001	55.4 ± 9.4	55.2 ± 9.8	0.777
White blood cell count ($10^3/\mu L$)	8.9 (7.2–11.1)	9.5 (7.5–11.5)	9.0 (7.2–11.2)	8.8 (6.9–11.1)	0.015	9.0 (2.2–21.2)	9.0 (7.0–11.5)	0.418
Hemoglobin (g/dL)	14.3 (12.9–15.4)	14.8 (13.7–15.8)	14.4 (13.2–15.5)	13.8 (12.2–15.0)	<0.001	14.4 (13.2–15.5)	14.5 (13.3–15.5)	0.858
Serum creatinine (mg/dL)	0.9 (0.7–1.0)	0.8 (0.7–1.0)	0.9 (0.7–1.0)	0.9 (0.7–1.1)	<0.001	0.9 (0.7–1.0)	0.9 (0.7–1.0)	0.526
Peak troponin-I (ng/mL)	11.1 (2.6–20.5)	7.8 (1.6–25.0)	10.0 (2.4–21.6)	8.7 (1.7–19.4)	0.105	10.0 (2.4–21.6)	10.9 (2.1–23.0)	0.599
GRACE score	123 (104–144)	111 (95–130)	120 (99–142)	132 (109–157)	<0.001	120 (99–142)	120 (101–142)	0.470
ACUITY-HORIZONS score	11 (7–16)	8 (5–12)	10 (7–15)	13 (8–19)	<0.001	10 (7–15)	10 (5–15)	0.800

Values are *n* (%), mean ± SD or median (interquartile range). BP, blood pressure; CAD, coronary artery disease; LVEF, left ventricular ejection fraction.

Table 2
Characteristics of procedures and medical treatment during hospitalization between potent P2Y12 blocker and clopidogrel groups before and after propensity score matching.

	All patients					Propensity-matched patients		
	Ticagrelor (*n* = 659)	Prasugrel (*n* = 242)	Potent P2Y12 blocker (*n* = 901)	Clopidogrel (*n* = 3180)	*p*-value	Potent P2Y12 blocker (*n* = 901)	Clopidogrel (*n* = 901)	*p*-value
Time from admission to PCI (h)	10.4 (3.1–22.4)	7.8 (2.6–18.7)	9.8 (3.0–21.3)	14.9 (3.7–26.9)	<0.001	9.8 (3.0–21.3)	12.6 (3.3–22.0)	0.204
Radial artery access	450 (68.3%)	155 (64.0%)	605 (67.1%)	1375 (43.2%)	<0.001	605 (67.1%)	611 (67.8%)	0.763
Infarct-related vessel					0.043			0.187
Left anterior descending artery	276 (41.9%)	102 (42.1%)	378 (42.0%)	1370 (43.1%)		378 (42.0%)	397 (44.1%)	
Left circumflex artery	188 (28.5%)	74 (30.6%)	262 (29.1%)	793 (24.9%)		262 (29.1%)	226 (25.1%)	
Right coronary artery	179 (27.2%)	62 (25.6%)	241 (26.7%)	915 (28.8%)		241 (26.7%)	263 (29.2%)	
Left main coronary artery	16 (2.4%)	4 (1.7%)	20 (2.2%)	102 (3.2%)		20 (2.2%)	15 (1.7%)	
ACC/AHA lesion type B2 or C	590 (89.5%)	204 (84.3%)	794 (88.1%)	2640 (83.0%)	<0.001	794 (88.1%)	794 (88.1%)	1.000
Number of diseased vessels					<0.001			0.768
1-vessel disease	305 (46.3%)	135 (55.8%)	440 (48.8%)	1322 (41.6%)		440 (48.8%)	431 (47.8%)	
2-vessel disease	197 (29.9%)	68 (28.1%)	265 (29.4%)	1004 (31.6%)		265 (29.4%)	283 (31.4%)	
3-vessel disease	129 (19.6%)	32 (13.2%)	161 (17.9%)	634 (19.9%)		161 (17.9%)	150 (16.6%)	
Left-main, isolated	5 (0.8%)	0 (0.0%)	5 (0.6%)	19 (0.6%)		5 (0.6%)	3 (0.3%)	
Left-main, complex	23 (3.5%)	7 (2.9%)	30 (3.3%)	201 (6.3%)		30 (3.3%)	34 (3.8%)	
Pre-PCI TIMI flow grade					0.001			0.806
0 or 1	219 (33.2%)	91 (37.6%)	310 (34.4%)	1272 (40.0%)		310 (34.4%)	304 (33.7%)	
2	129 (19.6%)	42 (17.4%)	171 (19.0%)	636 (20.0%)		171 (19.0%)	182 (20.2%)	
3	311 (47.2%)	109 (45.0%)	420 (46.6%)	1272 (40.0%)		420 (46.6%)	415 (46.1%)	
PCI with DES								
Second-generation DES	617 (93.6%)	231 (95.5%)	848 (94.1%)	3046 (95.8%)	0.034	848 (94.1%)	854 (94.8%)	0.537
Maximum stent diameter (mm)	3.12 ± 0.43	3.15 ± 0.43	3.13 ± 0.43	3.09 ± 0.43	0.037	3.13 ± 0.43	3.12 ± 0.44	0.695
Total stent length (mm)	30.0 ± 14.6	29.6 ± 16.1	29.9 ± 15.0	30.3 ± 15.6	0.514	29.9 ± 15.0	30.1 ± 15.0	0.859
Number of stents	1.19 ± 0.43	1.20 ± 0.43	1.19 ± 0.43	1.21 ± 0.46	0.134	1.19 ± 0.43	1.20 ± 0.44	0.664
Post-PCI TIMI flow grade					0.223			0.419
0 or 1	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.1%)		0 (0.0%)	1 (0.1%)	
2	7 (1.1%)	2 (0.8%)	9 (1.0%)	55 (1.7%)		9 (1.0%)	13 (1.4%)	
3	652 (98.9%)	240 (99.2%)	892 (99.0%)	3123 (98.2%)		892 (99.0%)	887 (98.4%)	
Medical treatment during hospitalization								
Glycoprotein IIb/IIIa inhibitor	75 (11.4%)	29 (12.0%)	104 (11.5%)	239 (7.5%)	<0.001	104 (11.5%)	103 (11.4%)	0.941
Aspirin	658 (99.8%)	242 (100.0%)	900 (99.9%)	3179 (100.0%)	0.393	900 (99.9%)	900 (99.9%)	1.000
Beta-blocker	550 (83.5%)	218 (90.1%)	768 (85.2%)	2698 (84.8%)	0.769	768 (85.2%)	774 (85.9%)	0.687
ACEI/ARB	542 (82.2%)	204 (84.3%)	746 (82.8%)	2609 (82.0%)	0.602	746 (82.8%)	752 (83.5%)	0.706
Statin	645 (97.9%)	233 (96.3%)	878 (97.4%)	2965 (93.2%)	<0.001	878 (97.4%)	880 (97.7%)	0.760

Values are *n* (%), mean ± SD or median (interquartile range). ACC/AHA, American College of Cardiology/American Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DES, drug-eluting stents; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

greedy matching protocol (1:1 nearest neighbor matching without replacement) with a caliper width of 0.2 of the standard deviation [17,18]. We were able to match 901 patients receiving potent P2Y12 blockers to 901 patients receiving clopidogrel. We estimated standardized differences for all the covariates before and after matching to assess the balance of the covariates between ticagrelor and clopidogrel groups. After matching, none of the covariates showed a standardized difference exceeding 10%, suggesting that all of the measured covariates were well balanced between the matched groups [19,20]. Differences between the matched pairs were evaluated using the paired *t* test or the Wilcoxon signed rank test for continuous variables and the McNemar's test for categorical variables. The risks of clinical endpoints in the matched cohort were compared by using a Cox proportional hazards regression model stratified on matched pairs, including factors deemed significant (*p*-value <0.1) by univariate analysis or considered clinically important in the multivariate model. We further tested the impact of potent P2Y12 blockers versus clopidogrel on 12-month net adverse clinical events in multiple subgroups of age, sex, body weight, Killip class, diabetes, glycoprotein IIb/IIIa inhibitor use, statin use, estimated glomerular filtration rate (eGFR), time to PCI, radial artery access, ACC/AHA lesion type, Global Registry of Acute Coronary Events (GRACE) score categorized into low to intermediate (0–140) or high risk (>140) [21–23], and Acute Catheterization and Urgent Intervention Triage Strategy-Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (ACUITY-HORIZONS) bleeding risk score classified into low to moderate (<15) or high to very high (≥15) [24]. For subgroup analysis, we repeated the same propensity score matching process while matching on both the score and the subgroup variable, forcing exact matches on the subgroup characteristics. Conditional logistic regression was then used to identify treatment-subgroup interactions. All *p*-values were two-tailed, with statistical significance set at a level of <0.05. Statistical analyses were conducted using SPSS version 21 (SPSS Inc., Chicago, IL, USA) and R version 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline clinical, procedural characteristics, and treatment during hospitalization

Baseline clinical characteristics of the patients are shown in Table 1. In the overall study population, patients with higher ischemic and bleeding risks more often received clopidogrel compared to potent P2Y12 blockers. Patients receiving clopidogrel were older, had lower body weight, hypertension, diabetes, prior history of MI, angina pectoris, stroke, longer time from symptom to presentation, faster heart rate, higher Killip class, lower left ventricular systolic function, lower white blood cell count, lower hemoglobin, lower renal function, and higher GRACE and ACUITY-HORIZONS scores. Patients receiving potent P2Y12 blockers were more often men, smokers, had typical chest pain at presentation.

Table 3
Unadjusted and adjusted clinical outcomes at 12 months between potent P2Y12 blocker and clopidogrel groups before and after propensity score matching.

	All patients						Propensity-matched patients			
	Ticagrelor (n = 659)	Prasugrel (n = 242)	Potent P2Y12 blocker (n = 901)	Clopidogrel (n = 3180)	Unadjusted HR (95% CI)	p-Value	Potent P2Y12 blocker (n = 901)	Clopidogrel (n = 901)	Adjusted HR (95% CI)	p-Value
Death from any cause	18 (2.7%)	3 (1.2%)	21 (2.3%)	165 (5.2%)	0.44 (0.28–0.70)	<0.001	21 (2.3%)	25 (2.8%)	0.85 (0.47–1.52)	0.577
MI	11 (1.7%)	5 (2.1%)	16 (1.8%)	64 (2.0%)	0.87 (0.50–1.51)	0.620	16 (1.8%)	10 (1.1%)	1.60 (0.73–3.52)	0.246
Repeat PCI	26 (3.9%)	8 (3.3%)	34 (3.8%)	181 (5.7%)	0.64 (0.45–0.93)	0.019	34 (3.8%)	56 (6.2%)	0.59 (0.39–0.91)	0.016
TLR	6 (0.9%)	3 (1.2%)	9 (1.0%)	38 (1.2%)	0.81 (0.39–1.67)	0.560	9 (1.0%)	10 (1.1%)	0.87 (0.35–2.15)	0.872
TVR	10 (1.5%)	4 (1.7%)	14 (1.6%)	71 (2.2%)	0.67 (0.38–1.18)	0.164	14 (1.6%)	19 (2.1%)	0.70 (0.35–1.40)	0.317
Non-TVR	3 (0.5%)	1 (0.4%)	4 (0.4%)	48 (1.5%)	0.28 (0.10–0.78)	0.015	4 (0.4%)	15 (1.7%)	0.26 (0.09–0.78)	0.016
CABG	2 (0.3%)	1 (0.4%)	3 (0.3%)	14 (0.4%)	0.75 (0.22–2.61)	0.653	3 (0.3%)	3 (0.3%)	1.00 (0.20–4.94)	0.997
Stent thrombosis	2 (0.3%)	0 (0.0%)	2 (0.2%)	17 (0.5%)	0.41 (0.09–1.77)	0.231	2 (0.2%)	3 (0.3%)	0.66 (0.11–3.93)	0.656
Stroke	9 (1.4%)	2 (0.8%)	11 (1.2%)	64 (2.0%)	0.60 (0.32–1.14)	0.116	11 (1.2%)	12 (1.3%)	0.90 (0.40–2.03)	0.897
Death from any cause, MI, stroke	43 (6.5%)	17 (7.0%)	60 (6.7%)	247 (7.8%)	0.84 (0.63–1.11)	0.218	40 (4.4%)	49 (5.4%)	0.81 (0.54–1.24)	0.335
MACCE	53 (8.0%)	13 (5.4%)	66 (7.3%)	390 (12.3%)	0.57 (0.44–0.75)	<0.001	66 (7.3%)	91 (10.1%)	0.72 (0.52–0.98)	0.038
TIMI major bleeding	17 (2.6%)	8 (3.3%)	25 (2.8%)	45 (1.4%)	1.97 (1.21–3.22)	0.006	25 (2.8%)	8 (0.9%)	3.15 (1.42–6.98)	0.005
TIMI major or minor bleeding	39 (5.9%)	14 (5.8%)	53 (5.9%)	106 (3.3%)	1.79 (1.29–2.49)	0.001	53 (5.9%)	20 (2.2%)	2.69 (1.61–4.51)	<0.001
Death from any cause, MI, stroke, or TIMI major bleeding	46 (7.0%)	15 (6.2%)	61 (6.8%)	285 (9.0%)	0.75 (0.57–0.99)	0.039	61 (6.8%)	49 (5.4%)	1.26 (0.87–1.84)	0.224

CABG, coronary artery bypass graft surgery; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; TLR, target-lesion revascularization; TVR, target-vessel revascularization.

Procedural characteristics and in-hospital medical treatment are presented in Table 2. Potent P2Y12 blocker group more often underwent PCI via the radial artery access, had ACC/AHA lesion type B2 or C, higher rate of pre-PCI TIMI flow grade 3, and received glycoprotein IIb/IIIa inhibitor and statin. Clopidogrel group had longer time from admission to PCI and was more likely to have multi-vessel disease and lesions in the right coronary artery and the left main stem, and to receive second-generation DES with smaller stent diameter. After propensity-score matching, there were no differences between potent P2Y12 blocker and clopidogrel groups in baseline clinical and procedural characteristics and medical treatment during hospitalization (Tables 1 and 2).

Clinical outcomes

Unadjusted and adjusted 12-month clinical outcomes before and after propensity matching are shown in Table 3. In all patients, patients receiving potent P2Y12 blockers, compared to those receiving clopidogrel, had lower rates of death, repeat PCI mainly driven by non-target vessel revascularization, and MACCE, but

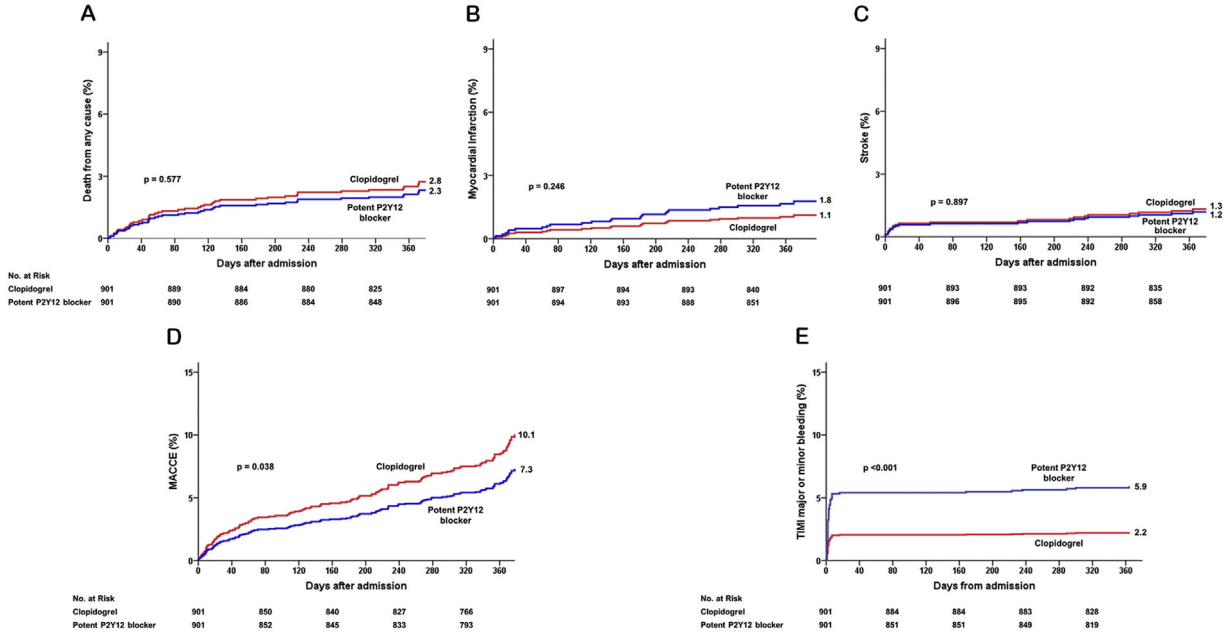

Fig. 2. Adjusted cumulative incidences of death from any cause (A), MI (B), stroke (C), MACCE (D), and TIMI major or minor bleeding (E) at 12 months in the propensity-score matched cohort. MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

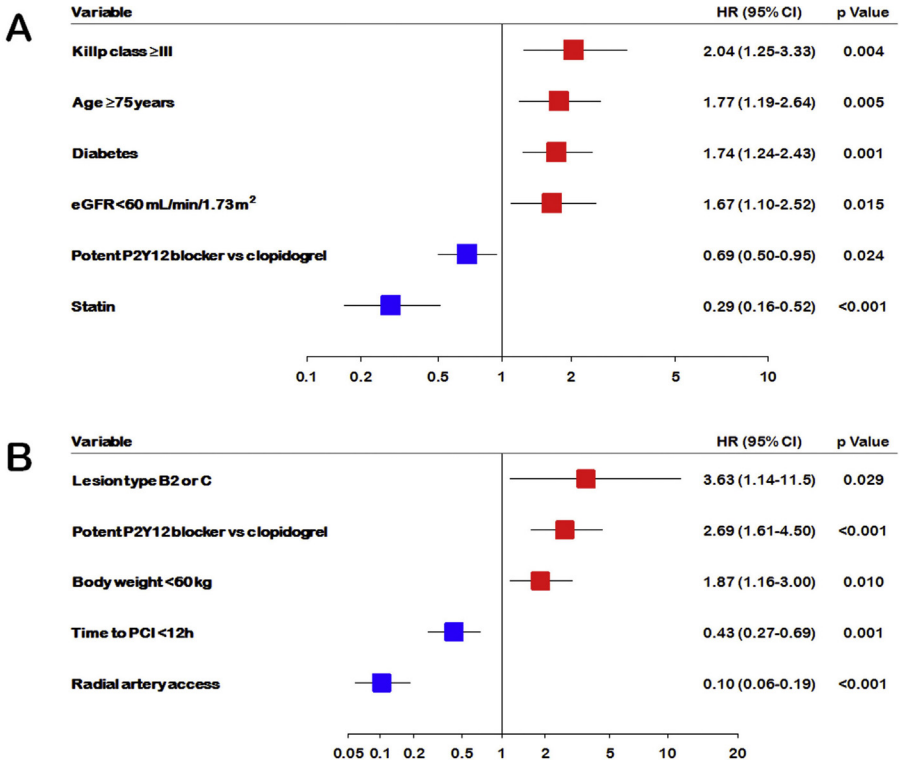

Fig. 3. Independent predictors of 12-month MACCE (A) and 12-month TIMI major or minor bleeding (B) in the propensity-matched cohort. CI, confidence interval; HR, hazard ratio; eGFR, estimated glomerular filtration rate; MACCE, major adverse cardiac and cerebrovascular events; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

higher rates of TIMI major bleeding, TIMI major or minor bleeding, and net adverse clinical events. After propensity score matching (n = 901 in each group), 12-month rates of death, MI, and stroke were not different between the groups (Fig. 2A–C). However, patients treated with potent P2Y12 blockers had lower rates of repeat PCI (3.8% vs. 6.2%; HR: 0.59; 95% CI: 0.39–0.91; p = 0.016) largely contributed by non-target vessel repeat PCI (0.4% vs. 1.7%; HR: 0.26; 95% CI: 0.09–0.78; p = 0.016) and of MACCE (7.3% vs. 10.1%; HR: 0.72; 95% CI: 0.52–0.98; p = 0.038) (Fig. 2D), but higher rates of TIMI major bleeding (2.8% vs. 0.9%; HR: 3.15; 95% CI: 1.42–6.98; p = 0.005), TIMI major or minor bleeding (5.9% vs. 2.2%; HR: 2.69; 95% CI: 1.61–4.51; $p < 0.001$) (Fig. 2E). Twelve-month rates of net adverse clinical events were not different between the two groups.

On multivariate analysis, 12-month risk of MACCE was higher with Killip class ≥III (HR: 2.04; 95% CI: 1.25–3.33; p = 0.004), age ≥75 years (HR: 1.77; 95% CI: 1.19–2.64; p = 0.005), diabetes (HR: 1.74; 95% CI: 1.24–2.43; p = 0.001), eGFR <60 mL/min/1.73 m^2 (HR: 1.67; 95%; CI: 1.10–2.52; p = 0.015), but lower with use of potent P2Y12 blockers compared to clopidogrel (HR: 0.69; 95% CI: 0.50–0.95; p = 0.024) and statin (HR: 0.29; 95% CI: 0.16–0.52; $p < 0.001$) (Fig. 3A). The risk of 12-month TIMI major or minor bleeding was higher with ACC/AHA type B2 or C lesion (HR: 3.63; 95% CI: 1.14–11.5; p = 0.029), use of potent P2Y12 blockers compared to clopidogrel (HR: 2.69; 95% CI: 1.61–4.50; $p < 0.001$), body weight <60 kg (HR: 1.87; 95% CI: 1.16–3.00; p = 0.010), but lower with time to PCI <12 h (HR: 0.43; 95% CI: 0.27–0.69; p = 0.001) and radial artery access (HR: 0.10; 95% CI: 0.06–0.19; $p < 0.001$) (Fig. 3B). Further comparison of the bleeding risk according to time to PCI (with PCI ≥24 h as a reference) showed that the reduction in the rate of 12-month TIMI major or minor bleeding was consistent across all strata for earlier PCI, regardless of the potency of the P2Y12 blocker (Fig. 4). Subgroup analysis for 12-month net adverse clinical events in the propensity-matched cohort showed that the treatment effects of potent P2Y12 blockers versus clopidogrel were not significantly different across the subgroups (Fig. 5).

Discussion

The present study showed that in patients with acute NSTEMI undergoing PCI with DES, the use of potent P2Y12 blockers, compared to clopidogrel, was associated with reduced ischemic risk but higher bleeding events with similar net clinical benefits. At 12-month follow-up, patients treated with potent P2Y12 blockers had lower rates of non-target vessel repeat PCI and MACCE, but higher rates of TIMI major or minor bleeding. On multivariate analysis, the risk of TIMI major or minor bleeding was higher with potent P2Y12 blockers, but lower with shorter time to PCI and radial artery access.

Current guidelines recommend DAPT with potent P2Y12 blockers such as ticagrelor or prasugrel in preference to clopidogrel in patients with NSTEMI undergoing invasive strategy [25,26]. However, increased bleeding risk is of serious concern, particularly to East Asians, who are known to be more susceptible to bleeding [8,9]. In the Study of Platelet Inhibition and Patient Outcomes (PLATO) [4] and the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction (TRITON–TIMI) 38 [3], both ticagrelor and prasugrel, compared to clopidogrel, increased non-CABG bleeding. Observational studies in Korean patients with acute MI showed that the use of potent P2Y12 blockers was associated with significantly increased risk of bleeding with similar rates of ischemic events [5–7]. Furthermore, a recent randomized trial on ACS patients from Japan, Taiwan, and South Korea showed higher incidences of major bleeding and of death, MI, or stroke, albeit not significantly, with ticagrelor

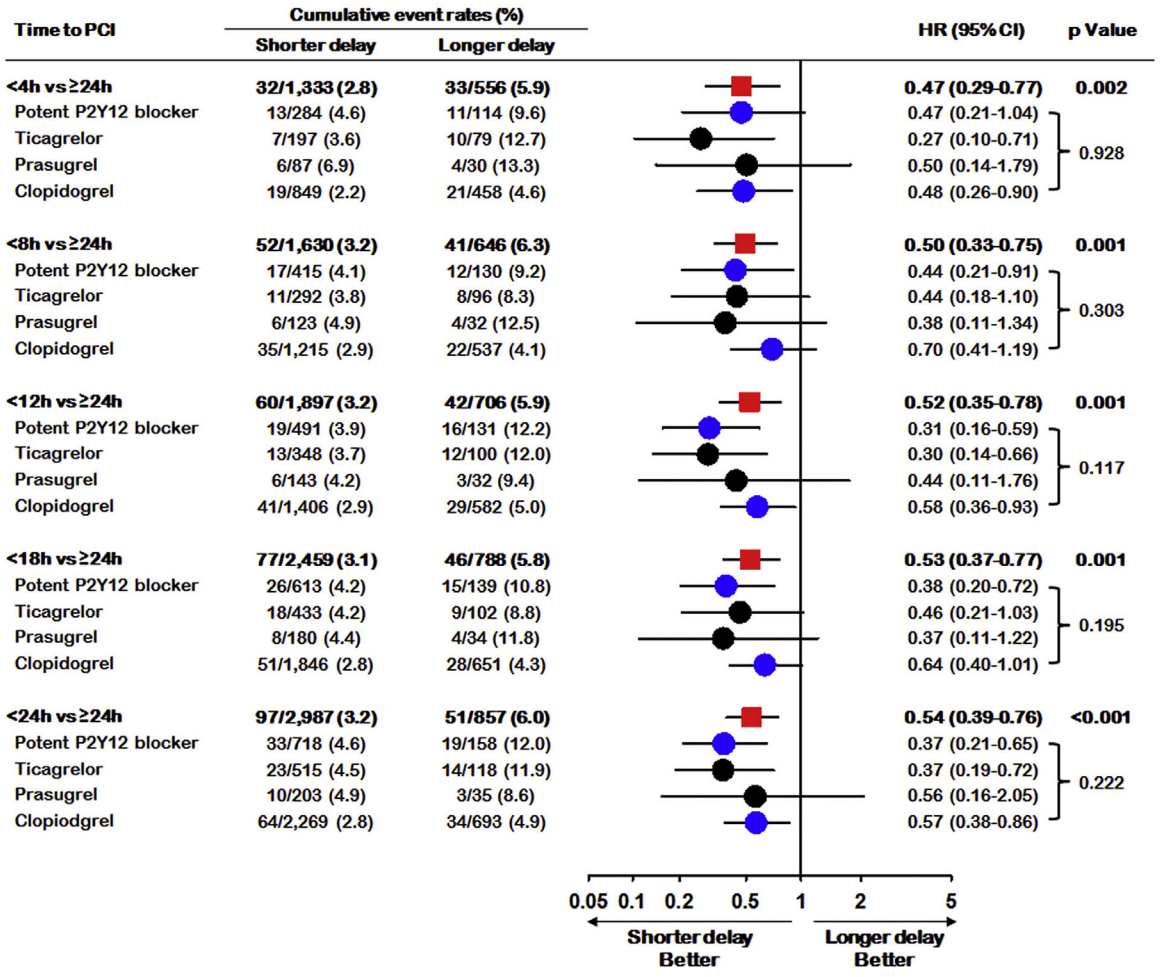

Fig. 4. Comparison of propensity-adjusted 12-month TIMI major or minor bleeding according to the time to PCI (PCI ≥24 h as reference). CI, confidence interval; HR, hazard ratio; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

compared to clopidogrel [27]. In the present study on patients with NSTEMI, the risk of bleeding was higher, but the risk of ischemic events was lower with potent P2Y12 blockers, compared to clopidogrel, with similar net clinical benefits. The findings of our study may suggest an individualized approach in selecting P2Y12 blockers weighing the risks and benefits, especially in the East Asian population.

As part of the strategies to reduce bleeding risk related to PCI, radial over femoral artery approach and new-generation DES are recommended in the current guidelines [1,2]. In line with this suggestion, multivariate analysis in the present study showed the risk of TIMI major or minor bleeding was lower with radial artery access. In addition, most patients in both potent P2Y12 blocker (94.1%) and clopidogrel (94.8%) groups received second-generation DES.

The timing of PCI may be another important contributing factor related to the risk of major bleeding with NSTEMI undergoing invasive management. Meta-analyses showed that early PCI in patients with NSTE-ACS was associated with lower rates of bleeding events [28–31]. The risk of major bleeding was also lower with immediate invasive strategy compared to delayed intervention for patients with NSTE-ACS in a number of randomized and observational clinical studies [32–37]. Consistent with these results, in the present study, earlier PCI was associated with lower risk of TIMI major or minor bleeding than delayed PCI (≥24 h), regardless of the potency of the P2Y12 blocker. This time-dependent risk of bleeding may be associated with the crescendo effects of antiplatelet therapy over time [38] and may suggest that patients at high risk of bleeding could benefit from even earlier invasive management [31].

The present study has several limitations. Firstly, although these results come from a large cohort and adjustment was made using propensity score analysis for confounding variables, unmeasured factors may still exist. In the overall population, patients with clopidogrel had higher ischemic and bleeding risks at baseline and higher mortality and ischemic events at 12 months. Although this discrepancy was not observed after propensity matching, the possible role of unmeasured residual confounding cannot be ruled out. Secondly, side effects and medication adherence status during clinical follow-up were not included in the analysis. Thirdly, for patients who developed bleeding events, detailed information on the causes of bleeding including vascular access complications was not available. Finally, in patients receiving prasugrel, it was not available from our registry whether prasugrel was given before or after coronary angiography, even though it is recommended that prasugrel be given after coronary angiography in patients with NSTEMI undergoing PCI based on the Comparison of Prasugrel at the Time of PCI or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial [39].

In conclusion, potent P2Y12 blockers in patients with NSTEMI undergoing PCI with DES were associated with reduced ischemic

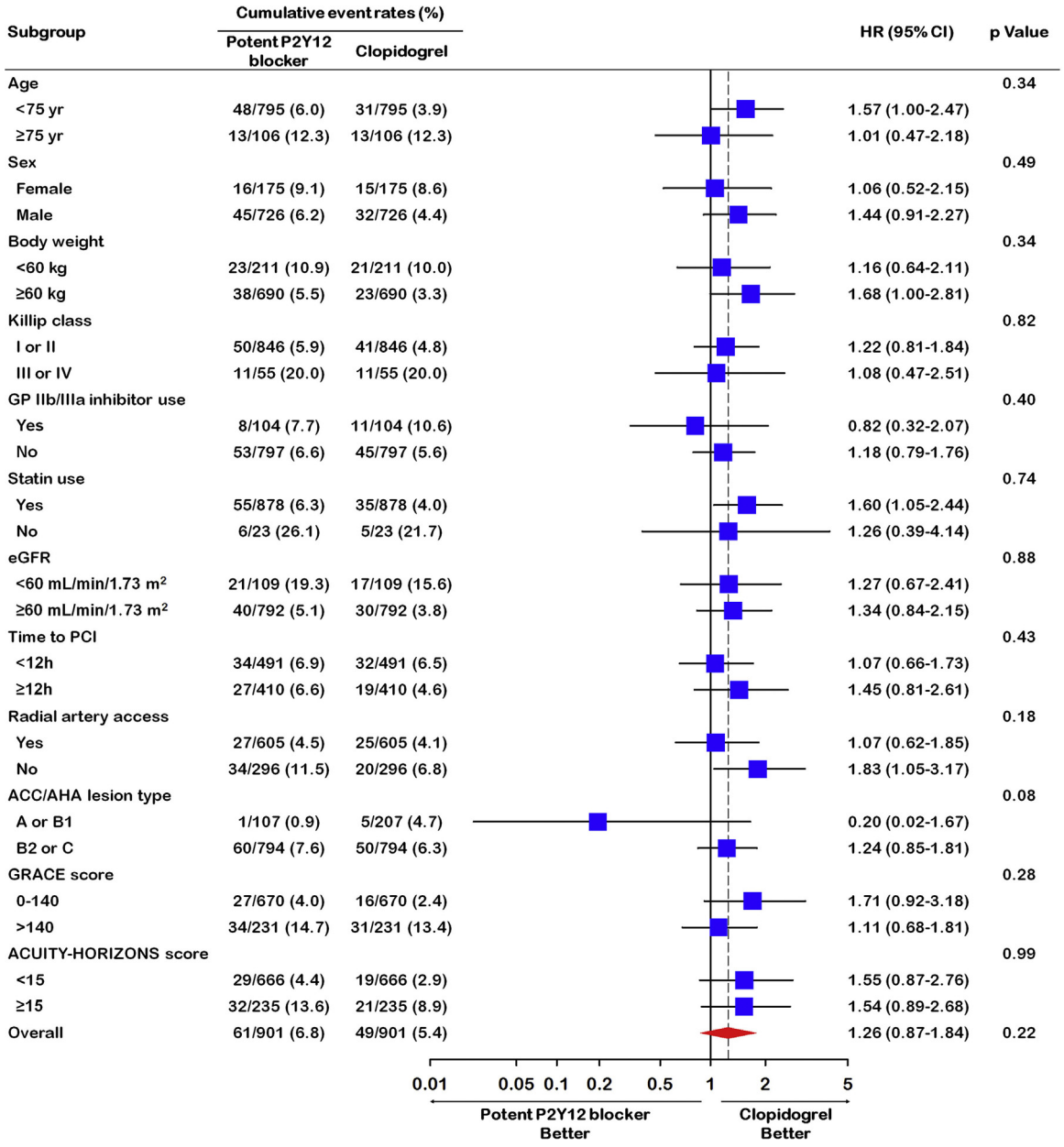

Fig. 5. Subgroup analysis for adjusted 12-month net adverse clinical events in the propensity-matched cohort. ACC/AHA, American College of Cardiology/American Heart Association; CI, confidence interval; eGFR, estimated glomerular filtration rate; GP, glycoprotein; HR, hazard ratio; PCI, percutaneous coronary intervention.

but increased bleeding risk with similar net clinical benefits. The results of our study warrant further studies on the optimal use of potent P2Y12 blockers in East Asian patients with NSTEMI.

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Conflicts of interest

The authors declare that there is no conflict of interest.

References

[1] Amsterdam EA, Wenger NK, Brindis RG, Casey Jr DE, Ganiats TG, Holmes Jr DR, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;130:e344–426.

[2] Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

[3] Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–15.

[4] Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–57.

[5] Park KH, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea Acute Myocardial Infarction Registry-National Institute of Health. Int J Cardiol 2016;215:193–200.

[6] Park KH, Jeong MH, Kim HK, Ahn TH, Seung KB, Oh DJ, et al. Comparison of prasugrel versus clopidogrel in Korean patients with acute myocardial infarction undergoing successful revascularization. J Cardiol 2018;71:36–43.

[7] Kang J, Han JK, Ahn Y, Chae SC, Kim YJ, Chae IH, et al. Third-generation P2Y12 inhibitors in East Asian acute myocardial infarction patients: a nationwide prospective multicentre study. Thromb Haemost 2018;118:591–600.
[8] Jeong YH. "East asian paradox": challenge for the current antiplatelet strategy of "one-guideline-fits-all races" in acute coronary syndrome. Curr Cardiol Rep 2014;16:485.
[9] Bae JS, Ahn JH, Tantry U, Gurbel PA, Jeong YH. Should antithrombotic treatment strategies in East Asians differ from Caucasians? Curr Vasc Pharmacol 2018;16:459–76.
[10] Kim JH, Chae SC, Oh DJ, Kim HS, Kim YJ, Ahn Y, et al. Multicenter cohort study of acute myocardial infarction in Korea – Interim analysis of the Korea Acute Myocardial Infarction Registry-National Institutes of Health Registry. Circ J 2016;80:1427–36.
[11] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.
[12] Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction, Jaffe AS, Apple FS, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634–53.
[13] Mauri L, Hsieh WH, Massaro JM, Ho KK, D'Agostino R, Cutlip DE. Stent thrombosis in randomized clinical trials of drug-eluting stents. N Engl J Med 2007;356:1020–9.
[14] Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial – phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.
[15] D'Agostino Jr RB. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17:2265–81.
[16] Joffe MM, Rosenbaum PR. Invited commentary: propensity scores. Am J Epidemiol 1999;150:327–33.
[17] Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. Am Stat 1985;39:33–8.
[18] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011;10:150–61.
[19] Cohen J. The *t* test for means. In: Cohen J, editor. Statistical power analysis for the behavioral sciences. 2nd ed., Hillsdale, NJ: Lawrence Erlbaum Associates; 1988. p. 19–74.
[20] Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, et al. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 2001;54:387–98.
[21] Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003;163:2345–53.
[22] de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 2005;26:865–72.
[23] Aragam KG, Tamhane UU, Kline-Rogers E, Li J, Fox KA, Goodman SG, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. PLoS One 2009;4:e7947.
[24] Mehran R, Pocock SJ, Nikolsky E, Clayton T, Dangas GD, Kirtane AJ, et al. A risk score to predict bleeding in patients with acute coronary syndromes. J Am Coll Cardiol 2010;55:2556–66.
[25] Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2016;68:1082–115.
[26] Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–60.
[27] Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome – randomized, double-blind, phase III PHILO study. Circ J 2015;79:2452–60.
[28] Katritsis DG, Siontis GC, Kastrati A, van't Hof AW, Neumann FJ, Siontis KC, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. Eur Heart J 2011;32:32–40.
[29] Zhang S, Ge J, Yao K, Qian J. Meta-analysis of early versus deferred revascularization for non-ST-segment elevation acute coronary syndrome. Am J Cardiol 2011;108:1207–13.
[30] Rajpurohit N, Garg N, Garg R, Choudhary A, Fresen J, Boren S, et al. Early versus delayed percutaneous coronary intervention for patients with non-ST segment elevation acute coronary syndrome: a meta-analysis of randomized controlled clinical trials. Catheter Cardiovasc Interv 2013;81:223–31.
[31] Sanchez PL, Fernandez-Aviles F. Catheterization laboratories open 24 hours a day, every day: does stable non-ST-elevation acute coronary syndrome need the offer? Eur Heart J 2012;33:1992–5.
[32] Neumann FJ, Kastrati A, Pogatsa-Murray G, Mehilli J, Bollwein H, Bestehorn HP, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. JAMA 2003;290:1593–9.
[33] Montalescot G, Cayla G, Collet JP, Elhadad S, Beygui F, Le Breton H, et al. Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. JAMA 2009;302:947–54.
[34] Riezebos RK, Ronner E, Ter Bals E, Slagboom T, Smits PC, ten Berg JM, et al. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. Heart 2009;95:807–12.
[35] Thiele H, Rach J, Klein N, Pfeiffer D, Hartmann A, Hambrecht R, et al. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI Trial). Eur Heart J 2012;33:2035–43.
[36] Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, Marinkovic J, Vukcevic V, Stefanovic B, et al. Immediate versus delayed invasive intervention for non-STEMI patients: The RIDDLE-NSTEMI Study. JACC Cardiovasc Interv 2016;9:541–9.
[37] Sim DS, Jeong MH, Ahn Y, Kim YJ, Chae SC, Hong TJ, et al. Clinical impact of immediate invasive strategy in patients with non-ST-segment elevation myocardial infarction. Int J Cardiol 2016;221:937–43.
[38] Riezebos RK, Verheugt FW. Timing of angiography in non-ST elevation myocardial infarction. Heart 2013;99:1867–73.
[39] Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, et al. Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes. N Engl J Med 2013;369:999–1010.