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Comparison of prescription rates and clinical outcomes in acute coronary syndrome patients who underwent percutaneous coronary intervention using different $P2Y_{12}$ inhibitors in a large observational study☆

Jeong Cheon Choe [a], Kwang Soo Cha [a,*], Jinhee Ahn [a], Jin Sup Park [a], Hye Won Lee [a], Jun-Hyok Oh [a], Jung Hyun Choi [a], Han Cheol Lee [a], Taek Jong Hong [a], Myung Ho Jeong [b], the Korea Acute Myocardial Infarction Registry–National Institutes of Health Investigators

[a] Department of Cardiology, Pusan National University Hospital, Busan, South Korea
[b] Department of Cardiology, Chonnam National University Hospital, Gwangju, South Korea

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ABSTRACT

Background: To compare the prescription rates, safety, and efficacy of contemporary $P2Y_{12}$ inhibitors in acute coronary syndrome (ACS) patients following percutaneous coronary intervention (PCI).
Methods: From 9684 ACS patients who underwent PCI in a nationwide, real-world registry, we compared prescription rates, bleeding, and major adverse cardiac events (MACEs: cardiac death, nonfatal myocardial infarction, or stroke) according to ticagrelor, prasugrel, or clopidogrel use.
Results: The prescription rates of ticagrelor, prasugrel, and clopidogrel were 15.2%, 11.7%, and 73.0%, respectively. In-hospital bleeding occurred in 565 (5.8%) patients, with 108 (7.3%), 80 (7.9%), and 377 (5.3%) patients using ticagrelor, prasugrel, and clopidogrel, respectively, with significantly higher incidence in ticagrelor ($p = 0.008$) and prasugrel ($p = 0.026$) users than in clopidogrel users. Ticagrelor and prasugrel were not different in terms of in-hospital bleeding ($p = 0.159$). MACEs occurred in 804 patients (8.3%), with 82 (5.6%), 69 (6.1%), and 653 (9.2%) patients in ticagrelor, prasugrel, and clopidogrel, respectively (median follow-up, 468 days). Ticagrelor ($p = 0.001$) and prasugrel ($p = 0.001$) were associated with fewer MACEs than clopidogrel; the difference between ticagrelor and prasugrel for fewer MACEs was nonsignificant ($p = 0.235$).
Conclusions: In real-world ACS patients following PCI, ticagrelor and prasugrel were not prescribed at higher rates than clopidogrel, but were found to improve clinical outcomes, albeit they induced bleeding more frequently. No differences were observed in bleeding and outcomes in ticagrelor versus prasugrel.

1. Introduction

Dual antiplatelet therapy (DAPT), involving aspirin and a $P2Y_{12}$ inhibitor, is essential in acute coronary syndrome (ACS) patients following percutaneous coronary intervention (PCI) to reduce potential atherothrombic risk [1–3]. However, clopidogrel has insufficient efficacy because its ability to inhibit platelets is slow, modest, and uneven [2,3]. Because ticagrelor and prasugrel exhibit faster, stronger, and more consistent potency than does clopidogrel and have more favorable clinical benefits in randomized trials [2–6], they were recommended over clopidogrel in ACS patients undergoing PCI [1]. The Prasugrel Versus Ticagrelor in Patients with Acute Myocardial Infarction Treated with Primary Percutaneous Coronary Intervention (PRAGUE-18) trial reported that in acute myocardial infarction (MI) patients who underwent PCI, ticagrelor and prasugrel had a comparable efficacy and safety [7,8]. However, real-world data on contemporary $P2Y_{12}$ inhibitors, particularly those used in ACS patients undergoing PCI, are limited and inconsistent [9–12]. Based on the reported association between contemporary $P2Y_{12}$ inhibitors and outcomes, we investigated the prescription patterns, safety, and efficacy of contemporary $P2Y_{12}$ inhibitors in ACS patients undergoing PCI, using a nationwide, real-world registry.

2. Methods

2.1. Study population

The study population was selected from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH) registry, which is a nationwide, prospective, multicenter online registry of patients presenting with ACS in Korea, maintained at 20 centers since November 2011. This registry was sponsored by the Korea Centers for

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* Corresponding author at: Department of Cardiology and Medical Research Institute, Pusan National University Hospital, 179 Gudeok-ro Seo-gu, Busan 49241, South Korea.
E-mail address: chakws1@hanmail.net (K.S. Cha).

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Disease Control and Prevention and managed by the Korean working group of acute MI. Participating centers are mainly academic and have high volumes of patients and facilities for primary PCI and on-site cardiac surgery. From November 2011 to June 2015, 12,431 consecutive patients with diagnosis of ACS were prospectively enrolled. The study's protocol conformed to the guidelines of the Declaration of Helsinki and was approved by each institution's human research committee. Informed consent was obtained from each patient. Trained study coordinators collected all medical data and study end points, using a standardized protocol and case report forms. Standardized definitions of all variables were determined by the Steering Committee Board of KAMIR-NIH.

Patients aged ≥18 years, those with a confirmed final diagnosis of ACS, those who underwent PCI, and those prescribed aspirin and a $P2Y_{12}$ inhibitor (ticagrelor, prasugrel, or clopidogrel) from admission and at discharge were included. Patients with invalid or incomplete data (aged <18 years, without follow-up, with inaccurate data on the coronary procedure and $P2Y_{12}$ inhibitor use, with a dating error, and with a missing value rate > 30%), those who discontinued or switched antiplatelet medications during hospitalization, and those who did not undergo PCI were excluded.

Among the registered patients, 9684 were included. Supplementary Fig. 1 shows the patient selection flowchart. Patients were divided into three groups based on $P2Y_{12}$ inhibitor use from admission and at discharge: ticagrelor ($n = 1474$), prasugrel ($n = 1137$), and clopidogrel ($n = 7073$) groups. After propensity score (PS) matching, there were 1203 ticagrelor-clopidogrel-, 968 prasugrel-clopidogrel-, and 526 ticagrelor-prasugrel-matched patients.

2.2. Management and follow-up

When patients with angina-like symptoms (chest or non-chest origin) suspected of having ACS presented to the emergency department, clinicians in the cardiology department typically made a diagnosis and drafted a treatment plan. If necessary, clinicians discussed the case with an interventional cardiologist. Before PCI, each patient routinely received antiplatelet agents, including aspirin 200–300 mg, and a $P2Y_{12}$ inhibitor (ticagrelor 180 mg, prasugrel 60 mg, or clopidogrel 300–600 mg) after the procedure, followed by daily aspirin (100 mg) indefinitely and a P2Y12 inhibitor (ticagrelor 90 mg twice daily, prasugrel 10 mg once daily, or clopidogrel 75 mg once daily) for at least 1 year. Prasugrel was not prescribed in patients >75 years old, <60 kg in weight, or with prior stroke/transient ischemic attack. The antiplatelet agents were chosen largely based on the discretion of individual cardiologists. Unfractionated heparin (50–70 U/kg) was administered before or during PCI to maintain the activated clotting time at 250–300 s. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, platelet glycoprotein IIb/IIIa inhibitors, statins, and β-blockers were administered per the physician's discretion. All patients underwent coronary angiography during PCI according to current standard procedural guidelines. The interventional cardiologist determined the specific PCI technique and stent type for the coronary lesion. Patients were provided with standard care and medications for secondary prevention.

After discharge, all patients were prescribed medications and were followed up with their clinicians regularly (1- to 3-month intervals) by office visit. During follow-up, patients who developed angina-like symptoms underwent complete clinical evaluations. If deemed necessary, patients received hospital care and revascularization. Information on clinical events was obtained from hospital records or via telephone contact with the patients' relatives or referring physicians.

2.3. Study end points and definitions

The primary safety end point was cumulative in-hospital bleeding events unrelated to coronary artery bypass grafting (CABG), as defined by the Thrombolysis in Myocardial Infarction bleeding criteria [13]. Major bleeding included intracranial bleeding, clinically overt sign of hemorrhage, and a decline in hemoglobin level of ≥5 g/dL or in hematocrit levels of ≥15%. Minor bleeding was defined as any bleeding requiring medical intervention but not meeting the major bleeding criteria. The primary efficacy end point was incidence of major adverse cardiac events (MACEs; cardiac death, nonfatal MI, or stroke) during follow-up. Secondary end points were MACE components, all-cause death, non-cardiac death, any revascularization including repeat PCI (re-PCI), and CABG during follow-up. All events were identified by the patient's physician and confirmed by the principal investigator of each hospital. All-cause death was defined as any case of death intra- or post-procedure; death was considered to be of a cardiac origin, unless a definite non-cardiac cause was established. Nonfatal MI was defined as recurrent symptoms with new electrocardiographic changes compatible with MI or cardiac marker levels at least twice the upper limit of normal. Stroke was defined as a new, sudden, focal neurological deficit due to a presumed cerebrovascular cause that was not reversible within 24 h and not due to a readily identifiable cause (e.g., tumors or seizures). Any revascularization was defined as revascularization involving either the target or non-target vessels.

2.4. Statistical analysis

Continuous variables are presented as medians with the 25th and 75th percentiles and were compared using the Mann-Whitney *U* test. Categorical variables are presented as numbers with percentages and were compared using the chi-square or Fisher exact tests, as appropriate. Multivariate logistic regression was performed to identify independent predictors for safety endpoints after adjusting for baseline, laboratory, and angiographic variables (age, sex, body mass index [BMI], diabetes mellitus [DM], prior myocardial infarction [MI], Killip class III/IV, ST-elevation MI [STEMI], baseline creatinine, maximum troponin I, left ventricular ejection fraction [LVEF], culprit lesion, transfemoral approach [TFA], multiple treated vessels [≥2], and $P2Y_{12}$ inhibitor type). Kaplan-Meier estimations were used to identify the survival free from major adverse cardiac events (MACEs) and the components of MACE among the three groups. Cox regressions were used to determine independent predictors for efficacy endpoints.

To eliminate the bias that is inherent to non-randomized studies, we performed 3 propensity score (PS)]-matched cohort analyses to compare (1) ticagrelor versus clopidogrel; (2) prasugrel versus clopidogrel; (3) ticagrelor versus prasugrel. PS was estimated using multivariate logistic regression, with each $P2Y_{12}$ inhibitor as the dependent variable. The adjusted covariates in the PS-matched analysis included age, sex, BMI, cardiovascular risk factors (hypertension, DM, dyslipidemia, prior MI, prior heart failure, and smoking history), Killip class, STEMI, primary percutaneous coronary intervention, laboratory characteristics (maximum creatine kinase–MB, maximum troponin I, B-type natriuretic peptide, baseline creatinine, and low-density lipoprotein cholesterol levels), LVEF, angiographic and procedural characteristics (extent of coronary lesion, culprit lesion, lesion type, TFA, multiple treated vessels [≥2], multiple stents [≥2], and procedural success), and medication at discharge (β-blocker, renin-angiotensin aldosterone system blocker, and statin). We matched the patients in each cohort using the 1:1 nearest-neighbor matching, without replacement, and with a caliper width of 0.2. To assess the differences within each PS-matched cohort, paired t and McNemar's test were used for continuous and categorical variables, respectively. Kaplan-Meier analyses and Cox regression were used to evaluate the influence of $P2Y_{12}$ inhibitor type on efficacy endpoints. Because combining multiple strategies for PS methods may lead to a better analysis of treatment effect than that using only one of the three PS methods (i.e., matching, stratification, or regression adjustment) [14], we performed an additional Cox regression with "PS" and "$P2Y_{12}$ inhibitor type" as covariates and "efficacy end point" as dependent variables. A two-sided p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS 22.0 (IBM, Armonk, NY, USA) and R 3.1.0 (R Development Core Team, Vienna, Austria).

3. Results

3.1. Baseline, laboratory, and angiographic characteristics

Among all patients, ticagrelor, prasugrel, and clopidogrel were prescribed to 15.2%, 11.7%, and 73.0% of patients, respectively. Supplementary Table 1 shows baseline, laboratory, and angiographic characteristics. Clopidogrel-treated patients were older, more likely to be a woman, and had higher incidences of diabetes mellitus, previous heart failure, Killip class III/IV, and left main or three-vessel disease. However, they were less likely to be current smokers or have a history of hypertension, ST-elevation MI (STEMI), type B2 or C lesions, and multiple stents. Additionally, they were more likely to have lower maximum creatine kinase-MB, maximum troponin I, and low-density lipoprotein-cholesterol levels than did ticagrelor- or prasugrel-treated patients. After PS matching, all absolute standard differences were <10%, indicating proper matching. There were no significant differences in clinical characteristics between the groups in each matched cohort (Supplementary Table 2).

3.2. Safety end points

In-hospital bleeding occurred in 565 patients, in 108 ticagrelor (7.3%), 80 prasugrel (7.9%), and 377 clopidogrel (5.3%) users. Table 1 and Supplementary Table 3 show the cumulative in-hospital bleeding in the entire cohort and each PS-matched cohort. In-hospital bleeding rates were significantly higher in the ticagrelor or prasugrel groups than in the clopidogrel group, but no significant differences existed in any bleeding between the ticagrelor and prasugrel groups. The minor bleeding rates tended to increase significantly in the ticagrelor or prasugrel groups compared with those in the clopidogrel group; however, there was no increase in the rates of major bleeding. No significant differences were noted in rates of in-hospital bleeding components between the ticagrelor and prasugrel groups (Tables 1 and 2 and Supplementary Table 3). Among STEMI patients undergoing primary PCI, ticagrelor or prasugrel users had higher rates of any and minor bleeding than did clopidogrel users, but not of major bleeding (Supplementary Table 4). After multivariate adjustment, ticagrelor or prasugrel use, age, transfemoral approach, and multiple treated vessels were independent predictors of both any and minor bleeding, but not major bleeding (Table 2 and Supplementary Fig. 2).

Table 1
Safety and Efficacy Endpoints in Entire Cohort.

	Ticagrelor group ($n = 1474$)	Prasugrel group ($n = 1137$)	Clopidogrel group ($n = 7073$)	P
In-hospital bleeding	108 (7.3%)†	80 (7.9%)†	377 (5.3%)	0.027
Major bleeding	48 (3.3%)	35 (3.1%)	197 (2.8%)	0.487
Minor bleeding	60 (4.1%)†	45 (4.0%)†	180 (2.5%)	0.021
MACEs*	82 (5.6%)†	69 (6.1%)†	653 (9.2%)	0.014
All-cause death	48 (3.3%)†	34 (3.0%)†	435 (6.2%)	0.017
Cardiac death	21 (1.4%)†	18 (1.6%)†	292 (4.1%)	0.022
Non-cardiac death	27 (1.8%)	16 (1.4%)†	143 (2.0%)	0.087
Nonfatal MI	36 (2.4%)	30 (2.6%)	209 (3.0%)	0.149
Stroke	25 (1.7%)†	21 (1.8%)	152 (2.1%)	0.216
Any revascularization	34 (2.3%)†	30 (2.6%)†	232 (3.3%)	0.047
Repeat percutaneous coronary intervention	28 (1.9%)†	25 (2.2%)†	199 (2.8%)	0.038
Coronary artery bypass graft	6 (0.4%)	5 (0.4%)	33 (0.5%)	0.249

Values are n (%).
MACEs, major adverse cardiac events; MI, myocardial infarction.
* MACEs included cardiac death, nonfatal MI, or stroke.
† significant *p*-value compared with Clopidogrel group.

3.3. Efficacy end points

Table 1 and Supplementary Table 3 present the cumulative efficacy end points in the entire cohort and each PS-matched cohort. MACEs occurred in 804 patients during a median follow-up period of 468 days (interquartile range, 253–718 days) and occurred significantly less frequently in patients in the ticagrelor or prasugrel groups than in those in the clopidogrel group. Patients in the ticagrelor or prasugrel groups had significantly lower rates of both all-cause and cardiac death, any revascularization, and re-PCI than did those in the clopidogrel group. In STEMI patients undergoing primary PCI, the MACEs, all-cause death, and cardiac death rates were significantly lower in patients in the ticagrelor or prasugrel groups than in those in the clopidogrel group (Supplementary Table 4). Similarly, in each PS-matched cohort, MACEs (in addition to all-cause and cardiac death) occurred significantly less frequently in patients in the ticagrelor or prasugrel groups than in those in the clopidogrel group. However, the incidences of MACEs, all-cause death, and cardiac death were comparable between the ticagrelor and prasugrel groups in both cohorts. No significant differences existed in the nonfatal MI and stroke rates among the three groups (Table 1 and Supplementary Table 3).

MACE- and cardiac death-free survival rates were significantly higher in ticagrelor or prasugrel groups than in the clopidogrel group, but nonfatal MI- and stroke-free survival were not (Fig. 1 and Supplementary Fig. 3). After adjustment for prognostic covariates, we found that ticagrelor or prasugrel use, age, presence of chronic kidney disease, use of a transfemoral approach during treatment, and multiple treated vessels were significantly associated with the risk of MACE and cardiac death (Table 3 and Supplementary Fig. 4). However, the impact of ticagrelor and prasugrel on MACE and secondary end point were comparable. In the PS-adjusted regression analysis, ticagrelor or prasugrel remained associated with a lower MACE risk than did clopidogrel, whereas ticagrelor and prasugrel had similar MACE risks (Table 3). Additionally, in the PS-matched and adjusted analyses, the ticagrelor and prasugrel groups in any of the subgroups were comparable regarding MACE risk (Supplementary Fig. 5).

4. Discussion

Using data from a recent, prospective, nationwide registry, we investigated prescription rates, incidence of clinical outcomes in 9684 consecutive ACS patients who underwent PCI after using ticagrelor, prasugrel, or clopidogrel. Prescription rates were ~15.0% for ticagrelor, ~12.0% for prasugrel, and 73.0% for clopidogrel. In-hospital bleeding was observed in ~6% of patients, but was observed more frequent in the ticagrelor or prasugrel groups; however, most of these bleeding events were minor. MACE occurred in ~8.0% during a median follow-up of 468 days. Moreover, ticagrelor or prasugrel versus clopidogrel use was associated with a decreased risk of MACE in addition to cardiac death. However, no significant differences in all clinical outcomes were noted between the use of ticagrelor and prasugrel. Our findings indicate that ticagrelor- or prasugrel-based DAPT is not prescribed frequently to ACS patients undergoing PCI, although it is likely to improve clinical efficacies by decreasing the rate of cardiac death. However, this may be because it is accompanied by a higher bleeding tendency that consisted of mostly minor events. Additionally, ticagrelor and prasugrel did not show any differences regarding safety and efficacy, which has not thoroughly been documented previously.

In ACS patients undergoing PCI, traditional clopidogrel-based DAPT is widely administered, but low or non-responders to clopidogrel showed worse outcomes [2,3]. Ticagrelor and prasugrel have overcome the pharmacokinetic limitations of clopidogrel [2,3], were proven to have better outcomes than clopidogrel [2–6,15,16] and are used increasingly [9,10]. However, data comparing contemporary $P2Y_{12}$ inhibitor use in ACS patients undergoing PCI are conflicting and scarce, and most existing studies studied Western populations [9–12,16,17].

Although prescription rates of contemporary $P2Y_{12}$ inhibitors have increased, they range widely [9–12,16,17]. Herein, ticagrelor and prasugrel prescribed in approximately 15% and 12% of patients, respectively, representing only approximately 27% of our population. These different rates may be explained by differences in the study populations, variation in health insurance among countries, and the heterogeneous therapeutic indication for $P2Y_{12}$ inhibitors. Some clinicians prefer conventional clopidogrel over new $P2Y_{12}$ inhibitors because the latter are associated with higher bleeding risks.

After PCI, bleeding was observed in 1.2%–12.1% of ticagrelor and 2.2%–8.2% of prasugrel users [11,12,17]. The bleeding rates in our study were lower than those reported previously. Differences in bleeding rates may be explained by differences in institutional practice patterns, clinical situations, and bleeding definitions in each study. Furthermore, ticagrelor or prasugrel have increased bleeding risks compared with clopidogrel [4–6,11,15]. Herein, ticagrelor or prasugrel users had a higher in-hospital bleeding tendency than do clopidogrel users, which was mainly due to increased minor bleeding, not major bleeding. This higher bleeding risk due to new $P2Y_{12}$ inhibitors could be attributed to greater potency by relatively simple biotransformation courses [2,3]. Thus, clinicians should carefully predict, monitor, and manage bleeding risks of ACS patients who undergo PCI and are treated with new $P2Y_{12}$ inhibitors. Additionally, ticagrelor and prasugrel were reported to have similar bleeding frequencies [11,12,17]. The PRAGUE-18 trial showed that ticagrelor and prasugrel had equivalent bleeding rates [7,8]. We noted that ticagrelor and prasugrel had comparable in-hospital bleeding risks.

Studies have reported that patients who take new $P2Y_{12}$ inhibitors have a favorable prognosis compared with those who use clopidogrel [2–6,9,11,15]. In this study, in all ACS patients undergoing PCI, ticagrelor or prasugrel versus clopidogrel use was associated with improved efficacy end points, including MACEs and all-cause and cardiac death, any revascularization, and re-PCI. Thus, these agents could be the preferred choice to prevent future cardiovascular events. These new drugs are clinically beneficial as they are faster, stronger, and exert a more consistent platelet inhibitory effect due to their fewer in vivo transformation (ticagrelor), and only one hepatic CYP450 metabolism step (prasugrel) is involved in yielding the active metabolites compared to clopidogrel, which requires two hepatic CYP450 metabolism steps [2,3]. However, current studies on ticagrelor and prasugrel showed that patients taking these agents had comparable prognoses [11,12,15,16]. Although the PRAGUE-18 trial found that ticagrelor and prasugrel had similar efficacy

Table 2
Safety Endpoints According to Different Adjustment Methods.

Variable	Ticagrelor versus clopidogrel (referent to clopidogrel)	Prasugrel versus clopidogrel (referent to clopidogrel)	Ticagrelor versus prasugrel (referent to prasugrel)
	Adjusted OR (95% CI), p	Adjusted OR (95% CI), p	Adjusted OR (95% CI), p
Standard logistic regression analysis			
In-hospital bleeding	1.32 (1.08–1.61), 0.008	1.17 (1.02–1.89), 0.026	0.79 (0.56–1.59), 0.159
Major bleeding	1.21 (0.89–1.71), 0.237	1.11 (0.88–1.56), 0.348	0.56 (0.18–1.79), 0.315
Minor bleeding	1.21 (1.14–1.72), 0.007	1.16 (1.04–1.75), 0.016	0.78 (0.53–1.70), 0.341
Propensity score-matched analyses			
In-hospital bleeding	1.27 (1.01–1.54), 0.031	1.19 (1.01–1.68), 0.041	0.69 (0.22–2.05), 0.302
Major bleeding	1.16 (0.86–1.86), 0.711	1.09 (0.59–2.03), 0.218	0.52 (0.14–2.44), 0.269
Minor bleeding	1.21 (1.01–1.59), 0.039	1.18 (1.02–1.66), 0.043	0.76 (0.27–4.36), 0.581

CI, confidence interval; OR, odds ratio.

[7,8], an ongoing randomized trial (NCT01944800) is expected to elucidate this issue further. Herein, ticagrelor and prasugrel had equivalent efficacies. Although new $P2Y_{12}$ inhibitors had a different mechanism than that of other $P2Y_{12}$ receptors, the platelet inhibition levels were nearly similar [8].

Our nationwide finding reflects the new $P2Y_{12}$ inhibitors use in non-selected and real-world patients, rather than in a homogenous study population of randomized trials, and provides further information to guide the clinician in the choice of contemporary $P2Y_{12}$ inhibitors. To achieve a better net clinical benefit in ACS patients following PCI, updated, novel drug-based DAPT should be tailored to the individual patient's ischemic and bleeding risks. Particularly, this novel regimen should be used in those with a high thrombotic or low bleeding risk. Patients with decreased or no response to clopidogrel [2,3] could be prescribed new $P2Y_{12}$ inhibitors. However, in patients with a high bleeding risk, the new $P2Y_{12}$ inhibitors use should be avoided. Clopidogrel may be restricted to patients who are ineligible for treatment with new $P2Y_{12}$ inhibitors. However, in ACS patients who are prescribed new $P2Y_{12}$ inhibitors following PCI, the DAPT duration, dosage, and concurrent use of other agents and new-generation drug-eluting stents should be investigated to minimise these agents' risks and maximise their benefits.

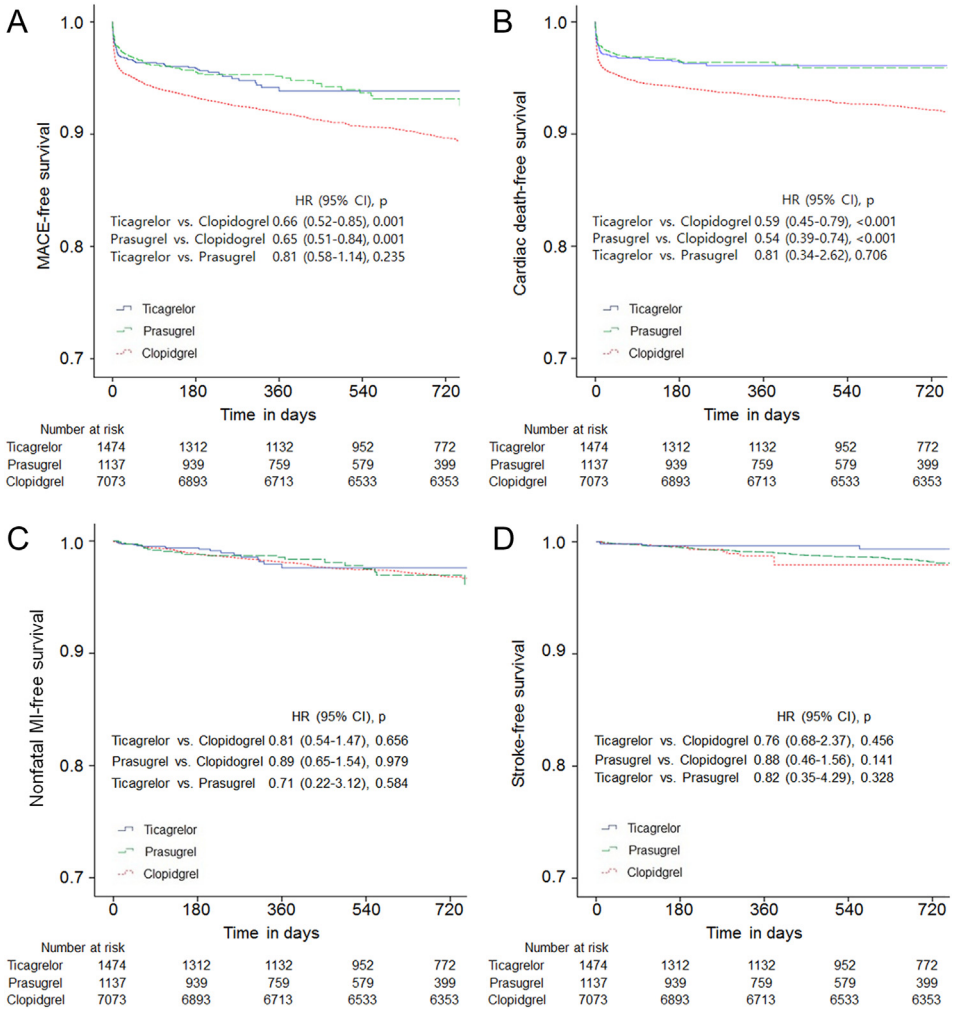

Fig. 1. Kaplan-Meier estimation of cumulative survival-free from MACEs (A), cardiac death (B), nonfatal MI (C), and stroke (D). CI, confidence interval; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction.

Table 3
Efficacy Endpoints According to Different Adjustment Methods.

Variable	Ticagrelor versus clopidogrel (referent to clopidogrel)	Prasugrel versus clopidogrel (referent to clopidogrel)	Ticagrelor versus prasugrel (referent to prasugrel)
	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p
Standard cox regression			
MACEs*	0.66 (0.52–0.85), 0.001	0.65 (0.51–0.84), 0.001	0.81 (0.58–1.14), 0.235
All-cause death	0.71 (0.43–0.89), 0.033	0.67 (0.49–0.83), 0.026	1.11 (0.38–4.19), 0.748
Cardiac death	0.59 (0.45–0.79), <0.001	0.54 (0.39–0.74), <0.001	0.81 (0.34–2.62), 0.706
Non-cardiac death	0.91 (0.61–1.38), 0.664	0.50 (0.29–0.85), 0.010	1.51 (0.35–5.27), 0.348
Nonfatal MI	0.81 (0.54–1.47), 0.656	0.89 (0.65–1.54), 0.979	0.71 (0.22–3.12), 0.084
Stroke	0.76 (0.68–2.37), 0.456	0.88 (0.46–1.56), 0.141	0.82 (0.35–4.29), 0.328
Any revascularization	0.81 (0.52–0.97), 0.023	0.85 (0.61–0.98), 0.035	0.79 (0.25–5.31), 0.569
Re-PCI	0.79 (0.53–0.89), 0.034	0.88 (0.52–0.95), 0.041	0.84 (0.41–5.58), 0.156
CABG	0.40 (0.10–1.68), 0.213	0.59 (0.18–1.93), 0.385	0.97 (0.12–1.29), 0.659
Propensity score-matched analyses			
MACEs*	0.68 (0.47–0.97), 0.025	0.55 (0.33–0.90), 0.017	0.39 (0.12–1.29), 0.123
All-cause death	0.61 (0.34–0.93), 0.032	0.53 (0.38–0.96), 0.041	1.02 (0.59–6.29), 0.759
Cardiac death	0.56 (0.35–0.91), 0.012	0.49 (0.23–0.83), 0.007	0.62 (0.05–1.30) 0.156
Non-cardiac death	0.89 (0.59–2.24), 0.247	0.93 (0.74–4.19), 0.422	1.11 (0.72–5.88), 0.649
Nonfatal MI	0.70 (0.34–1.43), 0.416	0.68 (0.32–1.46), 0.249	0.87 (0.05–8.31), 0.843
Stroke	0.61 (0.47–2.61), 0.219	0.38 (0.12–1.19), 0.157	0.78 (0.22–4.84), 0.469
Any revascularization	0.71 (0.42–1.61), 0.194	0.82 (0.48–2.03), 0.689	0.81 (0.35–6.92), 0.786
Re-PCI	0.82 (0.67–1.72), 0.258	0.98 (0.59–1.64), 0.428	0.76 (0.24–3.27), 0.512
CABG	0.19 (0.02–1.57), 0.648	0.50 (0.09–2.75), 0.785	0.92 (0.22–5.12), 0.611
Propensity score-adjusted analyses			
MACEs*	0.71 (0.48–0.99), 0.021	0.67 (0.38–0.95), 0.028	0.78 (0.26–1.48), 0.459
All-cause death	0.64 (0.41–0.95), 0.038	0.58 (0.41–0.99), 0.045	1.14 (0.68–5.75), 0.529
Cardiac death	0.61 (0.45–0.96), 0.024	0.59 (0.37–0.85), 0.012	0.81 (0.17–1.74) 0.428
Non-cardiac death	0.87 (0.61–2.14), 0.437	0.89 (0.71–3.87), 0.361	1.31 (0.63–4.98), 0.574
Nonfatal MI	0.72 (0.37–1.52), 0.326	0.65 (0.31–1.71), 0.443	0.78 (0.14–7.15), 0.637
Stroke	0.65 (0.45–2.24), 0.149	0.42 (0.21–1.56), 0.278	0.84 (0.42–3.97), 0.571
Any revascularization	0.75 (0.51–1.87), 0.254	0.79 (0.45–2.47), 0.592	0.76 (0.32–5.85), 0.613
Re-PCI	0.81 (0.72–1.89), 0.358	0.85 (0.54–1.72), 0.327	0.72 (0.32–3.48), 0.496
CABG	0.34 (0.14–1.78), 0.437	0.45 (0.13–2.86), 0.542	0.84 (0.28–4.72), 0.513

CI, confidence interval; HR, hazard ratio; MACEs, major adverse cardiac events; MI, myocardial infarction; Re-PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
* MACE included cardiac death, Nonfatal MI, or stroke.

4.1. Limitations

The nonrandomized nature of the registry data can possibly result in selection bias, despite the large nationwide, prospectively collected data set. Moreover, certain unmeasured variables could not be corrected for, but we performed multivariate adjustment and PS-matched and PS-adjusted analyses to adjust for potential confounding factors. To establish the practical advantages of newer $P2Y_{12}$ inhibitors, a randomized trial comparing ticagrelor, prasugrel, and clopidogrel with a larger number of participants and longer follow-up period is needed. We could not evaluate other side effects, except bleeding, in the KAMIR-NIH data set, which might affect the prescription pattern and outcomes. Furthermore, we could not evaluate the information on $P2Y_{12}$ inhibitor switching during the follow-up because the KAMIR-NIH data only provide information on $P2Y_{12}$ inhibitors upon admission and at discharge. Finally, we demonstrate the efficacy and safety of these new $P2Y_{12}$ inhibitors in Korean ACS patients undergoing PCI, which could limit our ability to generalize our results.

5. Conclusions

In this nationwide registry cohort of ACS patients who underwent PCI, ticagrelor or prasugrel use versus clopidogrel use was uncommon but was associated with improved ischemic events and a higher risk of bleeding. In addition, the equivalent clinical outcomes between ticagrelor and prasugrel use were noted. Thus, under proper periprocedural management regarding bleeding risk, the increased use of new $P2Y_{12}$ inhibitors could result in a better net clinical effect in ACS patients undergoing PCI.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.09.011.

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Conflict of interest

The authors declare no conflicts of interest.

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