ORIGINAL RESEARCH

Safety and Effectiveness of Contemporary $P2Y_{12}$ Inhibitors in an East Asian Population With Acute Coronary Syndrome: A Nationwide Population-Based Cohort Study

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***Background*—**Prior reports indicate that the effect of $P2Y_{12}$ inhibitors may be different in East Asian patients ("East Asian paradox"); therefore, understanding the outcomes associated with potent $P2Y_{12}$ inhibitors in different populations is clinically important.

***Methods and Results*—**In this observational cohort study using administrative healthcare data sets, we compared safety and effectiveness of contemporary $P2Y_{12}$ inhibitors in patients with acute coronary syndrome. The primary safety outcomes were major and any bleeding, and the primary effectiveness outcomes were major cardiovascular events (a composite of cardiovascular death, myocardial infarction, or stroke) and all-cause mortality. Among 70 715 patients with acute coronary syndrome, 56 216 (79.5%) used clopidogrel, 11 402 (16.1%) used ticagrelor, and 3097 (4.4%) used prasugrel. The median follow-up period was 18.0 months (interquartile range: 9.6–26.4 months). In a propensity-matched cohort, compared with clopidogrel, ticagrelor was associated with a higher risk of any bleeding (hazard ratio: 1.23; 95% CI, 1.14–1.33) but a lower risk of mortality (hazard ratio: 0.76; 95% CI, 0.63–0.91). Prasugrel, compared with clopidogrel, was associated with higher risks of any bleeding (hazard ratio: 1.23; 95% CI, 1.06–1.43) and major bleeding (hazard ratio: 1.50; 95% CI, 1.01–2.21) but a similar risk of effectiveness outcomes. No significant difference was noted between ticagrelor and prasugrel with respect to key safety or effectiveness outcomes. Several sensitivity analyses showed similar results.

***Conclusions*—**In East Asian patients with acute coronary syndrome, compared with clopidogrel, ticagrelor was associated with an increased risk of bleeding but a decreased risk of mortality. Prasugrel was associated with an increase of any bleeding without difference in effectiveness outcomes. The risks of bleeding and ischemic events were similar between ticagrelor and prasugrel.
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Key Words: acute coronary syndrome • antiplatelet agent • ethics

Dual-antiplatelet therapy involving aspirin and a $P2Y_{12}$ antagonist is the standard antithrombotic therapy in patients with acute coronary syndrome (ACS) and in those undergoing percutaneous coronary intervention (PCI).[1] Given greater and more consistent platelet inhibition and a documented clinical benefit of newer $P2Y_{12}$ antagonists (ticagrelor or prasugrel) over clopidogrel,[2,3] current European and US guidelines recommend that use of ticagrelor or prasugrel in preference to clopidogrel is reasonable for ACS patients with or without PCI.[4,5] However, compared with a Western population, a differential propensity for thromboembolic and bleeding risks in response to $P2Y_{12}$ inhibitors was reported in an East Asian population ("East Asian paradox").[6,7] Although East Asian ethnic groups are among the most populous (>1.5 billion people), few East Asian patients were included in the large, phase III,

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Clinical Perspective

What Is New?

- Some previous reports indicate that the effect of $P2Y_{12}$ inhibitors might be different in East Asian patients ("East Asian paradox"); therefore, understanding the outcomes associated with diverse $P2Y_{12}$ inhibitors in different populations is clinically important.
- This population-based study was the first with a specific focus on East Asian patients with acute coronary syndrome to investigate the comparative safety and effectiveness of different oral $P2Y_{12}$ inhibitors (clopidogrel, ticagrelor, and prasugrel).

What Are the Clinical Implications?

- Compared with clopidogrel, ticagrelor was associated with increased rates of bleeding, a significant reduction in mortality rate, and no decrease in the rate of major cardiovascular events.
- Compared with clopidogrel, prasugrel was associated with an increase in bleeding events but no differences in effectiveness outcomes.
- No significant differences were noted between ticagrelor and prasugrel with respect to the rate of any bleeding and ischemic events, and further randomized clinical trials are necessary to confirm the findings of this study regarding different levels of risk for bleeding and ischemic events among different $P2Y_{12}$ inhibitors.

randomized controlled trials (RCTs) of potent $P2Y_{12}$ antagonists for atherosclerotic cardiovascular disease.[2,3,8–11] Consequently, concerns exist regarding whether potent $P2Y_{12}$ inhibitors have acceptable safety and efficacy profiles in an East Asian population with differential ischemic and bleeding tendency.

Although an RCT setting with strict inclusion and exclusion criteria is required to obtain high-quality scientific evidence on the effects of antithrombotic drugs, well-conducted postapproval observational studies might complement the RCTs and provide additional clinical information in diverse groups of patients or in clinical circumstances encountered in daily practice. In this study, we sought to evaluate the relative safety and effectiveness of contemporary $P2Y_{12}$ inhibitors using a nationwide population-based cohort of Korean patients presenting with ACS.

Methods

Data Sources

Anonymized data and study materials have been made publicly available. The analytic methods have been made available within the article to other researchers for purposes of reproducing the results or replicating the procedure.

This study is based on data from nationwide administrative claims–based databases of the National Health Insurance Service (NHIS), which is the universal health coverage system in South Korea. All residents must be enrolled in the NHIS either as an National Health Insurance beneficiary or a Medical Aid recipient. Consequently, these data sets can enable unrestricted collection of large ACS cohorts with information about medical visits and prescriptions and no specific inclusion or exclusion criteria apart from the beneficiary status, minimizing selection bias. The NHIS databases maintain comprehensive healthcare data sets for diagnoses, treatments, procedures, surgeries, prescriptions, hospital admissions, and discharge records of all insured patients who are reimbursed by the government according to the National Health Insurance Act.[12] The prescription claims data identify dispensed prescriptions, including medications, date filled, days supplied, number of pills, and dosage. Medical claims include diagnostic and procedure information coded in accordance with the *International Classification of Diseases, Tenth Revision* (*ICD-10*) for inpatient and outpatient encounters. Based on these data sets, we collected information on demographics, clinical covariates, all diagnostic and procedure information, study drugs, and concomitant cardioactive medications (for details, see Table S1). We also collected the available self-reported medical history, smoking status, and general laboratory variables from the general health examination data, which were provided periodically by NHIS to all insured persons.[13] The NHIS databases were validated in prior antithrombotic studies.[14,15]

Study Population

We constructed a study cohort of adult patients who presented with ACS (ie, unstable angina or acute myocardial infarction [MI]) who had newly initiated $P2Y_{12}$ inhibitors between January 1, 2013, and November 30, 2015 (Figure 1). A new-user cohort design was used to compare patients who were prescribed clopidogrel, ticagrelor, or prasugrel as the initial treatment for ACS. Exclusion criteria were as follows: (1) prior use of any $P2Y_{12}$ inhibitor in the 12 months preceding the index date, (2) concomitant use of anticoagulants, (3) receipt of fibrinolytic therapy, (4) history of any cancer before the index date, (5) cardiogenic shock, (6) no hospital admission for a principal diagnosis of ACS, and (7) use of antiplatelet drugs <30 days. We also excluded users of dual $P2Y_{12}$ inhibitors. This study was approved by the institutional review board of the National Evidence-Based Healthcare Collaborating Agency (no. NECAIRB16-009-2), and informed consent was waived.

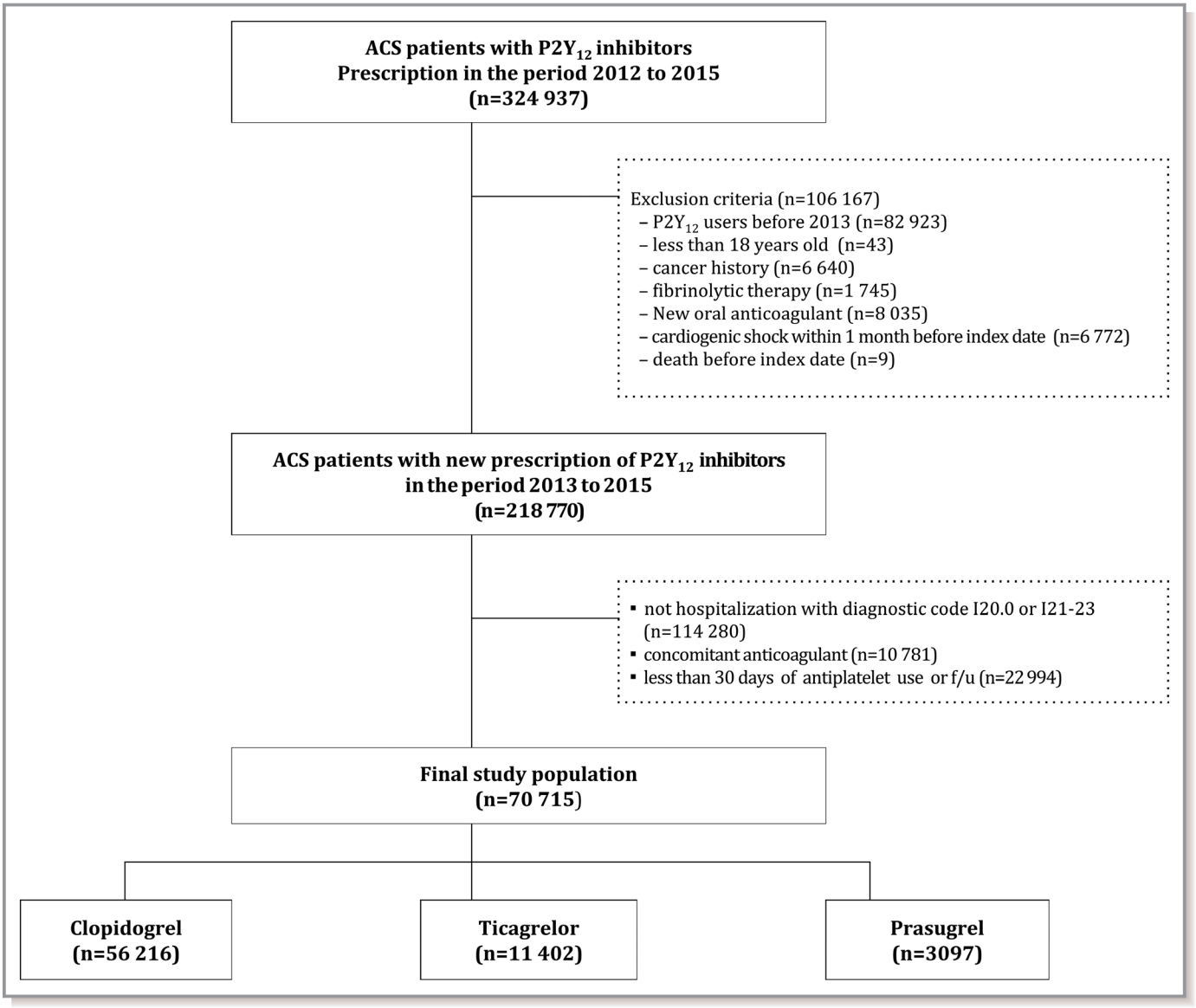

Figure 1. Flowchart of the study population. ACS indicates acute coronary syndrome; f/u, follow-up.

In Korea, the recommended dose of $P2Y_{12}$ inhibitors for the management of ACS was identical for standard-dose labeling: clopidogrel at 300- to 600-mg loading dose, 75-mg daily maintenance dose; ticagrelor at 180-mg loading dose, 90-mg twice maintenance dose; and prasugrel at a 60-mg loading dose, 10-mg daily maintenance dose.

Outcomes and Definition

The primary safety outcomes were any bleeding and major bleeding. Bleeding events were also assessed according to the site of the bleeding source. The primary effectiveness outcomes were major cardiovascular events and all-cause mortality. Detailed definitions of the safety and effectiveness outcomes on the basis of *ICD-10* codes are summarized in Table S2.

Major bleeding was defined as a fatal bleeding event, bleeding necessitating hospitalization, or bleeding that occurred in the critical sites (intracranial, intraspinal, intra-articular, intraocular, pericardial, retroperitoneal, or intramuscular with compartment syndrome).[16] *Any bleeding* included intracranial bleeding, gastrointestinal bleeding, urogenital bleeding, respiratory bleeding (hemoptysis), nasal bleeding, intraocular bleeding, intra-articular or intramuscular bleeding, and other types of bleeding. *Major cardiovascular events* were defined as the composite of cardiovascular death, MI, or stroke. Death certificate linkage data were provided by the Korean National Statistical Office. According to the *ICD-10* codes for primary cause of death, mortality was categorized into cardiovascular disease (disease of the circulatory system: I00–I99; sudden death: R96) and other (non–cardiovascular disease) causes (all other *ICD-10* codes).

Table 1. Baseline Characteristics Before and After Propensity-Score Matching Among Patients With Ticagrelor and Clopidogrel Use

Characteristic	Before Matching			After Matching		
	Ticagrelor (n=11 402)	Clopidogrel (n=56 216)	Standardized Difference (%)	Ticagrelor (n=11 402)	Clopidogrel (n=11 402)	Standardized Difference (%)
Age						
Mean, y	60.9 (12.1)	65.4 (12.1)	37.6	60.9 (12.1)	60.8 (12.1)	0.5
≥75 y	1741 (15.3)	14 404 (25.6)	25.9	1741 (15.3)	1741 (15.3)	0.0
Sex						
Male	8876 (77.9)	36 770 (65.4)	27.9	8876 (77.9)	8963 (78.6)	1.8
Female	2526 (22.1)	19 446 (34.6)	28.0	2526 (22.1)	2439 (21.4)	1.7
Socioeconomic status						
Low tertile	3623 (31.8)	18 287 (32.5)	1.6	3623 (31.8)	3703 (32.5)	1.5
Middle tertile	3995 (35.0)	18 165 (32.3)	5.8	3995 (35.0)	3907 (34.3)	1.6
High tertile	3784 (33.2)	19 764 (35.2)	4.2	3784 (33.2)	3792 (33.3)	0.1
Body mass index*						
Mean	24.8 (2.7)	24.52 (2.7)	9.2	24.8 (2.7)	24.8 (2.7)	1.5
<20.0	392 (3.4)	2444 (4.4)	4.7	392 (3.4)	379 (3.3)	0.7
20.0 to <22.5	1458 (12.8)	7725 (13.7)	2.8	1458 (12.8)	1385 (12.2)	1.9
22.5 to <25.0	4275 (37.5)	23 719 (42.2)	9.6	4275 (37.5)	4211 (36.9)	1.2
25.0 to <27.5	3759 (33.0)	15 550 (27.7)	11.6	3759 (33.0)	3905 (34.3)	2.7
27.5 to <30.0	1053 (9.2)	4759 (8.5)	2.7	1053 (9.2)	1038 (9.1)	0.5
≥30.0	465 (4.1)	2019 (3.6)	2.6	465 (4.1)	484 (4.2)	0.8
Hypertension	5267 (46.2)	33 565 (59.7)	27.3	5267 (46.2)	5233 (45.9)	0.6
Dyslipidemia	1487 (13.0)	10 540 (18.8)	15.7	1487 (13.0)	1459 (12.8)	0.7
Current smoking	3323 (29.1)	11 425 (20.3)	20.6	3323 (29.1)	3311 (29.0)	0.2
Diabetes mellitus						
Any	4214 (37.0)	26 515 (47.2)	20.8	4214 (37.0)	4203 (36.9)	0.2
Requiring insulin	66 (0.6)	582 (1.0)	5.1	66 (0.6)	78 (0.7)	1.3
Prior MI	379 (3.3)	2576 (4.6)	6.5	379 (3.3)	383 (3.4)	0.2
Prior PCI	45 (0.4)	481 (0.9)	6.0	45 (0.4)	51 (0.5)	0.9
Prior CABG	1 (0.0)	7 (0.0)	0.0	1 (0.0)	0 (0.0)	1.4
Prior CHF	58 (0.5)	812 (1.4)	9.5	58 (0.5)	79 (0.7)	2.3
Prior stroke	127 (1.1)	1285 (2.3)	9.1	127 (1.1)	113 (1.0)	1.2
PVD	1479 (13.0)	9972 (17.7)	13.3	1479 (13.0)	1373 (12.0)	2.8
Chronic renal failure	273 (2.4)	2728 (4.9)	13.2	273 (2.4)	270 (2.4)	0.1
Chronic lung disease	627 (5.5)	4892 (8.7)	12.5	627 (5.5)	675 (5.9)	1.8
Charlson comorbidity index						
Mean (±SD)	2 (2.1)	2.8 (2.5)	33.9	2 (2.1)	2 (2.1)	1.4
0	3420 (30.0)	10 440 (18.6)	26.9	3420 (30.0)	3465 (30.4)	0.9
1–2	4273 (37.5)	19 678 (35.0)	5.2	4273 (37.5)	4324 (37.9)	0.9
≥3	3709 (32.5)	26 098 (46.4)	28.7	3709 (32.5)	3613 (31.7)	1.8
Clinical presentation						
Unstable angina	2306 (20.2)	28 893 (51.4)	68.8	2306 (20.2)	2315 (20.3)	0.2
Acute MI	9096 (79.8)	27 323 (48.6)	68.8	9096 (79.8)	9087 (79.7)	0.2

Continued

Table 1. Continued

Characteristic	Before Matching			After Matching		
	Ticagrelor (n=11 402)	Clopidogrel (n=56 216)	Standardized Difference (%)	Ticagrelor (n=11 402)	Clopidogrel (n=11 402)	Standardized Difference (%)
Index treatment						
PCI	10 938 (95.9)	48 291 (85.9)	35.4	10 938 (95.9)	10 941 (96.0)	0.2
CABG	128 (1.1)	1648 (2.9)	12.9	128 (1.1)	132 (1.2)	0.4
Medical therapy	336 (3.0)	6277 (11.2)	32.5	336 (3.0)	329 (2.9)	0.4
Concomitant mediations at index hospitalization						
Aspirin	11 368 (99.7)	55 347 (98.5)	13.1	11 368 (99.7)	11 366 (99.7)	0.4
Statins	11 225 (98.5)	52 767 (93.9)	24.0	11 225 (98.5)	11 212 (98.3)	1.0
β-Blockers	9544 (83.7)	41 440 (73.7)	24.6	9544 (83.7)	9559 (83.8)	0.4
Calcium-channel blockers	4052 (35.5)	27 155 (48.3)	26.1	4052 (35.5)	4104 (36.0)	0.9
ACEIs or ARBs	8543 (74.9)	40 429 (71.9)	6.8	8543 (74.9)	8596 (75.4)	1.1
Diuretics	2215 (19.4)	13 725 (24.4)	12.1	2215 (19.4)	2237 (19.6)	0.5

Data are mean (SD) or number (percentage). The standardized differences are reported as percentages; a difference of <10.0% indicates a relatively small imbalance. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
*Weight in kilograms divided by the square of the height in meters.

Statistical Analysis

Given the differences in the baseline characteristics among eligible participants in the treatment groups, propensity-score matching was used to identify a cohort of patients with similar baseline characteristics.[17] In each cohort for comparison, the propensity score was estimated using a nonparsimonious logistic regression model,[18] with the treatment group of $P2Y_{12}$ inhibitors as the dependent variable and all the baseline characteristics outlined in Table 1 as covariates. Propensity-score matching was performed using bootstrapping with 1:1 nearest neighbor matching without replacement (caliper distance of 0.2 SD of the pooled propensity scores) to identify matched cohorts representing the 2 treatment groups. Covariate balance was evaluated using standardized differences of means, and standardized differences of <10.0% for a given covariate indicate a relatively small imbalance.[19]

In the matched cohort, paired comparisons were performed with the use of the McNemar test for binary variables and a paired Student *t* test or paired-sample test for continuous variables. The comparative risks of safety and effectiveness outcomes were compared using Cox proportional hazards regression models with robust standard errors that accounted for the clustering of matched pairs. Kaplan–Meier survival curves were estimated in each matched cohort of $P2Y_{12}$ inhibitors, and the survival curves were compared according to methods appropriate for matched data.[20] All analyses for outcomes were truncated at 2 years of follow-up, owing to the different follow-up durations according to type of $P2Y_{12}$ inhibitor and the small number of patients with data thereafter.

Several sensitivity analyses were performed considering that drug switching occurred over time. Adherence to $P2Y_{12}$ inhibitors was shown at 3, 6, 9, 12, 18, and 24 months (Table S3). Drug exposure was considered as a time-dependent variable. These same time points were used in the time-dependent variable analysis of the Cox model. Several supplementary analyses were also performed to confirm the risk of safety and effectiveness outcomes in the various groups: (1) patients including a population with <30 days use of $P2Y_{12}$ inhibitors; (2) ST-segment–elevation MI patients; (3) patients according to initial presentation (acute MI versus unstable angina cohort); and (4) healthy PCI cohort (body weight ≥60 kg, <75 years old, and no history of stroke or transient ischemic attack). We conducted many sensitivity and subgroup analyses. The hazard ratios (HRs) were adjusted for propensity score in the each propensity-score–matched cohort. In case of stratified analysis according to initial presentation, HRs used all data and were adjusted for covariates directly in the Cox model.

This observational data analysis used administrative claims–based data sets. To carefully define the population of interest and to minimize the data-dredging processes, we prespecified study objectives, a hypothesis, and a statistical approach using a statistical analysis plan.[21] All reported *P* values are 2-sided, and those <0.05 were considered statistically significant. For all statistical analyses, SAS v9.3 (SAS Institute) was used.

Table 2. Baseline Characteristics Before and After Propensity-Score Matching Among Patients With Prasugrel and Clopidogrel Use

Characteristic	Before Matching			After Matching		
	Prasugrel (n=3097)	Clopidogrel (n=56 216)	Standardized Difference (%)	Prasugrel (n=3097)	Clopidogrel (n=3097)	Standardized Difference (%)
Age						
Mean, y	55.9 (9.5)	65.4 (12.1)	88.1	55.9 (9.5)	55.9 (9.4)	0.2
≥75 y	55 (1.8)	14 404 (25.6)	73.9	55 (1.8)	55 (1.8)	0.0
Sex						
Male	2767 (89.3)	36 770 (65.4)	59.7	2767 (89.3)	2772 (89.5)	0.6
Female	330 (10.7)	19 446 (34.6)	59.7	330 (10.7)	325 (10.5)	0.6
Socioeconomic status						
Low tertile	962 (31.1)	18 287 (32.5)	3.2	962 (31.1)	933 (30.1)	2.0
Middle tertile	1143 (36.9)	18 165 (32.3)	9.7	1143 (36.9)	1200 (38.8)	3.8
High tertile	992 (32.0)	19 764 (35.2)	6.6	992 (32.0)	964 (31.1)	1.9
Body mass index*						
Mean	25.3 (2.7)	24.52 (2.7)	30.1	25.3 (2.7)	25.3 (2.6)	3.0
<20.0	52 (1.7)	2444 (4.4)	15.7	52 (1.7)	52 (1.7)	0.0
20.0 to <22.5	282 (9.1)	7725 (13.7)	14.6	282 (9.1)	262 (8.5)	2.3
22.5 to <25.0	962 (31.1)	23 719 (42.2)	23.3	962 (31.1)	1008 (32.6)	3.2
25.0 to <27.5	1313 (42.4)	15 550 (27.7)	31.3	1313 (42.4)	1314 (42.4)	0.1
27.5 to <30.0	313 (10.1)	4759 (8.5)	5.7	313 (10.1)	288 (9.3)	2.7
≥30.0	175 (5.7)	2019 (3.6)	9.8	175 (5.7)	173 (5.6)	0.3
Hypertension	1185 (38.3)	33 565 (59.7)	43.9	1185 (38.3)	1157 (37.4)	1.9
Dyslipidemia	370 (12.0)	10 540 (18.8)	18.9	370 (12.0)	359 (11.6)	1.1
Current smoking	1027 (33.2)	11 425 (20.3)	29.3	1027 (33.2)	1031 (33.3)	0.3
Diabetes mellitus						
Any	964 (31.1)	26 515 (47.2)	33.3	964 (31.1)	935 (30.2)	2.0
Requiring insulin	17 (0.6)	582 (1.0)	5.5	17 (0.6)	16 (0.5)	0.4
Prior MI	99 (3.2)	2576 (4.6)	7.1	99 (3.2)	96 (3.1)	0.6
Prior PCI	11 (0.4)	481 (0.9)	6.4	11 (0.4)	14 (0.5)	1.4
Prior CABG	1 (0.0)	7 (0.0)	1.4	1 (0.0)	1 (0.0)	0.0
Prior CHF	8 (0.3)	812 (1.4)	12.9	8 (0.3)	12 (0.4)	2.3
Prior stroke	20 (0.7)	1285 (2.3)	13.7	20 (0.7)	13 (0.4)	3.2
PVD	306 (9.9)	9972 (17.7)	22.9	306 (9.9)	282 (9.1)	2.6
Chronic renal failure	43 (1.4)	2728 (4.9)	20.0	43 (1.4)	39 (1.3)	1.1
Chronic lung disease	125 (4.0)	4892 (8.7)	19.2	125 (4.0)	133 (4.3)	1.3
Charlson comorbidity index						
Mean (±SD)	1.7 (1.9)	2.8 (2.5)	50.4	1.7 (1.9)	1.6 (1.9)	4.8
0	1044 (33.7)	10 440 (18.6)	35.0	1044 (33.7)	1134 (36.6)	6.1
1–2	1225 (39.6)	19 678 (35.0)	9.4	1225 (39.6)	1206 (38.9)	1.2
≥3	828 (26.7)	26 098 (46.4)	41.7	828 (26.7)	757 (24.4)	5.3
Clinical presentation						
Unstable angina	734 (23.7)	28 893 (51.4)	59.7	734 (23.7)	734 (23.7)	0.0
Acute MI	2363 (76.3)	27 323 (48.6)	59.7	2363 (76.3)	2363 (76.3)	0.0

Continued

Table 2. Continued

Characteristic	Before Matching			After Matching		
	Prasugrel (n=3097)	Clopidogrel (n=56 216)	Standardized Difference (%)	Prasugrel (n=3097)	Clopidogrel (n=3097)	Standardized Difference (%)
Index treatment						
PCI	3033 (97.9)	48 291 (85.9)	45.2	3033 (97.9)	3041 (98.2)	1.9
CABG	18 (0.6)	1648 (2.9)	18.0	18 (0.6)	16 (0.5)	0.8
Medical therapy	46 (1.5)	6277 (11.2)	40.6	46 (1.5)	40 (1.3)	1.7
Concomitant mediations at index hospitalization						
Aspirin	3083 (99.6)	55 347 (98.5)	11.1	3083 (99.6)	3082 (99.5)	0.4
Statins	3043 (98.3)	52 767 (93.9)	22.8	3043 (98.3)	3049 (98.5)	1.5
β-Blockers	2521 (81.4)	41 440 (73.7)	18.5	2521 (81.4)	2538 (82.0)	1.4
Calcium-channel blockers	1034 (33.4)	27 155 (48.3)	30.7	1034 (33.4)	1015 (32.8)	1.3
ACEIs or ARBs	2334 (75.4)	40 429 (71.9)	7.8	2334 (75.4)	2347 (75.8)	1.0
Diuretics	495 (16.0)	13 725 (24.4)	21.1	495 (16.0)	490 (15.8)	0.4

Data are mean (SD) or number (percentage). The standardized differences are reported as percentages; a difference of <10.0% indicates a relatively small imbalance. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
*Weight in kilograms divided by the square of the height in meters.

Results

Study Population and Patient Characteristics

In the initial cohort of 324 937 patients with a diagnosis of ACS who were prescribed $P2Y_{12}$ inhibitors, we identified 218 770 incident users of $P2Y_{12}$ inhibitors. Among them, a total of 70 715 patients requiring hospitalization with a principal diagnosis of ACS met the study inclusion criteria and none of the exclusion criteria (Figure 1). Of these, 56 216 (79.5%) received clopidogrel, 11 402 (16.1%) received ticagrelor, and 3097 (4.4%) received prasugrel. In the study period, clopidogrel use steadily decreased, but ticagrelor use rapidly increased over time, and prasugrel use was consistently low at <5% (Figure S1). Before propensity-score matching, there were between-group differences regarding several of the baseline variables in each cohort for comparisons (Tables 1 through 3). Prematched data showed that users of potent $P2Y_{12}$ inhibitors (ticagrelor or prasugrel) were generally younger, were predominantly male, had higher body mass index, and had fewer comorbidities than users of clopidogrel. After propensity-score matching was completed, there were 11 402 matched pairs for ticagrelor versus clopidogrel, 3097 matched pairs for prasugrel versus clopidogrel, and 3095 matched pairs for ticagrelor versus prasugrel. After matching, the standardized differences were <10.0% for most of variables, indicating only small differences between the 2 groups (Tables 1 through 3).

Comparative Safety and Effectiveness Outcomes

The median follow-up period was 17.5 months (interquartile range: 9.0–26.2 months). During the follow-up period, adherence to the index $P2Y_{12}$ regimen was shown in Table S3. Absolute event rates at 2 years were shown in Table S4. In a propensity-matched cohort, compared with clopidogrel, ticagrelor use was associated with a higher risk of any bleeding (HR: 1.23; 95% CI, 1.14–1.33; $P<0.001$; Table 4 and Figure 2). With respect to effectiveness outcomes, ticagrelor was associated with a similar risk of major cardiovascular events (HR: 1.00; 95% CI, 0.92–1.09; $P=0.96$) but a lower risk of all-cause mortality (HR: 0.76; 95% CI, 0.63–0.91; $P=0.002$). With regard to each component of major cardiovascular events, compared with clopidogrel, ticagrelor was significantly associated with a lower risk of cardiovascular death or stroke, but the risk of MI was similar. In a matched cohort of prasugrel versus clopidogrel, prasugrel was associated with a higher risk of any bleeding (HR: 1.23; 95% CI, 1.06–1.43; $P=0.01$) and major bleeding (HR: 1.50; 95% CI, 1.01–2.21; $P=0.04$), but there was no statistically significant difference in effectiveness outcomes (Table 5 and Figure 3). In a matched cohort of ticagrelor versus prasugrel, there was no statistically significant between-group difference with respect to safety or effectiveness outcomes except nasal bleeding (Table 6 and Figure 4).

Table 3. Baseline Characteristics Before and After Propensity-Score Matching Among Patients With Ticagrelor and Prasugrel Use*

Characteristic	Before Matching			After Matching		
	Ticagrelor (n=11 402)	Prasugrel (n=3097)	Standardized Difference (%)	Ticagrelor (n=3095)	Prasugrel (n=3095)	Standardized Difference (%)
Age						
Mean, y	60.9 (12.1)	55.9 (9.5)	46.2	55.9 (9.4)	55.9 (9.5)	0.1
≥75 y	1741 (15.3)	55 (1.8)	49.8	55 (1.8)	55 (1.8)	0.0
Sex						
Male	8876 (77.9)	2767 (89.3)	31.4	2766 (89.4)	2765 (89.3)	0.1
Female	2526 (22.2)	330 (10.7)	31.4	329 (10.6)	330 (10.7)	0.1
Socioeconomic status						
Low tertile	3623 (31.8)	962 (31.1)	1.6	919 (29.7)	961 (31.1)	3.0
Middle tertile	3995 (35.0)	1143 (36.9)	3.9	1191 (38.5)	1143 (36.9)	3.2
High tertile	3784 (33.2)	992 (32.0)	2.5	985 (31.8)	991 (32.0)	0.4
Body mass index†						
Mean	24.8 (2.7)	25.3 (2.7)	20.9	25.3 (2.6)	25.3 (2.7)	0.8
<20.0	392 (3.4)	52 (1.7)	11.2	41 (1.3)	52 (1.7)	3.0
20.0 to <22.5	1458 (12.8)	282 (9.1)	11.8	285 (9.2)	282 (9.1)	0.3
22.5 to <25.0	4275 (37.5)	962 (31.1)	13.6	946 (30.6)	962 (31.1)	1.1
25.0 to <27.5	3759 (33.0)	1313 (42.4)	19.6	1334 (43.1)	1311 (42.4)	1.5
27.5 to <30.0	1053 (9.2)	313 (10.1)	2.9	324 (10.5)	313 (10.1)	1.2
≥30.0	465 (4.1)	175 (5.7)	7.3	165 (5.3)	175 (5.7)	1.4
Hypertension	5267 (46.2)	1185 (38.3)	16.1	1181 (38.2)	1184 (38.3)	0.2
Dyslipidemia	1487 (13.0)	370 (12.0)	3.3	367 (11.9)	370 (12.0)	0.3
Current smoking	3323 (29.1)	1027 (33.2)	8.7	1025 (33.1)	1027 (33.2)	0.1
Diabetes mellitus						
Any	4214 (37.0)	964 (31.1)	12.3	963 (31.1)	964 (31.2)	0.1
Requiring insulin	66 (0.6)	17 (0.6)	0.4	5 (0.2)	17 (0.6)	6.6
Prior MI	379 (3.3)	99 (3.2)	0.7	117 (3.8)	99 (3.2)	3.2
Prior PCI	45 (0.4)	11 (0.4)	0.5	9 (0.3)	11 (0.4)	1.2
Prior CABG	1 (0.0)	1 (0.0)	1.4	0 (0.0)	1 (0.0)	2.4
Prior CHF	58 (0.5)	8 (0.3)	4.0	6 (0.2)	8 (0.3)	1.5
Prior stroke	127 (1.1)	20 (0.7)	4.9	18 (0.6)	20 (0.7)	0.9
PVD	1479 (13.0)	306 (9.9)	9.7	322 (10.4)	306 (9.9)	1.7
Chronic renal failure	273 (2.4)	43 (1.4)	7.3	31 (1.0)	43 (1.4)	3.6
Chronic lung disease	627 (5.5)	125 (4.0)	6.9	124 (4.0)	125 (4.0)	0.2
Charlson comorbidity index						
Mean (±SD)	2 (2.1)	1.7 (1.9)	16.0	1.7 (1.9)	1.7 (1.9)	0.0
0	3420 (30.0)	1044 (33.7)	8.0	1080 (34.9)	1044 (33.7)	2.4
1–2	4273 (37.5)	1225 (39.6)	4.3	1170 (37.8)	1223 (39.5)	3.5
≥3	3709 (32.5)	828 (26.7)	12.7	845 (27.3)	828 (26.8)	1.2
Clinical presentation						
Unstable angina	2306 (20.2)	734 (23.7)	8.4	709 (22.9)	734 (23.7)	1.9
Acute MI	9096 (79.8)	2363 (76.3)	8.4	2386 (77.1)	2361 (76.3)	1.9
Index treatment						
PCI	10 938 (95.9)	3033 (97.9)	11.6	3033 (98.0)	3031 (97.9)	0.5
CABG	128 (1.1)	18 (0.6)	5.9	18 (0.6)	18 (0.6)	0.0
Medical therapy	336 (3.0)	46 (1.5)	9.9	44 (1.4)	46 (1.5)	0.6

Continued

Table 3. Continued

Characteristic	Before Matching			After Matching		
	Ticagrelor (n=11 402)	Prasugrel (n=3097)	Standardized Difference (%)	Ticagrelor (n=3095)	Prasugrel (n=3095)	Standardized Difference (%)
Concomitant mediations at index hospitalization						
Aspirin	11 368 (99.7)	3083 (99.6)	2.5	3086 (99.7)	3082 (99.6)	2.2
Statins	11 225 (98.5)	3043 (98.3)	1.5	3053 (98.6)	3042 (98.3)	2.8
β-Blockers	9544 (83.7)	2521 (81.4)	6.1	2522 (81.5)	2520 (81.4)	0.2
Calcium-channel blockers	4052 (35.5)	1034 (33.4)	4.5	1044 (33.7)	1032 (33.3)	0.8
ACEIs or ARBs	8543 (74.9)	2334 (75.4)	1.0	2311 (74.7)	2332 (75.4)	1.6
Diuretics	2215 (19.4)	495 (16.0)	9.0	515 (16.6)	495 (16.0)	1.8

Data are mean (SD) or number (percentage). The standardized differences are reported as percentages; a difference of <10.0% indicates a relatively small imbalance. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CABG, coronary artery bypass grafting; CHF, congestive heart failure; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.
[†]Weight in kilograms divided by the square of the height in meters.

Sensitivity and Subgroup Analyses

Results of the sensitivity analyses with P2Y$_{12}$ inhibitors exposures as a time-varying covariate were similar to those of the overall analysis (Table S5). We performed additional analyses including a population with <30 days' use of P2Y$_{12}$ inhibitors (Tables S6 and S7). As a result, risks in safety and effectiveness outcomes were similar for the main results. We

Table 4. Risk of Safety and Effectiveness Outcomes in the Propensity-Score–Matched Cohort of Ticagrelor and Clopidogrel*

Outcomes	Outcome Rate at 2 Years (%)[†]		HR (95% CI)[‡]	*P* Value
	Ticagrelor (n=11 402)	Clopidogrel (n=11 402)		
Safety outcomes				
Any bleeding	18.1	15.1	1.23 (1.14–1.33)	<0.001
Major bleeding	3.1	2.5	1.18 (0.98–1.43)	0.07
Site of bleeding events				
Intracranial bleeding	0.8	1.0	0.85 (0.61–1.18)	0.33
Gastrointestinal bleeding	6.1	5.3	1.10 (0.96–1.26)	0.15
Urogenital bleeding	2.3	2.1	1.12 (0.89–1.39)	0.33
Respiratory bleeding	1.0	0.8	1.29 (0.93–1.78)	0.13
Nasal bleeding	4.4	2.8	1.73 (1.47–2.04)	<0.001
Intraocular bleeding	5.0	4.4	1.18 (1.01–1.36)	0.03
Other bleeding	0.5	0.5	1.21 (0.78–1.86)	0.40
Transfusion	1.8	1.5	1.22 (0.96–1.56)	0.10
Effectiveness outcomes				
Major cardiovascular events[§]	13.1	13.0	1.00 (0.92–1.09)	0.96
Death from cardiovascular causes	1.0	1.7	0.62 (0.47–0.82)	0.001
MI	10.6	10.0	1.07 (0.97–1.18)	0.20
Stroke	2.1	2.5	0.82 (0.66–1.00)	0.05
All-cause mortality	3.1	3.9	0.76 (0.63–0.91)	0.002

HR indicates hazard ratio; MI, myocardial infarction.
*The propensity-score–matched cohort included 11 402 patients in the ticagrelor user group and 11 402 patients in the clopidogrel user group.
[†]Outcome rates were derived from paired Kaplan–Meier curves.
[‡]HRs are for ticagrelor compared with clopidogrel.
[§]Major cardiovascular events were defined as a composite of death from cardiovascular causes, MI, or stroke.

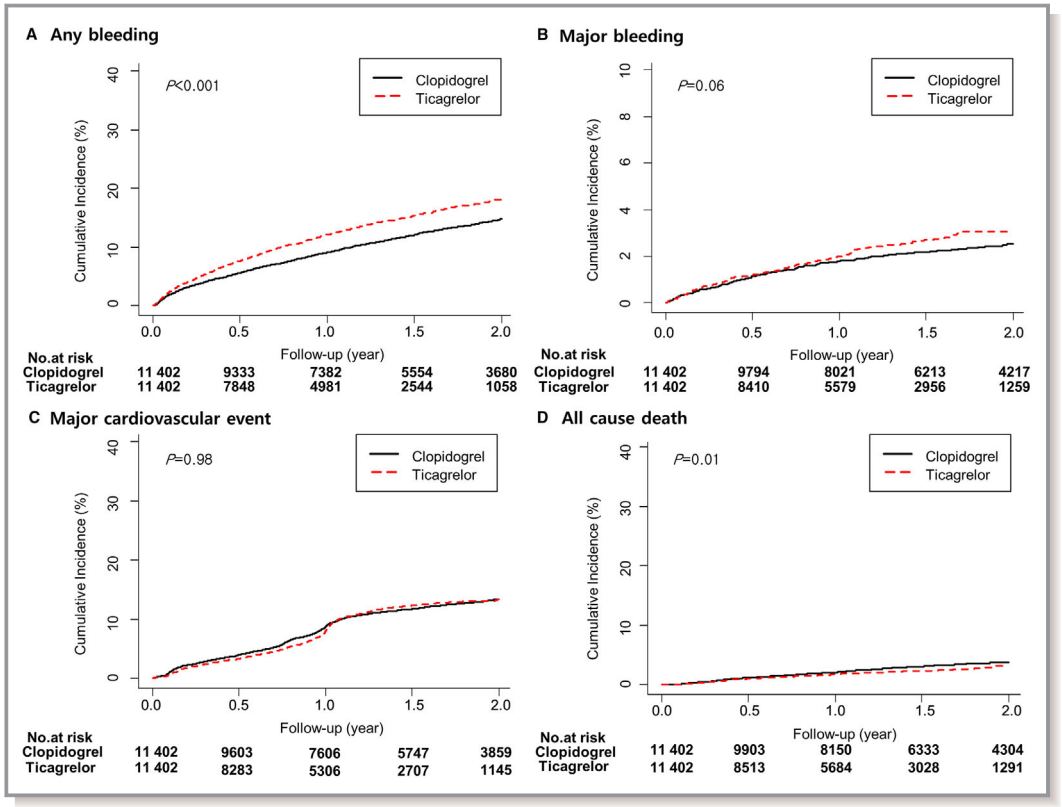

Figure 2. Cumulative risks of the study outcomes in the matched cohort of ticagrelor and clopidogrel. Cumulative incidence curves are shown for any bleeding (**A**), major bleeding (**B**), major cardiovascular events (**C**), and all-cause mortality (**D**).

conducted focused analysis of ST-segment–elevation MI patients, which ensured a more homogeneous patient group for comparison (Table S8). In the ST-segment–elevation MI cohort, compared with clopidogrel, ticagrelor and prasugrel were associated with higher risk of bleeding. Compared with prasugrel, ticagrelor was associated with lower risk of major

Table 5. Risk of Safety and Effectiveness Outcomes in the Propensity-Score–Matched Cohort of Prasugrel and Clopidogrel*

Outcomes	Outcome Rate at 2 Years (%)†		HR (95% CI)‡	*P* Value
	Prasugrel (n=3097)	Clopidogrel (n=3097)		
Safety outcomes				
Any bleeding	14.8	12.5	1.23 (1.06–1.43)	0.01
Major bleeding	2.6	1.8	1.50 (1.01–2.21)	0.04
Site of bleeding events				
Intracranial bleeding	0.8	0.5	1.21 (0.59–2.49)	0.60
Gastrointestinal bleeding	5.2	3.9	1.33 (1.02–1.73)	0.03
Urogenital bleeding	1.8	1.6	1.13 (0.73–1.75)	0.58
Respiratory bleeding	0.6	0.5	1.48 (0.71–3.10)	0.30
Nasal bleeding	4.0	2.3	1.88 (1.36–2.60)	<0.001
Intraocular bleeding	4.0	4.1	0.95 (0.71–1.26)	0.72

Continued

Table 5. Continued

Outcomes	Outcome Rate at 2 Years (%)†		HR (95% CI)‡	*P* Value
	Prasugrel (n=3097)	Clopidogrel (n=3097)		
Other bleeding	0.3	0.2	1.88 (0.63–5.61)	0.26
Transfusion	1.5	1.0	1.60 (0.96–2.64)	0.07
Effectiveness outcomes				
Major cardiovascular events§	10.3	11.4	0.88 (0.74–1.05)	0.17
Death from cardiovascular causes	0.6	0.9	0.66 (0.35–1.26)	0.21
Myocardial infarction	9.0	9.8	0.91 (0.75–1.10)	0.32
Stroke	1.3	1.3	0.95 (0.58–1.57)	0.85
All-cause mortality	1.6	1.9	0.78 (0.50–1.22)	0.28

HR indicates hazard ratio; MI, myocardial infarction.
*The propensity-score–matched cohort included 3097 patients in the prasugrel user group and 3097 patients in the clopidogrel user group.
†Outcome rates were derived from paired Kaplan–Meier curves.
‡HRs are for prasugrel compared with clopidogrel.
§Major cardiovascular events were defined as a composite of death from cardiovascular causes, MI, or stroke.

bleeding. With respect to effectiveness outcomes, no significant between-group difference was noted in all matched subcohorts. The outcomes of stratification analyses according to the patient's initial presentation (acute MI versus unstable angina cohort) are shown in Table S9. The results for both groups of acute MI and the unstable angina cohort were

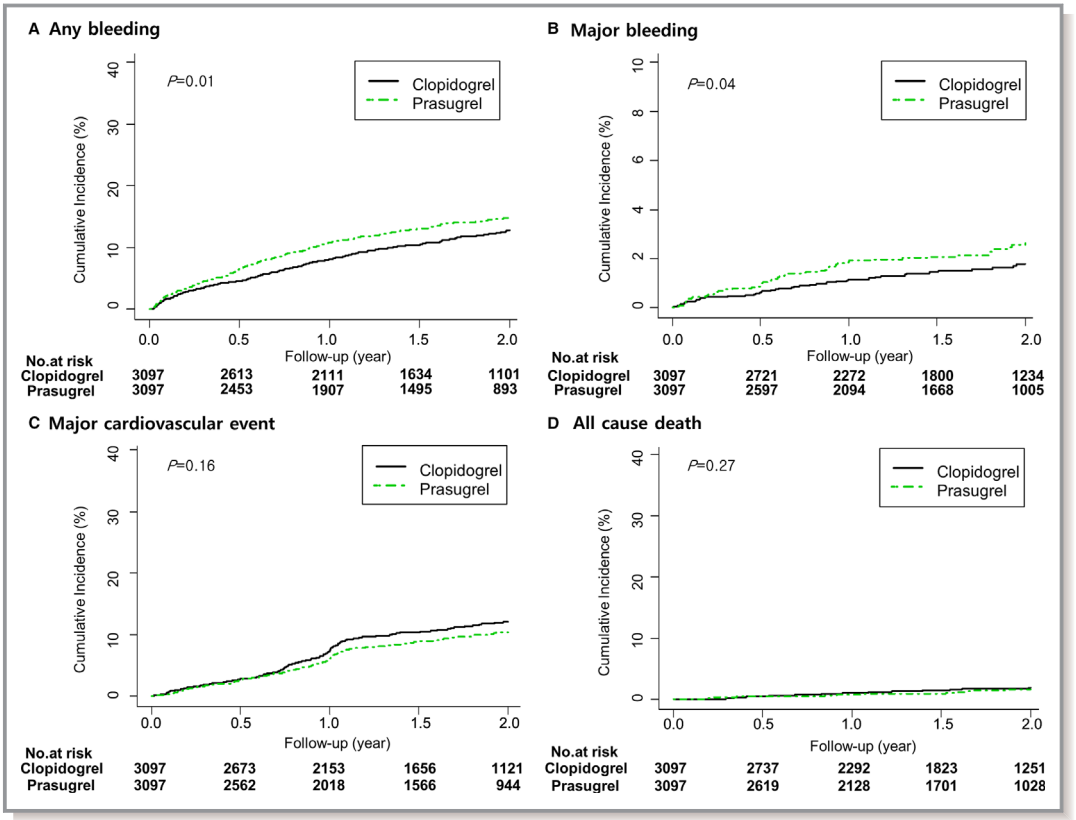

Figure 3. Cumulative risks of the study outcomes in the matched cohort of prasugrel and clopidogrel. Cumulative incidence curves are shown for any bleeding (**A**), major bleeding (**B**), major cardiovascular events (**C**), and all-cause mortality (**D**).

Table 6. Risk of Safety and Effectiveness Outcomes in the Propensity-Score–Matched Cohort of Ticagrelor and Prasugrel*

Outcomes	Outcome Rate at 2 Years (%)†		HR (95% CI)‡	*P* Value
	Ticagrelor (n=3095)	Prasugrel (n=3095)		
Safety outcomes				
Any bleeding	18.0	14.8	1.16 (1.00–1.35)	0.05
Major bleeding	2.6	2.6	0.99 (0.67–1.44)	0.94
Site of bleeding events				
Intracranial bleeding	0.6	0.8	1.10 (0.52–2.30)	0.80
Gastrointestinal bleeding	5.6	5.2	1.00 (0.77–1.31)	0.98
Urogenital bleeding	2.2	1.8	1.08 (0.68–1.69)	0.75
Respiratory bleeding	0.6	0.6	1.01 (0.50–2.02)	0.99
Nasal bleeding	6.1	4.0	1.38 (1.05–1.80)	0.02
Intraocular bleeding	4.8	4.0	1.13 (0.83–1.53)	0.44
Other bleeding	0.4	0.3	1.25 (0.51–3.09)	0.63
Transfusion	1.6	1.5	0.95 (0.59–1.54)	0.84
Effectiveness outcomes				
Major cardiovascular events§	11.1	10.3	1.14 (0.94–1.37)	0.18
Death from cardiovascular causes	0.5	0.6	0.76 (0.33–1.75)	0.52
MI	9.6	9.1	1.11 (0.90–1.36)	0.33
Stroke	1.3	1.3	1.18 (0.70–2.01)	0.54
All-cause mortality	1.4	1.6	0.92 (0.53–1.59)	0.77

HR indicates hazard ratio; MI, myocardial infarction.
*The propensity-score–matched cohort included 3095 patients in the ticagrelor user group and 3095 patients in the prasugrel user group.
†Outcome rates were derived from paired Kaplan–Meier curves.
‡HRs are for ticagrelor compared with prasugrel.
§Major cardiovascular events were defined as a composite of death from cardiovascular causes, MI, or stroke.

similar. Results for another sensitivity analysis in the healthy PCI cohort are shown in Table S10. The risk of any bleeding was significantly higher in the ticagrelor group than in the clopidogrel group. No significant between-group difference was noted in any matched subcohorts with respect to any safety and effectiveness outcomes.

Discussion

This nationwide population-based cohort study had several major findings. First, potent P2Y$_{12}$ inhibitors were prescribed substantially less often for Asian patients than for Western patients.[22,23] Second, compared with clopidogrel, ticagrelor was associated with an increased risk of bleeding but with lower risks of mortality for any cause and for cardiovascular causes and stroke. Third, compared with clopidogrel, prasugrel was associated with an increased risk of bleeding but with similar risks for effectiveness outcomes. Fourth, no significant differences were noted in the risk of bleeding and ischemic events between ticagrelor and prasugrel.

The key findings of our study conflicted with those of the pivotal RCTs of ticagrelor and prasugrel.[2,3] In our study, compared with clopidogrel, ticagrelor use significantly increased the rate of bleeding events without reducing major cardiovascular events. Some prior data suggested that the advantages of ticagrelor over clopidogrel and its net clinical benefit varied according to geography and ethnicity.[24,25] Similar to our findings, the PHILO trial showed that the 1-year rates of major bleeding events (10.3% versus 6.8%) and minor bleeding events (15.2% versus 9.2%) were higher in the ticagrelor group than in the clopidogrel group without a clear benefit regarding ischemic events.[26] Nevertheless, although our study used relatively weak criteria for major bleeding, the risk of major bleeding seems to be lower compared with the PHILO trial. This disparity might be explained by the differences in study design, population, definition and coding of events, and adjudication process. Similar to the PLATO (Platelet Inhibition and Patient Outcomes) trial,[2] our study also showed that ticagrelor was associated with mortality reduction. In PLATO, the improved survival rate with ticagrelor might be due to a decrease in ischemic events without a concomitant

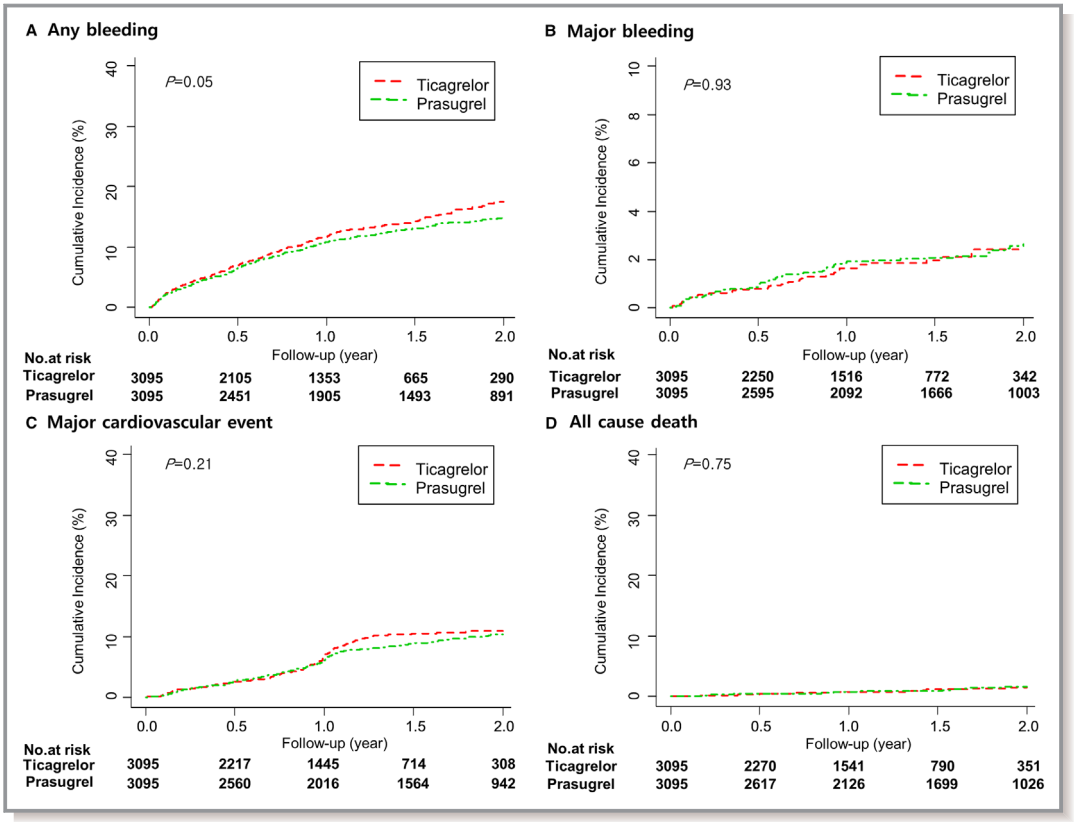

Figure 4. Cumulative risks of the study outcomes in the matched cohort of ticagrelor and prasugrel. Cumulative incidence curves are shown for any bleeding (**A**), major bleeding (**B**), major cardiovascular events (**C**), and all-cause mortality (**D**).

increase in major bleeding. However, in our study, the plausible reasons for the mortality benefit of ticagrelor use without a significant reduction of major cardiovascular events are still unclear. With regard to each component of the composite major cardiovascular event, compared with clopidogrel, ticagrelor was significantly associated with lower risk of death from cardiovascular causes and stroke but not risk of MI. Because the proportion of MI was largest in the composite outcome, the benefit of ticagrelor on reduction of major cardiovascular events seems to be not significant. A differential effect of ticagrelor on mortality or MI needs to be addressed in future investigations (ie, the pleiotropic effects of ticagrelor associated with inhibition of adenosine reuptake).

In the current study, although the limited number of prasugrel users might provide less robust findings, prasugrel was associated with an increased risk of bleeding events and was not associated with a benefit for major cardiovascular events and mortality compared with clopidogrel. Given the lower body mass index and greater bleeding tendency of Asian patients, physicians were less likely to prescribe the usual dose of prasugrel. The PRASFIT-ACS (Prasugrel Compared With Clopidogrel for Japanese Patients With ACS Undergoing PCI) trial, involving Japanese patients with ACS, showed that a reduced dose of prasugrel (a 20-mg loading dose and a 3.75-mg daily maintenance dose) was associated with a lower risk of ischemic and bleeding events compared with clopidogrel.[27] After this trial, a low dose of prasugrel was approved as the recommended dosing for Japanese population. Further studies are required to define the optimal dosing of prasugrel targeting an East Asian population.

A head-to-head comparison of newer P2Y$_{12}$ inhibitors remains a significant challenge. The PRAGUE-18 trial showed that the 30-day and 1-year rates of ischemic, bleeding, and net clinical end points were similar for ticagrelor and prasugrel.[28,29] Similarly, our postapproval observational study showed no significant differences in bleeding or ischemic outcomes for ticagrelor and prasugrel. These observations might highlight the practical challenges faced by treating physicians considering head-to-head evaluations of active therapies for ACS care. However, because previous trials were underpowered and observational studies have inherent limitations, a definitive answer regarding the comparative effectiveness of ticagrelor and prasugrel warrants further investigation and should be confirmed or refuted through large RCTs.

Although East Asian data have come from several registries and cohorts, the results are conflicting. KAMIR-NIH and this cohort's result favored for the concept of the East Asian paradox,[30] whereas the Taiwan National Database and the international multicenter BleeMACS registry favored potent $P2Y_{12}$ inhibitors for ACS patients.[31,32] Although exact reasons for the different results across these registries are still unknown, they might be explained in part by differences in patient characteristics, clinical practice or pattern, and end point definitions, as well as by confounding factors. The underlying mechanism of East Asian paradox with response to antiplatelet drugs has not been fully determined.[6,33] This phenomenon may be partly explained by interethnic differences in intrinsic thrombogenicity, pharmacokinetic and pharmacodynamic profiles, and propensity for bleeding complications.[34] In addition, differences in genetic polymorphisms (ie, factor V Leiden [G1691A] and prothrombin [G20210A] gene mutations), plasma hemostatic factors (ie, fibrinogen, D-dimer, and factor VIII), and endothelial activation markers (ie, VWF [von Willebrand factor], ICAM1 [intercellular adhesion molecule 1], and E-selectin) may at least contribute to this disparity.[35,36]

Our study has some potential limitations. First, our results rely on the completeness and accuracy of data from electronic and administrative databases. There is a possibility of coding errors, missing data, lack of clinically relevant data due to unmeasured variables, or concomitant over-the-counter drug use that usually cannot be captured in such data sources. However, the definition and coding of clinically relevant outcomes in our study were validated in recent clinical studies using the NHIS database.[14,15] Second, this study was observational and may have selection or ascertainment bias. Although all measured baseline differences were accounted for using robust propensity-score matching, unmeasured confounder might influence observed results. Unfortunately, we did not have data on coronary lesion characteristics that affect clinical outcomes; therefore, this factor could not be included in the propensity scores. Third, the primary end points were not adjudicated, leaving substantial risk of bias and misclassification of the end points. Finally, we cannot accurately quantify the effects of treatment retention and adherence. Over time, $P2Y_{12}$ de-escalation (switching from ticagrelor/prasugrel to clopidogrel) was common (Table S3). However, even after additional adjustment of the status of $P2Y_{12}$ inhibitors as a time-varying covariate, the overall findings were similar.

Conclusions

Among East Asian patients who presented with ACS, compared with clopidogrel, ticagrelor was associated with an increased rate of bleeding but with a significant reduction in death from all causes and from cardiovascular causes and stroke. Compared with clopidogrel, prasugrel was associated with an increase in bleeding events without differences in effectiveness outcomes. No significant differences were noted between ticagrelor and prasugrel with respect to bleeding and ischemic events.

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Disclosures

None.

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Supplemental Material

Table S1. Definitions of Clinical Risk Factors or Comorbid Conditions and Concomitant Cardioactive Medications on the Basis of Codes and Prescriptions in the 365 Days before Exposure.

Variable	Definition
Clinical history or risk factors	
Malignancy or cancer	ICD-10 diagnosis codes: C00.X–C99.X
Diabetes mellitus	ICD-10 diagnosis codes: E10.X–E14.X or hypoglycemic agents
Hypertension	ICD-10 diagnosis codes: I10.X–I13.X, I15.X or hypotensive agents* *Beta blocker, Calcium channel blocker, ACEi, ARB, Diuretics
Dyslipidemia	ICD-10 diagnosis codes: E78.0
Prior myocardial infarction	ICD-10 diagnosis codes: I21.X-I23.X
Prior percutaneous coronary intervention #	Procedure codes: M6551, M6552, M6561, M6562, M6563, M6564, M6571, M6572
Prior coronary-artery bypass grafting#	Procedure codes: O1641, O1642, O1647, OA641, OA642, OA647
Chronic renal failure	ICD-10 diagnosis codes: N18.X or specific dialysis code* * hemodialysis (V001, O7020, O9991), Peritoneal dialysis (V003, O7061, O7062, O7071, O7072, O7073, O7074)
COPD	ICD-10 diagnosis codes: J43, J43.0, J43.1, J43.2, J43.8, J43.9, J44, J44.0, J44.1, J44.8, J44.9
Unstable angina	ICD-10 diagnosis codes: I20.0
Acute MI	ICD-10 diagnosis codes: I21.X, I22.X, I23.X
Acute coronary syndrome	ICD-10 diagnosis codes: Unstable angina or acute MI
Charlson comorbidity index	
1. Myocardial infarction	ICD-10 diagnosis codes: I21.X, I22.X, I25.2
2. Congestive heart failure	ICD-10 diagnosis codes: I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.X, I50.X, P29.0
3. Peripheral vascular disease	ICD-10 diagnosis codes: I70.X, I71.X, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
4. Cerebrovascular disease	ICD-10 diagnosis codes: G45.X, G46.X, H34.0, I60.X–I69.X
5. Dementia	ICD-10 diagnosis codes: F00.X–F03.X, F05.1, G30.X, G31.1

6. COPD	ICD-10 diagnosis codes: I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3
7. Rheumatic disease (connective tissue disease)	ICD-10 diagnosis codes: M05.x, M06.x, M31.5, M32.x–M34.x, M35.1, M35.3, M36.0
8. Peptic ulcer disease	ICD-10 diagnosis codes: K25.x–K28.x
9. Diabetes mellitus (1 point if uncomplicated, 2 points if end organ damage)	ICD-10 diagnosis codes: (1point) E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, El2.6, E12.8, El2.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9; (2 points) E10.2–E10.5, E10.7, E11.2, E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
10. Moderate to severe chronic kidney disease (2 points)	ICD-10 diagnosis codes: I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18.x, N19.x, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
11. Hemiplegia (2 points)	ICD-10 diagnosis codes: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0–G83.4, G83.9
12. Leukemia (2 points) 13. Malignant lymphoma (2 points) 14. Solid tumor (2 points)	ICD-10 diagnosis codes: C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x
14. Metastatic solid tumor (6 points if metastatic)	ICD-10 diagnosis codes: (6 points) C77.x–C80.x
15. Liver disease (1 point if mild, 3 points if moderate to severe)	ICD-10 diagnosis codes: (1point) B18.x, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73.x, K74.x, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4; (3 points) I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Concomitant cardioactive medications	
Aspirin	acetylsalicylic acid
Unfractionated heparin	heparin calcium, heparin sodium
LMWH	bemiparin sodium, dalteparin sodium, diclofenac epolamine, enoxaparin sodium, nadroparin calcium, parnaparin sodium
Statins	atorvastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, pitavastatin, ezetamibe/simvastatin
β-blockers	atenolol, betaxolol, bevantolol, bisoprolol, carteolol, carvedilol, celiprolol, esmolol, labetalol, propranolol, sotalol, metoprolol combinations, bisoprolol combinations, s-atenolol, nebivolol
Calcium-channel blocker	amlodipine, barnidipine, benidipine, cilnidipine, diltiazem, felodipine, isradipine, lacidipine, lercanidipine, manidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nitrendipine, verapamil, nisoldipine

ACE inhibitors or ARBs	benazepril, candesartan, captopril, cilazapril, enalapril, fosinopril, imidapril, irbesartan, isinopril, losartan, moexipril, perindopril, zofenopril, quinapril, ramipril, temocapril, valsartan, telmisartan, eprosartan, olmesartan medoxomil
Diuretics	furosemide, hydrochlorothiazide, amiloride, indapamide, spironolactone, torasemide, xipamide, metolazone

[##]On the basis of the procedure codes provided by the national claims data in the National Health Insurance Service.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; LMWH, low-molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table S2. Definitions of Safety and Efficacy Outcomes.

Variable	Definition
Safety Outcomes	
Any bleeding	ICD-10 diagnosis codes: Intracranial, Gastro-intestinal, Urogenital, Respiratory, Nasal, Intraocular, Intraarticular or intramuscular, or Other bleeding (see below)
Major bleeding	ICD-10 diagnosis codes: D62, H05.2, H35.6, H431, M25.0, R04, R04.1, R04.2, R04.8, R04.9, J94.2 or intracranial bleeding, gastro-intestinal bleeding (see below)
Intracranial bleeding	ICD-10 diagnosis codes: I60.X, I61.X, I62.X, S06.4
Gastro-intestinal bleeding	ICD-10 diagnosis codes: I850, K22.11, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.81, K55.21, K57.01, K57.03, K57.11, K57.13, K57.21, K57.23, K57.31, K57.33, K57.41, K57.43, K57.51, K57.53, K57.81, K57.83, K57.91, K57.93, K62.5, K66.1, K92.0, K92.1, K92.2
Urogenital bleeding	ICD-10 diagnosis codes: N50.1, N83.0, R31, R31.0, R31.8
Respiratory bleeding (Hemoptysis)	ICD-10 diagnosis codes: J94.2, R04, R04.1, R04.2, R04.8, R04.9
Nasal bleeding	ICD-10 diagnosis codes: R04.0
Intraocular bleeding	ICD-10 diagnosis codes: H05.2, H11.3, H21.0, H31.3, H35.6, H43.1, H47.0
Intraarticular or intramuscular bleeding	ICD-10 diagnosis codes: M25.0
Other bleeding	ICD-10 diagnosis codes: D62, D68.3, E27.4, R58
Effectiveness Outcomes	
Composite of cardiovascular death, MI, or stroke	cardiovascular death, MI, or stroke
Cardiovascular death	ICD-10 diagnosis codes: I00.X–I99.X or R96, R98, R99
MI	ICD-10 diagnosis codes: I21.X, I22.X
Stroke	ICD-10 diagnosis codes: I60.X, I61.X, I62.X, I63.X, I64.X

MI, myocardial infarction.

Table S3. Adherence to the Index Drug during the Follow-up Period.

Characteristic	Clopidogrel Group (N=56,216)		Ticagrelor Group (N=11,402)		Prasugrel Group (N=3,097)	
At discharge	56,216		11,402		3,097	
Clopidogrel use	56,216	(100.0)	2,189	(19.2)	434	(14.0)
Ticagrelor use	742	(1.3)	11,402	(100.0)	26	(0.8)
Prasugrel use	436	(0.8)	115	(1.0)	3,097	(100.0)
Aspirin use	55,016	(97.9)	11,366	(99.7)	3,083	(99.5)
3 Mo after index discharge	48,031		10,176		2,724	
Clopidogrel use	46,450	(96.7)	2,844	(28.0)	404	(14.8)
Ticagrelor use	627	(1.3)	7,468	(73.4)	29	(1.1)
Prasugrel use	425	(0.9)	164	(1.6)	2,361	(86.7)
Aspirin use	41,925	(87.3)	9,730	(95.6)	2,638	(96.8)
6 Mo after 3 Mo	47,766		9,197		2,742	
Clopidogrel use	45,659	(95.6)	3,273	(35.6)	595	(21.7)
Ticagrelor use	597	(1.3)	5,933	(64.5)	24	(0.9)
Prasugrel use	416	(0.9)	185	(2.0)	2,173	(79.3)
Aspirin use	41,082	(86.0)	8,623	(93.8)	2,642	(96.4)
9 Mo after 6 Mo	42,030		7,486	(100.0)	2,422	
Clopidogrel use	39,317	(93.6)	3,087	(41.2)	635	(26.2)
Ticagrelor use	528	(1.3)	4,287	(57.3)	15	(0.6)
Prasugrel use	354	(0.8)	137	(1.8)	1,766	(72.9)
Aspirin use	35,272	(83.9)	6,867	(91.7)	2,285	(94.3)
12 Mo after 9 Mo	37,074		5,949	(100.0)	2,122	
Clopidogrel use	33,750	(91.0)	2,893	(48.6)	762	(35.9)
Ticagrelor use	449	(1.2)	2,888	(48.6)	17	(0.8)
Prasugrel use	263	(0.7)	102	(1.7)	1,317	(62.1)
Aspirin use	29,888	(80.6)	5,197	(87.4)	1,945	(91.7)
18 Mo after 12 Mo	35,356		5,114		2,010	
Clopidogrel use	28,849	(81.6)	3,058	(59.8)	1,018	(50.7)
Ticagrelor use	449	(1.3)	1,178	(23.0)	16	(0.8)
Prasugrel use	190	(0.5)	64	(1.3)	591	(29.4)
Aspirin use	26,430	(74.8)	3,959	(77.4)	1,654	(82.3)
24 Mo after 18 Mo	26,140		2,601		1,565	
Clopidogrel use	19,646	(75.2)	1,496	(57.5)	795	(50.8)
Ticagrelor use	286	(1.1)	321	(12.3)	10	(0.6)
Prasugrel use	112	(0.4)	26	(1.0)	214	(13.7)
Aspirin use	17,917	(68.5)	1,842	(70.8)	1,208	(77.2)

Data are numbers (percentages).

Table S4. Observed Rates of 2-Year Clinical Outcomes in the Overall Population.

Outcomes	Outcome Rate at 2 Years (%)*			P Value
	Clopidogrel (N=56,216)	Ticagrelor (N=11,402)	Prasugrel (N=3,097)	
Safety outcomes				
Any bleeding	17.0	18.1	14.8	<0.001
Major bleeding	3.2	3.1	2.6	0.27
Site of bleeding events				
Intracranial bleeding	1.1	0.8	0.8	0.005
Gastrointestinal bleeding	5.9	6.1	5.2	0.57
Urogenital bleeding	2.5	2.3	1.8	0.06
Respiratory bleeding	1.0	1.0	0.6	0.28
Nasal bleeding	2.8	4.4	4.0	<0.001
Intraocular bleeding	4.9	5.0	4.0	0.08
Other bleeding	0.6	0.5	0.3	0.37
Transfusion	1.9	1.8	1.5	0.62
Effectiveness outcomes				
Major cardiovascular events†	12.1	13.1	10.3	0.001
Death from cardiovascular causes	2.6	1.0	0.6	<0.001
Myocardial infarction	7.1	10.6	9.0	<0.001
Stroke	3.9	2.1	1.3	<0.001
All-cause mortality	5.8	3.1	1.6	<0.001

*Outcome rates were derived from paired Kaplan–Meier curves.

†Major cardiovascular events were defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Table S5. Time-Dependent Covariate Analysis*.

Outcomes	Hazard Ratio (95% CI)*	P Value
Ticagrelor vs. Clopidogrel (referent) (N=11,402 vs. N=11,402)		
Any bleeding	1.59 (1.45, 1.74)	<0.001
Major bleeding	1.56 (1.25, 1.95)	<0.001
Major cardiovascular events†	1.18 (1.06, 1.30)	0.002
All-cause mortality	0.79 (0.63, 0.99)	0.04
Prasugrel vs. Clopidogrel (referent) (N=3,097 vs. N=3,097)		
Any bleeding	1.63 (1.37, 1.94)	<0.001
Major bleeding	2.10 (1.37, 3.24)	0.001
Major cardiovascular events†	1.07 (0.89, 1.30)	0.47
All-cause mortality	0.47 (0.25, 0.88)	0.02
Ticagrelor vs. Prasugrel (referent)) (N=3,095 vs. N=3,095)		
Any bleeding	1.08 (0.89, 1.33)	0.43
Major bleeding	0.86 (0.51, 1.43)	0.56
Major cardiovascular events†	1.09 (0.86, 1.38)	0.48
All-cause mortality	1.58 (0.70, 3.58)	0.28

CI, confidence intervals; MI, myocardial infarction.

*Hazard ratios were adjusted for propensity score and time-dependent covariate (P2Y12 inhibitors at each time point shown in Online Table 3).

†Major cardiovascular events were defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Table S6. Baseline Characteristics Between Included Study Population and Excluded Population with Less Than 30 Days Use of P2Y12 Inhibitors.

Characteristic	Final Study Population (N=70,715)	Excluded Population (N=22,994)	P Value
Age			
Mean (yr)	64.3 (12.2)	65.7 (13.3)	<0.001
Age ≥75 yr	16,200 (22.9)	6,489 (28.2)	<0.001
Sex			
Male	48,413 (68.5)	13,039 (56.7)	<0.001
Female	22,302 (31.5)	9,955 (43.3)	<0.001
Socio-economic status			
Low tertile	22,872 (32.3)	8,003 (34.8)	<0.001
Middle tertile	23,303 (33.0)	7,187 (31.3)	<0.001
High tertile	24,540 (34.7)	7,804 (33.9)	<0.001
Body mass index†			
Mean (±SD)	24.6 (2.7)	24.5 (2.9)	<0.001
<20.0	2,888 (4.1)	1,230 (5.4)	<0.001
20.0 ≤ BMI < 22.5	9,465 (13.4)	3,035 (13.2)	<0.001
22.5 ≤ BMI < 25.0	28,956 (41.0)	10,035 (43.6)	<0.001
25.0 ≤ BMI < 27.5	20,622 (29.2)	5,719 (24.9)	<0.001
27.5 ≤ BMI < 30.0	6,125 (8.7)	1,993 (8.7)	<0.001
≥30.0	2,659 (3.8)	982 (4.3)	<0.001
Hypertension	40,017 (56.6)	13,599 (59.1)	<0.001
Dyslipidemia	12,397 (17.5)	4,445 (19.3)	<0.001
Current smoking	15,775 (22.3)	3,885(16.9)	<0.001
Diabetes			
Any	31,693 (44.8)	10,597 (46.1)	<0.001
Requiring insulin	665 (0.9)	196 (0.9)	0.22
Prior MI	3,054 (4.3)	1,167 (5.1)	<0.001
Prior PCI	537 (0.8)	63 (0.3)	<0.001
Prior CABG	9 (0.0)	1 (0.0)	0.29
Prior congestive heart failure	878 (1.2)	466 (2.0)	<0.001
Prior stroke	1,432 (2.0)	482 (2.1)	0.51

Peripheral vascular disease	11,757 (16.6)	4,064 (17.7)	<0.001
Chronic renal failure	3,044 (4.3)	1,328 (5.8)	<0.001
Chronic lung disease	5,644 (8.0)	2,351 (10.2)	<0.001
Charlson comorbidity index			
Mean (±SD)	2.6 (2.4)	3.0 (2.5)	<0.001
0	14,904 (21.1)	3,768 (16.4)	<0.001
1–2	25,176 (35.6)	7,888 (34.3)	<0.001
≥3	30,635 (43.3)	11,338 (49.3)	<0.001
Clinical presentation			
Unstable angina	31,933 (45.2)	14,862 (64.6)	<0.001
Acute MI	38,782 (54.8)	8,132 (35.4)	<0.001
Index treatment			
PCI	62,262 (88.1)	6,378 (27.7)	<0.001
CABG	1,794 (2.5)	407 (1.8)	<0.001
Medical therapy	6,659 (9.4)	16,209 (70.5)	<0.001
P2Y12 inhibitors			
Clopidogrel	56,216 (79.5)	19,731 (85.8)	<0.001
Ticagrelor	11,402 (16.1)	2,821 (12.3)	<0.001
Prasugrel	3,097 (4.4)	442 (1.9)	<0.001
Concomitant mediations at index hospitalization			
Aspirin	69,798 (98.7)	22,317 (97.1)	<0.001
Statins	67,035 (94.8)	17,833 (77.6)	<0.001
β-blockers	53,505 (75.7)	11,397 (49.6)	<0.001
Calcium-channel blockers	32,241 (45.6)	12,668 (55.1)	<0.001
ACE inhibitors or ARBs	51,306 (72.6)	11,889 (51.7)	<0.001
Diuretics	16,435 (23.2)	5,058 (22.0)	<0.001

*Data are mean (SD) or numbers (percentages).

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; LMWH, low-molecular weight heparin; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table S7. Risk of Safety and Effectiveness Outcomes in the Propensity-Score–Matched Cohort of Each P2Y12 Inhibitors in Sensitivity Analyses Including Population with Less Than 30 Days Use of P2Y12 Inhibitors.

Outcomes	Outcome Rate at 2 Years (%)*		Hazard Ratio (95% CI)†	P Value
Matched Cohort of Ticagrelor vs. Clopidogrel	**Ticagrelor (N=14,223)**	**Clopidogrel (N=14,223)**		
Any bleeding	17.6	14.6	1.24 (1.16, 1.34)	<0.001
Major bleeding	2.9	2.6	1.18 (0.99, 1.40)	0.07
Major cardiovascular events‡	14.5	14.5	1.01 (0.94, 1.09)	0.83
All-cause mortality	5.7	6.2	0.94 (0.85, 1.05)	0.31
Matched Cohort of Prasugrel vs. Clopidogrel	**Prasugrel (N=3,539)**	**Clopidogrel (N=3,539)**		
Any bleeding	14.7	14.0	1.07 (0.93, 1.23)	0.32
Major bleeding	2.6	2.3	1.21 (0.86, 1.72)	0.27
Major cardiovascular events‡	10.4	11.1	0.93 (0.79, 1.10)	0.41
All-cause mortality	2.2	2.3	0.91 (0.64, 1.29)	0.61
Matched Cohort of Ticagrelor vs. Prasugrel	**Ticagrelor (N=3,537)**	**Prasugrel (N=3,537)**		
Any bleeding	18.3	14.7	1.21 (1.05, 1.40)	0.01
Major bleeding	2.4	2.6	0.89 (0.61, 1.28)	0.53
Major cardiovascular events‡	12.1	10.4	1.21 (1.02, 1.44)	0.03
All-cause mortality	2.6	2.2	1.23 (0.86, 1.76)	0.26

CI, confidence intervals; MI, myocardial infarction.

*Outcome rates were derived from paired Kaplan–Meier curves.

†Hazard ratios are for the first drug as compared with the second drug.

‡Major cardiovascular events were defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Table S8. Risk of Safety and Effectiveness Outcomes in the Propensity-Score–Matched Cohort of Each P2Y12 Inhibitors in Subgroup of STEMI Patients.

Outcomes	Outcome Rate at 2 Years (%)*		Hazard Ratio (95% CI) †	P Value
Matched Cohort of Ticagrelor vs. Clopidogrel	**Ticagrelor (N=3,725)**	**Clopidogrel (N=3,725)**		
Any bleeding	16.9	13.3	1.31 (1.13, 1.50)	<0.001
Major bleeding	2.7	2.1	1.32 (0.94, 1.86)	0.11
Major cardiovascular events‡	13.6	13.2	1.06 (0.91, 1.23)	0.46
All-cause mortality	3.2	3.3	1.04 (0.76, 1.42)	0.80
Matched Cohort of Prasugrel vs. Clopidogrel	**Prasugrel (N=1,204)**	**Clopidogrel (N=1,204)**		
Any bleeding	15.4	12.5	1.29 (1.02, 1.64)	0.04
Major bleeding	3.0	1.8	1.80 (1.01, 3.22)	0.05
Major cardiovascular events‡	8.7	11.5	0.82 (0.62, 1.09)	0.17
All-cause mortality	1.9	1.4	1.35 (0.66, 2.78)	0.42
Matched Cohort of Ticagrelor vs. Prasugrel	**Ticagrelor (N=1,198)**	**Prasugrel (N=1,198)**		
Any bleeding	16.7	15.5	1.06 (0.84, 1.35)	0.61
Major bleeding	1.7	3.1	0.47 (0.24, 0.92)	0.03
Major cardiovascular events‡	11.2	8.8	1.25 (0.92, 1.70)	0.16
All-cause mortality	1.5	1.9	0.82 (0.37, 1.80)	0.62

CI, confidence intervals; MI, myocardial infarction.

*Outcome rates were derived from paired Kaplan–Meier curves.

†Hazard ratios are for the first drug as compared with the second drug.

‡Major cardiovascular events were defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Table S9. Stratified Analysis According to Initial Presentation (AMI vs. Unstable Angina Cohort).

	Acute MI		Unstable Angina		
Outcomes	**Hazard Ratio (95% CI)***	**P**	**Hazard Ratio (95% CI)***	**P**	**P-for Interaction**
Ticagrelor vs. Clopidogrel (referent)	**(N=9,096 vs. N=27,323)**		**(N=2,306 vs. N=28,893)**		
Any bleeding	1.24 (1.16, 1.34)	<0.001	1.30 (1.16, 1.47)	<0.001	0.43
Major bleeding	1.14 (0.96, 1.35)	0.12	1.25 (0.93, 1.69)	0.14	0.69
Major cardiovascular events†	0.97 (0.90, 1.04)	0.39	0.84 (0.65, 1.09)	0.19	0.08
All-cause mortality	0.73 (0.62, 0.86)	0.00	0.87 (0.62, 1.24)	0.45	0.20
Prasugrel vs. Clopidogrel (referent)	**(N=2,363 vs. N=27,323)**		**(N=734 vs. N=28,893)**		
Any bleeding	1.08 (0.95, 1.22)	0.26	1.15 (0.93, 1.41)	0.20	0.45
Major bleeding	1.15 (0.85, 1.56)	0.36	1.29 (0.76, 2.21)	0.35	0.60
Major cardiovascular events†	0.90 (0.78, 1.03)	0.13	0.82 (0.49, 1.37)	0.45	0.25
All-cause mortality	0.70 (0.47, 1.04)	0.08	0.96 (0.45, 2.03)	0.91	0.27
Ticagrelor vs. Prasugrel (referent)	**(N=2,363 vs. N=9,096)**		**(N=734 vs. N=2,306)**		
Any bleeding	1.13 (0.98, 1.30)	0.09	1.11 (0.88, 1.42)	0.37	0.99
Major bleeding	1.06 (0.76, 1.48)	0.75	1.02 (0.55, 1.91)	0.95	0.94
Major cardiovascular events†	1.19 (1.02, 1.38)	0.03	1.01 (0.56, 1.83)	0.97	0.93
All-cause mortality	0.89 (0.57, 1.40)	0.63	0.91 (0.38, 2.16)	0.82	0.66

CI, confidence intervals; MI, myocardial infarction.

*Hazard ratio were adjusted for Age, Sex, Socio-economic status, Body mass index, Hypertension, Dyslipidemia, Current smoking, Diabetes, Prior MI, Prior congestive heart failure, Prior stroke, Peripheral vascular disease, Chronic renal failure, Chronic lung disease, Charlson comorbidity index, Clinical presentation, Index treatment, Concomitant mediations

†Major cardiovascular events were defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Table S10. Risk of Safety and Effectiveness Outcomes in the Propensity-Score–Matched Cohort of Each P2Y12 Inhibitors in Healthy PCI Cohort (body weight >=60 kg, <75 years old, and no history of stroke or TIA).

Outcomes	Outcome Rate at 2 Years (%)*		Hazard Ratio (95% CI)†	P Value
Matched Cohort of Ticagrelor vs. Clopidogrel	**Ticagrelor (N=4,141)**	**Clopidogrel (N=4,141)**		
Any bleeding	19.5	16.6	1.21 (1.07, 1.37)	0.002
Major bleeding	3.4	3.0	1.12 (0.83, 1.52)	0.45
Major cardiovascular events‡	12.3	11.5	1.07 (0.92, 1.25)	0.37
All-cause mortality	2.5	3.4	0.76 (0.55, 1.05)	0.10
Matched Cohort of Prasugrel vs. Clopidogrel	**Prasugrel (N=1,021)**	**Clopidogrel (N=1,021)**		
Any bleeding	16.5	18.0	0.98 (0.77, 1.24)	0.85
Major bleeding	2.8	2.2	1.23 (0.65, 2.31)	0.52
Major cardiovascular events‡	11.7	9.8	1.18 (0.87, 1.61)	0.29
All-cause mortality	2.7	1.6	1.61 (0.78, 3.34)	0.20
Matched Cohort of Ticagrelor vs. Prasugrel	**Ticagrelor (N=1,021)**	**Prasugrel (N=1,021)**		
Any bleeding	21.2	16.5	1.22 (0.96, 1.55)	0.10
Major bleeding	3.6	2.8	1.26 (0.68, 2.32)	0.46
Major cardiovascular events‡	11.6	11.7	1.07 (0.78, 1.47)	0.68
All-cause mortality	2.4	2.7	0.90 (0.43, 1.89)	0.79

CI, confidence intervals; MI, myocardial infarction.

*Outcome rates were derived from paired Kaplan–Meier curves.

†Hazard ratios are for the first drug as compared with the second drug.

‡Major cardiovascular events were defined as a composite of death from cardiovascular causes, myocardial infarction, or stroke.

Figure S1. Proportion of New Antiplatelet Drug Use Compared to Clopidogrel Use Over Time.