Arteriosclerosis, Thrombosis, and Vascular Bi

CLINICAL AND POPULATION STUDIES

Comparison of Cardiovascular Events in Patients Receiving Concomitant Clopidogrel and Proton Pump Inhibitors Classified by CYP2C19 Inhibitory Potency

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BACKGROUND: Proton pump inhibitors (PPIs) may potentially reduce clopidogrel's antiplatelet effect and increase cardiovascular risk. The degree of CYP (cytochrome P450) 2C19 inhibition varies among PPIs. Few studies have evaluated individual PPIs by CYP2C19 inhibition strength across countries. This study aimed to compare the incidence of cardiovascular events between strong CYP2C19-inhibiting potency and weak CYP2C19-inhibiting potency (weak or non-CYP2C19–inhibiting PPIs) in patients receiving clopidogrel.

METHODS: We conducted an international observational cohort study using 14 databases from the United States, South Korea, and Taiwan. We included patients aged ≥18 years who received clopidogrel with PPIs from 1985 to 2023. PPIs were classified into strong CYP2C19-inhibiting PPIs and weak or non-CYP2C19–inhibiting PPIs based on CYP2C19 inhibition. We compared the hazard ratios and 95% CIs for major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality, using the Cox proportional hazards model after 1:1 propensity score matching. Secondary outcomes included cardiovascular mortality, myocardial infarction, stroke, and all-cause mortality. A random-effects model calculated pooled hazard ratios and 95% CIs. Only databases meeting all diagnostic criteria were included in the meta-analysis.

RESULTS: Large-scale propensity score matching identified 166 005 patient pairs. During the 365-day follow-up, the risk of major adverse cardiovascular events did not differ significantly between patients receiving clopidogrel plus strong CYP2C19-inhibiting PPIs and those receiving clopidogrel plus weak or non-CYP2C19–inhibiting PPIs (17.63 per 1000 person-years versus 16.82 per 1000 person-years; calibrated hazard ratio, 1.00 [95% CI, 0.79–1.26]). No significant difference was observed in the risk of secondary outcomes (calibrated hazard ratio, cardiovascular mortality 1.10 [95% CI, 0.87–1.39], myocardial infarction 0.98 [95% CI, 0.81–1.19], stroke 1.05 [95% CI, 0.87–1.27], and all-cause mortality 1.18 [95% CI, 0.93–1.50]).

CONCLUSIONS: Concomitant use of clopidogrel and strong CYP2C19-inhibiting PPIs was not associated with a higher cardiovascular risk compared with concomitant use of clopidogrel and weak or non-CYP2C19–inhibiting PPIs. This large-scale study does not support the clinical significance of potential interactions between PPIs and clopidogrel.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: cardiovascular diseases ■ clopidogrel ■ mortality ■ myocardial infarction ■ proton pump inhibitors ■ stroke

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Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
COGENT	Clopidogrel and the Optimization of Gastrointestinal Events Trial
CYP	cytochrome P450
EASE	expected absolute systematic error
H2RA	histamine-2 receptor antagonist
HR	hazard ratio
IRB	institutional review board
MACE	major adverse cardiovascular events
MI	myocardial infarction
PPI	proton pump inhibitor
PS	propensity score
sPPI	strong CYP2C19-inhibiting proton pump inhibitor
wPPI	weak or non-CYP2C19–inhibiting proton pump inhibitor

What Are the Clinical Implications?

This large-scale, multinational observational study provides important real-world evidence regarding the clinical safety of concomitant proton pump inhibitor use in patients treated with clopidogrel. Despite longstanding concerns that strong CYP (cytochrome P450) 2C19–inhibiting proton pump inhibitors may attenuate clopidogrel's antiplatelet effect and increase cardiovascular risk, our findings demonstrate no significant difference in major adverse cardiovascular events between patients receiving clopidogrel with strong versus weak CYP2C19-inhibiting proton pump inhibitors across diverse healthcare systems. These results suggest that pharmacokinetic interactions observed in experimental settings do not necessarily translate into clinically meaningful harm at the population level. From a clinical perspective, this supports greater flexibility in proton pump inhibitor selection for patients receiving clopidogrel, allowing clinicians to prioritize gastrointestinal bleeding prevention without compromising cardiovascular safety. This is particularly relevant for high-risk populations in whom gastroprotection is essential. Future research should integrate clinical outcomes with pharmacogenetic and mechanistic data to better identify patient subgroups in whom such interactions may be clinically relevant, ultimately enabling more individualized and evidence-based prescribing decisions.

Clopidogrel is a cornerstone of antiplatelet therapy for preventing ischemic cardiovascular events, but its use is associated with an increased bleeding risk. Recent evidence suggests that bleeding events carry a prognostic significance comparable to that of postdischarge myocardial infarction (MI) in patients with acute coronary syndrome (ACS).[1] Gastrointestinal bleeding, the most common bleeding complication,[2] can be effectively prevented by proton pump inhibitors (PPIs).[3] However, concerns persist about potential drug interactions between PPIs and clopidogrel via CYP (cytochrome P450) 2C19, the enzyme responsible for converting clopidogrel into its active metabolite.

See accompanying editorial by Navarese et al

The strength of CYP2C19 inhibition varies substantially among PPIs. Pharmacodynamic studies have demonstrated that PPIs with strong CYP2C19-inhibiting potency (sPPIs), such as omeprazole, significantly reduce the antiplatelet effect of clopidogrel compared with those with weak or non-CYP2C19–inhibiting PPIs (wPPIs), such as pantoprazole and rabeprazole.[4,5] The US Food and Drug Administration and the European Medicines Agency issued a cautionary statement on the concomitant use of clopidogrel and omeprazole or esomeprazole.[6,7] The recent European Society of Cardiology guideline recommends against prescribing omeprazole and esomeprazole to patients receiving clopidogrel.[8]

Nevertheless, strong CYP2C19 inhibitors such as omeprazole and esomeprazole remain widely prescribed in real-world clinical practice.[9] These agents provide potent and consistent acid suppression, with extensive evidence supporting their efficacy and safety for gastroprotection, particularly in patients at high risk of gastrointestinal bleeding.[10–13] In such patients, avoiding potent PPIs solely due to potential pharmacokinetic interactions may paradoxically increase the risk of serious gastrointestinal complications. From a gastroenterological perspective, omeprazole and esomeprazole therefore remain essential therapeutic options, making it clinically important to clarify whether their concomitant use with clopidogrel truly increases cardiovascular risk.

Despite ongoing debate, the clinical significance of differential PPI effects on cardiovascular outcomes remains largely unexplored. Most previous studies used nonusers as a control group,[14] which may introduce bias in observational studies, as patients prescribed PPIs often have more comorbidities and a higher baseline risk for adverse outcomes than those who do not receive PPIs.[15] This imbalance can exaggerate the association between PPI use and adverse clinical events. Therefore, we conducted an international cohort study using data from the United States, South Korea, and Taiwan to compare the risk of major adverse cardiovascular events (MACEs) between sPPIs and wPPIs when added to established clopidogrel therapy.

MATERIALS AND METHODS

Data Sources

Electronic medical records and administrative claims data converted to the Observational Medical Outcomes Partnership

Common Data Model were used from 14 data sources. Details of the included databases are provided in Table S1. All databases consisted of deidentified, patient-level electronic health records transformed into a common data model–standardized vocabulary using the same analysis program.[16–18] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines.

This study was approved by the institutional review board (IRB) of the Severance Hospital (IRB No. 4-2023-0200), Kangdong Sacred Heart Hospital (IRB No. 2021-07-011-001), and all data partners in the United States and Taiwan (N202503060). The other 7 hospitals in Korea joined the Research Border Free Zone of the common data model data network, which recognizes the IRB approval of research institutions and exempts IRB approval at each institution. The requirement for informed consent was waived because of the retrospective nature of the study. This study was registered in the European Union electronic register of post-authorization studies (EU PAS [European Union Electronic Register of Post-Authorisation Studies]; registration number: EUPAS1000000203).

Cohort Design and Study Population

We conducted a population-based, retrospective cohort study. We enrolled patients aged ≥18 years who received clopidogrel at the time of PPI initiation and had an observation period of at least 1 year before the index date. The study population included only patients who received clopidogrel for >30 consecutive days. The first prescription date of a PPI added on top of this ongoing clopidogrel treatment was defined as the index date. Patients with a history of MI or stroke within 1 year before the index date were excluded to avoid misclassification when estimating the incidence rates of the primary outcome.

PPIs were classified according to their CYP2C19 inhibitory potency and metabolic characteristics based on previous studies.[4,11,19–23] Esomeprazole and omeprazole were categorized as sPPIs because they act as irreversible or quasi-irreversible metabolism-dependent inhibitors of CYP2C19, whereas dexlansoprazole, lansoprazole, pantoprazole, and rabeprazole were defined as wPPIs. wPPIs were defined as active comparators because they have similar indications and a weak or no effect on CYP2C19 compared with observations in sPPIs.[19,24]

The index date was defined as the first prescription date of a PPI while continuing clopidogrel therapy. Continuous drug exposure was inferred by allowing gaps of <30 days between prescription records based on our previous study.[25] A schematic description of the study design is shown in Figure S1.

Outcome and Covariates

The primary outcome was MACE, which included cardiovascular mortality and hospitalization or emergency department visits for MI and stroke within 365 days after the index date (Table S2).[26] Secondary outcomes were defined as the individual components of MACE (cardiovascular mortality, MI, and stroke) and all-cause mortality (Table S2). The study population was censored at the earliest occurrence of death, the last date of the observation period, a 30-day treatment gap indicating PPI discontinuation, use of comparator drugs in the target group, or use of target drugs in the comparator group.

Covariates were used to match the target and comparator cohorts and included patient demographics (age, sex, and race), index year, prior comorbidities and medication use, historical procedures and measurements, device exposures within 30 and 365 days before the index date, and the Charlson Comorbidity Index over 365 days before the index date.

Statistical Analysis

Proportions and standardized mean differences of baseline patient characteristics were calculated. We used 1:1 propensity score (PS) matching to adjust for potential confounders and balance the target and comparator cohorts, using large-scale logistic regression models with covariates from the 12 months preceding the index date. A PS model was constructed for each target-comparator pair.

The primary analysis used an intention-to-treat analysis up to 365 days of the index date. Sensitivity analyses were performed using different comparators, time-at-risk windows, PS methods, and populations. First, comparator drugs: histamine-2 receptor antagonists (H2RAs), which have a weak or no effect on CYP2C19, were added as comparators. H2RAs included cimetidine, famotidine, lafutidine, nizatidine, ranitidine, and roxatidine. In addition, we compared the overall clopidogrel+overall PPI population (including both sPPIs and wPPIs) with the clopidogrel+H2RA population. Second, time-at-risk windows: 4 different risk periods were defined: (1) 30 days after PPI treatment initiation; (2) 365 days after PPI treatment initiation; (3) intention-to-treat: patients were followed until the end of the observation period; (4) during treatment: patients were followed until discontinuation of either PPIs or clopidogrel. Third, PS models: we applied 3 PS methods: 1:1 PS matching, 1:variable-ratio PS matching, and PS stratification (10 strata). Fourth, study population subgroups: 8 population pairs were analyzed: (1) concomitant use of clopidogrel and sPPIs versus clopidogrel and wPPIs; (2) concomitant use of clopidogrel and sPPIs versus clopidogrel and H2RAs; (3) concomitant use of clopidogrel and sPPIs in patients with ACS versus clopidogrel and wPPIs in patients with ACS; and (4) concomitant use of clopidogrel and sPPIs in patients without previous gastrointestinal bleeding versus clopidogrel and wPPIs in patients without previous gastrointestinal bleeding. The presence of ACS and gastrointestinal bleeding was determined based on diagnoses recorded within 1 year before the index date. Each of these 4 pairs was further stratified based on the presence or absence of a history of MI or stroke. Subgroup analyses were conducted by age (<65 versus ≥65 years), sex, region (Asia versus non-Asia), with versus without diabetes, and with versus without aspirin among data sources that met the predefined diagnostic criteria, excluding the Kyung Hee University Medical Center database.

Cumulative incidence of the primary outcome was estimated using the Kaplan-Meier curve, and differences between groups were assessed using the log-rank test. Calibrated hazard ratios (HRs) and 95% CIs were calculated using the Cox proportional hazards model.[27] Statistical significance was defined as a 2-sided $P<0.05$. A random-effects meta-analysis was performed, and heterogeneity was assessed using the I^2 statistic.[28,29] Database construction and statistical analyses were performed using R software version 4.1.2 (R Foundation for Statistical Computing), using open-source statistical packages from the Observational

Health Data Sciences and Informatics HADES (Health-Analytics Data to Evidence Suite) software collection.[30]

Predefined Diagnostics

Three prespecified objective study diagnostic rules were implemented to ensure reliable analysis.[18] The rules included: (1) assessment of baseline characteristics to check covariate balance after PS methods; (2) preference score distributions (a transformation of PS) to evaluate empirical equipoise; and (3) expected absolute systematic error (EASE) to assess residual bias. PS adjustment was used to reduce the effects of confounding factors by balancing the confounder proportions. Covariate balance was assessed using the standardized mean difference, with values <0.25 indicating adequate balance.[31,32] In the 2 treatment groups, clinical equipoise was measured by the proportion of overlap in the treatment groups' preference score distributions. We set indifference in treatment selection between the target and comparator cohorts if >30% of participants in clinical equipoise had preference scores in the range of 0.3 to 0.7.[33] For each analysis, we estimated the EASE to check for systematic error.[34] The EASE score is a measurement tool to determine how much the observed risk differs from the actual risk of 257 negative control outcomes (Table S3). If systematic errors exist, the EASE score is high. The threshold for the EASE score was set at <0.25. The prespecified study diagnostic rules were considered satisfied when all 3 conditions were met, and only databases that met all rules were included in each meta-analysis.

Data Availability

This study was conducted using a distributed research network based on a common data model, in which patient-level data remain under the control of the respective data partners. The patient-level data used in this study were not shared due to concerns regarding patient privacy. The study protocol and open, executable source code used in this study are available at https://github.com/ohdsi-studies/DdiPpiClo.

RESULTS

Cohort Selection and Characteristics

Among the 14 databases, 3 were from the United States, 1 was from Taiwan, and 10 were from South Korea. Between January 1985 and December 2023, 479,041 new eligible users of clopidogrel and sPPIs (239 427 patients) or wPPIs (239 614 patients) were identified (Figure 1). Among the study population, women comprised 45% of sPPI users and 44% of wPPI users (Table). Among 168 738 PS-matched pairs, the prevalence of comorbidities was as follows: hypertension (78%), ischemic heart disease (56%), gastroesophageal reflux disease (50%), and diabetes (37%). In addition, lipid-modifying agents were prescribed to 75% of patients in both groups. The prescription rate of aspirin was 40% in the clopidogrel+sPPIs and 39% in the clopidogrel+wPPIs. Comparing clopidogrel+sPPIs with clopidogrel+H2RA, the prescription rate of aspirin was also comparable between the 2 groups (39% versus 42% before PS matching). After PS matching, among 168 738 matched pairs, the standardized mean differences for all baseline characteristics between sPPI and

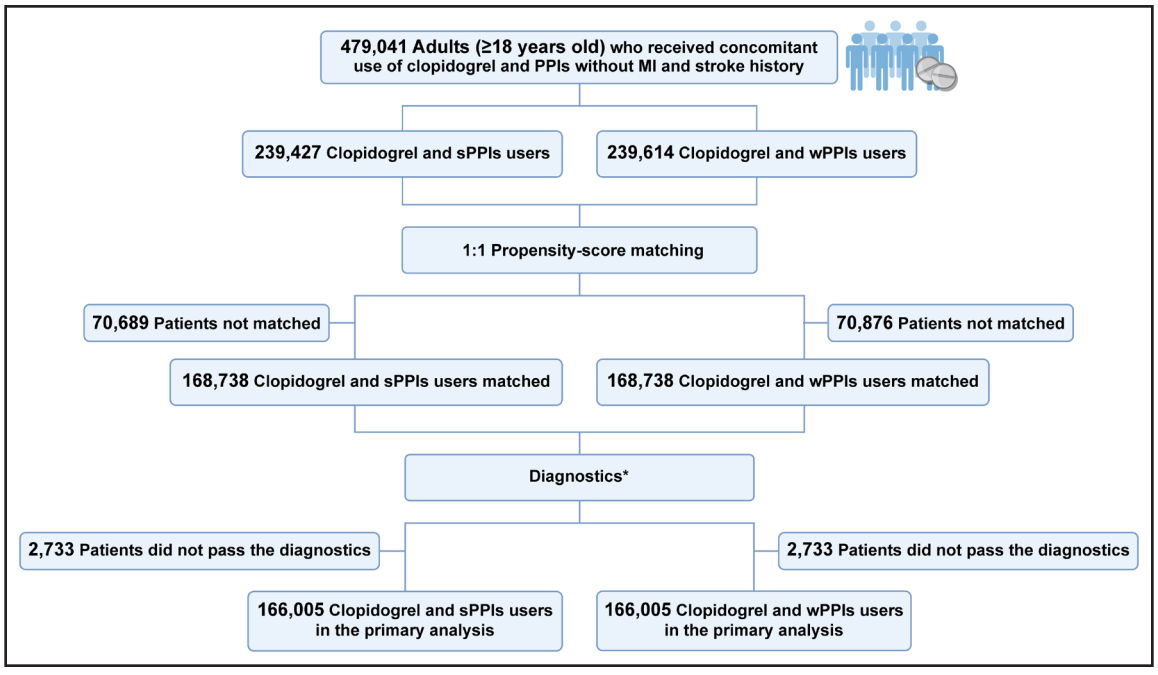

Figure 1. Study flowchart.
CYP indicates cytochrome P450; sPPI, strong CYP2C19-inhibiting proton pump inhibitor; and wPPIs, weak or non-CYP2C19–inhibiting proton pump inhibitor. *The objective study diagnostics included (1) assessment of baseline characteristics to check covariate balance after propensity score (PS) methods; (2) preference score distributions (a transformation of PS) to evaluate empirical equipoise; and (3) expected absolute systematic error to assess residual bias. All 3 diagnostic rules needed to be satisfied for the analysis to be included in the analysis.

Table. Baseline Characteristics of Patients Before and After Propensity Score Matching Between Clopidogrel+sPPIs and Clopidogrel+wPPIs

Characteristic	Before propensity score matching			After propensity score matching		
	Clopidogrel+sPPIs (N=239 427)	Clopidogrel+wPPIs (N=239 614)	SMD	Clopidogrel+sPPIs (N=168 738)	Clopidogrel+wPPIs (N=168 738)	SMD
Age group, y, %						
<55	11.3	11.4	0.00	11.5	11.3	0.00
55–59	12.0	11.6	0.01	11.9	11.9	0.00
60–64	17.2	16.9	0.01	17.5	17.5	0.00
65–69	15.1	15.0	0.00	15.1	15.1	0.00
70–74	15.7	16.0	−0.01	15.7	15.7	0.00
75–79	14.1	14.3	0.00	14.1	14.1	0.00
80–84	9.4	9.6	−0.01	9.2	9.3	0.00
85+	5.0	5.3	−0.01	5.1	5.1	0.00
Sex: women, %	44.6	44.2	0.01	41.6	41.8	0.00
Medical history, %						
Hyperlipidemia	81.7	80.7	0.03	82.0	81.9	0.00
Hypertensive disorder	77.4	77.0	0.01	77.8	77.6	0.00
Acute respiratory disease	59.7	59.1	0.01	63.0	62.7	0.01
Ischemic heart disease	56.4	57.1	−0.01	56.4	56.1	0.01
Gastroesophageal reflux disease	46.8	47.4	−0.01	50.0	49.4	0.01
Diabetes	40.1	40.3	0.00	37.0	36.8	0.00
Peripheral vascular disease	35.6	34.4	0.03	35.5	35.3	0.00
Osteoarthritis	31.8	28.2	0.08	28.6	28.6	0.00
Cerebrovascular disease	25.6	25.3	0.01	25.5	25.5	0.00
Heart failure	18.0	18.0	0.00	17.9	17.8	0.00
Depressive disorder	17.5	17.5	0.00	17.5	17.3	0.01
Renal impairment	8.2	9.4	−0.05	8.7	8.7	0.00
Dementia	7.4	7.7	−0.01	7.5	7.5	0.00
Rheumatoid arthritis	4.9	4.4	0.03	4.5	4.5	0.00
Medication use, %						
Anti-inflammatory and antirheumatic products	84.5	81.9	0.07	81.6	81.6	0.00
Drugs for acid-related disorders	83.9	84.3	−0.01	84.1	83.9	0.00
Lipid-modifying agents	75.1	75.4	−0.01	75.2	75.2	0.00
Agents acting on the renin-angiotensin system	61.5	62.7	−0.02	61.7	61.8	0.00
Angiotensin II antagonists	54.1	54.9	−0.01	54.3	54.4	0.00
Calcium channel blockers	52.5	53.3	−0.02	52.6	52.5	0.00
β-Blockers	43.6	45.4	−0.04	44.1	44.0	0.00
Aspirin	39.2	41.6	−0.05	39.5	39.4	0.00
Diuretics	38.4	40.6	−0.04	38.9	38.8	0.00
Warfarin	1.5	1.8	−0.03	1.6	1.6	0.00

CYP indicates cytochrome P450; SMD, standardized mean difference; sPPI, strong CYP2C19-inhibiting proton pump inhibitor; and wPPI, weak or non-CYP2C19–inhibiting proton pump inhibitor.

wPPI users were <0.1 within each data source, indicating better balance than that before matching (Figures S2 and S3).

Results From Study Diagnostics Rules

The diagnostic results are shown in Table S4. After PS matching, the maximum values of absolute standardized mean difference for the 8 databases (167 648 pairs; database names: Health Insurance Review and Assessment, IBM Health MarketScan Commercial Claims and Encounters Database, Columbia University Medical Center, Ajou University School of Medicine, Gyeongsang National University Hospital, Kyung Hee University Medical Center, Pusan National University Hospital, and Yonsei University Health System) were lower than

0.25. For preference score distribution overlap (clinical equipoise), all databases except Taipei Medical University Clinical Research Database met the threshold value (Table S4; Figures S4 and S5). The range of preference score overlap in the passed data sources was 0.47 to 0.93. The EASE values, representing systematic bias, were <0.25 in 6 databases. The range of EASE was 0.01 to 0.19 in these 6 databases. Among the 168 783 pairs, there were 5 databases (166 005 pairs; database names: Health Insurance Review and Assessment, IBM Health MarketScan Commercial Claims and Encounters Database, Columbia University Medical Center, Kyung Hee University Medical Center, and Yonsei University Health System) where all 3 study diagnostic rules were passed. Only 5 databases that passed all objective study diagnostics were included in the meta-analysis.

Association of Concomitant Use of Clopidogrel and sPPIs With Cardiovascular Risk

During the 365 days after the index date, the MACE incidence rates were 17.63 per 1000 person-years (2822 patients) in the clopidogrel plus sPPIs group and 16.82 per 1000 person-years (2696 patients) in the clopidogrel plus wPPIs group (Figure 2). The incidence rates and cumulative incidence curves of the primary outcome in each database are shown in Figures 2 and 3, respectively. The risk of MACE was not statistically different between clopidogrel plus sPPIs and clopidogrel plus wPPIs (calibrated HR, 1.00 [95% CI, 0.79–1.26]; Figure 2). In the Kaplan-Meier curves, a statistically significant difference in cumulative MACE incidence between the 2 groups was observed in the IBM Health MarketScan Commercial Claims and Encounters Database, whereas no significant differences were detected in the remaining databases (Columbia University Medical Center, Health Insurance Review and Assessment, Kyung Hee University Medical Center, and Yonsei University Health System; Figure 3). Among the 120 negative control outcomes, 117 (97.5%) in the clopidogrel+sPPIs group versus the clopidogrel+wPPIs group had meta-analytic HRs with 95% CIs covering one after calibration (Figure S6).

There were no significant differences in the risk of cardiovascular mortality (incidence rate at 1 year, 11.74 per 1000 person-years in the clopidogrel+sPPIs group versus 11.36 per 1000 person-years in the clopidogrel+wPPIs group; calibrated HR, 1.10 [95% CI, 0.87–1.39]), MI (<7.42 per 1000 person-years in the clopidogrel+sPPIs group versus 7.68 per 1000 person-years in the clopidogrel+wPPIs group; calibrated HR, 0.98 [95% CI, 0.81–1.19]), stroke (<13.06 per 1000 person-years in the clopidogrel+sPPIs group versus 13.20 per 1000 person-years in the clopidogrel+wPPIs group; calibrated HR, 1.05 [95% CI, 0.87–1.27]), or all-cause mortality (30.66 per 1000 person-years in the clopidogrel+sPPIs group versus 30.89 per 1000 person-years in the clopidogrel+wPPIs group; calibrated HR, 1.18 [95% CI, 0.93–1.50]; Figure 4).

Sensitivity Analyses and Subgroup Analyses

The results of the sensitivity analyses using diverse time windows and PS models are shown in Table S5. The risk of MACE was slightly higher in the clopidogrel+sPPIs group than in the clopidogrel+wPPIs group in the 30-day posttreatment analysis (calibrated HR, 1.19 [95% CI, 1.01–1.40]) and the on-treatment analysis (calibrated HR, 1.32 [95% CI, 1.10–1.59]). However, no significant difference was observed in the intention-to-treat analysis (calibrated HR, 1.06 [95% CI, 0.91–1.23]). Concomitant use of clopidogrel and sPPIs, compared with concomitant use of clopidogrel and wPPIs, was not associated with an increased risk of MACE using 1:variable-ratio PS matching (calibrated HR, 0.93 [95%

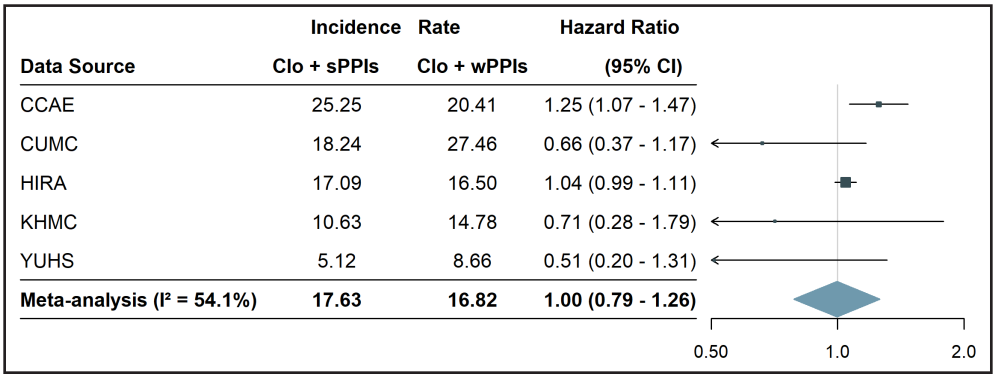

Figure 2. Comparative risks of the primary outcome (major adverse cardiovascular events) between clopidogrel (Clo)+strong CYP (cytochrome P450) 2C19–inhibiting proton pump inhibitors (sPPIs) and Clo+weak or non-CYP2C19–inhibiting proton pump inhibitors (wPPIs) in meta-analysis.
CCAE indicates IBM Health MarketScan Commercial Claims and Encounters Database; CUMC, Columbia University Medical Center; HIRA, Health Insurance Review and Assessment; KHMC, Kyung Hee University Medical Center; and YUHS, Yonsei University Health System.

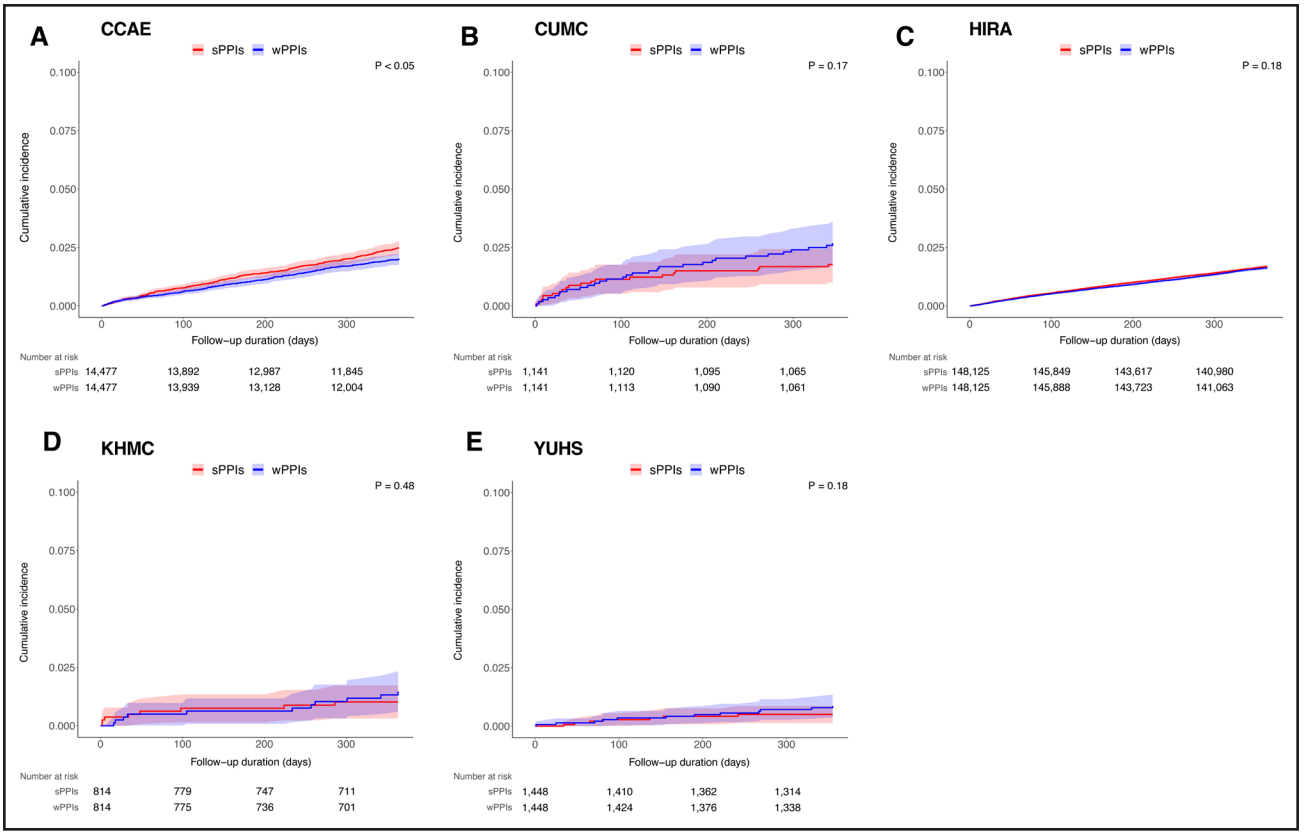

Figure 3. Kaplan-Meier plots for risk of the primary outcome (major adverse cardiovascular events) between clopidogrel (Clo)+strong CYP (cytochrome P450) 2C19-inhibiting proton pump inhibitors (sPPIs) vs Clo+weak or non-CYP2C19–inhibiting proton pump inhibitors (wPPIs).

CCAE indicates IBM Health MarketScan Commercial Claims and Encounters Database; CUMC, Columbia University Medical Center; HIRA, Health Insurance Review and Assessment; KHMC, Kyung Hee University Medical Center; and YUHS, Yonsei University Health System.

CI, 0.69–1.24]) or PS stratification (calibrated HR, 1.00 [95% CI, 0.83–1.21]).

The results of the sensitivity analyses for each outcome across the various target-comparator cohort pairs are shown in Table S6. The results using H2RA as an alternative active comparator were consistent (calibrated HR for MACE, 0.90 [95% CI, 0.60–1.34]) with those of the primary analysis. When comparing the overall

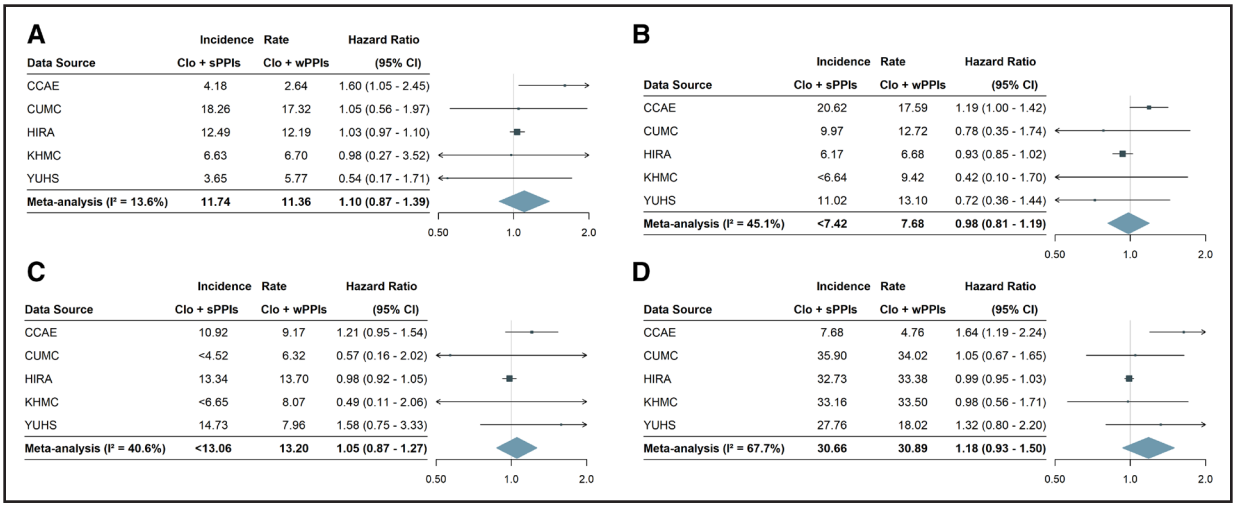

Figure 4. Comparative risks of the secondary outcome (cardiovascular mortality, myocardial infarction, stroke, and all-cause mortality) between clopidogrel (Clo)+strong CYP (cytochrome P450) 2C19-inhibiting proton pump inhibitors (sPPIs) and Clo+weak or non-CYP2C19–inhibiting proton pump inhibitors (wPPIs) in meta-analysis.

CCAE indicates IBM Health MarketScan Commercial Claims and Encounters Database; CUMC, Columbia University Medical Center; HIRA, Health Insurance Review and Assessment; KHMC, Kyung Hee University Medical Center; and YUHS, Yonsei University Health System.

clopidogrel+PPI population with the clopidogrel+H2RA group, the risk of MACE was also not significantly different between the 2 groups (meta-analytic HR, 0.99 [95% CI, 0.87–1.13]). There was no significantly higher MACE risk in patients with ACS (calibrated HR, 0.99 [95% CI, 0.89–1.10]) or in those without previous gastrointestinal bleeding (calibrated HR, 1.03 [95% CI, 0.90–1.18]). In addition, we confirmed that there was no association with cardiovascular events when comparing the cohorts, even after including individuals with a history of MI and stroke.

The results of the subgroup analyses are shown in Figure S7. Across all subgroups stratified by age, sex, region, diabetes comorbidity, and concomitant aspirin use, the risk of MACE did not differ between patients treated with clopidogrel+sPPIs and those treated with clopidogrel+wPPIs.

DISCUSSION

This study evaluated the comparative cardiovascular risk associated with the concomitant use of clopidogrel and sPPIs versus clopidogrel and wPPIs across 14 databases, including populations from the United States, Taiwan, and South Korea. This study analyzes the clinical interaction between clopidogrel and sPPIs versus that between clopidogrel and wPPIs across countries. In the large-scale observational study, the meta-analysis found no significant difference in the risk of MACE between the 2 groups (calibrated HR, 1.00 [95% CI, 0.79–1.26]) or in secondary outcomes. Sensitivity analyses across various time windows and comparison groups confirmed these findings. However, a short-term effect was observed, with a statistically significant increase in MACE risk in the early exposure windows.

The potential interaction with pharmacodynamic consequences has been reported between PPIs and clopidogrel in several studies.[20,35] One proposed mechanism suggests that drug absorption is more efficient in an acidic environment; therefore, the use of PPIs or other acid-reducing agents may elevate gastric pH, potentially hindering or delaying the absorption process.[36] A more widely recognized mechanism suggests that PPIs interfere with the activation of clopidogrel by inhibiting CYP2C19, a key enzyme involved in its metabolic conversion to active metabolites.[37] Because PPIs, particularly omeprazole and esomeprazole, also rely on CYP2C19 for their own metabolism, their concurrent use with clopidogrel may lead to competitive inhibition at the enzymatic level. This interaction can reduce the bioavailability of clopidogrel's active metabolite, potentially diminishing its antiplatelet efficacy.[15,35–37]

Omeprazole and esomeprazole exhibit irreversible or quasi-irreversible, metabolism-dependent inhibition of CYP2C19, whereas other PPIs, such as lansoprazole, act as mild inhibitors, and pantoprazole and rabeprazole exert minimal or no inhibition of this hepatic enzyme.[11,38,39] Several pharmacokinetic studies and randomized clinical trials have demonstrated that omeprazole and esomeprazole may attenuate the antiplatelet activity of clopidogrel by competitively inhibiting CYP2C19-mediated biotransformation to its active metabolite.[4,11,20–23] Consequently, both the European Medicines Agency and US Food and Drug Administration issued warnings regarding the potential interaction of clopidogrel with omeprazole or esomeprazole.[6,7] As a precaution, they advised against the concurrent use of these medications unless there was a compelling clinical need. However, findings from the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial), the only large-scale randomized controlled trial evaluating the effects of PPIs in patients receiving dual antiplatelet therapy, showed that omeprazole significantly reduced gastrointestinal events without increasing cardiovascular risks.[40] Nevertheless, the aforementioned trial specifically investigated omeprazole and was not adequately powered to definitively rule out a potential interaction between PPI use and cardiovascular outcomes.

Given these concerns, the 2023 European guideline advised against the use of sPPIs for gastric protection in patients with diabetes receiving clopidogrel for cardiovascular disease management.[8] This recommendation was based on a meta-analysis reporting a significantly increased risk of MACE with omeprazole (odds ratio, 1.40 [95% CI, 1.15–1.70]) and esomeprazole (odds ratio, 1.59 [95% CI, 1.29–1.95]).[8,14] However, a closer examination of the meta-analysis reveals several limitations. Some observational studies included in the analysis lacked robust methodologies, such as PS analysis, leading to baseline characteristic differences and potential uncontrolled confounding.[41] In addition, in observational studies, PPI users often had more comorbidities and higher baseline risks compared with those not receiving PPIs, which may have introduced bias and exaggerated adverse outcomes.[15] However, all observational studies in the meta-analysis used nonuse as a control group. To mitigate this, we selected weak competitive inhibitors, such as wPPIs and H2RAs, as active comparators. Third, the odds ratios were derived from unadjusted event counts rather than the risk values from original studies. Finally, combining randomized controlled trials with observational studies in a single meta-analysis may have introduced a potential source of bias.

Strengths and Limitations

Our study has several methodological strengths. To enhance the methodological rigor and reliability of our findings, we applied 3 prespecified diagnostic criteria when selecting databases for meta-analysis: covariate balance assessment, clinical equipoise evaluation, and residual bias estimation. Only databases that satisfied all 3 conditions were included: (1) ensuring well-balanced covariates, (2) maintaining sufficient overlap in preference score distributions (clinical equipoise), and (3)

minimizing residual bias, as assessed through an extensive range of negative control outcomes. By restricting our analysis to databases that met these strict criteria, we reduced confounding, maintained equipoise, and controlled for systematic error, thereby strengthening the validity and robustness of our meta-analysis compared with previous studies.[31,33,34] Defining decision thresholds in advance mitigates biases arising from the retrospective justification of diagnostic shortcomings or assumption breaches.[42] Moreover, we included a large number of study participants from 14 data sources that were converted to the Observational Medical Outcomes Partnership Common Data Model, which reduces the potential for bias specific to individual databases.

Despite its strengths, this observational cohort study has some limitations. First, prescriptions did not account for actual patient use or potential over-the-counter purchases. However, only certain PPIs, such as omeprazole and lansoprazole, have been approved for over-the-counter use.[23] Furthermore, PPIs are not available as over-the-counter drugs in South Korea. Second, although we used a previously validated outcome definition, using diagnostic codes in the operational definition of the outcome may result in potential misclassification bias.[43] Third, the potential for residual confounding factors cannot be excluded from this observational study. To enhance comparability between the exposure groups, we implemented a large-scale PS matching. Fourth, we did not assess genetic polymorphisms because CYP2C19 genotype information was unavailable. Therefore, the applicability of our findings to patients carrying CYP2C19 loss-of-function alleles should be interpreted with caution. Although the IBM Health MarketScan Commercial Claims and Encounters Database showed a numerically higher risk of MACE among clopidogrel–sPPI users, no significant difference in treatment effects was observed between Asian and non-Asian databases, and this pattern was not reproduced in the overall meta-analysis or regional subgroup analyses. However, given that CYP2C19 allele frequencies are known to differ substantially across populations, a genotype-related effect cannot be completely excluded. Although residual confounding cannot be fully ruled out, the large-scale PS model used in this study, which incorporated thousands of baseline clinical and medication covariates, may have partly mitigated unmeasured or indirectly measured confounding through correlated covariates, as demonstrated in recent methodological research.[44] The potential influence of CYP2C19 genetic polymorphisms on the clopidogrel and PPI interaction warrants further investigation.

Conclusions

When a rigorous study design with predefined diagnostic rules was used to assess bias, there was no difference in the incidence of major cardiovascular events between sPPIs and wPPIs in patients taking clopidogrel. This large-scale study did not support the clinical significance of potential interactions between PPIs and clopidogrel. Still, a transient early increase in risk was noted, and enhanced clinical attention during the early phase of sPPI initiation in clopidogrel users may be reasonable.

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Author Contributions

Seonji Kim, S.C. You, and S.I. Seo contributed to concept and design. Seonji Kim, S.C. You, and S.I. Seo drafted the manuscript. Seonji Kim contributed to other editorials/conceptuals. G. Hripcsak, J.C. Hsu, P. Nagy, W.G. Shin, S.C. You, and S.I. Seo contributed to critical review of the manuscript for important intellectual content. Seonji Kim, J. Park, H.Y. Chen, C.H. Setiawan, H. Lee, B. Martin, K.J. Lee, Subin Kim, P.-A. Nguyen, P. Thanh-Phuc, M.S. Muhtar, and M.-H. Hsu contributed to the statistical analysis. S.C. You and S.I. Seo obtained funding and supervised the study. All authors contributed to the acquisition, analysis, or interpretation of data.

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Disclosures

S.C. You reports grants from Daiichi Sankyo. He is a coinventor of granted Korean patents DP-2023-1223 and DP-2023-0920 and has pending Patent Applications DP-2024-0909, DP-2024-0908, DP-2022-1658, DP-2022-1478, and DP-2022-1365, unrelated to the current work. He is also the Chief Executive Officer of PHI Digital Healthcare. The other authors report no conflicts of interest.

Supplemental Material

Tables S1–S6
Figures S1–S7

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Supplemental Materials

Comparison of cardiovascular events in patients receiving concomitant clopidogrel and proton pump inhibitors classified by CYP2C19 inhibitory potency

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Major Resources Table

Major Resources Table

Data & Code Availability

Description	**Source / Repository**	**Persistent ID / URL**
Electronic medical records and administrative claims data converted to the Observational Medical Outcomes Partnership Common Data Model (OMOP-CDM) were used from 14 data sources. All databases consisted of de-identified, patient-level electronic health records transformed into a CDM-standardized vocabulary using the same analysis program.	OMOP-CDM from 14 data sources (Details of the included databases are provided in Table S1)	The study protocol and source code are available at https://github.com/ohdsi-studies/DdiPpiClo.

Supplementary Tables

Table S1. Data Source

Data source	Population	Patients (millions)	History	Description
Health Insurance Review and Assessment (HIRA)	Korea, general	50	2012-2021	National administrative claims database covering the South Korea population
IBM Health MarketScan Commercial Claims and Encounters Database (CCAE)	USA, general	119	2008-2017	Health insurance claims adjudicated for treatment (e.g., inpatient, outpatient, pharmacy) by large employers and health insurance plans that provide private health insurance to employees, spouses, and dependents
Columbia University Medical Center (CUMC)	USA, general	6.9	1989-2022	Electronic health record database from academic medical center
Johns Hopkins Medicine (JHM)	USA, general	2.2	2016-2023	Electronic health record database from academic medical center
Taipei Medical University Clinical Research Database (TMUCRD)	Taiwan, general	3.6	2001 to 2020	Electronic health record database from 3 academic medical centers (Taipei Medical University Hospital, Wanfang Hospital, and Shuang Ho Hospital)
Ajou University School of Medicine (AUSOM)	Korea, general	2.8	1994-2023	Electronic health record database from academic medical center
Daegu Catholic University Medical Center (DCMC)	Korea, general	0.9	2005-2022	Electronic health record database from academic medical center
Gyeongsang National University Changwon Hospital (GNUCH)	Korea, general	0.3	2016-2022	Electronic health record database from academic medical center
Gyeongsang National University Hospital (GNUH)	Korea, general	0.6	2009-2022	Electronic health record database from academic medical center

Kangdong Sacred Heart Hospital (KDH)	Korea, general	1.2	1986-2022	Electronic health record database from academic medical center
Kyung Hee University Medical Center (KHMC)	Korea, general	1.2	2008-2022	Electronic health record database from academic medical center
Kyung Hee University Hospital at Gangdong (KHNMC)	Korea, general	0.8	2006-2021	Electronic health record database from academic medical center
Pusan National University Hospital (PNUH)	Korea, general	1.8	2011-2020	Electronic health record database from academic medical center
Yonsei University Health System (YUHS)	Korea, general	5.4	1997-2023	Electronic health record database from academic medical center

Table S2. Outcome definitions

Outcome	Logical description	ICD-9-CM	ICD-10
Major adverse cardiovascular events	Earliest record of myocardial infarction or stroke occurring during an inpatient or ER visit, or cardiovascular mortality		
Myocardial infarction	Record of myocardial infarction during an inpatient or ER visit	410; 410.01; 410.02; 410.1; 410.11; 410.12; 410.2; 410.21; 410.22; 410.3; 410.31; 410.32; 410.4; 410.41; 410.42; 410.5; 410.51; 410.52; 410.6; 410.61; 410.62; 410.7; 410.71; 410.72; 410.8; 410.81; 410.82; 410.9; 410.91; 410.92 (Excluded: 412)	I21.0; I21.1; I21.2; I21.3; I21.4; I21.9; I22.0; I22.1; I22.8; I22.9 (Excluded: I25.2)
Stroke	Earliest record of stroke during an inpatient or ER visit	290.4; 290.41; 290.42; 290.43; 346.6; 346.61; 346.62; 346.63; 430; 431; 432; 432.1; 432.9; 433.01; 433.11; 433.21; 433.31; 433.81; 433.91; 434.0; 434; 434.01; 434.1; 434.11; 434.9; 434.91; 767; 772.1; 772.11; 772.12; 772.13; 772.14; 772.2; 779.7; 800.2; 800.21; 800.22; 800.23; 800.24; 800.25; 800.26; 800.29; 800.3; 800.31; 800.32; 800.33; 800.34; 800.35; 800.36; 800.39; 800.7; 800.71; 800.72; 800.73; 800.74; 800.75; 800.76; 800.79; 800.8; 800.81; 800.82; 800.83; 800.84; 800.85; 800.86; 800.89; 801.2; 801.21; 801.22; 801.23; 801.24; 801.25; 801.26; 801.29; 801.3; 801.31; 801.32; 801.33; 801.34; 801.35; 801.36; 801.39; 801.7; 801.71; 801.72; 801.73; 801.74; 801.75; 801.76; 801.79; 801.8; 801.81; 801.82; 801.83; 801.84; 801.85; 801.86; 801.89; 803.2; 803.21; 803.22; 803.23; 803.24; 803.25; 803.26; 803.29; 803.3; 803.31; 803.32; 803.33; 803.34; 803.35; 803.36; 803.39; 803.7; 803.71; 803.72; 803.73; 803.74; 803.75; 803.76; 803.79; 803.8; 803.81; 803.82; 803.83; 803.84; 803.85; 803.86; 803.89; 804.2; 804.21; 804.22; 804.23; 804.24; 804.25; 804.26; 804.29; 804.3; 804.31; 804.32; 804.33; 804.34; 804.35; 804.36; 804.39; 804.7; 804.71; 804.72; 804.73; 804.74; 804.75; 804.76; 804.79; 804.8; 804.81; 804.82; 804.83; 804.84; 804.85; 804.86;	F01.0; F01.1; F01.3; G36.1; G46.5; G46.6; G46.7; I60; I60.0; I60.1; I60.2; I60.3; I60.4; I60.5; I60.6; I60.7; I60.8; I60.9; I61; I61.0; I61.1; I61.2; I61.3; I61.4; I61.5; I61.6; I61.8; I61.9; I62; I62.0; I62.1; I62.9; I63; I63.0; I63.1; I63.2; I63.3; I63.4; I63.5; I63.6; I63.8; I63.9; I67.0; P10.0; P10.1; P10.2; P10.3; P52; P52.0; P52.1; P52.2; P52.3; P52.4; P52.5; P52.6; P52.8; P52.9; S06.4; S06.40; S06.41; S06.5; S06.50; S06.51; S06.6; S06.60; S06.61

		804.89; 852; 852.01; 852.02; 852.03; 852.04; 852.05; 852.06; 852.09; 852.1; 852.11; 852.12; 852.13; 852.14; 852.15; 852.16; 852.19; 852.2; 852.21; 852.22; 852.23; 852.24; 852.25; 852.26; 852.29; 852.3; 852.31; 852.32; 852.33; 852.34; 852.35; 852.36; 852.39; 852.4; 852.41; 852.42; 852.43; 852.44; 852.45; 852.46; 852.49; 852.5; 852.51; 852.52; 852.53; 852.54; 852.55; 852.56; 852.59; 853; 853.01; 853.02; 853.03; 853.04; 853.06; 853.09; 853.1; 853.11; 853.12; 853.13; 853.14; 853.15; 853.16; 853.19; 854.02; 854.03; 854.04; 854.12; 854.13; 997.02	
Cardiovascular mortality	Death record indicating at least one heart failure event during hospitalization or ER visit, or cardiovascular-related condition (myocardial infarction, stroke, or sudden cardiac death) recorded between 30 and 7 days before death	Heart failure: 402.01; 402.11; 402.91; 404.01; 404.03; 404.11; 404.13; 404.91; 404.93; 415; 428; 428.1; 428.2; 428.21; 428.22; 428.23; 428.3; 428.31; 428.32; 428.33; 428.41; 428.42; 428.43; 428.9 (Excluded: 398.91) Sudden cardiac death: 427.5; 779.85; 798; 798.1; 798.2 (Excluded: 427.4; 427.41)	Heart failure: I11.0; I11.00; I11.01; I11.02; I11.09; I13.0; I13.00; I13.01; I13.02; I13.09; I13.2; I13.20; I13.21; I13.22; I13.29; I26.0; I50; I50.0; I50.00; I50.01; I50.02; I50.09; I50.1; I50.10; I50.11; I50.12; I50.19; I50.9; P29.0 Sudden cardiac death: I46; I46.0; I46.1; I46.9; R95.0; R95.9; R96; R96.0
All-cause mortality	Death record of any type		

Table S3. List of negative control outcomes

OMOP Concept ID	Outcome Name
4175583	3-Methylglutaconic aciduria type 2
443698	Abnormal anal Papanicolaou smear
375824	Abnormal auditory perception
435574	Abnormal form of root of tooth
4262562	Abnormal heart beat
439935	Abnormal posture
436409	Abnormal pupil
443702	Abnormal response to nerve stimulation
443585	Abrasion and/or friction burn of multiple sites
4088768	Absent nipple
380818	Acquired deformity of head
31668	Acquired deformity of neck
4319325	Acquired deformity of trunk
432411	Acquired equinus deformity of foot
439673	Acute hepatitis B with delta-agent (coinfection) without hepatic coma
441481	Adult victim of abuse
435720	Adverse anesthesia outcome
4218106	Alcoholism
4303805	Allergic reaction to bite and/or sting
4254371	Altered growth and development
434916	Amphetamine or psychostimulant dependence, continuous
4101660	Amputated below knee
4198962	Amputated thumb
4155909	Anesthesia of skin
4171556	Ankle ulcer
45757682	Anomaly of jaw size
77650	Aseptic necrosis of bone
439237	Assault
76744	Azoospermia
4216219	Bizarre personal appearance

141797	Black piedra
433813	Bladder neck obstruction
436230	Blood chemistry abnormal
74698	Breech presentation
256449	Bronchiectasis
79232	Burn of ankle
134765	Cachexia
4172458	Candidiasis of skin
4228429	Carnitine deficiency
42709838	Cellulitis of lower limb
4213540	Cervical somatic dysfunction
443570	Cervicovaginal cytology: Low grade squamous intraepithelial lesion
439674	Chronic viral hepatitis B without delta-agent
438262	Chyluria
4066505	Clicking hip
196454	Colostomy and enterostomy malfunction
4201390	Colostomy present
134734	Compartment syndrome
46269889	Complication due to Crohn's disease
4173078	Complication due to immunization
438624	Complication of renal dialysis
72995	Contracture of joint of hand
80492	Contracture of knee joint
439666	Contracture of multiple joints
199978	Contusion of lower limb
433071	Contusion of multiple sites
4022071	Convalescence
432729	Crying infant
75389	Current tear of lateral cartilage AND/OR meniscus of knee
80242	Current tear of medial cartilage AND/OR meniscus of knee
73575	Deformity of toe
436233	Delayed milestone
443737	Dental restoration lost

438183	Denture occlusion incorrect
438759	Descemet's membrane fold
4101282	Dietary selenium deficiency
4115402	Difficulty sleeping
4022078	Discord with counselor
436906	Disease caused by rickettsiae
4135080	Dislocation of radial head
201091	Disproportion - major pelvic abnormality
372329	Dissociated deviation
4155818	Does climb
4196636	Dysarthria
433441	Ectopic production of endocrine substance
433111	Effects of hunger
78834	Effusion of joint of hand
4247710	Effusion of joint of pelvic region
72407	Effusion of joint of shoulder region
439791	Emotional upset
4150043	Epididymitis
4029271	Essential fatty acid deficiency
197607	Excessive and frequent menstruation
40480271	Extra unidentified structurally abnormal chromosome
193598	Extravasation of urine
439128	Extreme prematurity of infant
4059015	Falls
4092896	Feces contents abnormal
4182437	Female genital cutting
4118057	Fetal or neonatal effect of maternal oligohydramnios
4229403	Flat anterior chamber of eye
4069540	Flexion deformity of knee
374801	Foreign body in ear
4096540	Foreskin deficient
441487	Frostbite
73564	Full thickness rotator cuff tear

439788	Galactosemia
40481632	Ganglion cyst
435775	Genetic anomaly of leukocyte
74855	Genital herpes simplex
437744	Heat exhaustion
440021	Herpes simplex without complication
437489	Herpes zoster with complication
440329	Herpes zoster without complication
4012570	High risk sexual behavior
77364	Hypermobility of coccyx
441829	Hyperosmolality and or hypernatremia
4287416	Hyperphenylalaninemia
192298	Hypersplenism
74731	Hypertrophic osteoarthropathy
440129	Hypertrophy of nasal turbinates
4029280	Hypervitaminosis B6
435522	Hypervitaminosis D
434004	Hypervolemia
4024266	Hypocupremia
440072	Hypogammaglobulinemia
437390	Hypoxemia
443447	Iatrogenic hypotension
432596	Immune defect
4344500	Impingement syndrome of shoulder region
4090353	Incompetent urethral closure mechanism
441417	Incoordination
434485	Increase in body fat
440276	Infection AND/OR inflammatory reaction due to internal prosthetic device, implant AND/OR graft
434872	Infection by Trichomonas
4057662	Infestation by Phthirus
440053	Infestation by insect
442120	Injection site extravasation

4168222	Intra-abdominal and pelvic swelling, mass and lump
440710	Intraretinal microvascular abnormality
72994	Jaccoud's syndrome
78512	Joint contracture of the ankle and/or foot
78228	Joint derangement
77072	Joint effusion of ankle AND/OR foot
72404	Joint stiffness
4115991	Knee joint effusion
4093346	Large prostate
133088	Late amputation stump complication
436041	Leech infestation
4228331	Leukokeratosis nicotina palati
377873	Lid lag
4027782	Lipid storage disease
435516	Lipoprotein deficiency disorder
4297984	Local infection of wound
440638	Lyme disease
4083487	Macular drusen
438067	Malaria
4051630	Malingering
436426	Malleus mobility reduced
44783760	Mammographic calcification of breast
258540	Marfan's syndrome
438297	Mechanical complication of cardiac device, implant AND/OR graft
432798	Mechanical complication of internal orthopedic device, implant AND/OR graft
439082	Menopausal syndrome
436940	Metabolic syndrome X
435247	Metallosis
45757258	Minimal keratinized residual ridge mucosa
40480000	Multiple complications due to diabetes mellitus
137967	Muscle, ligament and fascia disorders
4271024	Musculoskeletal fibromatosis
134315	Myelophthisis

4195085	Nasal congestion
4209423	Nicotine dependence
4035269	Non-ketotic hyperglycinemia
434016	Nondependent opioid abuse, continuous
201792	Nongonococcal urethritis
40480893	Nonspecific tuberculin test reaction
72413	Nontraumatic rupture of muscle
198802	Occlusion of ureter
4215978	Onychomycosis
140648	Onychomycosis due to dermatophyte
4129408	Open wound of ankle
4053600	Open wound of elbow
77139	Open wound of finger without complication
444426	Open wound of foot except toes without complication
137426	Open wound of forearm without complication
77421	Open wound of hand except fingers without complication
4051004	Open wound of scalp
4129404	Open wound of upper arm
438130	Opioid abuse
438120	Opioid dependence
4171915	Orchitis
315361	Orthopnea
74080	Orthostatic proteinuria
75920	Osteitis condensans
437359	Osteochondritis dissecans
378160	Otorrhea
439035	Otosclerosis
77356	Pathological dislocation of joint
4022076	Patient dependence on care provider
375292	Perforation of tympanic membrane
78162	Peripheral vertigo
437092	Physiological development failure
253796	Pneumothorax

4295261	Postmenopausal state
4202045	Postviral fatigue syndrome
433542	Precipitate labor
4094448	Pregnancy test negative
434319	Premature ejaculation
198715	Premature menopause
439081	Premenstrual tension syndrome
46286594	Problem related to lifestyle
199876	Prolapse of female genital organs
4295888	Prolapse of intestine
194997	Prostatitis
439790	Psychalgia
440068	Psychosexual dysfunction
435028	Puerperal pyrexia of unknown origin
4245252	Raised prostate specific antigen
436246	Reduced libido
45772079	Retinopathy of prematurity stage 0
436828	Saliva abnormal
435088	Senility
4052226	Sequelae of injuries of lower limb
4056577	Sequelae of open wound of head
4233565	Severe protein-calorie malnutrition (Gomez: less than 60% of standard weight)
4250163	Sexual arousal disorder
4096999	Short rib
4305303	Sleep deprivation
195926	Slowing of urinary stream
4125590	Slurred speech
4019836	Social exclusion
444127	Specimen satisfactory for evaluation but limited
4345332	Spinal instability
443172	Splinter of face, without major open wound
443082	Starvation
440233	Strain of supraspinatus muscle AND/OR tendon

135852	Teething syndrome
4195698	Tenosynovitis
4339088	Testicular mass
440457	Threatened miscarriage
374907	Tics of organic origin
80946	Tinea manus
4163280	Tinea of perianal region
133141	Tinea pedis
433244	Tooth loss
440268	Toxic effect of carbon monoxide
81930	Transient arthropathy
4029731	Trimethylaminuria
74719	Ulcer of foot
443593	Ulcer of thigh
4199550	Unable to mobilize
4002572	Uncomplicated sedative, hypnotic AND/OR anxiolytic withdrawal
4092743	Unsteady when standing
195591	Urethral overactivity
4216708	Urgent desire for stool
80070	Uric acid urolithiasis
4088910	Uterine cervix absent
4092565	Uterine prolapse
4088920	Uterus absent
435131	Victim of neglect
261599	Vocal cord paralysis
4104132	Vomit contains feces
439405	Walking disability
132834	White piedra
435723	Wound seroma
440193	Wristdrop

Table S4. Results of pre-defined study diagnostics

Data source	Max SMD[a]	Preference score overlap[b]	EASE[c]	Overall[d]
Health Insurance Review and Assessment (HIRA)	0.03	0.76	0.01	PASS
IBM Health MarketScan Commercial Claims and Encounters Database (CCAE)	0.05	0.90	0.03	PASS
Columbia University Medical Center (CUMC)	0.21	0.66	0.07	PASS
Johns Hopkins Medicine (JHM)	0.33	0.54	0.18	FAIL
Taipei Medical University Clinical Research Database (TMUCRD)	0.47	0.16	0.45	FAIL
Ajou University School of Medicine (AUSOM)	0.20	0.47	0.38	FAIL
Daegu Catholic University Medical Center (DCMC)	0.27	0.49	-	FAIL
Gyeongsang National University Changwon Hospital (GNUCH)	0.51	0.64	-	FAIL
Gyeongsang National University Hospital (GNUH)	0.21	0.65	-	FAIL
Kangdong Sacred Heart Hospital (KDH)	0.35	0.59	-	FAIL
Kyung Hee University Medical Center (KHMC)	0.20	0.81	0.19	PASS
Kyung Hee University Hospital at Gangdong (KHNMC)	0.33	0.74	-	FAIL
Pusan National University Hospital (PNUH)	0.21	0.93	0.42	FAIL
Yonsei University Health System (YUHS)	0.16	0.84	0.18	PASS

[a] If the standardized mean difference for all predefined covariates is less than 0.25, the balance diagnostic passes, indicating sufficient covariate balance has been achieved. [b] In both cohorts, if greater than 30% of patients had a preference score between 0.3 and 0.7, the equipoise diagnosis was considered passed. [c] If the EASE score is less than 0.25, the EASE diagnosis is passed. If there are not enough results for the negative control results (less than 4), the EASE estimation becomes infeasible. [d] The final study diagnostics are passed if all pre-defined diagnostics are passed.

Abbreviations: SMD, standardized mean difference; EASE, Expected Absolute Systematic Error.

Table S5. Risk of primary outcome between clopidogrel + sPPIs vs. clopidogrel + wPPIs by times of risk definition and propensity score models

	Target subjects		IR (per 1,000 person-year)		Hazard ratio (95% CI)
	Target subjects	Comparator subjects	Target subjects	Comparator subjects	
Times of risk definition					
30-day after treatment	344/163,743	293/163,743	25.61	21.81	1.19 (1.01-1.40)
Intention-to-treat	13,026/166,005	12,781/166,005	17.31	16.88	1.06 (0.91-1.23)
During treatment	256/151,580	216/151,580	13.96	10.90	1.32 (1.10-1.59)
Propensity score models					
1:variable-ratio PS matching	2,822/166,005	4,104/231,258	17.63	18.41	0.93 (0.69-1.24)
PS stratification [strata: 10]	3,736/235,089	4,129/232,068	16.44	18.47	1.00 (0.83-1.21)

Abbreviations: sPPIs, proton pump inhibitors with strong CYP2C19-inhibiting potency; wPPIs, proton pump inhibitors with weak or minimal CYP2C19-inhibiting potency; IR, incidence rate; CI, confidence interval.

Table S6. Risk of incident cardiovascular event between clopidogrel + sPPIs vs. clopidogrel + wPPIs by study population

	Target subjects		IR (per 1,000 person-year)		Hazard ratio (95% CI)
	Target subjects	Comparator subjects	Target subjects	Comparator subjects	
Patients (without prior MI or stroke): Clopidogrel and sPPIs vs. Clopidogrel and H2RAs					
MACE	<257/12,410	<259/12,410	<22.72	<22.81	0.90 (0.60-1.34)
Cardiovascular mortality	<76/12,410	<60/12,410	<6.67	<5.24	1.27 (0.89-1.82)
MI	194/12,410	194/12,410	17.13	17.05	0.97 (0.78-1.20)
Stroke	118/12,410	107/12,410	10.39	9.37	1.07 (0.81-1.40)
All-cause mortality	146/12,410	123/12,410	12.83	10.75	1.15 (0.89-1.48)
Patients (without prior MI or stroke): Clopidogrel and overall PPIs vs. Clopidogrel and H2RAs					
MACE	1,261/74,476	<1,277/74,476	17.55	<17.76	0.99 (0.87-1.13)
Cardiovascular mortality	794/74,476	<807/74,476	11.01	<11.18	0.99 (0.86-1.14)
MI	598/74,476	588/74,476	8.32	8.18	1.02 (0.88-1.19)
Stroke	1,051/74,476	1,136/74,476	14.67	15.85	1.00 (0.81-1.25)
All-cause mortality	2,156/74,476	2,178/74,476	29.90	30.18	0.99 (0.88-1.12)
ACS patients (without prior MI or stroke): clopidogrel + sPPIs vs. clopidogrel + wPPIs					
MACE	738/36,541	743/36,541	20.86	20.98	0.99 (0.89-1.10)
Cardiovascular mortality	498/36,541	484/36,541	14.02	13.61	1.02 (0.90-1.16)
MI	354/36,541	391/36,541	10.02	11.05	0.98 (0.69-1.40)
Stroke	460/36,541	521/36,541	13.03	14.75	0.88 (0.77-1.00)
All-cause mortality	1,201/36,541	1,191/36,541	33.82	33.48	1.22 (0.66-2.26)
Patients without GI bleeding (without prior MI or stroke): Clopidogrel + sPPIs vs. clopidogrel + wPPIs					
MACE	2,516/156,096	2,480/156,096	16.68	16.44	1.03 (0.90-1.18)
Cardiovascular mortality	<1,652/156,096	<1,653/156,096	<10.92	<10.92	1.00 (0.93-1.07)
MI	1,093/156,096	1,114/156,096	7.25	7.39	0.99 (0.89-1.09)
Stroke	<1,930/156,096	1,940/156,096	<12.83	12.90	1.07 (0.84-1.37)
All-cause mortality	4,316/156,096	4,401/156,096	28.53	29.08	1.08 (0.90-1.29)
Clopidogrel and sPPIs vs. Clopidogrel and wPPIs					
MACE	6,824/282,361	6,858/282,361	25.19	25.30	1.00 (0.88-1.13)
Cardiovascular mortality	5,772/282,361	5,812/282,361	21.23	21.37	1.07 (0.84-1.35)
MI	1,841/282,361	1,894/282,361	6.79	6.99	0.85 (0.61-1.17)
Stroke	<2,343/282,361	2,395/282,361	<8.65	8.84	0.98 (0.91-1.05)
All-cause mortality	11,413/282,361	11,777/282,361	41.97	43.30	1.09 (0.93-1.28)
Clopidogrel and sPPIs vs. Clopidogrel and H2RAs					
MACE	329/16,808	316/16,808	21.54	20.59	1.01 (0.85-1.21)

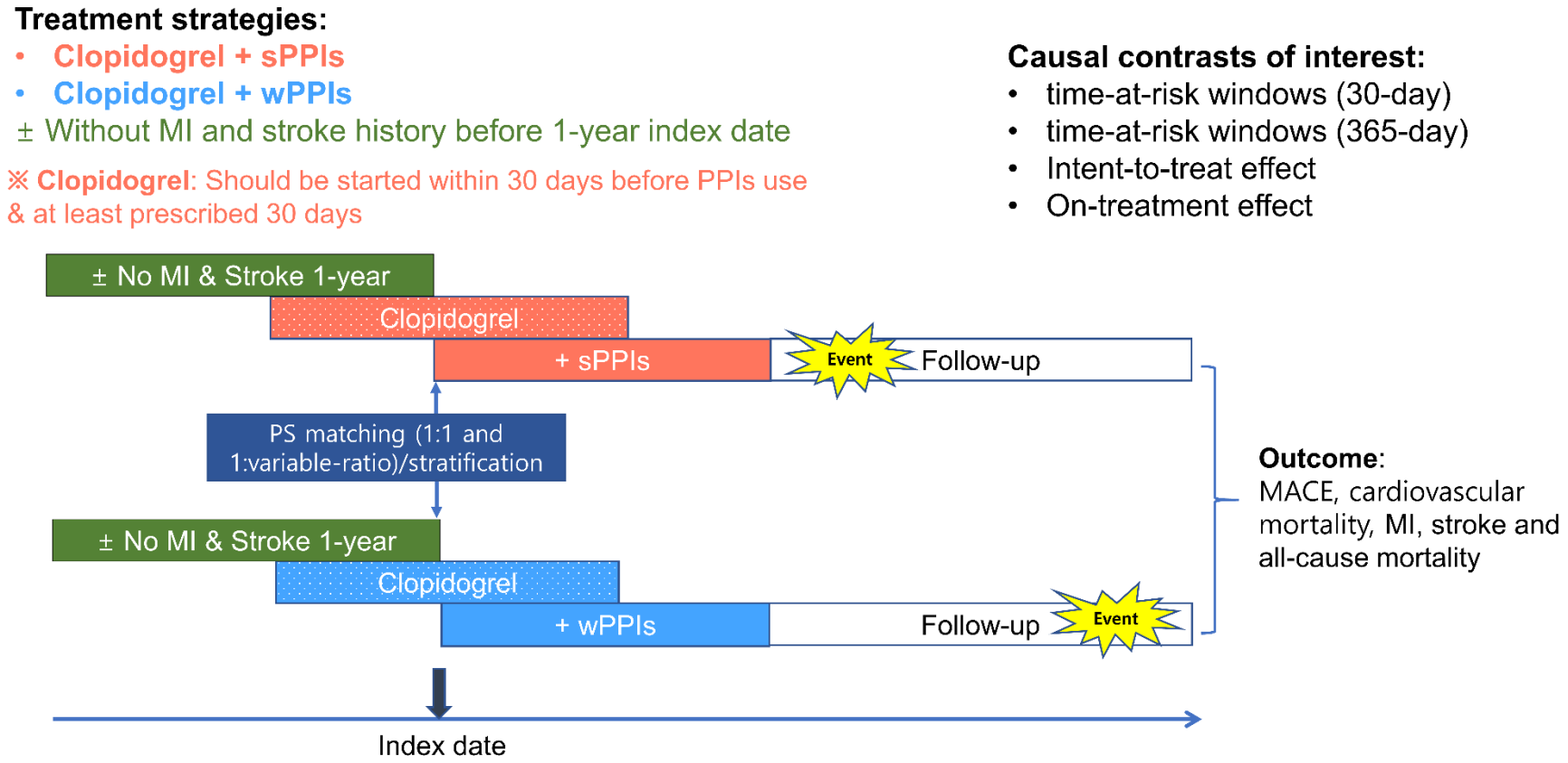
Cardiovascular mortality	115/16,808	112/16,808	7.48	7.25	1.00 (0.76-1.31)
MI	233/16,808	<229/16,808	15.23	<14.90	0.99 (0.81-1.22)
Stroke	<146/16,808	<117/16,808	<9.51	<7.58	1.20 (0.93-1.56)
All-cause mortality	233/16,808	228/16,808	15.17	14.77	0.99 (0.81-1.21)
ACS patients: Clopidogrel + sPPIs vs. clopidogrel + wPPIs					
MACE	2,073/67,809	2,081/67,809	32.01	32.07	1.00 (0.93-1.07)
Cardiovascular mortality	1,652/67,809	1,624/67,809	25.32	24.84	1.02 (0.95-1.10)
MI	439/67,809	481/67,809	6.75	7.38	0.91 (0.80-1.04)
Stroke	748/67,809	790/67,809	11.52	12.15	0.95 (0.85-1.05)
All-cause mortality	3,039/67,809	3,052/67,809	46.58	46.68	1.05 (0.84-1.31)
Patients without GI bleeding: Clopidogrel + sPPIs vs. clopidogrel + wPPIs					
MACE	5,995/264,647	6,017/264,647	23.55	23.63	0.94 (0.75-1.18)
Cardiovascular mortality	4,913/248,084	4,951/248,084	20.43	20.60	0.89 (0.62-1.26)
MI	1,690/264,647	1,740/264,647	6.64	6.83	0.97 (0.77-1.22)
Stroke	<2,191/264,647	<2,205/264,647	<8.61	<8.66	0.99 (0.93-1.06)
All-cause mortality	9,837/264,647	10,153/264,647	38.51	39.74	1.00 (0.90-1.11)

In databases where the number of outcome events was less than 5, the exact count was not collected to protect patient privacy.

Abbreviations: IR, incidence rate; CI, confidence interval; sPPIs, proton pump inhibitors with strong CYP2C19-inhibiting potency; wPPIs, proton pump inhibitors with weak or minimal CYP2C19-inhibiting potency; MI, myocardial infarction; MACE, major adverse cardiovascular event; ACS, acute coronary syndrome; GI bleeding, gastrointestinal bleeding.

Supplementary Figures

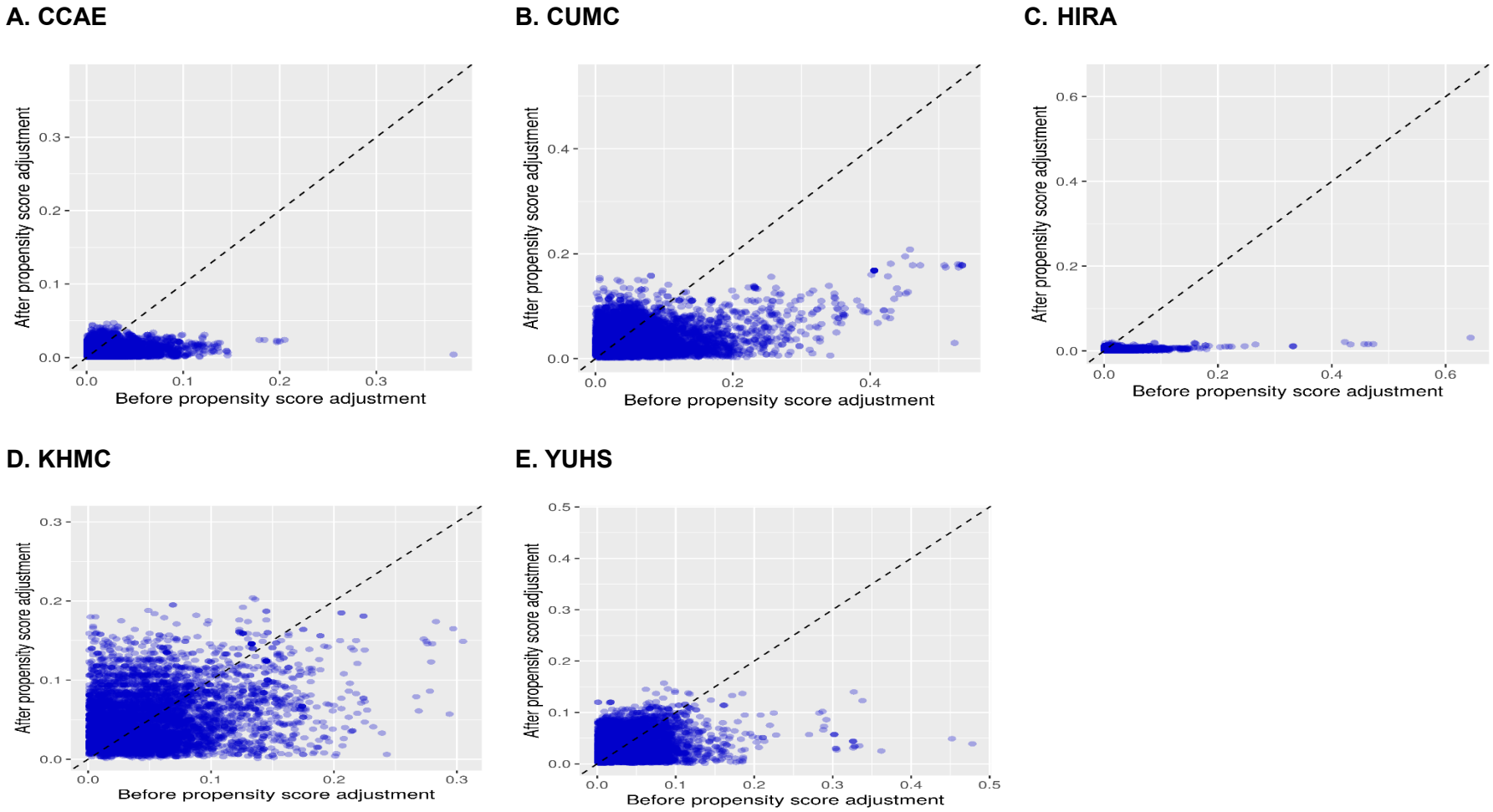
Figure S1. Overview of cohort definitions



Abbreviations: sPPIs, proton pump inhibitors with strong CYP2C19-inhibiting potency; wPPIs, proton pump inhibitors with weak or minimal CYP2C19-inhibiting potency; MI, myocardial infarction; PPIs, proton pump inhibitors; H2RAs, histamine receptor type 2 blockers; PS, propensity score; MACE, major

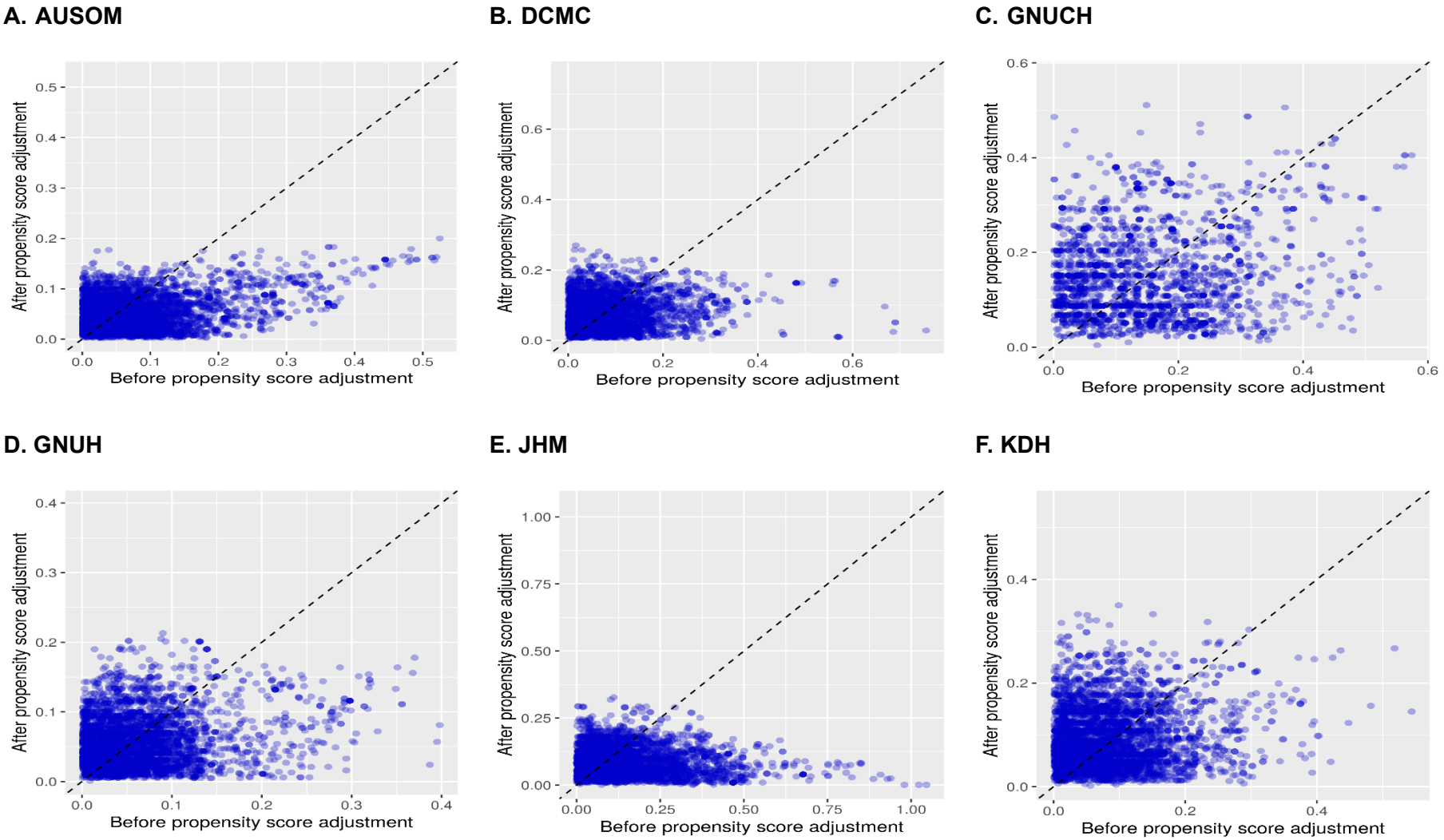
adverse cardiovascular event.

Figure S2. Covariate balance plot before and after propensity score matching for databases included in the meta-analysis

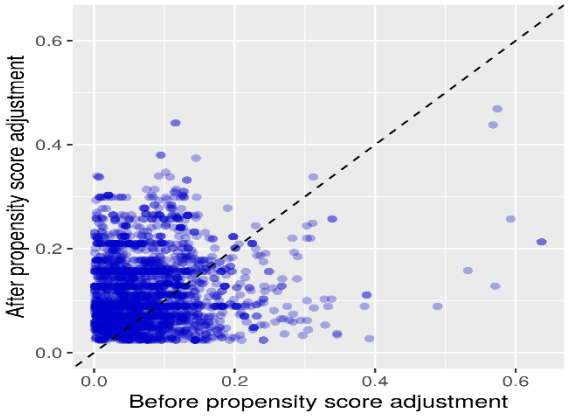


Abbreviations: CCAE, IBM Health MarketScan Commercial Claims and Encounters Database; CUMC, Columbia University Medical Center; HIRA, Health Insurance Review and Assessment; KHMC, Kyung Hee University Medical Center; YUHS, Yonsei University Health System.

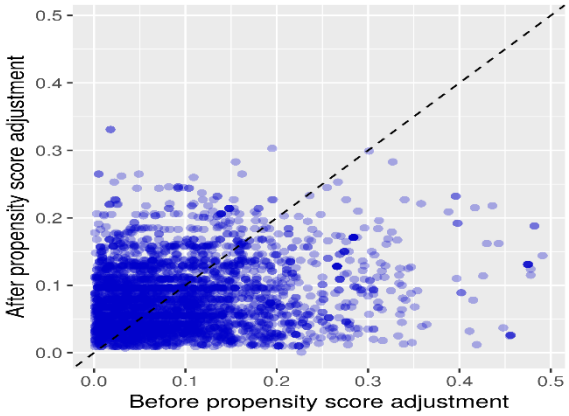
Figure S3. Covariate balance plot before and after propensity score matching for databases not included in the meta-analysis



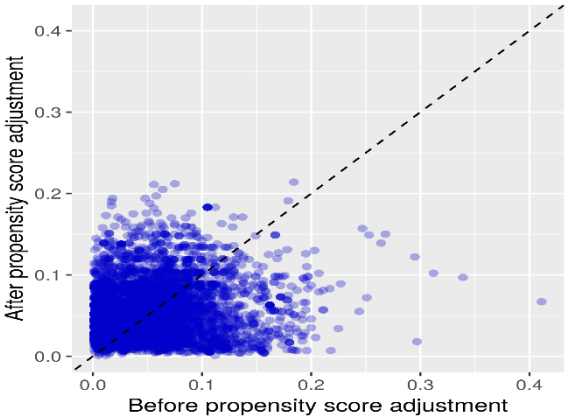
G. TMUCRD



H. KHNMC

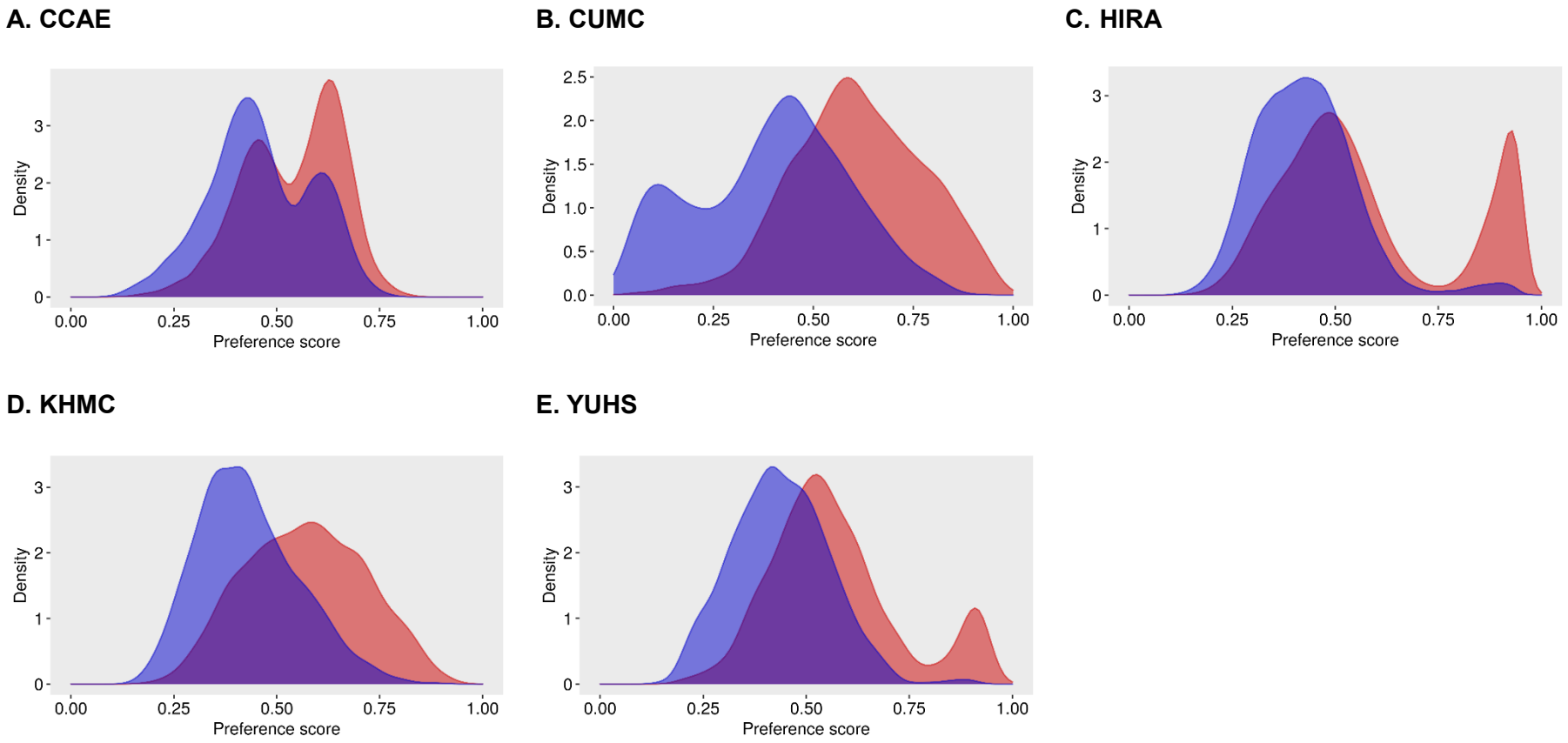


I. PNUH



Abbreviations: AUSOM, Ajou University School of Medicine; DCMC, Daegu Catholic University Medical Center; GNUCH, Gyeongsang National University Changwon Hospital; GNUH, Gyeongsang National University Hospital; JHM, Johns Hopkins Medicine; KDH, Kangdong Sacred Heart Hospital; TMUCRD, Taipei Medical University Clinical Research Database; KHNMC, Kyung Hee University Hospital at Gangdong; PNUH, Pusan National University Hospital.

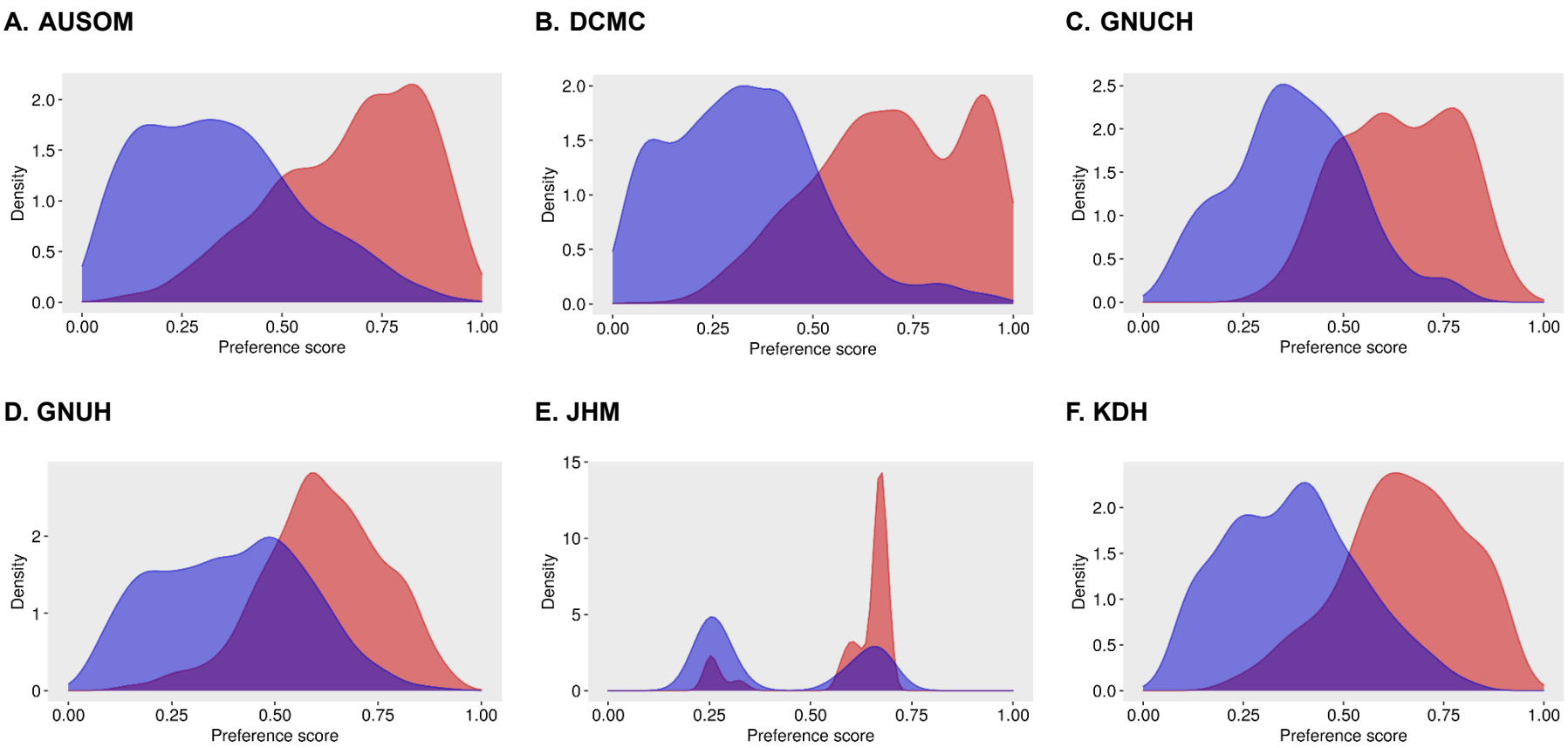
Figure S4. Preference score distributions in the target and comparator cohorts for databases included in the meta-analysis

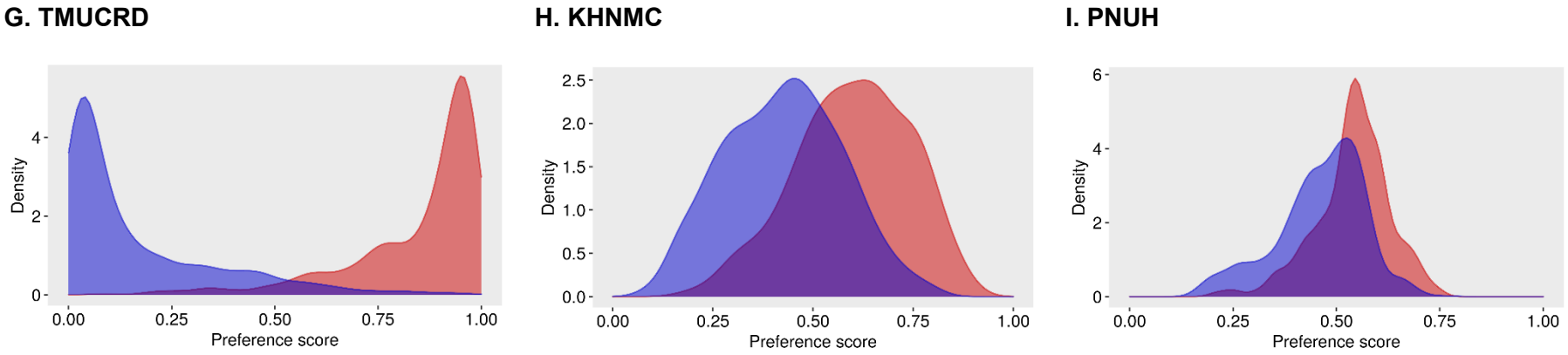


The preference score is a transformation of propensity score that adjusts for differences in prevalence across populations. For each pair, we fit large-scale propensity score model using baseline characteristics of the study population. A higher overlap between distributions indicates that cohorts in the target (left, red) and comparator (right, blue) are more similar in terms of their predicted probability of receiving one treatment over the other.

Abbreviations: CCAE, IBM Health MarketScan Commercial Claims and Encounters Database; CUMC, Columbia University Medical Center; HIRA, Health Insurance Review and Assessment; KHMC, Kyung Hee University Medical Center; YUHS, Yonsei University Health System.

Figure S5. Preference score distributions in the target and comparator cohorts for databases not included in the meta-analysis

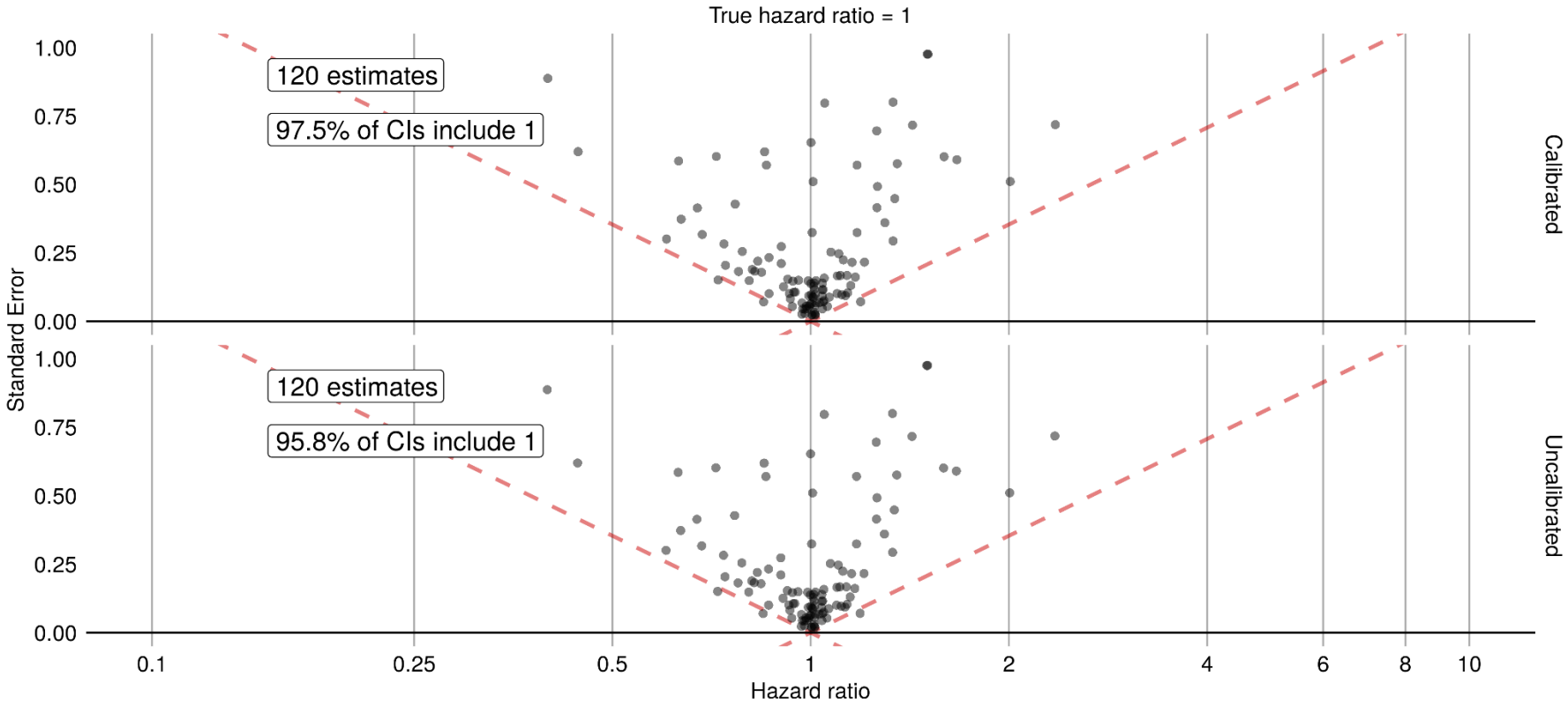




The preference score is a transformation of propensity score that adjusts for differences in prevalence across populations. For each pair, we fit large-scale propensity score model using baseline characteristics of the study population. A higher overlap between distributions indicates that cohorts in the target (left, red) and comparator (right, blue) are more similar in terms of their predicted probability of receiving one treatment over the other.

Abbreviations: AUSOM, Ajou University School of Medicine; DCMC, Daegu Catholic University Medical Center; GNUCH, Gyeongsang National University Changwon Hospital; GNUH, Gyeongsang National University Hospital; JHM, Johns Hopkins Medicine; KDH, Kangdong Sacred Heart Hospital; TMUCRD, Taipei Medical University Clinical Research Database; KHNMC, Kyung Hee University Hospital at Gangdong; PNUH, Pusan National University Hospital.

Figure S6. Systematic error control of effect estimation in the meta-analysis

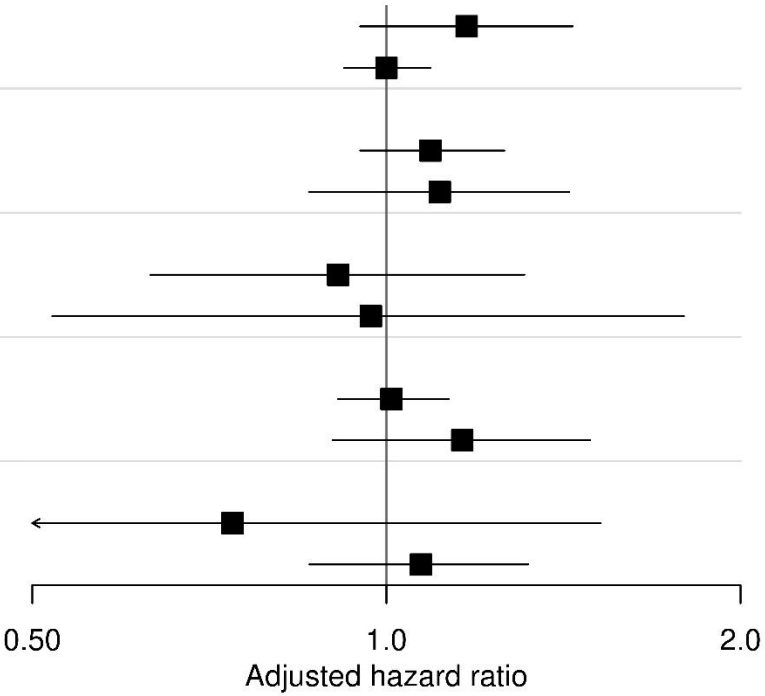


The funnel plots present the hazard ratio and standard error of negative controls in the meta-analysis of comparison of clopidogrel + sPPIs group versus clopidogrel + wPPIs group. In each panel, bottom plot is the result before calibration and top plot is the result after calibration of confidence interval. Nominal 95% confidence intervals cover 95.8% (115/120) and 97.5% (117/120) before and after calibration of confidence interval, respectively.

Abbreviations: CI, confidence interval; sPPIs, proton pump inhibitors with strong CYP2C19-inhibiting potency; wPPIs, proton pump inhibitors with weak or minimal CYP2C19-inhibiting potency.

Figure S7. Subgroup analyses of the primary outcome (MACE) between clopidogrel + sPPIs and clopidogrel + wPPIs

Subgroup	Incidence Rate		Hazard Ratio
	Clo + sPPIs	Clo + wPPIs	(95% CI)
Age group			
<65 years	<10.98	9.28	1.17 (0.95–1.44)
≥65 years	<22.52	<22.11	1.00 (0.92–1.09)
Sex			
Men	<18.42	16.92	1.09 (0.95–1.26)
Women	<16.97	16.42	1.11 (0.86–1.43)
Region			
Asia	16.94	16.42	0.91 (0.63–1.31)
Non–Asia	24.71	20.95	0.97 (0.52–1.79)
Comorbidity			
With DM	<22.39	21.81	1.01 (0.91–1.13)
Without DM	14.60	13.89	1.16 (0.90–1.49)
Comedication			
With aspirin	<18.09	21.51	0.74 (0.36–1.52)
Without aspirin	<15.19	14.41	1.07 (0.86–1.32)



In databases where the number of outcome events was less than 5, the exact count was not collected to protect patient privacy.

Abbreviations: IR, incidence rate; CI, confidence interval; sPPIs, proton pump inhibitors with strong CYP2C19-inhibiting potency; wPPIs, proton pump inhibitors with weak or minimal CYP2C19-inhibiting potency; DM, diabetes mellitus.