Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethod 1. Data source

Optum® de-identified Electronic Health Record dataset

Optum electronic health record (EHR) is an aggregated and de-identified electronic health record repository from US health systems. The medical record data includes clinical information, inclusive of prescriptions as prescribed and administered, lab results, vital signs, body measurements, diagnoses, procedures, and information derived from clinical notes using natural language processing (NLP). The data from November 20, 2011 to March 3, 2019 were used for this study. New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subject research.

IQVIA-Hospital Charge Data Master

Anonymized patient level data are sourced from hospital charge data masters and collected from resource management software within short-term, acute-care and non-federal hospitals in the United States. Data covers over 86 million patients, 122,000 providers, 230 specialties and more than 530 million unique visits from 2007 to 2018. The data from November 14, 2011 to June 29, 2018 were used for this study. A retrospective database study on this de-identified data is deemed not human subject research. Approval is provided for OHDSI community studies.

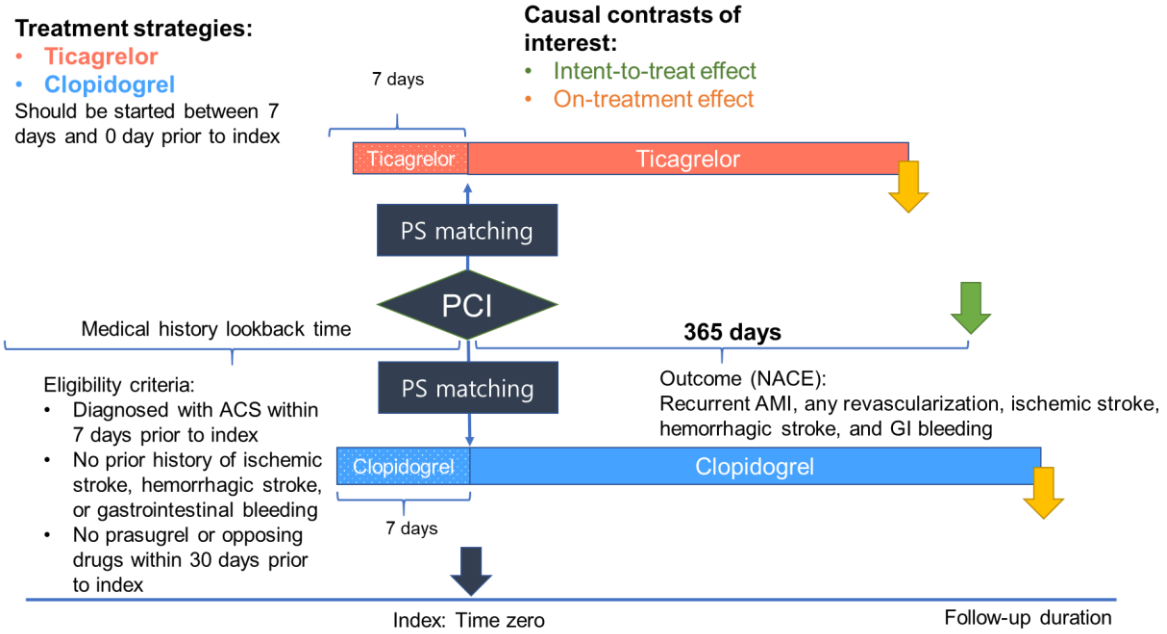
HIRA

HIRA claims data include healthcare utilization information of the entire population of South Korea, consisting of diagnosis, procedure, drug, medical material, healthcare resource, etc. The current study is conducted based on the converted CDM data[1] of the patients who received PCIs between 2007 and 2016. The CDM data include 462,486 patients with more than 155 million claims information. The data from February 28, 2013 to December 31, 2016 were used for this study. The present study was approved by the Scientific and Ethical Advisory Board of the HIRA (Project number: 2017-034-002)

eMethod 2. Cohort definitions

OHDSI's ATALS is an open source software tool (http://www.ohdsi.org/web/atlas/#/home) for researchers to conduct scientific analyses on standardized observational data converted to the OMOP Common Data model v5. Researchers can create cohorts by defining groups of people based on an exposure to a drug or diagnosis of a particular condition using healthcare data.

Supplementary Figure. Graphical overview of the cohorts and study design



Abbreviation: ACS, acute coronary syndrome; AMI, acute myocardial infarction; GI, gastrointestinal; NACE, net adverse clinical event; PCI, percutaneous coronary intervention; PS, propensity score.

Ticagrelor cohort

We define a cohort of ticagrelor user in the following way.
Index rule defining the patient index date:

- A procedure of percutaneous coronary intervention for the first time in the person's history with age ≥ 20.

Inclusion rule based on the index date:

- At least 365 days of observation time prior to the index date
- A diagnosis of acute coronary syndrome within 7 days prior to the index date
- Initiation of ticagrelor within 7 days prior to the index date

Exclusion rule based on the index date:

- Drug exposure of clopidogrel or prasugrel within 30 days prior to the index date
- Previous history of ischemic or hemorrhagic stroke
- Previous history of gastrointestinal bleeding

Censoring rule

- The cohort was censored when the patient stopped to continue ticagrelor more than 7 days

A parameterized SQL translation for cohort generation in any OMOP CDM v5 databases is available in: https://github.com/ohdsi-studies/TicagrelorVsClopidogrel/blob/master/inst/sql/sql_server/Ticagrelor.sql.

Clopidogrel cohort

We define a cohort of clopidogrel user in the following way.

Index rule defining the patient index date:

- A procedure of percutaneous coronary intervention for the first time in the person's history with age ≥ 20.

Inclusion rule based on the index date:

- At least 365 days of observation time prior to the index date
- A diagnosis of acute coronary syndrome within 7 days prior to the index date
- Initiation of clopidogrel within 7 days prior to the index date

Exclusion rule based on the index date:

- Drug exposure of ticagrelor or prasugrel within 30 days prior to the index date
- Previous history of ischemic or hemorrhagic stroke
- Previous history of gastrointestinal bleeding

Censoring rule

- The cohort was censored when the patient stopped to continue clopidogrel more than 7 days

A parameterized SQL translation for cohort generation in any OMOP CDM v5 databases is available in: https://github.com/ohdsi-studies/TicagrelorVsClopidogrel/blob/master/inst/sql/sql_server/Clopidogrel.sql.

eMethod 3. Individual outcome definitions

For each outcome, we developed an operational phenotype definition to determine if observational data could in fact support evaluation of the outcome. Where possible, concept sets originated with published code lists (eg ICD-9-CM and ICD-10). We developed definition of outcome cohorts and query to extract them using ATLAS, the OHDSI open-source platform (https://github.com/OHDSI/atlas). We executed these definitions on EHR data of Korean tertiary hospital to validate the definitions. Positive predictive values were estimated by a physician's manual chart review of discharge notes.

Supplementary Table. Outcome definition

Outcome	Logical description	ICD-9-CM	ICD-10	CPT4	PPV, % (n)
Acute myocardial infarction	Record of acute 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;410.7;410.71;410.72;410.8;410.81;410.82;410.9;410.91;410.92	I21.0;I21.1;I21.2;I21.3;I21.4;I21.9		83.8 (83/99)
Revascularization	Record of PCI or CABG during an inpatient or ER visit			566;567;33510;33511;33512;33513;33514;33516;33517;33518;33519;33521;33522;33523;33533;33534;33535;33536;33542;33545;33548;33572;33621;35506;35694;92920;92921;92924;92925;92928;92929;92933;92934;92937;92938;92941;92943;92944;1006199;1006200;1006208;1006216;1006217	100.0 (30/30)
Ischemic stroke	Earliest record of ischemic stroke during an inpatient or ER visit	346.6;346.6;346.61;346.62;346.63;433.01;433.11;433.21;433.31;433.81;433.91;434.01;434.11;434.91;997.02	I63.9;I63.8;I63.6;I63.5;I63.4;I63.3;I63.2;I63.1;I63.0;I63;G46.7;G46.6;G46.5;F01.3;F01.1;F01.0		72.9 (70/96)

Supplementary Table. Outcome definition (continued)

Hemorrhagic stroke	Earliest record of intracranial hemorrhage without concomitant ischemic stroke during an inpatient or ER visit	430;431;432;432;432.1;432.9	I60;I60.0;I60.5;I60.6;I60.7;I60.8;I60.9;I61.0;I61.1;I61.2;I61.3;I61.4;I61.5;I62;I62.0;I62.1;I62.9		100.0 (46/46)
Gastrointestinal bleeding	Gastrointestinal hemorrhage condition record during an inpatient or ER visit	530.21;530.7;530.82;531;531;531.01;531.2;531.2;531.21;531.4;531.4;531.41;531.6;531.6;531.61;532;532;532.01;532.2;532.2;532.21;532.4;532.4;532.41;532.6;532.6;532.61;533;533;533.01;533.2;533.2;533.21;533.4;533.4;533.41;533.6;533.6;533.61;534;534;534.01;534.2;534.2;534.21;534.4;534.4;534.41;534.6;534.6;534.61;535.01;535.11;535.21;535.31;535.41;535.51;535.61;535.71;537.83;537.84;562.02;562.03;562.12;562.13;569.3;569.85;578;578;578.1;578.9	K22.6;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;K62.5;K92.0;K92.1;K92.2		95.8 (68/71)
Dyspnea	Record of dyspnea	786.02;786.05	R06.0		94.7 (18/19)
All-cause mortality	Death record of any type				

PPV was represented as % (number of true positive cases / number of examined cases).
Abbreviation: PPV, positive predictive value; ER, emergency room

eMethod 4. Weighted incidence of net adverse clinical event

Similar to the paper of Eikelboom et al.[3], we estimated the weighted incidence of net adverse clinical event using following formula:

$$\text{net adverse clinical event} = \left[Incidence\ rate(IR)_{ischemic\ stroke} + \text{w1}IR_{acute\ myocardial\ infarction} + \text{w2}IR_{revascularization} + \text{w3}IR_{GI\ bleeding} + \text{w4}IR_{hemorrhagic\ stroke}\right]$$

Weights for each event represent the ratio of the adjusted hazard ratios of that event for 1-year mortality, using the hazard ratio for ischemic stroke as a reference. We used Korean National Health Insurance Service-National Sample Cohort[1,4] to calculate estimated the weights for each outcome (ischemic stroke, acute myocardial infarction, revascularization, gastrointestinal bleeding, and hemorrhagic stroke), since this database has complete record of mortality of randomly sampled 2% of Korean general population from 2002 to 2013. Until 2013, ticagrelor was not approved to use in Korea. Hazard ratios for 1-year mortality between patients with the outcome versus without outcome are estimated in the cohort with identical inclusion criteria with clopidogrel group of the study.
The estimate of weighted net adverse clinical event was higher in ticagrelor group than clopidogrel (461.82 per 1000 person-year in ticagrelor vs 374.0 per 1000 person-year in clopidogrel; absolute rate difference = 87.8 per 1000 person-year). We did not perform the statistical analysis to identify the significance.

Supplementary Table. Hazards ratios for death and weights for ischemic and bleeding events in the clopidogrel group

	Clopidogrel group in NHIS-NSC (n=3 205)			
	Events/Deaths	HR (95% CI)	*P*	Weight*
Ischemic stroke	55/6	2.50 (0.92-5.73)	.05	1
Acute myocardial infarction	386/37	3.31 (2.16-4.98)	<.001	1.32
Revascularization	247/4	0.42 (0.13-1.03)	.10	0.17
Gastrointestinal bleeding	51/11	6.27 (2.88-12.70)	<.001	2.51
Hemorrhagic stroke	12/6	25.94 (7.44-89.89)	<.001	10.37

*Weights (w1, w2, w3, and w4) are the ratio of the HR using for ischemic stroke as a reference.

Weighted incidence of Net Adverse Clinical Event in Ticagrelor group per 1000 person*year =
7.5(ischemic stroke) + 81.1 * 1.32 (Acute MI) + 42.7 * 0.17 (Revascularization) + 19.0 * 6.27 (gastrointestinal bleeding) + 21.3 * 10.37 (Hemorrhagic stroke)
= 461.82 / 1000 PY
Weighted incidence of Net Adverse Clinical Event in Clopidogrel group per 1000 person*year =
8.1 (ischemic stroke) + 81.8 * 1.32 (Acute MI) + 43.0 * 0.17 (Revascularization) + 14.1 * 6.27 (gastrointestinal bleeding) + 15.7 * 10.37 (Hemorrhagic stroke)
= 373.98 / 1000 PY

eMethod 5. Falsification endpoints

Falsification endpoints (negative control outcomes) are concepts known to not be associated with the target or comparator cohorts, such that we can assume the true relative risk between the two cohorts is 1. Total of 96 falsification endpoints are selected using a similar process to that outlined by Voss et al.[2] The concept IDs and SNOMED codes are described below.

Supplementary Table. Falsification endpoint list

OMOP Concept ID	SNOMED code	Outcome Name
378256	46670006	Abnormal reflex
4218106	7200002	Alcoholism
440424	87486003	Aphasia
439237	52684005	Assault
378424	82649003	Astigmatism
261880	46621007	Atelectasis
134118	400190005	Atrophic condition of skin
4224118	40492006	Bladder dysfunction
80509	203465002	Bone cyst
434626	20010003	Borderline personality disorder
438407	78004001	Bulimia nervosa
134765	238108007	Cachexia
4172458	49883006	Candidiasis of skin
436740	17382005	Cervical incompetence
381581	1482004	Chalazion
4307254	423125000	Closed fracture
4047787	123971006	Colles' fracture
198075	240542006	Condyloma acuminatum
73302	64217002	Curvature of spine
4242416	58588007	Cutis laxa
433163	238107002	Deficiency of macronutrients
4047269	229844004	Deformity of foot
133228	80967001	Dental caries
4095288	26298008	Diabetic coma with ketoacidosis
4044391	230572002	Diabetic neuropathy
443767	25093002	Diabetic oculopathy
4147672	30415006	Disease due to Papilloma virus
4140510	3305006	Disorder of lymphatic vessel
433440	78667006	Dysthymia
376132	62909004	Ectropion
440695	302690004	Encopresis
438872	267023007	Excessive eating - polyphagia
78804	27431007	Fibrocystic disease of breast
4131595	12676007	Fracture of radius
74855	33839006	Genital herpes simplex
441788	240532009	Human papilloma virus infection
76737	55434001	Hydrocele
4029582	237793004	Hyperandrogenization syndrome
195212	47270006	Hypercortisolism
438134	77692006	Hypersomnia
45768449	706882009	Hypertensive crisis
140362	36976004	Hypoparathyroidism
4322737	427898007	Infection of tooth
4207688	55184003	Infectious enteritis
79072	266579006	Inflammatory disorder of breast
139099	400097005	Ingrowing nail
4288544	396232000	Inguinal hernia

Supplementary Table. Falsification endpoint list (continued)

444191	125593007	Injury of face
444130	125604000	Injury of foot
134222	125597008	Injury of forearm
4297984	76844004	Local infection of wound
4018050	10443009	Localized infection
439840	1415005	Lymphangitis
4163232	45198002	Mastitis
440389	91138005	Mental retardation
436100	60380001	Narcolepsy
4262178	397732007	Neurogenic dysfunction of the urinary bladder
193874	8009008	Nocturnal enuresis
4171549	419153005	Nodular goiter
442274	52073004	Oligomenorrhea
4215978	414941008	Onychomycosis
4171915	274718005	Orchitis
380731	3135009	Otitis externa
378160	65668001	Otorrhea
192606	60389000	Paraplegia
253796	36118008	Pneumothorax
195501	69878008	Polycystic ovaries
4164337	399505005	Polyp of large intestine
4153877	269406001	Post-traumatic wound infection
434319	44001008	Premature ejaculation
373478	41256004	Presbyopia
199876	73998008	Prolapse of female genital organs
4295888	76641005	Prolapse of intestine
194997	9713002	Prostatitis
4146239	267802000	Pruritus of genital organs
4285569	68633000	Pupillary disorder
81336	57773001	Rectal prolapse
380395	314407005	Retinal dystrophy
141825	267369002	Simple goiter
137054	201066002	Skin striae
434630	3745000	Sleep-wake schedule disorder
4195698	67801009	Tenosynovitis
4339088	87860000	Testicular mass
133141	6020002	Tinea pedis
440814	70070008	Torticollis
435140	67426006	Toxic effect of alcohol
4270490	62994001	Tracheitis
4028970	13617004	Tracheobronchitis
4114197	254968009	Tumor of hypothalamus
193326	87557004	Urge incontinence of urine
4092565	24976005	Uterine prolapse
140641	57019003	Verruca vulgaris
197036	197811007	Vesicoureteric reflux
133551	402567004	Vesicular eczema of hands and/or feet
4223947	40468003	Viral hepatitis, type A
261326	75570004	Viral pneumonia

eTable 1. Baseline characteristics of the Optum EHR database

	Before PS matching			After PS matching		
	Ticagrelor (n= 22 967)	Clopidogrel (n=69 764)	Std. diff	Ticagrelor (n= 16 414)	Clopidogrel (n= 16 414)	Std. diff
Age group, %[a]						
30-34	0.4	0.3	0.02	0.4	0.4	0.01
35-39	1.3	0.9	0.04	1.2	1.3	0.01
40-44	3.1	2.2	0.05	2.8	2.7	<0.01
45-49	6.3	4.6	0.07	5.7	5.8	<0.01
50-54	11.0	8.4	0.09	9.7	9.9	0.01
55-59	15.1	11.9	0.09	14.0	14.1	<0.01
60-64	16.4	13.8	0.07	15.7	15.9	<0.01
65-69	14.7	14.5	0.01	14.9	15.0	<0.01
70-74	12.3	14.1	0.05	13.1	12.9	<0.01
75-79	9.5	12.0	0.08	10.4	10.5	<0.01
80-84	7.0	13.2	0.21	8.4	8.0	0.02
85-89	2.9	4.1	0.07	3.5	3.5	<0.01
Gender: men, %	67.8	65.2	0.05	66.8	66.9	<0.01
Gender: women, %	32.2	34.8	0.05	33.2	33.1	<0.01
Race, %[b]						
Asian	1.2	1.0	0.02	1.3	1.2	0.01
Black or African American	7.0	6.6	0.01	7.0	7.1	<0.01
White	88.1	88.9	0.02	88.1	87.9	0.01
Inclusion year, %						
2011	0.0	2.2	0.21	0.1	0.1	0.03

2012	2.2	13.6	0.43	3.0	2.8	0.01
2013	6.0	15.1	0.30	7.7	7.0	0.03
2014	10.5	16.3	0.17	12.4	11.4	0.03
2015	16.0	16.1	<0.01	17.5	17.2	0.01
2016	16.1	13.2	0.08	16.9	16.8	<0.01
2017	21.5	11.8	0.26	19.7	20.4	0.02
2018	21.9	9.7	0.34	18.4	19.6	0.03
2019	5.5	2.0	0.18	4.3	4.7	0.02
Type of ACS, %[c]						
ST-elevation myocardial infarction	22.4	19.3	0.08	19.9	19.8	<0.01
Non-ST-elevation myocardial infarction	31.3	35.4	0.09	32.4	32.0	<0.08
Unstable angina	49.7	56.0	0.13	52.9	52.3	0.01
Medical history, %[d]						
Congestive heart failure	15.0	21.4	0.17	16.2	15.9	0.01
Essential hypertension	76.7	78.8	0.05	77.8	77.9	<0.01
Hyperlipidemia	72.0	76.2	0.10	73.4	72.7	0.01
Peripheral arterial occlusive disease	0.5	1.0	0.06	0.7	0.7	<0.01
Persistent atrial fibrillation	0.6	0.8	0.03	0.7	0.8	0.01
Renal failure syndrome	0.7	1.2	0.05	0.9	0.8	0.01
Type 1 diabetes mellitus	0.9	0.9	<0.01	1.0	0.9	0.01
Type 2 diabetes mellitus	14.4	12.0	0.07	14.1	14.3	<0.01
Medication, %[e]						
Abciximab	2.0	2.5	0.03	1.9	1.8	<0.01
Apixaban	1.2	1.4	0.02	1.4	1.5	0.01
Aspirin	97.9	97.1	0.05	97.6	97.7	0.01
Dabigatran	0.2	0.4	0.05	0.2	0.3	0.02

Tirofiban	4.2	2.8	0.07	3.6	3.8	0.01
Warfarin	2.0	5.5	0.18	2.6	2.6	<0.01
ACE inhibitors	46.7	47.6	0.02	46.0	45.9	<0.01
Angiotensin II antagonists	16.7	17.5	0.02	17.6	17.0	0.01
Beta blocking agents	84.7	86.4	0.05	84.8	84.6	0.01
Calcium channel blockers	58.1	52.0	0.12	56.6	57.6	0.02
Diuretics	31.0	38.5	0.16	32.7	32.2	0.01
HMG CoA reductase inhibitors	92.0	89.4	0.09	90.8	91.0	0.01
Blood glucose lowering drugs, except. Insulins	17.8	19.6	0.05	18.6	18.4	<0.01
Insulins and analogues	27.7	31.4	0.08	28.7	28.5	<0.01
Proton pump inhibitors	35.7	39.4	0.08	36.9	36.8	<0.01
Laboratory values, mean (%)[f]						
Body mass index, kg/m^2	28.9 (94.8)	28.3 (93.7)	0.06	28.6 (94.3)	28.7 (94.7)	<0.01
Systolic blood pressure, mmHg	129.6 (98.8)	127.2 (97.8)	0.08	129.3 (98.5)	129 (98.7)	0.01
Diastolic blood pressure, mmHg	74.7 (98.8)	70.7 (97.8)	0.22	73.5 (98.5)	73.6 (98.7)	<0.01
Hemoglobin, g/dL	11.5 (91.9)	10.8 (89.9)	0.13	11.1 (90.3)	11.1 (90.6)	<0.01
Blood glucose, mg/dL	126.9 (93.3)	122.6 (92)	0.06	123.6 (92)	123.6 (92.5)	<0.01
Cholesterol in LDL, mg/dL	41.9 (41.2)	39.9 (41.9)	0.04	41.5 (41.3)	40.8 (41.2)	0.01
Creatine kinase.MB, ng/ml	8.7 (24.2)	8.3 (32.9)	0.01	8.6 (26.1)	7.7 (25)	0.02

Values are presented as proportion of the patients (%) unless otherwise indicated.

To account for baseline differences between patients with ticagrelor and clopidogrel, PS-based matching was used. PSs were calculated in each database independently, based on available demographic characteristics, as well as the medical, medication, procedure, device exposure history, and baseline laboratory values of in each database. Here, we reported the aggregated balance before and after matching only for limited covariates from three databases. The whole balance data before and after PS adjustment for more than 10,000 baseline covariates in each database are available at https://github.com/OHDSI/ShinyDeploy/tree/master/TicagrelorVsClopidogrel/data.

[a]Age group under 30 or over 90 was omitted.

[b]The Optum EHR data dictionary reports race as fixed categories (African American, Asian, Caucasian, and Other/Unknown) dependent on statistical de-identification rules for race based on geography, if insufficient Asians are represented in a particular geography they are “rolled up” to Unknown.

[c]Types of ACS were identified by coded medical diagnosis within 7 days to the catheterization. The proportion of each type of ACS can be over- or under-estimated, because some patients might have more than 1 diagnoses for ACS while more specific diagnoses (eg, ST-elevation myocardial infarction of anterior wall) were not reported here.
[d]Medical history was identified by coded medical diagnosis within 1 year prior to the catheterization.

[e]Short-term medication use was identified by medication records within 7 days of catheterization. Both ATC class-level and ingredient-level drug uses were used to fit PS model. We reported ingredient-level balances for antithrombotic agents, while class-level balances for other drugs before and after PS matching.

[f]The proportions in performance of laboratory test in each population are reported as percent (eg, 94.8% of ticagrelor group before matching were tested for body mass index, and mean of body mass index among them was 28.9 kg/m^2)

Abbreviation: EHR, electronic health record; Std.diff, standardized difference; PS, propensity score; ACS, acute coronary syndrome; ACE, angiotensin converting enzyme

eTable 2. Baseline characteristics of the IQVIA-Hospital database

	Before PS matching			After PS matching		
	Ticagrelor (n= 5 276)	Clopidogrel (n= 15 463)	Std. diff	Ticagrelor (n=3 998)	Clopidogrel (n=3 998)	Std. diff
Age group, %[a]						
30-34	0.3	0.3	<0.01	0.3	0.4	0.01
35-39	1.0	0.9	0.01	1.1	0.9	0.02
40-44	3.0	2.3	0.04	2.9	2.9	<0.01
45-49	5.9	4.7	0.05	5.4	5.2	0.01
50-54	10.2	8.5	0.06	9.7	9.4	0.01
55-59	14.6	12.4	0.06	14.1	13.5	0.02
60-64	16.0	14.1	0.05	15.2	15.2	<0.01
65-69	16.1	16.1	<0.01	16.2	16.8	0.02
70-74	14.3	15.5	0.03	15.2	15.3	<0.01
75-79	11.3	13.3	0.06	11.5	11.9	0.01
80-84	6.1	9.8	0.14	7.3	6.9	0.01
85-89	1.1	2.0	0.08	1.3	1.5	0.02
Gender: male, %	65.4	63.4	0.04	63.1	62.8	0.01
Gender: female, %	34.4	36.4	0.04	36.7	37.0	0.01
Inclusion year, %						
2011	0.1	2.6	0.22	0.2	0.2	0.01
2012	3.3	17.6	0.48	5.0	3.7	0.07
2013	9.5	18.6	0.26	13.1	11.5	0.05
2014	14.7	17.4	0.07	18.3	17.9	0.01
2015	16.4	14.9	0.04	18.6	18.6	<0.01
2016	16.1	10.4	0.17	16.1	15.9	<0.01

2017	25.4	12.1	0.35	19.1	22.0	0.07
2018	14.5	6.4	0.27	9.7	10.2	0.02
Type of ACS[b]						
ST-elevation myocardial infarction	3.7	4.5	0.04	4.4	4.6	0.01
Non-ST-elevation myocardial infarction	10.9	22.2	0.31	14.6	13.7	0.02
Unstable angina	41.4	49.7	0.17	42.4	40.4	0.04
Medical history, %[c]						
Congestive heart failure	5.7	9.7	0.15	6.7	6.4	0.01
Essential hypertension	47.1	51.0	0.08	48.5	46.9	0.03
Hyperlipidemia	37.4	44.0	0.14	38.0	36.9	0.02
Peripheral arterial occlusive disease	0.1	0.2	0.03	0.1	0.2	0.01
Persistent atrial fibrillation	0.1	0.2	0.01	0.1	0.3	0.06
Renal failure syndrome	0.1	0.3	0.04	0.1	0.2	0.02
Type 1 diabetes mellitus	0.6	0.9	0.03	0.7	0.6	0.02
Type 2 diabetes mellitus	15.4	23.4	0.20	18.2	16.7	0.04
Medication, %[d]						
Abciximab	1.5	1.6	0.01	1.5	1.9	0.03
Apixaban	0.3	0.3	<0.01	0.5	0.4	0.01
Aspirin	75.2	76.5	0.03	75.3	75.0	0.01
Dabigatran	0.0	0.1	0.03	0.1	0.1	0.01
Tirofiban	5.3	2.7	0.13	4.8	4.9	<0.01
Warfarin	0.7	2.2	0.12	1.0	1.4	0.04
ACE inhibitors	25.6	29.0	0.08	26.3	25.4	0.02
Angiotensin II antagonists	9.9	10.7	0.03	9.7	10.1	0.01
Beta blocking agents	68.0	70.8	0.06	68.4	69.3	0.02
Calcium channel blockers	46.7	40.7	0.12	42.8	44.6	0.04

Diuretics	17.4	22.1	0.12	18.6	18.0	0.01
HMG CoA reductase inhibitors	73.4	73.2	<0.01	73.0	72.9	<0.01
Blood glucose lowering drugs, except. Insulins	4.2	6.7	0.11	4.5	4.3	0.01
Insulins and analogues	8.3	13.1	0.15	9.9	9.6	0.01
Proton pump inhibitors	24.4	27.1	0.06	25.2	24.4	0.02

Values are presented as proportion of the patients (%) unless otherwise indicated.

To account for baseline differences between patients with ticagrelor and clopidogrel, PS-based matching was used. PSs were calculated in each database independently, based on available demographic characteristics, as well as the medical, medication, procedure, device exposure history, and baseline laboratory values of in each database. Here, we reported the aggregated balance before and after matching only for limited covariates from three databases. The whole balance data before and after PS adjustment for more than 10,000 baseline covariates in each database are available at https://github.com/OHDSI/ShinyDeploy/tree/master/TicagrelorVsClopidogrel/data.

[a]Age group under 30 or over 90 was omitted.

[b]Types of ACS were identified by coded medical diagnosis within 7 days to the catheterization. The proportion of each type of ACS can be over- or under-estimated, because some patients might have more than 1 diagnoses for ACS while more specific diagnoses (eg, ST-elevation myocardial infarction of anterior wall) were not reported here.
[c]Medical history was identified by coded medical diagnosis within 1 year prior to the catheterization.

[d]Short-term medication use was identified by medication records within 7 days of catheterization. Both ATC class-level and ingredient-level drug uses were used to fit PS model. We reported ingredient-level balances for antithrombotic agents, while class-level balances for other drugs before and after PS matching.

Abbreviation: Std.diff, standardized difference; PS, propensity score; ACS, acute coronary syndrome; ACE, angiotensin converting enzyme

eTable 3. Baseline characteristics of the HIRA database

	Before PS matching			After PS matching		
	Ticagrelor (n= 15 335)	Clopidogrel (n= 54 774)	Std. diff	Ticagrelor (n= 10 878)	Clopidogrel (n= 10 878)	Std. diff
Age group, %						
30-34	0.8	0.4	0.05	0.8	0.7	0.02
35-39	2.3	1.2	0.08	2.0	2.2	0.01
40-44	5.9	3.2	0.13	5.1	5.2	0.01
45-49	10.2	6.2	0.15	9.3	9.6	0.01
50-54	14.2	10.3	0.12	13.4	13.6	<0.01
55-59	17.2	13.3	0.11	16.5	15.9	0.02
60-64	14.7	14.0	0.02	14.8	15.6	0.02
65-69	11.2	13.5	0.07	12.0	11.9	<0.01
70-74	10.0	14.2	0.13	10.9	10.5	0.02
75-79	7.4	12.4	0.17	8.4	8.1	0.01
80-84	3.9	7.4	0.15	4.5	4.3	0.01
85-89	1.5	3.0	0.10	1.7	1.8	<0.01
Gender: men, %	81.2	69.3	0.28	79.1	79.6	0.01
Gender: women, %	18.8	30.7	0.28	20.9	20.4	0.01
Inclusion year, %						
2013	7.8	26.8	0.52	10.6	9.7	0.03
2014	23.3	27.0	0.08	26.6	26.8	0.01
2015	30.6	23.0	0.17	29.9	29.8	<0.01
2016	38.2	23.2	0.33	32.9	33.7	0.02
Type of ACS						
ST-elevation myocardial infarction	49.6	30.9	0.39	44.9	46.2	0.03

Non-ST-elevation myocardial infarction	19.9	14.2	0.15	20.2	20.7	0.01
Unstable angina	24.8	55.8	0.67	32.8	29.9	0.06
Medical history, %						
Congestive heart failure	6.7	9.0	0.08	7.2	7.3	0.01
Essential hypertension	71.8	78.3	0.15	73.3	72.8	0.01
Hyperlipidemia	70.3	71.1	0.02	70.8	70.9	<0.01
Peripheral arterial occlusive disease	0.8	1.1	0.03	0.9	0.7	0.02
Persistent atrial fibrillation	0.1	0.3	0.04	0.1	0.2	0.02
Renal failure syndrome	0.5	0.9	0.05	0.5	0.7	0.02
Type 1 diabetes mellitus	0.2	0.1	0.01	0.2	0.1	0.03
Type 2 diabetes mellitus	0.4	0.5	0.01	0.5	0.4	0.01
Medication, %						
Abciximab	17.6	7.6	0.30	12.9	14.0	0.03
Apixaban	0.1	0.2	0.03	0.1	0.1	0.01
Aspirin	99.8	99.7	0.03	99.8	99.9	<0.01
Dabigatran	0.0	0.1	0.04	0.0	0.1	0.03
Warfarin	0.9	2.2	0.10	1.1	1.1	<0.01
ACE inhibitors	40.2	34.0	0.13	40.0	40.6	0.01
Angiotensin II antagonists	37.1	42.1	0.10	39.1	39.1	<0.01
Beta blocking agents	78.4	72.8	0.13	78.5	79.3	0.02
Calcium channel blockers	44.0	55.1	0.22	47.3	45.8	0.03
Diuretics	34.3	37.9	0.08	33.8	33.5	0.01
HMG CoA reductase inhibitors	96.3	93.5	0.13	96.8	97.0	0.01
Blood glucose lowering drugs, except. Insulins	23.8	27.9	0.09	25.0	23.6	0.03
Insulins and analogues	12.6	13.0	0.01	11.9	11.6	0.01
Proton pump inhibitors	41.8	36.9	0.10	40.7	41.5	0.02

Device, %						
Drug-eluting coronary artery stent	94.8	93.9	0.04	95.0	95.1	<0.01

Values are presented as proportion of the patients (%) unless otherwise indicated.

To account for baseline differences between patients with ticagrelor and clopidogrel, PS-based matching was used. PSs were calculated in each database independently, based on available demographic characteristics, as well as the medical, medication, procedure, device exposure history, and baseline laboratory values of in each database. Here, we reported the aggregated balance before and after matching only for limited covariates from three databases. The whole balance data before and after PS adjustment for more than 10,000 baseline covariates in each database are available at https://github.com/OHDSI/ShinyDeploy/tree/master/TicagrelorVsClopidogrel/data.

[a]Age group under 30 or over 90 was omitted.

[b]Types of ACS were identified by coded medical diagnosis within 7 days to the catheterization. The proportion of each type of ACS can be over- or under-estimated, because some patients might have more than 1 diagnoses for ACS while more specific diagnoses (eg, ST-elevation myocardial infarction of anterior wall) were not reported here.
[c]Medical history was identified by coded medical diagnosis within 1 year prior to the catheterization.

[d]Short-term medication use was identified by medication records within 7 days of catheterization. Both ATC class-level and ingredient-level drug uses were used to fit PS model. We reported ingredient-level balances for antithrombotic agents, while class-level balances for other drugs before and after PS matching.

Abbreviation: HIRA, health insurance review and assessment service; Std.diff, standardized difference; PS, propensity score; ACS, acute coronary syndrome; ACE, angiotensin converting enzyme

eTable 4. Patient cohort sizes, primary endpoint events, incidence rates, and minimum detectable relative risk

	Patients, n		PYs, n*year		Events, n		IR, /1000PYs		MDRR
	T	C	T	C	T	C	T	C	
1 year									
Before PSM	43 578	140 001	31 197	110 939	4 824	15 851	154.63	142.88	1.05
After PSM	31 290	31 290	23 116	22 587	3 484	3 290	150.71	145.65	1.07
5 year									
Before PSM	43 578	140 001	65 203	300 759	6 613	25 093	101.42	83.43	1.04
After PSM	31 290	31 290	51 201	49 191	4 920	4 616	96.09	93.84	1.06
On-treatment									
Before PSM	31 002	99 520	7 834	49 262	2 365	9 226	301.89	187.28	1.06
After PSM	13 802	13 802	4 845	6 907	1 328	1 627	274.07	235.54	1.11

We report total number of patients, follow-up duration (in years), number of incident NACE (recurrent acute myocardial infarction, revascularization, ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding) during time-at-risks, incidence rate of NACE before and after propensity score matching from three databases. We also report MDRR for each comparison. Note that the incidence rate does not account for propensity score adjustment. The complete set of results is available at an interactive website (www.data.ohdsi.org/TicagrelorVsClopidogrel).

Abbreviation: T, ticagrelor; C, clopidogrel; PSM, propensity score matching; PY, person-year; IR, incidence rate; MDRR, minimum detectable relative risk; NACE, net adverse clinical event

eTable 5. Drug adherence after the index date in the HIRA database

		Ticagrelor	Clopidogrel	*P*[c]
MPR at 1 month	Observed patients, n	10424	10402	
	Mean (SD)	0.63 (0.40)	0.78 (0.35)	
	Median (IQR)	0.84 (0.18-1.00)	1.00 (0.58-1.00)	
	High adherence, %[a]	51.4	69.8	<0.001
	Full adherence, %[b]	40.6	60.5	<0.001
MPR at 6 months	Observed patients, n	8850	8608	
	Mean (SD)	0.61 (0.40)	0.76 (0.36)	
	Median (IQR)	0.76 (0.14-1.00)	1.00 (0.54-1.00)	
	High adherence, %[a]	48.4	68.4	<0.001
	Full adherence, %[b]	36.3	57.8	<0.001
MPR at 1 year	Observed patients, n	6865	6738	
	Mean (SD)	0.59 (0.40)	0.77 (0.36)	
	Median (IQR)	0.72 (0.13-1.00)	1.00 (0.55-1.00)	
	High adherence, %[a]	47.0	68.2	<0.001
	Full adherence, %[b]	32.9	56.4	<0.001

MPR is defined by the sum of the days supplied of all prescriptions filled for the allocated drug (ticagrelor or clopidogrel) in a given time period divided by the number of the days in the time-at-risk period until certain time points (30, 180 days and 365 days). The MPRs were calculated as the measures of adherence at 1 month, 6 months, and 1 year after the percutaneous coronary intervention.

[a]High adherence to the allocated drug is defined as MPR of 80% or higher

[b]Full adherence to the allocated drug is defined as MPR of 100%

[c]The proportions of high and full adherence to the allocated drug in the ticagrelor and clopidogrel group were compared by using $\chi 2$ test at each time point.

Abbreviation: HIRA, health insurance review and assessment service; MPR, medical possession ratio; SD, standard deviation; IQR, interquartile range

eTable 6. Incidence rate difference using random-effects meta-analysis

Outcome	Patients, n		PYs, n*year		IR, / 1000 PYs[a]		Random-effects meta-analysis			
	T	C	T	C	T	C	I^2	Incidence rate difference, / 1000 PYs[b]	95% CI	*P*
NACE	31 290	31 290	23 116	22 587	150.71	145.65	0.00	5.9	-0.6 to 12.4	0.078
NACE or mortality	31 290	31 290	23 101	22 569	168.34	165.53	0.00	2.8	-4.3 to 10	0.437
Ischemic event	31 290	31 290	23 274	22 711	135.21	133.50	0.00	3.1	-2.9 to 9.2	0.313
Ischemic stroke	31 290	31 290	24 985	24 292	7.48	8.15	0.00	-0.9	-2.3 to 0.6	0.248
Recurrent AMI	31 290	31 290	23 941	23 331	81.16	81.82	0.14	-0.2	-5.4 to 5.1	0.951
Revascularization	31 290	31 290	24 521	23 889	42.74	42.99	0.81	0.5	-9.4 to 10.5	0.914
Hemorrhagic event	31 290	31 290	24 811	24 212	21.36	15.69	0.49	5.6	1.8 to 9.4	0.004
Hemorrhagic stroke	31 290	31 290	25 031	24 372	2.96	1.85	0.00	1.1	0.3 to 2	0.009
GI bleeding	31 290	31 290	24 839	24 229	19.00	14.11	0.68	4.8	0.1 to 9.5	0.043
All-cause mortality	31 290	31 290	25 048	24 373	19.60	21.29	0.72	-0.9	-5.8 to 4	0.718
Dyspnea	31 290	31 290	21 390	21 518	272.64	226.32	0.97	42.6	-10 to 95.2	0.112
Cardiovascular-related mortality	27 292	27 292	22 469	21 887	14.29	15.49	0.78	-0.7	-5.1 to 3.7	0.754
MACE	27 292	27 292	21 716	21 183	72.85	71.85	0.76	1.9	-8.2 to 12.1	0.710

NACE includes recurrent acute myocardial infarction, revascularization, ischemic stroke, hemorrhagic stroke, and GI bleeding. MACE includes cardiovascular-related mortality, recurrent AMI, and stroke. The complete set of results is available at an interactive website (www.data.ohdsi.org/TicagrelorVsClopidogrel).

[a]The Incidence rate of each outcome was calculated by simple mean of incidence rates from three databases.

[b]The incidence rate difference of each outcome between ticagrelor and clopidogrel group was calculated by using random-effects meta-analysis. The positive value indicates more outcome occurred in ticagrelor group than clopidogrel group, and vice versa.

Abbreviation: T, ticagrelor; C, clopidogrel; PY, person-year; IR, incidence rate; NACE, net adverse clinical event; AMI, acute myocardial infarction; GI, gastrointestinal; MACE, major adverse cardiovascular event

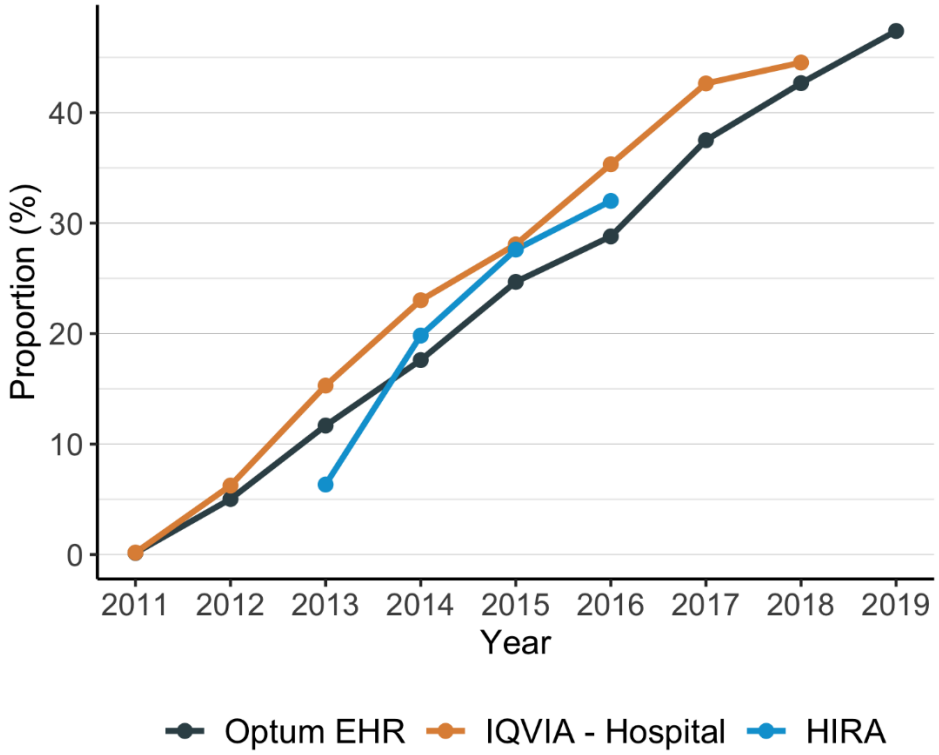
eTable 7. Incidence rates of secondary endpoint events at one year in the ticagrelor groups from this study and TICA-KOREA.

Outcomes	Study	Event / PYs	95% CI
GI bleeding	Our study	472 / 24 839	1.90-2.08
	TICA-KOREA	6 / 387	0.64-3.20
ICH	Our study	74 / 25 031	0.23-0.37
	TICA-KOREA	1 / 387	0.02-1.20
Recurrent AMI	Our study	1943 / 23 941	7.76-8.48
	TICA-KOREA	20 / 387	3.26-7.82
Ischemic stroke	Our study	187 / 24 985	0.65-0.86
	TICA-KOREA	5 / 387	0.49-2.83
Revascularization	Our study	1048 / 24 504	4.02-4.54
	TICA-KOREA	10 / 387	1.33-4.58

We compared confidence intervals of incidences for individual secondary endpoints of ischemic and hemorrhagic events in the ticagrelor group from our study with those from the most recent head-to-head randomized trials between ticagrelor vs clopidogrel (TICA-KOREA).[5] As shown in the table, all of the confidence intervals are overlapped between our results and the results from the TICA-KOREA.

Abbreviation: T, ticagrelor; C, clopidogrel; PY, person-year; CI, confidence interval; GI, gastrointestinal; ICH, intra-cerebral hemorrhage; AMI, acute myocardial infarction

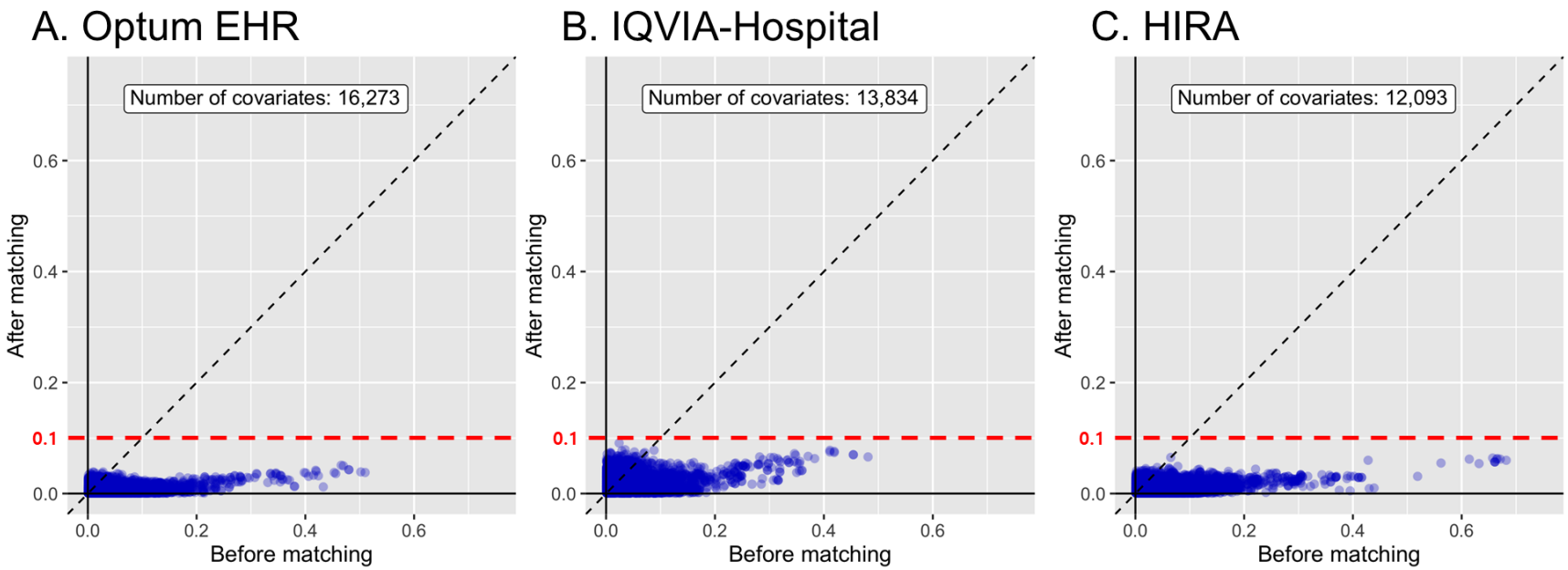
eFigure 1. Proportion of ticagrelor group among the whole study population, 2011-2019



The lines represent the proportion of patients who allocated to ticagrelor group among the whole study population in three different databases from US (Optum EHR and IQVIA-Hospital) and South Korea (HIRA).

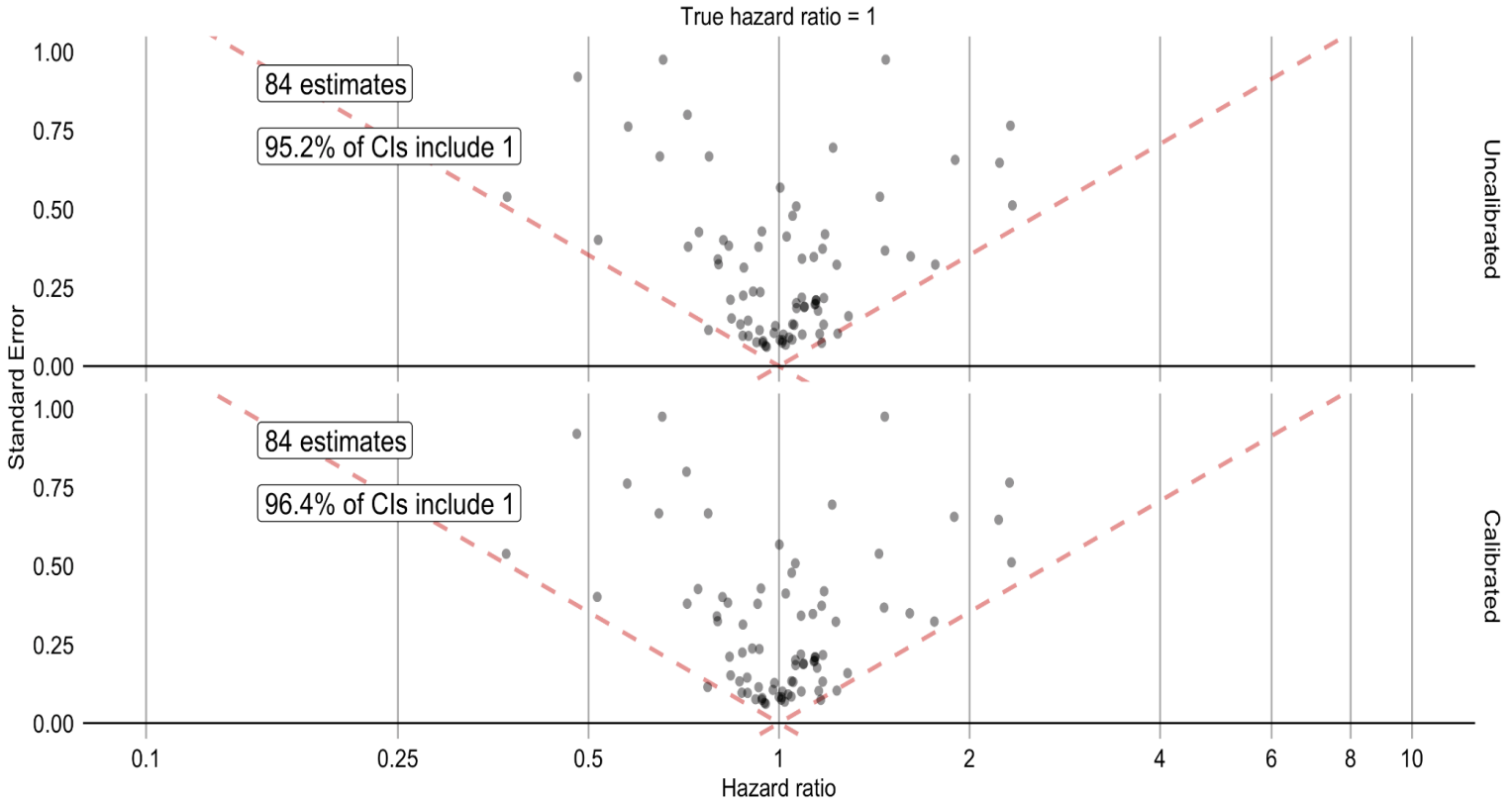
Abbreviation: Optum EHR, Optum electronic health record; HIRA, health insurance review and assessment service

eFigure 2. Covariate balance plot before and after propensity score matching



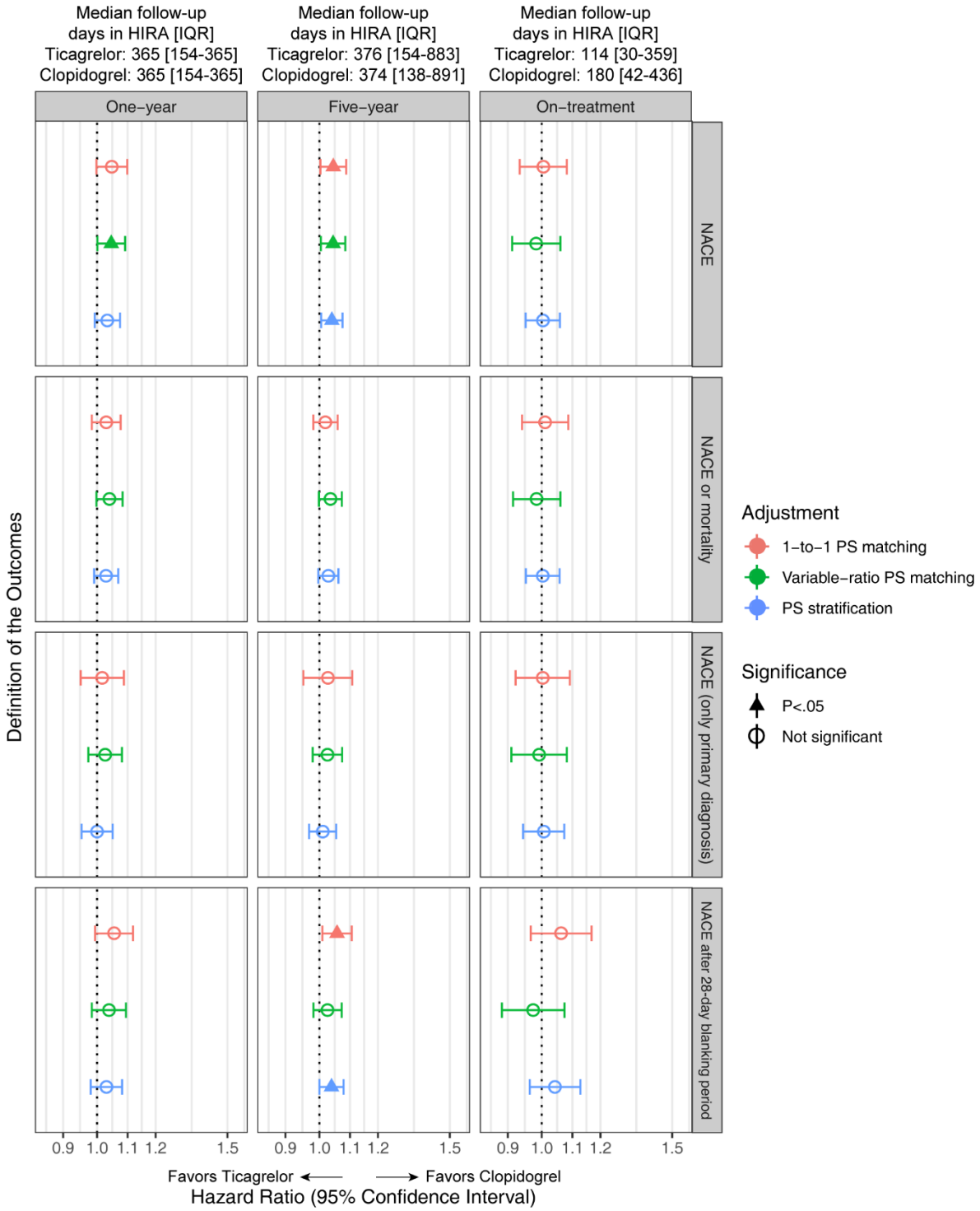
The covariate balances before and after PS matching were depicted. After PS matching, every standardized mean difference from more than 10,000 covariates does not exceed 0.1, which is depicted by red line. The complete set of results is available at an interactive website (www.data.ohdsi.org/TicagrelorVsClopidogrel).
Abbreviation: Optum EHR, Optum electronic health record; HIRA, health insurance review and assessment service; PS, propensity score

eFigure 3. Systematic error control of effect estimation in the meta-analysis comparing the risk of net adverse clinical event between the ticagrelor and clopidogrel group under one-year, 1-to-1 propensity score matching design



The funnel plots describe the hazard ratio and standard error of each summary estimate of falsification endpoints in meta-analysis. Top plot is the result before calibration and bottom plot is the result after calibration of confidence interval. Nominal 95% confidence intervals cover 95.2% (80/84) and 96.4% (81/84) before and after calibration of confidence interval, respectively. The complete set of results is available at an interactive website (www.data.ohdsi.org/TicagrelorVsClopidogrel).

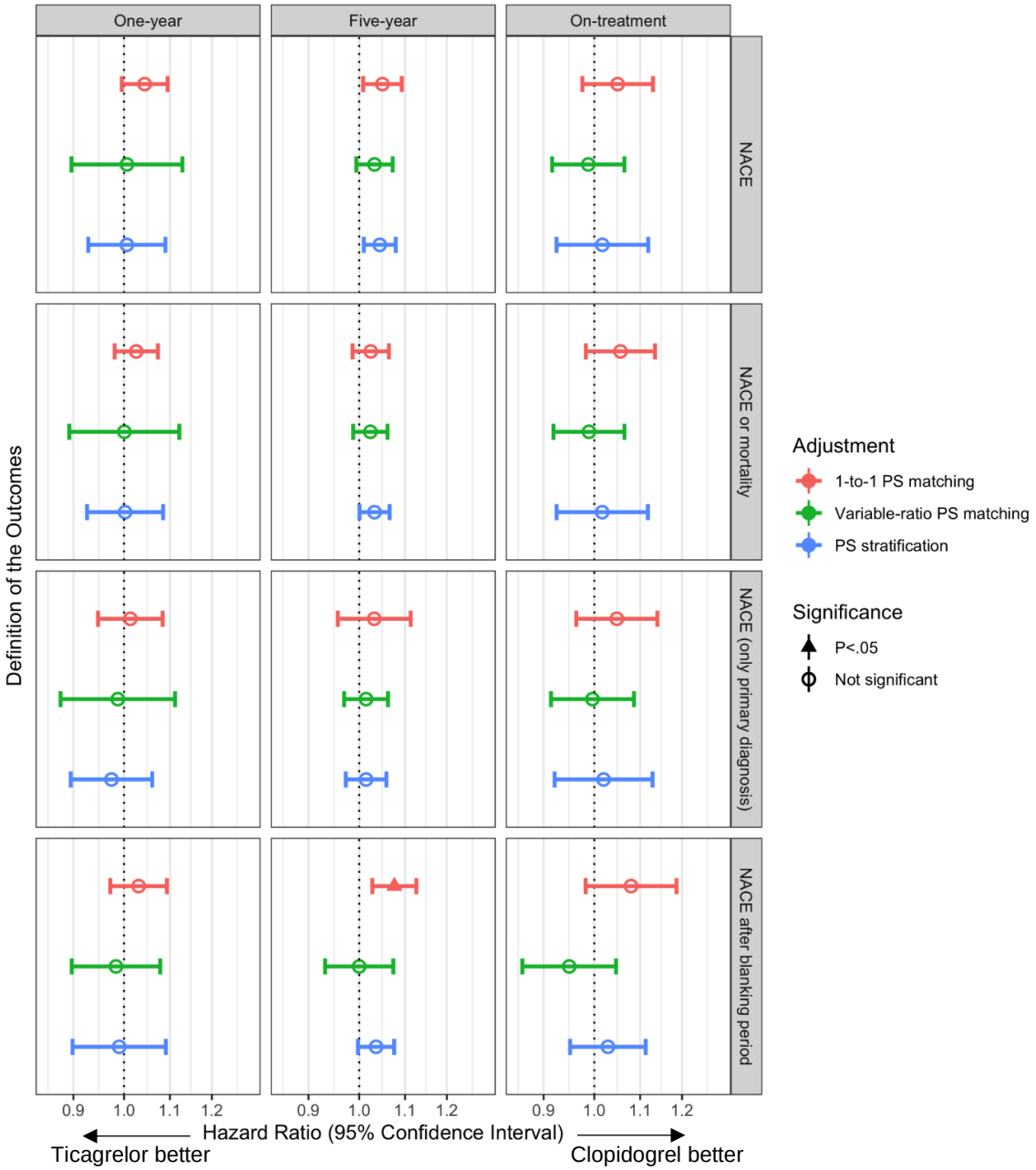
eFigure 4. Sensitivity analyses for risks of the primary outcome (NACE) associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



NACE includes ischemic events (recurrent acute myocardial infarction, revascularization, or ischemic stroke) and hemorrhagic events (hemorrhagic stroke or gastrointestinal bleeding). The points indicate HR estimates and the lines their 95% CIs, based on 36 analyses with three different times-at-risk, three different statistical models, and four different clinical definitions of NACE. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is an extended risk window from the 1-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-

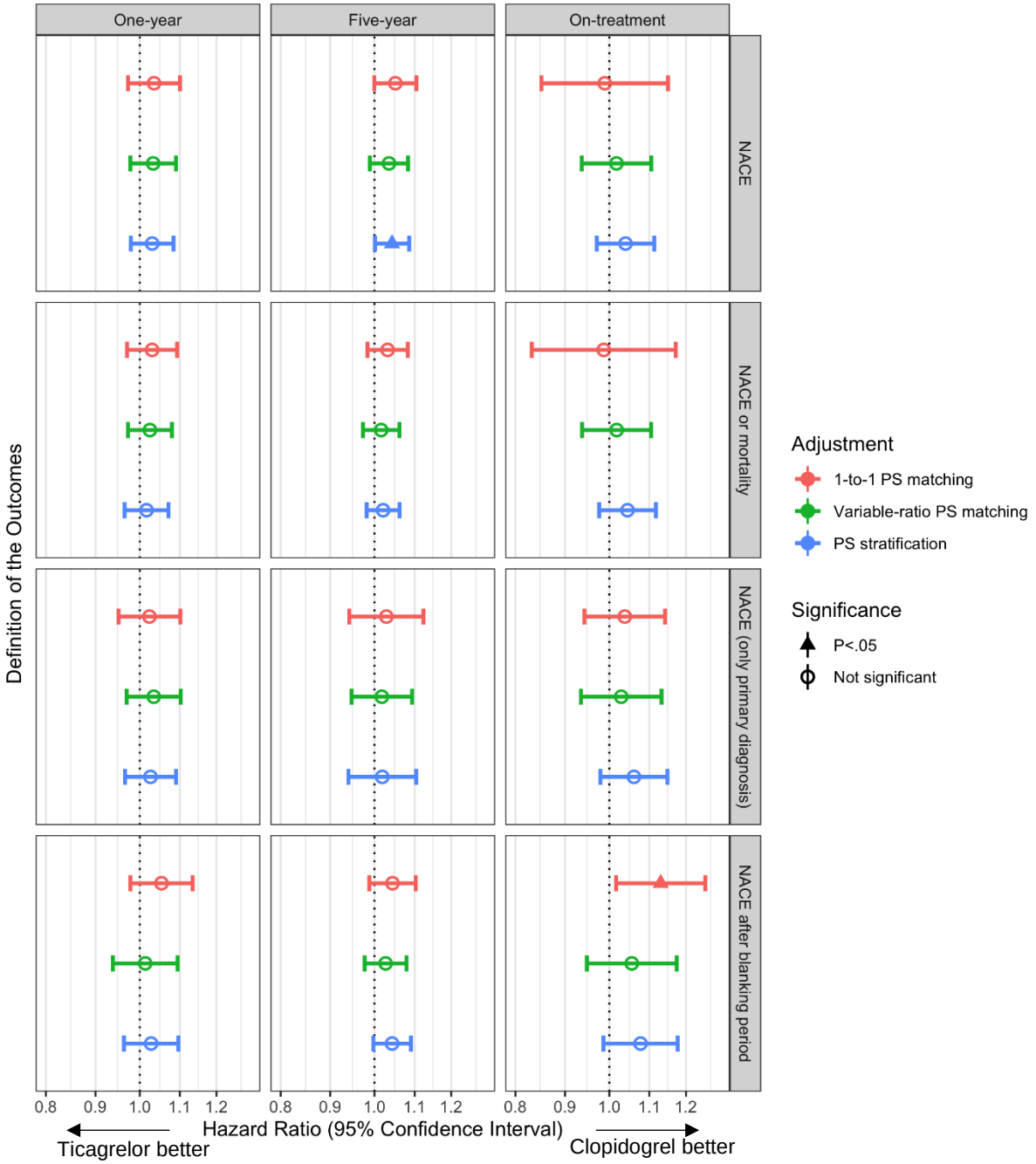
day gap or the end of patients' record. The median follow-up days and IQRs in the HIRA database for NACE in the ticagrelor and clopidogrel group are described on the top of the graph. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.
Abbreviations: NACE, net adverse clinical event; PS, propensity score; HR, hazard ratio; CI, confidence interval; IQR, interquartile range; HIRA, Health Insurance Review and Assessment Service.

eFigure 5. Risks of NACE associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings after empirical calibration



The points indicate HR estimates and the lines their 95% CIs, based on 36 analyses with three different times-at-risk, three different statistical models, and four different clinical definitions of NACE (recurrent acute myocardial infarction, revascularization, ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding) after empirical calibration. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.
Abbreviations: NACE, net adverse clinical event; PS, propensity score; HR, hazard ratio; CI, confidence interval.

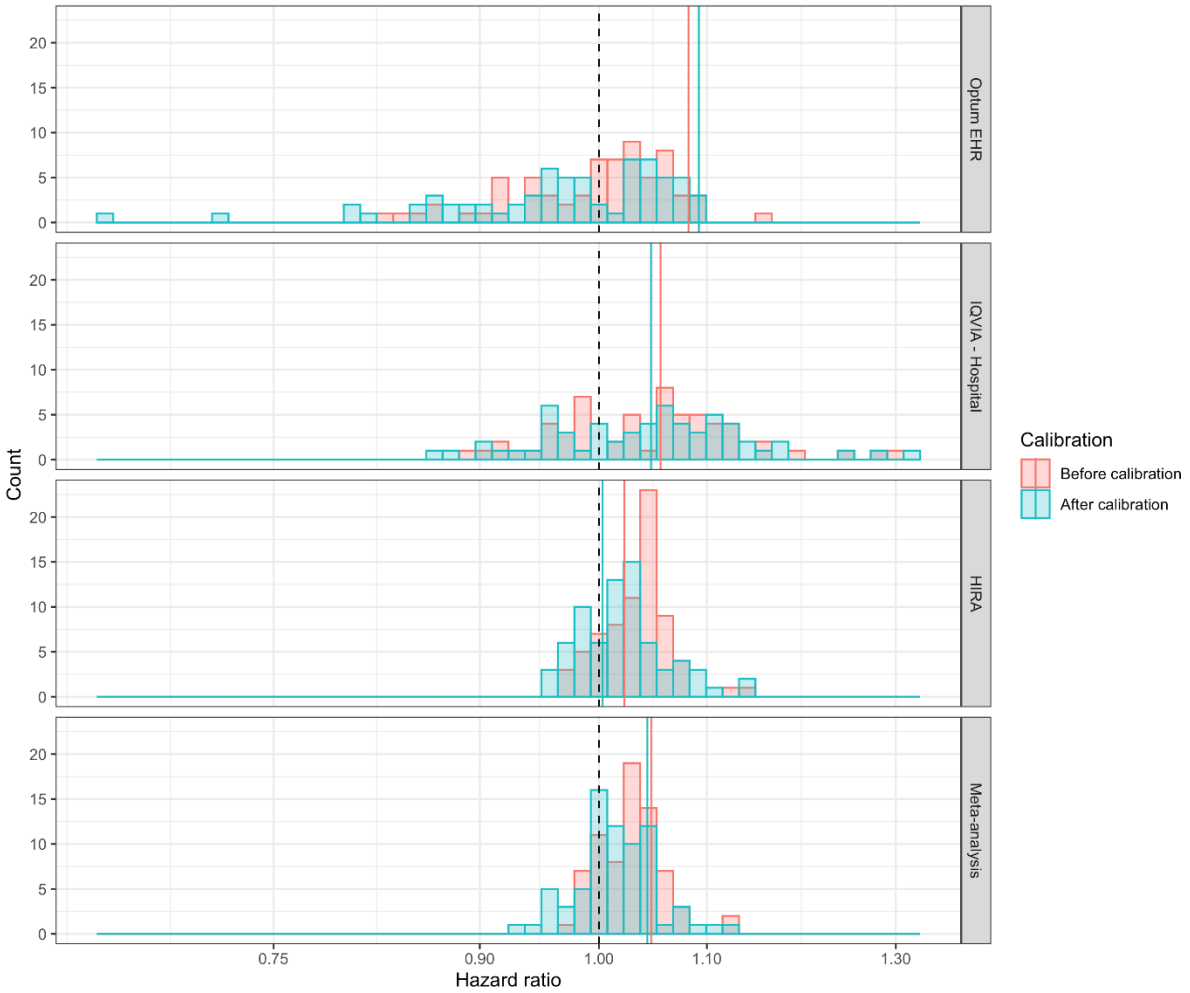
eFigure 6. Risks of NACE associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings from 2013 to 2015



Points report HR estimates and line mark their 95% CIs from 36 analyses with 3 different time-at-risk, 3 different statistical model, and 4 different clinical definition of NACE (recurrent acute myocardial infarction, revascularization, ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding) from March 2013 to 2015. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. The hazard ratio greater than 1 means increased risk in the ticagrelor group. Open round circle points demarcate HRs with CIs covering 1, and closed triangle points indicate HRs with statistical significance.

Abbreviation: NACE, net adverse clinical event; PS, propensity score; HR, hazard ratio; CI, confidence interval

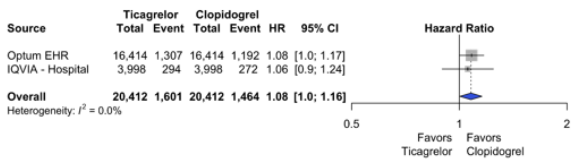
eFigure 7. Distribution of risk estimates for NACE from 144 analyses before and after empirical calibration



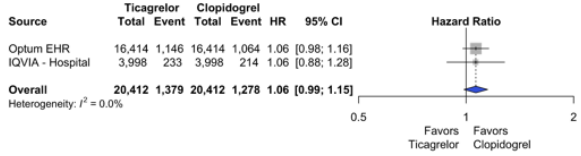
Histograms of point estimates (hazard ratios) for NACE (recurrent acute myocardial infarction, revascularization, ischemic stroke, hemorrhagic stroke, or gastrointestinal bleeding) from 72 different analyses before and after empirical calibration in three different databases and the meta-analysis. The vertical black dash line depicts hazard ratio of 1. Hazard ratios greater than 1 mean increased risk of NACE in the ticagrelor group. The vertical solid pink and aquamarine line depict the hazard ratios from the primary analysis (one-year NACE risk after 1-to-1 propensity score matching) before and after empirical value calibration, respectively. The results from the 135 analyses among these 144 analyses (93.8%) were not statistically significant, and the results from the rest 9 analyses (6.3%) indicated increased risk of NACE in ticagrelor group in the meta-analysis (range of summary HR 1.04-1.13, all $P<.05$). The complete set of results is available at an interactive website (www.data.ohdsi.org/TicagrelorVsClopidogrel).
Abbreviation: NACE, net adverse clinical event; Optum EHR, Optum electronic health record; HIRA, health insurance review and assessment service

eFigure 8. Meta-analysis results using only US databases

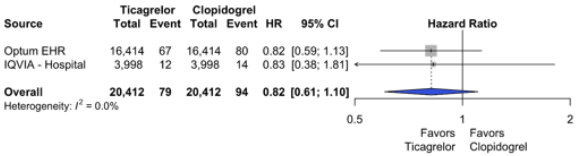
A. NACE



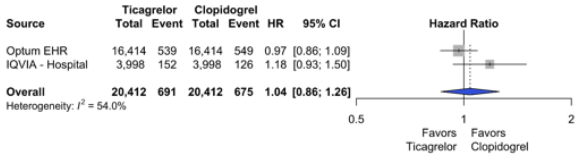
B. Ischemic event



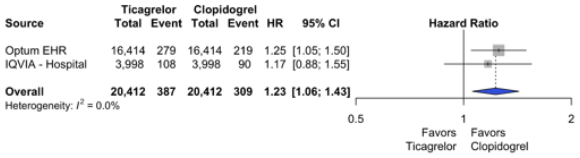
C. Ischemic stroke



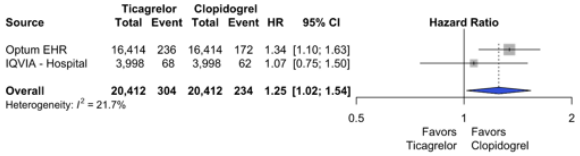
D. Recurrent acute MI



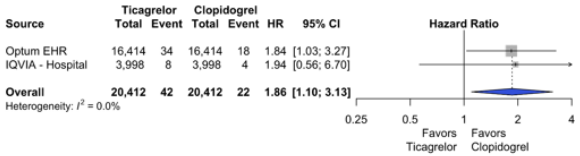
E. Revascularization



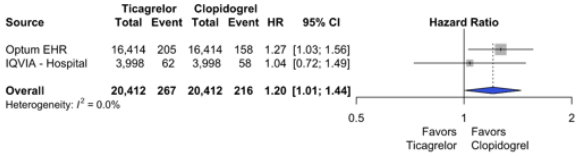
F. Hemorrhagic event



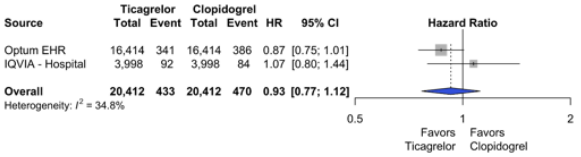
G. Hemorrhagic stoke



H. GI bleeding



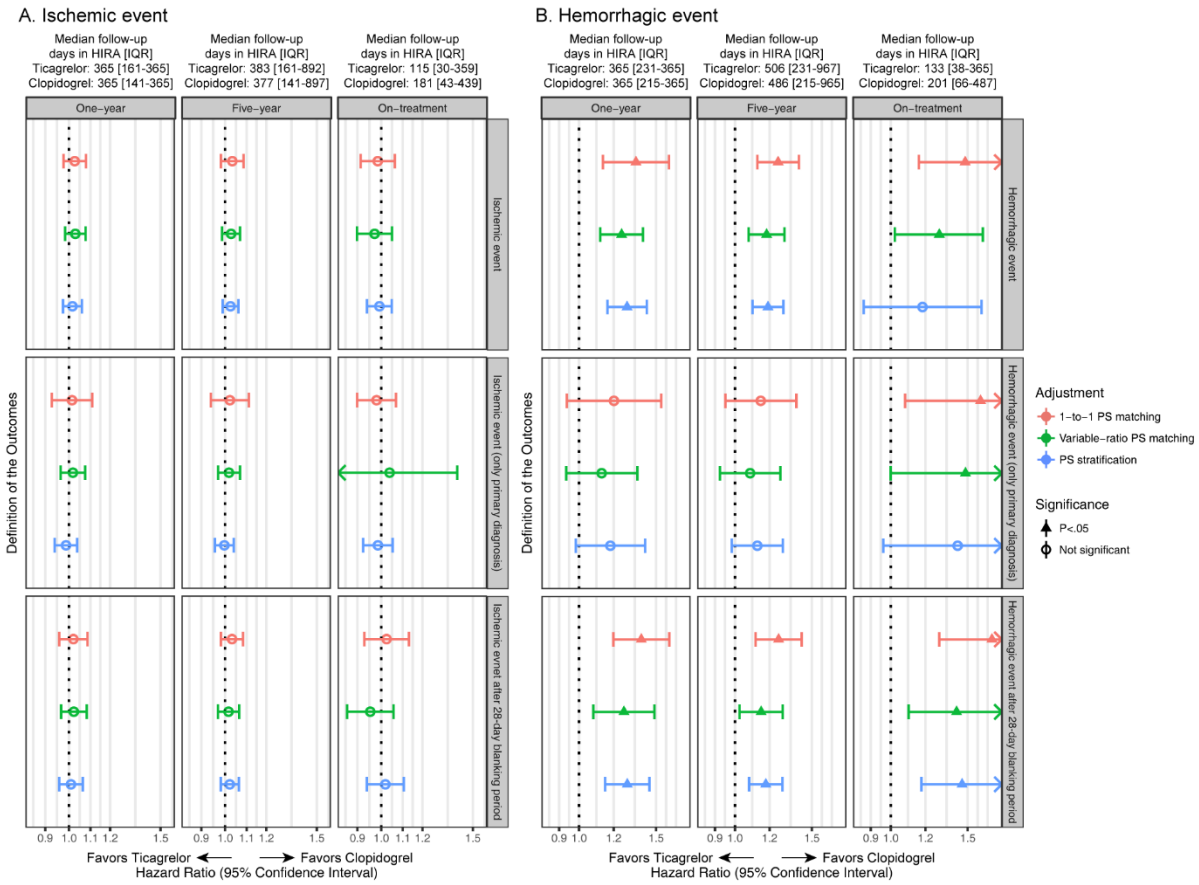
I. All-cause mortality



Forest plots depict HR and 95% CI for primary and secondary outcomes in two US data sources. The summary HR were calculated through random-effects model. The hazard ratio greater than 1 means increased risk in the ticagrelor group. The size of data marker indicates the weight of the study. Error bars indicate 95% CIs. (A) NACE (recurrent AMI, revascularization, ischemic stroke, hemorrhagic stroke, or GI bleeding), (B) Ischemic event (ischemic stroke, recurrent AMI, and revascularization), (C) ischemic stroke, (D) recurrent AMI, (E) revascularization, (F) hemorrhagic event (hemorrhagic stroke and GI bleeding), (G) hemorrhagic stroke, (H) GI bleeding, (I) all-cause mortality

Abbreviation: Optum EHR, Optum electronic health record; MI, myocardial infarction; GI, gastrointestinal; NACE, net adverse clinical event; HR, hazard ratio, CI, confidence interval.

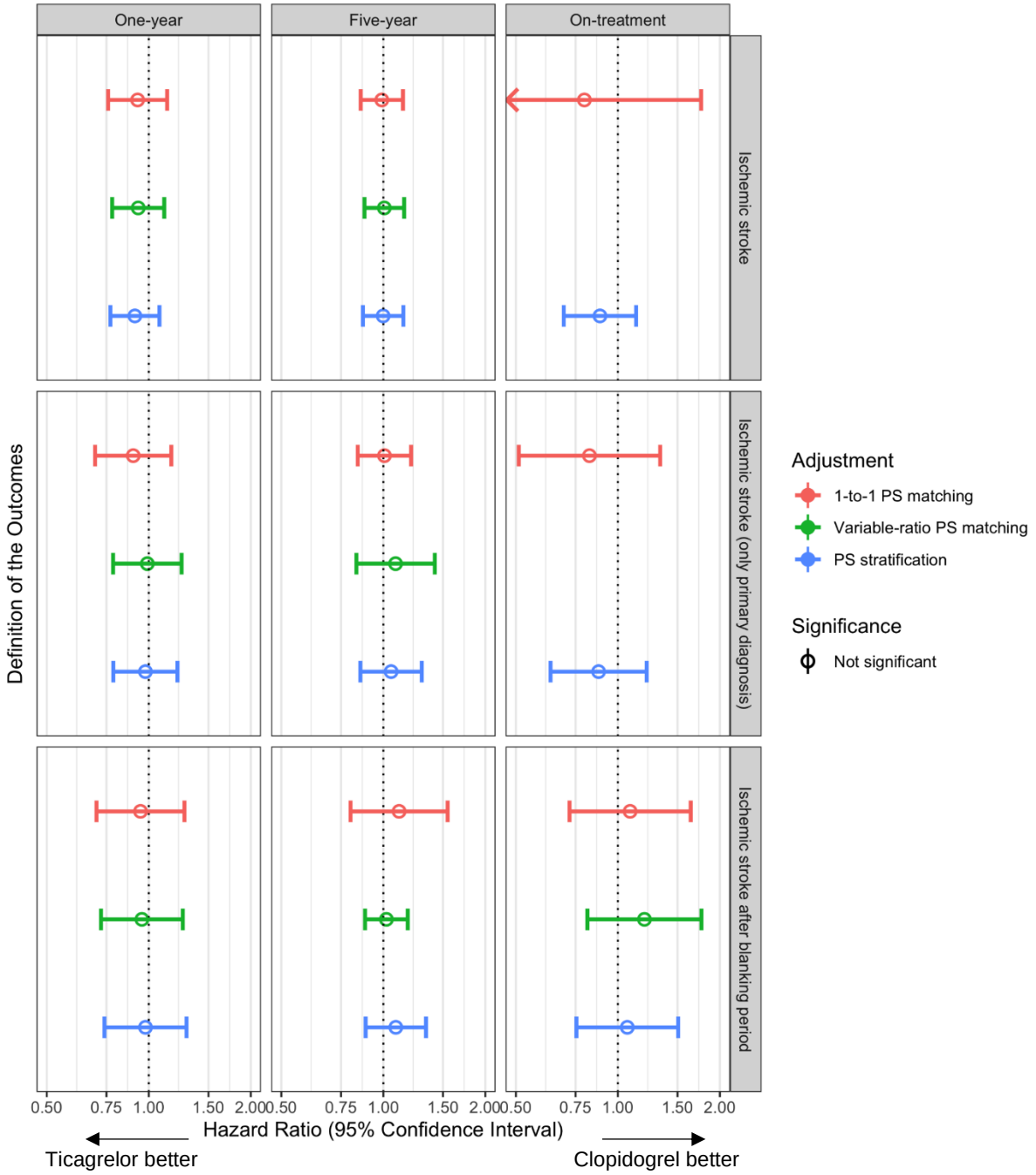
eFigure 9. Sensitivity analyses for risks of ischemic event (recurrent acute myocardial infarction, revascularization, or ischemic stroke) and hemorrhagic event (hemorrhagic stroke or gastrointestinal bleeding) associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points represent HR estimates and the lines their 95% CIs, based on 27 analyses with three different times-at-risk, three different statistical models, and three different clinical definitions of the secondary outcomes. The 1-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after the index date, which is an extended risk window from the 1-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. The median follow-up days and IQRs in the HIRA database for ischemic event and hemorrhagic event in ticagrelor and clopidogrel group are described on the top of the graphs. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and closed triangles represent HRs that were statistically significant. (A) ischemic event and (B) hemorrhagic event.

Abbreviations: PS, propensity score; HR, hazard ratio; CI, confidence interval; IQR, interquartile range; HIRA, Health Insurance Review and Assessment Service.

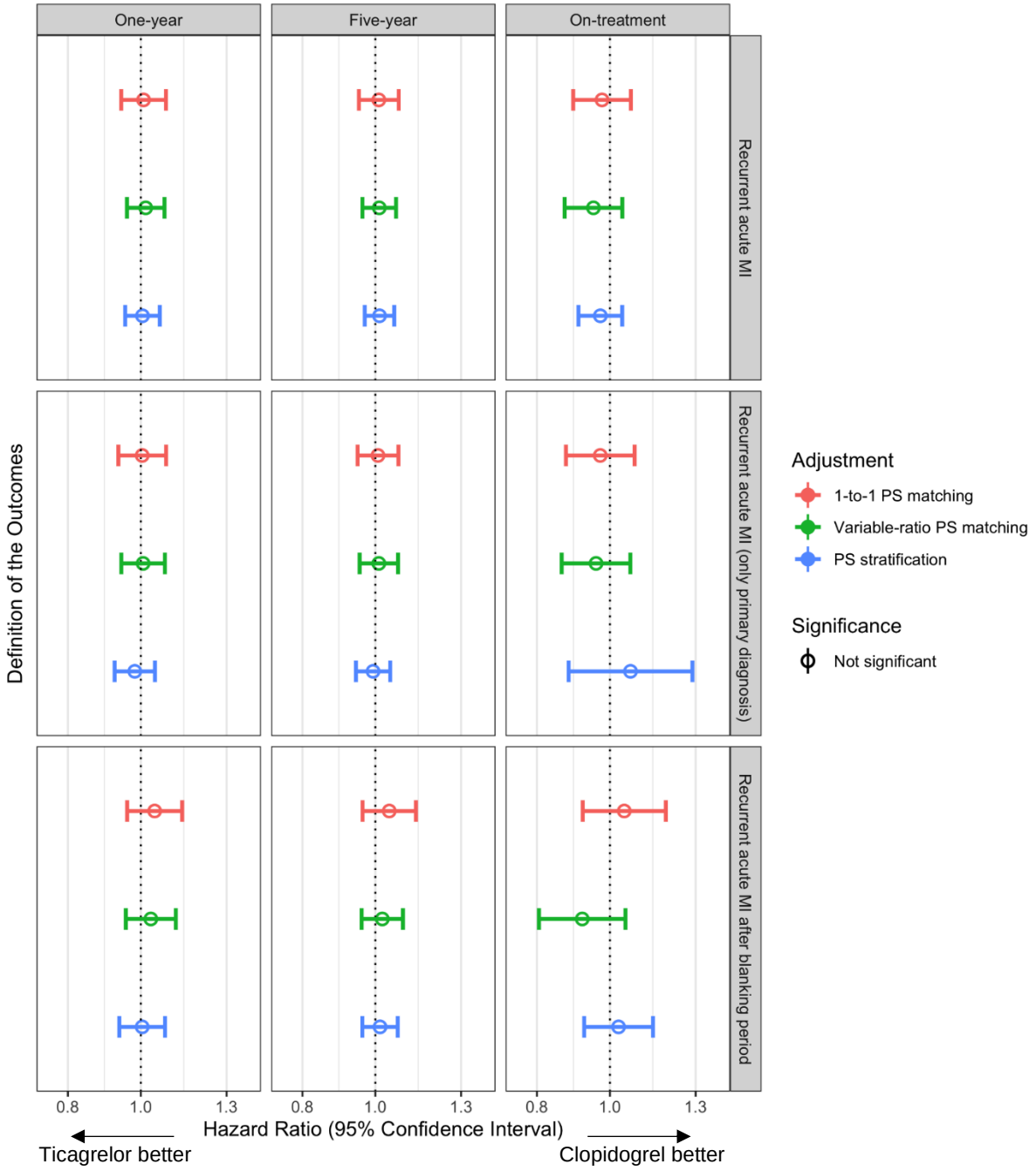
eFigure 10. Risks of ischemic stroke associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 25 analyses with three different times-at-risk, three different statistical models, and three different clinical definitions of ischemic stroke. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant. The results of meta-analysis were omitted to show when the result from Optum EHR was not available.

Abbreviation: PS, propensity score; HR, hazard ratio; CI, confidence interval; EHR, electronic health record

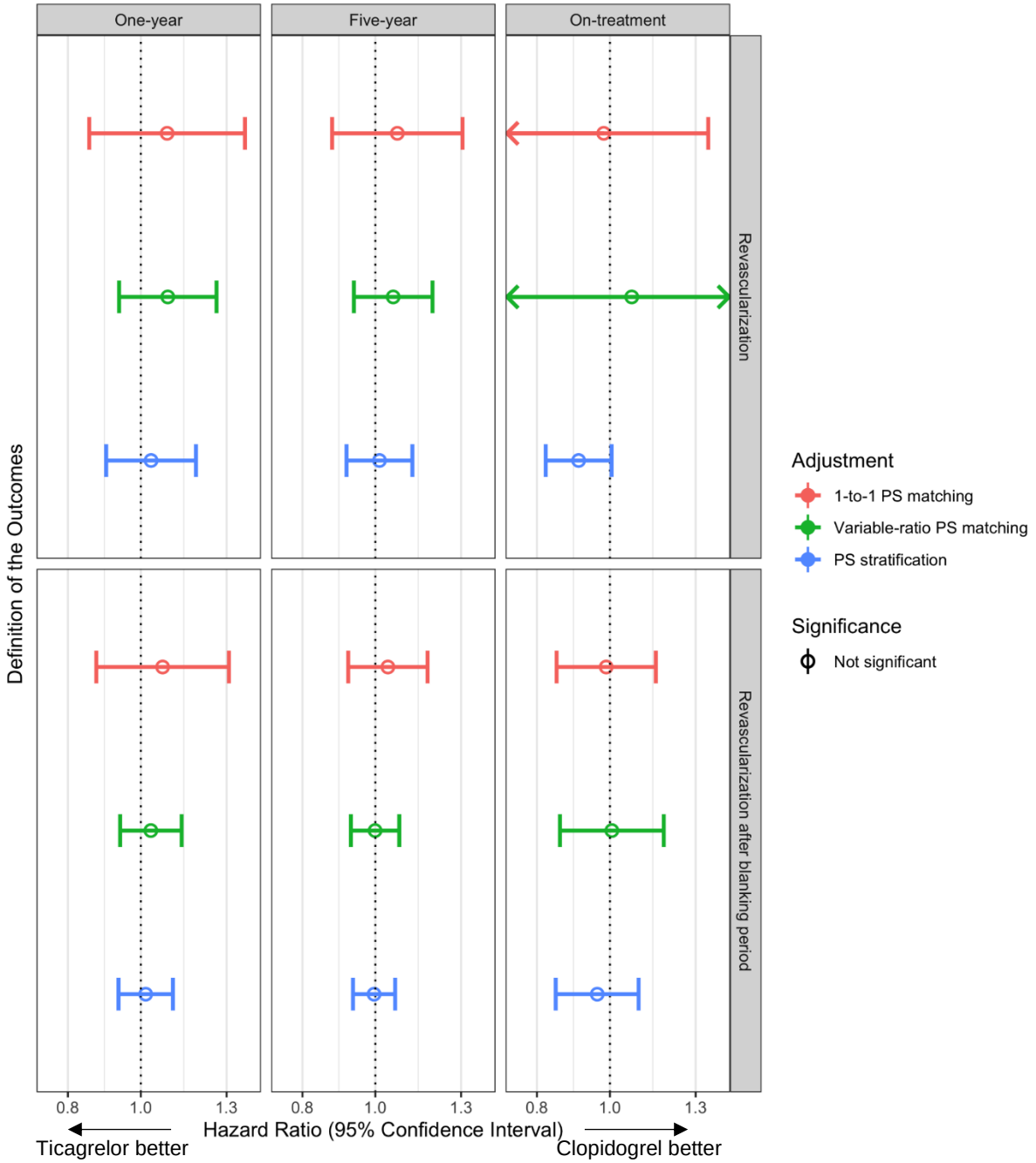
eFigure 11. Risks of recurrent acute myocardial infarction associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 27 analyses with three different times-at-risk, three different statistical models, and three different clinical definitions of acute MI. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.

Abbreviation: MI, myocardial infarction; PS, propensity score; HR, hazard ratio; CI, confidence interval

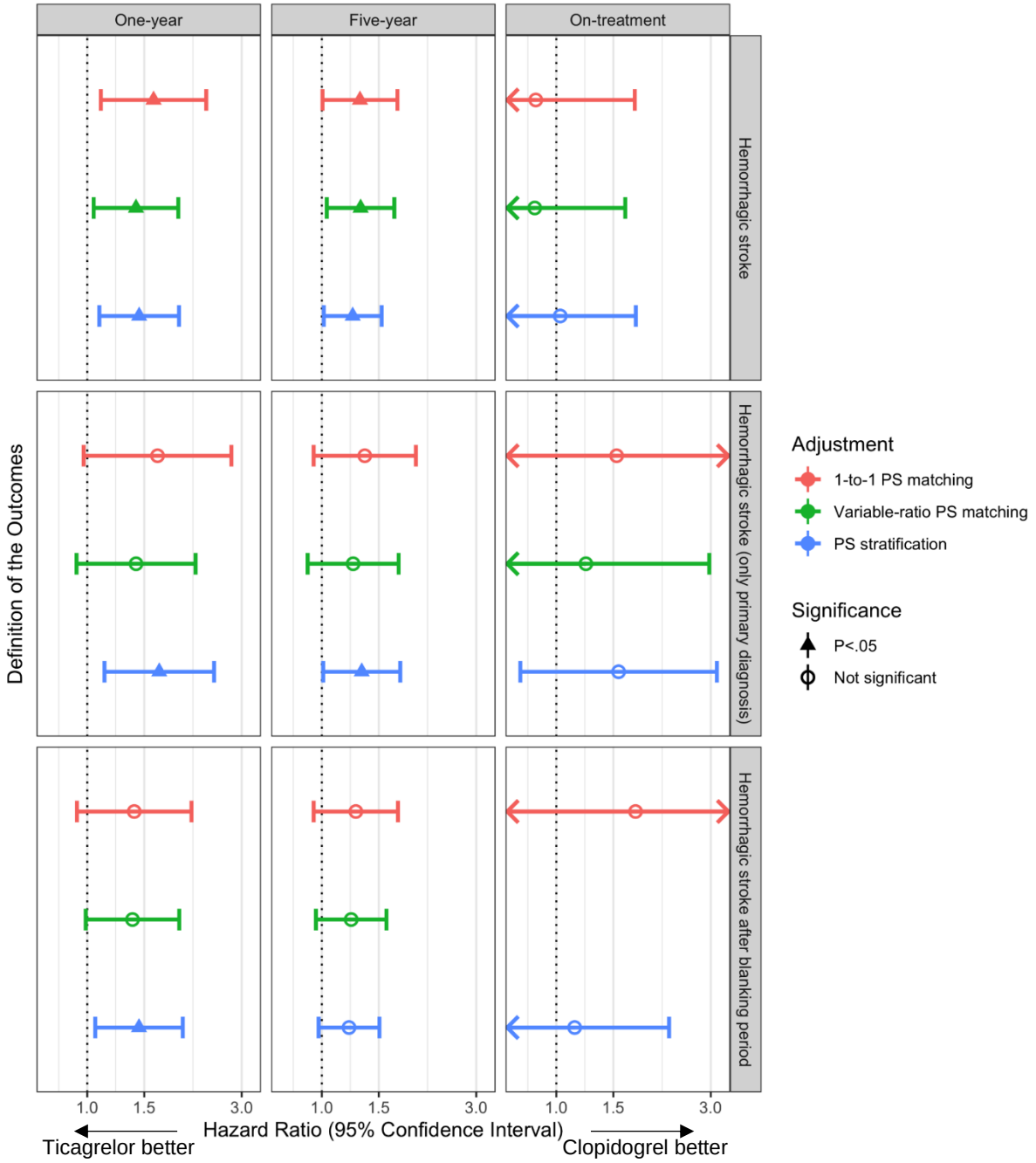
eFigure 12. Risks of revascularization associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 18 analyses with three different times-at-risk, three different statistical models, and two different clinical definitions of revascularization. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.

Abbreviation: PS, propensity score; HR, hazard ratio; CI, confidence interval

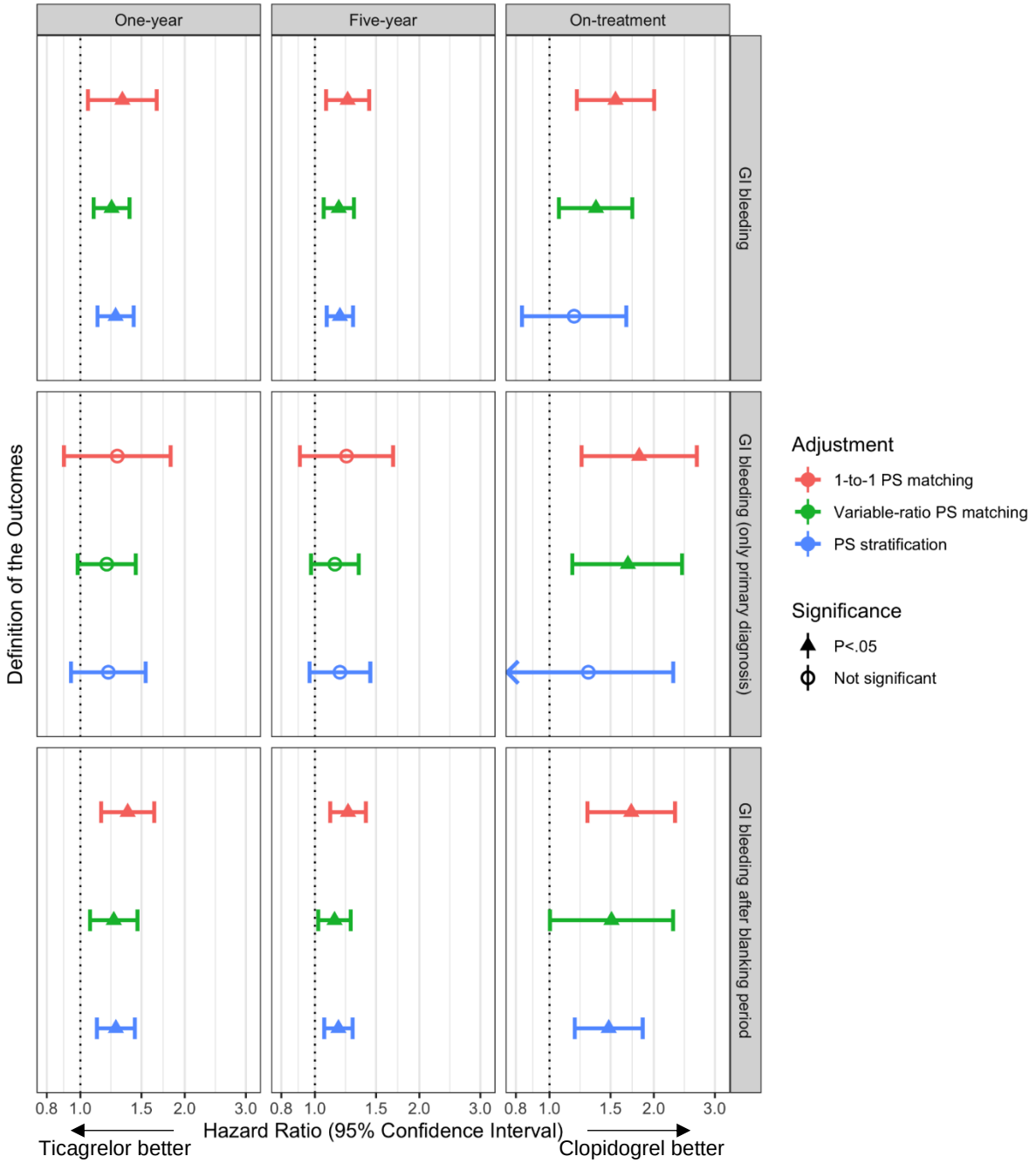
eFigure 13. Risks of hemorrhagic stroke associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 26 analyses with three different times-at-risk, three different statistical models, and three different clinical definitions of hemorrhagic stroke. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant. The results of meta-analysis were omitted to show when the result from Optum EHR was not available.

Abbreviation: PS, propensity score; HR, hazard ratio; CI, confidence interval; EHR, electronic health record

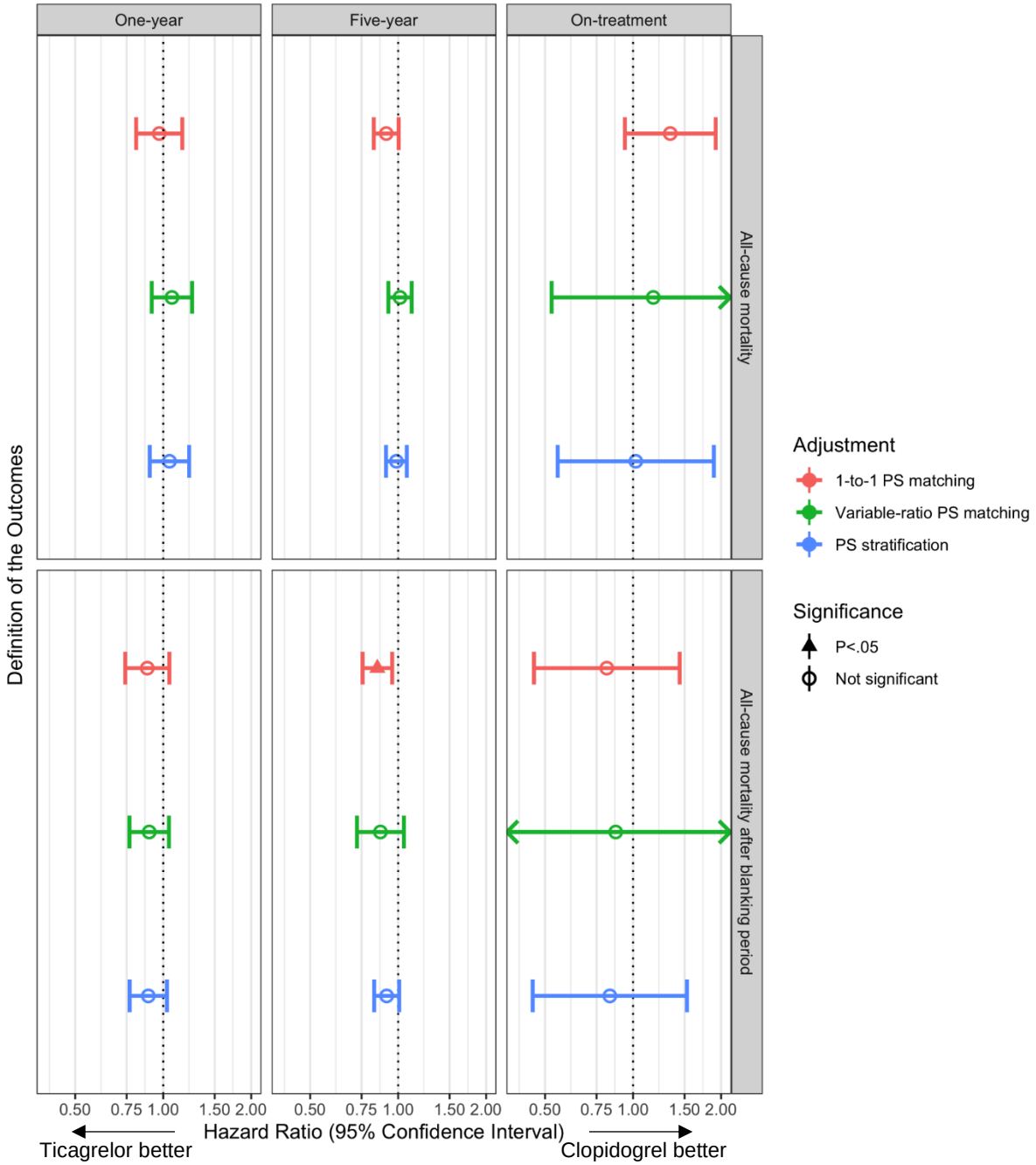
eFigure 14. Risks of GI bleeding associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 27 analyses with three different times-at-risk, three different statistical models, and three different clinical definitions of GI bleeding. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.

Abbreviation: GI, gastrointestinal, PS, propensity score; HR, hazard ratio; CI, confidence interval

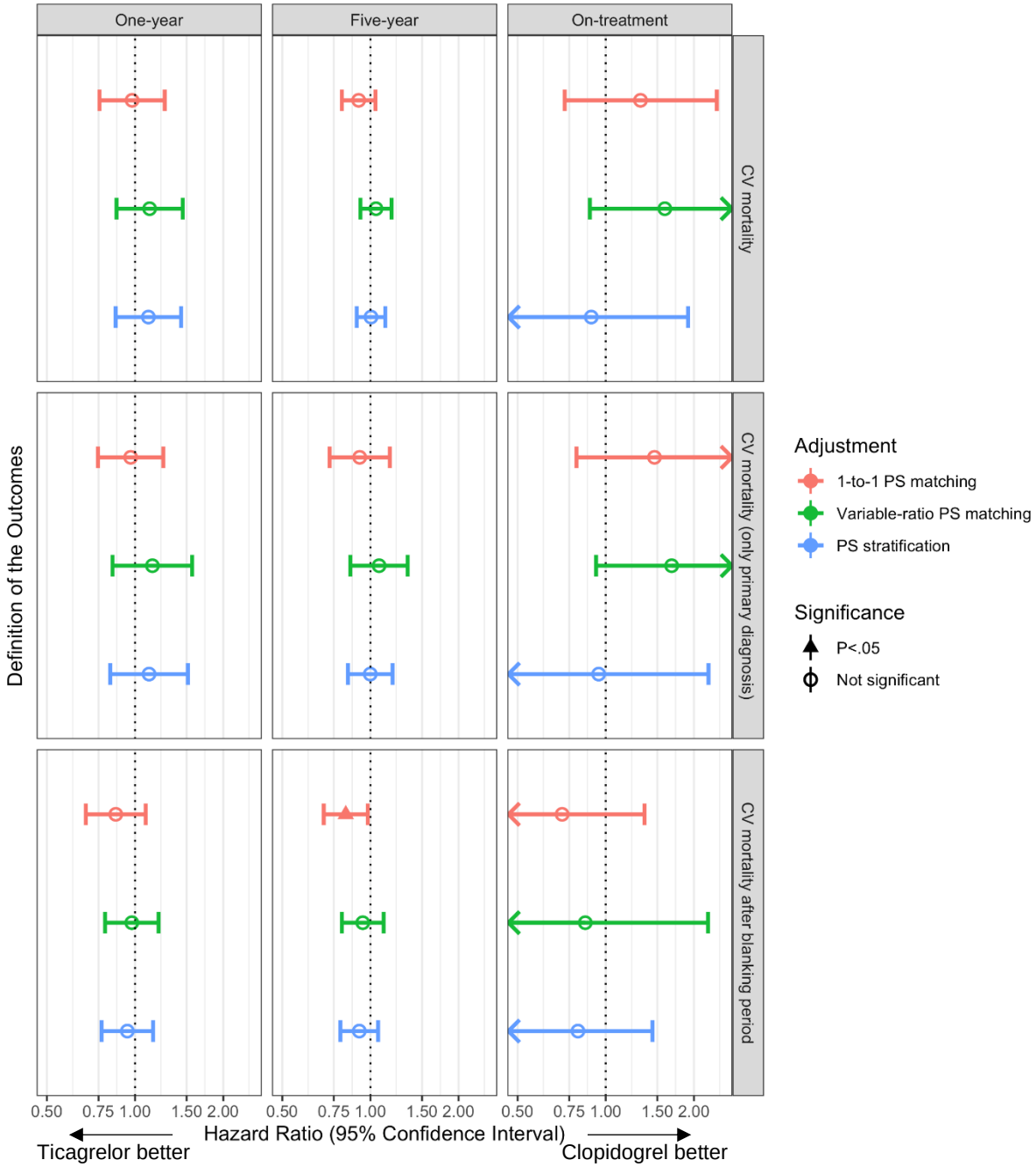
eFigure 15. Risks of all-cause mortality associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 18 analyses with three different times-at-risk, three different statistical models, and two different clinical definitions of overall mortality. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.

Abbreviation: PS, propensity score; HR, hazard ratio; CI, confidence interval

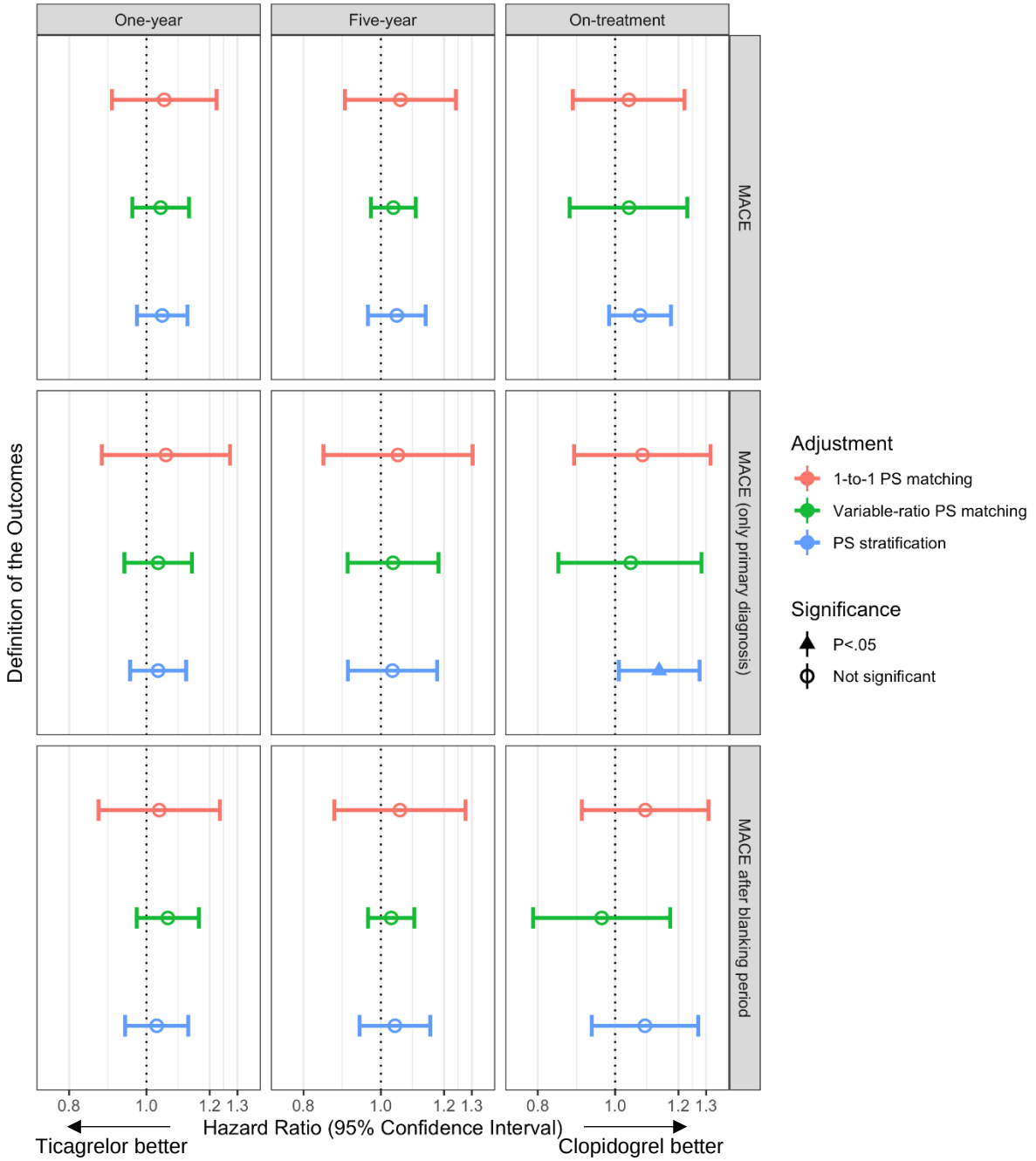
eFigure 16. Risks of cardiovascular-related mortality associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 18 analyses with three different times-at-risk, three different statistical models, and two different clinical definitions of cardiovascular-related mortality. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.

Abbreviation: CV, cardiovascular-related; PS, propensity score; HR, hazard ratio; CI, confidence interval

eFigure 17. Risks of major adverse cardiovascular event associated with ticagrelor and clopidogrel use, analyzed using a meta-analysis and various time-at-risk, statistical, and clinical definition settings



The points indicate HR estimates and the lines their 95% CIs, based on 27 analyses with three different times-at-risk, three different statistical models, and two different clinical definitions of major adverse cardiovascular event (cardiovascular-related mortality, recurrent acute myocardial infarction, and stroke) overall mortality. The one-year risk window was defined as the time from 1 day after the index date to the 365 days after the index date or the end of patients' record. Five-year risk window starts from 1 day to 1825 days after index date, which is extended risk window from the one-year risk window. The on-treatment risk window was defined as the time from 1 day after the index date until the end of persistent exposure to the drug of interest, allowing a 7-day gap or the end of patients' record. Blanking period means initial 28 days after the index date. An HR >1 implies a higher risk in the ticagrelor group. Open circles represent HRs with CIs that included 1, and triangles represent HRs that were statistically significant.

Abbreviation: MACE, major adverse cardiovascular event; PS, propensity score; HR, hazard ratio; CI, confidence interval

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