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Association of Ticagrelor vs Clopidogrel With Major Adverse Coronary Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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IMPORTANCE Guidelines currently recommend ticagrelor over clopidogrel for patients with acute coronary syndrome (ACS) based on randomized clinical trial data in which ticagrelor reduced major adverse coronary events (MACE) vs clopidogrel but increased bleeding and dyspnea.

OBJECTIVE To compare the risk of MACE with ticagrelor vs clopidogrel in patients with ACS treated with percutaneous coronary intervention (PCI), to compare major bleeding and dyspnea, and to evaluate the association between $P2Y_{12}$ inhibitor adherence and MACE.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study using data of patients discharged alive after PCI for ACS from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry from April 1, 2012, to March 31, 2016, with follow-up to 1 year. Analysis began April 2018.

EXPOSURES Outpatient prescription for ticagrelor or clopidogrel within 31 days after PCI. Adherence was defined as a medication refill adherence value of 80% or higher.

MAIN OUTCOMES AND MEASURES Major adverse coronary events, a composite of all-cause death, hospitalization for ACS, unplanned coronary revascularization, or stent thrombosis within 365 days after index PCI. Secondary outcomes included hospitalization for major bleeding and emergency department visit for dyspnea.

RESULTS Of 11 185 individuals who underwent PCI, the median (interquartile range) age was 61 (54-71) years, and 2760 (24.7%) were women. Ticagrelor users (4076 [36.4%]) were generally younger and had fewer cardiac and noncardiac comorbidities than clopidogrel users. Ticagrelor was not associated with lower risk of MACE (adjusted hazard ratio [aHR], 0.97; 95% CI, 0.85-1.10); however, it was associated with an increased risk of major bleeding (aHR, 1.51; 95% CI, 1.29-1.78) and dyspnea (aHR, 1.98; 95% CI, 1.47-2.65). A total of 3328 ticagrelor users (81.6%) were adherent during the study vs 5256 of clopidogrel users (73.9%) ($P < .001$; $\chi^2 = 86.4$). In the full cohort, adherence was associated with a lower MACE risk (aHR, 0.79; 95% CI, 0.69-0.90 for adherence of ≥80% vs <80%). Differences in other secondary outcomes were not statistically significant. Sensitivity and subgroup analyses were consistent with primary analyses.

CONCLUSIONS AND RELEVANCE In this population-based cohort study of patients with ACS who underwent PCI, outpatient use of ticagrelor was not associated with a statistically significant reduction in MACE vs clopidogrel; however, it was associated with more major bleeding and dyspnea.

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Supplemental content

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Guidelines recommend ticagrelor over clopidogrel as part of dual antiplatelet therapy with acetylsalicylic acid (or aspirin) in the treatment of individuals with acute coronary syndrome (ACS), regardless of plans for invasive management.[1,2] This recommendation is primarily based on the Platelet Inhibition and Patient Outcomes (PLATO) trial,[3] in which patients with ACS receiving ticagrelor had a 16% relative risk reduction in major adverse coronary events (MACE) and 22% relative risk reduction in all-cause death compared with those treated with clopidogrel. This improvement in efficacy was counterbalanced by a 19% relative risk increase in major bleeding not associated with coronary artery bypass grafting and an 84% relative risk increase in dyspnea, which was generally reported as mild and transient.[3-6]

Patients seen in routine practice may differ in several ways from those enrolled in clinical trials, including having higher risks of MACE and bleeding, more comorbidities, and lower likelihood of being prescribed and adhering to evidence-based therapies.[7] One registry study reported that 32% of consecutively enrolled patients with myocardial infarction were ineligible for contemporary antiplatelet trials including PLATO.[8] Observational studies can complement clinical trials by evaluating the associations of interventions in representative populations that reflect these factors and can identify barriers to replicating the results observed in randomized clinical trials.

The primary study objective was to assess the comparative association of ticagrelor and clopidogrel with reduced MACE using data from a population-based registry including all patients undergoing percutaneous coronary intervention (PCI) for ACS in a geographic region with universal access to health care. We hypothesized that ticagrelor would be associated with a lower risk of MACE than clopidogrel. Secondary objectives included the evaluation of the safety of ticagrelor compared with clopidogrel, as well as associations between adherence, persistence, and switching with MACE.

Key Points

Question What is the association between ticagrelor vs clopidogrel and major adverse coronary events, major bleeding, and dyspnea in patients with acute coronary syndrome treated with percutaneous coronary intervention?

Findings In this cohort study of 11 185 patients, ticagrelor was not associated with a statistically significantly lower risk of major adverse coronary events compared with clopidogrel. However, it was associated with statistically significantly more major bleeding and dyspnea.

Meaning Ticagrelor was not associated with a lower risk of major adverse coronary events in patients with acute coronary syndrome who underwent percutaneous coronary intervention.

Methods

Data Sources

The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry prospectively collects detailed clinical data on all patients undergoing coronary angiography in Alberta, Canada (population of approximately 4.3 million).[9] There are 3 sites where coronary angiography is performed that serve the entire province. The Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry was used to define the study cohort, determine baseline clinical and procedural characteristics, and obtain data on death and coronary procedures. The Pharmaceutical Information Network contains data on all outpatient prescriptions filled at pharmacies in Alberta, including fill dates and quantities. The Pharmaceutical Information Network was used to collect data on exposure to $P2Y_{12}$ inhibitors and other prescription medications, as well as data on $P2Y_{12}$ inhibitor adherence, persistence, and switching. Data on baseline hemoglobin concentration, creatinine concentration, and estimated glomerular filtration rate were obtained from the Alberta Health Services Laboratory Services. The Discharge Abstract Database and National Ambulatory Care Reporting System, which contain data on emergency department visits and hospitalizations in Alberta (eg, admission and discharge dates and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*] diagnosis codes) were used to identify history of atrial fibrillation (*ICD-10* code I48.x recorded within 2 years prior to index) and study outcomes. The University of Alberta Research Ethics Office approved this study with a waiver of informed consent because the data were deidentified when provided to the investigators.

Cohort Definition

Included participants were older than 18 years, underwent PCI for ACS between April 1, 2012, and March 31, 2016, were discharged alive from index hospitalization, and filled a first prescription for clopidogrel or ticagrelor within 31 days after undergoing PCI. Both clopidogrel and ticagrelor were approved for ACS in Canada during the entire study, and ticagrelor was available on the Alberta acute care formulary from October 1, 2012. Prevalent $P2Y_{12}$ inhibitor users, defined as individuals with a prescription for clopidogrel, prasugrel, or ticagrelor within 120 days prior to the index PCI, were excluded, as the present study was restricted to new users of $P2Y_{12}$ inhibitor therapy.

Exposure

Exposure was defined by a prescription fill in the Pharmaceutical Information Network for clopidogrel or ticagrelor. Three additional measures of exposure were calculated: adherence, persistence, and switch, assuming an intended $P2Y_{12}$ inhibitor duration of 12 months according to guideline recommendations.[1,2] Adherence was estimated using the medication refill adherence (MRA),[10,11] defined as: MRA (%) = (total days' supply within an interval / total days in interval) × 100, where the days' supply for clopidogrel equaled the number of tablets filled in that time interval, and the days' supply for ticagrelor equaled half the total tablets filled (because it is taken twice daily). Medication refill adherence was censored at time of death, such that adherence for patients who died prior to the next fill could not

exceed 100%. Patients with MRA of 80% or higher during the study were classified as adherent, as defined in previous ACS studies.[3,12] Participants were classified as persistent during the 365 days after the index event if they had gaps between $P2Y_{12}$ inhibitor prescription fills of less than the days' supply plus a 15-day grace period.[11] Switch was defined as 1 or more prescription fills for a $P2Y_{12}$ inhibitor different from the first fill within 365 days after the index event. For patients who switched $P2Y_{12}$ inhibitors during the study, all $P2Y_{12}$ inhibitor fill information was considered for calculation of adherence and persistence (ie, patients were considered adherent if they filled the second $P2Y_{12}$ inhibitor at appropriate intervals).

During the study, administration of acetylsalicylic acid, 81 mg, daily, for all patients without contraindication was the standard of care after ACS in Alberta and was incorporated in all standardized preprinted order sets for ACS management and post-ACS care. Acetylsalicylic acid, 81 mg, is not routinely recorded in the Pharmaceutical Information Network because it is available without a prescription in Alberta. For the purposes of this study, all patients were assumed to receive acetylsalicylic acid, 81 mg, daily, during follow-up.

Outcomes

The primary outcome was the first occurrence of MACE, defined as a composite of all-cause death, hospitalization with nonfatal ACS (*ICD-10* codes I20.0, I21, or I22 as most responsible diagnosis), coronary revascularization excluding planned staged PCI procedures (which is a prospectively filled data field in the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease registry), or stent thrombosis within 365 days after the index hospitalization. Secondary outcomes included a composite of all-cause death, hospitalization with ACS, or ischemic stroke (*ICD-10* codes I63.0 to I63.9 and I64); hospitalization for major bleeding (*ICD-10* codes listed in eAppendix in the Supplement as first or second diagnosis code); and emergency department visit for dyspnea (*ICD-10* code R06.0 as most responsible diagnosis). The *ICD-10* codes for ACS and major bleeding have been validated.[13-15]

Statistical Analyses

Baseline characteristics were summarized for each group as proportions for categorical variables and as medians with interquartile ranges for continuous variables. Proportions and medians were compared using the χ^2 and Mann-Whitney test, respectively. Hazard ratios (HR) and 95% confidence intervals for ticagrelor vs clopidogrel were obtained using Cox proportional hazard models, censored at time of $P2Y_{12}$ inhibitor switch. Models for nonfatal outcomes were also censored at time of death. To account for baseline differences, fully adjusted Cox models were constructed for each outcome. Baseline characteristics, including all variables listed in **Table 1**, with a *P* value less than .20 in the univariable model, were included in a multivariable model; factors with a *P* value less than .05 in multivariable analysis remained in the final model. Additionally, the model was further adjusted for adherence using MRA as a continuous variable. To assess the association between adherence, persistence, and switching and outcomes, comparisons of MACE between ticagrelor and clopidogrel were stratified based on adherence of 80% or more vs less than 80%, persistence vs nonpersistence, and switching vs nonswitching. Furthermore, risk of MACE was compared between those with adherence of 80% or more and less than 80%, persistent vs nonpersistent, and switchers vs nonswitchers.

To ensure robustness of the primary analysis, several sensitivity analyses were performed. First, ticagrelor and clopidogrel were compared in a propensity score–matched cohort, in which logistic regression was used to estimate the probability of ticagrelor use based on baseline variables listed in Table 1, and patients treated with ticagrelor were matched with those who received clopidogrel using 1:1 nearest-neighbor matching. Outcomes were compared using χ^2 tests and HRs from proportional hazards models stratified by matched pairs to account for correlation between each matched pair. Second, the primary analysis was repeated with adjustment for a cardiac-specific comorbidity index.[16] Subgroup analyses for MACE, major bleeding, and dyspnea were performed for the following: age (<65, 65-74, or ≥75 years), diabetes, estimated glomerular filtration rate (≥60 vs <60 mL/min), by fiscal year, with exclusion of patients receiving oral anticoagulants or with atrial fibrillation at baseline, exclusion of patients who switched $P2Y_{12}$ inhibitors, and high-risk criteria using 2 definitions: PLATO inclusion criteria (defined as either ST-segment elevation myocardial infarction, excluding those treated with rescue PCI following failed fibrinolysis, or non–ST-segment elevation myocardial infarction plus any of the following: age ≥60 years, multivessel coronary artery disease on coronary angiography, prior myocardial infarction, coronary artery bypass grafting, cerebrovascular disease, peripheral vascular disease, diabetes or renal disease, or estimated glomerular filtration rate <60 mL/min), and the TIMI Risk Score for Secondary Prevention.[17] The threshold for statistical significance was set at 2-sided *P* values less than .05. All analyses were performed using SAS, version 9.4 (SAS Institute) and R, version 3.4.3 (R Project for Statistical Computing). Analysis began April 2018.

Results

Cohort Characteristics

From April 1, 2012, to March 31, 2016, a total of 13 897 patients underwent PCI for ACS in Alberta, Canada. Of these, 11 185 patients (80.5%) filled at least 1 prescription for a $P2Y_{12}$ inhibitor within 31 days of PCI and met all study eligibility criteria (**Figure**). Overall, clopidogrel was the most frequently prescribed $P2Y_{12}$ inhibitor during the study (7109 of 11 185 [63.6%]); however, ticagrelor use steadily increased and was used in 3112 of 5523 patients (56.3%) by the second half of the study (Table 1 and eFigure in the Supplement).

The median (interquartile range) age was 61 (54-71) years, 2760 (24.7%) were women, and 4953 (44.3%) presented with ST-segment elevation myocardial infarction. Patients filled their first outpatient prescription for a $P2Y_{12}$ inhibitor a median (interquartile range) of 3 (1-4) days after

Table 1. Baseline Clinical and Angiographic Characteristics and $P2Y_{12}$ Inhibitor Use During Study Follow-up

Characteristic	No. (%)		P Value
	Clopidogrel Group (n = 7109)	Ticagrelor Group (n = 4076)	
Age, y			
Median (IQR)	62 (54-72)	60 (53-69)	<.001
≥75	1434 (20.2)	554 (13.6)	<.001
Women	1831 (25.8)	929 (22.8)	<.001
Fiscal year[a]			
2013	2593 (93.6)	177 (6.4)	<.001
2014	2105 (72.8)	787 (27.2)	
2015	1311 (48.3)	1406 (51.7)	
2016	1100 (39.2)	1706 (60.8)	
ACS type			
STEMI	3170 (44.6)	1783 (43.7)	.007
NSTEMI	2829 (39.8)	1683 (41.3)	
Unstable angina	1081 (15.2)	576 (14.1)	
Unknown	29 (0.4)	34 (0.8)	
Cardiovascular history and risk factors			
Prior MI	858 (12.1)	287 (7.0)	<.001
Prior coronary artery bypass grafting	294 (4.1)	172 (4.2)	.83
Prior PCI	951 (13.4)	478 (11.7)	.01
Cerebrovascular disease	326 (4.6)	120 (2.9)	<.001
Peripheral vascular disease	696 (9.8)	135 (3.3)	<.001
Heart failure	434 (6.1)	126 (3.1)	<.001
Atrial fibrillation	662 (9.3)	147 (3.6)	<.001
Diabetes mellitus	1807 (25.4)	968 (23.7)	.05
Hyperlipidemia	4163 (58.6)	2091 (51.3)	<.001
Hypertension	4857 (68.3)	2532 (62.1)	<.001
Smoking status			
Current	2301 (32.4)	1060 (26.0)	<.001
Former	1580 (22.2)	715 (17.5)	
Never/not recorded	3228 (45.4)	2301 (56.5)	
Other comorbidities			
Chronic pulmonary disease	714 (10.0)	147 (3.6)	<.001
Renal disease	295 (4.1)	108 (2.6)	<.001
Dialysis dependence	62 (0.9)	14 (0.3)	.001
Liver disease	51 (0.7)	15 (0.4)	.02
Malignancy	239 (3.4)	95 (2.3)	.002
Coronary anatomy			
1 Vessel	2395 (33.7)	1325 (32.5)	.54
2 Vessels	1849 (26.0)	1107 (27.2)	
2 Vessels including proximal LAD	551 (7.8)	300 (7.4)	
3 Vessels	1159 (16.3)	641 (15.7)	
3 Vessels including proximal LAD	908 (12.8)	555 (13.6)	
Left main	228 (3.2)	136 (3.3)	
Minimal CAD	19 (0.3)	12 (0.3)	
Ejection fraction, %			
>50	2638 (37.1)	1298 (31.8)	<.001
35-50	1220 (17.2)	482 (11.8)	
20-34	198 (2.8)	67 (1.6)	
<20	19 (0.3)	4 (0.1)	
Missing	3034 (42.7)	2225 (54.6)	
Meets PLATO trial eligibility criteria	5639 (79.3)	3223 (79.1)	.75
TIMI Risk Score for Secondary Prevention			
Median (IQR)	2 (1-3)	1 (1-2)	<.001
≥3	2014 (28.3)	770 (18.9)	<.001

(continued)

Table 1. Baseline Clinical and Angiographic Characteristics and $P2Y_{12}$ Inhibitor Use During Study Follow-up (continued)

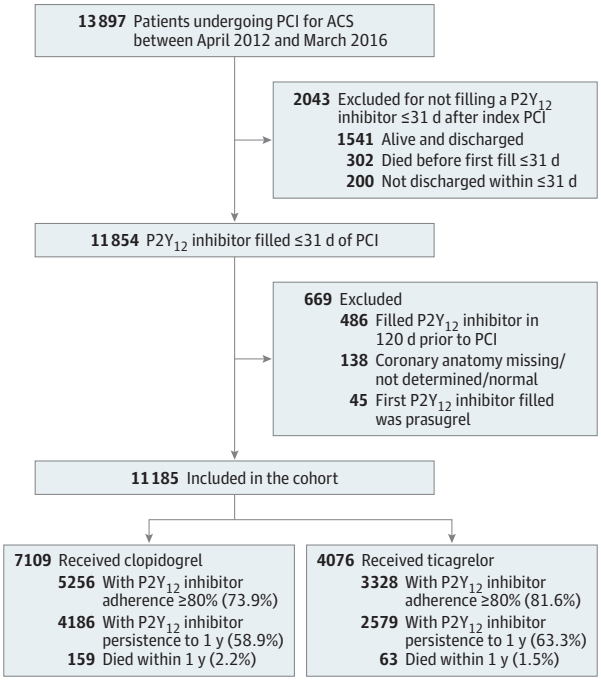
Characteristic	No. (%) Clopidogrel Group (n = 7109)	Ticagrelor Group (n = 4076)	*P* Value
Stent placement	6747 (94.9)	3827 (93.9)	.02
Drug-eluting stent	3989 (56.1)	3127 (76.7)	<.001
Laboratory values, median (IQR)			
Hemoglobin, g/dL	13.7 (12.5-14.8)	14.1 (13.0-15.1)	<.001
Serum creatinine, mg/dL	0.95 (0.81-1.11)	0.95 (0.81-1.09)	.41
eGFR, mL/min	62 (61-85)	81 (65-93)	<.001
Other medications ≤31 d after PCI			
Oral anticoagulant	1060 (14.9)	134 (3.3)	<.001
Proton pump inhibitor	2630 (37.0)	1270 (31.2)	<.001
Study $P2Y_{12}$ inhibitor utilization			
MRA, median (IQR), %	98 (78-101)	99 (88-102)	<.001
At month 0 to 6	100 (89-104)	101 (96-107)	<.001
At month 7 to 12	95 (67-100)	95 (81-100)	<.001
MRA ≥80%	5256 (73.9)	3328 (81.6)	<.001
At months 0 to 6	5732 (80.6)	3602 (88.4)	<.001
At months 7 to 12	4892 (68.8)	3048 (74.8)	<.001
Persistence	4186 (58.9)	2579 (63.3)	<.001
Switch	162 (2.3)	571 (14.0)	<.001

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; LAD, left anterior descending artery; MI, myocardial infarction; MRA, medication refill adherence; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

SI conversion factors: To convert hemoglobin to g/L, multiply by 10.0; serum creatinine to μmol/L, multiply by 88.4.

[a] Percentages represent proportion of cohort initially prescribed that $P2Y_{12}$ inhibitor during the indicated fiscal year.

Figure. Cohort Derivation



Derivation of the study cohort from APPROACH between April 1, 2012, and March 31, 2016, is shown. Included patients from Alberta, Canada, who were 18 years or older who underwent percutaneous coronary intervention (PCI) for an acute coronary syndrome (ACS), were not receiving a $P2Y_{12}$ inhibitor in the 120 days preceding the ACS, and filled a prescription for clopidogrel or ticagrelor within 31 days after their PCI.

index PCI and 1 (0-3) day after hospital discharge. Table 1 lists baseline characteristics by $P2Y_{12}$ inhibitor group. Patients receiving ticagrelor were statistically significantly younger, less likely to be women, and had a lower prevalence of prior myocardial infarction, other cardiovascular disease, cardiac risk factors, and comorbidities compared with clopidogrel users. Ticagrelor users were also more likely to receive a drug-eluting stent than clopidogrel users and less likely to receive a prescription for an oral anticoagulant within 31 days after PCI.

Major Adverse Coronary Events

In unadjusted analyses, outpatient use of ticagrelor was associated with a lower risk of MACE than clopidogrel (HR, 0.84; 95% CI, 0.74-0.95) (**Table 2**). Unadjusted death rates were also lower with ticagrelor but not hospitalization for ACS, coronary revascularization or the composite of death, ACS, or ischemic stroke. After multivariable adjustment including baseline characteristics listed in Table 1 and adherence, differences in MACE (adjusted HR [aHR], 0.97; 95% CI, 0.85-1.10) and other cardiovascular outcomes were no longer statistically significant between ticagrelor and clopidogrel (Table 2).

Safety

In unadjusted analyses, ticagrelor was not associated with a statistically significantly greater risk of major bleeding compared with clopidogrel (HR, 1.09; 95% CI, 0.93-1.27). However, ticagrelor was associated with a higher risk of major bleeding compared with clopidogrel in the fully adjusted model (aHR, 1.51; 95% CI, 1.29-1.78) (Table 2). This difference was mainly driven by an increase in gastrointestinal hemorrhage (aHR, 2.02; 95% CI, 1.52-2.68) and pulmonary hemorrhage (aHR, 1.49; 95% CI, 1.15-1.93). Furthermore, ticagrelor was associated with a statistically significantly greater risk of an emergency department visit for dyspnea, which persisted in the fully adjusted model (aHR, 1.98; 95% CI, 1.47-2.65) (Table 2).

Table 2. Association of Clopidogrel vs Ticagrelor With Outcomes Within 1 Year After Percutaneous Coronary Intervention for Acute Coronary Syndrome

Outcome	No. (%)		*P* Value	HR (95% CI)		
	Clopidogrel Group (n = 7109)	Ticagrelor Group (n = 4076)		Unadjusted	Adjusted for Age and Sex	Fully Adjusted[a]
MACE	828 (11.6)	419 (10.3)	.03	0.84 (0.74-0.95)[b]	0.88 (0.78-0.995)[b]	0.97 (0.85-1.10)
All-cause death	159 (2.2)	63 (1.5)	.01	0.73 (0.54-0.98)[b]	0.91 (0.67-1.23)	1.19 (0.87-1.62)
ACS	505 (7.1)	259 (6.4)	.13	0.85 (0.73-1.00)	0.88 (0.75-1.03)	0.93 (0.79-1.09)
Coronary revascularization	338 (4.8)	178 (4.4)	.35	0.83 (0.69-1.01)	0.85 (0.70-1.04)	0.90 (0.73-1.10)
PCI	249 (3.5)	133 (3.3)	.50	0.87 (0.70-1.09)	0.88 (0.71-1.11)	0.87 (0.69-1.09)
Coronary artery bypass grafting	94 (1.3)	46 (1.1)	.38	0.72 (0.49-1.06)	0.75 (0.51-1.11)	1.01 (0.68-1.52)
Stent thrombosis	25 (0.4)	19 (0.5)	.35	1.30 (0.71-2.38)	1.29 (0.70-2.36)	1.66 (0.88-3.12)
Composite of death, ACS, or ischemic stroke	676 (9.5)	328 (8.0)	.009	0.82 (0.72-0.94)[b]	0.87 (0.76-1.00)	0.93 (0.80-1.09)
Ischemic stroke	40 (0.6)	20 (0.5)	.62	0.91 (0.52-1.57)	1.02 (0.59-1.78)	1.35 (0.75-2.40)
Major bleeding	449 (6.3)	277 (6.8)	.32	1.09 (0.93-1.27)	1.23 (1.05-1.43)[b]	1.51 (1.29-1.78)[b]
Intracranial	11 (0.2)	5 (0.1)	.67	0.68 (0.22-2.15)	0.71 (0.22-2.24)	0.88 (0.26-2.90)
Gastrointestinal	135 (1.9)	99 (2.4)	.06	1.33 (1.02-1.74)[b]	1.55 (1.19-2.04)[b]	2.02 (1.52-2.68)[b]
Pulmonary	175 (2.5)	111 (2.7)	.40	1.12 (0.88-1.43)	1.24 (0.97-1.58)	1.49 (1.15-1.93)[b]
Urologic	74 (1.0)	38 (0.9)	.58	0.86 (0.58-1.30)	1.01 (0.67-1.52)	1.16 (0.76-1.78)
Other	85 (1.2)	42 (1.0)	.43	0.89 (0.61-1.30)	0.99 (0.68-1.44)	1.18 (0.79-1.75)
Dyspnea	116 (1.6)	119 (2.9)	<.001	1.80 (1.39-2.34)[b]	2.01 (1.54-2.61)[b]	1.98 (1.47-2.65)[b]

Abbreviations: ACS, acute coronary syndrome; HR, hazard ratio; MACE, major adverse coronary event; PCI, percutaneous coronary intervention.

[a] Adjusted for age, sex, and medication refill adherence as a continuous variable over the entire year and statistically significant variables from stepwise variable selection: MACE (prior PCI, diabetes, hyperlipidemia, coronary anatomy, drug-eluting stent, hemoglobin, creatinine, proton pump inhibitor use); major bleeding (malignancy, hemoglobin, creatinine, oral anticoagulant use); dyspnea (fiscal year, prior myocardial infarction, heart failure, diabetes, chronic pulmonary disease, renal disease); and ischemic stroke (diabetes, hypertension, oral anticoagulant use).

[b] Statistically significant results.

Table 3. Major Adverse Coronary Events Within 1 Year After Percutaneous Coronary Intervention for Acute Coronary Syndrome Based on Adherence, Persistence, and Switching of Study $P2Y_{12}$ Inhibitor

Characteristic	MACE, No./Total No. (%)			HR (95% CI)[a]
	Full Cohort (N = 11 185)	Clopidogrel Group (n = 7109)	Ticagrelor Group (n = 4076)	Ticagrelor vs Clopidogrel
Adherence				
MRA ≥80%	881/8584 (10.3)	550/5256 (10.5)	311/3328 (9.9)	1.00 (0.86-1.16)
MRA <80%	366/2601 (14.1)	278/1853 (15.0)	88/748 (11.8)	0.88 (0.68-1.14)
MRA ≥80% vs <80%, HR (95% CI)[a]	0.79 (0.69-0.90)[b]	0.77 (0.66-0.89)[b]	0.86 (0.67-1.11)	NA
Persistence				
Yes	697/6765 (10.3)	433/4186 (10.3)	264/2579 (10.2)	1.02 (0.87-1.20)
No	550/4420 (12.4)	395/2923 (13.5)	155/1497 (10.4)	0.89 (0.73-1.09)
Persistent vs nonpersistent, HR (95% CI)[a]	0.90 (0.80-1.01)	0.85 (0.74-0.98)[b]	1.01 (0.81-1.24)	NA
Switch[c]				
Yes	NA	6/92 (6.5)	47/521 (9.0)	1.49 (0.62-3.61)
No	NA	752/6947 (10.8)	322/3505 (9.2)	0.98 (0.86-1.12)
Switch vs no switch, HR (95% CI)[a]	NA	0.56 (0.25-1.25)	0.88 (0.65-1.20)	NA

Abbreviations: HR, hazard ratio; MACE, major adverse coronary event; MRA, medication refill adherence; NA, not applicable.

[a] Adjusted for age, sex, prior percutaneous coronary intervention, diabetes, hyperlipidemia, coronary anatomy, drug-eluting stent, hemoglobin, creatinine, and proton pump inhibitor use.

[b] Statistically significant results.

[c] Excludes switches occurring after MACE event.

Association of Adherence, Persistence, and Switching With Major Adverse Coronary Events

Ticagrelor users were more likely to be adherent to $P2Y_{12}$ inhibitor therapy during the entire study than clopidogrel users (3328 [81.6%] vs 5256 [73.9%]; $P < .001$; $\chi^2 = 86.4$). Median MRA declined in both groups between months 0 to 6 and months 7 to 12, and 2579 ticagrelor users (63.3%) vs 4186 clopidogrel users (58.9%) persisted on a $P2Y_{12}$ inhibitor for 1 year ($P < .001$; $\chi^2 = 20.9$) (Table 1). Major adverse coronary events were not statistically significantly different between ticagrelor and clopidogrel users regardless of adherence, persistence, and switching (**Table 3**). In the full cohort, MACE was lower in patients with $P2Y_{12}$ inhibitor adherence of 80% or higher compared with adherence under 80% (aHR, 0.79; 95% CI, 0.69-0.90).

Switching $P2Y_{12}$ inhibitors occurred in 571 ticagrelor users (14.0%) vs 162 clopidogrel users (2.3%) (Table 1) and was not associated with an increased risk of MACE (aHR, 0.56;

Table 4. Association of Clopidogrel vs Ticagrelor With Outcomes Within 1 Year After Percutaneous Coronary Intervention for Acute Coronary Syndrome in Propensity Score–Matched Cohort

Outcome	No. (%)		P Value	HR (95% CI)
	Clopidogrel Group (n = 3711)	Ticagrelor Group (n = 3711)		
MACE	368 (9.9)	380 (10.2)	.64	1.00 (0.86-1.17)
All-cause death	54 (1.5)	61 (1.6)	.51	1.10 (0.75-1.61)
ACS	228 (6.1)	235 (6.3)	.74	1.02 (0.84-1.24)
Coronary revascularization	168 (4.5)	157 (4.2)	.53	0.86 (0.67-1.09)
PCI	121 (3.3)	114 (3.1)	.64	0.90 (0.68-1.19)
CABG	50 (1.3)	44 (1.2)	.53	0.74 (0.47-1.15)
Stent thrombosis	7 (0.2)	18 (0.5)	.03	2.57 (1.07-6.16)[a]
Composite of all-cause death, ACS, or stroke	290 (7.8)	299 (8.1)	.70	1.02 (0.86-1.21)
Ischemic stroke	18 (0.5)	17 (0.5)	.87	0.94 (0.48-1.86)
Major bleed	182 (4.9)	261 (7.0)	<.001	1.52 (1.24-1.87)[a]
Intracranial	3 (0.1)	3 (0.1)	>.99	1.00 (0.14-7.10)
Gastrointestinal	53 (1.4)	95 (2.6)	<.001	2.10 (1.44-3.06)[a]
Pulmonary	81 (2.2)	105 (2.8)	.08	1.32 (0.97-1.80)
Urologic	29 (0.8)	37 (1.0)	.32	1.32 (0.79-2.22)
Other	32 (0.9)	38 (1.0)	.47	1.29 (0.78-2.11)
Dyspnea	46 (1.2)	116 (3.1)	<.001	2.42 (1.70-3.45)[a]

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; HR, hazard ratio; MACE, major adverse coronary event; PCI, percutaneous coronary intervention.

[a] Statistically significant results.

95% CI, 0.25-1.25 with initial clopidogrel use and aHR, 0.88; 95% CI, 0.65-1.20 with initial ticagrelor use) (Table 3). Within 30 days after an emergency department visit for dyspnea, 28 of 112 ticagrelor users (25.0%) switched $P2Y_{12}$ inhibitors compared with 1 of 115 clopidogrel users (0.9%) ($P < .001$; $\chi^2 = 29.6$). Similarly, more ticagrelor users than clopidogrel users switched their $P2Y_{12}$ inhibitor within 30 days after a major bleed (18 of 255 [7.1%] vs 2 of 439 [0.5%]; $P < .001$; $\chi^2 = 25.1$). Moreover, among ticagrelor users, switching occurred more frequently in those with an emergency department visit for dyspnea (54 of 119 [45.4%]) vs those without dyspnea (517 of 3957 [13.1%]) ($P < .001$; $\chi^2 = 100.1$) and among those with hospitalization for major bleed (53 of 277 [19.1%]) vs those without major bleed (518 of 3799 [13.6%]) ($P = .01$; $\chi^2 = 6.5$).

Sensitivity and Subgroup Analyses

Propensity score matching created a well-balanced cohort (n = 7422) with standardized differences for all baseline characteristics less than 0.1 (eTable 1 in the Supplement). Findings from the propensity score–matched analysis (**Table 4**) were consistent with the primary, multivariable-adjusted analyses, not demonstrating a statistically significant difference between ticagrelor and clopidogrel for MACE (HR, 1.00; 95% CI, 0.86-1.17) but higher risks of major bleeding (HR, 1.52; 95% CI, 1.24-1.87) and dyspnea (HR, 2.42; 95% CI, 1.70-3.45) with ticagrelor. Similarly, differences between ticagrelor and clopidogrel were not observed for MACE or any of its components when adjusted for a cardiac-specific comorbidity index (eTable 2 in the Supplement).

Subgroup analyses for MACE, major bleeding, and dyspnea based on age, diabetes, estimated glomerular filtration rate, high-risk criteria based on PLATO or TIMI Risk Score for Secondary Prevention criteria, fiscal year, and exclusion of patients with atrial fibrillation, receiving oral anticoagulants, or switching $P2Y_{12}$ inhibitors were all consistent with results for the overall cohort (eTable 3 in the Supplement). eTable 4 in the Supplement provides the full details of the multivariate models for MACE, major bleeding, and dyspnea. eTable 5 in the Supplement illustrates the change in the hazard ratio with stepwise addition of variables to the multivariate model for MACE.

Discussion

In this large, contemporary, population-based cohort study of patients who underwent PCI for ACS, outpatient use of ticagrelor was not associated with a lower risk of MACE compared with clopidogrel; however, it was associated with a higher risk of major bleeding and dyspnea. Conversely, adherence to any $P2Y_{12}$ inhibitor therapy was associated with 21% lower relative risk of MACE compared with $P2Y_{12}$ inhibitor nonadherence.

Our findings differ from prior studies on this topic, and this may be due to differences in methodology, patient populations, and advances in interventional cardiology. The randomized clinical trial that established the use of ticagrelor in ACS, PLATO,[3] was a multinational trial including all ACS subtypes regardless of planned invasive management, in whom PCI was performed predominantly using bare-metal stents and first-generation drug-eluting stents. Furthermore, outcome ascertainment in the PLATO trial included in-hospital outcomes. The large observational SWEDEHEART registry study,[18] which was also discordant with our findings, was not restricted to patients with ACS who underwent PCI, did not specify the proportion of patients receiving second-generation drug-eluting stents, and defined exposure based on intended choice and duration of $P2Y_{12}$ inhibitor therapy on discharge without confirmation of use and adherence using prescription fills or patient interview. Like our study, the SWEDEHEART study[18] did not include in-hospital events and only included patients who survived to discharge. Conversely, our observational study was

restricted to patients with ACS who all underwent PCI, survived to discharge, were new users of $P2Y_{12}$ inhibitor therapy, and primarily received second-generation drug-eluting stents, which have an improved safety profile, including a lower risk of stent thrombosis than bare-metal and older-generation drug-eluting stents.[19] The Dutch CHANGE DAPT cohort study, which enrolled patients with ACS who underwent PCI exclusively with second-generation drug-eluting stents, also found no statistically significant difference in MACE between ticagrelor and clopidogrel.[20] In aggregate, these study findings suggest that the increased potency of ticagrelor may not translate to improved efficacy in the era of second-generation drug-eluting stents, particularly after patients are hospital discharged. A 2019 randomized clinical trial of patients with ACS undergoing PCI found ticagrelor to be inferior to the once-daily potent $P2Y_{12}$ inhibitor prasugrel.[21]

Although the greater antiplatelet potency of ticagrelor did not translate to reduction in MACE in this study, it was associated with an increased risk of major bleeding. Given that patients who underwent coronary artery bypass grafting during the index hospitalization were excluded from this study, these findings emulate the increased risk of non–coronary artery bypass grafting–related major bleeding seen in PLATO.[3] Moreover, our cohort included patients at higher risk of bleeding than those generally included in clinical trials, as indicated by a rate of major bleeding in the ticagrelor group that was higher than that reported in PLATO (6.8% vs 4.5%) despite the stricter bleeding definition used in our study and exclusion of events (including periprocedural bleeding) occurring during the index hospitalization.[3] Similarly, patients in the ticagrelor group of this cohort had a 2-fold higher risk of emergency department visits for dyspnea vs those in the clopidogrel group. Although ticagrelor-related dyspnea is generally mild and transient, it persists and impairs quality of life in a subset of patients, leading to increased health care utilization, nonadherence, and premature discontinuation.[3-6,22]

This study found that adherence to a $P2Y_{12}$ inhibitor was more strongly associated with risk of MACE than choice of the $P2Y_{12}$ inhibitor itself. These findings extend prior observations that premature discontinuation of $P2Y_{12}$ inhibitors is associated with a greater risk of death, rehospitalization, and stent thrombosis.[23,24] Several factors associated with lower adherence to $P2Y_{12}$ inhibitors,[24] including greater comorbidity burden and use of oral anticoagulation, were more prevalent in clopidogrel users within the present study. This may have accounted in part for the lower adherence and persistence in clopidogrel users compared with ticagrelor users. These results should encourage clinicians to routinely ask patients whether they are taking their medications as prescribed and identify and resolve barriers to adherence, including cost, adverse events (including dyspnea with ticagrelor), and burden from number or frequency of medications administered. The steady decline in adherence during the course of the present study, consistent with prior studies,[25] warrants ongoing assessment of medication adherence starting at hospital discharge and continuing at every follow-up visit.

Limitations

This study has limitations inherent to its observational design. First, residual unmeasured confounding may persist despite measurement and adjustment for a variety of known clinical, angiographic, and laboratory variables. Second, we excluded outcomes occurring during the index hospitalization, as information on in-hospital $P2Y_{12}$ inhibitor use was not available within our databases. Third, the definitions for exposure, adherence, and persistence assume that patients took their $P2Y_{12}$ inhibitors as filled and may overestimate true adherence. However, these definitions have been validated, are consistent with those used in multiple prior studies, and provide the closest surrogate to medication use available using administrative data.[10,11] Fourth, the adherence definition assumed that all patients were intended to receive a $P2Y_{12}$ inhibitor for at least 12 months, which was routine standard of care during the study. Fifth, we used all-cause death for the composite primary outcome because cause of death was not reliably ascertained within available databases. Therefore, these results are not directly comparable with the primary outcome of PLATO. However, we included the secondary outcome of all-cause death, ACS, or stroke, which was also evaluated in PLATO. Sixth, we used a novel outcome definition for dyspnea using a nonspecific *ICD-10* symptom code that requires further validation. However, post hoc analyses further evaluating this outcome revealed higher switch rates in the ticagrelor group among those with dyspnea and more switches from ticagrelor than clopidogrel within 30 days after an emergency department visit for dyspnea, supporting an association between ticagrelor use and these events.

Conclusions

In a large, representative population-based cohort of patients who underwent PCI for ACS primarily using second-generation drug-eluting stents, ticagrelor was not associated with a lower risk of MACE compared with clopidogrel; however, it was associated with a higher risk of major bleeding and emergency department visits for dyspnea.

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REFERENCES

1. Mehta SR, Bainey KR, Cantor WJ, et al; members of the Secondary Panel. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol*. 2018;34(3):214-233. doi:10.1016/j.cjca.2017.12.012

2. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134(10):e123-e155. doi:10.1161/CIR.0000000000000404

3. Wallentin L, Becker RC, Budaj A, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327

4. Storey RF, Becker RC, Harrington RA, et al. Characterization of dyspnoea in PLATO study patients treated with ticagrelor or clopidogrel and its association with clinical outcomes. *Eur Heart J*. 2011;32(23):2945-2953. doi:10.1093/eurheartj/ehr231

5. Storey RF, Bliden KP, Patil SB, et al; ONSET/OFFSET Investigators. Incidence of dyspnea and assessment of cardiac and pulmonary function in patients with stable coronary artery disease receiving ticagrelor, clopidogrel, or placebo in the ONSET/OFFSET study. *J Am Coll Cardiol*. 2010;56(3):185-193. doi:10.1016/j.jacc.2010.01.062

6. Bonaca MP, Bhatt DL, Cohen M, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-1800. doi:10.1056/NEJMoa1500857

7. Kennedy-Martin T, Curtis S, Faries D, Robinson S, Johnston J. A literature review on the representativeness of randomized controlled trial samples and implications for the external validity of trial results. *Trials*. 2015;16(1):495. doi:10.1186/s13063-015-1023-4

8. Udell JA, Wang TY, Li S, et al. Clinical trial participation after myocardial infarction in a national cardiovascular data registry. *JAMA*. 2014;312(8):841-843. doi:10.1001/jama.2014.6217

9. Ghali WA, Knudtson ML. Overview of the Alberta provincial project for outcome assessment in coronary heart disease: on behalf of the APPROACH investigators. *Can J Cardiol*. 2000;16(10):1225-1230.

10. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *Ann Pharmacother*. 2006;40(7-8):1280-1288. doi:10.1345/aph.1H018

11. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15(8):565-574. doi:10.1002/pds.1230

12. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA*. 2007;297(2):177-186. doi:10.1001/jama.297.2.177

13. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of myocardial infarction diagnoses in administrative databases: a systematic review. *PLoS One*. 2014;9(3):e92286. doi:10.1371/journal.pone.0092286

14. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN. Rates of hemorrhage during warfarin therapy for atrial fibrillation. *CMAJ*. 2013;185(2):E121-E127. doi:10.1503/cmaj.121218

15. Arnason T, Wells PS, van Walraven C, Forster AJ. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. *Thromb Res*. 2006;118(2):253-262. doi:10.1016/j.thromres.2005.06.015

16. Azzalini L, Chabot-Blanchet M, Southern DA, et al. A disease-specific comorbidity index for predicting mortality in patients admitted to hospital with a cardiac condition. *CMAJ*. 2019;191(11):E299-E307. doi:10.1503/cmaj.181186

17. Bohula EA, Bonaca MP, Braunwald E, et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. *Circulation*. 2016;134(4):304-313. doi:10.1161/CIRCULATIONAHA.115.019861

18. Sahlén A, Varenhorst C, Lagerqvist B, et al. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. *Eur Heart J*. 2016;37(44):3335-3342. doi:10.1093/eurheartj/ehw284

19. Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379(9824):1393-1402. doi:10.1016/S0140-6736(12)60324-9

20. Zocca P, van der Heijden LC, Kok MM, et al. Clopidogrel or ticagrelor in acute coronary syndrome patients treated with newer-generation drug-eluting stents: CHANGE DAPT. *EuroIntervention*. 2017;13(10):1168-1176. doi:10.4244/EIJ-D-17-00634

21. Schüpke S, Neumann F-J, Menichelli M, et al; ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. *N Engl J Med*. 2019;381(16):1524-1534. doi:10.1056/NEJMoa1908973

22. Gaubert M, Laine M, Richard T, et al. Effect of ticagrelor-related dyspnea on compliance with therapy in acute coronary syndrome patients. *Int J Cardiol*. 2014;173(1):120-121. doi:10.1016/j.ijcard.2014.02.028

23. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation*. 2006;113(24):2803-2809. doi:10.1161/CIRCULATIONAHA.106.618066

24. Airoldi F, Colombo A, Morici N, et al. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation*. 2007;116(7):745-754. doi:10.1161/CIRCULATIONAHA.106.686048

25. Czarny MJ, Nathan AS, Yeh RW, Mauri L. Adherence to dual antiplatelet therapy after coronary stenting: a systematic review. *Clin Cardiol*. 2014;37(8):505-513. doi:10.1002/clc.22289