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ORIGINAL REPORT

Ticagrelor and bradycardia: a nested case–control study

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ABSTRACT

Purpose Ticagrelor increases serum adenosine concentrations, slowing conduction and possibly leading to bradycardia. Clinical trial data have shown numerically, though not statistically significantly, higher rates of bradyarrhythmias with ticagrelor versus clopidogrel. Additionally, recent case reports have further raised concerns for this adverse effect. We explored the association between ticagrelor and hospitalization for bradycardia in a real-world setting.

Methods We conducted a population-based, nested case–control study of Ontario residents, 66 years of age or older, discharged after a first acute coronary syndrome by linking multiple healthcare databases. Cases included patients hospitalized for bradycardia within 1 year of starting a $P2Y_{12}$ inhibitor. For each case, we identified 4 controls matched on age, sex, index date, and current use of a $P2Y_{12}$ inhibitor. The exposure of interest was a prescription for ticagrelor within 90 days, with clopidogrel use as the reference group.

Results From April 2012 to March 2014, we identified 140 cases and 560 controls who met the study criteria. We found no significant association between bradycardia and exposure to ticagrelor relative to clopidogrel in the previous 90 days prior to the index date (adjusted odds ratio 1.06, 95% confidence interval 0.65–2.21). Further adjustment for potential confounders also did not identify a significant association.

Conclusions Among older patients with a first acute coronary syndrome, use of ticagrelor was not associated with a greater risk of admission for bradycardia relative to clopidogrel. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—acute coronary syndrome; bradycardia; clopidogrel; myocardial infarction; p2y12 inhibitor; ticagrelor; pharmacoepidemiology

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INTRODUCTION

In the USA, approximately 683 000 patients are discharged from hospital each year following an acute coronary syndrome (ACS).[1] In patients with ACS, clinical practice guidelines recommend dual antiplatelet therapy with acetylsalicylic acid and a $P2Y_{12}$ inhibitor.[1–5] Several guidelines[3–5] preferentially recommend ticagrelor over clopidogrel based on the Platelet Inhibition and Patient Outcomes (PLATO) trial, which demonstrated a 1.9% absolute risk reduction in the composite of cardiovascular death, myocardial infarction, or stroke with ticagrelor compared with clopidogrel.[6]

Unlike other oral $P2Y_{12}$ inhibitors, ticagrelor inhibits the uptake of adenosine in erythrocytes, resulting in elevated serum adenosine concentrations.[7–9] Along with its other effects, adenosine slows conduction through the sinoatrial and atrioventricular nodes, which can lead to bradycardia. Data from a substudy of PLATO,[10] as well as a phase II trial,[11] suggest that ticagrelor increases the incidence of ventricular pauses. Although the incidence of syncope and bradycardia were numerically higher in the ticagrelor arm of the PLATO trial, this difference did not reach statistical significance. Similarly, the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a background of Aspirin–Thrombolysis in Myocardial Infarction 54

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(PEGASUS-TIMI 54) trial found a numerically higher risk of bradycardia with two doses of ticagrelor versus placebo, although neither was statistically significant.[12] Notably, however, PLATO and PEGASUS-TIMI 54 excluded patients at increased risk for bradycardia at the physician's discretion.[6,12] Further, exclusion of patients with a condition that increases risk for non-compliance or loss to follow-up may have systematically excluded patients more likely to be on certain interacting or bradycardia-inducing agents (e.g. antidepressants and cholinesterase inhibitors).

Two recent case reports implicating ticagrelor in severe bradycardia events raise concerns about the generalizability of the PLATO safety results to a real-world population.[13,14] In light of this ongoing uncertainty, we examined the association between ticagrelor use and hospitalization for bradycardia in patients with ACS.

METHODS

Setting and sources of data

We conducted a population-based, nested case–control study by linking multiple healthcare databases using unique, encoded individual identifiers from 1 April 2012 to 30 March 2014 in Ontario, Canada, as performed in previous studies by our research institution.[15,16] Ontario is Canada's most populous province, with a population of 13.6 million of whom approximately 2.1 million are aged 65 years or older.[17] These residents have universal access to hospital care, physicians' services, and prescription-drug coverage.

We examined the computerized prescription-fill records of the Ontario Drug Benefit database, which contains comprehensive records of prescription medications dispensed to Ontario residents 65 years of age or older.[18] We identified hospital visits with the use of the National Ambulatory Care Reporting System database and the Canadian Institute for Health Information Discharge Abstract Database, which contain detailed diagnostic and procedural information regarding emergency department visits and hospital admissions, respectively. We identified claims for inpatient and outpatient physician services using the Ontario Health Insurance Plan database. Furthermore, we obtained basic demographic information from the Registered Persons Database, a registry containing a single, unique record for all Ontario residents ever issued a health card. Finally, we estimated socio-economic status for each patient by linking the home postal code to Statistics Canada population census data to obtain the median household income quintile.

Nest cohort

We included Ontarians 66 years of age or greater with discharge for first ACS. We defined ACS using codes from the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) for unstable angina (I20.0) or acute myocardial infarction (I21 and I22).[19,20]

We restricted our cohort to individuals who were eligible for the Ontario Health Insurance Plan for at least 3 years in order to obtain sufficient information on covariates for our adjusted models. To ensure first use of a $P2Y_{12}$ inhibitor, we excluded patients with ACS or prescription filled for a $P2Y_{12}$ inhibitor within 1 year prior to ACS admission date, which required restriction to patients eligible for the Ontario Drug Benefit database for at least 1 year (i.e. patients greater than 66 years of age). We further excluded patients with a permanent pacemaker prior to nest entry and patients who died on the same date as nest entry. The observation period ended with either hospitalization for bradycardia, death, 1 year after nest entry, or end of the study period (whichever occurred first).

Case and control patients

From the nest cohort, we identified cases as patients treated in an emergency department or admission to hospital for bradycardia (ICD-10 code R001) or second-degree or third-degree atrioventricular block (I441, I442, or I443) within 1 year of cohort entry. The date of hospitalization served as the index date for all analyses. We included only the first hospitalization for bradycardia in our analysis for patients with multiple occurrences during the observation period. For each case, we selected 4 controls who had not experienced bradycardia on the index date. We matched controls for index date, age at index date (±1 year), sex, and exposure to a $P2Y_{12}$ inhibitor.

Exposure

We defined exposure as a prescription filled for ticagrelor or a control $P2Y_{12}$ inhibitor (clopidogrel or prasugrel) within 90 days prior to the index date. As there were no prasugrel users in our cases or controls, we focused on the comparison of ticagrelor and clopidogrel. We excluded from analysis any patients who filled a prescription for more than one $P2Y_{12}$ inhibitor from nest entry to the index date.

Statistical analysis

We used conditional logistic regression to estimate odds ratios and 95% confidence intervals for the association

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between bradycardia hospitalization and use of ticagrelor, with clopidogrel as the reference exposure. To avoid overfitting the model because of the low number of ticagrelor users in our nest cohort, the primary analysis included four conditions and medications associated with bradycardia.[21] The primary analysis adjusted for Charlson Comorbidity Index, number of prescription drugs filled in past year, arrhythmia in past 3 years, and exposure (within 90 days of index date) of a beta-blocker, clonidine, digoxin, diltiazem, or verapamil. The secondary analysis adjusted for nine covariables: income quintile; Charlson Comorbidity Index; number of prescription drugs filled in past year; previous arrhythmia; previous gastrointestinal bleed; cardiac procedure in past year; exposure to beta-blocker; exposure to clonidine, digoxin, diltiazem, or verapamil; and exposure to other bradycardia-causing drugs listed in Table 1. We performed all analyses at the Institute for Clinical Evaluative Sciences (ICES) using SAS software (version 9.3, SAS Institute) with a two-sided type I error rate of 0.05 as the threshold for statistical significance.

RESULTS

Between 1 April 2012 and 30 March 2014, we identified 242 patients hospitalized for bradycardia from a nest cohort of 17 831 patients. Of these, 140 cases were current users of a $P2Y_{12}$ inhibitor and had not used another $P2Y_{12}$ inhibitor between cohort entry and the index date. We successfully matched 4 controls for all cases (Table 1). The median age was 81 (interquartile range [IQR] 73 to 86) years, and 61% of the patients were male. Most hospitalizations for bradycardia occurred within 3 months of ACS discharge (median 82 days, IQR 23–168 days).

Eight of 140 cases (5.7%) filled a prescription for ticagrelor within 90 days of the index date. Compared with controls, patients hospitalized for bradycardia were not more likely to receive ticagrelor over clopidogrel (adjusted odds ratio 1.06, 95% confidence interval 0.65–2.21) (Table 2).

DISCUSSION

In this population-based study spanning 2 years, we found no association between bradycardia and ticagrelor use in elderly patients with ACS. Our findings provide reassurance that the numerically higher but not statistically significant incidences of bradycardia observed in the PLATO and PEGASUS-TIMI 54 studies may not be clinically meaningful in a real-world population. Further, in contrast to these clinical trials, our study included real-world patients with multiple risk factors for bradycardia, including older age, and a greater proportion of patients with heart failure and chronic kidney disease.

Some limitations of our study warrant mention. First, we used administrative data to identify hospitalizations relating to bradycardia, which would not detect bradycardia leading to death in the pre-hospital setting, or events not culminating in a hospital visit. Additionally, there is no validated definition of bradycardia for use in administrative databases. This may underestimate the true incidence of clinically relevant bradycardia in our study population. Nonetheless, our definition of bradycardia is similar to that used in previous research.[15]

Second, during our study follow-up period, the Ontario Drug Benefit program covered ticagrelor only in limited situations: ST-segment elevation myocardial infarction or non-ST-segment elevation ACS with high-risk angiographic features treated with percutaneous coronary intervention or patients with recurrent ACS while receiving clopidogrel. As a result, few patients in our study received ticagrelor (6.8% in the nest cohort). Additionally, restricted access may have produced confounding by indication whereby patients with more severe coronary disease and greater comorbidity received ticagrelor, favoring an association between ticagrelor and bradycardia. This potential difference would exaggerate the estimate of association between ticagrelor use and bradycardia, whereas the point estimates in all our analyses were close to 1.

Third, application of ticagrelor prescription fill claims as a surrogate for use may have led to non-differential exposure misclassification of patients who filled a prescription for a $P2Y_{12}$ without taking it regularly, thus attenuating an association. Nevertheless, based on the proposed adenosine mechanism for bradycardia induction by ticagrelor, even intermittent use would cause bradycardia if the effects were real. Furthermore, our study reflects real-world adherence to $P2Y_{12}$ inhibitors and its consequences.

Finally, our study design could not detect bradycardia events preceding ACS discharge, thus potentially missing an association if bradycardia occurred within the first ticagrelor dose, as in a recent case report.[14] Future studies with access to detailed inpatient medical records including vital signs may yet identify an increased risk of bradycardia with ticagrelor in this setting.

CONCLUSION

In a population-based nested case–control study of elderly patients with first ACS, we did not identify

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Table 1. Characteristics of cases and controls

Variable	Cases ($n = 140$)	Controls ($n = 560$)	Standardized difference
Years of age, median (IQR)	81 (73–86)	80 (73–85)	0.06
Male, *n* (%)	86 (61.4%)	344 (61.4%)	0
Income quintile, *n* (%)			
1	36 (25.7%)	95 (17.0%)	0.22
2	29 (20.7%)	138 (24.6%)	0.09
3	26 (18.6%)	118 (21.1%)	0.06
4	22 (15.7%)	105 (18.8%)	0.08
5	26 (18.6%)	101 (18.0%)	0.01
Missing	≤5 (0.7%)	≤5 (0.5%)	0.02
Charlson Comorbidity Index, median (IQR)	1 (1–3)	1 (1–2)	0.12
0	18 (12.9%)	62 (11.1%)	0.06
1	25 (17.9%)	94 (16.8%)	0.03
2+	32 (22.9%)	93 (16.6%)	0.16
No hospitalization	65 (46.4%)	311 (55.5%)	0.18
Previous medical conditions within 3 years, *n* (%)			
Arrhythmia	20 (14.3%)	38 (6.8%)	0.27
Atrial fibrillation	10 (7.1%)	20 (3.6%)	0.18
Bradycardia	≤5	9 (1.6%)	[a]
Angina	103 (73.6%)	407 (72.7%)	0.02
Cerebrovascular disease	19 (13.6%)	61 (10.9%)	0.08
Alcoholism	≤5	8 (1.4%)	[a]
Chronic kidney disease	32 (22.9%)	74 (13.2%)	0.27
Gastrointestinal bleed	≤5	25 (4.5%)	[a]
Heart failure	46 (32.9%)	111 (19.8%)	0.31
Hypothyroidism	≤5	9 (1.6%)	[a]
Previous cardiac procedure within 1 year, *n* (%)			
Left heart angiography	≤5	11 (2.0%)	[a]
Percutaneous coronary intervention	≤5	6 (1.1%)	[a]
Medications filled in past 1 year, median (IQR)	16 (12–21)	13 (10–18)	0.37
Medications in 90 days prior to index date, *n* (%)			
Beta-blockers	118 (84.3%)	430 (76.8%)	0.18
Diuretics	76 (54.3%)	232 (41.4%)	0.26
ACE inhibitors	75 (53.6%)	317 (56.6%)	0.06
Angiotensin receptor blockers	36 (25.7%)	112 (20.0%)	0.14
SSRIs	16 (11.4%)	37 (6.6%)	0.18
Diltiazem or verapamil	15 (10.7%)	20 (3.6%)	0.33
Digoxin	14 (10.0%)	17 (3.0%)	0.34
Insulin	13 (9.3%)	42 (7.5%)	0.07
Class 3 antiarrhythmic agents	12 (8.6%)	10 (1.8%)	0.39
Corticosteroids	11 (7.9%)	33 (5.9%)	0.08
Cholinesterase inhibitors	8 (5.7%)	21 (3.8%)	0.1
Antipsychotics	≤5	28 (5.0%)	[a]
SNRIs	≤5	17 (3.0%)	[a]
TCAs	≤5	17 (3.0%)	[a]
Days from nest entry to index date, median (IQR)	82 (23–168)	123 (60–227)	0.36
Cases who died during index hospitalization, *n* (%)	≤5	—	—

ACE: angiotensin converting enzyme, IQR: interquartile range, SNRI: serotonin-norepinephrine reuptake inhibitor, SSRI: selective serotonin reuptake inhibitor, TCA: tricyclic antidepressant.
Key characteristics that may be associated with exposure ($P2Y_{12}$ inhibitor selection) or outcome (hospitalization for bradycardia).
[a]In accordance with the ICES privacy policy, in cases where the number of total users is less than 6, the number and corresponding proportion have been suppressed to ensure confidentiality. In these cases, standardized differences have been suppressed to avoid residual disclosure issues.

Table 2. Association between hospitalization for bradycardia and ticagrelor or clopidogrel use within 90 days

	n (%) exposed				
	Cases ($n = 140$)	Controls ($n = 560$)	Univariate OR (95% CI)	Adjusted OR 1 (95% CI)	Adjusted OR 2 (95% CI)
Clopidogrel (reference)	132 (94.3)	526 (93.9)	1.00	1.00	1.00
Ticagrelor	8 (5.7)	34 (6.1)	0.93 (0.40–2.16)	1.06 (0.65–2.21)	1.07 (0.44–2.61)

CI: confidence interval, OR: odds ratio.
Unadjusted and adjusted logistic regression analyses estimating the measure of association between hospitalization for bradycardia and ticagrelor or clopidogrel use.

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an association between ticagrelor use and hospitalization for bradycardia relative to clopidogrel.

CONFLICT OF INTEREST

RT, KF, DJ, and JV: None.

MM: Dr Mamdani has served as an Advisory Board member for Astra Zeneca, Bristol-Myers Squibb, Eli Lilly and Company, Glaxo Smith Kline, Hoffman La Roche, Novartis, Novo Nordisk, and Pfizer.

KEY POINTS

- In a real-world population following discharge for acute coronary syndrome, ticagrelor use may not be associated with a substantially greater risk of subsequent bradycardia than clopidogrel.
- Future evaluation of association between ticagrelor use and bradycardia should focus on ticagrelor initiation using inpatient medical records.

ETHICS STATEMENT

The ethics review board of Sunnybrook and Women's College Health Sciences Centre, Toronto, approved this research project, and waived requirement for informed consent based on the de-identified and retrospective nature of the data sources.

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