Risk of Pneumonia with Ticagrelor Versus Clopidogrel: a Population-Based Cohort Study

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INTRODUCTION

Ticagrelor is a potent antiplatelet agent used in the management of acute coronary syndromes (ACS) that exerts pleiotropic effects, including anti-inflammatory¹ and anti-Gram-positive antibacterial² activity, and may reduce pneumonia complications.³

The objective of this study was to compare the risk of community-acquired pneumonia (CAP), predominantly caused by the Gram-positive pathogen *Streptococcus pneumoniae*, with ticagrelor versus clopidogrel among ACS patients who underwent percutaneous coronary intervention (PCI).

METHODS

We conducted a population-based cohort study by linking the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) registry with administrative data for hospitalizations, emergency department (ED) visits, outpatient prescription fills, and laboratory data. We previously compared major adverse coronary events with ticagrelor versus clopidogrel.⁴

We included patients ≥ 18 years old, discharged alive after undergoing PCI for ACS from April 2012 to March 2016, who filled a prescription for ticagrelor or clopidogrel ≤ 31 days after PCI. We excluded individuals already prescribed these medications prior to index admission. Medication exposure and adherence (assuming an intended standard 1-year therapy duration) were defined using outpatient prescription fills.⁴

The primary outcome was hospitalization or ED visit for non-viral CAP (discharge *International Classification of Diseases-10th Revision* codes J13.x to J18.x⁵) within 1 year after PCI. Secondary outcomes were individual components of hospitalization for CAP and ED visit for CAP. Hazard

ratios (HR) and 95% confidence intervals (CI) for ticagrelor versus clopidogrel were obtained using Cox proportional-hazard models, censored at time of P2Y₁₂ inhibitor switch, prescription fill gaps (greater than days' supply plus 15-day grace period) or death, and adjusted for potential confounders selected a priori: age, sex, Cardiac-Specific Comorbidity Index,⁶ smoking status, chronic pulmonary disease, proton pump inhibitor use, fiscal year, and adherence. Moreover, we evaluated the primary outcome based on P2Y₁₂ inhibitor adherence ($\geq 80\%$ versus $< 80\%$). A sensitivity analysis using propensity score matching was consistent with the primary analysis (not shown; available upon request). The University of Alberta Research Ethics Office approved this study with consent waived because investigators were provided de-identified data. Statistical significance was set at 2-sided $p < 0.05$. Analyses were performed using SAS 9.4 (SAS Institute) and R 3.4.3 (R Project for Statistical Computing).

RESULTS

Among 11,185 eligible patients, the median age was 61 years (interquartile range 54 to 71) and 2760 (24.7%) were women (Table 1). Ticagrelor users were younger, had fewer comorbidities, and were less likely to be women, current smokers, to have chronic pulmonary disease, or use a proton pump inhibitor than clopidogrel users. Ticagrelor users were more adherent, but more likely to switch to another P2Y₁₂ inhibitor.

Outpatient use of ticagrelor was associated with a lower risk of hospitalization or ED visit for CAP compared with clopidogrel in the year following PCI for ACS, which persisted in adjusted analysis (adjusted HR 0.64, 95% CI 0.47–0.88) (Table 2). These associations were consistent for hospitalizations for CAP (HR 0.65, 95% CI 0.44–0.97) and ED visits for CAP (HR 0.72, 95% CI 0.51–1.02), although the latter was not statistically significant. Adherence $\geq 80\%$ was associated with fewer CAP hospitalizations or ED visits compared with adherence $< 80\%$ in both clopidogrel users (2.7% versus 4.2%; adjusted HR 0.69, 95% CI 0.52–0.91) and ticagrelor users (1.4% versus 3.2%; adjusted HR 0.42, 0.25–0.71); however, this was more pronounced with ticagrelor.

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Table 1 Clinical Characteristics

Characteristic	Clopidogrel (n = 7109)	Ticagrelor (n = 4076)	p value
Age, median (IQR), years	62 (54, 72)	60 (53, 69)	< 0.0001
Women, No. (%)	1831 (25.8)	929 (22.8)	0.0005
ACS Type, No. (%)			0.0119
STEMI	3170 (44.6)	1783 (43.7)	
NSTEMI/unstable angina	3910 (55.0)	2259 (55.4)	
Unknown	29 (0.4)	34 (0.8)	
Cardiac-Specific Comorbidity Index, median (IQR)	− 5.4 (− 5.9, − 4.6)	− 5.5 (− 6.0, − 4.9)	< 0.0001
Medical history, No. (%)			
Prior MI	858 (12.1)	287 (7.0)	< 0.0001
Cerebrovascular disease	326 (4.6)	120 (2.9)	< 0.0001
Heart failure	434 (6.1)	126 (3.1)	< 0.0001
Diabetes mellitus	1807 (25.4)	968 (23.7)	0.0491
Smoking status			< 0.0001
Current	2301 (32.4)	1060 (26.0)	
Former	1580 (22.2)	715 (17.5)	
Never/not recorded	3228 (45.4)	2301 (56.5)	
Chronic pulmonary disease	714 (10.0)	147 (3.6)	< 0.0001
eGFR, mL/min, median (IQR)	62 (61, 85)	81 (65, 93)	< 0.0001
Proton pump inhibitor ≤ 31 days after PCI, No. (%)	2630 (37.0)	1270 (31.2)	< 0.0001
Study P2Y ₁₂ inhibitor utilization			
MRA, median (IQR), %	98 (78, 101)	99 (88, 102)	< 0.0001
MRA ≥ 80%, No. (%)	5256 (73.9)	3328 (81.6)	< 0.0001
Switch, No. (%)	162 (2.3)	571 (14.0)	< 0.0001

ACS, acute coronary syndrome; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRA, medication refill adherence; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction

Table 2 Outcomes with Ticagrelor Compared with Clopidogrel

Outcome	Clopidogrel (n = 7109)	Ticagrelor (n = 4076)	Unadjusted HR (95% CI)	Fully adjusted HR* (95% CI)
Primary outcome, n (%)	217 (3.1)	69 (1.7)	0.53 (0.40–0.71)	0.64 (0.47–0.88)
Hospitalization for CAP	140 (2.0)	41 (1.0)	0.48 (0.33–0.70)	0.65 (0.44–0.97)
ED visit for CAP	155 (2.2)	56 (1.4)	0.62 (0.45–0.85)	0.72 (0.51–1.02)

*Adjusted for baseline age, sex, current smoking, chronic pulmonary disease, Cardiac-Specific Comorbidity Index, proton pump use within 31 days after PCI, fiscal year, and adherence using MRA as a continuous variable

CAP, community-acquired pneumonia; CI, confidence interval; ED, emergency department; HR, hazard ratio

DISCUSSION

In this study, ticagrelor was associated with fewer hospitalizations or ED visits for CAP than clopidogrel. Moreover, adherent ticagrelor users had a lower risk of the primary outcome than non-adherent users. This study adds to recent promising data suggesting that ticagrelor may have clinically relevant antibacterial activity.^{1–3}

This study has limitations inherent to its observational design. First, residual confounding may persist despite adjustment for key confounders. Second, our definition for CAP (restricted to events that resulted in hospitalization or ED visit) may have excluded clinically relevant outcomes managed in the ambulatory setting. However, this compromise was made to maximize the likelihood that pneumonia diagnoses were confirmed by imaging.

Among patients with ACS managed with PCI, ticagrelor was associated with a reduced risk of hospitalization or ED

visit for community-acquired pneumonia compared with clopidogrel. Future studies will need to determine the mechanism so that targeted ticagrelor-derived agents without hemorrhagic risk can be developed for the management of pneumonia.

Ricky D. Turgeon, BSc(Pharm), PharmD¹

Erik Youngson, MMath²

Michelle M. Graham, MD³

¹Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada

²Alberta SPOR Support Unit, University of Alberta, Edmonton, Alberta, Canada

³Division of Cardiology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

Corresponding Author: Michelle M. Graham, MD; Division of Cardiology, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada (e-mail: mmg2@ualberta.ca).

Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

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