Changes in Treatment Patterns and Incremental Health Care Utilization Due to P2Y12-Associated Complications in Patients with Acute Coronary Syndrome

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ABSTRACT

BACKGROUND: P2Y12 antiplatelet therapy (APT) is highly efficacious in reducing the incidence of ischemic events in patients with acute coronary syndrome (ACS); however, it is associated with several adverse complications. Data on P2Y12-associated complications and adherence to APT are sparse.

OBJECTIVE: To describe the characteristics, frequency of P2Y12-associated complications, adherence and persistence to P2Y12 APT, and health care utilization among ACS patients on P2Y12 APT.

METHODS: This retrospective observational study of the MarketScan Commercial Claims and Encounters Database identified patients aged ≥ 18 years who were discharged from an ACS hospitalization in 2012-2014 and initiated P2Y12 APT (ticagrelor, prasugrel, or clopidogrel). The proportion of patients within each treatment group who experienced P2Y12-associated complications within 1 year and who were adherent to APT were determined. Frequencies of all-cause health care utilization (i.e., hospitalization, length of stay, emergency room [ER] visits, outpatient visits, cardiac events, and transfusions) were evaluated for each treatment group. Poisson regressions were conducted to evaluate the association between nonadherence with P2Y12 APT and health care utilization, after adjusting for demographics (age and gender), health insurance type, and comorbidities.

RESULTS: Among 11,629 ACS patients, most were male; 44.6% had hypertension; 20.6% had diabetes; and 53.4% had hyperlipidemia. Clopidogrel use was common (62.6%), with ticagrelor use less common (9.0%). Among all groups, approximately one third experienced P2Y12-associated complications. One-year adherence to APT was suboptimal (68% overall), with 73.3% adherence among prasugrel users, followed by 71.4% adherence among ticagrelor users and 65.6% adherence among clopidogrel users. Switching was most common with ticagrelor users. Inpatient hospitalizations, cardiac events, and transfusions were more common in clopidogrel users compared with prasugrel and ticagrelor users. Nonadherent patients experienced significantly more hospitalizations, ER visits, and transfusions (1.34, 1.09, and 1.85 [$P < 0.05$], respectively) compared with adherent patients. These trends of association remained consistent across all treatment groups. Also, patients not adherent to ticagrelor experienced 1.9 times as many cardiac events as adherent patients. However, this association was not significant for clopidogrel and prasugrel users. Patients not adherent to P2Y12 APT experienced significantly lower outpatient visits compared with adherent patients.

CONCLUSIONS: Complications associated with P2Y12 in ACS patients treated with P2Y12 APT were common, with dyspnea, heart block, and major or life-threatening bleeding as the most common. Adherence was significantly associated with lower health care utilization. Increased adherence to secondary prevention therapy among these very high-risk patients is crucial. Disease management strategies to improve adherence and reduce treatment-associated adverse events through individualized patient care,

alternative secondary treatment options, and physician awareness should be designed, implemented, and sustained.

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What is already known about this subject

- Although P2Y12 antiplatelet therapy (APT) is highly efficacious in reducing the incidence of ischemic events, it is highly associated with complications that may result in drug discontinuation, which affect health care utilization.
- A real-world study has confirmed a high rate of drug withdrawal in patients with acute coronary syndrome (ACS) who were treated with ticagrelor; however, the scope of the study was limited in both treatment and population.

What this study adds

- This study assessed the proportion of ACS patients who experienced P2Y12-associated complications and adherence and persistence to P2Y12 APT, along with its association with all-cause health care utilization, using a large U.S. commercial claims database.
- More patients treated with clopidogrel had inpatient hospitalizations, cardiac events, and transfusions compared with ticagrelor users and prasugrel users.
- Adherence to P2Y12 APT was suboptimal, and better adherence was highly associated with lower hospitalizations, emergency room visits, and transfusions.

Coronary heart disease remains a significant burden in developed and developing countries. Globally, cardiovascular disease is the major cause of death, accounting for over 17.5 million deaths (31% of the all global deaths) in 2012.¹ Acute coronary syndrome (ACS) is the initial presentation of a patient manifesting coronary artery disease. It is estimated that each year in the United States more than 780,000 people experience ACS. In 2010, ACS resulted in more than 1.14 million hospitalizations.²

To prevent any recurrent ischemic event for ACS patients, dual antiplatelet therapy with a combination of aspirin and a

P2Y12 inhibitor (clopidogrel, prasugrel, or ticagrelor) is recommended for a period of 12 months.^{3,4} Although clopidogrel is generally well tolerated in ACS patients, the irreversible nature of its antiplatelet action has raised concerns of increased bleeding risk, including a nonsignificant increase in life-threatening and fatal bleeding, severe and moderate bleeding, and dyspnea.⁵⁻⁷ A third-generation drug, prasugrel, is found to be effective as well, but there are also concerns regarding the higher bleeding risk associated with this drug.⁸⁻¹¹ The frequencies of Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding were higher, and fatal hemorrhage was more frequent with prasugrel than with clopidogrel.⁸

In the PLATelet inhibition and patient Outcomes (PLATO) trial, a relatively new P2Y12 receptor inhibitor, ticagrelor 90 mg, has shown better health outcomes in terms of morbidity and mortality, compared with clopidogrel in patients with ACS, although it is associated with increased incidence of intracranial bleeding, fatal intracranial bleeding, major or minor bleeding, dyspnea and ventricular pauses, syncope, heart block, and increase in level of serum uric acid and serum creatinine.¹² In addition, a recently published trial that assessed the benefit of ticagrelor 60 mg and 90 mg, both twice daily, in patients 1-3 years post-ACS reported nearly similar efficacy in reducing the risk of cardiovascular death, myocardial infarction, or stroke, although this benefit was associated with higher TIMI major or minor bleeding and serious dyspnea compared with placebo.¹³ However, the U.S. Food and Drug Administration and the European Medicines Agency approved and granted marketing authorization for the lower 60 mg dose for long-term use of ticagrelor after it demonstrated equal efficacy and an improved safety profile compared with the 90 mg dose.¹³⁻¹⁵

Although P2Y12 antiplatelet therapy (APT) is highly efficacious in reducing the incidence of ischemic events when used, it is associated with several adverse reactions, referred to as P2Y12-associated complications, including dyspnea, major or life-threatening bleeding, major gastrointestinal bleeding, bradycardia, heart block, and syncope. These P2Y12-associated complications may lead to higher discontinuation of APT by patients, which may ultimately affect treatment effectiveness and health care utilization. A real-world observational study that evaluated the effect of ticagrelor-related dyspnea on compliance with therapy in ACS patients reported that the rate of drug withdrawal was high, and drug-related dyspnea was the main reason for noncompliance with therapy followed by drug-related minor bleeding.¹⁶ However, this study was limited to only 1 P2Y12 antiplatelet drug (ticagrelor), focused on only 1 associated complication (dyspnea), and was geographically limited to a small French population.

Additional real-world information about P2Y12-associated complications in ACS patients and their effects on adherence to P2Y12 APT and consequent incremental health care utilization is much needed. A better understanding of patient

characteristics, adherence and persistence to APT, and its association with incremental health care utilization in ACS patients in the real-world setting could inform treatment guidelines and aid providers in clinical decision making.

The purpose of this study was to (a) assess the frequency of P2Y12-associated complications in ACS patients, along with their adherence and persistence to P2Y12 APT, in a large U.S. claims database, and (b) evaluate the association of nonadherence to P2Y12 APT with health care utilization in these patients.

Methods

Study Design and Data Source

This retrospective observational cohort study used the MarketScan Commercial Claims and Encounters Database (MCED), a HIPAA-compliant, employer-sponsored health care claims database. This database has covered approximately 200 million unique patients since 1995 and includes insured employees, early retirees, COBRA continuers, and their dependents from approximately 100 large, employer-sponsored health plans, as well as those who are Medicare eligible but choose to have supplemental employer-based insurance. The database contains enrollees residing in all 50 states and the District of Columbia. Although representation is greater from the South, the data are broadly representative of the United States as a whole.¹⁷ The MCED combines 2 separate databases: Commercial Claims and Encounters Database, and the Medicare Supplemental and Coordination of Benefit Database. The data components used in this study included health plan enrollment records, participant demographics, inpatient and outpatient medical services, and outpatient prescription drug dispensing records.

Study Cohort

The study cohort consisted of patients aged ≥ 18 years who were discharged from an ACS hospitalization between January 1, 2012, and December 31, 2014, and who initiated index P2Y12 APT (ticagrelor, prasugrel, or clopidogrel) within 30 days of their discharge. ACS was identified from the inpatient claims and defined as a primary diagnosis code from the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 410.xx (excluding 410.x2). The date of discharge for the ACS hospitalization was considered the index date. Eligible patients were required to be alive at discharge and have at least 12 months of baseline continuous enrollment before the index ACS hospitalization and at least 12 months of follow-up after the index event.

Patients who initiated more than 1 P2Y12 APT at the same time and who received P2Y12 APT for greater than 30 days or other oral anticoagulation therapy (except aspirin) during the baseline period were excluded. Use of P2Y12 APT was identified from outpatient pharmacy claims using all National Drug Code numbers associated with the respective generic names.

The final study sample was analyzed across 3 treatment groups based on the type of P2Y12 antiplatelet medication initiated after ACS hospitalization.

Measures

Baseline Characteristics. Baseline characteristics included basic demographics (age and gender), health insurance plan type, comorbidities, and concomitant prescription medications. Comorbidities were identified from medical claims from the 12 months before the index event. Concomitant prescription medications were assessed during the baseline period.

Complications Associated with P2Y12. Patients meeting the inclusion criteria were followed up to 12 months for episodes of P2Y12-associated complications. These complications included dyspnea, bradycardia, syncope, heart block, elevated serum creatinine and uric acid levels, intracranial bleeding or hemorrhage, major or life-threatening bleeding, and major gastrointestinal bleeding.¹⁸ These episodes were identified using the first claim originating from an emergency room (ER), inpatient claim, outpatient claim, or physician services claim with the respective ICD-9-CM codes as listed in Appendix A (available in online article).

P2Y12 Treatment Changes. During the follow-up period, switch, or discontinuation in therapy, adherence and persistence to the index P2Y12 APT were assessed. A switch in therapy was defined as patients who discontinued use of a current P2Y12 APT for 30 days or more and replaced it with another antiplatelet drug. Adherence is the degree to which a patient remains compliant to the prescribed medication and is operationally defined as the proportion of days covered (PDC) and calculated as the ratio of number of days P2Y12 APT was supplied and number of days in the follow-up period.¹⁹ Patients were considered to be adherent to APT if their PDCs were $\geq 80\%$.

Persistence is the patient's duration from medication initiation to discontinuation and is operationalized dichotomously, defined as continuation or discontinuation of P2Y12 APT where the gap in therapy of at least 30 days (between the refill date and the calculated run-out date of previous medication) was considered discontinuation and hence nonpersistence to the therapy. Nonpersistence during the follow-up period was defined as the first incident of failure to refill index medication within 30 days from the run-out date of the previous prescription.²⁰

Health Care Utilization. The measures of all-cause health care utilization included frequencies of all-cause inpatient hospitalization, ER visits, outpatient visits, cardiac events, and transfusions. In addition, length of hospital stay in days was also assessed. Cardiac events were identified from inpatient claims and were defined as having had acute myocardial infarction, which was identified using the ICD-9-CM code 410.x1, or having had revascularization, identified using the ICD-9-CM procedure codes 36.00, 36.06, 36.07, 36.09, and 36.10-36.19

during the follow-up period. Transfusions were identified from the inpatient claims using ICD-9-CM code 99.xx.

Statistical Analyses

Descriptive statistics of all patient demographic and clinical characteristics were conducted for the overall population, as well as for index treatment groups. Chi-square tests for categorical variables and t-tests or Kruskal-Wallis tests for continuous variables were used to assess significant differences between the treatment groups. The proportion of total patients and patients within treatment groups who experienced P2Y12-associated complications were determined. The proportion of patients who were adherent and persistent to APT and who switched to another APT were also estimated. Frequencies of hospitalizations, outpatient visits, ER visits, cardiac events, and transfusions, along with length of hospital days within each treatment group, were estimated and reported as mean (standard deviations [SDs]) or median (interquartile range [IQR]). Multivariate Poisson regressions were performed to evaluate if nonadherence with P2Y12 APT was associated with health care utilization within each treatment group. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Of the 143,238 patients hospitalized for ACS between January 1, 2012, and December 31, 2014, 11,629 met the inclusion criteria (Appendix B, available in online article). Patients were more often men (76.2%) and, on average, aged 57 years (Table 1). The majority (71.2%) of the study cohort was aged between 45 years and 64 years and had preferred provider organization insurance coverage (53.4%). Comorbid hyperlipidemia, hypertension, diabetes, and previous myocardial infarction were common (53.4%, 44.6%, 20.6%, and 42.2%, respectively) among these patients. The vast majority were taking prescription beta-adrenergic antagonists (73.3%) and statins (77.7%), while 49.5% were on angiotensin-converting enzyme inhibitors.

Among ACS patients treated with P2Y12, 9.0% initiated ticagrelor; 28.4% initiated prasugrel; and 62.6% initiated clopidogrel within 30 days of discharge. Treatment groups significantly differed across most baseline characteristics (Table 1), with the exception of exclusive provider organizations or health maintenance organizations and point-of-service insurance plans, previous myocardial infarction and coronary revascularization, peripheral arterial disease, and use of angiotensin II receptor antagonists and proton pump inhibitors.

Complications Associated with P2Y12

Of the 11,629 patients who met the inclusion criteria, 33% experienced P2Y12-associated complications during the

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TABLE 1 Baseline Characteristics of ACS Patients Who Initiated P2Y12 APT Within 30 Days of ACS Event

Variables	All Patients N = 11,629	Index P2Y12 Treatment			P Value
		Ticagrelor Users n = 1,049	Prasugrel Users n = 3,297	Clopidogrel Users n = 7,283	
Age, mean (SD)	57.4 (11.0)	56.1 (9.7)	54.6 (8.5)	58.9 (11.9)	<0.0001
Age group, years, %					
<35	0.9	1.0	0.8	0.9	0.9091
35-44	9.4	9.2	11.6	8.4	<0.0001
45-54	30.2	34.4	34.5	27.6	<0.0001
55-64	41.0	40.7	44.1	39.6	0.0001
65-74	10.5	9.3	7.8	11.9	<0.0001
75-84	5.6	4.8	1.1	7.7	<0.0001
>85	2.6	0.6	0.1	4.0	<0.0001
Gender, %					
Female	23.8	21.5	18.1	26.7	<0.0001
Benefit plan, %					
EPO/HMO	14.8	14.9	14.3	15.0	0.7149
PPO	53.4	55.2	56.3	51.8	0.0001
POS/POS with capitation	8.7	9.2	9.4	8.3	0.1856
Comprehensive	11.1	7.8	7.0	13.4	<0.0001
Other	8.0	9.7	8.6	7.6	0.0200
Unknown	4.0	3.2	4.4	4.0	0.2326
Comorbidities, %					
Hypertension	44.6	42.7	39.9	46.9	<0.0001
Hyperlipidemia	53.4	52.6	55.4	52.7	0.0276
Diabetes	20.6	19.0	18.3	21.9	0.0001
COPD	7.3	5.4	4.8	8.7	<0.0001
Previous MI	42.2	42.6	41.6	42.4	0.6973

^aIn baseline period.

^bDuring index hospitalization.

ACE=angiotensin-converting enzyme; ACS=acute coronary syndrome; AF=atrial fibrillation; APT=antiplatelet therapy; CABG=coronary artery bypass graft; CHF=chronic heart failure; COPD=chronic obstructive pulmonary disease; DVT=deep vein thrombosis; EPO=exclusive provider organization; HMO=health maintenance organization; MI=myocardial infarction; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; POS=point of service; PPO=preferred provider organization; revasc=revascularization; SD=standard deviation; TIA=transient ischemic attack.

follow-up period (Figure 1), with little variation across treatment groups (31.1%, 30.6%, and 34.8% among ticagrelor, prasugrel, and clopidogrel users, respectively). Dyspnea was reported in 14.5% of ticagrelor users, in 13.6% of prasugrel users, and in 16.5% of clopidogrel users. Also, heart block was more common in clopidogrel users (15.1%), followed by ticagrelor (12.2%) and prasugrel (11.8%) users. Overall, bradycardia and syncope were more infrequent (4.4% and 3.9%, respectively), but they were also more common in clopidogrel users than in ticagrelor and prasugrel users. In addition, major or life-threatening bleeding (7.9%) and major gastrointestinal bleeding (3.8%) occurred more commonly in clopidogrel users compared with ticagrelor or prasugrel users. Intracranial bleeding was rare in all groups (0.3%, 0.1%, and 0.2% among ticagrelor, prasugrel, and clopidogrel users, respectively).

There were significant differences between patients who experienced P2Y12-associated complications and those who did not across all treatment groups (Table 2). On average, those who experienced P2Y12-associated complications were younger, more often male, and had preferred provider organization insurance coverage, and they less often had comprehensive insurance and a history of chronic obstructive pulmonary disease (COPD), coronary artery bypass graft, congestive heart failure, atrial fibrillation, renal disease, and transient ischemic attack. Clopidogrel users who experienced P2Y12-associated complications less often had hypertension and diabetes but more often had hyperlipidemia and deep vein thrombosis during the baseline period. All the ACS patients within each treatment group who experienced P2Y12-associated complications were less often on proton pump inhibitors, while clopidogrel users who experienced P2Y12 complications were more often on

FIGURE 1 Proportion of ACS Patients Who Experienced P2Y12-Associated Complications Within 12 Months^a

^aOther P2Y12-associated complications with rate below 2.0% include elevated serum creatinine, elevated serum uric acid, and intracranial bleeding/hemorrhage—elevated serum creatinine: total (0.2%), ticagrelor (0.1%), prasugrel (0.3%), and clopidogrel (0.2%); elevated serum uric acid: total (2.0%), ticagrelor (2.0%), prasugrel (2.2%), and clopidogrel (1.9%); intracranial bleeding/hemorrhage: total (0.2%), ticagrelor (0.3%), prasugrel (0.1%), and clopidogrel (0.2%).

ACS=acute coronary syndrome.

statins and beta-adrenergic antagonists and less often on angiotensin II receptor antagonists and H2-receptor antagonists.

P2Y12 Treatment Changes

Sixty-eight percent of the study cohort was adherent to P2Y12 APT during the follow-up period (Table 3). Adherence was highest among prasugrel users (73.3%), followed by ticagrelor (71.4%) and clopidogrel users (65.6%). PDC was, on average, 80% in all patients, with little variation by treatment group (0.82 [SD 0.23], 0.83 [SD 0.23], and 0.78 [SD 0.29] among ticagrelor, prasugrel, and clopidogrel users, respectively). The proportion of ACS patients who were persistent with P2Y12 APT was similar at 78.8%, with slight variation among clopidogrel users (79.5%), followed by 78.5% among prasugrel users and 74.5% among ticagrelor users. A switch in P2Y12 APT was observed more often in ticagrelor (16.9%) and prasugrel (12.6%) users than in clopidogrel users (2.1%).

Health Care Utilization

Nearly all patients experienced outpatient visits following an ACS event, and a large portion also experienced hospitalizations (20.2%) and ER visits (30.9%; Table 3). On average, more patients treated with clopidogrel (22.1%) had inpatient hospitalizations with longer lengths of stay compared with those

patients treated with ticagrelor (17.1%) or prasugrel (17.1%). Cardiac events and transfusions were more common in clopidogrel users (5.7% and 2.2%, respectively) compared with ticagrelor and prasugrel users.

Associations Between Nonadherence to P2Y12 APT and Health Care Utilization

On average, patients not adherent to P2Y12 APT experienced all forms of health care utilization more frequently compared with adherent patients, with the exception of outpatient visits and cardiac events (Table 4). After adjusting for demographic and clinical characteristics, we observed that nonadherers had 1.34 (95% confidence interval [CI] = 1.25-1.44) times as many hospitalizations, with 1.83 (95% CI = 1.76-1.89) times the length of stay, 1.09 (95% CI = 1.04-1.15) times the number of ER visits, and 1.85 (95% CI = 1.45-2.37) times as many transfusions compared with adherent patients. These trends of association were similar across all treatment groups. Cardiac events differed by adherence group among ticagrelor users, where nonadherent patients had 1.90 (95% CI = 1.00-3.58) times the number of events compared with adherent patients. The mean number of outpatient visits among patients who were not adherent to P2Y12 APT was 8% lower than that among patients adherent to P2Y12 APT.

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TABLE 2 Description of ACS Patients By Experience of P2Y12-Associated Complications

	Ticagrelor Users			Prasugrel Users			Clopidogrel Users		
	With P2Y12 Complications	Without P2Y12 Complications	P Value	With P2Y12 Complications	Without P2Y12 Complications	P Value	With P2Y12 Complications	Without P2Y12 Complications	P Value
Age, mean (SD)	55.7 (9.5)	57.7 (10.7)	<0.0010	54.4 (8.3)	55.5 (8.7)	<0.0010	57.2 (10.9)	61.4 (13.0)	<0.0010
Age group, years, %									
<35	0.8	1.4	0.1620	1.1	0.6	0.1000	1.0	0.9	0.4291
35-44	10.7	8.5	0.0857	11.8	9.0	0.0015	9.8	6.4	<0.0010
45-54	32.7	28.0	0.0194	35.1	33.9	0.3970	29.8	24.2	<0.0010
55-64	41.5	42.6	0.6055	42.7	45.4	0.0530	41.2	37.1	<0.0010
65-74	10.7	10.8	0.9399	8.5	9.0	0.5190	11.0	14.1	<0.0010
75-84	2.9	7.2	<0.0010	0.8	1.8	0.0011	4.5	10.7	<0.0010
>85	0.6	1.6	0.0284	0.0	0.2	0.0166	2.7	6.7	<0.0010
Gender, %									
Female	19.4	25.5	0.0006	16.8	22.1	<0.0010	24.8	32.1	<0.0010
Medical history, %									
Hypertension	45.0	46.2	0.5718	42.2	43.3	0.4188	46.3	52.9	<0.0010
Hyperlipidemia	57.1	56.1	0.6629	59.2	56.4	0.0505	56.0	53.8	0.0137
Diabetes	19.1	20.4	0.4420	20.1	19.7	0.6957	22.9	26.9	<0.0010
COPD	5.4	8.2	0.0067	4.4	7.1	<0.0010	7.5	13.0	<0.0010
MI	39.4	41.8	0.2514	41.8	43.0	0.4243	42.2	42.5	0.7028
Coronary revasc ^a	6.9	8.7	0.1068	7.4	8.0	0.4474	6.8	7.6	0.0584
PCI ^a	6.5	7.8	0.2230	7.1	7.8	0.3612	5.8	6.2	0.3947
CABG ^a	0.6	1.4	0.0345	0.6	0.6	0.9910	1.3	2.1	0.0004
Coronary revasc ^b	94.7	94.7	0.9636	96.7	95.5	0.0254	82.8	80.1	0.0001
PCI ^b	94.5	94.3	0.7951	96.7	95.3	0.0130	80.6	77.1	<0.0010
CABG ^b	2.0	2.6	0.3422	1.5	1.8	0.5218	9.0	11.1	0.0002
CHF	8.1	13.9	<0.0010	7.4	10.9	<0.0010	11.0	19.0	<0.0010
AF	1.5	4.9	<0.0010	1.9	4.2	<0.0010	2.8	8.5	<0.0010
Renal disease	2.6	5.3	0.0007	2.1	3.8	0.0002	4.3	9.1	<0.0010
TIA	3.5	6.9	0.0002	3.0	3.8	0.1057	7.5	11.1	<0.0010
DVT	0.3	0.4	0.6962	0.3	0.6	0.1310	0.6	1.1	0.0044
PAD	2.3	3.6	0.0557	2.1	3.6	0.0007	3.5	6.6	<0.0010
Medication use, %									
Beta-adrenergic antagonists	75.5	75.5	0.9786	76.4	74.9	0.2162	73.7	70.7	0.0001
Angiotensin II receptor antagonists	6.5	8.3	0.0942	7.2	7.9	0.3765	6.5	8.7	<0.0010
Statins	80.6	80.2	0.8255	81.3	80.9	0.7104	77.9	73.6	<0.0010
Proton pump inhibitors	13.1	20.7	<0.0010	14.3	18.2	0.0001	13.9	18.3	<0.0010
H2-receptor antagonists	2.5	3.3	0.3078	2.9	3.6	0.1466	4.5	5.8	0.0006
ACE inhibitors	52.4	52.1	0.9012	52.6	52.3	0.8491	48.7	47.2	0.0967

^aIn baseline period.

^bDuring index hospitalization.

ACE=angiotensin-converting enzyme; ACS=acute coronary syndrome; AF=atrial fibrillation; CABG=coronary artery bypass graft; CHF=chronic heart failure; COPD=chronic obstructive pulmonary disease; DVT=deep vein thrombosis; EPO=exclusive provider organization; HMO=health maintenance organization; MI=myocardial infarction; PAD=peripheral arterial disease; PCI=percutaneous coronary intervention; POS=point of service; PPO=preferred provider organization; revasc=revascularization; SD=standard deviation; TIA=transient ischemic attack.

Discussion

This study assessed the proportion of ACS patients who experienced P2Y12-associated complications, adherence and persistence to P2Y12 APT, and its association with health care

utilization. We observed adherence to be associated with improved outcomes in a real-world setting using a large U.S. claims database (MarketScan) with 200 million unique patients and a wide national geographic coverage.

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TABLE 3 One-Year Treatment Patterns and Health Care Utilization Among P2Y12-Treated ACS Patients

	All Patients	Index P2Y12 Treatment		
		Ticagrelor Users	Prasugrel Users	Clopidogrel Users
Adherence ^a (PDC), mean (SD)	0.80 (0.267)	0.82 (0.232)	0.83 (0.230)	0.78 (0.285)
Adherence, ^b %	68.3	71.4	73.3	65.6
Persistence, ^c %	78.8	74.5	78.5	79.5
Switching, ^d %	6.4	16.9	12.6	2.1
Hospitalizations, %	20.2	17.1	17.1	22.1
Mean (SD)	1.41 (0.940)	1.33 (0.964)	1.36 (0.849)	1.44 (0.967)
Median (IQR)	1 (1-2)	1 (1-1)	1 (1-1)	1 (1-2)
Hospital length of stay ^e				
Mean (SD)	5.6 (8.6)	5.2 (10.7)	5.0 (7.6)	5.9 (8.6)
Median (IQR)	3 (2-6)	3 (2-5)	3 (1-5)	3 (2-7)
Emergency room visits, %	30.9	28.9	29.8	31.6
Mean (SD)	1.83 (1.778)	1.78 (1.948)	1.76 (1.258)	1.87 (1.937)
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	1 (1-2)
Outpatient visits, %	99.6	99.9	99.5	99.5
Mean (SD)	24.19 (21.185)	23.80 (20.126)	23.34 (18.825)	24.63 (22.303)
Median (IQR)	18 (10-32)	17 (10-33)	17 (10-31)	18 (10-32)
Cardiac events, %	5.1	3.9	4.2	5.7
Mean (SD)	1.07 (0.303)	1.05 (0.312)	1.08 (0.361)	1.07 (0.281)
Median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)
Transfusions, %	2.0	1.7	1.8	2.2
Mean (SD)	1.15 (0.475)	1.28 (0.752)	1.17 (0.378)	1.13 (0.468)
Median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)

^aPDC was calculated as the ratio of number of days P2Y12 APT was supplied and number of days in the follow-up period.

^bPatients with PDC ≥ 80% were considered adherent to P2Y12 APT.

^cContinuation or discontinuation of P2Y12 APT where the gap in therapy of at least 30 days was considered discontinuation and nonpersistent to therapy.

^dPatients on current P2Y12 APT that they discontinued for 30 days or more and replaced by another antiplatelet drug.

^eLength of stay (in days) was defined as the duration between hospital admission and discharge, among only those with at least 1 hospitalization.

ACS = acute coronary syndrome; APT = antiplatelet therapy; IQR = interquartile range; PDC = proportion of days covered; SD = standard deviation.

As expected, a smaller proportion of ACS patients had initiated ticagrelor within 30 days of their index event than those with an index APT of prasugrel and clopidogrel, a finding consistent with Kim et. al. (2017); however, this study focused

on ACS patients treated with percutaneous coronary intervention (PCI).²¹ This finding may be a result of low U.S. market penetration of ticagrelor close to the timing of drug launch in August 2011 (not long before this analysis initiated inclusion of ACS patients, from January 1, 2012, onwards). Our study findings indicate that a large proportion of ACS patients experienced P2Y12-associated complications and that adherence to P2Y12 APT among ACS patients was suboptimal and likely contributed to increased health care utilization.

In our study, we observed that a greater proportion of patients with index clopidogrel APT experienced dyspnea and several other P2Y12-associated complications compared with those patients using ticagrelor. These observations differ from the findings in the PLATO trial.¹² This difference may be because patients and physicians were aware of common complications and potential side effects associated with ticagrelor (by the time it was in use) so were less likely to use health care services when they experienced transient or mild-to-moderate side effects (e.g., dyspnea). While patients may have still experienced these side effects, they would not have been captured in the commercial claims database if they went untreated.

Patients who did not experience any P2Y12-associated complications more often had a higher proportion of certain baseline comorbidities, such as COPD, congestive heart failure, and atrial fibrillation, compared with those patients who did experience P2Y12 complications. This situation may also have led to underreporting of side effects if, for instance, ACS patients with COPD (for whom dyspnea is the most commonly occurring event) experienced dyspnea related to P2Y12 APT and did not report it.

Consistent with a previous report,¹² the rates of intracranial bleeding and hemorrhage in our study were 0.3% among ticagrelor users compared with 0.2% among clopidogrel users. However, we observed that 7.4% of ACS patients with index prasugrel treatment experienced major or life-threatening bleeding, with most of the patients switching to another APT, which was inconsistent with the TRITON-TIMI trial.⁸ A similar proportion (7.9%) of patients with index clopidogrel treatment experienced the same complication but did not switch to another APT. Switching to another APT was common among ticagrelor users (16.9%) compared with clopidogrel users (2.1%), even though a higher proportion of clopidogrel users experienced P2Y12-associated complications. This high switching rate among ticagrelor users was consistent with the ticagrelor withdrawal rate and ticagrelor switching rate from other published studies,^{16,22} although 1 of the studies evaluated the withdrawal rates over only a 1-month follow-up period in contrast to the 1-year follow-up assessed in our study.¹⁶

TABLE 4 Associations (Point Estimates and 95% CIs) Between Nonadherence to P2Y12 APT and Health Care Utilization^a

		All Patients	Ticagrelor Users	Prasugrel Users	Clopidogrel Users
Hospitalizations	Crude	1.58 (1.48-1.70)	1.64 (1.26-2.13)	1.57 (1.35-1.83)	1.54 (1.42-1.68)
	Adjusted ^b	1.34 (1.25-1.44)	1.55 (1.18-2.04)	1.42 (1.22-1.65)	1.31 (1.20-1.43)
Length of stay ^c	Crude	2.20 (2.12-2.27)	2.11 (1.86-2.41)	2.02 (1.88-2.18)	2.18 (2.10-2.28)
	Adjusted ^b	1.83 (1.76-1.89)	1.97 (1.71-2.25)	1.89 (1.75-2.04)	1.81 (1.73-1.89)
Emergency visits	Crude	1.18 (1.12-1.24)	1.18 (0.98-1.42)	0.99 (0.89-1.11)	1.24 (1.16-1.32)
	Adjusted ^b	1.09 (1.04-1.15)	1.11 (0.92-1.34)	0.93 (0.84-1.04)	1.16 (1.09-1.24)
Outpatient visits	Crude	0.96 (0.95-0.97)	0.83 (0.81-0.85)	0.90 (0.89-0.92)	0.99 (0.98-1.00)
	Adjusted ^b	0.92 (0.91-0.92)	0.79 (0.77-0.82)	0.88 (0.86-0.89)	0.95 (0.94-0.96)
Cardiac events	Crude	1.28 (1.09-1.51)	2.07 (1.14-3.78)	1.26 (0.89-1.79)	1.20 (0.99-1.45)
	Adjusted ^b	0.95 (0.81-1.13)	1.90 (1.00-3.58)	1.05 (0.73-1.50)	0.89 (0.73-1.09)
Transfusions	Crude	2.07 (1.63-2.64)	2.62 (1.14-6.04)	2.52 (1.57-4.04)	1.84 (1.37-2.48)
	Adjusted ^b	1.85 (1.45-2.37)	2.30 (0.92-5.75)	2.39 (1.47-3.89)	1.65 (1.21-2.23)

Note: Bold values represent significant results from Poisson regressions.

^aAssociations between nonadherence to APT and health care utilization were estimated using multivariable Poisson regression, where nonadherence was the independent variable and defined as PDC ≤ 80%, and counts of health care use were the dependent variables.

^bAdjusted for age, gender, benefit plan, hypertension, hyperlipidemia, diabetes, chronic obstructive pulmonary disease, previous myocardial infarction, coronary revascularization at index, congestive heart failure, atrial fibrillation, renal disease, stroke/transient ischemic attack, and peripheral arterial disease.

^cDefined as the duration between hospital admission and discharge; these analyses were done among only those with at least 1 hospitalization.

APT = antiplatelet therapy; CI = confidence interval.

Following the trend of the frequency of reported side effects, which was highest among clopidogrel users and lowest among prasugrel users, the converse was true when considering adherence. The proportion of patients adherent to prasugrel during the follow-up period was highest and was lowest among clopidogrel users. This study finding is consistent with a previous report of higher adherence rates in prasugrel users compared with ticagrelor users.²² The proportion of ACS patients adherent to clopidogrel was highly consistent with a 2011 study by Zhu et al.²³ Nordstrom et al. (2013) reported an adherence rate of 78.8% among ACS patients with PCI,²⁴ which is higher than that found in our study (68%). This discrepancy may be because the Nordstrom et al. study used medication possession ratio (MPR) to report adherence, while we used PDC estimates. MPR has been associated with overestimation of the true rate of medication adherence, while PDC has provided more conservative estimates of adherence.¹⁹ However, Nordstrom et al. reported lower adherence in both treatment groups than what we observed in our study,²⁴ most likely because of differences in databases (provider-based vs. insurance-based) and/or study cohorts (ACS with PCI vs. ACS).

Patients with index ticagrelor or prasugrel treatment in our study had similar rates of inpatient hospitalizations to that reported in the 2015 study conducted by Simeone et al.²² Nonadherence to all P2Y12 APT was significantly associated with higher rates of inpatient hospitalizations and increased length of hospital stay. Likewise, ACS patients not adherent to ticagrelor were more likely to experience cardiac events

compared with adherent patients, and patients not adherent to prasugrel or clopidogrel were also more likely to undergo blood transfusions compared with adherent patients.

These adherence findings highlight the need to improve adherence to P2Y12 APT, since poor adherence is associated with increased health care utilization and increased cardiac events among ticagrelor users.^{25,26} These findings should be interpreted with caution given the uncertainty in the direction and nature of the association between nonadherence and increased health care utilization. We hypothesized that the ACS patients on P2Y12 APT may be discontinuing, instead of adhering to, their regimens because of the associated complications that, in turn, lead to increased health care utilization. However, it is possible that P2Y12-associated complications may more likely be captured and reported in ACS patients who have frequent hospitalizations or that sicker patients are less likely to adhere to therapies.

Disease management strategies that may improve adherence and reduce treatment-associated adverse events through individualized patient care should be developed and practiced among high-risk patients. Alternative secondary treatment options that can further reduce cardiovascular risk with fewer side effects (and presumably better adherence) should be considered.²⁷⁻³⁰

Limitations

There are some limitations to this study that need to be considered. While the MarketScan database used in this study

represents a large number of commercially insured individuals in the United States with the advantages of integrated health care data, it is not without disadvantages. Although there is broad U.S. geographic coverage in these data, the southern region is overrepresented and may limit the generalizability of findings to the entire U.S. population. Such biases might encompass differences in disease prevalence and practice patterns by regions. The study population is a select sample of patients observed in a commercial claims database and likely is younger than the wider target population, so there is a possibility of underestimated event rates.

Also, there are certain limitations because of the observational nature of the study, including risk of bias by indication, and unmeasured residual confounding, including race and ethnicity information. In addition, we did not have information on medication consumption, but we assumed that calculations of medication adherence and persistence provided reasonable estimates of true treatment patterns.

Finally, date of death could not be captured, and the sample was restricted to patients with 12 months of follow-up, so results may not be applicable to patients who died during the 12 months after ACS discharge.

Conclusions

In this observational study, one third of the ACS patients treated with P2Y12 APT experienced at least 1 complication associated with P2Y12, the most common of which were dyspnea, heart block, and major or life-threatening bleeding. Adherence to P2Y12 APT was suboptimal during the 1-year follow-up period, and better adherence was highly associated with lower inpatient hospitalizations, shorter length of hospital stay, and fewer transfusions. Increased adherence to secondary prevention therapy among high-risk patients is critical. Disease management strategies to improve adherence and reduce treatment-associated adverse events through individualized patient care, alternative secondary treatment options, and physician awareness should be designed, implemented, and sustained.

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DISCLOSURES

Data analysis was conducted by Merck & Co., the manufacturer of vorapaxar (ZONTIVITY). At the time of this study, Vyas was an employee of Rutgers University, which received grant funding from Merck & Co. for this study, and is now employed with the University of Rhode Island. Patel was employed by Symphony Solutions and the University of North Carolina during the drafting and revising of the manuscript. Bash is employed by Merck & Co. Simpson received consulting fees from Merck & Co. for work on this study and has received fees for research from Amgen and Pfizer.

Study concept and design were contributed by Vyas, Bash, Patel, and Simpson. Patel took the lead in data collection, assisted by the other authors. All the authors contributed equally to data analysis and manuscript preparation.

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APPENDIX A ICD-9-CM Codes for P2Y12-Associated Complications

P2Y12 Complications	ICD-9-CM Codes
Dyspnea	786.0x
Bradycardia	427.89
Syncope	780.2
Heart block	426.xx, 427.xx
Elevated serum creatinine	794.4x
Elevated serum uric acid	790.6x
Intracranial bleeding/hemorrhage	430.xx, 431.xx, 432.0x, 432.1x, 432.9x
Major/life-threatening bleeding	430.xx-432.xx, 578.xx, 719.1x, 423.0x, 599.7x, 626.2x, 626.6x, 626.8x, 627.0x, 627.1x, 786.3x, 784.7x, 459.0x
Major gastrointestinal bleeding	531.xx-535.xx, 578.9x

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B Patient Selection Flowchart

ACS=acute coronary syndrome; APT=antiplatelet therapy.