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ARTICLE

Prescription patterns of P2Y12 inhibitors following revascularization in the United States: 2013–2018

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Abstract

P2Y12 inhibitors (i.e., clopidogrel, prasugrel, or ticagrelor) are effective at reducing adverse cardiovascular outcomes post-revascularization in coronary artery disease (CAD). However, the choice of a specific P2Y12 inhibitor may vary according to the patient's characteristics, and trends in the use of different P2Y12 inhibitors are not well studied in real-world settings. The objective of this study is to determine trends in the prescription patterns of P2Y12 inhibitors in patients with CAD. We studied 137,073 patients with CAD cross-sectionally using the IBM MarketScan database (2013–2018). Patients with CAD prescribed P2Y12 inhibitors within 14 days of index revascularization were included to compare the utilization of P2Y12 inhibitors based on age and clinical characteristics. There were differences in prescription patterns by age. Among patients aged less than or equal to 65 years ($N = 92,734$), a continuously increased utilization of ticagrelor was observed from 13.7% to 45.6% replacing clopidogrel as the most prescribed medication by 2018. Similarly, ticagrelor was the choice of drug among patients undergoing percutaneous coronary intervention. Among the patients at high bleeding risk, clopidogrel remained the most prescribed medication with use in 50.6% of patients in 2018 in patients aged less than or equal to 65 years. Contrarily, among the older adults with age 65 or above ($N = 44,339$), although ticagrelor use increased with time, clopidogrel remained the most utilized drug and was used by 66.2% of patients in 2018. Additionally, clopidogrel was the preferred medication among patients with stroke history. With the increasing use of ticagrelor in real-world practice, further research is needed to observe its impact on cardiovascular outcomes.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Current recommendations suggest the use of newer P2Y12 inhibitors (i.e., prasugrel or ticagrelor) over clopidogrel given the better efficacy found in the

randomized controlled trials. However, the choice of a particular P2Y12 inhibitor may differ based on the patient's clinical characteristics that has never been studied.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study determined the trends in the prescription patterns of P2Y12 inhibitors in patients with coronary artery disease from the year 2013 to 2018.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We observed a continuously increased utilization of ticagrelor among patients aged less than or equal to 65 years that replaced clopidogrel as the most utilized P2Y12 inhibitor in 2018. Contrarily, among the older adults aged greater than or equal to 65 years and those at a high risk of bleeding, clopidogrel remained the most utilized drug during the entire study period.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

With the increasing use of ticagrelor in the real-world population in the United States, future studies are warranted to study its impact on clinical outcomes.

INTRODUCTION

Coronary artery disease (CAD) is common in the United States affecting over 18.2 million Americans and resulting in more than $100 billion in indirect costs.[1] The manifestations of CAD include stable ischemic heart disease, unstable angina, and acute myocardial infarction (MI) resulting in myocardial injury and death.[2] Reperfusion is an essential part of the management of CAD to reduce ongoing myocardial damage.[3] Following reperfusion, the American Heart Association (AHA) recommends secondary prophylaxis with a P2Y12 inhibitor and aspirin, known as dual antiplatelet therapy (DAPT).[4] P2Y12 inhibitors utilized for secondary CAD prophylaxis include clopidogrel (approved by the US Food and Drug Administration [FDA] in 1997), and the newer agents prasugrel and ticagrelor, approved in 2009 and 2011,[5] respectively. Compared to clopidogrel, these newer agents have more potent and predictable antiplatelet aggregation profiles, attributed to consistent pharmacokinetics and dynamics.[6]

Newer P2Y12 inhibitors are generally recommended over clopidogrel in the AHA/American College of Cardiology Foundation (ACC) clinical practice guidelines.[7] Nevertheless, evidence suggests clopidogrel to be a safer option among elderly patients and those at a high risk of bleeding and a history of stroke.[8] Given this evidence, the AHA/ACC guidelines on the first choice P2Y12 agent to prescribe differs by (i) patient clinical characteristics (i.e., high bleeding risk and history of stroke), and (ii) type of revascularization technique (percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG], or fibrinolysis).[9] However, currently, there are no studies that have evaluated real-world prescribing patterns following different revascularization procedures and clinical characteristics. The main objective of this study is to examine differences in the prescribing of P2Y12 agents across important patients' clinical characteristics, such as high bleeding risk and the type of revascularization used and to determine the predictors of utilization of one P2Y12 inhibitor over the other.

METHODS

Data source

This study was done using the IBM MarketScan databases from January 1, 2013, to December 31, 2018. The Commercial Claims and Encounters (CCAE) database includes information on more than 30 million commercially insured beneficiaries and the Medicare Supplemental and Coordination of Benefits (MDCR) data includes information on more than one million Medicare beneficiaries with supplemental benefits.[10] The CCAE samples in our study included patients aged 18 to 65 years; whereas MDCR samples included patients aged greater than or equal to 65 years. These databases include enrollment information, inpatient and outpatient medical claims, and outpatient pharmacy claims.

Patient inclusion and exclusion

We included patients discharged from the hospital with a diagnosis of CAD. The CAD events were identified using validated International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM and ICD-10-CM) codes (ICD-9 and 10-CM codes),

Table S1. To be included, patients had to have at least 6 months of prior continuous enrollment in a health plan with medical and pharmacy benefits and initiate clopidogrel, prasugrel, or ticagrelor within 14 days of revascularization after a CAD event. Revascularization methods included fibrinolytic therapy, CABG, and PCI. The revascularization procedures were determined using Current Procedure Terminology codes and Healthcare Common Procedure Coding System as well as ICD-9 and 10 procedure codes published previously (Table S1).

Drug claims were identified from the IBM Micromedex Red Book[11] by National Drug Codes from outpatient pharmacy claims data using prescription fill date. We used an intention to treat approach,[12] using the first prescription fill to identify which P2Y12 inhibitor someone initiated on.

Study design

We used a cross-sectional study design to determine prescription patterns of P2Y12 inhibitors across patients' characteristics and type of revascularization procedure from January 1, 2013, to December 31, 2018. Patients with multiple revascularization procedures during a single admission were categorized by the most invasive procedure.[13–16] For example, patients experiencing both PCI and fibrinolytic therapy were categorized as PCI, and those having both PCI and CABG were categorized as CABG.

Predictors of drug selection were determined in the overall patient cohort (2013–2018) based on variables grouped using Andersen's Behavior Model (ABM) of Health Services Use.[17] A 6-month window prior to medication initiation was used to measure prescription predictors.

Prescription patterns were further described in two high-risk groups of patients: (1) with high bleeding risk, and (2) with a history of stroke or transient ischemic attack (TIA). High bleeding risk was defined as per AHA/ACC guidelines.[18] High bleeding risk included (i) any history of high-risk comorbid conditions (i.e., diabetes, anemia, chronic kidney disease, and low body weight), (ii) any major bleeding (i.e., intracranial, gastrointestinal, or any other major source of bleeding) in the last 6 months, and (iii) any concomitant use of the medication linked to higher bleeding risk (i.e., oral anticoagulants, prescription non-steroidal anti-inflammatory drugs, or corticosteroids). A history of stroke/TIA was identified in the prior 6 months.

In addition to cross-sectional descriptive comparisons, we examined longitudinal trends in prescription fill patterns for secondary CAD prophylaxis over time. We report the proportion of each P2Y12 inhibitor used among all patients initiating a P2Y12 inhibitor quarterly between 2013 and 2018 to show trends in treatment uptake over time.

Statistical analysis

The prevalence of each P2Y12 inhibitor was described using counts and percent estimates. To examine the association of patient characteristics on the decision to prescribe a particular P2Y12 inhibitor, we used χ^2 testing in bivariate analyses. The proportion of patients using P2Y12 inhibitors in every quarter was determined. To determine if significant trends existed in the quarterly prevalence of P2Y12 inhibitor prescriptions from the year 2013 to 2018, the Cochran-Armitage trend test was utilized.

We performed multivariate logistic regression (MLR) to examine the influence of all predictors on the decision to prescribe individual P2Y12 inhibitors in a single model. Variables were organized according to ABM of health service utilization into predisposing, enabling, and need variables (Figure S1). The rationale behind using these variables as confounders in the MLR is given in the Method S1. We tested for heterogeneity in age categories using the Breslow Day test and retained age as a categorical variable as it failed the null hypothesis of homogeneity. All comparisons were considered significant at α of 0.05. No adjustments for p values were made to account for multiple comparisons.

Given the differing age characteristics in CCAE and MDCR samples, we studied both CCAE and MDCR samples separately to gauge the effect of age on the prescribing pattern. Analyses were conducted using SAS 9.4.

RESULTS

We identified 137,073 unique patients (CCAE, $N = 92{,}734$ and MDCR, $N = 44{,}339$) with CAD who initiated a P2Y12 inhibitor within 14 days of revascularization between 2013 and 2018. Clopidogrel was the most utilized P2Y12 inhibitor with 60.9% of the prescription share followed by ticagrelor (25.1%) and prasugrel (13.6%).

Descriptive characteristics of P2Y12 inhibitor users in overall population (CCAE and MDCR combined) are given in Table 1 with detailed comparisons. A major portion of the patients included were men and with age 56–65 years enrolled in preferred provider organization plans regardless of the P2Y12 inhibitor used. Newer P2Y12 inhibitors, ticagrelor (97.62%) and prasugrel (97.40%), were utilized more often than clopidogrel (85.97%) when the mode of revascularization was a PCI. Additionally, when drug-eluting stents (DES) were used, newer P2Y12 inhibitors use was higher compared to clopidogrel. Furthermore, the use of newer agents was preferred compared to clopidogrel when patients were diagnosed with ST wave elevated myocardial infarction (STEMI).

TABLE 1 Demographics and baseline characteristics of P2Y12 inhibitors users from 2013 to 2018.

Characteristics	Clopidogrel (*N* = 83,998)		Prasugrel (*N* = 18,693)		Ticagrelor (*N* = 34,382)		*p* value
	n	%	*n*	%	*n*	%	
Predisposing demographic variables							
Age category, years							**<0.001**
>85	3,132	3.73	70	0.55	443	1.67	
76–85	12,418	14.78	600	3.98	2539	8.02	
66–75	16,565	19.72	2,673	14.44	4441	12.77	
56–65	31,886	37.96	8,516	44.47	14,948	42.60	
46–55	15,920	18.95	5,274	28.21	9,270	26.96	
36–45	3,722	4.43	1,412	7.55	2,456	7.14	
26–35	320	0.38	136	0.73	269	0.78	
18–25	35	0.04	12	0.06	16	0.05	
Sex							**<0.001**
Male	60,346	72.31	14,586	78.03	25,707	74.77	
Region							**<0.001**
Northeast	15,863	19.01	3,120	16.69	6,807	19.80	
Northcentral	23,633	28.32	3,927	21.01	8,676	25.23	
South	33,504	40.14	9,144	48.92	15,138	44.03	
West	10,267	12.30	2,242	11.99	3,533	10.28	
Unknown	741	0.89	260	1.39	228	0.66	
Enabling variables							
Plan type							**<0.001**
Comprehensive	15,346	18.39	2,000	10.70	3,682	10.71	
EPO	601	0.72	170	0.91	298	0.87	
HMO	8,753	10.49	1,683	9.00	3,194	9.29	
POS	5,069	6.07	1,153	6.17	2,249	6.54	
PPO	43,380	51.98	10,596	56.68	18,592	54.07	
POS with capitation	686	0.82	121	0.65	352	1.02	
CDHP	5,325	6.38	1,652	8.84	3,362	9.78	
HDHP	3,255	3.90	938	5.02	1,977	5.75	
Index year							**<0.001**
2013	12,492	14.97	2,963	15.85	2,221	6.46	
2014	20,986	25.15	5,078	27.17	5,159	15.00	
2015	15,711	18.83	3,232	17.29	5,488	15.96	
2016	14,476	17.35	3,273	17.51	6,464	18.80	
2017	11,231	13.46	2,387	12.77	7,240	21.06	
2018	9,102	10.91	1,760	9.42	7,810	22.72	
Need variables							
Mode of revascularization							**<0.001**
PCI	71,747	85.97	18,207	97.40	33,562	97.62	
CABG	11,447	13.72	455	2.43	752	2.19	
Fibrinolysis	804	0.96	31	0.17	68	0.20	
Type of stents							**<0.001**
DES	33,489	40.13	9,468	50.65	18,714	54.43	
BMS	3,904	4.68	705	3.77	1,544	4.49	

(Continues)

TABLE 1 (Continued)

Characteristics	Clopidogrel (*N* = 83,998)		Prasugrel (*N* = 18,693)		Ticagrelor (*N* = 34,382)		*p* value
	n	%	*n*	%	*n*	%	
Type of ACS							**<0.001**
NSTE-ACS	30,349	36.36	6,706	35.87	13,748	39.99	
STEMI	14,915	17.87	4,756	25.44	9,930	28.88	
Elixhauser index[a] (readmission)							**<0.001**
Category 0	23,354	27.98	5,858	31.34	11,108	32.31	
Category 1	18,146	21.74	5,120	27.39	8,602	25.02	
Category 2	6,372	7.63	1,283	6.86	2,602	7.57	
Category 3	19,812	23.74	4,211	22.53	7,252	21.09	
Category 4	16,314	19.55	2,221	11.88	4,818	14.01	
High bleeding risk [9]							
High-risk comorbid conditions in the past 6 months							
Diabetes	25,805	30.92	5,284	28.27	9,428	27.42	**<0.001**
Anemia	5,150	6.17	562	3.01	1,372	3.99	**<0.001**
Chronic kidney disease	5,996	7.18	677	3.62	1,629	4.74	**<0.001**
Low body weight	627	0.75	53	0.28	118	0.34	**<0.001**
History of prior bleeding[b]	10,389	12.45	1,017	5.44	2,216	4.21	**<0.001**
Concomitant use of high-risk medications[c]	10,839	12.99	1,372	7.34	2,639	7.68	**<0.001**
Medication history (past 6 months)							
Cardiac drugs							
Anticoagulants	7,723	9.25	501	2.68	1,112	3.23	**<0.001**
Antiplatelet drugs	15,458	18.52	3,383	18.10	4,915	14.30	**<0.001**
Anti-arrhythmic drugs	2,063	2.47	211	1.13	346	1.01	**<0.001**
Antihypertensive							
Ace inhibitors	24,571	29.44	4,898	26.20	8,430	24.52	**<0.001**
Angiotensin II antagonists	17,694	21.20	3,598	19.25	6,626	19.27	**<0.001**
Alpha-beta blockers	548	0.66	82	0.44	161	0.47	**<0.001**
Beta-blockers	40,252	48.23	7,402	39.60	12,307	35.79	**<0.001**
Calcium channel blockers	20,331	24.36	3,506	18.76	6,720	19.55	**<0.001**
Antidiabetics							
Miscellaneous[d]	17,054	20.43	3,713	19.86	6,416	18.66	**<0.001**
Meglitinides	341	0.41	45	0.24	89	0.26	**<0.001**
Sulfonylureas	7,849	9.40	1,449	7.75	2,595	7.55	**<0.001**
SGLT inhibitors	1,434	1.72	399	2.13	870	2.53	**<0.001**
TZD	1,213	1.45	263	1.41	416	1.21	**0.007**
Diuretics							
Loop diuretics	10,371	12.43	1,249	6.68	2,236	6.50	**<0.001**
Potassium-sparing diuretics	3,966	4.75	663	3.55	1,102	3.21	**<0.001**

TABLE 1 (Continued)

Characteristics	Clopidogrel (*N* = 83,998)		Prasugrel (*N* = 18,693)		Ticagrelor (*N* = 34,382)		
	n	%	*n*	%	*n*	%	*p* value
Thiazide diuretics	7,481	8.96	1,396	7.47	2521	7.33	**<0.001**
Carbonic anhydrase inhibitors	113	0.14	19	0.10	49	0.14	0.442
Lipid lowering agents	48,757	58.42	10,076	53.90	16,906	49.17	**<0.001**
Cardiac glycosides (Digoxin)	1,390	1.67	130	0.70	202	0.59	**<0.001**
Estrogens	1,483	1.78	337	1.80	538	1.56	**0.035**
Antidepressants	16,367	19.61	3,376	18.06	6,015	17.49	**<0.001**
Antacids							
PPIs	19,339	23.17	3,863	20.67	6,802	19.78	**<0.001**
H2RA	3,288	3.94	546	2.92	1,076	3.13	**<0.001**

Note: The *p* values in bold are statistically significant at $p = 0.05$.

Abbreviations: ACS, acute coronary syndrome; BMS, bare-metal stent; CABG, coronary artery bypass grafting; CCAE, Commercial Claims and Encounters database; CDHP, consumer-driven health plan; DES, drug-eluting stent; EPO, Exclusive Provider Organization; H2RA, H2 receptor blockers; HDHP, high-deductible health plan; HMO, health maintenance organization; MDCR, Medicare Supplemental and Coordination of Benefits (COB) Database; NSAIDS, non-steroidal anti-inflammatory drugs; NSTE ACS, Non-ST elevated myocardial infarction (NSTEMI) and unstable angina (UA); PCI, percutaneous coronary intervention; POS, point-of-service; PPIs, proton pump inhibitors; PPO, preferred provider organization; SGLT, Sodium-glucose co-transporter inhibitors; STEMI, ST wave elevated myocardial infarction; TZD, thiazolidinediones.

[a]Elixhauser Index (category 0: score = <0; category 1: score = 0; category 2: score = 1–5; category 3: score = 6–13; category 4 = score > = 14).

[b]History of intracranial, gastrointestinal bleeding, and other forms of major bleeding in the past 6 months.

[c]Any concomitant use of the medication linked to higher bleeding risk i.e., oral anticoagulants, prescription NSAIDs, or corticosteroids as an additional bleeding risk as per American Heart Association's recommendations.

[d]Miscellaneous Antidiabetic included *biguanides*, glucagon-like peptide 1 agonist, dipeptidyl peptidase 4 inhibitors, alpha-glucoside inhibitors, incretin mimetics, amylin analogues, glucagon, and combinations.

Trends in P2Y12 inhibitors use from 2013 to 2018

Due to the differences seen between the CCAE and MDCR datasets, results are stratified by age. For participants aged less than or equal to 65 years (the CCAE sample; *N* = 92,734), Figure 1, the prevalence of clopidogrel prescription decreased from 65.5% to 44.0% from 2013 to 2018. Ticagrelor use increased from 13.7% to 45.6% during this period, and surpassed clopidogrel use during the third quarter of 2018 (Table S2). Similar patterns were observed among patients aged greater than or equal to 65 years (MDCR sample; *N* = 44,339), Figure 1 with clopidogrel losing market-share. However, although ticagrelor use increased over time in the MDCR sample, it remained well below clopidogrel use throughout the study period (Figure 1, Table S3). The trends in use over time were significant for each P2Y12 inhibitor ($p < 0.05$) in both data samples (Tables S2 and S3).

For the prescription patterns across different revascularization techniques (Figure 2), it appears that patients undergoing PCI most commonly initiated ticagrelor (48.8%) in the CCAE (age ≤65 years) population in 2018. However, clopidogrel was the most often used P2Y12 inhibitor across other revascularization procedures (i.e., CABG and fibrinolysis in both the CCAE and MDCR samples; Figure 2).

In CCAE patients with high bleeding risk, clopidogrel use decreased whereas ticagrelor use increased from 12.0% to 40.1% over the study timeframe (Figure 3). Although a similar pattern was evident in the MDCR sample (Figure 3), clopidogrel was the most commonly used drug throughout the study with utilization declining from 82.2% in 2013 to 71.1% in 2018. Finally, among patients with stroke or TIA history (Figure 4), clopidogrel was favored in both the CCAE and MDCR populations (77.8% and 84.9%, respectively) followed by ticagrelor (14.6% and 9.9%, respectively), and prasugrel (7.6% and 5.2%, respectively).

Predictors of P2Y12 inhibitors utilization in both sample populations

Among participants less than or equal to 65 years, the use of clopidogrel decreased over time compared to ticagrelor in the CCAE sample (Table S4). For example, clopidogrel

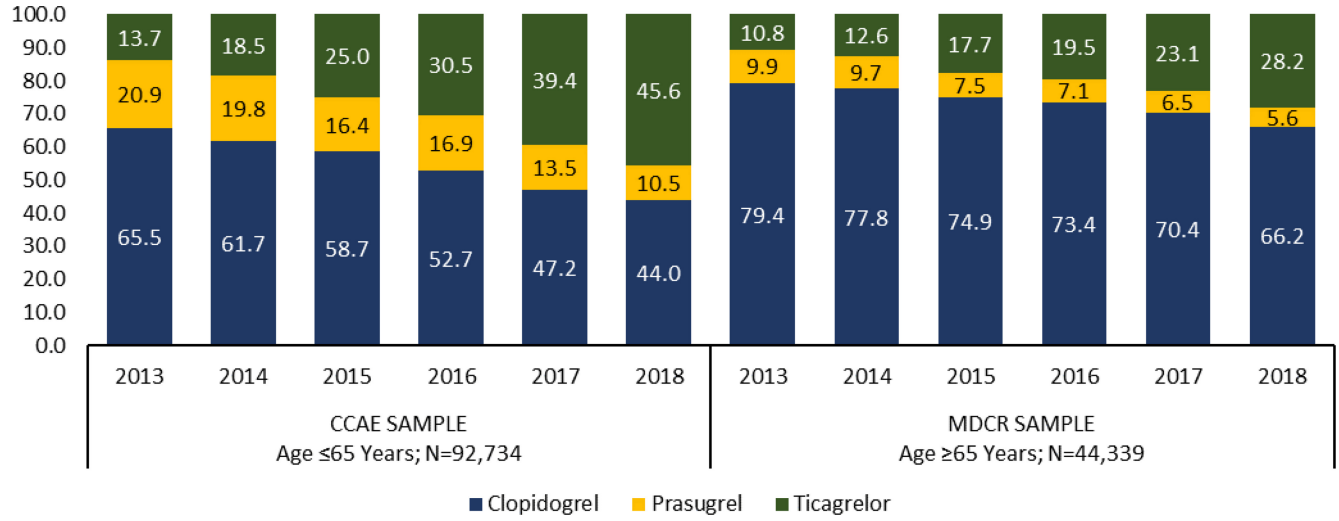

FIGURE 1 Prevalence of prescription of P2Y12 inhibitors in the CCAE (age ≤65 years) and MDCR (age ≥65 years) sample. CCAE, Commercial Claims and Encounters database; MDCR, Medicare Supplemental and Coordination of Benefits.

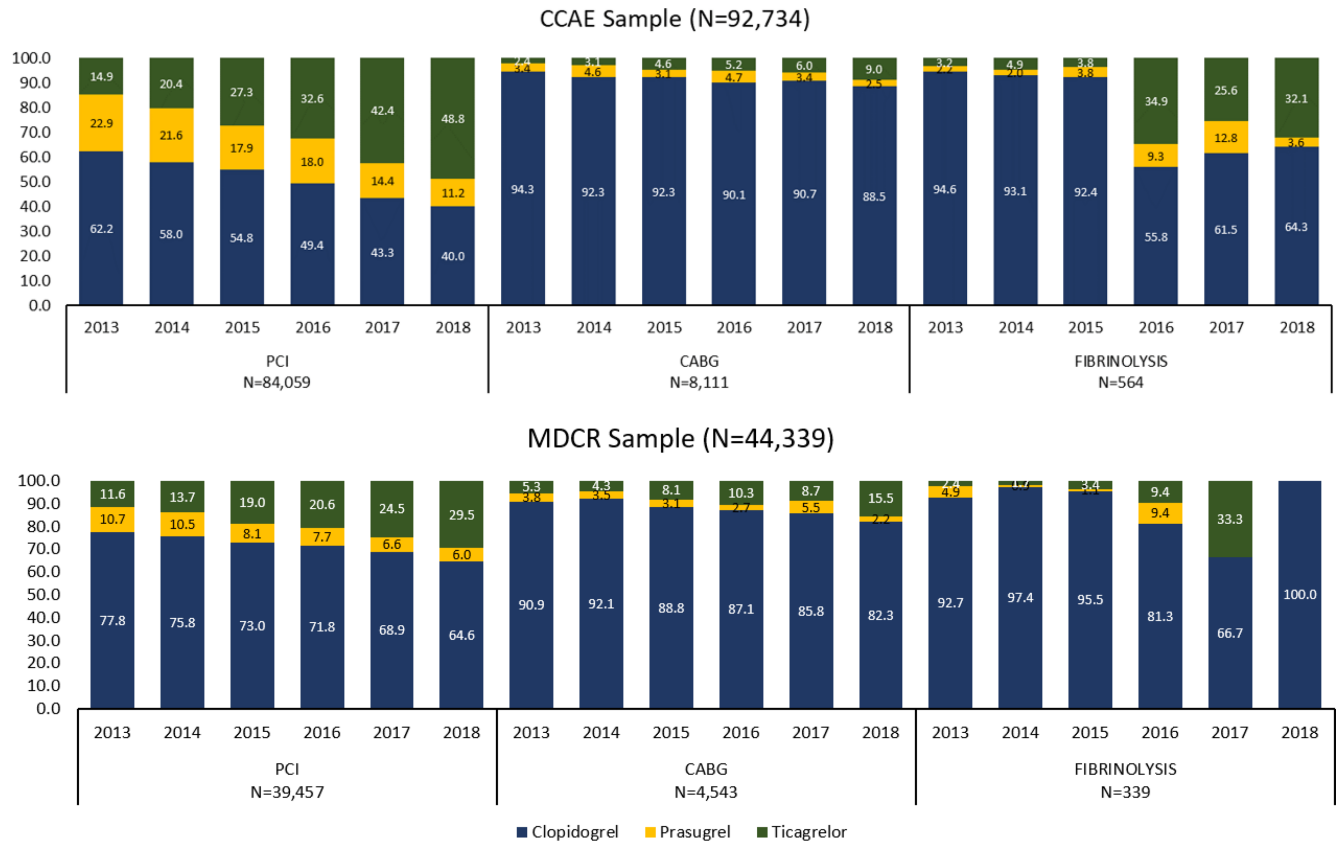

FIGURE 2 Prevalence of P2Y12 inhibitors as per the technique of revascularization in the CCAE (age ≤65 years) and MDCR (age ≥65 years) sample. CABG, coronary artery bypass grafting; CCAE, Commercial Claims and Encounters database; MDCR, Medicare Supplemental and Coordination of Benefits; PCI, percutaneous coronary intervention.

was associated with 37% to 85% lower odds of use compared to ticagrelor (odds ratio [OR] 0.63, 95% confidence interval [CI]: 0.57–0.70) and (OR 0.15, 95% CI 0.14–0.17), respectively, in years 2014 and 2018 compared to 2013. Similarly, ticagrelor had higher use than prasugrel. A similar pattern was observed for the MDCR sample (Table S5).

In the CCAE sample (Figure 5, Table S4), 8.7% of patients underwent CABG and 90.6% PCI. Patients undergoing CABG versus PCI were more likely to use clopidogrel

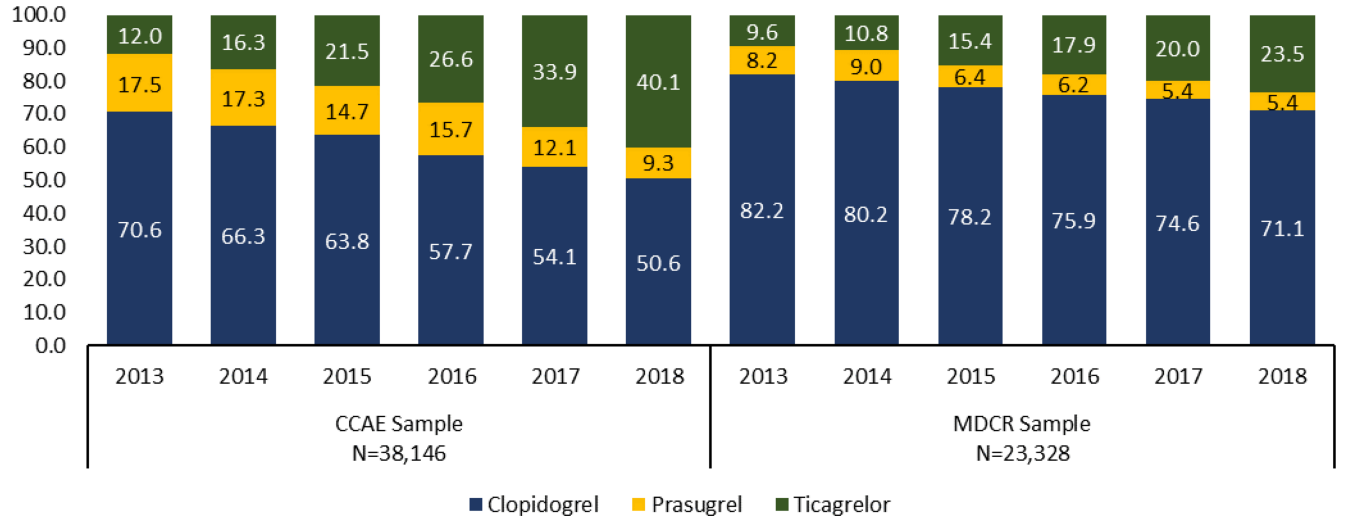

FIGURE 3 Prevalence of P2Y12 inhibitors among patients with high bleeding risk in the CCAE (age ≤65 years) and MDCR (age ≥65 years) sample. CCAE, Commercial Claims and Encounters database; MDCR, Medicare Supplemental and Coordination of Benefits.

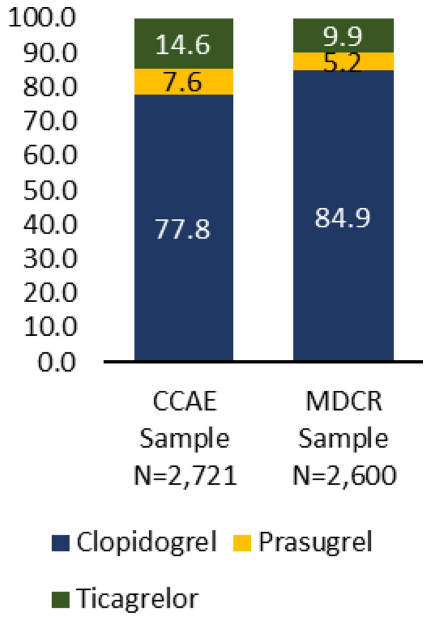

FIGURE 4 Prevalence of P2Y12 inhibitors among the patients with a history of stroke or trans ischemic events in the CCAE (age ≤65 years) and MDCR (age ≥65 years) sample. CCAE, Commercial Claims and Encounters database; MDCR, Medicare Supplemental and Coordination of Benefits.

than ticagrelor (OR 1.73, 95% CI 1.38–2.15). Similarly, the odds of prasugrel versus ticagrelor use were lower for CABG compared to PCI patients (OR 0.67, 95% CI 0.50–0.89). For the MDCR sample (Figure 6, Table S5), the odds of clopidogrel use were higher compared to ticagrelor and prasugrel for those undergoing CABG versus PCI.

Stents were implanted in 50.9% of our CCAE sample (Figure 5, Table S4). Of these 46.5% were DES and 4.4% bare-metal stents (BMS). The odds of clopidogrel use were 27% lower compared to ticagrelor when patients were revascularized using DES over BMS (OR 0.73, 95% CI 0.67–0.79). Similarly, clopidogrel was associated with lower use compared to prasugrel in patients revascularized using DES versus BMS (OR 0.70, 95% CI 0.63–0.77). For the MDCR sample (Figure 6, Table S5), a total of 46.6% of patients were implanted with stents. Similar to the CCAE sample, there was a greater likelihood of newer P2Y12 inhibitors use over clopidogrel if DES were used compared to BMS.

In regard to acute coronary syndrome (ACS) presentation, in the CCAE sample (Figure 5, Table S4), 25.0% of patients presented with STEMI and 38.3% with non-STEMI ACS (NSTE-ACS). NSTE-ACS included non-STEMI patients and patients with unstable angina. Among patients with STEMI compared to NSTE-ACS, in the CCAE sample, the odds of prescribing clopidogrel were lower in comparison to ticagrelor and prasugrel prescribing (OR 0.72, 95% CI 0.69–0.76) and (OR 0.76, 95% CI 0.72–0.81), respectively. Although a similar pattern was observed in the MDCR (Figure 6, Table S5), ticagrelor was also associated with 24% increased odds of being prescribed compared to prasugrel (OR 1.24, 95% CI 1.05–1.45), which was not seen in the CCAE sample.

Importantly, for the CCAE sample (Figure 5, Table S4), patients with a history of prior bleeding within the last 6 months, clopidogrel was associated with 19% and 28% higher odds of being prescribed compared to ticagrelor (OR 1.19, 95% CI 1.05–1.34) and prasugrel (OR 1.28, 95% CI 1.10–1.49). We also looked at the P2Y12 inhibitors use concomitantly with high-risk medications as a risk of bleeding. We continued to see that clopidogrel was associated with 52% and 77% higher odds of being prescribed compared to ticagrelor (OR 1.52, 95% CI 1.39–1.66) and prasugrel (OR 1.77, 95% CI

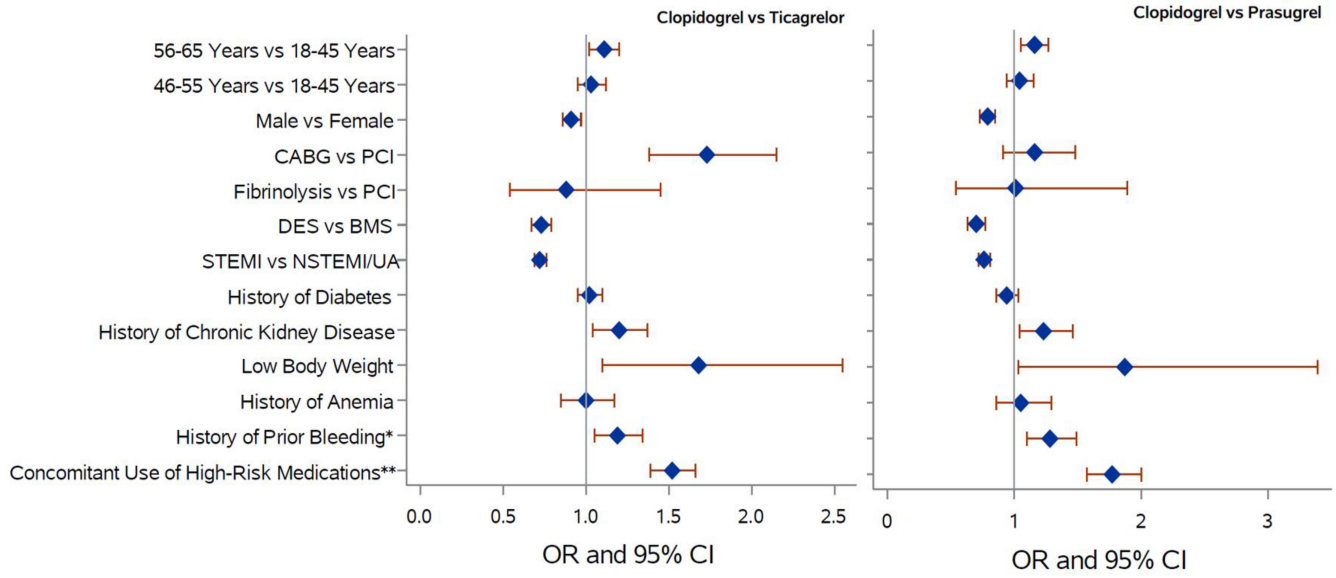

FIGURE 5 Predictors of P2Y12 inhibitors utilization in the CCAE (age ≤65 years) sample. ACS, acute coronary syndrome; BMS, bare-metal stent; CABG, coronary artery bypass grafting; CCAE, Commercial Claims and Encounters database; CI, confidence interval; DES, drug-eluting stent; NSAIDS, non-steroidal anti-inflammatory drugs; NSTEMI, non-ST elevated myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST wave elevated myocardial infarction; UA, unstable angina. *History of intracranial, gastrointestinal bleeding, and other forms of major bleeding in the past 6 months. ** Any concomitant use of the medication linked to higher bleeding risk (i.e., oral anticoagulants, prescription NSAIDs, or corticosteroids as an additional bleeding risk).

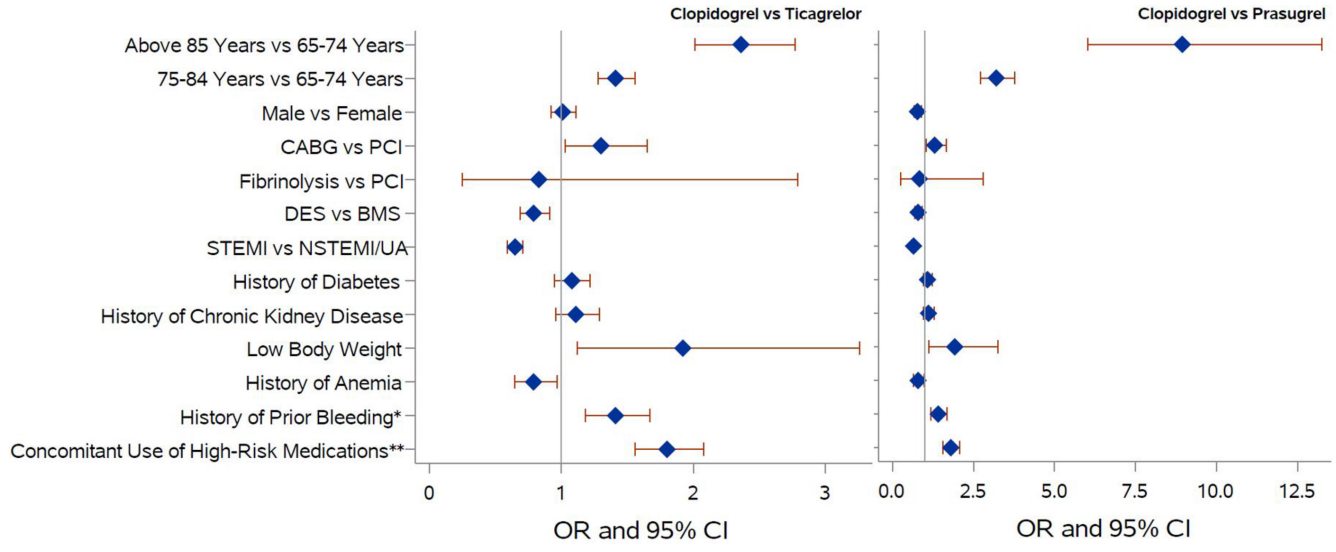

FIGURE 6 Predictors of P2Y12 inhibitors utilization in the MDCR (age ≥65 years) sample. ACS, acute coronary syndrome; AHA, American Heart Association; BMS, bare-metal stent; CABG, coronary artery bypass grafting; CI, confidence interval; DES, drug-eluting stent; MDCR, Medicare Supplemental and Coordination of Benefits Database; NSAIDS, non-steroidal anti-inflammatory drugs; NSTEMI, non-ST elevated myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; STEMI, ST wave elevated myocardial infarction; UA, unstable angina. *History of intracranial, gastrointestinal bleeding, and other forms of major bleeding in the past 6 months. ** Any concomitant use of the medication linked to higher bleeding risk (i.e., oral anticoagulants, prescription NSAIDs, or corticosteroids as an additional bleeding risk as per AHA recommendations.

1.57–2.00). We observed a similar pattern in the MDCR sample (Figure 6, Table S5).

Finally, when examining comorbidity, a higher category of the Elixhauser Index (EI)[19] was associated with increased odds of clopidogrel use over ticagrelor for both study samples (Tables S4 and S5). The detailed description of P2Y12 inhibitors as per the EI index is presented in Tables S6 and S7 for CCAE and MDCR populations, respectively.

DISCUSSION

This study provides comprehensive information on P2Y12 inhibitor utilization among patients with CAD with various clinical characteristics, and by revascularization-type, using a US real-world population from 2013 to 2018. Our results show ticagrelor use increased with time and became the preferred drug for secondary CAD prophylaxis for younger commercially insured patients (aged 65 years or less) in 2018. Newer P2Y12 inhibitors were preferred among the patients with STEMI versus NSTE-ACS and those managed with DES versus BMS. Whereas clopidogrel was the preferred P2Y12 inhibitor in high bleeding risk, higher comorbidity indices, history of stroke/TIA, but not in those undergoing PCI. Prescribing patterns generally followed AHA/ACC guidelines. For example, current guidelines recommend the use of newer P2Y12 inhibitors in preference to clopidogrel[7] that we observed in our analysis indicated by the increasing use of ticagrelor with time. Importantly, there was also evidence of potentially inappropriate medication use as patients with a stroke or TIA history were prescribed prasugrel, even though there is a black box warning by the FDA against its use in such patients.

In patients with age 18 to 65 years (CCAE sample), ticagrelor use in CAD increased substantially from 2013 to 2018 surpassing clopidogrel use in 2018 continuing a trend reported in prior studies up to 2014.[20] Increased adoption of ticagrelor may have been impacted by PLATO trial results[21] in which ticagrelor use resulted in a significant reduction of death and MI among patients with a median age of 62 years. Additionally, our previous retrospective cohort study using the IBM MarketScan database indicated a similar risk of composite major bleeding with ticagrelor and a higher risk of major bleeding with prasugrel versus clopidogrel in the CCAE population.[22] Although, we observed a similar risk of composite cardiovascular outcomes among users of P2Y12 inhibitors in our another study.[23] The increased adoption of ticagrelor in this study is in contrast to a reduction in prasugrel use observed in both the CCAE and MDCR sample. These results continue a trend reported using a 2 year period following the market introduction of ticagrelor in a prior study.[24]

Among older patients in the MDCR sample, clopidogrel remained the drug of choice for the entire study period. This trend is perhaps not surprising given that bleeding risk increases among older adults[8] and there is evidence to suggest that clopidogrel results in fewer bleeding events than prasugrel and ticagrelor in prior randomized controlled trial (RCT) studies.[21,25,26] These results are further supported when examining trends in prescribing among patients with high bleeding risk. In both the CCAE and MDCR samples, clopidogrel remained the most commonly prescribed P2Y12 inhibitor throughout our study between 2013 and 2018. It should be noted that despite a higher risk of bleeding in older adults treated with ticagrelor compared to clopidogrel,[27] the use of ticagrelor increased to 28% of prescriptions in the MDCR sample by 2018. The impact of this increasing utilization should be monitored to assess the risk of bleeding associated with this trend. Thus, given the altered physiologic changes because of the aging process affecting the drug pharmacokinetics, there is a need for an RCT studying the impact of DAPT, including potent P2Y12 inhibitors on safety in older adults in the United States.

In addition, we found that among patients undergoing PCI, ticagrelor was used preferentially over clopidogrel or prasugrel by 2018 in the CCAE sample. Contrarily, for the MDCR sample, clopidogrel was the preferred drug following PCI, which is perhaps again a result of the higher bleeding risk associated with newer drugs among older adults. Interestingly, for patients undergoing CABG, clopidogrel was the drug of choice in both study samples. Higher use of clopidogrel post CABG appears to be rational as clopidogrel has proven its efficacy in RCTs studying CABG patients.[28,29]

Finally, among patients with a history of stroke or TIA, clopidogrel use was more common than ticagrelor or prasugrel in both the CCAE and MDCR samples. Of concern, prasugrel was used in 7.6% of the CCAE and 5.2% in MDCR populations despite clear evidence of increased risk of fatal bleeding events found in the TRITON-TIMI 38 RCT[25] and the introduction of a black box warning cautioning against its use in patients with a history of stroke/TIA.[30] This suggests a need for further education related to the risks of prasugrel use in this high-risk population.

Strengths and limitations

Our study has several strengths. First, the sample size for both populations under this study was large and the results are more contemporary than prior studies on this topic. We were able to differentiate the prevalence of P2Y12 inhibitor use across a younger and older population, but also examine patterns of use in patient subgroups undergoing different revascularization techniques and across several important patients' characteristics that influence the effectiveness and safety of these agents. However, like any other observational study, this study also has several limitations. The trends observed in this study are only generalizable to the population studied. For example, the sample of patients in our Medicare sample had supplemental Medicare coverage and tend to be healthier and have higher income than the typical Medicare patient. This could potentially bias

the disease prevalence and prescription pattern of the P2Y12 inhibitors in our study. Furthermore, prescription patterns were analyzed in patients after discharge based on the first prescription. Thus, patients not surviving their hospital stay were not included. No data are available on the duration of the respective treatment and whether there have been changes thereafter. Additionally, MarketScan data lacks information related to race, ethnicity, socioeconomic status, frailty, and other factors that might have been of interest when examining trends in prescribing. These demographic factors are important as there are disparities in cardiovascular health reported in the previous studies.[31,32] It should be noted that several comparisons were made without adjusting for the multiplicity across different comparisons. Thus, a chance of results to show significance at $p < 0.05$ cannot be ruled out. Finally, claims data do not capture over-the-counter prescription fills, including low dose aspirin which is commonly prescribed and indicated in this patient population.[5]

CONCLUSION

This study concludes that ticagrelor use has increased over time in the United States replacing a major prescription share of clopidogrel. Generally, practitioners followed ACC/AHA evidence-based guidelines in prescribing P2Y12 inhibitors, yet we observed prasugrel use in patients with stroke or TIA history despite a black-box warning against its use. Given the greater use of more potent ticagrelor in the current practice and the associated bleeding tendency, further research is needed to observe the risk and benefit of its increasing use in CAD in real-world practice.

AUTHOR CONTRIBUTIONS

A.K., J.F.F., P.L.L., W.L.S., J.C.S., and J.R.V. designed the research. A.K. and J.F.F. performed the research and wrote the manuscript. A.K. and A.R. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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