Contemporary Trends in Oral Antiplatelet Agent Use in Patients Treated with Percutaneous Coronary Intervention for Acute Coronary Syndrome

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ABSTRACT

BACKGROUND: Recent trials demonstrated the efficacy of prasugrel and ticagrelor compared with clopidogrel in the reduction of cardiovascular complications in patients with acute coronary syndrome (ACS). However, it is unclear how use of the 3 antiplatelet medications has changed in commercially insured patients since the advent of the new agents.

OBJECTIVES: To (a) describe the adoption of prasugrel and ticagrelor in patients who received percutaneous coronary intervention (PCI) for the onset of ACS and (b) explore patient factors associated with the selection of the drug to provide insight into utilization patterns of these antiplatelet agents.

METHODS: Patients who received a new dispensing of an antiplatelet agent following a hospitalization for a PCI administered for ACS were identified from insurance claims between 2009 and 2013. Demographics and comorbid conditions were determined based on a 6-month period before the ACS event. Longitudinal trends in antiplatelet agent selection were illustrated using descriptive statistics segmented by month and quarter. Using logistic regressions with stepwise model selection, factors associated with use of the newer medications, as well as with the selection between ticagrelor and prasugrel, were identified.

RESULTS: The analysis included 66,335 subjects. The use of clopidogrel decreased from 100% to roughly 65% of total antiplatelet agent use by the end of 2011 and leveled off thereafter. The introduction of ticagrelor in 2011 coincided with a drop in prasugrel initiation from 35%-18% by December 2013. The use of new agents as opposed to use of clopidogrel was associated with younger age (< 65 years), male gender, and a diagnosis of ST-elevation myocardial infarction. In addition, conditions increasing mortality and risk of cardiovascular complication were associated with higher odds of using clopidogrel. The odds of using ticagrelor over prasugrel increased with older age and history of a cerebrovascular event.

CONCLUSIONS: In 2013, clopidogrel remained the most prescribed agent. Meanwhile, ticagrelor had gradually replaced a substantial portion of prasugrel initiation. Further investigation into outcomes associated with the newer agents, as well as reasons behind the conservative use of the antiplatelet agents, is warranted.

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What is already known about this subject

- Prasugrel and ticagrelor reduce cardiovascular complications in patients with acute coronary syndrome (ACS).
- Among patients receiving antiplatelet agents in hospitals registered in the National Cardiovascular Data Registry, the proportion of patients using prasugrel increased from 3% in October 2009 to 18% in September 2012, with a corresponding decrease in the use of clopidogrel use.

What this study adds

- As of 2013, clopidogrel continued to be a major option in ACS-percutaneous coronary intervention (PCI) patients, and a substantial portion of prasugrel initiation had been replaced by ticagrelor. This trend could not be fully explained by the efficacy profiles of the 3 antiplatelet agents.
- Clinical practice preferred clopidogrel to the newer agents even in patients having risk factors of further myocardial infarction or other complications.
- A sizable number of patients using the newer antiplatelet agents had a history of labeled conditions with increased risk of cardiovascular complications in which use of those agents are recommended to be avoided.

Acute coronary syndrome (ACS) imposes a major burden on the U.S. health care system. There were 1.14 million hospitalizations for ACS in 2010, and the annual medical cost for each commercially insured case ranged between \$34,000 and \$87,000, depending on the initial treatment.^{1,2} Surgical intervention is important to reduce cardiovascular complications.²⁻⁵ Further, across the wide spectrum of ACS care options, the use of antiplatelet therapy along with aspirin administration, referred to as dual antiplatelet therapy, is a key recommendation in the prevention of secondary events.^{3,5}

Antiplatelet management in ACS care has progressed substantially over the last 2 decades. In 1997, the U.S. Food and Drug Administration approved clopidogrel for the secondary prevention of cardiovascular events, and it experienced continuous growth in use.⁶⁻¹⁰ Recently, ACS care evolved with approvals of third-generation oral antiplatelet therapies that

included prasugrel and ticagrelor, which are commonly indicated as an adjunct to percutaneous coronary intervention (PCI) for a diagnosis of ACS.^{11,12} In randomized trials, prasugrel and ticagrelor reduced the risk of the composite endpoint of myocardial infarction, stroke, and cardiovascular death in comparison with clopidogrel.^{13,14} Further, using prasugrel or ticagrelor was cost-effective in comparison with the historic gold standard.^{15,16} Corresponding to all the evidence, clinical guidelines were updated with recommendations on using the recently approved agents.^{3,5,17-19}

A recent study involving the National Cardiovascular Data Registry showed that the proportion of patients using prasugrel increased from 3% in October 2009 to 18% in September 2012 in patients with ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI).²⁰ However, because ticagrelor was not included in this study, it is unclear how the availability of the third agent affected the choice of antiplatelet agents. In addition, the results from the National Cardiovascular Data Registry may not be generalizable to national practice, since being enrolled in the program is voluntary, which makes it more likely to reflect clinical practices that would adhere to guidelines.²⁰

The objective of this analysis was to describe trends in the use of 3 oral antiplatelet agents in commercially insured ACS patients who have newly received PCI.

Methods

Data Sources

Paid claims for a commercially insured population were obtained from Truven Health Analytics. The MarketScan Research Databases include de-identified patient-level medical and pharmacy claims for approximately 130 million subjects enrolled between the beginning of 2009 and the end of 2013. The research was deemed exempt by a local institutional review board.

Study Design and Analytic Cohort

A time-series analysis was performed for the patients who initiated 1 of the oral antiplatelet agents for post ACS-PCI care. Patients who were discharged from a hospitalization with a primary diagnosis of ACS (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 410.xx [except 410.x2], 411.1x, and 411.8x) between July 2009 and December 2013 were identified, and their PCI procedures during hospitalization were determined using ICD-9-CM codes and Current Procedural Terminology codes. Of the ACS-PCI subjects, patients who initiated clopidogrel, prasugrel, or ticagrelor within 14 days from the date of discharge were included in the analytic cohort. In order to avoid misinterpretation of the intended switching between loading and maintenance uses, the analytic cohort excluded patients who received 2 or more different antiplatelet agents during the

14-day assessment period. To focus on new users, patients were excluded who had received any antiplatelet medication during the 6 months before the ACS-PCI admission.²¹⁻²³ Over the same baseline period, medical history that potentially influenced the selection of an antiplatelet agent was collected using ICD-9-CM codes.²⁴⁻²⁸ For example, a past diagnosis of cerebrovascular encounter needs to be assessed before determining the medication strategy.^{3,5,6,11,12} Underlying myocardial infarction and other key comorbidities were also collected using a known coding algorithm for defining Charlson comorbidities.²⁹

Statistical Approach

Descriptive statistics segmented by calendar time were used to summarize the use of the 3 medications. The primary variable used in describing trends in new medication adoption was the monthly number and proportion of patients who newly initiated 1 of the oral antiplatelet agents. In addition to the proportions, the 95% confidence intervals (CIs) of the changes in the proportions were projected using a standard bootstrap resampling percentile approach with 1,000 replicates.

In order to provide additional insight into the use of these drugs, differences in patient characteristics across the 3 drug groups were compared. Age distributions were compared between clopidogrel and third-generation agent patients with a Student t-test and compared across the 3 groups using analysis of variance. Categorical variables were summarized using percentiles and χ^2 tests. Using frequency statistics, drug use was also looked at in patients with labeled contraindications, such as prasugrel use in patients with a history of transient ischemic attack (TIA), prasugrel in patients aged over 75 years without further risk factors of cardiovascular complication, or ticagrelor use in patients with a history of cerebrovascular hemorrhage.^{11,12}

Predictors in the selection between third-generation agents versus clopidogrel and between ticagrelor versus prasugrel were examined using logistic regression model adjusted for the semiannually segmented period and geographic location. Patient factors for consideration in the regression model were selected from the baseline characteristics whose *P* value in a bivariate analysis was less than 0.1. Independent variable selection was then performed using a stepwise forward selection approach with significance levels for entering effects of 0.1 and for the removing effect of 0.05. All of the statistical analysis was performed using SAS software version 9.3 (SAS Institute, Cary, NC).

Results

A total of 66,335 antiplatelet agent initiations over the 4.5-year period were identified. Of these, 33,307 initiated treatment between July 2009 and June 2011, the study period before ticagrelor was approved, and 85% of those cases were clopidogrel users. From July 2011 to the end of 2013, 68%, 25%,

FIGURE 1 Proportion of Each Incident, Antiplatelet Agent User, and Bootstrap 95% CIs: Monthly Segmentation

CI=confidence interval.

and 7% of the overall cohort were clonidogrel, prasugrel, and ticagrelor initiators, respectively (Appendix A, available in online article).

After prasugrel was approved, the proportion of prasugrel users increased by an average of 1 percentage point per month through March 2012, when the proportion plateaued. A decrease in the proportion of clonidogrel initiators had continued up to this point, but the proportion of clonidogrel use was essentially constant thereafter. Meanwhile, the use of ticagrelor increased by an average of 0.6 percentage points per month beginning March 2012 and reached 17% of the antiplatelet agent use at the end of 2013, which coincided with a decline in the proportion of prasugrel use. The bootstrapped CIs of prasugrel and ticagrelor uses overlapped each other after October 2013, but those intervals did not overlap with the range of the clonidogrel use (Figure 1). When the trends were stratified by diagnosis, proportions of the new agents increased faster in the STEMI group, with 20% and 19% of the STEMI subjects at the last quarter of 2013 being prescribed with prasugrel and ticagrelor, compared with non-ST-segment elevation ACS patients who had respective proportions of 17% and 15% during the same quarter ($P<0.01$). The recently approved

antiplatelet agents were adopted faster in male patients and in those aged younger than 55 years (Appendix B, available in online article).

The average proportion of patients with a STEMI diagnosis was higher in those using prasugrel or ticagrelor than the percentage in the clonidogrel group (57.1% vs. 50.5%, $P<0.01$). When clonidogrel users were compared with third-generation agents, the proportions of patients having a history of a cardiovascular disorder, including MI (9.1% vs. 8.2%), ischemic stroke (1.7% vs. 0.7%), intracerebrovascular bleedings (0.16% vs. 0.07%), and extracerebrovascular bleedings (7.0% vs. 5.5%), were significantly ($P<0.05$) higher in patients treated with clonidogrel. Also, patients using newer agents were younger than the clonidogrel patients, with average ages of 56.3 years and 61.0 years, respectively ($P<0.001$; see Appendix A for more detail).

From the logistic regression approach, being male and having STEMI were associated with a higher likelihood of using a third-generation agent, with adjusted odds ratios (OR) of 1.32 (95% CI=1.26-1.39) and 1.28 (95% CI=1.23-1.32), respectively. Risk factors for further cardiovascular events, including age over 54 years (OR=0.86, 95% CI=0.83-0.90) and 64 years (OR=0.39, 95% CI=0.37-0.42); congestive heart failure

TABLE 1 Factors Associated with Use of Third-Generation Antiplatelet Agents and Associated with Use of Ticagrelor

Patient Factors	Third-Generation Agents vs. Clopidogrel OR (95% CI)	Ticagrelor vs. Prasugrel OR (95% CI)
Male	1.32 (1.26-1.39)	0.76 (0.68-0.85)
Age (years): 55-64 vs. <55	0.86 (0.83-0.90)	1.03 (0.92-1.15)
Age (years): ≥65 vs. <55	0.39 (0.37-0.42)	1.55 (1.35-1.77)
STEMI vs. NSTEMI-ACS	1.28 (1.23-1.32)	—
Cardiac disorder: CHF	0.89 (0.84-0.94)	—
Cardiac disorder: underlying MI	0.89 (0.84-0.96)	—
Risk of bleeding: ECH	0.86 (0.79-0.93)	—
Risk of bleeding: ICH	0.51 (0.27-0.95)	7.23 (1.44-36.26)
Cerebrovascular event: ischemic stroke	0.47 (0.38-0.57)	1.70 (1.03-2.79)
Cerebrovascular event: TIA	0.76 (0.60-0.96)	—
Renal disorders	0.74 (0.68-0.82)	—
Substance abuse	0.87 (0.83-0.91)	0.84 (0.75-0.95)
Pulmonary disorder	0.86 (0.81-0.91)	—
Chronic liver disorders	0.89 (0.78-1.00)	—
Diabetes	1.05 (1.00-1.09)	—
Hemi or paraplegia	0.69 (0.45-1.06)	—
Dyslipidemia	1.07 (1.03-1.12)	0.90 (0.81-0.99)
Dementia	0.46 (0.28-0.76)	2.78 (0.87-8.91)
Cancer	0.84 (0.77-0.93)	—
Health plan: HMO vs. PPO	0.83 (0.78-0.88)	—
Health plan: comprehensive vs. PPO	0.98 (0.91-1.05)	—
Health plan: other vs. PPO	0.99 (0.94-1.04)	—

CHF=congestive heart failure; CI=confidence interval; ECH=extra cerebrovascular hemorrhage; HMO=health maintenance organization; ICH=intracerebrovascular hemorrhage; MI=myocardial infarction; NSTEMI-ACS=non-ST-segment elevation acute coronary syndrome; OR=odds ratio; PPO=preferred provider organization; STEMI=ST-segment elevation myocardial infarction; TIA=transient ischemic attack.

(OR=0.89, 95% CI=0.84-0.94); history of MI (OR=0.89, 95% CI=0.84-0.96); extra- and intracerebral bleedings (OR=0.86, 95% CI=0.79-0.93 and OR=0.51, 95% CI=0.27-0.95); and ischemic cerebrovascular events such as stroke and TIA (OR=0.47, 95% CI=0.38-0.57 and OR=0.76, 95% CI=0.60-0.96), were also associated with less use of third-generation agents. However, diabetes (OR=1.05, 95% CI=1.00-1.09) and dyslipidemia (OR=1.07, 95% CI=1.03-1.12) were positively related to the use of third-generation agents. When restricting the analysis to use of a third-generation drug, male gender (OR=0.76, 95% CI=0.68-0.85) was associated with less use of ticagrelor. On the other hand, underlying risk factors for cardiovascular complications, including ischemic stroke (OR=1.70, 95% CI=1.03-2.79); cerebrovascular hemorrhage (OR=7.23, 95% CI=1.44-36.26); and age older than 64 years (OR=1.55, 95% CI=1.35-1.77), were associated with greater use of ticagrelor (Table 1).

The analysis identified a sizable number of subjects using the newer antiplatelet agents with a history of conditions in which use of those agents are recommended to be avoided. Of the 13,609 subjects starting prasugrel, 268 (1.97%) were aged ≥75 years. Of those, 167 (1.77% of the prasugrel patients) did not report a diagnosis of MI or diabetes over the baseline assessment period. The number of patients having a history of ischemic stroke or TIA were 1,643, and 146 of those received prasugrel, which was also not a recommended use of the drug. With regard to the risk of bleeding, 12 of the prasugrel or ticagrelor users had a previous history of cerebrovascular hemorrhage.

Discussion

This study described broad trends of early antiplatelet agent use among commercially insured patients following PCI. While clopidogrel was used by the majority of the patients across the entire study period, an increase in the initiation of ticagrelor corresponded to a decrease in the use of prasugrel, resulting in the total percentage of patients starting the newer agents remaining constant. The results suggest a maximum loss of the clopidogrel market share beyond which the third-generation agents could not gain more.

Safety profiles of the novel agents that have to be considered potentially explain the use of clopidogrel by the majority of the ACS-PCI patients. Clinical trials demonstrated that prasugrel and ticagrelor are more effective than clopidogrel in the reduction of the composite of MI, stroke, and cardiovascular death over the 12- to 15-month period after the onset of ACS.^{13,30} However, the key safety endpoint, major bleeding, of the study assessing the outcomes of prasugrel significantly favored clopidogrel.¹³ Although statistically insignificant, an increase in bleeding was also observed in the trials for ticagrelor versus clopidogrel.³⁰ Potentially being associated with these risk-benefit profiles, guidelines added prasugrel and ticagrelor as an alternative to clopidogrel, but there was not an endorsement on one specific drug over the other.^{3,5,13,17,30} When this clinical evidence is taken into account, the adverse event profiles with the limited experience in the use of those newer agents likely outweighed the efficacy profiles in influencing clinical decisions.

Recent evaluations demonstrated that prasugrel and ticagrelor achieved an incremental cost per quality-adjusted life-years gain of less than \$100,000, and a genotype-guided therapy enabled the inclusion of the 2 new agents to be more cost-effective.³¹⁻³³ However, whether the high cost of the newer agents is offset by better clinical outcomes has been underinvestigated in real-world populations. In this regard, the national average drug acquisition costs show that the acquisition cost of generic clopidogrel 75 mg tablets was as low as \$0.08 per day, which was more than 100 times less than the daily cost of ticagrelor or prasugrel.³⁴ Similarly, the cost of clopidogrel in previous economic evaluations was also 45 to 70 times lower than that of the newer agents.^{16,33} Whether this high medication cost is a

barrier that cannot be paid off by better effectiveness needs to be investigated further.

Of the patients using a third-generation agent, ticagrelor gradually replaced prasugrel and reached 47% of the total third-generation antiplatelet agent use in December 2013. With the replacement of prasugrel with ticagrelor, contraindications in the use of prasugrel, such as older age and cerebrovascular events, acted as determinants. However, patients aged ≥ 75 years were 11% of the total ticagrelor use, and those patients with a history of ischemic stroke or TIA accounted for only 2% of the total ticagrelor initiators, meaning that the replacement was not limited to conditions in which prasugrel was recommended to be avoided. Interestingly, running counter to these trends, studies using a hospital charge data master found that resource use over 30 to 90 days after ACS discharge decreased more with prasugrel, not ticagrelor.^{35,36} Whether drug use in the near future will echo the observational studies is another area for investigation.

Our research provides multiple stakeholders with useful information. For the parts of the pharmaceutical industry with interest in ACS care, this research provides general insight into how new agents permeated the U.S. antiplatelet agent market and what conditions were considered in antiplatelet agent selection. In addition to previous drug use studies, this analysis included the newest oral antiplatelet agents and covered an extended period during which multiple options competed with each other.^{10,20} The observed drug initiation pattern suggests a need for further study regarding factors that encouraged the use of clopidogrel.

Limitations

Any interpretation of the results of this analysis should take into account substantial limitations. First, the low price of the generic version of clopidogrel and other marketing strategies likely influenced treatment patterns, but these business-related aspects were beyond the scope of this analysis. Nevertheless, describing contemporary practice helps health care providers understand how use of the novel agents has changed and what patient factors played a key role in the selection of antiplatelet agents. Second, the data covered only a commercially insured population. Therefore, the results may not be generalizable to underinsured groups. However, considering that our results were quite similar to the longitudinal trends identified in the National Cardiovascular Data Registry from 2009 to 2012, it is likely that drug use in the general U.S. population did not largely differ from what this study demonstrated.²⁰ Finally, general disadvantages in the use of an administrative database, such as miscoded diagnoses or omitted information in filing claims could not be excluded from the analysis. For example, the specific diagnosis of ACS was determined on the basis of the ICD-9-CM algorithm that has been employed in multiple studies.³⁶⁻³⁸ However, there remains concern regarding the validity of this coding because insurance claims are designed

for reimbursement purpose. Further, the data did not include full information regarding procedures provided during the index ACS-PCI admission, so some factors related to drug selection may not have been identified.

Conclusions

For PCI-treated ACS patients, especially those with a baseline risk of ACS complications, clopidogrel continued to be the most commonly used antiplatelet agent as of 2013. The uptake of ticagrelor in 2012 and 2013 encroached on about half of the prasugrel share. This replacement was associated with, but not limited to, patients having a history of cerebrovascular events. Use of the 3 antiplatelet agents did not fully correspond to the package labels and guideline recommendations, suggesting that future research should examine recommended use versus actual clinical practice.

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DISCLOSURES

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Study concept and design were contributed by Kim, Lee, Touchette, and Walton, with assistance from DiDomenico and Ardati. Kim and Lee collected the data, and data interpretation was performed by Lee, DiDomenico, and Ardati, along with Kim and Walton and assisted by Touchette. The manuscript was written by Kim and Walton, with assistance from the other authors, and revised by Kim, Walton, and Lee, with assistance from the other authors.

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APPENDIX A Prevalence of Baseline Characteristics in the 3 Antiplatelet Agent User Groups

	July 2009-June 2011			July 2011-December 2013				
	Prasugrel n = 4,482	Clopidogrel n = 25,945	P Value ^b	Ticagrelor n = 2,525	Prasugrel n = 9,127	P Value ^c	Clopidogrel n = 24,256	P Value ^b
Male	80.39	72.48	<0.01	74.73	80.15	<0.01	71.13	<0.01
Age, mean (± SD)	55.58 (± 8.78)	60.32 (± 12.03)	<0.01	58.81 (± 11.15)	56.03 (± 9.05)	<0.01	61.81 (± 12.36)	<0.01
Age group, years			<0.01			<0.01		<0.01
≤ 65	13.88	30.54		25.66	15.91		35.81	
55-64	45.76	38.38		39.88	44.01		36.60	
<55	40.36	31.08		34.46	40.08		27.59	
STEMI	59.48	52.85	<0.01	54.81	56.54	0.12	47.85	<0.01
CHF	13.32	15.70	<0.01	16.16	13.98	0.01	19.00	<0.01
Underlying MI	7.83	9.40	<0.01	8.24	8.37	0.83	0.24	<0.01
Ischemic stroke	0.54	1.61	<0.01	1.27	0.59	<0.01	2.05	<0.01
TIA	0.47	0.99	<0.01	0.83	0.51	0.06	1.13	<0.01
ICH	0.04	0.11	0.11 ^d	0.28	0.03	<0.01 ^d	0.25	<0.01
ECH	6.02	7.35	<0.01	5.47	5.37	0.85	7.63	<0.01
Para or hemiplegia	0.09	0.26	0.03	0.32	0.18	0.17	0.38	0.01
Diabetes	23.38	24.08	<0.01	25.11	25.61	0.61	27.28	<0.01
Diabetes w/complication	3.15	3.90	0.01	4.36	4.09	0.55	5.66	<0.01
Hypertension	54.40	56.10	0.03	60.40	58.83	0.16	62.53	<0.01
Dyslipidemia	58.39	54.02	<0.01	58.85	61.43	0.02	59.65	0.03
Pulmonary disorder	11.40	14.03	<0.01	12.71	10.77	0.01	16.08	<0.01
Liver disorder	2.16	2.13	<0.01	2.10	2.44	0.31	2.88	0.01
Renal disorder	2.59	4.92	<0.01	5.11	3.71	<0.01	7.15	<0.01
Rheumatic disease	1.07	2.02	0.15	2.14	1.97	0.60	2.37	0.03
Dementia	0.04	0.30	<0.01	0.32	0.09	0.01 ^d	0.52	<0.01
HIV	0.31	0.24	0.39	0.32	0.38	0.63	0.31	0.32
Cancer ^a	2.79	5.45	<0.01	5.43	3.96	<0.01	6.34	<0.01
Substance abuse	22.96	21.21	<0.01	20.44	25.38	<0.01	22.64	<0.01
Health plan			<0.01			<0.01		<0.01
PPO	58.05	52.14		58.93	60.20		55.19	
HMO	11.76	14.57		10.26	10.73		12.79	
Comprehensive	8.72	14.63		12.36	9.05		16.09	
Other	21.46	18.67		18.46	20.03		15.93	
Region			<0.01			<0.01		<0.01
Northeast	16.31	18.01		20.63	17.33		19.69	
North-Central	29.12	31.80		25.50	25.63		28.85	
South	39.67	33.89		40.71	39.16		33.12	
West	13.59	15.07		11.41	15.88		16.88	
Other	1.32	1.23		1.74	2.01		1.46	

Note: Results are presented in percentage points (%) unless otherwise specified.

^aCancer includes lymphoma and malignant solid tumor.

^bP value for the comparison between third-generation agents and clopidogrel.

^cP value for the comparison between ticagrelor and prasugrel.

^dResults from Fisher's exact test.

CHF = congestive heart failure; ECH = extracerebrovascular hemorrhage; HIV = human immunodeficiency virus infection; HMO = health maintenance organization; ICH = intracerebrovascular hemorrhage; MI = myocardial infarction; PPO = preferred provider organization; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

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APPENDIX B Adoption of New Antiplatelet Agents in Subgroups: Quarterly Segmented Statistics

A. Trends by ACS Diagnosis Category

Note: Left columns: STEMI; right columns: NSTE-ACS.

B. Trends by Age Group

Note: From left to right in each quarter: age <55 years, 55-64 years, and 65 years.

C. Trends by Gender

Note: Left columns: male; right columns: female.

D. Trends by Health Plan

Note: From left to right in each quarter: HMO, comprehensive, PPO, and other health plans.

■ Clonidogrel ■ Prasugrel ■ Ticagrelor

ACS=acute coronary syndrome; HMO=health maintenance organization; NSTE=non-ST-segment elevation; PPO=preferrred provider organization; Q=quarter; STEMI=ST-segment elevation myocardial infarction.