Title.

Contemporary Trends in Oral Anti-Platelet Agent Use in Patients Treated with Percutaneous Coronary Intervention for Acute Coronary Syndrome

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Main Text: 2497

1 Table and 1 Figures

Supplement has 1 table and 1 figure
Abstract

Background:
Recent trials demonstrated the efficacy of prasugrel and ticagrelor compared to clopidogrel in the reduction of cardiovascular complications in patients with acute coronary syndrome (ACS). However, it is unclear how utilization of the three anti-platelet medications has changed in commercially insured patients since the advent of the new agents.

Objective:
The primary aim of this study was to describe the adoption of prasugrel and ticagrelor in patients who received percutaneous coronary intervention (PCI) for the onset of ACS. We also explored patient factors associated with the selection of the drug to provide insight into utilization patterns of the anti-platelet agents.

Methods:
Patients who received a new dispensing of an anti-platelet 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 prior to the ACS event. Longitudinal trends in anti-platelet 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 medication, as well as with the selection between ticagrelor and prasugrel were identified.

Results:
The analysis included a total of 66,335 subjects. The use of clopidogrel decreased from 100% to roughly 65% of total anti-platelet 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% to 18% by December 2013. The use of new agents as opposed to use of clopidogrel was associated with younger age (<65), 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.

**Conclusion:**

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 anti-platelet agents is warranted.

**What is already known about this subject:**

Prasugrel and ticagrelor reduced cardiovascular complications in patients with acute coronary syndrome. Among patients receiving anti-platelet agents in the 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-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 three anti-platelet agents. Clinical practice preferred clopidogrel to the newer agents even in patients having risk factors of further MI or other complications. A sizable number of patients using the newer anti-platelet agents had a history of labeled conditions with increased risk of cardiovascular complications in which use of those agents are recommended to be avoided.
Background

Acute Coronary Syndrome (ACS) imposes a major burden on the US healthcare 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.\(^3\)\(^-\)\(^5\) Further, across the wide spectrum of ACS care options, the use of anti-platelet therapy along with aspirin administration, referred to as dual anti-platelet therapy (DAPT), is a key recommendation in the prevention of the secondary events.\(^3\)\(^,\)\(^5\)

Anti-platelet management in ACS care has progressed substantially over the last two decades. In 1997, the Food and Drug Administration (FDA) approved clopidogrel for the secondary prevention of cardiovascular events, and it experienced continuous growth in utilization.\(^6\)\(^-\)\(^10\) Recently, ACS care evolved with approvals of 3rd-generation oral anti-platelet therapies including 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, both prasugrel and ticagrelor reduced the risk of the composite endpoint of myocardial infarction, stroke, and cardiovascular death compared to clopidogrel.\(^13\)\(^,\)\(^14\) Further, using prasugrel or ticagrelor was cost-effective in comparison to 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 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). However, because ticagrelor was not included in this study, it is unclear how the availability of the third agent impacted the choice of anti-platelet agents. In addition, the results from the National Cardiovascular 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 our analysis was to describe trends in the use of three oral anti-platelet 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 Database include de-identified patient level medical and pharmacy claims for around 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 one of the oral anti-platelet agents for post ACS-PCI care. Patients who were discharged from a hospitalization with a primary diagnosis of ACS (ICD-9-CM: 410.xx [except 410.x2], 411.1x, and 411.8x) between July 2009 and December 2013 were identified, and their PCI procedures during the hospitalization were determined using ICD-9 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 also excluded patients who received two or more different anti-platelet agents during the 14-day assessment period. To focus on new users, we excluded patients who had received any anti-platelet medication during the 6-month prior to the ACS-PCI admission. Over the same baseline period, medical history that potentially influenced the selection of an anti-platelet agent were collected using ICD-9-CM codes. For example, a past diagnosis of cerebrovascular encounter needs to be assessed before determining the medication strategy. Underlying myocardial infarction and other key comorbidities were also collected using a known coding algorithm for defining Charlson Comorbidities.
Statistical Approach

We used descriptive statistics segmented by calendar time to summarize the use of the three medications. The primary variable used in describing trends in new medication adoption was the monthly number and proportion of patients who newly initiated one of the oral anti-platelet agents. In addition to the proportions, the 95% confidence intervals of the changes in the proportion were projected using a standard bootstrap re-sampling percentile approach with one thousand replicates.

In order to provide additional insight into the use of these drugs, differences in patient characteristics across the three drug groups were compared. Age distributions were compared between clopidogrel and 3rd-generation agent patients with a Student t-test, and compared across the three groups using ANOVA. Categorical variables were summarized using percentiles and $\chi^2$ tests. Using frequency statistics, we also looked at the drug use 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.\textsuperscript{11,12}

Predictors in the selection between 3rd-generation agents vs. clopidogrel, and between ticagrelor vs. prasugrel were examined using logistic regression model adjusted for the semi-annually 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 anti-platelet agent initiations over the 4.5 year period were identified. Of them, 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%
and 7% of the overall cohort were clopidogrel, prasugrel and ticagrelor initiators, respectively.
(Supplement)

After prasugrel was approved, the proportion of prasugrel users increased by an average of one
percentage point per month through March 2012 when the proportion plateaued. A decrease in the
proportion of clopidogrel initiator had continued up to this point, but the proportion of clopidogrel 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 anti-platelet agent use at the end of
2013, which coincided with a decline in the proportion of prasugrel use. The bootstrapped confidence
intervals of prasugrel and ticagrelor uses overlapped each other after October of 2013, but those intervals
did not overlap with the range of the clopidogrel use. (Figure 1) When the trends were stratified by
diagnosis, proportions of the new agent 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 to
non-ST-segment elevation ACS patients who had respective proportions of 17% and 15% during the
same quarter. (p<0.01). The recently approved anti-platelet agents were adopted faster in male patients
and in those younger than 55 years old. (Supplement)

The average proportion of patients with a STEMI diagnosis was higher in those on prasugrel or
ticagrelor than the percentage in the clopidogrel group (57.1% vs. 50.5 %, p<0.01). When we compared
clopidogrel users to 3rd-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%), intra- (0.16% vs. 0.07%) and
extra-cerebrovascular bleedings (7.0% vs. 5.5%) were significantly (p<0.05) higher in patients treated
with clopidogrel. Also, the patients on newer agents were younger than the clopidogrel patients, with
average ages of 56.3 and 61.0 respectively (p<0.01). (Supplement)

From the logistic regression approach, being male and having STEMI were associated with a
higher likelihood of use of a 3rd-generation agent, with adjusted odds ratios (OR) of 1.32 [95% CI: 1.26 –
1.39] and 1.28 [1.23 – 1.32], respectively. Risk factors for further cardiovascular events including age over 54 years (OR = 0.86 [0.83 – 0.90]) and 64 years (OR = 0.39 [0.37 – 0.42]), CHF (0.89 [0.84 – 0.94]), history of MI (0.89 [0.84 – 0.96]), extra- and intra- cerebral bleedings (0.86 [0.79 – 0.93] and 0.51 [0.27 – 0.95]), and ischemic cerebrovascular events such as stroke and TIA (0.47 [0.38 – 0.57] and 0.76 [0.60 – 0.96]) were also associated with less use of 3rd-generation agents. However, diabetes (1.05 [1.00 – 1.09]) and dyslipidemia (1.07 [1.03 – 1.12]) were positively related to the use of 3rd-generation agents. When restricting the analysis to use of a 3rd-generation drug, male gender (0.76 [0.68 – 0.85]) was associated with less use of ticagrelor. On the other hand, underlying risk factors for a cardiovascular complications including ischemic stroke (1.70 [1.03 – 2.79]), cerebrovascular hemorrhage (7.23 [1.44 – 36.26]) and age older than 64 (1.55 [1.35 – 1.77]) were associated with greater use of ticagrelor. (Table 1)

The analysis identified a sizable number using the newer anti-platelet 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 equal to or greater 75 years old. Of them, 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 them received prasugrel, which was also not a recommended use of the drug. With regard to the risk of bleeding, a total of 12 of the prasugrel or ticagrelor users had a prior history of a cerebrovascular hemorrhage.

Discussion

This study describes broad trends of early anti-platelet agent use among commercially insured patients following PCI. While clopidogrel was used in 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 3rd-generation agents could not gain more.
Safety profiles of the novel agents that have to be considered potentially explain the use of clopidogrel in the majority of the ACS-PCI patients. Clinical trials demonstrated that both prasugrel and ticagrelor are more effective than clopidogrel in the reduction of the composite of MI, stroke and cardiovascular death over 12 to 15 month period after the onset of ACS.\textsuperscript{13,30} However, the key safety endpoint, major bleeding, of the study assessing the outcomes of prasugrel significantly favored clopidogrel.\textsuperscript{13} Although statistically insignificant, an increase in the bleeding encounter was also observed in the trials for ticagrelor vs. clopidogrel.\textsuperscript{30} Potentially being associated with these risk-benefit profiles, guidelines added prasugrel and ticagrelor as an alternative to the clopidogrel, but there was not an endorsement on one specific drug over the other.\textsuperscript{3,5,13,17,30} When we take these clinical evidence 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 two new agents to be more cost-effective.\textsuperscript{31-33} However, whether the high cost of the newer agents offset by better clinical outcomes has been under-investigated in real-world populations. Regarding this, the National Average Drug Acquisition Costs shows that the acquisition cost of generic clopidogrel 75mg tablet was as low as $0.08 per day which was more than 100 times less than the daily cost of ticagrelor or prasugrel.\textsuperscript{34} Similarly, the cost of clopidogrel in previous economic evaluations was also 45 to 70 times lower than that of the newer agents.\textsuperscript{16,33} Whether this high cost of medication was a barrier which cannot be paid off by the better effectiveness needs to be investigated further.

Of the patients using a 3\textsuperscript{rd}-generation agent, ticagrelor gradually replaced prasugrel share and reached 47\% of the total 3\textsuperscript{rd}-generation anti-platelet agent use in December 2013. In the replacement of prasugrel with ticagrelor, contraindications in the use of prasugrel such as older age and cerebrovascular events acted as determinants. However, patients with age $\geq$ 75 were 11\% of the total ticagrelor use, and those who have a history of ischemic stroke or TIA accounted for only 2\% of the total ticagrelor
Main Text

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 utilization over 30 to 90-day post ACS discharge decreased more with prasugrel, not ticagrelor.\textsuperscript{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, the research provides general insight into how new agents permeated through the US anti-platelet agent market and what conditions were considered in anti-platelet agent selection. In addition to previous drug use studies, the analyses included the newest oral anti-platelet agents and covered an extended period during which multiple options competed with each other.\textsuperscript{10,20} The observed story suggests a need for further study regarding factors that encouraged the use of clopidogrel.

Any interpretation of the results should take into account substantial limitations. First, the low price of the generic version of clopidogrel and other marketing strategies were likely to influence the treatment patterns, but these business related aspects were beyond the scope of the current analysis. Nevertheless, describing contemporary practice helps healthcare providers understand how utilization of the novel agents has changed and what patient factors play a key role in the selection of anti-platelet agents. Second, the data solely covered the 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 from the National Cardiovascular Data Registry from 2009 to 2012, it is likely that drug use in the general US population did not largely differ from what our study demonstrated.\textsuperscript{20} Lastly, 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, we determined the specific diagnosis of ACS on the basis of the ICD-9-CM algorithm that has been employed in multiple studies already.\textsuperscript{36-38} However, there remains concern regarding the validity of the
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.

**Conclusion**

In the PCI treated ACS patients, especially in those with a baseline risk of ACS complications, clopidogrel continued to be the most commonly used anti-platelet agent by 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 a cerebrovascular event. Use of the three anti-platelet agents did not fully correspond to the package labels and guideline recommendations, suggesting that future research should examine recommended use versus actual clinical practice.
End Note

References


11. EFFIENT [Package Insert]. Eli Lilly and Company, Indianapolis, IN; Revised: July 2015.


End Note


End Note


38. Simeone JC, Molife C, Marrett E, et al. One-year post-discharge resource utilization and treatment patterns of patients with acute coronary syndrome managed with percutaneous
Figure 1. Proportion of each incident anti-platelet agent user and bootstrap 95% confidence interval. Monthly segmentation

Table 1. Factors associated with the use of 3rd-generation antiplatelet agents (vs. clopidogrel) and associated with the use of ticagrelor (vs. Prasugrel)

Abbreviation: CHF, Congestive Heart Failure; CI, Confidence Interval; ECH, Extra Cerebrovascular hemorrhage; HMO, Health Maintenance Organization; ICH, Intra Cerebrovascular Hemorrhage; MI, Myocardial Infarction; NSTE-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
Figure 1.

Proportion of Each Incident Antiplatelet Agent User and Bootstrap 95% Confidence Interval

- Clopidogrel
- Prasugrel
- Ticagrelor
Table 1.

<table>
<thead>
<tr>
<th>Patient Factors</th>
<th>3rd gen. agents vs. Clopidogrel OR [95% CI]</th>
<th>Ticagrelor vs. Prasugrel OR [95% CI]</th>
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<tbody>
<tr>
<td>Male</td>
<td>1.32 [1.26 – 1.39]</td>
<td>0.76 [0.68 – 0.85]</td>
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<tr>
<td>Age: 55-64 vs. &lt;55</td>
<td>0.86 [0.83 – 0.90]</td>
<td>1.03 [0.92 – 1.15]</td>
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<tr>
<td>Age: ≥65 vs. &lt;55</td>
<td>0.39 [0.37 – 0.42]</td>
<td>1.55 [1.35 – 1.77]</td>
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<tr>
<td>STEMI vs. NSTE-ACS</td>
<td>1.28 [1.23 – 1.32]</td>
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<tr>
<td>Cardiac Disorder: CHF</td>
<td>0.89 [0.84 – 0.94]</td>
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<tr>
<td>Cardiac Disorder: Underlying MI</td>
<td>0.89 [0.84 – 0.96]</td>
<td>-</td>
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<tr>
<td>Risk of Bleeding: ECH</td>
<td>0.86 [0.79 – 0.93]</td>
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<tr>
<td>Risk of Bleeding: ICH</td>
<td>0.51 [0.27 – 0.95]</td>
<td>7.23 [1.44 – 36.26]</td>
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<td>Cerebrovascular event: Ischemic Stroke</td>
<td>0.47 [0.38 – 0.57]</td>
<td>1.70 [1.03 – 2.79]</td>
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<td>Cerebrovascular event: TIA</td>
<td>0.76 [0.60 – 0.96]</td>
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<td>Renal Disorders</td>
<td>0.74 [0.68 – 0.82]</td>
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<td>Substance abuse</td>
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Table 1. Prevalence of baseline characteristics in the three anti-platelet agent user groups.

Note: Results are presented in percent point (%) unless otherwise specified.

Symbol: a Cancer includes lymphoma and malignant solid tumor; b p-value for the comparison between 3rd generation agents and clopidogrel; c p-value for the comparison between ticagrelor and prasugrel; d Results from Fisher’s exact test

Abbreviation: CHF, Congestive Heart Failure; DM, Diabetes Mellitus; ECH, Extra Cerebrovascular hemorrhage; HIV, Human Immunodeficiency Virus infection; HMO, Health Maintenance Organization; ICH, Intra Cerebrovascular Hemorrhage; MI, Myocardial Infarction; PPO, Preferred Provider Organization; STEMI, ST-segment elevation Myocardial infarction; TIA, Transient Ischemic Attack

Figure 1. Adoption of new anti-platelet agents in sub-groups. Quarterly segmented statistics

Figure 1A. Trends by ACS diagnosis category.
Note: Left columns: STEMI; Right Columns: NSTE-ACS

Figure 1B. Trends by Age group
Note: From left to right in each quarter: Age<55, 55-64, and ≥65

Figure 1C. Trends by Gender
Note: Left columns: Male; Right columns: Female

Figure 1D. Trends by Health plan
Note: From left to right in each quarter: HMO, Comprehensive, PPO, and Other Health Plans
### Supplement – Table 1.

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Supplement – Table 1.

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Supplement – Figure 1.

**Figure 1A.**

**Note**

**Figure 1C.**

**Note**

**Figure 1B.**

**Note**

**Figure 1D.**

**Note**