Prudent Formulary Management or Underutilization of the Novel P2Y12 Receptor Inhibitors in Patients with Acute Coronary Syndrome Who Received Percutaneous Coronary Intervention?

In the article “Contemporary Trends in Oral Antiplatelet Agent Use in Patients Treated with Percutaneous Coronary Intervention for Acute Coronary Syndrome,” published in the January 2017 issue of this journal, Kim et al. presented data on the adoption of prasugrel and ticagrelor in patients who received percutaneous coronary intervention for acute coronary syndrome (ACS) and the patient factors associated with the selection of the novel P2Y12 versus clopidogrel.¹ From the approval of prasugrel until the approval of ticagrelor, there was a slow uptake of prasugrel to approximately one third of P2Y12 use, at which point the erosion of clopidogrel use seemed to have leveled off. The introduction of ticagrelor did not result in further erosion of clopidogrel use. During the next couple of years, ticagrelor gained an almost 50% share of the novel P2Y12 use by the end of 2013.

In this study, Kim et al. showed that the use of new agents, as opposed to the use of clopidogrel, was associated with younger age (<65 years), male gender, and a diagnosis of ST-elevation myocardial infarction. The study also showed that the odds of using ticagrelor over prasugrel increased with older age and history of a cerebrovascular event. Although these differences were statistically significant, the table in Appendix A shows a lack of any clear patient factors associated with the choice of the P2Y12 inhibitor. This lack could indicate that it is physician preference, plan design, or affordability rather than the safety and efficacy profiles that influence the choice of P2Y12 antiplatelet therapy. As mentioned in the article, in clinical trials, prasugrel and ticagrelor have been shown to be more effective than clopidogrel in the reduction of the composite of myocardial infarction, stroke, and cardiovascular death over the 12- to 15-month period after the onset of ACS, albeit at the expense of some increased bleeding.

A key question must be whether the continued use of clopidogrel in approximately two thirds of the patients represents prudent formulary management or underutilization of the potentially more effective novel therapies. Studies from Sweden, Greece, and Israel have reported a much larger drop in clopidogrel use following the approval of the novel agents (see Table).²⁻⁴ The studies from Israel and Greece reported 1-year outcomes and showed that the death rate was lower for the novel agents versus clopidogrel with no statistical difference between the novel agents (Greece 6.2% vs. 2.9%, hazards ratio [HR]=0.46, 95% confidence interval [CI]=0.30-0.71; Israel 8.4% vs. 3.0%, $P<0.0001$). A recently published Swedish study showed a 24-month cumulative probability of death of 5.8%

TABLE Choice of P2Y12 Inhibitors in Patients Who Have Been Treated with PCI for ACS in Sweden, Greece, and Israel in 2013

Country (Inclusion Period)	Clopidogrel (%)	Prasugrel (%)	Ticagrelor (%)
Sweden (January-November 2013)	39	1	60
Greece (January 2012-August 2013)	47	18	35
Israel (March and April 2013)	35	43	22

PCI=percutaneous coronary intervention.

with ticagrelor and 12.9% with clopidogrel (adjusted HR=0.83, 95% CI=0.75-0.92).⁵

If the real-world effectiveness reported from European countries can be replicated in the U.S. setting, it would imply that the novel P2Y12 receptor inhibitors are underutilized in the United States.

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DISCLOSURES

The author is a former employee of AstraZeneca and owns stock in AstraZeneca. The author reports no conflicts of interest related to the subject of this letter.

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The Authors Respond

The letter by Dr. Ole Hauch regarding our article “Contemporary Trends in Oral Antiplatelet Agent Use in Patients Treated with Percutaneous Coronary Intervention for Acute Coronary Syndrome” provides thoughtful insight into the contemporary use of oral antiplatelet agents in patients who received percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS). As supported by other studies conducted in the United States and other countries, an increase in the use of ticagrelor among ACS-PCI patients has been universally observed, although the rates of replacement across countries has varied. In interpreting these utilization differences, characteristics of the underlying datasets, as well as the health care systems examined in each study, have to be carefully considered. For example, centrally regulated insurance systems such as those in Greece and Sweden use direct price controls, international price comparisons, and value-based administration, which may encourage the use of efficacious but costly medications.^{1,2} Conversely, lump sum medication cost reimbursement would be considered as a potential control for prescription drug use in a commercially insured U.S. population, likely furthering acceptance of ticagrelor in comparison with Europe.

Our trend analysis comes with limitations in terms of characterizing factors in the selection of oral antiplatelet agents. Nonetheless, the results illustrate that recent use of antiplatelet medication generally corresponds to guideline and package insert recommendations. For example, prasugrel appears to be relatively discouraged in older patients and in patients with a history of stroke, transient ischemic stroke, or intracranial hemorrhage. Further, the 3 studies cited in Dr. Hauch’s letter found that the prevalence of ST-segment elevation was higher in patients prescribed either prasugrel or ticagrelor rather than clopidogrel, which is generally consistent with our results. That said, we also observed contraindicated uses. Moreover, as the letter pointed out, prescriber preferences and factors other than clinical characteristics have to be considered. Because of the inherent limitations of retrospective analyses using an administrative claims database, the influence of prescriber preferences and plan design on the use of cardiovascular medication remain relevant areas for future research.

Dr. Hauch’s letter affirms that our results suggest that a real-world effectiveness study would be valuable in understanding the use of oral antiplatelet agents in ACS patients treated with PCI. With respect to real-world outcomes associated with the 3 oral antiplatelet agents, while there have been several retrospective cohort analyses, the outcomes associated with the 3 agents have not been comprehensively covered, and there is no conclusive recommendation.^{3,4} To help fill this void, our research team is following up with studies based on comparative

TABLE

Preliminary Data Analyses: Comparative Resource Utilization of 3 Oral P2Y₁₂ Antagonists over a 6-Month Period After ACS-PCI Discharge

	Third-Generation Agents vs. Clopidogrel	Ticagrelor vs. Prasugrel
Risk ratio, all-cause admissions	0.89 (0.78; 0.92)	1.02 (0.83; 1.19)
Risk ratio, all-cause office visits	0.99 (0.87; 1.03)	1.03 (0.87; 1.22)

effectiveness and health care resource utilization. Preliminary analyses, similar to the results from the pivotal randomized trials, have concluded that the use of third-generation antiplatelet agents, relative to clopidogrel, was associated with a decrease in the hazard rate of all-cause hospital admissions. In addition, patients who had initiated clopidogrel were associated with more hospital admissions, compared with those patients who were prescribed the newer agents, suggesting that there may be a meaningful cost offset to the higher price of ticagrelor or prasugrel (see Table). Whether these differences in prescription use in a commercially insured U.S. population, as compared with other countries, indicate underutilization of the newer agents will be further assessed in future studies.

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