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Editorial

The Use Pattern and Clinical Impact of Novel P2Y12 Receptor Antagonists for Acute Myocardial Infarction in Korea

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Dual antiplatelet treatment (DAPT) with aspirin and a P2Y12 receptor antagonist is essential for patients presenting with acute coronary syndrome (ACS) irrespective of their specific percutaneous coronary intervention (PCI). Clopidogrel (Bristol-Myers Squibb/Sanofi Pharmaceuticals, Bridgewater, NJ, USA), one of the most popular P2Y12 receptor antagonists of the past decade, has reduced the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with ACS by 20–30% when added to aspirin.[1] However, it has some limitations, including modest inhibition of platelet activity, delayed onset and offset of action, and inter-individual variability of pharmacodynamic responses. To overcome these drawbacks, 2 novel P2Y12 receptor antagonists, prasugrel (Eli Lilly and Company, Indianapolis, IN, USA) and ticagrelor (AstraZeneca Pharmaceuticals LP, Wilmington, DE, USA), have been developed and have demonstrated promising results. The TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with Prasugrel Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) trial found that prasugrel could reduce the composite risk of CV death, MI, or stroke in moderate-to-high-risk ACS patients undergoing PCI by 19% at the cost of higher risk of bleeding, including life-threatening hemorrhage, compared with clopidogrel.[2] Unfortunately, the use of prasugrel did not decrease CV death or overall mortality and has limitations of use in specific groups, such as elderly people (>75 years of age), patients with prior history of stroke, those with low body weight (<60 kg), or patients not concurrently receiving PCI. Ticagrelor has also shown to decrease the composite risk of CV death, MI, or stroke by 16% and the risk of CV death by 21% in ACS patients, irrespective of treatment strategy, compared with clopidogrel.[3] Despite increases in both major and minor bleeding, ticagrelor did not lead to any increase in fatal bleeding. With the advent of these novel P2Y12 receptor antagonists, the combination of aspirin and prasugrel or ticagrelor instead of clopidogrel as a DAPT has been increasingly used. Contemporary guidelines recommend the use of prasugrel or ticagrelor in the setting of acute myocardial infarction (AMI).[4] A few epidemiological studies from several countries have shown that the use of these novel P2Y12 receptor antagonists is rapidly increasing and has reduced the incidence of CV events or death in ACS patients compared with clopidogrel. A Danish nationwide population-based cohort study involving 28,449 patients demonstrated that the use of clopidogrel as a DAPT after AMI in 2009 had been reduced in favor of ticagrelor or prasugrel in 2012.[5] The Melbourne Interventional

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Group Registry in Australia also revealed that prasugrel and ticagrelor were increasingly being used in ACS patients treated with PCI from 2009–2013, especially in younger patients with fewer comorbidities.[6] The use of prasugrel increased early in that period but has since decreased with the introduction of ticagrelor. This pattern was also detected in Swedish national registries, which showed a rapid increase in the use of ticagrelor after its introduction in 2011.[7] Another nationwide population-based study that included 32,830 ACS patients in Austria demonstrated that prasugrel and ticagrelor were increasingly being used in ACS patients and were associated with lower risk of recurrence of ACS and death compared with clopidogrel.[8] In that study, the cumulative incidence rates of recurrence of ACS or death at 2 years were 18.7%, 8.7%, and 12.0% in patients receiving clopidogrel, prasugrel, or ticagrelor, respectively. These findings are consistent with the results of the GReek AntiPlatElet (GRAPE) Registry including 2,047 ACS patients treated with PCI in Greece, which revealed that the rate of 1-year major adverse cardiac event (MACE) was lower in prasugrel-treated patients (4.4%) than in clopidogrel-treated patients (10.1%) (hazard ratio [HR], 0.53; 95% confidence interval [CI], 0.30–0.91), although the results were not significantly different between the ticagrelor (6.8%) and clopidogrel groups (HR, 0.78; 95% CI, 0.54–1.12). The death rate was further reduced by these novel agents in comparison with clopidogrel (2.9% vs. 6.2%) along with an increased risk of bleeding (HR, 1.61; 95% CI, 1.33–1.95 with prasugrel; HR, 1.81; 95% CI, 1.55–2.10 with ticagrelor). In a direct comparison between prasugrel and ticagrelor, a real world United States study involving 16,098 ACS patients undergoing PCI reported that the rate of 30-day net adverse clinical events was 22% lower in prasugrel-treated than in ticagrelor-treated patients (risk ratio [RR], 0.78; 95% CI, 0.64–0.94). The 30-day adjusted MACE (RR, 0.80; 95% CI, 0.64–0.98) and major bleeding incidence (RR, 0.65; 95% CI, 0.45–0.95) rates were also lower in prasugrel-treated patients compared with ticagrelor-treated patients.[9]

Kim and colleagues[10] analyzed 40,706 AMI patients undergoing PCI between 2010 and 2015 using claim data from the Health Insurance Review and Assessment Service (HIRA) to evaluate the use pattern and clinical impact of novel P2Y12 receptor antagonists. They demonstrated that the use of the novel P2Y12 receptor antagonists, prasugrel and ticagrelor, had been rapidly increasing since 2013 and had surpassed clopidogrel as the preferred method of treatment in Korea since 2015. Despite similar levels of recommendations for prasugrel and ticagrelor by contemporary guidelines in AMI, the prescription rate of prasugrel has been gradually decreasing in Korea since 2013, which is in line with previous study results. At the same time, clopidogrel was more frequently prescribed in patients with longer hospital stays than prasugrel or ticagrelor. A previous study revealed that patients treated with clopidogrel were more likely to present with non-ST-elevation ACS, be older, and have more comorbidities. Therefore, it is reasonable to suggest that clopidogrel-treated patients might have more comorbidities or acute complications related to higher bleeding risks, which leads physicians to use clopidogrel more frequently than prasugrel or ticagrelor. Both prasugrel (odds ratio [OR], 0.45; 95% CI, 0.731–0.67; p<0.001) and ticagrelor (OR, 0.84; 95% CI, 0.71–0.98; p=0.032) had favorable effects on lowering the 30-day mortality in a weighted multivariable logistic regression model. However, there was no significant effect of these novel P2Y12 receptor antagonists on other clinical outcomes, including MI, stroke, bleeding, and hospital readmission, within 30 days. The strong point of this study is its study population. The use of the HIRA Korean database enabled an examination of the nationwide contemporary pattern of treatment for AMI patients in Korea. Although this study could not reveal the long-term effects of these novel P2Y12 receptor antagonists, it might suggest a trend for their use and short-term impacts on CV outcomes in Korean AMI patients.

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There are several limitations of the current study. First, the severity of disease at the time of the index AMI could not be evaluated. No severity indices, such as vital signs, left ventricular function, or cardiac biomarkers, and angiographic and procedural information (including the severity of diseased vessels and the number, size, and length of implanted coronary stents) were available. Second, the participants in this study were enrolled and analyzed using only diagnostic codes found in the HIRA database. Therefore, there is a chance that the analyses could have been inaccurate due to entry errors or omissions of diagnostic codes at the index hospitalization or during follow-up. For example, all cases with bleeding complications received the same particular diagnostic code regardless of clinical relevance. In addition, other adverse events that might have occurred during the index hospitalization might have been omitted. However, the implication of antiplatelet agents on the hard outcome like mortality might be more credible than that on other clinical events because mortality data have been independently recorded as they actually occurred, and all readmission events were contained in the database. Finally, information about other medications was unavailable to assess the optimization of the treatment for AMI.

In conclusion, there is a distinct tendency to use the novel P2Y12 receptor antagonist prasugrel or ticagrelor more frequently than clopidogrel in AMI patients undergoing PCI in Korea. In addition, the increasing use of these novel agents seems to be associated with a favorable effect on 30-day mortality. However, clopidogrel is still used frequently in AMI patients with longer hospital stays. Therefore, the selection of a specific P2Y12 receptor antagonist as a DAPT should be individualized, and further research must investigate whether one P2Y12 receptor antagonist is better or worse than the others in AMI patients with specific conditions, including comorbidities and a risk of bleeding.

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