

Newer P2Y₁₂ Inhibitors: How Does the Interventional Cardiologist Choose?

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Dual antiplatelet therapy remains the cornerstone of the medical management of patients with acute coronary syndrome (ACS). In ACS patients receiving a coronary stent, the combination of aspirin and a P2Y₁₂ inhibitor reduces rates of stent thrombosis and major adverse cardiovascular events. Given the well-known limitations of clopidogrel with variable antiplatelet effects and delayed onset of action, newer P2Y₁₂ inhibitors have been developed (Table). In randomized controlled clinical trials, prasugrel and ticagrelor reduce rates of major adverse cardiovascular events compared with clopidogrel, although both agents are associated with increased bleeding complications.^{1,2} Despite the clear benefits of these agents in randomized controlled clinical trials and meta-analyses, contemporary use in clinical practice appears to be low.³ Factors associated with the decision to select a particular P2Y₁₂ inhibitor for the management of patients with ACS are complex, multifactorial, and poorly described.

In this issue of the *Journal*, Vora et al studied 11 969 patients enrolled in the Treatment With ADP Receptor Inhibitors: Longitudinal Assessment of Treatment Patterns and Events After Acute Coronary Syndrome (TRANSLATE-ACS) study to explore how antiplatelet therapy is selected for patients with acute myocardial infarction (MI) undergoing percutaneous coronary intervention (PCI).⁴ TRANSLATE-ACS is a well-described contemporary registry of ACS patients treated at >200 hospitals throughout the United States.⁵ Prasugrel was used in 26% of patients, and those patients

tended to be younger, less likely female, and more likely to have private insurance than clopidogrel-treated patients. Factors associated with prasugrel use were cardiogenic shock, drug-eluting stent implantation, and presentation with an ST-segment elevation MI. To explore the relative importance of ischemia or mortality and bleeding when selecting a P2Y₁₂ inhibitor, patients were classified as having high or low Acute Coronary Treatment and Intervention Outcomes (ACTION) mortality and bleeding risk scores. The highest use of prasugrel was seen in patients with both a low bleeding score and a low mortality score. These findings suggest that physicians may perceive bleeding risk as a more important factor compared with ischemia or mortality risk when selecting a P2Y₁₂ inhibitor. The current study and others clearly show the difficulty that physicians face when weighing the benefits and risks of antiplatelet therapy. The benefits of enhanced antiplatelet therapy with a reduction in ischemic risk occur at the cost of increased bleeding events. The results of the current analysis apply only to patients with acute MI undergoing PCI. The selection of a specific P2Y₁₂ inhibitor in ACS patients receiving medical therapy alone without PCI is likely to be even more complex. The authors clearly outlined the limitations of the current analysis including the inability to account for unmeasured cofounders in this registry cohort, the lack of provider-reported rationales for P2Y₁₂ inhibitor selection, and the limited ability of the applied risk models to accurately assess mortality and bleeding risk. In addition, several other factors may be difficult and/or impossible to study and may also affect the selection of a particular P2Y₁₂ inhibitor. Participation in clinical trials evaluating new drugs often enhances a physician's ability to adopt newer agents into routine clinical practice following US Food and Drug Administration (FDA) approval. Although all hospitals participating in the TRANSLATE-ACS study were approved for inpatient prasugrel use, significant barriers often exist for long-term outpatient approval and receipt of prasugrel; physician knowledge of this difficulty could potentially discourage initial selection of this agent. Although a small number of patients initiated on >1 P2Y₁₂ inhibitor were excluded, and no information was provided for patients who switched between different P2Y₁₂

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Table. Comparison of P2Y₁₂ Inhibitors Currently Approved for Clinical Use

P2Y ₁₂ Receptor Inhibitor	Mechanism of Action	Time to Peak Activity	Loading Dose	Maintenance Dose, Route	Indications*
Clopidogrel	Thienopyridine that irreversibly inhibits the P2Y ₁₂ receptor	2–6 hours	300–600 mg [†]	75 mg daily, oral	ACS patients managed medically and those undergoing PCI; patients with STEMI; patients with recent MI, recent stroke, or established peripheral vascular disease
Prasugrel	Thienopyridine that irreversibly inhibits the P2Y ₁₂ receptor	30 minutes to 4 hours	60 mg	10 mg daily, [‡] oral	ACS patients undergoing PCI
Ticagrelor	Nonthienopyridine reversible direct-acting inhibitor of the ATP receptor P2Y ₁₂	30 minutes to 2 hours	180 mg	90 mg twice daily, oral	ACS patients managed medically and those undergoing PCI
Cangrelor	Nonthienopyridine ATP analogue that reversibly inhibits the P2Y ₁₂ receptor	2–30 minutes	None	4 µg/kg/min, intravenous infusion	Adjunct to PCI in patients who have not been treated with a P2Y ₁₂ inhibitor and who have not been given a glycoprotein IIb/IIIa inhibitor

ACS indicates acute coronary syndrome; ATP, adenosine triphosphate; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

*Indications based on the current U.S. Food and Drug Administration approval.

[†]Loading doses up to 1200 mg have been used in clinical trials.

[‡]Maintenance dose of 5 mg daily can be used in patients with body weight <60 kg.

inhibitors, which may happen frequently in clinical practice.^{6,7} Although these results are contemporary, patients were enrolled until October 2012; ticagrelor received FDA approval in 2011 and thus was not widely adopted during the study period. An intravenous P2Y₁₂ inhibitor (cangrelor) has also recently received FDA approval. The role of these 2 additional agents in contemporary practice remains unclear.

Several other investigators have explored similar issues regarding the contemporary selection of antiplatelet therapy.^{8,9} Using a national prospective registry within the country of Israel, Beigel et al studied 1093 patients with acute MI undergoing PCI at 25 hospitals who were discharged on a P2Y₁₂ inhibitor during March and April 2013.⁸ Importantly, from 2012 to the present in Israel, all 3 P2Y₁₂ inhibitors (clopidogrel, ticagrelor, and prasugrel) were uniformly available with a similar cost for acute MI patients undergoing PCI. The authors found that 35% received clopidogrel, 43% received prasugrel, and 22% received ticagrelor. Predictors of clopidogrel use were older age, chronic renal failure and stroke, and presentation with non-ST-segment elevation MI. Notably, patients discharged on ticagrelor had the highest rate of crossover to another P2Y₁₂ inhibitor. Sandhu et al evaluated 44 hospitals throughout the state of Michigan that were participating in a prospective multicenter registry that included >55 000 patients undergoing PCI from 2010 to 2011.⁹ Overall, 17% of the patients were prescribed prasugrel at hospital discharge, and the rates of prasugrel use increased from 8.4% to 22.5% throughout the

study period. Although the main indication for prasugrel use was unstable angina or non-ST-segment elevation MI, ≈33% of patients received prasugrel for indications other than ACS. Perhaps the most important finding of this study was that prasugrel was used in 34% of ACS patients with a documented contraindication (history of stroke or transient ischemic accident, age >75 years, and body weight <60 kg). The selection of newer P2Y₁₂ inhibitors may be even more complex in European countries.^{10,11} Indirectly related to the current discussion for coronary indications is that the use of P2Y₁₂ inhibitors in patients undergoing endovascular intervention appears to be even more variable, with less data from contemporary clinical practice.¹² A recent publication using data from the Centers for Medicare and Medicaid Services found that a P2Y₁₂ inhibitor was used in only 81% of patients undergoing an endovascular procedure.¹³ Physician specialty and the clinical setting in which the procedure was performed (inpatient, outpatient, or office) were strongly associated with P2Y₁₂ inhibitor use. In this particular study, all current P2Y₁₂ inhibitors were included as a single category, such that relative use of a particular agent could not be evaluated.

Additional studies should continue to explore reasons for selection of specific P2Y₁₂ inhibitors in both coronary and endovascular intervention. Targeting patients at the highest risk for ischemic events, with an acceptable bleeding risk, should allow the most effective and safest use of the newer P2Y₁₂ inhibitors.

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