Pharmacodynamic and Clinical Implications of Switching Between P2Y12 Receptor Antagonists: Considerations for Practice

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Abstract: Dual antiplatelet therapy with aspirin and a P2Y12 receptor antagonist, either clopidogrel or the newer more potent agents prasugrel or ticagrelor, is standard therapy in patients receiving a coronary stent and those with a recent acute coronary syndrome. Switching antiplatelet drug regimen may be required in some patients for efficacy, safety, adherence, and cost considerations. However, there are potential concerns when switching from one agent to another that gaps in effective antiplatelet inhibition could lead to thrombotic events, and overlap of agents might cause excessive platelet inhibition thereby increasing the risk of bleeding. This review considers pharmacodynamic and clinical data to guide clinicians when switching between antiplatelet drugs is considered. Loading dose of the new agent should be considered in nearly all situations to avoid any possible gap in adequate platelet inhibition, as overlap of the 2 agents is unlikely to result in bleeding in excess of that with the more potent drug.

Key Words: acute coronary syndrome, ADP receptor inhibitors, P2Y12 receptor antagonists

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Dual antiplatelet therapy with aspirin and a platelet P2Y12 receptor antagonist is the standard of treatment to prevent atherothrombotic events in patients treated with percutaneous coronary intervention (PCI) and those with recent acute coronary syndrome (ACS).[1,2] Although clopidogrel has been the primary P2Y12 receptor antagonist used over the last decade, the newer agents prasugrel and ticagrelor have demonstrated greater reduction in ischemic events compared with clopidogrel among ACS patients.[3,4] These agents provide more rapid, consistent, and potent antiplatelet effects but are associated with increased risk of bleeding and are more expensive.[5] When initiating a P2Y12 receptor antagonist, information on patient risk for ischemic and bleeding events, socioeconomic status, medication adherence, and preferences may not be known. In addition, after initiation of therapy, patients may develop adverse effects or contraindications for use with particular agents. Given availability of several P2Y12 receptor antagonists, switching antiplatelet agent may be a consideration for some individuals. Switching agents has potential hazards associated with increased thrombotic risk during a possible "gap" in platelet inhibition and risk of bleeding due to a possible "overlap" of the effect of the combined agents. This review considers pharmacodynamic and clinical issues and provides practice recommendations to minimize patient risk when P2Y12 receptor antagonists are switched.

Switching From Clopidogrel to a Novel P2Y12 Receptor Antagonist

Switching clopidogrel to a novel P2Y12 receptor antagonist may be considered for patients experiencing adverse effects (eg, hypersensitivity rash), clinical failure of adequate platelet inhibition (eg, stent thrombosis), and those with ACS deemed at increased risk for further ischemic events (eg, ST-segment elevation myocardial infarction [STEMI],[6] diabetes).[7] Despite the rationale for individualized antiplatelet therapy, the clinical benefit of a tailored approach based on platelet function testing has not yet been proven.[8–10] Thus, currently, there is no role for routine platelet aggregation studies to determine whether patients should be switched to an alternative P2Y12 agent.

The pharmacodynamic effect of switching from clopidogrel to prasugrel was examined in the Switching Antiplatelet study.[11] When ACS patients treated with clopidogrel 75 mg daily were switched to prasugrel with a 60 mg loading dose (LD), there was a significant increase in platelet inhibition at 24 hours and 7 days. However, when prasugrel was started without a LD, platelet inhibition was not increased at 24 hours, but increased by 7 days to similar platelet inhibition as the group receiving the LD. No increase in bleeding was observed when clopidogrel was switched to prasugrel in this small short-term study. In the Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome study,[12] among PCI-treated ACS patients, platelet reactivity with prasugrel 60 mg LD added to clopidogrel 600 mg LD was not significantly different compared with prasugrel 60 mg LD alone.

In the Response to Ticagrelor in Clopidogrel Nonresponders and Responders and Effect of Switching Therapies study of patients with stable coronary disease, switching from maintenance clopidogrel 75 mg daily to ticagrelor 180 mg loading followed by 90 mg twice daily maintenance dose for 14 days was associated with significant reduction in platelet aggregation both in clopidogrel nonresponders and responders.[13] Platelet aggregation was lowered within 30 minutes of ticagrelor administration with peak effect at 1 to 2 hours post-LD. Numerically, there was a small increase in bleeding in the patients switched to ticagrelor (ticagrelor 1 major, 3 minor bleeds; clopidogrel no bleeds), however, the study size was too small to adequately assess the bleeding risk.

The Study of Platelet Inhibition and Patient Outcomes study design allowed open-label clopidogrel to be administered before randomization; 46% of the ticagrelor treatment group was switched from clopidogrel in the first 24 hours after symptom onset, initiated with an LD of 180 mg ticagrelor.[4] These patients had similar outcome benefits from ticagrelor as the patients not pretreated

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with clopidogrel, without any additional safety concerns. Although the pharmacodynamic Platelet Aggregation During the Shift from Clopidogrel to Ticagrelor study suggested that an LD of ticagrelor may be unnecessary when switching from clopidogrel to ticagrelor, the number of patients studied was small (n = 50), and the study excluded clopidogrel "nonresponders".[14] The reassuring outcomes from the Platelet Inhibition and Patient Outcomes study indicate that for all-comers, a LD of 180 mg ticagrelor should be given, especially in patients at high thrombotic risk.

In US practice data from 2009 to 2011 from the National Cardiovascular Data Registry, the frequency of in-hospital switch from clopidogrel to prasugrel was approximately 5%, and most strongly associated with repeat PCI procedures during hospitalization, angiographic, and clinical characteristics predictive of higher risk for recurrent thrombotic events, and health insurance coverage.[15] Contemporary data from the Treatment with adenosine diphosphate (ADP) receptor inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome longitudinal registry indicates that rate of in-hospital switch from clopidogrel to a novel P2Y12 receptor antagonist in ACS patients treated with PCI in the United States is in excess of 10%.[16]

Switching From Novel P2Y12 Receptor Antagonists to Clopidogrel

Switching from a novel P2Y12 receptor antagonist to clopidogrel may be considered for patients in whom a novel inhibitor was initiated (possibly under emergent circumstances) and who were subsequently found to have a contraindication or to fall within the scope of safety concerns [eg, prasugrel: with history of prior stroke or transient ischemic attack or age >75 or weight <60 kg[17]; ticagrelor: a history of intracranial hemorrhage]. In addition, patients with active bleeding or at increased risk for bleeding (eg, those requiring concomitant treatment with an oral anticoagulant)[18] may require switching to clopidogrel. Prasugrel and ticagrelor are more expensive than generic clopidogrel, and switching to clopidogrel may be necessary when patients are unable to afford one of the novel agents.

Switching from prasugrel to clopidogrel results in increased platelet reactivity. Among ACS patients with low platelet reactivity on-treatment with prasugrel 10 mg daily, switching to clopidogrel 75 mg daily reduced the number of patients with low platelet reactivity, but unmasked a group of nonresponders to clopidogrel with unknown clinical consequences.[19] When switching stable coronary disease patients from ticagrelor to clopidogrel 75 mg daily in the RESPOND study, a brief carryover effect of ticagrelor was observed up to 4 hours. Beyond this, there was a consistent and significant rise in platelet aggregation.[13]

In US practice, data from the National Cardiovascular Data Registry of PCI-treated ACS patients, prasugrel is switched in-hospital to clopidogrel in approximately 11% with switching most strongly associated with in-hospital bleeding events and clinical characteristics predictive of bleeding (eg, prior stroke or transient ischemic attack, increased age).[15] In the Treatment with ADP receptor inhibitors: Longitudinal Assessment of Treatment Patterns and Events after Acute Coronary Syndrome study, avoidance of bleeding and cost considerations were the most frequent factors associated with switching drug regimen in-hospital.[16] In a single-center study of 365 ACS patients discharged on ticagrelor,[20] ticagrelor was either switched or discontinued at 30 days due to dyspnea in 19 patients, bleeding in 7 and skin reaction in 5 patients.

Switching Between Novel P2Y12 Receptor Antagonists

Patients on ticagrelor with severe dyspnea may require switching off the drug. Given that prasugrel is a once daily drug (as opposed to bid administration of ticagrelor), switching to a once daily drug may be considered in patients demonstrating or at increased risk for medication nonadherence. Switching between ticagrelor and prasugrel was reported in the Switching Antiplatelet-2 study.[21] Patients with stable coronary disease on ticagrelor maintenance therapy were transitioned to a maintenance dose of 10 mg prasugrel daily, with or without a 60 mg LD. A significant rise in mean platelet reactivity and high on-treatment platelet reactivity was noted within hours of prasugrel dose, which was partially mitigated by administering a LD of prasugrel. At 7 days, mean platelet reactivity was higher in the combined prasugrel group but high on-treatment platelet reactivity was infrequent and not significantly different when compared

TABLE 1. Switching Between Platelet P2Y12 Receptor Antagonists

From	To	Potential Clinical Reasons	Initial Dose of New Agent
Clopidogrel	Prasugrel	Clinical failure/stent thrombosis High recurrent thrombotic risk (STEMI, diabetes)	Prasugrel 60 mg
	Ticagrelor	Clopidogrel allergy/hypersensitivity Clinical failure/stent thrombosis High recurrent thrombotic risk (STEMI, diabetes)	Ticagrelor 180 mg
Prasugrel	Clopidogrel	Unrecognized prior stroke/transient ischemic attack, age >75, weight <60 kg Active bleeding Increased bleeding risk (concomitant oral anticoagulant use) Cost considerations	Clopidogrel 600 mg unless active bleeding
	Ticagrelor	Prasugrel allergy/hypersensitivity	Ticagrelor 180 mg
Ticagrelor	Clopidogrel	Unrecognized prior intracranial hemorrhage Off target adverse effects (dyspnea, bradycardia) Active bleeding Increased bleeding risk (concomitant anticoagulant use) Cost considerations	Clopidogrel 600 mg unless active bleeding
	Prasugrel	Ticagrelor intolerance (dyspnea) Nonadherence to bid medications	Prasugrel 60 mg

Suggestions in this table are made by author consensus opinion based upon currently available pharmacodynamic and clinical studies.

with the ticagrelor group. In contrast, when prasugrel is switched to ticagrelor, platelet reactivity is lower with ticagrelor than it had been while the patients were taking prasugrel. Mechanism for these findings including potential for pharmacodynamic drug interaction between ticagrelor and prasugrel, which bind to different sites of the P2Y12 receptor, requires further study.

CONCLUSIONS

Switching drug therapy to optimize patient ischemic and bleeding risk, adherence, side effects, and affordability is a consideration in some patients. Switching clopidogrel to more potent P2Y12 receptor antagonists with less variability may be considered in patients with clinical failure of adequate platelet inhibition, ACS patients at increased risk for further ischemic events, and those who experience hypersensitivity rash with clopidogrel. Switch from novel P2Y12 receptor antagonists to clopidogrel is relevant in patients with contraindications or precautions for use of the novel P2Y12 receptor antagonists, active or increased risk for bleeding, and those unable to afford these drugs. Switching from ticagrelor to prasugrel may be considered in patients with dyspnea or nonadherence to twice daily medications. LD of the new agent should be considered in nearly all situations to avoid any possible gap in adequate platelet inhibition, as overlap of the 2 agents is unlikely to result in bleeding in excess of that with the more potent drug.

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