The Art of Switching $P2Y_{12}$ Inhibitors: How to Mitigate Platelet Reactivation

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Introduction

While aspirin remains the gold standard in antiplatelet therapy, adding a second antiplatelet agent, a $P2Y_{12}$ inhibitor, to augment the antiplatelet effect of aspirin in highly thrombotic conditions such as acute coronary syndromes or post intervention, or to replace aspirin when the latter is not tolerated, is increasingly common [1]. The currently approved $P2Y_{12}$ inhibitors include clopidogrel, ticagrelor, and prasugrel in the oral form, while cangrelor is in an intravenous form. These agents have different properties, with variable degrees of platelet inhibition, bleeding risk, other side effects and cost [2].

Switching between $P2Y_{12}$ inhibitors is increasingly reported, with little science to guide this practice [3]. This prompted a recent white paper publication on the subject to guide clinicians on how to safely switch between these agents while mitigating the serious potential risk of platelet reactivation and subsequent thrombosis [4]. Much of the recommendation were based on the pharmacokinetic and pharmacodynamic properties of these agents, as little clinical data exist to guide this practice. In this review, we summarize the recommendations in table 1, in an attempt to simplify the recommendations. However, the decision to switch, and the method of switching may depend on many patient variables, calling for a tailored patient-specific approach.

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Reasons to Switch

Several reasons prompt clinicians to switch between oral $P2Y_{12}$ inhibitors, including allergy, side effects, risk of bleeding, need for other anticoagulants, potential drug-drug interactions and cost [5]. Table 2 summarizes some of those reasons. The clinician should always weigh the risks versus the benefits before switching between these agents to avoid the potential risk of heightened versus lessened antiplatelet effects.

Cangrelor is an approved intravenous $P2Y_{12}$ inhibitor with well demonstrated anti-ischemic properties in patients undergoing PCI, without a significant increase in major bleeding risk [6]. The timing to switch from cangrelor to oral $P2Y_{12}$ inhibitors is also critical to avoid the potential transient reactivation of platelets [7, 8].

Step Up or Step Down

The following effects on platelet inhibition of switching between $P2Y_{12}$ inhibitors have been reported.

1. Switching from clopidogrel to prasugrel or ticagrelor increases platelet inhibition [9].
2. Switching from ticagrelor to clopidogrel decreases platelet inhibition [10].
3. Switching from prasugrel to ticagrelor and from ticagrelor to prasugrel, ticagrelor appears to cause increased inhibition of platelets [11].
4. Despite the absence of large outcome data, smaller registries have not shown major safety issues related to switching $P2Y_{12}$ inhibitors [3].
5. Further clinical studies addressing the actual risk of bleeding or thrombosis related to switching $P2Y_{12}$ inhibitors are needed.

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Conclusion

Dual antiplatelet therapy has become the standard of care in many thromboembolic conditions and following coronary interventions. This strategy has greatly improved patient outcomes with regards to reduction of subsequent ischemic events. It has, however, introduced a set of challenges involving the tolerability of this treatment, the side effects of the medications, the increased bleeding risk and the cost. The need to switch from one $P2Y_{12}$ inhibitor to another is a challenge in itself, and an art that should be tailored to patient-specific factors, as large scientific outcomes data are lacking.

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Tables

Table 1. Recommendations for Switching $P2Y_{12}$ Inhibitors [4]

Switch		Loading dose	Maintenance dose	Timing
From	To			
Ticagrelor	Clopidogrel	300 mg	75 mg QD	Loading dose 12 hrs after last ticagrelor dose
	Prasugrel	60 mg	10 mg QD	
Prasugrel	Clopidogrel	None	75 mg QD	Maintenance dose 24 hours after last prasugrel dose
	Ticagrelor	None	90 mg BID	
Clopidogrel: *High coronary thrombosis risk*	Prasugrel	60 mg	10 mg QD	Loading dose irrespective of last clopidogrel dose
	Ticagrelor	180 mg	90 mg BID	
Clopidogrel: *Stable CAD*	Prasugrel	None	10 mg QD	Maintenance dose 24 hours after last clopidogrel dose
	Ticagrelor	None	90 mg BID	

Table 2. Potential Reasons Necessitating Switch Between $P2Y_{12}$ Inhibitors

Switch		Potential Reasons Necessitating Switch
From	To	
Ticagrelor	Clopidogrel /Prasugrel	1. Cost (formulary considerations with prasugrel) 2. Compliance (BID to QD dosing) 3. High bleeding risk (esp. with other anticoagulants); to clopidogrel 4. Anticipated need for higher ASA dose 5. Intolerance to ticagrelor (dyspnea, bradycardia) 6. Avoidance of CYP3A4 drug interaction; to prasugrel
Prasugrel	Clopidogrel /Ticagrelor	1. Cost (formulary considerations with ticagrelor) 2. High bleeding risk (esp. with other anticoagulants); to clopidogrel 3. Intolerance to prasugrel 4. Medical management decision; need for long-term therapy
Clopidogrel	Ticagrelor/ Prasugrel	1. Intolerance/allergy to clopidogrel (e.g. rash) 2. High risk of thrombosis (post ACS) 3. High risk intervention (left main, proximal LAD, multivessel PCI) 4. Avoidance of potential drug-drug interactions (PPIs, CYP3A4)