Switching $P2Y_{12}$ Receptor Inhibiting Therapies

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KEYWORDS

• $P2Y_{12}$ receptor inhibitors • Switching • Clopidogrel • Prasugrel • Ticagrelor • Cangrelor

KEY POINTS

- Antiplatelet therapy with aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, ticagrelor, or cangrelor) represents the cornerstone of acute and long-term treatment of patients with atherothrombotic disease manifestations.
- Switching between $P2Y_{12}$ inhibitors is common in clinical practice and attributed to multiple factors, including individual risk of bleeding and ischemic events, occurrence of adverse events, socioeconomic factors, and pharmacodynamic/genetic profiles.
- Pharmacologic properties of $P2Y_{12}$ inhibiting therapies (competitive vs noncompetitive binding and onset and offset of actions) and timing of clinical presentation (acute vs chronic) are key to define switching strategies.
- Drug interactions have been described when transitioning between $P2Y_{12}$ receptor inhibiting agents of different pharmacologic classes, raising concerns as to optimal switching strategies.
- Clinical trials evaluating the safety and efficacy of switching antiplatelet agents are lacking, and the only available data derive from pharmacodynamic studies and registries.

Dual antiplatelet therapy (DAPT) with aspirin and a platelet $P2Y_{12}$ receptor antagonist represents the keystone of treatment of acute coronary syndrome (ACS) patients and those undergoing percutaneous coronary intervention (PCI).[1–4] Although clopidogrel is still the most commonly used $P2Y_{12}$ receptor inhibitor,[5,6] the newer generation agents, prasugrel and ticagrelor, provide more rapid, consistent, and potent antiplatelet effects, which lead to a greater reduction in ischemic recurrences, including stent thrombosis, compared with clopidogrel in patients with ACS.[7–9] These agents are associated with increased risk of bleeding and higher costs, however, compared with clopidogrel.[7,8] For all these reasons, the treatment of choice for an individual patient takes into account a multitude of factors, which include clinical presentation, patient characteristics, and socioeconomic issues. In an acute setting, such as patients presenting with an ACS, when DAPT is started, information on patient risk for ischemic and bleeding events, socioeconomic status, medication adherence, and preferences may not be available. Moreover, patients may develop adverse effects or contraindications to the used agent during the treatment period. In all these scenarios, switching to another antiplatelet agent may be necessary. Switching between $P2Y_{12}$ agents is, therefore, not uncommon in clinical practice and represents a challenge due to potential drug interactions, which may lead to ineffective platelet inhibition, thus increasing the risk of thrombotic complications or, on the contrary, potential

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overdosing due to overlap in drug therapy, which might cause excessive platelet inhibition and increased bleeding.[9,10] These considerations are further enhanced by the recent introduction into clinical practice of intravenous $P2Y_{12}$ inhibitors (eg, cangrelor).[11,12] This article provides an overview of the literature on switching antiplatelet treatment strategies with $P2Y_{12}$ receptor inhibitors and provides practical considerations for switching therapies in the acute and chronic phases of presentation in patients requiring DAPT.

PHARMACOLOGIC PROPERTIES

Differences in the pharmacologic properties of ADP-$P2Y_{12}$ receptor inhibitors have a key role in the potential for drug interactions when switching from one agent to another, in particular with regard to their binding site to the $P2Y_{12}$ receptor (competitive vs noncompetitive), drug half-life, and speeds of onset and offset of action (Table 1).[9,11,13] Clopidogrel, a second-generation thienopyridine, is a prodrug that is up to 85% hydrolyzed into an inactive acid metabolite by human carboxylesterase-1 after intestinal absorption. The remaining 15% of the prodrug requires a 2-step oxidation process using multiple hepatic cytochrome P-450 (CYP) isoenzymes, mainly CYP2C19, to generate an active metabolite. Afterward, clopidogrel's active metabolite irreversibly blocks the ADP binding site on the $P2Y_{12}$ receptor.[9,14] Because ADP-induced $P2Y_{12}$ receptor activation plays a pivotal role in pathologic thrombosis, a clopidogrel-based antiplatelet regimen has represented for more than a decade the mainstay of secondary prevention in patients with ACS or PCI.[5,6,14]

Prasugrel is a third-generation thienopyridine with a more favorable pharmacologic profile compared with clopidogrel. In particular, metabolism of prasugrel is more efficient than that of clopidogrel given that it requires only a single-step hepatic oxidation to generate the active metabolite. Therefore, although prasugrel's active metabolite is equipotent to that derived from clopidogrel, the available plasma concentration is higher, which translates into more prompt, potent, and predictable platelet inhibitory effects compared with clopidogrel.[9,14] The active metabolites of thienopyrdines, however, are unstable, with a short half-life and thus are rapidly eliminated if they do not bind to the $P2Y_{12}$ receptor.[14,15] Given the irreversible binding, recovery time after treatment discontinuation is approximately equivalent to the life span of platelets, although it is longer after prasugrel discontinuation (7 days) compared with clopidogrel (5 days) due to the more profound level of platelet inhibition achieved.[14–16]

Reversibly binding inhibitors available for clinical use are ticagrelor and cangrelor. Ticagrelor is an oral cyclopentyl-triazolopyrimidine, which

Table 1
Pharmacologic properties of $P2Y_{12}$ receptor inhibitors

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Receptor blockade	Irreversible	Irreversible	Reversible	Reversible
Prodrug	Yes	Yes	No	No
Half-life	~6 h	~7 h	7 h	3–5 min
Competitive binding	Competitive	Competitive	Noncompetitive	Undetermined[a]
Administration route	Oral	Oral	Oral	Intravenous
Frequency	Once daily	Once daily	Twice daily	Bolus plus infusion
Onset of action	2–8 h	30 min–4 h	30 min–4 h	~2 min
Offset of action	7–10 d	7–10 d	3–5 d	30–60 min
CYP drug interaction	CYP2C19	No	CYP3A	No
Approved settings	ACS (invasive and noninvasively managed) and stable CAD PCI	ACS undergoing PCI	ACS (invasive or noninvasively managed)	PCI in patients with or without ACS

[a] The binding site of cangrelor at the $P2Y_{12}$ receptor level is not clearly defined; nevertheless, cangrelor is associated with high levels of receptor occupancy preventing ADP signaling.

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