Current and novel P2Y<sub>12</sub> ADP receptor antagonists and bleeding risk in dental surgery

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Abstract

Adenosine diphosphate (ADP) receptor antagonists are anti-platelet drugs used for treatment and prevention of thromboembolism. Clopidogrel, a second generation P2Y<sub>12</sub> ADP receptor antagonist, has been used over past decade with or without aspirin in acute coronary syndrome (ACS). Clopidogrel has several drawbacks due to two-step bioactivation by cytochrome P450 (CYP) leading to delayed onset and inter-individual variation. These lead to development of newer ADP receptor antagonists with more predictable pharmacokinetics and pharmacodynamics. The newly approved ADP receptor antagonists include oral prasugrel and ticagrelor, and intravenous cangrelor. During tooth extraction, significant bleeding may occur in patients receiving anti-platelet drugs especially aspirin plus ADP receptor antagonist therapy. This article describes the pharmacological properties and risk of bleeding especially in dental surgery of newly approved ADP receptor antagonists.

Keywords: clopidogrel, prasugrel, ticagrelor, cangrelor, bleeding, dental surgery

**Introduction**

Platelets play an important role in the formation of arterial thrombus, which is a common cause of ACS and ischemic complications following percutaneous coronary intervention (PCI)\(^1\), \(^2\). Anti-platelet agents are mainstay treatment for patients with ACS and patients who undergo PCI. Currently available anti-platelet drugs are concluded in figure 1\(^3\). Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1) leading to reduce thromboxane A\(_2\) (TXA\(_2\)) synthesized from platelets. Low-dose aspirin is prescribed indefinitely in single or combination with P2Y\(_{12}\) ADP receptor antagonist to prevent ischemic complications following PCI up to 1 year\(^4\). P2Y\(_{12}\) receptor antagonists are rapidly expanding group of anti-platelet drugs due to drawbacks of ticlopidine (the first P2Y\(_{12}\) receptor antagonist) and clopidogrel (the second P2Y\(_{12}\) receptor antagonist)\(^5\). Both drugs have delayed onset of action. Severe neutropenia is a serious adverse effect of ticlopidine\(^6\). The difference in inter-individual response to clopidogrel is responsible for unsuccessful treatment outcomes such as coronary ischemia and stent thrombosis\(^7\). In addition, the irreversible anti-platelet effect may increase risk of blood loss and transfusion requirement in patients undergoing coronary bypass surgery (CABG)\(^8\). The above limitations facilitated the search

**Figure 1** Metabolism and mechanism of action of P2Y\(_{12}\) receptor antagonists. Clopidogrel and prasugrel are pro-drugs required hepatic biotransformation to active metabolites whereas ticagrelor and cangrelor has direct antagonistic effect on platelet P2Y\(_{12}\) receptor. While 85% of absorbed clopidogrel is inactivated by esterase enzyme and then undergoes 2-step biotransformation by CYP to active metabolite, 100% of intermediate metabolite by esterase of prasugrel is changed by single CYP to active metabolite. The parental compound and active metabolite of ticagrelor have reversible antagonistic effect at P2Y\(_{12}\) receptor. Cangrelor is an intravenous direct active P2Y\(_{12}\) receptor antagonist. ADP = adenosine diphosphate; CYP = cytochrome P450; GPIIb/IIIa = glycoprotein IIb/IIIa.
for new P2Y<sub>12</sub> receptor antagonists. The new P2Y<sub>12</sub> receptor antagonists such as prasugrel (Effient<sup>®</sup>), ticagrelor (Brilinta<sup>®</sup>) and recently approved cangrelor (Kengreal<sup>®</sup>) are focused in this review.

**Pharmacological properties of P2Y<sub>12</sub> receptor antagonists**

ADP is secreted from dense granule of activated platelets. It plays a key role in physiological process of hemostasis and thrombosis. Extracellular nucleotides such as ADP and ATP activate two classes of purinergic receptors; namely P2X (ligand-gated calcium channel) and P2Y (G-protein coupling receptor)<sup>9</sup>. ATP activates P2X, leading to increase intracellular calcium while ADP activates P2Y<sub>1</sub> and P2Y<sub>12</sub> receptors<sup>10</sup>. The activation of P2Y<sub>1</sub> receptor induces rapid initiation of platelet activation by increasing the cytosolic calcium, which results in platelet shape change and aggregation via GPIIb/IIIa receptor. P2Y<sub>12</sub> is G<i>i</i>-coupling receptor. Activation of P2Y<sub>12</sub> leads to GPIIb/IIIa activation via phosphoinositide-3 kinase<sup>11, 12</sup> (figure 2). In addition, activation of P2Y<sub>12</sub> potentiates other agonists in inducing platelet aggregation<sup>13</sup>. P2Y<sub>12</sub> is the target of antiplatelet drugs because of selective distribution in platelets, whereas P2Y<sub>1</sub> receptors express in many tissues such as heart, blood vessel,
neural tissue, prostate, and ovary. Ticlopidine, clopidogrel and prasugrel are P2Y₁₂ inhibitors in thienopyridine family of ADP receptor antagonists (figure 3). They are prodrugs, which require hepatic conversion to active metabolites. The active metabolites irreversibly inhibit P2Y₁₂ receptor.

**Clopidogrel**

After absorption, 85% of clopidogrel is hydrolyzed by esterase to inactive metabolites. The remaining clopidogrel undergoes two-step biotransformation by CYP; first by CYP1A2, CYP2B6 and CYP2C19 to 2-oxo-clopidogrel, and second by CYP2B6, CYP2C9, CYP2C19 and CYP3A4 to form active metabolite (R-130964). The complex biotransformation to active metabolite of clopidogrel is responsible for the delay onset of platelet inhibition. In addition, genetic polymorphism of CYP2C19 causes significant inter-variation responses to clopidogrel.

**Prasugrel**

Prasugrel is a third-generation of thienopyridine that overcomes some limitations of clopidogrel. After metabolism, intermediate metabolite is converted to active form (R-138727) by a one-step CYP reaction (mainly either CYP3A4 or CYP2B6) leading to faster onset (30 min) and 10-fold more potent than clopidogrel. The active metabolites of prasugrel and clopidogrel have the same anti-platelet potency in vitro with 50% inhibitory concentration (IC₅₀) of 0.3 µM. However, more efficient and consistent conversion of prasugrel to active metabolite is responsible for greater anti-platelet effect compare to clopidogrel in human. Clinical trial demonstrated that prasugrel in combination with aspirin decreased mortality, rate of myocardial infarction and stent thrombosis (in both drug-eluting stents and bare-metal stents) significantly compared to clopidogrel plus aspirin. Prasugrel did not only decrease procedure-related myocardial infarction but also decreased

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**Figure 3** Currently available anti-platelet drugs including cyclooxygenase-1 inhibitors (aspirin, triflusal), P2Y₁₂ receptor antagonists (ticlopidine, clopidogrel, prasugrel, ticagrelor, and cangrelor), GPIIb/IIIa inhibitors (abciximab, eptifibatide and tirofiban), phosphodiesterase inhibitors (diprydiamole and cilostarol), prostacyclin analog (iloprost and beraprost), and PAR-1 inhibitor (vorapaxar). AA = arachidonic acid; AC = adenylate cyclase; AMP = adenosine monophosphate; cAMP = cyclic adenosine monophosphate; COX-1 = cyclooxygenase-1; GP Iib/IIa = glycoprotein Iib/IIa; PAR-1 = protease activated receptor-1; PDE = phosphodiesterase; TxA₂ = thromboxane A₂.
spontaneous myocardial infarction rate by 26% at 15-months follow-up after PCI²⁴.

**Ticagrelor**

Ticagrelor is a member in new class of P2Y₁₂ receptor antagonists²⁵. It has direct and allosteric reversible antagonistic effect at P2Y₁₂ receptor²⁶. The binding of ticagrelor to P2Y₁₂ receptor induces conformational change that prevents G-protein activation by ADP. Ticagrelor and its active metabolite (AR-C124910XX), which is converted by CYP3A4, have direct anti-platelet activity²⁷. In contrast to other P2Y₁₂ receptor antagonists, ticagrelor has to be administered twice daily due to its short half-life (8 hours)²⁸ (table 1). Ticagrelor has more rapid onset (30 minutes) and offset than clopidogrel. In addition, ticagrelor has markedly greater platelet inhibition than clopidogrel. Ticagrelor (180 mg) caused 88% platelet inhibition at 2 hours compared to 38% inhibition by clopidogrel (600 mg)²⁹. Prasugrel and ticagrelor showed effective anti-platelet effect in patients after PCI who resisted to clopidogrel treatment³⁰.

**Cangrelor**

Cangrelor, a structure related to ATP, is the first intravenous P2Y₁₂ inhibitor. Cangrelor cause reversible P2Y₁₂ inhibition by binding to P2Y₁₂ receptor at the same site as ADP²⁵. Cangrelor inhibits platelets immediately after intravenous administration. Cangrelor is inactivated by rapidly by ectoADPase located on surface of endothelial cells; thus platelet function is recovered within 1 hour after stop infusion³¹. It has very rapid onset (a few second) with duration of action about 1 hour after cessation of infusion. Cangrelor is a candidate drug used to reduce thrombotic events during PCI. Cangrelor reduced thrombotic events including stent thrombosis at 48 hours after PCI compared to clopidogrel (loading dose 300 or 600 mg)³². In bridging anti-platelet therapy, cangrelor was administrated to clopidogrel or prasugrel treated patients who underwent CABG or any urgent surgery. Discontinuation of clopidogrel or prasugrel for 7-10 days is required before surgery, resulting in increased risk of ischemia. After clopidogrel cessation, cangrelor maintained low platelet activity levels compared to placebo and no reported major bleeding prior

| **Table 1** Comparison of pharmacological properties of P2Y₁₂ receptor antagonists |
|---------------------------------|----------------------------|-----------------|-----------------|-----------------|
| **Chemical structure**          | Clopidogrel                 | Prasugrel       | Ticagrelor      | Cangrelor       |
| Thienopyridine                  | Thienopyridine              | CPTP            | ATP analog      |
| **Route and frequency of administration** | Oral (od)                  | Oral (od)      | Oral (bid)     | IV              |
| **Pro-drugs**                   | Yes                         | Yes            | No              | No              |
| **Binding to P2Y₁₂ receptor**   | Irreversibly                | Irreversibly   | Reversibly     | Reversibly     |
| **Metabolism**                  | Esterases and then two-step metabolism by CYP to active metabolite | Esterase and then CYP3A4 and CYP2B6 to active metabolite | No metabolism required or metabolized by CYP 3A4 | No metabolism required |
| **Time of reach steady state platelet inhibition** | 6 hours⁴⁵                  | 2 hours⁴⁵      | 2 hours²⁷      | Seconds³⁶      |
| **Time to restore platelet function** | 5 days²⁶, ³⁷    | 7 days         | 5 days         | 1 hour after stop infusion |

CPTP = cyclopentyltriazolopyrimidines; od = once daily; bid = twice daily; IV = intravenous; CYP = cytochrome P450
CABG\textsuperscript{33}. However, cangrelor antagonized anti-platelet effect of active metabolites of clopidogrel and prasugrel \textit{in vitro}\textsuperscript{34}. Therefore, it is uncertain how long cangrelor should be discontinued before starting clopidogrel.

**Risk of bleeding**

Aspirin plus clopidogrel has been showed to reduce myocardial ischemic events compared to aspirin alone. However, aspirin plus clopidogrel has been accompanied by an increases risk of bleeding. Severity of bleeding correlated with mortality rate of patients\textsuperscript{38}. Gastrointestinal bleeding was the most frequently bleeding reported\textsuperscript{39}.

**Prasugrel**

Patients receiving prasugrel had increased bleeding tendency together with decreased rates of ischemic events\textsuperscript{22}. In this study, ACS patients who planed to undergo PCI received aspirin (75-162 mg) plus either prasugrel (a 60-mg loading dose and followed by a 10-mg maintenance dose) or clopidogrel (a 300-mg loading dose and followed by a 75-mg maintenance dose). Major bleeding occurred more frequency in prasugrel compared to clopidogrel group. The fatal bleeding has been reported with odds ratio of 4.19 in prasugrel group. Gastrointestinal and intracranial sites were the most frequent sites of life-threatening bleeding in prasugrel treated patients. Patients who had history of stroke, transient ischemic attack, elderly (age \geq 75 years), and weight less than 60 kg might have less clinical efficacy and increased risk of bleeding\textsuperscript{22}.

**Ticagrelor**

In contrast to prasugrel, ticagrelor decreased mortality rate in ACS patients without increased incidence of major bleeding in comparison with clopidogrel\textsuperscript{40}. Ticagrelor was administrated (a 180-mg loading dose and 90-mg twice daily maintenance dose) plus aspirin to ACS patients. The incidences of major bleeding and CABG-related bleeding were not different between ticagrelor and clopidogrel treated patients\textsuperscript{41}. However, non-procedure related bleeding (spontaneous bleeding) increased in ticagrelor treated patients with odds ratio of 1.19\textsuperscript{40}. Ticagrelor has more potent platelet inhibition than clopidogrel but its effect is reversible therefore, the incidence of major bleeding did not increase compared to clopidogrel. Major bleeding of ticagrelor treated patients was not different among gender, age and race. The increase susceptibility of bleeding has been reported Asian people. However retrospective study showed that bleeding rates were similar between Asians and non-Asians\textsuperscript{42}.

**Cangrelor**

The rate of life-threatening bleeding in patients receiving cangrelor prior to PCI was very low, and incidences of moderate to severe bleeding were not different in comparison with clopidogrel treated patients\textsuperscript{32}. In addition, there were no significant differences in bleeding prior to CABG in patients bridging clopidogrel with cangrelor \textsuperscript{33}.

**Implication of P2Y\textsubscript{12} antagonists in dental practice**

Anti-platelet drugs increase bleeding, blood transfusion requirement and length of hospital stay in patients undergoing surgery. However, the cessation of anti-platelet drugs was associated with mortality especially within 6 weeks after PCI\textsuperscript{43}. In patients scheduled CABG, American College of Cardiology/American Heart Association (ACC/AHA) recommended to stop clopidogrel and ticagrelor for at least 5 days and prasugrel for 7 days prior surgery\textsuperscript{37}. However, data concerning about the risk of bleeding in non-cardiac surgery are very limited. Aspirin and aspirin plus clopidogrel continuation during non-
cardiac surgery led to an increase in bleeding time by 1.5 and 3.4 folds, respectively. However, the prolongation of surgical bleeding had not affect surgical outcome and mortality rate of patients.

The risk of excessive oral bleeding after dental procedure has been concerned. Risk of bleeding in patients who receive single or dual anti-platelet drugs and undergo dental extraction has been studied. No postoperative bleeding was found in patients receiving single anti-platelet drugs (n = 117), which was aspirin or clopidogrel. One of 43 patients in aspirin plus clopidogrel group experienced postoperative bleeding after extraction of three upper molars. In this study, patients required more complex tooth extraction were excluded. However, in another report, prolonged immediate postoperative bleeding was observed in patients received aspirin plus clopidogrel (n = 33). Local hemostatic measures successfully stopped postoperative bleeding. The hemorrhagic complication after dental extractions was also studied in 176 patients receiving aspirin plus clopidogrel. In this study, post-operative bleeding was managed by the gauze compression with tranexamic acid. Mild hemorrhage (bleeding less than 30 minutes) was found in most patients (90.9 %) however, only 9.1 % reported prolong bleeding for more than 30 minutes. Patients were instructed for using mouth washing with tranexamic acid every 6 hours. At 24 hours, only 8.3% of patients reported mild hemorrhage. The increased incidences of bleeding in this study might due to the difference in local anesthetic procedure that used 3% mepivacaine without vasoconstrictor. The risk of post-operative hemorrhage was associated with the presence of inflammation (odds ratio = 10.07) and number of extracted roots (odds ratio = 7.34).

Bleeding tendency increased in periodontitis because of hyperemia and fragility of blood vessels from local inflammation. In periodontal treatment, post-operative bleeding was not found in patients receiving single anti-platelet drug including aspirin (n = 48) or ticlopidine (n = 12). However, a case report showed the severe gingival hemorrhage following non-surgical periodontal procedures (scaling and root planning) in a patient received dual anti-platelet therapy. In this case, post-operative hemostasis was confirmed before leaving dental clinic without the used of hemostatic measures. Twenty-four hours later, patients admitted with severe bleeding of inter-dental papilla between teeth #25-26. However, bleeding was well-controlled by local hemostatic measures.

In contrast to clopidogrel, evidence for risk of bleeding in patients receiving prasugrel or ticagrelor who undergo dental surgery was limited. Bleeding especially life-threatening bleeding found more frequently in patients receiving prasugrel, which is ten-fold, more potent than clopidogrel. A recent clinical trial investigated risk of bleeding among dental patients (n = 129) receiving antiplatelet therapy (aspirin combined with either clopidogrel or prasugrel). Prolonged bleeding time about 10 minutes (21% increased) was found in prasugrel treated patients. In addition, wound suture decreased bleeding time significantly compared with gauze swab hemostasis in the presence or absence of epinephrine. This evidence suggested that tooth extraction performed safely in patients receiving aspirin plus prasugrel. However, there is no clinical trial or evidence-based data for bleeding risk in patients received ticagrelor plus aspirin in dental surgery.

Minor surgery including tooth extraction is associated with minor risk of bleeding. No indication for cessation of anti-platelet therapy in stent implantation patients who undergo dental surgery. However, elective surgery should be delayed by at least 6 months or ideally 12 months after PCI. Although uninterrupted aspirin plus clopidogrel therapy prolonged...
bleeding in dental surgery, most evidences suggested that dental surgery especially tooth extraction should perform safely with proper hemostatic measures. However, evidence for risk of hemorrhage in patients treated with aspirin plus prasugrel or ticagrelor in dental surgery was very limited. Dentists should concern about prolong bleeding time and should provide proper hemostatic measures. Discontinuation of anti-platelet should not be advised to patients without consulting cardiologist.

**Conclusion**

Newer P2Y\textsubscript{12} antagonists cause more rapid and potent platelet inhibition than clopidogrel leading to decreased incidence of ischemic events and stent thrombosis. However, risk of bleeding is significantly increased. The evidence of hemorrhage in patients treated with prasugrel or ticagrelor in dental surgery is limited. Prolong bleeding might be found in dental surgery without clinical significance. Local hemostatic measures are sufficient to stop bleeding. From the existing evidence, there is no indication to stop anti-platelet therapy before invasive dental procedure. The risk of thromboembolism is outweighed bleeding risk from dental surgery.

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