Antiplatelet Therapy in Percutaneous Coronary Intervention

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KEYWORDS

• Antiplatelet agents • ^{P2Y}12 receptor antagonists • Glycoprotein IIb/IIIa inhibitors
• Percutaneous coronary intervention • Bleeding • Stent thrombosis

KEY POINTS

- Balancing the risks of stent thrombosis and major bleeding is key to the effective use of antiplatelet agents during and after percutaneous coronary intervention (PCI).
- The new oral ^{P2Y}12 inhibitors prasugrel and ticagrelor have onsets of action considerably faster than that of clopidogrel and reduce the incidence of recurrent ischemic events when administered to patients with acute coronary syndrome undergoing PCI.
- Despite the theoretic benefits of ^{P2Y}12 inhibitor preloading and platelet function testing–guided selection of antiplatelet agents, clinical trials have failed to show the benefit of these strategies.

INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin and a ^{P2Y}12 inhibitor is the evidence-based, guideline-recommended cornerstone of antithrombotic therapy for patients undergoing percutaneous coronary intervention (PCI) across a spectrum of indications. Fundamental to DAPT use is the balance of bleeding with the risk of recurrent myocardial infarction (MI) and stent thrombosis.

Until recently, the only available ^{P2Y}12 inhibitors were clopidogrel and ticlopidine, both prodrugs metabolized into active metabolites that irreversibly bind the adenosine ^{P2Y}12 receptor on platelet surfaces, inhibiting platelet aggregation. Because of the requirement for first pass metabolism in the liver, neither drug achieves steady state levels of platelet inhibition for several hours following dosing, leaving a window of inadequate platelet inhibition during which post-PCI patients are theoretically vulnerable to acute stent thrombosis if they are not loaded with a ^{P2Y}12 inhibitor before PCI.

Over the past 5 years, 3 highly potent, fast-acting ^{P2Y}12 inhibitors have been introduced to the market: prasugrel, ticagrelor, and cangrelor. Prasugrel and ticagrelor are oral agents, and cangrelor is an intravenous agent. These agents all achieve maximal platelet inhibition within 1 hour of loading dose in healthy volunteers. However, these drugs exhibit different pharmacokinetics in real-world patients undergoing PCI, especially patients with ST segment elevation MI (STEMI) and non–ST segment elevation acute coronary syndrome (NSTE-ACS), which may have important implications for their use as antiplatelet agents in urgent and primary PCI. These agents are additions to the antiplatelet armamentarium that also includes aspirin and glycoprotein IIb/IIIa inhibitors, creating an array of combinations available for use in patients undergoing PCI.

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This article focuses on the pharmacokinetic and pharmacodynamics properties of the newer and older $^{P2Y}12$ inhibitors as well as glycoprotein IIb/IIIa inhibitors, and the clinical trial evidence supporting the use of each of the available antiplatelet agents. Their effects on periprocedural major bleeding and early stent thrombosis are also discussed, as are the optimal combinations and usage to achieve the best clinical outcomes.

THE CENTRAL ROLE OF PLATELETS IN OUTCOMES AFTER PERCUTANEOUS CORONARY INTERVENTION: STENT THROMBOSIS AND BLEEDING

Platelets are integrally involved in the pathogenesis of adverse events after PCI. In particular, stent thrombosis is a platelet-mediated phenomenon, and the antithrombotic effect of antiplatelet therapy predisposes patients to bleeding complications. Inhibitors of platelet activation and aggregation are therapeutic options for patients undergoing PCI. Fig. 1 shows potential receptor targets on the platelet surface, some of which are targets of available antiplatelet agents used for PCI.

In the immediate post-PCI period, acute stent thrombosis and periprocedural bleeding are events of concern. Both events are associated with increased mortality. Stent thrombosis can be grouped into acute (<24 hours after PCI), subacute (24 hours to 30 days), late (30 days to 1 year), and very late (>1 year). In an analysis of the Risk Model to Predict Adverse Outcomes after Primary PCI (RISK-PCI) clinical trial, the 30-day risk-adjusted mortality was more than 5-fold higher in patients with early (acute or subacute) stent thrombosis than in those without, and 1-year risk-adjusted mortality was more than 4-fold higher.[1] In an analysis of the Drug Eluting Stent in Primary Angioplasty (DESERT) primary PCI registry, patients with stent thrombosis had a raw mortality of 23.6%, compared with 6% in those without stent thrombosis.[2] This increase in mortality with stent thrombosis persists in patients without STEMI: in an analysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, which enrolled patients undergoing urgent PCI for NSTE-ACS, 30-day mortality was 24.7% in patients with stent thrombosis, compared with 0.5% in those without.[3]

Similarly, post-PCI bleeding has long been identified as an independent predictor of mortality in patients undergoing elective, urgent, and emergent PCI. In a pooled analysis of 3 clinical trials enrolling patients undergoing PCI for stable coronary artery disease (CAD), NSTE-ACS, and STEMI, post-PCI major bleeding increased risk-adjusted 1-year mortality 4.2-fold, an increase in mortality greater than that of recurrent MI within 30 days.[4] Analyses of the Global Registry of Acute Coronary Events (GRACE) and CathPCI registries found similar links between major bleeding and mortality,[5,6] with one CathPCI study showing an additional in-hospital death for every 29 patients with PCI-related major bleeding.[7]

Stent thrombosis carries a greater risk of death, but is rarer than bleeding, leading to differences in attributable deaths for the two

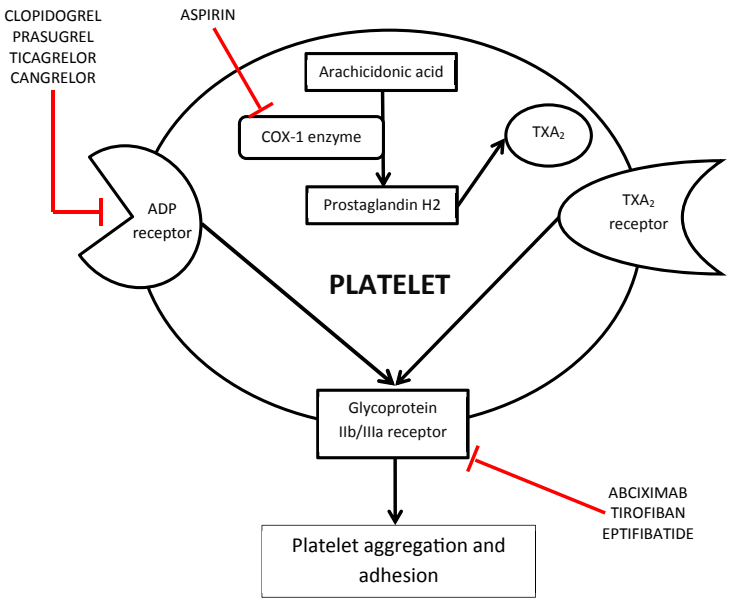

Fig. 1. Targets of antiplatelet agents used in patients undergoing PCI. Cyclooxygenase-1 (COX-1), the Adenosine diphosphate (ADP) receptor, and glycoprotein IIb/IIIa receptors are the targets of available antiplatelet agents. The ADP receptor and COX-1 mediate processes that activate the glycoprotein IIb/IIIa receptor, which is the major molecule mediating platelet aggregation and adhesion. TXA_2, thromboxane A_2.