Intensity of Antiplatelet Therapy in Patients with Acute Coronary Syndromes and Percutaneous Coronary Intervention: the Promise of Prasugrel?

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• Percutaneous coronary intervention

Platelet activation and aggregation are key contributors to the pathophysiology of acute coronary syndromes (ACS) and to ischemic complications of percutaneous coronary intervention (PCI), including spontaneous and periprocedural myocardial infarction (MI) and stent thrombosis. Platelets adhere to the site of vascular injury (whether spontaneous with ACS or iatrogenic with PCI). This initial adherence is followed by activation, which includes shape change and secretion of various procoagulant, proinflammatory, and vasoconstrictive secondary messengers, including ADP, thromboxane A2, and serotonin. Among the effects of these messengers is further activation of platelets, resulting in a feedback loop and explosive amplification of activation. ADP in particular interacts with puranergic receptors (P2Y1 and P2Y12) to amplify and sustain this activation.[1] In addition to shape change and secretion, platelet activation leads to the exposure of glycoprotein IIb/IIIa integrin receptors, which allows for crosslinking of platelets and fibrinogen to form platelet aggregates. Local vasoconstriction and inflammation, combined with the accumulation and embolization of platelet aggregates, result in thrombosis, ischemia, and infarction.

With this pathophysiology, it is not surprising that antiplatelet agents play a key role in the prevention of ischemic complications of ACS and PCI.[2–6] Three key classes of antiplatelet agents play major roles in the management of patients with these conditions: aspirin, intravenous glycoprotein IIb/IIIa integrin receptor antagonists, and thienopyridine antiplatelet agents. Aspirin inhibits the cyclooxygenase enzyme, a key mediator of arachadonic acid metabolism, resulting in a decrease in the production of proinflammatory and procoagulant mediators, including thromboxane A2, and has been demonstrated to reduce ischemic events in the setting of ST-elevation and non–ST-elevation ACS.[7,8] The glycoprotein IIb/IIIa integrin receptor antagonists block platelet aggregation by interfering with the formation of platelet fibrinogen crosslinks and have also been demonstrated to improve clinical outcomes of selected patients with ACS, especially those at high risk of recurrent ischemic events and those being managed with an invasive (coronary angiography directed) strategy of care.[9,10]

The thienopyridine class of antiplatelet agents has three members: ticlopidine, clopidogrel, and the subject of this review, prasugrel. All three

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drugs are prodrugs, orally inactive, and require metabolism to an active metabolite. The active metabolite of the thienopyridine binds irreversibly to the P2Y12 receptor, blocking the binding of ADP, and thereby inhibiting platelet activation and aggregation.[11] Ticlopidine, the first-generation thienopyridine was initially developed and tested in patients with previous transient ischemic attack or stroke.[12,13] The major utility of ticlopidine, however, was as a component of dual antiplatelet therapy in combination with aspirin for patients with PCI and intracoronary stents.[14–17] The utility of this agent was shown in a series of trials comparing dual antiplatelet therapy to aspirin plus an oral anticoagulant.[14,15] The utility of ticlopidine, however, was limited by the need to take the drug twice daily, and by issues with tolerability, including gastrointestinal distress and, most importantly, rare but severe hematological side effects, such as bone marrow aplasia,[18] which required frequent monitoring. As such, the clinical use of ticlopidine is largely historical. However, the results of studies of ticlopidine in cardiovascular disease set the stage for the use of the second-generation thienopyridine, clopidogrel, in cardiovascular disease, including ACS and PCI.

Clopidogrel plus aspirin dual antiplatelet therapy has become the standard of care for the support of patients undergoing PCI with stenting regardless of the indication for PCI.[19] In the Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS)[20] comparing ticlopidine plus aspirin to clopidogrel (with or without a loading dose) plus aspirin in patients with stenting, clopidogrel was found to have a significantly better safety/tolerability profile, but no difference between the two agents was observed in recurrent ischemic events.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial compared clopidogrel plus aspirin with aspirin alone in patients with non–ST-elevation ACS[21] and observed an improvement ischemic outcomes and an increase in minor bleeding events. Of the patients enrolled in the CURE trial who underwent PCI, reported as the PCI-CURE,[22] analysis demonstrated 30% relative reduction in the key composite end point of cardiovascular death, MI, and urgent revascularization.[22] On the basis of these and other studies, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend dual antiplatelet therapy with aspirin and clopidogrel in patients with ACS for up to 1 year regardless of treatment strategy (medical, PCI, or surgery).[5]

Patients with ST-segment elevation MI (STEMI) were not included in the CURE trial but also have strong clinical trial evidence for the use of dual antiplatelet therapy, including aspirin and clopidogrel. In the Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction 28 (CLARITY-TIMI 28) trial, subjects with STEMI receiving fibrinolytic therapy were randomized to dual antiplatelet therapy with aspirin or to aspirin alone. The composite end point of death, MI, or an occluded infarct-related artery was reduced by 36%, which was highly statistically significant, without an observed increase in major bleeding or a difference in intracranial hemorrhage.[23] The results of CLARITY-TIMI 28 were complemented by the report of the Clopidogrel and Metoprolol in Myocardial Infarction Trial—Second Chinese Cardiac Study (COMMIT-CCS 2),[24] a large simple trial with more than 45,000 subjects enrolled within 24 hours of MI and allocated to clopidogrel daily plus aspirin or aspirin alone until hospital discharge. Clopidogrel resulted in a 0.9% absolute reduction in death, which was statistically significant.[24] These studies together have resulted in the recommendation by national guidelines committees for the use of clopidogrel in patients with STEMI treated medically with or without fibrinolytic therapy.[3]

PHARMACOLOGIC LIMITATIONS OF CLOPIDOGREL

Despite the profound successes of clopidogrel alone and in combination with aspirin for patients with ACS and those undergoing PCI, there are pharmacologic limitations of this agent.[25] The antiplatelet effects of clopidogrel have a delayed onset and substantial variability among patients. With a growing number of studies using a variety of measures linking poor antiplatelet response to clopidogrel and in turn to adverse clinical outcomes, particularly coronary ischemia and stent thrombosis,[26–29] an interest has emerged in the development of antiplatelet therapy that is more intensive than that offered with clopidogrel.

One such agent, prasugrel, a third-generation thienopyridine, is the focus of this review.

PHARMACOLOGY AND EARLY PHASE CLINICAL STUDIES OF PRASUGREL

Like ticlopidine and clopidogrel, prasugrel is a prodrug that requires activation (**Fig. 1**) to form an active metabolite with platelet inhibitory properties.[30] Prasugrel is metabolized in a two-step process, including initial activation by plasma esterases followed by a single cytochrome P-450 (CYP)–dependent step.[31] In contrast, clopidogrel is largely inactivated by plasma esterases before a two-step CYP-dependent activation.[31] These