

Old and New Players in Oral Antiplatelet Therapy in Treatment of Acute Coronary Syndrome

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ABSTRACT

Oral antiplatelet therapy plays an important role in treating patients with acute coronary syndrome (ACS), including patients with unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) and patients with ST-segment elevation myocardial infarction (STEMI). All antiplatelet drugs in addition to inhibiting acute arterial thrombosis have danger of interfering with the physiologic role of platelet hemostasis. Bleeding is a major factor in evaluating the utility of available and upcoming antiplatelet drugs and their combination regimes. The role of antiplatelet agents in the treatment of ACS has undergone significant changes over the past several years. Aspirin, thienopyridines, and glycoprotein (GP) IIb/IIIa inhibitors are now standard parts of the treatment of STEMI, NSTEMI and UA whether an early invasive or an initial conservative strategy is chosen. Antiplatelet drugs have an important role in secondary prevention in the patients of ischaemic heart disease.

Keywords: Acute Coronary Syndrome; antiplatelet therapy; thienopyridines.

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Introduction

As the intricacies of platelet biology and mechanisms of thrombus formation are revealed, novel antiplatelet therapies have emerged. Platelets play a key role in the pathogenesis of atherosclerosis and atherothrombosis, contributing to both the initiation and progression of coronary artery disease. Antiplatelet therapy therefore features prominently in the treatment of acute coronary syndromes (ACS) and in patients undergoing percutaneous coronary intervention. As our understanding of platelet biology continues to evolve, new targets for the inhibition of platelet function have emerged. A computerised medical literature search of all English language articles was done from the “PubMed” online database with the keywords “antiplatelet therapy”, “thienopyridines”, “acute coronary syndromes” and “proton pump inhibitors”.

Irreversible platelet cyclooxygenase-1 inhibitors

Aspirin

Aspirin is most widely used antiplatelet agent and serves as the foundation of most strategies. After years of use and numerous clinical trials, the role of aspirin for patients with ACS is well established.¹ It produces its antithrombotic effect by irreversibly acetylating and inhibiting platelet cyclooxygenase (COX)-1, a critical enzyme in the biosynthesis of thromboxane A₂, a potent platelet activator.¹⁻³ Long-term aspirin therapy confers a conclusive net benefit on the risk of subsequent myocardial infarction (MI), stroke, or vascular death among subjects with an intermediate-to-high risk of vascular complications. These include patients with chronic stable angina, patients with prior MI,² patients with unstable angina,^{1,2} as well as

other high-risk categories.¹ The proportional effects of long-term aspirin therapy on vascular events in these different clinical settings are rather homogenous, ranging between 20% and 25% odds reduction based on an overview of all randomized trials.¹ Aspirin is also used for primary prevention in patients whose estimated annual risk of MI is >1%, a point where its benefits are likely to outweigh harms. In men, aspirin mainly reduces the risk of MI, while in women aspirin lowers the risk of stroke.⁴ Aspirin doses of 75–100 mg are recommended for most indications.⁵ However, its low potency due to a partial inhibition of platelet aggregation, some patients resistance to aspirin, and its gastrointestinal side effects prompted the search for more consistent, and more specific platelet inhibiting agents.⁵⁻⁷

Irreversible P2Y12 purinoreceptors inhibitors

Clopidogrel

The key role of adenosine diphosphate (ADP) in the process of platelet aggregation, and thrombus formation led to the development of drugs targeting P2Y12 receptor.⁸ The thienopyridine class of antiplatelets—Ticlopidine, Clopidogrel, and Prasugrel—selectively and irreversibly inhibit the P2Y12 purinoreceptors throughout the lifespan of the platelet. Clopidogrel is an irreversible thienopyridine ADP receptor antagonist. It can be considered an alternative to aspirin in patients with aspirin intolerance or who are allergic to aspirin.⁹ In patients with established atherosclerotic cardiovascular (CV) disease. Clopidogrel alone reduced (5.8% to 5.3%), the combined risk of major CV events, ischemic stroke, MI, and vascular death compared with aspirin alone⁶ and led to less (GI) bleeding (2.7% to 2.0%). Clopidogrel is recommended as an alternative agent for patients with CV disease unable to take aspirin.⁹⁻¹¹

Clopidogrel and Aspirin are combined to capitalize on their capacity to block complementary pathways on platelet activation.¹⁰⁻¹³ The combination of Clopidogrel and Aspirin is also effective in patients with unstable angina.⁴ Thus in such patients, the risk of cardiovascular death, MI or stroke was 9.3 % in those randomized to combination of Clopidogrel and Aspirin and 11.4 % in those given aspirin alone. This relative risk reduction with combination was highly statistically significant.^{4,14,15} In primary prevention settings, dual antiplatelet therapy with Clopidogrel and aspirin did not significantly reduce major CV events compared to aspirin alone (6.8 %) versus (7.3 %) but increased severe bleeding (1.3 % to 1.7 %). Therefore, the combination of Clopidogrel and aspirin should only be used when there is a clear benefit.^{13,14}

All the orally administered thienopyridines are prodrugs which require biotransformation into their active metabolites by fixed sets of hepatic cytochrome P450 (CYP) enzymes,

in particular, the CYP3A4 isozyme. The limitations of Clopidogrel — delayed onset of action, large interindividual variability in platelet response, irreversibility of its inhibitory effect on platelet, the two-step activation process, involving a series of cytochrome P-450 (CYP) isoenzymes, rendering it susceptible to the interference of genetic polymorphisms¹⁶⁻¹⁸ and drug–drug interactions¹⁷ encouraged the investigation of novel antiplatelet agents.^{19,20}

Prasugrel

Prasugrel is a new thienopyridine derivative with a rapid onset and consistent inhibition of platelet aggregation. In contrast to Clopidogrel's esterase inactivation and two-step CYP-dependent activation, Prasugrel has a more efficient and simpler metabolism, which requires only one reaction by the liver enzymes to yield its active metabolite.²¹⁻²³ This difference in the metabolism of these thienopyridines translates clinically into different patient responses and drug interactions with these antiplatelet agents.¹⁷ Patients with a poor response to Clopidogrel have an increased risk of coronary thrombosis.¹⁹ The increased risk of bleeding due to prolonged persistence of the Clopidogrel effect is of concern when patients need non-deferrable surgery such as urgent coronary-artery bypass grafting (CABG). To compare Prasugrel with Clopidogrel, in TRITON–TIMI 38 trial,²³ 13,608 patients were randomly assigned with moderate-to-high-risk acute coronary syndromes with scheduled percutaneous coronary intervention (PCI) to receive Prasugrel (a 60-mg loading dose and a 10-mg daily maintenance dose) or Clopidogrel (a 300-mg loading dose and a 75-mg daily maintenance dose) for 6 to 15 months. The primary efficacy end point was death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke. The key safety end point was major bleeding. In patients with ACS and planned PCI, Prasugrel reduced major CV events from 12.1% to 9.9% compared with Clopidogrel but increased major bleeding from 1.8% to 2.4% and fatal bleeding from 0.1% to 0.4%. Because patients older than age 75 years and those with a history of prior stroke or transient ischemic attack have a particularly high risk of bleeding, Prasugrel should generally be avoided in older patients, and the drug is contraindicated in those with a history of cerebrovascular disease. Caution is required if Prasugrel is used in patients weighing less than 60 kg or in those with renal impairment.

Reversible P2Y12 receptor inhibitor

Ticagrelor

However, the limitations of the irreversibility of the thienopyridine effect are also evident with Prasugrel. Ticagrelor, is a novel, reversible, direct-acting P2Y12 receptor blocker. Report on the results of the study of

Platelet Inhibition and Patient outcome – PLATO²⁴ showed the reduced primary endpoint of vascular death, MI, or stroke from 11.7% to 9.8% compared with Clopidogrel, with no significant difference in major bleeding (11.6% versus 11.2%) but with an increased risk of noncoronary artery bypass graft major bleeding (3.8% to 4.5%). PLATO²⁴ is the third randomized trial evaluating novel antagonist of the platelet ADP receptors in patients with acute coronary syndromes, following the Clopidogrel in Unstable Angina to Prevent Recurrent Events – CURE trial⁹ and TRITON-TIMI 38.²³ Two striking differences among the outcomes of these three trials deserve special consideration. First, in both the CURE trial and TRITON-TIMI 38,²³ stronger platelet inhibition was associated with an increased risk of bleeding, whereas in PLATO²⁴ the risk of major bleeding was not increased with Ticagrelor. As compared to Clopidogrel, Ticagrelor was associated with more frequent non-CABG – related bleeding but it was safer than Clopidogrel in patients undergoing CABG. Genetic variations in CYP isoenzymes do not appear to affect metabolism of Ticagrelor.

In PLATO trial,²⁴ Ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, $P=0.03$), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types. Therefore in patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with Clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding. Ticagrelor therapy may also be preferred in patients whose coronary anatomy is unknown and for whom CABG procedure is deemed probable. Dyspnoea occurred more frequently with Ticagrelor than Clopidogrel. Discontinuation of Ticagrelor due to dyspnoea occurred in 0.9 % of patients in Ticagrelor group. Holter monitoring detected more ventricular pauses during the first week in Ticagrelor group than in the Clopidogrel group but these episodes were infrequent at 30 days and were rarely associated with symptoms. There were no significant differences in rates of clinical manifestations of bradyarrhythmias between the two groups. Ticagrelor therapy should be discouraged in patients who have chronic pulmonary disease, hyperuricemia, moderate to severe renal failure, bradyarrhythmias unprotected by pacemaker and history of syncope.²⁴ Ticagrelor has been included in 2011 AHA/ACC recommendations for use in ACS.²⁵ The availability of three agents for antagonizing platelet ADP receptors may make it possible to individualize antiplatelet therapy. In particular, Ticagrelor therapy may be preferred in patients whose coronary anatomy is unknown and for whom a CABG procedure is deemed probable.²⁶

Proton pump inhibitors and antiplatelet agents

Proton pump inhibitors (PPIs) are often prescribed prophylactically when Clopidogrel is started, to prevent gastrointestinal complications such as ulceration and related bleeding²⁷ due to dual-antiplatelet therapy, in particular Acetyl Salicylic Acid (ASA) and Clopidogrel.²⁸ PPI medications have been found to interfere with the metabolism of Clopidogrel.²⁹ There have been retrospective reports of adverse cardiovascular outcomes (e.g., readmission for ACS) when the antiplatelet regimen of Clopidogrel and ASA is accompanied by PPIs, assessed as a group, compared with the use of this regimen without a PPI.²⁹⁻³¹ In a retrospective cohort study from the Veterans Affairs' medical records and pharmacy database, concomitant Clopidogrel and PPI therapy (with Omeprazole, Rabeprazole, Lansoprazole, or Pantoprazole) at any time point during follow-up of 8205 patients discharged for ACS was associated with an increased risk of death or rehospitalization for ACS.²⁹ Other post hoc study,³¹ a retrospective data analysis from the NHLBI Dynamic Registry³² in which PPIs were assessed as a class in combination with a Clopidogrel and an ASA regimen have not found an effect of PPI therapy on the clinical effect of Clopidogrel in ACS patients, after ACS, or in a general post-PCI population respectively.

Some studies have suggested that adverse cardiovascular outcomes with combination of Clopidogrel and a Proton Pump Inhibitor (PPI) are explained the individual PPI, in particular the use of a PPI that inhibits CYP450 2C19, which includes Omeprazole, Lansoprazole and Rabeprazole. The PPI Omeprazole notably has been reported to significantly decrease the inhibitory effect of Clopidogrel on platelet aggregation.^{33,34} One study reported that the PPI Pantoprazole was not associated with recurrent MI, possibly because of lack of inhibition of CYP450 2C19.³⁰

An open-label drug study evaluated the effects of the PPI Lansoprazole on the pharmacokinetics and pharmacodynamics of Prasugrel and Clopidogrel in healthy subjects given single doses of Prasugrel (60 mg) and Clopidogrel (300 mg) with and without concurrent Lansoprazole (30 mg) per day. The data suggest that inhibition of platelet aggregation was reduced in patients who took the combination of Clopidogrel and Lansoprazole, whereas it was unaffected after a Prasugrel dose.³⁵ The PRINCIPLE (Prasugrel In Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation) TIMI-44 trial^{36,37} and the TRITON-TIMI 38 trial. The findings indicated that first PPI treatment attenuated the pharmacodynamics effects of Clopidogrel and to a lesser extent those of Prasugrel. Secondly, PPI treatment did not affect the clinical outcome of patients given Clopidogrel or Prasugrel. This finding was true for all PPIs that were studied, including Omeprazole

and Pantoprazole.

A selected review of the published literature done in a study on the indications for gastric protection with PPI in patients on mono- or dual antiplatelet therapy focusing on the possible interaction between Clopidogrel and PPI revealed that in ex vivo analyses of platelet function, a reduced efficacy of Clopidogrel was observed in patients on comedication with Omeprazole. This was not the case with the comedication of other PPIs. It further stated that “To date, clear evidence is missing to state that comedication with PPI reduces the efficacy of Clopidogrel IN VIVO. If both Clopidogrel and PPI need to be prescribed, a split dosage regimen of PPI in the morning and Clopidogrel in the evening can be recommended. The short half-life of both medications explains the rationale of this recommendation.”³⁸

The use of H2 antagonists as an alternative to PPIs in the setting of dual-antiplatelet therapy, although they cannot be relied on to protect as well as PPIs, and there are few data about their use with ASA needs further consideration. The FAMOUS (Famotidine for the Prevention of Peptic Ulcers in Users of Low-Dose Aspirin), a phase II, double-blind, randomized, placebo-controlled trial, found that among patients with a history of coronary heart disease, diabetes mellitus, or cerebrovascular disease who were taking low-dose ASA, 12 weeks of Famotidine 20 mg twice daily (n=204) compared with placebo twice daily (n=200) was beneficial in reducing the incidence of peptic ulcer or oesophagitis during follow-up endoscopy at 12 weeks. In the Famotidine group, Clopidogrel use was 19% and Dipyridamole use was 6%.³⁹

AHA /ACC focused update 2009 has noted that additional data, notably randomized controlled clinical trial data that have been peer reviewed and published, are needed before an official recommendation can be made about the use of dual antiplatelet therapy with PPIs in the setting of ACS.⁴⁰

European College of Cardiology (ESC) has issued the following recommendations for oral antiplatelet agents in the management of acute coronary syndromes in 2011.⁴¹

Esc Recommendations for Oral Antiplatelet Agents

Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.

Class I

- A P2Y12 inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.^{42,43}

- A proton pump inhibitor (preferably not Omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (*Helicobacter pylori* infection, age ≥ 65 years, concurrent use of anticoagulants or steroids).^{9,23,24}
- Prolonged or permanent withdrawal of P2Y12 inhibitors within 12 months after the index event is discouraged unless clinically indicated.^{28,44,45}
- Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y12-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life threatening bleeding or other contraindications.²⁴
- Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive Ticagrelor or Prasugrel.²³
- A 600-mg loading dose of Clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when Ticagrelor or Prasugrel is not an option.^{9,46,47}
- A higher maintenance dose of Clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.^{19,43,48}

Class IIa

- Increasing the maintenance dose of Clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.⁴⁴

Class IIb

- Genotyping and/or platelet function testing may be considered in selected cases when Clopidogrel is used.⁴⁹

Class IIb

- In patients pre-treated with P2Y12 inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of Ticagrelor or Clopidogrel, and 7 days for Prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.^{50,51}

Abbreviations: CABG: coronary artery bypass graft; COX: cyclo-oxygenase; DAPT -dual (oral) antiplatelet therapy; NSAID -non-steroidal anti-inflammatory drug; PCI: percutaneous coronary intervention.

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