

2012


Anti-Platelet Therapy in Acute Coronary Syndromes: Updates in Therapy After Stent Implantation

Ryan McKenzie
Midwestern University

Andrew Park
Midwestern University

Laura Tsu
Chapman University, ltsu@chapman.edu

Follow this and additional works at: https://digitalcommons.chapman.edu/pharmacy_articles

 Part of the [Cardiovascular Diseases Commons](#), [Medical Education Commons](#), [Other Pharmacy and Pharmaceutical Sciences Commons](#), and the [Science and Mathematics Education Commons](#)

Recommended Citation

McKenzie R, Park A, Tsu LV. Anti-platelet therapy in acute coronary syndromes: Updates in therapy after stent implantation. *Arizona Journal of Pharmacy* 2012;33-40.

This Article is brought to you for free and open access by the School of Pharmacy at Chapman University Digital Commons. It has been accepted for inclusion in Pharmacy Faculty Articles and Research by an authorized administrator of Chapman University Digital Commons. For more information, please contact laughtin@chapman.edu.

Anti-Platelet Therapy in Acute Coronary Syndromes: Updates in Therapy After Stent Implantation

Comments

This article was originally published in *Arizona Journal of Pharmacy* in 2012. Those receiving articles through Chapman University Digital Commons may not receive Continuing Education (CE) credit.

Copyright

Arizona Journal of Pharmacy. All rights reserved. This publication may not be republished or re-distributed without authorization from the Arizona Pharmacy Association.

Anti-platelet Therapy in Acute Coronary Syndromes: Updates in Therapy after Stent Implantation

by Ryun McKenzie, Pharm.D. Candidate Class of 2013; Andrew Park, Pharm.D. Candidate Class of 2013; Laura Tsu, Pharm.D., BCPS; Midwestern University College of Pharmacy - Glendale

Goal:

This home-study CPE activity has been developed to educate pharmacists on updates in anti-platelet therapy after stent implantation.

Objectives:

At the conclusion of this lesson, successful participants should be able to:

1. Identify the mechanism of action and unique characteristics of the FDA-approved P2Y₁₂ receptor antagonists used in secondary prevention of cardiovascular disease.
2. Describe the recent recommendations regarding safety and efficacy for oral anti-platelet therapy post cardiac-stent placement.
3. Compare the benefits and risks associated with each P2Y₁₂ receptor antagonists based on presented clinical data.
4. Select the appropriate anti-platelet therapy using patient-specific parameters for prevention of recurrent cardiac events.

Introduction

Despite advances in pharmacotherapy and technology, acute coronary syndromes (ACS) remains a significant healthcare issue with more than 1.2 million Americans suffering an ACS event annually.¹ The usual culprit in ACS is an atheromatous plaque rupture which causes platelet activation and aggregation, leading to the propagation of the coagulation cascade. If untreated, the formation of a platelet-rich “white” clot will lead to an ACS event, which includes ST segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI) or unstable angina (UA). Treatment options for ACS include percutaneous coronary interventions (PCI) with stent implantation, thrombolytic therapy, and/or medical management.

After the acute treatment of patients with ACS, the pharmacotherapy focus shifts to secondary prevention of cardiovascular events. In patients who receive a stent implantation, one of the most important preventative measures is anti-platelet therapy to prevent both

stent restenosis and in-stent thrombosis.

Anti-platelet therapy for secondary prevention of cardiac events in the first year after ACS with PCI therapy and stent placement centers on several options: clopidogrel, prasugrel, ticagrelor, and aspirin. The first 3 agents are P2Y₁₂ receptor antagonists while aspirin inhibits platelet cyclooxygenase-1. Regardless of the mechanism, inhibition of these platelet pathways ultimately results in decreased platelet activation and aggregation.

For patients with implanted coronary stents, there are differing lengths of anti-platelet therapy based on the type of stent placed.^{2,3} The recommended therapy for bare metal stent placement include dual anti-platelet therapy with aspirin 75 - 325 mg daily and clopidogrel 75 mg for 1 month, then low dose aspirin 81 mg daily and clopidogrel 75 mg daily for the subsequent 11 months, and then single anti-platelet therapy with aspirin 81 mg daily indefinitely thereafter. The recommended therapy for drug-eluting stent placement include dual anti-platelet therapy with aspirin 75 - 325 mg with clopidogrel 75 mg daily for 3 - 6 months (minimum of 3 months for sirolimus-eluting stent and 6 months for paclitaxel-eluting stent), then low dose aspirin with clopidogrel 75 mg daily for 6 - 9 months thereafter, and then single anti-platelet therapy with aspirin 81 mg daily indefinitely (see Figure 1. for algorithm).⁴ The 2011 American College of Cardiology Foundation/American Heart Association Task force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions (ACCF/AHA/SCAI) recommend indefinite aspirin 81 mg therapy in preference over higher doses in combination with P2Y₁₂ receptor antagonists. A minimum of 12 months of therapy with P2Y₁₂ receptor antagonists is recommended with either a bare metal stent or drug-eluting stent if the patient is not at high risk of bleeding. Continuation of therapy beyond 12 months may be considered for those with drug-eluting stent placement and low risk of bleeding (see Figure 2. for algorithm).²

Both the CHEST and 2011 ACCF/AHA/SCAI practice guidelines recommend

the use of aspirin therapy with a P2Y₁₂ receptor antagonist post-cardiac stent implantation. In contrast, the guidelines differ with regard to the preference given to the individual P2Y₁₂ receptor antagonist. The recent CHEST guidelines give preference to ticagrelor therapy over clopidogrel and prasugrel.^{2,4} Therefore, the focus of this review is to compare the similarities and differences in efficacy and safety between the 3 FDA-approved P2Y₁₂ receptor antagonist: clopidogrel, prasugrel, and ticagrelor.

Clopidogrel (Plavix®)

Clopidogrel is a second-generation thienopyridine which irreversibly inhibits the P2Y₁₂ receptor on platelets. It is a pro-drug that requires hepatic biotransformation via CYP enzymes, particularly CYP2C19, to produce the active metabolite necessary to exert its pharmacological actions.⁵ The active metabolite formed in this process targets the P2Y₁₂ receptor, one of the adenosine diphosphate (ADP) receptors on the platelet surface, to prevent platelet recruitment and activation of the GPIIb/IIIa receptor complex; in so doing, platelet aggregation is reduced.⁶ Clopidogrel's pharmacokinetic profile exhibits rapid dose absorption with or without food.⁷ The conversion of the parent drug to active metabolite with maintenance dosing at 75 mg daily takes, on average, about two days to see inhibition of platelet aggregation (IPA) with peak effect occurring in 5 - 7 days.⁸ Due to the potential need for rapid inhibition of platelet aggregation, loading doses have been used to achieve faster therapeutic goals as studies have shown that peak IPA was able to be achieved within 6 hours with higher loading doses (300 mg, 600 mg, 900 mg).⁹

Although approximately half of the systemically circulating clopidogrel is cleared through the kidneys and the other half in the feces, there is limited data on the safety of this medication in renal impairment. No adjustment is necessary for those with hepatic impairment. It is also important to consider that while the half-life of clopidogrel is relatively

short (~ 0.5 hour) compared to the parent compound (~ 6 hours), it binds irreversibly to the platelet receptors resulting in normal platelet function of those blocked by clopidogrel to return with the development of new platelets. Platelet turnover takes approximately 7-10 days which is how long it would take for normal platelet function to return after the last dose of clopidogrel is administered.^{4,7}

Efficacy of clopidogrel in PCI

For patients with newly placed coronary stents, dual anti-platelet therapy with clopidogrel in addition to aspirin has shown to improve outcomes with long-term therapy. Data from studies such as the PCI-CURE trial which found significantly lower rates of cardiovascular (CV) death, myocardial infarction (MI), or any revascularization in patients undergone PCI with dual anti-platelet therapy beyond 4 weeks of treatment have helped to focus subsequent studies on the optimal length of therapy.¹⁰ The CREDO trial did just that and provided optimization for long-term anti-platelet therapy post-PCI when they found that there was relative reduction (26.9%) in combined CV events with at least a year of long-term dual therapy with clopidogrel and aspirin.¹¹ These trials highlight the significant use of clopidogrel in this patient population; however, the following sections will address several considerations that should be made when choosing this agent.

Drug Interactions with Proton Pump Inhibitors

In an effort to maintain high therapeutic efficacy but minimize gastrointestinal (GI) toxicity from clopidogrel use, clinicians began adding on proton-pump inhibitor (PPI) treatment. While effective, *in vitro* data supported the notion that competitive inhibition by PPIs of CYP2C19 may alter the necessary metabolic step needed to produce the active metabolite of clopidogrel.¹² The focus of current discussion is the therapeutic effect this interaction has on therapy outcomes. In the prospective randomized placebo-controlled COGENT trial of 3,873 patients, investigators assigned patients on dual anti-platelet therapy (clopidogrel 75 mg and aspirin 75 mg - 325 mg daily) to either omeprazole 20 mg or placebo. The primary endpoint of composite gastrointestinal event as determined by

bleeding ulcers, obstruction, or perforation addressed the potential benefits of gastrointestinal protection while on anti-platelet therapy. In addition, the primary safety endpoint composite of CV events as determined by death from CV causes, MI, revascularization, or stroke addressed the proposed interaction between clopidogrel and omeprazole on decreased anti-platelet activity. The study found lower gastrointestinal events rates with omeprazole when compared to placebo; supportively, in the safety endpoint comparison, there was no difference in the risk of CV events or MI in the treatment groups.¹³

In order to evaluate the effects of this interaction even further, a meta-analysis of twenty five studies (159,138 patients) was performed to assess the association of adverse events with combination therapy. They found that combination therapy with PPIs (searched keywords of ‘pantoprazole,’ or ‘omeprazole’ or ‘esomeprazole’ or ‘lansoprazole’ or ‘rabeprazole’) with clopidogrel was associated with increased risks of major adverse CV events and MI at 29% and 31%, respectively. However, PPI use was not associated with an overall increase in mortality. Subgroup analyses of concomitant use of clopidogrel with either pantoprazole or omeprazole were not associated with an increased risk of major CV events. While the analysis showed no influence on mortality, the investigators did find a decrease in the risk of developing GI bleed under PPI treatment by 50%.¹²

In lieu of the results presented in these trials, the Food and Drug Administration continues to warn against concomitant use of clopidogrel and PPIs, and recommends that combination treatment be used with caution. It should be noted that this warning advisory does not apply to all PPIs as not all PPIs affect the CYP enzymes similarly.¹⁴ The ACCF/ACG/AHA released a 2010 update on the 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use stating that a small to moderate association can be made based on available evidence; however, further randomized controlled trials are needed to validate the associations found in observational studies. While several trials showed no significant association of CV events, the potential relative risk of CV events may warrant

caution in combination therapy. The lack of consensus among trials confounds a clear association of PPI use with clopidogrel as the data is weak to establish decreased anti-platelet activity with coadministration. Ultimately, treatment decisions need to assess whether the potential benefits outweighs potential harm as patients with prior upper GI bleeding and risk factors may benefit from prophylaxis against GI bleeding.¹⁵

Decreased platelet responsiveness

In regards to anti-platelet efficacy, clopidogrel has a black box warning notifying that patients with genetic variability in CYP2C19 function, such as those with two nonfunctional alleles termed “poor metabolizers” of clopidogrel, may have reduced anti-platelet activity. Studies have suggested that high on-treatment platelet reactivity, those that require higher doses to achieve therapeutic effect, occurs in one-third of those prescribed clopidogrel.⁴ As a result, there have been higher cardiovascular event rates when this patient population is exposed to normal recommended doses when compared to those that do not have the decreased CYP2C19 function. A meta-analysis compared the risk of major adverse cardiovascular events of clopidogrel administration between noncarriers (71.5%), heterozygotes (26.3%), or homozygotes (2.2%) of reduced-function CYP2C19 alleles that underwent PCI that had an ACS. This study found that there was a significantly increased risk in both the patient populations with 1 reduced-function CYP2C19 allele and 2 reduced-function CYP2C19 alleles when compared to noncarriers. The analysis also found a significantly increased risk of stent thrombosis in both carriers of the reduced-function allele suggesting those patient populations with even 1 reduced-function CYP2C19 allele may not be fully protected from cardiovascular events despite standard doses of clopidogrel.¹⁶ Considering this patient population, there currently lacks support for the use genetic testing or platelet function testing to individualize anti-platelet therapy.³

Dosing and monitoring of clopidogrel

Clopidogrel is recommended to be administered as a 600 mg loading dose during PCI, followed by 75 mg daily maintenance dose.² In addition to the

forementioned precautions regarding PPIs, healthcare providers should be aware of other medications that are CYP2C19 inhibitors. Examples include fluconazole, voriconazole, and fluoxetine.

As with other medications in the thienopyridine class, there are risks of bleeding present with clopidogrel. Careful consideration in certain patient populations should be made as clopidogrel is contraindicated in those with active bleeding such as peptic ulcer or intracranial hemorrhage. Bleeding concerns have also prompted the recommendation to discontinue clopidogrel 5 days prior to surgery. When clopidogrel was stopped beyond 5 days before a coronary artery bypass graft (CABG), rates of major bleeding were similar to those taking placebo. In comparison, patients who remained on clopidogrel within 5 days of a CABG, rates of major bleeding were higher at 9.3% compared to 6.3% in the placebo group (see Table 1 for comparison chart).¹⁷

Newer anticoagulants options: prasugrel and ticagrelor

Clopidogrel has been clinically proven to reduce recurrent cardiovascular events but clopidogrel has several limitations: it is a pro-drug that requires hepatic conversion, has a delayed onset, and demonstrates a wide inter-patient variability and delayed recovery due to irreversible receptor binding. Prasugrel and ticagrelor, two relatively new P2Y₁₂ receptor antagonists have been approved as alternatives to clopidogrel for patients with ACS undergoing PCI with stent placement.²⁴ Both seek to address some of the issues faced with clopidogrel.

Prasugrel (Effient®)

Prasugrel was approved in 2009 for the reduction of recurrent cardiovascular events in patients with ACS who are undergoing PCI. Similar to clopidogrel, prasugrel is a thienopyridine which irreversibly inhibits the P2Y₁₂ receptor on the platelet.¹⁸ Prasugrel seeks to improve upon the shortcomings of clopidogrel with some key differences. While it is also a pro-drug, prasugrel is metabolized in the gastrointestinal tract and liver more rapidly than clopidogrel and the resulting metabolite binds irreversibly to the P2Y₁₂ receptors on platelets inhibiting their aggregation without the need for a second activation step compared to two

for clopidogrel. Also, prasugrel is not as adversely affected by individual genetic variations, which results in faster and more predictable platelet inhibition.⁵ It can reach peak concentration in as quickly as 30 minutes and last up to 7 hours.¹⁹

Efficacy and safety of prasugrel

The TRITON-TIMI 38 phase 3 study sought to determine the safety and efficacy of prasugrel compared to clopidogrel in 13,608 patients with ACS who were undergoing PCI. Clopidogrel was administered as a 300 mg loading dose then 75 mg daily while the comparator group was administered prasugrel 60 mg loading dose then 10 mg daily for 6 to 15 months. The study measured the primary efficacy endpoints of death from CV causes, nonfatal MI, and nonfatal stroke, while the incidence of major bleeding was the major safety endpoint. It was observed that in addition to a significantly lower number of primary efficacy endpoint events with prasugrel (9.9%) as compared with clopidogrel (12.1%), the prasugrel group also had fewer rates of MI, target-vessel revascularization, and stent thrombosis. However, the added benefit of increased efficacy came with the drawback of a higher incidence of major and life-threatening bleeding events in the prasugrel group.²⁰

Due to this increased risk of bleeding in the total study population, further subgroup analyses were performed to determine whether or not certain patient populations would experience a greater net clinical benefit from prasugrel, with the reduction in cardiovascular events outweighing the bleeding risk. To answer these questions, 2 separate subgroup analyses were performed on patients with diabetes and with a STEMI. Of the total 13,608 patients in the TRITON-TIMI 38 trial, the first subgroup analysis trial explored the safety and efficacy of prasugrel versus clopidogrel in the 3,146 patients with diabetes mellitus (DM). From a primary efficacy standpoint, there were significantly fewer incidents of (CV death, non-fatal MI, or non-fatal stroke) with prasugrel compared to clopidogrel in both the diabetic (9.2% versus 10.6%) and non-diabetic (12.2% versus 17%) groups. In contrast to the findings in the original TRITON-TIMI 38 trial, the diabetic subgroup in this study did not have an increased risk of major bleeding compared to clopidogrel (2.6% versus 2.5%). For

patients on prasugrel, the greater relative reduction in incidents of the primary end point and MI events without an observed increase in major bleeding provided a greater net clinical benefit when compared to clopidogrel.²¹

The other subgroup analysis included 3,534 participants with STEMI treated with either prasugrel or clopidogrel. The primary endpoint was a composite of CV death, non-fatal MI, or non-fatal stroke at 30 days and at 15 months. Compared to clopidogrel, the prasugrel group had a significantly lower incidence of the primary efficacy endpoint at both 30 days (9.5% vs. 6.5%) and at 15 months (12.4% vs. 10%). There was no significant difference in major bleeding unrelated to CABG surgery between both groups; similarly, no difference was reported in life-threatening bleeding, intracranial hemorrhage, or minor bleeding at 15 months. However, it was observed that patients on prasugrel who underwent CABG surgery experienced an increased risk for major bleeding compared to those on clopidogrel.²² Therefore, STEMI patients may also be a population in which prasugrel demonstrates a greater net clinical benefit when compared to clopidogrel.

Although prasugrel showed additional benefits for diabetics and those who have STEMIs, it is important to note that neither of these subgroup analyses were designed or powered for all clinical endpoints in the population, and the small sample size may have skewed the results.^{21, 22}

Dosing and monitoring of prasugrel

In patients undergoing PCI with stent placement, prasugrel is typically administered as a single 60 mg loading dose followed by a maintenance dose of 10 mg once daily if the patient weighs more than 60 kg. Patients with lower body weights may have an increased risk of bleeding and it is recommended that a lower 5 mg maintenance dose be used for those weighing less than 60 kg.^{2, 23} It must be noted, however, that although a lower maintenance dose is recommended for lower weight patients, safety and efficacy at this dose has not yet been studied.

Most of the contraindications and warnings center on patients with these risks due to the increased incidence of major and potentially fatal bleeding seen in the prasugrel trials when compared

to clopidogrel. It is contraindicated in patients with active pathological bleeding, history of transient ischemic attack (TIA) or stroke. Other high risk populations with an increased risk of bleeding include patients older than 75 years, weigh less than 60 kg, have a propensity to bleed, and are using concomitant medications that increase bleeding risk. Examples of these medications include warfarin, NSAIDs or fibrinolytic therapy. While it is generally not recommended to use prasugrel in patients older than 75 years, it may be considered in patients with diabetes or STEMI, as those groups demonstrated a greater net clinical benefit compared to the total study population.²¹

Prasugrel should be stopped at least 7 days before CABG with the extra time required due to the longer half-life.²¹ If possible, it is recommended that any bleeding be managed without discontinuing the medication due to increased risk of cardiovascular events if stopped prematurely. Practitioners managing these patients should also consider other common adverse drug events, including hypertension, hyperlipidemia, head and backaches, dyspnea, nausea and vomiting. Concomitant use of medications that increase bleeding risk should be avoided if possible, but interactions with CYP inducers or inhibitors were not significant. Fortunately, there is no renal dosing and the lower CYP activation means that no dose adjustment is needed in patients with mild to moderate hepatic impairment (see Table 1 for comparison chart).²³

Ticagrelor (Brilinta®)

Ticagrelor is classified as a cyclopentyl-triazolopyrimidine. It binds reversibly to the P2Y₁₂ receptor at an allosteric site, changes the receptor conformation, and prevents ADP-stimulated activation of the glycoprotein IIb/IIIa receptor and attenuating platelet aggregation.⁵ Unlike clopidogrel and prasugrel, ticagrelor is not a pro-drug and does not require metabolism to an active form. It is also broken down into at least one active metabolite with a similar potency to the parent drug. This combination of properties produces a rapid onset of action within 30 minutes, and a peak inhibitory effect in 2 hours.⁵

Efficacy and safety of ticagrelor

The landmark phase 3 PLATO trial

compared the safety and efficacy of ticagrelor with clopidogrel for prevention of cardiovascular events in patients with ACS.²⁶ Ticagrelor was given as a 180 mg loading dose then 90 mg twice daily and clopidogrel was given as a 300 – 600 mg loading dose then 75 mg daily. This study followed 18,624 patients over 12 months to determine the outcomes for a primary efficacy end point designated as time to the first occurrence of a composite of death from vascular causes, MI or stroke and primary safety endpoints of first occurrence of major bleeding.²⁶ It was observed that ticagrelor (9.8%) showed greater efficacy in preventing the primary efficacy end points than clopidogrel (11.7%) and the incidents of major bleeding were similar between the two groups (ticagrelor 11.6% vs. clopidogrel 11.2%). Unfortunately, patients on ticagrelor did experience a higher rate of non-CABG-related major bleeding, intracranial bleeding and dyspnea.²⁶

The PLATO trial discovered an anomaly in which ticagrelor was significantly less effective in North American patients compared to the rest of the world. The North American sub-study sought to determine the possible causes of this difference, and identified an underlying statistical interaction with aspirin maintenance dose. Of the 37 factors explored, only the maintenance aspirin dose emerged as a possible explanation for the regional differences.²³ Analysis revealed that more patients in the United States (53.6%) took a higher maintenance dose of aspirin > 300 mg than the rest of world (1.7%) and that low-dose maintenance aspirin concomitantly with ticagrelor had better outcomes compared to clopidogrel. The authors of the study theorized that aspirin's dose dependent inhibition of endothelial prostacyclin may reduce the anti-platelet effect of ticagrelor at higher doses. However, they do acknowledge that further research is needed to elucidate the possible mechanism of this interaction and that chance cannot be ruled out given the current data.²³ Based on the current available data, it is recommended that ticagrelor should only be administered with low-dose maintenance aspirin.²³

Dosing and monitoring of ticagrelor

Patients being started on ticagrelor should be given an initial loading dose of 180 mg at the time of PCI, and then

continued on a maintenance dose of 90 mg twice daily.²⁴ Ticagrelor is primarily metabolized by hepatic CYP3A4 enzymes so it is susceptible to drug interactions with medications that inhibit or induce these enzymes. Concomitant use of inducers such as rifampin or phenytoin and inhibitors such as azoles, clarithromycin or protease inhibitors should be avoided. Ticagrelor can reduce the metabolism of other drugs which are CYP3A4 substrates such as simvastatin, resulting in a higher serum simvastatin concentration and an increased risk of rhabdomyolysis. Serum levels of digoxin, a medication with a narrow therapeutic window, must also be monitored closely if used concomitantly with ticagrelor.²⁴

Due to an increased risk of bleeding, ticagrelor has a black box warning cautioning against use in patients with a history of intracranial hemorrhage and active bleeding.²⁴ It is also recommended to discontinue ticagrelor at least 5 days prior to CABG. It is important to note that the warning label advises to try managing bleeding episodes while remaining on ticagrelor as premature discontinuation increases the risk of cardiovascular events. Also included in the black box warning is the recommendation for use with aspirin 81 mg for efficacy. It is also advised against the use in patients with severe hepatic impairment.²⁴ Dyspnea was a common adverse effect noted with ticagrelor, occurring in approximately 14% of patients studied within the first few weeks after medication initiation. Other noted adverse events include, asymptomatic bradycardia, and ventricular pauses.²⁴ There have been reported cases of increase in uric acid levels as well, so caution should be taken in patients with a history of gout (see Table 1 for comparison chart).

The safety and efficacy of ticagrelor in elderly patients is of particular concern because while this population is at increased risk of cardiac complications, they are also at higher risks of bleeding. Fortunately, the PLATO trial did not identify any difference in safety or efficacy between younger and older patients, although it is recommended that older patients be monitored more carefully for bleeding complications.

General Considerations: P2Y₁₂ receptor antagonists

Patients should be counseled on the

importance of continuing dual anti-platelet therapy for the full recommended duration because early discontinuation can result in recurrent cardiovascular events. Another important counseling area includes the increased risk for bleeding and patients should be taught to be aware of certain things, such as signs and symptoms of bleeding (dark colored urine and stool). These patients will bruise more easily, and take longer than usual to stop bleeding. They should promptly report any unanticipated, prolonged, or excessive bleeding immediately to their health care provider.

Pharmacist's Role

With these newer anti-platelet agents, pharmacists can play a pivotal role in both monitoring and educating patients, whether in hospital, clinic, or community settings. Each of the agents discussed may provide enhanced benefit to specific patient populations. However, they also come with additional precautions, possible adverse events and interactions that must be carefully evaluated along with patient specific information, evidenced based research and clinical judgment to determine the best course of treatment. These new drugs provide extra tools in the healthcare provider arsenal for treating patients undergoing PCI with stent placement. As the medication experts, pharmacists are uniquely qualified to help match up the right drug to the right patient and ensure optimal treatment outcomes.

References

1. Spinler SA, Denus SD. Acute coronary syndromes. In: Dipiro JT, Talbert RL, Yee GC et al. *Pharmacotherapy: A Pathophysiologic Approach*. New York: McGraw Hill; 2008;249-277.
2. Levine GN, Bates ER, Blankenship JC et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124(23):e574-651.
3. Eikelboom JW, Hirsh J, Spencer FA et al. Antiplatelet drugs: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141:e89S-e119S.
4. Vandvik PO, Lincoff AM, Gore JM et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2)(Suppl):e637S-e668S.
5. Damman P, Woudstra P, Kuijt WJ et al. P2Y12 platelet inhibition in clinical practice. *J Thromb Thrombolysis*. 2012;33(2):143-153.
6. Savi P, Pereillo JM, Uzabiaga MF et al. Identification and biological activity of the active metabolite of clopidogrel. *Thromb Haemost*. 2000;85(5):891-896.
7. Plavix (clopidogrel) package insert. Bridgewater, NJ: Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership; 2011 Dec.
8. Herbert JM, Frehel D, Vallee E et al. Clopidogrel, a novel antiplatelet and antithrombotic agent. *Cardiovascular Drug Rev*. 1993;11(2):180-198.
9. Montalescot G, Sideris G, Meuleman C et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol*. 2006;48(5):931-938.
10. Mehta SR, Yusuf S, Peters RJ et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-533.
11. Steinhubl SR, Berger PB, Mann III JT et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized trial. *JAMA*. 2002;288(19):2411-2420.
12. Siller-Matula JM, Jilma B, Schror K et al. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost*. 2010;8(12):2624-2641.
13. Bhatt DL, Cryer BL, Contant CF et al. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med*. 2010;363(20):1909-1917.
14. Food and Drug Administration. Information for healthcare professionals: update to labeling of clopidogrel bisulfate (marketed as Plavix) to alter healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm190787.htm>. (accessed 2012 September 11th).
15. Abraham NS, Hlatky MA, Antman EM et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;122(24):2619-2633.
16. Mega JL, Simon T, Collet JP et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA*. 2010;304(16):1821-1830.
17. Yusuf S, Zhao F, Mehta SR et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
18. Höchtl T, Sinnaeve PR et al. Oral antiplatelet therapy in acute coronary syndromes: update 2012. *Eur Heart J*. 2012(1):79-86.
19. Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-15.
20. Wiviott SD, Braunwald E, Angiolillo DJ et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. *Circulation*. 2008;118(16):1626-36.
21. Montalescot G, Wiviott SD, Braunwald E et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomized controlled trial. *The Lancet*. 2009;373(9665):723-731.
22. Effient (prasugrel) package insert. Indianapolis, IN: Daiichi Sankyo, Inc. and Eli Lilly and Company; 2011 Sept.
23. Mahaffey KW, Wojdyla DM, Carroll K et al. Ticagrelor compared with clopidogrel by geographic region in the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation*. 2011;124(5):544-54.
24. Brilinta (ticagrelor) package insert. Wilmington, DE: AstraZeneca; 2011 July.
25. Guyatt GH, Akl EA, Crowther M et al. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2)(Suppl):7S-47S.
26. James SK, Storey RF, Khurmi NS et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes and a history of stroke or transient ischemic attack. *Circulation*. 2012;125(23):2914-21.

CPE MONITOR INSTRUCTIONS:

Beginning January 1, 2013 Statements of Credit for home-study activities will no longer be provided. All activities will be reported to the NABP CPE Monitor system as mandated by ACPE.

Licenses may obtain additional information and set up their NABP e-Profile at www.MyCPEmonitor.net.

An additional continuing pharmacy education home-study article titled *GLP-1 Agonists Therapy in Individuals with Type 2 Diabetes Mellitus: A Review of Safety and Tolerability* is available on the AzPA website in the AJP Archives. Member login is required.

Free CPE credit from home study articles published in the Arizona Journal of Pharmacy is a member benefit for AzPA Members.

Not a member? Visit the AzPA website and join today!

	Clopidogrel	Prasugrel	Ticagrelor
Mechanism of action	Irreversible P2Y ₁₂ receptor antagonist	Irreversible P2Y ₁₂ receptor antagonist	Reversible P2Y ₁₂ receptor antagonist
Activation	Pro-drug with 2-step activation	Pro-drug with 1-step activation	Active drug
Loading dose	300 - 600 mg	60 mg	180 mg
Maintenance dose	75 mg QD	10 mg QD	90 mg BID
Inhibition of platelet aggregation	Dose-dependent: 300-600 mg within 6 hours	Dose-dependent: 60 mg <30 minutes	Dose-dependent: 180 mg <30 minutes
Renal adjustment	No	No	No
Hepatic adjustment	No	No	No
Warnings /precautions	Reduced 2C19 function (BBW)	History of TIA or stroke (BBW), age≥75, weight <60 kg	Use with low dose aspirin only, history of ICH (both BBWs)
Drug interactions	2C19 inhibitors	None significant	3A4 inhibitors and inducers
Notes	Hold 5 days prior to CABG	Hold 7 days prior to CABG, benefits in STEMI and DM	Hold 5 days prior to CABG, increased dyspnea, moderate hepatic impairment

Table 1. Comparison of P2Y₁₂ receptor antagonists^{7,22,24}

BBW=Black Box Warning
 TIA= Transient ischemic attack
 STEMI= ST segment elevation
 CABG= Coronary Artery Bypass Grafting
 DM=Diabetes Mellitus
 ICH=Intracranial hemorrhage

Figure 1. Anti-platelet therapy recommendations from ACCP CHEST 2012 practice guidelines⁴

Clopidogrel	Prasugrel	Ticagrelor
<ul style="list-style-type: none"> Patients that have undergone PCI with stent placement, give dual antiplatelet therapy with clopidogrel 75 mg/day and aspirin therapy daily (1B) 	<ul style="list-style-type: none"> Patients that have undergone PCI with stent placement, give dual antiplatelet therapy with prasugrel 10 mg/day and aspirin therapy daily(1B) 	<ul style="list-style-type: none"> Patients that have undergone PCI with stent placement, give dual antiplatelet therapy with ticagrelor 90 mg/BID and aspirin therapy daily(1B)
<ul style="list-style-type: none"> Continue aspirin therapy 75 -325 mg/day: <ul style="list-style-type: none"> BMS: 1 month (1A), then 75 – 100 mg/day for 11 months (2C) Sirolimus-eluting stent: 3 months (1A), then 75 – 100 mg/day until 12 months (2C) Paclitaxel-eluting stent: 6 months (1A), then 75 – 100 mg/day until 12 months (2C) 	<ul style="list-style-type: none"> Continue aspirin therapy 75 -325 mg/day: <ul style="list-style-type: none"> BMS: 1 month (1A), then 75 – 100 mg/day for 11 months (2C) Sirolimus-eluting stent: 3 months (1A), then 75 – 100 mg/day until 12 months (2C) Paclitaxel-eluting stent: 6 months (1A), then 75 – 100 mg/day until 12 months (2C) 	<ul style="list-style-type: none"> Continue aspirin therapy 75 -325 mg/day: <ul style="list-style-type: none"> BMS: 1 month (1A), then 75 – 100 mg/day for 11 months (2C) Sirolimus-eluting stent: 3 months (1A), then 75 – 100 mg/day until 12 months (2C) Paclitaxel-eluting stent: 6 months (1A), then 75 – 100 mg/day until 12 months (2C)

1A= Strong recommendation, high-quality evidence
 1B= Strong recommendation, moderate-quality evidence
 2C= Weak recommendation, low-quality or very low-quality evidence
 PCI= Percutaneous coronary intervention
 BMS = bare metal stent

Figure 2. Anti-platelet therapy recommendations from 2011 ACCF/AHA/SCAI practice guidelines²

Evidence classification	Clopidogrel	Prasugrel	Ticagrelor
Class I: Benefit >>> Risk	B	<ul style="list-style-type: none"> Before PCI, give nonenteric aspirin 325 mg If on previous therapy, continue aspirin 81 mg to 325 mg 	<ul style="list-style-type: none"> Before PCI: give nonenteric aspirin 325 mg If on previous therapy, continue aspirin 81 mg to 325 mg
	B	<ul style="list-style-type: none"> Patients undergoing PCI, add clopidogrel 600 mg load followed by 75 mg/day to aspirin therapy then continue clopidogrel: <ul style="list-style-type: none"> BMS: ≥ 12 months DES: ≥ 12 months 	<ul style="list-style-type: none"> Patients undergoing PCI, add prasugrel 60 mg load followed by 10 mg/day to aspirin therapy then continue prasugrel: <ul style="list-style-type: none"> BMS: ≥ 12 months DES: ≥ 12 months
	A	<ul style="list-style-type: none"> After PCI, aspirin should be continued indefinitely 	<ul style="list-style-type: none"> After PCI, aspirin should be continued indefinitely
Class III: Benefit ≈ Risk	C	<ul style="list-style-type: none"> Dual therapy > 12 months may be considered 	<ul style="list-style-type: none"> Dual therapy > 12 months may be considered

A= Multiple populations evaluated
 B= Limited populations evaluated
 C= Very limited populations evaluated
 PCI= Percutaneous coronary intervention
 BMS= Bare metal stent
 DES= Drug-eluting stent

CONTINUING EDUCATION QUIZ

Anti-platelet Therapy in Acute Coronary Syndromes: Updates in Therapy after Stent Implantation

1. Clopidogrel acts primarily by :
 - a. Stimulating the ADP receptors on the platelet surface
 - b. Increasing platelet aggregation via P2Y₁₂ receptors
 - c. Inhibiting the P2Y₁₂ receptor on platelets
 - d. None of the above
2. Which of the following statements is correct and may explain the differences in onset of action of the 3 drugs?
 - a. Clopidogrel , prasugrel and ticagrelor are all pro drugs
 - b. Only clopidogrel is a pro drug. Prasugrel and ticagrelor are active medications
 - c. Only ticagrelor is a pro drug. Clopidogrel and prasugrel are active medications
 - d. Both clopidogrel and prasugrel are pro drugs. Ticagrelor is an active medication
3. The black box warning for ticagrelor:
 - a. Cautions against use in patients with a history of intracranial hemorrhage and active bleeding
 - b. Warns that patients with genetic variability in their CYP2C19 allele may have reduced anti-platelet activity
 - c. Advises against use in patients ≥ 75 years with the exception of high risk situations
 - d. Advises to avoid use in patients with unstable angina due to increased bleeding risk
4. Which potential drug-drug interaction has continued warnings because of the potential increase in cardiovascular events with concomitant use?
 - a. Clopidogrel and aspirin
 - b. Ticagrelor and proton pump inhibitors
 - c. Prasugrel and aspirin
 - d. Clopidogrel and proton pump inhibitors
5. What is the minimum length of time for thromboembolic prophylaxis for PCI patients with a sirolimus-eluting stent on clopidogrel, ticagrelor or prasugrel?
 - a. Patients may be transitioned off prophylaxis after 1 month if they are at low risk for a thromboembolic event.
 - b. Treatment should be discontinued immediately after PCI if the patient is not in a high risk group
 - c. Treatment should be continued indefinitely due to the high risk for thromboembolic events following PCI
 - d. ost patients should be treated for a minimum of 12 months
6. The North American sub study of ticagrelor found that:
 - a. Patients on lower maintenance doses of aspirin (< 300 mg) concomitantly with ticagrelor had better outcomes
 - b. Ticagrelor is best taken on an empty stomach as higher gastrointestinal pH increases bioavailability
 - c. Ticagrelor is teratogenic and should be avoided in patients who are pregnant or planning to become pregnant within 6 months
 - d. Ticagrelor patients on aspirin therapy experienced significantly lower gastrointestinal complications when using a PPI for prophylaxis
7. Which of the following statements is incorrect?
 - a. The active metabolite for ticagrelor binds reversibly to the P2Y₁₂ receptor
 - b. Clopidogrel requires dose adjustment for hepatic impairment
 - c. Inter-patient genetic variability has less effect on prasugrel than clopidogrel.
 - d. All of the above statements are correct
8. Which of the following statements is correct regarding platelet inhibition?
 - a. Clopidogrel has a faster platelet inhibition time than prasugrel but slower than ticagrelor
 - b. All three drugs have similar platelet inhibition times
 - c. Ticagrelor and prasugrel have faster platelet inhibition times than clopidogrel
 - d. None of the above statements are correct
9. Which of the following is an appropriate protocol for dosing prior to a CABG procedure?
 - a. Hold ticagrelor for 1 day prior to CABG
 - b. Hold prasugrel for 7 days prior to CABG
 - c. Hold clopidogrel for 2-3 days prior to CABG
 - d. All of the drugs should be held no longer than 1-2 days prior to CABG
10. 55 year-old, 50 kg patient is admitted for STEMI, and is taken to the cardiac catheterization lab for primary PCI. The patient has a past medical history of hypertension and a transient ischemic attack in 2005. Her renal and hepatic function are within normal limits. Current medications include aspirin 325 mg daily, metoprolol 25 mg twice daily, and atorvastatin 20 mg daily. Which of the following is the BEST recommendation for anti-platelet therapy for this patient?
 - a. Clopidogrel 600 mg loading dose, then 75 mg daily
 - b. Prasugrel 20mg mg loading dose, then 10 mg daily
 - c. Prasugrel 60 mg loading dose, then 10 mg daily
 - d. Ticagrelor 180 mg loading dose, then 90 mg twice daily



This activity was developed by the Arizona Pharmacy Association for pharmacists as a knowledge-based learning activity. The Arizona Pharmacy Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.