P2Y12 Antagonists: Pharmacology, Efficacy and Patient Considerations

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Abstract

Today atherothrombotic disease accounts for up to 40% of deaths in Western countries. The role of platelets in the pathogenesis of atherothrombosis disease is well known. Anti-platelet drugs have been shown to prevent formation and progression of thrombosis and are used to prevent complications in acute coronary syndrome. Aspirin and clopidogrel have been the conventional anti-platelet therapy for many years. Despite this, clopidogrel has well known disadvantages that include bleeding, delayed onset, and inter-patient response variability that may equate to negative ischemic outcomes. This has led to the development of alternative oral P2Y12 antagonists such as prasugrel and ticagrelor that have undergone large randomized controlled trials. In these trials, clopidogrel has been compared to the newer oral P2Y12 antagonists in terms of efficacy and safety. Lack of experience with the newer agents, combined with fears about higher rates of bleeding compared with clopidogrel and cost, may have slowed the rate of prasugrel and ticagrelor adoption. In this article we review the pharmacology and individual patient considerations that affect the decision of which P2Y12 antagonist to use.

Keywords — Anti-Platelet, Efficacy, Patient Consideration, Pharmacology, P2Y12 Antagonist


I. INTRODUCTION

It is critical to find the optimal management in Acute Coronary Syndrome (ACS) as atherothrombotic disease accounts for 40% of deaths in western countries and is the fastest growing cause of death in the developing world.1, 2 Anti-platelet therapies such as aspirin and clopidogrel have been the cornerstone medical therapy for ACS, which is comprised of unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and STElevation myocardial infarction (STEMI).

Aspirin acts via irreversible inhibition of thromboxane A2 mediated platelet aggregation. Clopidogrel belongs to the thienopyridine family, which inhibits the P2Y12 receptor. Ticlopidine was the P2Y12 antagonist approved by the United States Food and Drug Administration (FDA). However, since ticlopidine use was associated with neutropenia and thrombotic thrombocytopenia purpura, it has been replaced by clopidogrel in the clinical setting.3

Clopidogrel has proven to be efficacious in the setting of ACS but there are notable disadvantages with its use such as bleeding, delayed onset, recurrence of ischemic events, and inter-patient response variability.3,4 This had led to the search for alternative P2Y12 antagonists such as prasugrel, ticagrelor and cangrelor, which may provide greater efficacy and safety but also come with undesirable drawbacks that should be considered.

Making the important decision of what P2Y12 antagonist to treat an ACS patient is not a simple choice and in this article we review the pharmacology and individual patient’s considerations that may affect the choice of optimal anti-platelet therapy.

II. PHARMACOLOGY OF CLOPIDOGREL

Clopidogrel principally acts via irreversible inhibition of adenosine diphosphate (ADP) P2Y12 receptor. With binding of ADP to the P2Y12 receptor there is an inhibition of subsequent IIb/IIIa activation, preventing amplification and stabilization of platelet aggregation.4

Clopidogrel is a pro-drug that requires a two-step hepatic cytochrome P450 (CYP) metabolic activation to produce the active metabolite.1 Approximately 85% of the drug is hydrolyzed by esterases to an inactive carboxylic derivative and the remaining 15% is transformed by CYP enzymes.1 Thus, a small amount of the active drug is available for clinical effect.

Clopidogrel has a delayed onset of action of 2-6 hours, which is problematic when immediate intervention is desired. The maximum plateau of inhibition is seen 4-5 days after daily administration of clopidogrel 75mg.5 Due to an irreversible inhibition of the P2Y12 receptor, clopidogrel’s effect lasts for the life span of platelets (7-10 days). The prolonged half-life of 8 hours increases the risk of bleeding in ACS patients that need to undergo coronary artery bypass grafting (CABG).1

Clopidogrel treatment within 4 to 5 days of revascularization procedures is associated with increased blood loss, transfusion requirements, and prolonged hospital stay.5

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Genetic Polymorphisms

Certain genetic polymorphisms can reduce the amount of active drug in populations. A variant allele of the gene that encodes for CYP2C19, the enzyme that is involved in the transformation of the pro-drug, is found be at a reduced function in certain patients using clopidogrel. This leads to a decreased production of active metabolites necessary for platelet aggregation. These clopidogrel “high on-treatment platelet reactivity” individuals are a considerable percentage (5-40%) of the general population. Reduced function of the CYP2C19 allele occurs in approximately 30% of individuals of European ancestry, 40% of individuals of African ancestry, and greater than 50% of individuals of Asian ancestry. The greatest fear of clopidogreg sub-optimal response is worse clinical outcomes with ischemic recurrence. In an analysis of 22 studies the summarized sensitivity of the CYP2C19 genotype for predicting “high on-treatment platelet reactivity” was 37.6% (95% CI: 32.2-43.3%), with a summarized negative predictive value of only 52.3% (95% CI: 44.7 to 59.7%). These findings indicate that CYP2C19 genotyping is not effective for both excluding the risk of “high on-treatment platelet reactivity” and ischemic events.

Drug Interaction

Due to the multiple interactions with CYP enzymes, clopidogrel is subject to pharmacodynamic interactions with other drugs. This is a notable concern because patients treated with P2Y12 antagonists also are receiving therapy with different classes of drugs that require metabolism by CYP enzymes. Implications of drug interactions are most pronounced in the early phase of treatment for ACS and immediately after stent implantation. Atorvastatin and other lipophilic statins (Simvastatin and Lovastatin) utilize the CYP3A4 isoenzyme for elimination while proton pump inhibitors require both the CYP2C19 and CYP3A4 for their metabolism. Both classes of drugs may competitively inhibit the conversion of the clopidogrel prodrug to active metabolites as suggested by several ex-vivo studies. Data regarding drug interactions between calcium channel blockers (CCBs) which are moderate CYP3A4 inhibitors and clopidogrel have been shown to be largely inconsistent with an absence of negative clinical outcomes seen in randomized study.

The COGENT (Clopidogrel with or without Omeprazole in Coronary Artery Disease) trial revealed no significant difference in adverse cardiovascular events in patients receiving dual anti-platelet therapy when assigned to either the omeprazole or placebo arms (event rate of 4.9% with omeprazole and 5.7% with placebo, (HR = 0.99; [95% CI: 0.68 to 1.44]; P = 0.96). A post-hoc analysis of CREDO (Clopidogrel for the reduction of Events During Observation) trial revealed no significant differences in 1-year acute myocardial infarction, death, and/or stroke in patients treated with clopidogrel and atorvastatin or other CYP3A4-metabolized statins compared to treatment with non-CYP3A4 metabolized statins (ex: pravastatin, fluvastatin). These trials have provided some reassurance that pharmacological interactions with clopidogrel may not equate to negative clinical outcomes. Despite this, there is no guarantee that pharmacological drug interactions will not equate to ischemic outcomes given the multiple confounding factors that may decrease the efficacy of P2Y12 antagonists, such as genetic polymorphisms, drug response variability, and the pleiotropic effects of drugs on an individualized level.

Dosing

Clopidogrel loading dose ranges from 300-600mg and the maintenance dose is 75mg once a day. The benefits and risks of opting for a higher clopidogrel dose were elucidated in a sub group analysis of the CURRENT-OASIS 7 (Clopidogrel optimal loading dose Usage to Reduce Recurrent EveNTs-Organization to Assess Strategies in Ischemic Syndromes) trial. At 30 days, the overall primary outcome (MI, stroke, or CV death) occurred in 4.2% of patients with the double dose (loading dose 600 mg on day 1, followed by 150 mg from Day 2-7) vs. 4.4% in the standard dose group (loading dose of 300 mg on day 1, and followed by 75 mg daily from day 2-7) (HR= 0.94, [95% CI: 0.83-1.06]; P= 0.3). For patients that underwent percutaneous coronary intervention (PCI) decreased cardiovascular events and stent thrombosis were significantly reduced in the double dose group compared to the standard dose group (HR = 0.68, [95% CI: 1.0 - 1.27]; P = 0.04). Similar differences were not seen in patients that did not undergo PCI (P = 0.14). Regarding the safety outcome, doubling the doses was associated with significant higher rate of CURRENT major bleeding events (2.5%) compared with the standard dose group (2%);(HR = 1.24, [95% CI: 1.05-1.46]; P=0.01). Even though higher doses may appear to be beneficial in certain patients this also comes with increased bleeding events. As of today, the decision on the specific dose of clopidogrel is based upon the center’s preference and the individual patient being treated.

III. PHARMACOLOGY OF P2Y12 ANTAGONISTS

A. PARASUGREL

Prasugrel is a third-generation thienopyridine, which also irreversibly inhibits the P2Y12 platelet receptor. Prasugrel is administered orally with a loading dose of 60mg and maintenance dose of 10mg once a day. The time to onset of action is 2 hours with a half-life of 3.7 hours. Its pharmacological properties are considered more favorable than clopidogrel with its more rapid and consistent platelet inhibition secondary to more efficient in-vivo generation of the active metabolite of prasugrel. After ingestion, prasugrel is hydrolyzed in the gastrointestinal system into an intermediary metabolite, which is transformed via a CYP450 mediated one-step process into the active metabolite. There is a rapid appearance of active metabolite within 15 minutes of dosing; with maximal plasma concentration reached at approximately 30 minutes. A recent in-vivo study has commented on beneficial effects of the combination of the active metabolite of prasugrel and glycoprotein (GP) IIb-IIIa antagonists.

Combination therapy yields additive inhibitory effects on collagen-stimulated platelet aggregation and on the collagen.
plus ADP- stimulated level of activated platelet surface glycoprotein IIb-IIIa.15

Lack of genetic polymorphism and drug interaction
In contrast to clopidogrel, there is no significant influence of CYP genetic polymorphisms on the metabolic activation of prasugrel. Therefore there is lower inter-individual variability in platelet inhibition and extremely low prevalence of patients who display resistance to prasugrel.5

In addition prasugrel’s drug pamphlet states that the drug can be administered with medications that are inhibitors and inducers of the CYP450 enzymes.16 However, the protease inhibitor ritonavir is a potent CYP3A4 inhibitor that substantially reduces prasugrel bio-activation and should be avoided in HIV patients being treated for ACS.7

Statins have not been shown to negatively impact prasugrel mediated inhibition of platelet aggregation and exposure of its active metabolites.7 As with clopidogrel, there is an increased bleeding risk with co-administration of warfarin due to bleeding time prolongation up to 36%.7

B. TICAGRELOR
Unlike clopidogrel and prasugrel, ticagrelor, a cyclo-pentyl-triazolo-pyrimidine, is a reversible oral P2Y12 antagonist that acts at a different site from the ADP binding site. It is orally active and no metabolic activation necessary to achieve its anti-platelet effect.17

Ticagrelor undergoes enzymatic degradation by CYP3A4 to an active metabolite that is as potent as the original drug.1 Strong CYP3A4 inducers and inhibitors alter the pharmacokinetics of the drug, and concomitant use should be avoided.18

The loading dose is 180mg with a maintenance dose of 90mg three times a day. The multiple daily doses required for maintenance therapy may be problematic for patients with poor compliance. Time to peak onset is 2 hours with a half-life of 6-13 hours.19 With a reversible action, the anti-platelet effect dissipates more rapidly than with thienopyridines. This is a notable advantage in patients who require immediate intervention and less procedure related bleeding is expected.

C. CANGRELOR
Similar to ticagrelor, cangrelor is a non–thienopyridine P2Y12 receptor antagonist but is intravenously administered. The half-life is 3- 6 minutes, and it acts directly on the P2Y12 platelet receptor, with an initial administration of the bolus dose resulting in instantaneous platelet inhibition. This inhibition can be maintained with continuous infusion with quick normalization of platelet function achieved within the first hour after the cessation of infusion.

Cangrelor’s rapid onset is favorable in situations requiring urgent PCI and cases warranting urgent surgeries.20 The studied bolus dose of 30 µg/kg and the maintenance infusion rate of 4 µg/kg per min, was used in the CHAMPION-PCI (Platelet Inhibition with Cangrelor in patients Undergoing PCI) trial.21

### Table 1. Comparison of Oral P2Y12 Antagonists

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of P2Y12 inhibition</strong></td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td><strong>Metabolic Activation</strong></td>
<td>Required</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td><strong>Pharmacogenetic Variability in Anti-platelet Response</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Loading Dose</strong></td>
<td>300-600mg</td>
<td>60mg</td>
<td>180mg</td>
</tr>
<tr>
<td><strong>Maintenance Dose</strong></td>
<td>75mg OD</td>
<td>10mg OD</td>
<td>90mg TID</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>8 hours</td>
<td>3.7 hours</td>
<td>8-12 hours</td>
</tr>
<tr>
<td><strong>Time to Peak Onset of Action</strong></td>
<td>2-6 hours</td>
<td>2 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td><strong>Time to Offset of Action</strong></td>
<td>5-7 days</td>
<td>5-7 days</td>
<td>3 days</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td>-Bleeding -Inter-patient Response Variability</td>
<td>-Bleeding -Contraindications in patients with a history of stroke OR TIA -Increased bleeding risk in patients &gt;75 years and &lt;60kg</td>
<td>-Bleeding -Dose-related dyspnea -Multiple daily dosing -Contraindicated in severe hepatic impairment</td>
</tr>
</tbody>
</table>

IV. EFFICACY

A. CLOPIDOGREL
The efficacy of dual therapy with aspirin and clopidogrel in the reduction of ischemic events in ACS patients has been proven.22,23 The CURE (Effect of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndrome without ST-Segment Elevation) trial reported a significant reduction in the primary outcome of cardiovascular death, non-fatal MI, and stroke with the addition of clopidogrel to aspirin therapy as compared to the placebo plus aspirin (RR = 0.80; [95% CI: 0.72 – 0.90]; P < 0.001).22 Aspirin and clopidogrel therapy was associated with an increased risk for major bleeding, defined to be the requirement of transfusion of at least two units (3.7% vs 2.7%; P = 0.001). However, there was no significant difference in episodes of life threatening bleeding (2.1% vs 1.8%; P = 0.13).22 The COMMITT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial ) study showed a significantly reduced mortality with clopidogrel and aspirin compared to placebo and aspirin in a population that included STEMI patients who did not undergo primary PCI, (7.5% vs 8.1%; P = 0.03).23 The CAPRIE (A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events) trial reported a relative risk reduction of the aggregate of CV death, Stroke and MI of 8.7% (95% CI: 0.3 – 16.5; P = 0.043), when comparing Clopidogrel 75 mg to Aspirin 325 mg in patients with recent atherothrombotic events.24
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Comparator</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Population</th>
<th>Efficacy Outcome</th>
<th>Safety Outcome</th>
<th>JUMBO-TIMI 36 (Randomized Comparison of Prasugrel, a Novel Thienopyridine P2Y12 Antagonist, With Clopidogrel in Percutaneous Coronary Intervention- Result of the joint Utilization of Medication to Block Platelet Optimally)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON TIMI-38 (Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndrome)</td>
<td>Prasugrel (60 mg LD and a 10 mg OD MD) or clopidogrel (300 mg LD and 75 mg OD MD)</td>
<td>Double-Blind, Interventional RCT</td>
<td>13,608</td>
<td>UA/NSTE-ACS scheduled for PCI, Must have: Sx lasting &gt; 10 minutes and presenting &lt; 72 hrs prior to randomization AND TIMI score ≥ 3 AND STE ≥ 1 mm or Elv. Of cardiac biomarkers. STEMI Scheduled for PCI if onset of sx ≤ 12 hrs OR 14 Days have passed since receiving Med Mx.</td>
<td>1° End point at 72 hrs: (5.6%) Clopidogrel vs (4.7%) Prasugrel; HR: 0.82; 95% CI [0.71 - 0.96]; P = 0.01</td>
<td>TIMI Bleeding: Life threatening bleeding (1.4%) Prasugrel vs (0.9%) Clopidogrel; HR: 1.52; 95% CI [1.08 - 2.13]; P = 0.01</td>
<td>MACE: all cause mortality/ MI/ Stroke/ Recurrent Ischemia requiring rehospitalization/clinical target vessel thrombosis</td>
</tr>
<tr>
<td>TRILogy-ACS (Prasugrel versus Clopidogrel for Acute Coronary Syndrome without Revascularization)</td>
<td>LD of 30 mg Prasugrel or 300 mg Clopidogrel followed by 75 mg Clopidogrel or Prasugrel 10 mg MD OD or Prasugrel 5 mg MD OD in pts with wt &lt; 60 kg or age ≥ 75 yrs</td>
<td>Double-blind, Double-dummy, active-control; event-driven RCT</td>
<td>7,243</td>
<td>Pts selected for Med Mx Must have had UA/NSTE-ACS ≤ 10 d</td>
<td>1° End point at 30 months among pts &lt; 75 yrs: (13.9%) Prasugrel vs (16.0%) Clopidogrel; HR 0.91; 95 CI [0.79 - 1.05]; P=0.21</td>
<td>TIMI Bleeding: major or minor bleeding for pts &lt; 75 yrs: (3.3%) Prasugrel vs (2.1%) Clopidogrel; HR: 1.54; 95% CI [1.06 - 2.23]; P=0.02</td>
<td>MACE end point at 30 days: (7.2%) Prasugrel vs (9.4%) Clopidogrel; HR 1.42; 95% CI [0.46 - 1.24]; P=0.260</td>
</tr>
<tr>
<td>JUMBO-TIMI 36</td>
<td>randomized to prasugrel: low dose (40 mg LD followed by 7.5 mg MD OD), Intermediate dose (60 mg LD and 10 mg MD OD) and High dose (60 mg LD and 15 mg MD OD) c/w Clopidogrel (300 mg LD and 75 mg MD OD)</td>
<td>Double-blind, dose-ranging, Double-Dummy</td>
<td>904</td>
<td>Loaded with ASA 325mg pre PCI AND Adult pts ≤ 75 yrs AND Elective or Planned PCI scheduled for stenting AND CAD ≥ 60 stn. amendable by ≤ 2 stents</td>
<td>1° End point from 72 hrs to the end of follow up period: (6.9%) Clopidogrel vs (5.6%) Prasugrel; HR: 0.80; 95% CI [0.70 - 0.93]; P=0.003</td>
<td>TIMI Bleeding: Fatal major bleeding: (0.4%) Prasugrel vs (0.1%) Clopidogrel; HR: 4.19; 95% CI [1.58 - 11.11]; P=0.002</td>
<td>TIMI Bleeding: Non-CABG TIMI major and minor bleeding: (1.7%) Prasugrel vs (1.2%) Clopidogrel; HR: 1.42; 95% CI [0.40 - 5.08]; P=0.592</td>
</tr>
</tbody>
</table>

Table 2. Comparison of the Major Clinical Trials Involving Prasugrel and Clopidogrel.

Abbreviations: PCI = Percutaneous Coronary Intervention, SA = Stable Angina, UA = Unstable Angina, NSTE-ACS = Non ST Elevation Acute Coronary Syndrome, STEMI= ST Elevation Myocardial Infarction, 1°= Primary, 2°= Secondary, MI = Myocardial Infarction, CAGB = Coronary artery Bypass Grafting, OR= Odds Ratio, P = P value, CIE = Confidence Interval, HR = Hazard Ratio, Stn = stenosis , vs= Versus. c/w = compared with, OD = Once Daily, LD = Loading Dose, MD = Maintenance Dose, wt = weight, yrs = years (age), pts= patients, RCT = Randomized Controlled Trial, Med Mx = Medical Management, STE = ST segment elevation, Elv. = Elevated, DM = Diabetes, MACE = Major Adverse Cardiovascular Events, TIMI = The Thrombolysis in Myocardial Infarction, d = Days, sx = Symptoms.
B. PARASUGREL

Based on pharmacological properties prasugrel is considered to have greater efficacy in platelet inhibition compared to clopidogrel but with the disadvantage of an increased risk of bleeding (Table 1). In the TRITON-TIMI 38 study prasugrel was compared to clopidogrel in moderate to high risk ACS patient scheduled for PCI. 25

The primary efficacy point was a composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke. 25 Major safety end point was major bleeding based on the TIMI classification. 25 Overall prasugrel was shown to significantly reduce the primary efficacy end point. However, individually there was no significant difference in nonfatal stroke or cardiovascular death where the major clinical benefit was seen with a reduction in non-fatal MI. 25 No mortality benefit was seen with prasugrel treatment.

An increase in fatal and nonfatal non-CABG related bleeding was seen in the prasugrel group. 25 Bleeding events may be even higher in real-life situations because exclusions to participation in the study included an increased risk of bleeding, history of anemia, thrombocytopenia, known intracranial pathology, or the use of a P2Y12 receptor antagonist within five days before randomization. 25

The Trilogy-ACS (Prasugrel versus Clopidogrel for Acute Coronary Syndrome without Revascularization) study compared prasugrel and clopidogrel in the treatment of high-risk ACS patients without STEMI undergoing medical management. 26 There was no significant difference in the primary end point (cardiovascular death, MI, or stroke) (13.9% vs 16.0%; P = 0.21) or the safety end point with both the severe GUSTO (Global Use of Strategies to Open Occluded Arteries); (P = 0.87), and major TIMI (Thrombolysis in Myocardial Infarction); (P = 0.27) bleeding criteria at median follow-up of 17 months. 26 The study found itself in uncharted waters with prolonged follow-up compared to previous studies (Table 2).

There was an observed divergence of treatment effect among patients under the age of 75 years after the pre-specified 12-month time point. The frequency of the primary end point through 12 months was similar between both groups, with a weak trend toward a reduced risk in the prasugrel group after 12 months (p=0.07). 26

C. TICAGRELOR

There has been great interest in the possibility of ticagrelor being a replacement for clopidogrel. One of the most attractive features of ticagrelor is its reversible action, where it can be given at initial presentation ACS with relative flexibility allowing for more rapid initiation of CABG or other invasive interventions after discontinuation. The PLATO (PLATelet inhibition and patient Outcome) study compared ticagrelor to clopidogrel in the treatment of ACS patients (NSTEMI and STEMI) with the primary efficacy point a composite of death from vascular causes, MI, or stroke.19

The primary end point was significantly reduced in the ticagrelor group at 12 months. 19 Favorable reductions in ischemic events were seen from 30 days after randomization to the completion of the study. 19

The rate of stroke did not significantly differ between both groups, however more hemorrhagic strokes were seen with ticagrelor compared to clopidogrel (0.2% vs. 0.10%; P = 0.1). 19 The study chose to use its own major bleeding definition for the primary safety endpoint where no significant difference in major bleeding was seen (Table 3). However, using the TIMI definition major bleeding episodes were increased by 25% with ticagrelor compared to clopidogrel. 19

Probably one of the most discussed findings of the PLATO study is the so-called “US paradox.” Prior to FDA approval in 2011, PLATO’s reliability was scrutinized with data suggesting favorable primary endpoint outcomes from clinical sites monitored directly by the parent drug company AstraZeneca compared to the sites overseen by independent research parties (OR = 0.74; [95% CI: 0.64 – 0.85]) vs (OR = 1.21; [95% CI: 0.91 – 1.59]). 27

This may shed light on why ticagrelor failed to show superiority over clopidogrel in the North American population, but a significant benefit was seen in the international population especially in Poland and Czech Republic.

While historically, European guidelines have recommended lower aspirin doses compared to American guidelines, the findings of the study may be due to chance because currently there is no definitive biological rationale for why high aspirin dose therapy should influence the efficacy of ticagrelor. 28 However, as of today ticagrelor has a “black box” warning prohibiting concurrent aspirin treatment of >100mg a day. 18

D. CANGRELOR

Previously in CHAMPION-PCI and CHAMPION-PLATFORM, cangrelor failed to demonstrate superiority over clopidogrel or the placebo in reducing primary end point (death, MI or ischemic revascularization) at 48 hours after PCI. 21,22 In the CHAMPION-PHENIX trial, the primary efficacy end point which was a composite of death, MI, ischemia driven re-vascularization was significantly decreased in the cangrelor group compared to the clopidogrel group (4.7% vs 5.9%; OR: 0.78; [95% CI: 0.66 - 0.93]; P = 0.005). 30 The favorable result for cangrelor in the CHAMPION-PHENIX trial was likely secondary to the utilization of the uniform definition of myocardial infarction. In contrast, previous studies (CHAMPION-PCI and CHAMPION-PLATFORM) obtained only one baseline sample of cardiac enzymes to determine peri-procedural MI events (Table 4).

Today, the intravenous route of cangrelor administration remains an attractive feature that could be of benefit in patients experiencing nausea and vomiting, or those who are intubated or in cardiogenic shock. 30

V. PATIENT CONSIDERATION

A. COST

In 2011, a generic version of Plavix (clopidogrel) became available for patients as an alternative for those not able to pay more than $4 per day. 31
### Table 3. Comparison of the Major Trial features Involved in Ticagrelor and Clopidogrel

| Abbreviation | PCI = Percutaneous Coronary Intervention, SA = Stable Angina, UA = Unstable Angina, NSTE-ACS = Non ST Elevation Acute Coronary Syndrome, STEMI= ST Elevation Myocardial Infarction, 1° = Primary, 2° = Secondary, MI = Myocardial Infarction, AZD6140 = Ticagrelor, OR= Odds Ratio, HR= Hazard Ratio, 95% CI= Confidence Interval, ST= Stent Thrombosis, ACUTY= Acute Catheterization and Urgent Intervention Triage Strategy, GUSTO= The Global Use of Strategies to Open Occluded Arteries, vs=Versus, OD = Once daily, BID =Twice Daily, ECG = Electrocardiogram, DM = Diabetes, PAD = Peripheral Artery Disease, CAD = Coronary Artery Disease, Art. = Artery, St= Stenosis, CRF = Chronic Renal Failure, CABG = Coronary artery By-Pass, 2V = 2 Vessels, LBBB = Left Bundle Branch Block.  

The availability of a generically priced clopidogrel changes the discussion of using the more expensive newer P2Y12 antagonists.  

In a cost analysis of patients in the TRITON-TIMI-38 study where prasugrel was compared to generic clopidogrel in ACS patients with planned PCI, prasugrel was shown to be more cost-effective. Over a median follow-up of 14.7 months, average cumulative cost of prasugrel was $221 per patient lower than clopidogrel (95% CI: 759 to 299). The lower cost was largely secondary to reduced re-hospitalizations involving PCI with prasugrel (+$500 per patient in cost offsets). In sub-group analyses, prasugrel was an economic dominant strategy for high-risk patients with diabetes and STEMI. However, for patients with a previous history of stroke or TIA, there were worse clinical outcomes with increased bleeding events translating into lower life expectancy by 0.14 years for prasugrel.

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| Trial Name | PLATO  
| (Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes) | DISPERSE-2  
| (Safety, Tolerability, and Initial Efficacy of AZD6140, the first Reversible Oral Adenosine Diphosphonate Receptor Antagonist, Compared with Clopidogrel in Patients with Non STE-ACS) |
| Comparator | Ticagrelor 90mg BID vs 75 mg OD clopidogrel, in patients undergoing PCI for ACS, 75mg to 100mg of ASA was given prior to PCI if tolerated. | Randomized to either receive a) Ticagrelor 90 mg BID b) Ticagrelor 180mg BID or c) Clopidogrel 75 mg OD with 325 mg as a loading dose. |
| Study Design | Double-blind, double-dummy, randomized | Double-blind, double-dummy, randomized |
| Sample Size | 18,624 | 990 |
| Population | UA/NSTE-ACS, have met at least two of these criteria: DM or CRF or PAD or CAD with 50% St in 2V or ST segment changes or Biomarkers elv. Or TIA/Stroke/Carotid Art. St >50% or >60yrs/prior MI/prior CABG | NSTE-ACS patients who experienced: symptoms > 10 minutes at rest AND biomarkers elevation or ECG evidence of ischemia. |
| Duration | 12 months | 12 months |
| End Point Definition | 1° End Point: Death from Vascular cause/MI/Stroke  
2° End Point: Death from any cause/MI/Stroke | Clinical End Point: Cardiovascular Death/MI/Stroke |
| Efficacy Outcome | 1° End Point at 12 months: (9.8%) Ticagrelor vs (11.7%) Clopidogrel; HR:0.84; 95% CI [0.77-9.92]; P<0.001 | Clinical End Point at 4 weeks: (4.3%) AZD6140 90 mg Twice daily vs (3.8%) Clopidogrel; P=0.71; (19.9%) AZD6140 180 mg Twice Daily vs (3.8%) Clopidogrel; P=0.17 |
| Safety Outcome | Any Dyspnea: (13.8%) Ticagrelor vs (7.5%) Clopidogrel; HR:1.84; 95% CI [1.68 - 2.02]; P<0.001 | Dyspnea : (10.5%) AZD6140 90 mg b.dvs (6.4%) Clopidogrel od; P=0.07; (15.8%) AZD6140 180 mg b.dvs (6.4%) Clopidogrel 75 mg od; P=0.0002 |

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**The TRITON-TIMI-38 study**
The study also compared a hypothetical $1 per day generic clopidogrel prior to the patent expiration in 2011, to prasugrel. Generic clopidogrel was economically beneficial at up to 30 days of treatment. However, after 30 days it was no longer more cost-effective than prasugrel. For treatment up to 30 days, prasugrel remained a dominant strategy as long as the difference in the price was < $ 7.67 per day. This assumption can carry significant clinical implications as contemporary generic clopidogrel prices ranges from $0.32 to $ 5.50 per day.

In the treatment of ACS for 12 months, ticagrelor was not shown to be more cost-effective than generic clopidogrel based on an analysis of the PLATO study results.

Ticagrelor was associated with a cost per quality-adjusted life year (QALY) equivalent to $3530 using Swedish unit costs. Additional cost-effectives analyses with the most current generic clopidogrel prices based on US unit costs are necessary for further investigation.

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**Table 4.** Comparison of the Major Trial features Involving Cangrelor and Clopidogrel

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Comparator</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Duration</th>
<th>End Point Definition</th>
<th>Efficacy Outcome</th>
<th>Safety Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMPION-PCI</td>
<td>Scheduled to receive either pre procedure placebo or cangrelor and loading with clopidogrel 600 mg pre PCI.</td>
<td>Double-blind, double-dummy, randomized</td>
<td>8,877</td>
<td>12 months</td>
<td>1°Death/MI/IDR at 48 hrs</td>
<td>1° End point at 48 hrs: (7.5%) Cangrelor vs (7.1%) Clopidogrel; OR: 1.05; 95 CI 0.88 - 1.24; P=0.59</td>
<td>ACUITY BLEEDING: Minor Bleeding 17.6% (cangrelor) vs 15.2% (Clopidogrel); OR: 1.19; 95% CI [1.06 - 1.33]; P=0.003</td>
</tr>
<tr>
<td>CHAMPION-PLATFORM</td>
<td>Scheduled to receive either pre procedural placebo or cangrelor and loading with clopidogrel 600 mg post PCI.</td>
<td>Double-blind, double-dummy, randomized</td>
<td>5,362</td>
<td>12 months</td>
<td>1°Death/MI/IDR at 48 hrs</td>
<td>1° End point at 48 hrs: (7.0%) Cangrelor vs (8.0%) Placebo; OR: 0.87; 95% CI [0.71 - 1.07]; P = 0.17</td>
<td>GUSTO BLEEDING:Minor bleeding 19.6% (Cangrelor) vs 16.9% (Clopidogrel); OR: 1.20; 95% CI [1.07 - 1.34]; P=0.001</td>
</tr>
<tr>
<td>CHAMPION-PHEONIX</td>
<td>Cangrelor compared to Placebo, with Clopidogrel (300 mg or 600 mg) loaded at the start of the PCI or at the end of it.</td>
<td>Double-blind, double-dummy, randomized</td>
<td>11,145</td>
<td>12 months</td>
<td>1°Death/MI/IDR/ST at 48 hrs</td>
<td>1° End point at 48 hrs: (4.7%) Cangrelor vs (5.9%) Clopidogrel; OR: 0.78; 95 CI [0.66 - 0.93]; P=0.005</td>
<td>ACUITY BLEEDING: Major Bleeding 11.8% (Cangrelor) vs 8.6% (Clopidogrel); OR: 1.42; 95% CI [1.26 - 1.61]; P&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviation: PCI = Percutaneous Coronary Intervention, SA = Stable Angina, UA = Unstable Angina, NSTE-ACS = Non ST Elevation Acute Coronary Syndrome, STEMI= ST Elevation Myocardial Infarction, 1°= Primary, 2°= Secondary, MI= Myocardial Infarction, IDR= Ischemia Driven Revascularization, OR= Odds Ratio, P = P value, CI= Confidence Interval, ST= Stent Thrombosis, ACUITY=Acute Catheterization and Urgent Intervention Triage Strategy, GUSTO=The Global Use of Strategies to Open Occluded Arteries, vs=Versus.
B. PLATELET REACTIVITY

As mentioned earlier, a disadvantage of clopidogrel therapy is inter-patient response variability, which has been believed to equate to a greater number of ischemic events. This variability is not seen with prasugrel or ticagrelor due to their different pharmacological properties. Since clopidogrel “high on-treatment platelet reactivity” patients do not consistently achieve an adequate anti-platelet response it has been considered that better clinical outcomes could potentially be seen with targeting clopidogrel low-responder. As of now the role of pharmacogenetics with clopidogrel has been well established but its utility in clinical practice is uncertain as it is cumbersome, time-consuming, expensive, and not effective in all patients. The ARCTIC (Bedside Monitoring to Adjust Anti platelet Therapy for Coronary Stenting) trial revealed no significant benefit in the primary endpoint outcome in high platelet reactivity (monitored via the VerifyNow P2Y12 and aspirin point-of-care assays used prior to stenting) and subsequent treatment adjustments with an additional bolus of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors, compared with standard treatment for coronary stenting, (34.6 % vs 31.1%; HR = 1.13, [95% CI: 0.98 – 1.29], P = 0.10).35

The GRAVITAS (Gauging Responsiveness with a VerifyNow assay – Impact on Thrombosis and Safety) trial evaluated the effect of high-dose clopidogrel (loading and maintenance doses of 600 mg and 150 mg respectively) and low-dose clopidogrel (loading and maintenance doses of 300 mg and 75 mg respectively) in patients with high on platelet reactivity after PCI with drug eluting stent (DES) placement.26 In the trial, treatment with larger loading and maintenance doses of clopidogrel were not shown to significantly reduce ischemic events in the study population.18 The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel) study enrolled stable coronary artery disease patients with high on-treatment platelet reactivity after elective PCI, with at least one drug-eluting stent placed, and compared the efficacy of 10mg of prasugrel to 75mg of clopidogrel once a day.37 Even though switching treatment to prasugrel significantly decreased platelet-reactivity, measured via platelet reactivity units (PRU) testing, the trial was prematurely terminated due to lower than expected ischemic events.25 In both GRAVITAS and TRIGGER-PCI, platelet reactivity values where significantly reduced with high-dose clopidogrel and prasugrel respectively however, this did not equate to improved clinical outcomes. Also both studies measured platelet reactivity with the VerifyNow P2Y12 test (Accumetrics, San Diego, California) but with different cut-off values.6,35 Currently there is no established single best to identify patients with high platelet reactivity with clopidogrel treatment.5

C. ELDERLY, HISTORY OF TIA AND/ OR STROKE AND WEIGHT <60 KG

In a post-hoc analysis of the TRITON-TIMI 38 (Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndrome) study, no net benefit of prasugrel over clopidogrel was due to the potential ischemic benefit being offset with the increased bleeding events that were seen in patients with a history of TIA, weight less than 60kg, and age greater than 75 years. Prasugrel’s prescribing information contains a “black box” warning for it not to be used in patients with a history of TIA or stroke and age ≥ 75 years.19 The FDA recommends halving the daily maintenance dose of prasugrel to 5mg in elderly patients when additional risk factors such as previous AMI or presence of diabetes. The Trilogy ACS (Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization) study showed the safety of a reduced dose of prasugrel (5mg) in patients >75 years of age and <60 kg, however patients with a history of stroke or TIA were excluded from the study.26 The increased bleeding in the patient population may be due to altered disposition of the drug or a smaller body size increasing the levels of the active metabolite of prasugrel.25 According to a recent homogenous randomized meta-analysis, no benefit was observed with prasugrel or ticagrelor therapy for lowering the total risk of stroke when compared to clopidogrel (1.14% vs 1.11%; ARD: + 0.03%; OR = 1.06; [95% CI: 0.88 – 1.26]; P = 0.55).26 In a prospective randomized cross-over study, elderly patients with ACS undergoing PCI exhibiting High On-Treatment platelet reactivity after standard treatment with clopidogrel (75 mg per day), achieved lower platelet reactivity in patients receiving 5 mg per day of prasugrel than those receiving clopidogrel 150 mg per day (least squares estimates 190.8 [95% CI: 161.5 -220.1] and 240.8 [95% CI: 211.0 – 270.6], respectively; P = 0.008).39

Interestingly, in acute ischemic stroke patients with history of prior stroke and/or diabetes, improved outcomes were seen with thrombolytic therapy in comparison to no thrombolytic therapy.40 These results potentially can be extrapolated to ACS patients for making the decision of which P2Y12 antagonist to administer when a past history of stroke and/or diabetes is present. In addition, outcomes in ischemic stroke are likely complex with multiple factors such as genetic background playing a role. For instance, GP IIb/IIIa P1A2 polymorphisms have been shown to be an additive risk factor for ischemic stroke in high-risk patients.41

D. DIABETES MELLITUS

It should be understood by physicians that diabetics are at increased risk for both the incidence of ACS and its complications; this may be attributed to an increase in platelet reactivity and reduced generation of active clopidogrel metabolites.42 In the TRITON TIMI-38 sub-set population an increased benefit was seen with prasugrel (60 mg loading dose and 10 mg maintenance dose) over clopidogrel (loading dose 300 mg, maintenance dose 75 mg) over 6 to 15 months, with significant reduction in the primary end point of MI, CV death and stroke in diabetics, (12.2 % vs 17.0 %, [HR = 0.70]; P = 0.09) respectively without an increase in TIMI major bleeding when compared to clopidogrel (2.6% vs 2.5%, [ HR = 1.06], P = 0.81).28,42 Prasugrel’s greater platelet inhibition compared to clopidogrel may explain its favorable effect. The similar rates of bleeding seen in diabetics may be due to multiple reasons such as increased body weight and/or platelet reactivity.1 In the sub group analysis of PLATO trial, ticagrelor (loading dose of...
180 mg and twice daily maintenance dose of 90 mg) was tested against clopidogrel (loading dose 300 mg, maintenance dose of 75 mg). In diabetic patients, ticagrelor lowered the primary composite endpoint and all cause mortality but did not reach statistical significance, (14.1% vs 16.2%; HR = 0.88; [95% CI: 0.76 - 0.93]) and (7.0% vs 8.7%; HR = 0.82; [95% CI: 0.66 – 1.01]) respectively. However, ticagrelor did significantly reduce the primary end point and all cause mortality in patients with median hemoglobin A1C levels above 6.0%, (11.4% vs 14.2%; HR = 0.80; [95% CI: 0.70 – 0.91]) and (5.6% vs 7.4%; HR = 0.78; [95% CI: 0.65 – 0.93]) respectively.

E. RENAL AND HEPATIC IMPAIRMENT

Renal impairment is an important consideration given that renal disease is a known risk factor for coronary artery disease and increases the risk of bleeding. The summary of product characteristics of clopidogrel advises caution in the setting of moderate and severe renal impairment due to limited clinical experience. Since the pharmacokinetics of the active metabolite of prasugrel and its inhibition of platelet aggregation is not altered in patients with moderate renal impairment (CrCl 30-50ml/min) the summary of product characteristics does not recommend any dose adjustments in renal impairment but does caution its use due to limited clinical data. Dose adjustments due to renal impairment are also not recommended in ticagrelor’s summary of product characteristics however safety in dialysis patients has not been studied. Further research of the safety of P2Y12 antagonists in the context of severe renal impairment is necessary.

Currently there are no recommendations for dose adjustments in the setting of hepatic impairment. It is believed that because metabolism occurs in the liver, hepatic impairment may increase the risk of bleeding for the P2Y12 antagonists. Clopidogrel’s inhibition of platelet aggregation has not been shown to be affected by hepatic impairment. Pharmacokinetics and pharmacodynamics of prasugrel have not been studied in severe hepatic impairment. Ticagrelor has also not been studied in patients with moderate or severe hepatic impairment. Ticagrelor should be used with caution in moderate hepatic impairment and is contraindicated in patients with severe hepatic impairment.

F. SIDE EFFECTS

In the PLATO study an increased incidence of dyspnea was seen with ticagrelor compared to clopidogrel (13.8% vs 7.8%; p<0.001), which required discontinuation of ticagrelor in 0.9% of patients. The dose-related side effect of dyspnea was not secondary to cardiac or pulmonary conditions and is believed to be secondary to an increase in adenosine levels, due to inhibition of its clearance by ticagrelor. Even though not life threatening, the complaint of dyspnea is problematic for clinicians. A patient with a recent admission for acute coronary syndrome who presents with new onset dyspnea has a low-threshold for hospital admission. Ticagrelor induced dyspnea has the potential to increase emergency department visits and hospital admissions equating to increased healthcare costs.

Patients treated with ticagrelor also had more ventricular pauses observed during the first week of treatment. This appears to be an innocuous finding because as the majority of pauses were asymptomatic and sinoatrial in origin and the two treatment groups did not differ significantly in the incidence of syncope or pacemaker implantation. Cangrelor also has been associated with an increased incidence of dyspnea (1.2% vs 0.3%).

VI. CONCLUSIONS

The decision of which drug to use should be done on a case-by-case basis. Despite superiority in large randomized controlled trials neither prasugrel nor ticagrelor have dominated the market place. Physicians continue to use clopidogrel despite notable disadvantages of a delayed onset and inter-patient response variability. Perhaps the most important factor driving clopidogrel use is familiarity and the introduction of generic clopidogrel makes it an attractive choice for those with financial constraints. The combination of clopidogrel and aspirin has been used for many years, with satisfactory clinical results. Since severe bleeding has been uncommon with this combination, the risk of bleeding with clopidogrel may not concern physicians nearly as much as the risk of thrombosis with drug cessation. Lack of experience with the newer agents, combined with concerns about higher rates of bleeding compared with clopidogrel and cost, may have slowed the rate of prasugrel, ticagrelor, and cangrelor adoption. Finding the ideal balance between cost efficacy in ischemic event reduction and avoidance of bleeding will require additional studies. Direct comparative studies are needed to evaluate differences, if any, between prasugrel and ticagrelor.

REFERENCES


