Comparative Review of Oral P2Y12 Inhibitors
Renee Koski, PharmD, FMPA, CACP; and Blake Kennedy, PharmD

INTRODUCTION
According to the American Heart Association, cardiovascular disease mortality decreased by 38% between 2003 and 2013.1 Despite that, heart disease remains the leading cause of death in the United States, with approximately one in four individuals dying from the disease.2 Individuals who have had a myocardial infarction (MI) are at increased risk of having another event compared with the general population.3 MIs are classified as ST-elevation MI (STEMI) and non–ST-elevation MI based on electrocardiogram findings. A STEMI is usually the result of complete blockage, while a non–ST-elevation MI results from a partial obstruction of a coronary artery. Acute coronary syndrome (ACS) covers a spectrum of clinical presentations including STEMI, non–ST-elevation MI, and unstable angina. All are considered medical emergencies. Antiplatelet drugs can greatly reduce the risk of a recurrent MI and are considered standard therapy following an MI.3

Both the 2013 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Guideline for the Management of STEMI and the 2014 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Non–ST-elevation ACS recommend dual antiplatelet therapy (DAPT) comprised of aspirin and a purinergic signaling receptor Y12 (P2Y12) inhibitor for 12 months, followed by aspirin indefinitely, for patients without contraindications who are treated with either early invasive or ischemia-guided strategies.4,5 The 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease recommends DAPT for at least 12 months post-ACS whether managed medically, with percutaneous coronary intervention (PCI) (bare metal or drug-eluting stent), with thrombolytic and PCI, or coronary artery bypass graft (class I recommendation). It may be reasonable to continue DAPT longer than 12 months if ischemic risk warrants and if there is not a high risk of bleeding or history of significant overt bleeding with DAPT. Low-dose aspirin should be continued indefinitely in most clinical settings for both STEMI and non–ST-elevation ACS.6

Three oral P2Y12 inhibitors are available: clopidogrel, prasugrel, and ticagrelor (Brilinta, AstraZeneca). Clopidogrel, the first P2Y12 inhibitor, was the standard for DAPT until newer options became available. All three agents are recommended equally in the STEMI guidelines.4 The non–ST-elevation ACS guidelines recommend clopidogrel or ticagrelor (class I recommendation) or ticagrelor over clopidogrel (class IIa recommendation) in early invasive or ischemia-guided strategy.5

Keywords: antiplatelet, clopidogrel, prasugrel, ticagrelor, acute coronary syndrome, P2Y12 inhibitors

Both the STEMI and non–ST-elevation ACS guidelines recommend a clopidogrel 600-mg loading dose prior to PCI followed by 75 mg daily or a ticagrelor 180-mg loading dose prior to PCI followed by 90 mg twice daily.4,5 The STEMI guidelines also recommend a prasugrel 60-mg loading dose prior to PCI followed by 10 mg daily as an option.4 Clopidogrel’s loading dose should be reduced to 300 mg if given within 24 hours of a fibrinolytic or if medical management is pursued.4,5 This article will compare the three oral P2Y12 inhibitors in terms of efficacy, safety, and other drug characteristics.

Efficacy and Safety: Key Clinical Trials
Clopidogrel
Before the discovery of P2Y12 inhibitors, aspirin alone was the standard antiplatelet regimen post-MI. The CURE trial compared clopidogrel and aspirin (DAPT) to aspirin with or without revascularization in patients with ACS without ST elevation, and the COMMIT trial compared them post-STEMI. Patients undergoing primary PCI were excluded from the COMMIT trial. DAPT reduced the risk of adverse cardiovascular events compared with aspirin in both trials.7,8 In CURE but not COMMIT, there was an increase in major bleeding with clopidogrel.7 These trials led to guideline recommendations for DAPT following ACS with and without STEMI. Post-hoc analyses of CURE found DAPT to be cost-effective, beneficial despite clopidogrel polymorphisms, effective with and without PCI or surgery, effective despite timing of PCI, and effective despite dose of aspirin used.9–12 A post-hoc analysis of COMMIT found DAPT to be cost-effective post-MI.14

The CLARITY-TIMI 28 trial evaluated the use of clopidogrel plus aspirin (DAPT) versus aspirin with or without angiography in patients with STEMI also receiving fibrinolytic therapy and found DAPT reduced adverse cardiovascular events without an increase in major bleeding compared to aspirin.15 This trial established the safety and efficacy of DAPT plus a fibrinolytic post-STEMI.

The CURRENT-OASIS 7 trial was conducted to determine optimal doses of clopidogrel and aspirin in patients with ACS referred for early invasive strategy. Patients were assigned to double loading and maintenance doses or standard loading and maintenance doses of clopidogrel for seven days followed by standard doses daily for 23 days. Patients were also given high- or low-dose daily aspirin. There was no difference in adverse cardiovascular events with clopidogrel at double versus standard dose, but there was more major bleeding with the double dose. The primary efficacy and safety endpoints did not differ between high- and low-dose aspirin.16 This study proved that low-dose aspirin is equally effective compared with high-dose aspirin. A post-hoc subgroup analysis of patients who underwent PCI found double-dose clopidogrel reduced the primary efficacy endpoint (3.9% versus

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<table>
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<tr>
<th>Trial Name and Design</th>
<th>Inclusion Criteria</th>
<th>Study Arms</th>
<th>Primary Efficacy Endpoint</th>
<th>Primary Safety Endpoint</th>
<th>Results</th>
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<tr>
<td>CURE&lt;sup&gt;7&lt;/sup&gt; Clopidogrel vs. placebo (double-blind, randomized)</td>
<td>ACS without STEMI</td>
<td>Clopidogrel 300 mg x 1, then 75 mg (n = 6,259) OR placebo (n = 6,303) daily AND aspirin 75–325 mg daily</td>
<td>Death from CV causes, nonfatal MI, stroke at end of study follow-up</td>
<td>Major bleeding</td>
<td>Efficacy (P &lt; 0.001): • Clopidogrel: 9.3% • Placebo: 11.4% Safety (P = 0.001): • Clopidogrel: 3.7% • Placebo: 2.7%</td>
</tr>
<tr>
<td>COMMIT&lt;sup&gt;8&lt;/sup&gt; Clopidogrel vs. placebo (double-blind, randomized)</td>
<td>STEMI Clopidogrel 75 mg (n = 22,961) OR placebo (n = 22,891) daily AND aspirin 162 mg daily</td>
<td>Death, reinfarction, or stroke at 28 days</td>
<td>Any bleeding</td>
<td>Efficacy (P = 0.002): • Clopidogrel: 9.2% • Placebo: 10.1% Safety (P = 0.59): • Clopidogrel: 0.58% • Placebo: 0.55%</td>
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<tr>
<td>CLARITY-TIMI 28&lt;sup&gt;15&lt;/sup&gt; Clopidogrel vs. placebo (double-blind, randomized)</td>
<td>STEMI Clopidogrel 300 mg x 1, then 75 mg (n = 1,752) OR placebo (n = 1,739) AND fibrinolytic + aspirin 150–325 mg x 1, then 75–162 mg daily</td>
<td>Occluded infarct-related artery, death, or recurrent MI before or after angiography or day 8 if no angiography</td>
<td>TIMI-defined major bleeding after angiography or day 8 if no angiography</td>
<td>Efficacy: • Clopidogrel 150 mg: 4.2% • Clopidogrel 75 mg: 4.4% (P = 0.61) Safety (P = 0.01): • 150 mg: 2.5% • 75 mg: 2.0%</td>
<td></td>
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<tr>
<td>CURRENT-OASIS 7&lt;sup&gt;6&lt;/sup&gt; High-dose clopidogrel vs. low-dose clopidogrel; high-dose aspirin vs. low-dose aspirin (double-blind [clopidogrel], open-label [aspirin], randomized)</td>
<td>ACS referred for invasive strategy within 72 hours</td>
<td>Clopidogrel 600 mg x 1, 150 mg days 2–7, then 75 mg daily (n = 12,520) OR 300 mg x 1, then 75 mg daily (n = 12,566) AND aspirin 300–325 mg OR 75–100 mg daily</td>
<td>CV death, stroke, or MI at 30 days</td>
<td>Study-defined major bleeding at 30 days</td>
<td>Efficacy: • Clopidogrel 150 mg: 4.2% • Clopidogrel 75 mg: 4.4% (P = 0.30) Aspirin–high: 4.2% Aspirin–low: 4.4% (P = 0.61) Safety (P = 0.01): • 150 mg: 2.5% • 75 mg: 2.0%</td>
</tr>
<tr>
<td>TRITON-TIMI 38&lt;sup&gt;18&lt;/sup&gt; Clopidogrel vs. prasugrel (double-blind, randomized)</td>
<td>ACS undergoing PCI</td>
<td>Clopidogrel 300 mg x 1, then 75 mg daily (n = 6,795) OR prasugrel 60 mg x 1, then 10 mg daily (n = 6,813) AND aspirin 75–100 mg daily</td>
<td>Death from CV causes, nonfatal stroke, or nonfatal MI at 15 months</td>
<td>Non-CABG-related TIMI major bleeding at 15 months</td>
<td>Efficacy (P &lt; 0.001): • Prasugrel: 9.9% • Clopidogrel: 12.1% Safety (P = 0.03): • Prasugrel: 2.4% • Clopidogrel: 1.8%</td>
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<td>TRILOGY-ACS&lt;sup&gt;21&lt;/sup&gt; Clopidogrel vs. prasugrel (double-blind, randomized)</td>
<td>ACS not undergoing PCI</td>
<td>Clopidogrel 300 mg x 1, then 75 mg daily (n = 3,623) OR prasugrel 30 mg x 1, then 10 mg daily (n = 3,620) AND aspirin daily</td>
<td>Death from CV causes, nonfatal MI, or nonfatal stroke at 30 months</td>
<td>GUSTO-defined severe or life-threatening bleeding</td>
<td>Efficacy (P = 0.21): • Prasugrel: 10.1% • Clopidogrel: 12.1% Safety (P = 0.87): • Prasugrel: 0.4% • Clopidogrel: 0.4%</td>
</tr>
<tr>
<td>PLATO&lt;sup&gt;22&lt;/sup&gt; Clopidogrel vs. ticagrelor (double-blind, randomized)</td>
<td>ACS</td>
<td>Clopidogrel 300 mg x 1, then 75 mg daily (n = 9,291) OR ticagrelor 180 mg x 1, then 90 mg twice daily (n = 9,333) AND aspirin 75–100 mg daily</td>
<td>Death from vascular causes, stroke, or MI at 12 months</td>
<td>PLATO-defined major bleeding at 12 months</td>
<td>Efficacy (P &lt; 0.001): • Ticagrelor: 9.8% • Clopidogrel: 11.7% Safety (P = 0.43): • Ticagrelor: 11.6% • Clopidogrel: 11.2%</td>
</tr>
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</table>

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; CV = cardiovascular; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries trial; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction; TIMI = thrombolysis in myocardial infarction.
4.5%, respectively; \( P = 0.039 \) but increased major bleeding (1.6% versus 1.1%, respectively; \( P = 0.009 \) compared with the standard dose.17

**Clopidogrel Versus Prasugrel**

The TRITON-TIMI 38 trial compared DAPT with clopidogrel or prasugrel in patients with ACS undergoing PCI. There was a decrease in adverse cardiovascular events and an increase in major bleeding with prasugrel compared with clopidogrel. A subgroup analysis showed a reduction in adverse cardiac events with prasugrel in patients with diabetes, no history of stroke or transient ischemic attack (TIA), and age younger than 75 years with body weight of at least 60 kg.18 This trial led to prasugrel’s approval by the Food and Drug Administration (FDA). A post-hoc subgroup analysis of patients with STEMI undergoing PCI found a decrease in the primary endpoint without an increased risk of bleeding in the prasugrel versus clopidogrel group.19 A post-hoc cost-effectiveness analysis found 30-day treatment with prasugrel to be a dominant cost-effectiveness strategy compared with generic clopidogrel if the price difference per tablet was less than $7.67 per day. Beyond 30 days, the incremental cost-effectiveness ratio was greater than $50,000 per life-year gained when the drug price difference was greater than $9.30 per day.20

The TRILOGY ACS trial compared DAPT with clopidogrel or prasugrel in patients with ACS medically managed without revascularization. There was no difference in adverse cardiovascular events or severe or life-threatening bleeding between the two groups.21

**Clopidogrel Versus Ticagrelor**

The PLATO trial compared DAPT with clopidogrel or ticagrelor in patients with ACS treated with or without PCI. Adverse cardiovascular events occurred less often with ticagrelor than with clopidogrel, and there was no difference in major bleeding.22 This trial led to ticagrelor’s FDA approval. A post-hoc subgroup analysis found no difference in the primary efficacy or safety endpoints between the two groups in patients with ACS undergoing PCI.23 An additional post-hoc subgroup analysis found ticagrelor to have efficacy and safety outcomes similar to the original trial in patients with ACS managed non-invasively.24 Yet another post-hoc subgroup analysis found ticagrelor to have efficacy and safety outcomes similar to the original trial in patients with ACS managed non-invasively.24 Yet another post-hoc subgroup analysis found ticagrelor to have efficacy and safety outcomes similar to the original trial in patients with ACS managed non-invasively.25

The two ticagrelor doses were not compared.27 A recent meta-analysis of randomized controlled trials that evaluated long-term use of DAPT for secondary prevention of atherothrombotic events found long-term DAPT (longer than 12 months) was associated with a lower risk of death, MI, and stroke but a higher risk of bleeding compared with DAPT of less than 12 months or long-term aspirin alone. This meta-analysis included all three P2Y12 inhibitors but did not compare them.28 A different meta-analysis comparing the newer oral P2Y12 inhibitors with clopidogrel after non–ST-elevation ACS concluded that the newer agents are more effective in preventing adverse cardiac events but have an increased risk of major bleeding compared with clopidogrel.29

All the trials above excluded patients on oral anticoagulants. A recent large meta-analysis found no difference in major adverse cardiac events, stroke, all-cause mortality, or stent thrombosis with triple therapy (TT)—dual antiplatelet therapy plus warfarin—compared with DAPT after PCI. It also found a lower rate of MI and major bleeding with TT compared with DAPT and equal efficacy and safety outcomes with TT compared with the combination of warfarin and clopidogrel.30 Both the STEMI and non–ST-elevation ACS guidelines acknowledge the use of warfarin for patients with atrial fibrillation who also need DAPT.4,5 Studies evaluating direct-acting oral anticoagulants (DOACs) with DAPT are under way or recently completed (with promising results), but no recommendations regarding DOAC dosing with DAPT or which DOAC to use with DAPT have been published.31–34

Both the non–ST-elevation ACS guidelines and the duration of DAPT guidelines recommend adding a proton pump inhibitor (PPI) to DAPT in patients with a history of gastrointestinal bleeding and considering a PPI in patients with an increased risk of gastrointestinal bleeding on DAPT plus an oral anticoagulant. The duration of DAPT guidelines also recommend keeping TT duration as short as possible, considering a target international normalized ratio of 2.0–2.5 when warfarin is used, making clopidogrel the P2Y12 inhibitor of choice, and using low-dose aspirin (100 mg daily or less).3,5

**PERIOPERATIVE ANTIPLATELET MANAGEMENT**

Patients on DAPT may require its interruption for cardiac or noncardiac surgeries or procedures. It is recommended to assess thrombotic risk (high, intermediate, low) based on PCI (which one and how long ago it occurred) and hemorrhagic risk (high, intermediate, low) of the procedure. It is usually recommended to continue aspirin regardless of PCI thrombotic risk and procedure hemorrhagic risk. The P2Y12 inhibitor should be held for procedures of intermediate or high hemorrhagic risk regardless of PCI thrombotic risk. For procedures with low hemorrhagic risk, P2Y12 inhibitors should be continued if there is a high thrombotic risk, but held for intermediate or low thrombotic risk. Bridging with short-acting intravenous antiplatelet therapy (e.g., cangrelor [Kengreal, Chiesi USA, Inc.], eptifibatide, tirofiban [Aggrastat, Medicure, Inc.]) can be considered for high-thrombotic-risk PCI with intermediate- or high-hemorrhagic-risk procedures.35 Prior to the procedure, clopidogrel and ticagrelor should be held for five days and prasugrel should be held for seven days.36 The P2Y12 inhibitor should generally be resumed within 24 to 72 hours after...
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Table 2  Comparison of Oral P2Y12 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
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<tbody>
<tr>
<td></td>
<td>(Plavix, Bristol-Myers Squibb/Sanofi)</td>
<td>(Effient, Eli Lilly)</td>
<td>(Brilinta, AstraZeneca)</td>
</tr>
<tr>
<td>Initial FDA approval</td>
<td>1997</td>
<td>2009</td>
<td>2011</td>
</tr>
<tr>
<td>Current FDA-approved indications</td>
<td>ACS (invasively or noninvasively managed); recent MI or stroke; established PAD</td>
<td>ACS with PCI</td>
<td>ACS (invasively or noninvasively managed) or MI history</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Bind to ADP P2Y12 receptor on platelets, preventing ADP from binding and activating the glycoprotein GPIIb/IIIa complex, which is necessary for platelet aggregation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Onset of action</td>
<td>2–8 hours</td>
<td>0.5–4 hours</td>
<td>0.5–4 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>Parent: 6 hours</td>
<td>Active metabolite: 30 minutes</td>
<td>Active metabolite: 7 hours</td>
</tr>
<tr>
<td>Offset of action</td>
<td>5–7 days</td>
<td>7–10 days</td>
<td>3–5 days</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Thienopyridine prodrug metabolized mostly by CYP2C19 to active metabolite</td>
<td>Thienopyridine prodrug metabolized mostly by esterases in GI tract to active metabolite</td>
<td>Nonthienopyridine metabolized by CYP3A4; parent and metabolite equally inhibit P2Y12</td>
</tr>
<tr>
<td>Dosage forms</td>
<td>75-mg and 300-mg tablets</td>
<td>5-mg and 10-mg tablets</td>
<td>60-mg and 90-mg tablets</td>
</tr>
<tr>
<td>Loading dose</td>
<td>300 mg or 600 mg</td>
<td>60 mg</td>
<td>180 mg</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>75 mg daily</td>
<td>10 mg daily (consider 5 mg daily if weight &lt; 60 kg)</td>
<td>90 mg twice daily for 1 year post-ACS; then 60 mg twice daily</td>
</tr>
<tr>
<td>AWP for 30-day supply at maintenance dose</td>
<td>$232 (brand); $184 (lowest generic)</td>
<td>$551 (brand); $495 (lowest generic) (5-mg or 10-mg tablets)</td>
<td>$424 (60-mg or 90-mg tablets) (No generic available)</td>
</tr>
<tr>
<td>Use in renal/hepatic impairment</td>
<td>No dose adjustments necessary</td>
<td>Use caution in moderate-to-severe renal or severe hepatic impairment</td>
<td>Use caution in moderate and avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Periprocedural hold</td>
<td>5 days</td>
<td>7 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Nonbleeding noteworthy side effects</td>
<td>None</td>
<td>None</td>
<td>Dyspnea (14.2%); elevated serum creatinine; elevated uric acid</td>
</tr>
<tr>
<td>Boxed warnings and contraindications</td>
<td>• Diminished antiplatelet effect in CYP2C19 poor metabolizers. Consider alternative P2Y12 inhibitor in this population. • Contraindicated in active bleeding and CYP2C19 poor metabolizers.</td>
<td>• Bleeding risk: Significant and sometimes fatal bleeding may occur; contraindicated in patients with active bleeding, stroke/TIA history, or CABG surgery within 7 days. • Not recommended in patients ≥ 75 years of age unless high risk (diabetes or prior MI history) due to increased fatal and intracranial bleeding risk and uncertain benefit. • Not recommended in patients weighing &lt; 60 kg.</td>
<td>• Bleeding risk: Significant and sometimes fatal bleeding may occur; contraindicated in patients with active bleeding or intra- cranial hemorrhage history. • Aspirin doses and ticagrelor effectiveness: After initial aspirin dose, give aspirin 75–100 mg daily with ticagrelor. Aspirin maintenance doses greater than 100 mg daily reduce the effectiveness of ticagrelor and should be avoided.</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; ADP = adenosine diphosphate; AWP = average wholesale price; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; CYP = cytochrome P450; FDA = Food and Drug Administration; GI = gastrointestinal; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

the procedure with a loading dose (clopidogrel 300–600 mg, prasugrel 60 mg, ticagrelor 180 mg). Elective procedures should be postponed if possible until PCI thrombotic risk decreases to low risk (based on time since PCI).35

SWITCHING BETWEEN P2Y12 INHIBITORS

Patients may need to switch from one P2Y12 inhibitor to another for various reasons, including treatment failure, side effects, cost, nonadherence, and contraindications. Registries and pharmacodynamic studies have evaluated switching between P2Y12 inhibitors under both emergent and non-
emergent circumstances. Based on these studies, to avoid a gap in adequate platelet inhibition in the acute/early phase (30 days or less after the index event), a one-time loading dose (clopidogrel 600 mg, prasugrel 60 mg, ticagrelor 180 mg) of the new agent is recommended. The loading dose should be administered 24 hours after the last dose of the initial P2Y12 inhibitor for all situations, except switching from clopidogrel to ticagrelor or prasugrel, where the timing of the loading dose is irrespective of the timing and dosing of clopidogrel. In the late or very late phase (more than 30 days from the index event), no loading dose of the new agent is recommended, except when switching from ticagrelor to clopidogrel or prasugrel, when a 600-ng or 60-mg loading dose, respectively, is recommended 24 hours after the last ticagrelor dose.41,42 If switching to ticagrelor, the concurrent aspirin dose should not exceed 100 mg daily.42

Two recent, randomized, open-label trials studied the efficacy and safety of initiating prasugrel (TROPICAL-ACS) or prasugrel or ticagrelor (TOPIC) post-ACS and switching to clopidogrel one week (TROPICAL-ACS) or one month (TOPIC) later and continuing them for one year. In TROPICAL-ACS, patients were assessed for high on-treatment platelet reactivity (HPR) two weeks after initiation. If they were on clopidogrel and HPR was noted, patients were switched back to prasugrel. HPR was found in 39% of patients taking clopidogrel and 14% of patients taking prasugrel. This study found guided de-escalation to clopidogrel to be noninferior to continued prasugrel for both ischemic and bleeding outcomes. TOPIC found de-escalation to clopidogrel to be superior to continued prasugrel or ticagrelor in preventing bleeding complications without increasing ischemic events.43,44

CHARACTERISTICS, ADVANTAGES, AND DISADVANTAGES

The activity level of cytochrome P450 (CYP) 2C19 varies widely in the general population, so poor metabolizers (common in the Asian population) and patients on concomitant CYP2C19 inhibitors may not achieve adequate levels of platelet inhibition with clopidogrel and could face an increased risk for recurrent MI.45 Genetic phenotype testing is available but not routinely recommended.4 The PPIs are a common class of CYP2C19 inhibitors, and the PPI that inhibits CYP2C19 the most is omeprazole. One study measured the level of platelet inhibition and the rate of adverse cardiac events in patients taking clopidogrel with or without omeprazole. Platelet inhibition was significantly diminished in the omeprazole group, but there was no significant difference in adverse cardiac events.46 A recent meta-analysis of trials looking at clinical outcomes using clopidogrel with or without a PPI following coronary angioplasty found an increase in major adverse cardiac events with clopidogrel plus PPI versus clopidogrel without PPI. Omeprazole was considered to have more of an adverse effect than the other PPIs.47 Cost is an advantage of clopidogrel. It is the least expensive P2Y12 inhibitor and available as a generic.46 Disadvantages of clopidogrel include its potentially variable efficacy and boxed warning regarding poor CYP2C19 metabolizers.7,8,15,16,45

There is minimal variation in platelet inhibition with prasugrel in the general population compared to clopidogrel because it is metabolized mostly by esterases in the intestinal tract with minimal CYP metabolism in the liver. Advantages of prasugrel include potentially fewer drug interactions due to lack of significant CYP activity and its once-daily dosing.46 Disadvantages include: 1) the most reported fatal bleeding of the three drugs;18,21 2) an extensive boxed warning regarding its bleeding risk; 3) its contraindication in patients with a history of stroke or TIA; and 4) cost.48,49 Although less-expensive generic prasugrel is now available, its cost is greater than that of clopidogrel or ticagrelor.48

There is no variation in antiplatelet effect with ticagrelor in the general population because metabolism is not required for its activation. The reversible binding of ticagrelor is both an advantage and a disadvantage. While it leads to a quicker onset and offset, which may be beneficial in certain situations, the relatively short duration of antiplatelet activity could pose a problem if patients are not adherent to therapy. Other disadvantages of ticagrelor include: 1) twice-daily dosing, which can affect adherence; 2) its association with dyspnea, which can significantly limit daily activities; 3) a boxed warning regarding bleeding risk and concomitant aspirin dose;42 and 4) cost.48

The three drugs’ FDA-approved indications, pharmacokinetics, dosing, average wholesale prices, noteworthy side effects, boxed warnings, and contraindications are summarized in Table 2.

CONCLUSION

DAPT is key to preventing recurrent MIs and post-MI-related death. All three P2Y12 inhibitors are safe and effective post-MI. Data suggest that prasugrel and ticagrelor are more efficacious than clopidogrel at preventing adverse cardiac events and recurrent MI. One major comparative study and a meta-analysis found an increased risk of bleeding with prasugrel and ticagrelor compared with clopidogrel. The P2Y12 inhibitors have unique characteristics that may lead to one being preferred over another in different situations. Recognizing differences in the agents in terms of efficacy, safety, indications, cost, dosing, contraindications, drug interactions, and other characteristics can help providers choose the best agent for individual patients.

REFERENCES


