

## Therapeutic Class Overview Platelet Inhibitors

### Therapeutic Class

- Overview/Summary:** Platelet inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. The agents in the class are Food and Drug Administration (FDA)-approved for a variety of indications including treatment and/or prevention of acute coronary syndromes (ACS), stroke/transient ischemic attack (TIA), and thrombocytopenia. The platelet inhibitors are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery. The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action.<sup>1-9</sup> One of the newest platelet inhibitors to be FDA-approved is vorapaxar (Zontivity<sup>®</sup>), which is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).<sup>7</sup> Vorapaxar (Zontivity<sup>®</sup>), is the first in a new class of antiplatelet agents called protease-activated receptor-1 (PAR-1) antagonists. It is a competitive and selective antagonist of PAR-1, the major thrombin receptor on human platelets. It works by inhibiting thrombin-induced platelet aggregation and thus blood clot formation. In addition, vorapaxar is not a prodrug and does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.<sup>7</sup> Vorapaxar is available for once-daily dosing in combination with other antiplatelet agents (either clopidogrel and/or aspirin). Clopidogrel and prasugrel are administered once-daily, while ticagrelor is dosed twice daily.<sup>2,4,5</sup>

**Table 1. Current Medications Available in the Therapeutic Class<sup>1-9</sup>**

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
<b>Single-Entity Agents</b>			
Anagrelide (Agrylin <sup>®*</sup> )	Treatment of thrombocytopenia associated with myeloproliferative disorders <sup>†</sup>	Capsule: 0.5 mg 1 mg	✓
Aspirin extended-release (Durlaza <sup>®</sup> )	Reduce the risk of death and myocardial infarction in patients with chronic coronary artery disease as well as to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or transient ischemic attack	Capsule: 162.5 mg	-
Clopidogrel (Plavix <sup>®*</sup> )	Recent myocardial infarction, recent stroke, or established peripheral arterial disease, reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome <sup>‡</sup>	Tablet: 75 mg 300 mg	✓
Dipyridamole (Persantine <sup>®*</sup> )	Prevention of postoperative thromboembolic complications of cardiac valve replacement <sup>§</sup>	Tablet: 25 mg 50 mg 75 mg	✓
Prasugrel (Effient <sup>®</sup> )	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention <sup>  </sup>	Tablet: 5 mg 10 mg	-
Ticagrelor (Brilinta <sup>®</sup> )	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome <sup>¶</sup> ; reduce the rate of cardiovascular death, myocardial infarction, and stroke in patients with acute coronary syndrome or a history of myocardial infarction	Tablet: 60 mg 90 mg	-
Ticlopidine	Reduce the incidence of subacute stent	Tablet:	✓

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
(Ticlid <sup>®*</sup> )	thrombosis in patients undergoing successful coronary stent implantation <sup>#</sup> , reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke	250 mg	
Vorapaxar (Zontivity <sup>®</sup> )	Reduce the risk of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease: Tablet: 2.08 mg QD in combination with other antiplatelet agents (clopidogrel and/or aspirin)	Tablet: 2.08 mg	-
<b>Combination-Products</b>			
Aspirin/ extended-release dipyridamole (Aggrenox <sup>®</sup> )	Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	Capsule: 25/200 mg	✓

\*Generic available in at least one dosage form or strength.

†To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events.

‡For patients with non-ST-segment elevation acute coronary syndrome, including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction.

§As adjunct to coumarin anticoagulants.

|| Patients who are to be managed with percutaneous coronary intervention as follows: patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed percutaneous intervention.

¶Patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction.

#As adjunct to aspirin.

### Evidence-based Medicine

- Clopidogrel, Food and Drug Administration-approved in 1997, has been the principle platelet inhibitor for several years as the clinical data supporting its use is well established.<sup>11-16</sup>
- The RAPID Primary PCI study compared prasugrel to ticagrelor in patients who had a ST-Segment elevation myocardial infarction (STEMI) who were to undergo percutaneous coronary intervention (PCI). Prasugrel was noninferior as compared with ticagrelor in terms of residual platelet reactivity two hours after the loading dose (P=0.207).<sup>17</sup>
- Approval of prasugrel for use in ACS was based on the clinical evidence for safety and efficacy derived from the TRITON-TIMI 38 study (N=13,608). Within the study, prasugrel was significantly more effective compared to clopidogrel in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention. Prasugrel did not demonstrate a mortality benefit and a significantly higher rate of major, minor, life-threatening, and fatal bleeding events was observed with prasugrel.<sup>18</sup>
  - Of note, a benefit with prasugrel was not observed in certain patient subgroups within TRITON-TIMI 38, specifically those who were ≥75 years of age, those weighing <60 kg, and those with a past history of stroke or TIA.
- The approval of ticagrelor for use in ACS was based on the clinical evidence for safety and efficacy derived from the PLATO study. Within the trial, hospitalized patients with documented ACS, with or without ST-elevation, were randomized to either ticagrelor or clopidogrel (N=18,624). After 12 months of treatment, ticagrelor was significantly more effective compared to clopidogrel in reducing the primary composite endpoint of cardiovascular death, MI, or stroke; without increasing the risk of major bleeding. Ticagrelor demonstrated a mortality benefit compared to clopidogrel.<sup>19</sup>
  - There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS.<sup>20</sup>

- Brener et al evaluated prasugrel-treated patients to clopidogrel-treated patients with STEMI. The prasugrel group had higher rates of procedural success ( $P=0.03$ ), TIMI 3 flow ( $P=0.06$ ), and lower corrected TIMI frame counts ( $P=0.008$ ).<sup>21</sup>
- Approval of vorapaxar was based on the results of the TRA2°P-TIMI 50 trial. The composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or TIA the vorapaxar group showed a significant 17% relative risk reduction over the three years of the study (HR, 0.83; 95%CI, 0.76 to 0.90;  $P<0.001$ ).<sup>22</sup>
  - Patients who had a previous stroke were removed from the study after 24 month follow-up assessments. Among the patients with a history of stroke, the rate of intracranial hemorrhage in the vorapaxar group higher ( $P<0.001$ ), without a history of stroke and was significantly increased as compared with the group without a prior stroke ( $P=0.049$ ).<sup>22</sup>

### Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Use of the platelet inhibitors, as monotherapy or combination therapy, is based on the specific clinical indication and the patient's risk for thromboembolic events.<sup>23-43</sup>
  - According to the 2016 guideline update from the American College of Cardiology and American Heart Association, aspirin therapy should be continued indefinitely in patients with coronary artery disease. In those treated with dual antiplatelet therapy (DAPT), the daily aspirin dose should be 81 mg (range 75 to 100 mg).<sup>42</sup>
    - Patients with stable ischemic heart disease treated with DAPT after bare metal stent (BMS) implantation, should be given P2Y<sub>12</sub> inhibitor therapy with clopidogrel for a minimum of one month and for a minimum of six months following drug-eluting stent (DES) implantation.
    - Patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after BMS or DES implantation should be given therapy with a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel or ticagrelor) for at least 12 months.
    - Prasugrel should not be administered to patients with a prior history of stroke or TIA.
    - It may be reasonable to continue DAPT for longer than the above recommendations in patients who have tolerated DAPT without a bleeding complication and who are not considered at a high risk for bleeding.
  - Antiplatelet therapy (aspirin plus extended-release [ER] dipyridamole or clopidogrel > aspirin) is recommended for long-term secondary prevention in patients with an acute ischemic stroke who are not receiving thrombolysis. Combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. Dual antiplatelet therapy should be used with caution and is favored in patients who have had a recent acute MI, other ACS, or recently placed coronary stent.<sup>24,25</sup>
  - According to the 2012 guideline on Antithrombotic Therapy and Prevention of Thrombosis by the American College of Chest Physicians, dual therapy aspirin with clopidogrel or ticagrelor or prasugrel monotherapy is recommended in the first year following ACS in patients regardless of PCI status.<sup>24</sup>
    - The guideline recommends ticagrelor plus low-dose aspirin over clopidogrel plus low-dose aspirin in patients post-ACS independent of whether PCI has been conducted.<sup>24</sup>
  - The 2013 guidelines for managing patients with STEMI by American College of Cardiology Foundation and American Heart Association recommend clopidogrel, prasugrel or ticagrelor for one year following PCI, without recommendation for one antiplatelet drug over another.<sup>28</sup>
  - The 2011 and 2015 European Society of Cardiology guideline for the management of ACS in patients presenting without persisting ST-elevation recommends ticagrelor first-line in patients at moderate to high risk of ischemic events, regardless of treatment strategy and including those pretreated with clopidogrel.<sup>27,43</sup>
    - If coronary anatomy is known and PCI is planned, prasugrel is recommended.
    - Clopidogrel is recommended in patients who cannot receive prasugrel or ticagrelor.

- The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for percutaneous intervention recommends clopidogrel, prasugrel, and ticagrelor as treatment options.<sup>28</sup>
  - Treatment with all agents should be continued for at least one year.
- Other Key Facts:
  - Anagrelide, aspirin/dipyridamole, clopidogrel, dipyridamole and ticlopidine are available generically.

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