OPTUMRx®

Therapeutic Class Overview
Platelet Aggregation Inhibitors

INTRODUCTION

- Cardiovascular (CV) disease is the underlying cause of approximately 17.8 million deaths globally on an annual basis according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2020 update. Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, unintentional injuries/accidents, and chronic lower respiratory disease. Each year, about 795,000 people experience a new or recurrent stroke (*Virani et al 2020*).

- Platelet inhibitors play a major role in the management of CV, cerebrovascular, and peripheral vascular diseases. These agents are indicated for a variety of Food and Drug Administration (FDA)-approved indications including treatment and/or prevention of acute coronary syndromes (ACS) (myocardial infarction [MI], unstable angina [UA]), stroke/transient ischemic attack [TIA], intermittent claudication, prevention of postoperative thromboembolic complications, thrombocythemia, and valvular heart disease. The use of these agents as both monotherapy or combination therapy by national and international clinical guidelines is based on the specific clinical indication and the patient's risk for thromboembolic events (*Aboyans et al 2018, Amsterdam et al 2014, Anderson et al 2013, Baumgartner et al 2017, Bushnell et al 2014, Culebras et al 2014, Fihn et al 2012, Gerhard-Herman et al 2016, Guyatt et al 2012, Ibanez et al 2018, January et al 2014, January et al 2019, Jauch 2013, Kernan et al 2014, Knuuti et al 2020, Lansberg et al 2012, Levine et al 2011, Levine et al 2016a, Levine et al 2016b, Lip et al 2018, Meschia et al 2014, Nishimura, 2017, O'Gara et al 2013, Powers et al 2015, Powers et al 2018, Powers et al 2019, Smith et al 2011, Smith et al 2017, Valgimigli et al 2018*).

- The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action and have characteristics that distinguish agents from one another.
  - Aspirin (ASA), a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A2, a platelet aggregate and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that ASA reduces adverse clinical events among a broad group of patients treated for both acute and chronic vascular disease (*Harrington et al 2008*).
    - Omeprazole, a component of Yosprala (ASA delayed-release [DR]/omeprazole), in combination with ASA, is an antisecretory compound, which suppresses gastric acid secretion by inhibiting the $[H^+/K^+]$-ATPase enzyme system of the gastric parietal cells. Omeprazole has been characterized as a gastric acid-pump inhibitor as it blocks the final step of gastric acid production, and inhibits both basal and stimulus-induced acid secretion.
  - Zontivity is unique to the class as a selective antagonist of the protease-activated receptor-1 (PAR-1), a primary thrombin receptor, and should only be used with ASA and/or Plavix (clopidogrel) according to their indication or standards of care.
  - Plavix, Effient, and Brilinta inhibit $P2Y_{12}$, an adenosine phosphate receptor on the surface of platelets. Brilinta is the only reversible inhibitor of $P2Y_{12}$ and unlike Plavix does not require hepatic activation. Plavix has a slower onset of action, incomplete platelet inhibition, and poor response in certain patients including those with CYP2C19 polymorphisms. Compared to Plavix, the benefits of Effient have been seen as early as 3 days. Effient and Zontivity are both contraindicated in patients with a history of TIAs.
  - Agrylin has multiple mechanisms in which it exerts its action and is unique in class as it has the ability to reduce platelet counts without affecting white or red blood cell counts.
  - Cilostazol reversibly inhibits platelet aggregation through cyclic AMP phosphodiesterase inhibition. Cilostazol also has vasodilating activity, which has benefits in treating certain diseases.
  - Dipyridamole is a non-nitrate coronary vasodilator that also inhibits platelet aggregation. The mechanism of action of dipyridamole may involve its ability to vasodilate and to increase concentrations of adenosine, a platelet aggregation inhibitor.

- Products included in this class review include Agrylin (anagrelide), Aggrenox (ASA/extended-release [ER] dipyridamole), Brilinta (ticagrelor), cilostazol, Plavix (clopidogrel), dipyridamole, Durlaza (ASA ER), Effient (prasugrel), Yosprala (ASA DR/omeprazole), and Zontivity (vorapaxar). Other platelet aggregation inhibitors used only in inpatient acute care

settings, such as the glycoprotein IIb/IIIa inhibitors and Kengreal (cangrelor); and convenience kits such as clopidogrel 75 mg/ASA 81 mg are not discussed in this review.

- Medispan Class: Platelet Aggregation Inhibitors – Platelet Aggregation Inhibitors, Platelet Aggregation Inhibitors Combinations, Protease-Activated Receptor-1 (PAR-1) Antagonists, Direct-Acting P2Y$_{12}$ Inhibitors, Dipyridamole, Quinazoline Agents, Thienopyridine Derivatives, and Aspirin (Platelet Aggregation Inhibitor).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
Agrylin (anagrelide)	✔
Durlaza (aspirin ER)	-
Plavix (clopidogrel)	✔
cilostazol	✔
dipyridamole	✔
Effient (prasugrel)	✔
Brilinta (ticagrelor)	-*
Zontivity (vorapaxar)	-
Combination Products	
Aggrenox (aspirin/dipyridamole ER)	✔
Yosprala (aspirin DR/omeprazole)	✔

* Although generic ticagrelor has been approved by the FDA, the generic product has not been launched.

(*Drugs@FDA.gov 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

Table 2. Food and Drug Administration Approved Indications

Indication	Agrylin (anagrelide)	cilostazol	Plavix (clopidogrel)	dipyridamole	Effient (prasugrel)	Brilinta (ticagrelor)	Zontivity (vorapaxar)	Durlaza (aspirin ER)	Aggrenox (aspirin/ dipyridamole ER)	Yosprala (aspirin DR/ omeprazole)
Treatment of patients with thrombocythemia, secondary to myeloproliferative neoplasms, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events	✔ *									
Reduce the risk of death and MI in patients with chronic coronary artery disease (CAD), such as patients with a history of MI or UA pectoris or with chronic stable angina, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA								✔ †		
Reduction of symptoms of intermittent claudication, as demonstrated by an increased walking distance		✔								
Recent MI, recent stroke, or established peripheral arterial disease (PAD)			✔ ‡							
Reduce the rate of thrombotic CV events in patients with ACS			✔ ‡§							
Prevention of postoperative thromboembolic complications of cardiac valve replacement				✔ ‖						
Reduce the rate of thrombotic CV events in patients with ACS who are being managed with percutaneous coronary intervention (PCI)					✔ ¶					
Reduce the rate of CV death, MI, and stroke in patients with ACS or a history of MI. Also reduces the rate of stent thrombosis in patients who have been stented for the treatment of ACS						✔ #				
Reduce the risk of a first MI or stroke in patients with CAD at high risk for such events						✔ §§				
Reduce thrombotic CV events in patients with a history of MI or with PAD							✔ ††			
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis									✔	
ASA component: Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, reducing the combined risk of death and nonfatal MI in patients with previous MI or UA pectoris, reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, and for patients who have undergone coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) when there is a pre-existing condition for which ASA is already indicated. Omeprazole component: Decrease the risk of developing ASA-associated gastric ulcers in at-risk patients due to age (≥55 years) or documented history of gastric ulcers.										✔ †**

* Approved in adult and pediatric patients (studied in patients aged ≥ 7 years).
† Not indicated for use in situations where a rapid onset of action is required (such as acute treatment of MI or before PCI).
‡ Plavix has been shown to reduce the rate of MI and stroke.
§ For patients with non-ST-elevation ACS (UA/non-ST-elevation myocardial infarction [NSTEMI]), 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 (STEMI). Plavix should be administered in conjunction with ASA.
‖ As an adjunct to coumarin anticoagulants.
¶ Patients who are to be managed with PCI as follows: patients with UA or NSTEMI and patients with STEMI when managed with primary or delayed PCI.

\# Administer with a daily maintenance dose of ASA of 75 to 100 mg. For at least the first 12 months following ACS, it is superior to Plavix.
†† Has only been studied as an addition to ASA and/or Plavix. There is limited experience with other antiplatelet drugs or with Zontivity as monotherapy.
** Has not been shown to reduce the risk of gastrointestinal (GI) bleeding due to ASA.
§§Administer with a daily maintenance dose of ASA of 75 to 100 mg. While use is not limited to this setting, efficacy was established in a population with type 2 diabetes mellitus.

(Prescribing information: Aggrenox 2019, Agrylin 2020, Brilinta 2020, Cilostazol 2020, Durlaza 2015, Effient 2019, Persantine 2019, Plavix 2019, Yosprala 2018, Zontivity 2019)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Antiplatelet therapy plays an important role in the long-term prevention of stroke or TIAs. In a large, meta-analysis (MA) of patients with a previous MI, acute MI, previous TIA/stroke, and acute stroke, as well as patients with an increased risk of atherothrombotic events, it was demonstrated that overall, antiplatelet therapy reduced the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 25%. With regard to individual endpoints, antiplatelet therapy reduced the odds of nonfatal MI by 34%, nonfatal stroke by 25% and vascular death by 15% (*Antithrombotic Trialists' Collaboration 2002*).

- There are few head-to-head studies comparing the various antiplatelet agents. In 2013, the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (SR) of antiplatelet and anticoagulant treatments. The study authors concluded that Effient reduced rates of CV death, MI or stroke at 30 days in patients undergoing early invasive treatments when compared to Plavix and in UA/NSTEMI patients after 1 year, as did Plavix and Brilinta (*Melloni et al 2013*). Another SR of large, quality trials observing dual antiplatelet therapy (DAPT) of Plavix, Effient, or Brilinta plus ASA when compared to ASA monotherapy found DAPT with Effient or Brilinta and ASA vs DAPT with Plavix and ASA was not associated with a risk reduction of stroke. The authors also noted conflicting results within trials (*Gouya et al 2014*). A double-blind (DB), randomized controlled trial (RCT) compared the efficacy of Brilinta vs Plavix to lower the risk of CV death, MI, or ischemic stroke in 13,885 patients with symptomatic PAD, with a median follow-up of 30 months. The primary efficacy endpoint occurred in 10.8% of patients receiving Brilinta vs 10.6% receiving Plavix (hazard ratio [HR] 1.02; 95% confidence interval [CI], 0.92 to 1.13; p = 0.65). Major bleeding occurred at the same frequency with both treatments (1.6%), and Brilinta was discontinued more often than Plavix, mainly due to dyspnea (4.8 vs 0.8%) (*Hiatt et al 2017*).

- Recently, network MAs assessing the use of $P2Y_{12}$ inhibitors in ACS have been conducted (*Baldetti et al 2020, Navarese et al 2020*). Baldetti and colleagues performed a network MA of 14 studies involving 145,019 patients (*Baldetti et al 2020*). Endpoints included MACE, all-cause death, MI, definite stent thrombosis, and major bleeding at 30 days and 1 year all-cause death and MI. Results revealed that Effient had the highest efficacy in reducing adverse outcomes in patients with ACS and the highest probability of being the best $P2Y_{12}$ inhibitor to reduce hard adverse events at 30 day and 1 year follow-up. In a network MA of 52,816 patients from 12 randomized trials, Navarese and colleagues concluded that Effient and Brilinta reduced ischemic events and increased bleeding in comparison with Plavix, a significant CV and all-cause mortality reduction was seen with Brilinta as compared to Plavix, and there was no efficacy and safety difference between Effient and Brilinta (*Navarese et al 2020)*.

- Chiarito and colleagues performed a SR and MA involving 9 randomized trials that compared $P2Y_{12}$ inhibitor monotherapy vs ASA monotherapy for secondary prevention in 42,108 patients with established atherosclerosis (*Chiarito et al 2020*). Results revealed that $P2Y_{12}$ inhibitor monotherapy is associated with comparable risks of all-cause death, vascular death, and stroke, and a marginal risk reduction for MI, as compared to ASA monotherapy in this setting. However, the high number needed to treat and the absence of any major effect on death questions the clinical relevance of the marginally lower risk of MI seen with $P2Y_{12}$ inhibitor monotherapy.

- The CAPRIE study demonstrated that patients with a recent ischemic stroke or MI, or those with symptomatic PAD who were treated with Plavix experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death compared to 5.83% of patients treated with ASA (relative risk reduction [RRR], 8.7% in favor of Plavix; 95% CI, 0.3 to 16.3; p = 0.043) (*Antithrombotic Trialists' Collaboration 2002, CAPRIE 1996*). Results from the MATCH study demonstrated that the addition of ASA to Plavix in high-risk patients with a recent ischemic stroke or TIA was associated with a nonsignificant difference in reducing major vascular events. In this trial, DAPT was associated with more life-threatening, major, and minor bleeds (*Diener et al 2004*). In the ESPRIT study, patients within 6 months of a TIA or minor stroke of presumed arterial origin were randomized to receive ASA with or without dipyridamole. The rate of the primary composite outcome, death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complications (whichever occurred first), was 13% with combination therapy vs 16% with ASA (HR, 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction [ARR], 1% per year; 95% CI, 0.1 to 1.8) (*Halkes et al 2006*). One MA compared DAPT (ASA plus Plavix) with ASA alone in patients with acute minor ischemic stroke or TIA and found that starting DAPT within 24 hours of symptom onset reduced the absolute risk of non-fatal recurrent stroke, but had no impact on all-cause mortality (*Hao et al 2018*). There was a 0.2% absolute increase in moderate or severe extracranial bleeding with DAPT vs ASA alone. The results were similar to 2 MAs for secondary stroke prevention in patients with TIA or ischemic stroke (*Kheiri et al 2018, Ye et al 2019*). Another MA in elderly patients (≥ 65 years) with ischemic stroke or TIA found that DAPT was superior to ASA monotherapy (RR, 0.79; 95% CI, 0.69 to 0.91), but similarly effective for stroke prevention as Plavix monotherapy (RR, 1.01; 95% CI, 0.93

- With regard to the treatment of ACS, in the CLARITY-TIMI 28 study, patients who presented within 12 hours of a STEMI were randomized to receive either Plavix or placebo for 30 days. Treatment with Plavix was associated with a reduction of the composite endpoint of occluded infarct-related artery on angiography, death, or recurrent MI before angiography (*Sabatine et al 2005a*). Patients included in the COMMIT study were admitted within 24 hours of a suspected acute MI and received either combination therapy with Plavix and ASA or ASA monotherapy. In this study, there was a significant reduction in the risk of the composite endpoint of death, re-infarction, or stroke (p = 0.002), and in death from any cause (p = 0.03) in patients receiving combination therapy after 15 days (*COMMIT 2005*). In the CURE study, investigators compared long-term (3 to 12 months) combination therapy with Plavix plus ASA to ASA monotherapy in patients with a NSTEMI who presented within 24 hours of symptom onset. The results demonstrated that combination therapy resulted in a 20% RRR in the composite outcome of nonfatal MI, stroke, or vascular death (p < 0.001). The compelling benefit of combination therapy noted in the CURE study was in the reduction of nonfatal MI. Due to the low number of strokes that occurred during the study, the associated reduction was not significant. There was also a weak trend suggesting the possibility of small reductions in death associated with combination therapy that was not significant (*CURE 2001, Harrington et al 2008, Lansberg et al 2012*). MAs of ACS patients or those undergoing PCI to reduce thrombotic events, have conflicting results. Results reported Plavix was superior to placebo in reducing the risk of CV death and stroke. Effient or Brilinta treatment when compared to Plavix provided additional benefit regarding CV mortality and MI, but no advantage in stroke (*Aradi et al 2013*). A secondary analysis of the TRILOGY ACS trial found intensive antiplatelet therapy with Effient may be beneficial in reducing CV deaths, MIs, or strokes when an angiography is performed prior to treatment and anatomic coronary disease is confirmed (*Roe et al 2012, Wiviott et al 2013*). The CHARISMA study was another long-term trial (median, 28 months) that enrolled and randomized patients with clinically evident CV disease to either combination treatment with Plavix and ASA or to monotherapy with ASA. The rate of the primary composite endpoint of MI, stroke, or death from CV causes was not different between the 2 treatments (6.8 vs 7.3%; relative risk [RR], 0.93; 95% CI, 0.83 to 1.05; p = 0.22) (*Bhatt et al 2006*). There is also limited evidence that Plavix has a greater impact on preventing the composite of CV death, MI, and stroke in smokers compared to non-smokers (*Gagne et al 2013*). A MA evaluated the clinical efficacy and safety of $P2Y_{12}$ inhibitors in patients with STEMI undergoing primary PCI, as defined by composite major adverse CV events (MACE). At 1 month, the analysis suggested that Effient was associated with lower MACE vs Plavix (standard dose odds ratio [OR] 0.59; 95% CI, 0.50 to 0.69) and Brilinta (standard dose OR 0.69; 95% CI, 0.56 to 0.84); lower mortality and MI vs Plavix and standard Brilinta; and lower stroke risk vs standard Plavix and Brilinta. At 1 year, Effient was associated with lower mortality and MACE vs Plavix and Brilinta. In general, Effient and Brilinta were more efficacious vs Plavix in this analysis (*Rafique et al 2016*). However, another network meta-analysis (NMA) evaluated the efficacy of $P2Y_{12}$ inhibitors (Plavix, Effient, Brilinta, and cangrelor) in patients undergoing PCI for any indication (STEMI or non-ST elevated ACS) and did not find any significant differences between any of the agents in terms of all-cause mortality, CV death, MI, probable or definite stent thrombosis, stroke, major bleeding, or MACE (*Westman et al 2017*). When used post fibrinolytic therapy in patients with a STEMI, Brilinta and Plavix demonstrated similar rates of bleeding, MACE, mortality, MI, and stroke in a 2018 MA of 5 RCTs, as well as a 2019 RCT (*Kheiri et al 2019, Berwanger et al 2019*).
- The duration of DAPT has been highly debated and often controversial. Evolving evidence has consistently demonstrated that estimated benefits are accompanied by a certain proportion of risk; therefore, not all patients would benefit from DAPT treatment. To further complicate interpretations, often first-generation stents were studied for DAPT; however, newer stents have improved safety benefits, but studies and analyses often have ≥ 1 methodological limitations. Current evidence includes an analysis of the National Heart, Lung, and Blood Institute (NHLBI) observational registry which followed over 3,000 ACS patients following PCI with a drug-eluting stent (DES); this study found that patients who continued on DAPT (Plavix plus ASA) experienced lower mortality after 1 year, but had a higher risk of repeat PCI within 4 years (*Mulukutala et al 2013*). The PRODIGY trial demonstrated that Plavix plus ASA administered in patients who received a DES or bare metal stent for 24 months was not significantly more effective than a 6-month Plavix regimen in reducing the composite of death due to any cause, MI, or cerebrovascular accident (*Valgimigli et al 2012*). However, the DAPT trial found patients who continued DAPT beyond 1 year after the placement of a DES compared with ASA therapy alone, significantly reduced the risk of stent thrombosis, MACE and cerebrovascular events, including MI; but was associated with an increased risk of bleeding and all-cause mortality (*Mauri et al 2014*). Several MAs/systematic reviews have concluded there is no increased risk of stent thrombosis with shorter duration DAPT, and treatment is associated with a lower risk of bleeding. MAs restricted to predominantly newer generation DES have demonstrated increased trends of increased all-cause mortality associated with prolonged duration of DAPT, although

not all analyses reached statistical significance (*Elmariah et al 2015, Navarese et al 2015, Udell et al 2016, Misumida et al 2018*). Another MA determined that long-term DAPT was associated with a significant decrease in risk of death, MI, and stroke, primarily in patients with prior MI or stroke, but not PAD, while long-term DAPT was also associated with increased major bleeding. Of note, the study was not able to evaluate the impact of DES on atherothrombotic events (*Fanari et al 2017*). Another MA assessed the efficacy and safety of duration of DAPT in patients with implantation of predominantly newer-generation DES. The analysis determined treatment with DAPT for 12 months vs 3 to 6 months resulted in no significant differences in incidences of death, major hemorrhage, or MI. DAPT for 18 to 48 months vs 6 to 12 months was also associated with no difference in incidence of all-cause death, but showed decreased MI and stent thrombosis, and increased major hemorrhage. A risk-benefit analysis found 3 fewer stent thromboses and 6 fewer MIs but 5 more major bleeds per 1,000 patients/year treated with prolonged DAPT. Also, treatment with DAPT > 1 year after MI reduced the composite risk of CV death, MI, or stroke but increased major bleeding (*Bittl et al 2016*).

- A MA of 16 RCTs looking at the effects of antiplatelet agents (eg, ASA, Aggrenox, and ASA plus Plavix) and vitamin K antagonists for the prevention of thrombosis in patients with lower limb atherosclerosis undergoing bypass grafting found therapy with ASA or Aggrenox had an effect on peripheral bypass grafts and prosthetic graft patency, but not venous grafts alone. Treatment with Plavix plus ASA had greater increases of bleeding, but no difference in primary graft patency compared to ASA alone (*Bedenis et al 2015*).

- A major clinical study demonstrating the safety and efficacy of Brilinta is the PLATO study. PLATO was an international, DB, double-dummy (DD), multicenter (MC), RCT that compared Brilinta to Plavix in adult patients hospitalized with documented ACS, with or without ST-segment elevation within the previous 24 hours (n = 18,624). After 12 months, the risk of the primary composite endpoint of vascular death, MI, or stroke was significantly reduced with Brilinta (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.95; p < 0.001). Brilinta also significantly reduced the risk of the secondary endpoints of the composite of all-cause mortality, MI, or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; p < 0.001); the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event (14.6 vs 16.7%; HR, 0.88; 95% CI, 0.81 to 0.95; p < 0.001); MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; p = 0.005), and vascular death (4 vs 5.1%; HR, 0.79; 95% CI, 0.69 to 0.91). Furthermore, Brilinta significantly reduced the risk of all-cause mortality (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89). Rates of major bleeding were not different between the 2 treatments (p = 0.43) (*Wallentin et al 2009*).

  ○ Several subanalyses of the PLATO study have been conducted (*James et al 2011, Cannon et al 2010, Steg et al 2010, James et al 2010a, James et al 2010b, Held et al 2011, Wallentin et al 2010, Mahaffey et al 2011, Storey et al 2011, Becker et al 2011, Banerjee et al 2008, Kohli et al 2013, Husted et al 2014, Varenhorst et al 2014, Velders et al 2016*). One subanalysis found Brilinta was associated with fewer first and recurrent composite CV events based on the entire international study population (*Kohli et al 2013*). In patients with ACS undergoing noninvasive (p = 0.045) or invasive procedures (p = 0.0025), Brilinta remained more efficacious compared to Plavix (*James et al 2011, Cannon et al 2010*). However, in patients with ST-elevation or left bundle branch block (p = 0.07), chronic kidney disease (CKD) (p = 0.13), or diabetes (p-value = not reported), and in those who underwent CABG surgery (p = 0.29), there was no difference between Brilinta and Plavix with regard to the primary composite endpoint (*Steg et al 2010, James et al 2010a, James et al 2010b, Held et al 2011*). In patients with or without ST-elevated ACS, gender was not a risk factor for outcomes, but some signals alluded to men benefiting most. The number of primary events that occurred in men was double that of women (*Husted et al 2014*). A genetic substudy was also conducted and demonstrated Brilinta to be more efficacious than Plavix, irrespective of cytochrome P450 2C19 and ABCB1 polymorphisms (p = 0.0380) (*Wallentin et al 2010*). In the original PLATO study, a significantly higher rate of dyspnea was observed with Brilinta; however, data from a substudy revealed Brilinta had no effect on pulmonary function (*Wallentin et al 2009, Storey et al 2011*). In terms of causes of death, Brilinta appeared to have a greater effect on sudden death over Plavix within the study population (*Varenhorst et al 2014*). Another post-hoc subgroup analysis of patients with STEMI treated with primary PCI demonstrated treatment with Brilinta resulted in a reduction of the primary end point compared with Plavix (7.9 vs 8.6%; p = 0.38) (*Velders et al 2016*).

  ○ Mahaffey et al compared the effects of Brilinta and Plavix among patients enrolled in the PLATO study who were from the United States (U.S.) (N = 1413). The superior benefits of Brilinta in reducing thrombotic CV events were not observed among this specific patient population. Specifically, there was no difference between Brilinta and Plavix in the rate of the primary composite endpoint (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 7.75; p = 0.15). The authors discussed that among these patients who were treated with Brilinta, the lowest event rates were observed in patients also receiving low-dose ASA maintenance therapy. In contrast, event rates in those treated with Plavix were similar regardless of concurrent high- or low-dose ASA. Despite the potential role that ASA maintenance dosing may play in explaining the regional differences observed within the PLATO study, the authors noted that the pattern of results are

consistent with what might be expected by chance alone in a large, multiregional clinical study with multiple exploratory analyses. A potential mechanism by which high-dose ASA is thought to reduce the effects of Brilinta relates to its ability to inhibit the endothelial release of prostacyclin in a dose-dependent fashion at doses greater than 80 mg/day. Prostacyclin reduces platelet reactivity and may contribute synergistically in vivo to the antiplatelet effects of P2Y$_{12}$ inhibitors. Therefore, the therapeutic effects of a higher mean level of P2Y$_{12}$ inhibition achieved with Brilinta in the PLATO study may be attenuated when endogenous prostacyclin production is inhibited (*Mahaffey et al 2011*). Until a prospective clinical study comparing the effects of low- vs high-dose ASA maintenance therapy and its effect on the efficacy of Brilinta is conducted, it remains unclear as to why the diminished effects of Brilinta in the U.S. population were observed. Of note, the FDA-approved dosing of Brilinta recommends that after the initial loading dose of ASA (325 mg), a daily maintenance dose of ASA of 75 to 100 mg should be used.

- The GLOBAL LEADERS RCT compared DAPT (ASA plus Brilinta) for 1 month followed by Brilinta monotherapy for 23 months vs standard DAPT (ASA plus either Plavix or Brilinta) for 12 months followed by ASA monotherapy for 12 months for patients undergoing PCI with a DES for either CAD or ACS (*Vranckx et al 2018*). After 2 years, there was no differences between groups for the primary composite outcome of all-cause mortality, or non-fatal MI (RR, 0.87; 95% CI, 0.75 to 1.01). A pre-specified ancillary analysis (GLASSY) found that Brilinta monotherapy after 1 month of DAPT was noninferior, but not superior, to standard DAPT in terms of all-cause death, nonfatal MI, nonfatal stroke, or urgent target vessel revascularization (RR, 0.85; 95% CI, 0.72 to 0.99); rates of bleeding were not significantly different between groups (*Franzone et al 2019*).

- The TWILIGHT trial compared DAPT (ASA plus Brilinta) for 3 months followed by Brilinta monotherapy for 12 months vs DAPT (ASA plus Brilinta) for 15 months in patients at high risk for bleeding or ischemic events undergoing PCI with a DES (*Mehran et al 2019*). At 15 months, Brilinta monotherapy was associated with a lower risk of bleeding (HR, 0.56; 95% CI, 0.45 to 0.68) and no increased risk of death, MI, or stroke (HR, 0.99; 95% CI, 0.78 to 1.25).

- In the TICO randomized multicenter trial, 3056 patients with ACS treated with DES were randomized to Brilinta monotherapy 90 mg twice daily after 3 months of DAPT (n = 1527) or Brilinta-based 12-month DAPT (n = 1529) (*Kim et al 2020*). The primary outcome was a 1-year net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events. Results revealed that the primary outcome occurred in 59 patients (3.9%) administered Brilinta monotherapy after 3 month DAPT vs 89 patients (5.9%) given Brilinta-based 12-month DAPT (absolute difference: -1.98%; 95% CI, -3.50% to -0.45%; HR, 0.66; 95% CI, 0.48 to 0.95; p = 0.01). Major bleeding occurred significantly less frequently in patients administered Brilinta monotherapy after 3 month DAPT vs Brilinta-based 12 month DAPT (1.7% vs 3%; HR, 0.56; 95% CI, 0.34 to 0.91; p = 0.02); however, the incidence of major adverse cardiac and cerebrovascular events was not significantly different between the groups (2.3% vs 3.4%; HR, 0.69; 95% CI, 0.45 to 1.06; p = 0.09).

- The FDA approval of Brilinta for the reduction in the rate of CV death, MI, and stroke in patients with a history of MI was based on results from the PEGASUS TIMI-54 trial. Approximately 21,000 patients who had a MI at least 1 to 3 years prior and had a high-risk factor for another event were randomized to treatment with Brilinta 90 mg twice daily, 60 mg twice daily, or placebo in addition to ASA 75 to 150 mg and followed for a median time of 33 months. The primary composite endpoint of time to first event of CV death, MI, or stroke was significantly reduced by 16% with Brilinta 60 mg twice daily plus ASA with event rates 1.27% lower at 3 years in the Brilinta 60 mg twice daily plus ASA group compared to those patients treated with ASA alone (p = 0.004) (*Bonaca et al 2015*). Subgroup analyses have also demonstrated similar outcomes for the primary endpoint of MACE between patients with and without diabetes and between patients with and without prior coronary stenting (*Bhatt et al 2016, Furtado et al 2019*). The primary safety endpoint, TIMI major bleeding, was significantly increased with Brilinta treatment but to a lesser degree with the 60 mg twice daily dose (Brilinta 60 mg twice daily plus ASA, 2.3% vs ASA monotherapy, 1.1%; p < 0.001) (*Bonaca et al 2015*). The rates of CV mortality or all-cause mortality alone were not significantly different from ASA monotherapy.

- In a 2018 MA, dual or triple antithrombotic therapy with Brilinta vs Plavix significantly increased the risk of clinically significant bleeding (OR, 1.52; 95% CI, 1.12 to 2.06, and OR, 1.7; 95% CI, 1.24 to 2.33, respectively). Among those on triple therapy, a higher risk of MACE was seen with Brilinta compared to Plavix (OR, 1.88; 95% CI, 1.26 to 2.80); patients who received dual therapy exhibited a similar risk of MACE and stroke (*Andreou et al 2018*).

- A MA comparing Brilinta-based antiplatelet regimens to conventional antiplatelet regimens found that, among patients with CAD, Brilinta demonstrated a lower risk of death (HR, 0.84; 95% CI, 0.77 to 0.91) and MI (HR, 0.87; 95% CI, 0.80 to 0.94) (*Cassese et al 2020*).

- The SOCRATES trial evaluated approximately 13,200 patients with an acute, non-severe ischemic stroke or high-risk TIA who had not received intravenous or intra-arterial thrombolysis, were not considered to have had a cardioembolic

stroke, and were treated with either Brilinta or ASA for 90 days. Brilinta was not significantly superior to ASA in reducing stroke, MI, or death at 90 days, the primary endpoint (6.7% of the Brilinta group vs 7.5% of those treated with ASA; p = 0.07). Additionally, no secondary endpoints were considered significantly different between treatment groups but generally trended towards favoring Brilinta (with the exception of death and CV death). Exploratory analyses indicated that Brilinta may be more effective at 7 days in reducing ischemic stroke and all stroke. However, more patients discontinued treatment in the Brilinta group (17.5%) vs the ASA group (14.7%), mainly due to dyspnea and any bleeding (*Johnston et al 2016*).

- A subgroup analysis of SOCRATES assessed patients from Asian countries (N = 3858), as the composite of stroke, MI, or death occurred at an increased rate in patients from Asia compared with patients outside of Asia (10.6 vs 5.7%, nominal p < 0.01), with higher incidence of major or minor bleeding events in patients from Asia (2.1 vs 1.2%, respectively). In the patients from Asia, treatment with Brilinta significantly reduced the rate of the composite endpoint compared with ASA treatment (9.6 vs 11.6%; HR, 0.81; 95% CI, 0.67 to 0.99), with no significant differences in the rates of major bleeding between treatment groups (*Wang et al 2017*).

- In the randomized, placebo-controlled (PC), DB, THALES trial, Johnston and colleagues assessed the effects of Brilinta plus ASA vs ASA monotherapy for 30 days in 11,016 patients with a mild to moderate acute noncardioembolic ischemic stroke or TIA who were not undergoing thrombolysis or thrombectomy (*Johnston et al 2020*). Brilinta was administered as a 180 mg loading dose followed by 90 mg twice daily and ASA was given as 300 to 325 mg on the first day followed by 75 to 100 mg daily. The primary outcome was a composite of stroke or death within 30 days; severe bleeding was the primary safety outcome. Results revealed that a primary outcome event occurred in 303 (5.5%) patients in the Brilinta-ASA group vs 362 (6.6%) patients in the ASA monotherapy group (HR, 0.83; 95% CI, 0.71 to 0.96; p = 0.02). Ischemic stroke also occurred less frequently in the combination group (5% vs 6.3%; HR, 0.79; 95% CI, 0.68 to 0.93; p = 0.004). Severe bleeding occurred significantly less in the ASA monotherapy group (7 vs 28 patients; p = 0.001).

- The TiCAB trial compared Brilinta 90 mg twice daily to ASA 100 mg daily in patients undergoing CABG (*Schunkert et al 2019*). Study enrollment was prematurely halted, with only 1859 of the planned 3850 patients enrolled. No significant differences in major CV events or bleeding were demonstrated between the groups, but the study was underpowered to detect between-group differences.

- The THEMIS trial evaluated DAPT with Brilinta plus ASA vs ASA alone in 19,220 diabetic patients with stable CAD (ie, history of PCI or CABG, or documented angiographic stenosis of > 50% in at least 1 coronary artery) (*Steg et al 2019*). Ischemic CV event rates were slightly lower among patients receiving DAPT (HR, 0.90; 95% CI, 0.81 to 0.99), but major bleeding rates were also higher with DAPT (HR, 2.32; 95% CI, 1.82 to 2.94). Adding Brilinta to ASA was not found to have a favorable risk-benefit profile in the overall trial population. A prespecified analysis of patients in the THEMIS trial who had previously undergone PCI (N = 11,154) found that, although major bleeding was still increased (HR, 2.03; 95% CI, 1.48 to 2.76) in this patient population, there may be a net clinical benefit with DAPT (HR, 0.85; 95% CI, 0.75 to 0.95) (*Bhatt et al 2019*).

- The major clinical trial demonstrating the safety and efficacy of Effient for its FDA-approved indication was TRITON-TIMI 38 (N = 13,608). Results demonstrated that Effient was significantly more effective than Plavix in reducing ischemic events in patients with ACS who underwent PCI. However, the trial did not demonstrate a decrease in the mortality rate with Effient. In addition, the results from TRITON-TIMI 38 did show a significantly higher rate of major, minor, life-threatening, and fatal bleeding events with Effient. Of note, certain patient subgroups, specifically those who were ≥ 75 years of age, those weighing < 60 kg and those with a past history of stroke or TIA, did not demonstrate a clinical benefit with Effient (*Wiviott et al 2007*). In addition, several subgroup analyses were also conducted based on TRITON-TIMI 38 and 1 patient subgroup in particular, those with diabetes, were found to have a significantly greater reduction in ischemic events with Effient when compared to nondiabetic patients being treated with either Effient or Plavix (*Antman et al 2008, Montalescot et al 2009, Murphy et al 2008, O'Donoghue et al 2009, Pride et al 2009, Wiviott et al 2008a, Wiviott et al 2008b*).

- In a 2018 MA, adverse CV outcomes were significantly lower with the use of Effient in comparison to Plavix following PCI. In an evaluation of bleeding outcomes, both agents yielded similar rates of major and minor bleeding episodes (*Brundhun et al 2018*).

- One MA compared Brilinta and Effient following PCI, both agents demonstrated similar efficacy in reducing all-cause mortality, MACE, and stroke; however, the risk of major bleeding was higher with Brilinta (OR, 1.57; 95% CI, 1.30 to 1.89) (*Guan et al 2018*). Another MA compared these agents in patients with type 2 diabetes following PCI that failed to find any significant differences between agents for mortality, MACE, MI, stroke, or major bleeding (*Yang et al 2018*). A 2020 SR and MA also compared Brilinta and Effient for DAPT therapy in patients with ACS undergoing PCI and

==concluded that there were no significant differences between the agents with regard to MACE, all-cause mortality, CV mortality, MI, stent thrombosis, and bleeding (*Al-Abdouh et al 2020*).==

- The ISAR-REACT 5 trial compared Brilinta and Effient in patients (n = 4018) with ACS for whom invasive evaluation was planned (*Schupke et al 2019*). The incidence of the composite primary endpoint (death, MI, or stroke at 1 year) was significantly higher in the Brilinta group (HR, 1.36; 95% CI, 1.09 to 1.70); major bleeding was not significantly different between groups.

- Another MA compared antiplatelet agents (Brilinta and Effient) to Plavix in patients with CKD and ACS. The other antiplatelets were associated with a reduced risk of MACE (HR, 0.88; 95% CI, 0.79 to 0.99) and no difference in bleeding vs Plavix (*Bonello et al 2018*).

- As concluded in the TRILOGY ACS study, in patients with UA/NSTEMI who do not undergo revascularization, when added to ASA therapy, Effient did not significantly reduce the frequency of death from CV causes, MI, or stroke, as compared with DAPT with Plavix and ASA, and similar risks of bleeding were observed (*Kohli et al 2014, Roe et al 2012*). However, a secondary analysis of patients who underwent angiography prior to Effient treatment experienced fewer CV deaths, MIs, or strokes than those who were in the Plavix arm (*Roe et al 2012, Wiviott et al 2013*).

- First-in-class PAR-1 antagonist, Zontivity, was FDA-approved based on a post-hoc analysis of patients with a history of MI or PAD who were taking ASA and/or a thienopyridine (mainly Plavix) concomitantly. A safety review terminated the full TRACER trial and patients with stroke in the TRA 2°P-TIMI 50 trial due to significantly increased risks for bleeding, including intracranial hemorrhage (ICH). Both trials were PC. In the TRA 2°P-TIMI 50 trial, Zontivity demonstrated effectiveness in the secondary prevention of CV events, mainly MI and the composite endpoint of CV death, MI, or stroke, primarily driven by the reduction in MI. Although TRA 2°P-TIMI 50 was not designed to evaluate the benefits and risks of Zontivity in individual patient subgroups, an analysis of patients who were comprised of post-MI and PAD without a history of stroke or TIA was evaluated by the FDA for approval. Those results showed three-year Kaplan Meier (K-M) event rate for the primary efficacy endpoint of 7.9% in the Zontivity group compared to 9.5% in the placebo group (HR, 0.8; 95% CI, 0.73 to 0.89; p < 0.001). The benefit of Zontivity is tempered by the significant increase of bleeding with Zontivity use compared to placebo. Significantly increased bleeding rates were also observed in the TRA 2°P-TIMI 50 trial for GUSTO moderate or severe bleeding, TIMI clinically significant bleeding, and GI bleeding (NNH = 97, 25, 98, respectively). However, there was no significant difference between placebo and Zontivity for fatal bleeds (*Morrow et al 2012, Tricoci et al 2012, FDA Summary Review [Zontivity] 2014, FDA Advisory Committee Transcript [Zontivity] 2014*). Subgroup analyses have concluded that increased bleeding risks may not be observed in all populations. A pre-specified subgroup analysis of stable patients with a history of previous MI determined that Zontivity reduced the primary endpoint, whether treated concomitantly with a thienopyridine or not, and the risks of GUSTO moderate or severe bleeding were similarly increased irrespective of thienopyridine use (P-interaction = 0.37) (*Bohula et al 2015*). Other subgroup analyses have been published and include a number of the TRA 2°P–TIMI 50 primary study authors. These subgroup analyses found a significant difference in the composite primary endpoint of CV death, MI, or stroke for patients with a prior MI but no statistically significant difference in PAD patients; treatment with Zontivity in patients with a prior MI was also associated with greater reductions in CV death, MI, or stroke in patients with ≥ 1 risk factors for recurrent events, with greatest risk reductions in patients with ≥ 3 risk factors (*Bohula et al 2016, Bonaca et al 2013, Scirica et al 2013*). However, the quality of the sub-group analyses is not superior to that of the primary study and the validity of the results is uncertain as methodological limitations were noted. A MA of 5 RCTs (N = 40,630) demonstrated treatment with Zontivity vs placebo resulted in a statistically non-significant reduction in risk of MI (risk reduction [RR] 0.86; 95% CI, 0.80 to 0.93; p = 0.427) and ischemic stroke (RR, 0.84; 95% CI, 0.72 to 0.97; p = 0.92), with no observed differences in all-cause mortality or TIMI bleeding (*Sharma et al 2017*).

- The FDA approval of Yosprala (ASA DR/omeprazole) was based on 2 identically-designed, 6-month, phase 3, MC, DB, active-control (AC), RCTs conducted in the U.S. The trials compared Yosprala 325/40 mg (n = 524) to enteric-coated (EC) ASA 325 mg (n = 525), each administered orally once daily for secondary CV disease prevention in patients who had been taking ASA 325 mg daily for ≥ 3 months and who were at risk for ASA-associated gastric ulcers. Patients taking non-ASA non-steroidal anti-inflammatory drugs (NSAIDs) at baseline were allowed to continue therapy if use was chronic and expected to continue throughout the study period. The primary endpoint was the cumulative incidence of endoscopically-determined gastric ulceration over 6 months. Yosprala significantly reduced the cumulative incidence of gastric ulcers vs EC ASA 325 mg in the pooled analysis (3.2 vs 8.6%, respectively; p < 0.001). Among NSAID-users at baseline, the cumulative incidence of endoscopic gastric ulcer at month 6 was 4.5% with Yosprala vs 10.2% in the EC ASA group, while rates among patients not taking NSAIDs were 3.1% with Yosprala vs 8.4% in the EC ASA group.

Significantly fewer patients treated with Yosprala discontinued therapy due to pre-specified upper GI AEs vs patients treated with EC ASA arm (1.5 vs 8.2%, respectively; p < 0.001) (*Whellan et al 2014*).

- The long-term CV and GI safety of Yosprala were evaluated in a 12-month, phase 3, MC, open-label, single-arm trial among patients who were taking ASA 325 mg daily for ≥ 3 months for secondary CVD prevention and were at risk for ASA-associated upper GI events (n = 379). After 12 months, no new or unexpected safety events were noted with Yosprala, while the most common treatment-emergent GI AEs were diarrhea, dyspepsia, and nausea (each occurred in 4 to 5% of the overall safety population). Gastroesophageal reflux disease (GERD) was reported in 1.8% of the overall population (*Goldstein et al 2016*).
- Durlaza 162.5 mg was the first ASA ER formulation approved by the FDA to reduce the risk of death and MI in patients with chronic CAD, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA. New efficacy studies were not submitted to the FDA for the approval of Durlaza. While Durlaza 162.5 mg has a similar pharmacodynamic effect as immediate-release ASA 81 mg, the clinical benefits of the ER formulation vs immediate-release formulations of ASA are not yet known (*Drugs@FDA.gov 2020*).
- There is no evidence to support the use of dipyridamole in the acute treatment of patients presenting with a non-ST-segment elevation ACS (*Harrington 2008*). In addition, the results of a large MA of 29 RCTs demonstrated that in patients with arterial vascular disease, dipyridamole had no clear effect on the secondary prevention of vascular death. Compared to control (no drug or another antiplatelet inhibitor), dipyridamole appeared to reduce the risk of vascular events; however, the effect was only significant in patients presenting with cerebral ischemia (*De Schryver et al 2007*).
- In patients with stable intermittent claudication, cilostazol therapy has been shown to provide improvement in walking distance and speed as determined by standardized exercise treadmill tests and functional status questionnaires (*Beebe et al 1999, Bedenis et al 2014, Money et al 1998, Reilly 2001*). Results of several randomized, DB, PC studies of 6 to 24 weeks' duration indicate that cilostazol is more effective than placebo in increasing initial (until onset of claudication pain) and absolute (intolerable pain) claudication distances (*Bedenis et al 2014, Beebe et al 1999, Money et al 1998, O'Donnell et al 2009a, O'Donnell et al 2009b, Reilly 2001*). Limited data suggest that cilostazol (100 mg twice daily) also may be more effective than pentoxifylline (400 mg 3 times daily) in improving walking distance in patients with intermittent claudication (*Bedenis et al 2014, Beebe et al 1999, Dawson et al 2000, Hiatt 2001, Reilly 2001*).
- Because of its antiplatelet activity, cilostazol has been used alone or in combination with other antiplatelet agents (eg, ASA, Plavix) to prevent thrombosis and restenosis following coronary angioplasty/stent implantation (*Douglas et al 2005, Guyatt et al 2012, Kunishima et al 1997, Park et al 1999, Park et al 2000, Schömig et al 2005, Take et al 1997, Tsuchikane et al 1999, Xu et al 2016, Yoon et al 1999, Zou et al 2015*). In a randomized, DB, PC study, patients undergoing coronary artery stent implantation with bare-metal stents who received cilostazol (100 mg twice daily for 6 months) in addition to therapy with ASA and Plavix (75 mg daily for 30 days) had a larger minimal coronary artery lumen diameter (primary end point) and a 36% reduction in the risk of restenosis (defined as narrowing of the stented coronary artery lumen by at least 50% as documented by quantitative coronary angiography) (*Douglas et al 2005, Schömig et al 2005*). However, more studies, including a RCT and a SR of 10 RCTs, comparing triple antiplatelet therapy (ASA, Plavix, and cilostazol) with DAPT (ASA and Plavix), failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes (eg, reinfarction, major bleeding, mortality, periprocedural MI) when added to Plavix and ASA therapy (*Guyatt et al 2012, Xu et al 2016*). For patients undergoing DES implantation in coronary arteries, a MA of 7 RCTs evaluated the long-term efficacy and safety of adding cilostazol to conventional DAPT (ASA and Plavix). The analysis demonstrated that the addition of cilostazol was associated with a significant reduction in MACE vs DAPT (RR, 0.66; 95% CI, 0.50 to 0.88), without increasing bleeding, but was associated with significantly higher rates of rash, GI adverse effects, headache, and drug discontinuation (*Zou et al 2015*).
- Agrylin is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (*Anagrelide study group 1992, Birgegard et al 2004, Dombi et al 2017, Harrison et al 2005, Penninga et al 2004, Silver 2005, Steurer et al 2004, Wiviott et al 2007*).

CLINICAL GUIDELINES

- Antiplatelet therapy is recommended for a variety of indications. The selection of P2Y$_{12}$ inhibitor therapy for patients with CAD varies greatly by individual patient characteristics and bleeding risks. All guidelines agree and recommend long-term treatment with ASA, or Plavix for those who cannot tolerate ASA in patients with ACS (*Amsterdam et al 2014, Guyatt et al 2012, Ibanez et al 2018, January et al 2014, January et al 2019, Levine et al 2011, Levine et al 2016a, Levine et al 2016b, Lip et al 2018, O'Gara et al 2013, Piepoli et al 2016*).

- The 2016 American College of Cardiology (ACC)/AHA guidelines for DAPT in patients with CAD have updated duration recommendations for 6 previously published guidelines based on data around newer generation stents. Recommendations vary based on the benefit/risk profiles of CAD patients but overall, minimum courses of DAPT therapy are now recommended in certain patients. Newer key recommendations include: (1) Plavix therapy for a minimum of 6 months for patients treated with DES; (2) any P2Y$_{12}$ inhibitor treatment for 12 months in those with ACS; (3) extended DAPT continuation in patients who have low bleeding risk; and (4) shorter duration of DAPT for patients at lower ischemic risk with high bleeding risk and longer DAPT periods for patients at elevated ischemic risk with lower bleeding risk (*Levine et al 2016a*). In 2017, the European Society of Cardiology (ESC) also published guidelines for DAPT in patients with CAD. Recommendations are largely consistent with the 2016 ACC/AHA guidelines for DAPT with several additions. In patients with CAD treated with coronary stent implantation, Plavix plus ASA is recommended for 6 months, irrespective of stent type. In patients with CAD treated with bioresorbable vascular scaffolds, DAPT should be considered for at least 12 months. Brilinta plus ASA is recommended for patients with ACS who do not have contraindications to the drug. For patients with NSTEMI undergoing PCI who are P2Y$_{12}$ inhibitor-naïve, or those with STEMI initially managed with conservative strategies, but now requiring a PCI, Effient plus ASA is recommended unless contraindications exist (*Valgimigli et al 2018*).
- The 2016 ESC guidelines updated recommendations on CV disease prevention. Key recommendations include: (1) in patients with ACS, DAPT with a P2Y$_{12}$ inhibitor (no agent recommended over another) and ASA for 12 months is recommended, unless there are contraindications (e.g., excessive risk of bleeding); (2) a shorter duration of P2Y$_{12}$ inhibitor administration (ranging from 3 to 6 months) should be considered for patients with higher bleed risks after DES implantation; (3) in non-cardioembolic ischemic stroke or TIA, prevention with ASA only, or Aggrenox or Plavix alone is recommended; and (4) in patients with stable CAD, Effient is not recommended and Brilinta is not recommended in stable CAD without a prior ACS (*Piepoli et al 2016*). Many of these recommendations are echoed in the 2017 ESC guidelines for DAPT (*Valgimigli et al 2018*). Additionally, the 2017 guidelines note that continuation of DAPT with Plavix for 6 to 30 months may be considered for patients with stable CAD who have tolerated therapy without complications but continue to have a high thrombotic risk. One month of DAPT can also be considered for patients with stable CAD in whom a 3-month DAPT poses safety concerns. The 2019 ESC guidelines for chronic coronary syndromes recommend DAPT with Plavix and ASA for 6 months following coronary stenting (assuming a normal risk of bleeding); duration of DAPT may be shortened to 3 months or 1 month, depending on risk of bleeding (*Knuuti et al 2020*). ASA monotherapy is recommended for patients with chronic coronary syndromes and previous MI or revascularization, but Plavix may be used as an alternative, particularly for patients with ASA intolerance or history of PAD or stroke/TIA. Adding another antithrombotic drug (no preferred agent) to ASA for long-term prevention may be considered in patients who have a moderate or high risk of ischemic events and no high bleeding risk.
- Other guidelines come from the American College of Chest Physicians (ACCP), which recommend Plavix plus ASA for 6 to 12 months in patients undergoing PCI and stent placement. Effient should not be used in patients < 60 kg, > 75 years of age or with a prior history of stroke. In patients who are stopping anticoagulant therapy and do not have a contraindication to ASA, it is recommended to administer ASA over no ASA to prevent recurrent venous thromboembolism (*Guyatt et al 2012, Kearon et al 2016*).
- The AHA/ACC, 2020 ESC guidelines for the management of patients with NSTEMI ACS, and 2017 ESC guidelines for DAPT provide more specific P2Y$_{12}$ inhibitor recommendations compared to other reputable society groups. For those patients with moderate to severe risk of ischemic events, DAPT with ASA is recommended; however, Brilinta is specifically recommended over Plavix for up to 12 months of treatment. From the 2020 ESC updates for the treatment of NSTEMI ACS, Effient may be considered preferred over Brilinta in patient with NSTEMI-ASC patients who proceed to PCI. A switch from Effient or Brilinta to Plavix may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition. According to the 2015 ESC guidelines, Zontivity may be added to ASA and Plavix for patients with a history of MI, but efficacy is modest and must be weighed against the risk for bleeds. Routine pre-treatment with a P2Y$_{12}$ inhibitor in patients in whom coronary anatomy is not known and early invasive therapy is planned (*Amsterdam et al 2014, Collet et al 2020, January et al 2014, January et al 2019, O'Gara et al 2013, Valgimigli et al 2018*).
- According to the 2019 AHA/ACC focused update for the management of atrial fibrillation (AF), if triple therapy (oral anticoagulant, ASA, and P2Y$_{12}$ inhibitor) is prescribed in AF patients at increased risk of stroke and have undergone PCI, it is reasonable to choose Plavix over Effient. Double therapy with a P2Y$_{12}$ inhibitor (Plavix or Brilinta) and dose-adjusted warfarin or double therapy with a P2Y$_{12}$ inhibitor (Plavix) and certain oral anticoagulants (eg, low dose rivaroxaban 15 mg once daily or dabigatran 150 mg twice daily) are reasonable to reduce the risk of bleeding compared

to triple therapy. The 2018 ACCP guidelines for antithrombotic therapy for patients with AF recommend antiplatelet agents (preferably Plavix) for patients with AF undergoing PCI/stenting; the use and duration of triple therapy (2 antiplatelet agents plus an oral anticoagulant) and dual therapy (single antiplatelet agent plus an oral anticoagulant) is dependent on the risk of bleeding and thrombosis (*January et al 2014, January et al 2019, Lip et al 2018*).

- The 2017 ESC guidelines for the management of patients with a STEMI provide the following recommendations for the periprocedural use of platelet aggregation inhibitors in patients undergoing primary PCI: (1) unless there are contraindications such as excessive risk of bleeding, Effient or Brilinta (or Plavix if these are not available or are contraindicated), is recommended before (or at latest at the time of) PCI and should be continued for 12 months; (2) ASA should be administered as soon as possible for patients without contraindications. For patients undergoing fibrinolytic therapy, Plavix plus ASA is recommended. However, patients who undergo PCI should be switched to Effient or Brilinta 48 hours after fibrinolysis. DAPT (ASA plus a $P2Y_{12}$ inhibitor) is recommended for up to 1 year in patients undergoing fibrinolysis plus PCI (*Ibanez et al 2018*). According to the 2017 ESC guidelines for DAPT, pre-treatment with Plavix may be warranted for patients with stable CAD who have a high probability of PCI (*Valgimigli et al 2018*).

- The 2011 AHA/American College of Cardiology Foundation (ACCF) guidelines for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommends ASA, or Plavix if ASA is not tolerated, in all patients with CAD. A $P2Y_{12}$ inhibitor in combination with ASA is recommended in patients after ACS or PCI with stent placement, while patients receiving a bare-metal stent or DES during PCI for ACS should be given Plavix, Effient, or Brilinta for at least 12 months. Patients undergoing coronary artery bypass grafting should be given ASA for 1 year after surgery (*Smith et al 2011*). According to the 2017 ESC guidelines for DAPT, Brilinta or Effient plus ASA may be considered instead of Plavix in stable CAD patients undergoing PCI, taking into account ischemic and bleeding risks (*Valgimigli et al 2018*). These guidelines also recommend Plavix plus ASA in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive Brilinta or Effient, including those with prior intracranial bleeding or an indication for oral anticoagulation.

- According to the 2017 ESC guidelines for DAPT, a proton pump inhibitor (PPI) in combination with DAPT is recommended to minimize bleeding (*Valgimigli et al 2018).*

- The 2012 ACCP guidelines have included recommendations for ASA monotherapy or Aggrenox twice daily for initial therapy for TIA or ischemic stroke in order to prevent stroke (*Guyatt et al 2012*). The AHA/American Stroke Association (ASA) guidelines for acute ischemic stroke reinforce that the combination of ASA and Plavix might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (*Kernan et al 2014, Powers et al 2018*). A 2019 update to the AHA/ASA guidelines for early management of acute stroke recommends that ASA be started within 24 to 48 hours after stroke onset; in patients with minor noncardioembolic strokes who did not receive alteplase, dual therapy with ASA and Plavix has been shown to reduce recurrent ischemic stroke if initiated within 24 hours of symptom onset and continued for 21 days (*Powers et al 2019*). Other guidelines state Plavix plus ASA is probably more effective at reducing stroke compared with ASA monotherapy, but is less effective than warfarin (*Culebras et al 2014, Kernan et al 2014*). The 2014 AHA/ASA guidelines for the primary prevention of stroke state that current clinical data reflect risk but no benefit of ASA for the prevention of a first stroke in the general population, and that there is no evidence that antiplatelet medications reduce the risk of stroke in the general population at low risk (*Meschia et al 2014*). A 2017 AHA/ASA statement on the prevention of stroke in patients with silent cerebrovascular disease recommends that it is reasonable to avoid antiplatelet agents when there is no specific CV or cerebrovascular indication, but to otherwise use them according to currently recommended indications (*Smith et al 2017*). The 2011 AHA/ACCF guidelines recommend that patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA should be given ASA alone, Plavix alone, or a combination of Aggrenox (*Smith et al 2011*). The 2018 AHA/ASA guidelines for acute ischemic stroke note that Brilinta is not recommended over ASA in the treatment of minor stroke; this recommendation is echoed in the 2019 update (*Powers et al 2018, Powers et al 2019*).

- For the treatment of PAD, treatment with ASA is recommended for asymptomatic disease, and ASA or Plavix is recommended for secondary prevention of CV events in symptomatic PAD but not as dual therapy (*Alonso-Coello et al 2012, Smith et al 2011*). However, the 2011 ACC/AHA guidelines do state the combination of ASA and Plavix may be considered to reduce the risk of CV events in patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity (*Anderson et al 2013*). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend antiplatelet therapy with ASA alone (75 to 325 mg per day) or Plavix alone (75 mg per day) to reduce MI, stroke, and vascular death in patients with symptomatic PAD (*Gerhard-Herman et al 2016*). The 2017 ESC guidelines for patients with PAD also recommend single-agent antiplatelet therapy (Plavix is preferred over ASA) for symptomatic patients, but recommend ASA plus Plavix for at least 1 month after coronary artery

stenosis. Other indications for DAPT in the setting of PAD include after infra-inguinal stent implantation for at least 1 month, and in below-the-knee bypass with a prosthetic graft. Antiplatelet therapy is not routinely recommended for patients with isolated asymptomatic lower extremity arterial disease (*Aboyans et al 2018*).

- The 2012 ACCP guidelines recommend the addition of cilostazol to ASA or Plavix therapy in patients with refractory intermittent claudication who do not respond to conservative measures (*Guyatt et al 2012, Alonso-Coello et al 2012*). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend cilostazol as an effective therapy to improve symptoms and increase walking distance in patients with claudication (*Gerhard-Herman et al 2016*). The 2017 ESC guidelines for patients with PAD do not specifically recommend cilostazol for patients with intermittent claudication, but do acknowledge that this agent may yield mild-to-moderate improvements in walking distance (*Aboyans et al 2018*).
- The 2017 AHA/ACC guidelines for the management of patients with valvular heart disease recommend antithrombotic therapy with ASA in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical valve prosthesis, and daily ASA in all patients with a bioprosthetic aortic or mitral valve. Compared with oral anticoagulation alone, the addition of DAPT increases bleeding complications by at least 2- to 3-fold. Plavix 75 mg daily may be a reasonable antithrombotic therapy option for the first 6 months after transcatheter aortic valve replacement (TAVR), in addition to life-long ASA 75 mg to 100 mg daily (*Nishimura et al 2017*). The 2017 ESC guidelines for the management of valvular heart disease provide the following recommendations for patients with mechanical prosthesis: (1) triple therapy with ASA, Plavix, and a vitamin K antagonist for at least 1 month for patients treated with coronary stent implantation, irrespective of type of stent used; (2) triple therapy for 1 to 6 months is recommended for those with high ischemic risk due to ACS or other characteristics, when the benefits of therapy outweigh the bleeding risk; (3) dual therapy with a vitamin K antagonist and Plavix should be considered for patients in whom the bleeding risk outweighs the ischemic risk. The following are recommendations for patients with bioprostheses: (1) dual antiplatelet therapy should be considered for the first 3 to 6 months after transcatheter aortic valve implantation, followed by lifelong single antiplatelet therapy (in patients who do not need oral anticoagulation for other reasons); (2) antiplatelet therapy with a single agent can be considered after transcatheter aortic valve implantation for patients with a high risk of bleeding) (*Baumgartner et al 2018*).
- The updated 2019 Beers Criteria published by the American Geriatric Society (AGS) recommends avoiding short-acting dipyridamole and cilostazol in elderly patients, and recommends cautious use of ASA and Effient in older adults (*AGS 2019*). The criteria also recommends against scheduled use of proton-pump inhibitors, such as omeprazole, for more than 8 weeks unless they are used for high-risk patients.

SAFETY SUMMARY

- Boxed warnings associated with antiplatelet treatment include significant, sometimes fatal, bleeding with Brilinta, Effient, and Zontivity treatment. Additionally, Effient should not be prescribed in patients ≥ 75 years of age, body weight < 60 kg, those with a propensity to bleed, and with concomitant use of medications that increase the risk of bleeding. Brilinta should not be used with ASA in doses > 100 mg due to reduced effectiveness. The effectiveness of Plavix is dependent on the activation of CYP2C19; therefore, there is a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (termed "CYP2C19 poor metabolizers"). The use of another platelet $P2Y_{12}$ inhibitor should be considered in patients identified as CYP2C19 poor metabolizers. Additionally, Plavix has a warning and precaution for diminished antiplatelet activity with concomitant use of drugs that interfere with CYP2C19 (e.g., omeprazole, esomeprazole). Concomitant use with omeprazole or esomeprazole and Plavix should be avoided. Cilostazol is contraindicated in patients with heart failure of any severity.
- Plavix, Effient, Brilinta, and Zontivity are contraindicated in patients with active pathological bleeding such as bleeding peptic ulcer or ICH, and active pathologic bleeding is cited as a warning and precaution within the cilostazol labeling. Withholding Zontivity for a brief period will not be useful in managing an acute bleeding event because of its long half-life. There is no known treatment to reverse the antiplatelet effect of Zontivity, and significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Because of the short half-life of Plavix's active metabolite, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
- Effient and Zontivity are also contraindicated in patients with a history of prior TIA or stroke, and Brilinta and Zontivity are contraindicated in patients with a history of ICH. Aggrenox, Durlaza, and Yosprala are contraindicated in patients with a known allergy to NSAIDs, in patients with asthma, rhinitis, and nasal polyps, or in children or adolescents with viral infections due to the risk of Reye's syndrome. Other contraindications are included within boxed warnings.
- Agrylin has no contraindications.

- Plavix, Brilinta, and Effient should be discontinued prior to surgery. Thrombotic thrombocytopenic purpura (TTP) may occur after brief exposure (< 2 weeks) of Plavix, Brilinta, or Effient. Premature discontinuation of Plavix, Brilinta, or Effient may increase the risk of CV events. Dyspnea has been reported in patients administered Brilinta; continuation with Brilinta without interruption or another antiplatelet should be considered. Brilinta can cause ventricular pauses, bradyarrhythmias including AV block. Brilinta has not been studied in patients with severe hepatic impairment. The concentrations of Brilinta and its metabolite and platelet inhibition are expected to be similar in patients with end-stage renal disease on intermittent hemodialysis vs patients with normal renal function. In patients with severe hepatic impairment, concentrations of Brilinta are likely to be increased. Brilinta may cause false negative platelet functional test results in patients with heparin-induced thrombocytopenia. Hypersensitivity reactions, including rash and angioedema, have been reported with Plavix and Effient use in patients with a history of prior thienopyridine hypersensitivity.
- Aggrenox, Durlaza, and Yosprala should be used with caution in patients at increased bleeding risk such as patients with GI ulcers, a history of active peptic ulcer disease, and/or concomitant alcohol (≥ 3 drinks daily). Agents containing ASA may cause fetal harm, especially during the third trimester. ASA and Agrylin should not be co-administered as use increases the risk of bleeding.
- Concomitant use of Yosprala with Plavix should be avoided, as omeprazole reduces the pharmacologic activity of Plavix. Omeprazole has also been associated with acute interstitial nephritis, *Clostridium difficile*-associated diarrhea, increased risk of bone fracture, cutaneous and systemic lupus erythematosus, hypomagnesemia, and vitamin B-12 deficiency. Concomitant Yosprala and PPI use is associated with an increased risk of fundic gland polyps that increase with long-term use, especially beyond 1 year.
- Agrylin may cause vasodilation, tachycardia, palpitations, pulmonary hypertension, and congestive heart failure (CHF). Other drugs that inhibit PDE-3 have caused decreased survival when compared with placebo in patients with CHF (Class III to IV). Because of the positive inotropic effects and side effects of Agrylin, a pre-treatment CV examination is recommended in addition to careful monitoring during treatment. Agrylin increased QT prolongation in healthy volunteers; therefore, Agrylin should not be used in patients with known risk factors for QT prolongation. In addition, interstitial lung diseases, mostly as progressive dyspnea with lung infiltrations, have been reported to be associated with the use of Agrylin in postmarketing reports.
- Cilostazol may induce tachycardia, palpitation, tachyarrhythmia or hypotension, with an associated increase in heart rate of approximately 5 to 7 bpm. Increased risks of exacerbations of angina pectoris or MI may occur in patients with a history of ischemic heart disease. Left ventricular outflow tract obstruction has been reported in patients with sigmoid shaped interventricular septum after starting cilostazol. Patients should be monitored for the development of a new systolic murmur or cardiac symptoms. Cilostazol has not been studied in patients with hemostatic disorders or active bleeding and should be avoided in these groups. Patients should be monitored periodically for complete blood count (CBC) abnormalities. Cilostazol has not been studied in patients with moderate or severe hepatic impairment.
- Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe CAD or in patients with hypotension. Chest pain may be aggravated in patients with underlying CAD who are receiving dipyridamole. Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.
- Patients undergoing pharmacological stress testing with adenosinergic agents should not take Aggrenox or dipyridamole within 48 hours prior to stress testing.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Agrylin (anagrelide)	Capsules	Oral	Pediatric: Once daily Adult: 2 to 4 times daily	Adjust to the lowest effective dosage required to reduce and maintain platelet count < 600,000/μL in adults. Avoid with severe hepatic impairment.
Durlaza (ASA ER)	Capsules	Oral	Once daily	Do not take 2 hours before or 1 hour after consuming alcohol.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				==Take with a full glass of water at the same time each day. Swallow whole. Do not cut, crush, or chew capsules.== Avoid with severe renal or hepatic impairment.
cilostazol	Tablets	Oral	Twice daily	Reduce dose with concomitant CYP3A4 or CYP2C19 inhibitors. Take at least half an hour before or 2 hours after breakfast and dinner. If symptoms are not improved after 3 months, discontinue treatment. Moderate or severe hepatic impairment have not been studied.
Plavix (clopidogrel)	Tablets	Oral	Once daily[†]	--
dipyridamole	Tablets, IV solution	Oral, IV	Tablets: Four times daily[‡]	--
Effient (prasugrel)	Tablets	Oral	Once daily[§ǁ]	Take with or without food. Consider a lower dose for patients < 60 kg. Patients should also take ASA daily. Not studied in severe hepatic impairment, generally at higher risk of bleeding.
Brilinta (ticagrelor)	Tablets	Oral	Twice daily	Take with or without food. Administer with ASA. May be crushed, mixed with water, and drunk or administered via nasogastric tube. Avoid with severe hepatic impairment.
Zontivity* (vorapaxar)	Tablets	Oral	Once daily	Take with or without food. Use with ASA and/or Plavix according to their indications or standard of care. There is limited experience with other antiplatelets and none with Zontivity as the only antiplatelet agent. Avoid with severe hepatic impairment.
Aggrenox (ASA/ ER dipyridamole)	Capsules	Oral	Twice daily	Take with or without food. ==Do not chew capsule.==

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				In case of intolerable headaches during initial treatment, switch to 1 capsule at bedtime and low-dose ASA in the morning; resume twice daily dosing within 1 week. Avoid with severe renal and hepatic impairment.
Yosprala (ASA DR/omeprazole)	Tablets	Oral	Once daily	Take at least 60 minutes before a meal. Swallow whole with liquid. Do not split, chew, crush, or dissolve the tablet. Avoid with severe renal impairment and any degree of hepatic impairment.

See the current prescribing information for full details
*There is limited clinical experience with other antiplatelet drugs or with Zontivity as a monotherapy agent. Also due to the risk of bleeding, Zontivity should be avoided in patients taking warfarin or other anticoagulants. Withholding Zontivity for a brief period will not be useful in managing acute bleeding events because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation.
† Initiating Plavix without a loading dose will delay establishment of an antiplatelet effect by several days for certain indications.
‡ As adjunct to the usual warfarin therapy. ASA is not to be administered concomitantly with coumarin anticoagulants.
§ In the clinical trial, the loading dose of Effient was not administered until coronary anatomy was established in UA/NSTEMI patients and in STEMI patients presenting >12 hours after symptom onset. In STEMI patients presenting within 12 hours of symptom onset, the loading dose was administered at the time of diagnosis, although most received Effient at the time of PCI. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial.
‖ The safety and efficacy of the 5 mg dose have not been prospectively studied.

CONCLUSION

- The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and CV diseases.
- Antiplatelet agents have different sites of action. ASA is a COX-1 inhibitor. Plavix and Effient irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Brilinta is a reversible inhibitor of $P2Y_{12}$. Zontivity is a first-in-class selective antagonist of the PAR-1, which is a receptor on thrombin. The mechanism of action of dipyridamole, Agrylin, and cilostazol are not completely understood, but each is believed to inhibit platelet aggregation. Plavix has incomplete platelet inhibition, a slower onset of action, and poor response in some patients.
- Plavix has been shown to significantly reduce the odds of a serious vascular event in high-risk patients. Study data has demonstrated that Plavix significantly reduced the risk of stroke, MI, and vascular death compared to ASA in patients with a recent ischemic stroke, MI, or established peripheral vascular disease. On the basis of the CURE, COMMIT, and CLARITY studies, Plavix received an FDA-approved indication for the reduction of atherothrombotic events in patients with ACS and MI, and Plavix has been incorporated into the current treatment guidelines for the management of these conditions (*Amsterdam et al 2014, Collet et al 2020, COMMIT 2005, Culebras et al 2014, CURE 2001, Gerhard-Herman et al 2016, Ibanez et al 2018, January et al 2014, January et al 2019, Lip et al 2018, O'Gara et al 2013, Sabatine et al 2005a, Sabatine et al 2005b, Valgimigli et al 2018*).
- Plavix's effectiveness is dependent on its conversion to its active metabolite mostly by CYP2C19. Patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel, diminished antiplatelet responses, and generally exhibit higher CV event rates following MI than patients with normal CYP2C19 function. In addition, concomitant use of Plavix with proton pump inhibitors, particularly those extensively inhibiting CYP2C19, may also increase CV events.
- Effient may be the most potent of these agents, with more desirable characteristics compared to Plavix with regard to drug-drug interactions and interpatient enzyme variability (*Serebruany et al 2009, Wiviott et al 2007*). Initial FDA-approval of Effient was based on the results from the TRITON-TIMI 38 study, which compared Plavix to Effient. Effient has demonstrated efficacy in reducing ischemic events in patients with ACS who underwent PCI. Although compared to Plavix, there were no differences in the important outcomes of all-cause and CV mortality, and Effient demonstrated more major bleeding. The overall recommendation is for a thienopyridine to be used in ACS patients who are managed with PCI, with Plavix, Effient, and Brilinta listed as potential options. Of note, the use of Effient in STEMI patients with a

prior history of stroke or TIA for which primary PCI is planned is not recommended (*Levine et al 2011, Levine et al 2016b*).

- Brilinta is FDA-approved to reduce the rate of thrombotic CV events in patients with ACS, including UA, NSTEMI, and STEMI and to ==reduce the risk of a first MI or stroke in patients with CAD at high risk for such events==. Brilinta works in a similar manner to the other thienopyridine platelet inhibitors (Plavix and Effient). Brilinta is not a prodrug; therefore, it is not subject to potential drug interactions associated with the other agents (*Micromedex 2020*). PLATO was a pivotal clinical study establishing the safety and efficacy of Brilinta in reducing the rate of thrombotic CV events in patients with ACS, which compared Brilinta and Plavix in hospitalized patients with documented ACS, with or without ST-segment elevation. After 12 months of treatment, there was no difference in major bleeding; however, Brilinta significantly reduced all-cause and CV mortality. This efficacy benefit was not observed in North American patients (*Mahaffey et al 2011, Wallentin et al 2009*). The PEGASUS TIMI-54 trial reinforced benefit in patients with a history of MI in which a reduction in the rate of CV death, MI, and stroke was observed in patients treated with Brilinta 60 mg twice daily plus ASA over ASA monotherapy. The rates of CV mortality or all-cause mortality alone were not significantly different between groups, and increased risk of major bleeding was observed with Brilinta treatment (*Bonaca et al 2015*).
- Zontivity is FDA-approved for use in patients with a history of MI or PAD. Zontivity should be prescribed with ASA and/or Plavix according to their indications or standard of care, and not be used as monotherapy or concomitantly with warfarin or other anticoagulants. There is limited clinical experience with other antiplatelet drugs or with Zontivity as a monotherapy agent. Increased hemorrhagic stroke and bleeding rates in patients with a history of stroke or TIA caused the Zontivity phase 3 studies to be terminated early. In the TRA2°P-TIMI 50 trial, Zontivity demonstrated lower rates of the composite of CV mortality, MI, or stroke vs placebo when added to standard antiplatelet therapy for secondary prevention of CV events in PAD or MI who have not undergone PCI. Significance was driven by MI reductions (*Morrow et al 2012, Tricoci et al 2012, FDA Summary Review [Zontivity] 2014, FDA Advisory Committee Transcript [Zontivity] 2014*).
  - When managing acute bleeding events, withholding Zontivity may not be helpful because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Also, the optimal time for initiation and duration of Zontivity therapy remain poorly defined (*FDA Summary Review [Zontivity] 2014, Morrow et al 2012, Tricoci et al 2012*).
  - The 2016 ESC guidelines for CV disease prevention stipulate that Zontivity cannot be recommended systematically in patients with stable atherosclerotic disease; however, the 2015 ESC guidelines state Zontivity may be added to ASA and Plavix for patients with a history of MI. The ESC acknowledges that efficacy is modest and must be weighed against the risk for bleeds (*Piepoli et al 2016*).
- Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo but has not been shown to be more effective than ASA (*Diener et al 1996, Leonardi-Bee et al 2005*). Aggrenox significantly reduced the risk of stroke by 37% compared to 18% with ASA and 16% with ER dipyridamole. There was no significant difference in all-cause mortality among the active treatment groups (*Diener et al 1996*). Aggrenox significantly reduced the composite of death, nonfatal stroke or MI and major bleeding to 13% of patients compared to 16% for ASA monotherapy; however, the combination regimen was discontinued more often, mainly because of headache (*Halkes et al 2006*).
- Cilostazol is used for the symptomatic treatment of intermittent claudication and is recommended as an effective therapy to improve symptoms and increase walking distance in patients with claudication due to lower extremity PAD (*Gerhard-Herman et al 2016*). Long-term effects of the drug on limb preservation and hospitalization have not been fully elucidated. Studies and SRs have failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes when added to Plavix and ASA therapy. Currently, experts generally do not recommend the use of cilostazol for the prevention of postprocedural complications in patients undergoing coronary artery stent placement, with the possible exception of those with an allergy or intolerance to ASA or Plavix. In such cases, ACCP states that cilostazol may be used as a substitute for either ASA or Plavix as part of the DAPT regimen (*Alonso-Coello et al 2012, Guyatt et al 2012, Levine et al 2011, Levine et al 2016b*).
- Agrylin is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (*Anagrelide study group 1992, Birgegard et al 2004, Dombi et al 2017, Harrison et al 2005, Penninga et al 2004, Silver 2005, Steurer et al 2004, Wiviott et al 2007*).
- ASA is the most frequently studied platelet inhibitor and is generally the reference drug to which other treatments are compared. ASA is the platelet inhibitor recommended as first-line in most treatment guidelines for general use, including

initial management of noncardioembolic stroke or TIA, ACS, and MI, and for primary and secondary prevention in patients with cerebrovascular, CV, and peripheral vascular diseases (*Aboyans et al 2018, Amsterdam et al 2014, Culebras et al 2014, Gagne et al 2013, Gerhard-Herman et al 2016, Guyatt et al 2012, Ibanez et al 2018, Lip et al 2018, January et al 2014, January et al 2019, Kernan et al 2014, Knuuti et al 2020, Kohli et al 2014, O'Gara et al 2013, Powers et al 2018, Powers et al 2019, Smith et al 2011, Smith et al 2017, Valgimigli et al 2018*). Evidence supporting the efficacy of ASA has demonstrated a reduction in vascular death of ~15% and in nonfatal vascular events of ~30% (*Eikelboom et al 2012*). In the US, nearly 40% of adults > 50 years of age use ASA for the primary or secondary prevention of CV disease (*Bibbins-Domingo et al 2016*).

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