

## Therapeutic Class Overview

### Platelet Aggregation Inhibitors

#### INTRODUCTION

- Cardiovascular (CV) disease was the cause of 30.8% of all deaths, or approximately 1 of every 3 in the United States (US) in 2014 according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2017 update. Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after CV disease, cancer, chronic lower respiratory disease, and unintentional injuries/accidents, in which more women die (58% of all US stroke deaths) from stroke every year than men (Benjamin et al, 2017).
- 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, thrombocytopenia, 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 (Amsterdam et al, 2014; Anderson et al, 2013; Bushnell et al, 2014; Culebras et al, 2014; Fihn et al, 2012; Gerhard-Herman et al, 2016; Guyatt et al, 2012; January et al, 2014; Jauch, 2013; Kernan et al, 2014; Lansberg et al, 2012; Levine et al, 2011; Levine et al, 2016a; Levine et al, 2016b; Meschia et al, 2014; Nishimura, 2017; O'Gara et al, 2013; Powers et al, 2015; Roffi et al, 2016; Smith et al, 2011; Smith et al, 2017; Vandvick et al, 2012).
- The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action and have characteristics that distinguish agents from one another.
  - Aspirin, a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A<sub>2</sub>, a platelet aggregant and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that aspirin 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 (aspirin delayed-release [DR]/omeprazole), in combination with aspirin, is an antisecretory compound which suppresses gastric acid secretion by inhibiting the [H<sup>+</sup>/K<sup>+</sup>]-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.
  - Vorapaxar is a newer agent and 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 aspirin and/or clopidogrel according to their indication or standards of care.
  - Clopidogrel, prasugrel, ticagrelor, and ticlopidine inhibit P2Y<sub>12</sub>, an adenosine phosphate receptor on the surface of platelets. Ticagrelor is the only reversible inhibitor of P2Y<sub>12</sub> and unlike clopidogrel does not require hepatic activation. Clopidogrel has a slower onset of action, incomplete platelet inhibition, and poor response in certain patients including those with CYP2C19 polymorphisms. Ticlopidine can cause severe neutropenia. Compared to clopidogrel, the benefits of prasugrel have been seen as early as 3 days. Prasugrel and vorapaxar are both contraindicated in patients with a history of TIAs.
  - Anagrelide 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 anagrelide, aspirin/extended-release (ER) dipyridamole, BRILINTA® (ticagrelor), cilostazol, clopidogrel, dipyridamole, DURLAZA™ (aspirin extended release [ER]), EFFIENT® (prasugrel), ticlopidine, YOSPRALA™ (aspirin 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) are not discussed in this review.
- Medispan Class: Platelet Aggregation Inhibitors – Platelet Aggregation Inhibitors, Platelet Aggregation Inhibitors Combinations, Phosphodiesterase III Inhibitors, Direct-Acting P2Y<sub>12</sub> Inhibitors, Quinazoline Agents, Thienopyridine Derivatives, and Cyclopentyltriazolopyrimidine (CPTP) Derivatives.

**Table 1. Medications Included Within Class Review**

Drug	Manufacturer	FDA Approval Date	Generic Availability
<b>Single-Entity Agents</b>			
AGRYLIN® (anagrelide)	Various	03/14/1997	✓
DURLAZA (aspirin ER)	New Haven	09/04/2015	-
PLAVIX® (clopidogrel)	Various	11/17/1997	✓
PLETAL® (cilostazol)	Various	01/15/1999	✓*
PERSANTINE® (dipyridamole)	Various	12/06/1961	✓*
EFFIENT (prasugrel)	Eli Lilly	07/10/2009	-†
BRILINTA (ticagrelor)	AstraZeneca	07/20/2011	-
TICLID® (ticlopidine)	Various	10/31/1991	✓*
ZONTIVITY(vorapaxar)	Merck & Co	05/08/2014	-
<b>Combination Products</b>			
AGGRENOX (aspirin/ER dipyridamole)	Various	11/22/1999	✓
YOSPRALA™ (aspirin DR/omeprazole)	Aralez	09/14/2016	-

\* Brand no longer available.

† The earliest a generic will launch is anticipated is 2023 due to pediatric exclusivity.

(DRUGS@FDA.com, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

## INDICATIONS

**Table 2. Food and Drug Administration Approved Indications**

Indication	Drug
Treatment of patients with thrombocytopenia, secondary to myeloproliferative neoplasms, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events	anagrelide*
Reduce the risk of death and MI in patients with chronic coronary artery disease (CAD), such as patients with a history of MI or unstable angina 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	DURLAZA (aspirin ER) <sup>†</sup>
Reduction of symptoms of intermittent claudication, as demonstrated by an increased walking distance	cilostazol
Recent MI, recent stroke, or established peripheral arterial disease (PAD)	clopidogrel <sup>‡</sup>
Reduce the rate of thrombotic CV events in patients with ACS	clopidogrel <sup>‡§</sup>
Prevention of postoperative thromboembolic complications of cardiac valve replacement	dipyridamole <sup>  </sup>
Reduce the rate of thrombotic CV events in patients with ACS who are being managed with percutaneous coronary intervention (PCI)	EFFIENT (prasugrel) <sup>¶</sup>
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	BRILINTA (ticagrelor) <sup>#</sup>
Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation	ticlopidine <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	ticlopidine <sup>††</sup>
Reduce thrombotic CV events in patients with a history of MI or with PAD	ZONTIVITY (vorapaxar) <sup>‡‡</sup>
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	aspirin/ER dipyridamole
Aspirin 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 unstable angina 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 aspirin is already indicated.	YOSPRALA (aspirin DR/omeprazole) <sup>†§§</sup>
Omeprazole component: Decrease the risk of developing aspirin-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).

‡ Clopidogrel 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). Clopidogrel should be administered in conjunction with aspirin.

|| 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 aspirin of 75 to 100 mg. For at least the first 12 months following ACS, it is superior to clopidogrel.

\*\* As adjunctive therapy with aspirin.

†† Due to the potential for life-threatening blood dyscrasias (eg, thrombotic thrombocytopenic purpura [TTP], neutropenia/agranulocytosis, and aplastic anemia), ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.

‡‡ Has only been studied as an addition to aspirin and/or clopidogrel. 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 aspirin.

Prescribing information: AGGRENOX, 2015; AGRYLIN, 2015; BRILINTA, 2016; DURLAZA, 2015; EFFIENT, 2016; PERSANTINE, 2011; PLAVIX, 2016; PLETAL, 2016; ticlopidine, 2016; YOSPRALA, 2016; ZONTIVITY, 2015)

Information on indications, mechanism of action, pharmacokinetics, and safety information 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 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 antiplatelets. In 2013, the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review of antiplatelet and anticoagulant treatments. The study authors concluded that prasugrel reduced rates of CV death, MI or stroke at 30 days in patients undergoing early invasive treatments when compared to clopidogrel and in UA/NSTEMI patients after 1 year, as did clopidogrel and ticagrelor (Melloni et al, 2013). Another systematic review of large, quality trials observing dual antiplatelet therapy (DAPT) of clopidogrel, prasugrel, or ticagrelor plus aspirin when compared to aspirin monotherapy found DAPT with prasugrel or ticagrelor and aspirin vs DAPT with clopidogrel and aspirin was not associated with a risk reduction of stroke. The authors also noted conflicting results within trials (Gouya et al, 2014). A double-blind, randomized controlled trial compared the efficacy of ticagrelor vs clopidogrel 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 end point occurred in 10.8% of patients receiving ticagrelor vs 10.6% receiving clopidogrel (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 ticagrelor was discontinued more often than clopidogrel, mainly due to dyspnea (4.8% vs 0.8% (Hiatt et al, 2017). A 6-month, open-label, randomized trial of 181 Chinese patients with poor/intermediate metabolizer phenotypes of CYP2C19 with ACS undergoing PCI, demonstrated that ticagrelor significantly reduced the composite risk of death, stroke, or recurrent MI vs high-dose clopidogrel (4.4% vs 20%, P<0.001) There were no significant differences in major bleeding events between groups, but dyspnea (16.5%) was more common with ticagrelor treatment (Zhang et al, 2016).
- For individual platelet inhibitors, data from clinical studies demonstrated that ticlopidine reduced the risk of stroke and other vascular outcomes in patients with cerebrovascular disease (Gent et al, 1989; Hass et al, 1989). The CAPRIE study demonstrated that patients with a recent ischemic stroke or MI, or those with symptomatic PAD who were treated with clopidogrel experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death compared to 5.83% of patients treated with aspirin (relative risk reduction [RRR], 8.7% in favor of clopidogrel; 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 aspirin to clopidogrel 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 aspirin 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 aspirin (HR, 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction, 1% per year; 95% CI, 0.1 to 1.8) (ESPRIT Study Group, 2006).
- 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 clopidogrel or placebo for 30 days. Treatment with clopidogrel 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 clopidogrel and aspirin or aspirin 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 clopidogrel plus aspirin to aspirin 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). Meta-analyses of ACS patients or those undergoing PCI to reduce thrombotic events, have conflicting results. Results reported clopidogrel was superior to placebo in reducing the risk of CV death and stroke. Prasugrel or ticagrelor treatment when compared to clopidogrel 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 prasugrel 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 clopidogrel and aspirin or to monotherapy with aspirin. 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, 0.93; 95% CI, 0.83 to 1.05; P=0.22) (Bhatt et al, 2006). There is also limited evidence that clopidogrel 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 meta-analysis evaluated the clinical efficacy and safety of P2Y<sub>12</sub> inhibitors in patients with STEMI undergoing primary PCI, as defined by composite major adverse CV events (MACE). At one month, the analysis suggested that prasugrel was associated with lower MACE vs clopidogrel (standard dose odds ratio [OR] 0.59; 95% CI, 0.50 to 0.69) and ticagrelor (standard dose OR 0.69; 95% CI, 0.56 to 0.84); lower mortality and MI vs clopidogrel and standard ticagrelor; and lower stroke risk vs standard clopidogrel and ticagrelor. At one year, prasugrel was associated with lower mortality and MACE vs clopidogrel and ticagrelor. In general, prasugrel and ticagrelor were more efficacious vs clopidogrel (Rafique et al, 2016).

- 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  $\geq 1$  methodological limitations reducing publication strengths. 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) found that patients who continued on DAPT (clopidogrel plus aspirin) were associated with 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 clopidogrel plus aspirin administered in patients who received a DES or bare metal stent for 24 months was not significantly more effective than a 6 month clopidogrel 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 aspirin therapy alone, significantly reduced the risk of stent thrombosis, major adverse CV and cerebrovascular events, including MI; but was associated with an increased risk of bleeding and all-cause mortality (Mauri et al, 2014). Several meta-analyses/systemic 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. Meta-analyses restricted to predominantly newer generation DES have demonstrated increased trends of increased all-cause mortality associated with prolonged durations of DAPT (Elmariah et al, 2015; Navarese et al, 2015; Udell et al, 2016). A recent meta-analysis 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 meta-analysis 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 meta-analysis of 16 randomized controlled trials looking at the effects of antiplatelet agents (e.g., aspirin, aspirin plus dipyridamole, and aspirin plus clopidogrel) and vitamin K antagonists for the prevention of thrombosis in patients with lower limb atherosclerosis undergoing bypass grafting found therapy with aspirin or aspirin plus dipyridamole had an effect on peripheral bypass grafts and prosthetic graft patency, but not venous grafts alone. Treatment with clopidogrel plus aspirin had greater increases of bleeding, but no difference in primary graft patency compared to aspirin alone (Bedenis et al, 2015).
- The major clinical study demonstrating the safety and efficacy of ticagrelor for its FDA-approved indication is the PLATO study. PLATO was an international, double-blind, double-dummy, multicenter, randomized-controlled trial that compared ticagrelor to clopidogrel 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 ticagrelor (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.95; P<0.001). Ticagrelor 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, ticagrelor 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 ticagrelor 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 ( $P = 0.0025$ ), ticagrelor remained more efficacious compared to clopidogrel (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 ( $P = 0.13$ ), or diabetes ( $P$  value not reported), and in those who underwent coronary artery bypass graft surgery ( $P = 0.29$ ), there was no difference between ticagrelor and clopidogrel 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 ticagrelor to be more efficacious than clopidogrel, 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 ticagrelor; however, data from a substudy revealed ticagrelor had no effect on pulmonary function (Wallentin et al, 2009; Storey et al, 2011). In terms of causes of death, ticagrelor appeared to have a greater effect on sudden death over clopidogrel within the study population (Varenhorst et al, 2014). Another post-hoc subgroup analysis of patients with STEMI treated with primary PCI demonstrated treatment with ticagrelor resulted in a reduction of the primary end point compared with clopidogrel (7.9% versus 8.6%;  $P = 0.38$ ) (Velders et al, 2016).
- Mahaffey et al compared the effects of ticagrelor and clopidogrel among patients enrolled in the PLATO study who were from the United States ( $N = 1,413$ ). The superior benefits of ticagrelor in reducing thrombotic CV events were not observed among this specific patient population. Specifically, there was no difference between ticagrelor and clopidogrel in the rate of the primary composite endpoint (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 1.75;  $P = 0.1459$ ). The authors discussed that among these patients who were treated with ticagrelor, the lowest event rates were observed in patients also receiving low-dose aspirin maintenance therapy. In contrast, event rates in those treated with clopidogrel were similar regardless of concurrent high- or low-dose aspirin. Despite the potential role that aspirin 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 aspirin is thought to reduce the effects of ticagrelor 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<sub>12</sub> inhibitors. Therefore, the therapeutic effects of a higher mean level of P2Y<sub>12</sub> inhibition achieved with ticagrelor 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 aspirin maintenance therapy and its effect on the efficacy of ticagrelor is conducted, it remains unclear as to why the diminished effects of ticagrelor in the United States population were observed. Of note, the FDA-approved dosing of ticagrelor recommends that after the initial loading dose of aspirin (325 mg), a daily maintenance dose of aspirin of 75 to 100 mg should be used.
- The FDA approval of ticagrelor 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 ticagrelor 90 mg twice daily, 60 mg twice daily, or placebo in addition to aspirin 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 ticagrelor 60 mg twice daily plus aspirin with event rates 1.27% lower at 3 years in the ticagrelor 60 mg twice daily plus aspirin group compared to those patients treated with aspirin 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 (Bhatt et al, 2016). The primary safety endpoint, TIMI major bleeding, was significantly increased with

ticagrelor treatment but to a lesser degree with the 60 mg twice daily dose (ticagrelor 60 mg twice daily plus aspirin, 2.3% vs aspirin 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 aspirin monotherapy.

- 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 ticagrelor or aspirin for 90 days. Ticagrelor was not significantly superior to aspirin in reducing stroke, MI, or death at 90 days, the primary endpoint (6.7% of the ticagrelor group vs 7.5% of those treated with aspirin;  $P = 0.07$ ). Additionally, no secondary endpoints were considered significantly different between treatment groups but generally trended towards favoring ticagrelor (with the exception of death and CV death). Exploratory analyses indicated that ticagrelor may be more effective at 7 days in reducing ischemic stroke and all stroke. However, more patients discontinued treatment in the ticagrelor group (17.5%) vs the aspirin group (14.7%), mainly due to dyspnea and any bleeding (Johnston et al, 2016).
  - A subgroup analysis of SOCRATES assessed patients from Asian countries ( $N = 3,858$ ), 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 ticagrelor significantly reduced the rate of the composite endpoint compared with aspirin 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).
- The major clinical trial demonstrating the safety and efficacy of prasugrel for its FDA-approved indication was the TRITON-TIMI 38 ( $N = 13,608$ ). Results demonstrated that prasugrel was significantly more effective than clopidogrel in reducing ischemic events in patients with ACS who underwent PCI. However, the trial did not demonstrate a decrease in the mortality rate with prasugrel. In addition, the results from TRITON-TIMI 38 did show a significantly higher rate of major, minor, life-threatening, and fatal bleeding events with prasugrel. Of note, certain patient subgroups, specifically those who were  $\geq 75$  years of age, those weighing  $< 60$  kg and those with a past history of stroke or TIA, did not demonstrate a clinical benefit with prasugrel (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 prasugrel when compared to nondiabetic patients being treated with either prasugrel or clopidogrel (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).
  - As concluded in the TRILOGY ACS study, in patients with UA/NSTEMI who do not undergo revascularization, when added to aspirin therapy, prasugrel did not significantly reduce the frequency of death from CV causes, MI, or stroke, as compared with DAPT with clopidogrel and aspirin, 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 prasugrel treatment experienced fewer CV deaths, MIs, or strokes than those who were in the clopidogrel arm (Roe et al, 2012; Wiviott et al, 2013).
- First-in-class PAR-1 antagonist, vorapaxar, was FDA-approved based on a post-hoc analysis of patients with a history of MI or PAD who were taking aspirin and/or a thienopyridine (mainly clopidogrel) 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 placebo-controlled. In the TRA 2°P-TIMI 50 trial, vorapaxar 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 vorapaxar 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 vorapaxar 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 vorapaxar is tempered by the significant increase of bleeding with vorapaxar 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 vorapaxar 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 vorapaxar in patients with a prior MI was also associated with greater reductions in CV death, MI, or stroke in patients with  $\geq 1$  risk factors for recurrent events, with greatest risk reductions in patients with  $\geq 3$  risk factors (Bohula et al, 2016; Bonaca et al, 2012; 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 recent meta-analysis of five randomized controlled trials (N=40,630) demonstrated treatment with vorapaxar 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=0.920), with no observed differences in all-cause mortality or TIMI bleeding (Sharma et al, 2017).

- The FDA approval of YOSPRALA (aspirin DR/omeprazole) was based on 2 identically-designed, 6-month, phase 3, multi-center, double-blind, active-control, randomized controlled trials conducted in the US. The trials compared aspirin DR/omeprazole 325/40 mg (n=524) against enteric-coated (EC) aspirin 325 mg (n=525), each administered orally once daily for secondary CV disease prevention in patients who had been taking aspirin 325 mg daily for  $\geq 3$  months and who were at risk for aspirin-associated gastric ulcers. Patients taking non-aspirin 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. Aspirin DR/omeprazole significantly reduced the cumulative incidence of gastric ulcers vs EC aspirin 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 aspirin DR/omeprazole vs 10.2% in the EC aspirin group, while rates among patients not taking NSAIDs were 3.1% with aspirin DR/omeprazole vs 8.4% in the EC aspirin group. Significantly fewer patients treated with aspirin DR/omeprazole discontinued therapy due to pre-specified upper GI AEs vs patients treated with EC aspirin arm (1.5% vs 8.2%, respectively; P<0.001) (Whellan et al, 2014).
  - The long-term CV and GI safety of aspirin DR/omeprazole were evaluated in a 12-month, phase 3, multi-center, open-label, single-arm trial among patients who were taking aspirin 325 mg daily for  $\geq 3$  months for secondary CVD prevention and were at risk for aspirin-associated upper GI events (N=379). After 12 months, no new or unexpected safety events were noted with aspirin DR/omeprazole, 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 (aspirin ER) 162.5 mg was the first aspirin 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 aspirin ER. While aspirin ER 162.5 mg has a similar pharmacodynamic effect as immediate-release aspirin 81 mg, the clinical benefits of the ER formulation vs immediate-release formulations of aspirin are not yet known (DRUGS@FDA.com, 2017).
- 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 meta-analysis of 29 randomized-controlled studies 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, double-blind, placebo-controlled 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 (e.g., aspirin, clopidogrel) 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, double-blind, placebo-controlled 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 aspirin and clopidogrel (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 recent studies, including a recent randomized controlled trial and a systematic review of 10 randomized controlled trials, comparing triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) with DAPT (aspirin and clopidogrel), failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes (e.g., reinfarction, major bleeding, mortality, periprocedural MI) when added to clopidogrel and aspirin therapy (Guyatt et al, 2012; Xu et al, 2016). For patients undergoing DES implantation in coronary arteries, a meta-analysis of 7 randomized controlled trials evaluated the long-term efficacy and safety of adding cilostazol to conventional DAPT (aspirin and clopidogrel). The analysis demonstrated that the addition of cilostazol was associated with a significant reduction in MACE vs DAPT (relative risk 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).

- Anagrelide 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).

## 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  $\geq 75$  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 aspirin in doses  $> 100$  mg due to reduced effectiveness. The effectiveness of clopidogrel 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<sub>12</sub> inhibitor should be considered in patients identified as CYP2C19 poor metabolizers. Additionally, clopidogrel 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 clopidogrel should be avoided. Cilostazol is contraindicated in patients with heart failure of any severity. Ticlopidine has a boxed warning of life-threatening hematological adverse reactions when used in the presence of certain hematopoietic disorders.
- Clopidogrel, EFFIENT, BRILINTA, ZONTIVITY, and ticlopidine 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 four weeks after discontinuation. Because of the short half-life of clopidogrel'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 in ZONTIVITY patients with a history of ICH. Ticlopidine and clopidogrel are contraindicated in severe hepatic impairment. Aspirin/ER dipyridamole, DURLAZA (aspirin ER), and YOSPRALA (aspirin DR/omeprazole) 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.
- Anagrelide has no contraindications.
- Clopidogrel, BRILINTA, EFFIENT, and ticlopidine should be discontinued prior to surgery. Thrombotic thrombocytopenic purpura (TTP) may occur after brief exposure ( $< 2$  weeks) of clopidogrel, BRILINTA, or EFFIENT. Premature discontinuation of clopidogrel, 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 and ticlopidine have not been studied in patients with severe hepatic or renal impairment. Hypersensitivity reactions, including rash and angioedema, have been reported with clopidogrel and EFFIENT use in patients with a history of prior thienopyridine hypersensitivity. Ticlopidine has been associated with

increased cholesterol within one month of therapy and has not been studied concomitantly with heparin, oral anticoagulants, or fibrinolytic agents.

- Aspirin/ER dipyridamole, **DURLAZA (aspirin ER)**, and **YOSPRALA (aspirin DR/omeprazole)** 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 ( $\geq 3$  drinks daily). Agents containing aspirin may cause fetal harm, especially during the third trimester. Aspirin and anagrelide should not be co-administered as use increases the risk of bleeding.
- **Concomitant use of YOSPRALA (aspirin DR/omeprazole) with clopidogrel should be avoided, as omeprazole reduces the pharmacologic activity of clopidogrel. 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.**
- Anagrelide may cause vasodilation, tachycardia, palpitations, 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 anagrelide, a pre-treatment CV examination is recommended in addition to careful monitoring during treatment. Anagrelide increased QT prolongation in healthy volunteers; therefore, anagrelide 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 anagrelide 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. 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.

## DOSING AND ADMINISTRATION

**Table 3. Dosing and Administration**

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Anagrelide	Capsule: 0.5 mg, 1 mg	<u>Thrombocythemia, secondary to myeloproliferative disorders:</u> Pediatric - Initial, 0.5 mg once daily; Adult - Initial, 0.5 mg 4 times daily or 1 mg twice daily for $\geq 1$ week; maintenance, adjust to the lowest effective dosage required to reduce and maintain platelet count $< 600,000/\mu\text{L}$ (most doses range from 1.5 to 3 mg/day); maximum, 10 mg/day or 2.5 mg in a single dose	Increase dose by no more than 0.5 mg/day in any 1 week	
<b>DURLAZA (aspirin ER)</b>	<b>Capsule: 162.5 mg</b>	<b><u>Patients with chronic CAD:</u> 162.5 mg once daily</b>  <b><u>Patients who have had an ischemic stroke or TIA:</u> 162.5 mg once daily</b>		<b>Do not take 2 hours before or 1 hour after consuming alcohol</b>

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Cilostazol	Tablets: 50 mg, 100 mg	<u>Intermittent Claudication:</u> 100 mg twice daily	Reduce dose to 50 mg twice daily 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.
Clopidogrel	Tablet: 75 mg, 300 mg	<u>ACS:</u> Initial, 300 mg as a single loading dose; maintenance, 75 mg once daily <sup>†</sup>  <u>Recent MI, stroke or established PAD:</u> 75 mg once daily without a loading dose		
Dipyridamole	Tablet: 25 mg, 50 mg, 75 mg	<u>Prevention of postoperative thromboembolic complications of cardiac valve replacement:</u> 75 to 100 mg 4 times daily <sup>‡</sup>		
EFFIENT (prasugrel)	Tablet: 5 mg, 10 mg	<u>ACS who are being managed with PCI:</u> Initial, 60 mg as a single loading dose (risk of bleeding was increased with early administration [loading dose] <sup>§</sup> in patients undergoing PCI or early CABG); maintenance, 5 to 10 mg once daily <sup>  </sup>	Consider 5 mg once daily for patients <60kg.  Patients should also take aspirin (75 mg to 325 mg) daily.	Take with or without food
BRILINTA (ticagrelor)	Tablet: 60 mg, 90 mg	<u>ACS or a history of MI:</u> Initial, 180 mg (2 tablets) as a single loading dose; maintenance, 90 mg twice daily for the first year and then after 1 year 60 mg twice daily <sup>  </sup>		Take with or without food.  May be crushed, mixed with water, or administered via nasogastric tube.  Do not administer with another oral P2Y <sub>12</sub> platelet inhibitor.  In healthy patients, platelet transfusion did not reverse the effects of BRILINTA and is not likely beneficial for bleeding incidences.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Ticlopidine	Tablet: 250 mg	<u>Patients undergoing successful coronary stent implantation:</u> 250 mg twice daily for up to 30 days#  <u>Patients who have had a completed thrombotic stroke:</u> 250 mg twice daily		Take with food.
ZONTIVITY* (vorapaxar)	Tablet: 2.08 mg (equivalent to 2.5 mg vorapaxar sulfate)	<u>A history of MI or with PAD:</u> Take 1 (2.08 mg) tablet orally once daily	Use with aspirin and/or clopidogrel according to their indications or standard of care. There is limited experience with other antiplatelets and none with ZONTIVITY as the only antiplatelet agent.	Take with or without food.
Aspirin/ ER dipyridamole	Capsule: 25/200 mg	<u>Patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis:</u> 25/200 mg twice daily	In case of intolerable headaches during initial treatment, switch to 1 capsule at bedtime and low-dose aspirin in the morning; resume twice daily dosing within 1 week.	Take with or without food.  Do not chew capsule
YOSPRALA (aspirin DR/ omeprazole)	Tablet: 81/40 mg 325/40 mg	<u>Secondary prevention of CV and cerebrovascular events:</u> 81/40 mg once daily	81 mg has been accepted as an effective dose for secondary CV prevention; providers should consider need for 325 mg and refer to current clinical practice guidelines	Take at least 60 minutes before a meal

\*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. Also, the optimal time for initiation and duration of ZONTIVITY therapy also remain poorly defined.

† Initiating clopidogrel without a loading dose will delay establishment of an antiplatelet effect by several days.

‡ As adjunct to the usual warfarin therapy. Aspirin 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.

¶ Administer with a daily maintenance dose of aspirin of 75 to 100 mg.

# Take with antiplatelet doses of aspirin

**SPECIAL POPULATIONS**

**Table 4. Special Populations**

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Anagrelide	No overall differences in response in the elderly; however, greater sensitivity cannot be ruled out.	Based on an OL, PK/PD study in 18 patients aged 7 to 16 years, no apparent differences in adverse events vs adults. Initiate at lower dose of 0.5 mg/day.	No dosage adjustments	For moderate hepatic impairment initiate dose at 0.5 mg/day and maintain for a minimum of 1 week with careful monitoring of CV effects. Avoid in severe impairment.	Pregnancy Category: C  Unknown whether excreted in breast milk; discontinue nursing or discontinue drug.
<b>DURLAZA (aspirin ER)</b>	No overall differences in safety and efficacy have been observed between elderly and younger subjects.	Safety and efficacy have not been established. Due to aspirin, use is not recommended.	Avoid with severe renal failure	Avoid with severe hepatic dysfunction	Should be avoided during the third trimester of pregnancy, and 1 week prior to and during labor and delivery  Due to potential for serious AEs in nursing infants, discontinue nursing or discontinue drug.
Cilostazol	No overall differences in safety and efficacy have been observed; but greater sensitivity cannot be ruled out.	Safety and efficacy have not been established.	No dose adjustment. Dialysis patients have not been studied, but unlikely drug will be removed.	No dose adjustment required in mild hepatic impairment. Moderate or severe hepatic impairment have not been studied; dosing recommendations are not provided.	Pregnancy Category: C  Reported in milk of animal models; discontinue nursing or discontinue drug
Clopidogrel	No dosage adjustment necessary	Safety and efficacy have not been established.	No dosage adjustment	No dosage adjustment	Pregnancy Category: B  Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
Dipyridamole	No dosage adjustment	Safety and effectiveness in patients <12 years have not been established.	No dosage adjustment	No dosage adjustment; Elevations of liver enzymes have been reported.	Pregnancy Category: B  Drug is excreted in breast milk; exercise caution

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
EFFIENT (prasugrel)	Risk of bleeding increases with advancing age. Not recommended in patients 75 years and older except in high-risk situations <sup>†</sup>	Safety and efficacy have not been established.  In a PC, RCT, the primary objective, reducing the rate of vaso-occlusive crisis, was not met in sickle-cell anemia patients aged 2 to 17 years.	No dosage adjustment	No dosage adjustment with mild to moderate hepatic impairment; Not studied in severe impairment, generally at higher risk of bleeding.	Pregnancy Category: B  Unknown whether excreted in breast milk; use only if benefits outweigh risks
BRILINTA (ticagrelor)	No overall differences in safety and efficacy in patients 65 years and older. However, greater sensitivity of some older patients cannot be ruled out.	Safety and efficacy have not been established.	No dosage adjustment	Contraindicated with severe hepatic impairment; Consider carefully with moderate impairment; No dosage adjustment with mild impairment	Pregnancy Category: C  Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
Ticlopidine	Clearance decreases with age. No overall differences in efficacy or safety were observed in elderly patients (mean age 70 years). However, greater sensitivity cannot be ruled out.	Safety and efficacy have not been established.	Dose reduction or discontinuation if hemorrhagic or hematopoietic issues occur with renal impairment	Dose adjustment may be needed; Not recommended with severe liver impairment.	Pregnancy Category: B  Unknown whether excreted in breast milk; discontinue nursing or discontinue drug
ZONTIVITY (vorapaxar)	In the TRA 2°P – TIMI 50 study, 33% of patients were ≥65 years of age. The relative risk of bleeding was similar across groups. ZONTIVITY increases the risk of bleeding in proportion to the underlying risk. Older patients are generally at a higher risk of bleeding; consider patient age before initiating ZONTIVITY.	Safety and efficacy have not been established.	No dosage adjustments are required in patients with renal impairment.	No dosage adjustments are required in patients with mild to moderate hepatic impairment. ZONTIVITY is not recommended in patients with severe impairment due to increased risk of bleeding.	Pregnancy Category B  Unknown whether excreted in breast milk. Discontinue nursing or drug because of the potential for serious effects

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Aspirin/ER dipyridamole	No overall differences in safety and efficacy have been observed; but greater sensitivity cannot be ruled out.	Safety and efficacy have not been established. Due to aspirin, use is not recommended	Avoid aspirin with severe renal failure	Avoid with severe hepatic dysfunction	Pregnancy Category: D  Drug is excreted in breast milk; exercise caution
YOSPRALA (aspirin DR/omeprazole)	No overall differences in safety and efficacy have been observed; but greater sensitivity cannot be ruled out.	Safety and efficacy have not been established. Due to aspirin, use is not recommended	Avoid with severe renal failure	Avoid with any degree of hepatic impairment	Should be avoided during the third trimester of pregnancy, and 1 week prior to and during labor and delivery  Due to potential for serious AEs in nursing infants, discontinue nursing or discontinue drug.

Abbreviations: CV=cardiovascular; OL=open label; PC=place-controlled; PD=pharmacodynamic; PK=pharmacokinetic; RCT=randomized-controlled trial  
 \*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women; Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; **Pregnancy Category D = Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may justify the use of the drug in pregnant women despite potential risks.**

† American College of Chest Physicians (ACCP) 2012 guidelines state that evidence suggests that neither prasugrel results in neither benefit nor harm in patients with age greater than 75 years.

## CONCLUSION

- The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and CV diseases. Those agents which are available generically include anagrelide, cilostazol, clopidogrel, dipyridamole, ticlopidine, and aspirin/ER dipyridamole. Antiplatelet agents available only by brand name are BRILINTA (ticagrelor), **DURLAZA (aspirin ER)**, EFFIENT (prasugrel), **YOSPRALA (aspirin DR/omeprazole)**, and ZONTIVITY (vorapaxar).
- Antiplatelet agents have different sites of action. Aspirin is a COX-1 inhibitor. Ticlopidine, clopidogrel, and prasugrel irreversibly block P2Y<sub>12</sub>, a key adenosine phosphate receptor on the platelet surface. Ticagrelor is a reversible inhibitor of P2Y<sub>12</sub>. Vorapaxar is a first-in-class selective antagonist of the PAR-1, which is a receptor on thrombin. The mechanism of action of dipyridamole, anagrelide, and cilostazol are not completely understood, but each is believed to inhibit platelet aggregation. Clopidogrel has incomplete platelet inhibition, a slower onset of action, and poor response in some patients. Ticlopidine is generally not prescribed due to cases of rare but serious neutropenia (Micromedex, 2017).
- Clopidogrel has been shown to significantly reduce the odds of a serious vascular event in high-risk patients. Study data has demonstrated that clopidogrel significantly reduced the risk of stroke, MI, and vascular death compared to aspirin in patients with a recent ischemic stroke, MI or established peripheral vascular disease. On the basis of the CURE, COMMIT, and CLARITY studies, clopidogrel received a FDA-approved indication for the reduction of atherothrombotic events in patients with ACS and MI, and clopidogrel has been incorporated into the current treatment guidelines for the management of these conditions (Amsterdam et al, 2014; COMMIT, 2005; Culebras et al, 2014; CURE, 2001; **Gerhard-Herman et al, 2016**; January et al, 2014; O’Gara et al, 2013; Roffi et al, 2016; Sabatine et al, 2005a; Sabatine et al, 2005b).

- Clopidogrel'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 proton pump inhibitors, particularly those extensively inhibited by CYP2C19, with clopidogrel may also increase CV events.
- Prasugrel may be the most potent of these agents, with more desirable characteristics compared to clopidogrel with regard to drug-drug interactions and interpatient enzyme variability (Serebruany et al, 2009; Spinler, Rees, 2009; Wiviott et al, 2007). FDA-approval of prasugrel was based on the results from the TRITON-TIMI 38 study, which compared clopidogrel to prasugrel. Prasugrel has demonstrated efficacy in reducing ischemic events in patients with ACS who underwent PCI. Although compared to clopidogrel, there were no differences in the important outcomes of all-cause and CV mortality; and prasugrel demonstrated more major bleeding. The overall recommendation is for a thienopyridine to be used in ACS patients who are managed with PCI, with clopidogrel, prasugrel and ticagrelor listed as potential options. Of note, the use of prasugrel 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).
- Ticagrelor is FDA-approved to reduce the rate of thrombotic CV events in patients with ACS, including UA, NSTEMI, and STEMI. Ticagrelor works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel and ticlopidine). Ticagrelor is not a prodrug; therefore not subject to potential drug interactions associated with the other agents (Micromedex, 2017). PLATO was a pivotal clinical study establishing the safety and efficacy of ticagrelor in reducing the rate of thrombotic CV events in patients with ACS, which compared ticagrelor and clopidogrel 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, ticagrelor 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 ticagrelor 60 mg twice daily plus aspirin over aspirin 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 ticagrelor treatment (Bonaca et al, 2015).
- Clinical studies have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Randomized studies comparing ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin (Gent et al, 1989; Gorelick et al, 2003; Hass et al, 1989). When compared to aspirin alone and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis following coronary stenting (Leon et al, 1998). Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.
- Vorapaxar is FDA-approved for use in patients with a history of MI or PAD. Vorapaxar should be prescribed with aspirin and/or clopidogrel 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 vorapaxar as a monotherapy agent. Increased hemorrhagic stroke and bleeding rates in patients with a history of stroke or TIA caused the vorapaxar phase 3 studies to be terminated early. In the TRA2°P-TIMI 50 trial, vorapaxar 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 vorapaxar 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 vorapaxar therapy also 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 vorapaxar cannot be recommended systematically in patients with stable atherosclerotic disease; however, the 2015 ESC guidelines state vorapaxar may be added to aspirin and clopidogrel 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; Roffi 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 aspirin (Diener et al, 1996; Leonardi-Bee et al, 2005). Aspirin plus ER dipyridamole significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with ER dipyridamole. There was no significant difference in all-cause mortality among the active treatment groups (Diener et al, 1996). Aspirin plus ER dipyridamole significantly reduced the composite of death, nonfatal stroke



or MI and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache (ESPRIT, 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. Recent studies and systematic reviews have failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes when added to clopidogrel and aspirin 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 aspirin or clopidogrel; in such cases, ACCP states that cilostazol may be used as a substitute for either aspirin or clopidogrel as part of the DAPT regimen (Alonso-Coello et al, 2012; Guyatt et al, 2012; Levine et al, 2011; Levine et al, 2016b).
- Anagrelide 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).
- Aspirin is the most frequently studied platelet inhibitor and is generally the reference drug to which other treatments are compared. Aspirin 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 (Amsterdam et al, 2014; Culebras et al, 2014; Gagne et al, 2013; Gerhard-Herman et al, 2016; Guyatt et al, 2012; January et al, 2014; Kernan et al, 2014; Kohli et al, 2014; O'Gara et al, 2013; Roffi et al, 2016; Smith et al, 2011; Smith et al, 2017). Evidence supporting the efficacy of aspirin 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 aspirin for the primary or secondary prevention of CV disease (Bibbins-Domingo et al, 2016).
- Antiplatelet therapy is recommended for a variety of indications:
  - Selection of P2Y<sub>12</sub> inhibitor therapy for patients with CAD varies greatly by individual patient characteristics and bleeding risks:
    - All guidelines agree and recommend long-term treatment with aspirin, or clopidogrel for those who cannot tolerate aspirin in patients with ACS (Amsterdam et al, 2014; Guyatt et al, 2012; January et al, 2014; Levine et al, 2011; Levine et al, 2016a; Levine et al, 2016b; O'Gara et al, 2013; Piepoli et al, 2016; Roffi 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 range based on the benefit/risk profiles of CAD patients but overall, minimum courses of DAPT therapy are now recommended in certain patients. New key recommendations include: (1) clopidogrel therapy for a minimum of 6 months for patients treated with DES; (2) any P2Y<sub>12</sub> 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).
    - The 2016 ESC guidelines updated recommendations on CV disease prevention. Key recommendations include: (1) in patients with ACS, DAPT with a P2Y<sub>12</sub> inhibitor (no agent recommended over another) and aspirin for 12 months is recommended, unless there are contraindications (e.g., excessive risk of bleeding); (2) a shorter duration of P2Y<sub>12</sub> 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 aspirin only, or dipyridamole plus aspirin or clopidogrel alone is recommended; and (4) in patients with stable CAD, prasugrel is not recommended and ticagrelor is not recommended in stable CAD without a prior ACS (Piepoli et al, 2016).
    - Other guidelines include the ACCP which recommends general guidance of clopidogrel plus aspirin for 6 to 12 months in patients undergoing PCI and stent placement. Prasugrel 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 aspirin, it is recommended to administer aspirin over no aspirin to prevent recurrent venous thromboembolism (Guyatt et al, 2012; Kearon et al, 2016).

- The AHA/ACC and 2015 ESC guidelines for the management of patients with NSTEMI ACS provide more specific P2Y<sub>12</sub> inhibitor recommendations compared to other reputable society groups. For those patients with moderate to severe risk of ischemic events, DAPT with aspirin is recommended; however, ticagrelor is specifically recommended over clopidogrel for up to 12 months of treatment. Prasugrel is preferred over clopidogrel in post-PCI patients, except in those at high risk for bleeding. According to the 2015 ESC guidelines, vorapaxar may be added to aspirin and clopidogrel for patients with a history of MI, but efficacy is modest and must be weighed against the risk for bleeds (Amsterdam et al, 2014; January et al, 2014; O'Gara et al, 2013; Roffi et al, 2016).
- 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 aspirin, or clopidogrel if aspirin is not tolerated, in all patients with CAD. A P2Y<sub>12</sub> inhibitor in combination with aspirin 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 clopidogrel, prasugrel, or ticagrelor for at least 12 months. Patients undergoing coronary artery bypass grafting, should be given aspirin for 1 year after surgery (Smith et al, 2011).
- The 2012 ACCP guidelines have included recommendations for aspirin monotherapy or aspirin/ER dipyridamole twice daily for initial therapy for TIA or ischemic stroke in order to prevent stroke (Guyatt et al, 2012). The AHA/ASA reinforce that the combination of aspirin and clopidogrel 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). For minor ischemic stroke or TIA the combination of aspirin and clopidogrel might be reasonable, but adding antiplatelet therapy to vitamin K antagonist therapy is uncertain (January et al, 2014). Other guidelines state clopidogrel plus aspirin probably more effective at reducing stroke compared with aspirin 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 aspirin 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 to 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 aspirin alone, clopidogrel alone, or a combination of aspirin plus ER dipyridamole (Smith et al, 2011).
- For the treatment of PAD, treatment with aspirin is recommended for asymptomatic disease, and aspirin or clopidogrel 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 aspirin and clopidogrel 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 aspirin alone (75 to 325 mg per day) or clopidogrel alone (75 mg per day) to reduce MI, stroke, and vascular death in patients with symptomatic PAD (Gerhard-Herman et al, 2016).
- The 2012 ACCP guidelines recommend the addition of cilostazol to aspirin or clopidogrel 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 AHA/ACC guidelines for the management of patients with valvular heart disease recommend antithrombotic therapy with aspirin in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical valve prosthesis, and daily aspirin 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. Clopidogrel 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 aspirin 75 mg to 100 mg daily (Nishimura, 2017).

- Due to the risk of GI complications, ACCF/ACG/AHA recommends that gastroprotective therapy be prescribed for the treatment and prevention of aspirin-associated GI injury in patients at sufficient risk. Proton pump inhibitors are considered the preferred gastroprotective agents over histamine-2 (H<sub>2</sub>) receptor antagonists and misoprostol (Bhatt et al, 2008).
- The updated 2015 Beers Criteria published by the American Geriatric Society (AGS) recommends avoiding short-acting dipyridamole, ticlopidine, and cilostazol in certain elderly patients (AGS, 2015). 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.

## REFERENCES

- AGGRENOX prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. November 2015.
- AGRYLIN prescribing information. Shire US Inc. Wayne, PA. July 2015.
- Alonso-Coello P, Bellmunt S, McGorrian C, et al. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl):e669S-90S.
- American Geriatrics Society (AGS). American Geriatrics Society 2015 Updated Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2015 Nov;63(11):2227-46.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Dec 23; 130(25):e344-426.
- Anagrelide Study Group. Anagrelide, a therapy for thrombocytopenic states: experience in 577 patients. Am J Med. 1992;92:69-72.
- Anderson JL, Halperin JL, Albert N, et al. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 March epub doi:10.1016/j.jacc.2013.01.004.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71-86.
- Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 analysis. J Am Coll Cardiol. 2008;51(21):2028-33.
- Aradi D, Komocsi A, Vorobcsuk A, et al. Impact of clopidogrel and potent P2Y<sub>12</sub>-inhibitors on mortality and stroke in patients with acute coronary syndrome or undergoing percutaneous coronary intervention. Systematic review and meta-analysis. Thromb Haemost 2013; 109(1):93-101.
- Banerjee S, Varghese C, Samuel J, et al. Comparison of the impact of short (<1 year) and long-term (≥1 year) clopidogrel use following percutaneous coronary intervention on mortality. Am J Cardiol. 2008;102:1159-62.
- Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y<sub>12</sub> receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2011 Dec;32(23):2933-44.
- Beebe HG, Dawson DL, Cutler BS, et al. A new pharmacological treatment for intermittent claudication: results of a randomized, multicenter trial. Arch Intern Med. 1999; 159:2041-50.
- Bedenis R, Steward M, Cleanthis M, et al. Cilostazol for intermittent claudication. Cochrane Database Syst Rev. 2014; Issue 10. Art No. CD003748. Doi: 10.1002/14651858.CD003748.pub4.
- Bedenis R, Lethaby A, Maxwell H, et al. Antiplatelet agents for preventing thrombosis after peripheral arterial bypass surgery. Cochrane Database Syst Rev. 2015; Issue 10. Art No. CD003748. Doi: 10.1002/14651858.CD003748.pub4.
- Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017 Mar 7;135(10):e146-e603.
- Bhatt DL, Bonaca MP, Bansilal S, et al. Reduction in Ischemic Events With Ticagrelor in Diabetic Patients With Prior Myocardial Infarction in PEGASUS-TIMI 54. J Am Coll Cardiol. 2016 Jun 14;67(23):2732-40
- Bhatt DL, Fox KAA, Hacke W, et al; for the CHARISMA Investigators. Clopidogrel and aspirin vs aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006;354(16):1706-17.
- Bibbins-Domingo K, on behalf of the U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2016;164(12):836-45.
- Birgegard G, Bjorkholm M, Kutti J, et al. Adverse effects and benefits of two years of anagrelide treatment for thrombocytopenia in chronic myeloproliferative disorders. Haematologica. 2004;89:520-7.
- Bittl JA, Baber U, Bradley SM, et al. Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016 Sep 6;134(10):e156-78. doi: 10.1161/CIR.0000000000000405.
- Bohula EA, Aylward PE, Bonaca MP, et al. Efficacy and safety of vorapaxar with and without a thienopyridine for secondary prevention in patients with previous myocardial infarction and no history of stroke or transient ischemic attack: Results from TRA 2°P-TIMI 50. Circulation. 2015;132:1871-79.
- Bohula EA, Bonaca MP, Braunwald E et al. Atherothrombotic risk stratification and the efficacy and safety of vorapaxar in patients with stable ischemic heart disease and previous myocardial infarction. Circulation. 2016 Jul 26;134(4):304-13. doi: 0.1161/CIRCULATIONAHA.115.019861.
- Bonaca MP, Bhatt DL, Cohen M, et al. Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction (PEGASUS-TIMI 54). N Engl J Med. 2015; 372(19):1791.
- Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA 2°P-TIMI 50. Circulation. Apr 9, 2013;127(14):1522-9.
- BRILINTA prescribing information. AstraZeneca. Wilmington, DE. July 2016.
- Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the Prevention of Stroke in Women: A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association. Stroke. 2014 Jul;45(7):2160-236.

- Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomized double-blind study. *Lancet*. 2010 Jan 23;375(9711):283-93.
- CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel vs aspirin in patients at risk of ischemic events (CAPRIE). *Lancet*. 1996;348(9038):1329-39.
- COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet*. 2005;366:1607-21.
- Culebras A, Messe SR, Chaturvedi S, et al. Summary of evidence-based guideline update: Prevention of stroke in nonvalvular atrial fibrillation: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. Feb 25, 2014;82(8):716-24.
- The CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502.
- Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med*. 2000; 109:523-30.
- De Schryver EL, Algra A, van Gijn J. Dipyridamole for preventing stroke and other vascular events in patients with vascular diseases. *Cochrane Database Syst Rev*. 2007;(3):CD001820. DOI: 10.1002/14651858.CD001820.pub3.
- Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared to clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331-7.
- Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143(1-2):1-13.
- Dombi P, Illés Á, Demeter J, et al. Anagrelide reduces thrombotic risk in essential thrombocythaemia vs. hydroxyurea plus aspirin. *Eur J Haematol*. 2017 Feb;98(2):106-111. doi: 10.1111/ejh.12806.
- Douglas JS Jr, Holmes DR Jr, Kereiakes DJ, et al. Coronary stent restenosis in patients treated with cilostazol. *Circulation*. 2005; 112:2826-32.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>. Accessed March 9, 2017.
- DURLAZA prescribing information. New Haven Pharmaceuticals, Inc. North Haven, CT. September 2015.
- EFFIENT prescribing information. Eli Lilly and Company. Indianapolis, IN. July 2016.
- Eikelboom JW, Hirsh J, Spencer FA, Baglin TP, Weitz JI. Antiplatelet drugs. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(suppl 2):e89S-e119S.
- Elmariah S, Mauri L, Doros G, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. *Lancet*. 2015 Feb 28;385(9970):792-8.
- ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole vs aspirin alone after cerebral ischemia of arterial origin (ESPRIT): a randomized controlled trial. *Lancet*. 2006;367(9523):1665-73.
- Fanari Z, Malodiya A, Weiss SA, et al. Long-term use of dual antiplatelet therapy for the secondary prevention of atherothrombotic events: Meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med*. 2017 Jan - Feb;18(1):10-15. doi: 10.1016/j.carrev.2016.07.006
- FDA Advisory Committee Transcript (ZONTIVITY). Transcript for the January 15, 2014 Meeting of the Cardiovascular and Renal Drugs Advisory Committee. January 15, 2014. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM396033.pdf>. Accessed March 15, 2017.
- FDA Summary Review for Regulatory Action. ZONTIVITY. April 18, 2014. Available at: [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2014/204886Orig1s000SumR.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204886Orig1s000SumR.pdf). Accessed March 15, 2017.
- Fihn SD, Gardin JM, Abrams J, et al. ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease: Executive Summary. *Circulation*. 2012;126:3097-3137.
- Gagne JJ, Bykov K, Choudhry NK, et al. Effect of smoking on comparative efficacy of antiplatelet agents: systematic review, meta-analysis, and indirect comparison. *BMJ*. Sept 17, 2013;347:f5307.
- Gent M, Blakely JA, Easton JD, et al. The Canadian American ticlopidine study (CATS) in thromboembolic stroke. *Lancet*. 1989;1(8649):1215-20.
- Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the management of patients with lower extremity peripheral artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016 Nov 8. pii: S0735-1097(16)36902-9. doi:10.1016/j.jacc.2016.11.007.
- Goldstein JL, Whellan DJ, Scheiman JM, et al. Long-term safety of a coordinated delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg for secondary cardiovascular disease prevention in patients at GI risk. *Cardiovasc Ther*. 2016;34(2):59-66.
- Gorelick PB, Richardson D, Kelly M, et al. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. *JAMA*. 2003;289(2):2947-57.
- Gouya G, Arrich J, Wolzt M, et al. Antiplatelet treatment for prevention of cerebrovascular events in patients with vascular diseases: a systematic review and meta-analysis. *Stroke*. 2014 Feb;45(2):492-503.
- Guyatt GH, Akl EA, Crowther M, et al; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 Feb;141(2 Suppl):7S-47S.
- Harrington RA, Becker RC, Cannon CP, et al. Antithrombotic therapy for non-ST-segment elevation acute coronary syndromes: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (9th edition). *Chest*. 2008;133(6 Suppl):776S-814S.
- Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared to anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353:33-45.
- Hass W, Easton J, Adams H, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. Ticlopidine Aspirin Stroke Study (TASS) Group. *N Engl J Med*. 1989;8(321):501-7.
- Held C, Asenblad N, Bassand JP, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. *J Am Coll Cardiol*. 2011 Feb 8;57(6):672-84.
- Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001; 344:1608-21.
- Hiatt WR, Fowkes FG, Heizer G, et al. Ticagrelor versus clopidogrel in symptomatic peripheral artery disease. *N Engl J Med*. 2017 Jan 5;376(1):32-40. doi: 10.1056/NEJMoa1611688.

- Husted S, James SK, Bach RC, et al. The efficacy of ticagrelor is maintained in women with acute coronary syndromes participating in the prospective, randomized, platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J*. 2014;35(23):1541-50.
- James S, Angiolillo DJ, Corenal JH, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndrome and diabetes: a substudy from the platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J*. 2010a;31:3006-16.
- James S, Budaj A, Aylward P, et al. Ticagrelor vs clopidogrel in acute coronary syndromes in relation to renal function: results from the platelet inhibition and patient outcomes (PLATO) trial. *Circulation*. 2010b;122:1056-67.
- James SK, Roe MT, Cannon CP, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomized PLATElet inhibition and patient Outcomes (PLATO) trial. *BMJ*. 2011 Jun 17;342:d3527.
- January CT, Wann S, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary. *Circulation*. 2014 Dec 2;130(23):2071-104.
- Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013 Jan;44:870-947.
- Johnston SC, Amarenco P, Albers GW, et al for the SOCRATES Investigators. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med*. 2016 Jul 7;375(1):35-43.
- Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest*. 2016;149(2):293-294.
- Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014 Jul;45(7):2160-236.
- Kohli P, Wallentin L, Reyes E, et al. Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO study. *Circulation*. Feb 12, 2013;127(6):673-80.
- Kohli P, Udell JA, Murphy SA, et al. Discharge aspirin dose and clinical outcomes in patients with acute coronary syndromes treated with prasugrel vs clopidogrel: an analysis from the TRITON-TIMI 38 study (trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38). *J Am Coll Cardiol*. Jan 28, 2014;63(3):225-32.
- Kunishima T, Musha H, Eto F, et al. A randomized trial of aspirin vs cilostazol therapy after successful coronary stent implantation. *Clin Ther*. 1997; 19:1058-66.
- Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141(2 Suppl):e601S-36S.
- Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med*. 1998;339(23):1665-71.
- Leonardi-Bee J, Bath PMW, Boussier MG, et al. Dipyridamole for preventing recurrent ischemic stroke and other vascular events: a meta-analysis of individual patient data from randomized controlled trials. *Stroke*. 2005;36(1):162-8.
- Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. *J Am Coll Cardiol*. 2011 Dec 6;58(24):e44-122.
- Levine GN, Bates ER, Blankenship JC, et al. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the society for cardiovascular angiography and interventions. *Circulation*. 2016b Mar 15;133(11):1135-47.
- Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. *Circulation*. 2016a Sep 6;134(10):e123-55.
- Mahaffey KW, Wojdyla DM, Carroll K, et al. Ticagrelor compared to clopidogrel by geographic region in the platelet inhibition and patient outcomes (PLATO) trial. *Circulation*. 2011;124:544-54.
- Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. Nov 2014;371: 2155-66.
- Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014 Dec;45(12):3754-832. doi: 10.1161/STR.0000000000000046.
- Melloni C, Jones WS, Washam JB, et al. Antiplatelet and anticoagulant treatments for unstable angina/non-ST elevation myocardial infarction. Rockville MD: Agency for Healthcare Research and Quality; Nov 2013. Report No: 13(14)-EHC125-EF.
- Micromedex<sup>®</sup> Solutions [database on the Internet]. Truven Health Analytics; 2017. Available from: <http://www.micromedexsolutions.com/home/dispatch>. Accessed March 14, 2017.
- Money SR, Herd A, Isaacsohn JL et al. Effect of cilostazol on walking distances in patients with intermittent claudication caused by peripheral vascular disease. *J Vasc Surg*. 1998; 27:267-75.
- Montalescot G, Wiviott SD, Murphy SA, et al. Prasugrel compared to clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double blind, randomized controlled trial. *Lancet*. 2009;373:723-31.
- Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events (TRA 2°P-TIMI 50). *N Engl J Med*. April 12, 2012;366(15):1404.
- Mulukutla SR, Marroquin OC, Vlachos HA, et al. Benefit of long-term dual anti-platelet therapy in patients treated with drug-eluting stents: from the NHLBI dynamic registry. *Am J Cardiol*. 2013 Feb 15;111(4):486-92. doi: 10.1016/j.amjcard.2012.10.030.
- Murphy SA, Antman EM, Wiviott SD, et al. Reduction in recurrent cardiovascular events with prasugrel compared to clopidogrel in patients with acute coronary syndromes from the TRITON-TIMI 38 trial. *Eur Heart J*. 2008;29:2473-9.
- Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomized controlled trials. *BMJ*. 2015 Apr 16;350:h1618.

- Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2017 Mar 15. doi: 10.1161/CIR.0000000000000503. [Epub ahead of print]
- O'Donnell ME, Badger SA, Sharif MA, et al. The vascular and biochemical effects of cilostazol in patients with peripheral arterial disease. *J Vasc Surg*. 2009a May;49(5):1226-34.
- O'Donnell ME, Badger SA, Sharif MA, et al. The effects of cilostazol on exercise-induced ischaemia-reperfusion injury in patients with peripheral arterial disease. *Eur J Vasc Endovasc Surg*. 2009b Mar;37(3):326-35.
- O'Donoghue M, Antman EM, Braunwald E, et al. The efficacy and safety of prasugrel with and without a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes undergoing percutaneous intervention. *J Am Coll Cardiol*. 2009;54:678-85.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary. *Circulation*. 2013;127:529-555.
- Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations [database on the internet]. Silver Spring (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available at: <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>. Accessed March 9, 2017.
- Park SW, Lee CW, Kim HS, et al. Comparison of cilostazol vs ticlopidine therapy after stent implantation. *Am J Cardiol*. 1999; 84:511-4.
- Park SW, Lee CW, Kim HS, et al. Effects of cilostazol on angiographic restenosis after coronary stent placement. *Am J Cardiol*. 2000; 86:499- 503.
- Penninga E, Jensen BA, Hansen PB, et al. Anagrelide treatment in 52 patients with chronic myeloproliferative diseases. *Clin Lab Haem*. 2004;26:335-40.
- PERSANTINE prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT. December 2011.
- Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice: The sixth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016 Aug 1;37(29):2315-81.
- PLAVIX prescribing information. Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership. Bridgewater, NJ. September 2016.
- PLETAL prescribing information. Otsuka Pharmaceutical Co., LTD. Rockville, MD. January 2016.
- Powers WJ, Derdeyn CP, Biller J, et al. 2015 AHA/ASA Focused Update of the 2013 Guidelines for the Early Management of Patients with Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015 Oct;46(10):3020-35.
- Pride YB, Wiviott SD, Buros JL, et al. Effect of prasugrel vs clopidogrel on outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention without stent implantation: a trial to assess improvement in therapeutic outcomes by optimizing platelet inhibitor with prasugrel (TRITON)-thrombolysis in myocardial infarction (TIMI) 38 substudy. *Am Heart J*. 2009;158:e21-6.
- Rafique AM, Nayyar P, Wang TY, et al. Optimal P2Y12 inhibitor in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: A network meta-analysis. *JACC Cardiovasc Interv*. 2016 May 23;9(10):1036-46. doi: 10.1016/j.jcin.2016.02.013.
- Reilly MP, Mohler ER. Cilostazol: treatment of intermittent claudication. *Ann Pharmacother*. 2001; 35:48-56.
- Roe MT, Armstrong PW, Fox KAA, et al. Prasugrel vs clopidogrel for acute coronary syndromes without revascularization. *NEJM*. 2012;367:1297-1309.
- Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management for acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315. doi: 10.1093/eurheartj/ehv320
- Sabatine MS, Cannon CP, Gibson CM, et al; the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY Study. *N Engl J Med*. 2005a;294(10):1224-32.
- Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005b;352(12):1179-89.
- Schömgig A, Kastrati A, Wessely R. Prevention of restenosis by systemic drug therapy: back to the future? *Circulation*. 2005;112; 2759-2761.
- Scirica BM, Bonaca MP, Braunwald E, et al. Vorapaxar for secondary prevention of thrombotic events for patients with previous myocardial infarction: a prespecified subgroup analysis of the TRA 2°P-TIMI 50 trial. *Lancet*. Oct 13, 2012;380(9850):1317-24.
- Serebruany V, Shalito I, Kopyleva O. Prasugrel development-Claims and achievements. *Thromb Haemost*. 2009;101:14-22.
- Sharma A, Helft G, Garg A et al. Safety and efficacy of vorapaxar in secondary prevention of atherosclerotic disease: A meta-analysis of randomized control trials. *Int J Cardiol*. 2017 Jan 15;227:617-624. doi: 10.1016/j.ijcard.2016.10.088.
- Silver RT. Anagrelide is effective in treating patients with hydroxyurea-resistant thrombocytosis in patients with chronic myeloid leukemia. *Leukemia*. 2005;19:39-43.
- Smith SC, Benjamin EJ, Bonow RO, et al. AHA/ACC secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. A guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation*. 2011;124:2458-73.
- Smith EE, Saposnik G, Biessels GJ, et al. Prevention of stroke in patients with silent cerebrovascular disease: A scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017 Feb;48(2):e44-e71. doi: 10.1161/STR.0000000000000116.
- Spinler SA, Rees C. Review of prasugrel for the secondary prevention of atherothrombosis. *J Manage Care Pharm*. 2009;15(5):383-95.
- Steg PG, James S, Harrington RA, et al. Ticagrelor vs clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*. 2010 Nov 23;122(21):2131-41.
- Steurer M, Gastl G, Jedrzejczak WW, et al. Anagrelide for thrombocytosis in myeloproliferative disorders. *Cancer*. 2004;101(10):2239-46.
- Storey RF, Becker RC, Harrington RA, et al. Pulmonary function in patients with acute coronary syndrome treated with ticagrelor or clopidogrel (from the Platelet Inhibition and Patients Outcomes [PLATO] Pulmonary Function Substudy). *Am J Cardiol*. 2011;108:1542-6.
- Take S, Matsutani M, Ueda H, et al. Effect of cilostazol in preventing restenosis after percutaneous transluminal coronary angioplasty. *Am J Cardiol*. 1997; 79:1097-9.

- Ticlopidine prescribing information. Carilion Materials Management for Teva Pharmaceuticals. Sellersville, PA. August 2016.
- Tricoci P, Huang Z, Held C, et al. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes (TRACER trial). *N Engl J Med.* Jan 5, 2012;366(1):20-33.
- Tsuchikane E, Fukihara A, Kobayashi T, et al. Impact of cilostazol on restenosis after percutaneous coronary balloon angioplasty. *Circulation.* 1999; 100:21-6.
- Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. *Eur Heart J.* 2016 Jan 21;37(4):390.
- Vandvik PO, Lincoff M, Gore JM, et al. Primary and secondary prevention of cardiovascular disease. Antithrombotic therapy and prevention of thrombosis, 9<sup>th</sup> ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2012;141(suppl 2):e637S-e668S.
- Varenhorst C, Alstrom U, Braun O, et al. Causes of mortality with ticagrelor compared with clopidogrel in acute coronary syndromes. *Heart.* 2014; 100(22):1762-9.
- Valgimigli M, Campo G, Monti M, et al. Short versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial (PRODIGY). *Circulation.* 2012;125:2015–2026.
- Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. *Heart.* 2016 Apr;102(8):617-25. doi: 10.1136/heartjnl-2015-308963.
- Wallentin L, Becker RC, Budaj A, et al. Ticagrelor vs clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009 Sep 10;361(11):1045-57.
- Wallentin L, James S, Storey RF, et al. Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor vs clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. *Lancet.* 2010 Oct 16;376(9749):1320-8.
- Wang Y, Minematsu K, Wong KS, et al. Ticagrelor in acute stroke or transient ischemic attack in Asian patients: from the SOCRATES trial (acute stroke or transient ischemic attack treated with aspirin or ticagrelor and patient outcomes). *Stroke.* 2017 Jan;48(1):167-173. doi: 10.1161/STROKEAHA.116.014891.
- Whellan DJ, Goldstein JL, Cryer BL, et al. PA32540 (a coordinated-delivery tablet of enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) versus enteric-coated aspirin 325 mg alone in subjects at risk for aspirin-associated gastric ulcers: results of two 6-month, phase 3 studies. *Am Heart J.* 2014;168(4):495-502.
- Wiviott SD, White HD, Ohman EM, et al. Prasugrel vs clopidogrel for patients with unstable angina or non-ST-segment elevation myocardial infarction with or without angiography: a secondary, prespecified analysis of the TIOLOGY ACS trial. *Lancet.* July 2013;382:605-13. Correction published 30 Aug, 2013.
- Wiviott SD, Braunwald E, Angiolillo DJ, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes mellitus in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel thrombolysis in myocardial infarction 38. *Circulation.* 2008a;118:1626-36.
- Wiviott SD, Braunwald E, McCabe CH, et al. Intensive oral antiplatelet therapy for reduction of ischemic events including stent thrombosis in patients with acute coronary syndromes treated with percutaneous coronary intervention and stenting in the TRITON-TIMI 38 trial: a subanalysis of a randomized trial. *Lancet.* 2008b;371:1353-63.
- Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel vs clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2007;357(20):2001-15.
- Wiviott SD, Trenk D, Frelinger AL, et al; PRINCIPLE-TIMI 44 Investigators. Prasugrel compared to high loading- and maintenance-dose clopidogrel in patients with planned percutaneous coronary intervention: the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation Thrombolysis in Myocardial Infarction 44 trial. *Circulation.* 2007;116(25):2923-32.
- Xu LX, Chen KY, Liu T et al. Adjunctive loading dose of cilostazol in preventing periprocedural myocardial infarction. *Cardiovasc Ther.* 2016 Aug;34(4):225-33. doi: 10.1111/1755-5922.12192.
- Yoon YS, Shim WH, Lee DH, et al. Usefulness of cilostazol vs ticlopidine in coronary artery stenting. *Am J Cardiol.* 1999; 84:1375-80.
- YOSPRALA prescribing information. Aralez Pharmaceuticals US, Inc. Princeton, NJ. October 2016.
- Zhang Y, Zhao Y, Pang M, et al. High-dose clopidogrel versus ticagrelor for treatment of acute coronary syndromes after percutaneous coronary intervention in CYP2C19 intermediate or poor metabolizers: a prospective, randomized, open-label, single-centre trial. *Acta Cardiol.* 2016 Jun;71(3):309-16. doi: 10.2143/AC.71.3.3152091.
- ZONTIVITY prescribing information. Merck & Co., Inc. Whitehouse Station, NJ. April 2015.
- Zou Y, Hu C, Ye W, et al. Long-term clinical efficacy and safety of adding cilostazol to dual antiplatelet therapy after drug-eluting stent implantation in coronary arteries: A meta-analysis of randomized controlled trials. *Thromb Res.* 2015 Nov;136(5):870-7. doi: 10.1016/j.thromres.2015.08.018.

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