



# Platelet Aggregation Inhibitors

## Therapeutic Class Review (TCR)

January 14, 2015

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s)
aspirin/dipyridamole ER (Aggrenox®) <sup>1</sup>	Boehringer-Ingelheim	<ul style="list-style-type: none"> <li>Risk reduction of stroke in patients who have had transient ischemia of the brain or completed ischemic thrombotic stroke due to thrombosis</li> </ul>
clopidogrel (Plavix®) <sup>2</sup>	generic, Bristol-Myers Squibb	<ul style="list-style-type: none"> <li>Secondary prevention of atherosclerotic events (fatal or nonfatal myocardial infarction (MI), fatal or nonfatal ischemic stroke, and vascular death) in patients with recent MI, recent stroke or established peripheral arterial disease (PAD)</li> <li>Acute coronary syndrome:               <ul style="list-style-type: none"> <li>Non-Q-wave acute MI or unstable angina during medical management or percutaneous intervention (with or without stenting) or coronary artery bypass graft (CABG) to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke, as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia</li> <li>For ST-segment elevation acute MI to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke; this benefit is not known to pertain to patients who receive primary angioplasty</li> </ul> </li> </ul>
dipyridamole (Persantine®) <sup>3</sup>	generic, Boehringer-Ingelheim	<ul style="list-style-type: none"> <li>Adjunctive therapy to coumarin anticoagulants in the prevention of postoperative thromboembolic complications of cardiac valve replacement</li> </ul>
prasugrel (Effient™) <sup>4</sup>	Eli Lilly	<ul style="list-style-type: none"> <li>Reduction of thrombotic CV events (including stent thrombosis) in patients with acute coronary syndrome (ACS) who are to be managed with percutaneous coronary intervention (PCI) as follows: patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI), or patients with ST-elevation myocardial infarction (STEMI) when managed with either primary or delayed PCI.</li> </ul>
ticagrelor (Brilinta™) <sup>5</sup>	AstraZeneca	<ul style="list-style-type: none"> <li>Reduction of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).</li> <li>Reduces the rate of stent thrombosis in patient treated with percutaneous coronary intervention (PCI)</li> </ul>
ticlopidine <sup>6</sup>	generic	<ul style="list-style-type: none"> <li>Secondary prevention of thrombotic stroke (fatal or nonfatal); second-line therapy</li> <li>Adjunct to aspirin to reduce the incidence of subacute stent thrombosis for patients undergoing coronary stent placement</li> </ul>
vorapaxar (Zontivity™) <sup>7</sup>	Merck	<ul style="list-style-type: none"> <li>Reduction of thrombotic cardiovascular events in patients with a history of MI or PAD. It has been shown to reduce the rate of the combined endpoint of cardiovascular death, MI, stroke, and urgent cardiovascular revascularization</li> </ul>

Aspirin is available over the counter and used for secondary prevention of myocardial infarction (MI), stable and unstable angina, including coronary artery disease (CAD), arterial thromboembolism prophylaxis for patients with prosthetic heart valves in combination with warfarin, secondary prevention of stroke/transient ischemic attack (TIA), and acute treatment of stroke in patients not eligible for thrombolysis.

## OVERVIEW

The 2014 Heart Disease and Stroke Statistics update cites cardiovascular (CV) disease as the cause of 31 percent of all deaths in the United States (US) in 2010; however, death rates attributable to CV disease have decreased by 31 percent in the 10-year period from 2000 to 2010.<sup>8</sup> Stroke also causes significant morbidity and mortality in the US and is the fourth leading cause of death behind heart disease, cancer, and chronic lower respiratory disease.<sup>9</sup>

Inhibitory effects on platelet aggregation have led to a significant decrease in the rate of vascular events for both primary and secondary CV prevention trials.<sup>10,11</sup> Aspirin has been shown to reduce CV morbidity and mortality in both primary and secondary prevention trials.<sup>12,13,14,15,16</sup> The 2012 American College of Chest Physicians (ACCP) evidence-based practice guidelines state that aspirin therapy slightly reduces total mortality, regardless of CV risk profile, if taken over 10 years. In people at moderate to high risk of CV events, the reduction in myocardial infarction (MI) is closely balanced with an increase in major bleeds.<sup>17</sup> For primary prevention in persons aged 50 years or older without symptomatic CVD, ACCP suggests aspirin low-dose (75-100 mg daily) (Grade 2B). However, the FDA guidance from May 2014 states that aspirin should not be used for primary prevention of CVD or stroke which contradicts the ACCP guidelines.<sup>18</sup> For secondary prevention in patients with established CAD, defined as one-year post-acute coronary syndrome (ACS), with prior revascularization, coronary stenosis > 50 percent, and/or evidence for cardiac ischemia, ACCP recommends long-term low-dose aspirin or clopidogrel (Plavix) (Grade 1A); for patients undergoing elective PCI but no stenting, ACCP suggests aspirin 75 to 325 mg daily and clopidogrel for the first month; for patients in the first year after an ACS with stent placement, ACCP recommends low-dose aspirin plus ticagrelor (Brilinta), clopidogrel, or prasugrel (Effient) (Grade 1B), with a preference of aspirin plus ticagrelor over aspirin plus clopidogrel (Grade 2B).

Studies have identified inter-patient variability of response to the antiplatelet agents. A small percentage of patients with CV disease have aspirin resistance and, therefore, may be at higher risk for CV events.<sup>19</sup> The definition of aspirin resistance is quite variable in the literature and has been described as the failure to prevent a thrombotic event, the inability to inhibit platelet thromboxane formation, or the inability to cause prolongation of bleeding time. Guidelines for the management of aspirin resistance have not been developed. It is unknown if aspirin resistance can be overcome by increasing the dose of aspirin or adding another agent.<sup>20,21,22,23,24,25,26</sup> More high quality clinical trials evaluating aspirin resistance are needed.

Variability in responsiveness to clopidogrel has also been documented.<sup>27,28,29,30</sup> Inconsistencies in response to clopidogrel may be due to pre-existing variability in platelet response to adenosine diphosphate (ADP), genetic variability (polymorphisms in the hepatic enzymes [i.e., CYP2C19] involved in clopidogrel metabolism, or within the platelet P2Y<sub>12</sub> receptor), or drug interactions (e.g., proton pump inhibitors).<sup>31,32,33,34,35,36</sup> An association between a CYP2C19 variant and recurrent thrombotic coronary events in patients taking clopidogrel has been reported.<sup>37,38,39,40</sup> Unpredictability in response to thienopyridines has led to the development of point-of-care devices to assess ADP induced platelet aggregation.<sup>41</sup> Currently, recommendations are not in place regarding the use of these devices.

In addition, dual aspirin and clopidogrel non-responsiveness has been documented and linked to patients at very high risk of drug-eluting stent thrombosis or death.<sup>42</sup>

Other antithrombotic drugs have been developed to improve the platelet aggregation inhibition and to improve the safety profile of platelet aggregation inhibitor therapy. Clopidogrel (Plavix), aspirin/dipyridamole ER (Aggrenox), and ticlopidine are platelet aggregation inhibitors and are useful in the treatment and prevention of CV and cerebrovascular thrombotic events. Prasugrel (Effient) has shown better efficacy compared to clopidogrel in preventing MI and stent thrombosis in ACS patients undergoing PCI.<sup>43</sup> Studies have shown ticagrelor (Brilinta) to be favored over clopidogrel in preventing deaths from CV causes, MI, or stroke.<sup>44</sup> While safety information is still limited with the use of prasugrel, it has been associated with significantly more major bleeding episodes when compared to clopidogrel-treated patients.<sup>45</sup>

## Prevention of Stroke and TIAs

Several scientific statements and guidelines have been published on the prevention and treatment of ischemic stroke.<sup>46,47,48</sup>

The 2012 ACCP evidence-based practice guidelines recommend early (within 48 hour of stroke onset) aspirin therapy (initial dose 160 mg to 325 mg) for acute ischemic stroke or TIA (Grade 1A).<sup>49</sup> For long-term stroke prevention in patients who have experienced a noncardioembolic stroke or TIA, aspirin (75 to 100 mg daily), aspirin/dipyridamole ER (Aggrenox) (25 mg/200 mg twice daily), clopidogrel (75 mg daily), or cilostazol (Pletal®) are all acceptable options for initial therapy (Grade 1A). In these patients, clopidogrel or aspirin/dipyridamole ER are recommended over aspirin or cilostazol (Grade 2B-2C).

The 2014 American Heart Association/American Stroke Association (AHA/ASA) Stroke and TIA guidelines state that aspirin 50 to 325 mg daily monotherapy (Class I recommendation, Level of Evidence A) or aspirin/dipyridamole ER (Aggrenox) 25 mg/200 mg twice daily (Class I recommendation, Level of Evidence B) are indicated as initial therapy for TIA or ischemic stroke for prevention of future stroke.<sup>50</sup> Clopidogrel (Plavix) 75 mg daily monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or aspirin/dipyridamole ER, especially for patients allergic to aspirin (Class IIa, Level of Evidence B). The combination of aspirin and clopidogrel might be considered within 24 hours of a minor ischemic stroke or TIA and continued for 90 days (Class IIb, Level of Evidence B). The addition of aspirin to clopidogrel increases the risk of hemorrhage and is not recommended for routine secondary prevention after ischemic stroke or TIA (Class III; Level of Evidence A). For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin (Class IIb; Level of Evidence C).

The 2009 U.S. Preventative Services Task Force updated the recommendations for aspirin for the primary prevention of CV disease.<sup>51</sup> Aspirin is recommended in men ages 45 to 79 years to prevent MI. Aspirin is recommended in women ages 55 to 79 years to prevent ischemic stroke. There is not enough information regarding benefit versus risk to recommend aspirin in patients 80 years or older. The optimal aspirin dose is unknown, but a dose of approximately 75–100 mg per day seems as effective as higher doses, which can increase GI bleeding. However, newer information, from the FDA guidance from May 2014, specifies that aspirin should not be used for primary prevention of CVD or stroke contradicts the US Preventative Services Task Force guidelines.<sup>52</sup> The 2014 American Heart Association/American Stroke Association Guidelines for the Primary Prevention of Stroke address this contradiction.<sup>53</sup> While these guidelines state that aspirin is not useful for preventing a first stroke in low-risk individuals, the use of aspirin for cardiovascular prophylaxis (including but not limited to

stroke) is reasonable for people whose risk is sufficiently high (10-year risk >10 percent) for the benefits to outweigh the risks associated with treatment.

## Cardiac Uses

In 2014, the American College of Cardiology (ACC) and the American Heart Association (AHA) released new practice guidelines for the management of patients with non-ST-elevation acute coronary syndromes (NSTEMI-ACS).<sup>54</sup> The majority of patients who present with acute coronary syndrome (ACS) have unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI). Since the presentation of these conditions is similar, the ACC/AHA now refers to both as NSTEMI-ACS. The document replaces their 2007 guideline and the 2012 focused update. The 2014 guideline recommends non-enteric-coated, chewable aspirin, at a dose of 162 mg to 325 mg, should be given to all NSTEMI-ACS patients without contraindications as soon as possible after presentation, and a maintenance dose of aspirin, at a dose of 81 mg to 325 mg per day, should be continued indefinitely. For NSTEMI-ACS patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance, a loading dose of clopidogrel is recommended followed by a daily maintenance dose. For NSTEMI-ACS patients who are treated with an early invasive procedure or ischemia-guided therapy, the guideline recommends a P2Y<sub>12</sub> receptor inhibitor (either ticagrelor or clopidogrel, Class 1 recommendation) be added to aspirin therapy for up to 12 months of therapy, with ticagrelor preferred over clopidogrel (Class IIa). P2Y<sub>12</sub> inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be continued for at least 12 months in NSTEMI-ACS post-PCI patients treated with coronary stents (Class 1). Ticagrelor and prasugrel are preferred over clopidogrel in post-PCI NSTEMI-ACS patients (Class IIa); however, prasugrel should not be used in patients who are at high risk for bleeding.

According to the 2013 ACCF/AHA guidelines for the management of patients with STEMI, a loading dose of a P2Y<sub>12</sub> platelet inhibitor is recommended for STEMI patients for whom PCI is planned in addition to aspirin (162-325 mg).<sup>55</sup> The guidelines recommend aspirin 162 to 325 mg before primary PCI (Level of Evidence B); after PCI, aspirin should be continued indefinitely (Level of Evidence A); Class I recommendation for both. The guidelines also recommend use of prasugrel (Effient) and ticagrelor (Brilinta) as alternatives to clopidogrel (Plavix). These agents should be given as a loading dose as early as possible to patients with STEMI or at time of PCI, and continued for at least one year after stent placement, depending on type of stent (Class I, Level of Evidence B for all three agents).

Use of prasugrel is not recommended in STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned.

For patients with anterior MI and left ventricular (LV) thrombus, or at high risk for LV thrombus who do not undergo stenting, the 2012 ACCP guidelines recommend warfarin plus aspirin (75 to 100 mg daily) for the first three months (Grade 1B) and dual antiplatelet therapy with aspirin plus ticagrelor or clopidogrel for up to 12 months, as per their ACS recommendation.<sup>56</sup> After 12 months, single antiplatelet therapy with aspirin (75 to 100 mg daily) or clopidogrel is recommended as per the ACCP established CAD recommendation. If a stent is placed, clopidogrel is added during the first month after bare metal stent (BMS) placement, and for three to six months after DES placement.

Both clopidogrel (Plavix) and ticlopidine, with the addition of aspirin, are efficacious in reducing major cardiac adverse events following successful coronary stent implantation. Clopidogrel may be better tolerated than ticlopidine and have a faster onset of action. Serious hematologic adverse effects limit the use of ticlopidine.<sup>57,58,59,60</sup> After the placement of a drug-eluting or bare-metal stent, the 2013

ACC/AHA STEMI guidelines recommend dual antiplatelet therapy with aspirin indefinitely and a P2Y<sub>12</sub> platelet inhibitor (clopidogrel, prasugrel or ticagrelor) for at least 12 months (Level of Evidence B). It is reasonable to consider continuation of therapy for more than 12 months for patients undergoing DES placement (Level of Evidence C). In STEMI patients with a prior history of stroke and TIA for whom primary PCI is planned, prasugrel is not recommended as part of a dual-antiplatelet therapy regimen (Level of Evidence C).<sup>61</sup>

Early discontinuation of dual antiplatelet therapy greatly increases the risk of stent thrombosis, MI, and death and poor adherence in post-drug-eluting stent patients within the first 30 days of therapy and has been shown to reduce the beneficial effects on mortality.<sup>62,63</sup> The 2011 ACCF/AHA/Society for Cardiovascular Angiography and Interventions (SCAI) guidelines for PCI intervention recommend dual antiplatelet therapy pre-treatment and long-term therapy following PCI.<sup>64</sup> As noted above, the 2012 ACCP evidence-based clinical practice guidelines recommend the combination of aspirin and ticagrelor or clopidogrel for up to 12 months in patients who undergo bare metal stent or drug-eluting stent placement (Grade 1A).<sup>65</sup>

The 2011 AHA/ACCF guidelines for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommend a P2Y<sub>12</sub> receptor antagonist in combination with aspirin in patients with ACS or PCI with stent placement (Class I, Level of Evidence A).<sup>66</sup> For patients receiving a bare-metal stent or drug-eluting stent during PCI for ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily, or ticagrelor 90 mg twice daily should be given for at least 12 months (Class I, Level of Evidence A). After PCI, aspirin 81 mg daily is preferred to higher aspirin maintenance doses (Class IIa, Level of Evidence B).

The 2011 ACCF/AHA/SCAI PCI guidelines state that patients already on aspirin therapy should take 81 mg to 325 mg before PCI (Class I, Level of Evidence B). Patients not on aspirin therapy should be given non-enteric aspirin 325 mg before PCI (Class I, Level of Evidence B).<sup>67</sup> After PCI, aspirin should be continued indefinitely (Class I, Level of Evidence A). Clopidogrel, prasugrel, and ticagrelor should be initiated with a loading dose and maintenance dose continued for at least 12 months, depending on the type of stent placed. After PCI, it is reasonable to take aspirin 81 mg/day over higher maintenance doses (Class IIa, Level of Evidence B). Treatment with an alternate P2Y<sub>12</sub> inhibitor (e.g., prasugrel or ticagrelor) might be considered in patients with inadequate genetic platelet inhibition (via genetic testing) or in patients with high platelet reactivity (via platelet function testing [Class IIb, Level of Evidence C]). The 2011 ACCF/AHA CABG guidelines state that, for elective CABG, clopidogrel and ticagrelor should be discontinued for at least five days before surgery (Class I, Level B) and prasugrel for at least seven days (Class I, Level C).<sup>68</sup> In urgent CABG, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications (Class I, Level B).

The 2012 ACCP guidelines suggest that, in patients who are receiving dual antiplatelet drug therapy and require CABG surgery, aspirin should be continued around the time of surgery and clopidogrel/prasugrel should be interrupted five days before surgery (Grade 2C).<sup>69</sup>

### **Use in Peripheral Arterial Disease (PAD)**

The 2011 ACCF/AHA guidelines state that aspirin 75 to 325 mg per day is preferred over clopidogrel (Plavix) 75 mg per day to reduce the risk of MI, stroke, and vascular death in patients with PAD (Level of Evidence B).<sup>70</sup> The combination of aspirin and clopidogrel can be considered to reduce the risk of CV

events in certain high risk patients who are not at increased risk of bleeding and who are at high perceived CV risk (Level of Evidence B).

For the primary prevention of CV events in patients with asymptomatic PAD, 2012 ACCP guidelines suggest aspirin 75 to 100 mg daily (Grade 2B).<sup>71</sup> However, the FDA's guidance from May 2014 states that aspirin should not be used for primary prevention of CVD or stroke, which contradicts the ACCP's guidelines.<sup>72</sup> For secondary prevention in those with symptomatic PAD, ACCP recommends aspirin 75 to 100 mg daily or clopidogrel (Grade 1A). In patients with symptomatic carotid stenosis, ACCP recommends clopidogrel, aspirin/dipyridamole extended-release, or aspirin (75 to 100 mg daily) (Grade 1A), with preference to either clopidogrel or aspirin/dipyridamole extended-release over aspirin (Grade 2B).

## Other Uses

The 2014 ACC/AHA NSTEMI-ACS guidelines and the 2013 ACC/AHA STEMI guidelines state the duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y<sub>12</sub> receptor inhibitor should be minimized as much as possible in order to limit the risk of bleeding. Additionally, both of these guidelines suggest lowering the therapeutic INR range to 2.0–2.5 for NSTEMI-ACS patients treated with triple antithrombotic therapy (Class IIb).<sup>73,74</sup> The 2012 ACCP guidelines recommend a therapeutic INR range of 2.0–3.0 with warfarin therapy (Grade 1B).<sup>75</sup> Both the ACCP and the ACC/AHA guidelines recommend low dose aspirin with warfarin in most patients with an indication for warfarin therapy (e.g., atrial fibrillation).<sup>76</sup>

## PHARMACOLOGY<sup>77,78,79</sup>

Aspirin irreversibly inhibits platelet cyclooxygenase and thus inhibits the generation of thromboxane A<sub>2</sub>, a powerful inducer of platelet aggregation and vasoconstriction.

Dipyridamole increases intraplatelet cyclic-3',5'-adenosine monophosphate (cAMP) levels, a platelet inhibitor, by inhibiting cAMP degradation and uptake of adenosine into platelets, endothelial cells, and erythrocytes. Dipyridamole presumably inhibits adenosine deaminase, as well as phosphodiesterase, allowing levels of cAMP to remain increased.

Aspirin/dipyridamole ER (Aggrenox) provides two mechanisms of anti-aggregation effects on platelets by administration of aspirin and dipyridamole together.<sup>80</sup>

Clopidogrel (Plavix) is metabolized by CYP450 enzymes to its active metabolite that selectively inhibits the binding of adenosine diphosphate (ADP) to platelet P2Y<sub>12</sub> receptors and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex.<sup>81</sup> Activation of this complex leads to irreversible inhibition of platelet aggregation.

Prasugrel (Effient), a thienopyridine P2Y<sub>12</sub> platelet inhibitor, is converted to an active metabolite by CYP3A4 and CYP2B6 which inhibits platelet action by irreversibly binding to the platelet ADP receptor.<sup>82</sup>

Ticagrelor (Brilinta), a cyclopentyltriazolopyrimidine P2Y<sub>12</sub> platelet inhibitor, and its major metabolite reversibly inhibit the platelet P2Y<sub>12</sub> ADP-receptor and thereby prevent signal transduction and platelet activation and aggregation.<sup>83</sup>

Ticlopidine interferes with platelet membrane function by inhibiting ADP-induced platelet-fibrinogen binding and subsequent platelet-platelet interactions.<sup>84</sup> The effect on platelet function is irreversible for the life of the platelet.

Vorapaxar (Zontivity), a reversible antagonist of the protease-activated receptor-1 (PAR-1), inhibits thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation.

## PHARMACOKINETICS

Drug	Half-Life (hr)	Metabolites	Excretion (%)
aspirin	0.33	metabolites	Renal: pH dependent Feces: varies
dipyridamole (Aggrenox) <sup>85</sup>	13.6	monoglucuronide metabolite (low activity)	Renal: <5 Feces: 95
clopidogrel (Plavix) <sup>86</sup>	6–parent drug 8–inactive metabolite	carboxylic acid derivative is inactive; parent is inactive	Renal: 50 Feces: 46
dipyridamole (Persantine) <sup>87</sup>	10	inactive glucuronide metabolite	Predominately feces
prasugrel (Effient) <sup>88</sup>	7 (2 to15)-active metabolite	active and inactive metabolites	Renal: 68 Feces: 27
ticagrelor (Brilinta) <sup>89</sup>	7–parent drug 9–active metabolite	active metabolite	Renal: 26 Feces: 58
ticlopidine <sup>90</sup>	At steady state, 4–5 days	>20 inactive metabolites	Renal: 60 Feces: 23
vorapaxar (Zontivity) <sup>91</sup>	3–4 days	active metabolites	Renal: 25 Feces: 58

nr = not reported

The pharmacokinetics of the individual agents of aspirin/dipyridamole ER (Aggrenox) are not affected by concurrent administration.<sup>92</sup>

Clopidogrel is converted to its active form by the CYP2C19 enzyme. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects differ according to CYP2C19 genotype.<sup>93</sup> Patients with a CYP2C19 variant may be poor metabolizers of the drug and do not effectively convert clopidogrel to its active form, making clopidogrel less effect on platelets and less able to prevent MI, stroke, and CV death. The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to race. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately two percent for Whites, four percent for Blacks, and 14 percent for Chinese.<sup>94,95</sup> The CYP2C19\*2 and CYP2C19\*3 alleles account for 85 percent of reduced function alleles in Whites and 99 percent in Asians. The impact of CYP2C19 genotype on the pharmacokinetics of clopidogrel's active metabolite has been evaluated in several studies. Reduced CYP2C19 metabolism in intermediate and poor metabolizers decreased the maximum concentration (C<sub>max</sub>) and exposure (area under the curve [AUC]) of the active metabolite by 30 to 50 percent following 300 or 600 mg loading doses and 75 mg maintenance doses. The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in post-hoc analyses and several cohort studies.<sup>96,97,98,99,100,101,102</sup> The results ranged from increased CV events in impaired metabolizers to no CV event rate difference in various genotypes. In addition, paraoxonase-1 (PON1) has been recently identified as a new enzyme for

clopidogrel bioactivation, with the Q19R polymorphism determining both the rate of active metabolite and clopidogrel clinical activity.<sup>103</sup>

In March 2010, the FDA added a boxed warning to the label for clopidogrel (Plavix) regarding patients that are poor metabolizers of clopidogrel who may not receive the full benefits of the drug.<sup>104</sup> The warning informs healthcare professionals of the availability of tests to identify genetic differences in CYP2C19 function and advises consideration of alternative anti-platelet medications or alternative dosing strategies for clopidogrel in patients identified as poor metabolizers.

ACCF/AHA recommends that genetic testing may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes (e.g., patients undergoing elective high-risk PCI procedures). If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel for coronary patients, should be considered. Higher loading doses (600 mg versus 300 mg), double-dose loading (600 mg twice over two hours), and higher maintenance doses of clopidogrel (150 mg daily) have been found to improve platelet inhibition and might be considered alternatives for high-risk patients who respond poorly to standard dosages of clopidogrel, although there is uncertainty of the long-term safety and efficacy of this approach.

Prasugrel (Effient) is a prodrug that must be metabolized to its active metabolite. Prasugrel (Effient) and ticagrelor (Brilinta) are not significantly affected by genetic variations that reduce CYP2C19 enzymes, therefore are not expected to be affected by pharmacogenomics.<sup>105,106,107</sup> Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors.<sup>108</sup> The major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite is CYP3A4.

## CONTRAINDICATIONS/WARNINGS

Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), ticlopidine, and vorapaxar (Zontivity) are contraindicated in patients with active pathological bleeding, such as bleeding peptic ulcer or intracranial hemorrhage.<sup>109,110</sup> Ticlopidine should not be used in patients with a hemostatic disorder. Clopidogrel, prasugrel, and ticagrelor are contraindicated in patients with hypersensitivity to their active ingredient or any of the excipients. Prasugrel and vorapaxar are also contraindicated in patients with prior TIA or stroke.<sup>111,112</sup> Ticagrelor is contraindicated in patients with severe hepatic impairment, which may increase drug exposure. It is also contraindicated in patients with hypersensitivity to ticagrelor.<sup>113</sup>

Ticlopidine is contraindicated in patients with a presence of neutropenia and thrombocytopenia, or a history of TTP or aplastic anemia.<sup>114</sup> Ticlopidine should not be used in patients with severe liver impairment.

Aspirin/dipyridamole ER (Aggrenox) is contraindicated in patients with hypersensitivity to dipyridamole, aspirin, or any excipients.<sup>115</sup> Aspirin/dipyridamole ER should not be administered to patients with known allergy to NSAIDs or to patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin/dipyridamole ER, due to the aspirin component, should not be given to children or teenagers with viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.

Aspirin/dipyridamole ER (Aggrenox) has several warnings in the package labeling.<sup>116</sup> Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic heavy alcohol use while taking aspirin. Due to the aspirin component, the

increase in bleeding time may adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders. Aspirin has known gastrointestinal (GI) adverse effects that include stomach pain, heartburn, nausea, vomiting, and GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, it is important to monitor for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Patients with a history of active peptic ulcer disease should avoid using aspirin due to the potential for gastric mucosal irritation and bleeding.

Clopidogrel (Plavix) has a boxed warning stating that poor metabolizers of clopidogrel treated at recommended doses exhibit higher CV event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.<sup>117</sup> Genetic tests to determine a patient's CYP2C19 genotype could assist in determining treatment strategy. Alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers should be considered. The metabolism of clopidogrel to its active metabolite can also be impaired by concomitant medications that interfere with CYP2C19. Avoid concomitant use of clopidogrel with omeprazole or esomeprazole since both significantly reduce clopidogrel antiplatelet activity.

Clopidogrel impairs angiogenesis, a process critical for repair of GI mucosal disruptions. However, this may not be a primary cause of gastroduodenal ulcers; the anti-angiogenic effects may impair healing of gastric erosions or small ulcerations that develop because of other medications or *Helicobacter pylori* infection. In presence of acid, this can lead to clinically significant ulceration and related complications. PPIs inhibit the parietal cell proton pump, thereby exerting a suppressive effect on gastric acid. Combining a PPI with clopidogrel appears to result in less GI bleeding.<sup>118,119</sup> However, clopidogrel effectiveness can be decreased in the presence of PPIs.<sup>120,121,122,123,124</sup> Avoid use of clopidogrel in patients with impaired CYP2C19 function due to known genetic variation.

Clopidogrel has been rarely associated with thrombotic thrombocytopenic purpura (TTP).<sup>125</sup> Onset of TTP is generally within the first two weeks of therapy.<sup>126</sup> Clopidogrel should be discontinued five days prior to surgery, if possible, to reduce the risk of bleeding.

Hypersensitivity, including angioedema, has been reported in patients on prasugrel, including patients with a history of hypersensitivity reaction to other thienopyridines. Other warnings include increased risk of bleeding (boxed warning), particularly CABG bleeding, and increased risk of stent thrombosis, MI, and death when prasugrel is discontinued prematurely. Prasugrel should not be started if CABG is anticipated, and it should be discontinued at least seven days prior to any surgery. Other bleeding risk factors include weight less than 60 kg, propensity to bleeding, or use of other medications that increase bleeding risk. Prasugrel is generally not recommended in patients who are  $\geq 75$  years old due to increased risk of fatal and intracranial bleeding and uncertain benefit except in high-risk patients who are  $\geq 75$  years (e.g., with prior MI, diabetes). Thrombotic thrombocytopenia purpura (TTP) has been reported with the use of prasugrel (Effient), sometimes with brief exposures of  $< 2$  weeks.

Ticagrelor has boxed warnings regarding potential for significant, sometimes fatal, bleeding; recommendation against use in patients planned to undergo urgent CABG, when possible discontinue at least five days prior to any surgery; bleeding should be a suspected cause in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures when ticagrelor is used; bleeding should be managed without discontinuing ticagrelor whenever possible, since stopping the drug may increase the risk of subsequent CV events; maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be

avoided. After any initial dose, use with aspirin 75-100 mg per day. Ticagrelor is contraindicated in patients with hypersensitivity to ticagrelor or any component of the product. Dyspnea was reported more frequently with ticagrelor than clopidogrel and the resulting dyspnea was self-limiting.<sup>127</sup>

Ticlopidine has a boxed warning stating that ticlopidine has been associated with life-threatening hematologic adverse reactions, including neutropenia, agranulocytosis, TTP, and aplastic anemia. Periodic monitoring of complete blood count is recommended, especially during the first three months of therapy.<sup>128</sup>

Vorapaxar increases the risk of bleeding, including intracranial hemorrhage (ICH) and fatal bleeding, in proportion to the patient's underlying bleeding risk.<sup>129</sup> Consider the underlying risk of bleeding before initiating vorapaxar. General risk factors for bleeding include older age, low body weight, reduced renal or hepatic function, history of bleeding disorders, and use of certain concomitant medications that increase the risk of bleeding. Avoid concomitant use of warfarin or other anticoagulants. Withholding vorapaxar 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 vorapaxar. Significant inhibition of platelet aggregation remains four weeks after discontinuation.

### Risk Evaluation and Mitigation Strategy (REMS)<sup>130,131</sup>

Clopidogrel (Plavix) and prasugrel (Effient) also had REMS requirements but they have subsequently been removed. As of October 2013, the REMS requirement for ticagrelor (Brilinta) has been removed.

## DRUG INTERACTIONS

Drug	theophylline	warfarin	NSAIDs	Comment
aspirin/dipyridamole ER (Aggrenox) <sup>132</sup>	-	May be at higher risk for bleeding	May be at higher risk for bleeding	Dipyridamole may increase the CV effects of adenosine
clopidogrel (Plavix) <sup>133</sup>	-	May be at higher risk for bleeding	May increase risk of GI bleeding	-
dipyridamole (Persantine) <sup>134</sup>	-	-	-	Dipyridamole may increase the CV effects of adenosine
prasugrel (Effient) <sup>135</sup>	-	May be at higher risk for bleeding	May increase the risk of bleeding	Can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes
ticagrelor (Brilinta) <sup>136</sup>	-	May be at higher risk for bleeding	May be at higher risk for bleeding	Use with aspirin maintenance doses above 100 mg reduced the effectiveness of ticagrelor
ticlopidine <sup>137</sup>	Increased theophylline level	-	Ticlopidine potentiates the effect of NSAIDs on platelet aggregation	Monitor theophylline level
vorapaxar (Zontivity) <sup>138</sup>		May be at higher risk for bleeding	May be at higher risk for bleeding	Avoid concomitant use with warfarin

Ticagrelor (Brilinta) is predominantly metabolized by CYP3A4 and to a lesser extent by CYP3A5.<sup>139</sup> Ticagrelor is metabolized to the active metabolite AR C124910XX which produces systemic exposure approximately 30–40 percent of ticagrelor. Ticagrelor use with strong inhibitors of CYP3A (e.g.,

ketoconazole, clarithromycin, ritonavir) or potent inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine) should be avoided. Do not administer ticagrelor with aspirin maintenance doses above 100 mg, due to reduced effectiveness of ticagrelor.

Simvastatin and lovastatin are metabolized by CYP3A4 and coadministration of either agent with ticagrelor may result in an increase in their concentration.<sup>140</sup> Avoid simvastatin and lovastatin doses above 40 mg. Ticagrelor inhibits the P-glycoprotein transporter; therefore, digoxin levels should be monitored with initiation of, or change in, ticagrelor therapy.<sup>141</sup>

Vorapaxar (Zontivity) is metabolized by CYP3A4 and CYP2J2. Concomitant use of vorapaxar with strong inhibitors CYP3A (e.g., ketoconazole, clarithromycin, ritonavir) or strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine) should be avoided.

## Proton Pump Inhibitors

Clopidogrel is a prodrug which requires hepatic conversion in part via CYP2C19 to its active metabolite.<sup>142,143</sup> Impaired clopidogrel conversion to its active metabolite may be due to concomitant use of certain drugs that inhibit the activity of CYP2C19 resulting in reduced plasma concentrations of the active metabolite of clopidogrel and suboptimal antiplatelet activity. PPIs are CYP2C19 isoenzymes substrates and may decrease the conversion of clopidogrel to its active metabolite.

Several studies have examined the effects of concurrent clopidogrel with PPIs.<sup>144,145,146,147,148,149,150,151,152</sup> In clinical trials, omeprazole reduced the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. Although a higher dosage regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response, an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concurrently with clopidogrel. Dexlansoprazole (Dexilant), lansoprazole (Prevacid), and pantoprazole (Protonix) had less effect on the antiplatelet activity of clopidogrel than omeprazole or esomeprazole.

In October 2010, the FDA released a statement reiterating their warning against the concomitant use of clopidogrel and omeprazole because the coadministration can result in significant reductions in clopidogrel's active metabolite levels and antiplatelet activity.<sup>153</sup> The FDA emphasized additional facts that may be a source of confusion among healthcare professionals: (1) with regard to the PPI drug class, this recommendation applies only to omeprazole and not to all PPIs. Not all PPIs have the same inhibitory effect on the CYP2C19 enzyme that is crucial for conversion of clopidogrel into its active form; (2) pantoprazole (Protonix) may be an alternative PPI for consideration since it is a weak inhibitor of CYP2C19 and has less effect on the pharmacological activity of clopidogrel than omeprazole. But since this statement release, the clopidogrel label recommends against concomitant use of clopidogrel with omeprazole or esomeprazole.

In November 2010, based on new research, the American College of Cardiology Foundation (ACCF)/American College of Gastroenterology (ACG) and AHA updated the expert consensus document regarding gastrointestinal (GI) risk of antiplatelet and nonsteroidal inflammatory (NSAID) agents.<sup>154</sup> It states that clopidogrel alone, aspirin alone, and their combination are all associated with increased risk of GI bleeding and patients most at risk are those with prior GI bleeding; advanced age; concurrent use of anticoagulants, steroids, or NSAIDs, including aspirin; and *Helicobacter pylori* infection. Pharmacokinetic and pharmacodynamic studies suggest that concomitant use of clopidogrel and a PPI, particularly omeprazole, reduces the antiplatelet effects of clopidogrel. Observational studies and a

single randomized clinical trial (RCT) have shown inconsistent effects on CV outcomes of concomitant use of thienopyridines and PPIs. A clinically important interaction cannot be excluded, particularly in certain subgroups, such as poor metabolizers of clopidogrel. This statement does not recommend routine use of PPIs in patients on antiplatelet therapy, but advises that PPIs are appropriate to reduce GI bleeding among patients with multiple risk factors for GI bleeding who require antiplatelet therapy. Clinical decisions regarding concomitant use of PPIs and thienopyridines must balance overall risks and benefits, considering both CV and GI complications.

In December 2011, the clopidogrel (Plavix) label was revised to recommend against its concomitant use with omeprazole or esomeprazole and advising that when concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite.

Prasugrel is a prodrug which requires hepatic conversion via CYP3A4 and CYP2B6 (with lesser involvement of CYP2C9 and CYP2C19) to its active metabolite.<sup>155</sup> There are no significant drug interactions with CYP3A4 inhibitors (e.g., ketoconazole) and inducers (e.g., rifampin). Since prasugrel uses the CYP2C19 enzymes to a lesser extent for conversion to its active metabolite, it is also not significantly affected by the CYP2C19 inhibitors (e.g., omeprazole). Therefore, PPIs are not expected to interact with prasugrel or with ticagrelor (Brilinta).

## ADVERSE EFFECTS

Drug	Dyspepsia	Nausea	Rash	Dizziness	Headache	Diarrhea	Discontinuation Rate	Hemorrhage
aspirin/ dipyridamole ER (Aggrenox) <sup>156</sup> n=1,650	18.4	16	nr	nr	39.2	12.7	25	not specified 3.3
dipyridamole ER 200 mg twice daily n=1,654	17.4	15.4			38.3	15.5	25	1.5
aspirin 25mg twice daily n=1,649	18.1	12.7			33.8	6.8	19	2.8
placebo n=1,649 ESPS2 data	16.7	14.1			32.9	9.8	21	1.5
clopidogrel (Plavix) <sup>157,158</sup> n=9,599	5.2	3.4	4.2	6.2	7.6	4.5	13	GI 2
aspirin 325 mg daily n=9,586 CAPRIE data	6.1	3.8	3.5	6.7	7.2	3.4	13	2.7
prasugrel (Effient) + aspirin <sup>159</sup> n=6,741	nr	4.6	2.8	4.1	5.5	2.3	7.2	major bleeding non-CABG related 2.2
clopidogrel (Plavix) + aspirin n=6,716 TRITON-TIMI 38 data	nr	4.3	2.4	4.6	5.3	2.6	6.3	1.7 (p=0.029)
dipyridamole <sup>160</sup> n=147	reported	reported	2.3 (1.1)	13.6 (8.2)	2.3 (0)	reported	nr	reported with concurrent warfarin
ticagrelor (Brilinta) <sup>161,162</sup> (n=9,235)	nr	4.3	nr	4.5	6.5	3.7	7.4	major bleed 11.6
clopidogrel (Plavix) (n=9,186) PLATO data	nr	3.8	nr	3.9	5.8	3.3	5.4	11.2
ticlopidine <sup>163</sup> n=2,048	7.0 (0.9)	7.0 (1.7)	5.1 (0.6)	1.1 (0.0)	reported	12.5 (4.5)	21	reported

**Adverse Effects (continued)**

Drug	Dyspepsia	Nausea	Rash	Dizziness	Headache	Diarrhea	Discontinuation Rate	Hemorrhage
vorapaxar (Zontivity) <sup>164</sup> n=10,059	nr	nr	nr	nr	nr	nr	nr	severe 1.0 (0.8) moderate-severe 3.0 (2.0) by GUSTO bleeding (mild-sev.) 25.0 (17.6)

Adverse effects are indicated as percentage occurrence. Adverse effects data are compiled from package inserts and cannot be considered comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported

Within the fatal bleeding category in the PLATO study, the rate of fatal nonintracranial bleeding was greater in the clopidogrel group (n=21 [0.3 percent] than the ticagrelor group (n=9 [0.1 percent]); p=0.03) while a greater number of fatal intracranial bleeds occurred in the ticagrelor group (n=11 [0.1 percent]) versus the clopidogrel group (n=1 [0.01 percent]); p=0.02). Ticagrelor was associated with a higher rate of PLATO-defined non-CABG major bleeding than clopidogrel (4.5 percent versus 3.8 percent, respectively; p=0.03).

The most common non-hemorrhagic adverse event that occurred when comparing ticagrelor and clopidogrel was dyspnea which was reported in 13.8 and 7.8 percent of patients, respectively.<sup>165,166</sup>

Also, in a Holter substudy of about 3,000 patients in the PLATO study, more patients had ventricular pauses with ticagrelor than with clopidogrel (6 versus 3.5 percent, respectively, in the acute phase; and 2.2 versus 1.6 percent, respectively after one month).

Laboratory test changes in the PLATO study included greater increases in serum uric acid levels and creatinine levels in the ticagrelor group compared to the clopidogrel group.

The most common adverse effect that occurred when comparing vorapaxar (Zontivity) to placebo was bleeding.<sup>167</sup> Twenty-five percent of patients in the vorapaxar group experienced any GUSTO bleeding (mild-severe) compared to 17.6 percent in the placebo group. Other adverse reactions that occurred at a rate of at least two percent and at least 10 percent greater than placebo were anemia (five percent), depression (2.4 percent), and rashes, eruptions, and exanthemas (2.2 percent).

A meta-analysis evaluated the risk of bleeding complications associated with antiplatelet agents in 51 randomized trials with 338,191 patients.<sup>168</sup> Low-dose aspirin (less than 100 mg daily) and dipyridamole have the lowest risk of bleeding (3.6 and 6.7 percent, respectively). Aspirin doses exceeding 100 mg daily had a similar risk for bleeding as clopidogrel (Plavix) and ticlopidine. A systematic review of 22 clinical trials evaluated the adverse events with aspirin (75 to 325 mg daily) and clopidogrel (Plavix) associated with therapy for primary or secondary prophylaxis for CV events.<sup>169</sup> Aspirin was associated with an increased risk of major bleeding, major GI bleeding, and intracranial bleeding compared to placebo. The increased risk with low-dose aspirin was 1.7 to 2.1-fold; however, the absolute increased risk was only a 0.13 percent per year. A dose-related effect was not observed when dividing the aspirin

doses into two groups of 75 to 162.5 mg daily doses versus 162.5 to 325 mg daily doses in the analysis, which conflicts with other available data. Of the studies included, clopidogrel was not compared to placebo. One study included in the analysis had increased major GI bleeding with aspirin 325 mg compared to clopidogrel (RR=1.45; 95% CI, 1-2.1) with an absolute increase in risk of 0.12 percent per year associated with aspirin use (95% CI, 0-0.28).

## **SPECIAL POPULATIONS**<sup>170,171,172,173,174,175,176</sup>

### **Pediatrics**

Safety and effectiveness have not been established for clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta), ticlopidine, vorapaxar (Zontivity), or aspirin/dipyridamole ER (Aggrenox) in pediatric patients. Safety and effectiveness of dipyridamole in patients below the age of 12 years have not been established. The use of aspirin in children should be avoided due to the risk of Reye's syndrome with aspirin usage in certain viral illnesses.

The 2012 ACCP evidence-based clinical guidelines state that aspirin remains the most common antiplatelet agent used in pediatrics.<sup>177</sup> The dose of aspirin for optimal inhibition of platelet aggregation is not known, although empiric low doses of 1 to 5 mg/kg/day have been suggested (Grade 2C). Dipyridamole has also been used in pediatrics, as a second-line antiplatelet agent or in combination with aspirin therapy. Dipyridamole doses of 2 to 5 mg/kg per day are used. Little in the literature is available on the use of dipyridamole in pediatrics.

### **Pregnancy**

Clopidogrel (Plavix), prasugrel (Effient), ticlopidine, and vorapaxar (Zontivity) are Pregnancy Category B. Ticagrelor (Brilinta) is Pregnancy Category C. Aspirin should not be used within one week preceding or during labor and delivery, as the risk of hemorrhage is increased.

Aspirin/dipyridamole ER (Aggrenox) is classified as Pregnancy Category D. Due to the risk of low birth weight, increased incidence for intracranial hemorrhage in premature infants, stillbirths, and neonatal death, aspirin/dipyridamole ER (Aggrenox) should be avoided in the third trimester of pregnancy.

### **Renal Impairment**

Aspirin should be avoided in severe renal failure. No dosage adjustment is recommended for clopidogrel, dipyridamole, prasugrel, ticagrelor, or vorapaxar (Zontivity) in renal impairment. Dose reduction or discontinuation of ticlopidine (if hemorrhagic or hematopoietic problems are encountered) may be required in renal impairment.

### **Hepatic Impairment**

Aspirin should be avoided in severe hepatic insufficiency. No dosage adjustment is needed for clopidogrel in hepatic impairment. Elevations of hepatic enzymes and hepatic failure have been reported with dipyridamole. No dosage adjustment is needed for mild to moderate hepatic impairment with prasugrel. While prasugrel has not been studied in severe hepatic impairment, these patients are generally at higher risk of bleeding. Since ticlopidine is metabolized by the liver, dose adjustment may be needed for ticlopidine or other drugs metabolized in the liver and may require adjustment upon starting or stopping concomitant therapy. Because of limited experience in patients with severe hepatic disease who may have bleeding diatheses, the use of ticlopidine is not recommended in this

population. Impaired hepatic function can increase risk of adverse events, such as bleeding for ticagrelor. Ticagrelor is contraindicated in patients with severe hepatic impairment and should be considered carefully in patients with moderate impairment. No dosage adjustment of ticagrelor is needed in patients with mild hepatic impairment. Based on the increased inherent risk of bleeding in patients with severe hepatic impairment, vorapaxar is not recommended in such patients.

## Geriatrics

No dosage adjustment is recommended for elderly patients taking clopidogrel, dipyridamole, or vorapaxar. The risk of bleeding with use of prasugrel increases with advancing age. According to the manufacturer's label, for patients 75 years of age and older, the use of prasugrel is not recommended except in high-risk situations, such as the presence of diabetes or past history of MI. However, ACCP states in their 2012 guidelines that evidence suggests that prasugrel results in no net benefit or even harmed patients with age greater than 75 years.<sup>178</sup>

No overall differences in safety or effectiveness of ticagrelor have been observed between patients 65 years of age and older and younger patients; however, greater sensitivity of some older individuals cannot be ruled out. Relative risk of bleeding was similar in patients 65 years of age and older and those at least 75 years of age. Efficacy and overall safety of ticagrelor in high-risk patients including elderly patients ( $\geq 75$  years old) with ACS and those with prior history of stroke or TIA were consistent with the overall PLATO trial.<sup>179,180</sup>

Clearance of ticlopidine decreases with age. Steady state trough values in elderly patients (mean age 70 years) are about twice those in younger volunteer populations. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

## DOSAGES

Drug	Dose	Availability
aspirin 25 mg/ dipyridamole ER 200 mg (Aggrenox) <sup>181</sup>	one capsule twice daily  Alternative regimen for patients with intolerable headaches: during initial treatment, switch to one capsule at bedtime and low-dose aspirin in the morning. Because there are no outcomes data with this regimen and headaches become less of a problem as treatment continues, patients should return to the usual regimen (one capsule twice daily) as soon as possible, usually within one week.	25 mg/200 mg capsule  Aggrenox is not interchangeable with the individual components of aspirin and dipyridamole tablets.
clopidogrel (Plavix) <sup>182</sup>	75 mg daily  acute coronary syndrome: NSTEMI: 300 mg for one dose then 75 mg daily plus aspirin 75 to 325 mg daily STEMI: 75 mg daily in combination with aspirin	75, 300 mg tablets

**Dosages (continued)**

Drug	Dose	Availability
dipyridamole (Persantine) <sup>183</sup>	75-100 mg four times daily with concurrent coumarin anticoagulants	25, 50, and 75 mg tablets
prasugrel (Effient) <sup>184</sup>	60 mg for one dose then 10 mg daily plus aspirin 75 to 325 mg daily	5, 10 mg tablets
ticagrelor (Brilinta) <sup>185</sup>	Ticagrelor 180 mg for first dose, then 90 mg twice daily thereafter After initial aspirin loading dose (usually 325 mg), use ticagrelor with a daily maintenance dose of aspirin of 75-100 mg	90 mg tablets
ticlopidine <sup>186</sup>	250 mg twice daily	250 mg tablet
vorapaxar (Zontivity) <sup>187</sup>	2.08 mg daily	2.08 mg tablet

Pretreatment with clopidogrel (Plavix) therapy can reduce the risks associated with PCI. A loading dose of 600 mg instead of 300 mg has been studied in an effort to determine if this higher loading dose would shorten the time for clopidogrel to become effective and produce a greater antiplatelet effect, without an apparent adverse effect on safety.<sup>188,189,190,191,192,193,194,195</sup> Current recommendations exist for a loading dose up to 600 mg of clopidogrel in ACS patients undergoing PCI.<sup>196,197</sup>

The CURRENT-OASIS 7 investigated doubling the loading dose (from 300 mg to 600 mg) and the initial maintenance dose (from 75 mg to 150 mg) of clopidogrel for one week followed by 75 mg daily thereafter, with high (300 to 325 mg) or low dose (75 to 100 mg) aspirin daily in patients (n=25,086) with ST or non-ST-segment-elevation ACS managed with an early invasive strategy.<sup>198,199,200</sup> There was no significant difference between high dose and standard dose clopidogrel (4.2 versus 4.4 percent; HR 0.94; 95% CI, 0.83 to 1.06; p=0.30) for the primary outcome of CV death, MI, or stroke at 30 days. However, high-dose clopidogrel was associated with a significant reduction in the secondary outcome of stent thrombosis among patients who underwent PCI (n=17,263; 1.6 versus 2.3 percent; HR 0.68; 95% CI, 0.55 to 0.85; p=0.001). The primary safety endpoint of major bleeding was significantly greater for the high-dose group compared to the standard regimen (2.5 versus 2 percent; HR 1.24; 95% CI, 1.05 to 1.46; p=0.01). There was no significant difference between higher-dose and lower-dose aspirin with respect to the primary outcome (4.2 versus 4.4 percent; HR 0.97; 95% CI, 0.86 to 1.09; p=0.61) or major bleeding (2.3 versus 2.3 percent; HR 0.99; 95% CI, 0.84 to 1.17; p=0.9).

Use of ticagrelor with aspirin maintenance doses above 100 mg reduced the effectiveness of ticagrelor.

There is no experience with use of vorapaxar (Zontivity) alone as the only administered antiplatelet agent. Vorapaxar has been studied only as an addition to aspirin and/or clopidogrel and should only be used with aspirin and/or clopidogrel according to their indications or standard of care.<sup>201</sup>

## CLINICAL TRIALS

### Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled trials comparing agents in ambulatory patients who are at high risk or have documented vascular disease due to thrombotic episodes are considered the most relevant in this category. Studies included also reflect the FDA-approved indications. Comparative trials are the most important, but when comparative trials are not available, placebo-controlled trials were considered relevant. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

### aspirin

Aspirin has been extensively studied and found to prevent vascular events, both fatal and non-fatal, by 15 to 30 percent in many trials.<sup>202</sup> The Physicians' Health Study with 22,071 men (age >50 years without CAD) provided the first strong support for aspirin 325 mg daily in reducing the risk of a first MI; however, the relative risk reductions for stroke and mortality due to CV causes were less clear.<sup>203</sup> Further study confirmed aspirin use also reduced mortality in patients at higher risk for CVD.<sup>204,205</sup>

The Women's Health Study was a large randomized, double-blind, placebo-controlled trial of aspirin 100 mg daily in the primary prevention of CVD among 39,876 healthy women, with a majority of women less than age 65 years.<sup>206</sup> Patients were followed for a mean of 10 years for the major CV events of MI, stroke, and death from CV causes. The risk of major CV events was slightly lower with aspirin; however, the risk reduction was not statistically significant (nine percent relative risk reduction, 0.91; 95% CI, 0.8 to 1.03; p=0.13). Aspirin reduced the relative risk of stroke by 17 percent (relative risk, 0.83; 9% CI, 0.69 to 0.99; p=0.04) but not of MI.

The findings from the large preventive trials—Physician's Health Study in men and Women's Health Study—differ. Aspirin doses and rate of MI are examples of the many differences between the two studies. Aspirin therapy was associated with a 32 percent reduction in MI but no significant effect on stroke in men.<sup>207</sup>

### aspirin/dipyridamole ER (Aggrenox)

The second European Stroke Prevention Study (ESPS-2) evaluated the effectiveness of dipyridamole ER plus low-dose aspirin in the secondary prevention of stroke versus monotherapy for two years.<sup>208</sup> The double-blind study randomized 6,602 patients who had experienced a TIA or ischemic stroke within the previous three months to placebo, aspirin 25 mg twice daily, dipyridamole ER 200 mg twice daily, or the combination of aspirin 25 mg plus dipyridamole ER 200 mg twice daily. The primary endpoints

were stroke, death, or the combination. The aspirin/dipyridamole ER group showed a relative risk reduction for stroke of 37 percent versus placebo ( $p < 0.001$ ), 18 percent with ASA alone ( $p = 0.013$ ), and 16 percent with dipyridamole alone ( $p = 0.039$ ). The combination therapy had an absolute risk reduction of fatal and nonfatal stroke of three percent versus aspirin and dipyridamole monotherapy groups. Mortality rate was not significantly affected by any treatment. Beneficial effects of antiplatelet therapy were evident regardless of age.<sup>209</sup> Aspirin was associated with significantly more overall and gastrointestinal bleeding compared to dipyridamole or placebo.

In a randomized, placebo-controlled study of 149 patients from fibrinolytic trials who had a patent infarct-related artery three to four weeks after STEMI, quantitative coronary angiography of non-infarct arteries was performed on paired cine-angiograms at one year.<sup>210</sup> Patients had been randomized to either continue the daily combination of 50 mg aspirin and 400 mg dipyridamole or to placebo. There were no significant differences in these groups in changes in minimal luminal diameter (MLD) (-0.02 mm; 95% CI, -0.09 to 0.05). Progression of CAD was seen in two thirds of patients and did not independently predict long-term death and/or reinfarction.

### **clopidogrel (Plavix) versus aspirin**

In the CAPRIE study, clopidogrel 75 mg daily and aspirin 325 mg daily were compared for relative efficacy in reducing a composite outcome cluster of ischemic stroke, MI, or vascular death in a randomized, blinded trial.<sup>211</sup> A total of 19,185 patients with a documented stroke, MI, or symptomatic peripheral arterial disease were enrolled in the trial and followed for one to three years. Significant findings include an 8.7 percent relative risk reduction of all endpoints (ischemic stroke, MI, or vascular death) with clopidogrel (5.32 percent annual risk) versus aspirin (5.83 percent annual risk) (95% CI, 0.3-16.5;  $p = 0.043$ ). The absolute risk reduction of clopidogrel over aspirin was 0.5 percent for the combined endpoints. Hemorrhagic events were similar between the groups.<sup>212</sup>

### **clopidogrel (Plavix) plus aspirin**

The CURE study evaluated the efficacy and safety of clopidogrel when given with aspirin in 12,562 acute coronary syndrome patients.<sup>213</sup> Patients were randomized within 24 hours of onset of angina symptoms to clopidogrel 300 mg for one dose then 75 mg daily or placebo, in addition to aspirin (75 to 325 mg daily), for three to 12 months. The composite primary endpoint was CV death, nonfatal MI, or stroke, which occurred in 9.3 percent of the clopidogrel group and 11.4 percent in the placebo group (relative risk with clopidogrel as compared with placebo, 0.8; 95% CI, 0.72 to 0.9;  $p < 0.001$ ). Clopidogrel reduced the risk of the second primary endpoint defined as the composite of CV death, nonfatal MI, or stroke or the occurrence of refractory ischemia compared to the placebo group (16.5 percent clopidogrel group compared to 18.8 percent in the placebo group; relative risk, 0.86; 95% CI, 0.79 to 0.94;  $p < 0.001$ ). Rates of the individual outcome endpoints of CV death, stroke, and refractory ischemia showed numerical improvement with clopidogrel but did not achieve statistical significance. Significantly more major bleeding episodes were observed in the clopidogrel group (3.7 percent in the clopidogrel group versus 2.7 percent in the placebo group, relative risk 1.38;  $p = 0.001$ ). Hemorrhagic strokes and life-threatening bleeding episodes were similar in both groups. Higher doses of aspirin with or without clopidogrel were associated with a higher risk of major bleeding.<sup>214</sup> Minor bleeding episodes were significantly higher in the clopidogrel group (5.1 percent versus 2.4 percent in the placebo group,  $p < 0.001$ ). Benefits of the combination of clopidogrel and aspirin are seen at all doses of aspirin; however, bleeding risk increased with higher doses of aspirin.<sup>215</sup>

In an evaluation of the 2,658 patients that underwent percutaneous coronary intervention (PCI) after randomization in the CURE study (PCI-CURE study), clopidogrel and placebo in addition to aspirin were compared for safety and efficacy.<sup>216</sup> Patients received aspirin and the study drug (clopidogrel or placebo) for a median of 10 days prior to PCI. Open-label use of ticlopidine or clopidogrel in addition to aspirin 75 to 325 mg daily was permitted for two to four weeks after stent placement and then the randomly assigned medication resumed for a mean of eight months. The primary endpoint was the composite of CV death, MI, or urgent revascularization within 30 days of the PCI. The rate of composite endpoint in the clopidogrel group was 4.5 percent compared to 6.4 percent in the placebo group within the first 30 days (relative risk 0.7; 95% CI, 0.5–0.97;  $p=0.03$ ). As seen in the CURE study, clopidogrel patients had a lower incidence of CV death and MI or any revascularization compared to placebo ( $p=0.03$ ) and a lower rate of CV death or MI ( $p=0.047$ ). Bleeding rates between the groups did not differ significantly.

The COURAGE trial was a randomized, multi-center, 4.6-year study of 2,287 patients with stable coronary artery disease.<sup>217</sup> Patients underwent PCI plus optimal medical therapy (PCI group) or optimal medical therapy alone. All patients received aspirin 81 to 325 mg per day or clopidogrel 75 mg per day, if patients were intolerant to aspirin. Patients undergoing PCI received both aspirin and clopidogrel. Both groups received beta blockers, statins, ACE inhibitors, as well as made lifestyle modifications of diet, exercise, and smoking cessation. The median follow-up period was 4.6 years. The primary outcome of death from any cause and nonfatal MI occurred in 19 percent of the PCI group versus 18.5 percent of the optimal medical therapy group (hazard ratio 1.05, 95% CI, 0.87 to 1.27,  $p=0.62$ ). More patients in the optimal medical therapy group required revascularization (32.6 percent) versus the PCI group (21.1 percent;  $p<0.001$ ). PCI had the initial advantage of relieving angina; however, 74 percent of the PCI group versus 72 percent of the optimal medical therapy group did not experience angina at five years ( $p=0.35$ ). PCI did not reduce the risk of death, MI, or other major CV events in comparison to optimal medical therapy in patients with stable CAD.

In the CREDO study, 2,116 patients who planned to have angioplasty were randomized to clopidogrel or placebo and followed for one year for the combined event rate of death, MI, or stroke.<sup>218</sup> In the double-blind, placebo-controlled trial, patients randomized to clopidogrel received 300 mg prior to the revascularization or placebo. All patients received aspirin 325 mg daily and clopidogrel 75 mg daily for 28 days following stent placement. On day 29, patients then received clopidogrel or placebo, in addition to aspirin, as randomized prior to revascularization. At one year, 8.5 percent of the clopidogrel group had reached the composite endpoint (death, MI, or stroke at one year) compared to 11.5 percent in the placebo group (26.9 percent relative risk reduction; 95% CI, 3.9–44.4 percent;  $p=0.02$ ). Clopidogrel was not associated with a significant reduction in the combined event rate of death, MI, or urgent target vessel revascularization at 28 days. No significant difference was seen in the individual endpoints (death, MI, or death/MI) or bleeding over the one-year study period. During one year of follow-up, any bleeding (major or minor) occurred in 8.1 and 8.9 percent, major bleeding in 3.9 and 5.6 percent, and minor bleeding in 4.2 and 3.3 percent of placebo and clopidogrel treated patients, respectively.<sup>219</sup> These differences were not significant. Major GI bleeding occurred in significantly more patients on clopidogrel compared to placebo (1.4 versus 0.3 percent,  $p=0.011$ ).

In the MATCH trial, in patients who were already on clopidogrel 75 mg daily, the addition of aspirin 75 mg daily was compared to placebo to see if the combination had a greater benefit in preventing vascular events and to assess the potential for increased bleeding risk over 18 months.<sup>220</sup> The study was a randomized, double-blind, placebo-controlled trial in 7,599 high risk patients having had a recent

ischemic stroke or TIA and at least one additional risk factor who were already receiving clopidogrel therapy. The primary endpoint was a composite of ischemic stroke, MI, vascular death, or rehospitalization for acute ischemic attack (TIA, angina, worsening PAD). The primary endpoint was seen in 15.7 percent of the aspirin/clopidogrel group and 16.7 percent in the clopidogrel alone group (relative risk reduction of 6.4 percent [95% CI, -0.46 to 16.3], absolute risk reduction one percent [-0.6 to 2.71]). Combination therapy with clopidogrel and aspirin did not reduce the risk of major vascular events compared with clopidogrel monotherapy. The combination of aspirin and clopidogrel was associated with a higher rate of life-threatening bleeding episodes (2.6 percent) compared to clopidogrel monotherapy (1.3 percent). Major bleeding episodes were more common with the combination; however, mortality was unaffected.

CLARITY-TIMI-28 study: Clopidogrel was evaluated for safety and efficacy in the treatment of acute MI with ST-segment elevation in addition to standard treatment of fibrinolytics, aspirin, and weight-dosed heparin.<sup>221</sup> Patients were scheduled to undergo angiography 48 to 192 hours after the start of the study medication. Patients between ages 18 and 75 years (n=3,491) who presented within 12 hours of ST-elevation were randomized to clopidogrel 300 mg loading dose then 75 mg daily or placebo. The rates of primary efficacy endpoint of composite of angiography identified occluded infarct-related arteries (TIMI flow grade 0 or 1) or death or recurrent MI before angiography was reported in 21.7 percent of patients in the placebo group and 15 percent of patients in the clopidogrel group (6.7 percent difference; 95% CI, 24 to 47 percent; p<0.001). After 30 days, clopidogrel had a relative risk reduction of 20 percent for the composite of CV death, recurrent MI, or recurrent ischemia requiring revascularization (14.1 percent placebo versus 11.6 percent clopidogrel, p=0.03). Death from CV causes was similar between the groups and extremely low for the ST-segment acute MI population (2.6 and 2.2 percent for clopidogrel and placebo groups, respectively; p=0.49). Incidences of major bleeding (1.3 and 1.1 percent for clopidogrel and placebo groups, respectively) and intracranial hemorrhage were similar in both groups.

The PCI-CLARITY trial evaluated if pre-treatment with clopidogrel in the setting of PCI in patients with recent ST-segment elevation MI would affect the rate of major adverse CV events.<sup>222</sup> Patients (n=1,863) were those who underwent PCI after the required angiography as a part of the CLARITY trial discussed above. In the double-blind, placebo-controlled trial, patients received aspirin and were randomized to receive clopidogrel 300 mg once then 75 mg daily or placebo in addition to the fibrinolytics and weight-based heparin for two to eight days until angiography. In patients undergoing PCI with stenting, open-labeled clopidogrel including the loading dose were administered after the angiography but prior to PCI. The primary outcome was the composite of CV death, MI, or stroke from date of PCI to 30 days after randomization. Pre-treatment with clopidogrel was associated with a significant reduction in the composite outcome (3.6 versus 6.2 percent, adjusted OR, 0.54; 95% CI, 0.35–0.85; p=0.008). From randomization to 30 days, the clopidogrel group had a significant reduction in CV death, MI, or stroke (7.5 versus 12 percent; adjusted OR 0.59; [95% CI, 0.43–0.81]; p=0.001). Bleeding was not significantly different between the groups. Authors concluded that aspirin plus clopidogrel in addition to fibrinolytics and heparin reduce the composite outcome and should be administered prior to and after PCI.

In the CHARISMA trial, clopidogrel and aspirin were compared to aspirin alone in the prevention of the composite endpoint of MI, stroke, or CV death in a population of patients at high risk for CV diseases.<sup>223</sup> In the prospective, double-blind, randomized trial, a total of 15,603 patients with a history of CVD or multiple risk factors were randomized to clopidogrel 75 mg daily plus aspirin 75 to 162 mg

daily or placebo plus aspirin 75 to 162 mg daily. After a median of 28 months, 6.8 percent of the clopidogrel-aspirin group and 7.3 percent of the placebo-aspirin group reported the primary endpoint (relative risk, 0.93; 95% CI, 0.83 to 1.05;  $p=0.22$ ). The clopidogrel-aspirin group had significantly fewer patients report the secondary efficacy endpoint of the composite of MI, stroke, CV-related death, or hospitalizations due to unstable angina, TIA, or revascularization procedures (clopidogrel-aspirin: 16.7 percent, placebo-aspirin: 17.9 percent; relative risk 0.92 [95% CI, 0.86 to 0.995;  $p=0.04$ ]). A subgroup analysis found that patients with only risk factors (approximately 20 percent of total population) had a higher risk of death from all causes (5.4 versus 3.8 percent,  $p=0.04$ ) and CV death (3.9 versus 2.2 percent,  $p=0.01$ ) with both drugs than with aspirin alone. Those with established CVD (nearly 80 percent of total population) had a lower risk in the primary endpoint with clopidogrel (6.9 versus 7.9 percent with placebo; RR=0.88; 95% CI, 0.77 to 0.998;  $p=0.046$ ). The rate of severe bleeding was similar in both treatment groups with 1.7 percent and 1.3 percent for clopidogrel-aspirin and placebo-aspirin groups, respectively (relative risk, 1.25; 95% CI, 0.97 to 1.61 percent;  $p=0.09$ ). Moderate bleeding occurred more often in patients on the combination therapy (2.1 versus 1.3 percent; relative risk 1.62 (95% CI, 1.27 to 2.1;  $p<0.001$ ). The rate of intracranial hemorrhage was similar in the two treatment groups. Treatment discontinuation was reported in 20.4 and 18.2 percent of the clopidogrel-aspirin versus placebo-aspirin groups, respectively ( $p<0.001$ ).

The COMMIT trial was a randomized, double-blinded trial in which the combination of clopidogrel and aspirin was compared to aspirin alone in 45,852 patients with suspected acute MI in 1,250 sites in China.<sup>224</sup> Patients were randomized within 24 hours of suspected acute MI to clopidogrel 75 mg daily or placebo in addition to aspirin 162 mg daily until discharge or up to four weeks in the hospital. ST-segment elevation or bundle branch block was noted in 93 percent of patients, and ST-segment depression was noted in the remaining seven percent. Fibrinolysis was administered in half of the patients. Metoprolol use was also being evaluated in the same population. The two primary endpoints were 1) the composite of death, reinfarction, or stroke and 2) death from any cause. Clopidogrel-aspirin combination significantly reduced the risk of the composite of death, reinfarction, or stroke compared to aspirin alone [clopidogrel: 9.2 percent, ( $n=2,125$ ) versus aspirin alone: 10.1 percent, ( $n=2,311$ );  $p=0.002$ ]. All-cause mortality by hospital discharge was significantly lower in the clopidogrel group (7.5 versus 8.1 percent,  $p=0.03$ ). Any type of major bleed (fatal, transfused, and cerebral bleeds) occurred in 0.58 and 0.55 percent of the clopidogrel-aspirin and placebo-aspirin groups, respectively ( $p=NS$ ).

The Randomized Argentine Clopidogrel Stent (RACS) trial was a prospective, randomized, non-blinded study of 1,004 patients undergoing PCI who were randomized after successful bare metal stent placement to 30 versus 180 days of clopidogrel.<sup>225</sup> All patients also received aspirin. The primary endpoint was a composite of death, MI, and stroke at 180 days. At hospital discharge and 30 days (when both arms received the same treatment), there were no significant differences in frequency of death, MI, or stroke. In comparison from 30 days to 180 days, the patients in the 180 days of clopidogrel reached the primary endpoint (death, MI, and stroke) less frequently (4.99 versus 1.74 percent, 65 percent relative risk reduction,  $p=0.010$ ). No significant differences in frequency of total bleeding were reported.

Data from consecutive acute STEMI survivors and either concomitant therapy with aspirin or aspirin plus clopidogrel at discharge, who were prospectively enrolled in the Acute Coronary Syndromes (ACOS) registry, were analyzed.<sup>226</sup> The 5,886 patients were divided into three groups based on the initial reperfusion therapy (no reperfusion therapy  $n=1,445$ ; fibrinolysis  $n=1,734$ ; or primary PCI

n=2,707). Mortality was significantly lower in the clopidogrel plus aspirin group versus the aspirin group in the total group, as well as the reperfusion therapy [total group odds ratio (OR) 0.48, 95% CI, 0.48 to 0.61; no reperfusion therapy OR 0.96, 95% CI, 0.65 to 1.45; fibrinolysis OR 0.53, 95% CI, 0.32 to 0.87; primary PCI OR 0.38, 95% CI, 0.23 to 0.62].

### **clopidogrel (Plavix) versus ticlopidine in coronary stenting**

Clopidogrel and ticlopidine have been shown to reduce major adverse cardiac events at 30 days following successful coronary stent implantation.<sup>227,228,229,230,231,232</sup> Differences in the studies include patient populations, dose regimens, timing of initial therapy, duration of therapy, outcome parameters, and follow-up study period. Many of the studies are small and located in single centers. While both drugs have been shown to provide a reduction in major adverse cardiac events following successful coronary stent implantation, it is difficult to determine if one agent is superior as many studies are not powered to detect possible differences in efficacy.<sup>233,234,235</sup> In earlier studies, antiplatelet therapy with clopidogrel or ticlopidine with or without aspirin was given after PCI or stent placement whereas currently, clopidogrel and aspirin are given prior to PCI in much higher loading doses than previously studied.<sup>236,237,238,239,240</sup>

### **clopidogrel (Plavix) versus aspirin/dipyridamole ER (Aggrenox)**

The PRoFESS study was a randomized, double-blind, 2-by-2 factorial design, multicenter secondary stroke prevention trial.<sup>241</sup> A total of 20,332 patients, who had a noncardioembolic ischemic stroke within the previous 120 days, were randomized to aspirin 25 mg/dipyridamole ER 200 mg twice daily or to clopidogrel 75 mg daily and followed for a mean of 2.5 years. The comparison for the primary outcome of recurrent stroke did not meet the pre-defined criterion for non-inferiority (margin of 1.075 or a 75 percent noninferiority difference), and the number of recurrent strokes was similar between groups: recurrent stroke occurred in 9 percent and 8.8 percent of patients receiving aspirin/dipyridamole ER and clopidogrel, respectively, (HR, 1.01; 95% CI, 0.92 to 1.11). The secondary outcome of composite stroke, MI, or vascular death was identical between groups: 13.1 percent in each group (HR for aspirin/dipyridamole ER, 0.99; 95% CI, 0.92 to 1.07). More major hemorrhagic events were reported in the aspirin/dipyridamole ER group compared to clopidogrel, 4.1 percent versus 3.6 percent, respectively (HR, 1.15; 95% CI, 1 to 1.32), including intracranial hemorrhage (HR, 1.42; 95% CI, 1.11 to 1.83). Despite the increase in hemorrhage, the net risk of recurrent stroke or major hemorrhagic events was similar in the both groups: aspirin/dipyridamole ER 11.7 percent compared with clopidogrel 11.4 percent (HR, 1.03; 95% CI, 0.95 to 1.11).

### **dipyridamole (Persantine)**

Very little new clinical data are available for dipyridamole monotherapy. Older data with dipyridamole provides evidence that in patients with prosthetic heart valves, the addition of dipyridamole to warfarin therapy reduces the incidence of systemic emboli.<sup>242</sup> It should be noted that the extended-release dipyridamole formulation, not immediate-release dipyridamole, was used in the ESPS-2 and ESPIRIT trials.<sup>243,244</sup>

### **prasugrel (Effient) versus clopidogrel (Plavix)**

TRITON-TIMI 38: To compare prasugrel with clopidogrel, 13,608 patients with moderate to high risk acute ACS with scheduled PCI were randomized to receive prasugrel (60 mg loading dose, then 10 mg daily) or clopidogrel (300 mg loading dose, then 75 mg daily) for six to 15 months.<sup>245</sup> The primary

efficacy endpoint was death from CV causes, nonfatal MI, or nonfatal stroke. The key safety endpoint was major bleeding. The primary endpoint occurred in 12.1 percent of patients receiving clopidogrel and 9.9 percent of patients receiving prasugrel [hazard ratio (HR) versus clopidogrel, 0.81; 95% CI, 0.73 to 0.9;  $p < 0.001$ ]. There were also significant reductions in the prasugrel group in the rates of MI (9.7 versus 7.4 percent;  $p < 0.001$ ), urgent target-vessel revascularization (3.7 versus 2.5 percent;  $p < 0.001$ ), and stent thrombosis (2.4 versus 1.1 percent;  $p < 0.001$ ). Prasugrel patients experienced more major bleeding than those on clopidogrel (2.4 versus 1.8 percent; HR, 1.32; 95% CI, 1.03 to 1.68;  $p = 0.03$ ). Life-threatening bleeding (1.4 versus 0.9 percent;  $p = 0.01$ ), including nonfatal bleeding (1.1 versus 0.9 percent;  $p = 0.23$ ) and fatal bleeding (0.4 versus 0.1 percent;  $p = 0.002$ ), was also higher with prasugrel. The rate of study drug discontinuation because of adverse reactions was 7.2 percent for prasugrel and 6.3 percent for clopidogrel. Bleeding was the most common adverse reaction leading to study drug discontinuation for both drugs (2.5 percent for prasugrel and 1.4 percent for clopidogrel).

In patients undergoing PCI for STEMI, TIMI life-threatening bleeding and TIMI major or minor bleeding were similar with the two treatments. Only TIMI major bleeding after CABG surgery was significantly increased with prasugrel versus clopidogrel, 18.8 percent versus 2.7 percent, respectively ( $p = 0.0033$ ).<sup>246</sup> A post-hoc analysis of TRITON-TIMI 38 evaluated the efficacy and safety of prasugrel and clopidogrel in the setting of a glycoprotein (GP) IIb/IIIa inhibitor at 30 days.<sup>247</sup> A total of 54.5 percent received a GP IIb/IIIa inhibitor. There was a consistent benefit of prasugrel over clopidogrel for reducing CV death, MI, or stroke in patients who did (HR, 0.76; 95% CI, 0.64 to 0.90) or did not receive a GP IIb/IIIa inhibitor (HR, 0.78; 95% CI, 0.63 to 0.97,  $p = 0.83$ ). Although subjects treated with a GP IIb/IIIa inhibitor had greater rates of bleeding, the risk of major or minor bleeding with prasugrel versus clopidogrel was not significantly different in patients who were or were not treated with GP IIb/IIIa inhibitor ( $p = 0.19$ ).

A pre-specified analysis, compared prasugrel with clopidogrel in patients with diabetes mellitus (DM) in TRITON-TIMI 38.<sup>248</sup> A total of 3,146 subjects had a preexisting history of DM including 776 receiving insulin. The primary endpoint was reduced significantly with prasugrel among subjects without DM (9.2 percent versus 10.6 percent; hazard ratio [HR], 0.86;  $p = 0.02$ ) and with DM (12.2 percent versus 17 percent; HR, 0.7;  $p < 0.001$ ). A benefit for prasugrel was observed among DM patients on insulin (14.3 percent versus 22.2 percent; HR, 0.63;  $p = 0.009$ ) and those not on insulin (11.5 percent versus 15.3 percent; HR, 0.74;  $p = 0.009$ ). MI was reduced with prasugrel by 18 percent among subjects without DM (7.2 percent versus 8.7 percent; HR, 0.82;  $p = 0.006$ ) and by 40 percent among subjects with DM (8.2 percent versus 13.2 percent; HR, 0.6;  $p < 0.001$ ). The TIMI major hemorrhage was increased among subjects without DM on prasugrel (1.6 percent versus 2.4 percent; HR, 1.43;  $p = 0.02$ ), but the rates were similar among subjects with DM for clopidogrel and prasugrel (2.6 percent versus 2.5 percent; HR, 1.06;  $p = 0.81$ ). Net clinical benefit (death, nonfatal myocardial infarction, nonfatal stroke, and nonfatal TIMI major bleeding) with prasugrel was greater for DM patients (14.6 percent versus 19.2 percent; HR, 0.74;  $p = 0.001$ ) than for patients without DM (11.5 percent versus 12.3 percent; HR, 0.92;  $p = 0.16$ ).

TRILOGY ACS: In a randomized, double-blind trial, patients with UA/NSTEMI and receiving aspirin, who did not undergo revascularization, were evaluated for up to 30 months of treatment with prasugrel versus clopidogrel 75 mg.<sup>249</sup> Patients randomized to prasugrel who were under 75 years of age received 10 mg daily ( $n = 7,243$ ), while those 75 years of age and older received 5 mg daily ( $n = 2,083$ ). Median exposure to study drug was 14.8 months. Primary endpoint was death from CV causes, MI, or stroke. At a median follow-up of 17 months, the primary endpoint occurred in 13.9 of patients

receiving prasugrel and 16 percent receiving clopidogrel (HR 0.91; 95% CI, 0.79 to 1.05;  $p=0.21$ ). Results were similar regardless of age. At 30 months, there was no significant difference between the study groups in occurrence rate of primary endpoint. While there was no difference in the rate of the primary composite endpoint or its separate components between the two study groups in the first year of the study, the investigators found that prasugrel appeared to reduce the risk of events from 12 months onward; hazard ratio for the time period of  $\leq 12$  months versus the time period  $> 12$  months comparing prasugrel with clopidogrel for the primary efficacy endpoint were 0.99 (95% CI, 0.84 to 1.16) versus 0.72 (95% CI, 0.54 to 0.97) ( $p=0.07$  for interaction). There was no significant difference in the rate of severe, major, or life-threatening bleeding between the two study groups.

### **ticagrelor (Brilinta) versus clopidogrel (Plavix)**

The study of Platelet Inhibition and Patient Outcomes (PLATO) was a randomized, double-blind trial that compared ticagrelor and clopidogrel for the prevention of CV events in 18,624 patients admitted to the hospital with an acute coronary syndrome (ACS), unstable angina, and myocardial infarction with or without ST-segment elevation.<sup>250</sup> Patients were randomized to receive ticagrelor 180 mg loading dose, 90 mg twice daily thereafter, or clopidogrel 300 mg loading dose, 75 mg daily thereafter. All patients also received a maintenance dose of aspirin (75–100 mg recommended). The primary endpoint was a composite of death from vascular causes, MI, or stroke. At 12 months, the primary endpoint had occurred in 9.8 percent of patients receiving ticagrelor and 11.7 percent of those receiving clopidogrel (hazard ratio, 0.84; 95% CI, 0.77 to 0.92;  $p<0.001$ ). Secondary endpoints of MI alone occurred in 5.8 percent in the ticagrelor group and 6.9 percent in the clopidogrel group ( $p=0.005$ ); and death from vascular causes occurred in four versus 5.1 percent respectively ( $p=0.001$ ). There was no significant difference in stroke alone between the two groups (1.5 versus 1.3 percent, respectively,  $p=0.22$ ). The rate of death from any cause was also reduced with ticagrelor (4.5 versus 5.9 percent with clopidogrel;  $p<0.001$ ). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6 and 11.2 percent, respectively;  $p=0.43$ ), but ticagrelor was associated with a higher rate of major bleeding not related to CABG (4.5 versus 3.8 percent,  $p=0.03$ ), including more instances of fatal intracranial bleeding and fewer fatal bleeding of other types. In PLATO, use of  $>100$  mg of aspirin decreased the effectiveness of ticagrelor. In the North American (mostly US) PLATO subgroup, ticagrelor was numerically inferior to clopidogrel. Among 11,289 patients with PCI receiving any stent during PLATO, there was a lower risk of definite stent thrombosis for ticagrelor than with clopidogrel. The results were similar for drug-eluting and bare metal stents.

### **ticlopidine**

The Canadian American Ticlopidine Study (CATS) followed patients ( $n=1,072$ ) for a mean of 24 months and reported that ticlopidine 250 mg twice daily reduced the relative risk of stroke, MI, or vascular death by 30 percent (95% CI, 7.5 to 48.3,  $p=0.006$ ) compared with placebo in stroke patients.<sup>251</sup> An intention-to-treat analysis gave a smaller estimate of relative risk reduction for stroke, myocardial infarction, or vascular death (23.3 percent,  $p=0.02$ ). Adverse experiences associated with ticlopidine included neutropenia (severe in about one percent of cases) and skin rash and diarrhea (severe in two percent of cases each); all were reversible.

## ticlopidine versus aspirin

A randomized, double-blind trial enrolling 1,809 Black patients with a recent history of noncardioembolic ischemic stroke compared the efficacy and safety of aspirin and ticlopidine to prevent recurrent strokes, MI, and vascular death.<sup>252</sup> Patients were given either aspirin 650 mg daily or ticlopidine 250 mg twice daily and were followed for two years. The study was stopped early due to the low probability of ticlopidine being superior to aspirin. The primary composite outcome was recurrent stroke, MI, or vascular death that occurred in 14.7 percent of ticlopidine patients and 12.3 percent of aspirin patients (hazard ratio, 1.22; 95% CI, 0.94 to 1.57). Neutropenia was reported in 3.4 percent of ticlopidine patients compared to 2.2 percent of aspirin patients (p=0.12). One possible case of thrombotic thrombocytopenia purpura was reported in the ticlopidine treated group.

## vorapaxar (Zontivity)<sup>253,254</sup>

A multicenter, randomized, double-blind, placebo-controlled study (TRA 2P – TIMI) compared vorapaxar to placebo. There are two important differences between data in the TRA 2P publication and the approved prescribing information. The original cohort included patients with a history of MI ( $\geq$  two weeks but  $\leq$  12 months prior), ischemic stroke, or PAD (history of intermittent claudication and an ankle-brachial index of  $<0.85$ , or amputation or revascularization of the extremities secondary to ischemia). During the trial, after a median of 24 months of follow-up, an increased risk of ICH was observed in patients with a previous stroke; thus, all patients with a previous stroke were discontinued from the study. The prescribing information presents data from both the original cohort and the indicated population (post-MI and PAD). The protocol-defined primary endpoint was the composite of CV death, MI, stroke, or urgent coronary revascularization (UCR) and the major secondary endpoint was the composite of CV death, MI, or stroke. During the trial, prior to data lock or unblinding, the Steering Committee reordered the hierarchy of the efficacy endpoints based on another completed trial's results. The prescribing information considers the primary outcome measure to be the composite of CV death, MI, stroke, or UCR.

Patients who had evidence or a history of atherosclerosis involving the coronary, cerebral, or peripheral vascular systems were randomized to receive daily treatment with vorapaxar (n=13,225) or placebo (n=13,224) in addition to standard of care. Standard-of-care included antiplatelet therapy with aspirin and/or clopidogrel, statins, beta-blockers, and ACE-inhibitors or ARBs. The study's primary endpoint was the composite of CV death, MI, stroke, and UCR. The composite of CV, MI, and stroke was assessed as key secondary endpoint. The qualifying diagnosis was prior-MI in 67.3 percent and 67.2 percent of vorapaxar and placebo patients respectively, ischemic stroke in 18.4 percent and 18.5 percent, respectively of vorapaxar and placebo patients, and PAD in 14.3 percent in both groups. The median follow-up was 2.5 years (up to four years). In the original cohort (including those with a history of stroke), the findings in all randomized patients for the primary efficacy composite endpoint showed a three year Kaplan-Meier (K-M) event rate of 11.2 percent in the vorapaxar group compared to 12.4 percent in the placebo group (hazard ratio [HR]: 0.88; 95% CI, 0.82 to 0.95; p=0.001). The findings for the key secondary efficacy endpoint showed a three year K-M event rate of 9.3 percent in the vorapaxar group compared to 10.5 percent in placebo group (HR 0.87; 95% CI, 0.8 to 0.94; p<0.001). The difference between vorapaxar and placebo in the secondary endpoint of death or MI was significant favoring vorapaxar (p=0.002). The difference between groups in individual components of the composite endpoints was significant for MI (p=0.001) but not for the endpoints of stroke, UCR, or death from any cause. In patients weighing less than 60 kg, vorapaxar did not favorably influence

outcomes. The primary safety endpoint of GUSTO moderate or severe bleeding occurred in 4.2 percent in the vorapaxar group versus 2.5 percent in the placebo group (HR 1.66,  $p < 0.001$ ). Overall, ICH occurred in 102 patients (one percent) in the vorapaxar group versus 53 patients (0.5 percent) in the placebo group (HR 1.94;  $p < 0.001$ ). The difference between groups in fatal bleeding was not significant. Among those in the post-stroke cohort, the rate of ICH in the vorapaxar group was 2.4 percent versus 0.9 percent in the placebo group ( $p < 0.001$ ).

In the pre-defined sub-group analysis of patients with a qualifying diagnosis of MI, the CV death, MI, or stroke composite was reduced from 9.6 percent (K-M 3-year estimate) in the placebo group to 8.3 percent in the vorapaxar group (HR 0.80;  $p < 0.001$ ). The composite of CV death, MI, stroke, or UCR was reduced from 11.8 percent in the placebo group to 10.6 percent in the vorapaxar group (HR 0.83;  $p < 0.001$ ). In this cohort, GUSTO moderate or severe bleeding occurred in 3.4 percent of vorapaxar patients (K-M 3-year estimate) versus 2.1 percent of placebo patients (HR 1.61;  $p < 0.001$ ). The differences in rate of ICH and fatal bleeding were not significant.

In the pre-specified sub-group analysis of patients with a qualifying diagnosis of PAD, neither the CV death, MI, or stroke composite nor the CV death, MI, stroke or UCR composite were significant for vorapaxar versus placebo.<sup>255</sup> However, the secondary endpoint rates of hospitalization for acute limb ischemia occurred in 2.3 percent of vorapaxar patients versus 3.9 percent of placebo patients (HR 0.58;  $p = 0.006$ ). Peripheral revascularization occurred in 18.4 percent versus 22.2 percent of vorapaxar and placebo patients, respectively (HR 0.84;  $p = 0.0017$ ). The reduction was consistent for both urgent and elective revascularization. In this cohort, GUSTO moderate or severe bleeding occurred in 7.4 percent versus 4.5 percent of patients in the vorapaxar and placebo groups, respectively (HR 1.62;  $p = 0.001$ ). When patients with a history of cerebrovascular disease were excluded, the rates of ICH were 0.7 percent for vorapaxar versus 0.4 percent for placebo;  $p = 0.37$ .

## META-ANALYSIS

A meta-analysis of serious vascular events (MI, stroke, or vascular death) and major bleeds in six primary prevention trials and 16 secondary prevention trials compared long-term aspirin versus control.<sup>256</sup> In the primary prevention trials, aspirin allocation yielded a 12 percent proportional reduction in serious vascular events (0.51 percent aspirin versus 0.57 percent control per year,  $p = 0.0001$ ), due mainly to a reduction of about a fifth in non-fatal MI (0.18 percent versus 0.23 percent per year,  $p < 0.0001$ ). The net effect on stroke was not significant (0.2 percent versus 0.21 percent per year,  $p = 0.4$ ). Aspirin increased major GI and extracranial bleeds (0.1 percent versus 0.07 percent per year,  $p < 0.0001$ ). In the secondary prevention trials, aspirin yielded a greater absolute reduction in serious vascular events (6.7 percent versus 8.2 percent per year,  $p < 0.0001$ ), with a non-significant increase in hemorrhagic stroke but reductions of about one fifth in total stroke (2.08 percent versus 2.54 percent per year,  $p = 0.002$ ) and in coronary events (4.3 percent versus 5.3 percent per year,  $p < 0.0001$ ). In both primary and secondary prevention trials, the proportional reductions in the aggregate of all serious vascular events seemed similar for men and women.

Dipyridamole has no clear evidence of substantial benefit on vascular death compared to controls based on a systematic review evaluating the role of dipyridamole for preventing stroke and other vascular events in patients with vascular disease.<sup>257</sup> A total of 29 trials with 23,019 participants were included. Compared to the control group, dipyridamole had no effect on vascular death (relative risk 0.99, 95% CI, 0.87 to 1.12). The dose of dipyridamole did not influence the outcome nor did the type of vascular disease at presentation. For the risk of vascular events, dipyridamole did significantly reduce

the risk only for patients presenting with cerebral ischemia. There was no evidence that dipyridamole monotherapy was more efficacious than aspirin.

The combination of aspirin with dipyridamole ER (Aggrenox) has shown to be beneficial in the Second European Stroke Prevention Study (ESPS-2) in patients with cerebral ischemia.<sup>258</sup> A meta-analysis pooling data from five trials with a total of 11,459 patients with a history of TIA or ischemic stroke found that aspirin/dipyridamole reduced the composite of nonfatal stroke, nonfatal MI, and vascular death as compared with aspirin alone (OR, 0.84; 95% CI, 0.72 to 0.97), dipyridamole alone (OR, 0.76; 95% CI, 0.64 to 0.9), or control (OR, 0.66; 95% CI, 0.57 to 0.75).<sup>259</sup> It should be noted that 57 percent of the data were from the ESPS-2 trial.

A meta-analysis of six randomized trials with 7,648 patients showed a significant reduction in the overall stroke risk ratio with aspirin plus dipyridamole compared with aspirin alone (relative risk 0.77, 95% CI, 0.67 to 0.89) and composite outcome of stroke, MI, or vascular death with relative risk 0.85 (0.76 to 0.94).<sup>260</sup> Studies using immediate-release dipyridamole showed a nonstatistically significant trend in favor of the combination for stroke alone with relative risk 0.83 (0.59 to 1.15) and for the composite outcome with relative risk 0.95 (0.75 to 1.19). Studies using predominantly extended-release dipyridamole showed a statistically significant difference in favor of the combination for stroke alone with relative risk 0.76 (0.65 to 0.89) and for the composite outcome with relative risk 0.82 (0.73 to 0.92). Approximately 80 percent of the patients in this meta-analysis were from the ESPS-2 and ESPIRIT trials.

A meta-analysis of three randomized trials, PCI-CURE, CREDO, and PCI-CLARITY, was performed to evaluate the efficacy and safety of clopidogrel (Plavix) pre-treatment before PCI intervention with and without glycoprotein IIb/IIIa inhibitor (GPI) use.<sup>261</sup> A total of 6,325 patients were included; 32.4 percent of them received a GPI. There was a consistent benefit of clopidogrel pretreatment in reducing the incidence of CV death, MI, or stroke after PCI both in patients who did not receive a GPI (OR 0.72, 95% CI, 0.53 to 0.98,  $p=0.03$ ) and in those who did (OR 0.69, 95% CI, 0.47 to 1,  $p=0.05$ ). Clopidogrel pretreatment was not associated with a significant increase in bleeding.

## SUMMARY

Platelet aggregation inhibitors are used to prevent and treat a variety of thrombotic events including MI, stroke and TIA, and peripheral arterial disease. Various guidelines have specific recommendations for platelet aggregation inhibitor use. Current guidelines from ACCP and ACC/AHA include prasugrel and ticagrelor as options for dual therapy with aspirin for the treatment of patients with UA/NSTEMI/NSTE-ACS. Prasugrel and ticagrelor were also added to the ACC/AHA 2013 guidelines for STEMI

Serious hematologic adverse effects limit the utility of ticlopidine.

Clopidogrel has been established for use in the management of a variety of CV and cerebrovascular conditions associated with thrombotic events. The effectiveness of clopidogrel is dependent on its conversion to its active metabolite, largely by CYP2C19. However, recent evidence indicates that 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. Also, concomitant use of PPIs (particularly PPIs extensively inhibited by CYP2C19) with clopidogrel may increase CV events. The FDA

has updated the clopidogrel label to avoid concomitant use of clopidogrel with omeprazole or esomeprazole.

Prasugrel (Effient) is approved to reduce CV events in ACS patients undergoing PCI, and it is reported to be more effective than clopidogrel in preventing MI and stent thrombosis in this population. However, these gains are tempered by a significant increase in bleeding events. Prasugrel is not significantly affected by genetic variations that effect CYP enzymes, therefore is not expected to be affected by pharmacogenomics. PPIs are not expected to interact with prasugrel.

Ticagrelor (Brilinta) differs from the thienopyridines (clopidogrel and prasugrel) as it binds reversibly instead of irreversibly with P2Y<sub>12</sub> platelet receptor, and it has a more rapid onset of action than clopidogrel. Both ticagrelor and prasugrel result in more intense platelet inhibition compared to clopidogrel. Ticagrelor is not affected by CYP2C19 genotype; hence it is not expected to be affected by pharmacogenomics or to interact with PPIs.

Ticagrelor (Brilinta) is indicated for the reduction of thrombotic CV events in patients with acute coronary syndrome (ACS) (unstable angina, NSTEMI, or STEMI). Ticagrelor has shown to significantly reduce the rate of death from CV causes, MI, or stroke compared with clopidogrel. However, this benefit did not show in a subgroup analysis of patients enrolled in North America. Although ticagrelor does not increase the risk of major bleeding overall, it does increase major non-CABG bleeding. The daily maintenance doses of aspirin should not exceed 100 mg daily, when given with ticagrelor, since daily aspirin doses above 100 mg will decrease ticagrelor effectiveness.

Vorapaxar (Zontivity), the first protease-activated receptor-1 (PAR-1) antagonist, is an option to reduce thrombotic cardiovascular events as add-on therapy to standard-of-care treatment (aspirin and/or clopidogrel) to further reduce the risk of CV death, MI, stroke, and UCR in patients with a prior MI or with PAD. Although the place in therapy for vorapaxar has not yet been clearly established or addressed in the guidelines, the demonstrated benefit appears to be strongest in the stable post-MI population without risk factors for bleeding. Caution should be used when choosing vorapaxar therapy due to an increase in moderate and severe bleeding in the pivotal clinical trial.

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