Therapeutic Class Overview
Platelet Inhibitors

Therapeutic Class

- **Overview/Summary:** Platelet inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. The agents in the class are Food and Drug Administration (FDA)-approved for a variety of indications including treatment and/or prevention of acute coronary syndromes, stroke/transient ischemic attack, and thrombocythemia. The platelet inhibitors are also indicated to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery. The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action.[1-7] The newest platelet inhibitor to be FDA-approved is ticagrelor (Brilinta®), specifically to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndromes.[7] Ticagrelor is a cyclopentyltriazolopyrimidine; therefore, works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel and ticlopidine). However, unlike the other agents, ticagrelor is a reversible inhibitor of the $P2Y_{12}$ receptor located on the surface of platelets. In addition, ticagrelor is not a prodrug; therefore, does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[7,8] Ticagrelor is available for twice-daily dosing, while clopidogrel and prasugrel are administered once-daily.[2,4,7] Currently, anagrelide, clopidogrel, dipyridamole and ticlopidine are available generically.

Table 1. Current Medications Available in Therapeutic Class[1-7]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
Single-Entity Agents			
Anagrelide (Agrylin®*)	Treatment of thrombocytopenia associated with myeloproliferative disorders†	Capsule: 0.5 mg 1 mg	✔
Clopidogrel (Plavix®*)	Recent myocardial infarction, recent stroke, or established peripheral arterial disease, reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome‡	Tablet: 75 mg 300 mg	✔
Dipyridamole (Persantine®*)	Prevention of postoperative thromboembolic complications of cardiac valve replacement§	Tablet: 25 mg 50 mg 75 mg	✔
Prasugrel (Effient®)	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention‖	Tablet: 5 mg 10 mg	-
Ticagrelor (Brilinta®)	Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome¶	Tablet: 90 mg	-
Ticlopidine (Ticlid®*)	Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation#, reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke	Tablet: 250 mg	✔
Combination-Products			
Aspirin/ extended-release dipyridamole	Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	Capsule: 25/200 mg	-

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/ Strength	Generic Availability
(Aggrenox®)			

*Generic available in at least one dosage form or strength.
†To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events.
‡For patients with non-ST-segment elevation acute coronary syndrome, including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction.
§As adjunct to coumarin anticoagulants.
‖Patients who are to be managed with percutaneous coronary intervention as follows: patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed percutaneous intervention.
¶Patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction.
#As adjunct to aspirin.

Evidence-based Medicine

- Clopidogrel, Food and Drug Administration-approved in 1997, has been the principle platelet inhibitor for several years as the clinical data supporting its use is well established.[10-15]
- Approval of prasugrel for use in acute coronary syndromes (ACS) was based on the clinical evidence for safety and efficacy derived from the TRITON-TIMI 38 study (N=13,608). Within the study, prasugrel was significantly more effective compared to clopidogrel in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention. Prasugrel did not demonstrate a mortality benefit and a significantly higher rate of major, minor, life-threatening, and fatal bleeding events was observed with prasugrel.[16]
    - Of note, a benefit with prasugrel was not observed in certain patient subgroups within TRITON-TIMI 38, specifically those who were ≥75 years of age, those weighing <60 kg, and those with a past history of stroke or transient ischemic attack.
- The approval of ticagrelor for use in ACS was based on the clinical evidence for safety and efficacy derived from the PLATO study. Within the trial, hospitalized patients with documented ACS, with or without ST-elevation, were randomized to either ticagrelor or clopidogrel (N=18,624). After 12 months of treatment, ticagrelor was significantly more effective compared to clopidogrel in reducing the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke; without increasing the risk of major bleeding. Ticagrelor demonstrated a mortality benefit compared to clopidogrel.[17]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - Use of the platelet inhibitors, as monotherapy or combination therapy, is based on the specific clinical indication and the patient's risk for thromboembolic events.[18-28]
    - Antiplatelet therapy (aspirin, aspirin plus extended-release [ER] dipyridamole, or clopidogrel) is recommended for long-term secondary prevention in patients with an acute ischemic stroke who are not receiving thrombolysis. Combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. Dual antiplatelet therapy should be used with caution and is favored in patients who have had a recent acute myocardial infarction, other acute coronary syndrome (ACS), or recently placed coronary stent.[18,19]
    - According to the 2012 guideline on Antithrombotic Therapy and Prevention of Thrombosis by the American College of Chest Physicians, dual therapy with clopidogrel, prasugrel or ticagrelor in addition to low-dose aspirin is recommended in the first year following ACS in patients regardless of percutaneous coronary intervention (PCI) status.[20]
    - Furthermore, the guideline recommends ticagrelor plus low-dose aspirin over clopidogrel plus low-dose aspirin in patients post-ACS independent of whether PCI has been conducted.[20]
    - The 2011 European Society of Cardiology guideline for the management of ACS in patients presenting without persisting ST-elevation recommends ticagrelor first-line in patients at moderate to high risk of ischemic events, regardless of treatment strategy and including those pretreated with clopidogrel.[21]
        - If coronary anatomy is known and PCI is planned, prasugrel is recommended.

        - Clopidogrel is recommended in patients who cannot receive prasugrel or ticagrelor.
    - The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for percutaneous intervention recommends clopidogrel, prasugrel, and ticagrelor as treatment options.[22]
        - Treatment with all agents should be continued for at least one year.
- Other Key Facts:
    - Anagrelide, dipyridamole, and ticlopidine are available generically.

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Therapeutic Class Review
Platelet Inhibitors

Overview/Summary

Platelet inhibitors play a major role in the management of cardiovascular, cerebrovascular, and peripheral vascular diseases. These agents are indicated for a variety of Food and Drug Administration (FDA)-approved indications including treatment and/or prevention of acute coronary syndromes (myocardial infarction, unstable angina), stroke/transient ischemic attack, and thrombocythemia. The platelet inhibitors are also approved to prevent thrombosis in patients undergoing cardiovascular procedures and/or surgery.[1-7] The use of these agents as both monotherapy or combination therapy by national and international clinical guidelines is based on the specific clinical indication and the patient's risk for thromboembolic events.[8-19]

The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action. Aspirin, a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A_2, a platelet aggregant and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that aspirin reduces adverse clinical events among a broad group of patients treated for both acute and chronic vascular disease.[20] Of the available platelet inhibitors, aspirin is the only one that has been evaluated for the treatment of an acute ischemic attack; however, antiplatelet therapy plays an important role in long-term secondary prevention of ischemic stroke.[21]

Clopidogrel (Plavix®) and ticlopidine are both thienopyridines, which work by blocking the adenosine diphosphate receptors found on platelets, leading to a subsequent inhibition of both platelet aggregation and activation.[2,5] Both clopidogrel and ticlopidine are available generically. Clopidogrel is associated with a more favorable safety profile compared to ticlopidine, and is available for once-daily administration as opposed to twice-daily administration as required with ticlopidine. The platelet inhibition effects of the thienopyridines are delayed; therefore, a loading dose is typically required with these agents. As mentioned previously, these agents have been shown to be effective for the prevention of stroke and other vascular events in patients with cerebrovascular disease. In addition, the benefit of thienopyridines as monotherapy or in combination with aspirin in the treatment of coronary artery disease is well established.[20,21]

The mechanism of action of dipyridamole (Persantine®) is not completely understood; however, it may involve its ability to increase the concentrations of adenosine, a platelet aggregation inhibitor and a coronary vasodilator, and cyclic adenosine monophosphate, which decreases platelet activation.[3,22] Dipyridamole, particularly when combined with aspirin, is effective for the prevention of stroke.[21] Extended-release dipyridamole combined with aspirin (Aggrenox®) is available as a branded product, however, dipyridamole alone is available generically. Currently, there is no evidence to support the use of dipyridamole either instead of, or in addition to, aspirin and the thienopyridines in the acute treatment of patients presenting with a non-ST-segment elevation acute coronary syndrome.[20]

The mechanism of action of anagrelide (Agrylin®) is also not completely understood. It is believed that anagrelide reduces platelet production via a decrease in megakaryocyte hypermaturation. Of note, significant inhibition of platelet aggregation with anagrelide is observed only at doses higher than those required to reduce the platelet count.[1,22] Anagrelide is the only platelet inhibitor approved for the treatment of thrombocythemia associated with myeloproliferative disorders. Specifically, this agent is used to reduce elevated platelet counts and the risk of thrombosis, and to ameliorate associated symptoms, including thrombohemorrhagic events.[1] Anagrelide is currently available generically.

Prasugrel (Effient®) is a third generation thienopyridine adenosine diphosphate receptor antagonist; therefore, it has a similar mechanism of action to that of clopidogrel and ticlopidine. Prasugrel has been reported to be the most potent of these agents with a 10 mg dose of prasugrel being approximately 2.5 to

2.7 times more potent than a 75 mg dose of clopidogrel in inhibiting platelet aggregation and thrombus formation.[23] This reported greater efficacy in platelet inhibition is due to the difference in cytochrome activation between the agents. Clopidogrel requires a multi-step cytochrome activation process, whereas prasugrel requires only a single step.[24] Prasugrel has been shown to have more desirable characteristics when compared to clopidogrel with regard to drug-drug interactions and interpatient enzyme variability. Potent cytochrome P450 (CYP) 3A4 inhibitors have been shown to affect the metabolism of clopidogrel; however, no effect has been seen with prasugrel. Study results have demonstrated that clinical outcomes with prasugrel are not affected by patient genetic variations of the CYP2C9 and 2C19 enzymes, which have been reported with clopidogrel.[25]

The newest platelet inhibitor to be approved by the FDA, ticagrelor (Brilinta®), works in a similar manner to the other thienopyridine platelet inhibitors. Specifically, ticagrelor is a cyclopentyltriazolopyrimidine, and the agent and its equipotent active metabolite reversibly bind to the $P2Y_{12}$ receptor located on the surface of platelets, preventing platelet signal transduction and activation.[7,22] In contrast to ticagrelor, the other available thienopyridines work via the irreversible binding to the $P2Y_{12}$ receptor. In addition, these agents are all prodrugs, while ticagrelor is not. Since ticagrelor does not require enzymatic conversion to become pharmacologically active, it is not subject to potential drug interactions associated with the other platelet inhibitors. Ticagrelor is administered twice daily, while clopidogrel and prasugrel are administered once daily.[22] When compared to clopidogrel, ticagrelor resulted in lower platelet receptor expression and a greater extent of inhibition of platelet aggregation, suggesting increased potency at the $P2Y_{12}$ receptor.[26]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Anagrelide (Agrylin®*)	Platelet inhibitors	✔
Clopidogrel (Plavix®)	Platelet inhibitors	✔
Dipyridamole (Persantine®*)	Platelet inhibitors	✔
Prasugrel (Effient®)	Platelet inhibitors	-
Ticagrelor (Brilinta®)	Platelet inhibitors	-
Ticlopidine (Ticlid*)	Platelet inhibitors	✔
Combination Products		
Aspirin/extended-release dipyridamole (Aggrenox®)	Platelet inhibitors	-

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

Indications

Table 2. Food and Drug Administration-Approved Indications[1-7]

Indication	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Prevention of postoperative thromboembolic complications of cardiac valve replacement			✔ *				
Recent myocardial infarction, recent stroke, or established peripheral arterial disease		✔					
Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation						✔ †	
Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome		✔ ‡			✔ §		
Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome who are being managed with percutaneous coronary intervention				✔ ‖			
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis							✔
Reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke						✔	
Treatment of patients with thrombocythemia, secondary to myeloproliferative disorders	✔ ¶						

*As an adjunct to coumarin anticoagulants.
†As adjunctive therapy with aspirin.
‡For patients with non-ST-elevation acute coronary syndrome, including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction.
§Patients with unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction.
‖Patients who are to be managed with percutaneous coronary intervention as follows: patients with unstable angina or non-ST-elevation myocardial infarction and patients with ST-elevation myocardial infarction when managed with primary or delayed percutaneous intervention.
¶To reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events.

In addition to their respective Food and Drug Administration-approved indications, the platelet inhibitors have the potential to be used off-label for several other conditions, most of which are cardiovascular in nature. Clopidogrel may be used for thrombosis prophylaxis in patients with atrial fibrillation, chronic heart failure, or in patients who are undergoing percutaneous coronary intervention. Dipyridamole may be used to improve myocardial function and perfusion following a myocardial infarction, to reduce the rate of graft occlusion after aortocoronary-artery bypass grafting, to slow the progression of diabetic neuropathy or end stage renal failure, to reduce the risk of pressure ulcers, to treat fetal growth restriction, and to reduce the fall in platelet counts caused by hemodialysis. Ticlopidine may be used to lessen the complications of myocardial infarctions or transient ischemic attacks, to maintain saphenous vein graft patency after aortocoronary bypass, to manage angina, or to reduce post surgical deep vein thrombosis. Aspirin/extended-release dipyridamole may be used to reduce the graft occlusion rate in patients receiving an arterial bypass graft, to treat thrombocytopenic purpura, as prophylaxis for cerebrovascular accident, for the management of Kasabach-Merritt Syndrome, and for slowing the progression of peripheral occlusive arterial disease.[22]

Pharmacokinetics

Table 3. Pharmacokinetics[22]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents				
Anagrelide	75	72 to 90	Four detected but not identified	76
Clopidogrel	50	50	Thiol metabolite	6.0 (0.5 to 0.7*)
Dipyridamole	37 to 66	Minimal (not reported)	None	0.66 to 10.00
Prasugrel	≥79	68 to 70	R-138727	7 to 8*
Ticagrelor	36	26 to 27	AR-C124910XX	7
Ticlopidine	80 to 90	60	None	12.6
Combination Products				
Aspirin/extended-release dipyridamole	50 to 75/37	1/not reported	Not reported/none	0.3/14.0

*Metabolite.

Clinical Trials

The clinical studies demonstrating the safety and efficacy of the platelet inhibitors in their respective Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[27-87]

As mentioned previously, aspirin is the only platelet inhibitor that has been evaluated for the treatment of an acute ischemic attack; however, antiplatelet therapy plays an important role in the long-term prevention of stroke or transient ischemic attacks (TIAs).[21] In a large, meta-analysis of patients with a previous myocardial infarction (MI), acute MI, previous TIA/stroke, and acute stroke, as well as patients with an increased risk of atherothrombotic events, it was demonstrated that overall, antiplatelet therapy reduced the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 25%. With regard to individual endpoints, antiplatelet therapy reduced the odds of nonfatal MI by 34%, nonfatal stroke by 25% and vascular death by 15%.[42] Looking at the individual platelet inhibitors, data from clinical studies demonstrated that ticlopidine reduced the risk of stroke and other vascular outcomes in patients with cerebrovascular disease.[37,38] The CAPRIE study demonstrated that patients with a recent ischemic stroke or MI, or those with symptomatic peripheral arterial disease who were treated with clopidogrel experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death compared to 5.83% of patients treated with aspirin (relative risk reduction [RRR], 8.7% in favor of clopidogrel; 95% confidence interval [CI], 0.3 to 16.3; *P*=0.043).[42] Results from the MATCH study demonstrated that the addition of aspirin to clopidogrel in high-risk patients with a recent ischemic stroke or TIA was associated with a nonsignificant difference in reducing major vascular events. In this trial, dual antiplatelet therapy was associated with more life-threatening, major, and minor bleeds.[34] In the ESPRIT

study, patients within six months of a TIA or minor stroke of presumed arterial origin were randomized to receive aspirin with or without dipyridamole. The rate of the primary composite outcome, death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complications (whichever occurred first), was 13% with combination therapy and 16% with aspirin (hazard ratio [HR], 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction, 1.0% per year; 95% CI, 0.1 to 1.8).[28]

With regard to the treatment of acute coronary syndromes (ACS), in the CLARITY-TIMI 28 study, patients who presented within 12 hours of a ST-segment elevation MI were randomized to receive either clopidogrel or placebo for 30 days. Treatment with clopidogrel was associated with an absolute reduction of 6.7% in the composite endpoint of occluded infarct-related artery on angiography, death, or recurrent MI before angiography (*P* value not reported).[47] Patients included in the COMMIT study were admitted within 24 hours of a suspected acute MI and received either combination therapy with clopidogrel and aspirin or aspirin monotherapy. In this study, there was a significant reduction in the risk of the composite endpoint of death, re-infarction, or stroke (*P*=0.002), and in death from any cause (*P*=0.03) in patients receiving combination therapy after 15 days.[49] In the CURE study investigators compared long-term (three to 12 months) combination therapy with clopidogrel plus aspirin to aspirin monotherapy in patients with a non-ST-segment elevation MI who presented within 24 hours of symptom onset. The results demonstrated that combination therapy resulted in a 20% RRR in the composite outcome of nonfatal MI, stroke, or vascular death (*P*<0.001). The compelling benefit of combination therapy noted in the CURE study was in the reduction of nonfatal MI. Due to the low number of strokes that occurred during the study, the associated reduction was not significant. There was also a weak trend suggesting the possibility of small reductions in death associated with combination therapy that was not significant.[20,21,53] The CHARISMA study was another long-term trial (median, 28 months) that enrolled and randomized patients with clinically evident cardiovascular disease to either combination treatment with clopidogrel and aspirin or to monotherapy with aspirin. The rate of the primary composite endpoint of MI, stroke, or death from cardiovascular causes was not different between the two treatments (6.8 vs 7.3%; relative risk, 0.93; 95% CI, 0.83 to 1.05; *P*=0.22).[50] As mentioned previously, there is no evidence to support the use of dipyridamole in the acute treatment of patients presenting with a non-ST-segment elevation ACS.[20] In addition, the results of a large meta-analysis of 29 randomized-controlled studies demonstrated that in patients with arterial vascular disease, dipyridamole had no clear effect on the secondary prevention of vascular death. Compared to control (no drug or another antiplatelet inhibitor), dipyridamole appeared to reduce the risk of vascular events; however, the effect was only significant in patients presenting with cerebral ischemia.[44]

The major clinical trial demonstrating the safety and efficacy of prasugrel for its FDA-approved indication is the TRITON-TIMI 38 (N=13,608). Results demonstrated that prasugrel was significantly more effective than clopidogrel in reducing ischemic events in patients with ACS who underwent percutaneous intervention. However, the trial did not demonstrate a decrease in the mortality rate with prasugrel. In addition, the results from TRITON-TIMI 38 did show a significantly higher rate of major, minor, life-threatening, and fatal bleeding events with prasugrel. Of note, certain patient subgroups, specifically those who were ≥75 years of age, those weighing <60 kg and those with a past history of stroke or TIA, did not demonstrate a clinical benefit with prasugrel.[75] In addition, several subgroup analyses were also conducted based on TRITON-TIMI 38 and one patient subgroup in particular, those with diabetes, were found to have a significantly greater reduction in ischemic events with prasugrel when compared to nondiabetic patients being treated with either prasugrel or clopidogrel.[76-82]

The major clinical study demonstrating the safety and efficacy of ticagrelor for its FDA-approved indication is the PLATO study. PLATO was an international, double-blind, double-dummy, multicenter, randomized-controlled trial that compared ticagrelor to clopidogrel in adult patients hospitalized with documented ACS, with or without ST-segment elevation within the previous 24 hours (N=18,624). After 12 months, the risk of the primary composite endpoint of vascular death, MI, or stroke was significantly reduced with ticagrelor (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.95; *P*<0.001). Ticagrelor also significantly reduced the risk of the secondary endpoints of the composite of all-cause mortality, MI, or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; *P*<0.001); the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event (14.6 vs 16.7%; HR, 0.88; 95% CI,

0.81 to 0.95; *P*<0.001); MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; *P*=0.005), and vascular death (4.0 vs 5.1%; HR, 0.79; 95% CI, 0.69 to 0.91). Furthermore, ticagrelor significantly reduced the risk of all-cause mortality (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89). Rates of major bleeding were not different between the two treatments (*P*=0.43).[54]

Several subanalyses of the PLATO study have been conducted.[55-65] In patients with ACS undergoing noninvasive (*P*=0.045) or invasive procedures (*P*=0.0025), ticagrelor remained more efficacious compared to clopidogrel.[55,56] However, in patients with ST-elevation or left bundle branch block (*P*=0.07), chronic kidney disease (*P*=0.13), or diabetes (*P* value not reported), and in those who underwent coronary artery bypass graft surgery (*P*=0.2862), there was no difference between ticagrelor and clopidogrel with regard to the primary composite endpoint.[57-60] A genetic substudy was also conducted and demonstrated ticagrelor to be more efficacious than clopidogrel, irrespective of cytochrome P450 2C19 and ABCB1 polymorphisms (*P*=0.0380).[61] In the original PLATO study a significantly higher rate of dyspnea was observed with ticagrelor; however, data from a substudy revealed ticagrelor had no effect on pulmonary function.[54,63]

Mahaffey et al compared the effects of ticagrelor and clopidogrel among patients enrolled in the PLATO study who were from the United States (N=1,413). The "superior" benefits of ticagrelor in reducing thrombotic cardiovascular events were not observed among this specific patient population. Specifically, there was no difference between ticagrelor and clopidogrel in the rate of the primary composite endpoint (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 7.75; *P*=0.1459). The authors discussed that among these patients who were treated with ticagrelor, the lowest event rates were observed in patients also receiving low-dose aspirin maintenance therapy. In contrast, event rates in those treated with clopidogrel were similar regardless of concurrent high- or low-dose aspirin. Despite the potential role that aspirin maintenance dosing may play in explaining the regional differences observed within the PLATO study, the authors noted that the pattern of results are consistent with what might be expected by chance alone in a large, multiregional clinical study with multiple exploratory analyses. A potential mechanism by which high-dose aspirin is thought to reduce the effects of ticagrelor relates to its ability to inhibit the endothelial release of prostacyclin in a dose-dependent fashion at doses greater than 80 mg/day. Prostacyclin reduces platelet reactivity and may contribute synergistically in vivo to the antiplatelet effects of $P2Y_{12}$ inhibitors. Therefore, the therapeutic effects of a higher mean level of $P2Y_{12}$ inhibition achieved with ticagrelor in the PLATO study may be attenuated when endogenous prostacyclin production is inhibited.[62] Until a prospective clinical study comparing the effects of low- vs high-dose aspirin maintenance therapy and its effect on the efficacy of ticagrelor is conducted, it remains unclear as to why the diminished effects of ticagrelor in the United States population were observed. Of note, the FDA-approved dosing of ticagrelor recommends that after the initial loading dose of aspirin (325 mg), a daily maintenance dose of aspirin of 75 to 100 mg should be used.[7]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cerebrovascular Conditions (Ischemic Stroke, Transient Ischemic Attack)				
Uchiyama et al[27] JASAP Aspirin/dipyridamole ER 25/200 mg BID vs aspirin 81 mg QD Concomitant use of anticoagulation and antiplatelet therapies was prohibited.	AC, DB, MC, PG, RCT Patients ≥50 years of age with an ischemic stroke ≥1 week (but no more than 6 months) prior to enrollment, with ≥2 additional risk factors, stable neurological signs and symptoms, and responsible lesion confirmed by CT or MRI	N=1,294 12 months	Primary: Recurrent ischemic stroke (fatal or nonfatal) Secondary: Cerebral hemorrhage; subarachnoid hemorrhage; TIA; ACS; other vascular events; composite of ischemic stroke, TIA, MI, unstable angina, or sudden death attributable to thromboembolism; stroke (composite of ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage); safety A post hoc analysis was performed evaluating the event rate of intracranial hemorrhage and the composite of stroke or major bleeding for different subgroups	Primary: Recurrent ischemic stroke occurred in 6.9 (n=45) and 5.0% (n=32) of patients receiving combination therapy and aspirin, respectively. Noninferiority of combination therapy compared to aspirin was not shown (HR, 1.47; 95% CI, 0.93 to 2.31). Results were consistent in the PP population. Secondary: The event rate of stroke was significantly higher with combination therapy compared to aspirin. There was no difference between the two treatments for any other secondary endpoint. Combination therapy and aspirin were both well tolerated. There was a significantly higher total number of adverse events with combination therapy (640 vs 611; *P*=0.04). The difference in drug-related adverse events was mainly due to headache in the early stages of treatment with combination therapy. More patients receiving combination therapy discontinued treatment because of headache. Major bleeding events and clinically relevant minor bleeding events were comparable between the two treatments. No relevant changes in laboratory parameters, vital signs, and electrocardiography were noted with either treatment. There were four (0.6%) and 10 (1.6%) deaths with combination therapy and aspirin. A multivariate analysis taking into account potential confounders for recurrence of ischemic stroke but only keeping covariates with a significant contribution in the model revealed a similar result for the comparison between treatments as the primary analysis. The analysis also revealed that higher modified Rankin Scale values and established end organ damage at baseline had a deleterious effect on the primary outcome, whereas the concomitant therapy with statins had a beneficial effect.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ESPRIT Study Group[28] ESPRIT Aspirin 30 to 325 mg/day plus dipyridamole 200 mg BID vs aspirin 30 to 325 mg/day Aspirin plus dipyridamole was administered either as a fixed-dose combination or as the two agents administered separately.	MC, OL, RCT Patients who were referred to one of the participating hospitals within 6 months of a TIA or minor ischemic stroke of presumed arterial origin	N=2,739 Mean follow-up 3.5 years	Primary: Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (which ever happened first) Secondary: Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic events, all vascular events, major bleeding complications	Primary: Primary outcome events occurred in 173 (13%) patients receiving combination therapy compared to 216 (16%) patients receiving aspirin therapy (HR, 0.80; 95% CI, 0.66 to 0.98; absolute risk reduction 1.0% per year; 95% CI, 0.1 to 1.8). Patients receiving combination therapy discontinued trial medication more often than those receiving aspirin (470 vs 184 patients), mainly because of headache. Secondary: The HR for death from all causes and all vascular causes were 0.88 (93 vs 107 patients; 95% CI, 0.67 to 1.17) and 0.75 (44 vs 60 patients; 95% CI, 0.51 to 1.10). Ischemic events were less frequent with combination therapy (HR, 0.81; 95% CI, 0.65 to 1.01). Major bleeding complications arose in 35 patients receiving combination therapy compared to 53 patients receiving aspirin , whereas minor bleeding was reported in 171 patients receiving combination therapy compared to 168 patients receiving aspirin (RR, 1.03; 95% CI, 0.84 to 1.25).
Verro et al[29] Aspirin plus dipyridamole (IR and ER) vs aspirin	MA of 6 RCT (4 were DB) Patients with a history of non-cardioembolic stroke or TIA	N=7,648 Duration varied	Primary: Incidence of nonfatal stroke Secondary: Composite of stroke, MI or vascular death; subset analysis comparing outcomes with IR and ER dipyridamole	Primary: Combination therapy significantly reduced the risk of nonfatal ischemic and hemorrhagic stroke compared to aspirin therapy (RR, 0.77; 95% CI, 0.67 to 0.89). Secondary: Combination therapy significantly reduced the risk of the composite of stroke, MI or vascular death (RR, 0.85; 95% CI, 0.76 to 0.94). Based on four trials, aspirin plus IR dipyridamole did not show a significant reduction in the risk of stroke (RR, 0.83; 95% CI, 0.59 to 1.15) or the composite outcome (RR, 0.95; 95% CI, 0.75 to 1.19) compared to aspirin. Based on two trials, aspirin plus ER dipyridamole showed a significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				reduction in risk for stroke (RR, 0.76; 95% CI, 0.65 to 0.89) and for the composite outcome (RR, 0.82; 95% CI, 0.73 to 0.92) compared to aspirin.
Diener et al[30] ESPS 2 Aspirin 25 mg BID vs aspirin/dipyridamole 25/200 mg BID vs dipyridamole ER 200 mg* BID vs placebo	DB, MC, PC, RCT Patients who had an ischemic stroke or TIA within 3 months prior to study entry	N=6,602 24 months	Primary: Stroke (fatal or nonfatal), death (all cause mortality), combined stroke or death Secondary: TIA and adverse events	Primary: In comparison to placebo, stroke risk was reduced by 18% with aspirin (*P*=0.013), 37% with aspirin/dipyridamole (*P*<0.001) and 16% with dipyridamole ER (*P*=0.039). There was no significant difference in all cause mortality among the active treatment groups (*P* values not reported). In comparison to placebo, the risk of stroke or death was reduced by 13% with aspirin (*P*=0.016), 24% with aspirin/dipyridamole (*P*<0.001) and 15% with dipyridamole ER (*P*=0.015). Secondary: Aspirin (*P*<0.001), aspirin/dipyridamole (*P*<0.001) and dipyridamole ER (*P*<0.01) were significantly effective in preventing TIA compared to placebo. Headache was the most common adverse event, occurring more frequently in the dipyridamole-treated patients (*P* values not reported). All-site bleeding and gastrointestinal bleeding were significantly more common with aspirin in comparison to placebo or dipyridamole (*P* values not reported).
Sacco et al[31] Aspirin/dipyridamole 25/200 mg BID vs aspirin 25 mg BID	Post hoc analysis using data from the ESPS 2	N=3,299 Duration not reported	Primary: Rates of annual strokes, combined stroke or vascular events Secondary: Not reported	Primary: Compared to aspirin, combination therapy was more effective in reducing the risk of stroke (RRR, 23%; *P*=0.006) and combined stroke or vascular events (RRR, 22%; *P*=0.003). A more pronounced efficacy was observed for patients <70 years; those with hypertension or prior MI, stroke, TIA or prior cardiovascular disease and smokers (all *P*<0.01). The greatest relative hazard reduction (44.6%) was noted for patients with a stroke or TIA before the qualifying event. Significant hazard reductions were reported for the combined outcome of stroke or vascular events with the greatest reductions found in patients with prior stroke or TIA, previous MI and among current smokers.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The difference in efficacy increased in high-risk patients. Secondary: Not reported
Leonardi-Bee et al[32] Dipyridamole vs aspirin plus dipyridamole vs aspirin vs control (not specified)/placebo Two formulations of dipyridamole were assessed: conventional (150 to 300 mg/day) and modified-release (400 mg/day). The daily dose of aspirin was 50 to 1,300 mg.	MA of 5 RCT (including the ESPS 1 and 2) Patients with previous ischemic stroke and/or TIA	N=11,492 Follow-up at 15 to 72 months	Primary: Incidence of stroke (combined fatal and nonfatal) Secondary: Nonfatal stroke; MI (combined fatal and nonfatal); vascular death; composite of nonfatal stroke, nonfatal MI and vascular death	Primary: The incidence of recurrent stroke was reduced by dipyridamole therapy compared to control (OR, 0.82; 95% CI, 0.68 to 1.00; *P*<0.05), and by combination therapy compared to aspirin (OR, 0.78; 95% CI, 0.65 to 0.93; *P*<0.05), dipyridamole therapy (OR, 0.74; 95% CI, 0.60 to 0.90; *P*<0.05) or control (OR, 0.61; 95% CI, 0.51 to 0.71; *P*<0.05). Secondary: Dipyridamole therapy reduced nonfatal stroke as compared to control, and combination therapy reduced nonfatal stroke as compared to aspirin. Combination therapy significantly reduced the incidence of fatal and nonfatal MI compared to control (*P*<0.05), but not compared to aspirin or dipyridamole (*P*>0.05). Vascular death was not altered in any group. Combination therapy also significantly reduced the composite outcome of nonfatal stroke, nonfatal MI and vascular death as compared to aspirin (OR, 0.84; 95% CI, 0.72 to 0.97; *P*<0.05), dipyridamole (OR, 0.76; 95% CI, 0.64 to 0.90; *P*<0.05) or control (OR, 0.66; 95% CI, 0.57 to 0.75; *P*<0.05).
Sacco et al[33] Aspirin 25 mg plus dipyridamole ER 200 mg BID	AC, DB, PC, RCT Patients ≥50 years of age with a recent ischemic	N=20,332 2.5 years (mean)	Primary: Recurrent stroke of any type Secondary: Composite of stroke,	Primary: Confirmed first recurrence of stroke occurred in 1,814 patients. There was no interaction between the treatment benefit of antiplatelet plus telmisartan (*P*=0.35). The primary outcomes occurred in 916 (9.0%) and 898 (8.8%) patients in the aspirin plus dipyridamole ER and clopidogrel groups (HR, 1.01; 95% CI, 0.92 to 1.11). Although the HR is very close to 1.00, the upper limit of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs clopidogrel 75 mg/day plus placebo or telmisartan 80 mg/day	stroke (within <90 days before randomization, or 90 to 120 days before randomization if they had ≥2 additional vascular risk factors)		MI or death from vascular causes	the CI extends beyond the prespecified noninferiority margin of 1.075. Ischemic stroke accounted for 87.4% of the recurrent strokes. Secondary: The numbers of patients with the secondary endpoint were identical between the two groups (1,333 [13.1%]; HR for aspirin plus dipyridamole ER vs clopidogrel, 0.99; 95% CI, 0.92 to 1.07).
Diener et al[34] MATCH Clopidogrel 75 mg/day vs clopidogrel 75 mg/day plus aspirin 75 mg/day	DB, PC, RCT High-risk patients with a recent ischemic stroke or TIA, with ≥1 additional vascular risk factor who were already receiving clopidogrel	N=7,599 18 months	Primary: Composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event Secondary: Death, stroke, individual components and various combinations of the primary end points	Primary: There was no significant benefit of combination therapy compared to clopidogrel therapy in reducing the primary outcome (15.7 vs 16.7%, respectively; *P*=0.244). Secondary: There was no significant benefit of combination therapy compared to clopidogrel therapy in reducing the secondary outcomes. Life-threatening bleeds were higher in the group receiving combination therapy (2.6 vs 1.3%; *P*<0.0001). Major and minor bleeds were also significantly higher with combination therapy (*P*<0.0001). [Note: Although clopidogrel plus aspirin is recommended over aspirin for acute coronary syndromes, with most guidelines advocating for up to 12 months of treatment, the results of MATCH do not suggest a similar risk: benefit ratio for stroke and TIA survivors.]
Markus et al[35] CARESS Clopidogrel 300 mg on day 1, followed by clopidogrel 75 mg/day plus aspirin 75 mg/day on days 2 to 7 vs	DB, PC, RCT Patients >18 years of age with ≥50% carotid stenosis who experienced ipsilateral carotid territory TIA or	N=107 7 days	Primary: Proportion of patients who were microembolic signal positive on day seven Secondary: Proportion of	Primary: ITT analysis revealed a significant reduction in the primary end point: 43.8% of patients receiving combination therapy were microembolic signal positive on day seven, as compared to 72.7% of patients receiving aspirin (RRR, 39.8%; 95% CI, 13.8 to 58.0; *P*=0.0046). Secondary: Microembolic signal frequency/hour was reduced compared to baseline by 61.4% (95% CI, 31.6 to 78.2; *P*=0.0013) in the combination therapy group at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin 75 mg QD	stroke within the past 3 months		patients who were microembolic signal positive on day two, the rate of embolization on both days two and seven and their percent change from baseline, safety	day seven, and by 61.6% (95% CI, 34.9 to 77.4; *P*=0.0005) on day two. There were four recurrent strokes and seven TIAs in the aspirin group compared to no stroke and four TIAs in the combination therapy group that were considered treatment-emergent and ipsilateral to the qualifying carotid stenosis. Microembolic signal frequency was greater in the 17 patients with recurrent ipsilateral events compared to the 90 patients without (*P*=0.0003).
Kennedy et al[36] FASTER Clopidogrel 300 mg once, followed by 75 mg/day or placebo and simvastatin 40 mg once, followed by 40 mg/day or placebo All patients were also given aspirin 81 mg/day, with a 162 mg loading dose if naïve to aspirin.	Factorial design 2x2, DB, PC, RCT Patients ≥40 years of age with a TIA or minor stroke, randomized within 24 hours of symptom onset	N=392 90 days	Primary: Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis) Secondary: Composite of stroke, MI and vascular death	Primary: The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins. Within 90 days, 7.1% of patients on clopidogrel (with or without simvastatin) had a stroke compared to 10.8% of patients not taking clopidogrel (RR, 0.7; 95% CI, 0.3 to 1.2) for an absolute risk reduction of 3.8% compared to placebo (95% CI, -9.4 to 1.9; *P*=0.19). In the simvastatin group (with or without clopidogrel), 10.6% of patients had a stroke within 90 days compared to 7.3% of patients not taking simvastatin (RR, 1.3; 95% CI, 0.7 to 2.4) for an absolute risk increase of 3.3% compared to placebo (95% CI, -2.3 to 8.9; *P*=0.25). Two patients on clopidogrel had intracranial hemorrhage compared to none in patients not receiving clopidogrel (absolute risk increase, 1.0%; 95% CI, -0.4 to 2.4; *P*=0.5). There was no difference between groups for the simvastatin safety outcomes. Secondary: Clopidogrel was associated with a -3.3% risk difference in the secondary end point compared to placebo (95% CI, -9.3 to 2.7; *P*=0.28). Simvastatin was associated with a 2.7% risk difference compared to placebo (95% CI, -3.2 to 8.7; *P*=0.37).
Gent et al[37] CATS Ticlopidine 250 mg BID	DB, MC, PC, RCT Patients with	N=1,072 Up to 3 years (mean 24	Primary: Event rate/year for stroke, MI or vascular death	Primary: The event rate/year for stroke, MI or vascular death was 10.8% in the ticlopidine group and 15.3% in the placebo group. Compared to placebo, ticlopidine reduced the RR of stroke, MI or vascular death by 30% (*P*=0.006) in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	ischemic strokes occurring from 1 week to 4 months	months)	Secondary: Adverse events	the on-treatment analysis and by 23% (*P*=0.020) using the ITT approach. Ticlopidine reduced the RR of ischemic stroke by 33% (*P*=0.008) in the on-treatment analysis. Ticlopidine was beneficial for both men and women (RR, 28.1%; *P*=0.037 and RR, 34.2%; *P*=0.045, respectively). Secondary: Adverse events associated with ticlopidine included neutropenia (severe in about 1% of cases), skin rash (severe in about 2% of cases) and diarrhea (severe in about 2% of cases).
Hass et al[38] TASS Ticlopidine 250 mg BID vs aspirin 650 mg BID	Blinded, MC, RCT Patients with a minor stroke or TIA within the past 3 months	N=3,069 2 to 6 years	Primary: Nonfatal stroke or death Secondary: Adverse events	Primary: Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate, 17 vs 19%; *P*=0.048). Ticlopidine reduced the risk of stroke after three years by 21% (10 vs 13%; *P*=0.024). Secondary: Ticlopidine significantly increased total cholesterol compared to aspirin (9 vs 2%; *P*<0.01). Serious gastrointestinal adverse effects were 2.5 times more common in the aspirin group, but bleeding from other anatomic sites was infrequent and about equal in the two treatment groups. Severe neutropenia occurred in 0.9% of patients.
Gorelick et al[39] AAASPS Ticlopidine 250 mg BID vs aspirin 325 mg BID	DB, MC, RCT African American patients who recently had a non-cardioembolic ischemic stroke	N=1,809 Up to 2 years	Primary: Composite of recurrent stroke, MI or vascular death Secondary: Stroke (fatal and nonfatal)	Primary: There was no significant difference in the percent of patients reaching the primary outcome between ticlopidine and aspirin (14.7 vs 12.3%, respectively; *P*=0.12). Secondary: There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (*P*=0.08).
Fukuuchi et al[40] Ticlopidine 200 mg QD	DB, DD, MC, RCT	N=1,151 52 weeks	Primary: Safety (emphasis on hematologic	Primary: During the study period, 15.1 and 7.0 % of ticlopidine- and clopidogrel-treated patients had at least one primary safety end point (*P*<0.001). Significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs clopidogrel 75 mg QD	Japanese patients 20 to 80 years of age who experienced a non-cardioembolic cerebral infarction ≥8 days prior to enrollment		changes, hepatic dysfunction, non-traumatic hemorrhage and other serious adverse reactions) Secondary: Combined incidence of nonfatal or fatal cerebral infarction, MI or death due to other vascular causes	differences were primarily noted between ticlopidine and clopidogrel for hematologic disorders (2.4 vs 1.0%; *P*=0.043) and hepatic dysfunction (11.9 vs 4.2%; *P*<0.001). Study medication was discontinued prematurely due to safety end points in 27 and 17% of patients receiving ticlopidine and clopidogrel, respectively (*P*<0.001). The HR for the risk of discontinuing study medication due to a primary safety end point was 0.559 (95% CI, 0.434 to 0.721) in favor of clopidogrel. Secondary: The incidence of vascular events did not differ significantly between ticlopidine and clopidogrel (2.6 vs 3.0%, respectively; *P*=0.948; HR, 0.977; 95% CI, 0.448 to 1.957).
Uchiyama et al[41] Ticlopidine 200 mg QD vs clopidogrel 75 mg QD	2 DB, DD, Phase II, RCT Japanese patients 20 to 80 years of age, with a history of cerebral infarctions; the most recent stroke being >8 days prior to enrollment	N=1,921 26 to 52 weeks	Primary: Combined endpoint of accessory symptoms and abnormal laboratory changes Secondary: Combined incidence of vascular events (cerebral infarction, MI, vascular death, TIA, amaurosis fugax, angina pectoris, peripheral artery occlusion, retinal artery occlusion or other vascular event)	Primary: Fewer patients in the clopidogrel group (35.0%) experienced the combined safety endpoint compared to those in the ticlopidine group (48.7%). At one month, it was estimated that 83.4 and 69.9% of patients in the clopidogrel and ticlopidine groups were safety event free. At both two and 12 months, the estimated incidence of the safety events was significantly lower with clopidogrel compared to ticlopidine (*P* value not reported). It was estimated that almost twice as many patients (25.6%) in the ticlopidine group experienced symptoms and/or abnormal laboratory findings of hepatic dysfunction compared to the clopidogrel group (13.4%; HR, 0.455; 95% CI, 0.367 to 0.565; *P*<0.001). Secondary: There was no difference in the incidence of the combined efficacy endpoint of cerebral infarction, MI or vascular death with clopidogrel compared to ticlopidine (2.6 vs 2.5%; HR, 0.918; 95% CI, 0.518 to 1.626). There were no MIs or vascular deaths; only recurrence of cerebral infarctions. There was no difference in the total number of vascular events between the clopidogrel (3.6%) and ticlopidine (3.7%) groups (HR, 0.878; 95% CI, 0.545 to 1.412). The incidences of TIA, angina pectoris, PAD or other events were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				comparable between the two groups. There was no significant difference in the incidence of the combined efficacy endpoint between patients with prior lacunar stroke in the clopidogrel group (2.8%) and in the ticlopidine group (3.3%; *P* value not reported).
Cerebrovascular and Cardiovascular Conditions				
Antithrombotic Trialists' Collaboration[42] Antiplatelet agents vs control vs one antiplatelet regimen vs another	MA (197 RCTs compared antiplatelet therapy vs control and 90 trials compared different antiplatelet regimens) Patients at high risk of occlusive vascular events	N=135,640 Duration varied	Primary: Serious vascular event (nonfatal MI, nonfatal stroke or vascular death) Secondary: Not reported	Primary: Overall, antiplatelet therapy reduced the combined outcome of any serious vascular event by 25%, nonfatal MI by 34%, nonfatal stroke by 25% and vascular mortality by 15%, with no apparent adverse effect on other deaths. Aspirin was the most widely studied antiplatelet drug and low-dose (75 to 150 mg/day) was at least as effective as higher daily doses for long-term use. In acute settings an initial loading dose of ≥150 mg aspirin may be required. Clopidogrel reduced serious vascular events by 10% compared to aspirin, which was similar to the 12% reduction observed with ticlopidine. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone. Secondary: Not reported
CAPRIE Steering Committee[43] CAPRIE Clopidogrel 75 mg QD vs aspirin 325 QD	DB, MC, PG, RCT Patients with recent ischemic stroke (within 6 months with ≥1 week of residual neurological signs), recent MI (within 35 days) or symptomatic PAD	N=19,185 1 to 3 years (mean, 1.91 years)	Primary: Composite of ischemic stroke, MI or vascular death Secondary: Composite of ischemic stroke, MI, vascular death and amputation; vascular death; all cause mortality; safety	Primary: The ITT analysis showed that clopidogrel had an annual 5.32% risk of ischemic stroke, MI or vascular death compared to 5.83% with aspirin, for a RRR of 8.7% (95% CI, 0.3 to 16.5; *P*=0.043) in favor of clopidogrel. Corresponding on-treatment analysis yielded a RRR of 9.4% in favor of clopidogrel (*P* value not reported). For the 6,431 patients enrolled in the trial with prior stroke, the RRR for ischemic stroke, MI or vascular death was 7.3% in favor of clopidogrel (*P*=0.26), and the RRR for the end point of stroke was 8.0% (*P*=0.28). For the 6,302 patients enrolled in the trial with MI, a RR increase of 3.7% was associated with clopidogrel (*P*=0.66).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				For the 6,452 patients enrolled in the trial with PAD, a RRR of 23.8% was noted in favor of clopidogrel (*P*=0.0028). Secondary: Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (*P*=0.076). There was no significant difference between clopidogrel and aspirin with regards to vascular death (1.90 vs 2.06%; *P*=0.29) and all cause mortality (3.05 vs 3.11%; *P*=0.71). There were no major differences in terms of safety. Severe rash (*P*=0.017) and severe diarrhea (*P*=0.080) were reported more frequently with clopidogrel. Severe upper gastrointestinal discomfort (*P*=0.096), intracranial hemorrhage (*P*=0.23) and gastrointestinal hemorrhage (*P*=0.05) were reported more frequently with aspirin.
De Schryver et al[44] Dipyridamole with or without other antiplatelet drugs vs control (no drug or another antiplatelet drug)	MA of 29 RCTs Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA)	N=23,019 Duration varied (≥1 month in duration)	Primary: Secondary prevention of vascular death and vascular events (vascular death, any death from an unknown cause, nonfatal stroke or nonfatal MI) Secondary: Not reported	Primary: Compared to control, dipyridamole had no clear effect on vascular death (RR, 0.99; 95% CI, 0.87 to 1.12). The dose of dipyridamole or type of presenting vascular disease did not influence this result. Compared to control, dipyridamole appeared to reduce the risk of vascular events (RR, 0.88; 95% CI, 0.81 to 0.95). This effect was only significant in patients presenting with cerebral ischemia. There was no evidence that dipyridamole alone was more efficacious than aspirin. Secondary: Not reported
Cardiovascular Indications (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)				
Navarese et al[45] Ticagrelor 90 to 180 mg BID	MA of 7 RCTs Randomized controlled trials on adjunctive	N=58,591 30 days to 15 months	Primary: Mortality Secondary: MI, definite in-stent	Primary: Compared with clopidogrel, new antiplatelet therapies (ticagrelor or prasugrel) were associated with a statistically significant reduction in mortality (3.4 vs 2.9%; OR, 0.87; 95%CI, 0.79 to 0.95; *P*=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
or prasugrel 60 mg loading dose, followed by 10mg QD vs clopidogrel 300 to 600 mg loading dose, followed by 75 mg QD	ADP receptor antagonists among patients with ACS		thrombosis, safety	Secondary: Compared with clopidogrel, new antiplatelet therapies (ticagrelor or prasugrel) were associated with a statistically significant reduction in the incidence of recurrent MI (5.2 vs 4.2%; OR, 0.80; 95%CI, 0.74 to 0.87; *P*<0.0001). Compared with clopidogrel, new antiplatelet therapies (ticagrelor or prasugrel) were associated with a statistically significant reduction in the incidence of in-stent thrombosis (1.7 vs 0.9%; OR, 0.52; 95%CI, 0.43 to 0.63; *P*<0.0001). The rates of bleeding were comparable between clopidogrel and the new antiplatelet drugs (ticagrelor and prasugrel) (5 vs 4.7%; OR, 1.06; 95%CI, 0.96 to 1.17; *P*=0.25).
Ho et al[46] Clopidogrel, dose not specified	RETRO cohort Patients with ACS discharged on clopidogrel from 127 Veterans Affairs hospitals between October 2003 and March 2005	N=3,137 Duration varied (mean follow-up after stopping clopidogrel was 196 days for patients medically treated and 203 days for patients receiving PCI)	Primary: Rate of all cause mortality or acute MI after stopping clopidogrel Secondary: Not reported	Primary: Among medically treated patients the mean duration of clopidogrel treatment was 302 days. Death or acute MI occurred in 17.1% of these patients, with 60.8% of the events occurring during 0 to 90 days, 21.3% during 91 to 180 days and 9.7% during 181 to 270 days after stopping treatment with clopidogrel. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90 day interval after stopping treatment with clopidogrel was associated with a significantly higher risk of adverse events (IRR, 1.98; 95% CI, 1.46 to 2.69 vs the interval 91 to 180 days). Among the PCI-treated patients the mean duration of clopidogrel treatment was 278 days. Death or acute MI occurred in 7.9% of these patients, with 58.9% of the events occurring during 0 to 90 days, 23.4% during 91 to 180 days and 6.5% during 181 to 270 days after stopping clopidogrel treatment. In multivariable analysis including adjustment for duration of clopidogrel treatment, the first 90 day interval after stopping clopidogrel treatment was associated with a significantly higher risk of adverse events (IRR, 1.82; 95% CI, 1.17 to 2.83). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Sabatine et al[47] CLARITY-TIMI 28 Clopidogrel 300 mg once, followed by 75 mg/day vs placebo Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin. Patients were also scheduled to undergo angiography 48 to 192 hours after the start of the study medication.	DB, MC, PC, RCT Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI	N=3,491 30 days (study medication given up to, and including, the day of angiography, or up to day 8 or hospital discharge if no angiography)	Primary: Composite of an occluded infarct-related artery on angiography, death or recurrent MI before angiography (death or recurrent MI by day eight or hospital discharge in patients who did not undergo angiography) Secondary: Safety	Primary: The primary end point was reached in 15.0% of patients receiving clopidogrel compared to 21.7% of patients receiving placebo, representing an absolute reduction of 6.7% in the rate and 36% in the odds of reaching the end point with clopidogrel therapy (95% CI, 27 to 47; *P*<0.001). By 30 days, clopidogrel therapy reduced the odds of the composite end point of death from cardiovascular causes, recurrent MI or recurrent ischemia leading to the need for urgent revascularization by 20% (from 14.1 to 11.6%; *P*=0.03). Secondary: The rates of major bleeding and intracranial hemorrhage were similar in the two groups.
Ahmed et al[48] Clopidogrel 300 mg once, followed by 75 mg/day vs placebo Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin.	Substudy of CLARITY-TIMI 28 trial[46] Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI stratified by baseline GFR	N=3,252 30 days (study medication given up to, and including, the day of angiography, or up to day 8 or hospital discharge if no angiography)	Primary: Composite of an occluded infarct-related artery on angiography, all-cause mortality or recurrent MI prior to angiography (death or recurrent MI by day eight or hospital discharge in patients who did not undergo angiography) Secondary: Composite clinical	Primary: There was a significant trend for an increased rate of the primary composite endpoint with lower GFR and was the highest rate (23.4%) in patients with moderately reduced GFR (*P*=0.003). Secondary: By day 30, both the rates of the composite clinical endpoint (*P*<0.0001) and the safety endpoints of bleeding (*P*=0.0008) and intracranial hemorrhage (*P*=0.03) also trended towards a significant increase with lower GFRs. By day 30, there was a significant trend for an increased rate of cardiovascular death with lower GFR and was the highest rate (11.3%) in patients with moderately reduced GFR (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			endpoint of cardiovascular death, MI, or recurrent ischemia leading to urgent revascularization at 30 days; cardiovascular death; safety	
COMMIT Collaborative Group[49] COMMIT Clopidogrel 75 mg/day plus aspirin 162 mg/day vs aspirin 162 mg/day	MC, PC, RCT Patients admitted to the hospital within 24 hours of suspected acute MI	N=45,852 15 days (mean)	Primary: Composite of death, re-infarction or stroke; death from any cause Secondary: Safety	Primary: Combination therapy produced a highly significant nine percent proportional reduction in death, reinfarction or stroke compared to aspirin (actual reductions 9.2 vs 10.1%, respectively; *P*=0.002), corresponding to nine fewer events/1,000 patients treated for about two weeks. There was also a significant seven percent proportional reduction in any death in the combination therapy group compared to the aspirin group (7.5 vs 8.1%; *P*=0.03). Secondary: Considering all fatal, transfused or cerebral bleeds together, no significant excess risk was noted with combination therapy compared to aspirin; either overall (0.58 vs 0.55%, respectively; *P*=0.59), in patients >70 years of age (*P* value not reported) or in those given fibrinolytic therapy (*P* value not reported).
Bhatt et al[50] CHARISMA Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day vs aspirin 75 to 162 mg/day	DB, MC, PC, RCT Patients ≥45 years of age with clinically evident cardiovascular disease	N=15,603 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes or	Primary: The rate of the composite of MI, stroke or death from cardiovascular causes was 6.8% with combination therapy and 7.3% with aspirin (RR, 0.93; 95% CI, 0.83 to 1.05; *P*=0.22). The rate of the primary end point among patients with multiple risk factors was 6.6% with combination therapy and 5.5% with aspirin (RR, 1.2; 95% CI, 0.91 to 1.59; *P*=0.20), and the rate of death from cardiovascular causes also was higher with combination therapy (3.9 vs 2.2%; *P*=0.01). In the subgroup with clinically evident atherothrombosis, the rate was 6.9% with combination therapy and 7.9% with aspirin (RR, 0.88; 95% CI, 0.77 to 1.00; *P*=0.046).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			hospitalization for unstable angina, TIA or revascularization procedure; safety	Secondary: The secondary end point was reached in 16.7 and 17.9% (RR, 0.92; 95% CI, 0.86 to 1.00; *P*=0.04) of patients receiving combination therapy and aspirin, respectively. The rate of severe bleeding was 1.7 and 1.3% (RR, 1.25; 95% CI, 0.97 to 1.61; *P*=0.09) for patients receiving combination therapy and aspirin.
Dasgupta et al[51] Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day vs aspirin 75 to 162 mg/day	Post hoc analysis of CHARISMA[49] Post hoc analysis of patients with diabetic neuropathy in the CHARISMA trial, who were ≥45 years of age with clinically evident cardiovascular disease or multiple atherothrombotic risk factors	N=2,009 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes or hospitalization for unstable angina, TIA or revascularization procedure; safety	Primary: Almost all cardiovascular events occurred significantly more frequently in diabetic patients with neuropathy. Patients with diabetic neuropathy had a higher case fatality rate of MI compared to diabetic patients without nephropathy and nondiabetic patients (20 vs 14 vs 11%, respectively), but this higher rate was not significant (*P*=0.240). Secondary: Patients with nephropathy who were assigned clopidogrel experienced a significant increase in overall mortality (HR, 1.8; 95% CI, 1.2 to 2.7; *P*=0.006) compared to placebo, as well as significantly increased cardiovascular mortality (HR, 1.7; 95% CI, 1.1 to 2.9; *P*=0.028). The frequency of bleeding in patients with diabetic nephropathy who received clopidogrel tended to be higher compared to placebo, but this increase was not significant (2.6 vs 1.5%; HR, 1.8; *P*=0.075).
Hart et al[52] Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day vs aspirin 75 to 162 mg/day	Post hoc analysis of CHARISMA[49] Post hoc analysis of participants with a history of AF in the CHARISMA trial, who were ≥45 years of age with clinically evident cardiovascular disease or	N=593 Median 28 months	Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes Secondary: First occurrence of MI, stroke, death from cardiovascular causes, or hospitalization for	Primary: There was no difference in the composite of stroke, MI or vascular death between patients receiving combination therapy (35 of 298 patients) and patients receiving aspirin (27 of 285 patients; *P*=0.40). Secondary: There was no difference in the composite of stroke, MI, vascular death or rehospitalization (70 vs 66 patients; *P*=0.93) or all cause mortality (29 vs 25 patients; *P*=0.69) between the two groups. Stroke (ischemic and hemorrhagic) occurred in 15 patients receiving combination therapy (2.2% per year) and in 14 patients receiving aspirin (2.1% per year; HR, 1.03; 95% CI, 0.49 to 2.13; *P*=0.94).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	multiple atherothrombotic risk factors		unstable angina, TIA or revascularization procedure; safety	Severe or fatal extracranial hemorrhage occurred in six patients given combination therapy compared to three patients given aspirin alone (*P*=0.51), while intracranial bleeding occurred in three and one patients (*P*=0.62), respectively.
CURE Trial Investigators[53] CURE Clopidogrel (300 mg once, followed by 75 mg/day) plus aspirin vs aspirin	DB, PC, RCT Patients with NSTEMI, presenting within 24 hours of symptom onset	N=12,562 3 to 12 months	Primary: Composite of death from cardiovascular causes, nonfatal MI or stroke (first primary outcome); composite of the first primary outcome or refractory ischemia (second primary outcome) Secondary: Severe ischemia, heart failure, need for revascularization, safety	Primary: A composite of death from cardiovascular causes, nonfatal MI or stroke occurred in 9.3% of patients in the combination therapy group compared to 11.4% of patients in the aspirin group (RR, 0.80; 95% CI, 0.72 to 0.90; *P*<0.001). When refractory ischemia was included with the first primary outcome, the composite rate was 16.5 vs 18.8% (RR, 0.86; 95% CI, 0.79 to 0.94; *P*<0.001). Secondary: Significant reductions in nonfatal MI (5.2 vs 6.7%), and trends toward reduction in death (5.1 vs 5.5%) and stroke (1.2 vs 1.4%) with combination therapy compared to aspirin were noted (*P* values not reported). The percentages of patients with in-hospital refractory or severe ischemia, recurrent angina, heart failure and revascularization procedures were also significantly lower with combination therapy (all *P*<0.05 vs aspirin). There were significantly more patients with major bleeds in the combination therapy group than in the aspirin group (3.7 vs 2.7%; RR, 1.38; 95% CI, 1.13 to 1.67; *P*=0.001), but there were not significantly more patients with episodes of life-threatening bleeds (2.1 vs 1.8%; RR, 1.21; 95% CI, 0.95 to 1.56; *P*=0.13).
Wallentin et al[54] PLATO Ticagrelor 180 mg loading dose, followed by 90 mg BID vs	AC, DB, DD, MC, PG, PRO, RCT Adult patients hospitalized with documented ACS within the previous 24 hours, with or	N=18,624 12 months	Primary: Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding Secondary: Effect in patients for	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.92; *P*<0.001). A treatment effect was seen within 30 days and persisted throughout the trial. The rate of major bleeding was not different between ticagrelor and clopidogrel (11.6 vs 11.2%; HR, 1.04; 95% CI, 0.95 to 1.13; *P*=0.43).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	without ST-segment elevation		whom invasive treatment was planned; composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; individual components of the primary endpoint; all-cause mortality; other bleeding events; dyspnea; bradyarrhythmia; any other adverse event; results of laboratory safety tests	Secondary: In patients undergoing invasive procedures, significantly fewer composite events occurred with ticagrelor (8.9 vs 10.6%; HR, 8.4; 95% CI, 0.75 to 0.94; *P*=0.003). Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; *P*<0.001). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other thrombotic event (14.6 vs 16.7; HR, 0.88; 95% CI, 0.81 to 0.95; *P*<0.001). The rates of MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; *P*=0.005) and vascular death (4.0 vs 5.1%; HR, 0.84; 95% CI, 0.69 to 0.91; *P*=0.001) were significantly lower with ticagrelor. The rate of stroke was not different between the two treatments (1.5 vs 1.3%; HR, 1.17; 95% CI, 0.91 to 1.52; *P*=0.22). The rate of all-cause mortality was significantly lower with ticagrelor (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89; *P*<0.001). Data on minor bleeding events were not reported. Rates of fatal bleeding were not different between the two treatments (0.3 vs 0.3%; HR, 0.87; 95% CI, 0.48 to 1.59; *P*=0.66). The rate of fatal non-intracranial bleeding was significantly higher with clopidogrel (0.3 vs 0.1%, respectively; *P*=0.03). The rate of fatal intracranial bleeds was significantly higher with ticagrelor (0.10 vs 0.01%, respectively; *P*=0.02). The rate of dyspnea was significantly higher with ticagrelor (13.8 vs 7.8%; HR, 1.84; 95% CI, 1.68 to 2.02; *P*<0.001). From this group, 0.9 and 0.1% of patients discontinued treatment (HR, 6.12; 95% CI, 3.41 to 11.01; *P*<0.001). Rates of pacemaker insertion (*P*=0.87), syncope (*P*=0.08), bradycardia (*P*=0.21) and heart block (*P*=1.00) were not different between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Laboratory testing revealed significant increases in baseline serum uric acid with ticagrelor at one (*P*<0.001) and 12 months (*P*<0.001). Similar results were observed with serum creatinine (*P*<0.001 for both). One month after the end of treatment, there were no differences between the two treatments for either serum uric acid (*P*=0.56) or creatinine (*P*=0.59).
James et al[55] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	Substudy of PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing noninvasive procedures	N=5,216 12 months	Primary: Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding events Secondary: Individual components of the primary composite endpoint; all-cause mortality; nonvascular mortality; composite of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; subclasses of stroke; other bleeding events	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (12.0 vs 14.3%; HR, 0.85; 95% CI, 0.73 to 1.00; *P*=0.045). The rate of major bleeding did not differ between ticagrelor and clopidogrel (11.9 vs 10.3%; HR, 1.17; 95% CI, 0.98 to 1.39; *P*=0.079). Secondary: The rate of vascular death was significantly lower with ticagrelor (5.5 vs 7.2%; HR, 0.76; 95% CI, 0.61 to 0.96; *P*=0.019). The rates of MI (7.2 vs 7.8%; HR, 0.94; 95% CI, 0.77 to 1.15; *P*=0.555) and stroke (2.1 vs 1.7%; HR, 1.35; 95% CI, 0.89 to 2.07; *P*=0.162) were not different between the two treatments. The rates of all-cause mortality was significantly lower with ticagrelor (6.1 to 8.2%; HR, 0.75; 95% CI, 0.61 to 0.93; *P*=0.010). The rate of nonvascular death was not different between the two treatments (0.6 vs 1.0%; HR, 0.68; 95% CI, 0.35 to 1.31; *P*=0.252). The rate of the composite of vascular death, MI, stroke, composite ischemic events, or other arterial thrombotic events was not different between the two treatments (18.6 vs 20.3%; HR, 0.94; 95% CI, 0.82 to 1.06; *P*=0.309). The rates of ischemic (1.5 vs 1.4%; *P*=0.530), hemorrhagic (0.5 vs 0.2%; *P*=0.069) or unknown (0.20 vs 0.06%; *P*=0.124) strokes were not different between the two treatments. The rates of life threatening or fatal (5.5 vs 5.6%; HR, 0.99; 95% CI, 0.77 to 1.26; *P*=0.911) and intracranial bleeding (0.5 vs 0.2%; HR, 2.83; 95% CI, 0.90

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to 8.90; *P*=0.075) were not different between the two treatments. The rate of other major bleeding was significantly higher with ticagrelor (6.8 vs 4.9%; HR, 1.38; 95% CI, 1.09 to 1.76; *P*=0.009). The rates of non-CABG-related (*P*=1.03), CABG-related (*P*=0.335), coronary procedure related (*P*=0.231), noncoronary procedure related (*P*=0.072) bleeding were not different between the two treatments. The rate of major and minor bleeding was significantly higher with ticagrelor (16.4 vs 14.4%; HR, 1.17; 95% CI, 1.01 to 1.36; *P*=0.0358).
Cannon et al[56] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	Substudy of PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing invasive procedures	N=13,408 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; total major bleeding Secondary: Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; components of the primary endpoint; all-cause mortality; stent thrombosis; other bleeding events; safety	Primary: At 12 months, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (9.0 vs 10.7%; HR, 0.84; 95% CI, 0.75 to 0.94; *P*=0.0025). The rate of major bleeding did not differ between ticagrelor and clopidogrel (*P*=0.8803). Secondary: Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (9.4 vs 11.2%; HR, 0.84; 95% CI, 0.75 to 0.94; *P*=0.0016). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, composite ischemic events or other arterial thrombotic events (9.4 vs 11.2%; HR, 0.85; 95% CI, 0.77 to 0.93; *P*=0.0005). The rates of MI (5.3 vs 6.6%; HR, 0.80; 95% CI, 0.69 to 0.92; *P*=0.0023) and vascular death (3.4 vs 4.3%; HR, 0.82; 95% CI, 0.68 to 0.98; *P*=0.0250) were significantly lower with ticagrelor. The rate of stroke was not different between the two treatments (1.2 vs 1.1%; HR, 1.08; 95% CI, 0.78 to 1.50; *P*=0.6460). The rate of all-cause mortality was significantly lower with ticagrelor (3.9 vs 5.0%; HR, 0.81; 95% CI, 0.68 to 0.95; *P*=0.0054). The rates of definite (1.3 vs 2.0%; HR, 0.64; 95% CI, 0.46 to 0.88; *P*=0.0054), definite or probable (2.2 vs 3.0%; HR, 0.73; 95% CI, 0.57 to 0.94; *P*=0.0142)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and total (definite, probable or possible) (2.8 vs 3.8%; HR, 0.73; 95% CI, 0.59 to 0.92; *P*=0.0068) stent thrombosis were significantly lower with ticagrelor. The rates of life-threatening or fatal (*P*=0.6095), intracranial (*P*=0.4364) and other major bleeding (*P*=0.4030) were not different between the two treatments. The rates of total major or minor (*P*=0.0700), CABG-related (*P*=0.0710), coronary procedure-related (*P*=0.7768) and noncoronary procedure-related (*P*=0.3998) bleeding were not different between the two treatments. The rate of non-CABG-related bleeding was significantly higher with ticagrelor (8.9 vs 7.1%; HR, 1.26; 95% CI, 1.11 to 1.43; *P*=0.0004). The rate of dyspnea was significantly higher with ticagrelor (13.9 vs 8.0%; *P*<0.0001). Of the patients experiencing dyspnea, 0.8 and 0.2% discontinued treatment (*P* value not reported).
Steg et al[57] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed	Substudy of the PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with ST-segment elevation or left bundle-branch block	N=7,544 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: Composite endpoint of vascular death or MI (excluding silent); composite endpoint of all-cause mortality, MI (excluding silent), or stroke; composite endpoint of vascular death, total MI, stroke, severe recurrent cardiac ischemia, recurrent ischemia, TIA, or other arterial	Primary: At 12 months, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (9.4 vs 10.8%; HR, 0.87; 95% CI, 0.75 to 1.01; *P*=0.07). The rate of major bleeding did not differ between ticagrelor and clopidogrel (HR, 0.98; 95% CI, 0.8 to 1.14; *P*=0.76). Secondary: Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death and MI (8.4 vs 10.2%; HR, 0.82; 95% CI, 0.71 to 0.69; *P*=0.01). Ticagrelor was associated with significantly fewer events with regards to the composite of all-cause mortality, MI or stroke (9.8 vs 11.3%; HR, 0.87; 95% CI, 0.75 to 1.00; *P*=0.05). Ticagrelor was associated with significantly fewer events with regards to the composite of vascular death, MI, stroke, composite ischemic events or other arterial thrombotic events (13.3 vs 15.0%; HR, 0.87; 95% CI, 0.77 to 0.99; *P*=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 6 months.			thrombotic events; components of the primary endpoint; all-cause mortality; severe recurrent cardiac ischemia; recurrent ischemia; TIA; arterial thrombotic events; stent thrombosis; safety	The rates of MI (4.7 vs 5.8%; HR, 0.80; 95% CI, 0.65 to 0.98; *P*=0.03) and stroke (1.7 vs 1.0%; HR, 1.63; 95% CI, 1.07 to 2.48; *P*=0.02) were significantly lower with ticagrelor, but not vascular death (4.5 vs 5.5%; HR, 0.83; 95% CI, 0.67 to 1.02; *P*=0.07). The rate of all-cause mortality was significantly lower with ticagrelor (5.0 vs 6.1%; HR, 0.82; 95% CI, 0.67 to 1.00; *P*=0.05). The rates of severe recurrent cardiac ischemia (2.7 vs 3.2%; HR, 0.81; 95% CI, 0.61 to 1.06; *P*=0.13), TIA (0.2 vs 0.2%; *P* value not reported) and arterial thrombotic events (0.3 vs 0.4%; HR, 0.65; 95% CI, 0.28 to 1.51; *P*=0.32) were not different between the two treatments. The rate of recurrent ischemia was significantly lower with ticagrelor (4.3 vs 5.1%; HR, 0.81; 95% CI, 0.65 to 1.01; *P*=0.05). The rates of definite or probable stent thrombosis was not different between the two treatments (2.6 vs 3.4%; HR, 0.74; 95% CI, 0.55 to 1.00; *P*=0.05). The rates of definite, probable or possible (3.3 vs 4.3%; HR, 0.75; 95% CI, 0.57 to 0.99; *P*=0.04) and definite (1.6 vs 2.4%; HR, 0.66; 95% CI, 0.45 to 0.95; *P*=0.03) stent thromboses were significantly lower with ticagrelor. The rates of fatal (*P* value not reported), life-threatening (*P*=0.86), major (*P*=0.76), major and minor (*P*=0.43), CABG-related (major; *P*=0.30, major and minor; *P*=0.26), non-CABG-related (major; *P*=0.61, major and minor; *P*=0.11), procedure-related (major; *P*=0.83, major and minor; *P*=0.72) and major non-procedure-related (*P*=0.30) bleeding were not different between the two treatments. The rate of non-procedure-related major and minor bleeding was significantly lower with clopidogrel (5.1 vs 3.7%; HR, 1.31; 95% CI, 1.04 to 1.66; *P*=0.02). The rate of dyspnea was significantly higher with ticagrelor (12.6 vs 8.4%; *P*<0.0001), and caused significantly more treatment discontinuations (0.5 vs 0.1%; *P*=0.0004). Rates of bradycardia (*P*=0.83), syncope (*P*=0.18), heart block (*P*=0.64) and pacemaker insertion (*P*=0.20) were not different between the two treatments.
James et al[58]	Substudy of	N=15,202	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and CKD (creatine clearance <60 mL/minute)	12 months	Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: All-cause mortality, other bleeding events, safety	In patients with CKD, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (17.3 vs 22.0%; HR, 0.77; 95% CI, 0.65 to 0.90; *P*=0.13). In patients with CKD, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (15.1 vs 14.3%; HR, 1.07; 95% CI, 0.88 to 1.03; *P*=0.92). Secondary: In patients with CKD, the rate of all-cause mortality was not different between the two treatments (10.0 vs 14.0%; HR, 0.72; 95% CI, 0.58 to 0.89; *P*=0.16). In patients with CKD, the rates of major or minor (*P*=0.54), non-CABG-related major (*P*=0.77), fatal major (*P*=0.06) and intracranial bleeding (*P*=0.69) were not different between the two treatments. In patients with CKD, the rate of dyspnea was significantly less with clopidogrel (16.4 vs 11.5%; HR, 1.54; 95% CI, 1.27 to 1.88; *P*=0.04). In patients with CKD, the rate of ventricular pauses was no different between the two treatments (5.4 vs 4.6%; HR, 1.16; 95% CI, 0.51 to 2.52; *P*=0.56).
James et al[59] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance	Substudy of PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and diabetes	N=4,662 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major bleeding Secondary: All-cause mortality, MI, definite stent thrombosis, other bleeding events	Primary: In patients with diabetes, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (14.1 vs 16.2%; HR, 0.88; 95% CI, 0.76 to 1.03). In patients with diabetes, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (14.1 vs 14.8%; HR, 0.95; 95% CI, 0.81 to 1.12). Secondary: In patients with diabetes, the rate of all-cause mortality was not different between the two treatments (7.0 vs 8.7%; HR, 0.82; 95% CI, 0.66 to 1.01). In patients with diabetes, the rate of MI was not different between the two

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.				treatments (8.4 vs 9.1%; HR, 0.92; 95% CI, 0.75 to 1.13). In patients with diabetes, the rate of definite stent thrombosis was not different between the two treatments (1.6 vs 2.4%; HR, 0.65; 95% CI, 0.36 to 1.17). In patients with diabetes, the rates of non-CABG-related major (5.5 vs 4.9%; HR, 1.13; 95% CI, 0.86 to 1.49) and CABG-related major bleeding (9.3 vs 10.4%; HR, 0.90; 95% CI, 0.74 to 1.09) were not different between the two treatments.
Held et al[60] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	RETRO substudy of PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who underwent CABG	N=1,261 12 months	Primary: Composite endpoint of vascular death, MI, or stroke after CABG; major CABG-related bleeding Secondary: Individual components of the primary endpoint after CABG; all-cause mortality after CABG; other bleeding events after CABG	Primary: There was no difference between ticagrelor and clopidogrel with regards to the primary composite endpoint (10.6 vs 13.1%; HR, 0.84; 95% CI, 0.60 to 1.16; *P*=0.2862). There was no difference between ticagrelor and clopidogrel in the rate of major CABG-related bleeding (81.3 vs 80.1%; HR, 1.01; 95% CI, 0.90 to 1.15; *P*=0.84). Secondary: Rates of MI (excluding silent) (6.0 vs 5.7%; HR, 1.06; 95% CI, 0.66 to 1.68; *P*=0.8193) and stroke (2.1 vs 2.1%; HR, 1.17; 95% CI, 0.53 to 2.62; *P*=0.6967) were not different between the two treatments. The rate of vascular death was significantly less with ticagrelor (4.1 vs 7.9%; HR, 0.52; 95% CI, 0.32 to 0.85; *P*=0.0092). The rate of all-cause mortality was significantly less with ticagrelor (4.7 vs 9.7%; HR, 0.49; 95% CI, 0.32 to 0.77; *P*=0.0018). The rates of life-threatening or fatal CABG-related bleeding were not different between the two treatments (42.6 vs 43.7%; HR, 1.02; 95% CI, 0.87 to 1.21; *P*=0.77).
Wallentin et al[61] Ticagrelor 180 mg loading dose, followed by 90 mg	Genetic (CYP 2C19 and ABCB1) substudy of	N=10,285 12 months	Primary: Composite endpoint of vascular death, MI, or stroke; major	Primary: In patients with any loss-of-function allele, ticagrelor was associated with significantly fewer composite events compared to clopidogrel (8.3 vs 10.7%; HR, 0.77; 95% CI, 0.60 to 0.99; *P*=0.0380).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation		bleeding (loss-of-function allele) Secondary: Composite endpoint of vascular death or MI, definite stent thrombosis, major bleeding (gain-of-function allele), other bleeding events, net clinical benefit	In patients with any loss-of-function allele, there was no difference in the rate of major bleeding between ticagrelor and clopidogrel (10.8 vs 10.4%; HR, 1.04; 95% CI, 0.82 to 1.30; *P*=0.77). Secondary: In patients with any loss-of-function allele, ticagrelor was association with significantly fewer events with regards to the composite of vascular death or MI (7.4 vs 9.9%; HR, 0.73; 95% CI, 0.51 to 0.95; *P*=0.0184). In patients with any loss-of-function allele, the rate of definite stent thrombosis was not different between the two treatments (1.6 vs 2.2%; HR, 0.71; 95% CI, 0.36 to 1.37; *P*=0.30). In patients with any gain-of-function allele, the rate of major bleeding was not different between the two treatments (9.5 vs 10.8%; HR, 0.86; 95% CI, 0.71 to 1.05; *P*=0.13). In patients with any loss-of-function allele, the rates of non-CABG-related major (4.1 vs 3.0%; HR, 1.39; 95% CI, 0.93 to 2.08; *P*=0.11) and CABG-relate major bleeding (7.0 vs 7.8%; HR, 0.87; 95% CI, 0.66 to 1.14; *P*=0.31) were not different between the two treatments. In patients with any loss-of-function allele, the net clinical benefit was not different between the two treatments (14.7 vs 16.6%; HR, 0.88; 95% CI, 0.72 to 1.06; *P*=0.17). In patients with no loss-of-function, clopidogrel was significantly favored (13.4 vs 15.2%; HR, 0.86, 95% CI, 0.76 to 0.97; *P*=0.0172).
Mahaffey et al[62] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs	Substudy of PLATO[53] Adult patients hospitalized with documented ACS within the previous 24	N=1,413 12 months	Primary: Composite endpoint of the vascular death, MI, or stroke; major bleeding Secondary: Individual	Primary: Within the United States, there was no difference in the rate of the primary composite endpoint between ticagrelor and clopidogrel (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 1.75; *P*=0.1459). For the rest of world, ticagrelor was significantly favored (9.0 vs 11.0%; HR, 0.81; 95% CI, 0.74 to 0.90; *P*<0.001). Within the United States, there was no difference in the rates of major bleeding between ticagrelor and clopidogrel (11.3 vs 11.0%; HR, 1.05; 95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	hours, with or without ST-segment elevation who received treatment in the United States		components of the primary composite endpoint, all-cause mortality, other bleeding events	CI, 0.76 to 1.45; *P*=0.7572). Secondary: Within the United States, the rates of vascular death (3.4 vs 2.7%; HR, 1.26; 95% CI, 0.69 to 2.31; *P*=0.4468), MI (9.1 vs 6.7%; HR, 1.38; 95% CI, 0.95 to 2.01; *P*=0.0956) and stroke (1.0 vs 0.6%; HR, 1.75; 95% CI, 0.51 to 0.597; *P*=0.3730) were not different between the two treatments. For the rest of world, ticagrelor was significantly favored for reducing vascular death (3.8 vs 4.9%; HR, 0.77; 95% CI, 0.67 to 0.89; *P*=0.0005) and MI (5.1 vs 6.4%; HR, 0.80; 95% CI, 0.70 to 0.90; *P*=0.0004). Within the United States, the rate of all-cause mortality was not different between the two treatments (4.0 vs 3.4%; HR, 1.17; 95% CI, 0.68 to 2.01; *P*=0.5812). For the rest of world, ticagrelor was significantly favored (4.3 vs 5.6%; HR, 0.77; 95% CI, 0.67 to 0.88; *P*=0.0001). Within the United States, the rates of non-CAGB-related major (4.3 vs 3.7%; HR, 1.20; 95% CI, 0.70 to 2.04; *P*=0.5115) and major or minor bleeding (14.8 vs 13.6%; HR, 1.11; 95% CI, 0.84 to 1.84; *P*=0.4599) were not different between the two treatments. For the rest of the world, clopidogrel was significantly favored (3.9 vs 3.3%; HR, 1.19; 95% CI, 1.01 to 1.39; *P*=0.0330 and 14.5 vs 13.2%; HR, 1.11; 95% CI, 1.02 to 1.20; *P*=0.0114). For the entire population, results for the overall cohort yields an HR of 1.45 (95% CI, 1.01 to 2.09) favoring clopidogrel for maintenance aspirin doses ≥300 mg/day and HR of 0.77 (95% CI, 0.69 to 0.86) favoring ticagrelor for a maintenance aspirin dose ≤100 mg/day. The interaction between aspirin dose category and treatment is significant (*P*=0.00006). Within the United States, for patients receiving daily aspirin doses ≥300 mg, the event rate was 40 vs 27 with ticagrelor and clopidogrel (HR, 1.62; 95% CI, 0.99 to 2.94). The event rate was 19 vs 24 in patients receiving ≤100 mg/day of aspirin (HR, 0.73; 95% CI, 0.40 to 1.33).
Storey et al[63] Ticagrelor 180 mg loading dose, followed by 90 mg	Substudy of PLATO[53] Adult patients	N=199 12 months	Primary: FEV_1 after the completion of study treatment (six, nine,	Primary: FEV_1 values at the different evaluated time points were similar between treatments before and 20 minutes after inhalation of a β agonist (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.	hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation		or 12 months depending on phase of entry into the PLATO trial) Secondary: FEV_1 after one month of treatment and one month after the discontinuation of treatment, other measures of pulmonary function, safety	Secondary: There was no apparent change in FEV_1 before and 20 minutes after inhalation of a β agonist over time with either treatment and after the discontinuation of the study medication (*P* value not reported). Similar numbers of ticagrelor- and clopidogrel-treated patients showed >10% improvement in FEV_1 over time (seven and 12), with similar numbers of these patients showing improvement at the first visit after inhaled β agonist. The results of other pulmonary function parameters were also similar between the two treatments, with no apparent change over time and after discontinuation of study medication. Dyspnea or heart failure was noted in six and seven patients receiving ticagrelor and clopidogrel; pulmonary function parameters for these patients were consistent with findings in the rest of the treatment cohorts.
Becker et al[64] Ticagrelor 180 mg loading dose, followed by 90 mg BID vs clopidogrel 300 mg loading dose, followed by 75 mg QD Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. For patients who were	Substudy of PLATO[53] Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation	N=18,421 12 months	Primary: PLATO total major bleeding Secondary: Categories of PLATO major bleeding and minor bleeding combined, TIMI and GUSTO bleeding scales and transfusion of blood products	Primary: There was a similar incidence of PLATO major bleeding between patients randomized to receive clopidogrel and ticagrelor (11.6 vs 11.2%, respectively; *P*=0.43). The incidence of procedure-related (*P*=0.62), coronary procedure-related (*P*=0.73), and non-coronary procedure-related (*P*=0.22), non-CABG related procedural (*P*=0.55), CABG-related (*P*=0.31) and coronary angiography related (*P*=0.48) major bleeding were similar between the groups. There was a lower incidence of non-procedure related (spontaneous), total non-CABG-related and PCI related PLATO major bleeding with clopidogrel compared to ticagrelor (*P*=0.01, *P*=0.03 and *P*=0.05, respectively). Secondary: Total PLATO major or minor bleeding was significantly lower with clopidogrel compared to ticagrelor (14.6 vs 16.1%; *P*=0.01). Non-procedure-related

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin-naïve, 325 mg was the preferred loading dose. In patients receiving a stent, 325 mg was allowed for 6 months.				(spontaneous), non-CABG-related and PCI-related major or minor bleeding was also significantly lower with clopidogrel compared to ticagrelor (*P*<0.0001, *P*<0.0001 and *P*=0.01, respectively). Procedure-related, coronary procedure-related, non-coronary-related, CABG- and non-CABG-related and coronary angiography related bleeding did not differ between patients receiving clopidogrel or ticagrelor (*P*>0.05 for all). The percent of patients who experienced TIMI major bleeding was similar between the ticagrelor and clopidogrel treatment arms (7.9 vs 7.7%, respectively; *P*=0.57). Clopidogrel-treated patients experienced significantly less mild GUSTO bleeding compared to ticagrelor (*P*=0.01); however, no differences were reported for moderate (*P*=0.07) or major GUSTO bleeding (*P*=0.37). Transfusion of either packed red blood cells or whole blood for all clinical contexts did not differ between the treatment groups (8.5 vs. 8.3%; *P*=0.81).
Procedures and/or Surgery				
Banerjee et al[65] Clopidogrel for ≥1 year following PCI vs clopidogrel for <1 year following PCI Patients were free of cardiovascular events for 6 months after PCI, and had follow-up available for >12 months.	RETRO Patients who underwent PCI	N=530 2.4±0.8 years (mean follow-up)	Primary: All cause mortality Secondary: Incidence of major adverse cardiovascular events (composite of all cause death, nonfatal MI and repeat coronary revascularization by PCI or CABG)	Primary: Twelve (3.5%) patients who received clopidogrel for ≥1 year died compared to 28 (15%) patients who received clopidogrel for <1 year (*P*<0.001). On a multivariate analysis, the use of clopidogrel for ≥1 year was associated with lower mortality (HR, 0.28; 95% CI, 0.14 to 0.59; *P*<0.001), independent of traditional cardiovascular risk factors, clinical presentation and drug eluting stent use. Survival in the <1 and ≥1 year clopidogrel groups was 97 and 99%, respectively, at two years after PCI, and 80 and 93%, respectively, at three years after PCI. Secondary: There were no significant differences in the incidence of nonfatal MI (*P*=0.50), repeat coronary revascularization (*P*=0.16) or major adverse cardiovascular events between the two groups (*P*=0.10). Patients who experienced major

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				adverse cardiovascular events were significantly older and had preexisting CAD, and those who died were more likely to have chronic renal disease and heart failure.
CURRENT-OASIS 7[66] Clopidogrel 600 mg once, followed by 150 mg/day for 6 days, followed by clopidogrel 75 mg/day through day 30 (double dose) vs clopidogrel 300 mg once, followed by 75 mg/day for 6 days, followed by 75 mg/day through day 30 (standard dose) and aspirin ≥300 mg/day once, followed by 75 to 100 mg/day through day 30 (low-dose) vs aspirin ≥300 mg/day once, followed by 300 to 325 mg/day through day 30 (high-dose) All patients were to undergo early angiography	2x2 factorial design, RCT Patients ≥18 years of age who presented with a NSTE ACS or a STEMI	N=25,086 (n=17,263 underwent PCI) 30 days	Primary: Composite of cardiovascular death, MI or stroke Secondary: Composite of death from cardiovascular causes, MI, stroke or recurrent ischemia; the individual components of the primary endpoint; death from any cause; bleeding	Primary: The primary outcome occurred in 4.2% of patients in the double-dose group compared to 4.4% with the standard dose group (HR, 0.94; 95% CI, 0.83 to 1.06; *P*=0.30). Overall, 4.2% of the patients in the high-dose aspirin group had a primary outcome event compared to 4.4% of patients in the low-dose aspirin group (HR, 0.97; 95% CI, 0.86 to 1.09; *P*=0.61). A nominally significant interaction between the clopidogrel dose comparison and the aspirin dose comparison for the primary outcome was noted (*P*=0.04). Among patients assigned to high-dose aspirin, the primary outcome occurred in 3.8 and 4.6% in the double and standard clopidogrel dose groups (HR, 0.82; 95% CI, 0.69 to 0.98; *P*=0.03). Among patients assigned to low-dose aspirin, there was no significant difference between the double and standard clopidogrel groups (4.5 vs 4.2%; HR, 1.07; 95% CI, 0.90 to 1.26; *P*=0.46). Secondary: Consistent results were observed for each component of the primary outcome, as well as for the expanded composite endpoint for the clopidogrel and aspirin dose comparison. A nominally significant reduction in recurrent ischemia alone was associated with high-dose aspirin as compared to low-dose aspirin (0.3 vs 0.5%; HR, 0.63; 95% CI, 0.43 to 0.94; *P*=0.02). The rate of death from any cause did not differ significantly between the double and standard dose groups (2.3 vs 2.4%; HR with the double dose, 0.96; 95% CI, 0.82 to 1.13; *P*=0.61). Death from any cause occurred in 2.2 and 2.5% of patients in the high- and low-dose groups (HR, 0.87; 95% CI, 0.74 to 1.03; *P*=0.10). Major bleeding occurred in 2.5 and 2.0% of patients in the double and standard dose groups (HR, 1.24; 95% CI, 1.05 to 1.46; *P*=0.01). The aspirin groups did not differ significantly with respect to major bleeding (*P* value not reported). There was a nominally significant increase in the increase of minor bleeding among patients who received high-dose aspirin (HR, 1.13; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and PCI, if appropriate, no later than 72 hours after randomization.				1.00 to 1.27; *P*=0.04). There was a small increase in the incidence of major gastrointestinal bleeding among patients who received high-dose aspirin, as compared to those who received low-dose aspirin (0.4 vs 0.2%; *P*=0.04).
Sabatine et al[67] PCI-CLARITY Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 150 to 325 mg once, followed by 75 to 162 mg/day vs aspirin 150 to 325 mg once, followed by 75 to 162 mg/day	DB, MC, PC, RCT Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28)	N=1,863 30 days	Primary: Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization Secondary: MI or stroke before PCI, the primary end point from randomization to 30 days	Primary: Pretreatment with clopidogrel significantly reduced the primary end point following PCI compared to pretreatment without clopidogrel (3.6 vs 6.2%; adjusted OR, 0.54; 95% CI, 0.35 to 0.85; *P*=0.008). Pretreatment with clopidogrel also reduced the incidence of MI or stroke prior to PCI (4.0 vs 6.2%; OR, 0.62; 95% CI, 0.40 to 0.95; *P*=0.03). Secondary: Overall, pretreatment with clopidogrel significantly reduced the secondary outcome (7.5 vs 12.0%; adjusted OR, 0.59; 95% CI, 0.43 to 0.81; *P*=0.001). There was no significant excess in the rates of major or minor bleeding in patients receiving combination therapy compared to aspirin (2.0 vs 1.9%, respectively; *P*>0.99).
Mehta et al[68] PCI-CURE Prior to PCI, patients received aspirin plus clopidogrel or placebo After PCI, stented patients received OL aspirin plus a thienopyridine (clopidogrel or ticlopidine) for 2 to 4 weeks; after which administration of the randomly assigned study medication (clopidogrel or placebo) resumed until the end of the scheduled follow-up (3 to 12 months after initial randomization).	DB, RCT Patients with NSTE ACS from the CURE study undergoing PCI	N=2,658 8 months (average duration of follow-up after PCI)	Primary: Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of PCI; cardiovascular death or MI from time of PCI to scheduled end of trial Secondary: Not reported	Primary: Four and a half percent of patients in the aspirin plus clopidogrel group had the main primary end point compared to 6.4% in the aspirin group (*P*=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI or any revascularization (*P*=0.03), and of cardiovascular death or MI (*P*=0.047). Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or MI, including events before and after PCI (*P*=0.002). At follow-up, there was no significant difference in major bleeding between the groups (*P*=0.64). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Steinhubl et al[69] CREDO Clopidogrel 300 mg once (3 to 24 hours before PCI), followed by clopidogrel 75 mg/day vs placebo (3 to 24 hours before PCI), followed by clopidogrel 75 mg/day through day 28, followed by placebo All patients received aspirin 325 mg prior to PCI, followed by 325 mg/day through day 28, followed by 81 to 325 mg/day.	DB, MC, PC, RCT Patients undergoing PCI	N=2,116 12 months	Primary: One year incidence of the composite of death, MI or stroke; 28 day incidence of the composite of death, MI or urgent target vessel revascularization Secondary: Components of the composite end points, administration of clopidogrel <6 hours or ≥6 hours before PCI, need for target vessel revascularization or any revascularization at one year	Primary: Long-term (one year) clopidogrel plus aspirin was associated with a 26.9% RR in the combined risk of death, MI or stroke compared to aspirin (95% CI, 3.9 to 44.4; *P*=0.02; absolute reduction, 3.0%). Clopidogrel pretreatment did not significantly reduce the combined risk of death, MI or urgent revascularization at 28 days (-18.5%; 95% CI, -14.2 to 41.8; *P*=0.23). Secondary: A similar level of benefit was found in the individual components of the primary end point at one year, although individual outcomes were not significant (*P* values not reported). Treatment randomization did not appear to influence the rate of target vessel revascularization or any other revascularization during the follow-up period. Patients who had received clopidogrel at least six hours before PCI experienced a reduction in the relative combined risk of death, MI or stroke by 38.6% (95% CI, -1.6 to 62.9; *P*=0.051) compared to no reduction when treatment was given less than six hours before PCI (*P*=0.051). Risk of major bleeding at one year increased, but not significantly (8.8 vs 6.7%; *P*=0.07).
Lev et al[70] Clopidogrel 300 to 600 mg before PCI, followed by 75 mg/day for 3 to 12 months vs clopidogrel 300 to 600 mg immediately after PCI, followed by 75 mg/day for 3 to 12 months	PRO Patients with chest pain and STEMI undergoing emergency PCI	N=292 6 months	Primary: Occurrence of TIMI myocardial perfusion grade 3 after PCI Secondary: Incidence of re-infarction, stent thrombosis, target vessel revascularization, death	Primary: TIMI myocardial perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group (85 vs 71%; *P*=0.01). Secondary: The incidence of re-infarction at 30 days (0 vs 3.2%, respectively; *P*=0.04) and six months (0.6 and 3.9%, respectively; *P*=0.09) was lower in the pretreatment group. The incidence of stent thrombosis at 30 days (0 vs 2.4%, respectively; *P*=0.08) and six months (0 and 3.9%, respectively; *P*=0.02) was lower in the pretreatment group than in the no pretreatment group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients were treated with aspirin 325 mg before PCI, followed by aspirin (dose not specified) for 3 to 12 months.				The incidence of death and target vessel revascularization were not significantly different between the two groups at 30 days (*P*=0.6 and *P*=1.0) or six months (*P*=0.7 and *P*=0.9).
Han et al[71] Clopidogrel 600 mg once, followed by 75 mg/day vs clopidogrel 600 mg once, followed by 150 mg/day All patients received aspirin 300 mg/day. All patients received dual antiplatelet therapy on admission followed by maintenance dose administration according to study protocol and PCI was performed within 48 hours of admission.	RCT Patients ≥18 years of age, diagnosed with ACS, planned pretreatment with 600 mg clopidogrel loading dose, presence of ≥1 severe coronary stenosis requiring PCI located in native arteries and suitable for drug eluting stent implantation	N=813 30 days	Primary: Major adverse cardiac event (composite of cardiac death, nonfatal MI and urgent target vessel revascularization) Secondary: Stent thrombosis, major and minor bleeding events	Primary: A total of 13 patients reached the primary end points, including four (1.0%) patients in the 150 mg group and nine (2.2%) patients in the 75 mg group (*P*>0.05). There was no significant difference in cumulative major adverse cardiac event-free survival between the two groups. The incidences of MI (two vs five; *P*>0.05), urgent target vessel revascularization (three vs eight; *P*>0.05) and cardiac death (one vs one; *P*>0.05) were similar between the two groups. Secondary: The incidence of stent thrombosis (zero vs six; *P*<0.05) was significantly lower in the 150 mg group compared to the 75 mg group. There was no significant differences between both groups regarding the risk of major (one vs zero; *P*>0.05) or minor (two vs one; *P*>0.05) bleedings.
Bertrand et al[72] CLASSICS Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 325 mg/day vs clopidogrel 75 mg/day plus	RCT Patients receiving a stent placement	N=1,020 28 days	Primary: Major peripheral or bleeding complications, neutropenia, thrombocytopenia, early discontinuation due to non-cardiac adverse event	Primary: Primary end point occurred in 4.6% of patients in the combined clopidogrel groups and in 9.1% of patients in the ticlopidine group (RR, 0.50; 95% CI, 0.31 to 0.81; *P*=0.005). Secondary: Overall rates of major adverse cardiac events (cardiac death, MI, target lesion revascularization) were low and comparable between treatment groups (1.2% with clopidogrel loading dose, 1.5% with clopidogrel without the loading dose and 0.9% with ticlopidine; *P* values are nonsignificant for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
aspirin 325 mg/day vs ticlopidine 250 mg BID plus aspirin 325 mg/day			Secondary: Incidence of cardiac events	
Leon et al[73] Aspirin 325 mg/day vs aspirin 325 mg/day plus warfarin vs aspirin 325 mg/day plus ticlopidine 250 mg BID	MC, RCT Patients receiving a stent	N=1,653 30 days	Primary: Composite of death, revascularization of target lesion, angiographically evident thrombosis or MI within 30 days Secondary: Achievement of <50% residual stenosis without death or emergency bypass surgery, procedure-related MI, hematologic dyscrasias, hemorrhagic and vascular surgical complications	Primary: The primary end point was observed in 38 patients; 3.6% assigned to aspirin, 2.7% assigned to aspirin plus warfarin and 0.5% assigned to aspirin plus ticlopidine (*P*=0.001 for the comparison of all three groups). Secondary: Compared to aspirin and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis (*P*=0.001) following coronary stenting. Hemorrhagic complications occurred in 10 patients; 1.8% with aspirin, 6.2% with aspirin plus warfarin and 5.5% with aspirin plus ticlopidine (*P*<0.001 for the comparison of all three groups); the incidence of vascular surgical complications was 0.4, 2.0 and 2.0%, respectively (*P*=0.02). There were no significant differences in the incidence of neutropenia or thrombocytopenia among the three treatment groups and the overall incidence was 0.3% (*P* values not reported).
Lee et al[74] DECLARE-DIABETES Aspirin 200 mg/day plus clopidogrel 300 mg once, followed by 75 mg/day beginning ≥24 hours before stent placement and continued for ≥6 months	MC, PRO, RCT Diabetic patients ≥18 years of age undergoing drug eluting stent implantation	N=400 9 months	Primary: In-stent late loss at six months Secondary: In-segment late loss and restenosis rate at six months; stent thrombosis, target vessel	Primary: At six months, the in-stent late loss was significantly lower in the triple therapy vs dual therapy group (0.25±0.53 vs 0.38±0.54 mm; *P*=0.025). Secondary: At six months, the in-segment late loss (0.42±0.50 vs 0.53±0.49 mm; *P*=0.031) and restenosis (8.0 vs 15.6%; *P*=0.033) were significantly lower in the triple therapy group vs dual therapy group. At nine months, there was no difference in the rate of stent thrombosis (0 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs aspirin plus clopidogrel (as above) plus cilostazol 200 mg immediately after stent placement and continued for 6 months at 100 mg BID			revascularization, major adverse cardiac events (death, MI, and target lesion revascularization) at nine months; safety	0.5%; *P*=0.999). Target vessel revascularization was lower in the triple therapy group vs dual therapy group (3.5 vs 8.0%; *P*=0.053). At nine months, major adverse cardiac events tended to be lower in the triple therapy group than in the dual therapy group (3.0 vs 7.0%; *P*=0.066). Drug discontinuation was more common in the triple therapy group vs the dual therapy group (14.5 vs 2.5%; *P*<0.001) with skin rash and gastrointestinal disturbance the most common reasons for termination of cilostazol.
Wiviott et al[75] TRITON-TIMI 38 Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	DB, MC, PG, RCT Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours	N=13,608 6 to 15 months (median, 14.5 months)	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Composite of death from cardiovascular causes, nonfatal MI and need for urgent target vessel revascularization; composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or rehospitalization due to a cardiac ischemic event; urgent target vessel revascularization; stent thrombosis; safety	Primary: The rate of the composite endpoint was significantly lower in the prasugrel group (9.9%) than in the clopidogrel group (12.1%; HR, 0.81; 95% CI, 0.73 to 0.90; *P*<0.001). Each individual endpoint was analyzed separately and of the three, only nonfatal MI was reduced significantly greater in the prasugrel group (7.4%) than in the clopidogrel group (9.7%; HR, 0.76; 95% CI, 0.67 to 0.85; *P*<0.001).There were no significant differences reported in the rate of death from cardiovascular causes or in nonfatal stroke. A significant reduction was seen in the prasugrel group by day three with a 4.7% composite rate of death compared to 5.6% in the clopidogrel group (HR, 0.82; 95% CI, 0.71 to 0.96; *P*=0.01). Secondary: The composite endpoint of the rate of death from cardiovascular causes, nonfatal MI and need for urgent target vessel revascularization was significantly less in the prasugrel group (10.0%) compared to the clopidogrel group (12.3%; HR, 0.81; 95% CI, 0.73 to 0.89; *P*<0.001). The composite endpoint of the rate of death from cardiovascular causes, nonfatal MI, nonfatal stroke or rehospitalization due to a cardiac ischemic event was also significantly less in the prasugrel group (12.3%) than in the clopidogrel group (14.6%; HR, 0.84; 95% CI, 0.76 to 0.92; *P*<0.001). Urgent target vessel revascularization was found to be significantly less in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	after symptom onset if PCI was planned or within 14 days after receiving medical treatment for STEMI			prasugrel group (2.5%) than in the clopidogrel group (3.7%; HR, 0.66; 95% CI, 0.54 to 0.81; *P*<0.001). Stent thrombosis was found to be significantly less in the prasugrel group (1.1%) than in the clopidogrel group (2.4%; HR, 0.48; 95% CI, 0.36 to 0.64; *P*<0.001). The relative rate of non-CABG related TIMI major bleeding was increased by 32.0% in the prasugrel group compared to the clopidogrel group (HR, 1.32; 95% CI, 1.03 to 1.60; *P*=0.03). Life-threatening bleeding was significantly greater in the prasugrel group (1.4%) compared to the clopidogrel group (0.9%; HR, 1.52; 95% CI, 1.08 to 2.13; *P*<0.01). Fatal bleeding was significantly greater in the prasugrel group (0.4%) compared to the clopidogrel group (0.1%; HR, 4.19; 95% CI, 1.58 to 11.11; *P*=0.002). CABG related TIMI major bleeding was seen in 13.4% of patients in the prasugrel group compared to 3.2% in the clopidogrel group (HR, 4.73; 95% CI, 1.90 to 11.82; *P*<0.001). The rate of death from cardiovascular causes was not significantly different between the two treatment groups with a rate of 2.1% in the prasugrel group and 2.4% in the clopidogrel group (HR, 0.89; 95% CI, 0.70 to 1.12; *P*=0.31). Overall mortality was not significantly different between the two treatment groups (HR, 0.95; 95% CI, 0.78 to 1.16; *P*=0.64).
Wiviott et al[76] Prasugrel 60 mg once, followed by 10 mg/day vs	Subanalysis of TRITON-TIMI 38[73] TRITON-TIMI 38 patients with a median age of 63	N=13,608 (n=3,146 diabetes population) 6 to 15 months	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary:	Primary: The composite endpoint in patients with diabetes was significantly lower in the prasugrel group (12.2%) than in the clopidogrel group (17.0%; HR, 0.70; 95% CI, 0.58 to 0.85; *P*<0.001). A 14.0% overall reduction in the primary endpoint was seen in the prasugrel and no diabetes group compared to the clopidogrel group (HR, 0.86; 95% CI,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	stratified by diabetes	(median, 14.5 months)	Rate of cardiovascular death, MI (fatal or nonfatal) or stent thrombosis; safety; net clinical benefit	0.76 to 0.98; *P*=0.02). Among the diabetes group the reduction was 30% in the prasugrel group compared to the clopidogrel group (HR, 0.70; 95% CI, 0.58 to 0.85; *P*<0.001). Secondary: The rate of cardiovascular death in patients with diabetes was not significantly lower in the prasugrel group (3.4%) than in the clopidogrel group (4.2%; HR, 0.85; 95% CI, 0.58 to 1.24; *P*=0.40). The rate of MI in patients with diabetes was significantly lower in the prasugrel group (8.2%) than in the clopidogrel group (13.2%; HR, 0.60; 95% CI, 0.48 to 0.76; *P*<0.001). The rate of MI in patients without diabetes was also significantly lower in the prasugrel group (8.7%) than in the clopidogrel group (7.2%; HR, 0.82; 95% CI, 0.72 to 0.95; *P*=0.006). There was an 18.0% reduction in MI among nondiabetic prasugrel patients compared to a 40.0% reduction in MI among diabetic prasugrel patients. The rate of stent thrombosis in patients with diabetes was significantly lower in the prasugrel group (2.0%) than in the clopidogrel group (3.6%; HR, 0.52; 95% CI, 0.33 to 0.84; *P*=0.007). The rate of TIMI major non-CABG bleeding in patients with diabetes was not significantly greater in the prasugrel group (2.5%) compared to the clopidogrel group (2.6%; HR, 1.06; 95% CI, 0.66 to 1.69; *P*=0.81). The rate of TIMI major or minor non-CABG bleeding in patients with diabetes was not significantly greater in the prasugrel group (5.3%) compared to the clopidogrel group (4.3%; HR, 1.30; 95% CI, 0.92 to 1.82; *P*=0.13). The rate of net clinical benefit was significantly greater in the prasugrel group (14.6%) than in the clopidogrel group (19.2%; HR, 0.74; 95% CI, 0.62 to 0.89; *P*=0.001).
Montalescot et al[77] Prasugrel 60 mg once,	Subanalysis of TRITON-TIMI 38[73]	N=13,608 (n=3,534 STEMI	Primary: Composite of death from cardiovascular	Primary The composite rate of death in all patients with a STEMI was significantly lower in the prasugrel group (10.0%) than in the clopidogrel group (12.4%; HR,

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followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	TRITON-TIMI 38 patients with a median age of 58 and 59 in the prasugrel and clopidogrel groups respectively, with STEMI status stratified into either primary PCI (those enrolled within 12 hours of symptom onset) or secondary PCI (those enrolled between 12 hours and 14 days after symptom onset)	population) 6 to 15 months (median, 14.5 months)	causes, nonfatal MI or nonfatal stroke at 15 months Secondary: Composite of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization at 30 days; stent thrombosis; composite of cardiovascular death or nonfatal MI; all individual components of composite endpoints; all cause death rate; safety	0.79; 95% CI, 0.65 to 0.97; *P*=0.022). When examined by type of STEMI prasugrel only showed greater clinical efficacy in secondary PCI (9.6%) compared to clopidogrel (14.1%; HR, 0.65; 95% CI, 0.46 to 0.92; *P*=0.015). Secondary: The composite endpoint of the rate of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization was significantly lower in the prasugrel group (6.7%) than in the clopidogrel group (8.8%; HR, 0.75; 95% CI, 0.59 to 0.96; *P*=0.0205). This benefit continued to 15 months, with a rate of 9.6% in the prasugrel group and 12.0% in the clopidogrel group (HR, 0.79; 95% CI, 0.65 to 0.97; *P*=0.0250). When examined by type of STEMI, only secondary PCI patients treated with prasugrel (9.0%) had a lower rate of event compared to clopidogrel (13.9%; HR, 0.62; 95% CI, 0.43 to 0.89; *P*=0.009). Stent thrombosis was significantly lower in the prasugrel group (1.6%) than in the clopidogrel group (2.8%; HR, 0.58; 95% CI, 0.36 to 0.93; *P*=0.0232). The composite endpoint of cardiovascular death or nonfatal MI was significantly less in the prasugrel group (8.8%) than in the clopidogrel group (11.5%; HR, 0.75; 95% CI, 0.61 to 0.93; *P*=0.0071). When the clinical endpoints were examined individually the only event that was significantly less in the prasugrel group was nonfatal MI with a rate of 6.8% compared to 9.0% in the clopidogrel group (HR, 0.75; 95% CI, 0.59 to 0.95; *P*=0.016). All cause death was not found to be significantly different between the two groups (HR, 0.76; 95% CI, 0.54 to 1.07; *P*=0.113). TIMI major bleeding events unrelated to CABG surgery (*P*=0.645), and TIMI life-threatening bleeding events (*P*=0.750) were both not significantly different between the two treatment groups. TIMI major bleeding after CABG surgery was significantly greater in the prasugrel group (18.8%) than in the clopidogrel group (2.7%; HR, 8.19; 95% CI, 1.76 to 38.18; *P*=0.003).
Wiviott et al[78] Prasugrel 60 mg once,	Subanalysis of TRITON-TIMI 38[73]	N=13,608 (n=12,844 stent	Primary: Composite of death from cardiovascular	Primary: The primary endpoint was reduced significantly greater in stent patients in the prasugrel group (9.7%) compared to the clopidogrel group (11.9%; HR, 0.81;

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followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	TRITON-TIMI 38 patients who underwent PCI with stent implantation, with a median age of 60 and 61 for prasugrel and clopidogrel respectively in the bare metal stent group and 60 for both groups in the drug eluting stent cohort who received ≥1 coronary stent	population) 6 to 15 months (median 14.5 months)	causes, nonfatal MI or nonfatal stroke Secondary: Composite endpoint of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization; cardiovascular death; MI; urgent target vessel revascularization; stent thrombosis	95% CI, 0.72 to 0.90; *P*=0.0001). Drug eluting stent patients in the prasugrel group (9.0%) had a lower rate of the primary endpoint compared to the clopidogrel group (11.1%; HR, 0.82; 95% CI, 0.69 to 0.97; *P*=0.019). This was also seen in bare metal stent patients (10.0 vs 12.0%; HR, 0.80; 95% CI, 0.69 to 0.93; *P*=0.003). Secondary: The secondary endpoint was reduced significantly greater in stent patients in the prasugrel group (9.7%) compared to the clopidogrel group (11.9%; HR, 0.80; 95% CI, 0.72 to 0.89; *P*=0.0001). Drug eluting stent patients in the prasugrel group (9.0%) had a lower rate of primary endpoint compared to the clopidogrel group (11.0%; HR, 0.78; 95% CI, 0.66 to 0.92; *P*=0.004). This was also seen in bare metal stent patients in the prasugrel group (10.0%) compared to the clopidogrel group (12.0%; HR, 0.82; 95% CI, 0.71 to 0.95; *P*=0.009). Cardiovascular death was not significantly different in the entire stent cohort (*P*=0.17), nor was it significant in the drug eluting stent subgroup (*P*=0.25), or the bare metal stent subgroup (*P*=0.16). Rates of MI (fatal or nonfatal) were significantly less in the entire stent cohort that was treated with prasugrel (7.0%) than those treated with clopidogrel (10.0%; HR, 0.76; 95% CI, 0.67 to 0.86; *P*<0.0001). Rates were also significantly better in the individual prasugrel drug eluting stent (*P*=0.003) and bare metal stent (*P*=0.006) groups. Rates of urgent target vessel revascularization were significantly better in the entire stent cohort that was treated with prasugrel (2.0%) than those treated with clopidogrel (4.0%; HR, 0.68; 95% CI, 0.55 to 0.84; *P*<0.0003). Rates were only significantly better in the prasugrel drug eluting stent group (2.0%) compared to the clopidogrel group (4.0%; HR, 0.54; 95% CI, 0.38 to 0.76; *P*<0.0003). Rates of stent thrombosis were significantly better in the entire stent cohort

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				that was treated with prasugrel (0.88%) than those treated with clopidogrel (2.03%; HR, 0.42; 95% CI, 0.31 to 0.59; *P*<0.0001). Rates were significantly better in the prasugrel drug eluting stent group (0.70%) compared to the clopidogrel group (1.92%; HR, 0.35; 95% CI, 0.21 to 0.61; *P*<0.0001). Rates were significantly better in the prasugrel bare metal stent group (0.96%) compared to the clopidogrel group (1.92%; HR, 0.42; 95% CI, 0.31 to 0.59; *P*<0.0001). TIMI major bleeding not related to CABG was not significantly different with a rate of 2.0% seen in both treatment groups in the overall stent cohort (*P*=0.06).
Pride et al[79] Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	Subanalysis of TRITON-TIMI 38[73] TRITON-TIMI 38 patients who underwent PCI without stent implantation	N=13,608 (n=569 PCI population) 6 to 15 months (median, 14.5 months)	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or urgent target vessel revascularization; safety	Primary: The primary endpoint occurred in 14.2% of patients randomized to prasugrel and 17.1% of patients randomized to clopidogrel, a nonsignificant 18.0% RRR (HR, 0.82; 95% CI, 0.53 to 1.25; *P*=0.27). Overall, the unadjusted incidence of the primary composite outcome was significantly higher among patients who underwent PCI without stent implantation compared to those who received stents (15.6 vs 10.8%; *P*=0.001). Secondary: There were significant reductions in the incidence of urgent target vessel revascularization (3.6 vs 8.2%; HR, 0.46; 95% CI, 0.22 to 0.98; *P*=0.040), any target vessel revascularization (4.0 vs 10.1%; HR, 0.40; 95% CI, 0.20 to 0.82; *P*=0.009), the composite of any revascularization procedure (6.3 vs 12.9%; HR, 0.48; 95% CI, 0.27 to 0.87; *P*=0.014), and CABG surgery (12.5 vs 19.4%; HR, 0.62; 95% CI, 0.40 to 0.98; *P*=0.041) with prasugrel compared to clopidogrel. There were trends towards reductions in nonfatal MI (9.1 vs 13.5%; HR, 0.65; 95% CI, 0.39 to 1.10; *P*=0.11) and all MI (9.8 vs 13.9%; HR, 0.69; 95% CI, 0.41 to 1.14; *P*=0.14) favoring prasugrel. The incidence of all cause mortality, cardiovascular death and nonfatal and all stroke did not differ significantly between the groups. Non-CABG-related major bleeding was more frequent among patients randomized to prasugrel (2.1 vs 0.0%; *P*=0.033), and there was a trend toward

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				an increased incidence of non-CABG-related life-threatening bleeding (1.7 vs 0.0%; *P*=0.057). The incidence of intracranial hemorrhage and the composite of non-CABG TIMI major and minor bleeding did not differ significantly between the groups (4.3 vs 2.2%; HR, 1.85; 95% CI, 0.63 to 5.42), although there was no significant interactions between bleeding rates and treatment with prasugrel compared to clopidogrel as a function of PCI stent (stent vs no stent).
Antman et al[80] Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	Subanalysis of TRITON-TIMI 38[73] Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours after symptom	N=13,608 6 to 15 months (median, 14.5 months)	Primary: Rate of MI, stent thrombosis and urgent target vessel revascularization from randomization to day three and from day three to the end of the trial Secondary: Safety, percent net clinical benefit	Primary: The rate of MI was significantly lower in the prasugrel group (4.27%) than in the clopidogrel group by day three (5.24%; HR, 0.81; 95% CI, 0.70 to 0.95; *P*=0.008) and from day three until the end of the study (3.40 vs 4.79%; HR, 0.69; 95% CI, 0.58 to 0.83; *P*<0.0001). The rate of stent thrombosis was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.33 vs 0.67%; HR, 0.49; 95% CI, 0.29 to 0.82; *P*=0.006) and from day three until the end of the study (0.08 vs 1.74%; HR, 0.45; 95% CI, 0.32 to 0.64; *P*<0.0001). The rate of urgent target vessel revascularization was significantly lower in the prasugrel group than in the clopidogrel group by day three (0.54 vs 0.83%; HR, 0.66; 95% CI, 0.43 to 0.99; *P*=0.047) and from day three until the end of the study (1.94 vs 2.97%; HR, 0.65; 95% CI, 0.52 to 0.82; *P*=0.0003). Secondary: Through the first three days the rate of TIMI major non-CABG bleeding was numerically greater in the prasugrel group (0.74%) compared to the clopidogrel group (0.61%), however the difference between the two groups was not significant, (*P*=0.35). From day three to the end of the trial prasugrel was associated with a significantly greater risk of TIMI major non-CABG bleeding (1.71%) compared to clopidogrel (1.23%; HR, 1.39; 95% CI, 1.02 to 1.89; *P*=0.036). The rate of net clinical benefit was significantly greater in the prasugrel group than in the clopidogrel group by day three (6.19 vs 5.29%; HR, 0.85; 95% CI, 0.74 to 0.98; *P*=0.025) and from day three until the end of the study (8.33 vs

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	onset if PCI was planned or within 14 days after receiving medical treatment for STEMI			7.35%; HR, 0.87; 95% CI, 0.77 to 0.98; *P*=0.028).
Murphy et al[81] Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	Subanalysis of TRITON-TIMI 38[73] Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; for patients with unstable angina or NSTEMI ischemic symptoms lasting ≥10 minutes and occurring within 72 hours of randomization, a TIMI score ≥3 and either ST-segment deviation ≥1 mm or elevated cardiac necrosis biomarker levels; STEMI patients were included within 12 hours after symptom onset if PCI was	N=13,608 6 to 15 months (median, 14.5 months)	Primary: Total number of reoccurrences of the composite endpoint (rate of death from cardiovascular causes, nonfatal MI or nonfatal stroke), risk of second event following initial event, cardiovascular deaths following nonfatal event Secondary: Safety	Primary: Prasugrel demonstrated a significant overall reduction in subsequent events with 195 fewer total primary events compared to clopidogrel (HR, 0.79; 95% CI, 0.71 to 0.87; *P*<0.001). From the time of the first event to the recurrent event or last follow up a second event occurred in 10.8% of the prasugrel group compared to 15.4% in the clopidogrel group (HR, 0.65; 95% CI, 0.46 to 0.92; *P*=0.016). Cardiovascular death following the nonfatal event was also reduced in the prasugrel group (3.7%) compared to the clopidogrel group (7.1%; HR, 0.46; 95% CI, 0.25 to 0.82; *P*=0.008). Secondary: Recurrent bleeding events occurred infrequently, with TIMI major non-CABG bleeds in four patients treated with prasugrel and two with clopidogrel. There were also five repeat TIMI minor non-CABG bleeds in each treatment group. Among patients with at least one TIMI non-CABG major or minor bleeding event, 17 were reported in the prasugrel group and 13 were reported in the clopidogrel group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	planned or within 14 days after receiving medical treatment for STEMI			
O'Donoghue et al[82] Prasugrel 60 mg once, followed by 10 mg/day vs clopidogrel 300 mg once, followed by 75 mg/day Patients were also on concurrent aspirin (75 to 162 mg/day).	Subanalysis of TRITON-TIMI 38[73] TRITON-TIMI 38 patients stratified by GB IIb/IIIa inhibitor use	N=13,608 (n=7,414 GP IIb/IIIa inhibitor population) 30 days	Primary: Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke Secondary: Periprocedural MI, urgent target vessel revascularization, stent thrombosis, safety	Primary: There was a consistent benefit of prasugrel over clopidogrel in reducing cardiovascular death, MI or stroke at 30 days in patients who did (HR, 0.76; 95% CI, 0.64 to 0.90) and did not (HR, 0.78; 95% CI, 0.63 to 0.97; *P*=0.83) receive a GP IIb/IIIa inhibitor. Secondary: Prasugrel significantly reduced the risk of recurrent MI in subjects by approximately 25% regardless of the use of a GP IIb/IIIa inhibitor, including a comparable benefit toward a reduction in periprocedural MI across both subgroups. Patients treated with prasugrel also exhibited a significant reduction in urgent target vessel revascularization, irrespective of whether or not they were treated with a GP IIb/IIIa inhibitor (*P*=0.63). At the end of 30 days, prasugrel significantly reduced the risk of stent thrombosis by 54% in patients treated with a GP IIb/IIIa inhibitor (HR, 0.46; 95% CI, 0.29 to 0.71) and by 66% in patients not treated with a GP IIb/IIIa inhibitor (HR, 0.34; 95% CI, 0.17 to 0.65; *P*=0.46). In the overall cohort, prasugrel significantly increased the risk of TIMI non-CABG-related major or minor bleeding compared to clopidogrel (2.6 vs 2.1; HR, 1.26; 95% CI, 1.01 to 1.57; *P*=0.04). The excess risk of TIMI non-CABG-related major or minor bleeding observed with prasugrel was comparable regardless of whether a GP IIb/IIIa inhibitor was used (HR, 1.16; 95% CI, 0.89 to 1.50) or was not used (HR, 1.63; 95% CI, 1.05 to 2.52; *P*=0.19). The absolute excess in the risk of TIMI non-CABG-related major bleeding with prasugrel vs clopidogrel was 0.1% in patients treated with a GP IIb/IIIa inhibitor (1.2 vs 1.1%; HR, 1.06; 95% CI, 0.69 to 1.64) and 0.3% in subjects not treated with a GP IIb/IIIa inhibitor (0.9 vs 0.6%; HR, 1.47; 95% CI, 0.81 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				2.66), a difference that was not significantly different between subgroups (*P*=0.39). Similarly, the relative hazard of TIMI life-threatening bleeding with prasugrel compared to clopidogrel did not differ significantly in the presence or absence of a GP IIb/IIIa inhibitor (*P*=0.19). The incidence of procedure-related TIMI major bleeding was similar for subjects treated with prasugrel or clopidogrel and was not significantly influenced by the use of a GP IIb/IIIa inhibitor (*P* value not reported). Consistent with the overall trial, there was no significant difference in the incidence of intracranial hemorrhage between treatment arms in either stratum (*P* value not reported).
Wiviott et al[83] Prasugrel 60 mg loading dose, followed by 10 mg/day vs clopidogrel 600 mg loading dose, followed by 150 mg/day Maintenance dose administered upon PCI completion.	AC, DB, DD, RCT, XO Patients ≥18 years of age, who were scheduled to undergo cardiac catheterization with planned PCI for angina and ≥1 of the following: angiograph within 14 days with ≥1 PCI amendable legion, objective findings of ischemia within 8 weeks of study, or prior PCI or CABG	N=201 28 days (treatment periods were 14 days each)	Primary: Inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at six hours during the loading dose phase and at 14±2 days of the maintenance dose Secondary: Mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate, mean $P2Y_{12}$ assay percent inhibition, safety	Primary: For the loading dose phase, mean inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at six hours was significantly greater (higher inhibition of platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (74.8%) compared to the clopidogrel group (31.8%). The mean difference between the two groups was 43.2% (*P*<0.0001). For the maintenance dose phase mean inhibition of platelet aggregation with 20 μmol/L adenosine diphosphate at 14±2 days was significantly greater in the prasugrel group (61.3%) compared to the clopidogrel group (46.1%). The mean difference between the two groups was 14.9% (*P*<0.0001). Secondary: For the loading dose phase mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate was significantly lower (lower maximal platelet aggregation indication of greater antiplatelet effect) in the prasugrel group (18.9%) compared to the clopidogrel group (52.1%). The mean difference between the two groups was 33.1% (*P*<0.0001). For the maintenance dose phase mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate at 14±2 days was significantly lower in the prasugrel group (29.2%) compared to the clopidogrel group (40.9%). The mean difference between the two groups was 11.3% (*P*<0.0001). For the loading dose phase prasugrel also showed significantly greater platelet inhibition with the $P2Y_{12}$ assay (89.5%) compared to clopidogrel (38.4%). The mean difference between the two groups was 51.4% (*P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				For the maintenance dose phase prasugrel also showed significantly greater platelet inhibition with the $P2Y_{12}$ assay (83.3%) compared to clopidogrel (65.1%). The mean difference between the two groups was 18.9% (*P*<0.0001). There were no TIMI major bleeding episodes in either treatment group. For TIMI minor bleeding episodes 2% of patients in the prasugrel group experienced a minor bleed compared to 0% in the clopidogrel group. In the prasugrel group 18.6% of the patients reported a hemorrhagic event whether minor or major, compared to 14.1% in the clopidogrel group, however the difference was not significant (*P* value not reported).
Treatment of Thrombocythemia				
Anagrelide Study Group[84] Anagrelide 0.5 to 1 mg QID To be eligible, patients had to have responded to or have been treated for ≥4 weeks at 4 mg/day.	MC, Phase II Patients ≥18 years of age with a diagnosis of PV, CGL, ET or another myelo-proliferative process; with a history of thrombocytosis (>900,000/mm^3) on 2 occasions secondary to a myeloproliferative process	N=577 Duration not reported	Primary: Response to therapy (a reduction of platelet count from pretreatment levels by 50% or to <600,000 mm^3 for ≥4 weeks), changes in peripheral blood counts, dose of anagrelide to achieve a response, time to response, response duration, duration of therapy, maintenance dose of anagrelide, use with hydroxyurea, resistance to anagrelide, discontinuation of treatment, safety	Primary: Of the 577 patients, 424 were treated for at least four weeks. Of which, 396 (93%) met the criteria for response. Equivalent response rates were seen regardless of diagnosis (*P*=0.123). Time to a 50% reduction in platelet numbers after the start of treatment was a median of 11 days in the overall patient population. The pretreatment median platelet count (990,000/mm^3) was reduced to <500,000/mm^3 after six to 10 weeks in patients who responded, and remained at that level for up to two years. Longitudinal evaluation of platelet numbers showed a marked and sustained decrease relative to baseline for all responders (*P*<0.001) as well as for diagnostic subgroups (*P*<0.05). The median dose at first response was 2.57 mg/day (range, 2.52 to 2.88 mg/day) for all patients. The dose needed to achieve a response ranged from 0.5 to 9.0 mg/day; however, 95% of patients responded at a dose of ≤4 mg/day. The time to achieve a reduction in platelets ranged from a median of 2.6 to 3.9 weeks. No difference in the time to response was observed between diagnostic groups (*P*=0.447). The median duration of first response ranged from 7.7 months for PV patients

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Not reported	to >28.6 months for ET patients, with an overall median of 16.7 months. The median duration of therapy was 5.60 months, with a range of 0.03 to 61.00 months. A median daily dose of 1.7 to 2.8 mg/day was required to control platelet numbers at five to seven, 11 to 13 and 17 to 19 months after treatment. Eighty nine of the 114 patients with CGL also received hydroxyurea, and the median dose of anagrelide needed to control platelet numbers in these patients was the same as for the group as a whole. No enhanced toxicity was observed. Of the 577 patients, 424 were considered evaluable for response, and 396 had an initial response and maintained that response for at least four weeks at a constant dose of anagrelide. Of these, 16 (four percent) needed to have their dose increased by ≥0.5 mg/day on a long-term basis to maintain the same degree of control over platelet counts. Of the 195 patients who discontinued therapy, 94 did so because of an adverse effect of the drug, 68 for a reason unrelated to treatment, 21 because of death and 12 because the drug caused a response in platelet numbers but was not therapeutically adequate in the treating physician's opinion. In all patients who discontinued treatment, within four days the platelet count rose rapidly. In addition to the overall decrease in hemoglobin over time observed, it appears possible that anagrelide may affect red blood cell formation as well as thrombocytopoiesis. Although changes in blood pressure were noted in 12 patients, fluid retention was a much more common side effect; 132 (24%) patients had fluid retention or edema and 14 developed frank congestive heart failure. Two hundred nine (36%) patients complained of palpitations, forceful heartbeat or tachycardia; and 14 had an irregular pulse including four with atrial fibrillation or premature heart beats. The major neurologic side effect was headache, with dizziness as the second most frequent. Approximately 89 (19%) patients complained of nausea, which could possibly be related to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				treatment with anagrelide. Gas, eructation or bloating was noted by 49 (8%) and pain or gastric distress by a comparable number (n=48). The major lower gastrointestinal symptom was diarrhea (n=89; 15%). Secondary: Not reported
Silver et al[85] Anagrelide 0.5 to 1 mg QID Weekly adjustments to the dose were made to achieve and maintain a platelet count ≤600,000/µL. These patients previously received hydroxyurea therapy (hydroxyurea-resistant) before being treated with anagrelide. Patients fell into two groups: hydroxyurea-refractory patients and probably, but not definitely, hydroxyurea-refractory patients.	Subanalysis of Anagrelide Study Group[82] Patients with CML	N=38 Duration not reported	Primary: Efficacy, safety Secondary: Not reported	Primary: Of the 38 patients who previously received hydroxyurea, 27 (71%) patients met the criteria for response to anagrelide. After treatment, there were 27 responders, but 11 remained symptomatic. Following treatment, the mean platelet levels in responders and nonresponders were 250,000±360,400/µL. In one-third of the responders, the initial platelet count was reduced by 50%. At six to eight weeks, the median platelet count in two-thirds of the responders was <600,000/µL. The median time to best response in both subgroups was 7.1 weeks. Responders maintained their counts for a median of seven weeks and as long as eight months; thereafter, the platelet counts in each patient were affected by change in censored status of CML to accelerated or blast phase disease, by alternative chemotherapy for CML, marrow transplantation and by refusal of a physician to complete the paperwork. The symptoms of the group of patients with thrombosis included TIAs, MI, erythromelalgia, DVT, and ischemia with or without cutaneous ulceration of the extremities. Secondary: Not reported
Penninga et al[86] Anagrelide 0.5 mg/day for 7 days, followed by a dosage increase by 0.5 mg/week until an acceptable decline in platelet counts was recorded	MC, RETRO Patients with chronic myelo-proliferative disease	N=52 Duration not reported	Primary: Complete response (reduction in platelet counts to <$600x10^9$/L or to a minimum 50% of pre-treatment level for ≥4 weeks),	Primary: Forty one (79%) patients responded to treatment, with 39 (75%) patients being complete responders. All achieved a platelet count <$600x10^9$/L, and 34 (65%) patients achieved a platelet count <$400x10^9$/L. Eleven (21%) patients were nonresponders. The mean dose necessary to maintain response was 1.7 mg/day (range, 0.5

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			partial response (20 to 50% reduction of pretreatment level for ≥4 weeks), no response (<20% reduction in pretreatment platelet counts) Secondary: Adverse events	to 5 mg/day) and the mean daily dose for patients in the non-responder group was 2.7 mg/day (range, 0.5 to 8.5 mg/day). The time to response varied among the patients, mostly because some patients needed to have a temporary dose reduction because of adverse events. The mean time to response was 7.9 weeks. Secondary: Forty two (81%) patients developed adverse effects and 28 (54%) patients reported more than one adverse effect. The most common adverse effect was anemia. Headache and palpitations were the second most common adverse events. Most of the adverse events were seen within a month from initiation of treatment, with patients reporting them as generally mild and transient.
Birgegard et al[87] Anagrelide 1 to 8 mg/day Doses were evaluated until the lowest effective dose required to reduce and maintain platelet count <400 x10^9/L in symptomatic patients or <600 x10^9/L in asymptomatic patients was established. Patients who were receiving treatment with another agent to control platelets were switched over to anagrelide.	Noncomparative, OL, Phase II, PRO Patients with a diagnosis of myelo-proliferative disease and a platelet count >600 x10^9/L in symptomatic patients or >1,000 x10^9/L in all other patients	N=60 2 years	Primary: Clinical effects, short- and long-term tolerability, patient's management Secondary: Not reported	Primary: The overall response rate was 73% (67% complete responses [platelet count <400 x10^9/L or <600 x10^9/L in symptomatic and asymptomatic patients for ≥4 weeks], 6% partial response [reduction of the platelet count to ≥50% of the baseline value]) and the failure rate (platelet count that did not fall below <50% of the baseline value) was 27%. Primary treatment failure (n=16) was usually due to a lack of efficacy at a tolerable dose. In addition, another 14 patients withdrew from treatment before the end of the two year period. The most common reasons for discontinuing treatment were lack of efficacy at a tolerable dose and side effects while in complete response. Side effects included palpitations (70%), headache (52%), nausea (35%), diarrhea or flatulence (33%), edema (22%) and fatigue (23%). The frequency and severity of side effects was dose dependent. Patients and doctors rated the feasibility of anagrelide treatment on the 10-grade scale from 7.6 at three months to >9.0 at 24 months. The patients who continued treatment for the full two years (n=30) showed a high degree of satisfaction, as did their doctors. The hemoglobin level dropped significantly during treatment, this effect first occurring within one week after initiation of treatment (*P*=0.002). Two patients had a thromboembolic event occur during the study period.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Steurer et al[88] Anagrelide 0.5 mg BID for 14 days, followed by 1 mg BID and then the dosage was adjusted for each patient In patients pretreated with hydroxyurea or interferon-α, it was allowed to combine anagrelide with one of those compounds.	MC, Phase II Newly diagnosed or pretreated patients with ET, PV or CIMF	N=97 6 months	Primary: Platelet counts Secondary: Rate of clinical complications before and during anagrelide therapy, number of patients achieving response (complete, partial or failure to respond)	Primary: Platelet counts decreased significantly during the six month study period from a median baseline count of $743x10^9$/L (range, 335 to $1.912x10^9$/L) to $441x10^9$/L (range, 153 to $1.141x10^9$/L; *P*<0.001). Secondary: During the six months before the study, the rate of major thromboembolic complications was 5%. At the end of the study, the rate decreased to 2%. Seven patients had minor thromboembolic symptoms despite initiation of anagrelide treatment. At the start of the study, the rate of minor thromboembolic complications was 25%. After the study period, the rate decreased to 14%. Fifty patients qualified as complete responders and 25 patients had a very good partial response. The overall (complete, very good partial and partial; n=77) response rate was 79% when an ITT analysis was applied. Of the patient subgroups, the highest overall response rate of 82% was achieved in patients with no previous cytoreductive therapy. The lowest rate of 75% occurred among patients with PV.
Harrison et al[89] Hydroxyurea 0.5 to 1 mg/day vs anagrelide 0.5 mg BID Doses of hydroxyurea and anagrelide were adjusted to maintain the platelet count <400,000/mm^3. All patients received aspirin	OL, RCT Patients ≥18 years of age with ET who were at high risk for thrombotic or hemorrhagic events	N=809 39 months (median follow-up)	Primary: Composite of time from randomization until death from thrombosis, hemorrhage, arterial or venous thrombotic event or serious hemorrhage Secondary: Time to first arterial or venous thrombotic event or to the first serious	Primary: As compared to the hydroxyurea group, the anagrelide group had a significantly higher rate of the composite primary end point (OR, 1.57; 95% CI, 1.04 to 2.37; *P*=0.03). The estimated rate of the primary endpoint at five years was 16% (95% CI, 12 to 21) and 11% (95% CI, 7 to 14) in the anagrelide and hydroxyurea groups, with a median follow-up of 39 months. Secondary: Analyses of the secondary endpoints revealed significant differences between the two groups. Arterial thrombosis developed in more than twice as many anagrelide-treated patients compared to hydroxyurea treated patients (OR, 2.16; 95% CI, 1.27 to 3.69; *P*=0.004). There were significantly more TIAs in the anagrelide group as well (14 vs 1; OR, 5.72; 95% CI, 2.08 to 15.73; *P*<0.001). The rates of MI, unstable angina and thrombotic stroke were higher with anagrelide but not significantly different compared to hydroxyurea. There

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
75 mg/day. If aspirin was contraindicated, alternative agents were used (e.g., clopidogrel, dipyridamole).			hemorrhage; time to death; incidence of transformation to myelofibrosis, AML, myelodysplasia or PV; control of platelet count	was a significant increase in the rate of serious hemorrhage with anagrelide (OR, 2.61; 95% CI, 1.27 to 5.33; *P*=0.008), with gastrointestinal hemorrhage being most common (OR, 3.54; 95% CI, 1.33 to 9.44; *P*=0.01). The rate of venous thromboembolism with anagrelide was approximately one fourth that with hydroxyurea (OR, 0.27; 95% CI, 0.11 to 0.71; *P*=0.006), and there was a significantly lower rate of DVT with anagrelide (OR, 0.20; 95% CI, 0.06 to 0.71; *P*=0.009). Pulmonary emboli developed in seven patients, five of which were in the hydroxyurea group. The rates of death from any cause and death from thrombotic or hemorrhagic causes were not significantly different between the two groups, although the study was not powered to detect any difference in mortality. Anagrelide-treated patients had a significantly increased rate of transformation to myelofibrosis (OR, 2.92; 95% CI, 1.24 to 6.86; *P*=0.01). The estimated actuarial risk of myelofibrosis five years after trial entry was 2% (95% CI, 0 to 5) and 7% (95% CI, 3 to 10). Myelodysplasia or AML developed in 10 patients, four in the anagrelide group. Control of platelet count was similar in the two groups by nine months after trial entry and subsequently. At three and six months after trial entry, platelet counts in the anagrelide group were significantly higher than those in the hydroxyurea group (*P*<0.001 for both time points). PV developed in two patients, one in each treatment group.

*Agent not available in the United States.
Drug regimen abbreviations: BID=twice-daily, ER=extended-release, IR=immediate-release, QD=once-daily, QID=four times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, ITT=intention to treat, IRR=incidence rate ratio, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PP=per patient, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RRR=relative risk reduction, XO=cross over trial
Miscellaneous abbreviations: ACS=acute coronary syndrome, AF=atrial fibrillation, AML=acute myeloid leukemia, CABG=coronary artery bypass graft, CAD=coronary artery disease, CGL=chronic granulocytic leukemia, CML=chronic myeloid leukemia, CT=computerized tomography, DVT=deep vein thrombosis, ET=essential thrombocythemia, FEV_1=forced expiratory volume in one second, GFR=glomerular filtration rate, GP IIb/IIIa inhibitor=glycoprotein IIb/IIIa inhibitor, MI=myocardial infarction, MRI=magnetic resonance imaging, NSTE ACS=non-ST-segment elevation acute coronary syndromes, NSTEMI=non-ST-segment elevation myocardial infarction, PAD=peripheral arterial disease, PCI=percutaneous coronary intervention, PV=polycythemia ruba vera, STEMI=ST-segment elevation myocardial infarction, TIA=transient ischemic attack, TIMI=thrombolysis in myocardial infarction

Special Populations

Table 5. Special Populations[1-7]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Anagrelide	No dosage adjustment required in the elderly. Food and Drug Administration approved for use in children.	Not reported	Hepatic dosage adjustment is required; initiate therapy with 0.5 mg/day for ≥1 week with careful monitoring of cardiovascular effects. Contraindicated in severe hepatic impairment.	C	Unknown; use with caution.
Clopidogrel	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Not reported	No dosage adjustment required.	B	Unknown; use with caution.
Dipyridamole	No dosage adjustment required in the elderly. Safety and efficacy in children <12 years of age have not been established.	Not reported	Not reported	B	Yes (% not reported); use with caution.
Prasugrel	Use in patients ≥75 years of age is generally not recommended. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required in mild to moderate hepatic dysfunction. Not studied in severe hepatic dysfunction.	B	Unknown; use with caution.
Ticagrelor	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	No dosage adjustment required.	No dosage adjustment required in mild hepatic dysfunction; use with caution in moderate hepatic	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children have not been established.		dysfunction. Contraindicated with severe hepatic dysfunction.		
Ticlopidine	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Renal dosage adjustment may be required; a dosage reduction or the dis-continuation of therapy may be required.	Use is not recommended.	B	Unknown; use with caution.
Combination Products					
Aspirin/ extended-release dipyridamole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.*	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	D	Yes/Yes (% not reported for either component).

*****Due to the aspirin component, use of this product in children is not recommended.

Adverse Drug Events

Table 6. Adverse Drug Events[1-7]

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Cardiovascular							
Angina pectoris	1 to <5	-	✔	-	-	-	<1
Arrhythmia	1 to <5	-	-	-	-	-	<1
Atrial fibrillation/flutter	-	1 to 3	-	-	4.2	-	-
Cardiac failure	-	1 to 3	-	-	-	-	2
Cardiovascular disease	1 to <5	-	-	-	-	-	-
Chest pain	7.8	8	-	-	3.1	-	-
Edema	20.6	4	-	-	-	-	-
Heart failure	1 to <5	-	-	-	-	-	-
Hypertension	-	4	-	7.5	3.8	-	-
Hypotension	-	-	✔	-	3.2	-	-
Nodal arrhythmia	-	1 to 3	-	-	-	-	-
Palpitation	26.1	-	✔	-	-	-	-
Peripheral edema	8.5	-	-	-	-	-	-
Postural hypotension	1 to <5	-	-	-	-	-	-
Syncope	1 to <5	1 to 3	-	-	-	-	1
Tachycardia	7.5	-	✔	-	-	-	-
Vasodilation	1 to <5	-	-	-	-	-	-
Central Nervous System							
Amnesia	1 to <5	-	-	-	-	-	2
Anxiety	-	1 to 3	-	-	-	-	-
Cerebral edema	-	-	-	-	-	-	<1
Cerebral hemorrhage (includes intracranial and subarachnoid hemorrhage)	-	<1	-	-	-	<1	<1
Coma	-	-	-	-	-	-	<1
Confusion	1 to <5	<1	-	-	-	-	1
Depression	1 to <5	4	-	-	-	-	-
Dizziness	15.4	2 to 6	14	-	4.5	-	-
Fatigue	-	3	-	-	3.2	-	6

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Fever	-	1 to 3	-	-	-	-	-
Flushing	-	-	✔	-	-	-	-
Headache	43.5	3 to 8	2	5.5	6.5	-	38 (tolerance usually develops)
Insomnia	1 to <5	1 to 3	-	-	-	-	-
Lethargy/malaise	6.4	-	✔	-	-	-	2
Migraine	1 to <5	-	-	-	-	-	-
Nervousness	1 to <5	-	-	-	-	-	-
Pain	15	6	-	-	-	-	6
Seizure	-	-	-	-	-	-	2
Somnolence	1 to <5	-	-	-	-	-	1
Vertigo	-	1 to 3	-	-	-	-	-
Dermatologic							
Alopecia	1 to <5	-	✔	-	-	-	<1
Bullous eruption	-	<1	-	-	-	-	-
Eczema	-	1 to 3	-	-	-	-	-
Erythema multiforme	-	<1	-	-	-	<1	-
Erythema nodosum	-	-	-	-	-	<1	-
Exfoliative dermatitis	-	-	-	-	-	<1	-
Ischemic necrosis	-	<1	-	-	-	-	-
Lichen planus	-	<1	-	-	-	-	-
Maculopapular rash	-	<1	-	-	-	<1	-
Pruritus	5.5	3	✔	-	-	1	<1
Purpura	-	-	-	-	-	2	1
Rash	8.3	4	2	-	-	5	<1
Skin disease	1 to <5	-	-	-	-	-	-
Stevens-Johnson syndrome	-	-	-	-	-	<1	-
Toxic epidermal necrolysis	-	<1	-	-	-	-	-
Ulceration	-	-	-	-	-	-	<1
Urticaria	-	<1	-	-	-	<1	<1
Endocrine/Metabolic							
Dehydration	1 to <5	-	-	-	-	-	-

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Gout/hyperuricemia	-	1 to 3	-	-	-	-	-
Hypercholesterolemia/increased cholesterol	-	-	-	7	-	>10*	-
Hyponatremia	-	-	-	-	-	<1	-
Pancreatitis	-	<1	-	-	-	-	<1
Gastrointestinal							
Abdominal distress	-	-	6	-	-	-	-
Abdominal pain	16.4	2 to 6	-	-	-	4	18
Abnormal stools	-	-	-	-	-	1	-
Anorexia	7.7	-	-	-	-	-	1
Aphthous stomatitis	1 to <5	-	-	-	-	-	-
Bleeding	-	-	-	-	-	-	4
Chronic diarrhea	-	-	-	-	-	<1	-
Constipation	1 to <5	1 to 3	-	-	-	-	-
Diarrhea	25.7	2 to 5	✔	-	3.7	13	13
Dyspepsia	5.2	2 to 5	✔	-	-	7	>10
Dysuria	1 to <5	-	-	-	-	-	-
Eructation	1 to <5	-	-	-	-	-	-
Flatulence	10.2	-	-	-	-	2	-
Gastritis	1 to <5	-	-	-	-	-	-
Gastrointestinal distress	1 to <5	-	-	-	-	-	-
Gastrointestinal hemorrhage	-	1 to 3	-	-	-	<1	1
Hematemesis	-	-	-	-	-	-	<1
Hematuria	1 to <5	-	-	-	-	-	-
Hemorrhoids	-	-	-	-	-	-	1
Melena	1 to <5	-	-	-	-	-	-
Nausea	17.1	3	✔	-	4.3	7	16
Peptic ulcer	-	-	-	-	-	<1	-
Rectal bleeding	-	-	-	-	-	-	2
Retroperitoneal hemorrhage	-	<1	-	-	-	-	-
Vomiting	9.7	1 to 3	✔	-	-	2	8
Genitourinary							
Cystitis	-	1 to 3	-	-	-	-	-

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Hematuria	-	<1	-	-	-	<1	-
Interstitial nephritis	-	-	-	-	-	-	<1
Menorrhagia	-	-	-	-	-	<1	-
Papillary necrosis	-	-	-	-	-	-	<1
Renal failure	-	-	-	-	-	<1	<1
Serum creatinine increased	-	-	-	-	-	<1	-
Urinary tract infection	-	3	-	-	-	-	-
Uterine hemorrhage	-	-	-	-	-	-	<1
Hematologic							
Agranulocytosis	-	<1	-	-	-	<1	-
Anemia	1 to <5	1 to 3	-	-	-	-	2
Aplastic anemia	-	<1	-	-	-	<1	<1
Bleeding	-	Major, 4; minor, 5	-	Major, 2.2; minor, 2.4	Non-CABG-related, 8.7; CABG-related, 85.8	-	-
Disseminated intravascular coagulation	-	-	-	-	-	-	<1
Ecchymosis	1 to <5	-	-	-	-	-	-
Eosinophilia	-	-	-	-	-	<1	-
Epistaxis	1 to <5	3	-	-	-	-	-
Granulocytopenia	-	<1	-	-	-	-	-
Hematoma	-	1 to 3	-	-	-	-	-
Hemolytic anemia	-	-	-	-	-	<1	-
Hemorrhage	1 to <5	-	-	-	-	-	-
Hypochromic anemia	-	<1	-	-	-	-	-
Leukopenia	-	<1	-	-	-	-	-
Lymphadenopathy	1 to <5	-	-	-	-	-	-
Neutropenia	-	<1	-	-	-	2	-
Pancytopenia	-	<1	-	-	-	<1	<1
Prothrombin time prolonged	-	-	-	-	-	-	<1

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Purpura	-	5	-	-	-	-	-
Thrombocytopenia	1 to <5	<1	✔	-	-	<1	<1
Thrombocytosis	-	-	-	-	-	<1	-
Thrombosis	1 to <5	-	-	-	-	-	-
Thrombotic thrombocytopenic purpura	-	-	-	-	-	<1	-
Hepatic							
Acute liver failure	-	<1	-	-	-	-	-
Bilirubinemia	-	<1	-	-	-	-	-
Cholelithiasis	-	-	✔	-	-	-	<1
Elevated liver enzymes	1 to <5	-	-	-	-	-	-
Fatty liver	-	<1	-	-	-	-	-
Hepatic failure	-	-	-	-	-	-	<1
Hepatic necrosis	-	-	-	-	-	<1	-
Hepatitis	-	<1	✔	-	-	<1	<1
Jaundice	-	-	-	-	-	<1	<1
Liver dysfunction	-	-	✔	-	-	-	-
Liver function test abnormalities	-	<3	-	-	-	1	-
Neuromuscular/Musculoskeletal							
Arthralgia	1 to <5	6	-	-	-	-	6
Arthritis	-	1 to 3	✔	-	-	-	2
Arthropathy	-	-	-	-	-	<1	-
Arthrosis	-	-	-	-	-	-	1
Back pain	5.9	6	-	5	3.6	-	5
Fatigue	-	-	✔	-	-	-	-
Leg cramps	1 to <5	1 to 3	-	-	-	-	-
Myalgia	1 to <5	-	✔	-	-	-	1
Myositis	-	-	-	-	-	<1	-
Neuralgia	-	1 to 3	-	-	-	-	-
Paresthesia	5.9	1 to 3	✔	-	-	-	<1
Peripheral neuropathy	-	-	-	-	-	<1	-
Rhabdomyolysis	-	-	-	-	-	-	<1
Weakness	-	1 to 3	-	-	-	-	2

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Respiratory							
Asthma	1 to <5	-	-	-	-	-	-
Bronchiolitis obliterans-organized pneumonia	-	-	-	-	-	<1	-
Bronchitis	1 to <5	4	-	-	-	-	-
Bronchospasm	-	-	-	-	-	-	<1
Cough	6.3	3	-	-	4.9	-	2
Dyspnea	11.9	5	-	-	13.8	-	<1
Epistaxis	-	-	-	6.2	-	-	2
Hemoptysis	-	<1	-	-	-	-	<1
Hemothorax	-	<1	-	-	-	-	-
Intestinal pneumonitis	-	<1	-	-	-	-	-
Larynx edema	-	-	✔	-	-	-	-
Pharyngitis	6.8	-	-	-	-	-	-
Pneumonia	1 to <5	-	-	-	-	-	-
Pneumonitis	-	-	-	-	-	<1	-
Pulmonary edema	-	-	-	-	-	-	<1
Pulmonary hemorrhage	-	<1	-	-	-	-	-
Respiratory disease	1 to <5	-	-	-	-	-	-
Rhinitis	1 to <5	4	-	-	-	-	-
Sinusitis	1 to <5	-	-	-	-	-	-
Tachypnea	-	-	-	-	-	-	<1
Upper respiratory infection	-	-	-	-	-	-	1
Other							
Abnormal vision	1 to <5	-	-	-	-	-	-
Allergic reaction	-	<1	-	-	-	-	<1
Allergic vasculitis	-	-	-	-	-	-	<1
Amblyopia	1 to <5	-	-	-	-	-	-
Anaphylactoid reaction/anaphylaxis	-	<1	-	-	-	<1	<1
Angioedema	-	<1	-	-	-	<1	<1
Ante-/peri-/postpartum bleeding	-	-	-	-	-	-	<1
Asthenia	23.1	-	-	-	-	-	-

Adverse Event	Single-Entity Agents						Combination Products
	Anagrelide	Clopidogrel	Dipyridamole	Prasugrel	Ticagrelor	Ticlopidine	Aspirin/ER Dipyridamole
Cataract	-	1 to 3	-	-	-	-	-
Chills	1 to <5	-	-	-	-	-	-
Conjunctival bleeding	-	-	-	-	-	<1	-
Conjunctivitis	-	1 to 3	-	-	-	-	-
Deafness	-	-	-	-	-	-	<1
Diplopia	1 to <5	-	-	-	-	-	-
Fever	8.9	<1	-	-	-	-	-
Flu symptoms	1 to <5	8	-	-	-	-	-
Hypersensitivity reaction	-	<1	✔	-	-	-	-
Lower weight infants	-	-	-	-	-	-	<1
Non-cardiac chest pain	-	-	-	-	3.7	-	-
Ocular/retinal hemorrhage	-	<1	-	-	-	-	-
Photosensitivity	1 to <5	-	-	-	-	-	-
Positive antinuclear antibody	-	-	-	-	-	<1	-
Reye's syndrome	-	-	-	-	-	-	<1
Sepsis	-	-	-	-	-	<1	-
Serum sickness	-	<1	-	-	-	<1	-
Stillbirths	-	-	-	-	-	-	<1
Systemic lupus erythematosus	-	-	-	-	-	<1	-
Taste disorder	-	<1	-	-	-	-	-
Tinnitus	1 to <5	-	-	-	-	-	-
Vasculitis	-	<1	-	-	-	<1	-
Visual field abnormality	1 to <5	-	-	-	-	-	-

CABG=coronary artery bypass graft surgery
*Increases of eight to 10% within one month of therapy.
-Event not reported or incidence <1%.
✔ Percent not specified.

Contraindications/Precautions

Anagrelide is contraindicated with severe hepatic impairment.[1] Clopidogrel is contraindicated with active pathological bleeding such as peptic ulcer or intracranial hemorrhage, and with hypersensitivity to clopidogrel or any component of the product.[2] Dipyridamole is contraindicated with a hypersensitivity to dipyridamole and any other component of the product.[3] Prasugrel is contraindicated with active pathological bleeding such as peptic ulcer or intracranial hemorrhage, a history of prior transient ischemic attack or stroke, and with hypersensitivity to prasugrel or any component of the product.[4] Ticagrelor is contraindicated with known active bleeds which may include peptic ulcer disease or history of intracranial hemorrhage. Specifically, patients with intracranial hemorrhage may be at risk for recurrent episodes. Ticagrelor is also contraindicated with severe hepatic dysfunction.[7] Ticlopidine is contraindicated with hypersensitivity to the drug, a presence of hematopoietic disorders such as neutropenia and thrombocytopenia or a past history of either thrombotic thrombocytopenic purpura or aplastic anemia, a presence of a hemostatic disorder or active pathological bleeding, and severe liver impairment.[5] Aspirin/extended-release dipyridamole is contraindicated with known hypersensitivity to any of the product components. Aspirin, a component of the combination product, is contraindicated with known allergy to nonsteroidal anti-inflammatory drugs and with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may also cause severe urticaria, angioedema, or bronchospasm. In addition, aspirin should not be used in children or teenagers with viral infections due to the risk of Reye syndrome.[6]

Anagrelide should be used with caution in patients with known or suspected heart disease, and only if the potential benefits of therapy outweigh the potential risks. Because of the positive inotropic effects and side effects of anagrelide, a pre-treatment cardiovascular examination is recommended in addition to careful monitoring during treatment. In humans, therapeutic doses of anagrelide may cause cardiovascular effects, including vasodilation, tachycardia, palpitations, and congestive heart failure. The potential risks and benefits of anagrelide in a patient with mild and moderate hepatic impairment should be assessed before treatment is initiated. In addition, interstitial lung diseases have been reported to be associated with the use of anagrelide in postmarketing reports. In most cases, the symptoms improved after discontinuation of anagrelide.[1]

In general, thienopyridines increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, treatment with a thienopyridine should be discontinued five days prior to surgery.[2,7] Specific to treatment with prasugrel, the agent should be used with caution in patients with increased risk factors for bleeding. Risk factors include those patients who are ≥75 years of age. In this patient population prasugrel should be avoided except in high-risk situations such as diabetes or a history of myocardial infarction (MI), where the agent's effect appears to be greater and its use may be considered. Additional bleeding risk factors include patients planning on undergoing a coronary artery bypass graft (CABG) surgery or other surgical procedures. Patients who are planning on undergoing a CABG should not be started on prasugrel and those currently being treated with the medication should have it discontinued at least seven days prior to surgery.[4] Furthermore, ticagrelor increased the overall risk of bleeding, both major and minor, to a greater extent compared to clopidogrel. This was true for non-CABG-related bleeding as opposed to CABG-related bleeding. Fatal and life-threatening bleeds were not increased. Risk factors for bleeding associated with ticagrelor include older age, a history of bleeding disorders, performance of percutaneous intervention (PCI), and use of concomitant medications which increase bleeding risk. Bleeding with ticagrelor should be suspected in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. Managing bleeding without stopping ticagrelor is recommended, as stopping ticagrelor increases the risk of subsequent cardiovascular events.[7] Thienopyridines also inhibit platelet aggregation for the lifetime of the platelet (seven to 10 days); therefore, withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. In addition, thrombocytopenic purpura, sometimes fatal, has been reported following the use of clopidogrel, sometimes after a short exposure (less than two weeks).[2] This warning is applied to all theinopyridines[2,4,5]

Clopidogrel is a prodrug; therefore, inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in cytochrome P450 (CYP) 2C19 and by concomitant medications that interfere with CYP2C19. Concomitant use of clopidogrel with the proton pump inhibitors omeprazole and esomeprazole should be avoided as both agents significantly reduce the antiplatelet activity of clopidogrel. Lapses in clopidogrel therapy should be avoided, and if clopidogrel must be temporarily discontinued, the medication should be restarted as soon as possible. Premature discontinuation of clopidogrel may increase the risk of cardiovascular events.[2]

Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe coronary artery disease. Chest pain may be aggravated in patients with underlying coronary artery disease who are receiving dipyridamole. Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration. In addition, dipyridamole should be used with caution in patients with hypotension since it can produce peripheral vasodilation.[3]

In patients who are being managed with PCI or stent placement, premature prasugrel discontinuation can potentially lead to an increased risk of stent thrombosis, MI, or death; therefore, lapses in therapy should be avoided. If the agent is discontinued due to an adverse event it should be restarted as soon as possible. The medication should also be used with caution in patients with conditions that have the propensity to bleed such as recent surgery or trauma, or severe hepatic impairment. Thrombotic thrombocytopenic purpura has been reported with prasugrel use. Hypersensitivity including angioedema has also been reported with prasugrel use. Reports from patients with a history of hypersensitivity reaction to other thienopyridines have been made.[4]

In the PLATO study, use of ticagrelor with maintenance doses of aspirin >100 mg/day decreased the effectiveness of ticagrelor. Because of this, after the initial loading dose of aspirin, usually 325 mg, a maintenance dose of 75 to 100 mg/day should be used in patients receiving ticagrelor. In addition, dyspnea was reported in 14% of patients receiving ticagrelor compared to eight percent of patients receiving clopidogrel. Dyspnea was mild to moderate in intensity, and frequently resolved during continued treatment. If new, prolonged or worsened dyspnea develops in a patient receiving ticagrelor, exclude underlying disease that may require treatment. If dyspnea is determined to be related to ticagrelor, no specific treatment is required; continue therapy without interruption. As mentioned previously, avoid interruption of ticagrelor treatment. If therapy must be temporarily discontinued, restart it as soon as possible. Discontinuation of ticagrelor increases the risk of MI, stent thrombosis and death.[7]

Neutropenia may occur suddenly in patients receiving ticlopidine. After withdrawal of ticlopidine, the neutrophil count usually rises to >1,200/mm^3 within one to three weeks. Rarely, thrombocytopenia may occur in isolation or together with neutropenia. Aplastic anemia, characterized by anemia, thrombocytopenia and neutropenia together with a bone marrow examination that shows decreases in the precursor cells for red blood cells, white blood cells, and platelets may also develop in patients receiving ticlopidine. Prompt treatment, which may include the use of drugs to stimulate the bone marrow, can minimize the mortality associated with aplastic anemia. Patients receiving ticlopidine must be monitored every two weeks throughout treatment for hematologic adverse reactions. Rare cases of agranulocytosis, pancytopenia, or leukemia have been reported in post-marketing experience, some of which have been fatal. In addition, ticlopidine causes increased serum cholesterol and triglycerides levels. The tolerance and safety of coadministration of ticlopidine with heparin, oral anticoagulants, or fibrinolytic agents have not been established. If a patient is switched from an anticoagulant or fibrinolytic drug to ticlopidine, the former drug should be discontinued prior to initiating ticlopidine.[5]

Intracranial hemorrhage was observed in patients receiving aspirin/dipyridamole during clinical trials. Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. Use of aspirin/dipyridamole in patients with a history of active peptic ulcer disease should be avoided. In addition, because of the aspirin component, patients receiving aspirin/dipyridamole should be counseled about the bleeding risks involved with chronic and heavy alcohol intake. As mentioned previously,

dipyridamole has a vasodilatory effect; therefore, patients with underlying coronary artery disease who are receiving aspirin/dipyridamole may experience chest pain. In addition, for stroke and transient ischemic attack patients for whom aspirin is indicated to prevent recurrent MI or angina pectoris, the aspirin component in the aspirin/dipyridamole combination product may not provide adequate treatment for the cardiac indications. Finally, aspirin/dipyridamole capsules are not interchangeable with the individual components of aspirin and dipyridamole tablets.[6]

These contraindications/precautions have resulted in the assignment by the Food and Drug Administration of the Black Box Warnings outlined below.

Black Box Warning for Plavix® (clopidogrel)[90]

WARNING
Diminished effectiveness in poor metabolizers: The effectiveness of clopidogrel is dependent on its activation to an active metabolite by the cytochrome P450 (CYP 450) system, principally CYP2C19. Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome or percutaneous coronary intervention than patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype and can be used an as aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

Black Box Warning for Effient® (prasugrel)[90]

WARNING
Bleeding risk: Prasugrel can cause significant, sometimes fatal, bleeding. Do not use prasugrel in patients with active pathological bleeding or a history of transient ischemic attack or stroke. In patients 75 years of age and older, prasugrel is generally not recommended because of the increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior myocardial infarction) in which its effect appears to be greater and its use may be considered. Do not start prasugrel in patients likely to undergo urgent coronary artery bypass graft surgery. When possible, discontinue prasugrel at least seven days prior to any surgery. Additional risk factors for bleeding include body weight less than 60 kg, propensity to bleed, and concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of nonsteroidal anti-inflammatory drugs). Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention), coronary artery bypass graft surgery, or other surgical procedures in the setting of prasugrel. If possible, manage bleeding without discontinuing prasugrel. Discontinuing prasugrel, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events.

Black Box Warning for Brilinta® (ticagrelor)[90]

WARNING
Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding. Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage. Do not initiate therapy with ticagrelor in patients planning to undergo urgent coronary artery bypass graft (CABG) surgery. When possible, discontinue ticagrelor at least five days prior to any surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention, CABG, or other surgical procedures in the setting of ticagrelor. If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events. Maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor; avoid such doses. After any initial dose, use with aspirin 75 to 100 mg/day.

Black Box Warning for ticlopidine[90]

WARNING
Ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis and thrombotic thrombocytopenic purpura and aplastic anemia. Neutropenia/agranulocytosis: Among 2,048 patients in clinical trials, there were 50 cases (2.4%) of neutropenia (less than 1,200 neutrophils/mm^3), and the neutrophil count was below 450/mm^3 in 17 of these patients (0.8% of the total population). Thrombotic Thrombocytopenic Purpura: One case of thrombocytopenic purpura was reported during clinical trials. Based on postmarketing data, United States physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of two to four million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated thrombocytopenic purpura may be as high as one case in every 2,000 to 4,000 patients exposed. Aplastic anemia: Aplastic anemia was not seen during clinical trials in stroke patients, but United States physicians reported about 50 cases between 1992 and 1998. Based on an estimated patient exposure of two to four million, and assuming an event reporting rate of 10% (the true rate is not known), the incidence of ticlopidine-associated aplastic anemia may be as high as one case in every 4,000 to 8,000 patients exposed. Monitoring of clinical and hematologic status: Severe hematologic adverse reactions may occur within a few days of the start of therapy. The incidence of thrombocytopenic purpura peaks after about three to four weeks of therapy and neutropenia peaks at approximately four to six weeks. The incidence of aplastic anemia peaks after about four to eight weeks of therapy. The incidence of the hematologic adverse reactions declines thereafter. Only a few cases of neutropenia, thrombocytopenic purpura, or aplastic anemia have arisen after more than three months of treatment. Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first three months of treatment, patients receiving ticlopidine must, therefore, be hematologically and clinically monitored for evidence of neutropenia or thrombocytopenic purpura. If any such evidence is seen, ticlopidine should be immediately discontinued.

Drug Interactions

Table 7. Drug Interactions[2,22,90]

Generic Name	Interacting Medication or Disease	Potential Result
Platelet inhibitors (aspirin, prasugrel)	NSAIDs	NSAIDs may reduce the cardioprotective effect of low-dose, uncoated aspirin. Aspirin and NSAIDs are also gastric irritants. The risk of bleeding may be increased when prasugrel and NSAIDs are administered concurrently.
Platelet inhibitors (aspirin, prasugrel)	Warfarin	Anticoagulant activity may be enhanced; increasing the risk of bleeding.
Platelet inhibitors (aspirin)	Angiotensin converting enzyme Inhibitors	Aspirin may reduce the hypotensive and vasodilator effects of angiotensin converting enzyme Inhibitors.
Platelet inhibitors (aspirin)	β-blockers	Salicylates (aspirin) may attenuate the blood pressure lowering effects of β blockers. In addition, the beneficial effects of β-blockers on left ventricular ejection fraction in patients with chronic heart failure may be attenuated.
Platelet inhibitors (aspirin)	Carbonic anhydrase inhibitors	Concomitant use may result in carbonic anhydrase inhibitor accumulation and toxicity.

Generic Name	Interacting Medication or Disease	Potential Result
Platelet inhibitors (aspirin)	Clopidogrel	The risk of life-threatening bleeding may be increased in high-risk patients with transient ischemic attack or ischemic stroke.
Platelet inhibitors (aspirin)	Heparin	Concomitant use may increase the risk of bleeding.
Platelet inhibitors (aspirin)	Influenza virus vaccine, intranasal	The risk of Reye syndrome may be increased.
Platelet inhibitors (aspirin)	Insulin	The serum glucose lowering action of insulin may be potentiated.
Platelet inhibitors (aspirin)	Methotrexate	Increased toxic effects of methotrexate may occur.
Platelet inhibitors (aspirin)	Sulfinpyrazone	Concomitant use may suppress the uricosuria produced by sulfinpyrazone.
Platelet inhibitors (aspirin)	Sulfonylureas	Increased hypoglycemic effect of sulfonylureas.
Platelet inhibitors (aspirin)	Valproic acid	Increased free fraction of valproic acid, possibly leading to toxic effects of valproic acid.
Platelet inhibitors (clopidogrel)	Azole antifungals (ketoconazole)	Ketoconazole may inhibit the antiplatelet effect of clopidogrel.
Platelet inhibitors (clopidogrel)	Proton pump inhibitors	Proton pump inhibitors (omeprazole, esomeprazole) may decrease the antiplatelet activity of clopidogrel.
Platelet inhibitors (dipyridamole)	Adenosine	Dipyridamole may potentiate the pharmacologic effects of adenosine, resulting in profound bradycardia after rapid bolus adenosine administration.
Platelet inhibitors (ticagrelor)	Digoxin	Concurrent use may result in increased digoxin levels.
Platelet inhibitors (ticagrelor)	HMG CoA reductase inhibitors (lovastatin, simvastatin)	Concurrent use may result in increased lovastatin and simvastatin plasma concentrations.
Platelet inhibitors (ticagrelor)	Strong cytochrome P450 3A inducers/inhibitors	Concurrent use may result in decreased/increased ticagrelor plasma concentrations.
Platelet inhibitors (ticlopidine)	Cyclosporine	Cyclosporine whole blood concentrations may decrease, producing a decrease in pharmacologic effects.
Platelet inhibitors (ticlopidine)	Hydantoins	Plasma hydantoin concentrations may be increased, resulting in an increase in adverse effects.
Platelet inhibitors (ticlopidine)	Theophyllines	Increased theophylline levels have been noted when administered concomitantly with ticlopidine.

NSAIDs=nonsteroidal anti-inflammatory drugs

Dosage and Administration

If intolerable headaches occur during administration of aspirin/extended-release dipyridamole during initial treatment, patients should switch to one capsule in the evening plus a low-dose aspirin in the morning. As the headaches become less of a problem, patients should return to the usual dosing regimen as soon as possible, usually within one week.[6]

Table 8. Dosing and Administration[1-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Anagrelide	Treatment of patients with	Treatment of patients with	Capsule:

Generic Name	Adult Dose	Pediatric Dose	Availability
	thrombocythemia, secondary to myeloproliferative disorders: Capsule: initial, 0.5 mg QID or 1 mg BID for ≥1 week; maintenance, adjust to the lowest effective dosage required to reduce and maintain platelet count <600,000/µL; maximum, 10 mg/day or 2.5 mg in a single dose*	thrombocythemia, secondary to myeloproliferative disorders:† Capsule: initial, 0.5 mg/day; maintenance, adjust to the lowest effective dosage required to reduce and maintain platelet count <600,000/µL; maximum, 10 mg/day or 2.5 mg in a single dose*	0.5 mg 1 mg
Clopidogrel	Recent MI, recent stroke, or established peripheral arterial disease: Tablet: 75 mg QD Reduce the rate of thrombotic cardiovascular events in patients with ACS, non-ST-elevation: Tablet: initial, 300 mg as a single loading dose; maintenance, 75 mg QD‡ Reduce the rate of thrombotic cardiovascular events in patients with ACS, ST-elevation MI: Tablet: 75 mg QD§	Safety and efficacy in children have not been established.	Tablet: 75 mg 300 mg
Dipyridamole	Prevention of postoperative thromboembolic complications of cardiac valve replacement: Tablet: 75 to 100 mg QID‖	Safety and efficacy in children <12 years of age have not been established.	Tablet: 25 mg 50 mg 75 mg
Prasugrel	Reduce the rate of thrombotic cardiovascular events in patients with ACS who are being managed with PCI: Tablet: initial, 60 mg as a single loading dose; maintenance, 5 to 10 mg QD¶	Safety and efficacy in children have not been established.	Tablet: 5 mg 10 mg
Ticagrelor	Reduce the rate of thrombotic cardiovascular events in patients with ACS: Tablet: initial, 180 mg (two tablets) as a single loading dose, maintenance, 90 mg BID#	Safety and efficacy in children have not been established.	Tablet: 90 mg
Ticlopidine	Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation: Tablet: 250 mg BID for up to 30 days** Reduce the risk of thrombotic stroke	Safety and efficacy in children have not been established.	Tablet: 250 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	(fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke: Tablet: 250 mg BID††		
Combination Products			
Aspirin/ extended-release dipyridamole‡‡	Reduce the risk of stroke in patients who have had transient ischemia or the brain or completed ischemic stroke due to thrombosis: Capsule: 25/200 mg BID	Safety and efficacy in children have not been established.	Capsule: 25/200 mg

ACS=acute coronary syndrome, BID=twice-daily, MI=myocardial infarction, PCI=percutaneous coronary intervention, QD=once daily, QID=four times daily
*The dosage should be increased by no more than 0.5 mg/day in any one week.
†An open-label safety and pharmacokinetic and pharmacodynamic study was conducted in children seven to 14 years of age.
‡Administer with daily aspirin (75 to 325 mg).
§May be administered with or without a loading dose.
‖As adjunct to the usual warfarin therapy. Aspirin is not to be administered concomitantly with coumarin anticoagulants.
¶The safety and efficacy of the 5 mg dose have not been prospectively studied.
#Patients receiving ticagrelor should receive a typical initial loading dose of aspiring (325 mg), followed by a daily maintenance dose of aspirin of 75 to 100 mg.
**Take with food and with antiplatelet doses of aspirin.
††Take with food.
‡‡Aspirin/dipyridamole is not interchangeable with the individual components of aspirin and dipyridamole.

Clinical Guidelines

Current guidelines are summarized in Table 9. Please note that due to the complexity of treatment regimens for stroke, stable and unstable angina, acute coronary syndromes, myocardial infarction, peripheral arterial disease, and secondary prevention of coronary artery disease (or myocardial infarction), the associated clinical guideline summaries focus on the role of platelet inhibitors in disease management.

While not Food and Drug Administration-approved for the indication, the use of clopidogrel in combination with aspirin to reduce the risk of major vascular events, including stroke, can be considered in patients with atrial fibrillation in whom oral anticoagulation with warfarin is considered unsuitable. Patients with atrial fibrillation, who have undergone percutaneous coronary intervention or revascularization surgery, may also be considered for low-dose aspirin and/or clopidogrel in combination with anticoagulation therapy to prevent myocardial ischemic events. Of note, this treatment strategy has not been thoroughly evaluated and puts a patient at an increased risk of bleeding.[91-92]

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Chest Physicians: **Antithrombotic and Thrombolytic Therapy 9th Edition (2012)**[9]	Antithrombotic therapy for atrial fibrillation (AF): • Patients with nonrheumatic atrial fibrillation o For patients with AF who are at low risk for stroke ($CHADS_2$=0), antithrombotic therapy is not recommended. For patients who choose antithrombotic therapy, aspirin (75 to 325 mg daily) is recommended over oral anticoagulants or aspirin plus clopidogrel. o For patients with AF who are at intermediate risk for stroke ($CHADS_2$=1), oral anticoagulation is recommended over aspirin (75 to 325 mg daily) and over aspirin plus clopidogrel. o For patients with AF who are at high risk for stroke ($CHADS_2$=2), oral anticoagulation is recommended over no therapy, aspirin or aspirin plus clopidogrel. For patients who are unable or choose not to take an oral anticoagulant, combination therapy with aspirin and

Clinical Guideline	Recommendations
	clopidogrel rather than aspirin alone is recommended. o Vitamin K antagonists (VKA) therapy is recommended over aspirin (75 to 325 mg daily) or aspirin plus clopidogrel in patients with AF and mitral stenosis. For patients who are unable or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel rather than aspirin alone is recommended. • Patients with AF and stable coronary artery disease (CAD) o In patients with stable CAD (no acute coronary syndrome [ACS] in previous year), and who choose oral anticoagulation, dose-adjusted VKA therapy alone (INR 2 to 3) is recommended over dose-adjusted VKA therapy plus aspirin. • Patients with AF and placement of an intracoronary stent o For patients with AF at high risk of stroke ($CHADS_2$≥2) during the first month after placement of a bare-metal stent or the first three to six months after placement of a drug-eluting stent, triple therapy (e.g., VKA therapy, aspirin and clopidogrel) is recommended over dual antiplatelet therapy. o After this initial period of triple therapy, VKA therapy (INR 2 to 3) plus a single antiplatelet drug rather than VKA monotherapy is recommended. o Twelve months following intracoronary stent placement, continuing antithrombotic therapy is suggested for AF patients with stable CAD. o For patients with AF at low to intermediate risk of stroke during the first 12 months after intracoronary stent placement (bare metal or drug eluting), dual antiplatelet therapy rather than triple therapy is recommended. o At 12 months after intracoronary stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease • Patients with AF and ACS who do not undergo intracoronary stent placement o For patients with AF at intermediate to high risk of stroke ($CHADS_2$≥1) who experience an ACS but do not undergo intracoronary stent placement, dose-adjusted VKA therapy (INR 2 to 3) plus single antiplatelet therapy is recommended for the first 12 months rather than dual antiplatelet therapy (aspirin plus clopidogrel) or triple therapy (warfarin, aspirin and clopidogrel). o After 12 months, antithrombotic therapy is suggested as for patients with AF and stable CAD. o For patients with AF at low risk of stroke ($CHADS_2$=0), dual antiplatelet therapy (aspirin and clopidogrel) is recommended rather than dose-adjusted VKA therapy plus single antiplatelet therapy or triple therapy (warfarin, aspirin and clopidogrel). After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease. <u>Antithrombotic and thrombolytic therapy for valvular disease</u> • Patients with patent foramen ovale (PFO) and atrial septal aneurysm o In patients with cryptogenic stroke and PFO or atrial septal aneurysm, aspirin (50 to 100 mg daily) is recommended over no aspirin. o In patients with cryptogenic stroke and PFO or atrial septal

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	aneurysm who experience recurrent events despite aspirin therapy, treatment with VKA therapy (INR 2 to 3) and consideration of device closure over aspirin therapy should be considered. o In patients with cryptogenic stroke and PFO, with evidence of deep vein thrombosis (DVT), VKA therapy should be initiated for three months (INR 2 to 3) and consideration should be given to device closure over no VKA therapy or aspirin therapy. • Antithrombotic therapy in the first three months after surgery o In patients with aortic bioprosthetic valves who are in sinus rhythm with no other indication for VKA therapy, aspirin (50 to 100 mg daily) should be used over VKA therapy in the first three months. o In patients with transcatheter aortic bioprosthetic valves, aspirin (50 to 100 mg daily) plus clopidogrel (75 mg daily) is recommended over VKA therapy or no antiplatelet therapy in the first three months. o In patients with a bioprosthetic valve in the mitral position, VKA therapy (INR 2 to 3) is recommended over no VKA therapy for the first three months after valve insertion. • Long-term antithrombotic therapy for patients with bioprosthetic valves o Aspirin therapy is recommended over no aspirin therapy in patients with biprosthetic valves in normal sinus rhythm after three months postoperative. • Antiplatelet agent in addition to VKA therapy for patients with mechanical aortic or mitral valve prostheses o In patients with a mechanical mitral or aortic valve and a low risk of bleeding, the addition of an antiplatelet agent to VKA therapy is recommended. • Antiplatelet agent therapy instead of VKA therapy o For patients with mechanical aortic or mitral valves, VKA therapy is recommended over antiplatelet agents. • Antithrombotic therapy after mitral valve repair o In patients undergoing mitral valve repair with a prosthetic band in normal sinus rhythm, antiplatelet therapy is preferred for the first three months over VKA therapy. • Patients undergoing aortic valve repair o Aspirin (50 to 100 mg daily) is recommended over VKA therapy in patients undergoing aortic valve repair. <u>Antithrombotic therapy and thrombolytic therapy for ischemic stroke</u> • Aspirin in patients with acute ischemic stroke: o Early aspirin therapy (within 48 hours) is recommended (initial dose, 160 to 325 mg) over no aspirin therapy in patients with acute ischemic stroke or transient ischemic attack (TIA). • Anticoagulation in patients with acute ischemic stroke: o Early aspirin therapy (within 48 hours) is recommended (initial dose, 160 to 325 mg) over no therapeutic parenteral anticoagulation in patients with acute ischemic stroke or TIA. • Antithrombotic therapy for the secondary prevention of noncardioembolic stroke: o Long-term treatment with an antiplatelet drug is recommended in patients with a history of noncardioembolic ischemic stroke, or TIA. o Aspirin monotherapy (75 to 100 mg daily), the combination of

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	aspirin (25 mg) plus extended-release dipyridamole (200 mg twice-daily), clopidogrel (75 mg daily) or cilostazol (100 mg twice-daily) monotherapy are all acceptable options for initial therapy. Aspirin, at a dose of 50 to 100 mg daily, is recommended over high-dose aspirin. o Of the recommended regimens for initial therapy, clopidogrel or aspirin/extended-release dipyridamole is recommended over aspirin or cilostazol. • Antithrombotic therapy for the secondary prevention of cardioembolic stroke: o Oral anticoagulation is recommended over aspirin, combination therapy with aspirin and clopidogrel or no antithrombotic therapy in patients with a history of ischemic stroke or TIA and AF. o Combination therapy with aspirin and clopidogrel is recommended over aspirin monotherapy in patients with a history of ischemic stroke or TIA and AF who are unsuitable or choose not to take an oral anticoagulant. • Antithrombotic therapy for stroke prevention in patients with a history of intracerebral hemorrhage (ICH): o Long-term antithrombotic therapy is not recommended for the prevention of ischemic stroke in patients with a history of a symptomatic primary ICH. <u>The Primary and Secondary Prevention of Cardiovascular Disease</u> • Primary prevention of cardiovascular disease: o Daily low-dose aspirin (75 to 100 mg daily) is recommended over no aspirin therapy in adults ≥50 years of age without symptomatic cardiovascular disease. • Choice of long-term antithrombotic therapy in patients with established CAD: o Patients with established CAD, (one-year or more post- ACS with prior revascularization, coronary stenoses >50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing) long-term single antiplatelet therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) over no antiplatelet therapy is recommended. Single antiplatelet therapy is recommended over dual therapy with aspirin plus clopidogrel. • Choice of antithrombotic therapy following ACS: o For patients less than one year post-ACS who have <u>not</u> undergone percutaneous coronary intervention (PCI): ▪ Dual antiplatelet therapy (ticagrelor 90 mg twice-daily plus low-dose aspirin 75 to 100 mg daily or clopidogrel 75 mg daily plus low-dose aspirin 75 to 100 mg daily) is recommended over single antiplatelet therapy. ▪ Ticagrelor (90 mg twice-daily plus low-dose aspirin) is recommended over clopidogrel (75 mg daily plus low-dose aspirin). o For patients with anterior myocardial infarction (MI) and left ventricular (LV) thrombus, or at high risk for LV thrombus (ejection fraction , 40%, anteroapical wall motion abnormality), who do not undergo stenting: ▪ Warfarin (INR 2 to 3) plus low-dose aspirin (75 to 100 mg daily) is recommended over single antiplatelet therapy or

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	dual antiplatelet therapy for the first three months. After three months discontinue warfarin and continue with dual antiplatelet therapy for up to 12 months as per the recommendations above. After 12 months, single antiplatelet therapy is recommended. o For patients less than one year post-ACS who have undergone PCI with stent placement: ▪ Dual antiplatelet therapy (ticagrelor 90 mg twice-daily plus low-dose aspirin 75 to 100 mg daily, clopidogrel 75 mg daily plus low-dose aspirin, or prasugrel 10 mg daily plus low-dose aspirin) is recommended over single antiplatelet therapy. ▪ Ticagrelor (90 mg twice-daily plus low-dose aspirin) is recommended over clopidogrel (75 mg daily plus low-dose aspirin). o For patients with anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality), who undergo bare-metal stent (BMS) placement: ▪ Triple therapy (warfarin, low-dose aspirin and clopidogrel) for one month over dual antiplatelet therapy. ▪ Warfarin and single antiplatelet therapy is recommended for the second and third month post-BMS over alternative regimens and alternative time frames for warfarin use. Thereafter, discontinue warfarin and use dual antiplatelet therapy for up to 12 months as per the recommendations above. After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations. o For patients with anterior MI and LV thrombus, or at high risk for LV thrombus (ejection fraction <40%, anteroapical wall motion abnormality) who undergo drug-eluting stent (DES) placement: ▪ Triple therapy (warfarin, low-dose aspirin and clopidogrel) is recommended for three to six months over alternative regimens and alternative durations of warfarin therapy. ▪ Discontinue warfarin and continue of dual antiplatelet therapy for up to 12 months as per the ACS recommendations. After 12 months, antiplatelet therapy is recommended as per the established CAD recommendations. • Antithrombotic therapy following elective PCI o For patients who have undergone elective PCI with placement of BMS: For the first month, dual anti platelet therapy with aspirin (75 to 325 mg daily) and clopidogrel (75 mg daily) is recommended over single antiplatelet therapy. o For the subsequent 11 months, dual antiplatelet therapy with combination of low-dose aspirin (75 to 100) mg daily and clopidogrel (75 mg daily) is recommended over single antiplatelet therapy. o After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. • For patients who have undergone elective PCI with placement of DES: o For the first three to six months, dual antiplatelet therapy with aspirin (75 to 325 mg daily) and clopidogrel (75 mg daily) is

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	recommended over single antiplatelet therapy. o After three to six months, continuation of dual antiplatelet therapy with low dose aspirin (75 to 100 mg) and clopidogrel (75 mg daily) is recommended until 12 months over single antiplatelet therapy. o After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations. • For patients who have undergone elective BMS or DES stent placement: o Low-dose aspirin (75 to 100 mg daily) and clopidogrel (75 mg daily) together are recommended rather than cilostazol in addition to these drugs. o Aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) are recommended as part of dual antiplatelet therapy rather than the use of either drug with cilostazol. o Cilostazol (100 mg twice-daily) may be a substitute for either low-dose aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class. • For patients with CAD undergoing elective PCI but no stent placement: o Dual antiplatelet therapy with aspirin (75 to 325 mg daily) and clopidogrel (75 mg daily) is recommended over single antiplatelet therapy for the first month. Single antiplatelet therapy thereafter is recommended as per the established CAD recommendations. • Antithrombotic Therapy in Patients With Systolic LV Dysfunction o No antiplatelet or warfarin therapy is recommended in patients with systolic LV dysfunction without established CAD and no LV thrombus. o For patients with systolic LV dysfunction and established CAD, recommendations are as per the established CAD recommendations. <u>Antithrombotic therapy in peripheral artery disease (PAD)</u> • Primary prevention of cardiovascular events in patients with asymptomatic PAD: o Aspirin (75 to 100 mg daily) is recommended over no aspirin therapy. • Secondary prevention of cardiovascular events in patients with symptomatic PAD: o Long-term treatment with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended. Dual antiplatelet therapy with aspirin plus clopidogrel is not recommended and the use of an antiplatelet agent with moderate-intensity warfarin is not recommended. • Antithrombotic therapy for the management of patients with claudication: o For patients with intermittent claudication refractory to exercise therapy (and smoking cessation), cilostazol in addition to previously antithrombotic therapies (aspirin 75 to 100 mg daily or clopidogrel 75 mg daily) is recommended. o Prostanoids in addition to aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) are recommended for patients with symptomatic PAD and critical leg ischemia/rest pain who are not candidates for vascular intervention.

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	• Endovascular revascularization in patients with symptomatic PAD o For patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended. o For patients undergoing peripheral artery percutaneous transluminal angioplasty with stenting, single antiplatelet therapy is recommended over dual antiplatelet therapy. • Antithrombotic therapy following peripheral artery bypass graft surgery: o Long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel 75 mg daily is recommended. Single antiplatelet therapy over antiplatelet therapy and warfarin is recommended. o In patients undergoing below-knee bypass graft surgery with prosthetic grafts, clopidogrel (75 mg daily) plus aspirin (75 to 100 mg daily) should be used over aspirin alone for one year. For all other patients, single over dual antiplatelet therapy should be used. • Patients with carotid artery stenosis: o Aspirin (75 to 100 mg daily) is recommended in patients with asymptomatic carotid artery stenosis. o In patients with symptomatic carotid artery stenosis long-term antiplatelet therapy with clopidogrel (75 mg daily) or the combination of aspirin plus dipyridamole ER (25/200 mg twice-daily), or aspirin (75 to 100 mg daily) is recommended over no treatment. o Clopidogrel (75 mg daily) or the combination of aspirin plus extended-release dipyridamole (25/200 mg twice-daily) is recommended over aspirin (75 to 100 mg daily).
American Heart Association/American Stroke Association: **Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack (2011)**[8]	<u>Antithrombotic therapy for noncardioembolic stroke or TIA (specifically, atherosclerotic, lacunar, or cryptogenic infarcts)</u> • The use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. • Aspirin (50 to 325 mg/day) monotherapy, the combination of aspirin 25 mg and dipyridamole ER 200 mg twice-daily and clopidogrel (75 mg/day) monotherapy are all acceptable options for initial therapy. The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, and other clinical characteristics. • The risk of hemorrhage is increased when aspirin is added to clopidogrel; therefore, the combination is not recommended for routine secondary prevention after ischemic stroke or TIA. • For patients allergic to aspirin, clopidogrel is reasonable. • 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. <u>Recommendations for patients with cardioembolic stroke types</u> • AF: o For patients with ischemic stroke or TIA with paroxysmal or permanent AF, anticoagulation with a VKA (target INR, 2.0 to 3.0) is recommended. o For patients unable to take oral anticoagulants, aspirin alone is

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	recommended. o The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin. o For patients with AF at high risk for stroke who require temporary interruption of oral anticoagulation, bridging therapy with a low molecular weight heparin agent administered subcutaneously is reasonable. • Acute MI and left ventricular thrombus: o Patients with ischemic stroke or TIA in the setting of an acute MI complicated by left ventricular mural thrombus formation should be treated with oral anticoagulation (target INR, 2.5; range, 2.0 to 3.0) for at least three months. • Cardiomyopathy: o In patients with prior stroke or transient cerebral ischemic attack in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction, the benefit of warfarin has not been established. o Warfarin (INR, 2.0 to 3.0), aspirin (81 mg/day), clopidogrel (75 mg/day), or the combination of aspirin (25 mg twice-daily) plus ER dipyridamole (200 mg twice-daily) may be considered to prevent recurrent ischemic events in patients with pervious ischemic stroke or TIA and cardiomyopathy. • Native valvular heart disease: o For patients with ischemic stroke or TIA who have rheumatic mitral valve disease, whether or not AF is present, long-term warfarin therapy is reasonable with an INR target range of 2.5 (range 2.0 to 3.0). o To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin. o For patients with ischemic stroke or TIA and native aortic or non-rheumatic mitral valve disease who do not have AF, antiplatelet therapy may be reasonable. o For patients with ischemic stroke or TIA and mitral annular calcification, antiplatelet therapy may be considered. o For patients with mitral valve prolapse who have ischemic stroke or TIA, long-term antiplatelet therapy may be considered. • Prosthetic heart valves: o For patients with ischemic stroke or TIA who have mechanical prosthetic heart valves, warfarin is recommended with a target INR of 3.0 (range, 2.5 to 3.5). o For patients with prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 to 100 mg/day in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high risk of bleeding. o For patients with ischemic stroke or TIA who have bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered.
American College of Cardiology Foundation/American	<u>Early hospital care-antiplatelet therapy</u> • Aspirin should be administered as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.

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Heart Association: **2011 Focused Update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline) (2011)**[10]	• Clopidogrel should be administered to patients unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. • Patients with a definite diagnosis who are at medium or high risk and in whom an initial invasive strategy is selected should receive dual antiplatelet therapy on presentation. Aspirin should be initiated on presentation and the choice of a second antiplatelet agent to be initiated at presentation should include one of the following: before PCI: clopidogrel, an IV GP IIb/IIIa inhibitor; at the time of PCI: clopidogrel, prasugrel, or an IV GP IIb/IIIa inhibitor. • For an initial conservative strategy, clopidogrel should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for at least one month and ideally up to one year. • If recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear after an initial conservative strategy, diagnostic angiography should be performed. Either an IV GP IIb/IIIa inhibitor or clopidogrel should be added to aspirin and anticoagulant therapy before diagnostic angiography. • A loading dose of thienopyridine is recommended for whom PCI is planned. Regimens include one of the following: clopidogrel 300 to 600 mg given as early as possible before or at the time of PCI, or prasugrel 60 mg given promptly and no later than one hour after PCI once coronary anatomy is defined and a decision is made to proceed with PCI. • The duration of maintenance dose of thienopyridine therapy should be as follows: o Patients undergoing PCI: clopidogrel 75 mg/day or prasugrel 10 mg/day for at least 12 months. o If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. • If recurrent ischemia discomfort with clopidogrel, aspirin, and anticoagulant therapy is experienced with an initial conservative strategy, it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography. • For an initial conservative strategy, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least six hours earlier than planned catheterization or PCI. • For an initial conservative strategy, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy. • Prasugrel 60 mg may be considered for administration promptly upon presentation if PCI is planned, before definition of coronary anatomy if both the risk of bleeding is low and the need for CABG is considered unlikely. • The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk patients already receiving aspirin and a thienopyridine who are selected for an invasive strategy, who are not otherwise at high-risk for bleeding. • In patients with a definite diagnosis undergoing PCI as part of an early invasive strategy, the use of a loading dose of clopidogrel 600 mg, followed by a higher maintenance dose of 150 mg/day for six days, then 75 mg/day may be reasonable in patients not considered at high risk for bleeding. • Abciximab should not be administered to patients in whom PCI is not planned. • In patients at low risk for ischemic events or at high-risk of bleeding and

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	who are already receiving aspirin and clopidogrel, upstream GP IIb/IIIa inhibitors are not recommended. • In patients with a history of stroke and/or transient ischemic attack for whom PCI is planned, prasugrel is potentially harmful as part of dual antiplatelet therapy. <u>Additional antiplatelet and anticoagulation therapy</u> • In an initial conservative strategy with no subsequent features that would necessitate diagnostic angiography, a stress test should be performed. o If the patient is classified as not low-risk, diagnostic angiography should be performed. o If the patient is classified as low-risk, the following should take place in preparation for discharge: ▪ Continue aspirin indefinitely. ▪ Continue clopidogrel for at least one month and ideally up to one year. ▪ Discontinue IV GP IIb/IIIa inhibitor if started previously. ▪ Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy. • If CABG was selected as a postangiography management strategy, the following instructions should be followed: o Continue aspirin. o Discontinue IV GP IIb/IIIa inhibitor four hours before CABG. o Anticoagulant therapy should be managed as follows: ▪ Continue UFH. ▪ Discontinue enoxaparin 12 to 24 hours, fondaparinux 24 hours, and bivalirudin three hours before CABG and dose with UFH per institutional practice. • In patients taking a thienopyridine in whom CABG is planned and can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least five days in patients receiving clopidogrel and at least seven in those receiving prasugrel unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risk of excess bleeding. • When PCI has been selected as a postangiography management strategy, the following instructions should be followed: o Continue aspirin. o Administer a loading dose of a thienopyridine if not started before diagnostic angiography. o Discontinue anticoagulant therapy after PCI for uncomplicated cases. • When medical therapy is selected as a management strategy and no significant obstructive CAD on angiography is present, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician. For patients in whom evidence of coronary atherosclerosis is present, albeit without flow-limiting stenosis, long-term treatment with aspirin and other secondary prevention measures should be prescribed. • When medical therapy is selected and CAD is presence, the following approach is recommended: o Continue aspirin. o Administer a loading dose of clopidogrel if not given before

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	diagnostic angiography. o Discontinue IV GP IIb/IIIa inhibitor if started previously. o Anticoagulant therapy should be managed as follows: ▪ Continue IV UFH for at least 48 hours or until discharge if given before diagnostic angiography. ▪ Continue enoxaparin and fondaparinux for duration of hospitalization, up to eight days, if given before diagnostic angiography. ▪ Either discontinue bivalirudin or continue at a dose of 0.25 mg/kg per hour for up to 72 hours at the physician's discretion if given before diagnostic angiography. • When a conservative strategy is selected and no angiography or stress testing is performed, the following instructions should be followed: o Continue aspirin indefinitely. o Continue clopidogrel for at least one month and ideally up to one year. o Discontinue IV GP IIb/IIIa inhibitor if started previously. o Continue UFH for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy. • When an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography, left ventricular ejection fraction should be measured. • When PCI is selected as a postangiography management strategy, it is reasonable to administer an IV GP IIb/IIIa inhibitor if not started before diagnostic angiography, particularly for troponin-positive and/or other high-risk patients. • When PCI is selected as a management strategy, it is reasonable to omit administration of an IV GP IIb/IIIa inhibitor if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least six hours earlier. • If left ventricular ejection fraction is ≤4, it is reasonable to perform diagnostic angiography. • If left ventricular ejection fraction is >4, it is reasonable to perform a stress test. • Platelet function testing to determine platelet inhibitory response in patients on thienopyridine therapy may be considered if results of testing may alter management. • Genotyping for a cytochrome P450 2C19 loss of function variant on clopidogrel therapy might be considered if results of testing may alter management. • IV fibrinolytic therapy is not indicated in patients without acute ST-elevation, a true posterior MI, or a presumed new left bundle-branch block. <u>Long-term medical therapy and secondary prevention</u> • For patients treated medically without stenting, aspirin (75 to 162 mg/day) should be administered indefinitely. Clopidogrel (75 mg/day) should be administered for at least one month, and ideally for up to one year. • For patients with a BMS, aspirin 162 to 325 mg/day should be administered for at least one month, and then continued indefinitely at a dose of 75 to 162 mg/day. The duration and maintenance dose of thienopyridine therapy should be as follows:

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	o Clopidogrel 75 mg/day or prasugrel 10 mg/day for at least 12 months. o If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. • For patients treated with a DES, aspirin 162 to 325 mg/day should be administered for at least three months after sirolimus-eluting stent implantation and for six months after paclitaxel-eluting stent implantation, and then continued indefinitely at a dose of 75 to 162 mg/day. The duration and maintenance dose of thienopyridine therapy should be as follows: o Clopidogrel 75 mg/day or prasugrel 10 mg/day for at least 12 months. o If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by thienopyridine therapy, earlier discontinuation should be considered. • Clopidogrel 75 mg/day (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from unstable angina/non-ST-elevation MI (UA/NSTEMI) when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance. • For patients in whom the physician is concerned about the risk of bleeding, a lower initial aspirin dose (75 to 162 mg/day) after PCI is reasonable. • For patients who have an indication for anticoagulation, the addition of warfarin may be reasonable to maintain an INR 2.0 to 3.0. • Continuation of clopidogrel or prasugrel beyond 15 months may be considered in patients following DES placement. • Dipyridamole is not recommended as an antiplatelet in post-UA/STEMI patients because it has not been shown to be effective.
European Society of Cardiology: **Guideline for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-Segment Elevation (2011)**[11]	<u>Recommendations for oral antiplatelet agents</u> • Aspirin should be given to all patients without contraindications at an initial loading dose of 150 to 300 mg; maintenance doses should be between 75 to 100 mg daily regardless of treatment strategy. • A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications. • A proton pump inhibitor (preferably not omeprazole) is recommended in combination with dual antiplatelet therapy in patients with a history of gastrointestinal hemorrhage or peptic ulcer, and is appropriate for patients with multiple other risk factors (e.g., *Helicobacter pylori* infection, age ≥65 years, concurrent use of anticoagulants or steroids). • Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically warranted. • Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended for all patients at moderate to high risk of ischemic events (e.g., elevated troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel. Clopidogrel should be discontinued when ticagrelor is initiated. • Prasugrel (60 mg loading dose, 10 mg daily) is recommended for $P2Y_{12}$ inhibitor naïve patients (particularly diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications. • Clopidogrel (300 mg loading dose, 75 mg daily) is recommended for those who cannot receive ticagrelor or prasugrel. o A 600 mg loading dose (or a supplementary 300 mg dose at PCI

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	following an initial 300 mg loading dose) is recommended for patients scheduled for invasive strategy when ticagrelor or prasugrel is not an option. o A higher maintenance dose of 150 mg/day should be considered for the first seven days in patients managed with PCI and without increased risk of bleeding. o Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases. o Genotyping and/or platelet function testing can be considered in selected cases when clopidogrel is used. • In patients pretreated with $P2Y_{12}$ inhibitors who need to undergo nonemergency major surgery (including CABG), postponing surgery for at least five days after cessation of ticagrelor or clopidogrel, and seven days for prasugrel, if clinically feasible and unless the patient is at high risk of ischemic events should be considered. • Ticagrelor or clopidogrel should be considered to be re-started after CABG surgery as soon as it is safe. • The combination of aspirin with a non-steroidal anti-inflammatory is not recommended.
American College of Cardiology/American Heart Association and American College of Cardiology/American Heart Association/ Society for Cardiovascular Angiography and Interventions: **2009 Focused Update of the 2007 Focused Update and the 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction AND Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update) [2009])**[12]	<u>STEMI and PCI focused update section</u> • Recommendations for the use of thienopyridines: o A loading dose of thienopyridines is recommended for STEMI patients for whom PCI is planned. Regimens should be one of the following: ▪ At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or non-primary PCI. ▪ Prasugrel 60 mg should be given as soon as possible for primary PCI. ▪ For STEMI patients undergoing non-primary PCI, the following regimens are recommended: • If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the thienopyridine of choice. • If the patient has received fibrinolytic therapy without a thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the thienopyridine of choice. • If the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of prasugrel should be given promptly and no later than one hour after the PCI. o The duration of thienopyridine therapy should be as follows: ▪ In patients receiving a stent (BMS or DES) during PCI for ACS, clopidogrel 75 mg/day or prasugrel 10 mg/day should be given for at least 12 months. ▪ If the risk of morbidity because of bleeding outweighs the anticipated benefit afforded by thienopyridine therapy, earlier discontinuation should be considered. o In patients taking a thienopyridine in whom CABG is planned and

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	can be delayed, it is recommended that the drug be discontinued to allow for dissipation of the antiplatelet effect. The period of withdrawal should be at least five days in patients receiving clopidogrel and at least seven days in patients receiving prasugrel, unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the potential risks of excess bleeding. o Continuation of clopidogrel and prasugrel beyond 15 months may be considered in patients undergoing DES placement. o In STEMI patients with a prior history of stroke and transient ischemic attack for whom primary PCI is planned, prasugrel is not recommended as part of a dual antiplatelet therapy regimen. <u>Recommendations for the timing of angiography and antiplatelet therapy in UA/NSTEMI</u> • Patients with definite or likely UA/NSTEMI selected for an invasive approach should receive dual-antiplatelet therapy. Aspirin should be initiated on presentation. Clopidogrel (before or at the time of PCI) or prasugrel (at the time of PCI) is recommended as a second antiplatelet agent. • It is reasonable for initially stabilized high risk patients with UA/NSTEMI to undergo an early invasive strategy within 12 to 24 hours of admission. For patients not at high risk, an early invasive approach is also reasonable.
American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions: **2011 Guideline for Percutaneous Coronary Intervention (2011)**[13]	<u>Interventional pharmacotherapy-oral antiplatelet therapy</u> • Patients already taking daily aspirin therapy should take 81 to 325 mg before PCI. • Patients not on aspirin therapy should be given non-enteric aspirin 325 mg before PCI. • After PCI, use of aspirin should be continued indefinitely. • A loading dose of one of the following $P2Y_{12}$ receptor inhibitors should be given to patients undergoing PCI with stenting: clopidogrel 600 mg (ACS and non-ACS patients), prasugrel 60 mg (ACS patients), or ticagrelor 180 mg (ACS) patients. • The loading dose of clopidogrel for patients undergoing PCI after fibrinolytic therapy should be 300 mg within 24 hours and 600 mg more than 24 hours after receiving fibrinolytic therapy. • Patients should be counseled on the need for and risks of dual antiplatelet therapy before placement of intracoronary stents, especially DESs, and alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of dual antiplatelet therapy. • The duration of $P2Y_{12}$ inhibitor therapy after stent implantation should generally be as follows: o In patients receiving a stent (BMS or DES) during PCI for ACS, $P2Y_{12}$ inhibitor therapy with one of the following options should be given for at least 12 months: clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg twice-daily. o In patients receiving DES for a non-ACS indication, clopidogrel 75 mg/day should be given for at least 12 months if patients are not at high risk of bleeding. o In patients receiving BMSs for a non-ACS indication, clopidogrel should be given for a minimum of one month and ideally up to 12 months (unless the patient is at increased risk of bleeding; then it should be given for a minimum of two weeks).

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	• After PCI, it is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses. • If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. • Continuation of dual antiplatelet therapy beyond 12 months may be considered in patients undergoing DES implantation. • Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack. <u>Post-procedural recommendations for patients undergoing PCI</u> Aspirin: • Use of aspirin should be continued indefinitely. • It is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses. $P2Y_{12}$ inhibitors: • In patients receiving a stent (BMS or DES) during PCI for ACS, therapy with either clopidogrel 75 mg/day, prasugrel 10 mg/day, or ticagrelor 90 mg twice-daily should be given for at least 12 months. • In patients receiving DES for a non-ACS indication, clopidogrel 75 mg/day should be given for at least 12 months if patients are not at high risk of bleeding. • In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of one month and ideally up to 12 months (unless the patient is at an increased risk of bleeding; then it should be given for a minimum of two weeks). • Patients should be counseled on the importance of compliance with dual antiplatelet therapy and that therapy should not be discontinued before discussion with their cardiologist. • Proton pump inhibitors should be used in patients with a history of prior gastrointestinal bleeding who require dual antiplatelet therapy. • If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by a recommended duration of $P2Y_{12}$ inhibitor therapy after stent implantation, either discontinuation (e.g., <12 months) of $P2Y_{12}$ inhibitor therapy is reasonable. • Use of proton pump inhibitors is reasonable in patients with an increased risk of gastrointestinal bleeding (e.g., advanced age, concomitant use of warfarin, steroids, nonsteroidal anti-inflammatory drugs, *Helicobacter pylori* infection) who require dual antiplatelet therapy. • Continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of DES. • Routine use of a proton pump inhibitor is not recommended for patients at low risk of gastrointestinal bleeding, who have much less potential to benefit from prophylactic therapy. <u>Clopidogrel genetic testing</u> • Genetic testing might be considered to identify whether a patient at high risk for poor clinical outcomes is predisposed to inadequate platelet inhibition with clopidogrel. • When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternative

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	$P2Y_{12}$ inhibitor (e.g., prasugrel, ticagrelor) might be considered. • The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended.
National Institute for Health and Clinical Excellence: **Myocardial Infarction: Secondary Prevention in Primary and Secondary Care for Patients Following a Myocardial Infarction (2007)**[14]	• Aspirin is recommended in all patients after a MI and should be continued indefinitely. Clopidogrel should not be offered as first-line monotherapy after a MI. • Clopidogrel combined with low dose aspirin for 12 months is recommended in patients who have had a NSTE ACS who are at moderate to high risk of MI or death. Thereafter, patients may be treated with low dose aspirin without clopidogrel in the absence of indication for dual antiplatelet therapy. • Patients who have been treated with aspirin and clopidogrel within the first 24 hours of an STEMI should continue on dual antiplatelet therapy for at least four weeks. Thereafter, low-dose aspirin should be continued, and clopidogrel discontinued in the absence of indication for dual antiplatelet therapy. • If both clopidogrel and aspirin were not given during the acute phase of a MI, this combination should not routinely be initiated. • Dual antiplatelet therapy with aspirin and clopidogrel should not be used for longer than 12 months after an acute MI unless another indication for dual antiplatelet therapy exists. After a STEMI, the combination of aspirin and clopidogrel is usually recommended for a shorter duration than 12 months. • Clopidogrel monotherapy is an alternative treatment in patients with aspirin hypersensitivity. • Low dose aspirin and a proton pump inhibitor are recommended in patients with comorbid dyspepsia. A full dose proton pump inhibitor and low dose aspirin should be considered in patients with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for *Helicobacter pylori.* • Patients being treated with warfarin for another indication should continue on warfarin. Those being treated with moderate-intensity warfarin (INR 2.0 to 3.0) and are at low risk of bleeding, may be treated with aspirin. The combination of warfarin and clopidogrel is not routinely recommended.
American College of Cardiology/American Heart Association: **2007 Chronic Angina Focused Update of the 2002 Guidelines for the Management of Patients With Chronic Stable Angina (2007)**[15]	• Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients unless contraindicated. • The use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.
European Society of Cardiology: **Management of Stable Angina Pectoris (2006)**[16]	Therapy to improve prognosis • Aspirin 75 mg daily is recommended in all patients without specific contraindications (e.g., active gastrointestinal bleeding, aspirin allergy, previous aspirin intolerance). Clopidogrel is an alternative antiplatelet agent in patients who cannot take aspirin. • The use of unopposed cyclooxygenase-2 inhibition is not recommended in patients with stable angina pectoris. • Clopidogrel may be combined with aspirin after coronary stenting or an

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	ACS for a finite period of time, but combination therapy is currently not recommended in stable angina pectoris. • Dipyridamole is not recommended for antithrombotic treatment of stable angina.
National Institute for Health and Clinical Excellence: **Clopidogrel and Modified-Release Dipyridamole for the Prevention of Occlusive Vascular Events (2010)**[17]	• This guidance applies to people who have had an occlusive vascular event, or who have established peripheral arterial disease. This guidance does not apply to people who have had, or are at risk of, a stroke associated with AF, or who need treatment to prevent occlusive events after coronary revascularization or carotid artery procedures. • For people who have had an ischemic stroke, clopidogrel is recommended as a treatment option. For people who have a contraindication or intolerance to clopidogrel, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to both clopidogrel and aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a TIA, modified-release dipyridamole plus aspirin is recommended as a treatment option. For people who have a contraindication or intolerance to aspirin, modified-release dipyridamole alone is recommended as a treatment option. • For people who have had a MI, clopidogrel is recommended only when treatment with aspirin is contraindicated or not tolerated. • For people with peripheral arterial disease, clopidogrel is recommended as a treatment option. • For people with multi-vascular disease, clopidogrel is recommended as a treatment option. • Treatment with clopidogrel to prevent occlusive vascular events should be started with the least costly licensed preparation.
American College of Cardiology/American Heart Association: **2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): (2011)**[18]	Antiplatelet and antithrombotic drugs • Antiplatelet therapy is indicated to reduce the risk of MI, stroke, and vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. • Aspirin, (75 to 325 mg daily), is recommended to reduce the risk of MI, stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. • Clopidogrel (75 mg daily) is recommended as a safe and effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, ischemic stroke, or vascular death in individuals with symptomatic atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia. • Antiplatelet therapy can be useful to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with an ABI less than or equal to 0.90. • The usefulness of antiplatelet therapy to reduce the risk of MI, stroke, or vascular death in asymptomatic individuals with borderline abnormal ABI, defined as 0.91 to 0.99, is not well established. • The combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic

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	atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk. • In the absence of any other proven indication for warfarin, its addition to antiplatelet therapy to reduce the risk of adverse cardiovascular ischemic events in individuals with atherosclerotic lower extremity PAD is of no benefit and is potentially harmful due to increased risk of major bleeding.
European Society of Cardiology, Task Force on the Use of Antiplatelet Agents in Patients With Atherosclerotic Cardiovascular Disease: **Expert Consensus Document on the Use of Antiplatelet Agents (2004)**[19]	Major recommendations for individual antiplatelet agents Aspirin: • Aspirin once-daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. • Because of gastrointestinal toxicity and its potential impact on compliance, physicians are encouraged to use the lowest dose of aspirin that was shown to be effective in each clinical setting. • The available evidence supports daily doses of aspirin in the range of 75 to 100 mg for the long-term prevention of serious vascular events in high-risk patients (e.g., ≥3% per annum). • In clinical situations where an immediate antithrombotic effect is required (such as in ACS or in acute ischemic stroke), a loading dose of 160 to 300 mg should be given at diagnosis in order to ensure rapid and complete inhibition of thromboxane A2-dependent platelet aggregation. • No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient. • The routine use of proton pump inhibitors or cytoprotective agents is not recommended in patients taking daily doses of aspirin in the range of 75 to 100 mg, because of lack of randomized trials demonstrating the efficacy of such protective strategies in this setting. • Nonsteroidal anti-inflammatory drugs have been investigated inadequately in terms of their potential cardiovascular effects. Thus, physicians prescribing these drugs to arthritic patients with prior vascular complications should not discontinue treatment with low-dose aspirin. • Because of potential pharmacodynamic interactions between traditional nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) and aspirin, patients treated with low-dose aspirin requiring nonsteroidal ant-inflammatory drug therapy may benefit from the use of selective cyclooxegenase-2 inhibitors. Ticlopidine: • The role of ticlopidine in the present therapeutic armamentarium is uncertain. • Although there are no large head-to-head comparisons between the two thienopyridines, indirect comparisons are highly suggestive of a lower burden of serious bone-marrow toxicity with clopidogrel as compared to ticlopidine. • In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent MI. Clopidogrel: • Although clopidogrel may be slightly more effective than aspirin, the size of any additional benefit is statistically uncertain and the drug has not been granted a claim of “superiority” vs aspirin by regulatory authorities. • Clopidogrel 75 mg/day is an appropriate alternative for high-risk patients with coronary, cerebrovascular or peripheral arterial disease who have a

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	contraindication to low-dose aspirin. • The results of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial have led to Food and Drug Administration approval of a new indication for clopidogrel in patients with NSTE ACS. A loading dose of 300 mg clopidogrel should be used in this setting, followed by 75 mg daily. Revision of the existing guidelines will need a consensus agreement by the experts with respect to timing of PCI, length of clopidogrel treatment and combination with GP IIb/IIIa antagonists. Dipyridamole: • Although the combination of low-dose aspirin and extended-release dipyridamole (200 mg twice-daily) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no basis to recommend this combination in patients with ischemic heart disease.

Conclusions

The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and cardiovascular diseases. Anagrelide (Agrylin®), clopidogrel (Plavix®), dipyridamole (Persantine®), and ticlopidine are available generically, and single-entity aspirin is available in several over-the-counter formulations. Prasugrel (Effient®), ticagrelor (Brilinta®), and the fixed-dose combination product of aspirin and extended release dipyridamole (Aggrenox®) are not available generically. The aspirin/extended-release dipyridamole product is not interchangeable with the commercially available generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.[1-7]

Aspirin is the most frequently studied platelet inhibitor and is generally the reference drug to which other treatments are compared.[42] Aspirin is the platelet inhibitor recommended as first-line in most treatment guidelines for general use. Aspirin is recommended as a first-line option for the initial management of noncardioembolic stroke or transient ischemic attack (TIA), acute coronary syndrome (ACS), and myocardial infarction (MI), and for primary and secondary prevention in patients with cerebrovascular, cardiovascular, and peripheral vascular diseases. Low-dose aspirin (75 to 150 mg/day) is an effective platelet inhibitor regimen for long-term use, but in acute settings an initial loading dose of ≥150 mg may be required. Other platelet inhibitors are usually reserved for patients with contraindications or severe intolerance to aspirin or who have failed aspirin monotherapy, or in high-risk patients when dual antiplatelet therapy is recommended. Dual antiplatelet therapy with aspirin plus clopidogrel, prasugrel or ticagrelor is recommended for patients with ACS (non ST-elevation MI [STEMI] and unstable angina). Antiplatelet therapy is also recommended in patients with STEMI. For patients with noncardioembolic ischemic strokes or TIAs, aspirin/extended-release dipyridamole is suggested instead of aspirin alone, and clopidogrel may be considered instead of aspirin alone to reduce the risk of recurrent stroke and other cardiovascular events.[8-11,15] In a study comparing the fixed combination aspirin/extended-release dipyridamole to clopidogrel (with or without telmisartan), results demonstrated that neither treatment was "superior" to the other in the prevention of recurrent stroke.[33] 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 product has been studied in patients who have had an event while receiving aspirin.[8]

Clopidogrel and ticlopidine are adenosine diphosphate receptor antagonists that have been shown to significantly reduce the odds of a serious vascular event in high-risk patients. The CAPRIE study reported that clopidogrel significantly reduced the combined risk of ischemic stroke, MI and vascular death by 8.7% compared to aspirin in patients with a recent ischemic stroke, MI or established peripheral vascular disease. In a subanalysis of over 6,000 patients enrolled in the study based on a recent ischemic stroke, clopidogrel reduced the risk of the composite endpoint by 7.3% and stroke by 8.0% compared to aspirin; however, these differences were not statistically significant.[43] On the basis of the CURE, COMMIT, and

CLARITY studies, clopidogrel received a Food and Drug Administration (FDA) indication for the reduction of atherothrombotic events in patients with ACS and MI, and clopidogrel has been incorporated into the current treatment guidelines for the management of these conditions.[10,49,53,67] Prasugrel is a relatively new adenosine diphosphate receptor antagonist and may be the most potent of these agents, with more desirable characteristics compared to clopidogrel with regard to drug-drug interactions and interpatient enzyme variability.[23-25] FDA-approval of prasugrel was based on the results from the TRITON-TIMI 38 study, in which prasugrel was significantly more effective in reducing ischemic events in patients with ACS who underwent percutaneous coronary intervention (PCI) intervention. Of note, no reduction in the mortality rate was seen with prasugrel, and a significantly greater incidence of major, minor, life-threatening and fatal bleeding events was associated with prasugrel.[75] The overall recommendation is for a thienopyridine to be used in these patients, with clopidogrel, prasugrel and ticagrelor listed as potential options. Of note, the use of prasugrel in STEMI patients with a prior history of stroke or TIA for whom primary PCI is planned, is not recommended.[12]

Ticagrelor is the newest platelet inhibitor to be FDA-approved, specifically to reduce the rate of thrombotic cardiovascular events in patients with ACS, including unstable angina, non ST-elevation MI, and ST-elevation MI.[7] As a cyclopentyltriazolopyrimidine, ticagrelor works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel and ticlopidine); however, ticagrelor is a reversible inhibitor of the $P2Y_{12}$ receptors. Ticagrelor is not a prodrug and does not require enzymatic conversion to become pharmacologically active. It is therefore not subject to potential drug interactions associated with the other agents.[7,22] The pivotal clinical study establishing the safety and efficacy of ticagrelor in reducing the rate of thrombotic cardiovascular events in patients with ACS is the PLATO study. PLATO was a large, international, prospective, double-blind, randomized controlled study comparing ticagrelor and clopidogrel in hospitalized patients with documented ACS, with or without ST-segment elevation (N=18,624). After 12 months of treatment, ticagrelor significantly reduced the primary composite endpoint of cardiovascular death, MI or stroke, without increasing the risk of major bleeding.[54] The 2011 American College of Cardiology Foundation/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline for PCI recommends clopidogrel, prasugrel and ticagrelor as potential options in patients receiving PCI.[13] The 2012 guidelines for Antithrombotic Therapy and Prevention of Thrombosis guidelines by the American College of Chest Physicians recommends ticagrelor over clopidogrel in patients with ACS treated with or without PCI, and over prasugrel in patients undergoing PCI with stent placement.[9] The 2011 European Society of Cardiology guidelines recommend that patients presenting without persistent ST-elevation receive dual antiplatelet therapy with aspirin and a platelet inhibitor. Specifically, ticagrelor is recommended for all patients at moderate to high risk of ischemic events, regardless of initial treatment strategy (i.e., invasive vs noninvasive), including those pretreated with clopidogrel. Prasugrel is recommended for $P2Y_{12}$ inhibitor-naïve patients who are proceeding to PCI, while clopidogrel is recommended for patients who cannot receive ticagrelor or prasugrel.[11]

Clinical studies have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Randomized studies comparing ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin.[38,39] When compared to aspirin alone, and aspirin plus warfarin, treatment with aspirin plus ticlopidine resulted in a lower rate of stent thrombosis following coronary stenting.[73] Because ticlopidine is associated with a risk of life-threatening blood dyscrasias, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy.[5]

Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo, but has not been shown to be more effective than aspirin.[30,32] Aspirin plus extended-release dipyridamole significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with extended-release dipyridamole. There was no significant difference in all cause mortality among the active treatment groups.[30] Aspirin plus extended-release dipyridamole significantly reduced the composite of death, nonfatal stroke or MI and major bleeding to 13% of patients compared to 16% for aspirin monotherapy; however, the combination regimen was discontinued more often, mainly because of headache.[28]

Anagrelide is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication.[1,84-89]

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DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Brilinta® (ticagrelor) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
Authorization will be given if the following criteria are met and documented:

a. The recipient has a diagnosis of Acute Coronary Syndrome (unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction).
AND
b. The recipient does not have an active pathological bleed or history of intracranial hemorrhage.
AND
c. The recipient will be receiving concomitant treatment with aspirin in a dose of <100 mg/daily.
AND
d. The recipient has been started and stabilized on the requested medication.
OR
e. The recipient has experienced an adverse event with or has an allergy or contraindication with clopidogrel.
OR
f. Another clinically appropriate rationale is provided for why clopidogrel cannot be used.

2. PA Guidelines:
Prior Authorization approval will be for 1 year.

3. Quantity Limitations:
60 tablets per rolling 25 days