# *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.[1-8] The newest platelet inhibitor to be FDA-approved is vorapaxar (Zontivity®), which is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD).[7] Vorapaxar (Zontivity®), is the first in a new class of antiplatelet agents called protease-activated receptor-1 (PAR-1) antagonists. It is a competitive and selective antagonist of PAR-1, the major thrombin receptor on human platelets. It works by inhibiting thrombin-induced platelet aggregation and thus blood clot formation. In addition, vorapaxar is not a prodrug and does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[7] Vorapaxar is available for once-daily dosing in combination with other antiplatelet agents (either clopidogrel and/or aspirin). Clopidogrel and prasugrel are administered once-daily, while ticagrelor is dosed twice daily.[2,4,5]

**Table 1. Current Medications Available in the Therapeutic Class**[1-8]

| 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:<br>0.5 mg<br>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:<br>75 mg<br>300 mg | ✔ |
| Dipyridamole (Persantine®*) | Prevention of postoperative thromboembolic complications of cardiac valve replacement§ | Tablet:<br>25 mg<br>50 mg<br>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:<br>5 mg<br>10 mg | - |
| Ticagrelor (Brilinta®) | Reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome¶ | Tablet:<br>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:<br>250 mg | ✔ |
| Vorapaxar (Zontivity®) | Reduce the risk of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease: | Tablet:<br>2.08 mg | - |

| Generic Name (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/ Strength | Generic Availability |
|---|---|---|---|
| | Tablet: 2.08 mg QD in combination with other antiplatelet agents (clopidogrel and/or aspirin) | | |
| **Combination-Products** | | | |
| Aspirin/ extended-release dipyridamole (Aggrenox®) | Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis | Capsule: 25/200 mg | - |

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

**Evidence-based Medicine**

- Clopidogrel, Food and Drug Administration-approved in 1997, has been the principle platelet inhibitor for several years as the clinical data supporting its use is well established.[10-15]
- The RAPID Primary PCI study compared prasugrel to ticagrelor in patients who had a ST-Segment elevation myocardial infarction (STEMI) who were to undergo percutaneous coronary intervention (PC)I. Prasugrel was noninferior as compared with ticagrelor in terms of residual platelet reactivity two hours after the loading dose (P=0.207).[109]
- 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]
    - There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS.[76]
- Brener et al evaluated prasugrel-treated patients to clopidogrel-treated patients with STEMI. The prasugrel group had higher rates of procedural success (P=0.03), TIMI 3 flow (P=0.06), and lower corrected TIMI frame counts (P=0.008).[77]
- Approval of vorapaxar was based on the results of the TRA2ºP-TIMI 50 trial. The composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or transiet ischemic attack (TIA) the vorapaxar group showed a significant 17% relative risk reduction over the three years of the study (HR, 0.83; 95%CI, 0.76 to 0.90; P<0.001).[78]
    - Patients who had a previous stoke were removed from the study after 24 month follow-up assessments. Among the patients with a history of stroke, the rate of intracranial hemorrhage

in the vorapaxar group higher (P<0.001), without a history of stroke and was significantly increased as compared with the group without a prior stroke (P=0.049). [78]

**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.[24-40]
  - Antiplatelet therapy (aspirin plus extended-release [ER] dipyridamole or clopidogrel >aspirin) is recommended for long-term secondary prevention in patients with an acute ischemic stroke who are not receiving thrombolysis. Combination aspirin plus dipyridamole ER is recommended over aspirin, and clopidogrel is suggested over aspirin. Dual antiplatelet therapy should be used with caution and is favored in patients who have had a recent acute myocardial infarction, other ACS, or recently placed coronary stent.[24,25]
  - According to the 2012 guideline on Antithrombotic Therapy and Prevention of Thrombosis by the American College of Chest Physicians, dual therapy aspirin with clopidogrel or ticagrelor or prasugrel monotherapy is recommended in the first year following ACS in patients regardless of PCI status.[24]
    - 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.[24]
  - The 2013 guidelines for managing patients with STEMI by American College of Cardiology Foundation and American Heart Association recommend clopidogrel, prasugrel or ticagrelor for one year following PCI, without recommendation for one antiplatelet drug over another.[28]
  - 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.[27]
    - 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.[28]
    - 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.[1-8] 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.[9-25]

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.[9] 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.[10] The role of platelet inhibitors in other disease states are outlined in Table 11..[11-25]

Clopidogrel (Plavix®) and ticlopidine (Ticlid®) 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.[2,4] 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 seen with ticlopidine. The platelet inhibition effects of 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.[9]

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.[26] 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.[27] Prasugrel has been shown to have more desirable characteristics when compared to clopidogrel with regards to drug-drug interactions and interpatient enzyme variability. Looking more specifically at drug-drug interactions, potent cytochrome P450 (CYP) 3A4 inhibitors have been shown to affect clopidogrel; however, no effect has been seen with prasugrel, suggesting that no dosage adjustments are necessary when faced with this type of interaction. Regarding polymorphism, studies have shown that clinical outcomes with prasugrel are not affected by patient genetic variations of the CYP2C9 and 2C19 enzymes, which have been reported with clopidogrel.[28]

Ticagrelor (Brilinta®), also works in a similar manner to the other thienopyridine platelet inhibitors. Specifically, ticagrelor is a cyclopentyltriazolo-pyrimidine, 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.[5,29] 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. Therefore, ticagrelor does not require enzymatic conversion to become pharmacologically active, and 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.[2,4,5] 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.[30]

The newest platelet inhibitor to be approved by the FDA, vorapaxar (Zontivity®), is the first in a new class of antiplatelet agents called protease-activated receptor-1 (PAR-1) antagonists. It is a competitive and selective antagonist of PAR-1, the major thrombin receptor on human platelets. It works by inhibiting thrombin-induced platelet aggregation and thus blood clot formation. The FDA approved its use for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). Vorapaxar has been studied only as an addition to aspirin and/or clopidogrel. There is no experience with the use of vorapaxar as monotherapy. It is advised to administer it together with aspirin and/or clopidogrel.[7]

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.[3,29] Dipyridamole, particularly when combined with aspirin, is effective for the prevention of stroke.[9,10] Currently, there is no evidence to support the use of dipyridamole either instead of, or in addition to, aspirin and thienopyridines in the acute treatment of patients presenting with a non-ST-segment elevation acute coronary syndrome.[11]

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.[1,29] 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]

Currently, anagrelide, clopidogrel, dipyridamole and ticlopidine are the platelet inhibitors that are available generically. Aspirin, which is available over-the-counter, is available as a branded combination product with extended-release dipyridamole (Aggrenox®).[8]

## Medications

**Table 1. Medications Included Within Class Review**[1-8]

| 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 | ✔ |
| Vorapaxar (Zontivity®) | Platelet inhibitors | - |
| **Combination Products** | | |
| Aspirin/dipyridamole (Aggrenox®) | Platelet inhibitors | - |

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

## Indications

**Table 2. Food and Drug Administration-Approved Indications**[1-8]

| Indication | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ 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 | ✔ ¶ | - | - | - | - | - | - | - |
| Reduce the risk of thrombotic | - | - | - | - | - | - | ✔ | - |

| Indication | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease | | | | | | | | |

*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 the Food and Drug Administration-approved indications, the platelet inhibitors have the potential to be used off-label in 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 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 postsurgical deep vein thrombosis. Aspirin/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.[29]

## Pharmacokinetics

**Table 3. Pharmacokinetics**[1-8,29]

| 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 |
| Vorapaxar | 100 | 25 | M20 | 120 to 312 |
| **Combination Products** | | | | |
| Aspirin/dipyridamole | 50 to 75/37 | 1/not reported | Not reported/none | 0.3/14.0 |

*Metabolite.

## Clinical Trials

The clinical trials demonstrating the safety and efficacy of the platelet inhibitors in Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[27,31-115]

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).[9,10] 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%. Looking at the endpoints individually, antiplatelet therapy reduced the odds of nonfatal MI by 34%, nonfatal stroke by 25%, and vascular death by 15%.[47] Looking at the individual platelet inhibitors, data from clinical trials demonstrated that ticlopidine reduced the risk of stroke and other vascular outcomes in patients with cerebrovascular disease.[42,43] The CAPRIE trial 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).[48] Results from the MATCH trial 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.[39] The ESPRIT trial randomized patients within six months of a TIA or minor stroke of presumed arterial origin to 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 happened 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).[33] A meta-analysis of patients with acute ischemic stroke or TIA demonstrated that dual platelet inhibitor therapy was associated with a reduction in stroke recurrence (relative risk [RR], 0.67; 95% CI, 0.49 to 0.93) and a nonsignificant increase in major bleeding (RR, 2.09; 95% CI, 0.86 to 5.06) compared to monotherapy.[31]

With regard to the treatment of acute coronary syndromes (ACS), the CLARITY-TIMI 28 trial randomized patients who presented within 12 hours of a ST-segment elevation MI to 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).[51] The COMMIT trial randomized patients who were admitted within 24 hours of a

suspected acute MI to either combination therapy with clopidogrel and aspirin or to monotherapy with aspirin. In this trial, 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.[53] The CURE trial compared long-term (three to 12 months) combination therapy with clopidogrel plus aspirin to monotherapy with aspirin 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 trial was in the reduction of nonfatal MI. Due to the low number of strokes that occurred during the trial, 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.[57] The CHARISMA trial was also a long-term trial (median, 28 months) that enrolled patients with clinically evident cardiovascular disease and randomized them to either combination treatment with clopidogrel and aspirin or to monotherapy with aspirin. In this trial, 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).[54] 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.[10] In addition, a meta-analysis of 29 randomized-controlled trials 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.[49]

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, TRITON-TIMI 38 did report 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.[99] 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.[100-106] The RAPID Primary PCI study compared prasugrel to ticagrelor in patients who had a ST-Segment Elevation MI (STEMI) and were to undergo percutaneous coronary intervention (PCI). Both drugs provide an effective platelet inhibition two hours after the loading dose in only a half of patients. A majority of patients had achieved an effective platelet inhibition after four hours. Prasugrel showed to be noninferior as compared with ticagrelor in terms of residual platelet reactivity two hours after the loading dose (P=0.207).[109]

The major clinical trial demonstrating the safety and efficacy of ticagrelor for its FDA-approved indication is the PLATO trial. 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).[61]

Several subanalyses of the PLATO trial have been conducted.[62-76] In patients with ACS undergoing noninvasive (P=0.045) or invasive procedures (P=0.0025), ticagrelor remained more efficacious

compared to clopidogrel.[62,63,73] 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 regards to the primary composite endpoint.[64-67] Evaluation of the effects on biomarkers in non-ST-elevation ACS without revascularization found that elevated high sensitivity troponin T (hs-TnT) was significantly related to the rate of the primary composite endpoint of cardiovascular death, MI and stroke (P<0.001). Ticagrelor compared to clopidogrel reduced the composite of cardiovascular death, MI, and stroke with a larger effect in the patients in the upper tertiles of positive hs-TnT levels, (i.e., those with a higher risk) whereas there was a lack of effect in those with negative hs-TnT (<14 ng/L) (interaction P=0.042).[74] Mahaffey et al found that in patients with ACS, ticagrelor significantly reduced the incidence of MI compared with clopidogrel, with consistent results across most MI subtypes.[75] 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).[68] In the original PLATO trial, a significantly higher rate of dyspnea was observed with ticagrelor; however, data from a substudy revealed ticagrelor had no effect on pulmonary function.[60,69] There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS.[76]
Mahaffey et al compared the effects of ticagrelor and clopidogrel among patients enrolled in the PLATO trial 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 trial, the authors noted that the pattern of results are consistent with what might be expected by chance alone in a large, multiregional clinical trial 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 trial may be attenuated when endogenous prostacyclin production is inhibited.[69] Until a prospective clinical trial 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.[5]

Brener et al evaluated prasugrel-treated patients to clopidogrel-treated patients with STEMI. The prasugrel group had higher rates of procedural success (94% vs 89%, P=0.03), TIMI 3 flow (95% vs 90%, P=0.06), and lower corrected TIMI frame counts (21 ± 6 vs 23 ± 11, P=0.008). At 30 days, infarct size (percentage of left ventricular myocardium) was marginally lower in the prasugrel group (median [interquartile range], 16.4% [95% CI, 6.5 to 20.0] vs 17.6% [95% CI, 8.1 to 25.7], P=0.06). Although these differences did not retain statistical significance after controlling for the propensity to use prasugrel, it was at least as effective as clopidogrel with similar safety profile.[77]

Approval of vorapaxar was based on results from the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events -Thrombolysis in Myocardial Infarction (TRA2ºP-TIMI 50) trial. This study was designed to evaluate the efficacy and safety of vorapaxar in reducing atherothrombotic events in patients with established atherosclerosis who were receiving standard therapy. In January 2011, after completion of enrollment and a median of 24 months follow-up, the data and safety monitoring board reported an excess of intracranial hemorrhage (ICH) in patients with a history of stroke in the vorapaxar group and recommended the discontinuation of vorapaxar in all patients with a current or previous stroke. Among the patients with a history of stroke, the rate of ICH in the vorapaxar group was 2.4%, as compared with 0.9% in the placebo group (P<0.001). Among patients without a

history of stroke, the rates of ICH were lower in the two study groups (0.6% in the vorapaxar group and 0.4% in the placebo group, P=0.049). For the primary efficacy endpoint of the composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or TIA the vorapaxar group showed a significant 17% relative risk reduction over the three years of the study (10.1% in the vorapaxar group compared to 11.8% in the placebo group [HR 0.83; 95%CI, 0.76 to 0.90; p<0.001]).[78]

A subgroup analysis of 17,779 MI patients without a history of stroke or TIA taken from the original TRA2ºP-TIMI 50 trial was also followed using the same primary and secondary endpoints. The patients were randomized to vorapaxar 2.5 mg qd or placebo. The results showed a significant reduction in the primary efficacy endpoint for the vorapaxar group (10.5%) versus the placebo group (12.1%); p=0.0001 in addition to the secondary efficacy endpoint for the vorapaxar group (8.1%) versus the placebo group (9.7%); p<0.0001. However, safety endpoints showed a significant increase in the bleeding rates for the vorapaxar group versus the placebo group, p<0.0001.[79] Bonaca et al concluded that vorapaxar did not reduce the risk of cardiovascular death, MI, or stroke in patients with PAD; however, vorapaxar significantly reduced acute limb ischemia and peripheral revascularization which was accompanied by an increase in bleeding (P=0.006, P=0.017 and P=0.001, respectively).[80] Another subgroup analysis of patients with prior ischemic stroke, it was confirmed that adding vorapaxar increased the risk of intracranial hemorrhage without an improvement in major vascular events, including ischemic stroke (P<0.001 and P=0.75).[81]

The TRA*CER trial was another phase III, placebo-controlled, randomized trial of 12,944 patients that evaluated vorapaxar efficacy and safety when added to standard antiplatelet therapy to prevent cardiovascular complications in patients with unstable angina/Non-ST-Segment Elevation MI (UA/NSTEMI). PatientsThe study results reported no difference between vorapaxar and placebo groups for the primary outcome, a composite of cardiovascular deaths, MI, stroke, recurrent ischemia with re-hospitalization, or UCR using a 2-year K-M time to event analysis. However, it did show a significant increase in the risk of major bleeding, including ICH. The 2-year K-M global utilization of streptokinase and t-PA (GUSTO) moderate to severe bleeding was 6.1% in vorapaxar group vs 4.5% in placebo group (HR, 1.35; 95% CI, 1.16 to 1.58; P<0.001. The 2-year K-M estimate for ICH was 1.1% in vorapaxar group compared to 0.2% in placebo group (HR, 3.39; 95% CI, 1.78 to 6.45; P<0.001.[82] A subgroup analysis of TRA*CER found that
in NSTEMI ACS patients undergoing coronary artery bypass graft (CABG), vorapaxar was associated with a significant reduction in ischemic events and no significant increase in major CABG-related bleeding (P=0.005).[83] A second subgroup analysis found that patients taking high-dose aspirin with vorapaxar had a higher rate of ischemic and bleeding outcomes.[84]

**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)** | | | | |
| Geeganage et al[31]<br><br>Dual therapy with clopidogrel or dipyridamole plus aspirin<br><br>vs<br><br>monotherapy with aspirin, clopidogrel or dipyridamole | MA of 12 RCTs<br><br>Patients with acute ischemic stroke or TIA | N=3,766<br><br>Duration varied | Primary:<br>Recurrent stroke<br><br>Secondary:<br>Composite of stroke, TIA, ACS and death; composite of nonfatal stroke, nonfatal MI and vascular death; MI, severe stroke, intracerebral hemorrhage, major bleeding, all-cause death and vascular death | Primary:<br>Dual antiplatelet therapy was associated with a significant decrease in stroke recurrence in comparison to monotherapy (3.3 vs 5.0%; RR, 0.67; 95% CI, 0.49 to 0.93).<br><br>Secondary:<br>Compared to monotherapy, dual antiplatelet therapy was associated with a significant reduction in the risk of composite endpoint of stroke, TIA, ACS and death (1.7 vs 9.1%; RR, 0.71; 95% CI, 0.56 to 0.91) as well as the composite endpoint of nonfatal stroke, nonfatal MI and vascular death (4.4 vs 6.0%; RR, 0.75; 95% CI, 0.56 to 0.99).<br><br>No significant differences were seen between dual therapy and monotherapy with regard to the occurrence of MI (RR, 0.71; 95% CI, 0.25 to 2.03), severe stroke (RR, 1.01; 95% CI, 0.91 to 1.12), intracerebral hemorrhage (RR, 1.39; 95% CI, 0.22 to 8.75), all-cause death (RR, 1.34; 95% CI, 0.76 to 2.34) and vascular death (RR, 1.31; 95% CI, 0.59 to 2.93).<br><br>Major bleeding occurred more frequently with dual therapy compared to monotherapy, though this increase was not statistically significant (RR, 2.09; 95% CI, 0.86 to 5.06). |
| Uchiyama et al[32]<br>JASAP<br><br>Aspirin/dipyridamole ER 25/200 mg BID<br><br>vs<br><br>aspirin 81 mg QD<br><br>Concomitant use of anticoagulation and antiplatelet therapies was | AC, DB, MC, PG, RCT<br><br>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 | N=1,294<br><br>12 months | Primary:<br>Recurrent ischemic stroke (fatal or nonfatal)<br><br>Secondary:<br>Cerebral hemorrhage; subarachnoid hemorrhage; TIA; ACS; other vascular events; composite of ischemic stroke, | Primary:<br>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.<br><br>Secondary:<br>The event rate of stroke was significantly higher with combination therapy compared to aspirin.<br><br>There was no difference between the two treatments for any other secondary endpoint. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| prohibited. | neurological signs and symptoms, and responsible lesion confirmed by CT or MRI | | TIA, MI, unstable angina, or sudden death attributable to thromboembolism; stroke (composite of ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage); safety<br><br>A post hoc analysis was performed evaluating the event rate of intracranial hemorrhage and the composite of stroke or major bleeding for different subgroups | 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.<br><br>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. |
| ESPRIT Study Group[33]<br>ESPRIT<br><br>Aspirin 30 to 325 mg/day plus dipyridamole 200 mg BID<br><br>vs<br><br>aspirin 30 to 325 mg/day<br><br>Aspirin plus dipyridamole was administered either as a fixed-dose combination or as the two agents administered separately. | MC, OL, RCT<br><br>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<br><br>Mean follow-up 3.5 years | Primary:<br>Composite of death from all vascular causes, nonfatal stroke, nonfatal MI or major bleeding complication (which ever happened first)<br><br>Secondary:<br>Death from all causes, death from all vascular causes, death from all vascular causes and nonfatal stroke, all major ischemic | Primary:<br>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).<br><br>Patients receiving combination therapy discontinued trial medication more often than those receiving aspirin (470 vs 184 patients), mainly because of headache.<br><br>Secondary:<br>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).<br><br>Ischemic events were less frequent with combination therapy (HR, 0.81; 95% CI, 0.65 to 1.01). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | events, all vascular events, major bleeding complications | 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[34]<br><br>Aspirin plus dipyridamole (IR and ER)<br><br>vs<br><br>aspirin | MA of 6 RCT (4 were DB)<br><br>Patients with a history of non-cardioembolic stroke or TIA | N=7,648<br><br>Duration varied | Primary:<br>Incidence of nonfatal stroke<br><br>Secondary:<br>Composite of stroke, MI or vascular death; subset analysis comparing outcomes with IR and ER dipyridamole | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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.<br><br>Based on two trials, aspirin plus ER dipyridamole showed a significant 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[35]<br>ESPS 2<br><br>Aspirin 25 mg BID<br><br>vs<br><br>aspirin/dipyridamole 25/200 mg BID<br><br>vs<br><br>dipyridamole ER 200 mg* BID | DB, MC, PC, RCT<br><br>Patients who had an ischemic stroke or TIA within 3 months prior to study entry | N=6,602<br><br>24 months | Primary:<br>Stroke (fatal or nonfatal), death (all cause mortality), combined stroke or death<br><br>Secondary:<br>TIA and adverse events | Primary:<br>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).<br><br>There was no significant difference in all cause mortality among the active treatment groups (P values not reported).<br><br>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).<br><br>Secondary:<br>Aspirin (P<0.001), aspirin/dipyridamole (P<0.001) and dipyridamole ER (P<0.01) were significantly effective in preventing TIA compared to placebo. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>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[36]<br><br>Aspirin/dipyridamole 25/200 mg BID<br><br>vs<br><br>aspirin 25 mg BID | Post hoc analysis using data from the ESPS 2 | N=3,299<br><br>Duration not reported | Primary:<br>Rates of annual strokes, combined stroke or vascular events<br><br>Secondary:<br>Not reported | Primary:<br>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).<br><br>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.<br><br>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.<br><br>The difference in efficacy increased in high-risk patients.<br><br>Secondary:<br>Not reported |
| Leonardi-Bee et al[37]<br><br>Dipyridamole<br><br>vs<br><br>aspirin plus dipyridamole<br><br>vs<br><br>aspirin<br><br>vs | MA of 5 RCT (including the ESPS 1 and 2)<br><br>Patients with previous ischemic stroke and/or TIA | N=11,492<br><br>Follow-up at 15 to 72 months | Primary:<br>Incidence of stroke (combined fatal and nonfatal)<br><br>Secondary:<br>Nonfatal stroke; MI (combined fatal and nonfatal); vascular death; composite of nonfatal stroke, nonfatal MI and vascular death | Primary:<br>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).<br><br>Secondary:<br>Dipyridamole therapy reduced nonfatal stroke as compared to control, and combination therapy reduced nonfatal stroke as compared to aspirin.<br><br>Combination therapy significantly reduced the incidence of fatal and nonfatal MI compared to control (P<0.05), but not compared to aspirin or dipyridamole |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| control (not specified)/placebo<br><br>Two formulations of dipyridamole were assessed: conventional (150 to 300 mg/day) and modified-release (400 mg/day).<br><br>The daily dose of aspirin was 50 to 1,300 mg. | | | | (P>0.05).<br><br>Vascular death was not altered in any group.<br><br>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[38]<br><br>Aspirin 25 mg plus dipyridamole ER 200 mg BID<br><br>vs<br><br>clopidogrel 75 mg/day plus placebo or telmisartan 80 mg/day | AC, DB, PC, RCT<br><br>Patients ≥50 years of age with a recent ischemic stroke (within <90 days before randomization, or 90 to 120 days before randomization if they had ≥2 additional vascular risk factors) | N=20,332<br><br>2.5 years (mean) | Primary:<br>Recurrent stroke of any type<br><br>Secondary:<br>Composite of stroke, MI or death from vascular causes | Primary:<br>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 the CI extends beyond the prespecified noninferiority margin of 1.075. Ischemic stroke accounted for 87.4% of the recurrent strokes.<br><br>Secondary:<br>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[39]<br>MATCH<br><br>Clopidogrel 75 mg/day<br><br>vs | DB, PC, RCT<br><br>High-risk patients with a recent ischemic stroke or TIA, with ≥1 additional | N=7,599<br><br>18 months | Primary:<br>Composite of ischemic stroke, MI, vascular death or rehospitalization for an acute ischemic event | Primary:<br>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).<br><br>Secondary:<br>There was no significant benefit of combination therapy compared to |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| clopidogrel 75 mg/day plus aspirin 75 mg/day | vascular risk factor who were already receiving clopidogrel | | Secondary:<br>Death, stroke, individual components and various combinations of the primary end points | clopidogrel therapy in reducing the secondary outcomes.<br><br>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).<br><br>[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[40]<br>CARESS<br><br>Clopidogrel 300 mg on day 1, followed by clopidogrel 75 mg/day plus aspirin 75 mg/day on days 2 to 7<br><br>vs<br><br>aspirin 75 mg QD | DB, PC, RCT<br><br>Patients >18 years of age with ≥50% carotid stenosis who experienced ipsilateral carotid territory TIA or stroke within the past 3 months | N=107<br><br>7 days | Primary:<br>Proportion of patients who were microembolic signal positive on day seven<br><br>Secondary:<br>Proportion of 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 | Primary:<br>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).<br><br>Secondary:<br>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 day seven, and by 61.6% (95% CI, 34.9 to 77.4; P=0.0005) on day two.<br><br>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.<br><br>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[41]<br>FASTER<br><br>Clopidogrel 300 mg once, followed by 75 mg/day<br><br>or | Factorial design 2x2, DB, PC, RCT<br><br>Patients ≥40 years of age with a TIA or minor stroke, | N=392<br><br>90 days | Primary:<br>Incidence of stroke (ischemic and hemorrhagic), safety (hemorrhage, myositis)<br><br>Secondary: | Primary:<br>The trial was stopped early due to a failure to recruit patients at the prespecified minimum enrollment rate because of increased use of statins.<br><br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| placebo<br><br>and<br><br>simvastatin 40 mg once, followed by 40 mg/day<br><br>or<br><br>placebo<br><br>All patients were also given aspirin 81 mg/day, with a 162 mg loading dose if naïve to aspirin. | randomized within 24 hours of symptom onset | | Composite of stroke, MI and vascular death | 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).<br><br>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.<br><br>Secondary:<br>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[42]<br>CATS<br><br>Ticlopidine 250 mg BID<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients with ischemic strokes occurring from 1 week to 4 months | N=1,072<br><br>Up to 3 years (mean 24 months) | Primary:<br>Event rate/year for stroke, MI or vascular death<br><br>Secondary:<br>Adverse events | Primary:<br>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 the on-treatment analysis and by 23% (P=0.020) using the ITT approach.<br><br>Ticlopidine reduced the RR of ischemic stroke by 33% (P=0.008) in the on-treatment analysis.<br><br>Ticlopidine was beneficial for both men and women (RR, 28.1%; P=0.037 and RR, 34.2%; P=0.045, respectively).<br><br>Secondary:<br>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[43]<br>TASS<br><br>Ticlopidine 250 mg BID | Blinded, MC, RCT<br><br>Patients with a minor stroke or | N=3,069<br><br>2 to 6 years | Primary:<br>Nonfatal stroke or death<br><br>Secondary: | Primary:<br>Compared to aspirin, ticlopidine showed a 12% reduction in nonfatal stroke or death (three-year event rate, 17 vs 19%; P=0.048).<br><br>Ticlopidine reduced the risk of stroke after three years by 21% (10 vs 13%; |

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| vs<br><br>aspirin 650 mg BID | TIA within the past 3 months | | Adverse events | P=0.024).<br><br>Secondary:<br>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[44]<br>AAASPS<br><br>Ticlopidine 250 mg BID<br><br>vs<br><br>aspirin 325 mg BID | DB, MC, RCT<br><br>African American patients who recently had a non-cardioembolic ischemic stroke | N=1,809<br><br>Up to 2 years | Primary:<br>Composite of recurrent stroke, MI or vascular death<br><br>Secondary:<br>Stroke (fatal and nonfatal) | Primary:<br>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).<br><br>Secondary:<br>There was a nonsignificant trend for reduction of fatal or nonfatal stroke among those in the aspirin group (P=0.08). |
| Fukuuchi et al[45]<br><br>Ticlopidine 200 mg QD<br><br>vs<br><br>clopidogrel 75 mg QD | DB, DD, MC, RCT<br><br>Japanese patients 20 to 80 years of age who experienced a non-cardioembolic cerebral infarction ≥8 days prior to enrollment | N=1,151<br><br>52 weeks | Primary:<br>Safety (emphasis on hematologic changes, hepatic dysfunction, non-traumatic hemorrhage and other serious adverse reactions)<br><br>Secondary:<br>Combined incidence of nonfatal or fatal cerebral infarction, MI or death due to other vascular causes | Primary:<br>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 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).<br><br>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.<br><br>Secondary:<br>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[46]<br><br>Ticlopidine 200 mg QD | 2 DB, DD, Phase II, RCT | N=1,921<br><br>26 to 52 | Primary:<br>Combined endpoint of accessory | Primary:<br>Fewer patients in the clopidogrel group (35.0%) experienced the combined safety endpoint compared to those in the ticlopidine group (48.7%). At one |

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| vs<br><br>clopidogrel 75 mg QD | Japanese patients 20 to 80 years of age, with a history of cerebral infarctions; the most recent stroke being >8 days prior to enrollment | weeks | symptoms and abnormal laboratory changes<br><br>Secondary:<br>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) | 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).<br><br>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).<br><br>Secondary:<br>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.<br><br>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 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[47]<br><br>Antiplatelet agents<br><br>vs<br><br>control<br><br>vs<br><br>one antiplatelet regimen vs | MA (197 RCTs compared antiplatelet therapy vs control and 90 trials compared different antiplatelet regimens)<br><br>Patients at high risk of occlusive | N=135,640<br><br>Duration varied | Primary:<br>Serious vascular event (nonfatal MI, nonfatal stroke or vascular death)<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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.<br><br>Clopidogrel reduced serious vascular events by 10% compared to aspirin, which was similar to the 12% reduction observed with ticlopidine. |

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| another | vascular events | | | The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared to aspirin alone.<br><br>Secondary:<br>Not reported |
| CAPRIE Steering Committee[48]<br>CAPRIE<br><br>Clopidogrel 75 mg QD<br><br>vs<br><br>aspirin 325 QD | DB, MC, PG, RCT<br><br>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<br><br>1 to 3 years (mean, 1.91 years) | Primary:<br>Composite of ischemic stroke, MI or vascular death<br><br>Secondary:<br>Composite of ischemic stroke, MI, vascular death and amputation; vascular death; all cause mortality; safety | Primary:<br>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).<br><br>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).<br><br>For the 6,302 patients enrolled in the trial with MI, a RR increase of 3.7% was associated with clopidogrel (P=0.66).<br><br>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).<br><br>Secondary:<br>Clopidogrel reduced the risk of the primary outcome plus amputation by 7.6% compared to aspirin (P=0.076).<br><br>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).<br><br>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. |

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| De Schryver et al[49]<br><br>Dipyridamole with or without other antiplatelet drugs<br><br>vs<br><br>control (no drug or another antiplatelet drug) | MA of 29 RCTs<br><br>Patients with arterial vascular disease (angina, CAD, MI, nephropathy, PAD, retinopathy, stroke and TIA) | N=23,019<br><br>Duration varied (≥1 month in duration) | Primary:<br>Secondary prevention of vascular death and vascular events (vascular death, any death from an unknown cause, nonfatal stroke or nonfatal MI)<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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.<br><br>There was no evidence that dipyridamole alone was more efficacious than aspirin.<br><br>Secondary:<br>Not reported |
| **Cardiovascular Indications (Acute Coronary Syndrome, Myocardial Infarction, Angina Pectoris)** | | | | |
| Ho et al[50]<br><br>Clopidogrel, dose not specified | RETRO cohort<br><br>Patients with ACS discharged on clopidogrel from 127 Veterans Affairs hospitals between October 2003 and March 2005 | N=3,137<br><br>Duration varied (mean follow-up after stopping clopidogrel was 196 days for patients medically treated and 203 days for patients receiving PCI) | Primary:<br>Rate of all cause mortality or acute MI after stopping clopidogrel<br><br>Secondary:<br>Not reported | Primary:<br>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.<br><br>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).<br><br>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.<br><br>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). |

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| | | | | Secondary:<br>Not reported |
| Sabatine et al[51]<br>CLARITY-TIMI 28<br><br>Clopidogrel 300 mg once, followed by 75 mg/day<br><br>vs<br><br>placebo<br><br>Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin.<br><br>Patients were also scheduled to undergo angiography 48 to 192 hours after the start of the study medication. | DB, MC, PC, RCT<br><br>Patients 18 to 75 years of age who presented within 12 hours after the onset of an STEMI | N=3,491<br><br>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:<br>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)<br><br>Secondary:<br>Safety | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>The rates of major bleeding and intracranial hemorrhage were similar in the two groups. |
| Ahmed et al[52]<br><br>Clopidogrel 300 mg once, followed by 75 mg/day<br><br>vs<br><br>placebo<br><br>Patients received a fibrinolytic agent, aspirin, and when appropriate, heparin. | Substudy of CLARITY-TIMI 28 trial[51]<br><br>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<br><br>30 days (study medication given up to, and including, the day of angiography, or up to day 8 or hospital discharge if | Primary:<br>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) | Primary:<br>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).<br><br>Secondary:<br>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.<br><br>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 |
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| | | no angiography) | Secondary: Composite clinical endpoint of cardiovascular death, MI, or recurrent ischemia leading to urgent revascularization at 30 days; cardiovascular death; safety | |
| COMMIT Collaborative Group[53]<br>COMMIT<br><br>Clopidogrel 75 mg/day plus aspirin 162 mg/day<br><br>vs<br><br>aspirin 162 mg/day | MC, PC, RCT<br><br>Patients admitted to the hospital within 24 hours of suspected acute MI | N=45,852<br><br>15 days (mean) | Primary: Composite of death, re-infarction or stroke; death from any cause<br><br>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.<br><br>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).<br><br>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[54]<br>CHARISMA<br><br>Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day<br><br>vs<br><br>aspirin 75 to 162 mg/day | DB, MC, PC, RCT<br><br>Patients ≥45 years of age with clinically evident cardiovascular disease | N=15,603<br><br>Median 28 months | Primary: Composite of first occurrence of MI, stroke or death from cardiovascular causes<br><br>Secondary: First occurrence of | 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).<br><br>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 |

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| | | | MI, stroke, death from cardiovascular causes or hospitalization for unstable angina, TIA or revascularization procedure; safety | 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).<br><br>Secondary:<br>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.<br><br>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[55]<br><br>Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day<br><br>vs<br><br>aspirin 75 to 162 mg/day | Post hoc analysis of CHARISMA[54]<br><br>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<br><br>Median 28 months | Primary:<br>Composite of first occurrence of MI, stroke or death from cardiovascular causes<br><br>Secondary:<br>First occurrence of MI, stroke, death from cardiovascular causes or hospitalization for unstable angina, TIA or revascularization procedure; safety | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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[56]<br><br>Clopidogrel 75 mg/day plus aspirin 75 to 162 mg/day<br><br>vs<br><br>aspirin 75 to 162 mg/day | Post hoc analysis of CHARISMA[54]<br><br>Post hoc analysis of patients with a history of AF in the CHARISMA trial, who were ≥45 years of age with clinically | N=593<br><br>Median 28 months | Primary:<br>Composite of first occurrence of MI, stroke or death from cardiovascular causes<br><br>Secondary:<br>First occurrence of MI, stroke, death | Primary:<br>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).<br><br>Secondary:<br>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. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | evident cardiovascular disease or multiple atherothrombotic risk factors | | from cardiovascular causes, or hospitalization for unstable angina, TIA or revascularization procedure; safety | 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).<br><br>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[57]<br>CURE<br><br>Clopidogrel (300 mg once, followed by 75 mg/day) plus aspirin<br><br>vs<br><br>aspirin | DB, PC, RCT<br><br>Patients with NSTEMI, presenting within 24 hours of symptom onset | N=12,562<br><br>3 to 12 months | Primary:<br>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)<br><br>Secondary:<br>Severe ischemia, heart failure, need for revascularization, safety | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>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). |
| Roe et al[58]<br>TRILOGY ACS<br><br>Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who | AC, DB, DD, event-driven, RCT<br><br>Patients with ACS if selected | N=7,243 (primary analysis; patients <75 years of age) | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke among patients <75 | Primary:<br>At a median follow-up of 17 months, the primary endpoint occurred in 13.9 vs 16.0% of prasugrel- and clopidogrel-treated patients (HR in the prasugrel group, 0.91; 95% CI, 0.79 to 1.05; P=0.21). Similar results were observed in the overall population (18.7 vs 20.3%; HR, 0.96; 95% CI, 0.86 to 1.07; P=0.45). Because superiority was not established in the primary cohort, the |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| weighed <60 kg received 5 mg/day)<br><br>vs<br><br>clopidogrel 75 mg/day<br><br>Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization. | for a final treatment strategy of medical management without revascularization within 10 days after the index event; patients with MI without ST-segment elevation had elevated cardiac markers and patients with unstable angina with negative cardiac markers had an ST-segment depression of >1 mm in ≥2 electrocardiographic leads, and patients had ≥1 of 4 risk criteria: age ≥60 years of age, the presence of diabetes, previous MI, or previous revascularization with either PCI or CABG | N=2,083 (secondary analysis; patients ≥75 years of age)<br><br>Up to 30 months | years of age<br><br>Secondary: Incidence of cardiovascular death, MI, and stroke; all-cause mortality; bleeding events; safety | prespecified testing strategy did not direct further superiority testing.<br><br>The frequency of the primary end point in the two treatment groups did not differ significantly among prespecified subgroups of patients who were <75 years of age, but an interaction with prasugrel treatment was apparent in current or recent smokers, those who underwent angiography before randomization, and those taking a PPI at randomization.<br><br>The prespecified analysis that was performed to account for multiple recurrent ischemic events suggested a lower risk among patients <75 years of age with prasugrel (HR, 0.85; 95% CI, 0.72 to 1.00; P=0.04). Among patients who had an ischemic event, 364 patients treated with prasugrel (10.1%) had at least one ischemic event compared to 397 patients (11.0%) with clopidogrel, whereas 77 (2.1%) vs 109 (3.0%) had a least two recurrent ischemic events, and 18 (0.5%) vs 24 (0.7%) had at least three recurrent ischemic events, respectively.<br><br>Secondary:<br>Among patients <75 years of age, there were no differences in the incidences of cardiovascular death (6.6 vs 6.8%; HR, 0.93; 95% CI, 0.75 to 1.15; P=0.48), MI (8.3 vs 10.5%; HR, 0.89; 95% CI, 0.74 to 1.07; P=0.21), and stroke (1.5 vs 2.2%; HR, 0.67; 95% CI, 0.42 to 1.06; P=0.08) between prasugrel- and clopidogrel-treated patients. Similar results were observed in the overall population (P=0.38, P=0.58, and P=0.52)<br><br>Among patients <75 years of age, all-cause mortality was similar between the two treatments (7.8 vs 8.1%; HR, 0.96; 95% CI, 0.79 to 1.16; P=0.63). Similar results were observed in the overall population (P=0.40).<br><br>At 30 months, the key bleeding end points of non-CABG-related severe or life-threatening events and major bleeding occurred with similar frequency among patients <75 years of age in the two treatment groups. The only subgroup in which there was a significant treatment interaction for TIMI major bleeding was patients receiving a reduced dose of aspirin.<br><br>The frequency of new, benign neoplasms in the overall treated population did |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | not differ significantly between prasugrel and clopidogrel (1.9 vs 1.8%; P=0.79); similar findings were observed among treated patients with no history of cancer or a history of previous cancer that had been cured before randomization. The incidence of common (>1.0%) nonhemorrhagic serious adverse events was balanced between the two treatments among patients <75 years of age, and the only significant difference observed was a higher rate of heart failure with clopidogrel. |
| Gurbel et al[59]<br><br>Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day)<br><br>vs<br><br>clopidogrel 75 mg/day<br><br>Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel before randomization and were started on daily maintenance administration of a study drug after randomization | Substudy of TRILOGY ACS<br><br>Patients with ACS if selected for a final treatment strategy of medical management without revascularization within 10 days after the index event; patients with MI without ST-segment elevation had elevated cardiac markers and patients with unstable angina with negative cardiac markers had an ST-segment depression of >1 mm in ≥2 electrocardiograp | N=2,564<br><br>Up to 30 months | Primary:<br>Platelet reactivity (measured in $P2Y_{12}$ reaction units); composite of cardiovascular death, MI, or stroke through 30 months<br><br>Secondary:<br>Not reported | Primary:<br>Among patients <75 years of age and weighing ≥60 kg, median $P2Y_{12}$ reaction unit values at 30 days were 64 (interquartile range, 33 to 128) with prasugrel compared to 200 (interquartile range, 141-260) with clopidogrel (P<0.001), a difference that persisted through all subsequent time points. Among patients <75 years of age and weighing <60 kg, corresponding values were 139 (interquartile range, 86 to 203) vs 209 (interquartile range, 148 to 283) (P<0.001). Among patients >75 years of age, corresponding values were 164 (interquartile range, 105 to 216) vs 222 (interquartile range, 148 to 268) (P<0.001).<br><br>At 30 months, the rate of the composite endpoint was 17.2 (160 events) vs 18.9% (180 events) with prasugrel and clopidogrel (P=0.29). There were no significant differences in the continuous distributions of 30 day $P2Y_{12}$ reaction unit values for patients with a primary efficacy endpoint compared to patients without an event (P=0.07) and no significant relationship between the occurrence of the primary efficacy endpoint and continuous $P2Y_{12}$ reaction unit values (adjusted HR for increase of 60 $P2Y_{12}$ reaction units, 1.03; 95% CI, 0.96 to 1.11; P=0.44). Similar findings were observed with 30 day $P2Y_{12}$ reaction unit cut points used to define high on-treatment platelet reactivity; $P2Y_{12}$ reaction unit >280 (adjusted HR, 1.16; 95% CI, 0.89 to 1.52; P=0.28) and $P2Y_{12}$ reaction unit >230 (adjusted HR, 1.20; 95% CI, 0.90 to 1.61; P=0.21).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | hic leads, and patients had ≥1 of 4 risk criteria: age ≥60 years of age, the presence of diabetes, previous MI, or previous revascularization with either PCI or CABG | | | |
| Wiviott et al[60]<br><br>Prasugrel 10 mg/day or 5 mg/day (patients who were ≥75 years of age or who weighed <60 kg received 5 mg/day)<br><br>vs<br><br>clopidogrel 75 mg/day<br><br>Patients who underwent randomization within 72 hours after the first medical contact without previous clopidogrel treatment received a loading dose of 30 mg of prasugrel or 300 mg of clopidogrel. Patients who did not undergo randomization within 72 hours were required to be treated with OL clopidogrel | Substudy of TRILOGY ACS[58] | N=7,243<br><br>Up to 30 months | Primary:<br>Differences in cardiovascular death, myocardial infarction, or stroke at 30 months based on angiography status<br><br>Secondary:<br>Not reported | Primary:<br>Fewer patients who had angiography reached the primary endpoint at 30 months compared with those who did not have angiography (12.8% vs 16.5%; HR, 0.63; 95% CI, 0.53 to 0.75; P<0.0001).<br><br>The proportion of patients who reached the primary endpoint was lower in the prasugrel group than in the clopidogrel group for those who had angiography (10.7% vs 14.9%; HR,0.77; 95% CI, 0.61 to 0.98; P=0.032) but did not differ between groups in patients who did not have angiography (16.3% vs 16.7%; HR, 1.01; 95% CI, 0.84 to 1.20; P=0.94).<br><br>Overall, TIMI major bleeding and GUSTO severe bleeding were rare. Bleeding outcomes tended to be higher with prasugrel but did not differ significantly between treatment groups in either angiography cohort.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| before randomization and were started on daily maintenance administration of a study drug after randomization | | | | |
| Wallentin et al[61]<br>PLATO<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | AC, DB, DD, MC, PG, PRO, RCT<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation | N=18,624<br><br>12 months | Primary:<br>Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding<br><br>Secondary:<br>Effect in patients for 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 | Primary:<br>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.<br><br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>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).<br><br>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).<br><br>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). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | event; results of laboratory safety tests | 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).<br><br>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).<br><br>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.<br><br>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[62]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant. | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing noninvasive procedures | N=5,216<br><br>12 months | Primary:<br>Composite endpoint of the rate of vascular death, MI, or stroke; major bleeding events<br><br>Secondary:<br>Individual components of the primary composite endpoint; all-cause mortality; nonvascular mortality; composite of vascular death, | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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.<br><br>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). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | | | MI, stroke, severe recurrent cardiac ischemia, recurrent cardiac ischemia, TIA, or other arterial thrombotic event; subclasses of stroke; other bleeding events | 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).<br><br>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).<br><br>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.<br><br>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 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[63]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation, undergoing invasive | N=13,408<br><br>12 months | Primary:<br>Composite endpoint of vascular death, MI, or stroke; total major bleeding<br><br>Secondary:<br>Composite endpoint of all-cause mortality, MI, or stroke; composite endpoint of vascular death, MI, stroke, severe recurrent | Primary:<br>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).<br><br>The rate of major bleeding did not differ between ticagrelor and clopidogrel (P=0.8803).<br><br>Secondary:<br>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).<br><br>Ticagrelor was associated with significantly fewer events with regards to the |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | procedures | | 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 | 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).<br><br>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).<br><br>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).<br><br>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) 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.<br><br>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).<br><br>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[64]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs | Substudy of the PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the | N=7,544<br><br>12 months | Primary:<br>Composite endpoint of vascular death, MI, or stroke; major bleeding<br><br>Secondary: | Primary:<br>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).<br><br>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). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | previous 24 hours, with ST-segment elevation or left bundle-branch block | | 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 thrombotic events; components of the primary endpoint; all-cause mortality; severe recurrent cardiac ischemia; recurrent ischemia; TIA; arterial thrombotic events; stent thrombosis; safety | Secondary:<br>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).<br><br>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).<br><br>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).<br><br>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).<br><br>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).<br><br>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).<br><br>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. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 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).<br><br>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[65]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and chronic kidney disease (creatine clearance <60 mL/minute) | N=15,202<br><br>12 months | Primary:<br>Composite endpoint of vascular death, MI, or stroke; major bleeding<br><br>Secondary:<br>All-cause mortality, other bleeding events, safety | Primary:<br>In patients with chronic kidney disease, 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).<br><br>In patients with chronic kidney disease, 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).<br><br>Secondary:<br>In patients with chronic kidney disease, 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).<br><br>In patients with chronic kidney disease, 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.<br><br>In patients with chronic kidney disease, 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).<br><br>In patients with chronic kidney disease, the rate of ventricular pauses was no |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| for 6 months. | | | | 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[66]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation and diabetes | N=4,662<br><br>12 months | Primary:<br>Composite endpoint of vascular death, MI, or stroke; major bleeding<br><br>Secondary:<br>All-cause mortality, MI, definite stent thrombosis, other bleeding events | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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).<br><br>In patients with diabetes, the rate of MI was not different between the two treatments (8.4 vs 9.1%; HR, 0.92; 95% CI, 0.75 to 1.13).<br><br>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).<br><br>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[67]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD | RETRO substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment | N=1,261<br><br>12 months | Primary:<br>Composite endpoint of vascular death, MI, or stroke after CABG; major CABG-related bleeding<br><br>Secondary:<br>Individual components of the | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>Rates of MI (excluding silent) (6.0 vs 5.7%; HR, 1.06; 95% CI, 0.66 to 1.68; |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | elevation who underwent CABG | | primary endpoint after CABG; all-cause mortality after CABG; other bleeding events after CABG | 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).<br><br>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).<br><br>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[68]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Genetic (CYP 2C19 and ABCB1) substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation | N=10,285<br><br>12 months | Primary:<br>Composite endpoint of vascular death, MI, or stroke; major bleeding (loss-of-function allele)<br><br>Secondary:<br>Composite endpoint of vascular death or MI, definite stent thrombosis, major bleeding (gain-of-function allele), other bleeding events, net clinical benefit | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>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).<br><br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 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.<br><br>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[69]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who received treatment in the United States | N=1,413<br><br>12 months | Primary:<br>Composite endpoint of the vascular death, MI, or stroke; major bleeding<br><br>Secondary:<br>Individual components of the primary composite endpoint, all-cause mortality, other bleeding events | Primary:<br>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).<br><br>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% CI, 0.76 to 1.45; P=0.7572).<br><br>Secondary:<br>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).<br><br>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).<br><br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 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).<br><br>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[70]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation | N=199<br><br>12 months | Primary:<br>$FEV_1$ after the completion of study treatment (six, nine, or 12 months depending on phase of entry into the PLATO trial)<br><br>Secondary:<br>$FEV_1$ after one month of treatment and one month after the discontinuation of treatment, other measures of pulmonary function, safety | Primary:<br>$FEV_1$ 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).<br><br>Secondary:<br>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.<br><br>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.<br><br>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. |
| James et al[71] | Substudy of | N=18,624 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | PLATO[58]<br><br>Adult patients with and without a history of prior stroke or TIA and who were hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation | 12 months | Composite endpoint of the vascular death, MI or stroke and major bleeding<br><br>Secondary: Components of primary composite endpoint and all-cause mortality | A total of 1,152 patients (6.2%) had a history of stroke or TIA. Overall, patients with prior history of stroke had higher rates of the primary composite endpoint compared to those without prior stroke or TIA; however, safety and efficacy in these patients were similar in the overall study population.<br><br>The RRR of the primary composite endpoint with ticagrelor compared to clopidogrel was similar in patients with (HR, 0.87) and without (HR, 0.84) prior stroke or TIA (P=0.84).<br><br>The risk of major bleeding with ticagrelor vs clopidogrel in patients with prior history of stroke or TIA was similar in patients without prior history (P=0.77).<br><br>Secondary:<br>When comparing patients with prior history of stroke or TIA to those without prior history, the RRR of cardiovascular death (P=0.42), MI (P=0.19) and overall stroke (P=0.89) was similar.<br><br>The HR of all-cause mortality with ticagrelor compared to clopidogrel was 0.62 in patients with prior stroke or TIA and 0.81 in those without a prior history (P=0.19). |
| Kohli et al[72]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance | Substudy of PLATO[58]<br><br>Adult patients hospitalized with documented ACS within the previous 24 hours, with or without ST-segment elevation who experienced nonfatal events | N=18,624<br><br>12 months | Primary:<br>Total (i.e., first and recurrent) occurrences of any of primary outcome events (e.g., vascular death, MI and stroke), other ischemic events, (urgent revascularization, (severe) recurrent ischemia, transient ischemic attacks, | Primary:<br>Of the 1,888 patients who experienced a primary end point event during follow-up for six to 12 months, 1570 experienced a single event, but 318 patients experienced multiple occurrences of the composite end point of vascular death/MI/stroke. Patients who experienced multiple events were more likely to be older or have diabetes mellitus, a previous history of MI or CABG, impaired renal function and hypertension and were less likely to be male.<br><br>Patients with STEMI at study entry were more likely to experience a single vascular death/MI/stroke event during the trial compared to patients with NSTEMI, who were more likely to experience multiple events (P<0.001).<br><br>The risk of the second occurrence of the composite end point or all-cause |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | | | and arterial thrombotic events<br><br>Secondary: Recurrent bleeding events | death was significantly reduced by ticagrelor (HR, 0.80; 95% CI, 0.70 to 0.90; P<0.001).<br><br>Patients treated with ticagrelor had fewer total vascular death/MI/stroke events as compared to clopidogrel (1057 vs 1225; RR, 0.86; 95% CI, 0.79 to 0.93; P=0.003). Beyond the first event, there were numerically fewer additional events with ticagrelor; however, the difference was not statistically significant (189 vs 205; P=0.40).<br><br>Patients treated with ticagrelor experienced a lower risk of any first atherothrombotic event (vascular death/MI/Stroke/recurrent ischemia/severe recurrent ischemia/TIA/arterial thrombotic events) (RR, 0.88; 95% CI, 0.82 to 0.95; P<0.001).<br><br>Recurrent events were significantly reduced with ticagrelor compared to clopidogrel (740 vs 834) demonstrating a significant reduction in risk of second event or death (RR, 0.83; 95% CI, 0.75 to 0.91; P<0.001).<br><br>With regard to the other composite ischemic end point of vascular death/ MI/stroke/urgent revascularization, significantly fewer events were reported with ticagrelor compared to clopidogrel (1325 vs 1515; P<0.001), demonstrating a RR of 0.87 (95% CI, 0.81 to 0.94) and a NNT of 47.<br><br>Secondary:<br>In an on-treatment cohort, there were 961 first occurrences of PLATO major bleeding with ticagrelor compared to 929 with clopidogrel (HR, 1.04; P=0.43). The recurrent bleeding events were infrequent compared to the first occurrences in both ticagrelor and clopidogrel groups (70 vs 68; P=0.89). This resulted in a similar number of total PLATO major bleeding events between patients treated with ticagrelor or clopidogrel (1031 vs 997; P=0.53).<br><br>Ticagrelor was associated with a higher number of PLATO major or minor events in the on-treatment population (RR, 1.09; 95% CI, 1.01 to 1.17; P=0.02) and the ITT population (RR, 1.08; 95% CI, 1.01 to 1.16; P=0.03). Primarily, this was due to the first occurrences of the composite bleeding end point, as no difference in additional bleeding events were reported in either the ITT |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | cohort (228 vs 226; P=0.96) or the on-treatment cohort (168 vs 162; P=0.78).<br><br>There were significantly more TIMI major non-CABG bleeding events in the on-treatment cohort with ticagrelor compared to clopidogrel (234 vs 188; P=0.03). Although first occurrences of bleeding increased with ticagrelor, recurrent bleeding events were uncommon and similar by treatment for both the safety cohort (13 vs 11; P=0.69) as well as the ITT cohort (18 vs 13; P=0.38). |
| Steg et al[73]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Substudy of PLATO[58]<br><br>Patients who had a least one intracoronary stent | N=11,289<br><br>12 months | Primary:<br>Incidence and effect of treatment on stent thrombosis<br><br>Secondary:<br>Effect on stent thrombosis based on type of ACS, diabetes status, stent type, geographical location, aspirin loading dose, intended treatment strategy, genetic status of CYP2C19, clopidogrel dose, and use of glycoprotein IIb/IIIa inhibitors at randomization | Primary:<br>There were no differences at baseline between patients in the 2 treatment arms.<br><br>Ticagrelor reduced stent thrombosis compared with clopidogrel across all definitions: definite, 1.37% (N=71) compared to 1.93% (N=105; HR, 0.67; 95% CI, 0.50 to 0.90; P=0.0091); definite or probable, 2.21% (N=118) compared to 2.87% (N=157; HR, 0.75; 95% CI, 0.59 to 0.95; P=0.017); and definite, probable, and possible, 2.94% (N=154) compared to 3.77 (N=201; HR, 0.77; 95% CI, 0.62 to 0.95). The reduction in definite stent thrombosis was consistent regardless of acute coronary syndrome type, presence of diabetes mellitus, stent type (drug-eluting or bare metal stent), CYP2C19 genetic status, loading dose of aspirin, dose of clopidogrel before randomization, and use of glycoprotein IIb/IIIa inhibitors at randomization.<br><br>Secondary:<br>The reduction in stent thrombosis with ticagrelor was numerically greater for late (>30 days; HR, 0.48; 95% CI, 0.24 to 0.96) and subacute (4 hours to 30 days; HR, 0.60; 95% CI, 0.39 to 0.93) compared with acute (<24 hours; HR, 0.94; 95% CI, 0.43 to 2.05) stent thrombosis or for patients compliant to therapy (ie, taking blinded study treatment ≥80% of the time) compared with less compliant patients.<br><br>However, the benefit of ticagrelor appeared more marked in patients receiving ≥600 mg clopidogrel compared with those receiving a lower dose (P=0.07 for interaction). Although the interaction of treatment with region is nonsignificant, the HRs show trends similar to previously published results for the other study outcomes, that is, less benefit or a trend toward harm in North America. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Randomization to ticagrelor was a strong independent inverse predictor of definite stent thrombosis (HR, 0.65; 95% CI, 0.48 to 0.88). |
| Wallentin et al[74]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Substudy of PLATO[58]<br><br>Patients with NSTEMI ACS and provided blood samples at randomization | N=9,962<br><br>12 months | Primary:<br>Prognostic importance of hs-TnT, NT-proBNP, GDF-15 in relation to treatment and management strategy<br><br>Secondary:<br>Not reported | Primary:<br>In patients managed without revascularization, hs-TnT levels were significantly related to the rate of the primary composite end point of cardiovascular death, MI, and stroke (log-rank P<0.001). Ticagrelor compared to clopidogrel reduced the composite of CV death, MI, and stroke with a larger effect in the patients in the upper tertiles of positive hs-TnT levels, ie, those with a higher risk, whereas there was a lack of effect in those with negative hs-TnT (<14 ng/L) (interaction P=0.042). The treatment effect of ticagrelor in the noninvasive cohort with hs-TnT ≥14 ng/L was dominated by a reduction in CV mortality. In the same cohort, there also appeared numeric reductions in all types of MI, with the exception of type 5 (CABG-related) MI. There were no consistent relations between hs-TnT and the risk of major non–CABG-related bleeding in the in-hospital noninvasive cohort.<br><br>In the in-hospital revascularization group, the level of hs-TnT showed no relationship with the rate of the composite of CV death/spontaneous MI, CV death alone, spontaneous MI alone, or any of the different types of MI. Ticagrelor substantially reduced the rate of the primary composite and its individual components in the in-hospital invasive cohort. There was no association between the hs-TnT level and the risk of major non-CABG bleeding and no interaction with the effect of ticagrelor in comparison with clopidogrel. The levels of NT-proBNP and GDF-15 were significantly related to the rate of cardiovascular death, MI, and stroke (log-rank P<0.001) based on relations to both cardiovascular death and spontaneous MI in the in-hospital invasive group.<br><br>Concerning major non–CABG-related bleeding, there was a significant relationship to the levels of NT-proBNP and GDF-15 with higher rates of bleeding at higher levels. The increase in bleeding events with ticagrelor in comparison with clopidogrel in the invasive group was accordingly larger at higher levels of these biomarkers.<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Not reported |
| Mahaffey et al[75]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD<br><br>Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | Substudy of PLATO[58]<br><br>Patients who had an MI during the study period | N=1,097<br><br>12 months | Primary:<br>Treatment effect of ticagrelor on MI<br><br>Secondary:<br>Not reported | Primary:<br>Ticagrelor significantly reduced overall 12-month Kaplan-Meier MI rates (5.8% ticagrelor, 6.9% clopidogrel; HR,0.84; 95% CI, 0.75 to 0.95; P=0.005). The direction of the treatment effects was consistent across the MI types except for CABG-related, but there were few of these events, and CIs were wide.<br><br>Nonprocedural MI (HR,0.86; 95% CI, 0.74 to 1.01) and MI related to percutaneous coronary intervention or stent thrombosis tended to be lower with ticagrelor. MIs related to coronary artery bypass graft surgery were few, but numerical excess was observed in patients assigned ticagrelor. Analyses of overall MIs using investigator-reported data showed similar results but did not reach statistical significance (HR,0.88; 95% CI, 0.78 to 1.00).<br><br>Secondary:<br>Not reported |
| Levin et al[76]<br><br>Ticagrelor 180 mg loading dose, followed by 90 mg BID<br><br>vs<br><br>clopidogrel 300 mg loading dose, followed by 75 mg QD | Substudy of PLATO[58] | N=15,212<br><br>12 months | Primary:<br>Effects on health-related quality of life<br><br>Secondary:<br>Not reported | Primary:<br>The EuroQol five-dimensional questionnaire value at discharge among 7,631 patients assigned to ticagrelor was 0.847 and among 7,581 patients assigned to clopidogrel was 0.846 (P=0.71). At 12 months, the mean EuroQol five-dimensional questionnaire value was 0.840 for ticagrelor and 0.832 for clopidogrel (P=0.046). Excluding patients who died resulted in mean EuroQol five-dimensional questionnaire values of 0.864 among ticagrelor patients and 0.863 among clopidogrel patients (P=0.69).<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Patients received aspirin 70 to 100 mg/day maintenance therapy, unless intolerant.<br><br>For patients who were aspirin-naïve, 325 mg was the preferred loading dose.<br><br>In patients receiving a stent, 325 mg was allowed for 6 months. | | | | |
| Brener et al[77]<br><br>clopidogrel<br><br>vs<br><br>prasugrel<br><br>All patients received aspirin therapy. | Subgroup analysis of INFUSE-AMI | N=452<br><br>30 days | Primary:<br>Infarct size<br><br>Secondary:<br>Parameters of reperfusion, and major adverse cardiac events at 30 days and one year | Primary:<br>Prasugrel-treated patients had higher rates of procedural success (94% vs 89%, P=0.03), TIMI 3 flow (95% vs 90%, P=0.06), and lower corrected TIMI frame counts (21 ± 6 vs 23 ± 11, P=0.008). At 30 days, infarct size (percentage of left ventricular myocardium) was marginally lower in the prasugrel group (median [interquartile range] = 16.4% [98% CI, 6.5 to 20.0] vs 17.6% [8.1 to 25.7], P=0.06). These differences did not retain statistical significance after controlling for the propensity to use prasugrel.<br><br>Secondary:<br>At 30 days, the incidence of major adverse cardiac events was lower in the prasugrel group (1.9% vs 8.8%, P=0.005) because of lower rates of death and new-onset heart failure. Similarly, the incidence of major adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke, or ischemia-driven revascularization) was lower in the prasugrel-treated patients (0.7% vs 5.8%, P=0.009). There were no significant differences in stent thrombosis or major bleeding.<br><br>At one year, prasugrel-treated patients had significantly lower rates of major adverse cardiac events than clopidogrel-treated patients, driven predominantly by significantly less death (1.3% vs 8.3%, P=0.004) and fewer episodes of new-onset severe heart failure (2.0% vs 7.7%, P=0.02). The rate of major adverse cardiac and cerebrovascular events remained significantly lower in the prasugrel group as well (4.1% vs 11.4%, P=0.01). These findings persisted after propensity score adjustment. There were no significant differences in |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | major bleeding. Stent thrombosis (definite or probable) was 0% versus 2.5%, respectively, P=0.054. |
| Morrow et al[78]<br>TRA2ºP-TIMI 50<br><br>Vorapaxar 2.5 mg QD<br><br>vs<br><br>placebo QD<br><br>(in addition to standard of care) | MC, DB, PC, RCT<br><br>Men and women at least 18 years of age with evidence or a history of atherosclerosis involving the coronary (spontaneous MI ≥ 2 weeks but ≤ 12 months prior), cerebral (ischemic stroke), or PAD (documented PAD- defined as history of claudication and an ankle-brachial index of <0.85 or prior revascularization for limb ischemia) systems | N=26,449<br><br>Median follow-up 2.5 years (up to 4 years) | Primary:<br>The composite of cardiovascular death, MI, stroke, and UCR<br><br>Secondary:<br>The composite of cardiovascular death, MI, and stroke | Primary:<br>In all patients, the 3-year K-M event rate of 11.2% in the vorapaxar group compared to 12.4% in the placebo group (HR, 0.88; 95% CI, 0.82 to 0.95; P=0.001).<br><br>In post-MI or PAD patients without a history of stroke or TIA), the 3-year K-M event rate was 10.1% in the vorapaxar group compared to 11.8% in the placebo group (HR, 0.83; 95%CI, 0.76 to 0.90; P<0.001)<br><br>Secondary:<br>In all randomized patients, the 3-year K-M event rate of 9.3% in the vorapaxar group compared to 10.5% in the placebo group (HR, 0.87; 95% CI, 0.80 to 0.94; P<0.001). The 3-year K-M estimate of moderate or severe bleeding was 4.2% in vorapaxar group vs. 2.5% in placebo group (HR, 1.66, 95% CI,1.43 to 1.93; P<0.001.<br><br>In post-MI or PAD patients without a history of stroke or TIA, the 3-year K-M event rate of 7.9% in the vorapaxar group compared to 9.5% in the placebo group (HR, 0.80; 95% CI, 0.73 to 0.89; P<0.001). Thje 3-year K-M estimate of TIMI clinically significant bleeding was 15.8% in vorapaxar group vs. 11.1% in placebo group (HR, 1.46, 95% CI, 1.36 to 1.57; P<0.001). |
| Scirica et al[79]<br>TRA2ºP-TIMI 50<br>(parallel trial- subgroup analysis)<br><br>Vorapaxar 2.5 mg QD | MC, DB, PC, RCT<br><br>Men and women at least 18 years of age with evidence or a | N=17,779<br><br>Median follow-up 2.5 years | Primary:<br>The composite of cardiovascular death, MI, stroke, and UCR<br><br>Secondary: | Primary:<br>The 3-year K-M estimates were 10.5% in the vorapaxar group compared to 12.1% in the placebo group (HR, 0.83, 95% CI, 0.76 to 0.92; P=0.0001).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>placebo QD<br><br>(in addition to standard of care) | history of MI ≥ 2 weeks but ≤ 12 months prior | | Cardiovascular death, MI, or stroke | The 3-year K-M estimates were 8.1% in the vorapaxar group compared to 9.7% in the placebo group (H,R 0.80, 95% CI, 0.72 to 0.89; P<0.0001).<br><br>The 3-year K-M estimate of GUSTO moderate or severe bleeding was 3.4% in vorapaxar group compared to 2.1% in placebo group (HR, 1.61, 95% CI, 1.31 to 1.97; P<0.0001).<br><br>The3-year K-M estimate of TIMI clinically significant bleeding was 15.1% in vorapaxar group vs. 10.4% in placebo group (HR, 1.49, 95% CI, 1.36 to 1.63; P<0.0001). |
| Bonaca et al[80]<br>TRA2ºP-TIMI 50<br>(parallel trial- subgroup analysis)<br><br>Vorapaxar 2.5 mg QD<br><br>vs<br><br>placebo QD<br><br>(in addition to standard of care) | MC, DB, PC, RCT<br><br>Men and women at least 18 years of age with PAD (defined as history of claudication and an ankle-brachial index of <0.85 or prior revascularization for limb ischemia) | N=3,787<br><br>Median follow-up 36 months | Primary:<br>Composite of cardiovascular death, MI, stroke, and UCR<br><br>Secondary:<br>Cardiovascular death, MI, or stroke | Primary:<br>The 3-year K-M estimates were 12.7% in the vorapaxar group compared to 13.4% in the placebo group (HR, 0.95, 95% CI, 0.79 to 1.14; P=0.57).<br><br>Secondary:<br>The 3-year K-M estimates were 11.3% in the vorapaxar group compared to 11.9% in the placebo group (HR, 0.94, 95% CI, 0.78 to 1.14; P=0.53).<br><br>The 3-year K-M estimate of moderate or severe bleeding was 7.4% in vorapaxar group compared to 4.5% in placebo group (HR, 1.62, 95% CI, 1.21 to 2.18; P=0.001). |
| Morrow et al[81]<br>TRA2ºP-TIMI 50<br><br>Vorapaxar 2.5 mg QD<br><br>Vs<br><br>Placebo<br><br>Both treatments were added to standard antiplatelet therapy. | Subgroup analysis of TRA2ºP-TIMI 50[78]<br><br>TRA2ºP-TIMI 50 patients who had a prior ischemic stroke | N=4,883<br><br>Median follow-up 36 months | Primary:<br>Composite of cardiovascular death, MI, or stroke, followed by cardiovascular death, MI, stroke, or urgent coronary revascularization, and then cardiovascular death or MI | Primary:<br>For patients with a prior ischemic stroke, the three-year incidence of CV death, MI, or stroke was 13.0% in the vorapaxar group compared with 11.7% in the placebo group(HR, 1.03 (95% CI, 0.85 to 1.25; P=0.75). There was no significant difference between vorapaxar and placebo in any of the efficacy end points examined. In particular, recurrent stroke alone was not reduced with vorapaxar (10.1% vs 7.5%; HR, 1.13; 95% CI, 0.90 to 1.40; P=0.30) in this cohort.<br><br>Secondary:<br>GUSTO moderate or severe bleeding was higher in patients treated with vorapaxar compared with placebo (4.2% vs 2.4%; HR, 1.93; 95% CI, 1.33 to |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | Secondary:<br>GUSTO moderate or severe bleeding, subset of GUSTO severe bleeds that were intracranial hemorrhages | 2.79; P<0.001). Intracranial hemorrhage, inclusive of intracerebral and subdural bleeding, was significantly increased with vorapaxar (2.5% vs 1.0%; HR, 2.52; 95% CI, 1.46 to 4.36; P<0.001). Intracerebral bleeding was significantly increased by vorapaxar with a small number of subdural or epidural bleeding events. The increased risk of intracranial hemorrhage emerged early and persisted. Fatal bleeding was numerically higher with vorapaxar compared with placebo. |
| Leonardi et al[82]<br>TRA*CER<br><br>Vorapaxar 40 mg loading dose followed by 2.5 mg QD<br><br>vs<br><br>placebo loading dose followed by QD | MC, DB, PC, RCT<br><br>Patients ≥18 years of age with a current clinical manifestation of NSTE ACS confirmed by biomarker or EKG + 1 or more cardiovascular risk factors ( >55 years, diabetes mellitus,, previous MI, PCI or CABG, or PAD) | N=12,944<br><br>Median follow-up 502 days | Primary:<br>Composite of death from cardiovascular causes, MI, stroke, recurrent ischemia with rehospitalization or UCR<br><br>Secondary:<br>Composite of cardiovascular death or MI | Primary:<br>The 2-year K-M estimate were 18.5% in the vorapaxar group compared to 19.9% in the placebo group (HR, 0.92, 95% CI,0.85 to 1.01; P=0.07)<br><br>Secondary:<br>The2-year K-M estimate were 14.7% in the vorapaxar group compared to 16.4% in the placebo group (HR, 0.89, 95% CI, 0.81 to 0.98; P=0.02).<br>The 2-year K-M estimate of GUSTO moderate or severe bleeding was 7.2% in vorapaxar group compared to5.2% in placebo group (HR, 1.35, 95% CI, 1.16 to 1.58; P<0.001).<br><br>The 2-year K-M estimate of TIMI clinically significant bleeding was 20.2% in vorapaxar group vs. 14.6% in placebo group (HR, 1.43, 95% CI, 1.31 to 1.57; P<0.001).<br><br>For the rates of intracranial hemorrhage, 2-year K-M estimate was 1.1% in vorapaxar group compared to 0.2% in placebo group (HR, 3.39, 95% CI, 1.78 to 6.45; P<0.001). |
| Whellan et al[83]<br>TRA*CER | Subanalysis of TRA*CER[82]<br><br>TRA*CER patients who underwent CABG during index hospitalization after they were | N=1,312<br><br>Median follow-up 502 days | Primary:<br>Composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization | Primary:<br>In patients undergoing CABG during index hospitalization, the primary endpoint occurred in 43 patients in the vorapaxar group and in 70 patients in the placebo group (2-year Kaplan-Meier rates: 8.2% and 12.9%, respectively), corresponding to a 45% reduction (adjusted HR, 0.55; 95% CI, 0.36 to 0.83; P=0.005). The reduction in events post-discharge was higher among patients who underwent CABG during index hospitalization (HR, 0.46; 95% CI, 0.28 to 0.77; P=0.003) compared with those who did not undergo CABG during index hospitalization (HR, 0.97; 95% CI, 0.87 to 1.08; P=0.59). There was a |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | randomized and began the study drug | | Secondary:<br>The composite of cardiovascular death, MI, or stroke | statistically significant interaction between CABG and vorapaxar (P=0.012). All components of the primary endpoint were numerically lower with vorapaxar. When all patients who underwent CABG in the first 30 days after randomization were included, the effect on post-CABG events remained consistent, with a 48% reduction with vorapaxar (HR, 0.52; 95% CI, 0.36 to 0.76; P=0.001), and the interaction between CABG and vorapaxar treatment effect on post-discharge events remained significant with groups defined at 30 days (P=0.028).<br><br>Secondary:<br>Vorapaxar was also associated with lower occurrence of the key secondary endpoint (43 events; 2-year Kaplan-Meier rate of 8.2%) compared with placebo (58 events; 2-year Kaplan-Meier rate of 10.2%) in patients undergoing CABG (adjusted HR, 0.66; 95% CI, 0.43 to 1.01; P=0.057). The reduction in post-discharge events was numerically higher among patients who underwent CABG (HR, 0.54; 95% CI, 0.31 to 0.94; P=0.030) compared with those who did not undergo CABG (HR, 0.89; 95% CI, 0.78 to 1.01; P=0.065). The interaction between randomized treatment and CABG was not statistically significant (P=0.209). Results were comparable when all patients who underwent CABG in the first 30 days post-randomization were included (HR, 0.60; 95% CI, 0.40 to 0.88; P=0.010).<br><br>The CABG-related TIMI major bleeding was not a statistically significant difference between vorapaxar and placebo, although it was numerically higher with vorapaxar (HR, 1.36; 95% CI, 0.92 to 2.02; P=0.12), as it was for GUSTO severe bleeding related to CABG (HR, 1.35; 95% CI, 0.80 to 2.29; P=0.26). The number of patients who required repeated surgery to control bleeding was similar between groups (vorapaxar N= 30 [4.7%]; placebo N=31 [4.6%]). Fatal bleeding occurred in two placebo patients and in none of the vorapaxar patients. Among those who continued the study drug up to the time of surgery, TIMI major CABG-related bleeding occurred in 43 (8.0%) placebo patients and in 54 (11.0%) vorapaxar patients<br><br>Among those who discontinued the randomized drug throughout CABG, TIMI major CABG-related bleeding occurred in 9 (7.3%) placebo patients and in 13 (9.3%) vorapaxar patients. Reoperation for bleeding in this subgroup was |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | similar between the vorapaxar (N=7 [5.0%]) and placebo (N=7 [5.6%]) groups, and in the group of patients who continued the drug through the perioperative period (vorapaxar: N=23 [4.6%]; placebo: N=24 [4.4%]). In patients who received clopidogrel within five days of surgery (vorapaxar N=242; placebo N=263), TIMI major CABG-related bleeding occurred in 28 (11.6%) patients with vorapaxar and in 23 (8.7%) patients with placebo, and reoperation for bleeding occurred in 10 (4.1%) patients with vorapaxar and 13 (4.9%) patients with placebo. Among patients who received their last dose of clopidogrel ≥5 days before CABG (vorapaxar N=214; placebo N=231), TIMI major CABG-related bleeding occurred in 26 (12.1%) patients with vorapaxar and in 17 (7.4%) patients with placebo, and reoperation for bleeding occurred in 11 (5.1%) patients with vorapaxar and in 12 (5.2%) patients with placebo.<br><br>There was a mild excess in chest tube drainage in patients treated with vorapaxar versus placebo at eight hours (350 ml vs 308 ml), at 24 hours (635 ml vs 580 ml), and total (830 ml vs780 ml).<br><br>When all CABG surgeries performed during the first 30 days from randomization were included, the results for CABG-related major bleeding were similar.<br><br>In patients who underwent CABG during index hospitalization, bleeding after discharge increased with vorapaxar. In the CABG population, GUSTO moderate or severe bleeding at two years was 4.0% with vorapaxar and 2.2% with placebo (HR, 1.60; 95% CI, 0.75 to 3.42). The TIMI major bleeding was infrequent in the CABG cohort, but increased with vorapaxar (2-year Kaplan-Meier rates of 1.4% with vorapaxar and 0.8% with placebo; HR, 1.83; 95% CI, 0.54 to 6.26). In the CABG cohort, there was one patient (0.2%) with intracranial hemorrhage who received vorapaxar and no intracranial hemorrhage with placebo. In the non-CABG population, the GUSTO moderate or severe bleeding rate at two years was 4.1% with vorapaxar and 2.8% with placebo (HR, 1.38; 95% CI, 1.09 to 1.75). There was no statistically significant interaction (P=0.75). |
| Mahaffey et al[84]<br>TRA*CER | Subanalysis of TRA*CER[82] | N=12,944<br><br>Median | Primary:<br>Associations between baseline | Primary:<br>Most patients were treated with low-dose aspirin, and few patients were treated with medium-dose aspirin. A greater proportion of patients were |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | follow-up 502 days | and discharge aspirin dose and clinical efficacy and safety<br><br>Secondary:<br>Not reported | treated with low-dose aspirin at discharge compared with baseline. This is partially reflective of the higher dose given to patients when they arrived at the hospital.<br><br>Patients treated with ≥300 mg aspirin had higher event rates compared with patients treated with ≤100 mg aspirin. There were no statistically significant interactions between vorapaxar effect and aspirin dose. The unadjusted and adjusted hazard ratios in patients treated with ≤100 versus ≥300 mg of aspirin suggested a trend toward a greater treatment effect associated with vorapaxar compared with placebo in the low-dose aspirin group.<br><br>Compared with patients treated with ≤100 mg of aspirin, patients treated with ≥300 mg aspirin had similar GUSTO severe bleeding event rates and slightly higher Thrombolysis In Myocardial Infarction major bleeding rates. There were no statistically significant interactions between study treatment effect on bleeding and aspirin dose. The unadjusted and adjusted hazard ratios in patients treated with ≤100 versus ≥300 mg of aspirin suggested a trend toward more prominent bleeding risk associated with vorapaxar compared with placebo.<br><br>The adjusted hazard ratios showed trends suggesting that in patients treated with higher-dose aspirin, vorapaxar was associated with trends toward lesser efficacy in reducing cardiovascular outcomes compared with placebo. |
| **Procedures and/or Surgery** | | | | |
| Collet et al[85]<br><br>Clopidogrel with platelet-function evaluation and drug adjustment (monitoring)<br><br>vs<br><br>clopidogrel conventional treatment without platelet-function evaluation | OL, RCT<br><br>Patients scheduled to undergo PCI | N=2,440<br><br>1 year | Primary:<br>Composite of death from any cause, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis<br><br>Secondary:<br>Composite of stent | Primary:<br>After one year, there was no statistically significant difference in the composite of death from any cause, MI, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis between patients in the monitoring group and the conventional treatment group (34.6 vs 31.1%; HR, 1.13; 95% CI, 0.98 to 1.29; P=0.10).<br><br>Secondary:<br>The incidence of the composite of stent thrombosis (revascularized or not) and urgent revascularization was not significantly different between patients in the monitoring group compared to the conventional treatment group (4.6 vs 4.9%; HR, 1.06; 95% CI, 0.74 to 1.52; P=0.77). |

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| (conventional treatment)<br><br>Prior to stent implantation, if high platelet reactivity during treatment with clopidogrel occurred, a GP IIb/IIIa inhibitor was administered and an additional loading dose of clopidogrel (≥600 mg) or prasugrel (60 mg) was administered before the procedure, followed by a maintenance dose of 150 mg of clopidogrel or 10 mg of prasugrel following the procedure.<br><br>At 14 to 30 days after stent implantation, patients with high platelet reactivity with clopidogrel switched to prasugrel (10 mg) or increased the dose of clopidogrel by 75 mg. Patients with low platelet reactivity (≥90% inhibition), switched to clopidogrel 75 mg if they were receiving prasugrel 10 mg or clopidogrel 150 mg. | | | thrombosis (revascularized or not) and urgent revascularization; composite of death, recurrent ACS, or stroke; composite of death or resuscitation after cardiac arrest; the composite of death or MI; each individual component of the primary end point; major bleeding events | The composite of death, recurrent ACS, or stroke occurred in a similar proportion of patients managed by platelet monitoring and those who received conventional treatment (8.2 vs 7.0; HR, 1.17; 95% CI, 0.88 to 1.56; P=0.28).<br><br>The composite of death or resuscitation after cardiac arrest occurred in a similar proportion of patients managed by platelet monitoring and those who received conventional treatment (2.7 vs 1.7%; HR, 1.59; 95% CI, 0.92 to 2.74; P=0.10).<br><br>There was no statistically significant difference in the incidence of death or MI between patients randomized to the monitoring group and those in the conventional treatment group (31.7 vs 28.8%; HR, 1.11; 95% CI, 0.96 to 1.29; P=0.15).<br><br>There was no statistically significant difference between the platelet monitoring group and the conventional treatment group with regard to death (P=0.24), MI (P=0.32), stent thrombosis (P=0.51), stroke or TIA (P=0.78) or urgent revascularization (P=0.76).<br><br>The incidence of major bleeding events (2.3 vs 3.3; P=0.15), minor bleeding events (1.0 vs 1.7; P=0.12) and major or minor bleeding events (3.1 vs 4.5%; P=0.08) were not significantly different between the platelet monitoring group and the conventional treatment group, respectively. |
| Banerjee et al[86]<br><br>Clopidogrel for ≥1 year following PCI | RETRO<br><br>Patients who underwent PCI | N=530<br><br>2.4±0.8 years (mean follow-up) | Primary:<br>All cause mortality<br><br>Secondary:<br>Incidence of major | Primary:<br>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).<br><br>On a multivariate analysis, the use of clopidogrel for ≥1 year was associated |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>clopidogrel for <1 year following PCI<br><br>Patients were free of cardiovascular events for 6 months after PCI, and had follow-up available for >12 months. | | | adverse cardiovascular events (composite of all cause death, nonfatal MI and repeat coronary revascularization by PCI or CABG) | 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.<br><br>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.<br><br>Secondary:<br>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 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[87]<br><br>Clopidogrel 600 mg once, followed by 150 mg/day for 6 days, followed by clopidogrel 75 mg/day through day 30 (double dose)<br><br>vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day for 6 days, followed by 75 mg/day through day 30 (standard dose)<br><br>and<br><br>aspirin ≥300 mg/day once, followed by 75 to 100 | 2x2 factorial design, RCT<br><br>Patients ≥18 years of age who presented with a NSTE ACS or a STEMI | N=25,086 (n=17,263 underwent PCI)<br><br>30 days | Primary:<br>Composite of cardiovascular death, MI or stroke<br><br>Secondary:<br>Composite of death from cardiovascular causes, MI, stroke or recurrent ischemia; the individual components of the primary endpoint; death from any cause; bleeding | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| mg/day through day 30 (low-dose)<br><br>vs<br><br>aspirin ≥300 mg/day once, followed by 300 to 325 mg/day through day 30 (high-dose)<br><br>All patients were to undergo early angiography and PCI, if appropriate, no later than 72 hours after randomization. | | | | 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).<br><br>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, 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[88]<br>PCI-CLARITY<br><br>Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 150 to 325 mg once, followed by 75 to 162 mg/day<br><br>vs<br><br>aspirin 150 to 325 mg once, followed by 75 to 162 mg/day | DB, MC, PC, RCT<br><br>Patients with STEMI who received fibrinolytics and underwent PCI (after mandated angiography in CLARITY-TIMI 28) | N=1,863<br><br>30 days | Primary:<br>Composite of cardiovascular death, recurrent MI or stroke from PCI to 30 days after randomization<br><br>Secondary:<br>MI or stroke before PCI, the primary end point from randomization to 30 days | Primary:<br>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).<br><br>Secondary:<br>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).<br><br>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[89]<br>PCI-CURE<br><br>Prior to PCI, patients received aspirin plus clopidogrel or placebo | DB, RCT<br><br>Patients with NSTE ACS from the CURE study undergoing PCI | N=2,658<br><br>8 months (average duration of follow-up after PCI) | Primary:<br>Composite of cardiovascular death, MI or urgent target-vessel revascularization within 30 days of | Primary:<br>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).<br><br>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). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| 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). | | | PCI; cardiovascular death or MI from time of PCI to scheduled end of trial<br><br>Secondary:<br>Not reported | Overall, clopidogrel was associated with a 31% reduction in cardiovascular death or MI, including events before and after PCI (P=0.002).<br><br>At follow-up, there was no significant difference in major bleeding between the groups (P=0.64).<br><br>Secondary:<br>Not reported |
| Steinhubl et al[90]<br>CREDO<br><br>Clopidogrel 300 mg once (3 to 24 hours before PCI), followed by clopidogrel 75 mg/day<br><br>vs<br><br>placebo (3 to 24 hours before PCI), followed by clopidogrel 75 mg/day through day 28, followed by placebo<br><br>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<br><br>Patients undergoing PCI | N=2,116<br><br>12 months | Primary:<br>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<br><br>Secondary:<br>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:<br>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%).<br><br>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).<br><br>Secondary:<br>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.<br><br>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).<br><br>Risk of major bleeding at one year increased, but not significantly (8.8 vs 6.7%; P=0.07). |
| Lev et al[91] | PRO | N=292 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Clopidogrel 300 to 600 mg before PCI, followed by 75 mg/day for 3 to 12 months<br><br>vs<br><br>clopidogrel 300 to 600 mg immediately after PCI, followed by 75 mg/day for 3 to 12 months<br><br>All patients were treated with aspirin 325 mg before PCI, followed by aspirin (dose not specified) for 3 to 12 months. | Patients with chest pain and STEMI undergoing emergency PCI | 6 months | Occurrence of TIMI myocardial perfusion grade 3 after PCI<br><br>Secondary:<br>Incidence of re-infarction, stent thrombosis, target vessel revascularization, death | TIMI myocardial perfusion grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group (85 vs 71%; P=0.01).<br><br>Secondary:<br>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.<br><br>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.<br><br>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[92]<br><br>Clopidogrel 600 mg once, followed by 75 mg/day<br><br>vs<br><br>clopidogrel 600 mg once, followed by 150 mg/day<br><br>All patients received aspirin 300 mg/day.<br><br>All patients received dual antiplatelet therapy on admission followed by maintenance dose administration according to study protocol and PCI was | RCT<br><br>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<br><br>30 days | Primary:<br>Major adverse cardiac event (composite of cardiac death, nonfatal MI and urgent target vessel revascularization)<br><br>Secondary:<br>Stent thrombosis, major and minor bleeding events | Primary:<br>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.<br><br>Secondary:<br>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.<br><br>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. |

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| performed within 48 hours of admission. | | | | |
| Valgimigli et al[93]<br>PRODIGY<br><br>Clopidogrel 300 or 600 mg once, followed by 75 mg/day plus aspirin 160 to 325 mg orally or 500 mg intravenously once, followed by 80 to 160 mg/day for six months<br><br>vs<br><br>clopidogrel 300 or 600 mg once, followed by 75 mg/day plus aspirin 160 to 325 mg orally or 500 mg intravenously once, followed by 80 to 160 mg/day for 24 months<br><br>Patients in the six-month group who received bare metal stent were allowed to discontinue treatment after 30 days. | MC, OL, RCT<br><br>Patients ≥18 years of age with chronic stable CAD, NSTEMI or STEMI ACS who were receiving a stent placement | N=2,013<br><br>24 months | Primary:<br>Composite of death of any cause, nonfatal MI and cerebrovascular accident<br><br>Secondary:<br>Components of the composite primary endpoint, cardiovascular death, stent thrombosis and bleeding outcomes | Primary:<br>The cumulative risk of the primary endpoint at 24 months was 10.1% in the 24-month group and 10.0% in the six-month group (HR, 0.98; 95% CI, 0.74 to 1.29; P=0.91).<br><br>Secondary:<br>When individual components were analyzed separately, there were no differences between the six-month and 24-month groups with regard to risks of death of any cause (6.6% for both; HR, 1.00; 95% CI, 0.72 to 1.40; P=0.98), nonfatal MI (4.2 vs 4.0%; HR, 1.06; 95% CI, 0.69 to 1.63; P=0.80), cerebrovascular accident (1.4 vs 2.1%; HR, 0.60; 95% CI, 0.29 to 1.23; P=0.17), cardiovascular death (3.8 vs 3.7%; HR, 1.03; 95% CI, 0.66 to 1.61; P=0.89) and stent thrombosis (4.7 vs 3.9%; HR, 1.21; 95% CI, 0.79 to 1.86; P=0.38).<br><br>Safety end point was a composite end point of fatal bleeding, overt bleeding plus hemoglobin drop of ≥3 g/dL, bleeding that requires nonsurgical/medical intervention, bleeding that leads to hospitalization or increased level of care and bleeding that prompts evaluation. Dual-antiplatelet therapy for six months was associated with a lower risk of bleeding compared to the 24-month therapy (3.5 vs 7.4%; HR, 0.46; 95% CI, 0.31 to 0.69; P=0.00018). |
| Gwon et al[94]<br>EXCELLENT<br><br>Clopidogrel 75 mg/day plus aspirin 100 to 200 mg/day for six months then aspirin alone for six months | MC, OL, PRO, RCT<br><br>Korean patients with coronary vessel occlusion and who were undergoing PCI | N=1,443<br><br>12 months | Primary:<br>Target vessel failure defined as a composite of cardiac death, MI and target vessel revascularization | Primary:<br>Incidence of target vessel failure was similar between the six- and 12-month dual antiplatelet treatment groups (4.8 vs 4.3%; HR, 1.14; 95% CI, 0.70 to 1.86).<br><br>In the pre-specified subgroup analysis, the incidence of target vessel failure was higher with the six-month group compared to the 12-month group for patients with diabetes (HR, 3.16; 95% CI, 1.42 to 7.03). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>clopidogrel 75 mg/day plus aspirin 100 to 200 mg/day for 12 months<br><br>All patients received aspirin ≥300 mg plus clopidogrel 300 to 600 mg once before PCI. | with drug-eluting stent placement | | Secondary:<br>Components of the composite primary endpoint, death of any cause, death or MI, stent thrombosis, major bleeding according to TIMI criteria, major adverse cardiocerebral events and composite safety endpoint | Secondary:<br>No differences were seen between the six- and 12-month groups in the rate of cardiac death (0.3 vs 0.4%; HR, 0.67; 95% CI, 0.11 to 3.99), MI (1.8 vs 1.0%; HR, 1.86; 95% CI, 0.74 to 4.67) and target vessel revascularization (3.1 vs 3.2%; HR, 2.00; 95% CI, 0.75 to 5.34).<br><br>Risk of death of any cause was 0.6 and 1.0% in the six-month and 12-month groups (HR, 0.57; 95% CI, 0.17 to 1.95). Death or MI occurred in 2.4 and 1.9% of patients in the six- and 12-month groups (HR, 1.21; 95% CI, 0.60 to 2.47).<br><br>Incidence of stent thrombosis was higher with the six-month group but was not statistically different from the 12-month group (0.9 vs 0.1%; HR, 6.02; 95% CI, 0.72 to 49.96).<br><br>Risk of TIMI major bleeding was similar between the six- and 12-month groups (0.3 vs 0.6%; HR, 0.5; 95% CI, 0.09 to 2.73).<br><br>Risk of major cardiocerebral event, which is a composite of death, MI, stroke, stent thrombosis and any revascularization, was similar between the six- and 12-month groups (8.0 vs 8.5%; HR, 0.94; 95% CI, 0.65 to 1.35).<br><br>Safety endpoint, defined as a composite of death, MI, stroke, stent thrombosis and TIMI major bleeding, was also similar between the six- and 12-month groups (3.3 vs 3.0%; HR, 1.15; 95% CI, 0.64 to 2.06). |
| Bertrand et al[94]<br>CLASSICS<br><br>Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 325 mg/day<br><br>vs<br><br>clopidogrel 75 mg/day plus aspirin 325 mg/day | RCT<br><br>Patients receiving a stent placement | N=1,020<br><br>28 days | Primary:<br>Major peripheral or bleeding complications, neutropenia, thrombocytopenia, early discontinuation due to non-cardiac adverse event<br><br>Secondary: | Primary:<br>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).<br><br>Secondary:<br>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 |
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| vs<br><br>ticlopidine 250 mg BID plus aspirin 325 mg/day | | | Incidence of cardiac events | |
| Isshiki et al[96]<br>CLEAN<br><br>Clopidogrel 300 mg once, followed by 75 mg/day plus aspirin 81 to 100 mg/day<br><br>vs<br><br>ticlopidine 100 mg BID plus aspirin 81 to 100 mg/day | DB, MC, RCT<br><br>Japanese patients ≥20 years of with stable angina or history of MI and who were undergoing PCI | N=931<br><br>12 weeks | Primary:<br>Composite of clinically significant bleeding, blood disorders, elevated liver function tests and study drug discontinuation due to an adverse reaction<br><br>Secondary:<br>Composite of all-cause mortality, acute MI, revascularization, stent thrombosis or ischemic stroke | Primary:<br>The composite primary endpoint occurred in 10.1% of patients in the clopidogrel group and 34.2% in the ticlopidine group (HR, 0.259; 95% CI, 0.187 to 0.359; P<0.0001).<br><br>When individual components were analyzed separately, there were no differences between clopidogrel and ticlopidine with regard to the risks of clinically significant bleeding (0.9 vs 0.6%; HR, 1.328; 95% CI, 0.297 to 5.936) and blood disorder (1.7 vs 3.4%; HR, 0.495; 95% CI, 0.212 to 1.158). Clopidogrel was associated with lower risk of liver function test elevation (6.0 vs 30.3%; HR, 0.172; 95% CI, 0.115 to 0.258) and treatment discontinuation due to an adverse reaction (3.9 vs 13.1%; HR, 0.281; 95% CI, 0.166 to 0.476) compared to ticlopidine.<br><br>Secondary:<br>There was no difference in the cumulative risk of the composite cardiovascular endpoint between the clopidogrel and ticlopidine groups (9.2 vs 10.3%; HR, 0.886; 95% CI, 0.587 to 1.337). Acute MI was reported in 7.7 and 9.2% of patients in the clopidogrel and ticlopidine groups, revascularization in 1.5 and 0.4% of patients and ischemic stroke in 0.2 and 0.6% of patients in the respective treatment group (P values not reported). No death or stent thrombosis was reported during the study. |
| Leon et al[97]<br><br>Aspirin 325 mg/day<br><br>vs<br><br>aspirin 325 mg/day plus warfarin | MC, RCT<br><br>Patients receiving a stent | N=1,653<br><br>30 days | Primary:<br>Composite of death, revascularization of target lesion, angiographically evident thrombosis or MI within 30 days<br><br>Secondary: | Primary:<br>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).<br><br>Secondary:<br>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. |

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| vs<br><br>aspirin 325 mg/day plus ticlopidine 250 mg BID | | | Achievement of <50% residual stenosis without death or emergency bypass surgery, procedure-related MI, hematologic dyscrasias, hemorrhagic and vascular surgical complications | 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).<br><br>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[98]<br>DECLARE-DIABETES<br><br>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<br><br>vs<br><br>aspirin plus clopidogrel (as above) plus cilostazol 200 mg immediately after stent placement and continued for 6 months at 100 mg BID | MC, PRO, RCT<br><br>Diabetic patients ≥18 years of age undergoing drug eluting stent implantation | N=400<br><br>9 months | Primary:<br>In-stent late loss at six months<br><br>Secondary:<br>In-segment late loss and restenosis rate at six months; stent thrombosis, target vessel revascularization, major adverse cardiac events (death, MI, and target lesion revascularization) at nine months; safety | Primary:<br>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).<br><br>Secondary:<br>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.<br><br>At nine months, there was no difference in the rate of stent thrombosis (0 vs 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).<br><br>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).<br><br>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[99]<br>TRITON-TIMI 38<br><br>Prasugrel 60 mg once, followed by 10 mg/day | DB, MC, PG, RCT<br><br>Patients with ACS (unstable angina, NSTEMI | N=13,608<br><br>6 to 15 months (median, 14.5 months) | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke | Primary:<br>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).<br><br>Each individual endpoint was analyzed separately and of the three, only |

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| vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day<br><br>Patients were also on concurrent aspirin (75 to 162 mg/day). | 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 planned or within 14 days after receiving medical treatment for STEMI | | 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 | 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.<br><br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>Urgent target vessel revascularization was found to be significantly less in the prasugrel group (2.5%) than in the clopidogrel group (3.7%; HR, 0.66; 95% CI, 0.54 to 0.81; P<0.001).<br><br>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).<br><br>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).<br><br>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). |

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| | | | | 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).<br><br>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).<br><br>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).<br><br>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[100]<br><br>Prasugrel 60 mg once, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day<br><br>Patients were also on concurrent aspirin (75 to 162 mg/day). | Subanalysis of TRITON-TIMI 38[82]<br><br>TRITON-TIMI 38 patients with a median age of 63 stratified by diabetes | N=13,608 (n=3,146 diabetes population)<br><br>6 to 15 months (median, 14.5 months) | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke<br><br>Secondary:<br>Rate of cardiovascular death, MI (fatal or nonfatal) or stent thrombosis; safety; net clinical benefit | Primary:<br>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).<br><br>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, 0.76 to 0.98; P=0.02).<br><br>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).<br><br>Secondary:<br>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).<br><br>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% |

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| | | | | reduction in MI among nondiabetic prasugrel patients compared to a 40.0% reduction in MI among diabetic prasugrel patients.<br><br>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).<br><br>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).<br><br>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).<br><br>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[101]<br><br>Prasugrel 60 mg once, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day<br><br>Patients were also on concurrent aspirin (75 to 162 mg/day). | Subanalysis of TRITON-TIMI 38[82]<br><br>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 | N=13,608 (n=3,534 STEMI population)<br><br>6 to 15 months (median, 14.5 months) | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke at 15 months<br><br>Secondary:<br>Composite of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization at 30 days; stent thrombosis; composite of cardiovascular | Primary<br>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, 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).<br><br>Secondary:<br>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).<br><br>Stent thrombosis was significantly lower in the prasugrel group (1.6%) than in |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | symptom onset) or secondary PCI (those enrolled between 12 hours and 14 days after symptom onset) | | death or nonfatal MI; all individual components of composite endpoints; all cause death rate; safety | the clopidogrel group (2.8%; HR, 0.58; 95% CI, 0.36 to 0.93; P=0.0232).<br><br>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).<br><br>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.<br><br>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[102]<br><br>Prasugrel 60 mg once, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day<br><br>Patients were also on concurrent aspirin (75 to 162 mg/day). | Subanalysis of TRITON-TIMI 38[82]<br><br>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 | N=13,608 (n=12,844 stent population)<br><br>6 to 15 months (median 14.5 months) | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke<br><br>Secondary:<br>Composite endpoint of death from cardiovascular causes, nonfatal MI or urgent target vessel revascularization; cardiovascular death; MI; urgent target vessel revascularization; | Primary:<br>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; 95% CI, 0.72 to 0.90; P=0.0001).<br><br>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).<br><br>Secondary:<br>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).<br><br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | drug eluting stent cohort who received ≥1 coronary stent | | stent thrombosis | 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).<br><br>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).<br><br>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.<br><br>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).<br><br>Rates of stent thrombosis were significantly better in the entire stent cohort 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).<br><br>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[103]<br><br>Prasugrel 60 mg once, followed by 10 mg/day | Subanalysis of TRITON-TIMI 38[82]<br><br>TRITON-TIMI 38 | N=13,608 (n=569 PCI population)<br><br>6 to 15 | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke | Primary:<br>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). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day<br><br>Patients were also on concurrent aspirin (75 to 162 mg/day). | patients who underwent PCI without stent implantation | months (median, 14.5 months) | Secondary:<br>Composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke or urgent target vessel revascularization; safety | 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).<br><br>Secondary:<br>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.<br><br>The incidence of all cause mortality, cardiovascular death and nonfatal and all stroke did not differ significantly between the groups.<br><br>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 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[104]<br><br>Prasugrel 60 mg once, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 300 mg once, | Subanalysis of TRITON-TIMI 38[82]<br><br>Patients with ACS (unstable angina, NSTEMI or STEMI) with a | N=13,608<br><br>6 to 15 months (median, 14.5 months) | Primary:<br>Rate of MI, stent thrombosis and urgent target vessel revascularization from randomization to day three and from day three to | Primary:<br>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).<br><br>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, |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| followed by 75 mg/day<br><br>Patients were also on concurrent aspirin (75 to 162 mg/day). | 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 planned or within 14 days after receiving medical treatment for STEMI | | the end of the trial<br><br>Secondary:<br>Safety, percent net clinical benefit | 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).<br><br>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).<br><br>Secondary:<br>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).<br><br>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).<br><br>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 7.35%; HR, 0.87; 95% CI, 0.77 to 0.98; P=0.028). |
| Murphy et al[105]<br><br>Prasugrel 60 mg once, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day | Subanalysis of TRITON-TIMI 38[82]<br><br>Patients with ACS (unstable angina, NSTEMI or STEMI) with a scheduled PCI; | N=13,608<br><br>6 to 15 months (median, 14.5 months) | Primary:<br>Total number of reoccurrences of the composite endpoint (rate of death from cardiovascular causes, nonfatal MI or nonfatal stroke), risk of second event | Primary:<br>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).<br><br>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). |

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| Patients were also on concurrent aspirin (75 to 162 mg/day). | 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 planned or within 14 days after receiving medical treatment for STEMI | | following initial event, cardiovascular deaths following nonfatal event<br><br>Secondary:<br>Safety | 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).<br><br>Secondary:<br>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. |
| O'Donoghue et al[106]<br><br>Prasugrel 60 mg once, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 300 mg once, followed by 75 mg/day | Subanalysis of TRITON-TIMI 38[82]<br><br>TRITON-TIMI 38 patients stratified by GB IIb/IIIa inhibitor use | N=13,608 (n=7,414 GP IIb/IIIa inhibitor population)<br><br>30 days | Primary:<br>Composite of death from cardiovascular causes, nonfatal MI or nonfatal stroke<br><br>Secondary:<br>Periprocedural MI, urgent target vessel revascularization, | Primary:<br>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.<br><br>Secondary:<br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Patients were also on concurrent aspirin (75 to 162 mg/day). | | | stent thrombosis, safety | subgroups.<br><br>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).<br><br>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).<br><br>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 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). |
| Trenk et al[107]<br>TRIGGER-PCI<br><br>Prasugrel 60 mg loading dose followed by 10 mg/day | RCT<br><br>Patients 18 to 80 years of age with stable CAD who underwent PCI | N=423<br><br>6 months | Primary:<br>Composite of cardiovascular death and MI and non-CABG-related TIMI major bleeding | Primary:<br>Composite primary endpoint occurred in one patient in the clopidogrel group vs none in the prasugrel group (P>0.05).<br><br>Non-CABG-related TIMI major bleeding occurred in three patients in the prasugrel group and one in the clopidogrel group (P>0.05). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>clopidogrel 75 mg/day<br><br>All patients received clopidogrel 600 mg loading dose plus aspirin ≥250 mg within 24 hours before PCI and one-time clopidogrel 75 mg the morning after PCI. | with at least one drug-eluting stent placement and demonstrated high on-treatment platelet reactivity after clopidogrel loading dose followed by one-time clopidogrel 75 mg | | Secondary:<br>Composite of cardiovascular death, MI and target vessel revascularization, composite of cardiovascular death, MI, stroke and rehospitalization for cardiac ischemic event and composite safety endpoint | Secondary:<br>Composite endpoint of cardiovascular death, MI and revascularization occurred in two patients in each treatment group (P>0.05).<br><br>Composite endpoint of cardiovascular death, MI, stroke and rehospitalization for cardiac ischemic event occurred in two patients treated with prasugrel and six patients treatment with clopidogrel (HR, 0.493; 95% CI, 0.090 to 2.692).<br><br>Secondary safety endpoint, a composite of any non-CABG-related bleeding, occurred in 2.9 and 1.9% in the prasugrel and clopidogrel groups, respectively (HR, 1.517; 95% CI, 0.428 to 5.376).<br><br>The authors concluded that due to low event rate, the utility of prasugrel in patients with high on-treatment platelet reactivity could not be determined. |
| Wiviott et al[27]<br><br>Prasugrel 60 mg loading dose, followed by 10 mg/day<br><br>vs<br><br>clopidogrel 600 mg loading dose, followed by 150 mg/day<br><br>Maintenance dose administered upon PCI completion. | AC, DB, DD, RCT, XO<br><br>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<br><br>28 days (treatment periods were 14 days each) | Primary:<br>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<br><br>Secondary:<br>Mean maximal platelet aggregation with 20 μmol/L adenosine diphosphate, mean $P2Y_{12}$ assay percent inhibition, safety | Primary:<br>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).<br><br>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).<br><br>Secondary:<br>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).<br><br>For the maintenance dose phase mean maximal platelet aggregation with 20 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | 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).<br><br>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).<br><br>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).<br><br>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.<br><br>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). |
| Dasbiswas et al (abstract)[108]<br><br>Prasugrel 60 mg loading dose followed by 10 mg QD maintenance<br><br>vs<br><br>clopidogrel 300 mg loading dose followed by 75 mg QD maintenance<br><br>All the patients were co-prescribed aspirin 325 mg with both the drugs | DB, DD, MC, PG, RCT<br><br>Patients with acute coronary syndrome undergoing PCI | N=210<br><br>12 weeks | Primary:<br>Percentage inhibition of ADP induced platelet aggregation at four ± one hour after the loading dose and at 30 ± three days during maintenance treatment<br><br>Secondary:<br>Safety | Primary:<br>Patients in prasugrel group have demonstrated significantly higher inhibition of platelets as compared to clopidogrel group (82.5% vs 71.1%) at 4 hours and at 30 days (84.1% vs 67.4%). The difference in inhibition of platelets between prasugrel and clopidogrel after loading dose and maintenance dose was statistically significant (P≤0.01).<br><br>More patients on prasugrel have shown response to antiplatelet therapy than on clopidogrel (97.4% vs 87.6%). The difference between the two groups was statistically significant (P<0.05).<br><br>Secondary:<br>Both clopidogrel and prasugrel were well tolerated and have comparable safety profile. |
| Parodi et al[109] | NI, RCT | N=50 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| RAPID Primary PCI<br><br>Prasugrel 60 mg loading dose<br><br>Vs<br><br>Ticagrelor 180 mg loading dose<br><br>The following were concomitant medications: 1) aspirin: 500 mg LD followed by 100 mg daily dose; 2) bivalirudin: bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion during PCI, after PPCI a bivalirudin infusion of 0.25 mg/kg/h for 4 h was allowed; 3) unfractionated heparin use was discouraged; and 4) glycoprotein IIb/IIIa inhibitors were not allowed.<br><br>Dual antiplatelet therapy (100 mg aspirin associated with 5 or 10 mg prasugrel or 180 mg ticagrelor) was recommended for 12 months. | Patients 18 years of age or older who have a diagnosis of STEMI within 12 hours of symptoms onset | | Residual platelet activity two hours after loading dose<br><br>Secondary: Percentage of patients with a high residual platelet reactivity two hours after loading dose, acute stent thrombosis, and in-hospital major, minor or minimal bleedings | Platelet reactivity units (PRU) two hours after the loading were 217 (12 to 279) and 275 (88 to 305) in the prasugrel and ticagrelor groups, respectively (P=0.207), satisfying pre-specified noninferiority criteria.<br><br>There was no difference in platelet reactivity unit value at two hours between prasugrel and ticagrelor group: 217 (12 to 279) and 275 (88 to 305), respectively (P=0.207). Prasugrel showed to be noninferior as compared with ticagrelor in inhibiting platelet activity two hours after the loading dose (Δ: −41; 95% CI, −115 to 31; which was behind the predefined +35 noninferiority margin).<br><br>Secondary:<br>Residual platelet reactivity was 34 ± 14 and 39 ± 14 (P=0.215) in prasugrel and ticagrelor groups, respectively.<br><br>High residual platelet reactivity (HRPR) (PRU ≥240) was found in 44% and 60% of patients (P=0.258) at two hours. The mean time to achieve a PRU <240 was three ± two hours and five ± four hours in the prasugrel and ticagrelor groups, respectively. The independent predictors of HRPR at two hours were morphine use (OR: 5.29; 95% CI, 1.44 to 19.49; P=0.012) and baseline PRU value (OR: 1.014; 95% CI, 1.00 to 1.03; P=0.046).<br><br>There was no difference in event rates between the two study drugs, but a higher rate of dyspnea and contrast-induced nephropathy in the ticagrelor group. |
| **Treatment of Thrombocythemia** | | | | |
| Anagrelide Study Group[110] | MC, Phase II | N=577 | Primary:<br>Response to | Primary:<br>Of the 577 patients, 424 were treated for at least four weeks. Of which, 396 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Anagrelide 0.5 to 1 mg QID<br><br>To be eligible, patients had to have responded to or have been treated for ≥4 weeks at 4 mg/day. | 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 | Duration not reported | 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<br><br>Secondary:<br>Not reported | (93%) met the criteria for response. Equivalent response rates were seen regardless of diagnosis (P=0.123).<br><br>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).<br><br>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.<br><br>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).<br><br>The median duration of first response ranged from 7.7 months for PV patients to >28.6 months for ET patients, with an overall median of 16.7 months.<br><br>The median duration of therapy was 5.60 months, with a range of 0.03 to 61.00 months.<br><br>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.<br><br>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.<br><br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 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.<br><br>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.<br><br>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 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%).<br><br>Secondary:<br>Not reported |
| Silver et al[111]<br><br>Anagrelide 0.5 to 1 mg QID<br><br>Weekly adjustments to the dose were made to achieve and maintain a platelet count ≤600,000/μL. | Subanalysis of Anagrelide Study Group[91]<br><br>Patients with CML | N=38<br><br>Duration not reported | Primary:<br>Efficacy, safety<br><br>Secondary:<br>Not reported | Primary:<br>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. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| These patients previously received hydroxyurea therapy (hydroxyurea-resistant) before being treated with anagrelide.<br><br>Patients fell into two groups: hydroxyurea-refractory patients and probably, but not definitely, hydroxyurea-refractory patients. | | | | 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.<br><br>The symptoms of the group of patients with thrombosis included TIAs, MI, erythromelalgia, DVT, and ischemia with or without cutaneous ulceration of the extremities.<br><br>Secondary:<br>Not reported |
| Penninga et al[112]<br><br>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<br><br>Patients with chronic myelo-proliferative disease | N=52<br><br>Duration not reported | Primary:<br>Complete response (reduction in platelet counts to <600x$10^9$/L or to a minimum 50% of pre-treatment level for ≥4 weeks), partial response (20 to 50% reduction of pretreatment level for ≥4 weeks), no response (<20% reduction in pretreatment platelet counts)<br><br>Secondary:<br>Adverse events | Primary:<br>Forty one (79%) patients responded to treatment, with 39 (75%) patients being complete responders. All achieved a platelet count <600x$10^9$/L, and 34 (65%) patients achieved a platelet count <400x$10^9$/L.<br><br>Eleven (21%) patients were nonresponders.<br><br>The mean dose necessary to maintain response was 1.7 mg/day (range, 0.5 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.<br><br>Secondary:<br>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[113]<br><br>Anagrelide 1 to 8 mg/day | Noncomparative, OL, Phase II, PRO | N=60<br><br>2 years | Primary:<br>Clinical effects, short- and long-term | Primary:<br>The overall response rate was 73% (67% complete responses [platelet count <400 x$10^9$/L or <600 x$10^9$/L in symptomatic and asymptomatic patients for ≥4 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Doses were evaluated until the lowest effective dose required to reduce and maintain platelet count <400 x$10^9$/L in symptomatic patients or <600 x$10^9$/L in asymptomatic patients was established.<br><br>Patients who were receiving treatment with another agent to control platelets were switched over to anagrelide. | Patients with a diagnosis of myelo-proliferative disease and a platelet count >600 x$10^9$/L in symptomatic patients or >1,000 x$10^9$/L in all other patients | | tolerability, patient's management<br><br>Secondary:<br>Not reported | 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.<br><br>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.<br><br>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.<br><br>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.<br><br>Secondary:<br>Not reported |
| Steurer et al[114]<br><br>Anagrelide 0.5 mg BID for 14 days, followed by 1 mg BID and then the dosage was adjusted for each patient<br><br>In patients pretreated with hydroxyurea or interferon-α, it was allowed to combine anagrelide with one of those compounds. | MC, Phase II<br><br>Newly diagnosed or pretreated patients with ET, PV or chronic idiopathic myelofibrosis | N=97<br><br>6 months | Primary:<br>Platelet counts<br><br>Secondary:<br>Rate of clinical complications before and during anagrelide therapy, number of patients achieving response (complete, partial or failure to respond) | Primary:<br>Platelet counts decreased significantly during the six month study period from a median baseline count of 743x$10^9$/L (range, 335 to 1.912x$10^9$/L) to 441x$10^9$/L (range, 153 to 1.141x$10^9$/L; P<0.001).<br><br>Secondary:<br>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%. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 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[115]<br><br>Hydroxyurea 0.5 to 1 mg/day<br><br>vs<br><br>anagrelide 0.5 mg BID<br><br>Doses of hydroxyurea and anagrelide were adjusted to maintain the platelet count <400,000/mm$^3$.<br><br>All patients received aspirin 75 mg/day.<br><br>If aspirin was contraindicated, alternative agents were used (e.g., clopidogrel, dipyridamole). | OL, RCT<br><br>Patients ≥18 years of age with ET who were at high risk for thrombotic or hemorrhagic events | N=809<br><br>39 months (median follow-up) | Primary:<br>Composite of time from randomization until death from thrombosis, hemorrhage, arterial or venous thrombotic event or serious hemorrhage<br><br>Secondary:<br>Time to first arterial or venous thrombotic event or to the first serious hemorrhage; time to death; incidence of transformation to myelofibrosis, AML, myelodysplasia or PV; control of platelet count | Primary:<br>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.<br><br>Secondary:<br>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 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.<br><br>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.<br><br>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 |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 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.<br><br>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, GDF-15=growth differentiation factor-15, GFR=glomerular filtration rate, GP IIb/IIIa inhibitor=glycoprotein IIb/IIIa inhibitor, GUSTO= global utilization of streptokinase and t-PA, hs-TnT= high-sensitivity troponin T, MI=myocardial infarction, MRI=magnetic resonance imaging, NNT=number needed to treat, NSTE ACS=non-ST-segment elevation acute coronary syndromes, NSTEMI=non-ST-segment elevation myocardial infarction, NT-proBNP= N-terminal pro-brain natriuretic peptide, 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**[1-8]

| 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.<br><br>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.<br><br>Contraindicated in severe hepatic impairment. | C | Unknown; use with caution. |
| Clopidogrel | No dosage adjustment required in the elderly.<br><br>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.<br><br>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.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | No dosage adjustment required in mild to moderate hepatic dysfunction.<br><br>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 | 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. | | moderate hepatic dysfunction.<br><br>Contraindicated with severe hepatic dysfunction. | | |
| Ticlopidine | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>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. |
| Vorapaxar | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | No dose adjustment is required. | No dosage adjustment required for mild to moderate hepatic impairment. Use in severe hepatic impairment is not recommended. | B | Unknown; use with caution. |
| **Combination Products** | | | | | |
| Aspirin/ dipyridamole | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>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**[1-8]

| Adverse Event | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ 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 | 0.6 | <1 |
| Coma | - | - | - | - | - | - | - | <1 |
| Confusion | 1 to <5 | <1 | - | - | - | - | - | 1 |
| Depression | 1 to <5 | 4 | - | - | - | - | 2.4 | - |
| 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 | Vorapaxar | Aspirin/ 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 | 2.2 | <1 |
| Skin disease | 1 to <5 | - | - | - | - | - | - | - |
| Stevens-Johnson syndrome | - | - | - | - | - | <1 | - | - |
| Toxic epidermal necrolysis | - | <1 | - | - | - | - | - | - |
| Ulceration | - | - | - | - | - | - | - | <1 |
| Urticaria | - | <1 | - | - | - | <1 | - | <1 |
| **Endocrine/Metabolic** | | | | | | | | |

| Adverse Event | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Dehydration | 1 to <5 | - | - | - | - | - | - | - |
| 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 | 4.7 | 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** | | | | | | | | |

| Adverse Event | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Cystitis | - | 1 to 3 | - | - | - | - | - | - |
| 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 | - | - | - | - | 5 | 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 | - | Severe: 1.3 Moderate to Severe: 3.7 Any: 27.7 | - |
| 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 | - | - |

| Adverse Event | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Pancytopenia | - | <1 | - | - | - | <1 | - | <1 |
| Prothrombin time prolonged | - | - | - | - | - | - | - | <1 |
| 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 |

| Adverse Event | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Peripheral neuropathy | - | - | - | - | - | <1 | - | - |
| Rhabdomyolysis | - | - | - | - | - | - | - | <1 |
| Weakness | - | 1 to 3 | - | - | - | - | - | 2 |
| **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 |

| Adverse Event | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Angioedema | - | <1 | - | - | - | <1 | - | <1 |
| Ante-/peri-/postpartum bleeding | - | - | - | - | - | - | - | <1 |
| Asthenia | 23.1 | - | - | - | - | - | - | - |
| 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

**Table 7. Contraindications**[1-8]

| Contraindication | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Active pathological bleeding | - | ✔ | - | ✔ | ✔ | ✔ | ✔ | - |
| Children and teenagers with viral infection because of the risk of Reye syndrome | - | - | - | - | - | - | - | ✔ |
| Hematopoietic disorders or a past history of either thrombotic thrombocytopenic purpura or aplastic anemia | - | - | - | - | - | ✔ | - | - |
| Hemostatic disorder | - | - | - | - | - | ✔ | - | - |
| History of intracranial hemorrhage | - | - | - | - | ✔ | - | ✔ | - |
| History of stroke or transient ischemic attack | - | - | - | - | - | - | ✔ | |
| Hypersensitivity to any product ingredient | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ |
| Known allergy to nonsteroidal anti-inflammatory drugs | - | - | - | - | - | - | - | ✔ |
| Prior transient attack or stroke | - | - | - | ✔ | - | - | - | - |
| Severe hepatic impairment | ✔ | - | - | - | ✔ | ✔ | - | - |
| Syndrome of asthma, rhinitis and nasal polyps | - | - | - | - | - | - | - | ✔ |

**Black Box Warning for Plavix® (clopidogrel)**[2]

| WARNING |
|---|
| The effectiveness of Plavix® is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. Plavix® at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix® at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. |

**Black Box Warning for Effient® (prasugrel)**[4]

| WARNING |
|---|
| • Effient® can cause significant, sometimes fatal, bleeding.<br>• Do not use Effient® in patients with active pathological bleeding or a history of transient ischemic attack or stroke.<br>• In patients ≥75 years of age, Effient® is generally not recommended, because of increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of prior MI), where its effect appears to be greater and its use may be considered.<br>• Do not start Effient® in patients likely to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue Effient® at least 7 days prior to any surgery.<br>• Additional risk factors for bleeding include: body weight <60 kg; propensity to bleed; concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, fibrinolytic therapy, chronic use of non-steroidal anti-inflammatory drugs [NSAIDs])<br>• Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical Procedures in the setting of Effient®.<br>• If possible, manage bleeding without discontinuing Effient®. Discontinuing Effient®, particularly in the first few weeks after acute coronary syndrome, increases the risk of subsequent cardiovascular events. |

**Black Box Warning for Brilinta® (ticagrelor)**[5]

| WARNING |
|---|
| Bleeding Risk<br>• Brilinta®, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding.<br>• Do not use Brilinta® in patients with active pathological bleeding or a history of intracranial hemorrhage.<br>• Do not start Brilinta® in patients planning to undergo urgent coronary artery bypass graft (CABG) surgery. When possible, discontinue Brilinta® at least five days prior to any surgery.<br>• Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of Brilinta®.<br>• If possible, manage bleeding without discontinuing Brilinta®. Stopping Brilinta® increases the risk of subsequent cardiovascular events.<br><br>Aspirin Dose and Brilinta® Effectiveness<br>• Maintenance doses of aspirin above 100 mg reduce the effectiveness of Brilinta® and should be avoided. After any initial dose, use with aspirin 75 to 100 mg/day. |

**Black Box Warning for ticlopidine**[6]

| WARNING |
|---|
| Ticlopidine hydrochloride can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura (TTP) and aplastic anemia.<br><br>Neutropenia/agranulocytosis: Among 2,048 patients in clinical trials in stroke patients, 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).<br><br>TTP: One case of thrombocytopenic purpura was reported during clinical trials in stroke patients. 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 TTP may be as high as one case in every 2,000 to 4,000 patients exposed.<br><br>Aplastic anemia: Aplastic anemia was not seen during clinical trials, 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.<br><br>Monitoring of clinical and hematologic status: Severe hematological adverse reactions may occur within a few days of the start of therapy. The incidence of TTP 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, TTP, or aplastic anemia have arisen after more than three months of therapy. Hematological adverse reactions cannot be reliably predicted by any identified demographic or clinical characteristics. During the first three months of treatment, patients receiving ticlopidine hydrochloride must, therefore, be hematologically and clinically monitored for evidence of neutropenia or TTP. If any such evidence is seen, ticlopidine hydrochloride should be immediately discontinued. |

**Black Box Warning for Zontivity® (vorapaxar)**[7]

| WARNING |
|---|
| Bleeding Risk:<br>• Do not use Zontivity® in patients with a history of stroke, transient ischemic attack (TIA), or intracranial hemorrhage (ICH); or active pathological bleeding.<br>• Antiplatelet agents, including Zontivity®, increase the risk of bleeding, including ICH and fatal bleeding. |

## Warnings/Precautions

**Table 8. Warnings and Precautions**[1-8]

| Warning/Precaution | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Allergic cross-reactivity among thienopyridines (such as ticlopidine, prasugrel) have been reported; patient should be evaluated for history of hypersensitivity to another thienopyridine | - | ✔ | - | - | - | - | - | - |
| Anticoagulant drugs; the concurrent use of ticlopidine with heparin, oral anticoagulants or fibrinolytic agents have not been established; discontinue anticoagulants or fibrinolytic drugs prior to initiating ticlopidine | - | - | - | - | - | ✔ | - | - |
| Cardiovascular effects; vasodilation, tachycardia, palpitations and congestive heart failure may occur; use with caution in patients with known or suspected heart disease and only if the potential benefits of therapy outweigh the potential risks | ✔ | - | - | - | - | - | - | - |
| Cholesterol elevation; serum cholesterol and triglycerides may increase | - | - | - | - | - | ✔ | - | - |
| Coagulation abnormalities; aspirin can lead to an increase in bleeding time and adversely affect patients with inherited or acquired bleeding disorders | - | - | - | - | - | - | - | ✔ |

| Warning/Precaution | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Concomitant aspirin maintenance dose; aspirin doses above 100 mg decreases effectiveness of ticagrelor | - | - | - | - | ✔ | - | - | - |
| Concomitant aspirin use; risk of major hemorrhagic events is increased | ✔ | - | - | - | - | - | - | - |
| Coronary artery bypass surgery-related bleeding; risk increases in patients receiving prasugrel | - | - | - | ✔ | - | - | - | - |
| Coronary artery disease; use with caution; chest pain may be aggravated in patients with underlying coronary artery disease | - | - | ✔ | - | - | - | - | ✔ |
| CYP3A4 strong inhibitors and inducers should be avoided | - | - | - | - | - | - | ✔ | - |
| Discontinuation of treatment; abrupt discontinuation is followed by an increase in platelet counts | ✔ | - | - | - | - | - | - | - |
| Discontinuation of treatment; premature discontinuation may increase the risk of cardiovascular events | - | ✔ | - | - | - | - | - | - |
| Discontinuation of treatment; premature discontinuation may increase the risk of stent thrombosis, myocardial infarction and death | - | - | - | ✔ | ✔ | - | - | - |
| Dyspnea; self-limiting; rule out other causes | - | - | - | - | ✔ | - | - | - |
| Gastrointestinal bleeding; risk is increased in patients who are | - | - | - | - | - | - | - | ✔ |

| Warning/Precaution | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| heavy alcohol users, have a history of peptic ulcer disease or vitamin K deficiency | | | | | | | | |
| Hematological adverse reactions may occur; monitor at baseline, every two weeks through the third month of therapy and two weeks after discontinuation | - | - | - | - | - | ✔ | - | - |
| Hepatic impairment; consider the risks and benefits of treatment in this patient population; exposure to medication may be increased | ✔ | - | - | - | ✔ | - | - | - |
| Hepatic insufficiency; elevations of hepatic enzymes and hepatic failure have been reported | - | - | ✔ | - | - | - | - | ✔ |
| Hypersensitivity; incident including angioedema has been reported including in patients with a history of hypersensitivity reaction to other thienopyridines | - | - | - | ✔ | - | - | - | - |
| Hypotension; use with caution since dipyridamole can produce peripheral vasodilation | - | - | ✔ | - | - | - | - | ✔ |
| Increased risk of bleeding; discontinue treatment five days prior to elective surgery | - | ✔ | - | - | ✔ | - | ✔ | - |
| Increased risk of bleeding; do not use in patients with active bleeding, prior transient ischemic attack or stroke | - | - | - | ✔ | - | - | ✔ | - |
| Increased risk of bleeding, including intracranial hemorrhage as with other antiplatelets | - | - | - | - | - | - | - | ✔ |

| Warning/Precaution | Single-Entity Agents | | | | | | | Combination Products |
|---|---|---|---|---|---|---|---|---|
| | Anagrelide | Clopidogrel | Dipyridamole | Prasugrel | Ticagrelor | Ticlopidine | Vorapaxar | Aspirin/ Dipyridamole |
| Interstitial lung diseases; cases have been reported in post-marketing experience; time of onset ranged from one week to several years after initiating anagrelide | ✔ | - | - | - | - | - | - | - |
| Laboratory tests; blood counts, renal and hepatic function should be monitored during treatment | ✔ | - | - | - | - | - | - | - |
| Pregnancy; use of aspirin in pregnancy can cause fetal harm, especially during the third trimester | - | - | - | - | - | - | - | ✔ |
| Recent transient ischemic attack or stroke; concurrent use with aspirin in these patients was shown to increase major bleeding without being more effective than using medication alone | - | ✔ | - | - | - | - | - | - |
| Reduced effectiveness in impaired cytochrome P450 2C19 function; avoid concomitant use with omeprazole or esomeprazole | - | ✔ | - | - | - | - | - | - |
| Renal failure, severe; avoid aspirin in this patient population | - | - | - | - | - | - | - | ✔ |
| Thrombotic thrombocytopenic purpura; incidence has been reported with treatment, including fatal cases | - | ✔ | - | ✔ | - | ✔ | - | - |

## Drug Interactions

**Table 9. Drug Interactions**[1-8]

| 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. |
| 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 | Strong cytochrome P450 | Concurrent use may result in decreased/increased |

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| (ticagrelor, vorapaxar) | 3A inducers/inhibitors | ticagrelor or vorapaxar 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/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.[8]

**Table 10. Dosing and Administration**[1-8]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| **Single-Entity Agents** | | | |
| Anagrelide | Treatment of patients with thrombocythemia, secondary to myeloproliferative disorders:<br>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* | Treatment of patients with thrombocythemia, secondary to myeloproliferative disorders:‡<br>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* | Capsule:<br>0.5 mg<br>1 mg |
| Clopidogrel | Recent MI, recent stroke, or established peripheral arterial disease:<br>Tablet: 75 mg QD<br><br>Reduce the rate of thrombotic cardiovascular events in patients with ACS, non-ST-elevation:<br>Tablet: initial, 300 mg as a single loading dose; maintenance, 75 mg QD‡<br><br>Reduce the rate of thrombotic cardiovascular events in patients with ACS, ST-elevation MI:<br>Tablet: 75 mg QD§ | Safety and efficacy in children have not been established. | Tablet:<br>75 mg<br>300 mg |
| Dipyridamole | Prevention of postoperative thromboembolic complications of | Safety and efficacy in children <12 years of age | Tablet:<br>25 mg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | cardiac valve replacement:<br>Tablet: 75 to 100 mg QID‖ | have not been established. | 50 mg<br>75 mg |
| Prasugrel | Reduce the rate of thrombotic cardiovascular events in patients with ACS who are being managed with PCI:<br>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:<br>5 mg<br>10 mg |
| Ticagrelor | Reduce the rate of thrombotic cardiovascular events in patients with ACS:<br>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:<br>90 mg |
| Ticlopidine | Reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation:<br>Tablet: 250 mg BID for up to 30 days**<br><br>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:<br>Tablet: 250 mg BID†† | Safety and efficacy in children have not been established. | Tablet:<br>250 mg |
| Vorapaxar | Reduce the risk of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease:<br>Tablet: 2.08 mg QD in combination with other antiplatelet agents (clopidogrel and/or aspirin) | Safety and efficacy in children have not been established. | Tablet:<br>2.08 mg |
| **Combination Products** | | | |
| Aspirin/ dipyridamole‡‡ | Reduce the risk of stroke in patients who have had transient ischemia or the brain or completed ischemic stroke due to thrombosis:<br>Capsule: 25/200 mg BID | Safety and efficacy in children have not been established. | Capsule:<br>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 11. 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.

**Table 11. Clinical Guidelines**

| Clinical Guideline | Recommendations |
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| American College of Chest Physicians: **Antithrombotic Therapy and Prevention of Thrombosis, 9th edition (2012)**[9] | Antithrombotic therapy for atrial fibrillation (AF)<br>• Patients with AF, including those with paroxysmal AF, who are at low risk of stroke: no therapy is suggested over antithrombotic therapy. For patients who choose antithrombotic therapy, aspirin is suggested over oral anticoagulation or combination therapy with aspirin and clopidogrel.<br>• Patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke: oral anticoagulation is recommended over no therapy. Oral anticoagulation is suggested over aspirin or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel are suggested over aspirin.<br>• Patients with AF, including those with paroxysmal AF, who are at high risk of stroke: oral anticoagulation is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take an oral anticoagulant, combination therapy with aspirin and clopidogrel is recommended over aspirin.<br>• Patients with AF, including those with paroxysmal AF: for recommendations in favor of oral anticoagulation, dabigatran 150 mg twice daily is suggested over adjusted-dose vitamin K antagonist (VKA) therapy (target international normalized ratio [INR] range, 2.0 to 3.0).<br>• Patients with AF and mitral stenosis: adjusted-dose VKA therapy is recommended over no therapy, aspirin, or combination therapy with aspirin and clopidogrel. For patients who are unsuitable for or choose not to take adjusted-dose VKA therapy, combination therapy with aspirin and clopidogrel is recommended over aspirin alone.<br>• Patients with AF and stable coronary artery disease and who choose oral anticoagulation: adjusted-dose VKA therapy alone is suggested over the combination of adjusted-dose VKA therapy and aspirin.<br>• Patients with AF at high risk of stroke 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 suggested over dual antiplatelet therapy (e.g., aspirin and clopidogrel). After this initial period, a VKA plus a single antiplatelet agent is suggested over a VKA alone. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.<br>• Patients with AF at intermediate risk of stroke during the first 12 months after placement of a stent: dual antiplatelet therapy is suggested over triple therapy. At 12 months after stent placement, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.<br>• Patients with AF at intermediate to high risk of stroke who experience an acute coronary syndrome (ACS) and do not undergo stent placement, for the first 12 months: adjusted-dose VKA therapy plus single antiplatelet therapy is suggested over dual antiplatelet therapy or triple therapy. After |

| Clinical Guideline | Recommendations |
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| | the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.<br>• Patients with AF at low risk of stroke: dual antiplatelet therapy is suggested over adjusted-dose VKA therapy plus single antiplatelet therapy or triple therapy. After the first 12 months, antithrombotic therapy is suggested as for patients with AF and stable coronary artery disease.<br>• Patients with AF being managed with a rhythm control strategy: it is suggested that antithrombotic therapy decisions follow the general risk-based recommendations for patients with nonrheumatic AF, regardless of the apparent persistence of normal sinus rhythm.<br>• Patients with atrial flutter: it is suggested that antithrombotic therapy decisions follow the same risk-based recommendations as for AF.<br><br><u>Antithrombotic therapy for ischemic stroke</u><br>• In patients with acute ischemic stroke or transient ischemic attack (TIA), early (within 48 hours) aspirin 160 to 325 mg is recommended over therapeutic parenteral anticoagulation.<br>• In patients with a history of noncardioembolic ischemic stroke or TIA, aspirin (75 to 100 mg daily), clopidogrel (75 mg daily), aspirin/dipyridamole extended-release (ER) (25 mg/200 mg twice daily) or cilostazol (100 mg twice daily) is recommended over oral anticoagulants, the combination of clopidogrel plus aspirin or triflusal.<br>o Clopidogrel or aspirin/dipyridamole ER is recommended over aspirin or cilostazol.<br>• In patients with a history of ischemic stroke or TIA and AF, oral anticoagulation with dabigatran 150 mg twice daily is recommended over VKA therapy.<br>o In patients who are unable to or choose not to take an oral anticoagulant, the combination of aspirin plus clopidogrel is recommended over aspirin alone.<br><br><u>Primary and secondary prevention of cardiovascular disease</u><br>• Patients ≥50 years of age without symptomatic cardiovascular disease: low dose aspirin (75 to 100 mg/day) is suggested over no aspirin therapy.<br>• Patients with established coronary artery disease: long term single antiplatelet therapy with aspirin (75 to 100 mg/day) or clopidogrel (75 mg/day) is recommended over no antiplatelet therapy, and single antiplatelet therapy is suggested over dual antiplatelet therapy.<br>• Patients in the first year after ACS who have not undergone percutaneous coronary intervention (PCI): dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day or clopidogrel 75 mg/day plus low dose aspirin 75 to 100 mg/day) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin.<br>• Patients in the first year after an ACS who have undergone PCI with stent placement: dual antiplatelet therapy (ticagrelor 90 mg twice daily plus low dose aspirin 75 to 100 mg/day, clopidogrel 75 mg/day plus low dose aspirin, or prasugrel 10 mg/day plus low dose aspirin) is recommended over single antiplatelet therapy. Ticagrelor 90 mg twice daily plus low dose aspirin is suggested over clopidogrel 75 mg/day plus low dose aspirin.<br>• Patients with anterior myocardial infarction (MI) and left ventricular (LV) |

| Clinical Guideline | Recommendations |
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| | thrombus, or at high risk for LV thrombus, who do not undergo stenting: warfarin plus low dose aspirin (75 to 100 mg/day) is recommended over single antiplatelet therapy or dual antiplatelet therapy for the first three months. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, single antiplatelet therapy is recommended as per the established coronary artery disease recommendations.<br>• Patients with anterior MI and LV thrombus, or at high risk LV thrombus, who undergo bare-metal stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for one month is suggested over dual antiplatelet therapy. Warfarin and single antiplatelet therapy for the second and third month post-bare-metal stent is suggested over alternative regimens and alternative time frames for warfarin use. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations.<br>• Patients with anterior MI and LV thrombus, or at high risk for LV thrombus who undergo drug-eluting stent placement: triple therapy (warfarin, low dose aspirin, clopidogrel 75 mg/day) for up to three to six months is suggested over alternative regimens and alternative durations of warfarin therapy. Thereafter, it is recommended that warfarin be discontinued and dual antiplatelet therapy should be continued for up to 12 months. After 12 months, antiplatelet therapy is recommended as per the established coronary artery disease recommendations.<br>• Patients who have undergone elective PCI with placement of bare-metal stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for one month is recommended over single antiplatelet therapy. For the subsequent 11 months, dual antiplatelet therapy with combination low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy.<br>• Patients who have undergone elective PCI with placement of drug-eluting stent: dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day for three to six months is recommended over single antiplatelet therapy. After three to six months, continuation of dual antiplatelet therapy with low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is suggested to be continued until 12 months over antiplatelet therapy. After 12 months, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations.<br>• Patients who have undergone elective bare-metal stent or drug-eluting stent placement: low dose aspirin 75 to 100 mg/day and clopidogrel 75 mg/day is recommended over cilostazol in addition to these drugs. Aspirin 75 to 100 mg/day or clopidogrel 75 mg/day as part of dual antiplatelet therapy is suggested over the use of either drug with cilostazol. Cilostazol 100 mg twice daily as a substitute for either low dose aspirin or clopidogrel as part of a dual antiplatelet regimen in patients with an allergy or intolerance of either drug class is suggested.<br>• Patients with coronary artery disease undergoing elective PCI but no |

| Clinical Guideline | Recommendations |
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| | stent placement: for the first month dual antiplatelet therapy with aspirin 75 to 325 mg/day and clopidogrel 75 mg/day is suggested over single antiplatelet therapy. Single antiplatelet therapy thereafter is recommended as per the established coronary artery disease recommendations.<br>• Patients with systolic LV dysfunction without established coronary artery disease and no LV thrombus: it is suggested that antiplatelet therapy and warfarin not be used.<br>• Patients with systolic LV dysfunction without established coronary artery disease with identified acute left thrombus: moderate intensity warfarin for at least three months is suggested.<br>• Patients with systolic LV dysfunction and established coronary artery disease: recommendations are as per the established coronary artery disease recommendations.<br><br><u>Antithrombotic therapy in peripheral artery disease (PAD)</u><br>• In patients with asymptomatic PAD, aspirin 75 to 100 mg daily is recommended.<br>• In patients with symptomatic PAD, long-term therapy with aspirin (75 to 100 mg daily) or clopidogrel (75 mg daily) is recommended for secondary prevention of cardiovascular events. Dual antiplatelet therapy or the combination of an antiplatelet agent with moderate-intensity warfarin is not recommended.<br>• Use of cilostazol in addition to aspirin or clopidogrel is recommended in patients with intermittent claudication refractory to exercise therapy and smoking cessation.<br>• Use of prostanoids in addition to aspirin or clopidogrel is recommended in patients with symptomatic PAD and critical leg ischemia who are not candidates for vascular intervention.<br>• In patients undergoing peripheral artery percutaneous transluminal angioplasty with or without stenting, long-term therapy with aspirin or clopidogrel is recommended over dual antiplatelet therapy.<br>• Following peripheral artery bypass graft surgery, long-term therapy with aspirin or clopidogrel is recommended over the combination of antiplatelet agent plus warfarin. Clopidogrel plus aspirin for one year is recommended in patients undergoing below-knee bypass graft surgery with prosthetic grafts.<br>• In patients with asymptomatic carotid stenosis, aspirin 75 to 100 mg daily is recommended.<br>• In patients with symptomatic carotid stenosis, long-term therapy with clopidogrel (75 mg daily) or aspirin/dipyridamole ER (25 mg/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 (2014)**[10] | <u>Recommendations for Nonvalvular Atrial Fibrillation:</u><br>• For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (~30 days) for AF is reasonable within six months of the index event.<br>• VKA therapy, apixaban, dabigatran and rivaroxaban are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent.<br>o Selection of agent should be individualized based on risk factors, cost, tolerability, patient preference, drug interactions and other characteristics including renal function and time in INR |

| Clinical Guideline | Recommendations |
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| | therapeutic range if the patient has been taking VKA therapy.<br>• Target INR for patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent or permanent AF on VKA therapy is 2.5 (range 2.0 to 3.0).<br>• Combination oral anticoagulation (warfarin or a newer agent) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA.<br>o Combination therapy is reasonable in patients with clinically apparent coronary artery disease particularly an acute coronary syndrome or stent placement.<br>• For patients with ischemic stroke or TIA and AF who unable to take oral anticoagulants, aspirin alone is recommended.<br>o Adding clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable.<br>• For most patients with a stroke or TIA in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms.<br>• In the presence of high risk for hemorrhagic conversion, it is reasonable to delay initiation of oral anticoagulation beyond 14 days.<br>• For patients with AF and a history of stroke or TIA who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH (or equivalent) is reasonable, depending on perceived risk for thromboembolism and bleeding.<br>• The usefulness of closure of the left atrial appendage with the WATCHMAN device in patients with ischemic stroke or TIA and AF is uncertain.<br><br><u>Recommendations for Acute MI and LV Thrombus:</u><br>• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months is recommended in most patients with ischemic stroke or TIA in this setting.<br>o Additional antiplatelet therapy for cardiac protection may be guided by recommendations such as those from the American College of Chest Physicians.<br>• Treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) for three months may be considered in patients with ischemic stroke or TIA in the setting of acute anterior STEMI without demonstrable LV mural thrombus formation but with anterior apical akinesis or dyskinesis identified by echocardiography or other imaging.<br>• In patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation or anterior or apical wall-motion abnormalities with an LV ejection fraction <40% who are intolerant to VKA therapy because of nonhemorrhagic adverse events, treatment with an LMWH, dabigatran, rivaroxaban, or apixaban for three months may be considered as an alternative to VKA therapy for prevention of recurrent stroke or TIA.<br><br><u>Recommendations for Cardiomyopathy:</u><br>• In patients with ischemic stroke or TIA in sinus rhythm who have left atrial or LV thrombus, anticoagulant therapy with a VKA is recommended for ≥3 months.<br>• In patients with ischemic stroke or TIA in the setting of a mechanical |

| Clinical Guideline | Recommendations |
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| | LVAD, treatment with VKA therapy (target INR, 2.5; range, 2.0 to 3.0) is reasonable in the absence of major contraindications.<br>• In patients with ischemic stroke or TIA in sinus rhythm with either dilated cardiomyopathy (LV ejection fraction ≤35%) or restrictive cardiomyopathy without evidence of left atrial or LV thrombus, the effectiveness of anticoagulation compared with antiplatelet therapy is uncertain, and the choice should be individualized.<br>• In patients with ischemic stroke or TIA in sinus rhythm with dilated cardiomyopathy (LV ejection fraction ≤35%), restrictive cardiomyopathy, or a mechanical LVAD who are intolerant to VKA therapy because of nonhemorrhagic adverse events, the effectiveness of treatment with dabigatran, rivaroxaban, or apixaban is uncertain compared with VKA therapy for prevention of recurrent stroke.<br><br><u>Recommendations for Mitral Stenosis, Mitral Regurgitation, Mitral Prolapse, Mitral Annular Calcification, and Aortic Valve Disease</u>:<br>• For patients with ischemic stroke or TIA who have rheumatic mitral valve disease and AF, long-term VKA therapy with INR target of 2.5 (range, 2.0 to 3.0) is recommended.<br>• For patients with ischemic stroke or TIA who have rheumatic mitral valve disease without AF or another likely cause for their symptoms (e.g., carotid stenosis), long-term VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered instead of antiplatelet therapy.<br>• For patients with rheumatic mitral valve disease who are prescribed VKA therapy after an ischemic stroke or TIA, antiplatelet therapy should not be routinely added.<br>• For patients with rheumatic mitral valve disease who have an ischemic stroke or TIA while being treated with adequate VKA therapy, the addition of aspirin might be considered.<br>• For patients with ischemic stroke or TIA and native aortic or nonrheumatic mitral valve disease who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended.<br>• For patients with ischemic stroke or TIA and mitral annular calcification who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without the mitral annular calcification.<br>• For patients with mitral valve prolapse who have ischemic stroke or TIAs and who do not have AF or another indication for anticoagulation, antiplatelet therapy is recommended as it would be without mitral valve prolapse.<br><br><u>Recommendations for Prosthetic Heart Valves:</u><br>• For patients with a mechanical aortic valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 2.5 (range, 2.0 to 3.0).<br>• For patients with a mechanical mitral valve and a history of ischemic stroke or TIA before its insertion, VKA therapy is recommended with an INR target of 3.0 (range, 2.5 to 3.5).<br>• For patients with a mechanical aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and who are at low risk for bleeding, the addition of aspirin 75 to 100 mg/day to VKA therapy is recommended. |

| Clinical Guideline | Recommendations |
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| | • For patients with a mechanical heart valve who have an ischemic stroke or systemic embolism despite adequate antithrombotic therapy, it is reasonable to intensify therapy by increasing the dose of aspirin to 325 mg/day or increasing the target INR, depending on bleeding risk.<br>• For patients with a bioprosthetic aortic or mitral valve and a history of ischemic stroke or TIA before its insertion and no other indication for anticoagulation therapy beyond three to six months form the valve placement, long-term therapy with aspirin 75 to 100 mg/day is recommended in preference to long-term anticoagulation.<br>• For patients with a bioprosthetic aortic or mitral valve who have a TIA, ischemic stroke, or systemic embolism despite antiplatelet therapy, the addition of VKA therapy with an INR target of 2.5 (range, 2.0 to 3.0) may be considered.<br><br><u>Recommendations for Noncardioembolic Stroke or TIA</u>:<br>• For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events.<br>• Aspirin (50 to 325 mg/day) monotherapy or the combination of aspirin 25 mg and extended-release dipyridamole 200 mg twice daily is indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke.<br>• Clopidogrel (75 mg) monotherapy is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole. This recommendation also applies to patients who are allergic to aspirin.<br>• The selection of an antiplatelet agent should be individualized on the basis of patient risk facto profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics.<br>• The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stork or TIA and for continuation for 90 days.<br>• The combination of aspirin and clopidogrel, when initiated days to years after a minor stroke or TIA and continued for two to three years, increases the risk of hemorrhage relative to either agent alone and is not recommended for routine long-term secondary prevention after ischemic stroke or TIA).<br>• For patients who have an ischemic stroke or TIA 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 adequately studied in patients who have had an event while receiving aspirin.<br>• For patients with a history of ischemic stroke or TIA, AF and coronary artery disease, the usefulness of adding antiplatelet therapy to VKA therapy is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet or VKA therapy.<br>o For patients with noncardioembolic ischemic stroke or TIA, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. |
| American College of | <u>Early hospital care-antiplatelet therapy</u> |

| Clinical Guideline | Recommendations |
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| Cardiology Foundation/American Heart Association: **2012 Focused Update Incorporated Into the 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (2012)**[11] | • Aspirin should be administered as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it.<br>• A loading dose followed by daily maintenance dose of clopidogrel, prasugrel or ticagrelor should be administered to patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.<br>• 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 added to aspirin on presentation should include one of the following:<br>o Before PCI: clopidogrel, ticagrelor or an intravenous (IV) glycoprotein (GP) IIb/IIIa inhibitor.<br>o At the time of PCI: clopidogrel, prasugrel, ticagrelor or an IV GP IIb/IIIa inhibitor.<br>• For an initial conservative strategy, clopidogrel or ticagrelor (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to one year.<br>• If recurrent symptoms/ischemia, heart failure or serious arrhythmias subsequently appear after an initial conservative strategy, diagnostic angiography should be performed. An IV GP IIb/IIIa inhibitor, clopidogrel or ticagrelor should be added to aspirin and anticoagulant therapy before diagnostic angiography.<br>• A loading dose of $P2Y_{12}$ receptor inhibitor is recommended for whom PCI is planned. Regimens include one of the following:<br>o Clopidogrel 600 mg given as early as possible before or at the time of PCI.<br>o 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.<br>o Ticagrelor 180 mg given as early as possible before or at the time of PCI.<br>• The duration of maintenance dose of $P2Y_{12}$ receptor inhibitor therapy should be as follows:<br>o Patients undergoing PCI: clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily for at least 12 months.<br>o If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered.<br>• If recurrent ischemia discomfort with a $P2Y_{12}$ receptor inhibitor, aspirin and anticoagulant therapy is experienced with an initial conservative strategy, it is reasonable to add a GP IIb/IIIa inhibitor before diagnostic angiography.<br>• For an initial invasive 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.<br>• For an initial conservative strategy, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy.<br>• Prasugrel 60 mg may be considered for administration promptly upon presentation if PCI is planned, before definition of coronary anatomy if |

| Clinical Guideline | Recommendations |
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| | both the risk of bleeding is low and the need for coronary artery bypass graft (CABG) is considered unlikely.<br>• The use of upstream GP IIb/IIIa inhibitors may be considered in high-risk patients already receiving aspirin and a $P2Y_{12}$ receptor inhibitor who are selected for an invasive strategy and who are not otherwise at high-risk for bleeding.<br>• 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.<br>• Abciximab should not be administered to patients in whom PCI is not planned.<br>• In patients at low risk for ischemic events or at high-risk of bleeding and who are already receiving aspirin and a $P2Y_{12}$ receptor inhibitor, upstream GP IIb/IIIa inhibitors are not recommended.<br>• In patients with a history of stroke and/or TIA for whom PCI is planned, prasugrel is potentially harmful as part of dual antiplatelet therapy.<br><br><u>Additional antiplatelet and anticoagulation therapy</u><br>• In an initial conservative strategy with no subsequent features that would necessitate diagnostic angiography, a stress test should be performed.<br>o If the patient is classified as not at low-risk, diagnostic angiography should be performed.<br>o If the patient is classified as being at low-risk, the following should take place in preparation for discharge:<br>▪ Continue aspirin indefinitely.<br>▪ Continue clopidogrel or ticagrelor for up to one year.<br>▪ Discontinue IV GP IIb/IIIa inhibitor if started previously.<br>▪ Continue unfractionated heparin (UFH) for 48 hours or administer enoxaparin or fondaparinux for the duration of hospitalization, up to eight days, and then discontinue anticoagulant therapy.<br>• If CABG was selected as a post-angiography management strategy, the following instructions should be followed:<br>o Continue aspirin.<br>o Discontinue IV GP IIb/IIIa inhibitor four hours before CABG.<br>o Anticoagulant therapy should be managed as follows:<br>▪ Continue UFH.<br>▪ Discontinue enoxaparin 12 to 24 hours, fondaparinux 24 hours and bivalirudin three hours before CABG and dose with UFH per institutional practice.<br>• In patients taking a $P2Y_{12}$ receptor inhibitor 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 or ticagrelor and at least seven days in those receiving prasugrel unless the need for revascularization and/or the net benefit of the $P2Y_{12}$ receptor inhibitor outweighs the potential risk of excess bleeding.<br>• When PCI has been selected as a post-angiography management strategy, the following instructions should be followed:<br>o Continue aspirin. |

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| | o Administer a loading dose of a $P2Y_{12}$ receptor inhibitor if not started before diagnostic angiography.<br>o Discontinue anticoagulant therapy after PCI for uncomplicated cases.<br>• When medical therapy is selected as a management strategy and no significant obstructive coronary artery disease 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.<br>• When medical therapy is selected and coronary artery disease is present on angiography, the following approach is recommended:<br>o Continue aspirin.<br>o Administer a loading dose of clopidogrel or ticagrelor if not given before diagnostic angiography.<br>o Discontinue IV GP IIb/IIIa inhibitor if started previously.<br>o Anticoagulant therapy should be managed as follows:<br>▪ Continue IV UFH for at least 48 hours or until discharge if given before diagnostic angiography.<br>▪ Continue enoxaparin and fondaparinux for duration of hospitalization, up to eight days, if given before diagnostic angiography.<br>▪ 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.<br>• When a conservative strategy is selected and no angiography or stress testing is performed, the following instructions should be followed:<br>o Continue aspirin indefinitely.<br>o Continue clopidogrel or ticagrelor for up to 12 months.<br>o Discontinue IV GP IIb/IIIa inhibitor if started previously.<br>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.<br>• When an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography, LV ejection fraction should be measured.<br>• When PCI is selected as a post-angiography 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.<br>• 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.<br>• If LV ejection fraction is ≤0.4, it is reasonable to perform diagnostic angiography.<br>• If LV ejection fraction is >0.4, it is reasonable to perform a stress test.<br>• Platelet function testing to determine platelet inhibitory response in patients on $P2Y_{12}$ receptor inhibitor therapy may be considered if results of testing may alter management.<br>• Genotyping for a cytochrome P450 2C19 loss of function variant on |

| Clinical Guideline | Recommendations |
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| | $P2Y_{12}$ receptor inhibitor therapy might be considered if results of testing may alter management.<br>• IV fibrinolytic therapy is not indicated in patients without acute ST-elevation, a true posterior MI, or a presumed new left bundle-branch block.<br><br><u>Long-term medical therapy and secondary prevention</u><br>• For patients treated medically without stenting, aspirin should be administered indefinitely. Clopidogrel (75 mg/day) or ticagrelor (90 mg twice daily) should be administered for up to 12 months.<br>• For patients treated with a stent, aspirin should be continued indefinitely. The duration and maintenance dose of $P2Y_{12}$ receptor inhibitor should be:<br>o Clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily for at least 12 months for drug eluting stent and up to 12 months for bare metal stent.<br>o If the risk of morbidity because of bleeding outweighs the anticipated benefits afforded by $P2Y_{12}$ receptor inhibitor therapy, earlier discontinuation should be considered.<br>• Clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily should be given to patients recovering from unstable angina (UA)/non-ST-elevation MI (NSTEMI) when aspirin is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance.<br>• After PCI, it is reasonable to use aspirin 81 mg/day in preference to higher maintenance dose.<br>• For patients who have an indication for anticoagulation, the addition of warfarin may be reasonable to maintain an INR of 2.0 to 3.0.<br>• Continuation of a $P2Y_{12}$ receptor inhibitor beyond 12 months may be considered in patients following drug eluting stent placement.<br>• Dipyridamole is not recommended as an antiplatelet in post-UA/NSTEMI 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)**[12] | <u>Recommendations for oral antiplatelet agents</u><br>• 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.<br>• A $P2Y_{12}$ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications.<br>• 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).<br>• Prolonged or permanent withdrawal of $P2Y_{12}$ inhibitors within 12 months after the index event is discouraged unless clinically warranted.<br>• 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.<br>• 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- |

| Clinical Guideline | Recommendations |
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| | threatening bleeding or other contraindications.<br>• Clopidogrel (300 mg loading dose, 75 mg daily) is recommended for those who cannot receive ticagrelor or prasugrel.<br>  o A 600 mg loading dose (or a supplementary 300 mg dose at PCI following an initial 300 mg loading dose) is recommended for patients scheduled for invasive strategy when ticagrelor or prasugrel is not an option.<br>  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.<br>  o Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.<br>  o Genotyping and/or platelet function testing can be considered in selected cases when clopidogrel is used.<br>• 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.<br>• Ticagrelor or clopidogrel should be considered to be re-started after CABG surgery as soon as it is safe.<br>• The combination of aspirin with a non-steroidal anti-inflammatory is not recommended. |
| American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of ST-Elevation Myocardial Infarction (2013)**[13] | <u>Antiplatelet therapy to support primary PCI for STEMI</u><br>• Aspirin 162 to 325 mg should be given before primary PCI.<br>• After PCI, aspirin should be continued indefinitely.<br>• A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg.<br>• $P2Y_{12}$ inhibitor therapy should be given for one year to patients with STEMI who receive a stent (bare-metal or drug-eluting) during primary PCI using clopidogrel 75 mg/day, prasugrel 10 mg/day or ticagrelor 90 mg twice daily.<br>• It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI.<br>• It is reasonable to start treatment with an IV GP IIb/IIIa receptor antagonist such as abciximab, high bolus-dose tirofiban or double-bolus eptifibatide at the time of primary PCI (with or without stenting or clopidogrel pre-treatment) in selected patients with STEMI who are receiving UFH.<br>• It may be reasonable to administer IV GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, emergency department) to patients with STEMI for whom primary PCI is intended.<br>• It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI.<br>• Continuation of a $P2Y_{12}$ inhibitor beyond one year may be considered in patients undergoing drug-eluting stent placement.<br>• Prasugrel should not be administered to patients with a history of prior stroke or TIA.<br><br><u>Anticoagulant therapy to support primary PCI</u> |

| Clinical Guideline | Recommendations |
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| | • For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended: UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered or bivalirudin with or without prior treatment with UFH.<br>• In patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and a GP IIb/IIIa receptor antagonist.<br>• Fondaparinux should not be used as the sole anticoagulant to support primary PCI because of the risk of catheter thrombosis.<br><br><u>Adjunctive antiplatelet therapy with fibrinolysis</u><br>• Aspirin (162- to 325-mg loading dose) and clopidogrel (300 mg loading dose for ≤75 year of age, 75-mg dose for patients >75 years of age) should be administered to patients with STEMI who receive fibrinolytic therapy.<br>• Aspirin should be continued indefinitely and clopidogrel (75 mg daily) should be continued for at least 14 days and up to one year in patients with STEMI who receive fibrinolytic therapy.<br>• It is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses after fibrinolytic therapy.<br><br><u>Adjunctive anticoagulant therapy with fibrinolysis</u><br>• Patients with STEMI undergoing reperfusion with fibrinolytic therapy should receive anticoagulant therapy for a minimum of 48 hours, and preferably for the duration of the hospitalization, up to eight days or until revascularization if performed.<br>• Recommended regimens include UFH administered as a weight-adjusted IV bolus and infusion to obtain an activated partial thromboplastin time of 1.5 to 2.0 times control, for 48 hours or until revascularization; enoxaparin administered according to age, weight, and creatinine clearance, given as an IV bolus, followed in 15 minutes by subcutaneous injection for the duration of the index hospitalization, up to eight days or until revascularization; or fondaparinux administered with initial IV dose, followed in 24 hours by daily subcutaneous injections if the estimated creatinine clearance is greater than 30 mL/min, for the duration of the index hospitalization, up to eight days or until revascularization.<br><br><u>Antiplatelet therapy to support PCI after fibrinolytic therapy</u><br>• After PCI, aspirin should be continued indefinitely.<br>• Clopidogrel should be provided as a 300 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy; a 600 mg loading dose given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy; and a dose of 75 mg daily should be given after PCI.<br>• After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses.<br>• Prasugrel, in a 60 mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but |

| Clinical Guideline | Recommendations |
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| | prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent.<br>• Prasugrel, in a 10 mg daily maintenance dose, is reasonable after PCI.<br>• Prasugrel should not be administered to patients with a history of prior stroke or TIA.<br><br>Anticoagulant therapy to support PCI after fibrinolytic therapy<br>• For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with IV UFH, additional boluses of IV UFH should be administered as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered.<br>• For patients with STEMI undergoing PCI after receiving fibrinolytic therapy with enoxaparin, if the last subcutaneous dose was administered within the prior eight hours, no additional enoxaparin should be given; if the last subcutaneous dose was administered between eight and 12 hours earlier, enoxaparin 0.3 mg/kg IV should be given. |
| American College of Cardiology Foundation/American Heart Association/ Society for Cardiovascular Angiography and Interventions: **2011 Guideline for Percutaneous Coronary Intervention (2011)**[14] | Interventional pharmacotherapy-oral antiplatelet therapy<br>• Patients already taking daily aspirin therapy should take 81 to 325 mg before PCI.<br>• Patients not on aspirin therapy should be given non-enteric aspirin 325 mg before PCI.<br>• After PCI, use of aspirin should be continued indefinitely.<br>• 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.<br>• 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.<br>• Patients should be counseled on the need for and risks of dual antiplatelet therapy before placement of intracoronary stents, especially drug-eluting stents, and alternative therapies should be pursued if patients are unwilling or unable to comply with the recommended duration of dual antiplatelet therapy.<br>• The duration of $P2Y_{12}$ inhibitor therapy after stent implantation should generally be as follows:<br>o In patients receiving a stent (bare metal or drug eluting stent) 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.<br>o In patients receiving drug-eluting stent 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.<br>o In patients receiving bare-metal stents 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).<br>• After PCI, it is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses.<br>• If the risk of morbidity from bleeding outweighs the anticipated benefit |

| Clinical Guideline | Recommendations |
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| | 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.<br>• Continuation of dual antiplatelet therapy beyond 12 months may be considered in patients undergoing drug-eluting stent implantation.<br>• Prasugrel should not be administered to patients with a prior history of stroke or TIA.<br><br><u>Post-procedural recommendations for patients undergoing PCI</u><br>Aspirin:<br>• Use of aspirin should be continued indefinitely.<br>• It is reasonable to use aspirin 81 mg/day in preference to higher maintenance doses.<br>$P2Y_{12}$ inhibitors:<br>• In patients receiving a stent (bare-metal or drug-eluting stent) 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.<br>• In patients receiving drug-eluting stent 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.<br>• In patients receiving bare-metal stent 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).<br>• 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.<br>• Proton pump inhibitors should be used in patients with a history of prior gastrointestinal bleeding who require dual antiplatelet therapy.<br>• 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.<br>• 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.<br>• Continuation of clopidogrel, prasugrel, or ticagrelor beyond 12 months may be considered in patients undergoing placement of drug-eluting stent.<br>• 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.<br><br><u>Clopidogrel genetic testing</u><br>• 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.<br>• When a patient predisposed to inadequate platelet inhibition with clopidogrel is identified by genetic testing, treatment with an alternative $P2Y_{12}$ inhibitor (e.g., prasugrel, ticagrelor) might be considered.<br>• The routine clinical use of genetic testing to screen patients treated with |

| Clinical Guideline | Recommendations |
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| | 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 (2014)**[15] | Antiplatelet Therapy<br>• Offer all people who have had an acute MI treatment with dual antiplatelet therapy (aspirin plus a second antiplatelet agent)<br>• Offer aspirin to all people after an MI and should be continued indefinitely, unless they are aspirin intolerant or have an indication for anticoagulation. Clopidogrel should not be offered as first-line monotherapy after a MI.<br>• Offer aspirin to people who have had an MI more than 12 months ago and continue it indefinitely<br>• For patients with aspirin hypersensitivity, clopidogrel monotherapy should be considered as an alternative treatment<br>• Special considerations should be made for people with dyspepsia<br>• After appropriate treatment, people with a history of aspirin-induced ulcer bleeding whose ulcers have healed and who are negative for Helicobacter pylori should be considered for treatment in line with dyspepsia. Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with ACS (STEMI, PCI, or NSTEMI).<br>• Offer clopidogrel as a treatment option for up to 12 months to people who have had an NSTEMI, regardless of treatment, or people who have had a STEMI and received a bare-metal or drug-eluting stent.<br>• Offer clopidogrel as a treatment option for at least one month and consider continuing for up to 12 months in people who have had a STEMI and medical management with or without reperfusion treatment with a fibrinolytic agent.<br>• Continue the second antiplatelet agent for up to 12 months in people who have had a STEMI and who received CABG surgery.<br>• Offer clopidogrel instead of aspirin to people who also have other clinical vascular disease (had an MI and topped dual antiplatelet therapy or had an MI more than 12 months ago).<br><br>Antiplatelet Therapy in People with an Indication for Anticoagulation<br>• Take bleeding risk, thromboembolic risk and cardiovascular risk into account when deciding which people who have had an MI and have an indication for anticoagulation.<br>• Unless there is a high risk of bleeding, continue anticoagulation and add aspirin to treatment in people who have had an MI who otherwise need anticoagulation and who have had their condition managed medically or have undergone balloon angioplasty or have undergone CABG surgery.<br>• Continue anticoagulation and add clopidogrel to treatment in people who have had an MI, who have undergone PCI with bare-metal or drug-eluting stents and who otherwise need anticoagulation.<br>• Offer clopidogrel with warfarin to people with a sensitivity to aspirin who otherwise need anticoagulation and aspirin and who have had an MI.<br>• Do not routinely offer warfarin in combination with prasugrel or ticagrelor to people who need anticoagulation who have had an MI.<br>• After 12 months since the MI, continue anticoagulation and take into consideration the need for ongoing antiplatelet therapy, taking into account all of the following: indication for anticoagulation, thromboembolic risk, bleeding risk, cardiovascular risk and the person's wishes.<br>• Do not add a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in combination with dual antiplatelet therapy in people who |

| Clinical Guideline | Recommendations |
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| | otherwise need anticoagulation, who have had an MI.<br>• Consider using warfarin and discontinuing treatment with a new oral anticoagulant (rivaroxaban, apixaban or dabigatran) in people who otherwise need anticoagulation and who have had an MI, unless there is a specific clinical indication to continue it. |
| American College of Cardiology Foundation/American Heart Association/ American College of Physicians/American Association for Thoracic Surgery/ Preventive Cardiovascular Nurses Association/Society for Cardiovascular Angiography and Interventions/Society of Thoracic Surgeons: **Guideline for the Diagnosis and Management of Patients with Stable Ischemic Heart Disease (2012)**[16] | Lipid management<br>• Lifestyle modifications, including daily physical activity and weight management, are strongly recommended for all patients with stable ischemic heart disease (SIHD).<br>• Dietary therapy for all patients should include reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), and cholesterol (to <200 mg/d).<br>• In addition to therapeutic lifestyle changes, a moderate or high dose of a statin therapy should be prescribed, in the absence of contraindications or documented adverse effects.<br><br>Blood pressure management<br>• All patients should be counseled about the need for lifestyle modification<br>• In patients with SIHD with blood pressure 140/90 mm Hg or higher, antihypertensive drug therapy should be instituted in addition to or after a trial of lifestyle modifications.<br>• The specific medications used for treatment of high blood pressure should be based on specific patient characteristics and may include ACE-inhibitors and/or beta blockers, with addition of other drugs, such as thiazide diuretics or calcium channel blockers, if needed to achieve a goal blood pressure of less than 140/90 mm Hg.<br><br>Diabetes management<br>• For selected individual patients, such as those with a short duration of diabetes mellitus and a long life expectancy, a goal glycosylated hemoglobin A1c ($Hb_{A1c}$) of 7% or less is reasonable.<br>• A goal $Hb_{A1c}$ between 7 and 9% is reasonable for certain patients according to age, history of hypoglycemia, presence of microvascular or macrovascular complications, or presence of coexisting medical conditions.<br>• Initiation of pharmacotherapy interventions to achieve target $Hb_{A1c}$ might be reasonable.<br>• Therapy with rosiglitazone should not be initiated in patients with SIHD.<br><br>Antiplatelet therapy<br>• Treatment with aspirin 75 to 162 mg daily should be continued indefinitely in the absence of contraindications in patients with SIHD.<br>• Treatment with clopidogrel is reasonable when aspirin is contraindicated in patients with SIHD.<br>• Treatment with aspirin 75 to 162 mg daily and clopidogrel 75 mg daily might be reasonable in certain high-risk patients with SIHD.<br>• Dipyridamole is not recommended as antiplatelet therapy for patients with SIHD.<br><br>Renin-angiotensin-aldosterone blocker therapy<br>• ACE inhibitors should be prescribed in all patients with SIHD who also have hypertension, diabetes mellitus, LV ejection fraction 40% or less, or |

| Clinical Guideline | Recommendations |
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| | chronic kidney disease, unless contraindicated.<br>• Angiotensin-receptor blockers are recommended for patients with SIHD who have hypertension, diabetes mellitus, LV systolic dysfunction, or chronic kidney disease and have indications for, but are intolerant of, ACE inhibitors.<br>• Treatment with an ACE inhibitor is reasonable in patients with both SIHD and other vascular disease.<br>• It is reasonable to use angiotensin-receptor blockers in other patients who are ACE inhibitor intolerant.<br><br>Influenza vaccination<br>• An annual influenza vaccine is recommended for patients with SIHD.<br><br>Additional therapy to reduce risk of MI and death<br>• Estrogen therapy is not recommended in postmenopausal women with SIHD with the intent of reducing cardiovascular risk or improving clinical outcomes.<br>• Vitamin C, vitamin E, and beta-carotene supplementation are not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD.<br>• Treatment of elevated homocysteine with folate or vitamins B6 and B12 is not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD.<br>• Chelation therapy is not recommended with the intent of improving symptoms or reducing cardiovascular risk in patients with SIHD.<br>• Treatment with garlic, coenzyme Q10, selenium, or chromium is not recommended with the intent of reducing cardiovascular risk or improving clinical outcomes in patients with SIHD. |
| The American College of Cardiology/ American Heart Association: **Practice Guidelines for the Management of Patients with Peripheral Artery Disease (2011)**[17,18] | Exercise and lower extremity PAD rehabilitation<br>• A program of supervised exercise training is recommended as an initial treatment modality for patients with intermittent claudication.<br>• Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least three times/week for a minimum of 12 weeks.<br>• The usefulness of unsupervised exercise programs is not well established as an effective initial treatment modality for patients with intermittent claudication.<br><br>Smoking Cessation<br>• Patients who are smokers or former smokers should be asked about status of tobacco use at every visit. Patients with lower extremity PAD who use tobacco should be advised to stop smoking.<br>• Patients should be provided with counseling and assistance with developing a plan for smoking cessation.<br>• One or more of the following pharmacological therapies should be offered if not contraindicated: varenicline, bupropion and nicotine replacement therapy.<br><br>Antiplatelet and antithrombotic drugs<br>• Antiplatelet therapy is indicated to reduce the risk of MI, stroke and vascular death in patients with symptomatic atherosclerotic lower extremity PAD and in asymptomatic patients with ankle brachial index |

| Clinical Guideline | Recommendations |
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| | ≤0.90. The usefulness of antiplatelet therapy is not well established in asymptomatic patients with ankle brachial index between 0.91 and 0.99.<br>• Aspirin (75 to 325 mg/day) is recommended to reduce the risk of cardiovascular events. Clopidogrel (75 mg/day) is recommended as an alternative to aspirin.<br>• Combination of aspirin and clopidogrel may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD who are at high cardiovascular risk and not at increased risk of bleeding.<br>• The addition of warfarin to antiplatelet therapy is of no proven benefit and is potentially harmful due to increased risk of major bleeding.<br><br>Medical and pharmacological treatment for claudication<br>• Cilostazol (100 mg orally twice daily) is indicated as an effective therapy to improve symptoms and increase walking distance in patients with lower extremity PAD and intermittent claudication (in the absence of heart failure).<br>• A therapeutic trial of cilostazol should be considered in all patients with lifestyle-limiting claudication (in the absence of heart failure).<br>• Pentoxifylline (400 mg three times daily) may be considered as second-line alternative therapy to cilostazol to improve walking distance in patients with intermittent claudication.<br>• The clinical effectiveness of pentoxifylline as therapy for intermittent claudication is marginal and not well established.<br>• The effectiveness of L-arginine for patients with intermittent claudication is not well established.<br>• The effectiveness of propionyl L-carnitine as a therapy to improve walking distance in patients with intermittent claudication is not well established.<br>• The effectiveness of ginkgo biloba as a therapy to improve walking distance in patients with intermittent claudication is not well established.<br>• Oral vasodilator prostaglandins such as beraprost* and iloprost are not effective medications to improve walking distance in patients with intermittent claudication.<br>• Vitamin E is not recommended as a treatment for patients with intermittent claudication.<br>• Chelation (e.g. ethylenediaminetetraacetic acid) is not indicated for treatment of intermittent claudication and may have harmful adverse effects. |
| American Heart Association/American College of Cardiology/ Heart Rhythm Society: **Guideline for the Management of Patients with Atrial Fibrillation: Executive Summary (2014)**[19] | Recommendations for risk-based antithrombotic therapy:<br>Class I<br>• In patients with AF, antithrombotic therapy should be individualized based on shared decision-making after discussion of the absolute and relative risks of stroke, bleeding and the patient's values and preferences.<br>• Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF patter is paroxysmal, persistent, or permanent.<br>• In patients with nonvalvular AF, the $CHA_2DS_2$-VASc score is recommended for assessment of stroke risk.<br>• For patients with AF who have mechanical heart valves, warfarin is recommended and the target INR should be based on type and location of the prosthesis.<br>• For patients with nonvalvular AF with prior stroke, TIA, or a $CHA_2DS_2$- |

| Clinical Guideline | Recommendations |
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| | VASc score ≥2, oral anticoagulants are recommended. Options include warfarin (INR 2.0 to 3.0), dabigatran, rivaroxaban, or apixaban.<br>• Among patients treated with warfarin, the INR should be determined at least weekly during initiation of antithrombotic therapy and at least monthly when anticoagulation (INR in range) is stable.<br>• For patients with nonvalvular AF unable to maintain a therapeutic INR level with warfarin, use of a direct thrombin or factor Xa inhibitor is recommended.<br>• Re-evaluation of the need for and choice of antithrombotic therapy at periodic intervals is recommended to reassess stroke and bleeding risks.<br>• Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures that require interruption of warfarin. Decisions regarding bridging therapy should balance the risks of stroke and bleeding.<br>• For patients with AF without mechanical heart valves who require interruption of warfarin or newer anticoagulants for procedures, decisions about bridging therapy (LMWH or UFH) should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated.<br>• Renal function should be evaluated prior to initiation of direct thrombin or factor Xa inhibitors and should be re-evaluated when clinically indicated and at least annually.<br>• For patients with atrial flutter, antithrombotic therapy is recommended according to the same risk profile used for AF.<br>Class IIa<br>• For patients with nonvalvular AF and a $CHA_2DS_2$-VASc score of 0, it is reasonable to omit antithrombotic therapy.<br>• For patients with nonvalvular AF with a $CHA_2DS_2$-VASc score of ≥2 and who have end-stage chronic kidney disease (creatine clearance <15 mL/min) or who are on hemodialysis, it is reasonable to prescribe warfarin (INR 2.0 to 3.0) for oral anticoagulation.<br>Class IIb<br>• For patients with nonvalvular AF and a $CHA_2DS_2$-VASc score of 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered.<br>• For patients with nonvalvular AF and moderate-to-severe chronic kidney disease with a $CHA_2DS_2$-VASc score of ≥2, treatment with reduced doses of direct thrombin or factor Xa inhibitors may be considered (e.g., dabigatran, rivaroxaban, or apixaban), but safety and efficacy have not been established.<br>• In patients with AF undergoing PCI, bare-metal stents may be considered to minimize the required duration of dual antiplatelet therapy. Anticoagulation may be interrupted at the time of the procedure to reduce the risk of bleeding ant the site of peripheral arterial puncture.<br>• Following coronary revascularization (percutaneous or surgical) in patients with AF and a $CHA_2DS_2$-VASc score of ≥2, it may be reasonable to use clopidogrel (75 mg once daily) concurrently with oral anticoagulants but without aspirin.<br>Class III: No Benefit<br>• The direct thrombin inhibitor, dabigatran, and the factor Xa inhibitor, rivaroxaban, are not recommended in patients with AF and end-stage chronic kidney disease or on hemodialysis because of the lack of evidence from clinical trials regarding the balance of risks and benefits. |

| Clinical Guideline | Recommendations |
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| | Class III: Harm<br>• The direct thrombin inhibitor, dabigatran, should not be used in patients with AF and a mechanical heart valve.<br><br>Recommendations for thromboembolism prevention:<br>Class I<br>• For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion, regardless of the $CHA_2DS_2$-VASc score and the method used to restore sinus rhythm.<br>• For patients with AF or atrial flutter of more than 48 hours duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least four weeks after cardioversion unless contraindicated.<br>• For patients with AF or atrial flutter of less than 48-hour duration and with high risk stroke, intravenous heparin or LMWH, or administration of a factor Xa or direct thrombin inhibitor, is recommended as soon as possible before or immediately after cardioversion, followed by long-term anticoagulation therapy.<br>• Following cardioversion for AF of any duration, the decision regarding long-term anticoagulation therapy should be based on the thromboembolic risk profile.<br>Class IIa<br>• For patients with AF or atrial flutter of 48-hour duration or longer or of unknown duration who have not been anticoagulated for the preceding three weeks, it is reasonable to perform a TEE prior to cardioversion and proceed with cardioversion if no LA thrombus is identified, including in the LAA, provided that anticoagulation is achieved before TEE and maintained after cardioversion for at least four weeks.<br>• For patients with AF or atrial flutter of 48-hour duration or longer, or when the duration of AF is unknown, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for at least three weeks prior to and four weeks after cardioversion.<br>Class IIb<br>For patients with AF or atrial flutter of less than 48-hour duration who are at low thromboembolic risk, anticoagulation (heparin, LMWH, or a new oral anticoagulant) or no antithrombotic therapy may be considered for cardioversion, without the need for post cardioversion oral anticoagulation. |
| American Heart Association/American Stroke Association: **Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation (2012)**[20] | Primary prevention<br>• Antiplatelet therapy with aspirin is recommended for low-risk and some moderate-risk patients with AF on the basis of patient preference, bleeding risk and access to anticoagulation monitoring.<br>• In high-risk patients with AF who are unable to take oral anticoagulants, dual antiplatelet therapy with clopidogrel plus aspirin offers more protection against stroke than aspirin alone but is associated with an increased risk of major bleeding.<br><br>Secondary prevention<br>• In patients who are unable to take oral anticoagulants, aspirin alone is recommended. The risk of bleeding of the combination of clopidogrel plus aspirin is similar to warfarin and is therefore not recommended for |

| Clinical Guideline | Recommendations |
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| | patients with hemorrhagic contraindication to warfarin.<br><br>Combination therapy with new oral anticoagulants<br>• The safety and efficacy of combining dabigatran, rivaroxaban or apixaban with an antiplatelet agent have not been established. |
| 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)**[21] | • Aspirin should be started at 75 to 162 mg/day and continued indefinitely in all patients unless contraindicated.<br>• 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)**[22] | Therapy to improve prognosis<br>• 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.<br>• The use of unopposed cyclooxygenase-2 inhibition is not recommended in patients with stable angina pectoris.<br>• Clopidogrel may be combined with aspirin after coronary stenting or an ACS for a finite period of time, but combination therapy is currently not recommended in stable angina pectoris.<br>• Dipyridamole is not recommended for antithrombotic treatment of stable angina. |
| American Heart Association/American College of Cardiology Foundation: **Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2011 Update (2011)**[23] | Antiplatelet agents/anticoagulants<br>• Aspirin 75 to 162 mg daily is recommended in all patients with coronary artery disease unless contraindicated.<br>  o Clopidogrel 75 mg daily is recommended as an alternative for patients who are intolerant of or allergic to aspirin.<br>  o Combination therapy with both aspirin 75 to 162 mg daily and clopidogrel 75 mg daily may be considered in patients with stable coronary artery disease.<br>• A $P2Y_{12}$ receptor antagonist in combination with aspirin is indicated in patients after ACS or PCI with stent placement.<br>  o For patients receiving a bare-metal stent or drug-eluting stent during PCI or ACS, clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily should be given for at least 12 months.<br>  o If the risk of morbidity from bleeding outweighs the anticipated benefit afforded by thienopyridine therapy after stent implantation, earlier discontinuation (e.g., 12 months) is reasonable. The risk for serious cardiovascular events because of early discontinuation of thienopyridines is greater for patients with drug-eluting stents than those with bare-metal stents.<br>  o After PCI, it is reasonable to use aspirin 81 mg daily in preference to higher maintenance doses.<br>• For patients undergoing CABG, aspirin should be started within six hours after surgery to reduce saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg daily for one year appear to be efficacious. |

| Clinical Guideline | Recommendations |
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| | o For patients undergoing CABG, clopidogrel (75 mg daily) is a reasonable alternative in patients who are intolerant of or allergic to aspirin.<br>• In patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA, treatment with aspirin alone (75 to 325 mg daily), clopidogrel alone (75 mg daily) or the combination of aspirin plus dipyridamole ER (25 mg and 200 mg twice daily, respectively) should be started and continued.<br>• For patients with symptomatic atherosclerotic PAD of the lower extremity, antiplatelet therapy with aspirin (75 to 325 mg daily) or clopidogrel (75 mg daily) should be started and continued.<br>o The benefits of aspirin in patients with asymptomatic PAD of the lower extremities are not well established.<br>• Antiplatelet therapy is recommended in preference to anticoagulant therapy with warfarin or other VKA to treat patients with atherosclerosis.<br>o If there is a compelling indication for anticoagulant therapy, such as AF, prosthetic heart valve, LV thrombus or concomitant venous thromboembolic disease, warfarin should be administered in addition to the low-dose aspirin (75 to 81 mg daily).<br>o For patients requiring warfarin, therapy should be administered to achieve the recommended INR for the specific condition.<br>o Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely. |
| European Association for Cardiovascular Prevention and Rehabilitation: **European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)**[24] | Antithrombotic therapy<br>• Antiplatelet therapy, in particular low-dose aspirin, is recommended for hypertensive patients with cardiovascular events.<br>• Antiplatelet therapy with aspirin is not recommended for people with diabetes who do not have clinical evidence of atherosclerotic disease.<br>• In ACS and for the following 12 months, dual antiplatelet therapy with $P2Y_{12}$ inhibitor (ticagrelor or prasugrel) added to aspirin is recommended unless contraindicated due to such as excessive risk of bleeding.<br>o Clopidogrel (600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.<br>• In the chronic phase (>12 months) after MI, aspirin is recommended for secondary prevention.<br>• In patients with noncardioembolic TIA or ischemic stroke, secondary prevention with dipyridamole plus aspirin or clopidogrel alone is recommended.<br>o In the case of intolerance to dipyridamole or clopidogrel, aspirin alone is recommended.<br>• In patients with noncardioembolic cerebral ischemic events, anticoagulation is not superior to aspirin and is not recommended.<br>• Aspirin or clopidogrel cannot be recommended in individuals without cardiovascular or cerebrovascular disease due to the increased risk of major bleeding. |
| European Society of Cardiology, Task Force on the Use of Antiplatelet Agents in | Major recommendations for individual antiplatelet agents<br>Aspirin:<br>• Aspirin once-daily is recommended in all clinical conditions in which antiplatelet prophylaxis has a favorable benefit/risk profile. |

| Clinical Guideline | Recommendations |
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| Patients With Atherosclerotic Cardiovascular Disease: **Expert Consensus Document on the Use of Antiplatelet Agents (2004)**[25] | • 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.<br>• 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).<br>• 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.<br>• No test of platelet function is recommended to assess the antiplatelet effect of aspirin in the individual patient.<br>• 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.<br>• 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.<br>  • 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.<br>Ticlopidine:<br>• The role of ticlopidine in the present therapeutic armamentarium is uncertain.<br>• 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.<br>• In contrast to clopidogrel, ticlopidine does not have an approved indication for patients with a recent MI.<br>Clopidogrel:<br>• 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.<br>• Clopidogrel 75 mg/day is an appropriate alternative for high-risk patients with coronary, cerebrovascular or PAD who have a contraindication to low-dose aspirin.<br>• 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.<br>Dipyridamole:<br>• Although the combination of low-dose aspirin and dipyridamole ER (200 mg twice-daily) is considered an acceptable option for initial therapy of patients with noncardioembolic cerebral ischemic events, there is no |

| Clinical Guideline | Recommendations |
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| | 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 (Ticlid®) are available generically, and single-entity aspirin is available in several over-the-counter formulations. Prasugrel (Effient®), ticagrelor (Brilinta®), vorapaxar (Zontivity®) and the fixed-dose combination product of aspirin and dipyridamole extended-release (ER) (Aggrenox®) are not available generically. Aggrenox® is not interchangeable with the commercially available generic formulations of aspirin and dipyridamole since the strengths and delivery mechanisms are different among these products.[1-8]

Aspirin has been the most frequently studied platelet inhibitor and is usually the reference drug to which other treatments are compared.[47] 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) as well as 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 and unstable angina). Antiplatelet therapy is also recommended in patients with ST-elevation MI. For patients with noncardioembolic ischemic strokes or TIAs, aspirin/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.[9-15] In a trial comparing aspirin plus dipyridamole ER and clopidogrel (with or without telmisartan), results demonstrated that neither treatment was “superior” to the other in the prevention of recurrent stroke.[38] 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.[10]

Clopidogrel and ticlopidine are adenosine diphosphate receptor antagonists and have been shown to significantly reduce the odds of a serious vascular event in high-risk patients. The CAPRIE trial 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 who were enrolled in the trial 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.[48]

Prasugrel is a adenosine diphosphate receptor antagonist which has been reported to be the most potent of these agents and to have more desirable characteristics when compared to clopidogrel with regards to drug-drug interactions and interpatient enzyme variability.[26-28] Approval of this agent was based on the results from the TRITON-TIMI 38 trial, 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.[86] The American College of Cardiology/American Heart Association recommends the use of prasugrel in patients with a STEMI in which PCI is planned. The overall recommendation is for a thienopyridine to be used in these patients, with both clopidogrel and prasugrel listed as potential options.

Of note, use of prasugrel in STEMI patients with a prior history of stroke or TIA for whom primary PCI is not recommended.[13]

Ticagrelor is a platelet inhibitor 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.[5] As a cyclopentyltriazolopyrimidine, ticagrelor works in a similar manner to the other thienopyridine platelet inhibitors (clopidogrel, prasugrel, ticlopidine); however, ticagrelor is a reversible inhibitor of the $P2Y_{12}$ receptors. In addition, ticagrelor is not a prodrug and therefore does not require enzymatic conversion to become pharmacologically active, and is not subject to potential drug interactions associated with the other agents.[5,29] The pivotal clinical trial establishing the safety and efficacy of ticagrelor in reducing the rate of thrombotic cardiovascular events in patients with ACS is the PLATO trial. PLATO was a large, international, prospective, double-blind, randomized controlled trial 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.[61] There was no difference in quality of life scores between the clopidogrel group and the ticagrelor group in hospitalized patients with ACS during the PLATO trial.[76]

Approval of vorapaxar was based on the TRA2ºP-TIMI 50 trial. This study evaluated the efficacy and safety of vorapaxar in reducing atherothrombotic events in patients with established atherosclerosis who were receiving standard therapy. After completion of enrollment and a median of 24 months follow-up, the data and safety monitoring board reported an excess of intracranial hemorrhage (ICH) in patients with a history of stroke in the vorapaxar group and recommended the discontinuation of vorapaxar in all patients with a current or previous stroke. Among the patients with a history of stroke, the rate of ICH in the vorapaxar group was 2.4%, as compared with 0.9% in the placebo group (P<0.001). Among patients without a history of stroke, the rates of ICH were lower in the two study groups (0.6% in the vorapaxar group and 0.4% in the placebo group, P=0.049). Vorapaxar was effective at reducing the composite of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR) in post-MI or PAD patients without a history of stroke or TIA with significant relative risk reduction of 17% over the three years of the study (10.1% in the vorapaxar group compared to 11.8% in the placebo group [hazard ratio (HR), 0.83; 95%CI, 0.76 to 0.90; P<0.001]).[78] The TRA*CER trial evaluated vorapaxar efficacy and safety when added to standard antiplatelet therapy to prevent cardiovascular complications in patients with unstable angina/Non-ST-Segment Elevation MI (UA/NSTEMI). [82]

Clinical trials have shown that ticlopidine reduces the risk of stroke and other vascular outcomes in patients with cerebrovascular disease. Randomized trials that compared ticlopidine with aspirin in stroke or TIA patients produced conflicting results regarding whether ticlopidine is more effective than aspirin.[43,44] 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.[84] 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.[6]

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.[35,37] Aspirin plus dipyridamole significantly reduced the risk of stroke by 37% compared to 18% with aspirin and 16% with dipyridamole. There was no significant difference in all-cause mortality among the active treatment groups.[35] Aspirin plus 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.[33]

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.[1,110-115]

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